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Review article

A meta-analysis of blood and salivary cortisol levels in first-episode psychosis and high-risk individuals

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ABSTRACT

Dysregulated cortisol responses and glucose metabolism have been reported in psychosis. We performed a random-effects meta-analysis of cortisol responses in first-episode psychosis (FEP) and psychosis risk states, taking into consideration glucose metabolism. A total of 47 studies were included. Unstimulated blood cortisol levels were significantly higher ($g = 0.48$, 95 %CI: 0.25–0.70, $p < 0.001$) in FEP, but not in psychosis risk states ($g = 0.39$, 95 %CI: −0.42–1.21, $p = 0.342$), compared to controls. Cortisol awakening response (CAR) was attenuated in FEP ($g = -0.40$, 95 %CI: −0.68 - −0.12, $p = 0.006$), but not in psychosis risk states ($p = 0.433$). Glucose and insulin levels were positively correlated with unstimulated blood cortisol levels in FEP. Our meta-analysis supports previous findings of elevated blood cortisol levels and attenuated CAR in FEP. Future research should focus on identifying the common denominators for alterations in stress hormones and glucose metabolism.

1. Introduction

The hypothalamic–pituitaryadrenal (HPA) axis is one of the major biological systems responsible for the stress response. Activation of the HPA axis begins with the release of corticotropin-releasing hormone (CRH) by the hypothalamus, which in turn stimulates the production of the adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. Subsequently, ACTH stimulates the adrenal cortex to release glucocorticoids that include cortisol. The HPA axis acts through a negative feedback loop, whereby cortisol decreases the production of CRH and ACTH. Glucocorticoids regulate a number of metabolic and immune processes (Oppong and Cato, 2015; Vegiopoulos and Herzig, 2007). Chronic exposure to glucocorticoids leads to the development of obesity and insulin resistance through several mechanisms (Geer et al., 2014). Specifically, glucocorticoids have been shown to increase food intake by altering expression of appetite-regulating molecules, such as neuropeptide Y or leptin (Solano and Jacobson, 1999). Moreover, glucocorticoids decrease post-receptor insulin signaling by altering expression of downstream signaling molecules, such as IRS-1, p39MAPK and PTP1B (Almon et al., 2005, 2007). Finally, glucocorticoids promote hepatic gluconeogenesis (Goldstein et al., 2002), lipolysis (Harvey et al., 2018) and fat accumulation in the liver (Marino et al., 2016).

Accumulating evidence suggests that aberrant activity of the HPA axis might be involved in the pathophysiology of psychosis (Pruessner et al., 2017). Indeed, it has been shown that cortisol may enhance dopaminergic signaling in various brain regions, especially in the mesolimbic system (Walker et al., 2008). For instance, Pruessner et al. (2004) found that exposure to psychosocial stress triggers release of dopamine in the ventral striatum as measured by a decrease in [11C] raclopride binding in healthy volunteers. In this study, a positive correlation between dopamine release and cortisol response was observed. Apart from interactions with the mesolimbic system, glucocorticoids interact with their receptors located in other brain regions, including the hippocampus and the prefrontal cortex that are responsible for learning and memory processes. Chronically elevated levels of cortisol can lead to reduced neurogenesis and synaptic plasticity in the hippocampus,

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contributing to cognitive impairment (Kim et al., 2015). A recent meta-analysis of post mortem studies revealed decreased volume and neuron numbers in several subfields of the left hippocampus in patients with schizophrenia (Roeske et al., 2020). However, there are certain mechanisms that protect the hippocampus against neurotoxic effects of cortisol. For instance, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) pass through the blood-brain barrier, serve as the local source of neurosteroids and protect the hippocampus from the effects of corticosterone (Kimonides et al., 1999; Melcangi et al., 2011).

Previous meta-analyses of the HPA axis activity have demonstrated the following alterations: 1) blunted cortisol awakening response (CAR) in first-episode psychosis (FEP) and schizophrenia) (Berger et al., 2016); 2) attenuated cortisol response to social stress in schizophrenia (Ciufolini et al., 2014); 3) increased morning cortisol levels in blood and saliva of individuals with schizophrenia and FEP (Girshkin et al., 2014); 4) increased baseline cortisol levels in blood of individuals with FEP (Hubbard and Miller, 2019) and 5) increased baseline cortisol levels in saliva of individuals at clinical high risk (CHR) of psychosis (Chaumette et al., 2016). However, most meta-analyses in this field have addressed single parameters of the HPA axis activity and have not considered cortisol levels in blood and saliva separately as well as their association with other hormonal and metabolic alterations reported in this population, including impaired glucose homeostasis (Pillinger et al., 2017) and altered levels of DHEA or DHEA-S (Misiak et al., 2018). Importantly, assessment of blood cortisol levels provides the information on the total fraction of cortisol – free and bound to proteins. In turn, collection of saliva samples is non-invasive and provides the opportunity to determine the free fraction of cortisol that elicits biological activity (Kirschbaum and Hellhammer, 1989; Kudielka et al., 2012). Indeed, the acinar cells that are located in the salivary glands prevent the transition of proteins and protein-bound molecules to saliva (Kirschbaum and Hellhammer, 1994). Another shortcoming of previous research is the lack of a systematic comparison of baseline cortisol levels and cortisol levels in response to stimulation. Finally, there is some evidence that unaffected relatives of individuals with psychosis show increased emotional reactivity to daily life stress, increased ACTH levels in response to stress, increased pituitary volume and reduced hippocampal volume (Aiello et al., 2012). These observations provide the rationale for investigating the association between genetic liability for psychosis and the HPA axis responses. Therefore, in this study we aimed to perform a meta-analysis investigating baseline cortisol levels and cortisol levels in response to stimulation in blood and saliva in subjects with first-episode psychosis (FEP), CHR individuals, as well as unaffected relatives of individuals with schizophrenia, taking into consideration a number of potential moderators.

2. Methods

2.1. Search strategy

Five databases (MEDLINE, ERIC, CINAHL Complete, International Pharmaceutical Abstracts as well as the Academic Search Ultimate and the Health Source: Nursing/Academic Edition) were searched from their inception until 1st Feb 2021 by two independent reviewers (BS and MW). The following keywords were used: "chr" OR "uhr" OR "arms" OR "risk" OR "siblings" OR "relatives" OR "offspring" OR "first-episode" OR "antipsychotic-naïve" OR "drug-naïve" OR "unmedicated" OR "never medicated" AND "psychosis" OR "schizophr*" AND "cortisol" OR "HPA axis" OR "glucocorticoid". The third reviewer (BM) was involved in resolving all disagreements. Online searches were conducted in agreement with the PRISMA guidelines (Moher et al., 2009). The protocol of this meta-analysis was registered in the PROSPERO database (registration number: CRD42021185601). The PRISMA checklist was presented in Supplementary Table 1.

2.2. Eligibility criteria

Publications were considered eligible if they met the following criteria: 1) reported the blood and/or salivary levels of unstimulated (baseline) cortisol and/or CAR as measured by the area under the curve with respect to increase (AUCi) or ground (AUCg) (Pruessner et al., 2003); 2) necessary data (mean and SD for baseline blood and/or salivary levels of cortisol for the CAR as measured by the AUCi as well as sample size) were available in the article or upon request from the corresponding author; 3) cross-sectional studies comparing blood and/or salivary levels of cortisol and/or CAR as measured by the AUCi or AUCg between persons with FEP or CHR individuals or unaffected individuals at familial risk (FHR) of psychosis (first- and second-degree relative of individuals with schizophrenia) and healthy controls or between high-risk converters and non-converters and 4) English language full-text articles. Three subgroups of individuals were included: 1) patients with FEP; 2) CHR individuals diagnosed using the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al., 2005) or the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003), including those with schizotypal personality disorder and 3) FHR individuals (first- and second-degree relatives of patients with schizophrenia). The following types of publication records were excluded: 1) animal model studies; 2) non-original studies (e.g., reviews, commentaries and editorials); 3) publications without necessary data; 4) studies that did not include healthy controls or did not record transition to overt psychosis. In case of overlapping authorship of potentially eligible publications, corresponding authors were contacted to provide necessary data from the largest sample of non-overlapping participants. In case of a lack of response from the corresponding author, only the largest study was included. Similarly, corresponding authors of eligible publications were contacted in case of unclear findings or a lack of necessary data to perform meta-analysis.

