Brain, Behavior, and Immunity 128 (2025) 219–233

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Do biological alterations precede the onset of psychosis? A systematic review and *meta*-analysis of immune, cardiometabolic, prolactin and HPA axis alterations in clinical high-risk for psychosis

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ARTICLE INFO

Keywords:
Clinical high risk
Psychosis
Schizophrenia
Immune
Cortisol

ABSTRACT

First episode psychosis (FEP) individuals show biological abnormalities preceding antipsychotic treatment. However, it remains unclear whether such alterations are also present before the onset of psychosis. We aim to provide estimates of standardized mean differences for immune, cardiometabolic, prolactin, and HPA axis parameters in individuals at clinical high-risk for psychosis (CHR-P) compared to healthy controls (HC) and FEP individuals, and between CHR-P transitioning to psychosis (CHR-T) compared non-transitioning (CHR-NT). A multistep literature search was performed from database inception until September 25, 2023. PRISMA/MOOSE-compliant and pre-registered (PROSPERO: CRD42024507670) systematic review identified studies reporting on

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https://doi.org/10.1016/j.bbi.2025.04.009
Received 24 November 2024; Received in revised form 12 February 2025; Accepted 3 April 2025
Available online 7 April 2025

immune, cardiovascular or endocrine parameters in CHR-P samples compared with HC or FEP samples or comparing CHR-T vs CHR-NT. Inter-group differences in magnitude of effect were estimated using Hedges g and estimates were pooled using random-effects *meta*-analysis. Heterogeneity was high for most outcomes. 37 studies were included, total sample 2509 CHR-P, 710 FEP, and 1444 HC individuals. A statistically significant elevation of pro-inflammatory proteins was found among CHR-P compared with HC ($k = 12$; $N = 1710$; $g = 0.16$; $p < 0.01$) and FEP ($k = 7$; $g = 0.15$; $p = 0.04$) subjects. Interleukin-6 (IL-6) was increased in CHR-P compared to HC ($k = 9$; $N = 1243$; $g = 0.54$; $p < 0.01$), and interleukin-4 (IL-4) was increased in CHR-T compared with CHR-NT ($k = 2$; $N = 318$; $g = 0.36$; $p < 0.01$). CHR-P exhibited stronger cortisol awakening response than FEP subjects ($k = 3$; $N = 173$; $g = 0.51$; $p = 0.01$). CHR-P and FEP individuals did not show statistically significant differences in terms of prolactin levels. An inflammatory state (particularly marked by elevated IL-6 and IL-4 levels) and HPA axis alterations are present in CHR-P individuals.

1. Introduction

Schizophrenia is a complex and heterogeneous disorder affecting around 1 % of the population (Solmi et al., 2023). Individuals living with schizophrenia and related psychotic disorders experience a reduction in life expectancy by 10–15 years compared to the general population (Kilbourne et al., 2009). Physical illnesses, and particularly cardiovascular diseases (Correll et al., 2017), are the primary contributors to this increased rate of premature mortality. Furthermore, evidence indicates that individuals experiencing a first episode of psychosis (FEP) exhibit abnormalities across various organ systems, beyond the central nervous system (CNS), even before the initiation of antipsychotic treatment (Pillinger et al., 2019a). These abnormalities include elevated inflammatory proteins (Pillinger et al., 2019b; Pillinger et al., 2019c), activation of the hypothalamic–pituitary–adrenal (HPA) axis, and elevated prolactin levels in antipsychotic-naïve FEP patients (Aymerich et al., 2023), among others.

However, it remains unclear at what stage of the illness these alterations occur, whether they are associated with the onset of psychotic symptoms, or if they precede them. There is evidence that individuals at Clinical High-Risk for Psychosis (CHR-P) exhibit CNS alterations that are intermediate between healthy controls and those who have already experienced a FEP, both on a functional (Li et al., 2019) and a structural level (Zhu et al., 2024, Ellis et al., 2020). However, there is much less evidence regarding the presence of biological alterations in other systems involved in the development of psychosis, such as the immune system or the HPA axis.

Furthermore, while CHR-P individuals present a substantially higher risk of transitioning to a FEP compared to the general population, with around 25 % transitioning within 3 years (Salazar de Pablo et al., 2021), it remains challenging to detect on an individual level which individuals will develop psychosis. Establishing biomarkers associated with the transition to psychosis would allow for the identification of individuals at the highest risk and the development of potential preventive and therapeutic targets.

A recent *meta*-analysis evaluated the existence of immune alterations in populations with increased risk of psychosis compared to healthy controls, identifying elevated IL-6 levels in high-risk populations compared with healthy controls. However, it included a limited number of studies and patients, and the comparison between high-risk and FEP populations was not established (Misiak et al., 2021), which could help better identify the factors that trigger the onset of psychotic symptoms for the first time, as well as improve the detection of risk factors for transition. Moreover, this *meta*-analysis encompassed a broader and more heterogeneous study population, including not only CHR-P individuals but also unaffected siblings of individuals with schizophrenia and other first- and second-degree relatives (i.e. at genetic, not clinical risk). The evidence regarding the alteration of endocrine and cardiometabolic parameters in CHR-P is even more limited, with no systematic reviews or *meta*-analyses on the subject available to date.

To address these questions, we aimed to perform a systematic review and *meta*-analysis of the existence of alterations in immune, cardiometabolic, prolactin and HPA axis parameters in individuals at CHR-P, compared to (i) healthy controls, (ii) first episode psychosis patients, and (iii) transitioning to non-transitioning samples.

2. Methods and materials

This study protocol was registered on PROSPERO (registration number: CRD42024507670). The study was conducted in accordance with "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) (Moher et al., 2009) (eMethods1) and "Meta-analyses of Observational Studies in Epidemiology" (MOOSE) checklist (Stroup et al., 2000) (eMethods 2), following "EQUATOR Reporting Guidelines" (Altman et al., 2008).

2.1. Search strategy and selection criteria

A systematic literature search was carried out by two independent researchers (C.A. and B.P.). Web of Science database (Clarivate Analytics) was searched, including 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 September 25th, 2023. Subsequently, the search was updated to include studies published up to November 1st, 2024, to identify new articles released during this period.

The following keywords were used: (schizophren* OR psychosis) AND (high-risk OR high risk OR attenuated OR BLIPS OR CHR OR UHR OR genetic risk OR prodrom*) AND (immun* OR inflamm* OR cytokine OR antibody OR cardiac OR metabolic OR glucose OR diabetes OR lipid OR cholesterol OR triglyceride OR antioxidant OR cortisol OR hypothalamic pituitary adrenal OR HPA OR prolactin).

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.

2.2. Condition and individuals being studied

Inclusion criteria for the systematic review and *meta*-analysis were (a) individual studies with original data, (b) reporting on a sample of individuals at CHR-P of at least 18 years old (mean age of the sample), defined according to established psychometric instruments (e.g., CAARMS or SIPS) (eMethods 3 (Salazar de Pablo et al., 2021)), (c) comparing CHR-P groups with a healthy control group or a FEP group (defined as patients presenting with psychosis under 5 years from onset, according to any DSM (Anonymous 2022, Anonymous 2013, Anonymous 2000) or ICD (World Health Organization, 2021, World Health Organization, 2012) criteria, on their first treatment contact), or CHR-T groups vs CHR-NT groups, (d) including validated peripheral measurements of immune, cardiometabolic, or endocrine parameters (see Table 1 for the included parameters), (e) nonoverlapping samples (overlap was determined by looking at the specific program or university, inclusion dates, type of population and country in which the study was carried out); in case of overlapping the study with the largest sample comprising each studied parameter was selected). In the case of

Table 1
Included parameters.

Inflammatory proteins	
IL-6	Articles reporting on blood (either plasma or serum) samples measuring any of the included inflammatory proteins were included.
IL-2	
IL-1β	
TNF-β	
TNF-α	
IL-4	
IL-5	
IL-17	
IL-10	
IL-8	
IL-12p70	
CRP	
IFN-γ	
VEGF	
Cardiometabolic parameters	
Fasting glucose	Articles reporting on blood (either plasma or serum) samples measuring any of the included cardiometabolic parameters were included.
Glucose post-oral glucose tolerance test	
Fasting insulin	
Insulin resistance	
Total cholesterol	
LDLc	
HDLc	
Triglycerides	
Prolactin and HPA axis parameters	
Prolactin	Only studies reporting on antipsychotic naïve samples stratified by sex were included, due to the largely established effects of sex (Zhu et al., 2021) and D2 antagonism (Freeman et al., 2000b) over prolactin levels.
Cortisol Awakening Response – Area Under the Curve with respect to increase	To standardize the data from the included studies, the area under the curve with respect to the increase formula was used to calculate the cortisol awakening response. This formula was selected as it is more closely related to the changes in the cortisol response (Pruessner et al., 2003).
Awakening Cortisol	Cortisol samples obtained within the first 45 min after waking up were included. Where possible, blood samples were selected.
Evening Cortisol	Studies reporting on cortisol samples obtained after 7 pm were included. Where possible, blood samples were selected.
Morning cortisol	Studies reporting on cortisol samples obtained between 10am and 12am (except for those where it was specified that it was an awaking cortisol measurement) were included. Where possible, blood samples were selected.
Trier Social Stress Test	Articles using a standardized protocol for the TSST (Allen et al., 2017) were selected. To uniformize the results of each study, two values were calculated for each sample: the difference between the beginning and the end of the evaluation period (from now on *TSST increase*) and the difference between the end of the evaluation and the closest measure to + 20 min after finishing the protocol (from now on *TSTT decrease*).

