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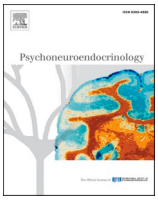

Blood concentrations of anterior pituitary hormones in drug-naïve people with first-episode psychosis: A systematic review and meta-analysis

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ABSTRACT

Introduction: The role of anterior pituitary hormones – i.e., adrenocorticotropic hormone (ACTH), luteinizing and follicle stimulating hormones (LH and FSH), growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH) – in early schizophrenia and psychoses unclear. We thus performed a systematic review and meta-analysis on the blood concentrations of ACTH, LH and FSH, GH, PRL, and TSH in drug-naïve people with first-episode psychosis (FEP) as compared with healthy controls.

Methods: We searched Embase, MEDLINE, and PsycInfo for articles indexed until September 2022. Data quality was appraised. Random-effects meta-analyses were carried out, generating pooled standardized mean differences (SMDs). Between-study heterogeneity was estimated using the I^2 statistic. Sensitivity and meta-regression analyses were performed.

Results: Twenty-six studies were included. Drug-naïve people with FEP, compared to healthy subjects, had higher blood concentrations of ACTH ($k = 7$; $N = 548$; SMD = 0.62; 95%CI: 0.29 to 0.94; $p < 0.001$; $I^2 = 60.9\%$) and PRL ($k = 17$; $N = 1757$; SMD = 0.85; 95%CI: 0.56 to 1.14; $p < 0.001$; $I^2 = 85.5\%$) as well as lower levels of TSH ($k = 6$; $N = 677$; SMD = –0.34; 95%CI: –0.54 to –0.14; $p = 0.001$; $I^2 = 29.1\%$). Meta-regressions did not show any moderating effect of age ($p = 0.78$), sex ($p = 0.21$), or symptom severity ($p = 0.87$) on PRL concentrations in drug-naïve FEP. Available data were not sufficient to perform meta-analyses on FSH, LH, and GH.

Conclusions: Drug-naïve people with FEP have altered ACTH, PRL, and TSH blood concentrations, supporting the hypothesis that an abnormal anterior pituitary hormone secretion may be involved in the onset of schizophrenia and psychoses. Further research is needed to elucidate the role of pituitary hormones in FEP.

1. Introduction

Schizophrenia spectrum and other psychotic disorders are characterized by psychopathological abnormalities, such as delusions and hallucinations, social withdrawal, affective flattening, disorganized thought and behavior, and cognitive disfunctions (McCutcheon et al., 2020). Among many different putative biological correlates of schizophrenia, neuroendocrine abnormalities involving the pituitary gland have been extensively studied (Brown, 2009). The pituitary gland (or hypophysis) is a small, pea-sized endocrine organ that represents a key link between the nervous and the endocrine systems (Le Tissier et al., 2017). It is formed by two main lobes, the anterior pituitary (or adenohypophysis) and the posterior pituitary (or neurohypophysis), separated by the *pars intermedia* (Ooi et al., 2004). While the posterior lobe secretes anti-diuretic hormone and oxytocin, the anterior one, constituting most of the gland's mass, is made of five unique endocrine cell types defined by the hormones they secrete: corticotropes, secreting adrenocorticotropic hormone (ACTH); gonadotropes, synthesizing gonadotropins, i.e., follicle stimulating and luteinizing hormones (FSH and LH); somatotropes, which produce growth hormone (GH) or somatotropin; lactotropes, secreting prolactin (PRL); and thyrotropes, producing thyroid-stimulating hormone (TSH) (Davis et al., 2013; Le Tissier et al., 2012). Indeed, anterior pituitary hormones are involved in neurotransmission and neuroregulation processes, which seem involved in the pathophysiology of schizophrenia. First, PRL has a bidirectional link with dopamine, because PRL regulates hypothalamic dopaminergic

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neurons whilst dopamine directly inhibits the basal secretory tone of lactotroph cells (Fitzgerald and Dinan, 2008). In addition, the hypothalamic-pituitary-adrenal (HPA) axis regulates dopamine activity in certain brain regions such as the mesolimbic system and is involved in stress response (Walker et al., 2008). Moreover, the hypothalamic-pituitary-thyroid (HPT) axis affects emotion regulation and cognitive functioning (Zhu et al., 2020), the hypothalamic-pituitary-gonadal (HPG) axis interacts with dopaminergic, serotonergic, and glutamatergic systems (Matuszewska et al., 2023), and GH regulates cognitive, behavioral, neuroendocrine, and metabolic functions (Wasinski et al., 2019). In sum, anterior pituitary hormones seem to have a central role in several fundamental pathophysiological processes that are putatively altered in schizophrenia (de Boer et al., 2015; Laporte and Vankelecom, 2022; Thomas et al., 2019). However, defining the neurobiological relevance of the anterior pituitary hormones for schizophrenia and other psychoses remains complex because of both the inherent impairing features of the disease and the effect of medications (Kahn et al., 2015). For these reasons, studies investigating people with first-episode psychosis (FEP) who have never received psychopharmacological treatment (drug-naïve) may provide unique insights (Pillinger et al., 2019). Nonetheless, published meta-analyses are limited to single hormones (PRL and TSH) (González-Blanco et al., 2016; Misiak et al., 2021a), while there is no systematic synthesis for other anterior pituitary hormones (i.e., ACTH, FSH and LH, and GH). With the aim of providing a comprehensive and up-to-date assessment of this research literature, we performed a systematic review and meta-analysis of studies investigating the differences in blood concentrations of the anterior pituitary hormones (i.e., ACTH, FSH and LH, GH, PRL, and TSH) between drug-naïve people with FEP and those without mental disorders, also taking into consideration possible effect modifiers such as sex, symptom severity, and quality of the available evidence.

2. Material and methods

2.1. Protocol

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement (Page et al., 2021). The protocol was registered in the Open Science Framework Registries on 20th July 2022 (doi: 10.17605/OSF.IO/NMJDB).

2.2. Search strategy and inclusion criteria

Systematic searches of Embase, Ovid MEDLINE(R), and APA PsycInfo databases (via Ovid) were performed for articles published up to 20th September 2022. The search phrase used was: *(adrenocorticotropic hormone OR ACTH OR gonadotropin OR follicle stimulating hormone OR FSH OR luteinizing hormone OR LH OR growth hormone OR hGH OR GH OR somatotropin OR prolactin OR PRL OR thyroid stimulating hormone OR TSH) AND (psychos* OR psychot* OR schizophreni* OR schizoaffective) AND (first OR naive OR untreated OR unmedicated OR nonmedicated OR minimally treated OR free).mp.* as a multiple purpose search of title, abstract, heading words, and keywords. No language or publication date restrictions were applied. The reference lists of the included studies and of relevant reviews (González-Blanco et al., 2016; Misiak et al., 2021a) were also searched to identify potential additional articles.