2.3. Data extraction

The following data were retrieved: 1) age; 2) sex; 3) body-mass index (BMI); 4) cigarette smoking status; 5) unstimulated (baseline) salivary levels of cortisol (i.e., single cortisol levels in the absence of stimulation or before stimulation or the values from the first measurement during the day); 6) unstimulated blood levels of cortisol; 7) CAR as measured by the AUCi or AUCg; 8) type of assay used to measure the level of cortisol; 9) type of biological material used to measure the level of cortisol (saliva, serum or plasma); 10) number of biological material samples used to calculate the level of cortisol; 11) conditions of biological material sampling (fasting or non-fasting, time of sampling); 12) medication status; 13) illness duration; 14) scores of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and 15) the levels of other biochemical parameters determined by at least six studies. The terms "baseline", and "unstimulated" with respect to cortisol levels are used interchangeably. Variables were retrieved as mean and SD or a number of cases.

Conversion methods were used to calculate mean and SD in case of data provided as median and interquartile range (IQR) or 95% confidence interval (95 %CI) or standard error (SE). The median was included as an approximation of the mean (Higgins and Green, 2011). In turn, SD was calculated using the following formulas: 1) SD = IQR/1.35; 2) SD = SE $\times \sqrt{N}$ or 3) SD = $\sqrt{N} \times$ (upper limit of 95 %CI – lower of 95 %CI)/3.92 (Higgins and Green, 2011; Hozo et al., 2005). Effect size estimates for biochemical parameters that were tested as potential moderators were calculated as described elsewhere (Lipsey and Wilson, 2001).

2.4. Quality assessment

The Newcastle-Ottawa Scale (NOS) (Wells et al., 2000) was used to assess quality of eligible studies. The NOS is a "star system" developed to

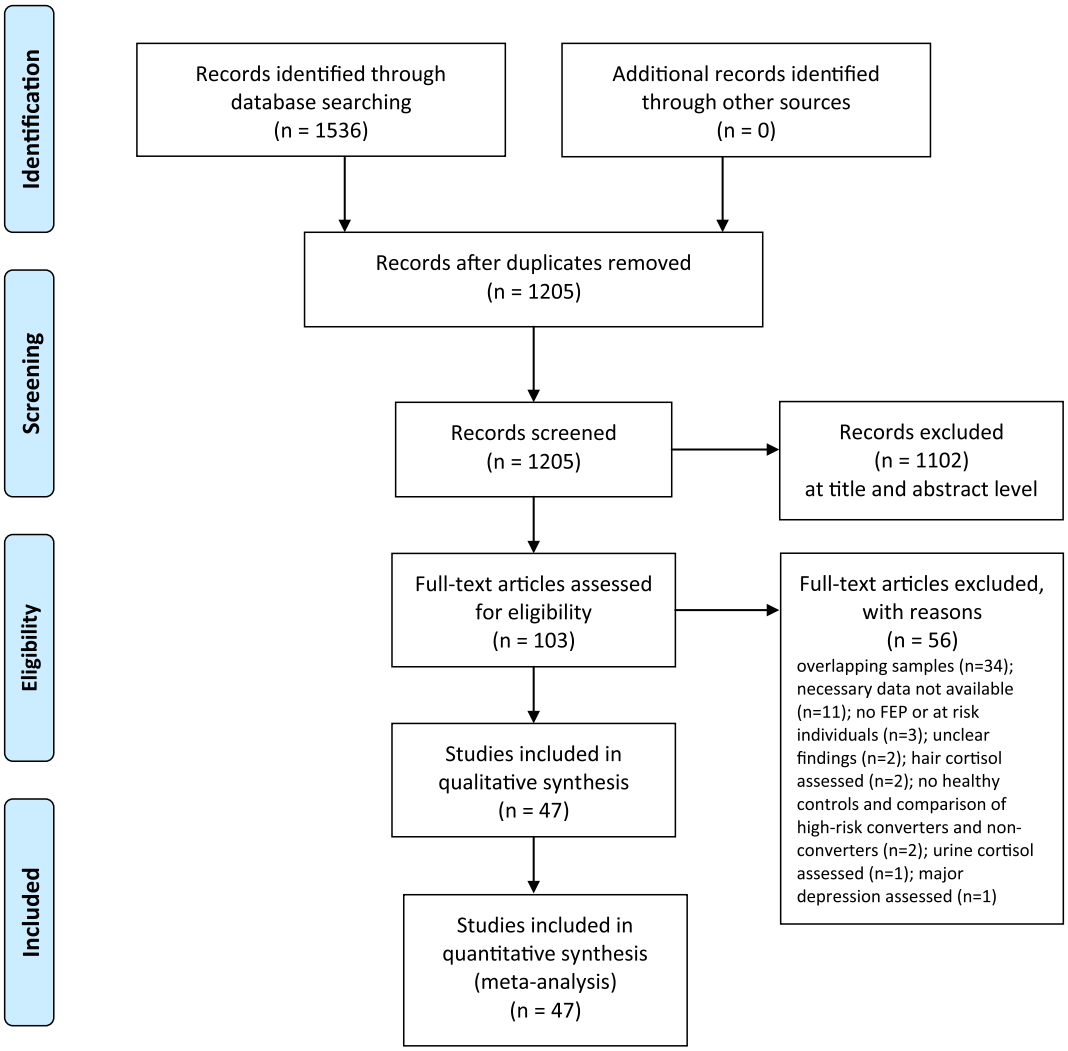

Fig. 1. The PRISMA flow chart (Moher et al. 2009).

evaluate three categories of quality: 1) the selection of study groups (the maximum score is 4 stars); 2) the comparability of study groups (the maximum score is 2 stars) and 3) the ascertainment of exposure or outcome of interest (the maximum score is 3 stars). The total NOS score ranges from 0 to 9 stars, where higher scores indicated better quality. Matching patients and healthy controls for age and sex was considered to allocate stars for the comparability of studied groups.

2.5. Data analysis

Between-group differences in baseline blood and salivary levels as well as CAR were tested as main outcome measures. The Cochran Q and I^2 statistics were used as the measures of heterogeneity. Random-effects models were used due to between-study differences in sample size, recruitment procedures, diagnoses or clinical manifestation captured by FEP or high-risk states and methods used to measure cortisol responses. Indeed, random-effects models are recommended if eligible studies are heterogeneous from a clinical and methodological point of view, and thus it is unreasonable to assume that they share a common effect (Tufanaru et al., 2015). The Hedges' g was calculated as the effect size estimate. The number of effect size estimates included in each analysis was reported as the "k" measure. The leave-one-out sensitivity analysis was performed to investigate if any single study accounted for heterogeneity. All analyses were carried out separately for studies of individuals with FEP, CHR and FHR. Meta-regression analyses were performed in case of continuous moderators that were assessed by at least six studies and categorical moderators if each category was represented by at least four studies (Fu et al., 2011). Publication bias was evaluated using the Egger's test if specific outcome measures were determined by at least 10 studies (Sterne et al., 2008). The level of significance was set at $p < 0.05$. The STATISTICA software, version 12.5, was used to perform data analyses.

