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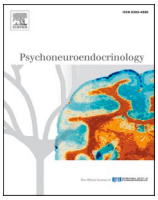

Prolactin and morning cortisol concentrations in antipsychotic naïve first episode psychosis: A systematic review and meta-analysis

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ABSTRACT

Importance: Alterations in prolactin and cortisol levels have been reported in antipsychotic naïve patients with first episode psychosis (FEP). However, it has been studied in very small samples, and inter-group variability has never been studied before.
Objective: To provide estimates of standardized mean differences (SMD) and inter-group variability for prolactin, cortisol awakening response (CAR) and morning cortisol concentrations in antipsychotic naïve FEP (AN-FEP) patients and healthy controls (HC).
Data sources: BIOSIS, KCI, MEDLINE, Russian Science Citation Index, SciELO, Cochrane, PsycINFO, Web of Science were searched from inception to February 28, 2022.
Study selection: Peer-reviewed cohort studies that reported on prolactin or cortisol blood concentrations in AN-FEP patients and HC were included.
Data extraction and synthesis: Study characteristics, means and standard deviations (SD) were extracted from each article. Inter group differences in magnitude of effect were estimated using Hedges g. Inter-group variability was estimated with the coefficient of variation ratio (CVR). In both cases estimates were pooled using random-effects meta-analysis. Differences by study-level characteristics were estimated using meta-regression. PRISMA guideline was followed (No. CRD42022303555).

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Main outcomes and measures: Prolactin, CAR and morning cortisol blood concentrations in AN-FEP group in relation to HC group.
Results: Fourteen studies for prolactin (N = 761 for AN-FEP group, N = 687 for HC group) and twelve studies for morning cortisol (N = 434 for AN-FEP group, N = 528 for HC group) were included. No studies were found in CAR in AN-FEP patients. Mean SMD for prolactin blood concentration was 0.88 (95% CI 0.57, 1.20) for male and 0.56 (95% CI 0.26, 0.87) for female. As a group, AN-FEP presented greater inter-group variability for prolactin levels than HC (CVR=1.28, 95% CI 1.02, 1.62). SMD for morning cortisol concentrations was non-significant: 0.34 (95% CI −0.01, 0.69) and no inter-group variability significant differences were detected: CVR= 1.05 (95% CI 0.91, 1.20). Meta-regression analyses for age and quality were non-significant. Funnel plots did not suggest a publication bias.
Conclusions and relevance: Increased prolactin levels were found in AN-FEP patients. A greater inter-group variability in the AN-FEP group suggests the existence of patient subgroups with different prolactin levels. No significant abnormalities were found in morning cortisol levels. Further research is needed to clarify whether prolactin concentrations could be used as an illness biomarker.

1. Introduction

Schizophrenia is a chronic and debilitating disease with a lifetime prevalence of around 0.9% (Perälä, 2007) and an economic burden of over US$60 billion per year in the US (Marcus and Olfson, 2008). In recent years, evidence has shown a wide range of organic alterations in patients with schizophrenia, not only in the central nervous system (Pillinger, D'Ambrosio, 2019) but also affecting cardiometabolic parameters, (Greenhalgh, 2016; Pillinger, 2017) as well as immune, (Goldsmith, 2016; Upthegrove, 2014) and in the pituitary-hypothalamus-adrenal axis (Chaumette, 2015; González-Blanco, 2016). Some of these alterations are related with the effects derived from the lifestyle associated with the disease itself (such as smoking (Sagud, 2019), or a sedentary lifestyle, linked to the negative symptoms (Correll, 2014)) or with antipsychotic treatment (Newcomer, 2007; Rojo, 2015). There is, however, less evidence regarding the presence of organic alterations in early phases of the disease, unrelated to its treatment.

This is the case for prolactin, a polypeptide hormone, the synthesis and secretion of which is regulated for the most part by dopaminergic neurons in the anterior pituitary (Freeman, 2000). Dopamine projections originating in the midbrain can be divided into two broad groups, those that project to the striatum and those that project to the cortex. Dopamine plays a major role in the pathophysiology of schizophrenia with evidence of both increased dopamine signaling from striatal projections, and reduced signaling from cortical ones (Howes, 2016). However, the situation for the tuberoinfundibular pathway, which innervates the anterior pituitary, is unclear. Dopamine inhibits prolactin release, which accounts for the fact that treatment with drugs that block D2 receptors (such as the vast majority of antipsychotics (Halbreich, 2003)) produce an increase in prolactin concentrations (Zhu, 2021). In antipsychotic naïve individuals decreased prolactin levels would suggest a hyperactivity of the tuberoinfundibular pathway similar to what is seen in the striatum, whereas raised levels would suggest the pattern of disruption is more in keeping with what is observed in cortex. Furthermore, characterizing prolactin levels it is also of interest, given that hyperprolactinemia can have serious adverse effects on general health such as amenorrhea (Klein, 2019), sexual disfunction (Drobnis and Nangia, 2017), osteoporosis (Samperi, 2019) and possibly breast cancer (De Hert, 2016; Ferrán Catalá-López, 2014). In addition, an increase in prolactin in situations of psychosocial stress has been described in healthy men and women (Lennartsson and Jonsdottir, 2011; Sonino, 2004).

