



# Morning cortisol levels in schizophrenia and bipolar disorder: A meta-analysis



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**Summary** Increased peripheral levels of morning cortisol have been reported in people with schizophrenia (SZ) and bipolar disorder (BD), but findings are inconsistent and few studies have conducted direct comparisons of these disorders. We undertook a meta-analysis of studies examining single measures of morning cortisol (before 10 a.m.) levels in SZ or BD, compared to controls, and to each other; we also sought to examine likely moderators of any observed effects by clinical and demographic variables. Included studies were obtained via systematic searches conducted using Medline, BIOSIS Previews and Embase databases, as well as hand searching. The decision to include or exclude studies, data extraction and quality assessment was completed in duplicate by LG, SM and AS. The initial search revealed 1459 records. Subsequently, 914 were excluded on reading the abstract because they did not meet one or more of the inclusion criteria; of the remaining 545 studies screened in full, included studies were 44 comparing SZ with controls, 19 comparing BD with controls, and 7 studies directly comparing schizophrenia with bipolar disorder. Meta-analysis of SZ ( $N=2613$ ,  $g=0.387$ ,  $p=0.001$ ) and BD ( $N=704$ ,  $g=0.269$ ,  $p=0.004$ ) revealed moderate quality evidence of increased morning cortisol levels in each group compared to controls, but no difference between the two disorders ( $N=392$ ,  $g=0.038$ ,  $p=0.738$ ). Subgroup analyses revealed greater effect sizes for schizophrenia samples with an established diagnosis (as opposed to 'first-episode'), those that were free of medication, and those sampled in an inpatient setting (perhaps reflecting an acute illness phase). In BD, greater morning cortisol levels were found in outpatient and non-manic participants (as opposed to those in a manic state), relative to controls. Neither age nor sex affected cortisol levels in any group. However, earlier greater increases in SZ morning cortisol were evident in samples taken before 8 a.m. (relative to those taken after 8 a.m.). Multiple meta-regression showed

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that medication status was significantly associated with morning cortisol levels in SZ, when the effects of assay method, sampling time and illness stage were held constant. Heightened levels of morning cortisol in SZ and BD suggest long-term pathology of the hypothalamic-pituitary-adrenal (HPA) axis that may reflect a shared process of illness development in line with current stress-vulnerability models.

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## 1. Introduction

Schizophrenia and bipolar disorder are severe neuropsychiatric disorders likely caused by an interaction of multiple biological and environmental factors, with a prominent role for stress-related pathology proposed within current diathesis-stress models of illness development (Rethelyi et al., 2013). Shared environmental risk factors have been estimated to account for 3–6% of vulnerability for schizophrenia and bipolar disorder (Lichtenstein et al., 2009), and include a higher prevalence of pre- or post-natal insults (Demjaha et al., 2012; Murray et al., 2004), early childhood maltreatment (Aas et al., 2011), and/or cannabis use in adolescence (Leweke and Koethe, 2008; Moore et al., 2007). The impact of early life stressors on the development and function of the hypothalamic-pituitary-adrenal (HPA) axis may be key to understanding the development of these disorders (Collip et al., 2013; Joels et al., 2012).

The HPA axis is a key component of the stress-response system (Belsky and Pluess, 2009). Cortisol is the primary hormone released by the HPA axis in response to stress, and operates to maintain homeostasis of various physiological systems (Peters et al., 2007). Cortisol levels have been shown to peak in the first 30–40 min after waking (known as the cortisol awakening response; CAR): cortisol first increases sharply, then declines gradually throughout the day, in line with a normal diurnal rhythm associated with the sleep-wake cycle (Edwards et al., 2001). This response has been shown to vary according to factors such as age (Nicolson et al., 1997) and sex (Kurina et al., 2005), and substantial evidence shows an increase in basal cortisol following childhood maltreatment (Braehler et al., 2005). Chronic hypercortisolemia has been shown to significantly affect neurophysiology, with evidence of anatomical changes in prefrontal, amygdala and hippocampal brain regions (Joels, 2008; Roozendaal et al., 2009; Wellman, 2001), altered stress responsiveness (Bollini et al., 2004), and reduced brain-derived neurotrophic factor (BDNF) expression (Hansen et al., 2006).