3. Results

3.1. Search results and general characteristics of included studies

Initial searches identified 1536 publication records (Fig. 1). After considering eligibility criteria, 47 studies were finally included in systematic review and meta-analysis (Appiah-Kusi et al., 2020; Berger et al., 2018; Beyazyüz et al., 2014; Bičíková et al., 2011; Brunelin et al., 2008; Cai et al., 2018; Carol et al., 2017; Chaumette et al., 2016; Cullen et al., 2014, 2020a; Day et al., 2014; Fernandez-Egea et al., 2009; Garner et al., 2011; Guest et al., 2011; Gunduz-Bruce et al., 2007; Hempel et al., 2010; Iftimovici et al., 2020; Kale et al., 2010; Karanikas et al., 2017; Knytl et al., 2019; Liu et al., 2020; Mittal et al., 2007; Mondelli et al., 2015; Nordholm et al., 2018; Petrikis et al., 2015; Piotrowski et al., 2019; Pruessner et al., 2013a; 2013b; 2015; 2017; 2003b;; Reed et al., 2020; Riahi et al., 2016; Ryan et al., 2003a; Seitz et al., 2019; Solanki et al., 2017; Spelman et al., 2007; Steiner et al., 2020; Strous et al., 2004;

Table 1
General characteristics of case-control studies.

Study	Country of recruitment	FEP or psychosis risk				Healthy controls			Cortisol measures	Biological material	Fasting	Time of sampling	Assay	%AP-naive
		Diagnosis	N	age	% males	N	age	% males						
Appiah-Kusi et al. (2020)	UK	CHR	32	23.8	53.1	26	23.9	46.2	cortisol (TSST)	serum	no	11 AM	ns	100
Berger et al. (2018)	Germany	FEP	28	33.0	53.6	53	36.9	67.9	cortisol	serum	yes	8 – 9 AM	MIA	85.7
Beyazyüz et al. (2014)	Turkey	FEP	32	25.2	100	24	26.7	100	cortisol	plasma	no	8 AM	RIA	100
Bičíková et al. (2011)	Czech Republic	FEP	13	31.0	100	22	31.0	100	cortisol	serum	yes	8 AM	RIA	100
Brunelin et al. (2008)	France	siblings	15	28.5	46.7	14	29.1	42.8	cortisol	plasma	yes	9 AM	HPLC	100
Cai et al. (2018)	USA	FEP	53	25.6	56.6	43	24.9	55.8	cortisol	plasma	yes	8 – 9 AM	ELISA	ns
Carol et al. (2017)	USA	CHR	43	18.9	48.8	29	17.3	44.8	cortisol	saliva	no	8:45 AM	ELISA	100
Chaumette et al. (2016)	France	CHR	93	21.0	ns	52	20.6	ns	cortisol	saliva	yes	8 – 10 AM	FIA	41.0
Chaumette et al. (2016)	France	FEP	24	20.8	ns	52	20.6	ns	cortisol	saliva	yes	8 – 10 AM	FIA	34.0
Cullen et al. (2014)	UK	1st- and 2nd-relatives	22	13.3	50.0	40	13.1	43.0	CAR	saliva	yes	0, 15, 30, 60 min. post awakening	ELISA	100
Cullen et al. (2020)	USA, Canada	CHR	457	19.0	57.5	205	20.3	49.3	cortisol	saliva	no	6:15 AM – 6:11 PM (3 samples)	ELISA	85.6
Day et al. (2014)	UK	CHR	43	22.9	53.8	38	24.3	59.5	cortisol	saliva	yes	0, 30, 60 min. post awakening, 12 PM, 8 PM	CLA	94.2
Fernandez-Egea et al. (2009)	Spain	FEP	50	29.4	70.0	50	28.8	70.0	cortisol	serum	yes	8 – 9 AM	RIA	100
Garner et al. (2011)	Australia	FEP	39	20.6	66.7	25	22.5	84.0	cortisol	serum	no	9 – 10 AM	ns	ns
Guest et al. (2011)	Germany, the Netherlands	FEP	236	31.0	68.2	230	30.0	66.1	cortisol	serum	no	ns	MIA	ns
Gunduz-Bruce et al. (2007)	USA	FEP	16	25.8	75.0	29	29.8	ns	cortisol	saliva	no	9 AM	RIA	62.5
Hempel et al. (2010)	the Netherlands	FEP	27	22.0	100	38	22.0	100	cortisol	saliva	no	30 min. after awakening	ELISA	18.5
Kale et al. (2010)	India	FEP	31	32.7	45.2	48	34.2	56.2	cortisol	plasma	yes	ns	CLA	100
Karanikas et al. (2017)	Greece	CHR	12	24.5	100	23	27.0	100	cortisol	saliva	yes	8:00	RIA	100
Knytl et al. (2019)	Czech Republic	FEP	16	25.8	ns	29	29.4	ns	cortisol	plasma	yes	ns	HPLC	
Knytl et al. (2019)	Czech Republic	siblings	22	29.3	ns	29	29.4	ns	cortisol	plasma	yes	ns	HPLC	100
Labad et al. (2015)	Spain	CHR	39	22.3	69.2	44	23.2	65.1	CAR	saliva	yes	0, 30, 60 min. post awakening	CLA	82.0
Labad et al. (2018)	Spain	FEP	34	23.9	60.6	34	24.3	60.6	CAR	saliva	yes	0, 30, 60 min. post awakening	CLA	0
Liu et al. (2020)	China	FEP	43	22.3	62.8	47	23.3	61.7	cortisol	serum	yes	7 – 8 AM	CLA	ns
Mittal et al. (2007)	USA	CHR	39	14.2	66.0	47	14.1	53.0	cortisol	saliva	ns	9 AM, 10 AM, 11 AM, 12 PM, 1 PM	ns	84.6
Mondelli et al. (2015)	UK	FEP	68	29.2	67.6	57	26.8	63.2	CAR	saliva	yes	0, 15, 30, 60 min. post awakening	ns	10.3
Nordholm et al. (2018)	Denmark	CHR	32	23.9	42.9	28	24.7	58.3	CAR	saliva	yes	0, 15, 30, 60 min. post awakening	ELISA	100
Nordholm et al. (2018)	Denmark	FEP	26	24.1	55.0	28	24.7	58.3	CAR	saliva	yes	0, 15, 30, 60 min. post awakening	ELISA	100
Petrikis et al. (2015)	Greece	FEP	40	32.45	67.5	40	31.9	62.5	cortisol	serum	yes	8 AM		100
Piotrowski et al. (2019)	Poland	FEP	42	27.7	50.0	42	27.8	38.1	cortisol	serum	yes	7 – 9 AM	CLA	4.8
Piotrowski et al. (2019)	Poland	offspring	37	36.9	32.4	42	27.8	38.1	cortisol	serum	yes	7 – 9 AM	CLA	100
Pruessner et al. (2013a)	Canada	CHR	21	20.8	57.1	21	20.8	57.1	cortisol (TSST)	saliva	no	1 – 4 PM	FIA	100
Pruessner et al. (2013b)	Canada	FEP	58	23.3	65.5	33	22.9	48.5	CAR	saliva	yes	0, 30, 60 min. post awakening	FIA	8.6
Pruessner et al. (2015)	Canada	FEP	58	23.9	67.2	27	22.3	55.6	CAR	saliva	yes	0, 30, 60 min. post awakening	FIA	5.2
Pruessner et al. (2017)	Canada	CHR	42	20.2	57.1	46	23.3	50.0	CAR	saliva	yes	0, 30, 60 min. post awakening	FIA	100
Reed et al. (2020)	USA	FEP	38	22.2	78.9	29	22.7	69.0	cortisol (TSST)	saliva	no	mid-afternoon	ns	ns
Riahi et al. (2016)	Iran	FEP	31	ns	64.5	190	24.5	49.5	cortisol	plasma	no	ns	ELISA	100
Ryan et al. (2003)	Ireland	FEP	26	33.6	57.7	26	34.4	57.7	cortisol	plasma	yes	8 AM	FIA	100
Seitz et al. (2019)	Canada	FEP	57	23.9	71.9	43	23.2	53.5	cortisol (TSST)	saliva	no	1 – 4 PM	FIA	
Solanki et al. (2017)	India	FEP	30	24.3	60.0	20	27.9	65.0	cortisol	serum	no	8:30 – 9:30 AM	ns	100
Spelman et al. (2007)	Ireland	FEP	44	33.7	59.1	38	25.2	73.7	cortisol	plasma	yes	8 AM	ns	100
Spelman et al. (2007)	Ireland	1st-degree relatives	38	25.2	73.7	38	25.2	73.7	cortisol	plasma	yes	8 AM	ns	100