Cortisol is a steroid hormone primarily synthetized in the adrenal cortex that also shows an increase in concentration in response to stress (Chrousos, 2009). It is released according to a diurnal circle, and several studies have shown cortisol abnormalities, such as elevated levels of morning cortisol (Girshkin, 2014; Venkatasubramanian, 2010; Yıldırım, 2011) or a capped response in cortisol awakening response (CAR) (Berger, 2016) in patients with stablished psychosis relative to healthy controls, although not all studies have replicated these results (Garcia-Rizo, 2011; van Venrooij, 2012). As in the case of prolactin, these abnormalities seem to be strongly influenced by antipsychotic medication (Hempel, 2010).

It is much less clear whether the disturbances in these hormones are already present in early stages of untreated psychosis. Some studies (Greenhalgh, 2016) have previously looked at these alterations in FEP populations. However, those systematic reviews included smaller samples, often containing both antipsychotic treated and antipsychotic-naïve patients.

Another unanswered question is whether these abnormalities are homogeneous across patients or heterogeneity exists. Former studies have found significant heterogeneity of striatal dopamine function in antipsychotic-naïve schizophrenia patients(Brugger, 2020), as well as in immune(Pillinger, Osimo, 2019) and metabolic (Pillinger, 2022) parameters. However, variability analyses have not been previously performed for prolactin and cortisol levels, and finding endocrine alterations specific to a subgroup of patients would suggest these parameters may have potential as response or prognosis biomarkers, potentially identifying a subgroup of patients with greater alterations in dopaminergic pathways in the case of prolactin, or with higher sensitivity to stress in the case of cortisol. To address these questions, we performed a systematic review and meta-analysis of blood prolactin concentrations, morning blood cortisol concentrations, and cortisol awakening response in antipsychotic naïve first episode of psychosis patients compared to healthy controls.

2. Methods

This study protocol was registered on PROSPERO (registration number: CRD42022303555). The study was conducted in accordance with "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) (Moher, 2009) (Table S1) and "Meta-analyses of Observational Studies in Epidemiology" (MOOSE) checklist (Stroup, 2000) (Table S2), following "EQUATOR Reporting Guidelines" (Altman, 2008).

2.1. Search strategy and selection criteria

A systematic literature search was carried out by two independent researchers (C.A. and M.P.). Web of Science database (Clarivate Analytics) was searched, incorporating the Web of Science Core Collection, the BIOSIS Citation Index, the KCI-Korean Journal Database, MEDLINE®, the Russian Science Citation Index, and the SciELO Citation Index as well as Cochrane Central Register of Reviews, and Ovid/PsycINFO databases, from inception until February 28th, 2022.

The following keywords were used: "Psychosis" OR "Schizophr*" AND "Prolactin" OR "Cortisol*".

Articles identified were first screened as abstracts, and after excluding those that did not meet the inclusion criteria, the full texts of

the remaining articles were assessed for eligibility and inclusion.

Inclusion criteria for the systematic review and meta-analysis were (a) individual studies with original data, (b) comparing patient groups with a healthy control group, and (c) patients meeting criteria for a first-episode of psychosis (defined as patients presenting with psychosis under 5 years from onset, according to DSM-5-TR (Anonymous, 2022) or ICD-11 (World Health Organization, 2019) criteria, on their first treatment contact), who have a maximum lifetime antipsychotic exposure of 1 week, and no antipsychotic use in the 30 days prior to the study, (d) including validated peripheral measurements of blood prolactin levels, morning (extracted between 7 am and 10 am) cortisol levels or cortisol awakening response (CAR), (e) nonoverlapping samples (overlap was determined by looking at the inclusion dates, type of population and country in which the study was carried out), and the

Table 1
Articles included in the systematic review and meta-analysis for serum prolactin measures. Prolactin values are expressed in ng/ml. HC Healthy Controls; FEP First Episode Psychosis.