We included any observational study investigating blood concentrations of ACTH, FSH, LH, GH, PRL, or TSH in people with first-episode schizophrenia spectrum or other psychotic disorders (American Psychiatric Association, 2022) who were never or minimally (for a maximum of 2 weeks (Egerton et al., 2018)) treated with psychotropic medications as compared with healthy controls (HCs). To improve the consistency and comparability of data, we excluded: i) studies on subjects described as prodromal or at clinical high risk for psychosis; ii) studies including participants suffering from disorders potentially characterized by psychotic symptoms but not included in the DSM-5-TR schizophrenia spectrum and other psychotic disorders section (American Psychiatric Association, 2022), e.g., bipolar or major depressive disorders with psychotic features; iii) studies including individuals with physical comorbidities that influence anterior pituitary hormone secretion and related metabolic axes (Higham et al., 2016); iv) "grey" literature, conference abstracts, dissertations, and all publications not having undergone a peer-review process.

When information from the same sample was reported in multiple publications we used the article providing the most comprehensive data to avoid duplication. If uncertainties remained, one investigator (DC) contacted the corresponding authors of potentially eligible studies for clarification.

After a preliminary screening based on titles and abstracts, full texts were retrieved to evaluate eligibility. Articles were independently screened and read in full text by five authors (DC, CAC, PG, GB, and MR), and reasons for exclusion were recorded (Supplementary Table 1). Any disagreement was resolved by discussion with the other authors.

2.3. Data extraction

Five authors (DC, CAC, PG, GB, and MR) independently extracted data and blindly cross-checked them for accuracy. A data extraction template was used to collect key information from the eligible studies, including: i) author(s) and year of publication; ii) country; iii) type of assay used to measure the blood concentrations of hormones; iv) diagnostic criteria and tools used to assess FEP; v) main characteristics of index and control groups, including sample size, mean age, sex distribution, diagnosis, duration of untreated psychosis (defined as the time between the onset of first-episode psychosis and first treatment (Penttilä et al., 2014)), and symptom severity; vi) anterior pituitary hormone blood concentrations. When the data were insufficient or unclear, one investigator (DC) contacted the corresponding author looking for clarification to reduce the risk of reporting bias.

2.4. Quality and comparability of data

Due to the lack of valid methods to assess the quality of non-randomized studies (e.g., Stang, 2010), we considered the following items from each included study to evaluate the potential risk of bias (Grimes and Schulz, 2002): i) age and ii) sex comparability between FEP and control groups, considering acceptable differences up to three years in mean age and 5% in proportion of men, respectively (Bartoli et al., 2020; Cavaleri et al., 2023); iii) representativeness of the FEP group, verifying that individuals were not selected from special populations in terms of demographic and clinical characteristics (e.g., studies predominantly based on males or females; studies restricted to early- or late-onset psychosis); iv) diagnosis of FEP, considering appropriate an assessment made using structured or semi-structured interviews based on DSM criteria, such as the Structured Clinical Interview for DSM (SCID) or the Mini-International Neuropsychiatric Interview (MINI). These items were then used to inform sensitivity analyses. Data quality and comparability was addressed independently by five authors (DC, CAC, PG, GB, and MR), and disagreements were resolved by discussion with other authors.

2.5. Data analysis

Random-effects meta-analyses were performed when data were available from at least three studies. Standardized mean differences (SMDs) and their 95% confidence intervals (95%CIs), estimated from means and standard deviations (SDs), were used to compare hormone concentrations between drug-naïve people with FEP and HCs (Higgins et al., 2022). If raw means and SDs were not reported, they were estimated using conventional transformation methods, when feasible

(Drevon et al., 2017; Higgins et al., 2022; Luo et al., 2018). To guarantee consistency, normalized and/or transformed data were excluded (Deeks et al., 2022). When data were reported by subgroups, they were combined into a single group using standard formulae (Higgins et al., 2022). Statistical significance was set at $p < 0.05$ (two-tailed). Conventional forest plots were used to summarize results. Effect sizes were evaluated according to standard cut-offs for SMDs (0.2: small; 0.5: medium; 0.8: large; 1.3: very large) (Rosenthal, 1996). Heterogeneity across studies was estimated with the I^2 statistic, defining low, moderate, and high levels of heterogeneity (I^2 values around 25%, 50%, and 75%, respectively) (Higgins et al., 2003). For analyses with an $I^2 > 50\%$, we carried out heterogeneity-based sequential sensitivity analyses, leaving out a single or a cluster of studies up to the minimum I^2 value below the desired pre-set threshold of 50% (Patsopoulos et al., 2008). Egger's test (Egger et al., 1997) and visual inspection of funnel plots were used to evaluate the risk of publication bias when at least ten studies were available (Page et al., 2022). Furthermore, for meta-analyses based on at least ten studies (Deeks et al., 2022), we performed random-effect meta-regression analyses with Monte Carlo permutation to explore whether the differences in pituitary hormone concentrations might have been influenced by possible moderators among people with FEP, including i) mean age and ii) proportion of males, iii) mean duration of untreated psychosis, and iv) symptom severity. Symptom severity was based on mean Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) scores, converting BPRS to equivalent PANSS scores for comparability (Leucht et al., 2013). To evaluate the impact of the quality of included studies on effect estimates (Grimes and Schulz, 2002), we carried out sensitivity analyses excluding studies not meeting each quality item (age or sex comparability, representativeness, diagnostic assessment). To account for possible differences in hormone concentrations, we performed sex-based meta-analyses when at least three studies were available. Analyses were performed using Stata Statistical Software, Release 17 (StataCorp, 2021).