(*continued on next page*)

Table 1 (*continued*)

Study	Country of recruitment	FEP or psychosis risk				Healthy controls			Cortisol measures	Biological material	Fasting	Time of sampling	Assay	%AP-naive
		Diagnosis	N	age	% males	N	age	% males						
Steiner et al. (2020)	Germany	FEP	43	29.0	60.5	133	35.0	60.9	cortisol	serum	yes	ns	ns	100
Strous et al. (2004)	Israel	FEP	37	27.3	45.9	27	28.1	55.6	cortisol	serum	no	8 – 10 AM	ns	ns
Sugranyes et al. (2012)	USA	CHR	33	18.6	91.0	13	20.3	46.0	cortisol	saliva	no	11:30 AM	ns	ns
Sun et al. (2016)	China	FEP	13	22.5	100.0	15	22.2	100.0	cortisol	plasma	no	ns	RIA	100
Van Venrooij et al. (2012)	the Netherlands	FEP	11	23.0	100.0	15	22.0	100.0	cortisol (TSST)	plasma	no	10 AM	CLA	100
Venkatasubramanian et al. (2007)	India	FEP	44	33.0	52.3	44	32.5	52.3	cortisol	serum	yes	8 – 9 AM	CLA	100
Yang et al. (2012)	China	offspring	32	27.6	53.1	37	26.6	54.1	cortisol	plasma	yes	8 – 9 AM	FIA	100
Yildirim et al. (2011)	Turkey	1st-degree relatives	70	39.3	55.7	60	37.3	50.0	cortisol	serum	ns	8 – 9 AM	CLA	100
Zhu et al. (2020)	China	FEP	92	27.2	ns	154	37.3	ns	cortisol	serum	yes	6 – 8 AM	CLA	100

Abbreviations: ARMS – at risk mental state; CAR – cortisol awakening response; CHR – clinical high risk; CLA – chemiluminescence; ELISA – enzyme-linked immunosorbent assay; FIA – fluoroimmunoassay; HPLC – high-performance liquid chromatography; MIA – multiplex immunoassay; ns – not specified; RIA – radioimmunoassay; TSST – the Trier Social Stress Test; CHR – ultra high risk.

Sugranyes et al., 2012; Sun et al., 2016; Van Venrooij et al., 2012; Venkatasubramanian et al., 2007; Yang et al., 2012; Yildirim et al., 2011; Zhu et al., 2020). In case of five publication records (Pruessner et al., 2015; 2013a; 2013b; 2017;; Seitz et al., 2019), data from a total sample of non-overlapping individuals were provided by the corresponding author, and are further referred to as Pruessner et al.. Altogether, these studies included 1327 patients with FEP (range of mean age: 20.6 – 33.7 years, range of percentage of males: 45.2 – 100%), 932 CHR individuals (range of mean age: 14.2 – 24.5 years, range of percentage of males: 42.9 – 100%), 242 FHR individuals (range of mean age: 13.3 – 39.3 years, range of percentage of males: 32.4 – 73.7%) and 2203 healthy controls (range of mean age: 13.1 – 37.3 years, range of percentage of males: 38.1 – 100%). Participants were recruited in Europe (23 studies, 48.9%), Asia (11 studies, 23.4%), North America (11 studies, 23.4%), Australia (1 study, 2.1%) as well as Europe and North America (1 study, 2.1%). General characteristics of eligible studies are shown in Table 1, Table 2 and Supplementary Table 2. The NOS score varied between 3 and 6 (Supplementary Table 3).

3.2. *Unstimulated blood cortisol levels*

There were 27 studies investigating the unstimulated (baseline) levels of blood cortisol (Appiah-Kusi et al., 2020; Berger et al., 2018; Beyazyüz et al., 2014; Bičíková et al., 2011; Brunelin et al., 2008; Cai et al., 2018; Garcia-Rizo et al., 2012; Garner et al., 2011; Guest et al., 2011; Kale et al., 2010; Knytl et al., 2019; Liu et al., 2020; Petrikis et al., 2015; Piotrowski et al., 2019; Riahi et al., 2016; Ryan et al., 2003a; 2003b;; Solanki et al., 2017; Spelman et al., 2007; Steiner et al., 2020; Strous et al., 2004; Sun et al., 2016; Van Venrooij et al., 2012; Venkatasubramanian et al., 2007; Yang et al., 2012; Yildirim et al., 2011; Zhu et al., 2020). Among them 22 studies included subjects with FEP (Berger et al., 2018; Beyazyüz et al., 2014; Bičíková et al., 2011; Cai et al., 2018; Garcia-Rizo et al., 2012; Garner et al., 2011; Guest et al., 2011; Kale et al., 2010; Knytl et al., 2019; Liu et al., 2020; Petrikis et al., 2015; Piotrowski et al., 2019; Riahi et al., 2016; Ryan et al., 2003a; 2003b;; Solanki et al., 2017; Spelman et al., 2007; Steiner et al., 2020; Strous et al., 2004; Sun et al., 2016; Van Venrooij et al., 2012; Venkatasubramanian et al., 2007; Zhu et al., 2020) and 7 studies (Appiah-Kusi et al., 2020; Brunelin et al., 2008; Knytl et al., 2019; Piotrowski et al., 2019; Spelman et al., 2007; Yang et al., 2012; Yildirim et al., 2011) included individuals at high-risk of psychosis (one study of CHR individuals and six studies of FHR individuals).

Blood cortisol levels were significantly higher in patients with FEP ($k = 22$, $g = 0.48$, 95 %CI = 0.25–0.70, $p < 0.001$) but not individuals at high risk of psychosis ($k = 7$, $g = 0.39$, 95 %CI = −0.42–1.21, $p = 0.342$) compared to healthy controls (Table 3, Fig. 2). Heterogeneity was significant in these analyses [FEP vs. controls: $I^2 = 83.3\%$, $Q = 125.5$, $p(Q) < 0.001$; high-risk individuals vs. controls: $I^2 = 94.6\%$, $Q = 110.8$, $p(Q) < 0.001$]

The leave-one-out sensitivity analysis revealed that no single study accounted for heterogeneity in studies investigating unstimulated blood cortisol levels in subjects with FEP and those at high risk of psychosis (Supplementary Table 4). Standardized mean differences for the levels of glucose ($k = 9$, $\beta = 0.85$, 95 %CI = 0.28 – 1.43, $p = 0.004$) and insulin ($k = 7$, $\beta = 2.11$, 95 %CI = 0.60 – 3.62, $p = 0.006$) were associated with significantly higher standardized mean differences for blood cortisol levels in studies of individuals with FEP (Supplementary Table 5, Supplementary Fig. 1, Supplementary Fig. 2). These moderators were not tested separately for high-risk individuals due to low number of studies. Other variables were not significantly associated with effect size estimates for blood levels of cortisol (mean difference in age, difference in percentage of males, type of assay, fasting, difference in percentage of smokers, mean difference in BMI, percentage of antipsychotic-naïve patients or high-risk individuals, the NOS score, as well as effect size estimates for blood lipids, DHEA and DHEA-S). Results of the Egger's test were not significant for studies of individuals with FEP, indicating

Table 2
General characteristics of studies investigating unstimulated salivary cortisol with respect to transition to psychosis.