Author year	Country	N FEP	N HC	Age mean (SD)	Prolactin FEP (SD)	Prolactin HC (SD)	NOS	Conclusions
(Abel, 1996)	United Kingdom	13	13	30.6 (2.55)	11.31 (0.41)	8.86 (0.38)	7	Prolactin responses were enhanced in FEP compared to HC and were correlated positively with BPRS items for depression, anxiety and guilt.
(Albayrak, 2014)	Turkey	♂ 30	♂ 32	26.06 (6.00)	♂ 34.1 (19.9)	♂ 9.7 (2.3)	7	Higher serum prolactin levels were found in male FES compared with male HC.
(Angelopoulos, 2002)	Greece	♂ 16	♂ 12	26.07 (5.17)	♂ 9.3 (5.5)	♂ 6.6 (2.1)	8	Prolactin responses to haloperidol challenge in the drug-free state were lower in the schizophreniform group than in the control and the schizophrenic groups.
(Bicikova, 2011)	Czech Republic	22 ♂ 13 ♀ 9	47 ♂ 22 ♀ 25	30.28 (5.93)	12.25 (6.82) ♂ 11.49 (6.86) ♀ 13.33 (6.62)	9.71 (4.98) ♂ 10.87 (2.35) ♀ 8.68 (6.29)	9	No significant difference was found in prolactin levels between FEP and HC groups.
(Del Cacho, 2019)	Spain	61 ♂ 38 ♀ 23	45 ♂ 25 ♀ 20	25.89 (9.69)	86.67 (101.99) ♂ 80.09 (68.15) ♀ 94.71 (143.02)	40.56 (67.77) ♂ 31.54 (54.10) ♀ 51.32 (81.4)	8	This study showed significantly higher levels of prolactin in drug-naïve patients compared to healthy controls.
(Delgado-Alvarado, 2018)	Spain	270 ♂ 137 ♀ 133	153 ♂ 93 ♀ 60	30.77 (9.51)	18.57 (15.54) ♂ 13.4 (9.3) ♀ 23.2 (18.3)	12.55 (8.49) ♂ 10.2 (5.0) ♀ 16.2 (11.1)	6	Antipsychotic naïve FEP patients have increased levels of prolactin compared to HC, which might be stress-induced.
(Gaber, 2020)	Egypt	♂ 40	♂ 40	34.64 (9.58)	♂ 26.06 (10.7)	♂ 17.75 (9.1)	6	In first-episode psychotic patients, the IIEF-5 score and total testosterone levels were significantly lower, while serum prolactin levels were higher than in HC.
(Garcia-Rizo, 2011)	Spain	33 ♂ 20 ♀ 13	33 ♂ 21 ♀ 12	27.7 (6.41)	22.9 (19.4) ♂ 15.1 (9.1) ♀ 35.1 (24.7)	9.8 (5.8) ♂ 7.6 (2.7) ♀ 13.6 (7.7)	8	Increased prolactin concentrations in antipsychotic-naïve FEP do not appear to be due to important confounding variables, or to the effects of elevated TSH, ghrelin, or cortisol.
(Petrikis, 2016)	Greece	40 ♂ 27 ♀ 13	40 ♂ 27 ♀ 13	32.4 (9.46)	28.77 (41.46) ♂ 14.4 (10.67) ♀ 17.0 (14.31)	15.25 (22.69) ♂ 8.2 (2.32) ♀ 11.4 (4.56)	9	A higher serum prolactin level was found in drug naïve FEP compared to HC.
(Rao, 1990)	Germany	20 ♂ 11 ♀ 9	90 ♂ 49 ♀ 41	26.45 (7.21)	9.35 (4.61) ♂ 7.43 (2.93) ♀ 11.7 (5.18)	10.75 (8.54) ♂ 6.75 (3.6) ♀ 15.53 (10.13)	8	Prolactin was higher in neuroleptic-treated men compared to drug-free male patients or HC.
(Srivastava)	India	38 ♂ 18 ♀ 20	60 ♂ 30 ♀ 30	N.A.	38.86 (21.77) ♂ 28.37 (11.26) ♀ 48.31 (24.46)	16.29 (8.33) ♂ 12.2 (5.05) ♀ 23.72 (7.98)	7	Prolactin levels in male but not female FEP at baseline were twice those of HC.
(Song, 2014)	China	60 ♂ 32 ♀ 28	60 ♂ 33 ♀ 27	25.4 (5.17)	30.42 (13.01) ♂ 28.61 (11.74) ♀ 32.48 (14.05)	20.91 (6.15) ♂ 16.21 (3.07) ♀ 26.66 (3.54)	8	Patients with normal weight, drug-naïve, first-episode schizophrenia present elevated serum levels of prolactin.
(Studerus, 2021)	Switzerland / Spain	87 ♂ 56 ♀ 31	45 ♂ 24 ♀ 21	26.48 (9.58)	22.74 (26.32) ♂ 16.59 (8.6) ♀ 33.84 (40.23)	14.47 (8.81) ♂ 10.72 (4.84) ♀ 18.75 (10.25)	6	FEP patients have higher stress levels than HC and frequently have hyperprolactinemia. There was no significant association between self-perceived stress and prolactin levels.
(Zhang, 2016)	China	31	71	28.8 (5.46)	51.3 (43.29)	20.04 (10.76)	8	A higher serum prolactin level was found in drug naïve FEP compared to HC.

study with the largest sample was then selected, and (f) written in English language. Exclusion criteria were (a) reviews, clinical cases, study protocols or qualitative studies, conferential proceedings, letters, and commentaries, (b) reporting on patients with multiple episodes of psychosis, (c) reporting on patients with an affective psychotic disorder, and (d) including patients previously or currently exposed to antipsychotic medication, and (d) written in languages other than English.

2.2. Data extraction

Three researchers (B.P., M.L. and J.H.) independently extracted data from all the included studies. The three databases were then cross-checked, and discrepancies were resolved through consensus under the supervision of a senior researcher (A.C.). A summary of selected variables included: first author and year of publication, country and city, sample size, age (mean ± standard deviation [SD], sex (% female), duration of untreated psychosis, clinical diagnosis, treatment, type of biological sample, quality assessment (see below), and key findings. When stratified data was available, data were extracted separately for male and female populations.

2.3. Risk of bias (quality) assessment

Risk of bias was assessed using Newcastle-Ottawa Scale for cross-sectional and cohort studies (Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al., 2012) (Table S3).

2.4. Strategy for data synthesis and statistics

First, we provided a systematic synthesis (Tables 1 and 2) of the findings from the included studies.

Second, we performed meta-analyses where data allowed for it. The comparison of effect sizes in each group was calculated using effect size (ES) formula. A positive ES indicates the AN-FEP group have higher serum prolactin or morning cortisol levels than the control. Effect sizes were calculated using the means, standard deviations (SDs), and sample sizes for the outcomes of interest for each sample. Meta-regressions were performed to determine the effect of the (a) age, and (b) Newcastle-Ottawa Scale (NOS) score on the outcomes of interest. Heterogeneity among studies was assessed using the Q statistic, with the proportion of the total variability in effect size estimates evaluated using the I^2 index, classifying the heterogeneity as low (I^2 =25%), medium (I^2 =50%), and high (I^2 =75%) (Lipsey and Wilson, 2009). Sensitivity analyses were performed to determinate the differences depending on sex. Estimates comparisons among subgroups (male vs female) were performed using Wald-type tests. The random-effects model was used. Publication bias was assessed by visually inspecting funnel plots.