IL-6 Interleukin-6; IL-2 Interleukin-2; IL-1β Interleukin-1β; TNF-β Tumour Necrosis Factor-β; TNF-α Tumour Necrosis Factor-α; IL-4 Interleukin-4; IL-5 Interleukin-5; IL-17 Interleukin-17; IL-10 Interleukin-10; IL-8 Interleukin-8; IL-12p70 Interleukin-12p70; CRP C-Reactive Protein; IFN-γ Interferon-γ; VEGF Vascular Endothelial Growth Factor; LDLc Low Density Lipoprotein Cholesterol, HDLc High Density Lipoprotein Cholesterol; HPA Hypothalamic-Pituitary-Adrenal.

prolactin, an additional inclusion criterion was stablished, (f) studies reporting on antipsychotic naïve samples stratified by sex, due to the largely established effects of sex (Zhu et al., 2021) and D2 antagonism (Freeman et al., 2000a) over prolactin levels. Exclusion criteria were (a) reviews, clinical cases, study protocols or qualitative studies, conferential proceedings, letters, and commentaries, (b) reporting on patients with already established psychotic disorders (not including FEP individuals when compared to CHR-P populations), (c) reporting on endocrine or immune conditions based on pre-defined diagnostic criteria (e.g. rates of hyperprolactinemia or hypercortisolemia).

2.3. Data extraction

Two researchers (C.Ay. and B.P.) independently extracted data from all the included studies. The two 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), clinical diagnosis, structured interview, treatment, substance use, control group (HC vs FEP), type of biological sample (e.g., blood, saliva), analytic parameter, quality assessment (see below), and key findings. The original units of measurement were preserved. When stratified data was available, data were extracted separately for transitioning CHR-P (CHR-T) and non-transitioning CHR-P (CHR-NT) samples at follow-up. Transition to psychosis was operationalized as defined by each CHR-P instrument (eMethods 3).

2.4. Risk of bias (quality) assessment

Risk of bias was assessed using Newcastle-Ottawa Scale for cross-sectional and cohort studies, which has been repeatedly used in the field (Salazar de Pablo et al., 2021, Salazar de Pablo et al., 2020). Studies were awarded 0–9 points according to their representativeness, exposure, outcomes, follow-up period and losses to follow-up (eMethods 4). Scores ≥ 7–9, 4–6, <4 are considered low, intermediate, and high risk of bias, respectively (Wells et al., 2012).

2.5. Strategy for data synthesis and statistics

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

Second, we performed *meta*-analyses when at least 2 articles reported data for a particular outcome. The comparison of effect sizes in each group was calculated as the Hedges' g. A positive Hedges' g indicates the CHR-P population (or, in the case of CHR-T versus CHR-NT, the transitioning group) have higher concentrations for that analytic parameter compared with the control group. Effect sizes were calculated using the means, standard deviations (SDs), and sample sizes for the outcomes of interest for each sample. Because the studies were expected to be heterogeneous, *meta*-analytical random-effects models were used.

Heterogeneity among study point estimates was assessed with the Q statistic, with the proportion of the total variability in effect size estimates due to between-study heterogeneity was evaluated using the I^2 index. Publication bias was examined by visually inspecting funnel plots.

Meta-regressions were performed when at least seven studies per outcome were available (Salazar de Pablo et al., 2023, Pacho et al., 2023). We investigated the influence of the following factors: % of females, mean age, quality score and publication year. All analyses were conducted using the metafor and meta packages within R software, version 4.2.2 (R Foundation for Statistical Computing, 2021). The significance level was set at $p < 0.05$, two-sided.

In addition to conducting individual *meta*-analyses for each inflammatory protein as outlined, a separate subgroup *meta*-analysis was also carried out, focusing on the pro-inflammatory mediator's data. In agreement with previous work in the field, only those cytokines and molecules reflecting a pro-inflammatory status were included – specifically IL-6, IL-1β, TNF-β, TNF-α, IL-17, IL-8, IL-12p70, IFN-γ, and CRP – (Sarah H. Ross and Doreen A. Cantrell, 2018, P C Ng, 2003, Charles A.

Table 2
Characteristics of the included studies.

Author & Year	City (Country)	N CHR-P	N FEP	N HC	Mean age (SD)	% Female	Parameters	NOS	Key findings
Inflammatory proteins									
(Ouyang et al., 2022)	Changsha (China)	14 CHR-T; 16 CHR-NT	40	30	18.6 (±3.3)	43 %	IL-6, IL-2, IL-1β, TNF-β, IL-4, IL-17, IFN-γ	8	Immune activation level is increased in the early stage of psychosis. IL-1β may be a potential selective predictive biomarker for future transition in CHR-P individuals.
(Zhang et al., 2022a)	Shanghai (China)	16 CHR-T; 68 CHR-NT	–	65	18.7 (±5.2)	46 %	IL-6, IL-1β	9	A specific pattern of decreased IL-1β/IL-6 ratios with lower serum IL-1β level is associated with an increased risk of transition in CHR-P individuals.
Zhang et al, 2023	Shanghai (China)	47 CHR-T; 216 CHR-NT	–	100	18.9 (±5.4)	50 %	IL-6, IL-2, IL-1β, IL-10, IL-8, VEGF	8	Alterations in the serum levels of inflammatory cytokines were found to precede the first episode psychosis in the CHR-P population, particularly for CHR-T.
Zeni-Graiff et al, 2016	Sao Paulo (Brazil)	12	–	16	18.0 (N.a.)	28 %	IL-6, IL-17, IFN-γ	7	Compared to HC, CHR-P individuals showed increased IL-6 levels and decreased IL-17 levels in serum.
Mondelli et al, 2023	London (UK)	50 CHR-T; 219 CHR-NT	–	56	22.7 (±5.3)	45 %	IL-6, IL-2, IL-1β, TNF-β, TNF-α, IL-4, IL-5, IL-10, IL-8, IL-12p70, IFN-γ, VEGF	8	VEGF levels and the IL-10/IL-6 ratio were significantly higher in CHR-T than in CHR-NT. Increased VEGF levels could reflect altered blood–brain-barrier permeability.
Michalczyk et al, 2022 (Michalczyk et al., 2022)	Szczecin (Poland)	12	19	29	29.8 (±5.1)	58 %	IL-6, TNF-α, IL-10, IL-8, IFN-γ	8	Levels of IL-6 and IFN-γ differed significantly between groups.
Michalczyk et al, 2023 (Michalczyk et al., 2023)	Szczecin (Poland)	16	30	34	30.6 (±8.1)	55 %	IL-6, TNF-α, IL-10, IL-8, IL-12p70, IFN-γ, CRP	8	No correlation was found between any of the cytokines and the integrity of white matter.
Martorell et al, 2019	Reus (Spain)	14	39	21	23.3 (±4.2)	37 %	IL-6, IL-12p70, CRP	7	Increased leptin levels were detected in the early stages of psychosis, along with significant correlations between leptin levels and IL-6 levels.
Stojanovic et al, 2014	Reus (Spain)	17	77	25	24.9 (±4.6)	40 %	IL-6, IL-12p70, CRP	8	IL-6 may be a biomarker for early psychotic symptoms.
Karanikas et al, 2016 (Karanikas et al., 2016)	Thessaloniki (Greece)	12	25	–	25.2 (±4.8)	0 %	IL-2, IL-1β, TNF-β, TNF-α, IL-4, IL-5, IL-10, IL-8, IL-12p70, IFN-γ	6	Higher levels of both pro-inflammatory and anti-inflammatory cytokines were found in the FEP group compared to the CHR-P group.
Karanikas et al, 2016	Thessaloniki (Greece)	12	–	23	26.2 (±3.2)	0 %	IL-2, IL-1β, TNF-β, TNF-α, IL-4, IL-5, IL-10, IL-8, IL-12p70, IFN-γ	6	CHR-P subjects presented increased IL-4 levels compared with both the HC and the chronic schizophrenia patients.
Nisha Aji et al., 2023	Toronto (Canada)	38	–	20	21.1 (±2.6)	44 %	IL-8	7	CRP, IL-1β, TNF-α, and IFN-γ levels were independent peripheral predictors of brain translocator protein in CHR-P individuals.
Pollak et al., 2021	Multiple (Multiple)	254	–	116	22.7 (±5.0)	23 %	IL-12p70, CRP	8	NMDAR autoantibodies are detectable in a subgroup of CHR-P subjects at equal rates in HC, and in CHR-P are associated with affective psychopathology and cognitive impairment.
Kelsven et al, 2020	Multiple (USA, Mexico)	11	7	–	21.4 (±5.6)	30 %	IL-6, IL-1β, IL-10, IL-8, IL-12p70	6	Higher levels of IL-10 were detected in CHR-P as compared to FEP and HC subjects.
Perkins et al, 2015	Multiple (USA)	72	–	35	19.6 (±4.6)	35 %	IL-6, IL-1β, IL-10, IL-4, IL5, IL-8, IL-12p70, CRP	8	CHR-P subjects displayed significantly higher levels of multiple inflammatory metabolites than HC, including IL-8 and IL-4.
Hypothalamus-Pituitary-Adrenal Axis Parameters									
Nordholm et al, 2023	Copenhagen (Denmark)	72	–	36	23.8 (±3.4)	56 %	Evening cortisol, CAR	7	No significant differences were found regarding cortisol between HC and CHR-P individuals.
Day et al, 2014	London (UK)	30	–	33	23.5 (±4.5)	44 %	Evening cortisol, awakening cortisol, CAR	7	CHR-P individuals displayed a blunted CAR compared with HC participants. No differences were found in daytime cortisol.
Labad et al, 2018 (Labad et al., 2018)	Reus (Spain)	21	34	21	23.3 (±5.0)	43 %	Morning cortisol, evening cortisol, awakening cortisol, CAR	8	No significant differences were found regarding CAR and diurnal cortisol slope between CHR-P, FEP, and HC individuals.
Pruessner et al, 2017	Quebec (Canada)	42	–	46	21.8 (±3.5)	46 %	Awakening cortisol, CAR	7	No significant differences were found regarding CAR between CHR-P and HC individuals.