Study	Country of recruitment	Converters			Non-converters			Fasting	Time of sampling	Assay	%AP-naive	Observation period
		N	Mean age	% males	N	Mean age	% males					
Cullen et al. (2020)	USA, Canada	69	18.5	60.9	388	19.1	57.0	no	6:15 AM – 6:11 PM (3 samples)	ELISA	85.6	24 months
Iftimovici et al. (2020)	France	42	20.6	69.0	91	21.3	53.8	ns	7:00 AM	FIA	77.4	12 months
Labad et al. (2015)	Spain	10	20.4	50.0	29	23.0	75.9	yes	At awakening	CLA	82.0	At least 12 months
Sugranyes et al. (2012)	USA	9	ns	ns	24	ns	ns	no	11:30AM	ns	ns	24 months

Abbreviations: CLA – chemiluminescence; ELISA – enzyme-linked immunosorbent assay; FIA – fluoroimmunoassay; ns – not specified.

Table 3
Results of subgroup analyses.

Measure	Analysis	k	g	95 %CI	p	I^2	Q	p(Q)
Unstimulated cortisol - blood	FEP	22	0.48	0.25 – 0.70	**< 0.001**	83.3%	125.5	**< 0.001**
	Psychosis risk	7	0.39	−0.42 – 1.21	0.342	94.6%	110.8	**< 0.001**
Unstimulated cortisol – saliva	FEP	7	0.09	−0.09 – 0.26	0.331	0%	4.7	0.581
	Psychosis risk	10	0.15	−0.01 – 0.31	0.062	34.2%	13.7	0.134
	CHR converters vs. non-converters	4	−0.13	−0.50 – 0.24	0.500	61.3%	7.8	0.051
CAR - saliva	FEP	4	−0.40	−0.68 – −0.12	**0.006**	46.1%	5.6	0.134
	Psychosis risk	5	−0.13	−0.44 – 0.19	0.433	59.4%	9.8	**0.043**

Abbreviations: CAR – cortisol awakening response; CHR – clinical high risk; FEP – first-episode psychosis k refers to the number of comparisons Significant results ($p < 0.05$) were marked with bold characters.

no evidence for publication bias (k = 22, regression intercept = -1.51, 95 %CI = -4.61 – 1.60, p = 0.324).

3.3. Unstimulated salivary cortisol levels

There were 18 studies allowing the extraction of unstimulated (baseline) salivary cortisol levels (Carol et al., 2017; Chaumette et al., 2016; Cullen et al., 2020a; Day et al., 2014; Gunduz-Bruce et al., 2007; Hempel et al., 2010; Karanikas et al., 2017; Labad et al., 2015; 2018; 2013a; 2015; 2017;; Mittal et al., 2007; Nordholm et al., 2018; Pruessner et al., 2013b; Reed et al., 2020; Seitz et al., 2019; Sugranyes et al., 2012). Among them, 9 studies included subjects with FEP (Chaumette et al., 2016; Gunduz-Bruce et al., 2007; Hempel et al., 2010; Labad et al., 2018; Nordholm et al., 2018; Pruessner et al., 2015, 2013b; Reed et al., 2020; Seitz et al., 2019) and 10 studies included CHR individuals (Carol et al., 2017; Chaumette et al., 2016; Cullen et al., 2020a; Day et al., 2014; Karanikas et al., 2017; Labad et al., 2015; Mittal et al., 2007; Nordholm et al., 2018; Pruessner et al., 2013a; 2017;; Sugranyes et al., 2012).

There were no significant differences in unstimulated salivary cortisol levels between patients with FEP and healthy controls (k = 7, g = 0.09, 95 %CI = -0.09 – 0.26, p = 0.331) as well as between CHR individuals and healthy controls (k = 10, g = 0.15, 95 %CI = -0.01 – 0.31, p = 0.062) (Table 3, Fig. 3). No significant differences were also found between CHR converters and non-converters (k = 4, g = -0.13, 95 %CI = -0.50 – 0.24, p = 0.500). Heterogeneity was not significant in these analyses [FEP vs. controls: I^2 = 0%, Q = 4.7, p(Q) = 0.581; CHR individuals vs. controls: I^2 = 34.2, Q = 13.7, p(Q) = 0.134; CHR converters vs. non-converters: I^2 = 61.3%, Q = 7.8, p = 0.051].

The leave-one-out sensitivity analysis revealed that after removing single studies (Chaumette et al., 2016; Day et al., 2014; Pruessner et al., 2013a; 2017) salivary cortisol levels were significantly higher in CHR individuals compared to healthy controls with no evidence of heterogeneity (Supplementary Table 4). However, no significant between-group differences in salivary cortisol levels were found after removing single studies from the subgroup analysis of patients with FEP. Meta-regression analysis (Supplementary Table 5, Supplementary Fig. 3) demonstrated that the NOS score was significantly associated with effect size estimates for salivary cortisol levels in the subgroup analysis of studies that included CHR individuals (k = 10, β = −0.22, 95 %CI = -0.39 - −0.06, p = 0.009). Other potential moderators were not found to be significantly associated with effect size estimates for salivary cortisol in studies of CHR individuals (mean difference in age, difference in the percentage of males, number of saliva samples, single measure at awakening vs. other sampling schedules, type of assay and the percentage of antipsychotic-naïve CHR individuals). Due to the low number of studies that included patients with FEP, only the mean difference in age and the NOS score were tested in meta-regression analyses. However, none of them was found to be significantly associated with the effect size estimates of salivary cortisol in studies of patients with FEP. Importantly, none of eligible studies investigating unstimulated salivary cortisol levels measured the parameters of glucose homeostasis. Results of the Egger's test were not significant for studies of CHR individuals (k = 10, regression intercept = 1.21, 95 %CI = -0.73 – 3.15, p = 0.189).

3.4. CAR

There were 9 studies investigating the CAR (Cullen et al., 2014; Day et al., 2014; Labad et al., 2015; 2018;; Mondelli et al., 2015; Nordholm et al., 2018; Pruessner et al., 2013b; 2015; 2017a). Among them, 4 studies included CHR individuals (Day et al., 2014; Labad et al., 2015; Nordholm et al., 2018; Pruessner et al., 2017), 1 study included FHR individuals (Cullen et al., 2014) and 5 studies were based on patients with FEP (Labad et al., 2018; Mondelli et al., 2015; Nordholm et al., 2018; Pruessner et al., 2013b, 2015). Data on AUCg were available only for studies by Pruessner et al. (2013b; 2015; 2017), and thus the AUCi measures provided by the authors were included in the analyses instead.