Inter-group variability was assessed by investigating the CVR (the logarithm of the ratio of the coefficients of variation, termed the log "CV ratio") across the different outcomes of interest in AN-FEP individuals compared to HC. A CVR of 1 demonstrates equal variability in the outcomes of interest in the AN-FEP group than in the HC group, whereas a CVR greater than 1 indicates greater variability in the AN-FEP group.

All analyses were conducted within R 1.4.1106 (R Foundation for Statistical Computing, 2021). CVR analyses were performed using the metafor package (Viechtbauer, 2015). The significance level was set at a $p < 0.05$, two-sided.

3. Results

3.1. Serum prolactin

The literature search yielded 3022 citations through electronic database, which were screened for eligibility; 102 articles were assessed in full text, and 88 were excluded. The final database for the systematic review and meta-analysis included 14 studies (Table 1) (Abel, 1996; Albayrak, 2014; Angelopoulos, 2002; Bicikova, 2011; Del Cacho, 2019; Delgado-Alvarado, 2018; Gaber, 2020; Garcia-Rizo, 2011; Petrikis, 2016; Rao, 1990; Song, 2014; Srivastava; Studerus, 2021; Zhang, 2016), on which 12 report stratified results for male population (Albayrak, 2014; Angelopoulos, 2002; Bicikova, 2011; Del Cacho, 2019; Delgado-Alvarado, 2018; Gaber, 2020; Garcia-Rizo, 2011; Petrikis, 2016; Rao, 1990; Song, 2014; Srivastava; Studerus, 2021) and 9 for female population (Bicikova, 2011; Del Cacho, 2019; Delgado-Alvarado, 2018;

Table 2
Articles included in the systematic review and meta-analysis for morning cortisol measures. Morning cortisol values are expressed in mcg/dl. HC Healthy Controls; FEP First Episode Psychosis.

Author year	Country	N FEP	N HC	Age mean (SD)	Cortisol FEP (SD)	Cortisol HC (SD)	NOS	Conclusions
(Beyazyüz, 2014)	Turkey	32	24	25.85 (5.5)	9.73 (3.59)	10.34 (3.65)	8	Blood levels of ACTH, cortisol, testosterone, and progesterone were similar among the FEP group and the HC.
(Bicikova, 2011)	Czech Republic	22	47	33.08 (5.93)	17.29 (2.82)	18.5 (4.99)	9	In male FEP patients, cortisol levels did not differ from HC. However, for female FEP patients a significantly higher cortisolemia was found compared to HC.
(Christou, 2021)	Greece	55	55	31.35 (8.8)	12.6 (4.5)	15.5 (4.9)	8	Serum cortisol levels and cortisol/DHEA-S ratio were statistically lower in FEP patients compared to HC.
(Fernandez-Egea, 2009)	Spain	50	50	29.1 (8.25)	19.0 (4.98)	20.2 (4.57)	8	Cortisol blood levels were slightly lower in the FEP group than in HC.
(Kale, 2009)	India	31	48	33.62 (8.73)	10.07 (4.1)	7.44 (3.42)	8	Plasma cortisol levels were also significantly higher in FEP patients as compared to HC.
(Rao, 1990)	Germany	20	90	26.45 (6.09)	20.3 (7.25)	21.02 (6.89)	8	Basal cortisol was not significantly different in FEP patients compared to HC.
(AimAek, 2017)	Turkey	23	23	14.5 (1.46)	9.93 (11.84)	5.7 (5.6)	8	No significant differences were found between the FEP patients and the HC in serum cortisol.
(Solanki, 2017)	India	30	20	25.74 (5.96)	9.1 (2.5)	7.88 (2.5)	8	No significant differences were found between the FEP patients and the HC in serum cortisol.
(Spelman, 2007)	Ireland	38	38	25.2 (5.66)	12.3 (4.3)	8.5 (2.4)	9	Serum cortisol was significantly higher in FEP patients compared with relatives and HC.
(Steiner, 2017)	Germany	24	24	31.56 (9.11)	32.15 (21.52)	20.35 (7.54)	8	FEP patients exhibit higher baseline cortisol levels and a blunted cortisol awakening response compared with HC.
(Venkatasubramanian, 2007)	India	44	44	32.75 (7.65)	16.2 (7.7)	9.5 (3.6)	8	FEP patients had a significantly higher mean cortisol level than HC.
(Yesilkaya, 2021)	Turkey	65	65	27.02 (7.4)	13.7 (5.59)	8.7 (4.03)	7	The levels of ACTH and cortisol were significantly higher in FEP patients compared to HC.

Garcia-Rizo, 2011; Petrikis, 2016; Rao, 1990; Song, 2014; Srivastava; Studerus, 2021), as it can be seen in Fig. S1A (PRISMA Flow Diagram) (PRISMA, 2021).