3. Results

3.1. Study selection and characteristics

Our systematic search generated 3589 records via Ovid (2042 from Embase, 917 from Ovid MEDLINE(R), and 630 from APA PsycInfo), reduced to 2379 unique articles after deduplication. No additional

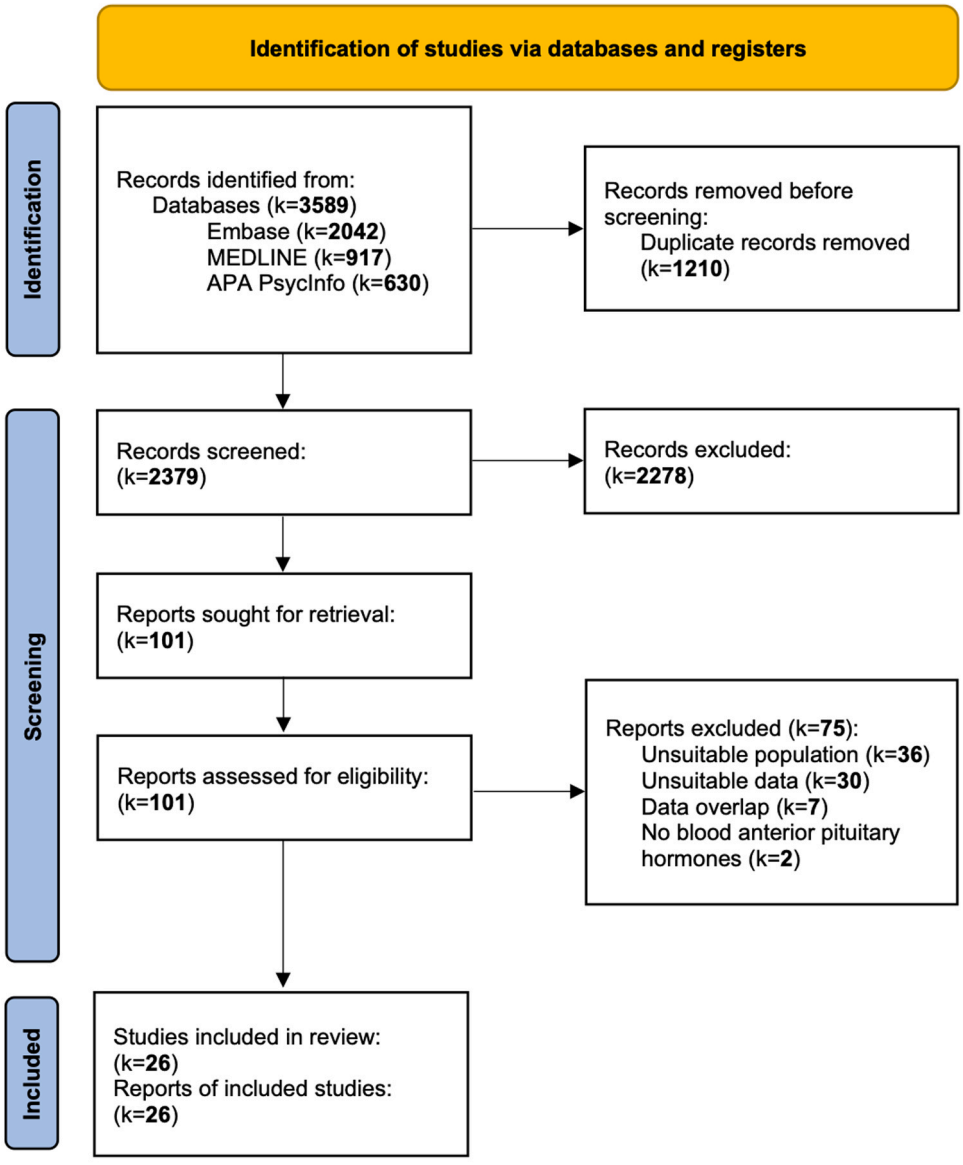

Fig. 1. PRISMA flowchart of study selection process.

articles were retrieved from the reference lists of the included studies and of relevant reviews (González-Blanco et al., 2016; Misiak et al., 2021a). The screening of titles and abstracts identified 101 potentially eligible studies. After a full-text review, 26 studies met eligibility criteria and were included in the systematic review (Abel et al., 1996; Albayrak et al., 2014; Angelopoulos et al., 2002; Beyazyüz et al., 2014; Bicikova et al., 2011; Del Cacho et al., 2019; Delgado-Alvarado et al., 2019; Garcia-Rizo et al., 2012; Hidalgo-Figueroa et al., 2022; Nerozzi et al., 1990; Petrikis et al., 2020; Petrikis et al., 2016; Rao et al., 1990; Ryan et al., 2004; Shrivastava et al., 2012; Şimşek et al., 2017; Song et al., 2014; Studerus et al., 2021; van Venrooji et al., 2012; Walsh et al., 2005; Yalçin et al., 2016; Yang et al., 2018; Yesilkaya et al., 2021; Yuan et al., 2016; Zhang et al., 2016; Zhu et al., 2020). We also used unpublished information provided by the authors of three articles (Hidalgo-Figueroa et al., 2022; Yalçin et al., 2016; Zhu et al., 2020). The study selection process is described in Fig. 1. The 75 articles excluded after full-text review, with relevant reasons, are listed in Supplementary Table 1.

Studies were published between 1990 (Nerozzi et al., 1990; Rao et al., 1990) and 2022 (Hidalgo-Figueroa et al., 2022). Seven studies reported on blood concentrations of ACTH, two on FSH, two on LH, one on GH, 17 on PRL, and six on TSH. All studies involved participants never treated with psychotropic medications, except for one (Garcia-Rizo et al., 2012), which included individuals with a previous minimal exposure to antipsychotic treatment (maximum lifetime exposure of one week) followed by no antipsychotic use in the 30 days prior to blood sampling.

The characteristics of the included studies are reported in Table 1. The quality assessment of data is reported in Supplementary Table 2.

3.2. Anterior pituitary hormones blood concentrations

3.2.1. Adrenocorticotropic hormone blood concentrations

Seven studies (Beyazyüz et al., 2014; Ryan et al., 2004; Şimşek et al., 2017; van Venrooij et al., 2012; Walsh et al., 2005; Yesilkaya et al., 2021; Zhu et al., 2020), including a total of 548 individuals (245 with drug-naïve FEP and 303 HCs), provided comparative data on ACTH blood concentrations.

The meta-analysis showed that drug-naïve individuals with FEP had higher ACTH concentrations compared to HCs, with a medium-to-large effect size (SMD = 0.62; 95%CI: 0.29 to 0.94; $p < 0.001$) and moderate-to-high heterogeneity across studies ($I^2 = 60.9\%$) (Fig. 2).

The heterogeneity-based sensitivity analysis, leaving out one study (Yesilkaya et al., 2021), confirmed this finding (SMD = 0.51; 95%CI: 0.17 to 0.84; $p = 0.003$; $I^2 = 47.6\%$).

Since there were less than ten studies, publication bias could not be assessed. For the same reason, no meta-regression analyses were performed.

