Eberhard Karls Universität Tübingen
Faculty of Science
Department of Psychology

MASTER THESIS

M. Sc. Psychology

Meta-Analyses Investigating Basal and Stress-Induced Cortisol Levels in Schizophrenia Patients and Healthy Controls

Teresa Luther

19 January 2022

Primary Supervision: Prof. Dr. Jennifer Svaldi
Secondary Supervision: Dr. Lydia Kogler

Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Abschlussarbeit selbstständig verfasst und ohne fremde Hilfe angefertigt habe sowie mich keiner anderen als den angegebenen Hilfsmitteln und Quellen bedient habe. Alle wörtlich oder sinngemäß aus anderen Werken entnommenen Textstellen sind als solche kenntlich gemacht. Die eingereichte elektronische Fassung entspricht dieser schriftlichen Fassung exakt. Die vorliegende Arbeit war bisher weder vollständig noch in wesentlichen Teilen Gegenstand eines anderen Prüfungsverfahrens und wurde bisher auch nicht veröffentlicht. Die Richtlinien zur Sicherung guter wissenschaftlicher Praxis und zum Umgang mit wissenschaftlichem Fehlverhalten wurden bei der Erstellung dieser Abschlussarbeit beachtet. Ich bin mir bewusst, dass eine unwahre Erklärung rechtliche Folgen haben kann.

Tübingen, den 19. Januar 2022

Teresa Luther

Abstract

Evidence is accumulating for dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in schizophrenia, with several studies pointing to a central role for cortisol in this severe psychiatric disorder. Elevated cortisol levels in the morning and a blunted cortisol awakening response (CAR) are common findings in patients with schizophrenia compared to healthy controls. However, inconsistent conclusions have been drawn regarding afternoon and evening cortisol levels, as well as with cortisol reactivity to psychosocial and physical stress in schizophrenia. Therefore, we performed meta-analyses comparing patients with schizophrenia to healthy controls on several cortisol outcomes to improve our understanding of HPA axis dysregulation in schizophrenia. Our analyses revealed schizophrenia to be associated with significantly elevated baseline cortisol levels both in the morning and in the evening. However, no significant group differences were found in afternoon cortisol levels and, contrasting previous meta-analytic findings, we also did not find evidence for an altered CAR in schizophrenia. Our results on cortisol stress reactivity indicate a similar pattern of cortisol secretion in patients with schizophrenia and healthy controls in response to mental and physiological stress. Overall, we found meta-analytic evidence of time-specific alterations in baseline cortisol secretion in association with schizophrenia. The lack of differences in cortisol response to stress in our findings should be interpreted cautiously given the paucity of studies investigating mental and physiological stress in schizophrenia. This work highlights the need for further empirical investigation and warrants replication studies related to the current findings in order to gain insight into how schizophrenia and HPA axis functioning are related.

Table of Contents

Meta-Analyses Investigating Basal and Stress-Induced Cortisol Levels in Schizophrenia Patients and Healthy Controls

Schizophrenia is a severe neuropsychiatric disorder that typically manifests in late adolescence or early adulthood and affects approximately 20 million of the world population, as estimated by the World Health Organization (2019b). The disorder is characterized by a wide spectrum of symptoms, with the core clinical features including hallucinations and delusions (i.e., positive symptoms), affective flattening, alogia, avolition (i.e., negative symptoms), and cognitive impairment, resulting in social and occupational dysfunctions according to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013, p. 99). Despite its relatively low lifetime prevalence rate, estimated at about 1% worldwide (Saha et al., 2005), schizophrenia has been repeatedly found to be associated with a range of adverse outcomes, ranking the disorder as the 22nd leading cause of disability-adjusted life years in the age group 25–49 worldwide according to the Global Burden of Disease Study (GBD 2019 Diseases and Injuries Collaborators, 2020). Compared to the general population, higher prevalence rates of co-occurring general medical conditions (de Hert et al., 2011; Leucht et al., 2007) and elevated suicide rates (Hor & Taylor, 2010; Palmer et al., 2005) represent major contributors to increased premature mortality risks among individuals with schizophrenia, with life expectancy reduced by an average of 15–20 years (E. E. Lee et al., 2018). Moreover, schizophrenia is associated with a higher unemployment rate (Evensen et al., 2016), a significantly lower quality of life (Dong et al., 2019), and a higher prevalence of psychiatric comorbidities (Buckley et al., 2009). The early onset and often chronic recurrent course of illness (Owen et al., 2016), as well as the often unsatisfactory response to treatment (Saha et al., 2005), further add to the substantial overall health and economic burden that is not only borne by the patients, but also by their families and society (Chong et al., 2016).

The diverse psychopathology which characterizes schizophrenia was already conveyed in the first conceptualization of the disorder by Bleuler through the term “group of schizophrenias” (Bleuler, 1950). Its complexity has since elicited continual debate and led to frequent changes and re-conceptions of the disorder over the last several decades (Tandon et al., 2013). Only recently has a tribute to the heterogeneity and variety of symptoms been given via revision of the two major diagnostic systems of psychiatric classifications. By eliminating the subtypes of schizophrenia and implementing a dimensional approach to diagnosis with symptom specification, symptoms of the disorder can be more reliably described in the revised versions of the DSM (DSM-5; American Psychiatric Association, 2013) and International Classification of Diseases (ICD-11; World Health Organization, 2019a). Furthermore, the

revised versions of the diagnostic systems may provide useful platforms for integrating ongoing ever-evolving scientific knowledge (Tandon et al., 2013). At the same time however, although huge efforts are being made to better understand the pathophysiological underpinnings of the disorder, the etiological factors implicated in schizophrenia still remain largely elusive (Biedermann & Fleischhacker, 2016; Tandon et al., 2013).

A variety of models and theories have been proposed to explain schizophrenia causation, ranging from biological approaches that focus on neurodevelopmental abnormalities (e.g., Fatemi & Folsom, 2009) to cognitive models that emphasize the role of dysfunctional cognitive processes and emotions as important factors in the etiology of schizophrenia (e.g., Sarin & Wallin, 2014). One of the most influential and widely accepted perspectives for conceptualizing the etiology of schizophrenia is the diathesis-stress theory or vulnerability-stress theory, respectively (Kendler, 2020). Even though several diathesis-stress models have been proposed for schizophrenia (e.g., Ciompi, 1989; Nuechterlein & Dawson, 1984; Zubin & Spring, 1977), the fundamental assumption of all these models is that the etiology of schizophrenia is most likely multifactorial and based on a dynamic interaction between multiple vulnerability factors (e.g., genetic predispositions) and stressors (Cheng et al., 2016). In particular, these models posit that a range of stressors, defined as external environmental factors, may precipitate schizophrenia in (genetically) predisposed individuals when the individual threshold point is reached at which the stress level exceeds the vulnerability level (Cheng et al., 2016). Twin studies suggest that schizophrenia is highly heritable, with estimates of around 80% (Owen et al., 2016). Genome-wide association studies have identified a large number of genetic risk loci for schizophrenia, indicating a substantial polygenic contribution to the genetic liability of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

There is evidence that individuals with a higher than average vulnerability to develop schizophrenia (i.e., high-risk individuals) have an increased stress sensitivity as they are more frequently exposed to adverse life events and minor daily stressors, report higher levels of perceived stress and experience greater emotional reactivity in relation to these events (Fusar-Poli et al., 2017; Myin-Germeys & van Os, 2007; Trotman et al., 2014). These findings are in accordance not only with diathesis/vulnerability-stress models, posing that vulnerability factors render an individual more or less reactive to stressors, but also with sensitization theory whereby repeated or chronic exposure to environmental stressors results in greater response to stressors over time in high-risk individuals (Collip et al., 2008). Moreover, similar to the findings in high-risk individuals, patients with an established diagnosis of schizophrenia also have reported a heightened number of stressful life events and traumas, and likewise have been

widely observed to have an altered response to stress (Mansueto & Faravelli, 2017; Myin-Germeys et al., 2001). The definite causes of altered stress reactivity have not yet been fully clarified, however, the biological counterparts of stress reactivity have been the focus of research in recent years, and models incorporating neurobiological mechanisms (such as the neural diathesis stress model; E. F. Walker & Diforio, 1997) suggest a pivotal role of the hypothalamic-pituitary-adrenal (HPA) axis in this regard.

Stress and the Role of the HPA Axis in the Physiological Stress Response

Stress, originally defined by Selye as "the non-specific response of the body to any demand" (Selye, 1975, p. 39), occurs when the dynamic equilibrium, or homeostasis, of an organism is challenged by internal or external "stressors" with potentially adverse effects (Deussing & Chen, 2018). When a stressor of any kind is appraised as stressful and exceeds a certain threshold, behavioral and physiological compensatory mechanisms are activated. Such a system enables the organism to adequately respond and adapt to the stressor, thereby helping the body to maintain homoeostasis in the presence of stressors (S. Cohen et al., 2016; Deussing & Chen, 2018).

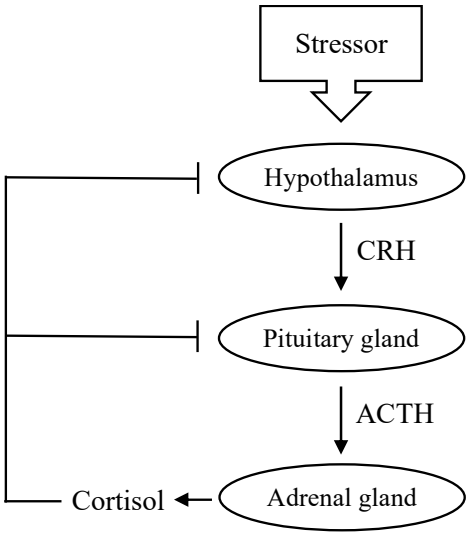
In humans, the stress system subserves the adaptive response by activating the two major stress-responsive systems, the locus caeruleus-norepinephrine-autonomic nervous system as well as the HPA axis (Chrousos, 2009). Following a stressor, excitatory projections from brain areas such as the amygdala and the medial prefrontal cortex activate the autonomic nervous system and the HPA axis (Chrousos, 2009). When a stressor is detected, the hypothalamic paraventricular nucleus (PVN) secretes corticotropin releasing hormone (CRH) and, to a lesser extent, arginine vasopressin (AVP) into the hypophyseal portal system where the neuropeptides CRH and AVP act on the anterior lobe of the pituitary gland to stimulate the production and release of adrenocorticotropic hormone (ACTH). Subsequently, circulating ACTH binds to receptors in the adrenal cortex and thereby induces the adrenal glands to synthesize and release corticosteroids, including the glucocorticoid hormone cortisol, into the bloodstream (Corcoran et al., 2003). The released cortisol in turn elicits cascading effects on various bodily functions involving the metabolic, immune, cardiovascular, and gastrointestinal systems (Chrousos, 2009).

In the short term, in acutely stressful situations, the activation of the HPA axis is highly adaptive as the rapid rise in cortisol levels mobilizes the critical energetic resources to cope with the stressful challenge and furthermore exerts effects that are necessary for the termination of the HPA axis response, i.e., for the rapid return of cortisol to pre-stress levels (Charmandari et al., 2004; Gjerstad et al., 2018). The latter is achieved via a negative feedback mechanism

which involves cortisol-mediated inhibition of HPA axis activity through inhibition of CRH and ACTH secretion from the PVN and anterior pituitary gland, respectively (Charmandari et al., 2004). See Figure 1 for an illustration of the basic functioning of the HPA axis. Long term activation of the HPA axis and hypersecretion of cortisol due to prolonged stressful conditions have been associated with hippocampal volume reduction (Lupien et al., 2009) and can result in dysregulation of adaptive mechanisms. This in turn has been linked to development and exacerbation of several mental and physical disorders (e.g., major depression, bipolar disorders, schizophrenia, and anxiety disorders; de Kloet et al., 2005).

Figure 1

Basic Physiology of the HPA Axis in the Occurrence of a Stressor



Note. CRH = corticotropin releasing hormone; ACTH = adrenocorticotropic hormone; the solid arrows represent excitatory-based interactions and lines with a bar indicate inhibitory connections that operate through negative feedback mechanisms.

In addition to its response to stressors, cortisol secretion exhibits a distinct 24-hour circadian rhythm under basal conditions, with the highest cortisol concentrations typically observed in the early hours of the morning just after awakening (Fries et al., 2009). This dynamic phenomenon of a sharp increase in cortisol concentration triggered by the process of awakening is known as the cortisol awakening response (CAR) and usually occurs during the first hour after awakening, with cortisol levels peaking between 30 and 45 minutes post-awakening (Steptoe & Serwinski, 2016; Wilhelm et al., 2007). Following this initial increase, cortisol levels steeply decline over the next three hours after awakening and throughout the

remainder of the day, cortisol concentration then gradually declines before a nadir is reached around midnight (Fries et al., 2009). Cortisol levels remain low during sleep and then begin to escalate again prior to awakening (Fries et al., 2009).

Experimental Stress Induction and Measurement of Cortisol Levels

In human stress research, cortisol secretion, which can reflect the function of the HPA axis, is commonly indexed using basal cortisol levels, the CAR, and the cortisol stress response. Cortisol levels are usually measured at multiple time points, within one hour after awakening in order to calculate the CAR represented as the area under the curve with respect to the cortisol increase (AUC_i; J. C. Pruessner et al., 2003), and as the difference between before and after stress induction for assessing the cortisol stress response. To investigate acute stress reactions in healthy individuals, as well as in individuals with psychiatric disorders, a wide range of stress induction methods can be applied in the laboratory setting, including methods to induce mental (or psychological) stress and physiological stress. While mental stress is usually induced by standardized laboratory paradigms which involve a social evaluation component or cognitive load, physiological stress is usually induced by laboratory stimuli which provoke cortisol increase due to physiological demands. Commonly applied paradigms for inducing mental stress include the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005), the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977), and mental arithmetic tasks; common methods for inducing physiological stress include the cold pressor test, noise exposure and tests with bicycle ergometer exercise.

Cortisol levels can be obtained from various biological specimens, the most common of which include peripheral samples (e.g., in saliva, blood, urine, and hair) and cerebrospinal fluid. While cortisol concentrations in saliva, blood and urine reflect stress-related changes over a relatively short period of time, hair has been suggested to provide a measure of chronic stress and has been established as method for retrospectively determining cumulative cortisol secretion over prolonged periods of time, up to several months (M. Pruessner et al., 2017).

Schizophrenia and Stress

According to the neural diathesis-stress model of schizophrenia proposed by Walker and Diforio (E. F. Walker & Diforio, 1997; E. Walker et al., 2008), predisposing biological vulnerability factors and environmental stressors synergistically increase the risk for developing schizophrenia. Biological vulnerability factors can lead to structural and functional alterations in hippocampal brain areas and repeated or chronic exposure to environmental stress can result in hyperactivation of the HPA axis and therewith elevate cortisol secretion (E. Walker

et al., 2008). The HPA axis plays a pivotal role in mediating the effects of environmental stressors on constitutional vulnerability. Dysregulation of the HPA axis can lead to triggering and exacerbating schizophrenic symptoms via reciprocal regulatory processes between the HPA axis and the subcortical dopamine system (E. Walker et al., 2008). The neural diathesis-stress model as a theoretical framework for the development of schizophrenia draws on early empirical findings which suggest a link between HPA axis function and psychosis, and has ever since its first publication approximately 20 years ago sparked a great research interest in the role of stress and HPA axis activity in schizophrenia. In accordance with the neural diathesis-stress model, alterations in hippocampal volume, particularly reductions in hippocampal volume, have been frequently reported in schizophrenia (Adriano et al., 2011). Furthermore, accumulated evidence highlights HPA axis dysfunction in association with disorders across the schizophrenia and psychosis spectrum (for a review on HPA axis function over the illness course, see M. Pruessner et al., 2017).

Regarding baseline cortisol levels, studies generally yielded results consistent with components of the neural diathesis-stress model, showing elevated salivary and blood cortisol levels both in the morning and throughout the day. These findings were observed in both patients with an established diagnosis of schizophrenia and those having had a first-episode (e.g., Borges et al., 2013; Girshkin et al., 2014). Elevated morning cortisol levels may be largely independent of patients' medication status as they have been reported in single salivary and blood samples among antipsychotic-naive and drug-free schizophrenia patients (e.g., Venkatasubramanian et al., 2010; Zhang et al., 2005), as well as among patients who were on antipsychotic medication at the time of sampling (e.g., Bulut et al., 2016; Yıldırım et al., 2011). Apart from heightened morning cortisol levels, research also indicates elevated afternoon cortisol levels in schizophrenia patients. These elevated levels of cortisol were evident in blood samples collected from antipsychotic-naive first-episode patients and medicated schizophrenia patients, respectively (Gallagher et al., 2007; Ryan, Sharifi, et al., 2004). Moreover, heightened cortisol levels in schizophrenia patients have also been found in saliva samples collected in the evening (Faravelli et al., 2017) and in indices of diurnal cortisol secretion calculated from repeated cortisol measurements throughout the day (Mondelli et al., 2010). Although these findings can collectively be seen as evidence for heightened baseline cortisol values in schizophrenia patients, not all studies have replicated these findings.

A meta-analysis focusing on salivary cortisol levels concluded that there is evidence of moderate elevations in salivary cortisol levels in ultra-high risk individuals relative to healthy controls, however, no significant group differences in cortisol levels were found between first-

episode patients and healthy controls (Chaumette et al., 2016). Consistent with these meta-analytic findings, there are also several more recent studies that have reported similar baseline concentrations of cortisol in schizophrenia patients and healthy controls. Two of which examined morning levels of blood cortisol obtained at a single time point and found no significant differences in cortisol levels between schizophrenia and first-episode patients compared to healthy controls (Allott et al., 2018; C. H. Lee et al., 2019). In addition to these results of non-significant differences, some studies even reported significantly lower cortisol levels in patients with schizophrenia compared to healthy controls, as measured in morning blood and afternoon saliva samples, respectively (Das et al., 2018; Phassouliotis et al., 2012).

Mixed results have also been reported in studies that have compared cortisol levels of schizophrenia patients and healthy controls at multiple time points during the day. While some studies reported heightened blood and saliva cortisol levels in schizophrenia patients both in the morning and in the afternoon (Altamura et al., 1989; Morphy et al., 1985; Nordholm et al., 2018), significantly reduced blood cortisol levels were found for these time windows in a study of Hoshino et al. (1984). Interestingly, different results have also been found when cortisol levels were compared at different time points during the day within the same studies. For example, while significantly elevated blood cortisol levels were found in the afternoon in an exclusively male sample of schizophrenia patients compared to healthy controls, no group differences in cortisol levels were found in morning and evening measurements (Whalley et al., 1985). Such findings may indicate disruptions of the normal circadian rhythm of cortisol secretion, however, overall, findings regarding baseline cortisol levels in schizophrenia remain inconclusive and further research is warranted to disentangle the empirical inconsistencies (Bradley & Dinan, 2010).

Regarding the CAR, findings are also inconsistent as indicated by a systematic review and meta-analysis of the CAR in high-risk individuals, first-episode patients and patients with an established diagnosis of schizophrenia (Berger et al., 2016). While some studies reported blunted awakening cortisol levels among first-episode patients relative to healthy controls (Mondelli et al., 2010; Mondelli et al., 2015), several other studies did not observe group differences in the CAR in first-episode patients compared to healthy controls (Girshkin et al., 2016; Hempel et al., 2010). One study assessed the CAR in two subgroups of patients and found the CAR to be significantly reduced among patients with schizophrenia who had been exposed to cannabis before illness onset, whereas schizophrenia patients not previously exposed to cannabis showed a CAR similar to healthy controls (Monteleone et al., 2014). Evidence from a meta-analysis and review suggests attenuated CAR in first-episode patients and patients with

schizophrenia (Berger et al., 2016; Borges et al., 2013), however, the number of studies assessing CAR in patients with schizophrenia is limited and the results of more recent studies are mixed (e.g., Aas et al., 2020; Nordholm et al., 2018; Seidenfaden et al., 2017).

Drawing on the crucial role of stress exposure in the onset of schizophrenia symptoms postulated by etiological models of schizophrenia, several studies have been conducted to investigate the HPA axis response to stressors in schizophrenia by examining the cortisol response to acute laboratory stress tasks, which can be considered to serve as a proxy for the stress response to real-life stressful situations (Zorn et al., 2017). Some of the paradigms most commonly used to induce acute stress in a laboratory setting include public speaking tasks that contain social evaluation of the individual's performance, and tasks that are cognitively or physiologically demanding.

Studies investigating the cortisol response to acute psychosocial stress tasks in disorders across the schizophrenia and psychosis spectrum have generally yielded mixed results. The TSST is a widely used experimental protocol to induce psychosocial stress that typically consists of a job interview and a mental arithmetic task which occurs in front of a panel of judges and is video recorded (Kirschbaum et al., 1993). Systematic reviews and meta-analyses focusing on the cortisol response to the original or modified versions of the TSST have proposed a blunted cortisol response in patients with schizophrenia compared to healthy controls (Ciufolini et al., 2014; Zorn et al., 2017). Interestingly, in their meta-analysis, Ciufolini et al. (2014) found significantly lower cortisol levels in the anticipatory phase and a significantly attenuated peak cortisol response in the patient sample, however, no significant group differences in cortisol levels were revealed for the recovery phase or for the total amount of cortisol released in response to the TSST. The results of a more recent study are partially consistent with these meta-analytic findings, demonstrating a lack of cortisol peak concentrations in response to the TSST in patients with schizophrenia (Lange et al., 2017). However, in the study by Lange et al. (2017), significant group differences in absolute cortisol levels were reported at all time points of cortisol measurement, with the patient sample exhibiting significantly blunted salivary cortisol levels compared to the sample of healthy controls, even 60 minutes after acute psychosocial stress exposure.