The CAR was significantly attenuated in subjects with FEP (k = 4, g = -0.40, 95 %CI = -0.68 – −0.12, p = 0.006) but not in high-risk individuals (k = 5, g = -0.13, 95 %CI = -0.44 – 0.19, p = 0.433) (Table 3, Fig. 4). Heterogeneity was significant in the analysis of high-risk individuals [I^2 = 59.4%, Q = 9.8, p(Q) = 0.043] but not in the analysis of individuals with FEP [I^2 = 46.1%, Q = 5.6, p(Q) = 0.134]. Notably, in the studies by Pruessner et al. (2013b; 2015), males with FEP had significantly lower CAR compared to females with FEP and male

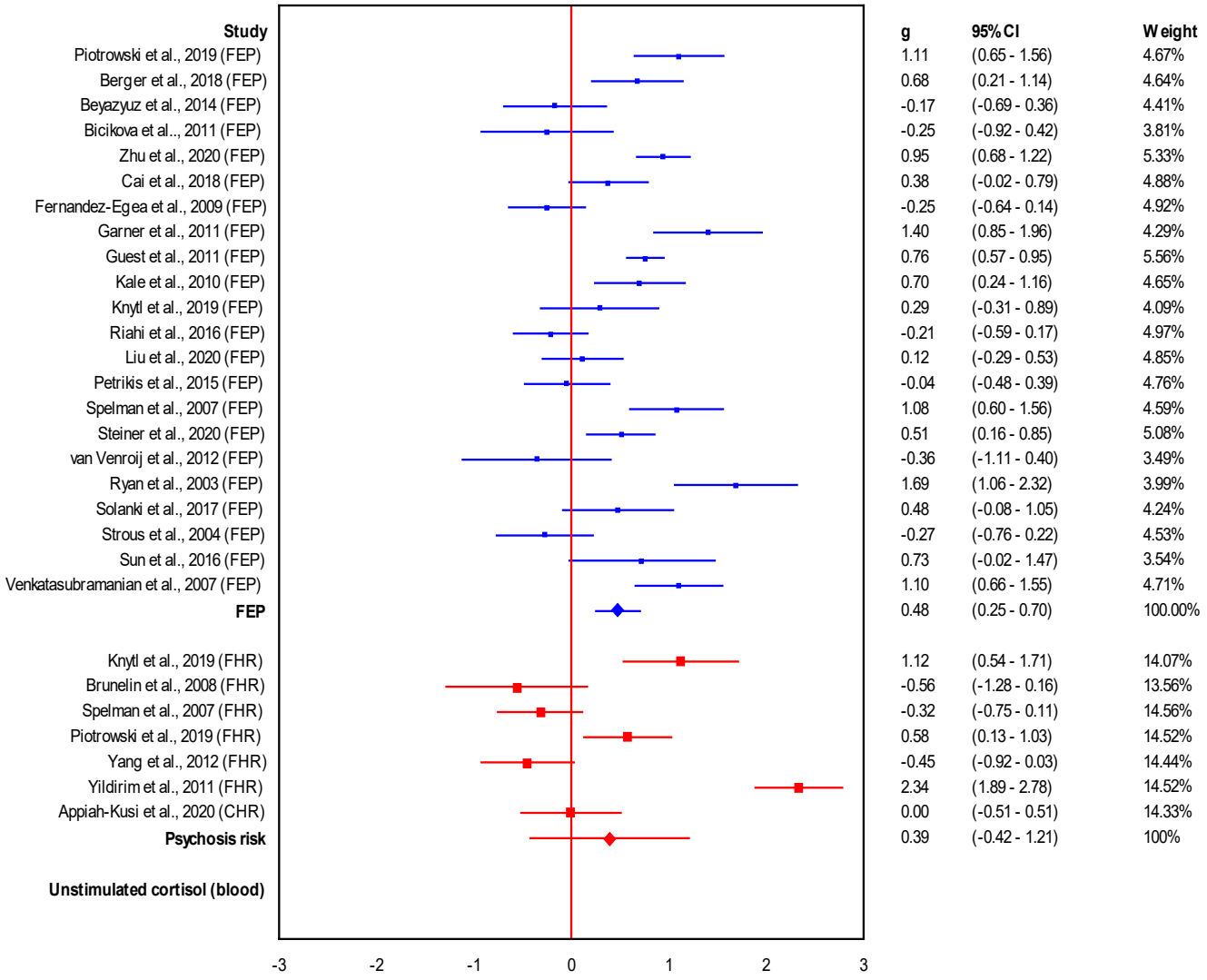

Fig. 2. Forrest plot of unstimulated blood cortisol levels. Abbreviations: CHR – clinical high risk; FEP – first-episode psychosis; FHR – familial high risk.

controls.

The leave-one-out sensitivity analysis (Supplementary Table 4) revealed that the CAR remained attenuated after removing any single study, except from the findings of the studies by Pruessner et al. (2013b; 2015) (k = 3, g = -0.42, 95 %CI = -0.83–0.01, p = 0.050). After removing these studies heterogeneity was not significant [$I^2 = 61\%$, Q = 5.1, p(Q) = 0.077]. Heterogeneity remained not significant in sensitivity analysis. The difference in CAR between high-risk individuals and controls was not significant after removing any single study in sensitivity analysis. Due to low number of studies, meta-regression analyses and the Egger's test were not performed. Moreover, none of eligible studies investigating CAR measured the parameters of glucose homeostasis.

4. Discussion

4.1. Unstimulated blood cortisol levels

Our systematic review and meta-analysis demonstrated significantly higher unstimulated levels of blood cortisol in patients with FEP but not in high-risk individuals with medium effect size estimates and significant heterogeneity. The difference in unstimulated levels of blood cortisol was not associated with between-group differences in age, sex, BMI and cigarette smoking status. Moreover, quality of studies, type of assay, fasting and the use of antipsychotics were not significantly correlated with effect size estimates. These findings are consistent with the results of previous meta-analysis of blood cortisol in patients with FEP (Hubbard and Miller, 2019). However, for the first time, we investigated a number of other biological alterations as potential moderators (the levels of glucose, insulin, DHEA and DHEA-S as well as lipid profile). We found that the effect size estimates for blood cortisol levels are significantly associated with those for the levels of glucose and insulin. It should be noted that abnormal glucose homeostasis parameters in unmedicated patients with FEP have previously been reported by several meta-analyses (Greenhalgh et al., 2017; Perry et al., 2016; Pillinger et al., 2017). Although a cross-sectional design of studies included in this meta-analysis does not allow to provide insights into causality, two scenarios need to be considered. First, it is likely that the enhanced activity of the HPA axis contributes to impaired glucose homeostasis. Indeed, glucocorticoids may liberate energy substrates through enhancing hepatic gluconeogenesis and reducing glucose utilization in fight-or-flight circumstances (Geer et al., 2014). Second, it cannot be ruled out that impaired glucose homeostasis in FEP accounts for elevated blood cortisol levels. For instance, it has been shown that glucose load amplifies cortisol responses to psychosocial stress in healthy volunteers (Gonzalez-Bono et al., 2002; von Dawans et al., 2021).

