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# Meta-analysis of blood cortisol levels in individuals with first-episode psychosis

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ABSTRACT

*Objective:* Schizophrenia is associated with abnormal neuroimmunoendocrine function. There is evidence for hypothalamic-pituitary-adrenal (HPA) axis abnormalities in individuals with first-episode psychosis (FEP). However, some previous meta-analyses have focused on heterogeneous sample sources and patient populations. We performed a meta-analysis of baseline (i.e., one sample) blood cortisol levels in individuals with FEP and minimal exposure to antipsychotics.

*Method:* Articles were identified by searching PubMed, PsycInfo, Web of Science, and Science Direct, and the reference lists of these studies.

*Results:* Twenty-six studies (comprising twenty-seven samples) met the inclusion criteria. Blood cortisol levels were significantly increased in individuals with FEP compared to controls with a small-to-medium effect size (standard mean difference [SMD] = 0.37, 95% CI 0.16-0.57, $p < 0.001$). In meta-regression analyses, geography was a significant moderator of this association, with larger effects seen in studies conducted in Asia versus the Middle East.

*Conclusion:* We found elevated blood cortisol levels in individuals with FEP, providing additional, complementary evidence for abnormal HPA axis function in this disorder. This finding, which does not inform on mechanism, is consistent with the "neural diathesis-stress" model of psychosis. Given the immunomodulatory effects of cortisol, methodologically rigorous longitudinal studies of cortisol parameters, inflammatory markers, and psychopathology in this patient population are warranted.

## 1. Introduction

The "neural diathesis-stress" model posits a role for hypothalamic-pituitary-adrenal HPA axis in the onset and exacerbation of schizophrenia (Walker and Diforio, 1997; Walker et al., 2008; Pruessner et al., 2017). According to this model, beginning in early life (i.e., conception), genetic and environmental factors/stressors increase psychosis risk through a cycle of HPA axis dysregulation (hyperactivation) and brain degenerative processes affecting neurons in the hippocampus and prefrontal cortex, altering the function of dopamine and other neurotransmitters. The HPA axis is the primary system that responds to physiological and psychological stress (Philips et al., 2006), and it is also involved in the regulation of multiple physiologic processes, including immune, metabolic, and brain function. In this system, corticotropin-releasing hormone (CRH) produced by the hypothalamus stimulates secretion of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland, which in turn stimulates production of glucocorticoid hormones, including cortisol, by the adrenal glands. In a negative feedback loop, cortisol inhibits production of ACTH and CRH. There is evidence for a circadian rhythm in cortisol levels with diurnal variation (levels peak in the morning, decrease throughout the day, and rise during sleep; Pruessner et al., 2017).

In the past decade, there has been exponential growth in research on the role of stress and the HPA axis in schizophrenia. HPA axis abnormalities are observed in individuals with first-episode psychosis (FEP) and in those with chronic schizophrenia. These abnormalities include abnormalities in daytime cortisol levels and the cortisol awakening response (CAR), as well as responses to psychosocial stress tasks (reviewed in Pruessner et al., 2017). The CAR is the rapid increase in cortisol levels that occurs in the first hour after waking, which may be a distinct feature of the diurnal cortisol rhythm. A previous meta-analysis found a blunted/flattened CAR (measured in saliva) in the setting of higher absolute cortisol levels, in individuals with FEP (Berger et al., 2016). Another meta-analysis found increased daytime cortisol levels in

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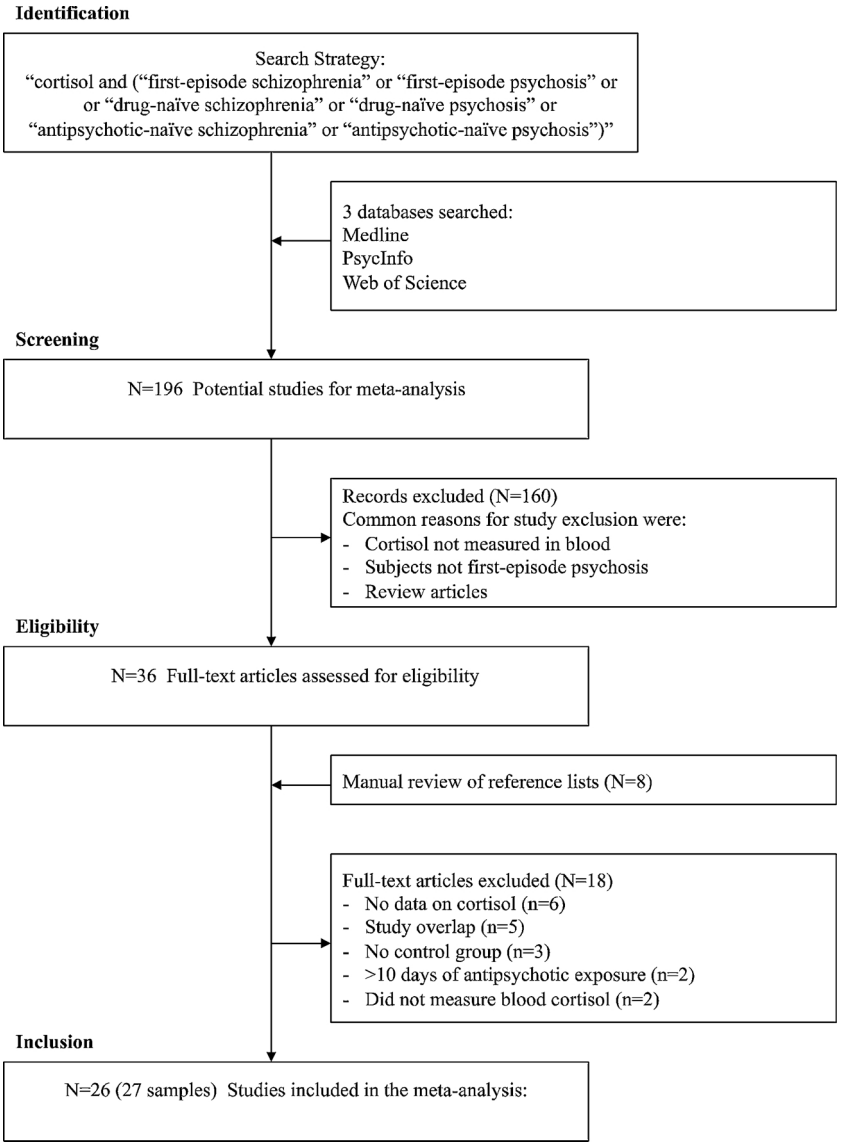