Inconsistent findings were also reported in studies that employed the MIST. This psychosocial stress paradigm consists of computerized mental arithmetic tasks presented during functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) and involves negative visual and verbal feedback from the experimenter, along with a task difficulty level and a time limit adjusted to be just beyond the individual's performance level in the

experimental condition (Dedovic et al., 2005). In the control (nonstress) condition, similar arithmetic tasks are presented, but without time constraints or negative feedback from the experimenter (Dedovic et al., 2005). Compared to healthy controls and individuals at high clinical risk for developing psychosis, patients with schizophrenia who were not on antipsychotic medication at the time of sampling demonstrated the largest changes in salivary cortisol following a PET scan with sample collection occurring every 12 minutes throughout the implemented MIST (Mizrahi et al., 2012). Another study using a very similar design with sample collection in intervals of 15 minutes throughout the MIST could not replicate those findings, reporting no significant group differences in cortisol stress response (Schifani et al., 2018). Interestingly, similar to the results of Mizrahi et al. (2012), a study that applied a mental arithmetic task without a social-evaluative component yielded higher blood cortisol levels in schizophrenia patients compared to a sample of healthy controls (Albus et al., 1982). The implementation of other cognitive paradigms such as the PASAT and the Mirror Tracing Persistence Task (MTPT-C; Strong et al., 2003) along with measurement of salivary cortisol levels however, have resulted in a lack of group differences for cortisol levels. (Chiappelli et al., 2016).

Physiological paradigms that have been used to assess the cortisol stress response in schizophrenia patients are very different in their nature while at the same time have also yielded mixed results. An early study comparing unmedicated patients with schizophrenia and healthy controls was comprised of a total of four standardized stress-induction tasks and reported elevated blood cortisol levels in patients both in response to the cold pressor test (i.e., alternately immersing the feet in ice cold water for 40 seconds) and to a noise stressor (Albus et al., 1982). In contrast, in a more recent study that measured cortisol in saliva rather an attenuated cortisol response to a noise stressor was observed in medicated patients with schizophrenia (Lincoln et al., 2015). Another more recent study assessed blood cortisol levels in response to administration of electrical stimulations just below the pain threshold and no significant group differences in cortisol response between unmedicated patients with schizophrenia and healthy controls were found (C. Z. Duval et al., 2016). This report of no group differences can be considered in line with an earlier study in which salivary levels of cortisol were assessed in medicated patients with schizophrenia and healthy controls during a 10-minute bicycle ergometry exercise period as part of a total two-hour test session (Jansen et al., 2000).

Taken together, research on HPA axis functionality in schizophrenia has been growing during the last decades, and scientific evidence on neuroendocrine mechanisms has progressively been integrated into etiological models of the disorder. An increasing number of

studies has focused on the evaluation of HPA axis hormones, particularly of the stress hormone cortisol, within this context, and studies conducted on basal cortisol concentrations (i.e., without an explicit stressor), frequently reported increased cortisol levels in patients with schizophrenia compared to healthy controls – a finding often taken as evidence for hyperactivation of the HPA axis in schizophrenia. However, as the above mentioned studies highlight, literature is still characterized by conflicting findings, particularly regarding schizophrenia patient's cortisol levels at specific time points during the day (morning, afternoon, evening) and in response to experimental stress induction. As of yet, most meta-analyses in this field have focused specifically on morning cortisol levels or have evaluated baseline cortisol levels by including cortisol measures from various single time points in one analysis. Metanalysis has not yet been performed in relation to cortisol levels at specific time points taken separately throughout the day. Importantly, there is evidence of altered cortisol levels in patients with schizophrenia at specific time points during the day (e.g., Whalley et al., 1985) and such alterations may not be adequately inferred from analyses that include measurements at various different time points. Findings from previous systematic reviews and meta-analyses indicate an attenuated cortisol response to psychosocial stress in schizophrenia, but these results are based on a small number of studies analyzed and should therefore be considered as preliminary (Ciufolini et al., 2014; Zorn et al., 2017). Furthermore, to our knowledge, as of yet, no meta-analysis has been conducted to examine the cortisol response to physiological stressors, and only one systematic review and meta-analysis has been carried out focusing specifically on the CAR among schizophrenia and first-episode patients (Berger et al., 2016).

The present meta-analytic study therefore seeks to expand the scope of previous meta-analyses by more rigorously analyzing published studies on the relationship of schizophrenia and baseline cortisol levels, the CAR, and stress-induced cortisol levels. To this end, we aimed to compare cortisol levels in patients with schizophrenia and healthy controls, and to deliberately separate studies that provide baseline cortisol levels based on time of cortisol sample collection in order to more rigorously assess potential differences in baseline cortisol levels. Additionally, we aimed to run separate meta-analyses on cortisol levels in response to mental and physiological stress induction. Given that various stressors generally elicit different endocrine responses (Pacák & Palkovits, 2001), focusing on these two types of stressors enables investigation of stressor-specific differences in cortisol secretion in schizophrenia patients compared to healthy controls. Building on previous meta-analyses that assessed cortisol reactivity exclusively to psychosocial stress, we aimed to extend these findings by including both psychosocial and cognitive stress tasks in our analysis on mental stress.

Regarding baseline cortisol levels, we expected to replicate previous findings of elevated morning cortisol levels in schizophrenia patients, while for afternoon and evening cortisol levels, our hypotheses were non-directional, as previous findings have yielded inconsistent results. Regarding the CAR, we expected to replicate the meta-analytic finding of a blunted CAR in patients with schizophrenia (Berger et al., 2016). Regarding cortisol stress reactivity, as there are currently no meta-analytic studies available that focus on both cortisol response to mental stress – with additional consideration of cognitive stress tasks – and to physiological stress, hence our hypotheses were non-directional for these two meta-analyses.

Method

Literature Search and Selection of Studies

Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), a systematic literature search of the electronic database PubMed (https://pubmed.gov) was performed from inception until April 20, 2021, to identify relevant studies investigating cortisol levels in individuals with schizophrenia. The search strategy was carried out using the search string consisting of the following key words: "schizophrenia" OR "psychosis" OR "psychotic disorder" OR "first episode" OR "prodromal" OR "clinical high risk" OR "ultra high risk" AND "cortisol". The search was confined to human studies, with no restrictions being imposed in terms of publication language or any other criteria. No gray literature was included in the search.

Inclusion and Exclusion Criteria

Studies were considered eligible for inclusion if they met the following criteria: (a) reporting cortisol levels, either unstimulated (baseline) values with specification of the time of sample collection and/or CAR or raw data from at least three repeated measures taken within the first hour after awakening that allowed calculation of CAR, and/or an index of stress-induced change in cortisol levels (single or multiple values pre- and post-stress, values during a stress/control condition, or respective delta values); (b) reporting cortisol levels either as mean and standard deviation, mean and standard error, or in the form of raw values that allowed calculation of these statistics; (c) reporting cortisol levels measured either in saliva, blood, urine or cerebrospinal fluid; (d) presenting cortisol in patients with a diagnosis on the schizophrenia spectrum (including schizophrenia, schizoaffective disorder, schizophreniform disorder or other non-affective psychoses) according to any version of the DSM, the ICD and/or the Research Diagnostic Criteria (RDC) in comparison to healthy individuals without a psychiatric diagnosis.

Study exclusion occurred based on the following criteria: (a) no available full-text version of the article (neither online nor upon request from the authors or through the document delivery service of local libraries); (b) review article or meta-analysis; (c) article written in a language other than English or German; (d) use of an incompatible sampling method (e.g., analyzing cortisol in post-mortem brain tissue); (e) measurement of cortisol levels in specimens other than saliva, blood, urine or cerebrospinal fluid (e.g., cortisol concentration in hair indicative of long-term stress); (f) reporting cortisol levels either exclusively or in comparison to those in healthy individuals, in participants without a diagnosis of a schizophrenia spectrum disorder according to the DSM, ICD or RDC diagnostic criteria (e.g., in participants diagnosed according to other criteria, such as those applied by Feighner et al. (1972), in healthy individuals reporting on schizotypal traits, in individuals at high risk of developing a schizophrenia spectrum disorder, in participants meeting the DSM criteria for a schizotypal personality disorder, or in participants with other psychiatric diagnoses, such as affective disorders); (g) lacking a comparison group comprised of healthy individuals without psychiatric diagnosis; (h) nonavailability of cortisol data in the article or upon request from the authors; (i) providing cortisol data that were considered incomplete or inadequate for inclusion in our analyses (i.e., only values for healthy controls were available and/or baseline cortisol levels were not reported for stress induction; time of sample collection was not specified for baseline cortisol; and/or only cortisol levels across the day or the total cortisol output during the day were provided; and/or only values of cortisol metabolites were available; and/or no units were given for cortisol values; and/or cortisol values were reported collectively and not individually for the patient groups included; and/or only the median values and interquartile ranges were available). In cases in which sample overlap was explicitly stated in the articles of potentially eligible studies, or if the assumption of sample overlap could be confirmed by the corresponding authors, only the study with the largest sample size was included.

The inclusionary and exclusionary criteria implementation was carried out in a two-step approach. In the first stage, the titles and abstracts of all retrieved articles were screened for relevance to the research question based on the selection criteria. Subsequently, the articles that passed the initial screening and for which the full text was available, underwent full eligibility assessment according to the inclusion and exclusion criteria.

Data Extraction and Statistical Analysis

If available the following data were extracted from included studies: Author(s), year of publication, type of participants, characteristics of participants per group (sample size, age, sex distribution, diagnosis and medication status of patients), source of cortisol (saliva, blood, urine,

cerebrospinal fluid), time of sample collection for baseline cortisol, type of stress induction, and respective cortisol values (either directly retrieved or calculated from raw data).

Baseline cortisol levels, measured either before a stressor was implemented or in the absence of a stressor at time of collection, were analyzed according to the time of sample collection using single cortisol raw values. Cortisol levels in response to awakening were analyzed based on the corresponding cortisol index CAR, as well as on cortisol raw values from at least three repeated measures within the first hour after awakening, which allowed for calculation of post-awakening cortisol changes through the formula of the area under the curve with respect to the increase (AUC_i):

$$AUC_i = \left(\sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2} \right) - \left(m_1 \cdot \sum_{i=1}^{n-1} t_i \right)$$

with m_i indicating the single measurements, t_i indicating the time distance between the measurements, and n indicating the total number of measurements (J. C. Pruessner et al., 2003). To assess the secretion of cortisol in response to stress induction, delta values of change (pre- versus post-stress) were used. In some cases, these delta values could be directly retrieved from the corresponding publications, in all other cases, we used the mean cortisol concentrations at baseline (pre-stress) and post-stress (peak) to calculate the mean peak cortisol change ($\text{Cortisol}_{\text{change}} = \text{Cortisol}_{\text{post-stress peak}} - \text{Cortisol}_{\text{pre-stress}}$). If cortisol levels peaked at different time points post-stress in schizophrenia patients and healthy individuals, the time point of peak in schizophrenia patients was used for calculations of the peak cortisol change in both groups.

Quantitative meta-analyses were performed using the open-source software OpenMetaAnalyst (Wallace et al., 2009). Before extracted cortisol data was entered into the software, values were transformed to standard international (SI) units of nmol/L through an online SI units Conversion Calculator (https://unitslab.com) in case the values were originally reported in other units of measurement. In the case that the data was provided as mean and standard error (SE), the following formula was used to calculate the standard deviation (SD) from the standard error: $\text{SD} = \text{SE} \times \sqrt{N}$ (Higgins et al., 2021). For all analyses, a random effects model (DerSimonian & Laird, 1986) was fitted to calculate the standardized mean difference (SMD) and the corresponding 95% confidence interval (CI), as we expected systematic differences between studies regarding patient characteristics and cortisol assays. Hedge's *g*, a measure of effect size that is considered optimal for analysis of studies with small sample sizes (Borenstein et al., 2009), was used in all analyses as a measure of SMD. Following established

conventions, an effect size was considered small, medium, and large for values 0.20, 0.50, and 0.80, respectively (J. Cohen, 1988). Heterogeneity among the studies in each analysis was quantified using Higgins' I^2 statistic (Higgins & Thompson, 2002), an estimate of the proportion of between-study variability in effect size estimates that cannot be accounted for by random sampling error but rather is due to heterogeneity. Based on commonly applied guidelines, I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). Forest plots for each meta-analysis were generated to graphically display the individual and pooled effect size estimate, and the corresponding 95% confidence interval. For all analyses, results were considered statistically significant at the alpha = .05 level ($p < .05$; two-tailed).

If studies reported cortisol levels separately for distinct diagnostic groups on the schizophrenia spectrum (e.g., for individuals diagnosed with schizophrenia and individuals with a diagnosis of schizoaffective disorder), only data from the schizophrenia sample were included in the corresponding analyses. If studies reported a comparison of cortisol levels in schizophrenia patients and healthy individuals separately for males and females, gender-specific data were extracted and entered separately into the corresponding analyses as the male and female subgroups can be considered independent samples (Borenstein et al., 2009). However, if cortisol levels were available for two subgroups of schizophrenia patients (medicated versus unmedicated) separately, we followed the recommendation of the Cochrane Handbook for Systematic Reviews and Meta-Analyses (Higgins et al., 2021) and calculated combined means and standard deviations in order to pool the subgroups together in the corresponding analyses. This approach avoided the inclusion of the same sample of healthy individuals twice in the same meta-analysis. The combined means and standard deviations were calculated using the following formulae:

$$\bar{X} = \frac{n_1\,\bar{X}_1 + n_2\,\bar{X}_2}{n_1 + n_2}$$

$$S = \sqrt{\frac{(n_1 - 1)\,S_1^2 + (n_2 - 1)\,S_2^2 + \frac{n_1\,n_2}{n_1 + n_2}\,(\bar{X}_1 - \bar{X}_2)^2}{n_1 + n_2 - 1}}$$

where $\bar{X}_1$ and $\bar{X}_2$ represent the subgroup means, n_1 and n_2 represent the subgroup sample sizes and S_1 and S_2 represent the subgroup standard deviations (Higgins et al., 2021). If studies reported cortisol levels in schizophrenia patients at two time points, once while medicated and

once while unmedicated, only the cortisol sample taken during the medicated period was included in the corresponding analyses as this sample was considered to be more comparable when taking into account that the patient sample in most studies comprised either medicated and unmedicated or only medicated schizophrenia patients. This approach further allowed us to avoid including the same sample of schizophrenia patients twice in the same meta-analysis.

Quality Assessment

Due to variation of study design types of the included studies, comprising observational and randomized controlled studies, two different tools were applied for quality assessment as recommended by Zeng et al. (2015).

Newcastle-Ottawa Scale

The methodological quality of included case-control studies was assessed using the Newcastle-Ottawa Scale (NOS; Wells et al., 2014). The NOS, designed to assess the quality of non-randomized case-control and cohort studies, consists of eight items representing the following three domains of study quality: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure (cohort studies) or study outcome (case-control studies). A star rating system is used by which a study can be awarded a maximum of one star for each item within each of the three domains, except in domain comparability where a maximum of two stars can be awarded to a study. Thus, the total NOS score ranges from zero to nine stars for each study, with higher scores indicating a better methodological quality. The NOS has been widely applied for study quality assessment in meta-analyses and is well accepted in the literature (Deeks et al., 2003; Farrah et al., 2019).

Revised Cochrane Risk-of-Bias Tool for Randomized Trials

We evaluated the methodological quality of included randomized controlled trials (RCTs) according to the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2; Sterne et al., 2019), which bases quality appraisal on the following five main domains: Bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in the selection of the reported result. Domain-level and overall risk of bias judgments across bias domains are formulated and differentiated as low risk, some concerns and high risk. No studies in our analyses were excluded based on quality assessment.

Assessment of Publication Bias

The potential for publication bias, defined as the propensity for selective publication of studies with a statistically significant outcome leading to possible overestimation of effect sizes in meta-analyses (e.g., Lin, 2018), was assessed using visual inspection of funnel plots (Sterne

& Egger, 2001) and Egger's regression test for funnel plot asymmetry (Egger et al., 1997). To ensure sufficient statistical power to distinguish between chance and real asymmetry (Egger et al., 1997), these methods to analyze publication bias were carried out only for meta-analyses that comprised at least 10 studies. The metafor package (Viechtbauer, 2010) in the statistical software R (Version 4.0.4) was used for creating the funnel plots and performing Egger's regression test. Results were considered statistically significant at the alpha = .05 level ($p < .05$; two-tailed).

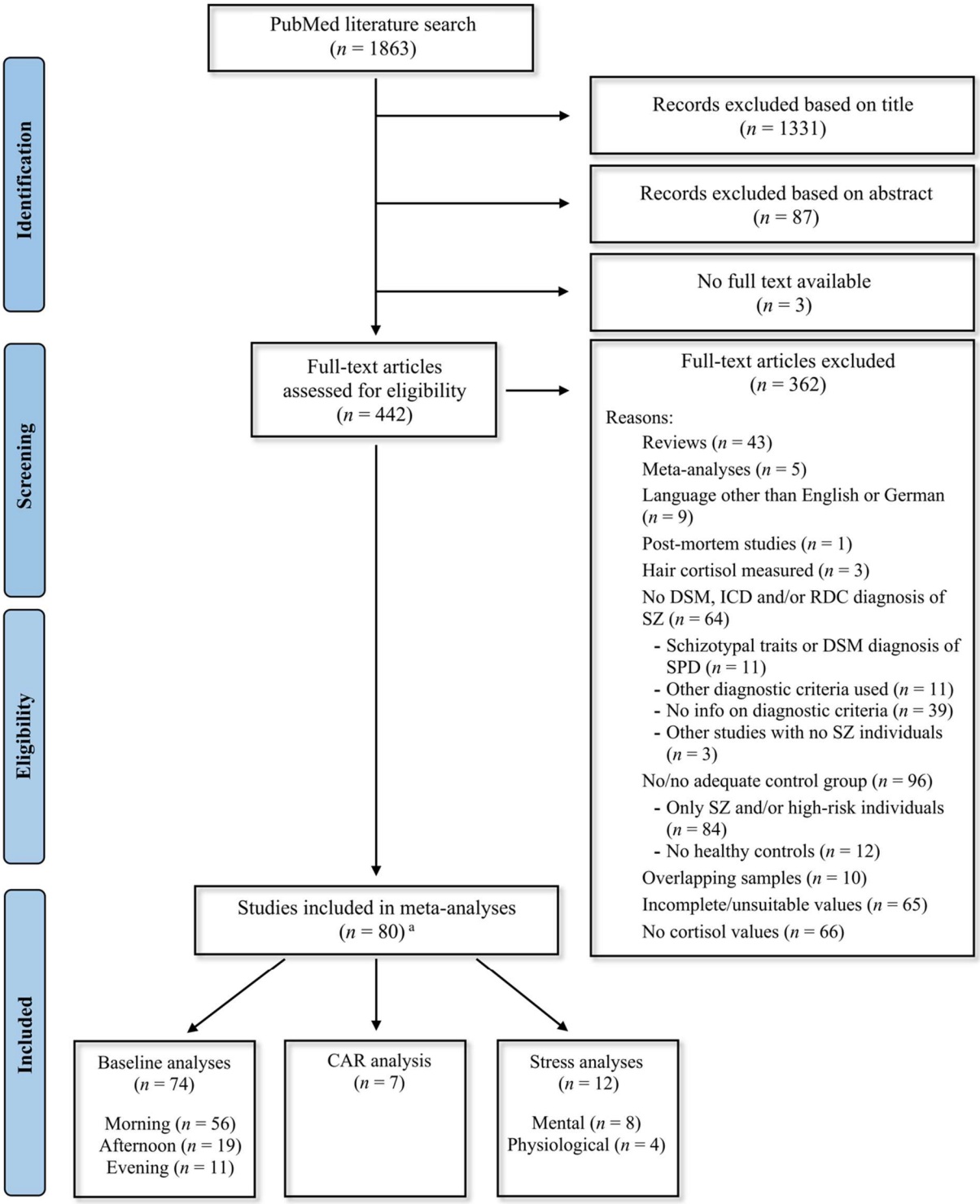
Results

Search Results

The database search yielded a total of 1863 records. Title and abstract screening resulted in exclusion of 1418 articles, and for 442 of the retained 445 articles, a full text was available or could be obtained (n = 3 excluded as unobtainable). The full-text articles were further evaluated for eligibility according to the inclusion and exclusion criteria described in the Method section. The study selection process is depicted in detail by the PRISMA flow diagram (see Figure 2).

Figure 2

PRISMA Flow Diagram of the Study Selection Process



Note. CAR = cortisol awakening response; SPD = schizophrenia personality disorder; SZ = schizophrenia.