(*continued on next page*)

Table 2 (*continued*)

Author & Year	City (Country)	N CHR-P	N FEP	N HC	Mean age (SD)	% Female	Parameters	NOS	Key findings
Nordholm et al, 2018	Copenhagen (Denmark)	41	40	46	24.2 (±5.0)	46 %	CAR	8	CHR-P individuals had stronger CAR compared to HC. There was a negative correlation between CAR and symptom severity among CHR-P individuals.
Ntouros et al, 2018	Thessaloniki (Greece)	12	25	–	26.2 (±3.2)	0 %	CAR	7	CHR individuals showed a stronger CHR-P than FEP and HC samples.
Labad et al, 2014	Reus (Spain)	10 CHR-T; 29 CHR-NT	–	44	22.8 (±4.5)	32 %	Morning cortisol, awakening cortisol, CAR	8	CHR-P individuals with a psychosis transition had an enhanced CAR and increased prolactin levels.
Valli et al, 2016	London (UK)	26	–	17	23.2 (±4.2)	37 %	CAR	8	CHR-P individuals who later developed psychosis had a blunted CAR, observed at trend level also in the whole CHR-P sample.
Carol et al, 2021	Belmont (USA)	38	–	38	18.6 (±2.2)	47 %	TSST	6	CHR-P individuals showed higher overall cortisol levels through the TSST test than HC, along with higher levels of subjective stress.
Davies et al, 2022	Multiple (UK)	17	–	19	24.2 (±4.6)	47 %	TSST	8	CHR-P individuals showed a dysfunction in fear processing and cortisol response during TSST.
Pruessner et al, 2013	Montreal (Canada)	21	–	21	20.8 (N.a.)	43 %	TSST	6	Cortisol levels and systolic blood pressure during TSST were significantly lower among CHR-P subjects than in HC.
Appiah-Kusi et al, 2020	London (UK)	17	–	25	24.4 (±4.6)	55 %	TSST	8	CHR-P individuals exhibited higher cortisol reactivity than HC, that significantly moderated with cannabidiol treatment.
Shah et al, 2023	Montreal (Canada)	28	61	45	21.6 (±4.1)	40 %	TSST	7	CHR-P and FEP individuals had greater perceived stress and blunted cortisol compared to HC. No significant differences in cortisol response were found between CHR-P and FEP samples.
Cullen et al, 2020	London (UK)	69 CHR-T; 388 CHR-NT	–	205	19.4 (±0.9)	44 %	Awakening cortisol	8	CHR-P sample reported greater exposure to life events and daily stressors; however, only CHR-T were characterized by elevated basal cortisol.
Manzanares et al, 2014	Reus (Spain)	16	65	25	24.6 (±4.7)	43 %	Morning cortisol	7	No significant differences were found in plasma o salivary cortisol levels between CHR-P and HC samples.
Martorell et al, 2019	Reus (Spain)	14	39	21	24.0 (±4.3)	38 %	Morning cortisol	7	No significant differences were found in cortisol levels between CHR-P, FEP and HC subjects.
Walker et al, 2013	Multiple (USA)	256	–	141	19.0 (±4.4)	44 %	Morning cortisol	6	CHR-P individuals showed higher morning cortisol levels compared with HC subjects. CHR-T showed higher cortisol levels than CHR-NT.
Montalvo et al, 2014	Reus (Spain)	23	55	29	24.2 (±4.9)	37 %	Morning cortisol	7	No significant differences were found in morning cortisol plasma levels between CHR-P, FEP, and HC samples.
Aston et al, 2010	Basel (Switzerland)	♂23 ♀19	♂13 ♀5	–	27.5 (±7.9)	*	Prolactin	7	Hyperprolactinemia was found in 25.6 % of CHR-P subjects and 46.2 % FEP subjects. No statistically significant differences were found between the two groups.
Studerus et al, 2021	Basel (Switzerland)	♂28 ♀3	♂56 ♀31	–	25.2 (±8.9)	*	Prolactin	8	Both CHR-P and FEP patients showed significantly higher levels of prolactin compared to HC.
Ittig et al, 2017	Basel (Switzerland)	♂82 ♀34	♂34 ♀15	–	26.1 (±6.9)	*	Prolactin	8	Hyperprolactinemia was found in 32.0 % of CHR-P subjects and 35.0 % FEP subjects. No statistically significant differences were found between the two groups.
Cardiometabolic Parameters									
Cropley et al, 2023	Multiple (Germany)	23	24	25	26.9 (±8.2)	17 %	Fasting glucose	8	No significant differences were found in serum glucose levels between CHR-P, FEP, and HC samples.
Martorell et al, 2019	Reus (Spain)	14	39	21	24.0 (±4.3)	38 %	HDLc, Triglycerides	7	CHR-P individuals showed significantly lower levels of HDLc compared with FEP and HC subjects. CHR-P sample showed significantly higher levels of triglycerides compared with HC, but no statistically significant differences with FEP.
Armio et al, 2024	Turku (Finland)	48	78	83	26.9 (±5.9)	48 %	Fasting glucose, fasting insulin, insulin resistance index (HOMA2-IR)	8	CHR-P had significantly higher serum glucose levels than HC, with no differences in fasting insulin or insulin resistance index. No significant differences were found between CHR-P and FEP for any outcomes.

CHR-P Clinical High Risk for Psychosis; CHR-T Clinical High Risk – Transitioners; CHR-NT Clinical High-Risk Non-Transitioners; FEP First Episode Psychosis; HC Healthy Control; SD Standard Deviation; NOS Newcastle-Ottawa Scale; IL Interleukin; IFN Interferon; VEGF Vascular Endothelial Growth Factor; TNF Tumoral

Necrotic Factor; CRP C-Reactive Protein; NMDAR N-methyl-D-aspartate Receptor; CAR Cortisol Awakening Response; TSST Trier Social Stress Task; HDLc High-Density Lipoprotein Cholesterol. * Indicates results are stratified by sex.

Dinarello, 2000). This approach was taken to minimize the confounding effect of cytokines with highly specific functions well-documented in the literature, such as IL-5 in allergic processes (Kiyoshi Takatsu and Hiroshi Nakajima, 2008). The magnitudes of subgroup summary effect sizes were determined by conducting a unified analysis of all studies molecules into a subgroup. If a single study reported outcomes for multiple subgroup parameters (for instance, results for various cytokines from one study population), the numbers of the CHR-P and comparison groups in that study were divided by the total number of parameters contributing to the summary *meta*-analyses, as done previously in similar studies in the field (Pillinger et al., 2019a).

3. Results

1947 citations were retrieved through electronic database and were screened for eligibility. 168 articles were assessed in full text, 132 were excluded, and 1 additional article was added through manual search. The final database for the systematic review and *meta*-analyses included 37 studies (eResults 1, Table 2).

