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Association of symptom severity and cerebrospinal fluid alterations in recent onset psychosis in schizophrenia-spectrum disorders – An individual patient data *meta*-analysis

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ABSTRACT

Neuroinflammation and blood-cerebrospinal fluid barrier (BCB) disruption could be key elements in schizophrenia-spectrum disorderś(SSDs) etiology and symptom modulation. We present the largest two-stage individual patient data (IPD) *meta*-analysis, investigating the association of BCB disruption and cerebrospinal fluid (CSF) alterations with symptom severity in first-episode psychosis (FEP) and recent onset psychotic disorder (ROP) individuals, with a focus on sex-related differences. Data was collected from PubMed and EMBASE databases. FEP, ROP and high-risk syndromes for psychosis IPD were included if routine basic CSF-diagnostics were reported. Risk of bias of the included studies was evaluated. Random-effects *meta*-analyses and mixed-effects linear regression models were employed to assess the impact of BCB alterations on symptom severity. Published (6 studies) and unpublished IPD from n = 531 individuals was included in the analyses. CSF was altered in 38.8 % of individuals. No significant differences in symptom severity were found between individuals with and without CSF alterations (SMD = -0.17, 95 %CI −0.55–0.22, p = 0.341). However, males with elevated CSF/serum albumin ratios or any CSF alteration had significantly higher positive symptom scores than those without alterations (SMD = 0.34, 95 %CI 0.05–0.64, p = 0.037 and SMD = 0.29, 95 %CI 0.17–0.41p = 0.005, respectively). Mixed-effects and simple regression models showed no association (p > 0.1) between CSF parameters and

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symptomatic outcomes. No interaction between sex and CSF parameters was found ($p > 0.1$). BCB disruption appears highly prevalent in early psychosis and could be involved in positive symptoms severity in males, indicating potential difficult-to-treat states. This work highlights the need for considering BCB breakdown and sex-related differences in SSDs clinical trials and treatment strategies.

1. Introduction

Neuroinflammation and blood-cerebrospinal fluid-barrier (BCB) disruption might play a substantial role in the etiology of schizophrenia spectrum disorders (SSDs) (Pollak et al., 2018; Benros et al., 2014; Khandaker et al., 2015). The gold standard technique for quantifying BCB permeability in human beings is measurement of the CSF/serum albumin ratio. An elevation of age-adjusted CSF/serum albumin ratio suggests that increased quantities of albumin, and by implication other macromolecules, have been able to pass from blood to CSF because of an impaired barrier (Pollak et al., 2018). The evidence for BCB disruption in at least a subgroup of people with SSDs is solid and rapidly increasing (Endres et al., 2020; Jeppesen et al., 2022; Orlovska-Waast et al., 2019; Campana et al., 2022; Oviedo-Salcedo et al., 2021; Romer et al., 2023). People with SSDs appear to also have other CSF abnormalities indicating BCB impairment, such as elevated CSF total protein and elevated CSF to serum immunoglobulin G (IgG) ratio compared to healthy controls (Romer et al., 2023). The reasons for BCB disruption are incompletely understood, but could relate to immune alterations which are present in SSDs (Pollak et al., 2018) and appear early in the disease with subsequent implications regarding difficult-to-treat states.

There is increasing evidence of the role of inflammation in SSDs etiopathogenesis. A recent large network *meta*-analysis reported a baseline level of inflammatory protein alteration in SSDs, including consistently elevated pro-inflammatory proteins such as interleukin (IL)-6. Interestingly, individuals early in their illness had significantly higher IL-2 and interferon (IFN)-γ as a sign of acute, superimposed immune activity (Halstead et al., 2023). Other well-known neurobiological alterations in SSDs, such as decreased postsynaptic density might be a consequence of increased complement component 4A (C4A) gene expression, which is involved in synaptic elimination and its concentration in CSF appear to be significantly elevated in patients with first-episode psychosis (FEP) who develop schizophrenia (Gracias et al., 2022).

Assessing CSF markers in FEP patients is clinically used to exclude organic brain disorders such as autoimmune encephalitis (Paval et al., 2023). Beyond its diagnostic role, CSF analysis provides a unique advantage compared to serum analysis in assessing neuroinflammation, as peripheral and CSF inflammatory biomarkers show low correlations (Gigase et al., 2023). Moreover, focusing on CSF in FEP individuals allows to elucidate the dynamic of BCB disruption at the earliest stage of the disease progression and to minimize the potential confounding effects of long-term antipsychotic medication (Elmorsy et al., 2014). Recent studies showed that a subgroup of FEP patients expresses an increased BCB permeability and peripheral inflammation (Jeppesen et al., 2022; Campana et al., 2022). However, most of the evidence to date is monocentric, relatively limited in sample size and lacks information regarding symptom severity.