**Fig. 1.** Flow Chart of the Study Selection Process.

individuals with schizophrenia compared to controls (Girshkin et al., 2014). However, this study focused on heterogeneous sample sources (e.g., combined data from blood and saliva) and patient populations (e.g., first-episode and chronic schizophrenia).

Indeed, research on HPA axis function has many inherent methodological complexities, and there are also many potential confounding and moderating factors (Pruessner et al., 2017). Some potential confounding and/or moderating factors that may influence cortisol levels include age (Halbreich et al., 1984; Platje et al., 2013), sex (Paris et al., 2010), race/ethnicity (DeSantis et al., 2007; Fuller-Rowell et al., 2012), body mass index (BMI; Champaneri et al., 2013), fasting (Kirschbaum et al., 1997), socioeconomic status (Cohen et al., 2006), smoking (Direk et al., 2011), diet (Maurer et al., 2003), exercise (Chen et al., 2017), and psychopathology in individuals with psychosis (Babinkostova et al., 2015; Zhang et al., 2005). Importantly, antipsychotic medications may also modulate HPA axis function. In particularly, there is evidence for a dampening of HPA axis activity with atypical antipsychotic treatment (Cohrs et al., 2006; Venkatasubramanian et al., 2010; Zhang et al., 2005). Also, as noted by Pruessner et al. (2017), given the potential novelty and stress of research study participation, baseline cortisol levels in the laboratory setting may be increased compared to those in a natural environment.

Meta-analysis is one approach that can bring increased clarity to an area of research with significant heterogeneity. In order to decrease heterogeneity and minimize some potential confounding factors, we performed a meta-analysis of cross-sectional, baseline (at a single time point) blood cortisol levels in individuals with FEP and no more than minimal exposure to antipsychotics compared to controls.

We chose to focus on individuals with FEP, rather than all persons with schizophrenia or those with chronic psychosis, as associations with cortisol in this patient population would be largely independent of the effects of long-term antipsychotic medication use. We also investigated the effects of many potential moderating factors regarding the association between baseline blood cortisol and FEP. We investigated blood cortisol, which was measured in many more studies than salivary cortisol, in order to include a larger cumulative sample size of individuals with FEP.

## 2. Methods

### 2.1. Study selection

Studies of baseline blood cortisol levels in individuals with FEP were identified by systematically searching Medline (PubMed, National

Center for Biotechnology Information, US National Library of Medicine, Bethesda, Maryland), PsycInfo (via Ovid, American Psychological Association, Washington, DC), Web of Science (Science Citation Index and Social Sciences Citation Index, Thomson Reuters, Charlottesville, Virginia), ScienceDirect (Elsevier B.V., Amsterdam), and the reference lists of studies that met the inclusion/exclusion criteria for the meta-analysis in January 2018. The primary search strategy was "cortisol and ("first-episode psychosis" or "drug-naïve psychosis" or "first-episode schizophrenia" or "drug-naïve schizophrenia")". From all sources, we identified 196 potential studies. The majority of initial matches were excluded because subjects were not first-episode psychosis, cortisol was not measured in the blood, or were review articles.

The inclusion criteria were studies assessing blood cortisol levels in adults with FEP and controls. Exclusion criteria were: 1) > 15% of patients with > 10 days of antipsychotic exposure prior to assessment of blood cortisol, and 2) significant overlap in study population, defined as the use of the same patient or control group in multiple publications (determined based on sample size and demographic data). Of the initial matches, 36 full-text articles were selected for further evaluation. After independent searches, review of study methods by both authors (DBH and BJM), 26 studies (comprising 27 samples) met the inclusion/exclusion criteria (Abel et al., 1996; Allot et al., 2018; Berger et al., 2018; Beyazyüz et al., 2014; Bicikova et al., 2011; Fernandez-Egea et al., 2009; Garner et al., 2011; Kale et al., 2010; Petrikis et al., 2015; Phassouliotis et al., 2013; Reniers et al., 2015; Riahi et al., 2016; Ryan et al., 2003, 2004a, 2004b; Schwarz et al., 2012; Solanki et al., 2017; Spelman et al., 2007; Steiner et al., 2018; Strous et al., 2004; Sun et al., 2016; van Venrooji et al., 2012; Venkatasubramanian et al., 2007; Walsh et al., 2005). One study reported cortisol levels for patients and controls stratified by sex (Riahi et al., 2016). A flowchart summarizing the study selection process is presented in Fig. 1. Details of the included studies are also presented as Supplementary Material. If multiple blood samples were collected, only the data for the baseline blood sample were used.