[a] Some of the included studies were considered in more than one meta-analysis. Thus, the number of studies included in the categories and in the analyses within a category may exceed the number of studies indicated overall and for the respective category.

In case of missing cortisol values (n = 78), the corresponding authors were contacted up to two times with a data request. Eighteen authors were unreachable and of the 60 authors contacted, 12 authors (35% of the responding authors) responded positively to the data request. This resulted in a total of 80 studies eligible for inclusion in our meta-analyses. We were able to categorize the literature based on the cortisol values reported in the studies for analyses: (a) baseline cortisol, (b) cortisol awakening response, and (c) stress induction. According to the time of cortisol sample collection, baseline cortisol could be further categorized in morning cortisol, afternoon cortisol, and evening cortisol. Based on the type of stressor applied, stress induction could be further categorized in mental stress and physiological stress. The categories and included studies are displayed in the PRISMA flow diagram and are listed in Appendix A.

General Characteristics of Included Studies

The 80 included studies were published between 1982 and 2020 and the total sample size comprised 5028 participants, 2675 patients diagnosed with schizophrenia (range of mean age: 14.3–51.9 years, percentage of females: 31.25%) and 2353 healthy individuals (range of mean age: 14.7–50.7 years, percentage of females: 32.64%). In most of the included studies, cortisol was measured in blood samples (n = 60; 75.00%), with 26 studies specifically measuring blood serum and 32 studies specifically measuring in blood plasma, while the remaining two studies provided no detailed information on the blood component. Seventeen studies measured cortisol in saliva, and two studies measured it both in the blood plasma and saliva. In one study, cortisol was measured in cerebrospinal fluid. None of the included studies assessed cortisol in urine. The majority of studies (n = 72; 90.00%) included exclusively adult samples, while in eight studies, adolescents were also eligible to participate. Regarding diagnosis, in most of the included studies, schizophrenia was diagnosed according to the DSM and/or ICD criteria (n = 72; 90.00%), whereas in six and two studies the RDC or both RDC and DSM criteria, respectively, were used. In about one third (n = 24; 30.00%) of the studies, the patient sample entirely or partially consisted of individuals experiencing their first or an early episode of illness. Based on the design, 76 of the included studies were observational studies and four were randomized controlled trials. For an overview regarding the general characteristics of included studies please refer to Appendix A.

Meta-Analyses Based on Different Categories

Baseline Cortisol

In total, 74 studies examined the basal levels of cortisol in schizophrenia patients and healthy individuals. To take into consideration the circadian variation of cortisol levels (M. Pruessner et al., 2017), we performed separate meta-analyses according to the time of cortisol

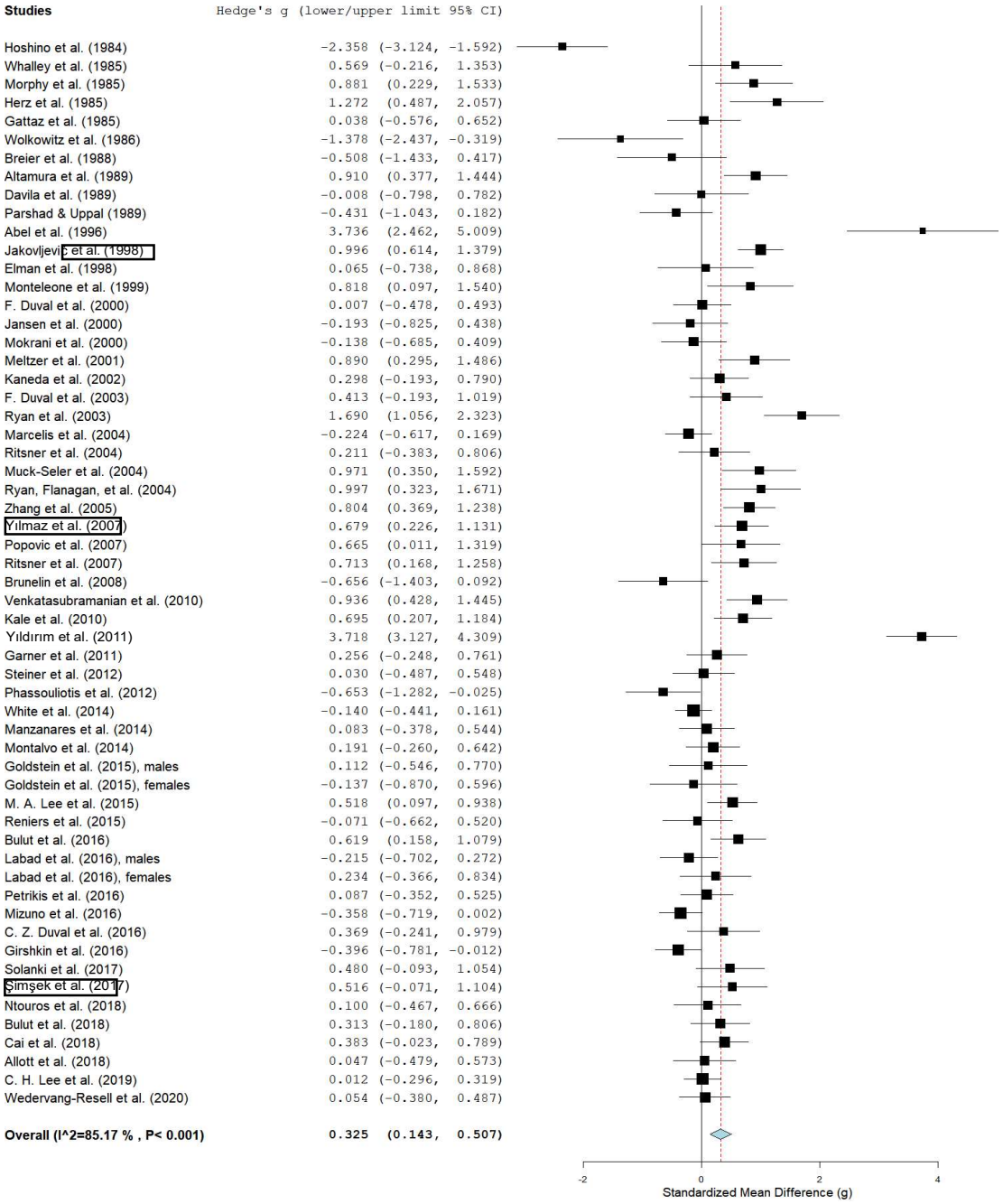
assessment: (a) morning (time window between 06:00 a.m. and 12:00 p.m.), (b) afternoon (from 12:00 p.m. to 06:00 p.m.), (c) evening (from 06:00 p.m. to 01:00 a.m.).

Morning Cortisol. Fifty-six studies provided data on morning cortisol levels. These studies comprised a total of 3639 participants, 1991 patients with schizophrenia and 1648 healthy individuals. Two of the included studies in this meta-analysis reported cortisol values separately for female and male participants (Goldstein et al., 2015; Labad et al., 2016).

The meta-analysis yielded a small, statistically significant effect, indicating higher cortisol levels in schizophrenia patients compared to healthy individuals in the morning (g = 0.33, 95% CI [0.14, 0.51], $p < .001$). Heterogeneity was high and significant in this analysis (I^2 = 85.17%, $p < .001$). See Figure 3 for the respective forest plot.

Figure 3

Baseline Morning Cortisol Levels



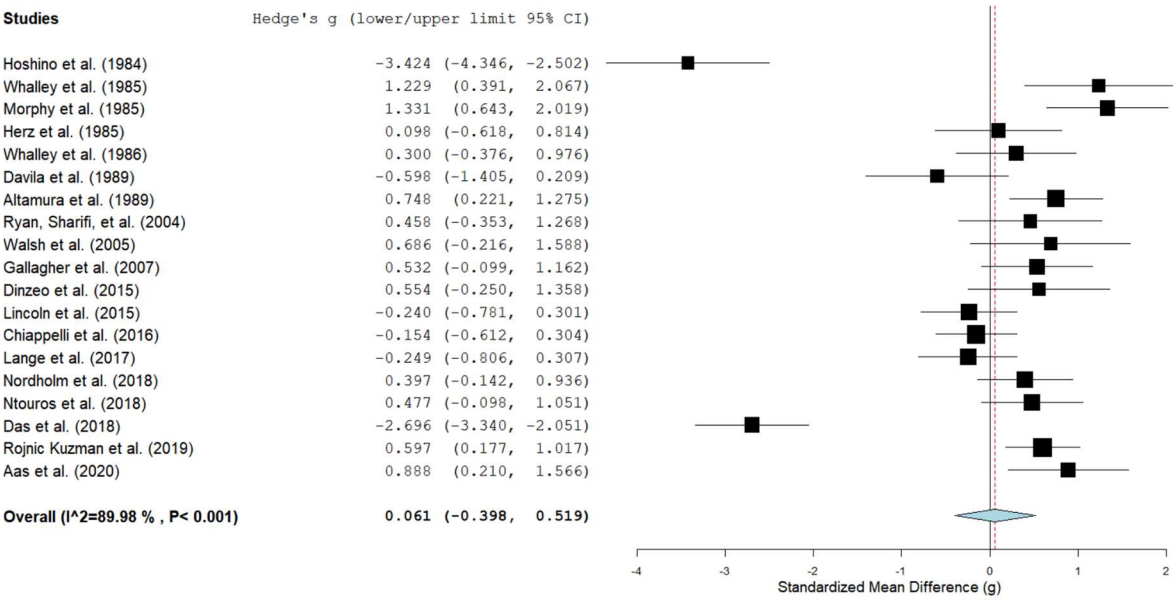
Note. Forest plot displaying random-effects meta-analysis comparing baseline morning cortisol levels between patients with schizophrenia and healthy controls. The black squares and the horizontal lines represent the individual studies' standardized mean difference (Hedge's *g*) effect size estimates and 95% confidence intervals, respectively. The center of the blue diamond and the vertical red dotted line represent the pooled effect size estimate, with the width of the blue diamond representing the corresponding 95% confidence interval. Positive effect size estimates indicate higher baseline morning cortisol levels in patients with schizophrenia than in healthy controls. CI = confidence interval; I^2 = Higgins' I^2 statistic.

Afternoon Cortisol. Nineteen studies provided data on afternoon cortisol levels. These studies comprised a total of 882 participants, 456 patients with schizophrenia and 426 healthy individuals. Two studies differed slightly from the rest of the included studies as they assessed cortisol in the time window between 11:30 a.m. and 12:30 p.m. (Whalley et al., 1986) or between 02:00 p.m. and 08:00 p.m. (Lincoln et al., 2015). Considering that the collection intervals specified in these two studies predominantly encompass the time around noon or the afternoon hours, these two studies were included in this analysis.

The meta-analysis yielded no effect, indicating no significant group differences in cortisol levels in the afternoon ($g = 0.06$, 95% CI [-0.40, 0.52], $p = .796$). Heterogeneity between studies was high and significant in this analysis ($I^2 = 89.98\%$, $p < .001$). See Figure 4 for the respective forest plot.

Figure 4

Baseline Afternoon Cortisol Levels



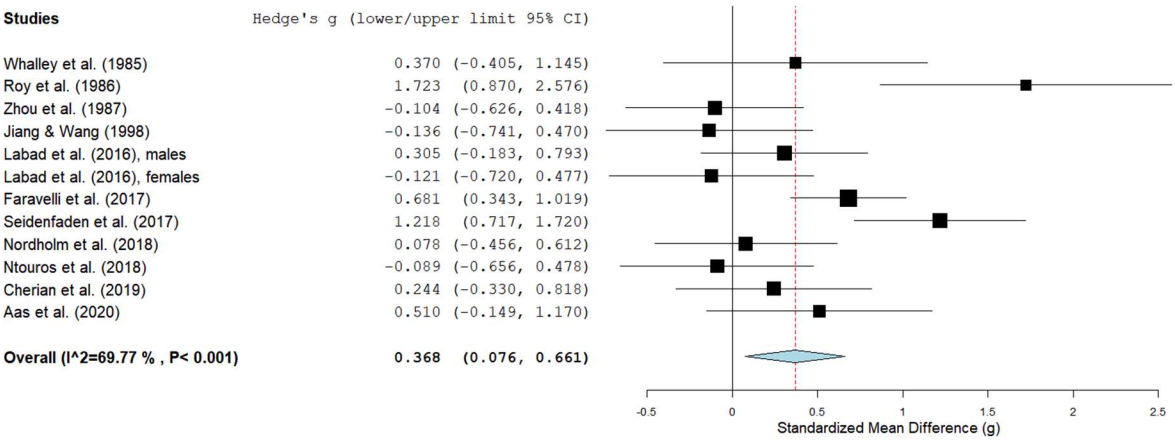
Note. Forest plot displaying random-effects meta-analysis comparing baseline afternoon cortisol levels between patients with schizophrenia and healthy controls. The black squares and the horizontal lines represent the individual studies' standardized mean difference (Hedge's *g*) effect size estimates and 95% confidence intervals, respectively. The center of the blue diamond and the vertical red dotted line represent the pooled effect size estimate, with the width of the blue diamond representing the corresponding 95% confidence interval. Positive effect size estimates indicate higher baseline afternoon cortisol levels in patients with schizophrenia than in healthy controls. CI = confidence interval; I^2 = Higgins' I^2 statistics.

Evening Cortisol. Eleven studies provided data on evening cortisol levels. These studies comprised a total of 716 participants, 323 patients with schizophrenia and 393 healthy individuals. One of the included studies in this meta-analysis reported cortisol values separately for female and male participants (Labad et al., 2016).

The meta-analysis yielded a small statistically significant effect, indicating elevated cortisol levels in schizophrenia patients compared to healthy individuals in the evening (g = 0.37, 95% CI [0.08, 0.66], p = .014). Heterogeneity between studies was moderate and significant in this analysis (I^2 = 69.77%, p < .001). See Figure 5 for the respective forest plot.

Figure 5

Baseline Evening Cortisol Levels



Note. Forest plot displaying random-effects meta-analysis comparing baseline evening cortisol levels between patients with schizophrenia and healthy controls. The black squares and the horizontal lines represent the individual studies' standardized mean difference (Hedge's g) effect size estimates and 95% confidence intervals, respectively. The center of the blue diamond and the vertical red dotted line represent the pooled effect size estimate, with the width of the blue diamond representing the corresponding 95% confidence interval. Positive effect size estimates indicate higher baseline evening cortisol levels in patients with schizophrenia than in healthy controls. CI = confidence interval; I^2 = Higgins' I^2 statistic.

Cortisol Awakening Response

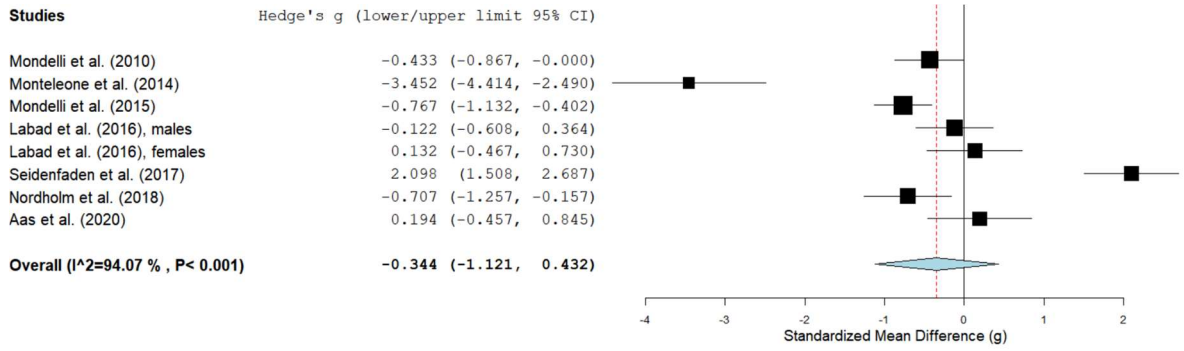
The CAR, defined as the increase in cortisol levels during the first 60 minutes following awakening, was examined by seven studies. These studies comprised a total of 534 participants, 283 patients with schizophrenia and 251 healthy individuals. One of the included studies in this

meta-analysis reported cortisol values separately for female and male participants (Labad et al., 2016).

The meta-analysis showed a small, statistically non-significant effect, indicating lower cortisol levels in schizophrenia patients compared to healthy individuals during the first 60 minutes after awakening (g = -0.34, 95% CI [-1.12, 0.43], p = .385). Heterogeneity was high and significant in this analysis (I^2 = 94.07%, p < .001). See Figure 6 for the respective forest plot.

Figure 6

Cortisol Awakening Response (CAR)



Note. Forest plot displaying random-effects meta-analysis comparing cortisol awakening response (CAR) between patients with schizophrenia and healthy controls. The black squares and the horizontal lines represent the individual studies' standardized mean difference (Hedge's g) effect size estimates and 95% confidence intervals, respectively. The center of the blue diamond and the vertical red dotted line represent the pooled effect size estimate, with the width of the blue diamond representing the corresponding 95% confidence interval. Positive effect size estimates indicate a higher cortisol awakening response in patients with schizophrenia than in healthy controls. CI = confidence interval; I^2 = Higgins' I^2 statistic.

Stress Induction

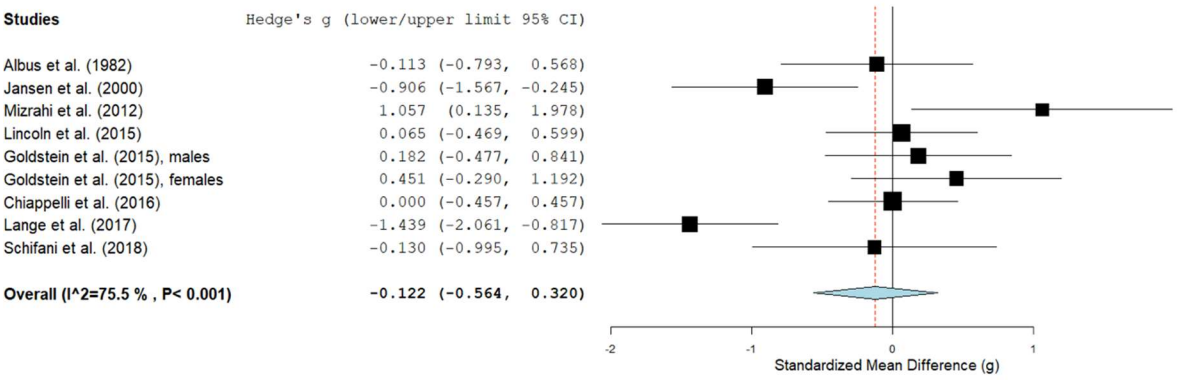
Mental Stress. The effect of mental stress paradigms on cortisol levels in schizophrenia patients and healthy individuals was assessed by eight studies, which comprised a total of 363 participants, 167 patients with schizophrenia and 196 healthy individuals. Five of the included studies focused on a psychosocial stress component by application of paradigms such as the MIST, variations of the TSST or other types of public speaking tasks, while three studies applied stress tasks related to a cognitive component such as a mental arithmetic task, an aversive affective arousal task using visual image stimuli, and computerized tasks to assess

cognitive function. One of the included studies in this meta-analysis reported cortisol values separately for female and male participants (Goldstein et al., 2015).

The meta-analysis showed no effect, indicating no group differences in cortisol change after induction of mental stress (g = -0.12, 95% CI [-0.56, 0.32], p = .589). Heterogeneity was medium and significant in this analysis (I^2 = 75.50%, p < .001). See Figure 7 for the respective forest plot.

Figure 7

Influence of Mental Stress on Cortisol Levels



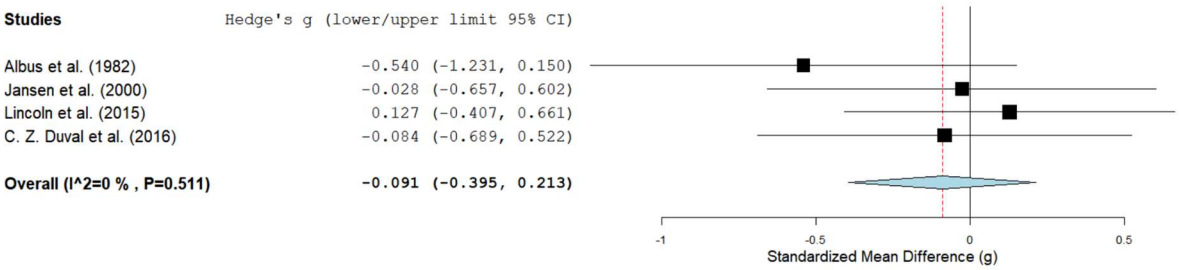
Note. Forest plot displaying random-effects meta-analysis comparing change in cortisol levels (from pre-to-post) in response to mental stress induction between patients with schizophrenia and healthy controls. The black squares and the horizontal lines represent the individual studies' standardized mean difference (Hedge's g) effect size estimates and 95% confidence intervals, respectively. The center of the blue diamond and the vertical red dotted line represent the pooled effect size estimate, with the width of the blue diamond representing the corresponding 95% confidence interval. Positive effect size estimates indicate either a higher increase or lower decrease in cortisol levels following mental stress induction in patients with schizophrenia than in healthy controls. CI = confidence interval; I^2 = Higgins' I^2 statistic.