Data were extracted for a total sample size of 2,509 CHR-P individuals (mean age 21.99 ± 2.41 years; 42.08 % females; 12.28 % were taking antipsychotics [AP] and 23.19 % antidepressants [AD]), 710 FEP individuals (mean age 24.79 ± 2.71 years; 35.44 % females; 51.08 % were taking AP), and 1444 healthy controls (mean age 24.27 ± 4.47 years; 43.61 % females). The mean age of the total sample was 23.16, ranging from 14 to 45 years (SD = 3.07). Studies included samples from

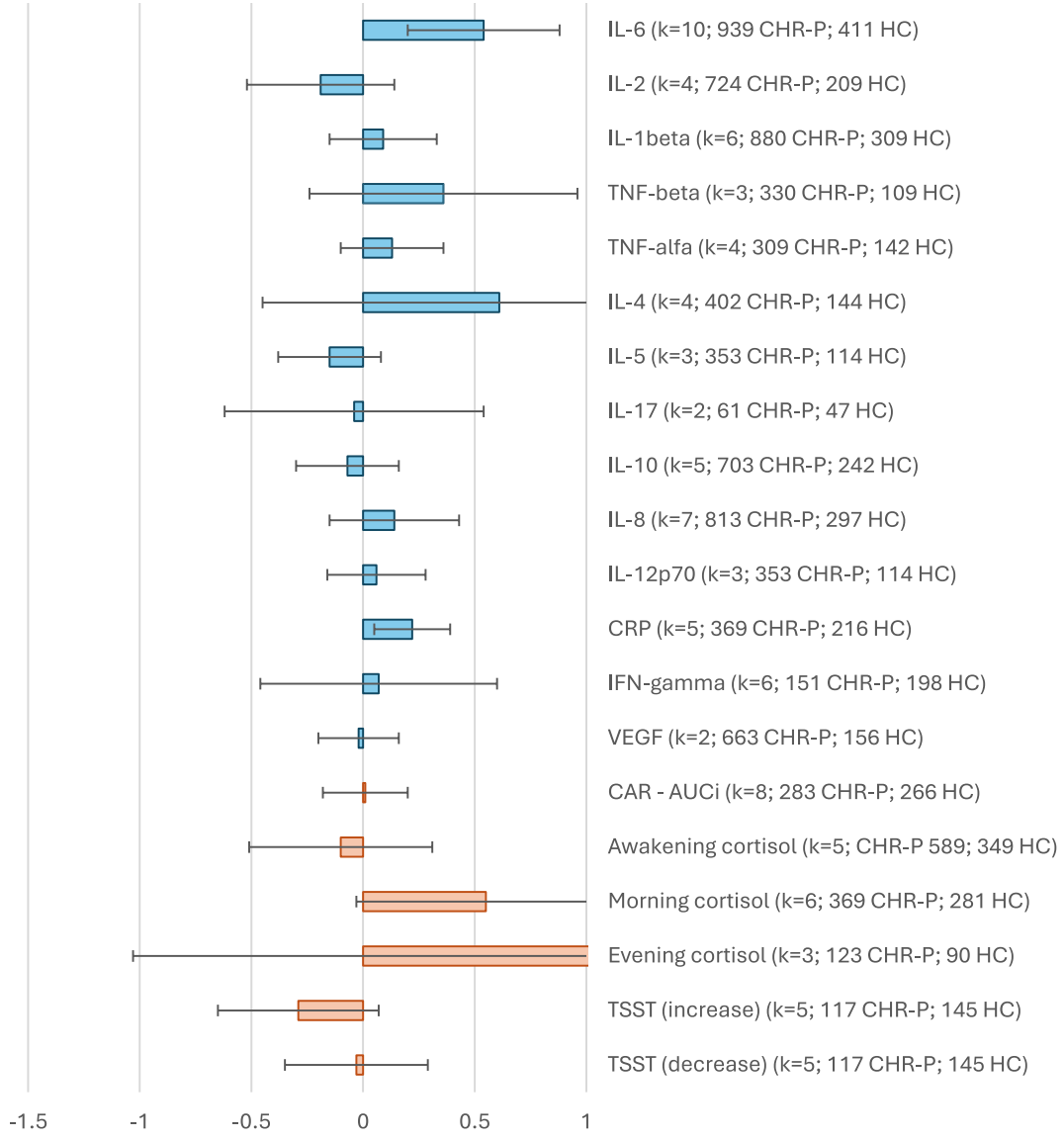

Fig. 1. Immune and hypothalamic–pituitary–adrenal axis parameters of individuals at clinical high-risk for psychosis (CHR-P) compared with healthy control (HC) individuals. Hedges *g* scores (mean and 95% CI) are given (negative values indicate lower levels of the studied parameter among individuals at CHR-P vs HC individuals), along with the number of studies (k) included and sample size. IL-6 Interleukin-6; IL-2 Interleukin-2; IL-1β Interleukin-1β; TNF-β Tumour Necrosis Factor-β; TNF-α Tumour Necrosis Factor-α; IL-4 Interleukin-4; IL-5 Interleukin-5; IL-17 Interleukin-17; IL-10 Interleukin-10; IL-8 Interleukin-8; IL-12p70 Interleukin-12p70; CRP C-Reactive Protein; IFN-γ Interferon-γ; VEGF Vascular Endothelial Growth Factor; CAR – AUCi Cortisol Awakening Response – Area Under the Curve increase; TSST Trier Social Stress Test.

12 countries in 4 continents: Europe (k = 24; 64.86 %), North America (k = 8; 21.62 %), South America (k = 1; 2.70 %) and Asia (k = 3; 8.11 %). Mean NOS score of the included studies was 7.34 (SD = 0.80), with 13.51 % studies being at moderate to high risk of bias.

3.1. Immune system alterations

15 articles examining immune system alterations in CHR-P were identified (Mondelli et al., 2023, Nisha Aji et al., 2023, Michalczyk et al., 2023, Zhang et al., 2023, Michalczyk et al., 2022, Zhang et al., 2022b, Ouyang et al., 2022, Pollak et al., 2021, Kelsven et al., 2020, Martorell et al., 2019, Karanikas et al., 2017, Karanikas et al., 2016, Zeni-Graiff et al., 2016, Stojanovic et al., 2014a). Of them, eleven included data on interleukin-6 (IL-6), eight on interleukin-8 (IL-8), seven on interleukin-12p70 (IL-12p70), seven on interleukin-1β (IL-1β), seven on interleukin-10 (IL-10), six on interferon-γ (IFN-γ), four on interleukin-2 (IL-2), five on c-reactive Protein (CRP), four on Tumour Necrosis Factor-α (TNF-α), three on Tumour Necrosis Factor-β (TNF-β), four on interleukin-4 (IL-4), three on interleukin-5 (IL-5), two on interleukin-17 (IL-17), and two on Vascular Endothelial Growth Factor (VEGF) (Table 2, Figs. 1-3). A detailed summary of *meta*-analytical results can be found in eResults 2, and the forest plots and funnel plots of the *meta*-analyzed inflammatory proteins are available in eResults 3 and eResults 4, respectively. Heterogeneity of studies was low to high (I^2 = 0 % – 94.0 %).Fig. 4.