Each of the included studies was assessed and assigned a "Quality Score" by one author (DBH), which was independently verified by another author (BJM). Quality scores for studies of cortisol were based on the sum of the presence or absence of ten factors (one point for each): whether the study considered potential effects of age, sex, race, fasting status, socioeconomic status (SES), body mass index (BMI), smoking, medications (including antipsychotic-naïve status), diet, and exercise by either 1) matching patients with FEP and controls, or 2) controlling for these variables in the analysis.

### 2.2. Data extraction and meta-analysis

Data were extracted (sample size, mean/standard deviation [SD] or median/interquartile range [IQR] for cortisol levels patients and controls), in each study that satisfied the inclusion and exclusion criteria for this study. As done in our previous study, if necessary, we estimated the mean/SD from the median/IQR using the following formulas: 1) $\text{mean} = (2m + a + b)/4$, where $m$ is the median and $a$ and $b$ are the 25th and 75th percentiles, respectively, and 2) IQR = 1.35xSD (Hernandez et al., 2014). One author (DBH) extracted all data, which was independently verified by another author (BJM). Effect size estimates (standard mean difference [SMD] and 95% confidence intervals [95% CIs]) were calculated using the random effects method (DerSimonian and Laird, 1986). Random effects methods are considered to be more representative of real-world data in comparison to the alternative fixed effect approach, and provide a more conservative estimate of the average weighted effect size (Hunter and Schmidt, 2000). The null hypothesis was a SMD = 0 (i.e., no difference in blood cortisol levels in individuals with FEP versus controls). One research group compared the same patient group to two different control groups in separate publications (Bicikova et al., 2011, 2013). We included only the study with the smaller SMD in the overall meta-analysis, which would bias findings toward the null hypothesis.

The meta-analysis procedure also calculates a $\chi^2$ value for the heterogeneity in effect size estimates, which is based on Cochran's Q-statistic (Cochran, 1950), and $I^2$, the proportion of the variation in effect size attributable to between-study heterogeneity. Between-study heterogeneity $\chi^2$ was considered significant for $p < 0.10$ (Song et al., 2001). For all studies, between-study heterogeneity $\chi^2$ was significant, so we performed a sensitivity analysis. Sensitivity analysis was done by removing one study at a time and repeating the meta-analysis procedure, to examine its impact on the effect size estimates and between-study heterogeneity (Higgins and Green, 2011). As between-study heterogeneity remained significant after removing each individual study, we then removed all combinations of two different studies and repeated the meta-analysis procedure.

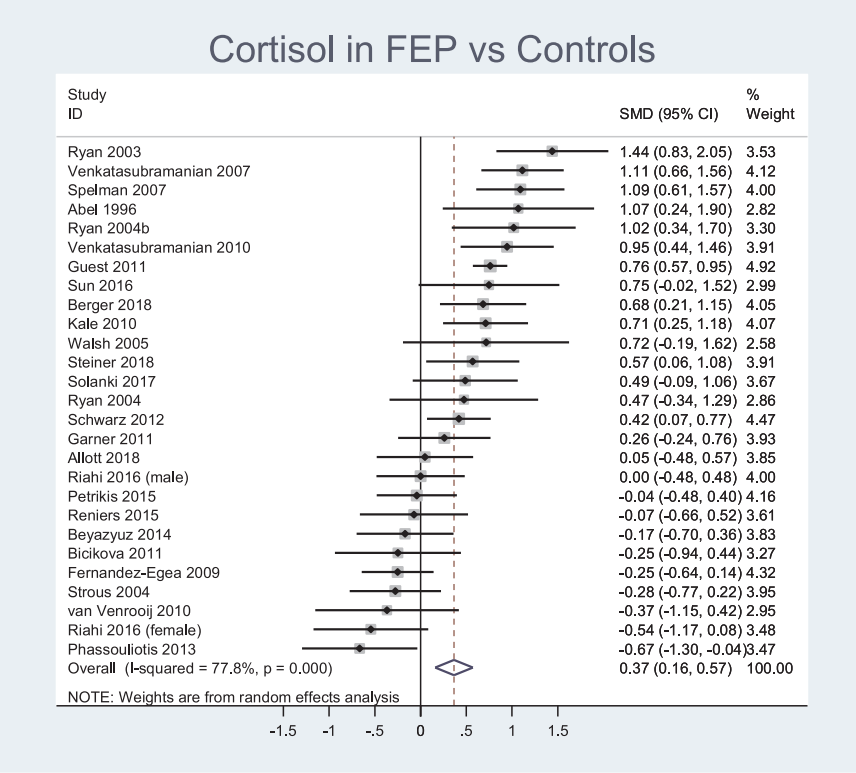
Due to the persistence of significant between-study heterogeneity $\chi^2$, we investigated potential moderating variables using a two-step process. First, for descriptive purposes, we repeated the meta-analysis procedure for the following subgroups of studies: 1) subjects fasting at the time of blood draw, 2) antipsychotic-naïve subjects, 3) studies measuring plasma and serum cortisol (considered separately), 4) studies of morning (8–10 am) cortisol, and 5) assay type (enzyme-linked immunosorbent assay [ELISA], fluoroimmunoassay, chemiluminescence, and radioimmunoassay [RIA], considered separately). We then performed a series of meta-regressions to investigate the statistical significance of these descriptive differences, and to explore other possible moderating variables to account for such heterogeneity. Meta-regression assesses and adjusts the effects of potential moderating variables on the effect size estimate from the meta-analysis. A positive slope (i.e., regression coefficient) means that the effect size estimate from the meta-analysis and the moderator variable change in the same direction, and a negative slope means they change in the opposite direction.