After allowing for overlapping studies, data were extracted for a total sample size of 761 patients (age range 14 – 56 years) and 687 controls (age range 14 – 64 years). Prolactin levels are elevated in antipsychotic naïve FEP, with an effect size of 0.92 (95% CI [0.43, 1.40]; p 0.0002), as shown in Fig. 1A. When stratifying the results by sex, prolactin was significantly increased for both groups, but this alteration was more prominent in males than in females, with effect sizes of 0.88 (95% [CI 0.57, 1.20]; $p < 0.0001$) and 0.56 (95% CI [0.26, 0.87]; p 0.0003), respectively (Fig. 1B and C). However, the difference between the two subgroups effect sizes' was not statistically significant (p 0.15).

The heterogeneity was significant with all of the studies included in the analysis ($I^2 = 93.96\%$; $p < 0.0001$). When results were stratified by sexes, heterogeneity remained significant for both female samples ($I^2 = 57.21\%$; $p < 0.026$) and male samples ($I^2 = 75.55\%$; $p < 0.0001$).

Meta-regressions showed no significant effect of age, NOS score or % of females. Funnel plots did not suggest the presence of a publication bias for any of the analyzed groups (Fig. S1).

The AN-FEP group also presented greater variability than HC in serum prolactin, both for the complete sample (CVR: 1.28; 95% CI [1.02, 1.62]; p 0.0002) and for male (CVR: 1.43; 95% CI [1.07, 1.91]; p 0.0001) and female (CVR: 1.76; 95% CI [1.29, 2.39]; $p < 0.0001$) populations, being this measure greater for the later (Fig. 2).

3.2. Morning cortisol

The literature search yielded 1660 citations through electronic database, which were screened for eligibility; 49 articles were assessed in full text, and 37 were excluded. The final database for the systematic review and meta-analysis included 12 studies (Table 2) (AimAek, 2017; Beyazyüz, 2014; Bicikova, 2011; Christou, 2021; Fernandez-Egea, 2009; Kale, 2009; Rao, 1990; Solanki, 2017; Spelman, 2007; Steiner, 2017; Venkatasubramanian, 2007; Yesilkaya, 2021), as it can be seen in Fig. 1B (PRISMA Flow Diagram).

After allowing for overlapping studies, data were extracted for a total sample size of 434 patients (age range 14 – 55 years) and 528 controls (age range 14 – 55 years). Morning cortisol did not significantly differ between AN-FEP patients and healthy controls (SMD: 0.34; 95% CI [−0.01, 0.69]; p 0.054), as shown in Fig. 3.

Heterogeneity was significant ($I^2 = 84.9\%$; $p < 0.0001$). Meta-regressions showed no significant effect of age and NOS score. Funnel plots did not suggest the presence of a publication bias (Fig. S3).

There was not a statistically significant difference in the variability between the two study groups (CVR: 1.05; 95% CI [0.91, 1.20]; p 0.071) (Fig. S4).

The literature search yielded no studies reporting on cortisol awakening response in antipsychotic-naïve AN-FEP patients, so there was no data available for meta-analysis.

4. Discussion

This is the first meta-analysis to date that includes the analysis of prolactin and morning cortisol blood concentrations in antipsychotic naïve patients with a first episode of psychosis, also assessing the intergroup variability of these concentrations compared to healthy controls.

We have found evidence that there is an increase in prolactin concentrations in AN-FEP patients, and that variability of prolactin concentrations is also increased in AN-FEP patients. These increases precede the introduction of medication and it is not explained by the age or sex of the patients. On the other hand, we have not observed a significant alteration in morning cortisol levels, nor a higher variability in the AN-FEP group compared to the HC group.

These abnormalities in prolactin concentrations are consistent with previous reports in the literature. However, such reports included a much smaller number of FEP patients included in this study, often mixing antipsychotic naïve and previously treated patients, and intergroup variability has never been analyzed before. González-Blanco et al. reported in a previous meta-analysis examining a smaller number of patients a significant increase in serum prolactin levels in antipsychotic naïve FEP patients, more pronounced in male patients (González-Blanco, 2016). Our study also found a greater estimated ES in males (0.88) than in females (0.56). However, differences between sexes were not statistically significant. Other studies that took into account combined cohorts of antipsychotic free and antipsychotic naïve patients also found a significant increase in the FEP group (Lally, 2017; PARIANTE, 2005), as well as hyperprolactinemia rates of up to 70% (Kahn, 2008).

As for morning cortisol concentrations, previous reports in the literature are inconclusive. Misiak et al. (Misiak, 2021) report in a recent meta-analysis (including both antipsychotic naïve and antipsychotic treated patients) a significant increase in morning cortisol in FEP populations, but not in ultra-high risk for psychosis (UHR-P) patients. On the other hand, Girshkin et al. (Girshkin, 2014) report an increase in cortisol levels in schizophrenia patients compared to HC. However, those patients were not antipsychotic naïve, and subgroup analyses already indicate a smaller effect size for FEP patients in relation to chronic patients.