Of note, our findings do not explain the mechanisms underlying elevated blood cortisol levels in patients with FEP and concomitant

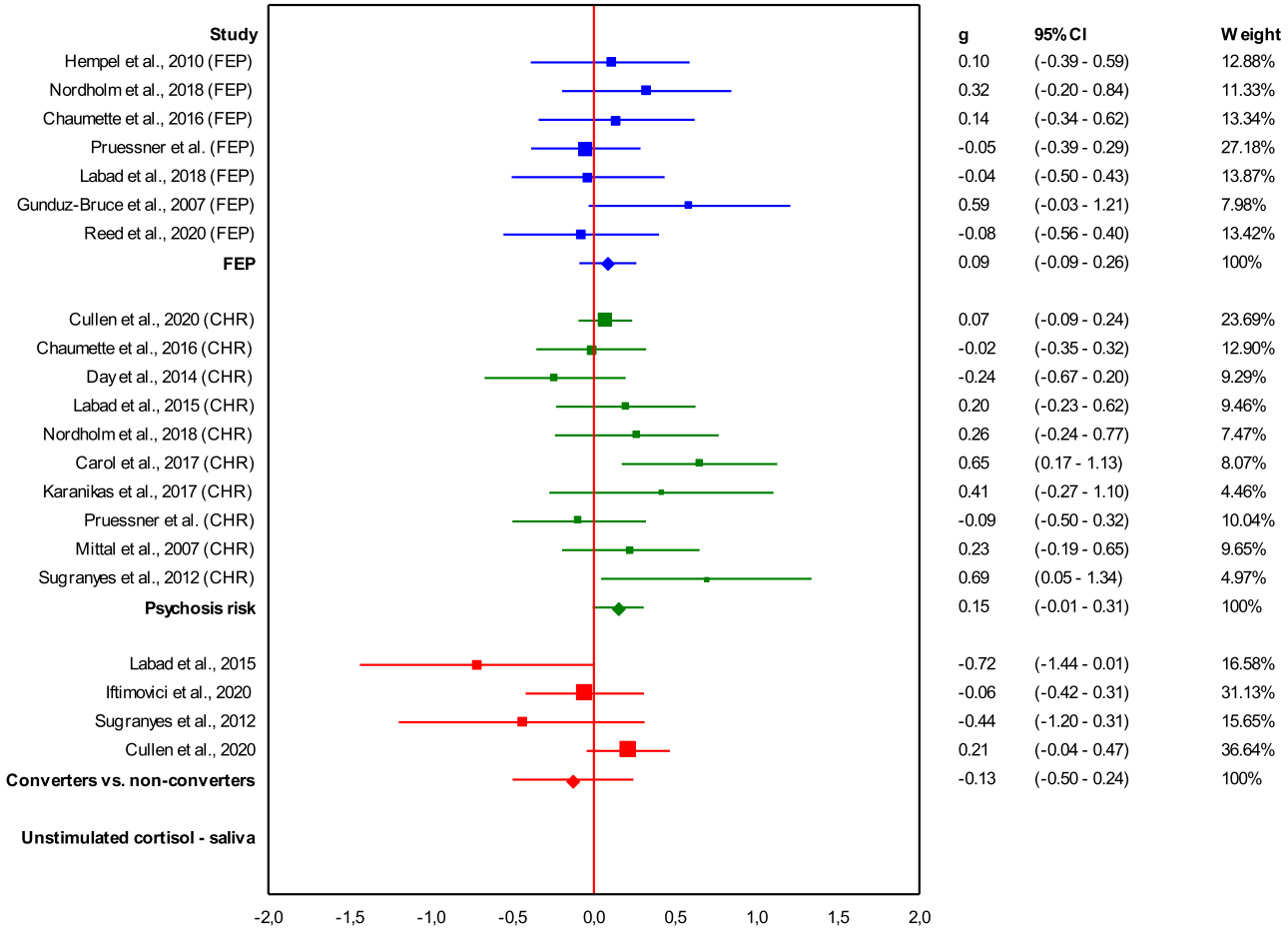

Fig. 3. Forrest plot of unstimulated salivary cortisol levels. Abbreviations: CHR – clinical high risk; FEP – first-episode psychosis.

glucose homeostasis alterations. However, certain processes should be taken into consideration. Convincing evidence indicates that traumatic life experiences, especially those acting in childhood, increase a risk of psychosis (Beards et al., 2013; Misiak et al., 2017; Varese et al., 2012). Their impact seems to be long-lasting as patients with psychosis and a history of childhood trauma show poor clinical and functional outcomes (Alameda et al., 2017; Misiak and Frydecka, 2016; Mondelli et al., 2015; Pruessner et al., 2019, 2021). Neuroimaging studies have also identified some neural substrates of childhood trauma in psychosis. Indeed, it has been reported that a history of early-life stress is associated with reduced volumes of the hippocampus and the amygdala in adult patients with psychosis (Aas et al., 2012; Hoy et al., 2012). In addition, more proximal stressors play an important role in triggering relapse of psychosis (Martland et al., 2020). However, it is important to note that a recent meta-analysis demonstrated poor concordance between naturally occurring psychosocial stressors and cortisol responses in psychosis (Cullen et al., 2020b). Nevertheless, the authors of this meta-analysis noted that this observation should be interpreted with caution due to limited statistical power at the level of meta-analysis and individual studies, heterogeneity of study measures and populations as well as differences in timing of cortisol measurement with respect to the onset of stressor. Moreover, experiencing psychosocial stress is neither necessary nor sufficient to trigger the onset of psychosis, and may contribute to the development of psychopathology that falls beyond the psychosis spectrum. This observation suggests that certain factors might moderate the association between psychosocial stress and a risk of psychosis or cortisol responses. These moderators might include individual psychological characteristics (e.g., personality traits, coping strategies or resilience) (Mizuno et al., 2016; Oswald et al., 2006; Piotrowski et al., 2020), social environments (Gayer-Anderson et al., 2015) or even genetic backgrounds (Stramecki et al., 2020). Interestingly, it has also been observed that a history of childhood trauma might contribute to insulin resistance in patients with schizophrenia and FEP (Misiak et al., 2020; Perry et al., 2021; Tosato et al., 2020). Apart from the associations with psychosocial stress, it cannot be excluded that elevated blood cortisol levels in FEP simply reflect a broad context of biological dysregulations. For instance, it has been shown that individuals with FEP show an elevated allostatic load index that captures a number of cardiovascular, metabolic, neuroendocrine and immune-inflammatory alterations, including elevated cortisol levels (Piotrowski et al., 2019). Finally, it is also important to note that we did not find significant correlations of effect size estimates for blood levels of cortisol with those for DHEA and DHEA-S. Elevated levels of DHEA and DHEA-S, two hormones that exert anti-glucocorticoid activities (Kimonides et al., 1999), have been well-documented in patients with FEP (Misiak et al., 2018). However, based on our meta-analysis, it might be implied that the HPA axis and DHEA/DHEA-S responses in FEP are not linearly associated.

4.2. *Unstimulated salivary cortisol levels*

Another important observation is that we found no convincing evidence that unstimulated salivary cortisol levels are altered in subjects at high risk of psychosis or those with FEP compared to healthy controls. Notably, heterogeneity was not significant in these analyses. After