Besides informing etiological hypothesis, larger CSF datasets in this population, ideally matched with longitudinal follow-up clinical measurements, could play a key role in detecting biological predictors of treatment response or difficult-to-treat-states and enable intensified treatment before the emergence of treatment-resistance. Up to 30 % of FEP patients fail to respond to two or more adequate treatment trials of antipsychotic medication fulfilling the criteria for treatment-resistant schizophrenia (TRS) (Chan et al., 2021; Siskind et al., 2022; Howes et al., 2022). Moreover, around 40 % of TRS patients do not respond to an adequate trial of clozapine, which is the most effective antipsychotic for TRS (Siskind et al., 2017). Hence, a CSF marker which could predict the disease trajectory or help stratify patient populations would be of crucial importance for future clinical trials or emerging prognostic algorithms (Osimo et al., 2023).

BCB integrity as well as CSF production rate have been known to decay with age accounting for higher CSF/serum albumin ratios in older subjects (Tumani and Bachhuber, 2024). For this reason albumin ratio reference values are usually adjusted for age (Tumani and Bachhuber, 2024; Trendelenburg, 1994). Additionally, recent studies in large non-psychiatric samples, reported a sex-related difference in BCB permeability, with males characterized, on average, by a more permeable BCB (Parrado-Fernandez et al., 2018; Castellazzi et al., 2020). These findings were later confirmed in a large cohort of patients with schizophreniform and affective psychosis (Meixensberger et al., 2020).

Various sex-related differences in schizophrenias clinical manifestation are robust and well known (Giordano et al., 2021; Ochoa et al., 2012). Usually male patients present at an earlier age of illness onset, a worse level of premorbid functioning, a greater severity of negative symptoms, a lower severity of affective symptoms and a higher rate of comorbid alcohol/substance abuse compared to females (Giordano et al., 2021). Furthermore, men are at a higher risk of developing TRS (Siskind et al., 2022), consequently bearing a higher socio-economic burden and experiencing a lower quality of life (Kennedy et al., 2014). Assessing sex-related CSF differences in FEP patients and their association with symptoms severity is of central interest in elucidating the interplay between BCB integrity and clinical manifestation of the disorder.

The goal of this work was to further investigate the association between BCB alterations and symptom severity in people with recent onset psychotic disorder (ROP) or FEP, as defined in the methods section. Moreover, we aimed to assess sex-related differences in BCB permeability and their association with symptom severity. Finally, we intended to strongly enrich the limited CSF dataset in the aforementioned clinical population by performing an individual patient data (IPD) *meta*-analysis of the largest, international database of FEP and ROP patients having received CSF routine diagnostics to date.

2. Methods

This study was pre-registered with PROSPERO (registration number CRD42022346833).

2.1. Searches

PubMed and EMBASE databases were searched from inception to date of search (July 18th, 2022). The following search terms were applied: ((“cerebrospinal fluid”) OR (“csf”)) AND ((“schizophrenia”) OR (“psychosis”) OR (“first-episode”) OR (“first episode”)). No language restrictions have been applied. Cross-sectional studies, cohort studies, case-control studies, unpublished data from contacted corresponding authors were considered eligible for inclusion. The following Inclusion criteria were applied: Individuals with first episode psychosis or early psychosis or high-risk syndromes for psychosis (definition of first episode will be taken from each study) of Schizophrenia Spectrum Disorder (SSDs) (DSM-III, DSM-IV, DSM-V, ICD-9, or ICD-10) that underwent a lumbar puncture.

For results completeness a new PubMed and EMBASE database search from July 2022 (PubMed) and from January 2022 (EMBASE) to date of search (November 1st, 2023) was run.

2.2. Data extraction

Two reviewers (MC, VY) screened the identified articles on the title and abstract level and assessed full texts independently. All corresponding authors of identified CSF studies matching our criteria were contacted twice via e-mail in order to share respective individual patient data (raw data). If no response was received from the corresponding author, co-authors were contacted. Since only three studies (Endres et al., 2020; Meixensberger et al., 2020; Orhan et al., 2018) reported aggregate data for few CSF parameters among individuals with FEP without corresponding symptom severity scores, aggregate data was not obtained.