Quality-based sensitivity analyses confirmed that ACTH concentrations were higher in drug-naïve FEP considering age ($k = 6$; $N = 302$; SMD = 0.61; 95%CI: 0.16 to 1.06; $p = 0.008$; $I^2 = 67.4\%$) and sex comparability ($k = 5$; $N = 172$; SMD = 0.45; 95%CI: 0.01 to 0.89; $p = 0.044$; $I^2 = 46.2\%$), and diagnostic assessment ($k = 6$; $N = 522$; SMD = 0.67; 95%CI: 0.32 to 1.02; $p < 0.001$; $I^2 = 64.0\%$) (Supplementary Table 3). The quality-based sensitivity analysis regarding the representativeness of the sample was not feasible due to the limited number of studies ($k = 2$).

Male drug-naïve participants with FEP showed higher ACTH concentrations as compared with HCs ($k = 4$; $N = 265$; SMD = 0.53; 95%CI: 0.02 to 1.03; $p = 0.041$; $I^2 = 64.7\%$) (Supplementary Figure 1). There were no sufficient data to perform an analysis on females ($k = 1$) (Zhu et al., 2020).

3.2.2. Gonadotropin blood concentrations

Only two eligible studies reported comparative data on gonadotropins (Petrikis et al., 2020; Yuan et al., 2016). The levels of FSH did not significantly differ between participants with FEP and HCs in either of the two studies (Petrikis et al.: $p = 0.09$; Yuan et al.: $p = 0.52$). Similarly, none of the two studies reported significantly different LH concentrations between index and control groups (Petrikis et al.: $p = 0.13$; Yuan et al.: $p = 0.18$). No meta-analysis was carried out because of insufficient data.

3.2.3. Growth hormone blood concentrations

Data on GH concentrations were available from one study only (Rao et al., 1990), which reported no statistically significant differences between drug-naïve FEP and HCs ($p = 0.27$). Due to the lack of data, no meta-analysis on GH levels was performed.

3.2.4. Prolactin blood concentrations

Seventeen studies (Abel et al., 1996; Albayrak et al., 2014; Angelopoulos et al., 2002; Bicikova et al., 2011; Delgado-Alvarado et al., 2019; Garcia-Rizo et al., 2012; Hidalgo-Figueroa et al., 2022; Nerozzi et al., 1990; Petrikis et al., 2016; Rao et al., 1990; Shrivastava et al., 2012; Song et al., 2014; Studerus et al., 2021; Yalçin et al., 2016; Yang et al., 2018; Yuan et al., 2016; Zhang et al., 2016) including a total of 1757 individuals (888 with drug-naïve FEP and 869 HCs), provided comparative data on PRL blood concentrations.

The meta-analysis showed that drug-naïve people with FEP had higher PRL concentrations compared to HCs, with a large (SMD = 0.85; 95%CI: 0.56 to 1.14; $p < 0.001$), though inconsistent ($I^2 = 85.5\%$), effect size (Fig. 3).

The heterogeneity-based sensitivity analysis, leaving out six studies (Albayrak et al., 2014; Rao et al., 1990; Shrivastava et al., 2012; Yang et al., 2018; Yuan et al., 2016; Zhang et al., 2016), confirmed this finding ($k = 11$; $N = 1150$; SMD = 0.58; 95%CI: 0.39 to 0.77; $p < 0.001$; $I^2 = 45.7\%$).

Both the visual inspection of the funnel plot (Supplementary Figure 2) and the Egger's test ($p = 0.27$) showed a low probability of publication bias.

Meta-regression analyses did not show any moderating effect of mean age ($p = 0.78$), proportion of males ($p = 0.21$), and symptom severity ($p = 0.87$) on PRL concentrations of the drug-naïve FEP group. It was not possible to perform a meta-regression analysis exploring the role of duration of untreated psychosis due to the limited number of studies ($k = 5$).

Quality-based sensitivity analyses considering age ($k = 13$; $N = 1387$; SMD = 0.91; 95%CI: 0.57 to 1.25; $p < 0.001$; $I^2 = 85.8\%$) and sex comparability ($k = 12$; $N = 913$; SMD = 0.88; 95%CI: 0.49 to 1.27; $p < 0.001$; $I^2 = 84.5\%$), representativeness ($k = 12$; $N = 1512$; SMD = 0.69; 95%CI: 0.42 to 0.96; $p < 0.001$; $I^2 = 81.7\%$), and diagnostic assessment ($k = 16$; $N = 1625$; SMD = 0.89; 95%CI: 0.58 to 1.20; $p < 0.001$; $I^2 = 85.8\%$) confirmed these findings (Supplementary Table 3).

Sex-based analyses showed that both males ($N = 891$; SMD = 0.85; 95%CI: 0.51 to 1.18; $p < 0.001$; $I^2 = 78.8\%$) (Supplementary Figure 3) and females ($N = 738$; SMD = 0.74; 95%CI: 0.34 to 1.13; $p < 0.001$; $I^2 = 81.1\%$) (Supplementary Figure 4) with drug-naïve FEP had higher PRL concentrations compared to HCs.

3.2.5. Thyroid stimulating hormone blood concentrations

Six studies (Bicikova et al., 2011; Del Cacho et al., 2019; Garcia-Rizo et al., 2012; Petrikis et al., 2016; Rao et al., 1990; Zhu et al., 2020), including a total of 677 individuals (268 drug-naïve individuals with FEP and 409 HCs), provided comparative data on TSH blood concentrations.

The meta-analysis showed that drug-naïve people with FEP had lower TSH concentrations compared to HCs, with a small-to-medium effect size (SMD = –0.34; 95%CI: –0.54 to –0.14; $p = 0.001$). Heterogeneity across studies was low ($I^2 = 29.1\%$) (Fig. 4).

Due to the lack of sufficient information, we could not perform publication bias assessment nor meta-regression analyses.

Quality-based sensitivity analyses suggested a possible influence of

Table 1
Characteristics of the included studies.