Continuous variables included in meta-regression analyses were age, sex (as percentage of males in the study sample), body-mass index (BMI), year of publication, psychopathology scores, and study quality scores. Geographic region (Asia, Europe, Middle East, and Australia), fasting status (yes/no), antipsychotic status (antipsychotic-naïve versus minimal antipsychotic exposure), sample source (plasma versus serum), assay type (ELISA, fluoroimmunoassay, chemiluminescence, RIA), and time of sampling (morning or not) were modeled as categorical variables. Each of these variables was first examined in univariate meta-regression models. Variables with a p-value < 0.05 in univariate models were then entered into a multivariate meta-regression model. We investigated age (Halbreich et al., 1984; Platje et al., 2013), sex (Paris et al., 2010), race/ethnicity (DeSantis et al., 2007; Fuller-Rowell et al., 2012), body mass index (BMI; Champaneri et al., 2013), fasting (Kirschbaum et al., 1997), socioeconomic status (Cohen et al., 2006), smoking (Direk et al., 2011), time of sampling (Pruessner et al., 2017) psychopathology (Babinkostova et al., 2015; Zhang et al., 2005) as potential moderating factors based on previous evidence that they may influence cortisol levels. We investigated year of publication and study quality scores as other potential proxy measures of publication bias. We also investigated geography as a potential proxy measure for other residual moderating factors, such as genetics, diet, exercise, and psychosocial stress (Dulin-Keita et al., 2012). Although we are not aware of evidence for differences in cortisol levels based on sample source and assay type, we chose to investigate them as potential moderating factors because this information was available for the vast majority of studies.

The potential for publication bias was examined by means of Sterne's funnel plot analysis (Sterne and Egger, 2001) and Egger's regression intercept (Egger et al., 1997). All statistical analyses were performed in Stata 10.0 (StataCorp LP, College Station, TX), and P-values were considered statistically significant at the $\alpha = 0.05$ level.

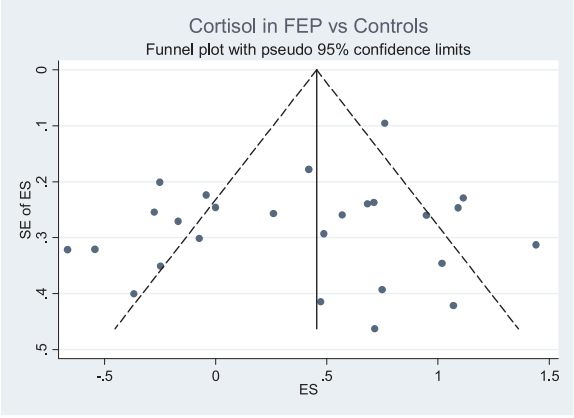
## 3. Results

The total sample consisted of 959 individuals with FEP and 1121




FEP = First-Episode Psychosis
SMD = Standard Mean Difference
95% CI = 95% Confidence Interval

**Fig. 2.** Meta-analysis of blood cortisol levels in individuals with first-episode psychosis (FEP).
FEP = First-Episode Psychosis.
SMD = Standard Mean Difference.
95% CI = 95% Confidence Interval.




ES = Effect Size
SE = Standard Error

**Fig. 3.** Funnel plot of studies of blood cortisol levels in individuals with first-episode psychosis (FEP).
ES = Effect Size.
SE = Standard Error.

controls. The mean study quality score was 4.6. In all studies, blood cortisol levels were significantly increased in individuals with FEP compared to controls with a small-to-medium effect size (SMD = 0.37, 95% CI 0.16-0.57, $p < 0.001$; see Fig. 2). Between-study heterogeneity was significant ($\chi^2 = 116.88$, $I^2 = 77.8\%$, $p < 0.001$). In sensitivity analyses, after removing all combinations of two different studies and repeating the meta-analysis procedure, between-study heterogeneity remained significant. A funnel plot and results of Egger's test showed no evidence for publication bias ($p > 0.05$) (see Fig. 3).

In subgroup analyses, the effect size for increased blood cortisol in individuals with FEP was stronger for studies in which subjects were fasting at the time of blood sampling (SMD = 0.65, 95% CI 0.35-0.95, $p < 0.001$), compared to the overall effect size. In studies where individuals with FEP were antipsychotic-naïve at the time of blood sampling, the effect size was SMD = 0.46 (95% CI 0.20-0.73, $p = 0.001$). The association was stronger in studies measuring cortisol in plasma (SMD = 0.50, 95% CI 0.17-0.83, $p = 0.003$) than in serum (SMD = 0.24, 95% CI -0.05-0.53, $p = 0.105$). In studies measuring blood cortisol levels in the morning (between 8–10 am), the effect size was SMD = 0.40 (95% CI 0.13-0.67, $p = 0.004$). An even stronger effect size was seen for the subset of 7 studies that measured fasting, morning, plasma cortisol in antipsychotic-naïve individuals with FEP (SMD = 0.67, 95% CI 0.15–1.20, $p = 0.011$). Variation in association was also found based on assay type, with significant effect size estimates in studies measuring cortisol using ELISA or fluoroimmunoassay, but not immune-chemiluminescence or (RIA). We note that these analyses were made for descriptive purposes, and we did not statistically test for differences between subgroups. These results are summarized in Table 1.