There are several hypotheses that could explain an alteration in prolactin concentrations in AN-FEP patients. The synthesis and secretion of prolactin are mainly regulated by dopaminergic neurons in the anterior pituitary gland, which exerts an inhibitory effect on the release of this hormone (Kopelman, 2000). It is well known that dopaminergic transmission is disturbed in psychosis, and a significant heterogeneity of striatal dopamine function in AN-FEP patients has been described before (Brugger, 2020). Previous authors have suggested that raised prolactin levels in psychosis may be stress induced and that the increase in dopamine found in striatal projections in psychotic states could be, at least in part, a regulatory mechanism in order to down-regulate increased prolactin levels (Aston, 2010). Conversely it could be that psychosis is associated with reduced dopamine signaling within tuberoinfundibular pathways and this leads to raised prolactin levels. A further hypothesis would suggest the existence of a pre-existing genetic vulnerability, which predisposes, in situations of stress, both to an increase in prolactin and to the presentation of psychotic symptoms, through a dysregulation of dopaminergic pathways. The evidence of an increase in prolactin already in UHR-P populations (Aston, 2010; Montalvo, 2014; Vingerhoets, 2018), with an effect size intermediary to HC and those with the FEP and more pronounced in UHR-P who transition to psychosis (Labad, 2014), supports this theory. This does not necessarily apply to all FEP patients but may only affect a subgroup. Some authors have found a consistent association between plasma prolactin and measures of positive symptoms (Rajkumar, 2014), interpreting these results as a further dysregulation in dopaminergic pathways in patients with paranoid symptoms (Segal, 2007). However, it remains a highly controversial issue, refuted by others (Akhondzadeh, 2006). It remains unclear whether this increase in prolactin concentrations precedes the onset of psychotic symptoms. If that were the case, measuring baseline prolactin concentrations in antipsychotic-naïve UHR-P patients, or in those patients with prodromal symptoms, could prove a valuable biomarker. If that was not the case and the prolactin increase was parallel or subsequent to the psychotic symptoms debut, it should be investigated whether prolactin could be a marker of severity or greater presence of positive symptoms. Further lines of research should examine the existence and identification of potential subgroups within FEP samples by latent class analysis, as it has already been done for other potential markers such as aggressive behaviour or certain susceptibility genes (Holliday, 2009; Lau, 2019).

On the other hand, cortisol is regulated by the pituitary-hypothalamic-adrenal axis, with little influence of dopamine secretion (Lightman, 2020). Although both prolactin and cortisol have been called

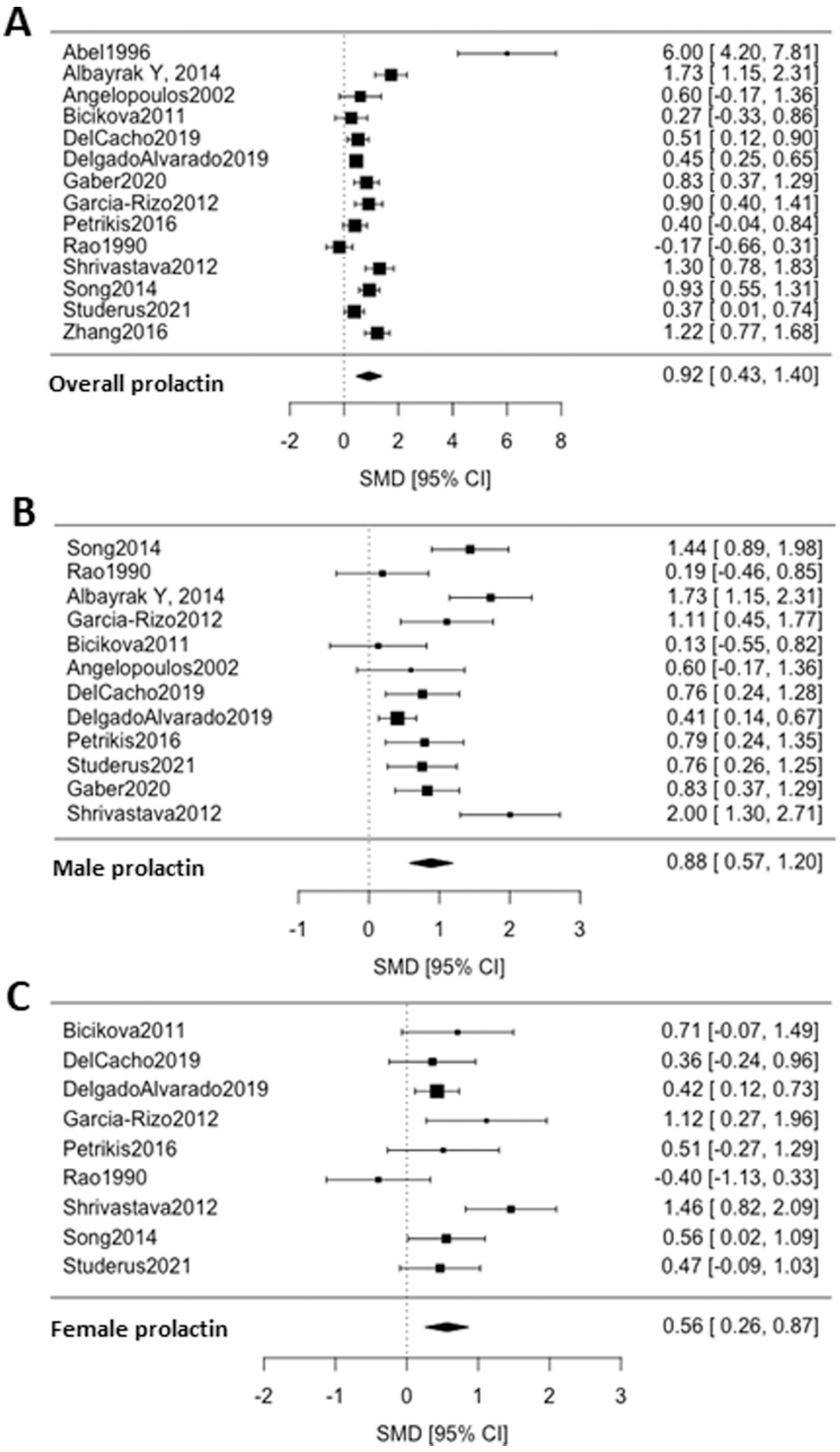

Fig. 1. Forest plot for the magnitude of blood prolactin alterations in antipsychotic naïve first episode psychosis vs. healthy controls (A). Stratified results are shown for male population (B) and female population (C).