CHR-P individuals exhibited statistically significant elevated levels

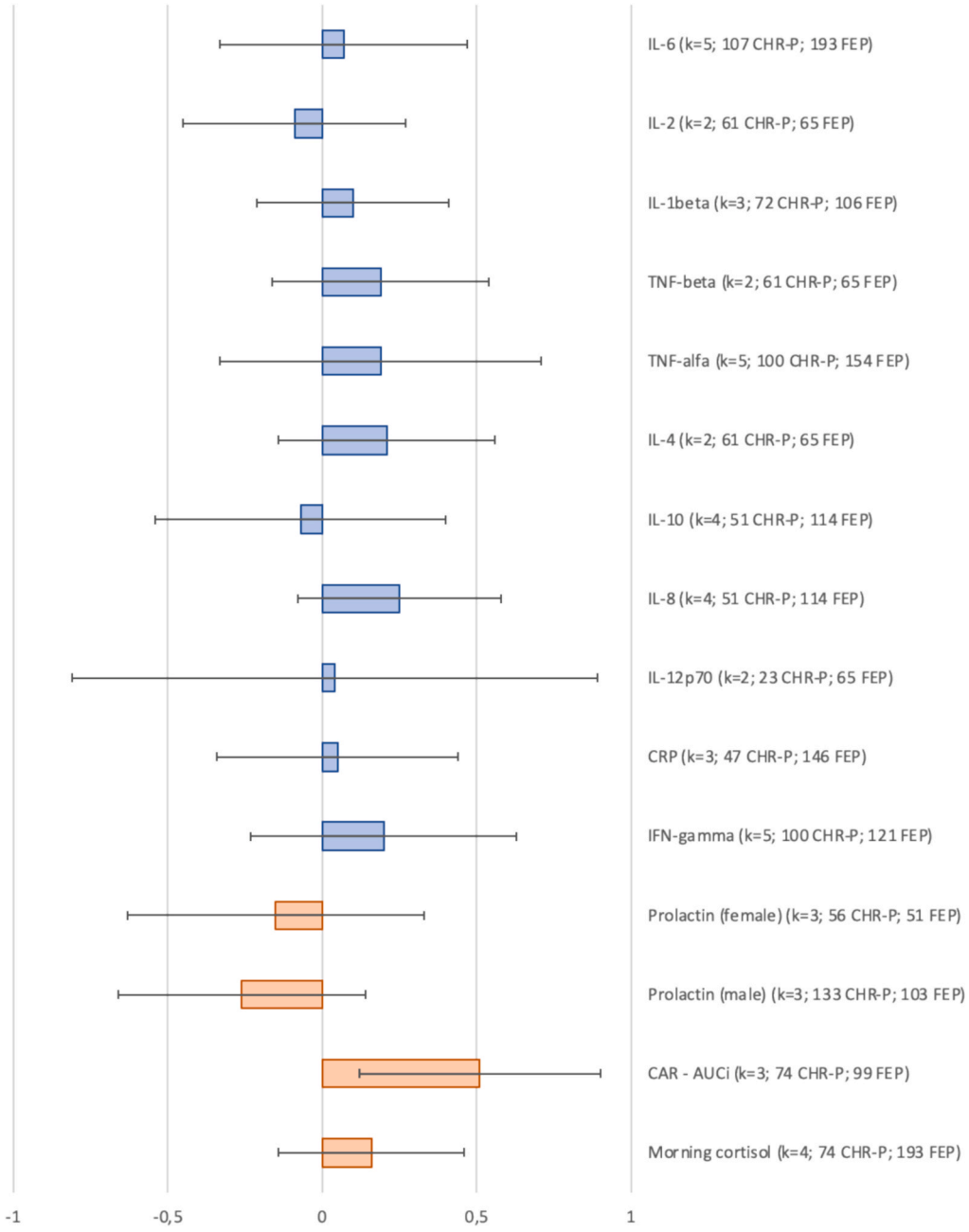

Fig. 2. Immune, prolactin, and hypothalamic–pituitary–adrenal axis parameters of individuals at clinical high-risk for psychosis (CHR-P) compared with First Episode Psychosis (FEP) individuals. Hedges *g* scores (mean and 95% CI) are given (negative values indicate lower levels of the studied parameter among individuals at CHR-P vs FEP individuals), along with the number of studies (k) included and sample size. IL-6 Interleukin-6; IL-2 Interleukin-2; IL-1β Interleukin-1β; TNF-β Tumour Necrosis Factor-β; TNF-α Tumour Necrosis Factor-α; IL-4 Interleukin-4; IL-10 Interleukin-10; IL-8 Interleukin-8; IL-12p70 Interleukin-12p70; CRP C-Reactive Protein; IFN-γ Interferon-γ; CAR – AUCi Cortisol Awakening Response – Area Under the Curve increase.

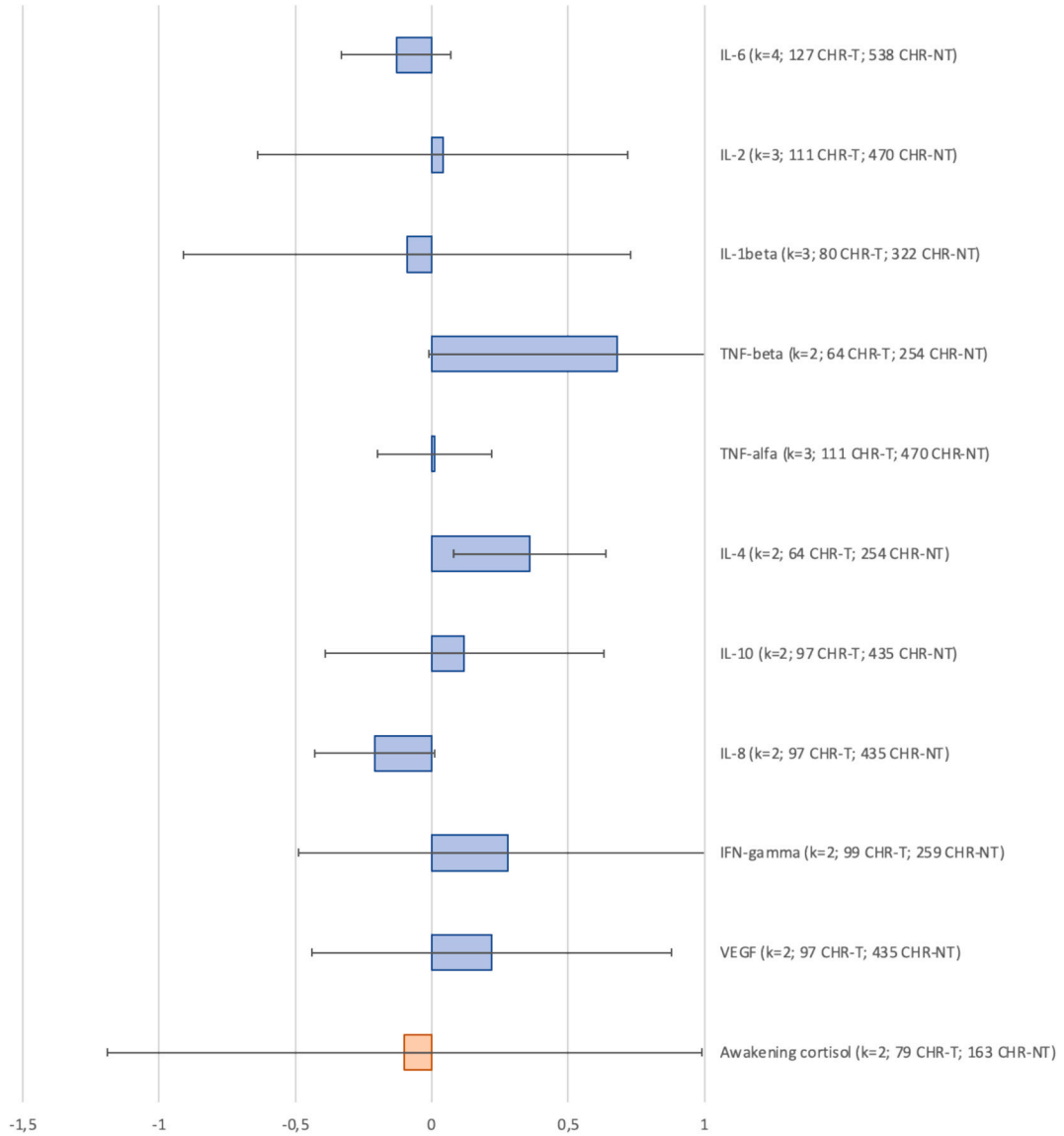

Fig. 3. Immune and hypothalamic–pituitary–adrenal axis parameters of individuals at clinical high-risk for psychosis developing psychosis (CHR-T) compared with those not developing psychosis (CHR-NT). Hedges *g* scores (mean and 95% CI) are given (negative values indicate lower levels of the studied parameter among individuals at CHR-T vs CHR-NT individuals), along with the number of studies (k) included and sample size. IL-6 Interleukin-6; IL-2 Interleukin-2; IL-1β Interleukin-1β; TNF-β Tumour Necrosis Factor-β; TNF-α Tumour Necrosis Factor-α; IL-4 Interleukin-4; IL-10 Interleukin-10; IL-8 Interleukin-8; IFN-γ Interferon-γ; VEGF Vascular Endothelial Growth Factor.

of IL-6 compared to HC (k = 10; N = 1350; g = 0.54; 95 % Confidence Interval [CI] 0.20; 0.88; p < 0.01) and in CRP compared to HC as well (k = 5; N = 585; g = 0.22; 95 % CI 0.05; 0.40; p < 0.01), while the rest of the studied cytokines levels did not present statistically significant differences compared to either HC or FEP individuals. Metaregressions did not find any significant effects of sex, mean age, quality score or publication year (eResults 5).

When comparing CHR-T vs CHR-NT individuals, the CHR-T group exhibited significantly higher levels of IL-4 (k = 2; N = 318; g = 0.36; 95 % CI 0.08; 0.64; p < 0.01), with no significant differences between groups for the rest of the studied parameters.