Disruptions to the 24-h diurnal rhythm of cortisol secretion are commonly reported in schizophrenia and bipolar disorder: both disorders show heightened afternoon (Gallagher et al., 2007; Ryan et al., 2004; Walsh et al., 2005) and evening levels of cortisol (Jabben et al., 2011; Linkowski et al., 1994). Heightened levels of cortisol and a flattened diurnal curve have been associated with greater clinical severity (Havermans et al., 2011; Belvederi Murri et al., 2012). In addition, both disorders show increased morning cortisol profiles and a blunted CAR (Braehler et al., 2005; Deshauer et al., 2003; Mondelli et al., 2010; Monteleone et al., 2014). The measurement of baseline levels of cortisol immediately at waking, unlike the dynamic CAR, is reflective

of basal cortisol (Clow et al., 2004; Wust et al., 2000) rather than the fluctuation of the cortisol rhythm. There is considerable evidence of increased levels of morning cortisol (here defined as a single measure taken before 10 a.m.) in both schizophrenia and bipolar disorder relative to controls. However, a number of studies have reported conflicting evidence of no increase in cortisol (Breier and Buchanan, 1992; Brunelin et al., 2008; Davila et al., 1989; Dewan et al., 1988; Duval et al., 2003; Fernandez-Egea et al., 2009; Garcia-Rizo et al., 2012; Garfinkel et al., 1979; Hardoy et al., 2006; Henderson et al., 2006; Jansen et al., 2000; Judd et al., 1981; Kaneda et al., 2002; Lerer et al., 1988; Maes et al., 1996; Maguire et al., 1997; Maj et al., 1984; Meltzer et al., 1984; Perini et al., 1984; Ritsner et al., 2004; Strous et al., 2004; van Nimwegen et al., 2008; Vieta et al., 1997; Whalley et al., 1985; Wolkowitz et al., 1986), or a significant decrease in morning cortisol levels in these disorders (Kirkpatrick et al., 2009; Phassouliotis et al., 2013).

Increased cortisol levels observed in schizophrenia and bipolar disorder have been proposed as endophenotypic markers of illness (Cheng et al., 2010), but the potential effects of moderating variables such as illness stage, mood-state, treatment setting and psychotropic medication deserve further exploration in this context. In particular, there remains uncertainty about differing fluctuations in cortisol levels in association with manic or depressive mood states, and whether dysregulated cortisol levels remain during euthymic periods of bipolar disorder (Cervantes et al., 2001; Manenshijn et al., 2012). Some evidence has shown the depressive phase to be associated with heightened cortisol levels (Maj et al., 1984), with an absence of cortisol dysfunction during mania (Swann et al., 1992) and euthymic periods of remission (Schmider et al., 1995). However, other evidence indicates no clear relationship between cortisol level and illness phase (Deshauer et al., 2006). Additionally, the influence of illness duration on cortisol level remains unclear, with several studies showing a positive relationship between illness duration and cortisol levels (Havermans et al., 2011; Yilmaz et al., 2007) that has not always been replicated (Hempel et al., 2010). Unfortunately, studies of the relationship between illness stage and cortisol levels are often confounded by the use of psychotropic medications (Lee et al., 2011; Venkatasubramanian et al., 2010; Zhang et al., 2005).

We set out to conduct a meta-analysis of the available evidence for aberrant morning cortisol levels, measured peripherally (in blood or saliva), in both bipolar disorder and schizophrenia, compared to controls, and directly compared to each other. It was hypothesized that individuals with schizophrenia or bipolar disorder would show greater levels of morning cortisol in comparison to controls, with no difference expected between the two disorders.

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