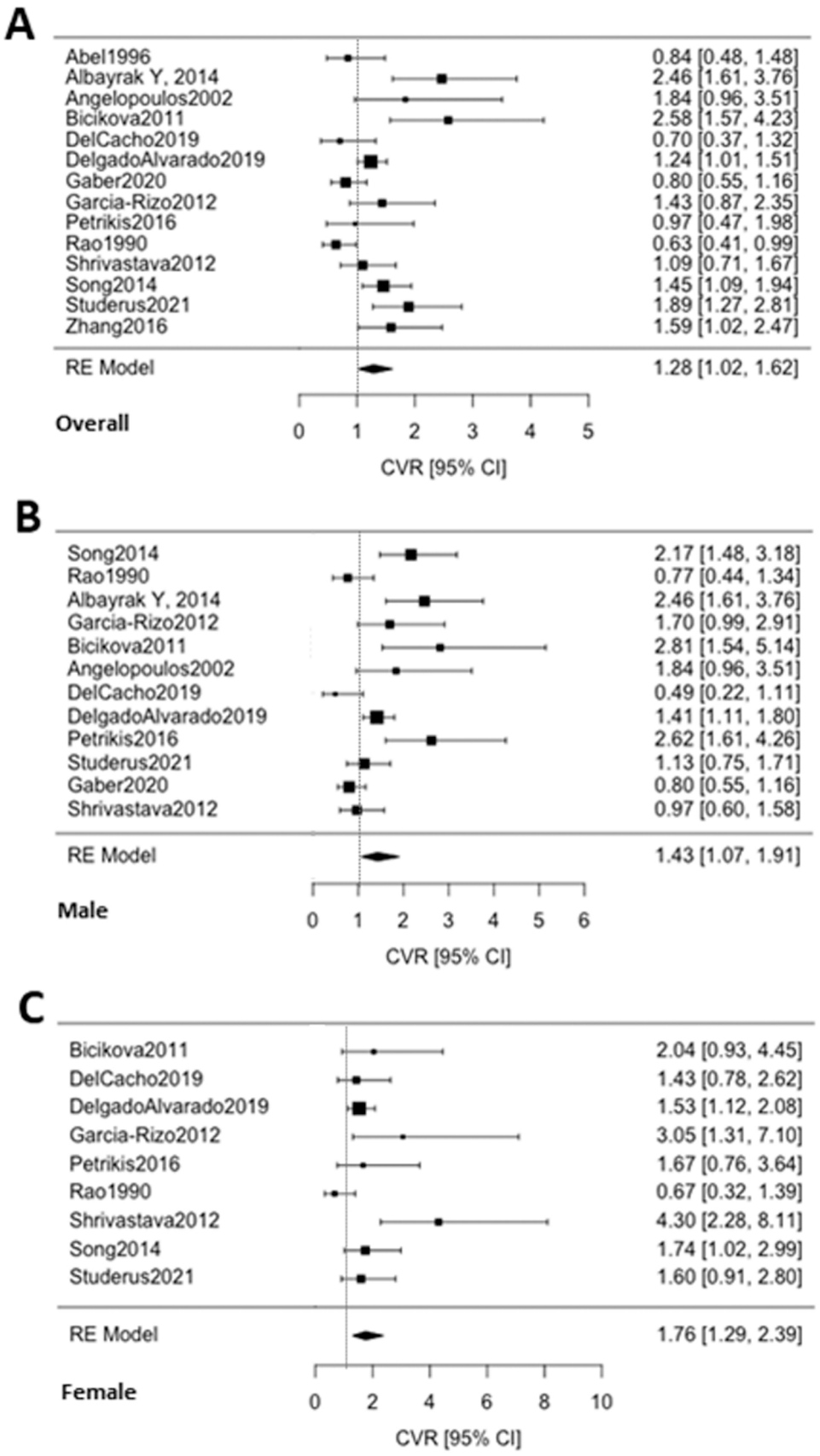

Fig. 2. Inter-group variability forest plot for blood prolactin concentrations in antipsychotic naïve first episode psychosis vs. healthy controls (A). Stratified results are shown for male population (B) and female population (C).