Data extraction was performed by two reviewers (EW, MC) following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Page et al., 2021). If a study reported multiple timepoints, only baseline values were considered. The following participant-level data were sought: age, sex, date of lumbar puncture, diagnosis, duration of illness, duration of untreated illness (DUI), number of antipsychotic drugs, body-mass index (BMI), concomitant cardiovascular disease, concomitant diabetes, concomitant lung disease, concomitant CNS disorder, smoker status, CSF white blood cell (WBC) count, serum WBC count, CSF albumin, serum albumin, CSF IgG, serum IgG, presence of oligoclonal bands (OCBs) in serum and/or CSF, CSF protein level, Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Trail-Making-Tests-A and −B (TMT-A and −B) (Bowie and Harvey, 2006); Montreal Cognitive Assessment (MoCA) scores (Nasreddine et al., 2005), Global Assessment of Functioning Scale (GAF) (Hall, 1995). Dichotomous variables were harmonized using the same numerical values. Continuous variables units were matched if necessary (mg/dl to g/l). Total WBC was corrected in cases where data on CSF red blood cell count was available and equal to or more than 1000 erythrocytes/µl. One cell was subtracted from the total WBC for every 1000 erythrocytes/µl (Oviedo-Salcedo et al., 2021; Wildemann and Reiber, 2006). Patients where only the DUI information "less than a year" was known were imputed with a DUI of 12 months.

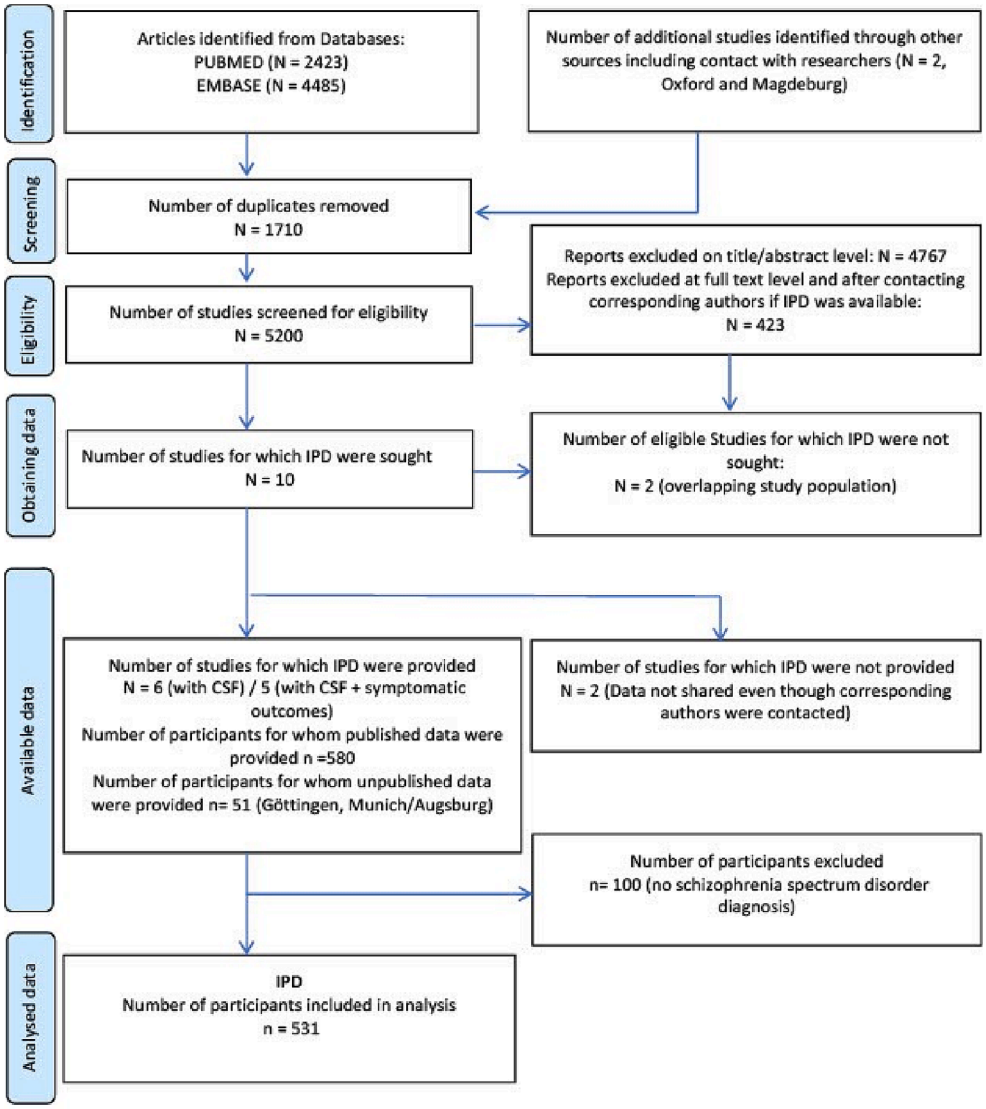

Fig. 1. The PRISMA IPD Flow Diagram.