Physiological Stress. Four studies provided cortisol values for the effect of a physiological stress paradigm on cortisol levels. These studies comprised a total of 174 participants, 79 patients with schizophrenia and 95 healthy individuals. The physiological stressors applied in the studies comprised the cold pressor test, noise paradigms, electrical stimulations, and a session of bicycle exercise. One study (Albus et al., 1982) applied two experimental conditions to assess cortisol stress response, the cold pressor task (alternately putting each foot into ice water for 40 seconds) and a noise condition (sine-wave and structured noise with a mean intensity of 95 dB).

The meta-analysis showed no effect, indicating no group differences in cortisol change after physiological stress induction (g = -0.09, 95% CI [-0.39, 0.21], p = .557). Heterogeneity was low and non-significant in this analysis (I^2 = 0.00%, p = .511). Meta-analysis did not yield different results when including the noise paradigm from the Albus et al. (1982) study (g = -0.09, 95% CI [-0.40, 0.21], p = .549), and there was low, non-significant between-study heterogeneity (I^2 = 0.00%, p = .498). See Figure 8 for the respective forest plot for the analysis which included the cold pressor task from the Albus et al. (1982) study.

Figure 8

Influence of Physiological Stress on Cortisol Levels



Note. Forest plot displaying random-effects meta-analysis comparing change in cortisol levels (from pre-to-post) in response to physiological stress induction between patients with schizophrenia and healthy controls. The black squares and the horizontal lines represent the individual studies' standardized mean difference (Hedge's g) effect size estimates and 95% confidence intervals, respectively. The center of the blue diamond and the vertical red dotted line represent the pooled effect size estimate, with the width of the blue diamond representing the corresponding 95% confidence interval. Positive effect size estimates indicate either a higher increase or lower decrease in cortisol levels following physiological stress induction in patients with schizophrenia than in healthy controls. CI = confidence interval; I^2 = Higgins' I^2 statistic.

Quality Assessment

The overall study quality of included observational studies, as assessed by the NOS, and expressed as the overall NOS quality score, varied between 1 and 8, with the rating median being 5 stars. For randomized controlled trials, the study quality, as assessed using the RoB 2, was low in two studies and rated as having some concerns in the other two studies. The primary methodological limitations of the included observational studies were that cortisol levels were not assessed blindly according to the sample's case/control status (n = 61), and that no response rate was indicated in the studies (n = 75). The methodological quality of two of the four

randomized controlled studies, both of which were rated as having some concerns, was limited by deviations from the intended interventions and missing outcome data. See Appendix A for the quality ratings of the included studies.

Assessment of Publication Bias

Visual inspection of the funnel plots for the analysis of morning, afternoon and evening cortisol did not indicate substantial asymmetry (see Appendix B for the respective funnel plots) and Egger's test did not yield significance. These results were consistent for the analysis of morning (z = 1.07, p = .284) and afternoon cortisol (z = -0.89, p = .372), as well as for the analysis of evening cortisol (z = 0.91, p = .364), overall indicating a low probability of publication bias in the three analyses of baseline cortisol levels.

Due to the insufficient number of studies included in the meta-analyses performed on CAR, mental stress, and physiological stress, no formal graphical or statistical assessment of publication was conducted for these meta-analyses.

Discussion

Summary and Interpretation of the Meta-Analytic Findings

Baseline Cortisol

Our meta-analysis on morning cortisol levels demonstrated significantly higher cortisol levels in patients with schizophrenia compared to healthy controls, with small effect size estimates. Of the nineteen studies showing significantly elevated cortisol levels among patients with schizophrenia, two studies (Abel et al., 1996; Yıldırım et al., 2011) showed a comparatively large effect. Three of the included studies in this analysis showed significantly reduced cortisol levels in patients compared to healthy controls with one study reporting exceptionally low cortisol levels (Hoshino et al., 1984) among patients compared with the other studies. Of the studies reporting significantly elevated cortisol levels in patients with schizophrenia, seven measured cortisol levels between 06:00 a.m. and 08:00 a.m., whereas 12 studies collected samples between 08:00 a.m. and 12:00 p.m., overall indicating that cortisol levels in schizophrenia are not only found to be elevated in the early morning hours until 08:00 a.m., but also in the later morning hours approaching noon. Of all included studies involving morning cortisol, 31 measured cortisol levels in patients on antipsychotic medication, whereas 25 reported cortisol levels in antipsychotic-naive or minimally treated patients. Twelve of the latter studies reported significantly elevated cortisol levels among patients. The majority of studies within this analysis comprised adult samples, seven did not explicitly exclude adolescents. In most of the included studies, cortisol levels were measured in blood, three

studies measured salivary cortisol and one study measured cortisol in cerebrospinal fluid. As has been pointed out in several of the included studies and in previous meta-analyses, it should be noted that results of blood cortisol may be confounded by potential stress associated with phlebotomy. However, while this factor may possibly have influenced some of the individual study findings, given the large number of studies included in this analysis, we consider it unlikely to have a substantial impact on our meta-analytic findings.

Overall, our finding of elevated morning cortisol levels in patients with schizophrenia is in line with our hypothesis and beyond replicating the findings of previous meta-analyses, we were also able to extend them. The meta-analysis conducted by Girshkin et al. (2014) focused on morning cortisol levels from single blood and salivary samples which had been collected from medicated and unmedicated schizophrenia and first-episode patients until 10:00 a.m. On the basis of 44 included studies, they found elevated cortisol levels among patients, with a small-to-medium effect size estimate (g = 0.387). In contrast to Girshkin et al. (2014), we based our analysis on a broader definition of morning and thus also included cortisol measurements between 10:00 a.m. and 12:00 p.m. This inclusion of cortisol measurements later in the morning could potentially explain the relatively smaller effect size in our meta-analysis compared to Girshkin et al. (2014), an assumption that would certainly require further statistical testing but would complement the results of the subgroup analysis performed by Girshkin et al. (2014), indicating cortisol levels in schizophrenia to be particularly elevated in the early morning (until 08:00 a.m.) but not after 08:00 a.m.

Our meta-analysis on afternoon cortisol levels did not reveal significant group differences. Measurements included in this analysis spanned a wide time interval, with seven studies measuring cortisol levels within the 12:00 p.m. to 01:00 p.m. time window and nine studies reporting cortisol levels within the 01:00 p.m. to 05:00 p.m. time window. Three studies reported cortisol levels in unique time windows (12:00 p.m. to 04:00 p.m. in Chiappelli et al., 2016; 01:00 p.m. to 20:00 p.m. in Lincoln et al., 2015; 11:30 a.m. to 12:30 p.m. in Whalley et al., 1986). Most of the studies reporting cortisol levels within the 12:00 p.m. to 01:00 p.m. time window found no significant group differences. Descriptively, however, one of these studies (Davila et al., 1989) found cortisol levels to be reduced in patients with schizophrenia, whereas five studies found elevated cortisol levels in patients with schizophrenia compared to healthy controls. Due to the within-subjects design of the study by Davila et al. (1989), only the cortisol levels of medicated patients could be included in this analysis. Although some of the other studies measuring cortisol levels within the time frame earlier in the afternoon and were also comprised of medicated patients, it cannot be ruled out that the finding of reduced cortisol levels

in the study by Davila et al. (1989) is due to all patients receiving their usual neuroleptic dose four hours before sample collection.

Significantly reduced cortisol levels were reported in two studies (Das et al., 2018; Hoshino et al., 1984), which measured cortisol at 04:00 p.m. (Hoshino et al., 1984) and in the time frame from 02:00 p.m. until 04:00 p.m. (Das et al., 2018). Das et al. (2018) assessed the relationship between cortisol and aggression in schizophrenia and found reduced afternoon cortisol levels in the subsample of patients with aggression compared to the subsample of patients without aggression. This finding within the patient subgroups may explain the particularly reduced afternoon cortisol levels in patients with schizophrenia compared to the healthy controls in this study. Contrasting the findings of Hoshino et al. (1984) and Das et al. (2018), four studies which also measured cortisol later in the afternoon (Altamura et al., 1989; Morphy et al., 1985; Rojnic Kuzman et al., 2019; Whalley et al., 1985) reported significantly elevated cortisol levels in patients with schizophrenia compared to healthy controls. Likewise, Aas et al. (2020) reported significantly elevated cortisol levels, albeit in women with postpartum psychosis and with samples collected at noon. Given that the studies included in this analysis spanned a wide time interval for afternoon cortisol samples, and given the different findings of studies with sample collection earlier and later in the afternoon, the topic deserves a more detailed examination to provide further insight into the potential time-specific differences in cortisol secretion.

The meta-analysis on evening cortisol demonstrated significantly higher cortisol levels in patients with schizophrenia compared to healthy controls, with a small effect size estimate. Of the 11 studies included in this analysis, three showed significantly elevated evening cortisol levels in patients with schizophrenia compared to healthy controls. One of these studies (Roy et al., 1986) found particularly high cortisol levels in patients who had been withdrawn from antipsychotic medication prior to sample collection at 08:00 p.m. Given the relatively small sample size of 36 participants, the impact of this study on the overall meta-analytic finding is comparatively small, but interestingly, the finding of significantly elevated evening cortisol levels in schizophrenia patients has been replicated in two more recent larger studies comprising 156 and 76 participants, and measuring cortisol levels at 08:00 p.m. and 06:00 p.m., respectively (Faravelli et al., 2017; Seidenfaden et al., 2017).

Our hypotheses regarding differences between patients with schizophrenia and healthy controls in afternoon and evening cortisol levels were non-directional as, to our knowledge, there have been no studies conducted to investigate cortisol levels in these two samples within the time frames spanning the afternoon and evening by means of separate meta-analyses. Our

meta-analytic findings differ from the results of individual studies that report cortisol levels at multiple time points. For example, Aas et al. (2020) and Whalley et al. (1985) found cortisol levels in patients with schizophrenia to be significantly elevated compared to healthy controls in the afternoon, while for the evening, they found no significant group differences in cortisol levels. In two other studies however, no significant group differences were found between the groups both in the afternoon and in the evening (Nordholm et al., 2018; Ntouros et al., 2018).

Altogether, our meta-analyses on baseline cortisol levels in schizophrenia are consistent with the relationship between schizophrenia and HPA axis dysfunction as proposed in the neural diathesis-stress model (E. F. Walker & Diforio, 1997; E. Walker et al., 2008) and add to a growing body of literature linking altered HPA axis regulation to schizophrenia which is manifested by altered cortisol secretion. Our findings replicate previous meta-analytic findings of elevated morning cortisol levels (Girshkin et al., 2014). Moreover, our results extend existing research that found disruptions in the 24-h diurnal rhythm of cortisol secretion in schizophrenia based on the area under the curve with respect to a baseline (AUC_g; J. C. Pruessner et al., 2003) and further samples collected over the course of a day (e.g., Aas et al., 2020; Mondelli et al., 2015). Crucially, on the basis of such aggregate values, no adequate inferences can be made about potential alterations of cortisol secretion at specific time points during the day. By carrying out separate meta-analyses for specific time intervals, we demonstrate that schizophrenia is associated with time-specific alterations in cortisol secretion, with significantly elevated baseline cortisol levels in the morning and evening, but no significant group differences in cortisol levels measured in the afternoon.

It is important to note that heterogeneity was significant in all three meta-analyses conducted on baseline cortisol levels and may reflect factors which confound the results. One factor that may potentially account for these heterogenous results is symptomatology. Several studies have found baseline plasma cortisol levels to be positively associated with the severity of negative symptoms (e.g., Altamura et al., 1989; Zhang et al., 2005), whereas others have reported an association with more severe positive symptoms (e.g., Belvederi Murri et al., 2012; Walder et al., 2000). Moreover, also related to illness characteristics, higher baseline cortisol levels have been reported in schizophrenia inpatients as compared to outpatients in the meta-analysis by Girshkin et al. (2014), a finding that may be explained by increased levels of stress due to admission to a psychiatric clinic (Bradley & Dinan, 2010). Between-study heterogeneity may also be related to medication status of schizophrenia patients. A body of research indicates that antipsychotic medication, in particular atypical antipsychotics, may reduce cortisol levels and thus lead to an underestimation of differences in cortisol levels between patients with

schizophrenia and controls (Venkatasubramanian et al., 2010; Zhang et al., 2005). Interestingly, Cohrs et al. (2006) examined the effects of antipsychotic drugs in healthy individuals and found that while first-generation antipsychotics have little effect on cortisol levels, second-generation drugs reduce cortisol levels. This finding suggests that the effect of antipsychotics in reducing cortisol levels may be independent of its influence on the symptoms of schizophrenia and rather be due to the direct pharmacologic actions inhibiting HPA axis activity (Cohrs et al., 2006).

Results regarding the influence of age and gender on cortisol levels have been divergent, with some studies reporting increased cortisol secretion during adolescence (E. F. Walker et al., 2001) and higher baseline cortisol levels in men compared to women (Klinger-König et al., 2021; Paris et al., 2010), and others finding no differences related to age in adult samples (Girshkin et al., 2014) and no sex differences in baseline cortisol levels (Kirschbaum et al., 1992; Liu et al., 2017). As in some of the studies included in our baseline analysis, adolescents have not been explicitly excluded from study participation, it cannot be ruled out that differences in effect sizes may also partly be due to age effects. Two of the studies included in our meta-analyses on baseline cortisol levels reported cortisol levels for the patient and control group stratified by sex (Goldstein et al., 2015; Labad et al., 2016). Although neither of these studies found significant sex differences in baseline cortisol levels, our results could nonetheless be confounded by sex-specific differences in cortisol levels, considering that the samples of the included studies were composed differently, with some consisting exclusively of male or female participants. Furthermore, studies did not always control for menstrual cycle phase and/or use of oral contraceptives. This may be problematic particularly in mixed gender samples as higher baseline cortisol levels have been reported in oral contraceptive users compared to non-users and in the follicular phase compared to the luteal phase in free-cycling women (Hamidovic et al., 2020; Hertel et al., 2017).

Another factor that has not always been controlled for in individual studies and thus may have influenced our meta-analytic results is smoking status. Compared to the general population, patients with schizophrenia exhibit a high incidence of tobacco smoking and nicotine dependence (de Leon & Diaz, 2005). In healthy individuals, tobacco smoking is associated with elevated cortisol levels, whereas results on an association between cortisol and smoking in patients with schizophrenia are more divergent (Nedic Erjavec et al., 2017) and few studies have been dedicated to the topic.

Cortisol Awakening Response

Our meta-analysis on CAR did not reveal significant group differences and thus did not replicate the finding of a previous meta-analysis of significantly blunted cortisol secretion in

response to awakening in patients with schizophrenia compared to healthy controls (Berger et al., 2016).

Due to this previous meta-analysis being published in 2016, we were able to identify and include some additional empirical findings in our meta-analysis, two studies partly comprised of first-episode patients and medicated (Labad et al., 2016) or antipsychotic-naive patients (Nordholm et al., 2018), one study comprised of women with a diagnosis of postpartum psychosis (Aas et al., 2020), and one study comprised of patients with schizophrenia who were on antipsychotic medication (Seidenfaden et al., 2017). Four of the studies included in the meta-analysis of Berger et al. (2016) were excluded from our meta-analysis due to missing values of cortisol (M. Pruessner et al., 2008; M. Pruessner et al., 2013), missing units for cortisol levels (M. Pruessner et al., 2015), overlap of study findings (Aas et al., 2011) with findings from a larger sample (Mondelli et al., 2010), and cortisol data only available for two time points (Hempel et al., 2010). The time points at which cortisol was measured differed between studies. While five studies reported values from 0, 15, 30 and 60 minutes after awakening (Aas et al., 2020; Mondelli et al., 2010; Mondelli et al., 2015; Monteleone et al., 2014; Nordholm et al., 2018), Labad et al. (2016) reported a CAR which was calculated based on the time points 0, 30 and 60 minutes after awakening, and an additional sampling point (45 minutes post-awakening) was considered in the study by Seidenfaden et al. (2017). From the study by Monteleone et al. (2014), which originally reported CAR for two days, only the measurements of the first testing day were considered for our analysis.

Since in the meta-analysis by Berger et al. (2016), no study had been included that reported significantly elevated CAR in patients with schizophrenia compared to healthy controls, the discrepancy with our meta-analysis, which did not reveal significant group differences in CAR, may be explained by the inclusion of the study by Seidenfaden et al. (2017) in our analysis. This study examined the relationship between schizophrenia and childhood adversities in a patient sample in which about half of the individuals reported a high frequency of experienced childhood adversities. In addition to methodological differences regarding the sampling protocol which may account for the significant between-study heterogeneity, it is important to note that none of the included studies objectively verified participants adherence with the timed cortisol sampling instructions. According to expert consensus guidelines, objective control of sample timing accuracy and wake time, for example through use of actigraphy and objective monitoring, is crucial for obtaining valid CAR measures as even small delays in sample collection can result in inaccurate estimation of CAR (Stalder et al., 2016). Some of the studies included followed earlier recommendations of extending the sampling

period to two days, however, cortisol data for two days was usually not available for all participants and more recent research highlights that state-related covariates such as examination context (e.g., whether samples are collected at home or in hospital facilities) cannot be controlled through sample period extension (Stalder et al., 2016). Except for the study by Seidenfaden et al. (2017) which measured cortisol levels in a subsample of inpatients at a psychiatric ward, all other studies instructed participants to sample cortisol at home.

Similar to our analyses on baseline cortisol levels, we did not consider potential confounders in our analysis on CAR, therefore, we cannot rule out that effects of medication (e.g., status, type, timing in relation to sampling), sex and age, as well as of menstrual cycle phase and use of oral contraceptives may have influenced our meta-analytic results.

Stress Induction

Our meta-analysis on the effect of mental stress on cortisol levels did not reveal significant group differences. Five of the included studies assessed responses to psychosocial stress tasks, while three applied cognitive tasks to invoke stress. Of the eight studies, three reported the cortisol response to stress as difference in aggregated cortisol levels (i.e., AUC_g; J. C. Pruessner et al., 2003) measured during a stress and a control task (Jansen et al., 2000; Mizrahi et al., 2012; Schifani et al., 2018). Regarding psychosocial stress, two studies (Mizrahi et al., 2012; Schifani et al., 2018) applied the MIST in a neuroimaging setting and assessed cortisol stress reactivity in unmedicated schizophrenia patients by collecting saliva samples. While one study found an increase of cortisol in patients with schizophrenia compared to healthy controls (Mizrahi et al., 2012), no significant group differences in change of cortisol levels were observed in the study by Schifani et al. (2018). In the other three studies that focused on psychosocial stress, mainly comprising medicated patients, cortisol saliva samples were collected while participants performed either a modified version of the TSST (Lange et al., 2017) or another type of public speaking task (Jansen et al., 2000; Lincoln et al., 2015). Whereas two studies reported a significantly blunted cortisol response in patients with schizophrenia compared to healthy controls (Jansen et al., 2000; Lange et al., 2017), the other study found no significant group differences in cortisol response to psychosocial stress.

Of the studies applying a cognitive stress task, one study assessed cortisol stress reactivity to a mental arithmetic task (Albus et al., 1982), Goldstein et al. (2015) reported sex-specific data of cortisol response to a visual-stress challenge, and in the study by Chiappelli et al. (2016), a behavioral paradigm comprising computerized tasks to assess cognitive function was used. With the exception of the study by Albus et al. (1982), which comprised patients who were not on medication at the time of sampling, in all studies the patient samples were at least

partially comprised of medicated individuals. None of the studies focusing on the cognitive component of mental stress found significant group differences in cortisol response.

Overall, our finding of an absence of group differences in cortisol response to mental stress induction contradicts the finding of significantly reduced cortisol stress response found in patients with schizophrenia compared to healthy controls in the meta-analysis by Zorn et al. (2017). The explanation of this divergence is potentially twofold. Firstly, it may be explained by the fact that we, apart from studies explicitly applying stressors with a social-evaluative component, also included studies that assessed cortisol stress response to cognitive stress paradigms. Secondly, the divergent findings may be due to the authors of the Zorn et al. (2017) meta-analysis only including studies that examined the total amount of cortisol released over the period of stress induction (i.e., aggregate measures of cortisol stress response).