Study	Country	Type of assay	Subjects with FEP						Healthy controls			Hormones measured
			Sample size *N*	Mean age *years*	Proportion of males *% (M/F)*	Sample characteristics	Mean DUP *months*	Severity score (PANSS/ BPRS) *total score*	Sample size *N*	Mean age *years*	Proportion of males *% (M/F)*	
Abel et al. (1996)	United Kingdom	RIA	13	29.5	76.9% (10 M/3 F)	Drug-naïve FES (except for one patient who was treated for two weeks one year prior to the study)	N/R	BPRS: 39.2 ± 10.1	13	31.7	76.9% (10 M/3 F)	PRL
Albayrak et al. (2014)	Turkey	RIA	30	25.7	100% (30 M/0 F)	Drug-naïve FES	N/R	BPRS: 29.3 ± 7.5	32	26.4	100% (32 M/0 F)	PRL
Angelopoulos et al. (2002)	Greece	RIA	16	25.3	100% (16 M/0 F)	Drug-naïve FES (n = 10) or schizophreniform disorder (n = 6)	24.5 months	PANSS: 120 ± 18	12	27.1	100% (12 M/0 F)	PRL
Beyazyüz et al. (2014)	Turkey	RIA	32	25.2	100% (32 M/0 F)	Drug-naïve FES	N/R	N/A	24	26.7	100% (24 M/0 F)	ACTH
Bicikova et al. (2011)	Czech Republic	IRMA (PRL), ECLIA (TSH)	22	32.6	59.1% (13 M/9 F)	Drug-naïve FES	N/R	N/R	47	33.1	46.8% (22 M/25 F)	PRL, TSH
Del Cacho et al. (2019)	Spain	CMIA	61	24.6	62.3% (38 M/23 F)	Drug-naïve non-affective FEP	N/R	N/R	45	27.6	55.6% (25 M/20 F)	TSH
Delgado-Alvarado et al. (2019)	Spain	CLIA	270	31.4	50.7% (137 M/ 133 F)	Drug-naive FES (n = 126), schizophreniform disorder (n = 84), brief psychotic disorder (n = 35), unspecified psychotic disorder (n = 19), schizoaffective disorder (n = 5), or delusional disorder (n = 1).	N/R	N/R	153	29.7	60.8% (93 M/60 F)	PRL
Garcia-Rizo et al. (2012)	Spain	CLIA	33	28.6	60.6% (20 M/13 F)	FES (n = 18), brief psychotic disorder (n = 9), schizophreniform disorder (n = 3), or psychosis NOS (n = 3) with maximum cumulative (lifetime) antipsychotic exposure of one week and no antipsychotic use in the 30 days prior to the study.	N/R	N/R	33	26.8	63.6% (21 M/12 F)	PRL, TSH
Hidalgo-Figueroa et al. (2022)	Spain	ELISA	18	23.7	66.7% (12 M/6 F)	Drug-naïve non-affective (n = 12) or affective (n = 6) FEP	2.5 months†	PANSS: 43.4 ± 17.4	83	25.3	69.9% (58 M/25 F)	PRL
Nerozzi et al. (1990)	Italy	RIA	5	N/R	100% (5 M/0 F)	Drug-naïve schizophreniform disorder	N/R	N/R	10	20.4	100% (10 M/0 F)	PRL
Petrikis et al. (2020)	Greece	CLIA	55	29.4	100% (55 M/0 F)	Drug-naïve FES (n = 7), schizophreniform disorder (n = 7), or brief psychotic episode (n = 18)	2.5 months	PANSS: 78.2 ± 5.9	55	31.2	100% (55 M/0 F)	FSH, LH
Petrikis et al. (2016)	Greece	CLIA	40	32.5	67.5% (27 M/13 F)	Drug-naïve FES, schizophreniform disorder, or brief psychotic episode	2.4 months	PANSS: 79.4 ± 9.1	40	32.3	67.5% (27 M/13 F)	PRL, TSH
Rao et al. (1990)	Germany	RIA	20	33	55.0% (11 M/9 F)	Drug-naïve FES	N/R	N/R	90	25	54.4% (49 M/41 F)	GH, PRL, TSH
Ryan et al. (2004)	Ireland	RIA	12	33.6	58.3% (7 M/5 F)	Drug-naïve FES	N/R	BPRS: 36.7 ± 8.4	12	35.8	58.3% (7 M/5 F)	ACTH
Shrivastava et al. (2012)	India	RIA	38	29.1	47.4% (18 M/20 F)	Drug-naïve FES	N/R	N/R	31	22.1	64.5% (20 M/11 F)	PRL
Şimşek et al. (2017)	Turkey	EIA	23	14.3	34.8% (8 M/15 F)	Drug-naïve early onset FES (aged between 11 and 17 years)	N/R	N/R	23	14.7	34.8% (8 M/15 F)	ACTH
Song et al. (2014)	China	ECLIA	60	24.6	53.3% (32 M/28 F)	Drug-naïve FES	7.3 months	PANSS: 72.2 ± 5.6	60	26.2	55.0% (33 M/27 F)	PRL

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Type of assay	Subjects with FEP						Healthy controls			Hormones measured
			Sample size *N*	Mean age *years*	Proportion of males *% (M/F)*	Sample characteristics	Mean DUP *months*	Severity score (PANSS/ BPRS) *total score*	Sample size *N*	Mean age *years*	Proportion of males *% (M/F)*	
Studerus et al. (2021)	Spain, Switzerland	ECLIA	87	25.7	64.4% (56 M/31 F)	Drug-naïve non-affective FEP	N/R	N/R	45	28.0	53.3% (24 M/21 F)	PRL
van Venrooij et al. (2012)	The Netherlands	CLIA	11	23.7	100% (11 M/0 F)	Drug-naïve FES (n = 8) or schizophreniform disorder (n = 3)	3.0 months	PANSS: 73.8 ± 16.1	15	22.4	100% (15 M/0 F)	ACTH
Walsh et al. (2005)	Ireland	RIA	10	26.8	100% (10 M/0 F)	Drug-naïve FES	18.5 months	BPRS: 42.9 ± 5.4	10	25.0	100% (10 M/0 F)	ACTH
Yalçin et al. (2016)	Turkey	CLIA	45	33.6	48.9% (22 M/23 F)	Drug-naïve FES	N/R	PANSS: 94.5 ± 16.7	45	N/R	48.9% (22 M/23 F)	PRL
Yang et al. (2018)	China	CLIA	79	34.3	0% (0 M/79 F)	Drug-naïve FES	N/R	PANSS: 84.2 ± 12.9	35	37.0	0% (0 M/35 F)	PRL
Yesilkaya et al. (2021)	Turkey	CLIA	65	27.4	69.2% (45 M/20 F)	Drug-naïve FES	N/R	PANSS: 107.4 ± 28.9	65	26.7	63.1% (41 M/24 F)	ACTH
Yuan et al. (2016)	China	ECLIA	81	26.6	48.1% (39 M/42 F)	Drug-naïve FES	8.5 months	PANSS: 85.5 ± 8.1	70	25.6	42.9% (30 M/40 F)	FSH, LH, PRL
Zhang et al. (2016)	China	ECLIA	31	25.6	48.4% (15 M/16 F)	Drug-naïve FES	N/R	PANSS: 87.6 ± 12.5	71	30.2	45.1% (32 M/39 F)	PRL
Zhu et al. (2020)	China	ECLIA	92	27.2	78.3% (72 M/20 F)	Drug-naïve FES	1.0 months	PANSS: 85.7 ± 9.8	154	37.3	60.4% (93 M/61 F)	ACTH, TSH

CLIA = chemiluminescent immunoassay; CMIA = chemiluminescent microparticle immunoassay; ECLIA = electrochemiluminescence immunoassay; EIA = enzyme immunoassay; ELISA = enzyme-linked immunosorbent assay; IRMA = immunoradiometric assay; RIA = radioimmunoassay.
BPRS = Brief Psychiatric Rating Scale; DUP = duration of untreated psychosis; FEP = first-episode psychosis; FES = first-episode schizophrenia; NOS = not otherwise specified; N/R = not reported; PANSS = Positive and Negative Syndrome Scale.
† Data available for n = 13 participants only.