In univariate meta-regression analyses, age, geography, fasting status, and study quality were significant moderators ($p < 0.05$ for each) of the association between cortisol levels and first-episode psychosis, with larger effect sizes in studies with older subjects, fasting samples, and studies with higher quality scores. Geography was a

**Table 1**
Meta-analysis of blood cortisol levels in individuals with first-episode psychosis (FEP).

| Included Studies | Studies (N) | FEP (n) | Controls (n) | SMD | 95% CI | p-value |
|---|---|---|---|---|---|---|
| All | 27 | 959 | 1121 | 0.37 | 0.16-0.57 | < 0.001 |
| Fasting | 14 | 381 | 451 | 0.65 | 0.35-0.95 | < 0.001 |
| Plasma | 15 | 335 | 545 | 0.50 | 0.17-0.83 | 0.003 |
| Antipsychotic-naïve | 18 | 534 | 545 | 0.46 | 0.20-0.73 | 0.001 |
| Morning (8-10 am) | 15 | 462 | 436 | 0.40 | 0.13-0.67 | 0.004 |
| Fasting, plasma, morning, and antipsychotic-naive | 7 | 224 | 242 | 0.67 | 0.15-1.20 | 0.011 |
| Assay type | | | | | | |
| ELISA | 5 | 366 | 532 | 0.38 | 0.02-0.73 | 0.049 |
| Fluoroimmunoassay | 3 | 48 | 48 | 0.94 | 0.31-1.56 | 0.003 |
| Immuno-chemiluminescence | 5 | 132 | 168 | 0.45 | −0.05-0.95 | 0.307 |
| RIA | 7 | 177 | 170 | 0.30 | −0.14-0.74 | 0.175 |

significant moderator of the association in studies from Asia versus both the Middle East and Australia ($p < 0.01$ for each), and studies from Europe versus the Middle East ($p = 0.019$). In a multivariate meta-regression analysis that included all four of these moderators, only geography remained a significant moderator of the association between FEP and cortisol in studies from Asia versus the Middle East (slope = -0.68, 95% CI = -1.31 - -0.006, $p = 0.037$). Otherwise, there were no significant moderators of the association in multivariate meta-regression.

In post-hoc analyses, we repeated the meta-analysis procedure stratifying by geographic region. Cortisol levels were significantly increased in individuals with FEP versus controls in studies from Asia (SMD = 0.84, 95% CI = 0.60–1.07, $p < 0.001$) and Europe (SMD = 0.57, 95% CI = 0.29-0.84, $p < 0.001$), but not Australia (SMD = -0.08, 95% CI = -0.45-0.30, $p = 0.688$). In contrast, there was a trend for lower cortisol in individuals with FEP in studies from the Middle East (SMD = -0.22, 95% CI = -0.47-0.03, $p = 0.082$).

## 4. Discussion

We found meta-analytic evidence for increased baseline blood cortisol levels in individuals with FEP and minimal antipsychotic exposure compared to controls with a small-to-medium effect size (SMD = 0.37). There was significant between-study heterogeneity for the effect size estimate. Importantly, in meta-regression analyses this association was not significantly moderated by age, sex, BMI, year of publication, fasting status, antipsychotic-naïve status, sample source (plasma versus serum), assay type, time of sampling, psychopathology, and study quality score. However, the association was moderated by geographic region, with greater effect sizes in studies from Asia and Europe versus the Middle East.

Our finding of increased baseline blood cortisol levels in FEP, which is consistent with the "neural diathesis-stress" model of psychosis, complements and extends previous findings in HPA axis research in individuals with early psychosis. Girshkin et al. (2014) performed a meta-analysis of morning cortisol levels in individuals with schizophrenia, which included medication exposed and non-exposed subjects, salivary and blood samples, and individuals with chronic and first-episode schizophrenia. In all subjects with schizophrenia, regardless of clinical status or sample source, they found a small-to-medium effect size for increased cortisol levels ($g = 0.39$) that was not moderated by age or sex. In contrast to our study, Girshkin et al. (2014) did not find evidence for increased cortisol in individuals with FEP ($g = -0.10$, 95% CI -0.51-0.31). Their estimate was based on 10 studies (8 measuring cortisol in blood and 2 in saliva), whereas we analyzed 26 studies (all measuring blood cortisol). Therefore, the larger sample size and a more homogenous sample source in our study likely contributed to the discordant findings. In another meta-analysis, Berger et al. (2016) found a significant decreased CAR among individuals with FEP compared to controls due to a change (flattening) in the diurnal cortisol curve, but still with increased absolute cortisol levels. The increased absolute cortisol levels in individuals with FEP in the meta-analysis by Berger et al. (2016) are consistent with increased baseline (i.e., one sample) blood cortisol in the present study. Taken together, these findings provide complementary evidence for HPA axis dysfunction in individuals with FEP.

Given the significant between-study heterogeneity in the effect size estimate for baseline blood cortisol in FEP, we also performed several subgroup analyses. The association was statistically significant, and numerically greater than the overall effect size, in studies where individuals with FEP were antipsychotic-naïve at the time of blood sampling (SMD = 0.46). This finding is particularly important, as it suggests an association between increased cortisol levels and FEP that is independent of effects of antipsychotic medications. Similarly, effect size estimates were statistically significant, and numerically greater than the overall effect size, in subgroups of studies with 1) fasting subjects (SMD = 0.65), 2) measurement of cortisol in plasma (SMD = 0.50), and 3) studies of morning (8–10 am) cortisol (SMD = 0.40). Furthermore, the largest numerical effect size was seen for the subset of seven studies that measured fasting, morning, plasma cortisol in antipsychotic-naïve individuals with FEP (SMD = 0.67). This is important because these studies are arguably more methodologically rigorous in their design, as evidenced by significantly higher mean study quality scores compared to the other studies (6.7 ± 1.5 versus 4.1 ± 1.8, $p = 0.002$), and therefore suggest the association is less likely to be due to residual confounding.