While our results are consistent with those of Ciufolini et al. (2014), it is important to note that their meta-analysis examined the cortisol stress response (delta) from the peak secretion in the recovery and anticipatory phases, and, similar to Zorn et al. (2017), solely focused on studies that applied social-evaluative stressors. Interestingly, apart from the stress-induced change in cortisol levels, Ciufolini et al. (2014) also meta-analytically assessed the peak in cortisol secretion during stress induction and found peak levels to be significantly lower in patients with schizophrenia compared to healthy controls. As the investigation of stress reactivity takes into account baseline cortisol levels and considering that these were measured at variable time points within variable time frames in the individual studies (e.g., between 10:00 a.m. and 04:00 p.m. in Jansen et al., 2000; between 02:00 p.m. and 08:00 p.m. in Lincoln et al., 2015), we would assume based on our analyses on baseline cortisol, that due to the time-specificity of altered cortisol secretion in schizophrenia, baseline cortisol levels differ both among participants within the same study as well as between the studies. Therefore, the finding of attenuated peak cortisol levels during stress induction as compared to the finding of no differences in cortisol stress response may be explained by ceiling effects of baseline cortisol elevations that are operating time-specifically (i.e., when baseline cortisol levels are elevated in patients with schizophrenia, that is in the morning and evening). The variability of the time frame in which the stressor was applied may be considered as one potential factor in explaining the significant between-study heterogeneity in this meta-analysis. Another potentially confounding factor that was not controlled for in our analysis and that would require further investigation by the means of subgroup analyses is participants' sex. In our analysis, only one study (Goldstein et al., 2015) analyzed cortisol response to stress stratified for sex. This shows a dearth of research evaluating gender effects despite results which have indeed suggested sex

differences in cortisol response to psychosocial stress (Kirschbaum et al., 1992). Equally important, it seems that whether or not sex differences are found also depends on methodological aspects such as sampling and procedural variations (Liu et al., 2017).

Neither our meta-analysis nor any of the underlying studies revealed significant group differences in cortisol response to physiological stress. There was great variability in tasks used to assess cortisol stress response and except for C. Z. Duval et al. (2016), all studies within this analysis applied at least two different types of stressors and were also included in our analysis on mental stress. Albus et al. (1982) applied two experimental conditions to assess cortisol stress response, the cold pressor test and a noise condition, while the other studies applied electrical stimulations (C. Z. Duval et al., 2016), noise (Lincoln et al., 2015) and bicycle exercise (Jansen et al., 2000), respectively.

Taken together it should be noted that we were able to include only a small number of studies in our meta-analyses on cortisol stress reactivity and that our meta-analytic findings should be interpreted cautiously due to the variety of stress induction paradigms that may have influenced heterogeneity of findings and the overall lack of significant group differences in cortisol response to mental and physiological stress in our analyses. Most of the included studies assessed other physiological stress measures (e.g., heart rate) in addition to cortisol levels, and also analyzed subjective stress response. Usually, these data confirmed the validity of the respective stress induction methods, as they elicited a similar increase in heart rate in patients and controls. However, some studies found higher ratings of subjective stress and state anxiety in patients compared to controls following stress induction, a finding that seems contradictory to the lack of significant group differences in cortisol response. Interestingly, despite higher self-reported state anxiety in patients, Jansen et al. (2000) observed group differences with attenuated cortisol stress response in patients specifically to psychosocial stress and not to physiological stress. According to Dickerson & Kemeny (2004), stressors are not uniformly likely to trigger a cortisol response, and they identified stressors characterized by explicit social evaluation, uncontrollability, and unpredictability as particularly likely to reliably provoke a cortisol response. This specificity may explain why in the study by Jansen et al. (2000), only psychosocial stress, but not physiological stress, led to group differences in cortisol response. Furthermore, the absence of at least one of these three components in mere cognitive and physiological challenge tasks may provide an explanation for why no significant group differences in cortisol response were observed in the respective studies.

Strengths and Limitations

To the best of our knowledge, this is the first study to meta-analyze a variety of cortisol outcomes in schizophrenia, including examining possible time-point specific variations in baseline cortisol levels in schizophrenia by separately analyzing studies according to the time point(s) at which cortisol was measured. In addition, to our knowledge, the present study is the first to evaluate patients with schizophrenia and healthy controls with respect to their cortisol response to physiological stress induction by means of meta-analysis. Thus, our analyses provide a broad picture of cortisol profiles in schizophrenia. We only included patients with a diagnosis according to the three classical diagnostic systems, the ICD, DSM or RDC, thereby minimizing heterogeneity of symptoms. It should also be noted that the assessment for a potential publication bias showed favorable results about the power of our meta-analytic findings, as none were indicative of being significantly influenced by small-study effects, thereby signaling a strength of our chosen methods.

We would also like to point out several limitations of our meta-analyses that should be considered when interpreting the present findings. One limitation pertains to our search strategy. We consulted only one database for relevant literature and did not consider screening reference lists of included articles or searching the gray literature. Thus, although our analyses did not indicate that our findings were significantly affected by publication bias, the possibility that some relevant studies were missed cannot be definitively excluded. Furthermore, due to significant between-study heterogeneity in almost all meta-analyses performed, findings should be interpreted with caution. In particular, it should be noted that our meta-analyses on cortisol stress reactivity were based on a rather small number of studies, most of which characterized by sample sizes of less than 50. Thus, these meta-analyses may have lacked sufficient statistical power to detect group differences in cortisol response to mental and physiological stress, and precision of pooled effect size estimates may have been limited. The influences of potential confounding variables that may have contributed to significant between-study heterogeneity, as well as the effects of potential moderators, such as characteristics of participants (e.g., age, sex and specific to patients, medication status) and methodological aspects related to cortisol sampling (e.g., assay type), were not examined. Important to note is that although the overall quality of the included studies can be considered adequate, ratings of study quality varied largely across the studies which may limit the validity of our results. Another limitation pertains to our analyses on cortisol stress reactivity. Our approach of only considering the pre-to-post change in cortisol levels in the two groups limits conclusions to whether cortisol levels changed differently in patients with schizophrenia compared to healthy controls, but does not allow

conclusions about the direction of change. Thus, higher delta values of change may either signify a greater increase or a smaller decrease in cortisol levels in the patient group. Furthermore, it is important to mention that our analyses did not distinguish between diagnoses on the schizophrenia and psychosis spectrum. This was due to the majority of studies grouping these diagnoses together and not reporting cortisol levels separately for patients with specific diagnoses. In this regard, it also should be noted that while we limited our study to patients with an ICD, DSM or RDC diagnosis, the criteria differ slightly across these diagnostic systems and across the different versions. Additionally, there were inconsistencies in the included studies with regard to controlling for comorbid psychiatric disorders as well as patients' duration of illness and medication status, a critical factor as blunted levels of cortisol have frequently been linked to use of antipsychotic medication (e.g., Cohrs et al., 2006). As alterations in cortisol secretion suggestive of HPA axis dysfunction have also been reported in other psychiatric diagnosis, for example in major depression (for a meta-analysis, see Burke et al., 2005), it remains unclear as to what extend the variations in cortisol secretion found in our meta-analyses are clearly attributable to the primary diagnosis of patients or as to whether they may also be influenced by alterations of cortisol secretion associated with psychiatric comorbidities. Overall, heterogeneity amongst the patient samples with regard to diagnosis, illness stage and medication status may on one hand increase the generalizability of our findings, however, on the other hand it considerably limits the conclusions about possible diagnosis-specific alterations in HPA axis functioning.

Directions for Future Research and Conclusion

The present meta-analytic study supports previous research of elevated baseline cortisol levels in schizophrenia. However, by applying an approach in which we performed several individual meta-analyses according to the time points that the baseline cortisol levels were measured in the primary studies, we were able to pinpoint these alterations in HPA axis functioning to specific time frames, demonstrating that schizophrenia is clearly associated with elevated cortisol levels in the morning and in the evening.

Our meta-analyses focusing on the CAR and on cortisol stress reactivity in schizophrenia highlight the paucity of further research on these topics. Specifically, to our knowledge, there has only been one previous meta-analysis conducted on the pattern of cortisol response to awakening in schizophrenia. While we were able to update the findings of Berger et al. (2016) with inclusion of more recent empirical findings, the results from our meta-analysis opposed their report related to significantly blunted CAR in schizophrenia patients, whereas our analyses showed no significant group differences in CAR. Considering the sparsity of

research and the inconsistencies in findings, future research is clearly warranted in examining the CAR in schizophrenia. It is strongly recommended that future studies employ methods to ensure objective verification of sampling times as even small delays in sampling can result in inaccurate estimates of CAR (Stalder et al., 2016).

With the aim to assess stressor-dependent cortisol response in schizophrenia, we performed two separate meta-analyses, one focusing on mental stress and one on physiological stress. As mentioned in the Strengths and Limitations section, both meta-analyses were characterized by a small number of included studies. Although our finding of no significant group differences in cortisol response to mental stress is consistent with the meta-analytic findings of Ciufolini et al. (2014), more studies are needed to replicate these results before any firm conclusions can be drawn. More recently, use of the Experience Sampling Method (ESM) as a more ecologically valid method to assess cortisol stress reactivity has replicated the finding of no group differences in cortisol response to psychosocial stress in a more naturalistic setting (Vaessen et al., 2018). As our results on cortisol response to mental stress are to be considered as preliminary, so are the results of our meta-analysis on cortisol response to physiological stress. Only four studies were considered in our meta-analysis on physiological stress and there was great variation in the physiological challenges applied. Thus, it is strongly recommended that future studies are designed in a way that allows for replication of these findings and thereby help to elucidate whether schizophrenia might be associated with stressor-specific variations in cortisol response. In general, accumulation of more research on the relationship between schizophrenia and cortisol stress reactivity would also allow to investigate potential sources of heterogeneity by employing subgroup analyses and meta-regression.

Additional meta-analyses are currently in the planning in which we aim to assess cortisol stress reactivity in schizophrenia across illness stages, including the high-risk stage, thereby hoping to shed more light on the role of stress in the etiology of schizophrenia.

Acknowledgements

First and foremost, I would like to express my immense gratitude to Prof. Dr. Jennifer Svaldi and Dr. Lydia Kogler for supervising my master thesis. I would like to thank Dr. Lydia Kogler for providing me with such an interesting topic to work on and Prof. Dr. Birgit Derntl for giving me the opportunity to be part of a great lab with an amazing work atmosphere. Additionally, I am deeply thankful to the authors who provided data via correspondence, thereby contributing to make the analyses as thorough as possible. Also, I would like to thank Bela Kittelberger, Fabian Kraft, Erola Pons, Lea Tanzer, Hannah Fandel, and Jiatong Liu for

their help in literature and data preparation. Finally, I would like to thank my wonderful family and all my friends. They all supported and encouraged me greatly.

References

References marked with an asterisk indicate studies included in the meta-analyses.

Aas, M., Dazzan, P., Mondelli, V., Toulopoulou, T., Reichenberg, A., Di Forti, M., Fisher, H. L., Handley, R., Hepgul, N., Marques, T., Miorelli, A., Taylor, H., Russo, M., Wiffen, B., Papadopoulos, A., Aitchison, K. J., Morgan, C., Murray, R. M., & Pariante, C. M. (2011). Abnormal cortisol awakening response predicts worse cognitive function in patients with first-episode psychosis. *Psychological Medicine, 41*(3), 463–476. https://doi.org/10.1017/S0033291710001170

*Aas, M., Vecchio, C., Pauls, A., Mehta, M., Williams, S., Hazelgrove, K., Biaggi, A., Pawlby, S., Conroy, S., Seneviratne, G., Mondelli, V., Pariante, C. M., & Dazzan, P. (2020). Biological stress response in women at risk of postpartum psychosis: The role of life events and inflammation. *Psychoneuroendocrinology, 113*, Article 104558. https://doi.org/10.1016/j.psyneuen.2019.104558

*Abel, K. M., O'Keane, V., & Murray, R. M. (1996). Enhancement of the prolactin response to D-fenfluramine in drug-naive schizophrenic patients. *The British Journal of Psychiatry, 168*(1), 57–60. https://doi.org/10.1192/bjp.168.1.57

Adriano, F., Caltagirone, C., & Spalletta, G. (2011). Hippocampal volume reduction in first-episode and chronic schizophrenia: A review and meta-analysis. *The Neuroscientist, 18*(2), 180–200. https://doi.org/10.1177/1073858410395147

*Albus, M., Ackenheil, M., Engel, R. R., & Müller, F. (1982). Situational reactivity of autonomic functions in schizophrenic patients. *Psychiatry Research, 6*(3), 361–370. https://doi.org/10.1016/0165-1781(82)90026-9

*Allott, K. A., Yuen, H. P., Bartholomeusz, C. F., Rapado-Castro, M., Phassouliotis, C., Butselaar, F., Wood, S. J., Proffitt, T.-M., Savage, G., Phillips, L. J., Bendall, S., Markulev, C., Reniers, R. L. E. P., Pantelis, C., Baldwin, L., McGorry, P. D., & Garner, B. (2018). Stress hormones and verbal memory in young people over the first 12 weeks of treatment for psychosis. *Psychiatry Research, 260*, 60–66. https://doi.org/10.1016/j.psychres.2017.11.044

*Altamura, C., Guercetti, G., & Percudani, M. (1989). Dexamethasone suppression test in positive and negative schizophrenia. *Psychiatry Research, 30*(1), 69–75. https://doi.org/10.1016/0165-1781(89)90173-X

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Belvederi Murri, M., Pariante, C. M., Dazzan, P., Hepgul, N., Papadopoulos, A. S., Zunszain, P., Di Forti, M., Murray, R. M., & Mondelli, V. (2012). Hypothalamic-pituitary-adrenal axis and clinical symptoms in first-episode psychosis. *Psychoneuroendocrinology, 37*(5), 629–644. https://doi.org/10.1016/j.psyneuen.2011.08.013

Berger, M., Kraeuter, A. K., Romanik, D., Malouf, P., Amminger, G. P., & Sarnyai, Z. (2016). Cortisol awakening response in patients with psychosis: Systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 68*, 157–166. https://doi.org/10.1016/j.neubiorev.2016.05.027

Biedermann, F., & Fleischhacker, W. W. (2016). Psychotic disorders in *DSM-5* and *ICD-11*. *CNS Spectrums, 21*(4), 349–354. https://doi.org/10.1017/S1092852916000316

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias.* International Universities Press.

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2009). *Introduction to meta-analysis.* John Wiley & Sons.

Borges, S., Gayer-Anderson, C., & Mondelli, V. (2013). A systematic review of the activity of the hypothalamic–pituitary–adrenal axis in first episode psychosis. *Psychoneuroendocrinology, 38*(5), 603–611. https://doi.org/10.1016/j.psyneuen.2012.12.025

Bradley, A. J., & Dinan, T. G. (2010). A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: Implications for mortality. *Journal of Psychopharmacology, 24*(4), 91–118. https://doi.org/10.1177/1359786810385491

*Breier, A., Wolkowitz, O., Rapaport, M., Paul, S., & Pickar, D. (1988). Metabolic stress effects in normal volunteers and schizophrenic patients. *Psychopharmacology Bulletin, 24*(3), 431–433.

*Brunelin, J., d'Amato, T., van Os, J., Cochet, A., Suaud-Chagny, M.-F., & Saoud, M. (2008). Effects of acute metabolic stress on the dopaminergic and pituitary–adrenal axis activity in patients with schizophrenia, their unaffected siblings and controls. *Schizophrenia Research, 100*(1), 206–211. https://doi.org/10.1016/j.schres.2007.11.009

Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin, 35*(2), 383–402. https://doi.org/10.1093/schbul/sbn135

*Bulut, S. D., Bulut, S., Gundogmus, A. G., & Aydemir, C. (2018). Serum DHEA-S, testosterone and cortisol levels in female patients with schizophrenia. *Endocrine, Metabolic & Immune Disorders-Drug Targets, 18*(4), 348–354. https://doi.org/10.2174/1871530318666180212102128

*Bulut, S. D., Bulut, S., & Güriz, O. (2016). The relationship between sex hormone profiles and symptoms of schizophrenia in men. *Comprehensive Psychiatry, 69*, 186–192. https://doi.org/10.1016/j.comppsych.2016.06.005

Burke, H. M., Davis, M. C., Otte, C., & Mohr, D. C. (2005). Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology, 30*(9), 846–856. https://doi.org/10.1016/j.psyneuen.2005.02.010

*Cai, H., Zhou, X., Dougherty, G. G., Reddy, R. D., Haas, G. L., Montrose, D. M., Keshavan, M., & Yao, J. K. (2018). Pregnenolone-progesterone-allopregnanolone pathway as a potential therapeutic target in first-episode antipsychotic-naïve patients with schizophrenia. *Psychoneuroendocrinology, 90*, 43–51. https://doi.org/10.1016/j.psyneuen.2018.02.004

Charmandari, E., Tsigos, C., & Chrousos, G. (2004). Endocrinology of the stress response. *Annual Review of Physiology, 67*(1), 259–284. https://doi.org/10.1146/annurev.physiol.67.040403.120816

Chaumette, B., Kebir, O., Mam-Lam-Fook, C., Morvan, Y., Bourgin, J., Godsil, B. P., Plaze, M., Gaillard, R., Jay, T. M., & Krebs, M.-O. (2016). Salivary cortisol in early psychosis: New findings and meta-analysis. *Psychoneuroendocrinology, 63*, 262–270. https://doi.org/10.1016/j.psyneuen.2015.10.007

Cheng, S. C., Walsh, E., & Schepp, K. G. (2016). Vulnerability, stress, and support in the disease trajectory from prodrome to diagnosed schizophrenia: Diathesis-stress-support model. *Archives of Psychiatric Nursing, 30*(6), 810–817. https://doi.org/10.1016/j.apnu.2016.07.008

*Cherian, K., Schatzberg, A. F., & Keller, J. (2019). HPA axis in psychotic major depression and schizophrenia spectrum disorders: Cortisol, clinical symptomatology, and cognition. *Schizophrenia Research, 213*, 72–79. https://doi.org/10.1016/j.schres.2019.07.003

*Chiappelli, J., Shi, Q., Kodi, P., Savransky, A., Kochunov, P., Rowland, L. M., Nugent, K. L., & Hong, L. E. (2016). Disrupted glucocorticoid—immune interactions during stress response in schizophrenia. *Psychoneuroendocrinology, 63*, 86–93. https://doi.org/10.1016/j.psyneuen.2015.09.010

Chong, H. Y., Teoh, S. L., Wu, D. B.-C., Kotirum, S., Chiou, C.-F., & Chaiyakunapruk, N. (2016). Global economic burden of schizophrenia: A systematic review. *Neuropsychiatric Disease and Treatment, 12*, 357–373.

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology, 5*(7), 374–381. https://doi.org/10.1038/nrendo.2009.106

Ciompi, L. (1989). The dynamics of complex biological-psychosocial systems: Four fundamental psycho-biological mediators in the long-term evolution of schizophrenia. *British Journal of Psychiatry, 155*(S5), 15–21. https://doi.org/10.1192/S0007125000295925

Ciufolini, S., Dazzan, P., Kempton, M. J., Pariante, C., & Mondelli, V. (2014). HPA axis response to social stress is attenuated in schizophrenia but normal in depression: Evidence from a meta-analysis of existing studies. *Neuroscience and Biobehavioral Reviews, 47*, 359–368. https://doi.org/10.1016/j.neubiorev.2014.09.004

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Lawrence Erlbaum Associates.

Cohen, S., Gianaros, P. J., & Manuck, S. B. (2016). A stage model of stress and disease. *Perspectives on Psychological Science, 11*(4), 456–463. https://doi.org/10.1177/1745691616646305

Cohrs, S., Röher, C., Jordan, W., Meier, A., Huether, G., Wuttke, W., Rüther, E., & Rodenbeck, A. (2006). The atypical antipsychotics olanzapine and quetiapine, but not haloperidol, reduce ACTH and cortisol secretion in healthy subjects. *Psychopharmacology, 185*(1), 11–18. https://doi.org/10.1007/s00213-005-0279-x

Collip, D., Myin-Germeys, I., & Van Os, J. (2008). Does the concept of "sensitization" provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophrenia Bulletin, 34*(2), 220–225. https://doi.org/10.1093/schbul/sbm163

Corcoran, C., Walker, E., Huot, R., Mittal, V., Tessner, K., Kestler, L., & Malaspina, D. (2003). The stress cascade and schizophrenia: Etiology and onset. *Schizophrenia Bulletin, 29*(4), 671–692. https://doi.org/10.1093/oxfordjournals.schbul.a007038

*Das, S., Sengupta, S., Pathak, K., Sah, D., Mehta, S., Avinash, P. R., Baruah, A., Deuri, S. K., Sarmah, A., Gogoi, V., Kalita, K. N., & Hazarika, J. (2018). Aggression as an independent entity even in psychosis – the role of cortisol. *Psychiatry Research, 259*, 405–411. https://doi.org/10.1016/j.psychres.2017.11.002

*Davila, R., Zumarraga, M., Andia, I., & Friedhoff, A. J. (1989). Persistence of cyclicity of the plasma dopamine metabolite. Homovanillic acid, in neuroleptic treated schizophrenic patients. *Life Sciences, 44*(16), 1117–1121. https://doi.org/10.1016/0024-3205(89)90339-1

Dedovic, K., Renwick, R., Mahani, N. K., Engert, V., Lupien, S. J., & Pruessner, J. C. (2005). The Montreal Imaging Stress Task: Using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain. *Journal of Psychiatry and Neuroscience, 30*(5), 319–325.