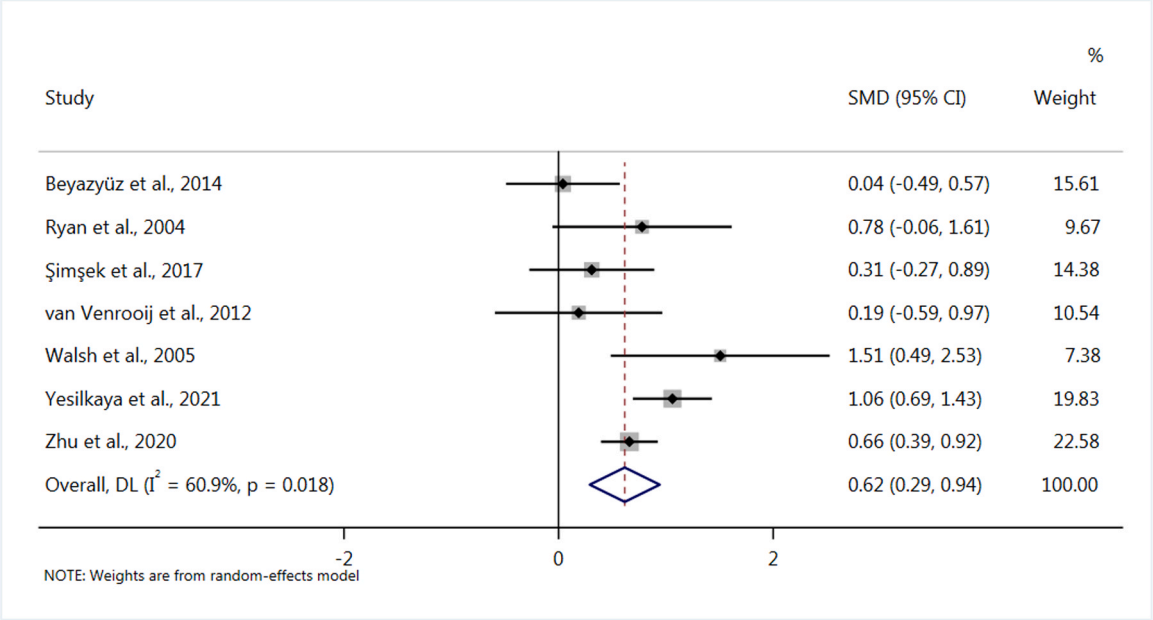

Fig. 2. Forest plot of the meta-analysis on blood concentrations of adrenocorticotrophic hormone (ACTH) in drug-naïve people with first-episode psychosis as compared with healthy controls.

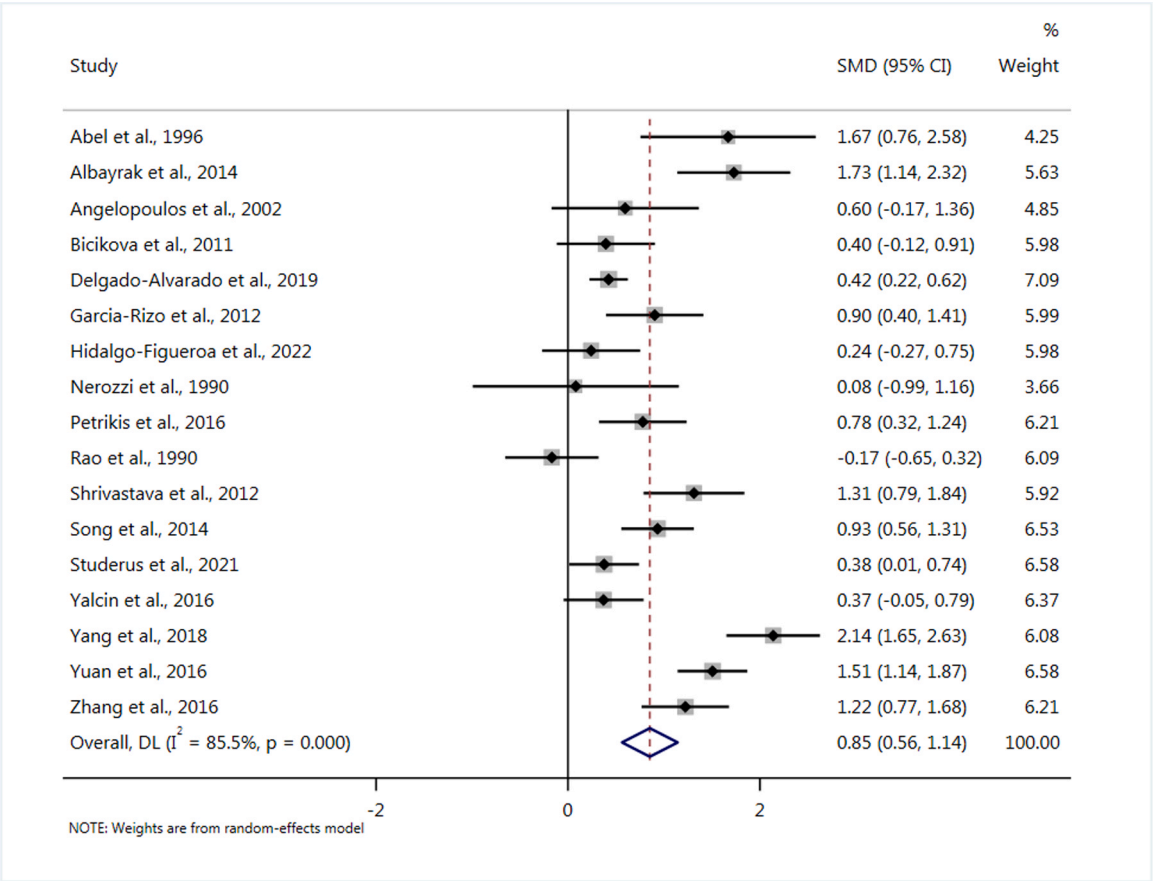

Fig. 3. Forest plot of the meta-analysis on blood concentrations of prolactin (PRL) in drug-naïve people with first-episode psychosis as compared with healthy controls.