2.3. Inclusion criteria

Data from individuals with FEP or ROP who underwent CSF diagnostic and had at least included the parameter CSF WBC count available (n, mean and SD) were included. All patients had received a diagnosis of non-organic, non-affective psychotic disorder (International Classification of Diseases, Tenth Revision (ICD10) F20/F22-29). FEP was defined as the first manifestation of psychotic symptoms at the time point of study inclusion. ROP was defined as having received the aforementioned diagnosis within a year prior to inclusion (Jeppesen et al., 2022).

A total of n = 100 patients were excluded from the analyses due to a diagnosis other than F2x or lacking CSF data. For more details, please see Fig. 1 and supplement S1.

The centers Munich and Augsburg were classified as one center since interviews within this prospective study were performed by the same study personnel (project nr. 21–1139).

2.4. Data synthesis and analysis

2.4.1. Groups and Main outcomes

CSF/serum albumin ratio cut-offs were age-adjusted according to the Reiber formula (4 + age/15) x10^{-3} (Reiber and Peter, 2001) and thus the binary outcome age-adjusted CSF/serum albumin ratio elevation was created.

"Any CSF alteration" was defined as follows: age-adjusted CSF/serum albumin ratio elevation or CSF WBC > 5/µl or CSF protein elevation according to study-specific definition or presence of OCBs in blood and/or CSF (type II, III or IV).

Main outcomes were Positive and Negative Syndrome Scale (PANSS) total, positive and negative scores (Kay et al., 1987), Trail-Making-Tests-A and −B (TMT-A and −B) (Bowie and Harvey, 2006) and Montreal Cognitive Assessment (MoCA) scores (Nasreddine et al., 2005) for male and female populations separately and for the whole sample.

2.4.2. IPD

Data analysis was performed in R studio (version.6.1) and *meta*-analyses were conducted using the *metafor* (version 3.4) package. Given the observational nature of primary studies and expected high rates of heterogeneity, a random-effects model with Hartung-Knapp adjustment was used for all analyses. For continuous outcomes, standardized mean differences (SMDs) and for dichotomous outcomes, relative risks (RRs) were used as summary statistics. Main outcomes were compared between patients with and without "Any CSF alterations" and "age-adjusted albumin CSF/Serum ratio elevation". To pool RRs, the Mantel-Haenszel method was used (Webb, 2010). RRs were used in order to investigate the dichotomous CSF outcomes "Any CSF alteration" and "age-adjusted albumin CSF/Serum ratio elevation" with regard to sex regardless of the symptomatic outcomes. Subgroup analyses were conducted according to sex. A significance level of $\alpha < 0.05$ was applied for all analyses. Heterogeneity was assessed using tau^2 and I^2 statistics. A restricted maximum-likelihood estimator was used for tau^2 and the Q-Profile method was used for the confidence interval of tau^2 and tau in order to quantify heterogeneity. Since sex is known to influence CSF outcomes, all cohorts were divided into male and female study population subgroups. Since aggregate data in respective studies was only available for few CSF parameters in three studies, but neither with symptom severity scores nor for our main outcome groups, only IPD was considered for our statistical analyses.

2.4.3. Mixed-effects linear regression models

In order to investigate the impact of continuous CSF outcomes on symptoms, regression models were computed. Mixed-effects regression models were computed using the "lme4" package of R for with CSF WBC as a predictor and symptom severity as outcome (PANSS positive, negative, general scores, MoCA_score, TMT-A and TMT-B scores), adjusting for sex, age, center and a random variable addressing repeated measurement from the same center. For the IgG CSF/Serum ratios only CSF and cognitive outcomes from one center (Munich/Augsburg) were available and thus used a simple regression model with similar characteristics as described above, excluding center. An interaction term between sex and CSF parameters were included in all the models to investigate the modulatory impact of sex on the association between CSF outcomes and symptoms.

2.4.4. Risk of bias

Risk of bias among included studies was assessed according to our modified Newcastle-Ottawa Scale for cross-sectional studies (see Supplement S6) (Wells and Connell, 2024). Studies that scored a total of 7 or 6 points were considered to have a low risk of bias; 4–5 points were considered to have a medium risk of bias; 3 points or less were considered to have a high risk of bias.