Deeks, J. J., Dinnes, J., D'Amico, R., Sowden, A. J., Sakarovitch, C., Song, F., Petticrew, M., & Altman, D. (2003). Evaluating non-randomised intervention studies. *Health Technology Assessment, 7*(27), iii–173. https://doi.org/10.3310/hta7270

De Hert, M., Correll, C. U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Möller, H.-J., Ndetei, D. M., Newcomer, J. W., Uwakwe, R., & Leucht, S. (2011). Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry 10*(1), 52–77. https://doi.org/10.1002/j.2051-5545.2011.tb00014.x

De Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews Neuroscience, 6*(6), 463–475. https://doi.org/10.1038/nrn1683

De Leon, J., & Diaz, F. J. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research, 76*(2), 135–157. https://doi.org/10.1016/j.schres.2005.02.010

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials, 7*(3), 177–188. https://doi.org/10.1016/0197-2456(86)90046-2

Deussing, J. M., & Chen, A. (2018). The corticotropin-releasing factor family: Physiology of the stress response. *Physiological Reviews, 98*(4), 2225–2286. https://doi.org/10.1152/physrev.00042.2017

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin, 130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

*Dinzeo, T. J., Sledjeski, E., Durner, C., & Docherty, N. M. (2015). Comparative study of personality trait characteristics and reactivity in schizophrenia using a film clip paradigm. *The American Journal of Psychology, 128*(4), 515–526. https://doi.org/10.5406/amerjpsyc.128.4.0515

Dong, M., Lu, L., Zhang, L., Zhang, Y.-S., Ng, C. H., Ungvari, G. S., Li, G., Meng, X., Wang, G., & Xiang, Y.-T. (2019). Quality of life in schizophrenia: A meta-analysis of comparative studies. *Psychiatric Quarterly, 90*(3), 519–532. https://doi.org/10.1007/s11126-019-09633-4

*Duval, C. Z., Goumon, Y., Kemmel, V., Kornmeier, J., Dufour, A., Andlauer, O., Vidailhet, P., Poisbeau, P., Salvat, E., Muller, A., Mensah-Nyagan, A. G., Schmidt-Mutter, C., & Giersch, A. (2016). Neurophysiological responses to unpleasant stimuli (acute electrical stimulations and emotional pictures) are increased in patients with schizophrenia. *Scientific Reports, 6*(1), Article 22542. https://doi.org/10.1038/srep22542

*Duval, F., Mokrani, M.-C., Crocq, M.-A., Bailey, P. E., Diep, T. S., Correa, H., & Macher, J.-P. (2000). Dopaminergic function and the cortisol response to dexamethasone in psychotic depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 24*(2), 207–225. https://doi.org/10.1016/S0278-5846(99)00098-6

*Duval, F., Mokrani, M.-C., Monreal, J., Bailey, P., Valdebenito, M., Crocq, M.-A., & Macher, J.-P. (2003). Dopamine and serotonin function in untreated schizophrenia: Clinical correlates of the apomorphine and D-fenfluramine tests. *Psychoneuroendocrinology, 28*(5), 627–642. https://doi.org/10.1016/S0306-4530(02)00047-1

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ, 315*(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

*Elman, I., Adler, C. M., Malhotra, A. K., Bir, C., Pickar, D., & Breier, A. (1998). Effect of acute metabolic stress on pituitary-adrenal axis activation in patients with schizophrenia. *American Journal of Psychiatry, 155*(7), 979–981. https://doi.org/10.1176/ajp.155.7.979

Evensen, S., Wisløff, T., Lystad, J. U., Bull, H., Ueland, T., & Falkum, E. (2016). Prevalence, employment rate, and cost of schizophrenia in a high-income welfare society: A

population-based study using comprehensive health and welfare registers. *Schizophrenia Bulletin, 42*(2), 476–483. https://doi.org/10.1093/schbul/sbv141

*Faravelli, C., Mansueto, G., Palmieri, S., Lo Sauro, C., Rotella, F., Pietrini, F., & Fioravanti, G. (2017). Childhood adversity, cortisol levels, and psychosis: A retrospective investigation. *The Journal of Nervous and Mental Disease, 205*(7), 574–579. https://doi.org/10.1097/NMD.0000000000000699

Farrah, K., Young, K., Tunis, M. C., & Zhao, L. (2019). Risk of bias tools in systematic reviews of health interventions: An analysis of PROSPERO-registered protocols. *Systematic Reviews, 8*(1), Article 280. https://doi.org/10.1186/s13643-019-1172-8

Fatemi, S. H., & Folsom, T. D. (2009). The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophrenia Bulletin, 35*(3), 528–548. https://doi.org/10.1093/schbul/sbn187

Feighner, J. P., Robins, E., Guze, S. B., Woodruff, R. A., Jr., Winokur, G., & Munoz, R. (1972). Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry, 26*(1), 57–63. https://doi.org/10.1001/archpsyc.1972.01750190059011

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): Facts and future directions. *International Journal of Psychophysiology, 72*(1), 67–73. https://doi.org/https://doi.org/10.1016/j.ijpsycho.2008.03.014

Fusar-Poli, P., Tantardini, M., De Simone, S., Ramella-Cravaro, V., Oliver, D., Kingdon, J., Kotlicka-Antczak, M., Valmaggia, L., Lee, J., Millan, M. J., Galderisi, S., Balottin, U., Ricca, V., & McGuire, P. (2017). Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry, 40*, 65–75. https://doi.org/10.1016/j.eurpsy.2016.09.003

*Gallagher, P., Watson, S., Smith, M. S., Young, A. H., & Ferrier, I. N. (2007). Plasma cortisol-dehydroepiandrosterone (DHEA) ratios in schizophrenia and bipolar disorder. *Schizophrenia Research, 90*(1), 258–265. https://doi.org/10.1016/j.schres.2006.11.020

*Garner, B., Phassouliotis, C., Phillips, L. J., Markulev, C., Butselaar, F., Bendall, S., Yun, Y., & McGorry, P. D. (2011). Cortisol and dehydroepiandrosterone-sulphate levels correlate with symptom severity in first-episode psychosis. *Journal of Psychiatric Research, 45*(2), 249–255. https://doi.org/10.1016/j.jpsychires.2010.06.008

*Gattaz, W. F., Hannak, D., & Beckmann, H. (1985). Increased CSF cortisol levels after neuroleptic treatment in schizophrenia. *Psychoneuroendocrinology, 10*(3), 351–354. https://doi.org/10.1016/0306-4530(85)90012-5

GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. *The Lancet, 396*(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9

Girshkin, L., Matheson, S. L., Shepherd, A. M., & Green, M. J. (2014). Morning cortisol levels in schizophrenia and bipolar disorder: A meta-analysis. *Psychoneuroendocrinology, 49*, 187–206. https://doi.org/10.1016/j.psyneuen.2014.07.013

*Girshkin, L., O'Reilly, N., Quidé, Y., Teroganova, N., Rowland, J. E., Schofield, P. R., & Green, M. J. (2016). Diurnal cortisol variation and cortisol response to an MRI stressor in schizophrenia and bipolar disorder. *Psychoneuroendocrinology, 67*, 61–69. https://doi.org/10.1016/j.psyneuen.2016.01.021

Gjerstad, J. K., Lightman, S. L., & Spiga, F. (2018). Role of glucocorticoid negative feedback in the regulation of HPA axis pulsatility. *Stress, 21*(5), 403–416. https://doi.org/10.1080/10253890.2018.1470238

*Goldstein, J. M., Lancaster, K., Longenecker, J. M., Abbs, B., Holsen, L. M., Cherkerzian, S., Whitfield-Gabrieli, S., Makris, N., Tsuang, M. T., Buka, S. L., Seidman, L. J., & Klibanski, A. (2015). Sex differences, hormones, and fMRI stress response circuitry deficits in psychoses. *Psychiatry Research: Neuroimaging, 232*(3), 226–236. https://doi.org/10.1016/j.pscychresns.2015.03.006

Gronwall, D. M. A. (1977). Paced Auditory Serial-Addition Task: A measure of recovery from concussion. *Perceptual and Motor Skills, 44*(2), 367–373. https://doi.org/10.2466/pms.1977.44.2.367

Hamidovic, A., Karapetyan, K., Serdarevic, F., Choi, S. H., Eisenlohr-Moul, T., & Pinna, G. (2020). Higher circulating cortisol in the follicular vs. Luteal phase of the menstrual cycle: A meta-analysis. *Frontiers in Endocrinology, 11*(311). https://doi.org/10.3389/fendo.2020.00311

Hempel, R. J., Tulen, J. H., Van Beveren, N. J., Röder, C. H., De Jong, F. H., & Hengeveld, M. W. (2010). Diurnal cortisol patterns of young male patients with schizophrenia.

Psychiatry and Clinical Neurosciences, 64(5), 548–554. https://doi.org/10.1111/j.1440-1819.2010.02121.x

Hertel, J., König, J., Homuth, G., Van der Auwera, S., Wittfeld, K., Pietzner, M., Kacprowski, T., Pfeiffer, L., Kretschmer, A., Waldenberger, M., Kastenmüller, G., Artati, A., Suhre, K., Adamski, J., Langner, S., Völker, U., Völzke, H., Nauck, M., Friedrich, N., & Grabe, H. J. (2017). Evidence for stress-like alterations in the HPA-axis in women taking oral contraceptives. *Scientific Reports, 7*(1), Article 14111. https://doi.org/10.1038/s41598-017-13927-7

*Herz, M. I., Fava, G. A., Molnar, G., & Edwards, L. (1985). The dexamethasone suppression test in newly hospitalized schizophrenic patients. *American Journal of Psychiatry, 142*(1), 127–129.

Higgins, J. P. T., Li, T., & Deeks, J. J. (2021). Choosing effect measures and computing estimates of effect. In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, V. A. Welch (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions* (Version 6.2). Cochrane. https://www.training.cochrane.org/handbook

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine, 21*(11), 1539–1558. https://doi.org/https://doi.org/10.1002/sim.1186

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Hor, K., & Taylor, M. (2010). Suicide and schizophrenia: A systematic review of rates and risk factors. *Journal of Psychopharmacology, 24*(4), 81–90. https://doi.org/10.1177/1359786810385490

*Hoshino, Y., Ohno, Y., Murata, S., Yokoyama, F., Kaneko, M., & Kumashiro, H. (1984). Dexamethasone suppression test in autistic children. *Psychiatry and Clinical Neurosciences, 38*(4), 445–449. https://doi.org/10.1111/j.1440-1819.1984.tb00793.x

*Jakovljević, M., Mück-Šeler, D., Pivac, N., & Crnčević, Ž. (1998). Platelet 5-HT and plasma cortisol concentrations after dexamethasone suppression test in patients with different time course of schizophrenia. *Neuropsychobiology, 37*(3), 142–145. https://doi.org/10.1159/000026493

*Jansen, L. M. C., Gispen-de Wied, C. C., & Kahn, R. S. (2000). Selective impairments in the stress response in schizophrenic patients. *Psychopharmacology, 149*(3), 319–325. https://doi.org/10.1007/s002130000381

*Jiang, H. K., & Wang, J. Y. (1998). Diurnal melatonin and cortisol secretion profiles in medicated schizophrenic patients. *Journal of the Formosan Medical Association, 97*(12), 830–837.

*Kale, A., Naphade, N., Sapkale, S., Kamaraju, M., Pillai, A., Joshi, S., & Mahadik, S. (2010). Reduced folic acid, vitamin B12 and docosahexaenoic acid and increased homocysteine and cortisol in never-medicated schizophrenia patients: Implications for altered one-carbon metabolism. *Psychiatry Research, 175*(1), 47–53. https://doi.org/10.1016/j.psychres.2009.01.013

*Kaneda, Y., Fujii, A., & Ohmori, T. (2002). The hypothalamic–pituitary–adrenal axis in chronic schizophrenic patients long-term treated with neuroleptics. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 26*(5), 935–938. https://doi.org/10.1016/S0278-5846(02)00208-7

Kendler, K. S. (2020). A prehistory of the diathesis-stress model: Predisposing and exciting causes of insanity in the 19th century. *American Journal of Psychiatry, 177*(7), 576–588. https://doi.org/10.1176/appi.ajp.2020.19111213

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology, 28*(1–2), 76–81. https://doi.org/10.1159/000119004

Kirschbaum, C., Wüst, S., & Hellhammer, D. (1992). Consistent sex differences in cortisol responses to psychological stress. *Psychosomatic Medicine, 54*(6), 648–657.

Klinger-König, J., Frenzel, S., Hannemann, A., Wittfeld, K., Bülow, R., Friedrich, N., Nauck, M., Völzke, H., & Grabe, H. J. (2021). Sex differences in the association between basal serum cortisol concentrations and cortical thickness. *Neurobiology of Stress, 15*, Article 100416. https://doi.org/10.1016/j.ynstr.2021.100416

*Labad, J., Gutiérrez-Zotes, A., Creus, M., Montalvo, I., Cabezas, Á., Solé, M., Ortega, L., Algora, M. J., Sánchez-Gistau, V., & Vilella, E. (2016). Hypothalamic-pituitary-adrenal axis measures and cognitive abilities in early psychosis: Are there sex differences? *Psychoneuroendocrinology, 72*, 54–62. https://doi.org/10.1016/j.psyneuen.2016.06.006

*Lange, C., Huber, C. G., Fröhlich, D., Borgwardt, S., Lang, U. E., & Walter, M. (2017). Modulation of HPA axis response to social stress in schizophrenia by childhood

trauma. *Psychoneuroendocrinology, 82*, 126–132. https://doi.org/10.1016/j.psyneuen.2017.03.027

*Lee, C. H., Sinclair, D., O'Donnell, M., Galletly, C., Liu, D., Weickert, C. S., & Weickert, T. W. (2019). Transcriptional changes in the stress pathway are related to symptoms in schizophrenia and to mood in schizoaffective disorder. *Schizophrenia Research, 213*, 87–95. https://doi.org/10.1016/j.schres.2019.06.026

Lee, E. E., Liu, J., Tu, X., Palmer, B. W., Eyler, L. T., & Jeste, D. V. (2018). A widening longevity gap between people with schizophrenia and general population: A literature review and call for action. *Schizophrenia Research, 196*, 9–13. https://doi.org/10.1016/j.schres.2017.09.005

*Lee, M. A., Jayathilake, K., Sim, M. Y., & Meltzer, H. Y. (2015). Decreased serotonin$_{2C}$ receptor responses in male patients with schizophrenia. *Psychiatry Research, 226*(1), 308–315. https://doi.org/10.1016/j.psychres.2015.01.007

Leucht, S., Burkard, T., Henderson, J., Maj, M., & Sartorius, N. (2007). Physical illness and schizophrenia: A review of the literature. *Acta Psychiatrica Scandinavica, 116*(5), 317–333. https://doi.org/10.1111/j.1600-0447.2007.01095.x

Lin, L. (2018). Bias caused by sampling error in meta-analysis with small sample sizes. *PLOS ONE, 13*(9), Article e0204056. https://doi.org/10.1371/journal.pone.0204056

*Lincoln, T. M., Köther, U., Hartmann, M., Kempkensteffen, J., & Moritz, S. (2015). Responses to stress in patients with psychotic disorders compared to persons with varying levels of vulnerability to psychosis, persons with depression and healthy controls. *Journal of Behavior Therapy and Experimental Psychiatry, 47*, 92–101. https://doi.org/10.1016/j.jbtep.2014.11.011

Liu, J. J. W., Ein, N., Peck, K., Huang, V., Pruessner, J. C., & Vickers, K. (2017). Sex differences in salivary cortisol reactivity to the Trier Social Stress Test (TSST): A meta-analysis. *Psychoneuroendocrinology, 82*, 26–37. https://doi.org/https://doi.org/10.1016/j.psyneuen.2017.04.007

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience, 10*(6), 434–445. https://doi.org/10.1038/nrn2639

Mansueto, G., & Faravelli, C. (2017). Recent life events and psychosis: The role of childhood adversities. *Psychiatry Research, 256*, 111–117. https://doi.org/10.1016/j.psychres.2017.06.042

*Manzanares, N., Monseny, R., Ortega, L., Montalvo, I., Franch, J., Gutiérrez-Zotes, A., Reynolds, R. M., Walker, B. R., Vilella, E., & Labad, J. (2014). Unhealthy lifestyle in early psychoses: The role of life stress and the hypothalamic–pituitary–adrenal axis. *Psychoneuroendocrinology, 39*, 1–10. https://doi.org/10.1016/j.psyneuen.2013.09.023

*Marcelis, M., Cavalier, E., Gielen, J., Delespaul, P., & Van Os, J. (2004). Abnormal response to metabolic stress in schizophrenia: Marker of vulnerability or acquired sensitization? *Psychological Medicine, 34*(6), 1103–1111. https://doi.org/10.1017/S0033291703001715

*Meltzer, H. Y., Lee, M. A., & Jayathilake, K. (2001). The blunted plasma cortisol response to apomorphine and its relationship to treatment response in patients with schizophrenia. *Neuropsychopharmacology, 24*(3), 278–290. https://doi.org/10.1016/S0893-133X(00)00201-3

*Mizrahi, R., Addington, J., Rusjan, P. M., Suridjan, I., Ng, A., Boileau, I., Pruessner, J. C., Remington, G., Houle, S., & Wilson, A. A. (2012). Increased stress-induced dopamine release in psychosis. *Biological Psychiatry, 71*(6), 561–567. https://doi.org/10.1016/j.biopsych.2011.10.009

*Mizuno, Y., Hofer, A., Suzuki, T., Frajo-Apor, B., Wartelsteiner, F., Kemmler, G., Saruta, J., Tsukinoki, K., Mimura, M., Fleischhacker, W. W., & Uchida, H. (2016). Clinical and biological correlates of resilience in patients with schizophrenia and bipolar disorder: A cross-sectional study. *Schizophrenia Research, 175*(1), 148-153. https://doi.org/10.1016/j.schres.2016.04.047

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The, P. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLOS Medicine, 6*(7), Article e1000097. https://doi.org/10.1371/journal.pmed.1000097

*Mokrani, M. C., Duval, F., Diep, T. S., Bailey, P. E., & Macher, J. P. (2000). Multihormonal responses to clonidine in patients with affective and psychotic symptoms. *Psychoneuroendocrinology, 25*(7), 741–752. https://doi.org/10.1016/S0306-4530(00)00024-X

*Mondelli, V., Ciufolini, S., Belvederi Murri, M., Bonaccorso, S., Di Forti, M., Giordano, A., Marques, T. R., Zunszain, P. A., Morgan, C., Murray, R. M., Pariante, C. M., & Dazzan, P. (2015). Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophrenia Bulletin, 41*(5), 1162–1170. https://doi.org/10.1093/schbul/sbv028

*Mondelli, V., Dazzan, P., Hepgul, N., Di Forti, M., Aas, M., D'Albenzio, A., Di Nicola, M., Fisher, H., Handley, R., Marques, T. R., Morgan, C., Navari, S., Taylor, H., Papadopoulos, A., Aitchison, K. J., Murray, R. M., & Pariante, C. M. (2010). Abnormal cortisol levels during the day and cortisol awakening response in first-episode psychosis: The role of stress and of antipsychotic treatment. *Schizophrenia Research, 116*(2), 234–242. https://doi.org/10.1016/j.schres.2009.08.013

*Montalvo, I., Gutiérrez-Zotes, A., Creus, M., Monseny, R., Ortega, L., Franch, J., Lawrie, S. M., Reynolds, R. M., Vilella, E., & Labad, J. (2014). Increased prolactin levels are associated with impaired processing speed in subjects with early psychosis. *PLOS ONE, 9*(2), Article e89428. https://doi.org/10.1371/journal.pone.0089428

*Monteleone, P., Filippo, C. D., Fabrazzo, M., Milano, W., Martiadis, V., Corrivetti, G., Monteleone, A. M., & Maj, M. (2014). Flattened cortisol awakening response in chronic patients with schizophrenia onset after cannabis exposure. *Psychiatry Research, 215*(2), 263–267. https://doi.org/10.1016/j.psychres.2013.12.016

*Monteleone, P., Tortorella, A., Borriello, R., Cassandro, P., & Maj, M. (1999). Prolactin hyperresponsiveness to D-fenfluramine in drug-free schizophrenic patients: A placebo-controlled study. *Biological Psychiatry, 45*(12), 1606–1611. https://doi.org/10.1016/S0006-3223(98)00270-4

*Morphy, M. A., Fava, G. A., Carson, S. W., Perini, G. I., Molnar, G., & Jusko, W. J. (1985). The metyrapone test in schizophrenic patients and healthy subjects. *Neuropsychobiology, 14*(1), 35–38. https://doi.org/10.1159/000118198

*Muck-Seler, D., Pivac, N., Mustapic, M., Crncevic, Z., Jakovljevic, M., & Sagud, M. (2004). Platelet serotonin and plasma prolactin and cortisol in healthy, depressed and schizophrenic women. *Psychiatry Research, 127*(3), 217–226. https://doi.org/10.1016/j.psychres.2004.04.001

Myin-Germeys, I., & van Os, J. (2007). Stress-reactivity in psychosis: Evidence for an affective pathway to psychosis. *Clinical Psychology Review, 27*(4), 409–424. https://doi.org/https://doi.org/10.1016/j.cpr.2006.09.005

Myin-Germeys, I., van Os, J., Schwartz, J. E., Stone, A. A., & Delespaul, P. A. (2001). Emotional reactivity to daily life stress in psychosis. *Archives of General Psychiatry, 58*(12), 1137–1144. https://doi.org/10.1001/archpsyc.58.12.1137

Nedic Erjavec, G., Uzun, S., Nikolac Perkovic, M., Kozumplik, O., Svob Strac, D., Mimica, N., Hirasawa-Fujita, M., Domino, E. F., & Pivac, N. (2017). Cortisol in schizophrenia:

No association with tobacco smoking, clinical symptoms or antipsychotic medication. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 77*, 228–235. https://doi.org/10.1016/j.pnpbp.2017.04.032

*Nordholm, D., Rostrup, E., Mondelli, V., Randers, L., Nielsen, M. Ø., Wulff, S., Nørbak-Emig, H., Broberg, B. V., Krakauer, K., Dazzan, P., Zunszain, P. A., Nordentoft, M., & Glenthøj, B. (2018). Multiple measures of HPA axis function in ultra high risk and first-episode schizophrenia patients. *Psychoneuroendocrinology, 92*, 72–80. https://doi.org/10.1016/j.psyneuen.2018.03.015

*Ntouros, E., Karanikas, E., Floros, G., Andreou, C., Tsoura, A., Garyfallos, G., & Bozikas, V. P. (2018). Social cognition in the course of psychosis and its correlation with biomarkers in a male cohort. *Cognitive Neuropsychiatry, 23*(2), 103–115. https://doi.org/10.1080/13546805.2018.1440201

Nuechterlein, K. H., & Dawson, M. E. (1984). A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin, 10*(2), 300–312. https://doi.org/10.1093/schbul/10.2.300

Owen, M. J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. *The Lancet, 388*(10039), 86–97. https://doi.org/10.1016/S0140-6736(15)01121-6

Pacák, K., & Palkovits, M. (2001). Stressor specificity of central neuroendocrine responses: Implications for stress-related disorders. *Endocrine Reviews, 22*(4), 502–548. https://doi.org/10.1210/edrv.22.4.0436

Palmer, B. A., Pankratz, V. S., & Bostwick, J. M. (2005). The lifetime risk of suicide in schizophrenia: A reexamination. *Archives of General Psychiatry, 62*(3), 247–253. https://doi.org/10.1001/archpsyc.62.3.247

Paris, J. J., Franco, C., Sodano, R., Freidenberg, B., Gordis, E., Anderson, D. A., Forsyth, J. P., Wulfert, E., & Frye, C. A. (2010). Sex differences in salivary cortisol in response to acute stressors among healthy participants, in recreational or pathological gamblers, and in those with posttraumatic stress disorder. *Hormones and Behavior, 57*(1), 35–45. https://doi.org/10.1016/j.yhbeh.2009.06.003

*Parshad, O., & Uppal, A. (1989). Thyroid-gonad relationship in chronic schizophrenia. *The West Indian Medical Journal, 38*(2), 83–87.