A secondary analysis was subsequently conducted to calculate a summary effect size of pro-inflammatory proteins, including IL-6, TNF-β, TNF-α, IL-1β, IL-8, IL-12p70, CRP, and IFN-γ (Sarah H. Ross and Doreen A. Cantrell, 2018, P C Ng, 2003, Charles A. Dinarello, 2000). The summary effect size in CHR-P vs HC was 0.17 (k = 13; N = 1814; 95 % CI 0.08; 0.26; p < 0.01), reflecting a statistically significant higher level of pro-inflammatory parameters among CHR-P individuals. A statistically significant elevation of pro-inflammatory parameters was also found in CHR-P when compared with FEP, with a summary effect size of 0.15 (k = 7; N = 364; 95 % CI 0.01; 0.29; p = 0.04). Conversely, no statistically significant differences were found in the summary effect sizes of CHR-T vs CHR-NT individuals (k = 4; N = 667; g = -0.08; 95 % CI −0.21; 0.6; p = 0.27) (Fig. 3).

3.2. Cardiometabolic alterations

Three articles examining cardiometabolic alterations in CHR-P met our inclusion criteria. However, there was insufficient data available to *meta*-analyze any of the studied parameters.

One study including 23 antipsychotic-naïve CHR-P individuals, reported on serum glucose levels and found no statistically significant differences between the CHR-P group and either the FEP group (p > 0.05) nor the HC group (p > 0.05) (Cropley et al., 2023).

Another study of 48 CHR-P individuals reported significantly higher fasting glucose levels compared to HC (t = 3.7; p < 0.01), with no

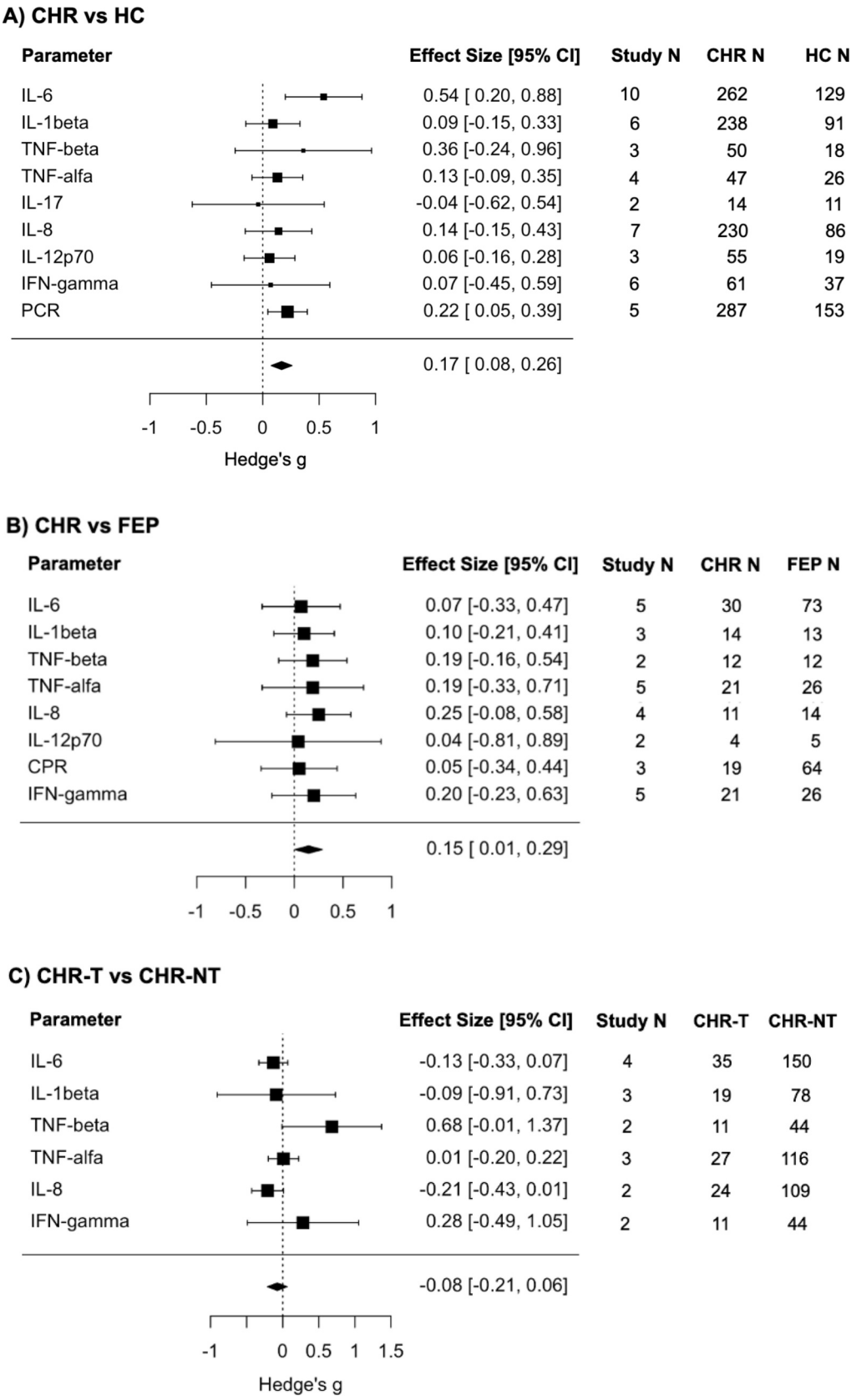

Fig. 4. Forest plots for pro-inflammatory cytokines. CHR Clinical High Risk; CHR-T Clinical High Risk – Transitioners; CHR-NT Clinical High-Risk Non-Transitioners; CI Confidence Interval; FEP First Episode Psychosis; HC Healthy Control; IL Interleukin; IFN Interferon; VEGF Vascular Endothelial Growth Factor; TNF Tumoral Necrotic Factor; CRP C-Reactive Protein.

significant differences in fasting insulin levels ($p > 0.05$) or insulin resistance index ($p > 0.05$). Additionally, no significant differences were observed between CHR-P and FEP for any of these three outcomes (Armio et al., 2024).

Finally, a third study including 14 CHR-P individuals, reported on serum high-density lipoprotein cholesterol (HDLc) and triglycerides (Martorell et al., 2019). The CHR-P individuals showed significantly lower levels of HDLc compared to both FEP individuals and HC individuals ($p = 0.03$). Conversely, the CHR-P group had higher levels of triglycerides compared to the HC group ($p < 0.01$), but no statistically significant differences compared to the FEP group ($p > 0.05$). It is important to note that 36 % of the CHR-P sample and 92 % of the FEP group were receiving antipsychotic treatment, so an effect from the medication cannot be ruled out.

3.3. Prolactin and hypothalamic–pituitary–adrenal system alterations

21 articles examining HPA alterations in CHR-P met our inclusion criteria (Nordholm et al., 2023, Shah et al., 2023, Studerus et al., 2021, Carol et al., 2021, Appiah-Kusi et al., 2020, Cullen et al., 2020, Martorell et al., 2019, Nordholm et al., 2018, Labad et al., 2018, Ntouros et al., 2018, Davies et al., 2018, Pruessner et al., 2017, Ittig et al., 2017, Valli et al., 2016, Montalvo et al., 2014a, Day et al., 2014, Labad et al., 2014, Manzanares et al., 2014, Pruessner et al., 2013, WALKER et al., 2013, Aston et al., 2010). Eight studies reported on cortisol awakening response (CAR), six on morning cortisol, five on awakening cortisol, five on Trier Social stress test (TSST), three on prolactin levels, and three on evening cortisol (Table 2, Figs. 1-3). A detailed summary of *meta*-analytical results can be found in eResults 6, and the forest plots and funnel plots of the *meta*-analyzed inflammatory proteins are available in eResults 7 and eResults 8, respectively. Heterogeneity of studies was low to high ($I^2 = 0\ \% - 97.0\ \%$)

No statistically significant differences in prolactin levels were found between antipsychotic naïve CHR-P individuals vs FEP individuals, neither for males ($k = 3$; $N = 236$; $g = -0.15$; 95 % CI −0.63; 0.32; $p = 0.52$) nor females ($k = 3$; $N = 107$; $g = -0.26$; 95 % CI −0.66; 0.16; $p = 0.20$).

CHR-P individuals exhibited statistically significant higher reactivity of CAR compared to FEP individuals ($k = 3$; $N = 173$; $g = 0.51$; 95 % CI 0.12; 0.91; $p = 0.01$).

No statistically significant differences were found between CHR-P and HC individuals for CAR ($k = 8$; $N = 603$; $g = 0.01$; 95 % CI −0.18; 0.20; $p = 0.91$), awakening cortisol ($k = 5$; $N = 938$; $g = -0.10$; 95 % CI −0.51; 0.30; $p = 0.61$), morning cortisol ($k = 6$; $N = 650$; $g = 0.55$; 95 % CI −0.03; 1.14; $p = 0.06$), evening cortisol ($k = 3$; $N = 213$; $g = 1.22$; 95 % CI −1.03; 0.30; $p = 3.46$), TSST (increase) ($k = 5$; $N = 262$; $g = -0.29$; 95 % CI −0.65; 0.07; $p = 0.11$) or TSST (decrease) ($k = 5$; $N = 262$; $g = -0.03$; 95 % CI −0.35; 0.29; $p = 0.87$). No statistically significant differences were found either between CHR-P and FEP individuals for morning cortisol ($k = 4$; $N = 267$; $g = -0.29$; 95 % CI −0.65; 0.07; $p = 0.11$). Metaregressions did not find any significant effects of sex, mean age, quality score or publication year (eResults 9) on the difference of CAR between CHR-P and HC individuals. When comparing transitioning vs non-transitioning CHR-P individuals, no statistically significant differences were found for awakening cortisol ($k = 2$; $N = 242$; $g = -0.10$; 95 % CI −1.19; 0.99; $p = 0.85$).