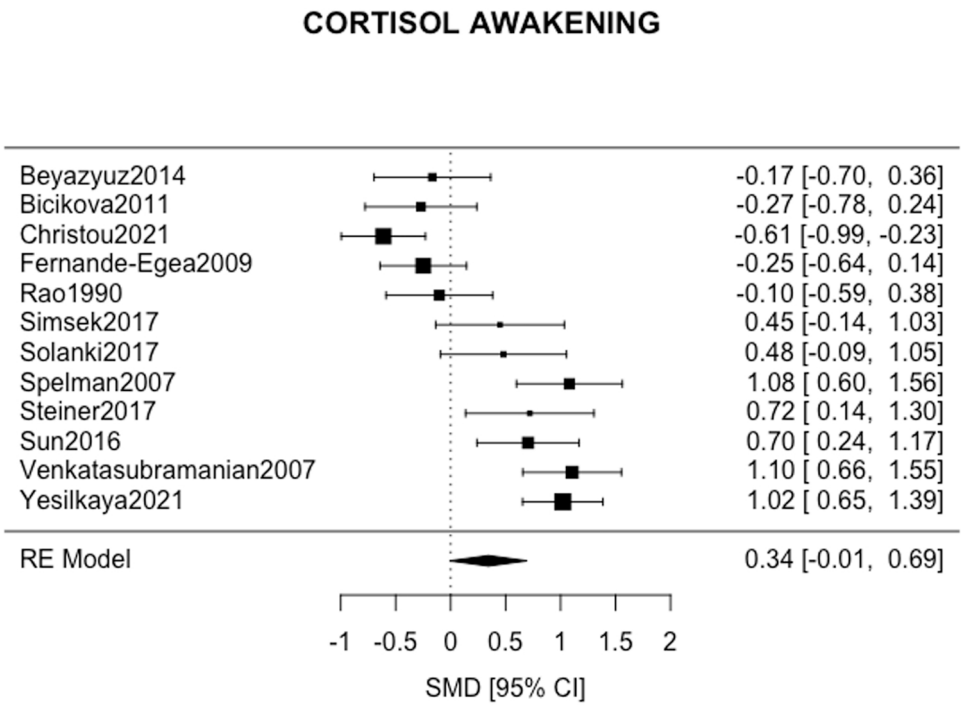

Fig. 3. Forest plot for the magnitude of morning cortisol alterations in antipsychotic naïve first episode psychosis vs. healthy controls.

stress hormones, proving to be elevated in situations of psychosocial stress – such as a FEP –, the independence of cortisol from the dopaminergic secretion could explain its absence of alteration in early phases of the disease. The presence of morning cortisol abnormalities in cohorts of patients with established psychosis (Duval, 2003; Jorgensen, 2013; Popovic, 2007) could indicate that this hormone may be elevated in later stages of the disease, and may play a role as a marker of evolution or severity. However, further research is needed to confirm or reject these hypotheses. Another interesting area for future investigation would be a sex difference analysis in the cortisol levels among the AN-FEP population, since not enough data was found to separately meta-analyze morning cortisol levels for both sexes.

No articles reporting on CAR were identified during the literature search, so no data was available to examine. Nevertheless, CAR seems to be a unique aspect of the diurnal cortisol rhythm that is not always connected to diurnal cortisol levels (Fries, 2009). A flattened CAR has previously been described in medicated patients with schizophrenia but not in individuals at ultra-high-risk mental states (Berger, 2016). In our opinion, it would be highly interesting to study CAR in AN-FEP and CHR-P populations to clarify if it could be a marker for a psychotic relapse or transition to psychosis.

4.1. Strengths and limitations

To the best of our knowledge, this systematic review and meta-analysis represents the most comprehensive synthesis to date on prolactin and baseline cortisol alterations in antipsychotic naïve, first episode psychosis patients, also analyzing inter-group variability. Focusing on this population, the confounding effects of illness course chronicity and treatment were limited. However, this study also has several limitations, the main one being the great heterogeneity present in our meta-analyses. Due to a lack of data, we were not able to address the effect of some known variables on prolactin levels, like BMI (Kopelman, 2000) and smoking (Xue, 2010), since most of the studies included in the meta-analyses matched their patients and control subjects without considering these variables. In addition, we included articles from a period comprising almost 30 years, so it is possible some methodological and laboratory factors could have an effect in the prolactin determinations from older articles. However, the random effects model used is robust to inconsistency, and would not explain our variability findings, because these reflect within-study variation (where methodological factors are the same in both patient and control groups in any given study). This reinforces the hypothesis of distinct subgroups in the FEP sample. Another limitation is related to the concept of first-episode psychosis. Although we excluded in our search those patients with an affective diagnosis of psychosis, our review still includes heterogeneous samples, including patients with several different psychotic disorders.

4.2. Implications

The implications of these findings are multiple. The existence of an increase in prolactin levels in AN-FEP patients highlights the need to use treatment strategies that do not aggravate this hyperprolactinemia, whose adverse effects at the organic level are well known (De Hert, 2016; Drobnis and Nangia, 2017; Ferrán Catalá-López, 2014; Klein, 2019). In addition, peripheral prolactin levels could provide a window into central dopaminergic dysfunction in, at least, some patients with psychosis. Some authors have already postulated that serial measurement of prolactin levels could be established as a biomarker of response to antipsychotic treatment (Agarwal, 2011; Gault, 2018; Souza, 2011), despite the clear limitations that the alteration of prolactin levels induced by the antipsychotics themselves, even at low doses, entails in said use. The results of this study suggest the possibility of using baseline prolactin as a marker of future treatment response in AN-FEP patients. Again, further research is needed to clarify these questions.

5. Conclusions

Our findings show the existence of a significant increase of blood prolactin, but not morning cortisol, in antipsychotic naïve FEP patients, as well as a higher inter-group variability of these concentrations compared with healthy controls. This suggests a prolactin physiopathology disturbance in at least some part of this group, beyond the effect of antipsychotic medications.

Conflicts of interest

The authors declare no potential conflicts of interest. This research has received no funding.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106049.

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