*Petrikis, P., Boumba, V. A., Tzallas, A. T., Voulgari, P. V., Archimandriti, D. T., Skapinakis, P., & Mavreas, V. (2016). Elevated levels of Insulin-Like Growth Factor-1 (IGF-1) in drug-naïve patients with psychosis. *Psychiatry Research, 246*, 348–352. https://doi.org/10.1016/j.psychres.2016.09.053

*Phassouliotis, C., Garner, B. A., Phillips, L. J., Bendall, S., Yun, Y., Markulev, C., Kerr, M., & McGorry, P. D. (2012). Enhanced cortisol suppression following administration of low-dose dexamethasone in first-episode psychosis patients. *Australian and New Zealand Journal of Psychiatry, 47*(4), 363–370. https://doi.org/10.1177/0004867412465125

*Popovic, V., Doknic, M., Maric, N., Pekic, S., Damjanovic, A., Miljic, D., Popovic, S., Miljic, N., Djurovic, M., Jasovic-Gasic, M., Dieguez, C., & Casanueva, F. F. (2007). Changes in neuroendocrine and metabolic hormones induced by atypical antipsychotics in normal-weight patients with schizophrenia. *Neuroendocrinology, 85*(4), 249–256. https://doi.org/10.1159/000103868

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28*(7), 916–931. https://doi.org/10.1016/S0306-4530(02)00108-7

Pruessner, M., Boekestyn, L., Béchard-Evans, L., Abadi, S., Vracotas, N., Joober, R., Pruessner, J. C., & Malla, A. K. (2008). Sex differences in the cortisol response to awakening in recent onset psychosis. *Psychoneuroendocrinology, 33*(8), 1151–1154. https://doi.org/10.1016/j.psyneuen.2008.04.006

Pruessner, M., Cullen, A. E., Aas, M., & Walker, E. F. (2017). The neural diathesis-stress model of schizophrenia revisited: An update on recent findings considering illness stage and neurobiological and methodological complexities. *Neuroscience and Biobehavioral Reviews, 73*, 191–218. https://doi.org/10.1016/j.neubiorev.2016.12.013

Pruessner, M., Lepage, M., Collins, D. L., Pruessner, J. C., Joober, R., & Malla, A. K. (2015). Reduced hippocampal volume and hypothalamus-pituitary-adrenal axis function in first episode psychosis: Evidence for sex differences. *NeuroImage: Clinical, 7*, 195–202. https://doi.org/10.1016/j.nicl.2014.12.001

Pruessner, M., Vracotas, N., Joober, R., Pruessner, J. C., & Malla, A. K. (2013). Blunted cortisol awakening response in men with first episode psychosis: Relationship to parental bonding. *Psychoneuroendocrinology, 38*(2), 229–240. https://doi.org/10.1016/j.psyneuen.2012.06.002

*Reniers, R. L. E. P., Garner, B., Phassouliotis, C., Phillips, L. J., Markulev, C., Pantelis, C., Bendall, S., McGorry, P. D., & Wood, S. J. (2015). The relationship between stress, HPA axis functioning and brain structure in first episode psychosis over the

first 12 weeks of treatment. *Psychiatry Research: Neuroimaging, 231*(2), 111–119. https://doi.org/10.1016/j.pscychresns.2014.11.004

*Ritsner, M., Gibel, A., Maayan, R., Ratner, Y., Ram, E., Modai, I., & Weizman, A. (2007). State and trait related predictors of serum cortisol to DHEA(S) molar ratios and hormone concentrations in schizophrenia patients. *European Neuropsychopharmacology, 17*(4), 257–264. https://doi.org/10.1016/j.euroneuro.2006.09.001

*Ritsner, M., Maayan, R., Gibel, A., Strous, R. D., Modai, I., & Weizman, A. (2004). Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. *European Neuropsychopharmacology, 14*(4), 267–273. https://doi.org/10.1016/j.euroneuro.2003.09.003

*Rojnic Kuzman, M., Makaric, P., Bosnjak Kuharic, D., Kekin, I., Rossini Gajsak, L., Boban, M., Bozina, N., Bozina, T., Celic Ruzic, M., & Darmopil, S. (2019). Integration of complementary biomarkers in patients with first episode psychosis: Research protocol of a prospective follow up study. *Psychiatria Danubina, 31*(2), 162–171. https://doi.org/10.24869/psyd.2019.162

*Roy, A., Pickar, D., Doran, A., Wolkowitz, O., Gallucci, W., Chrousos, G., & Gold, P. (1986). The corticotropin-releasing hormone stimulation test in chronic schizophrenia. *The American Journal of Psychiatry*, *143*(11), 1393–1397. https://doi.org/10.1176/ajp.143.11.1393

*Ryan, M. C. M., Collins, P., & Thakore, J. H. (2003). Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *American Journal of Psychiatry, 160*(2), 284–289. https://doi.org/10.1176/appi.ajp.160.2.284

*Ryan, M. C. M., Flanagan, S., Kinsella, U., Keeling, F., & Thakore, J. H. (2004). The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naive patients with schizophrenia. *Life Sciences, 74*(16), 1999–2008. https://doi.org/10.1016/j.lfs.2003.08.044

*Ryan, M. C. M., Sharifi, N., Condren, R., & Thakore, J. H. (2004). Evidence of basal pituitary–adrenal overactivity in first episode, drug naïve patients with schizophrenia. *Psychoneuroendocrinology, 29*(8), 1065–1070. https://doi.org/10.1016/j.psyneuen.2003.08.011

Saha, S., Chant, D., Welham, J., & McGrath, J. (2005). A systematic review of the prevalence of schizophrenia. *PLOS Medicine, 2*(5), Article e141. https://doi.org/10.1371/journal.pmed.0020141

Sarin, F., & Wallin, L. (2014). Cognitive model and cognitive behavior therapy for schizophrenia: An overview. *Nordic Journal of Psychiatry, 68*(3), 145–153. https://doi.org/10.3109/08039488.2013.789074

*Schifani, C., Tseng, H.-H., Kenk, M., Tagore, A., Kiang, M., Wilson, A. A., Houle, S., Rusjan, P. M., & Mizrahi, R. (2018). Cortical stress regulation is disrupted in schizophrenia but not in clinical high risk for psychosis. *Brain, 141*(7), 2213–2224. https://doi.org/10.1093/brain/awy133

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature, 511*(7510), 421–427. https://doi.org/10.1038/nature13595

*Seidenfaden, D., Knorr, U., Soendergaard, M. G., Poulsen, H. E., Fink-Jensen, A., Jorgensen, M. B., & Jorgensen, A. (2017). The relationship between self-reported childhood adversities, adulthood psychopathology and psychological stress markers in patients with schizophrenia. *Comprehensive Psychiatry, 72*, 48–55. https://doi.org/10.1016/j.comppsych.2016.09.009

Selye, H. (1975). Confusion and controversy in the stress field. *Journal of Human Stress, 1*(2), 37–44. https://doi.org/10.1080/0097840X.1975.9940406

*Şimşek, Ş., Gençoğlan, S., Yüksel, T., & Aktaş, H. (2017). Cortisol and ACTH levels in drug-naive adolescents with first-episode early onset schizophrenia. *Asia-Pacific Psychiatry, 9*(1), Article e12264. https://doi.org/10.1111/appy.12264

*Solanki, R. K., Sharma, P., Tyagi, A., & Singh, C. (2017). Serum levels of neuroactive steroids in firstepisode antipsychotic-naive schizophrenic patients and its correlation with aggression: A case-control study. *East Asian Archives of Psychiatry, 27*(2), 79–84. https://doi.org/10.3316/informit.904107475150316

Stalder, T., Kirschbaum, C., Kudielka, B. M., Adam, E. K., Pruessner, J. C., Wüst, S., Dockray, S., Smyth, N., Evans, P., Hellhammer, D. H., Miller, R., Wetherell, M. A., Lupien, S. J., & Clow, A. (2016). Assessment of the cortisol awakening response: Expert consensus guidelines. *Psychoneuroendocrinology, 63*, 414–432. https://doi.org/10.1016/j.psyneuen.2015.10.010

*Steiner, J., Westphal, S., Schroeter, M. L., Schiltz, K., Jordan, W., Müller, U. J., Bernstein, H.-G., Bogerts, B., Schmidt, R. E., & Jacobs, R. (2012). Increased $S100B_+$ NK cell counts in acutely ill schizophrenia patients are correlated with the free cortisol index, but not with S100B serum levels. *Brain, Behavior, and Immunity, 26*(4), 564–567. https://doi.org/10.1016/j.bbi.2012.01.018

Steptoe, A., & Serwinski, B. (2016). Cortisol awakening response. In G. Fink (Ed.), *Stress: Concepts, cognition, emotion, and behavior* (1st ed., Vol. 1, pp. 277–283). Academic Press. https://doi.org/10.1016/B978-0-12-800951-2.00034-0

Sterne, J. A. C., & Egger, M. (2001). Funnel plots for detecting bias in meta-analysis: Guidelines on choice of axis. *Journal of Clinical Epidemiology, 54*(10), 1046–1055. https://doi.org/10.1016/S0895-4356(01)00377-8

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., . . . Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, Article l4898. https://doi.org/10.1136/bmj.l4898

Strong, D. R., Lejuez, C. W., Daughters, S., Marinello, M., Kahler, C. W., & Brown, R. A. (2003). *The Computerized Mirror Tracing Task, version 1*. [Unpublished manual]. Department of Psychology, University of Maryland.

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., Malaspina, D., Owen, M. J., Schultz, S., Tsuang, M., Van Os, J., & Carpenter, W. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research, 150*(1), 3–10. https://doi.org/10.1016/j.schres.2013.05.028

Trotman, H. D., Holtzman, C. W., Walker, E. F., Addington, J. M., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Heinssen, R. K., Mathalon, D. H., Tsuang, M. T., Perkins, D. O., Seidman, L. J., Woods, S. W., & McGlashan, T. H. (2014). Stress exposure and sensitivity in the clinical high-risk syndrome: Initial findings from the North American Prodrome Longitudinal Study (NAPLS). *Schizophrenia Research, 160*(1), 104–109. https://doi.org/10.1016/j.schres.2014.09.017

Vaessen, T., Kasanova, Z., Hernaus, D., Lataster, J., Collip, D., van Nierop, M., & Myin-Germeys, I. (2018). Overall cortisol, diurnal slope, and stress reactivity in psychosis: An experience sampling approach. *Psychoneuroendocrinology, 96*, 61–68. https://doi.org/10.1016/j.psyneuen.2018.06.007

*Venkatasubramanian, G., Chittiprol, S., Neelakantachar, N., Shetty, T., & Gangadhar, B. N. (2010). Effect of antipsychotic treatment on Insulin-Like Growth Factor-1 and cortisol in schizophrenia: A longitudinal study. *Schizophrenia Research, 119*(1), 131–137. https://doi.org/10.1016/j.schres.2010.01.033

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software, 36*(3), 1–48. https://doi.org/10.18637/jss.v036.i03

Walder, D. J., Walker, E. F., & Lewine, R. J. (2000). Cognitive functioning, cortisol release, and symptom severity in patients with schizophrenia. *Biological Psychiatry, 48*(12), 1121–1132. https://doi.org/10.1016/S0006-3223(00)01052-0

Walker, E., Mittal, V., & Tessner, K. (2008). Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. *Annual Review of Clinical Psychology, 4*(1), 189–216. https://doi.org/10.1146/annurev.clinpsy.4.022007.141248

Walker, E. F., & Diforio, D. (1997). Schizophrenia: A neural diathesis-stress model. *Psychological Review, 104*(4), 667–685. https://doi.org/10.1037/0033-295X.104.4.667

Walker, E. F., Walder, D. J., & Reynolds, F. (2001). Developmental changes in cortisol secretion in normal and at-risk youth. *Development and Psychopathology, 13*(3), 721–732. https://doi.org/10.1017/S0954579401003169

Wallace, B. C., Schmid, C. H., Lau, J., & Trikalinos, T. A. (2009). Meta-analyst: Software for meta-analysis of binary, continuous and diagnostic data. *BMC Medical Research Methodology, 9*(1), Article 80. https://doi.org/10.1186/1471-2288-9-80

*Walsh, P., Spelman, L., Sharifi, N., & Thakore, J. H. (2005). Male patients with paranoid schizophrenia have greater ACTH and cortisol secretion in response to metoclopramide-induced AVP release. *Psychoneuroendocrinology, 30*(5), 431–437. https://doi.org/10.1016/j.psyneuen.2004.11.003

*Wedervang-Resell, K., Friis, S., Lonning, V., Smelror, R. E., Johannessen, C., Reponen, E. J., Lyngstad, S. H., Lekva, T., Aukrust, P., Ueland, T., Andreassen, O. A., Agartz, I., & Myhre, A. M. (2020). Increased interleukin 18 activity in adolescents with early-onset psychosis is associated with cortisol and depressive symptoms. *Psychoneuroendocrinology, 112*, Article 104513. https://doi.org/10.1016/j.psyneuen.2019.104513

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

*Whalley, L. J., Borthwick, N., Copolov, D., Dick, H., Christie, J. E., & Fink, G. (1986). Glucocorticoid receptors and depression. *British Medical Journal, 292*(6524), 859–861. https://doi.org/10.1136/bmj.292.6524.859

*Whalley, L. J., Christie, J. E., Bennie, J., Dick, H., Blackburn, I. M., Blackwood, D., Sanchez Watts, G., & Fink, G. (1985). Selective increase in plasma luteinising hormone concentrations in drug free young men with mania. *British Medical Journal, 290*(6462), 99–102. https://doi.org/10.1136/bmj.290.6462.99

*White, R. G., Lysaker, P., Gumley, A. I., McLeod, H., McCleery, M., O'Neill, D., MacBeth, A., Giurgi-Oncu, C., & Mulholland, C. C. (2014). Plasma cortisol levels and illness appraisal in deficit syndrome schizophrenia. *Psychiatry Research, 220*(3), 765–771. https://doi.org/10.1016/j.psychres.2014.08.043

Wilhelm, I., Born, J., Kudielka, B. M., Schlotz, W., & Wüst, S. (2007). Is the cortisol awakening rise a response to awakening? *Psychoneuroendocrinology, 32*(4), 358–366. https://doi.org/10.1016/j.psyneuen.2007.01.008

*Wolkowitz, O. M., Doran, A. R., Breier, A., Cohen, M. R., & Pickar, D. (1986). Endogenous opioid regulation of hypothalamo-pituitary-adrenal axis activity in schizophrenia. *Biological Psychiatry, 21*(4), 366–373. https://doi.org/10.1016/0006-3223(86)90164-2

World Health Organization. (2019a). *International statistical classification of diseases and related health problems* (11th ed.). https://icd.who.int/

World Health Organization. (2019b, October 4). *Schizophrenia*. https://www.who.int/news-room/fact-sheets/detail/schizophrenia

*Yıldırım, O., Dogan, O., Semiz, M., & Kilicli, F. (2011). Serum cortisol and dehydroepiandrosterone-sulfate levels in schizophrenic patients and their first-degree relatives. *Psychiatry and Clinical Neurosciences, 65*(6), 584–591. https://doi.org/10.1111/j.1440-1819.2011.02252.x

*Yılmaz, N., Herken, H., Cicek, H. K., Celik, A., Yürekli, M., & Akyol, Ö. (2007). Increased levels of nitric oxide, cortisol and adrenomedullin in patients with chronic schizophrenia. *Medical Principles and Practice, 16*(2), 137–141. https://doi.org/10.1159/000098367

Zeng, X., Zhang, Y., Kwong, J. S. W., Zhang, C., Li, S., Sun, F., Niu, Y., & Du, L. (2015). The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. *Journal of Evidence-Based Medicine, 8*(1), 2–10. https://doi.org/10.1111/jebm.12141

*Zhang, X. Y., Zhou, D. F., Cao, L. Y., Wu, G. Y., & Shen, Y. C. (2005). Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia:

Association with psychopathology and response to antipsychotics. *Neuropsychopharmacology, 30*(8), 1532–1538. https://doi.org/10.1038/sj.npp.1300756

*Zhou, D., Shen, Y., Shu, L., & Lo, H. (1987). Dexamethasone suppression test and urinary MHPG· SO4 determination in depressive disorders. *Biological Psychiatry, 22*(7), 883–891. https://doi.org/10.1016/0006-3223(87)90086-2

Zorn, J. V., Schür, R. R., Boks, M. P., Kahn, R. S., Joëls, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology, 77*, 25–36. https://doi.org/10.1016/j.psyneuen.2016.11.036

Zubin, J., & Spring, B. (1977). Vulnerability: A new view of schizophrenia. *Journal of Abnormal Psychology, 86*(2), 103–126. https://doi.org/10.1037/0021-843X.86.2.103

Appendix A

Characteristics of Included Studies

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Morning cortisol										
Hoshino et al. (1984)	19	10:9	35.0 (–)	RDC diagnosis of schizophrenia	medicated	26	12:14	27.0 (–)	plasma	NOS: 2
Whalley et al. (1985)	13	0:13	25.6 (7.5)	RDC diagnosis of schizophrenia	drug free	13	0:13	30.0 (8.6)	plasma	NOS: 6
Morphy et al. (1985)	18	3:15	38.9 (13.8)	DSM-III and RDC diagnosis of schizophrenia	medicated	22	15:7	34.2 (8.5)	serum	NOS: 4
Herz et al. (1985)	15	8:7	32.0 (9.6)	DSM-III diagnosis of schizophrenia or schizoaffective disorder	drug free	15	8:7	34.5 (6.7)	serum	NOS: 4
Gattaz et al. (1985)[d]	28	0:28	30.6 (1.5)	RDC diagnosis of schizophrenia	mixed	16	2:14	35.0 (3.9)	CSF	NOS: 3
Wolkowitz et al. (1986)	9	–	–	DSM-III and RDC diagnosis of schizophrenia or schizoaffective disorder	mixed	8	4:4	–	serum	NOS: 8
Breier et al. (1988)	8	1:7	–	DSM-III diagnosis of schizophrenia	mixed	11	7:4	–	plasma	NOS: 1
Altamura et al. (1989)	54	19:35	31.9 (10.2)	DSM-III diagnosis of schizophrenia	medicated	20	–	–	plasma	NOS: 4
Davila et al. (1989)	11	0:11	30.0 (–)	RDC diagnosis of schizophrenia	medicated	14	0:14	33.0 (–)	plasma	NOS: 2
Parshad & Uppal (1989)	20	0:20	28.9 (11.2)	DSM-III diagnosis of schizophrenia	medicated	22	0:22	31.6 (16.7)	serum	NOS: 4