sex (k = 3; N = 256; SMD = –0.27; 95%CI: –0.54 to 0.01; p = 0.06; I^2 = 2.6%). However, the results of the overall analysis were confirmed when considering age comparability (k = 4; N = 321; SMD = –0.38; 95%CI: –0.69 to –0.08; p = 0.015; I^2 = 45.3%), representativeness (k = 5; N = 431; SMD = –0.40; 95%CI: –0.65 to –0.16; p = 0.001; I^2 = 29.4%), and diagnostic assessment (k = 5; N = 571; SMD = –0.33; 95%CI: –0.58

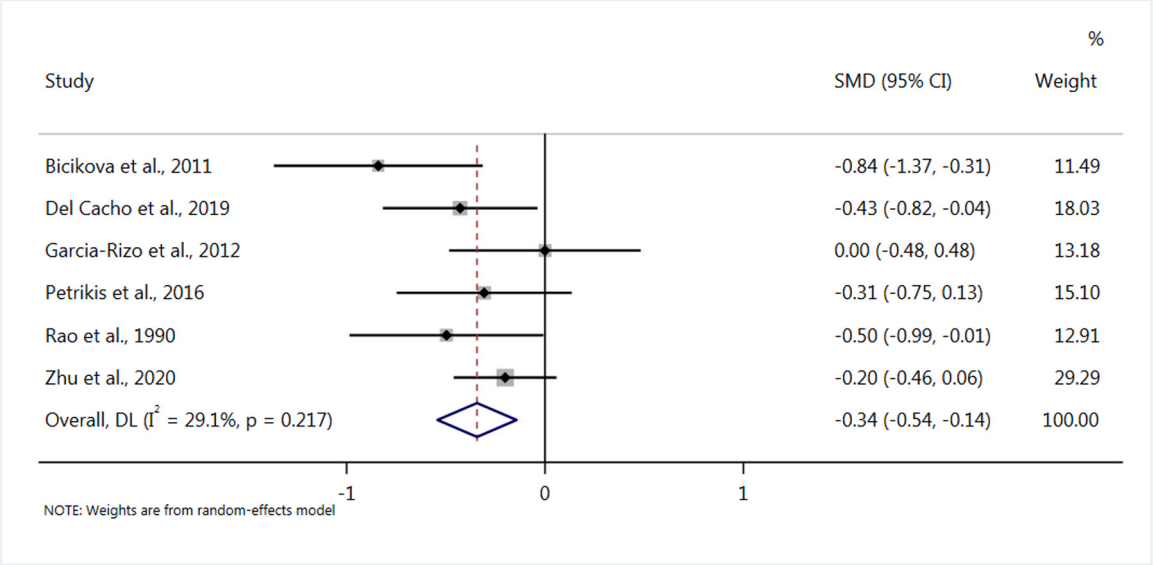

Fig. 4. Forest plot of the meta-analysis on blood concentrations of thyroid-stimulating hormone (TSH) in drug-naïve people with first-episode psychosis as compared with healthy controls.

to –0.09; p = 0.008; I^2 = 40.4%) (Supplementary Table 3).

Sex-based analyses could not be performed since data stratified by sex were available only from two studies (Bicikova et al., 2011; Zhu et al., 2020).

4. Discussion

4.1. Summary and interpretation of findings

To our knowledge, this is the first comprehensive quantitative synthesis of the existing body of evidence on the blood concentrations of anterior pituitary hormones in drug-naïve people with FEP. Benefiting from published and unpublished data from 26 eligible studies, several major findings emerged. First, pooled data from seven studies showed higher ACTH concentrations in drug-naïve people with FEP, with a medium-to-large effect size. Second, pooling results from 17 studies, we found significantly higher PRL concentrations in drug-naïve people with FEP in comparison to HCs, with a large effect size. No moderating role of age, sex, or symptom severity was found. Third, TSH concentrations were found to be lower in drug-naïve people with FEP compared to HCs, with a small-to-medium effect size. A possible – though slight – influence of sex comparability between index and control groups on the overall estimate of TSH levels was found. Lastly, data available on FSH, LH, and GH blood concentrations were not sufficient to carry out meta-analyses, preventing us to make any consideration regarding these three hormones in drug-naïve FEP.

The findings of this meta-analysis should be interpreted considering the potential neurobiological underpinnings of the estimated variations of ACTH, PRL, and TSH in FEP. The HPA axis represents the main biological system involved in stress response (Stephens and Wand, 2012). Hence, its assessment is critical for a better understanding of the biological mechanisms leading from stressful experiences to the onset of schizophrenia and other psychotic disorders (Borges et al., 2013; Mondelli et al., 2010). Our meta-analysis is the first to estimate higher ACTH concentrations in drug-naïve FEP, supporting the hypothesis of a basal over-activity of the HPA axis. Indeed, robust evidence from studies on FEP has shown elevated concentrations of cortisol (Misiak et al., 2021b), blunted cortisol awakening response, and non-suppression of cortisol secretion by dexamethasone (Borges et al., 2013). Such pattern indicates a dysregulation of the cortisol-driven negative feedback inhibition on pituitary ACTH secretion, suggesting that FEP might be characterized by an ACTH-dependent hypercortisolemia in a Cushing's disease-like manner (Lonser et al., 2017). Because of the cross-sectional nature of our data, it remains unclear whether the abnormal HPA axis response to stress in FEP is the consequence of the psychotic onset as such or, conversely, an enhanced stress response preceding FEP might represent a marker of biological vulnerability to environmental stimuli (Borges et al., 2013; Misiak et al., 2020; Misiak et al., 2017). Preliminary evidence seems to support the latter hypothesis (Borges et al., 2013) indeed, an impaired functioning of HPA axis is found in subjects at high risk for psychosis (Thompson et al., 2007), and the interaction between daily stressors and elevated cortisol levels may predict the subsequent onset of psychosis in this clinical population (Cullen et al., 2022).