We also found that geography was a strong moderating factor of the association between cortisol and FEP. Whether the moderating effects of geography reflect genetic (Li et al., 2008) or environmental factors, or both, in certain regions warrants further investigation. Sleep disturbances may modulate cortisol levels (Backhaus et al., 2004). There is some evidence for variation in sleep time by geographical region (Olds et al., 2010), but whether there were differences in the prevalence of sleep disturbance by geographical region for studies included in the present meta-analysis is unknown. Other possible environmental factors influencing cortisol levels that may vary by geography include diet, exercise, and psychosocial stress (Dulin-Keita et al., 2012; Filippidis et al., 2016). Future studies of cortisol in individuals with FEP should consider these potentially relevant factors.

Future studies should also investigate relationships between cortisol and other neuroimmunoendocrine abnormalities in individuals with FEP. Cortisol has potent immunosuppressive properties—including inhibition of pro-inflammatory cytokines and stimulation of anti-inflammatory cytokine. There is also evidence for increased levels of pro-inflammatory cytokines in the blood of individuals with FEP compared to controls (Goldsmith et al., 2016; Upthegrove et al., 2014). This raises the question of whether increased cortisol in individuals with FEP represents a response to the stress of acute psychosis, a separate (patho) physiologic process, or a potential counter-regulatory response to inflammation. Potential theories for the paradoxical finding of increases

in both cortisol and pro-inflammatory cytokine in individuals with FEP include: 1) reduced glucocorticoid signaling due to glucocorticoid resistance, which facilitates excessive activity of the immune system, and 2) pro-inflammatory activity of glucocorticoids under certain circumstances (Horowitz and Zunszain, 2015). Future longitudinal studies in early psychosis, including individuals with prodromal psychosis, with serial measurement of cortisol parameters, inflammatory markers, and psychopathology would help disentangle these associations, towards an increased understanding of potential pathophysiological mechanisms.

There are always strengths and limitations to studies. An important strength of our study was that we included a large number of studies and subjects. Another strength is that we only included studies of individuals with FEP and minimal antipsychotic exposure, thereby minimizing potential confounding effects of antipsychotic medications. Furthermore, we focused on a homogeneous sample source (i.e., blood), which may have increased the signal-to-noise ratio of our findings. We also performed meta-regression analyses to consider multiple potential moderating factors.

There are also several limitations of the present study. Findings should be interpreted with caution in light of significant between-study heterogeneity that remained after sensitivity analysis. The data in the present meta-analysis were cross-sectional in nature, and baseline blood cortisol from a single sample is much less informative on HPA axis function than other measures (Pruessner et al., 2017). Adequate data for a meta-analysis of longitudinal data for individuals with FEP, such as 1) changes in cortisol levels following a period of antipsychotic treatment for acute psychosis, and over the course of illness, and 2) the use of multiple samples throughout the day to estimate diurnal patterns of cortisol secretion, were not available. There were also inadequate data to investigate time periods of sample collection other than morning (8–10 am), due to a small number of studies. Correlation coefficients for cortisol levels and psychopathology scores were also not available for individual studies. However, mean psychopathology scores did not moderate the association between cortisol and FEP, suggesting that between-group differences were not attributable to the severity of psychopathology. Nevertheless, findings regarding psychopathology should be interpreted with some caution in light of smaller number of studies with psychopathology scores for specific scales ($n = 10$ for SANS, $n = 8$ for BPRS, and $n = 5$ for PANSS). Another limitation is that the fear and stress response associated with phlebotomy may have impacted on blood cortisol levels in some subjects, with an uncertain overall impact on findings from this meta-analysis. Although we investigated a number of potential moderating factors, inadequate data were available to evaluate other important, potential moderators (e.g., smoking, socioeconomic status, trauma, diet, exercise, and time of awakening).

## 5. Conclusion

In conclusion our meta-analysis found increased baseline blood cortisol levels in individuals with FEP and minimal exposure to antipsychotics compared to controls. In order to further understand and clarify the biological relevance of this association, methodologically rigorous longitudinal studies are needed, with serial measurement of cortisol parameters, other inflammatory markers, and psychopathology, in relation to the clinical course of schizophrenia. Taken together, our findings provide additional evidence of neuroimmunoendocrine dysfunction in early psychosis.

## Conflict of interest

Mr. Hubbard has nothing to disclose.

Dr. Miller has nothing to disclose for this study. In the past 12 months, Dr. Miller received research support from the National Institute of Mental Health, NARSAD, the Stanley Medical Research Institute, and Augusta University; and Honoraria from Psychiatric Times.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.03.014.