4. Discussion

To the best of our knowledge, this is the largest and most updated systematic review and *meta*-analysis examining the existence of immune, cardiometabolic, and endocrine parameters alterations among CHR-P individuals. An overall small but statistically significant elevation of pro-inflammatory parameters (including IL-6, TNF-β, TNF-α, IL-1β, IL-8, IL-12p70, IL-17, CRP, and IFN-γ) was found among CHR-P individuals compared to HC, suggesting a pro-inflammatory status among CHR-P subjects.

Surprisingly, pro-inflammatory parameters as a group were also elevated in CHR-P subjects compared with FEP individuals. This immune-inflammatory dysregulation has been described before both among CHR-P individuals (prior to psychotic conversion and antipsychotic treatment) (Kelsven et al., 2020) and in FEP samples (Pillinger et al., 2019a). It has also been related to more prominent cognitive (Zhang, L. et al., 2022) and negative (Dunleavy et al., 2022) symptoms. Our findings suggest inflammatory dysregulation may play a role in the very early stages of psychosis and subsequently attenuates as the disease progresses. This aligns with the 'vulnerability-stress-inflammation' model of schizophrenia development, which posits that stressor-induced pro-inflammatory situations in early life can cause chronic inflammation that perturbs neurotransmitter systems, eventually leading to psychotic symptom presentation (Norbert Müller, 2018). This pro-inflammatory state might attenuate over time, at least in the periphery (Halstead et al., 2023). Evidence from some anti-inflammatory treatments suggest stage-specific effects, with higher response rates among early psychosis patients (Chen, A. T. et al., 2015). However, evidence remains to be highly variable and heterogeneous, both in our *meta*-analyses and in the existing literature. This would also be consistent with the hypothesis that immune alterations are specific to a subgroup of individuals with psychosis, not only among those who have already experienced their FEP (Pillinger et al., 2019b) but also among individuals at CHR-P.

Among specific inflammatory proteins, two cytokines stood out in our analyses: IL-6 and IL-4. IL-6 was the only cytokine to show a statistically significant difference between CHR-P individuals and HC, with an effect size of 0.54 (95 % CI 0.17; 0.92). IL-6 is a multifunctional cytokine that plays a pivotal role in the organism's defense mechanism, contributing to host defense by stimulating the acute phase response, hematopoiesis, and immune reactions (Tanaka et al., 2014). It can be produced by astrocytes, microglia cells, and neurons in the brain (MÜLLER et al., 2000, Freidin et al., 1992). Furthermore, IL-6 receptors have been found in the CNS, and there is evidence of this interleukin's role in multiple brain physiological functions, including sleep-wake cycles, emotional reactivity, and the HPA axis, among others (Erta Cañabate et al., 2012). The relationship between schizophrenia and IL-6 levels has been extensively studied, with sometimes contradictory results. While elevated IL-6 levels have been found both in both serum (Potvin et al., 2008) and cerebrospinal fluid (Schwieler et al., 2015, GARVER et al., 2003) of patients with chronic schizophrenia, a previous *meta*-analysis indicated that IL-6 is primarily elevated in patients experiencing a FEP and in acute relapse (Miller et al., 2011) and tends to decrease following the treatment with antipsychotics (Capuzzi et al., 2017), thereby serving as a state marker of schizophrenia. This is consistent with our findings, which points to an elevation of IL-6 in the prodromal phases of the psychotic disease and the appearance of attenuated psychotic symptoms, supported by previous observational studies (Mondelli et al., 2023b, Stojanovic et al., 2014b).

Furthermore, within the CHR-P sample, we found that elevated IL-4 levels were significantly associated with a subsequent transition to psychosis, with an effect size of 0.36 (95 % CI 0.08; 0.64). IL-4 is an interleukin that serves as a regulator of the immune system, in health and in pathological conditions. However, accumulated evidence suggests it also has a significant role in the CNS's higher functions, including memory and learning processes (Gadani et al., 2012). Consistent with our results, IL-4 has been previously linked to the onset of psychotic disorders (Mondelli et al., 2023, Perkins et al., 2015a). Although the studied parameters are far from being able to constitute a biomarker for disease or prognosis at individual level, our findings suggest that there are interleukins with a more central role in the etiopathogenesis of psychotic disorders, particularly IL-6 and IL-4. Future research should longitudinally characterize the diagnostic and prognostic correlates of those two cytokines on larger CHR-P samples. It should also be noted that immune markers encompass a broader range than those examined in this study, which focuses on inflammatory proteins due to their

predominance in the available literature. However, immune parameters include a wider spectrum, such as cellular markers and other proteins, which have been gaining relevance in recent years(Cropley et al., 2023). Future research should also aim to further understand how these immune components interact in the onset and maintenance of psychotic symptoms.

As for the prolactin and HPA axis alterations, several important findings were made as well. First, no statistically significant differences in prolactin levels were found between antipsychotic-naïve CHR-P individuals vs antipsychotic-naïve FEP individuals, neither for males nor females. Although unfortunately no studies were found investigating the differences in prolactin levels between CHR-P and HC, this finding is interesting by itself, as increased prolactin levels among antipsychotic-naïve FEP patients compared to HC have been repeatedly reported in literature (Aymerich et al., 2023). Consistently, in a previous study increased prolactin levels were found among CHR-P individuals who later transitioned into a psychotic disorder compared to HC (Labad et al., 2015). Prolactin synthesis and secretion are regulated by dopaminergic neurons in the anterior pituitary gland, and dopamine inhibits the release of this hormone (Kopelman, 2000). Therefore, peripheral prolactin levels could provide a window into central dopaminergic dysfunction, that is already present in CHR-P individuals before they transition to psychosis (van Hooijdonk et al., 2022). However, an increase in prolactin has also been described in situations of psychosocial stress (Lennartsson and Jonsdottir, 2011, Sonino et al., 2004), which has led some authors to associate the stress induced by early psychosis to the elevation of prolactin levels (Aston et al., 2010). An alternative hypothesis posits that hyperprolactinemia in CHR-P individuals may result from altered prolactin regulation (Labad, 2019), given findings from previous challenge studies in drug-naïve patients with first-episode schizophrenia(SPOOV et al., 2010). These studies demonstrated an altered response to low doses of thyrotropin-releasing hormone, suggesting a 'hypersensitive' prolactin-stimulating system. However, challenge studies in CHR-P individuals are currently lacking.

Second, cortisol awakening response was significantly elevated in CHR-P individuals compared to FEP, with an effect size of 0.51 (95 % CI 0.12; 0.91), while no significant differences were found between CHR-P and HC samples. Cortisol awakening response (CAR) is defined as the increase in cortisol release in response to waking up and constitutes a proxy marker for HPA axis dysregulation that is not necessarily related to diurnal cortisol levels (Fries et al., 2009). Furthermore, CAR measurement is an inherently standardized method that allows for little variation, thus eliminating the heterogeneity of single cortisol measurements (Stalder et al., 2016). While an increased CAR has been consistently related with general stress (Chida and Steptoe, 2009), a blunted CAR has been found in both FEP and chronic schizophrenia patients (Berger et al., 2016). While it is possible that HPA axis-related dysfunction (such as an altered stress response and its consequent blunting of the CAR) appears only after the psychosis onset, it is also possible that some CHR-P subgroups (and particularly those who will later transition to a psychotic disorder, as reported by Labad et al (Labad et al., 2014) present distinct stress biomarkers as transition predictors.

A potential explanation for the concurrent findings of inflammatory proteins and HPA axis alterations in CHR-P individuals is the concept known as allostasis. The disruption of homeostasis due to stress situations leads to the activation of various biological processes in the organism. This includes the elevation of multiple hormonal mediators such as cortisol and noradrenaline, and pro-inflammatory mediators to meet demands and ensure short-term survival (MISIAK et al., 2014). However, when stress persists over time, the prolonged activation of these mediators can have detrimental effects on itself, accelerating disease progression on the long term (Chen et al., 2024, McEwen, 2000) in what is known as allostatic load (AL) (McEwen, 1998). In schizophrenia patients, a higher AL compared to HC has been consistently reported in literature (Misiak, 2020). Furthermore, an elevated AL index has also been linked to more severe cognitive impairments (Savransky et al., 2018), increased positive symptoms, and greater functional impairment (Berger et al., 2018). In CHR-P individuals, higher AL has been associated with poorer social and occupational functioning after 6 months (Berger et al., 2020). Moreover, common risk factors have been reported for both high allostatic load and risk for psychosis among CHR-P individuals, including childhood trauma, perceived stress and tobacco use (Finlay et al., 2022, Mauss and Jarczok, 2021, Fusar-Poli et al., 2017, Wiggert et al., 2016). Therefore, it seems plausible to understand the elevated immune and stress response hormone levels (including prolactin and CAR) as an allostatic process that could end up in multisystem dysfunction, including for instance a dysfunctional hormonal stress response (Gispen-de Wied, 2000), but also CNS symptoms and, eventually, psychosis.