Benefitting from the inclusion of ten additional, more recent studies, our work strengthens the findings of a previous meta-analysis (González-Blanco et al., 2016), showing higher blood concentrations of PRL in drug-naïve FEP on the basis of a large effect size, notably confirmed not only in males but also in females. Our findings seem to suggest that hyperprolactinemia in psychosis might be at least partly independent from – and not only secondary to – the D_2-blockade exerted by antipsychotic drugs. Consistently, increased baseline PRL levels have been found also in high-risk subjects who subsequently developed a psychotic disorder (Labad et al., 2015), suggesting that abnormalities in PRL secretion would even predate the psychotic experience. The release of PRL is part of the stress response (Levine and Muneyyirci-Delale, 2018) and is putatively linked to stress-induced alterations of dopaminergic and serotoninergic metabolism (Sonino et al., 2004). Thus, the increase in PRL might account – at least partially – for the concomitant increase in ACTH secretion (Levine and Muneyyirci-Delale, 2018). Although the larger pituitary volumes observed in FEP have historically been attributed to an increase in the size and number of ACTH-producing cells (Füchsl et al., 2013; Pariante et al., 2005), it has been shown that pituitary volume is sensitive also to the activation of lactotroph cells (MacMaster et al., 2007; Pariante et al., 2005). Hence, it could be argued that the large increase in PRL secretion in drug-naïve FEP uncovered by our meta-analysis could contribute to pituitary enlargement as much as the increased production of ACTH.

Finally, our findings on lower TSH concentrations in drug-naïve people with FEP confirm previous evidence (Misiak et al., 2021a). Once again, cortisol stress response seems to exert an inhibitory influence on blood TSH levels (Dogansen et al., 2018; Mathioudakis et al., 2012; Roelfsema et al., 2009), possibly due to both hypercortisolemia-induced

decrease in thyrotropin-releasing hormone gene expression (Alkemade et al., 2005) and blunted TSH response to thyrotropin-releasing hormone (Dogansen et al., 2018; Paragliola et al., 2021). Hypercortisolism might also mediate the inhibition of peripheral deiodination of thyroid hormones (Xiang et al., 2019), consistently with previous evidence of decreased levels of fT3 and elevated levels of fT4 in FEP (Misiak et al., 2021a). Moreover, the dopaminergic system, which is interconnected with the HPT axis, holds a direct effect on pituitary thyrotropic cells by downregulating TSH (Dogansen et al., 2018; Mohammadi et al., 2021).

4.2. Clinical and research implications

The findings of our meta-analysis highlight the importance of monitoring anterior pituitary hormones, whose imbalances may have clinical consequences since the first phases of schizophrenia along with other endocrine, metabolic, and inflammatory parameters (Misiak et al., 2021c, 2019). A dysregulation of the HPA axis, causing hypercortisolism, can lead to several health sequelae, including impaired glucose homeostasis and diabetes, hypertension, central obesity, osteoporosis, menstrual disturbances, higher inflammatory burden, and loss of cognitive performance (Melmed, 2020; Misiak et al., 2021d, 2020; Russell and Lightman, 2019). Elevated PRL levels, suppressing gonadotropins, can cause sexual disfunctions in both females and males, affecting desire, arousal, erection, ejaculation, and orgasm, all major reasons for poor quality of life in people with psychotic disorders (Marques et al., 2012; Riecher-Rössler, 2017). Hyperprolactinemia also leads to infertility and galactorrhea, and – in the longer term – to reduced bone density with osteoporosis, increased cardiovascular risk, and possible cognitive disturbances (Melmed, 2020; Riecher-Rössler, 2017). Finally, thyroid metabolism has effects on cardiovascular function, body weight regulation, sleep, thermoregulation, inflammation, and immune response (De Luca et al., 2021). All these abnormalities, with their impact on the general health of the patient, need to be taken into account among people with schizophrenia, considering also the additional metabolic burden driven by antipsychotic treatment (Bartoli et al., 2015a, 2015b; Riboldi et al., 2022) and unhealthy behaviors such as poor diet, smoking, lack of physical exercise, and alcohol and drug abuse (Carrà et al., 2016, 2014). Anterior pituitary hormone profile should be carefully scrutinized when assessing people in the earlier stages of psychotic disorders, even before the administration of antipsychotics (Riecher-Rössler, 2017). Indeed, abnormalities of anterior pituitary hormone secretion and relevant metabolic axes are found also in other severe mental conditions such as bipolar disorder (e.g., Daban et al., 2005) and major depressive disorder (e.g., Choi et al., 2018). However, research has to identify specific differences between FEP and first-episode affective spectrum disorders yet (Petruzzelli et al., 2020). Comparisons across various clinical populations might provide additional insights, especially as to whether abnormal concentrations of pituitary hormones are specific markers of FEP or are more generically linked to stress underlying severe mental disorders (Russell and Lightman, 2019; Davis et al., 2017).

4.3. Limitations

Some limitations should be acknowledged when interpreting the findings of our meta-analysis. First, the cross-sectional nature of the included studies does not allow any causal inference about the relationship between pituitary hormone concentrations and FEP. Second, although the included samples seemed satisfactorily consistent in terms of main characteristics, some meta-analyses were characterized by moderate (ACTH) or high (PRL) heterogeneity. Moreover, apart from the meta-analysis on PRL (for which the estimated probability was low), the relatively small number of included studies precluded a thorough evaluation of potential publication bias. In addition, while we tested the effects of some potential correlates such as age, sex, and symptom severity in analyses on PRL, we could not assess their role for the other hormones due to the shortage of relevant data. Finally, it should be considered that other characteristics, such as the duration of untreated psychosis, the type of assay used to measure hormone blood levels, or clinical variables (e.g., body mass index, physical comorbidities, cigarette smoking, substance use (Carrà et al., 2016, 2014)), were explored by a limited number of studies, making it impossible to assess their role on the concentrations of anterior pituitary hormones in FEP.

5. Conclusions

Drug-naïve people with FEP have altered blood pituitary hormone profiles, with higher ACTH and PRL as well as lower TSH. Our findings suggest that anterior pituitary metabolism is likely to be involved in the onset of schizophrenia spectrum and other psychotic disorders. However, further research is needed, particularly on the least investigated anterior pituitary hormones, to explore possible biological and clinical moderators of this complex relationship.

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CRediT authorship contribution statement

Daniele Cavaleri: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft; **Chiara A. Capogrosso**: Data curation, Investigation, Visualization, Writing - review & editing; **Pierluca Guzzi**: Data curation, Investigation, Writing - review & editing; **Gianna Bernasconi**: Data curation, Investigation, Writing - review & editing; **Martina Re**: Data curation, Investigation, Writing - review & editing; **Błażej Misiak**: Methodology, Writing - review & editing; **Cristina Crocamo**: Formal analysis, Software, Visualization, Writing - review & editing; **Francesco Bartoli**: Methodology, Project administration, Writing - review & editing; **Giuseppe Carrà**: Project administration, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106392.

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