## References

Abel, K.M., O'Keane, V., Murray, R.M., 1996. Enhancement of the prolactin response to d-fenfluramine in drug-naïve schizophrenic patients. Br. J. Psychiatry 68, 57–60.
Allot, K.A., Yuen, H.P., Bartholomeusz, C.F., et al., 2018. Stress hormones and verbal memory in young people over the first 12 weeks of treatment for psychosis. Psychiatry Res. 260, 60–66.
Babinkostova, Z., Stefanovski, B., Janicevic-Ivanovska, D., et al., 2015. Serum cortisol and DHEA-S levels in schizophrenic patients with different response to antipsychotic therapy: association with psychopathology. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 36, 175–183.
Backhaus, J., Junghanns, K., Hohagen, F., 2004. Sleep disturbances are correlated with decreased morning awakening salivary cortisol. Psychoneuroendocrinology 29, 1184–1191.
Berger, M., Kraeuter, A.K., Romanik, D., et al., 2016. Cortisol awakening response in patients with psychosis: systematic review and meta-analysis. Neurosci. Biobehav. Rev. 68, 157–166.
Beyazyüz, M., Albayrak, Y., Beyazyüz, E., et al., 2014. Increased serum dehydroepiandrosterone sulfate in the first episode but not in subsequent episodes in male patients with schizophrenia. Neuropsychiatr. Dis. Treat. 10, 687–693.
Bicikova, M., Hampl, R., Hill, M., et al., 2011. Neuro- and immunomodulatory steroids and other biochemical markers in drug-naïve schizophrenia patients and the effect of treatment with atypical antipsychotics. Neuroendocrinol. Lett. 32, 141–147.
Bicikova, M., Hill, M., Ripova, D., et al., 2013. Determination of steroid metabolome as a possible tool for laboratory diagnosis of schizophrenia. J. Steroid Biochem. Mol. Biol. 133, 77–83.
Champaneri, S., Xu, X., Carnethon, M.R., et al., 2013. Diurnal salivary cortisol is associated with body mass index and waist circumference: the Multiethnic Study of Atherosclerosis. Obesity (Silver Spring) 21, E56–63.
Chen, C., Nakagawa, S., An, Y., et al., 2017. The exercise-glucocorticoid paradox: how exercise is beneficial to cognition, mood, and the brain while increasing glucocorticoid levels. Front. Neuroendocrinol. 44, 83–102.
Cochran, W.B., 1950. The comparison of percentages in matched samples. Biometrika 37, 256–266.
Cohen, S., Schwartz, J.E., Epel, E., et al., 2006. Socioeconomic status, race, and diurnal cortisol decline in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Psychosom. Med. 68, 41–50.
Cohrs, S., Röher, C., Jordan, W., et al., 2006. The atypical antipsychotics olanzapine and quetiapine, but not haloperidol, reduce ACTH and cortisol secretion in healthy subjects. Psychopharmacology (Berl.) 185, 11–18.
DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188.
DeSantis, A.S., Adam, E.K., Doane, L.D., et al., 2007. Racial/ethnic differences in cortisol diurnal rhythms in a community sample of adolescents. J. Adolesc. Health 41, 3–13.
Direk, N., Newson, R.S., Hofman, A., et al., 2011. Short and long-term effects of smoking on cortisol in older adults. Int. J. Psychophysiol. 80, 157–160.
Dulin-Keita, A., Casazza, K., Fernandez, J.R., et al., 2012. Do neighbourhoods matter? Neighbourhood disorder and long-term trends in serum cortisol levels. J. Epidemiol. Community Health 66, 24–29.
Egger, M., Davey Smith, G., Schneider, M., et al., 1997. Bias in meta-analysis detected by a simple, graphical test. Br. Med. J. 315, 629–634.
Fernandez-Egea, E., Bernardo, M., Donner, T., et al., 2009. Metabolic profile of antipsychotic-naïve individuals with non-affective psychosis. Br. J. Psychiatry 194, 434–438.
Filippidis, F.T., Agaku, I.T., Vardavas, C.I., 2016. Geographic variation and socio-demographic determinants of the co-occurrence of risky health behaviours in 27 European Union member states. J. Public Health (Oxf.) 38, e13–20.
Fuller-Rowell, T.E., Doan, S.N., Eccles, J.S., 2012. Differential effects of perceived discrimination on the diurnal cortisol rhythm of African Americans and Whites. Psychoneuroendocrinology 37, 107–118.
Garner, B., Phassouliotis, C., Phillips, L.J., et al., 2011. Cortisol and dehydroepiandrosterone-sulphate levels correlate with symptom severity in first-episode psychosis. J. Psychiatr. Res. 45, 249–255.
Girshkin, L., Matheson, S.L., Shepherd, A.M., et al., 2014. Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. Psychoneuroendocrinology 49, 187–206.
Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry 21, 1696–1709.
Halbreich, U., Asnis, G.M., Zumoff, B., et al., 1984. Effect of age and sex on cortisol secretion in depressives and normals. Psychiatry Res. 13, 221–229.
Hernandez, A.V., Guarnizo, M., Miranda, Y., et al., 2014. Association between insulin