Previous authors have suggested that the allostatic load model might explain some differences in HPA axis measures in relation to the stage of illness (e.g. increased CAR in CHR-P individuals but blunted in FEP and chronic schizophrenia). CHR-P individuals might exhibit adaptive biological responses to stress before the onset of psychosis (lower allostatic load stage), which are lost upon the development of psychosis (higher allostatic load stage), thereby revealing maladaptive biological responses such as a blunted CAR. However, this remains to be highly speculative, and it is crucial that future studies prospectively establish the exact moment in the evolution of psychotic disorders at which biological alterations and their associated factors appear, due to the potential implications this could have in the etiopathogenesis of psychosis and in its prevention and treatment.

Finally, it is important to note that there was insufficient data to conduct a *meta*-analysis on significant differences in cardiometabolic parameters (including fasting glucose, cholesterol, or triglycerides, among others) between CHR-P individuals and either FEP or HC groups. This underscores a notable gap in the literature regarding the physical health of CHR-P individuals, a population with poorer lifestyle habits and higher alcohol and tobacco consumption than age-matched general population (Provenzani et al., 2023). Future research should aim to better characterize the cardiometabolic correlates of CHR-P populations. Given the previously identified need for monitoring physical health parameters and developing tailored health interventions in early psychosis and prodromic states (Carney et al., 2018), addressing this gap is crucial.

This systematic review and *meta*-analysis represents the most comprehensive synthesis to date on the biological alterations among CHR-P individuals, including immune, cardiometabolic, prolactin and HPA axis parameters, compared with both FEP and HC samples. However, the interpretation of this study's findings should be approached with caution due to certain limitations. First, the small number of studies and the overall sample size for some of the studied outcomes limits the generalization of the results (De Prisco and Vieta, 2024). Our mixed findings might reflect the relatively small number of CHR-P individuals in the included studies, which may have underpowered our analyses to identify significant effects. Moreover, our analyses include varying numbers of samples and subjects, leading to differences in statistical power across the different outcomes. It is important to also account for this variability in power. Second, it was no possible to analyze the effect of some important variables (i.e. antipsychotic treatment (Ilzarbe and Vieta, 2023) or the specific CHR-P subgroups) on the immune and endocrine parameters due to the lack of stratified information for those outcomes. The differences between groups in factors consistently associated with immunological alterations, such as average age or sex, are minimal, however, so a significant impact of these variables on the results is not expected. Nevertheless, other variables such as the duration of illness in FEP populations, could have had a significant impact on the results. Unfortunately, due to insufficient data in the included studies, we were unable to conduct sensitivity analyses or *meta*-regressions to explore this potential effect. Heterogeneity was high for some of the studied parameters, which might indicate a potential influence of these unstudied variables on the outcomes. Furthermore, CHR-P samples are

not homogeneous populations but instead exhibit significant inter-individual variability in terms of clinical presentation, prognosis, and risk of transition to psychosis (Fusar-Poli et al., 2016). While we have minimized heterogeneity as much as possible by applying more restrictive inclusion criteria compared to previous *meta*-analyses, it is possible that alterations in certain biomarkers are specific to particular patient subgroups (Misiak et al., 2021), which may have limited our findings. Finally, this synthesis includes articles spanning nearly three decades; therefore, there is the possibility that methodological and laboratory variations might influence the outcomes measurements in earlier studies.

Our findings show the existence of a pro-inflammatory state among CHR-P subjects compared with both FEP and HC populations, along with a stronger cortisol reactivity compared to FEP individuals, and undistinguishable prolactin levels to those of FEP samples at a group level. It is precise to conduct larger, longitudinal research on CHR-P samples to identify the relevance and potential causal relationships between these outcomes and the later transition to psychosis and overall prognosis.

CRediT authorship contribution statement

Claudia Aymerich: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Borja Pedruzo:** Writing – original draft, Data curation, Conceptualization. **Gonzalo Salazar de Pablo:** Methodology, Formal analysis, Conceptualization. **Javier Labad:** Supervision, Methodology, Formal analysis, Conceptualization. **Robert McCutcheon:** Supervision, Methodology. **Toby Pillinger:** Supervision, Methodology. **Miguel Ángel González-Torres:** Writing – review & editing, Supervision. **Vanessa Sanchez-Gistau:** Writing – review & editing, Supervision. **Dominic Oliver:** Supervision, Methodology, Investigation. **Daniel Alonso-Alconada:** Writing – review & editing, Supervision. **Pablo Navalón:** Investigation, Conceptualization. **Gisela Sugranyes:** Writing – review & editing, Supervision. **Eduard Vieta:** Writing – review & editing, Supervision. **Celso Arango:** Writing – review & editing, Supervision. **Philip McGuire:** Writing – review & editing, Supervision. **Paolo Fusar-Poli:** Writing – review & editing, Supervision, Conceptualization. **Ana Catalan:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Funding

This research has been supported by the European College of Neuropsychopharmacology (ECNP) Network on Prevention of mental disorders and mental health promotion. CAy is supported by the Alicia Koplowitz Foundation. PN is supported by the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (ISCIII), JR22/0030, and by the Asociación Española de Psiquiatría del Niño y del Adolescente (AEPNYA) 2023 Research Assistance. CAr has received support by the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (ISCIII), co-financed by the European Union, ERDF Funds from the European Commission, "A way of making Europe", financed by the European Union – NextGenerationEU (PMP21/00051), PI19/01024. CIBERSAM, Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds, European Union Seventh Framework Program, European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking: Project PRISM-2 (Grant agreement No.101034377), Project AIMS-2-TRIALS (Grant agreement No 777394), Horizon Europe, the National Institute of Mental Health of the National Institutes of Health under Award Number 1U01MH124639-01 (Project ProNET) and Award Number 5P50MH115846-03 (project FEP-CAUSAL), Fundación Familia Alonso, and Fundación Alicia Koplowitz. RAMs work is funded by a Wellcome Trust Clinical Research Career Development Fellowship (224625/Z/21/Z). GS has received support by the Spanish Ministry of Health, Instituto de Salud Carlos III «Health Research Fund»/ FEDER funds (PI2100330, FORT23/00002_SUGR_G6, PI24/00279), La Marató TV3 (grantnumber 202232-30-31), the Alicia Koplowitz Foundation, and Pons Bartran and Maria and Nuria Cunillera legacies. JL and his research group (2021 SGR 00789) are part of REIS (Red Temática Española de Investigación en Estrés), funded by the Ministerio de Ciencia e Innovación (REF. RED2022–134191-T).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CAy received personal fees or grants from Janssen Cilag and Neuraxpharm outside the current work. GSP received personal fees or grants from Janssen Cilag and Menarini. GSP has received honoraria from Janssen Cilag, Lundbeck and Angelini outside the current work. PFP has received grant support from Lundbeck and honoraria fees from Angelini, Menarini, and Lundbeck outside the current work. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Adamed, Angelini, Biogen, Beckley-Psytech, Biohaven, Boehringer-Ingelheim, Celon Pharma, Compass, Dainippon Sumitomo Pharma, Ethypharm, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, HMNC, Idorsia, Johnson & Johnson, Lundbeck, Luye Pharma, Medincell, Merck, Newron, Novartis, Orion Corporation, Organon, Otsuka, Roche, Rovi, Sage, Sanofi-Aventis, Sunovion, Takeda, Teva, and Viatris, outside the submitted work. CAr has been a consultant to or has received honoraria or grants from Abbot, Acadia, Angelini, Biogen, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Medscape, Menarini, Minerva, Otsuka, Pfizer, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion, Takeda and Teva. AC received personal fees or grants from Janssen Cilag, ROVI, and Lundbeck outside the current work. RAM has received speaker/consultancy fees from Boehringer Ingelheim, Janssen, Karuna, Lundbeck, Newron, Otsuka, and Viatris, and co-directs a company that designs digital resources to support treatment of mental ill health. GS has received travel support from Roche Pharma. JL has received grants and served as consultant, advisor or CME speaker from Janssen Cilag, Casen Recordati, Angelini, Rovi, Idorsia, Otsuka and Lundbeck. All other authors report no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.04.009.

Data availability

Data will be made available on request.

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