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Morning cortisol										
Abel et al. (1996)[b]	13	3:10	29.5 (8.3)	DSM-III-R diagnosis of schizophrenia	naive	13	3:10	31.7 (8.3)	plasma	NOS: 6
Jakovljević et al. (1998)	59	0:59	36.2 (6.5)	DSM-III-R diagnosis of schizophrenia	drug free	59	0:59	31.8 (5.4)	plasma	NOS: 4
Elman et al. (1998)	13	3:10	37.9 (8.7)	DSM-IV diagnosis of schizophrenia	medicated	11	2:9	32.4 (6.5)	plasma	NOS: 5
Monteleone et al. (1999)	16	8:8	28.1 (7.3)	DSM-IV diagnosis of schizophrenia	drug free	16	8:8	28.2 (6.3)	plasma	RoB 2: low risk
F. Duval et al. (2000)	41	13:28	34.6 (11.5)	DSM-IV diagnosis of schizophrenia	drug free	27	13:14	35.5 (9.4)	plasma	NOS: 5
Jansen et al. (2000)	18	7:11	27.7 (4.3)	DSM-IV diagnosis of schizophrenia	medicated	21	8:13	27.0 (5.4)	saliva	NOS: 3
Mokrani et al. (2000)	31	8:23	29.8 (9.1)	DSM-IV diagnosis of schizophrenia	drug free	22	13:9	34.8 (10.2)	serum	NOS: 4
Meltzer et al. (2001)	51	9:42	36.1 (8.3)	DSM-III-R diagnosis of schizophrenia or schizoaffective disorder	drug free	15	5:10	25.5 (5.7)	plasma	RoB 2: some concerns
Kaneda et al. (2002)	53	20:33	51.9 (10.3)	DSM-IV diagnosis of schizophrenia	medicated	23	10:13	50.7 (15.8)	plasma	NOS: 1
F. Duval et al. (2003)	20	9:11	32.5 (11.6)	DSM-IV diagnosis of schizophrenia	mixed	23	12:11	34.2 (7.2)	serum	NOS: 7

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Morning cortisol										
Ryan et al. (2003)[b]	26	11:15	33.6 (13.5)	DSM-IV diagnosis of schizophrenia	naive	26	11:15	34.4 (1.9)	plasma	NOS: 7
Marcelis et al. (2004)	50	24:26	31.2 (7.5)	RDC diagnosis schizophrenia or schizoaffective disorder	medicated	50	25:25	35.0 (8.9)	plasma	NOS: 8
Ritsner et al. (2004)	40	2:38	38.0 (11.1)	DSM-IV diagnosis of schizophrenia	medicated	15	2:13	35.1 (7.6)	plasma	NOS: 6
Muck-Seler et al. (2004)	20	20:0	33.1 (8.8)	DSM-IV diagnosis of schizophrenia	drug free	25	25:0	39.5 (7.7)	plasma	NOS: 6
Ryan, Flanagan, et al. (2004)[b]	19	4:15	31.0 (2.5)	DSM-IV diagnosis of schizophrenia	naive	19	4:15	32.6 (2.3)	plasma	NOS: 8
Zhang et al. (2005)	78	18:60	43.8 (7.2)	DSM-III-R diagnosis of schizophrenia	drug free	30	8:22	40.4 (10.3)	serum	RoB 2: low risk
Yılmaz et al. (2007)	66	0:66	33.6 (11.0)	DSM-IV diagnosis of schizophrenia	medicated	28	0:28	34.4 (12.0)	serum	NOS: 5
Popovic et al. (2007)	18	9:9	28.8 (1.6)	ICD-10 diagnosis of schizophrenia	medicated	20	12:8	30.4 (2.1)	serum	NOS: 4
Ritsner et al. (2007)	43	3:40	34.1 (9.2)	DSM-IV diagnosis of schizophrenia	medicated	20	2:18	37.2 (8.7)	serum	NOS: 6
Brunelin et al. (2008)	15	5:10	28.6 (7.5)	DSM-IV diagnosis of schizophrenia	medicated	14	8:6	29.1 (7.2)	plasma	NOS: 5

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Morning cortisol										
Venkatasubramanian et al. (2010)	33	13:20	33.8 (8.2)	DSM-IV diagnosis of schizophrenia	naive	33	13:20	32.2 (8.0)	serum	NOS: 6
Kale et al. (2010) b	31	17:14	32.7 (8.0)	DSM-IV diagnosis of schizophrenia, schizophreniform or schizoaffective disorder	naive	38	–	–	plasma	NOS: 8
Yıldırım et al. (2011)	60	29:31	36.3 (9.5)	DSM-IV diagnosis of schizophrenia	mixed	60	30:30	37.3 (9.9)	serum	NOS: 3
Garner et al. (2011) b	39	13:26	20.6 (2.6)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, delusional, or psychotic disorder, bipolar disorder or major depression with psychotic features	naive or minimally treated	25	4:21	22.5 (2.0)	serum	NOS: 7
Steiner et al. (2012)	26	9:17	34.7 (11.3)	DSM-IV diagnosis of schizophrenia	mixed	32	12:2	34.4 (10.8)	serum	NOS: 6
Phassouliotis et al. (2012) [b]	21	9:12	20.6 (2.9)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, delusional, psychotic disorder bipolar disorder or major depression with psychotic features	naive or minimally treated	20	8:12	22.4 (2.3)	serum	NOS: 6
White et al. (2014)	85	19:66	–	DSM-IV diagnosis of schizophrenia	medicated	85	–	–	plasma	NOS: 7
Manzanares et al. (2014) [b]	65	26:39	24.4 (4.7)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, or psychotic disorder	medicated	25	14:11	27.0 (3.9)	plasma, saliva	NOS: 7

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Morning cortisol										
Montalvo et al. (2014)[b]	55	25:30	24.5 (5.3)	DSM-IV diagnosis of schizophreniform, schizoaffective, or psychotic disorder	mixed	29	14:15	26.4 (4.3)	plasma	NOS: 6
Goldstein et al. (2015)[c]	32	16:16	41.9 (5.9)	DSM-IV diagnosis of non-affective psychoses or affective psychoses	medicated	33	–	–	blood, no details	NOS: 6
M. A. Lee et al. (2015)	69	0:69	33.7 (6.9)	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	drug free	33	0:33	28.6 (7.4)	plasma	RoB 2: some concerns
Reniers et al. (2015)[b]	22	4:18	20.6 (2.4)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, delusional, or psychotic disorder, bipolar disorder or major depression with psychotic features	naive or minimally treated	22	4:18	22.5 (2.0)	serum	NOS: 6
Bulut et al. (2016)	38	0:38	39.0 (10.5)	DSM-IV-TR diagnosis of schizophrenia	medicated	38	0:38	39.3 (12.5)	serum	NOS: 5
Labad et al. (2016)[b]	60	21:39	24.6 (5.4)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, or psychotic disorder	medicated	50	22:28	23.8 (4.7)	saliva	NOS: 5
Petrikis et al. (2016)[b]	40	13:27	32.5 (9.8)	DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or brief psychotic episode	naive	40	15:25	31.9 (8.3)	serum	NOS: 7
Mizuno et al. (2016)	60	38:22	45.9 (10.0)	DSM-IV diagnosis of schizophrenia	medicated	60	30:3	41.0 (17.6)	plasma	NOS: 4

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Morning cortisol										
C. Z. Duval et al. (2016)	21	5:16	37.7 (9.2)	DSM-IV-TR diagnosis of schizophrenia	drug free	21	5:16	37.4 (10.7)	blood, no details	NOS: 3
Girshkin et al. (2016)	56	24:32	42.8 (11.5)	ICD-10 diagnosis of schizophrenia or schizoaffective disorder	medicated	59	27:32	34.9 (11.8)	saliva	NOS: 6
Solanki et al. (2017) [b]	30	12:18	24.3 (5.4)	ICD-10 diagnosis of schizophrenia	naive	20	7:13	27.9 (6.1)	serum	NOS: 7
Şimşek et al. (2017) [b]	23	15:8	14.3 (1.4)	DSM-IV diagnosis of early onset schizophrenia	naive	23	15:8	14.7 (1.5)	serum	NOS: 5
Ntouros et al. (2018) [b]	25	0:25	25.5 (5.4)	DSM-IV-TR diagnosis of psychotic episode without affective features	drug free or naive	23	0:23	27.0 (2.9)	serum	NOS: 5
Bulut et al. (2018)	32	32:0	33.4 (7.5)	DSM-IV-TR diagnosis of schizophrenia	medicated	32	32:0	34.6 (7.7)	serum	NOS: 5
Cai et al. (2018) [b]	53	23:30	24.9 (8.6)	DSM-IV diagnosis of schizophrenia, schizophreniform or schizoaffective disorder	naive	43	19:24	25.6 (7.2)	plasma	NOS: 5
Allott et al. (2018) [b]	35	9:26	20.3 (2.5)	DSM-IV diagnosis of schizophreniform, schizoaffective, delusional, or psychotic disorder, bipolar disorder or major depression with psychotic features	naive or minimally treated	23	5:18	22.1 (1.8)	serum	NOS: 6
C. H. Lee et al. (2019)	86	33:53	35.8 (8.3)	DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder	medicated	77	38:39	31.7 (8.5)	serum	NOS: 5

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Morning cortisol										
Wedervang-Resell et al. (2020)[b]	31	20:11	16.3 (1.4)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, or psychotic disorders	mixed	60	31:29	15.9 (1.4)	serum	NOS: 3
Afternoon cortisol										
Whalley et al. (1986)	12	10:2	42.8 (–)	RDC diagnosis of schizophrenia	medicated	29	–	–	plasma	NOS: 6
Ryan, Sharifi, et al. (2004)[b]	12	5:7	33.6 (12.6)	DSM-IV diagnosis of schizophrenia	naive	12	5:7	35.8 (12.0)	plasma	NOS: 8
Walsh et al. (2005)[b]	10	0:10	26.8 (1.3)	DSM-IV diagnosis of schizophrenia	naive	10	0:10	25.0 (2.2)	plasma	NOS: 7
Gallagher et al. (2007)	20	2:18	42.1 (10.3)	DSM-IV diagnosis of schizophrenia	medicated	20	2:18	45.3 (12.4)	plasma	NOS: 7
Dinzeo et al. (2015)	16	7:9	41.1 (6.6)	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	medicated	10	5:5	36.7 (8.8)	saliva	NOS: 6
Lincoln et al. (2015)	28	10:18	–	ICD-10 diagnosis of schizophrenia or schizoaffective disorder	medicated	26	11:15	–	saliva	NOS: 7
Chiappelli et al. (2016)	34	14:20	39.9 (12.9)	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	medicated	40	20:20	38.1 (14.1)	saliva	NOS: 6
Lange et al. (2017)	25	7:18	38.3 (13.5)	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	medicated	25	9:16	41.2 (11.1)	saliva	NOS: 4

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Afternoon cortisol										
Nordholm et al. (2018)[b]	26	–	–	ICD-10 diagnosis of schizophrenia or schizoaffective psychosis	naive	28	–	–	saliva	NOS: 8
Das et al. (2018)	58	8:50	31.5 (9.8)	ICD-10 diagnosis of schizophrenia or psychosis	drug free	22	4:18	31.9 (8.6)	saliva	NOS: 3
Rojnic Kuzman et al. (2019)[b]	46	–	–	ICD-10 diagnosis of psychotic episode with schizophrenia features	naive	45	–	–	saliva	NOS: 6
Aas et al. (2020)	14	14:0	34.1 (3.9)	DSM-IV diagnosis of brief psychotic disorder with postpartum onset	–	26	26:0	34.4 (4.7)	saliva	NOS: 5
Further studies: Hoshino et al. (1984), Whalley et al. (1985), Morphy et al. (1985), Herz et al. (1985), Altamura et al. (1989), Davila et al. (1989), Ntouros et al. (2018)[b], see above section Morning cortisol										
Evening cortisol										
Roy et al. (1986)	9	5:4	30.0 (–)	DSM-III diagnosis of schizophrenia	drug free	27	–	–	plasma	NOS: 3
Zhou et al. (1987)	48	20:28	27.8 (9.0)	DSM-III and ICD-9 diagnosis of schizophrenia	–	20	10:10	33.8 (10.7)	plasma	NOS: 4
Jiang & Wang (1998)	21	0:21	27.3 (7.2)	DSM-IV diagnosis of schizophrenia	medicated	21	0:21	29.7 (11.0)	serum	NOS:4
Faravelli et al. (2017)[b]	54	24:30	43.7 (10.5)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, or delusional disorder	–	102	49:53	43.5 (12.2)	saliva	NOS:5

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Evening cortisol										
Seidenfaden et al. (2017)	37	20:17	32.3 (10.7)	ICD-10 diagnosis of schizophrenia	medicated	39	19:20	31.7 (9.7)	plasma, saliva	NOS: 4
Cherian et al. (2019)	16	–	–	DSM-IV diagnosis of schizophrenia or schizoaffective disorder	mixed	44	–	–	plasma	NOS: 4
Further studies: Whalley et al. (1985), Labad et al. (2016)[b], Ntouros et al. (2018)[b], see above section Morning cortisol; Nordholm et al. (2018)[b], Aas et al. (2020), see above section Afternoon cortisol										
Cortisol awakening response (CAR)										
Mondelli et al. (2010)[b]	50	18:32	29.2 (1.1)	DSM-IV diagnosis of schizophrenia, schizophreniform, delusional, schizoaffective, or psychotic disorder	mixed	36	10:26	27.3 (0.8)	saliva	NOS: 6
Monteleone et al. (2014)	28	8:20	41.0 (7.5)	DSM-IV-TR diagnosis of schizophrenia	medicated	15	3:12	37.6 (6.9)	saliva	NOS: 7
Mondelli et al. (2015)[b]	68	22:46	29.2 (1.3)	DSM-IV diagnosis of schizophrenia, schizophreniform, schizoaffective, delusional, or psychotic disorder	mixed	57	21:36	26.8 (0.6)	saliva	NOS: 6
Further studies: Labad et al. (2016)[b], see above section Morning cortisol; Nordholm et al. (2018)[b], Aas et al. (2020), see above section Afternoon cortisol; Seidenfaden et al. (2017), see above section Evening cortisol										
Mental stress										
Albus et al. (1982)	12	–	34.0 (8.5)	ICD diagnosis of schizophrenia	drug free	27	–	–	plasma	NOS: 2

(continued on the next page)

Appendix A (continued)

Study	Schizophrenia patients					Healthy individuals			Sample type	Study quality
	N	Sex (females: males)	Age, mean (*SD*)	Diagnosis	Medication status[a]	*N*	Sex (females: males)	Age, mean (*SD*)		
Mental stress										
Mizrahi et al. (2012)	9	–	–	DSM-IV diagnosis of schizophrenia or schizophreniform disorder	naive	12	5:7	26.1 (3.8)	saliva	NOS: 4
Schifani et al. (2018)	9	–	–	DSM-IV diagnosis of schizophrenia, schizoaffective, delusional, or schizophreniform disorder	drug free or naive	12	5:7	26.0 (6.5)	saliva	NOS: 3
Further studies: Jansen et al. (2000), Goldstein et al. (2015)[c], see above section Morning cortisol; Lincoln et al. (2015), Chiappelli et al. (2016), Lange et al. (2017), see above section Afternoon cortisol										
Physiological stress										
Studies: Jansen et al. (2000), C. Z. Duval et al. (2016), see above section Morning cortisol; Lincoln et al. (2015), see above section Afternoon cortisol; Albus et al. (1982), see above section Mental stress										

Note. The different sections accentuated with gray background represent the categories for which we performed meta-analyses. The dash (–) indicates that the data was not reported in the respective article and was not available upon request. CAR = cortisol awakening response; CSF = cerebrospinal fluid; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; *N* = number of subjects that had cortisol values available, not necessarily the total sample sizes of the respective studies; NOS = Newcastle-Ottawa Scale; RDC = Research Diagnostic Criteria; RoB 2 = Revised Cochrane Risk-of-Bias Tool for Randomized Trials.

[a] drug free = all or the majority of patients underwent a wash-out period or were antipsychotic-free at the time of sampling; medicated = all or the majority of patients were on antipsychotic treatment at the time of sampling; minimally treated = patients had received maximally 10 days of treatment with any psychotropic medication prior to study entry; mixed = at least some of the patients were on antipsychotic treatment at the time of sampling; naive = all patients were antipsychotic naive at study entry.

[b] All or the majority of patients in these studies were specified as experiencing an early or first episode of schizophrenia or psychosis. Early psychosis was defined as psychotic disorder with less than three years of illness duration in the studies by Labad et al. (2016) and Montalvo et al. (2014), and as psychotic disorder with less than five years of illness duration in the study by Manzanares et al. (2014). Early-onset psychosis in the study by Wedervang-Resell et al. (2020) was defined as psychosis with onset prior to 18 years of age. No explicit definition of early onset was available from the study by Şimşek et al. (2017).

[c] In this study, non-affective psychosis included the diagnoses schizophrenia, schizoaffective disorder and psychosis not otherwise specified.

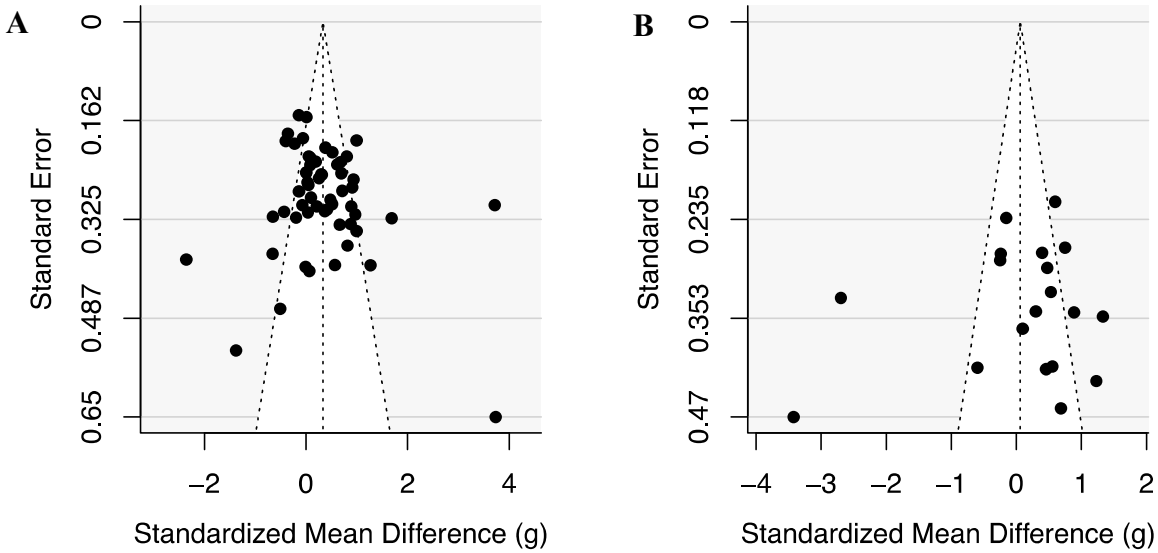
[d] In this study, two samples of schizophrenia patients were reported on, but only one patient sample was compared to healthy individuals and thus qualified for inclusion.

Appendix B

Funnel Plots for Assessment of Publication Bias

Figure B1

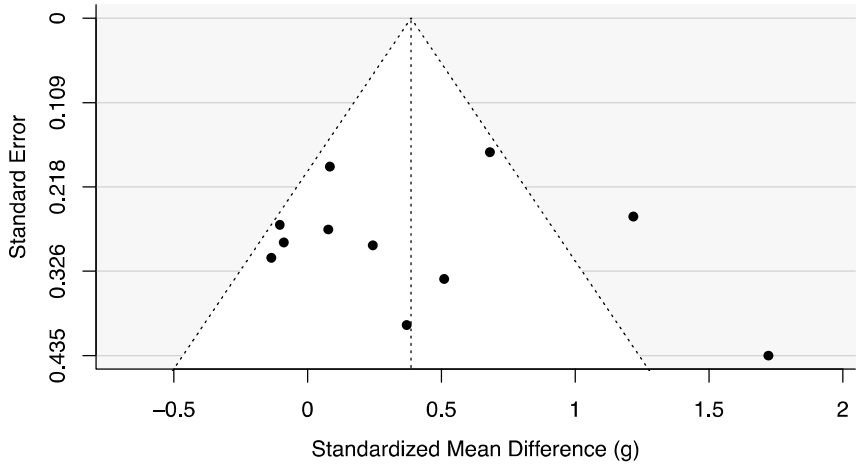
Funnel Plot for Publication Bias Assessment of the Meta-Analyses on (A) Baseline Morning and (B) Baseline Afternoon Cortisol Levels



Note. Funnel plots of individual studies' standardized mean difference (Hedge's *g*) effect size estimates representing the association between schizophrenia and cortisol levels against the standard error of the effect size estimates with pseudo 95% confidence intervals.

Figure B2

Funnel Plot for Publication Bias Assessment of the Meta-Analysis on Baseline Evening Cortisol Levels



Note. Funnel plot of individual studies' standardized mean difference (Hedge's *g*) effect size estimates representing the association between schizophrenia and cortisol levels against the standard error of the effect size estimates with pseudo 95% confidence interval.