resistance and breast carcinoma: a systematic review and meta-analysis. PLoS One 9, e99317.
Higgins, J.P.T., Green, S. (Eds.), 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 9.7. Sensitivity Analyses. The Cochrane Collaboration Available from. www.cochrane-handbook.org.
Horowitz, M.A., Zunszain, P.A., 2015. Neuroimmune and neuroendocrine abnormalities in depression: two sides of the same coin. Ann. N.Y. Acad. Sci. 1351, 68–79.
Hunter, J.E., Schmidt, F.L., 2000. Fixed effect vs. Random effects meta-analysis models: implications for cumulative research knowledge. Int. J. Select Assess 8, 275–292.
Kale, A., Naphade, N., Sapkale, S., et al., 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 Res. 175, 47–53.
Kirschbaum, C., Gonzalez Bono, E., Rohleder, N., et al., 1997. Effects of fasting and glucose load on free cortisol responses to stress and nicotine. J. Clin. Endocrinol. Metab. 82, 1101–1105.
Li, J.Z., Absher, D.M., Tang, H., et al., 2008. Worldwide human relationships inferred from genome-wide patterns of variation. Science 319, 1100–1104.
Maurer, M., Riesen, W., Muser, J., et al., 2003. Neutralization of Western diet inhibits bone resorption independently of K intake and reduces cortisol secretion in humans. Am. J. Physiol. Renal Physiol. 284 F32–40.
Olds, T., Blunden, S., Petkov, J., et al., 2010. The relationships between sex, age, geography and time in bed in adolescents: a meta-analysis of data from 23 countries. Sleep Med. Rev. 14, 371–378.
Paris, J.J., Franco, C., Sodano, R., et al., 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. Horm. Behav. 57, 35–45.
Petrikis, P., Tigas, S., Tzallas, A.T., et al., 2015. Parameters of glucose and lipid metabolism at the fasted state in drug-naïve first-episode patients with psychosis: evidence for insulin resistance. Psychiatry Res. 229, 901–904.
Phassouliotis, C., Garner, B.A., Phillips, L.J., et al., 2013. Enhanced cortisol suppression following administration of low-dose dexamethasone in first-episode psychosis patients. Aust. N. Z. J. Psychiatry 47, 363–370.
Philips, L.J., McGorry, P.D., Garner, B., et al., 2006. Stress, the hippocampus and the hypothalamic-pituitary-adrenal axis: implications for the development of psychotic disorders. Aust. N. Z. J. Psychiatry 40, 725–741.
Platje, E., Vermeiren, R.R., Branje, S.J., 2013. Long-term stability of the cortisol awakening response over adolescence. Psychoneuroendocrinology 38, 271–280.
Pruessner, M., Cullen, A.E., Aas, M., et al., 2017. The neural diathesis-stress model of schizophrenia revisited: an update on recent findings considering illness stage and neurobiological and methodological complexities. Neurosci. Biobehav. Rev. 73, 191–218.
Reniers, R.L., Garner, B., Phassouliotis, C., et al., 2015. The relationship between stress, HPA axis functioning and brain structure in first episode psychosis over the first 12 weeks of treatment. Psychiatry Res. 231, 111–119.
Riahi, F., Izadi-Mazidi, M., Ghaffari, A., et al., 2016. Comparison of plasma neurosteroid and prolactin levels in patients with schizophrenia and healthy individuals. Scientifica (Cairo) 2016, 3108689.
Ryan, M.C., Collins, P., Thakore, J.H., 2003. Impaired fasting glucose tolerance in first-episode drug-naïve patients with schizophrenia. Am. J. Psychiatry 160, 284–289.
Ryan, M.C., Flanagan, S., Kinsella, U., et al., 2004a. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naïve patients with schizophrenia. Life Sci. 74, 1999–2008.
Ryan, M.C., Sharifi, N., Condren, R., et al., 2004b. Evidence of basal pituitary-adrenal overactivity in first episode, drug naïve patients with schizophrenia. Psychoneuroendocrinology 29, 1065–1070.
Schwarz, E., Guest, P.C., Rahmoune, H., et al., 2012. Identification of a biological signature for schizophrenia in serum. Mol. Psychiatry 17, 494–502.
Solanki, R.K., Sharma, P., Tyagi, A., et al., 2017. Serum levels of neuroactive steroids in first-episode antipsychotic-naïve schizophrenic patients and its correlation with aggression: a case-control study. East Asian Arch. Psychiatry 27, 79–84.
Song, F., Sheldon, T.A., Sutton, A.J., et al., 2001. Methods for exploring heterogeneity in meta-analysis. Eval. Health Prof. 24, 126–151.
Spelman, L.M., Walsh, P.I., Sharifi, N., et al., 2007. Impaired glucose tolerance in first-episode drug-naïve patients with schizophrenia. Diabet. Med. 24, 481–485.
Steiner, J., Fernandes, B.S., Guest, P.C., et al., 2018. Glucose homeostasis in major depression and schizophrenia: a comparison among drug-naïve first-episode patients. Eur. Arch. Psychiatry Clin. Neurosci. https://doi.org/10.1007/s00406-018-0865-7.
Sterne, J.A.C., Egger, M., 2001. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J. Clin. Epidemiol. 54, 1046–1055.
Strous, R.D., Maayan, R., Lapidus, R., et al., 2004. Increased circulatory dehydroepiandrosterone and dehydroepiandrosterone-sulphate in first-episode schizophrenia: relationship to gender, aggression and symptomatology. Schizophr. Res. 71, 427–434.
Sun, H.Q., Li, S.X., Chen, F.B., et al., 2016. Diurnal neurobiological alterations after exposure to clozapine in first-episode schizophrenia patients. Psychoneuroendocrinology 64, 108–116.
Upthegrove, R., Manzanares-Teson, N., Barnes, N.M., 2014. Cytokine function in medication-naïve first episode psychosis: a systematic review and meta-analysis. Schizophr. Res. 155, 101–108.
van Venrooji, J.A., Fluitman, S.B., Lijmer, J.G., et al., 2012. Impaired neuroendocrine and immune response to acute stress in medication-naïve patients with a first episode of psychosis. Schizophr. Bull. 38, 272–279.
Venkatasubramanian, G., Chittiprol, S., Neelakantachar, N., et al., 2007. Insulin and insulin-like growth factor-1 abnormalities in antipsychotic-naïve schizophrenia. Am. J. Psychiatry 164, 1557–1560.
Walker, E.F., Diforio, D., 1997. Schizophrenia: a neural diathesis-stress model. Psychol. Rev. 104, 667–685.
Walker, E., Mittal, V., Tessner, K., 2008. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annu. Rev. Clin. Psychol. 4, 189–216.
Walsh, P., Spelman, L., Sharifi, N., et al., 2005. Male patients with paranoid schizophrenia have greater ACTH and cortisol secretion in response to metoclopramide-induced AVP release. Psychoneuroendocrinology 30, 431–437.
Zhang, X.Y., Zhou, D.F., Cao, L.Y., et al., 2005. Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. Neuropsychopharmacology 30, 1532–1538.