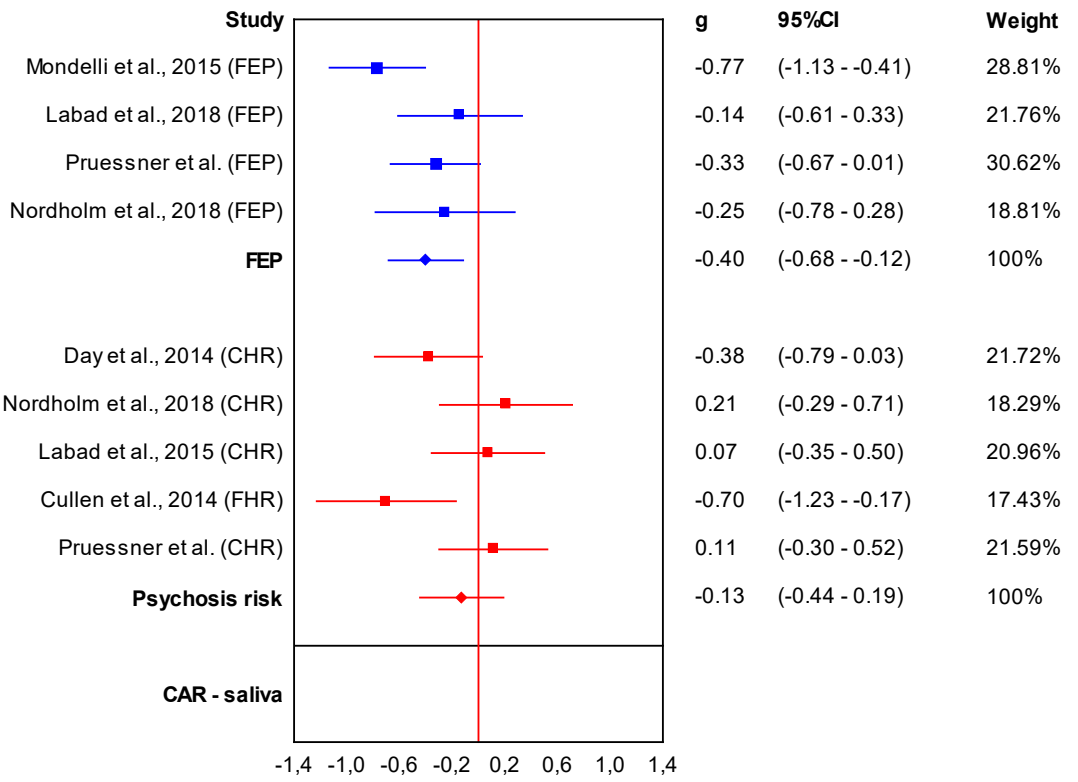

Fig. 4. Forrest plot of cortisol awakening response. Abbreviations: CAR – cortisol awakening response; CHR – clinical high risk; FEP – first-episode psychosis.

removing two single studies (Chaumette et al., 2016; Day et al., 2014) and the joint data from studies by Pruessner et al. from the subgroup analysis of CHR individuals, baseline salivary cortisol levels were significantly higher in CHR individuals compared to healthy controls. It should be noted that Chaumette et al. (2016) recruited help-seeking healthy controls as opposed to other eligible studies, which might explain why between-group differences in salivary cortisol were not significant. In case of other studies, it is difficult to indicate factors that might account for the results of sensitivity analysis. Importantly, the quality of studies was strongly and negatively associated with the effect size estimates. Nevertheless, a lack of significant difference with respect to unstimulated salivary cortisol levels between individuals with FEP and healthy controls might be surprising in light of our findings on blood cortisol levels. Although assessment of blood levels provides the information on total cortisol fraction, while salivary cortisol levels capture the unbound and biologically active fraction of cortisol, both measures are highly correlated (Kirschbaum and Hellhammer, 1989, 1994). Additional studies of salivary cortisol in psychosis are warranted, and should include multiple measurements, controlling for potential confounding factors. Moreover, methods like experience sampling, which allows to explore cortisol responses to daily hassles in real life environments, might provide more insights into the dynamics of salivary cortisol in subjects at the early phase of psychosis development (Myin-Germeys et al., 2018).

4.3. CAR

The present meta-analysis showed significantly attenuated CAR in subjects with FEP. Heterogeneity was not significant in this analysis. No significant differences with respect to the CAR were found between high-risk individuals and healthy controls. Only the study by Cullen et al. (2014) revealed a blunted CAR in children, who were relatives of individuals with schizophrenia, suggesting that the CAR might be associated with familial liability to psychosis. Notably, this was the only study that included unaffected FHR individuals. Altogether, these findings are in agreement with those of a previous meta-analysis (Berger et al., 2016), and would suggest that the CAR becomes attenuated after the onset of psychosis.

The CAR captures the marked increase in cortisol levels that appears during the first 30–45 min. after morning awakening (Stalder et al., 2016). It is independent of baseline or daytime cortisol levels and cortisol responses to psychosocial stress (Fries et al., 2009; Kidd et al., 2014). Studies included in the present meta-analysis also demonstrated interesting correlates of the CAR in subjects with FEP. Indeed, an attenuated CAR was associated with unfavorable paternal parenting under the age of 16 years (Pruessner et al., 2013b), greater cortical volume reductions (Pruessner et al., 2015; 2017a) and poor treatment response (Mondelli et al., 2015). However, it should be noted that we were not able to perform meta-regression analyses for the CAR.

4.4. Sex differences in cortisol response

It is important to note that the vast majority of eligible studies did not investigate sex differences in cortisol responses. Indeed, sex differences were investigated only in one dataset (Pruessner et al., 2013b; 2015). The authors found that the CAR was significantly lower in males with FEP compared to females with FEP and male controls. Also, a significant positive correlation between CAR and hippocampal volumes was found in males with FEP (Pruessner et al., 2015). Sex differences were also reported in a study by Carol et al. (2016) that was excluded from the present meta-analysis due to overlap with findings from a larger sample (Carol et al., 2017). More specifically, the authors found a significantly blunted CAR in CHR males but not in CHR females.

Sex differences with respect to cortisol responses might be of particular relevance to the pathophysiology of psychosis. For instance, females with schizophrenia tend to show later age of psychosis onset, more affective and less negative symptoms as well as less severe course of illness (Abel et al., 2010). These observations might be attributed to differences in hormonal homeostasis between females and males that are important with respect to cortisol responses. For instance, it has been

reported that testosterone and cortisol levels are positively correlated, and this association does not change with age (Harden et al., 2016). Sex differences in testosterone levels in patients with schizophrenia have also been explored in our previous meta-analysis (Misiak et al., 2018). Although we were not able to address these aspects in FEP due to a low number of studies, we found that total testosterone levels among individuals with multiple-episode schizophrenia are elevated in females and reduced in males, likely due to sex-dependent impact of antipsychotics. Moreover, greater hippocampal volume reductions have been reported in males with schizophrenia (Adriano et al., 2012).

4.5. Limitations

Our meta-analysis is characterized by certain limitations. Although it was based on a large number of studies, in the majority of them sample size was relatively low and representativeness was limited. In case of certain subgroup analyses, the number of eligible studies was also low. Moreover, it should be noted that we were unable to perform separate subgroup analyses of CHR and FHR individuals. In case of blood cortisol levels, subgroup analysis of high-risk individuals included only one study of CHR subjects. Moreover, due to a lack of data, we were unable to address the effects of clinical heterogeneity in the CHR construct. Another limitation is that our meta-analysis was based on a limited number of studies that compared cortisol measures in CHR converters and non-converters. Findings on the salivary cortisol levels should also be interpreted with caution due to the effects of quality scores. Importantly, the present meta-analysis does not provide insights into causal mechanisms underlying reported cortisol alterations. In addition, it is important to note that heterogeneity was not fully explained and was high in certain analyses, e.g., those of blood cortisol levels. Finally, results of this meta-analysis should be interpreted with caution due to the high number of statistical tests performed overall.

5. Conclusions

In summary, most robust findings of the present meta-analysis confirm elevated blood cortisol levels and attenuated CAR in patients with FEP. However, the present findings also allow to build new observations upon existing evidence (Berger et al., 2016; Chaumette et al., 2016; Hubbard and Miller, 2019; Pruessner et al., 2017). First, we showed that the HPA axis dysfunction is associated with impairments of glucose homeostasis widely demonstrated in FEP. This association needs to be explored further to clearly indicate direction of causality, and might open new possibilities to develop early interventions aimed to improve somatic health in FEP. Second, it is of importance to initiate studies that combine various measures of the HPA axis activity as discrepant observations together with the effects of methodological factors are reported in the present meta-analysis. These studies should strictly follow existing recommendations on the measurement of the HPA axis activity and take into consideration potential sex differences (Miller et al., 2013; Ryan et al., 2003a; 2003b;; Stalder et al., 2016). Third, available evidence does not support the utility of the HPA axis measures in predicting transition to psychosis in CHR individuals. However, these observations are based on limited number of studies, and thus additional research in this field is needed. A clear definition of HPA axis dysfunction is also warranted due to the fact that the efficacy of anti-glucocorticoid treatments in psychosis has not been sufficiently documented (Garner et al., 2016).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2021.100930.

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