3. Results

3.1. Data availability

A total of N = 2423 studies were identified on PUBMED and N = 4485 on EMBASE. After duplicate removal (N = 1710) and addition of studies identified through other sources (N = 2), N = 5200 studies were screened for eligibility according to the aforementioned inclusion and exclusion criteria. N = 423 studies were excluded at full text level. For N = 10 studies IPD were sought. The population of two studies (Campana et al., 2022; Gine-Serven et al., 2022) were overlapping with other publications from the same working groups (Oviedo-Salcedo et al., 2021; Guasp et al., 2021). In this case, the study with more FEP individuals was selected and the respective two studies were counted as one. Thus, eight cohorts were available with IPD on routine CSF parameters (and five with both IPD on routine CSF parameters and symptomatic outcomes) among people with FEP/ROP. For six cohorts (6/8, 75 %), IPD was provided while for N = 2 published studies (2/8, 25 %) IPD was not (Endres et al., 2020; Meixensberger et al., 2020) provided. Furthermore, N = 51 participants from unpublished cohorts were added after systematically contacting research groups to provide IPD in the field of immunopsychiatry. In order to investigate whether IPD was available, corresponding authors from the N = 423 aforementioned CSF publications in schizophrenia were contacted (see Fig. 1). In the additional database search from November 1st 2023, N = 3 relevant new publications were found (Singh et al., 2023; Maurus et al., 2023; Campana et al., 2023) which analyzed overlapping cohorts from which IPD were already available, thus no new IPD was sought.

3.2. Risk of bias

According to our modified Newcastle-Ottawa Scale for cross-sectional studies, 2 studies had a low risk of bias, 4 a moderate risk and 1 a high risk of bias (see Supplements S6).

3.2.1. Demographics – total sample

As summarized in Table 1 and Tables S2-S3, a total of n = 531 individuals were included in the descriptive sample with a mean age of 32.8 (SD = 13.7) years. N = 298 (56.1 %) were men. Duration of illness (DUI), for both FEP and ROP combined, at the timepoint of CSF diagnostics (n = 325) was 12.8 months (SD = 19.7). Patients where only the DUI information "less than a year" was known (n = 122) were imputed with a DUI of 12 months. Individuals with recent-onset psychosis (n = 101) were all by study-specific inclusion criteria diagnosed with SSDs within one year of CSF diagnostics (Jeppesen et al., 2022). The mean duration of untreated psychosis (n = 52) was 69.3 days (SD = 130.1). The majority of patients were diagnosed with paranoid schizophrenia (56.1 %). Almost all individuals were receiving at least one AP (n = 442/485, 91.1 %) with n = 85 (17.5 %) being treated with two (15.9 %) or three (1.6 %) APs. Duration of antipsychotic treatment was

Table 1
Symptom severity and cerebrospinal fluid alterations in recent onset psychosis – IPD *meta*-analysis, Campana et al.

Whole sample Continuous variables	N	Mean	SD (±)
Age (years)	531	32.81	13.74
Duration of illness at Timepoint of lumbar puncture (months)	325	12.76	19.70
PANSS positive	178	18.17	6.44
PANSS negative	178	16.11	6.63
PANSS general	178	34.10	10.73
PANSS total	178	68.39	19.91
MoCA score	93	26.62	2.53
TMT-A (sec)	123	25.76	10.26
TMT-B (sec)	122	69.84	37.71
Albumin CSF/serum ratio	455	5.53	2.49
CSF WBC	531	1.64	2.09
Serum WBC	326	6.94	2.19
Duration untreated psychosis (days)	52	69.31	130.06
Number of APs	485	1.10	0.55
Duration of treatment (months)[a]	70	1.94	2.31
BMI (kg/m^2)	240	23.57	4.10
GAF	93	35.22	13.91
IgG CSF/serum ratio	320	2.81	1.88
Categorical variables	**N**	**Total N**	**Percentage**
Male sex	298	531	56.12 %
ICD-10 diagnosis			
F20	238	531	44.82 %
F21	12	531	2.26 %
F22	40	531	7.53 %
F23	146	531	27.50 %
F24	1	531	0.19 %
F25	49	531	9.23 %
F28	3	531	5.65 %
F29	23	531	4.33 %
No specified ICD-10 diagnosis	13	531	2.45 %
Prodromal schizophrenia	6	531	1.13 %
Medicated with APs	442	485	91.1 %
1 AP	357	485	73.6 %
2 APs	77	485	15.9 %
3 APs	8	485	1.6 %
Cardiovascular disease	37	322	11.49 %
Diabetes	11	323	3.41 %
Lung disease	24	404	5.94 %
Active smoker	177	464	38.15 %
Any CSF alteration[b]	206	531	38.79 %
CNS disorder[c]	13	304	4.28 %
Elevated age-corrected albumin CSF/serum ratio	111	455	24.40 %
CSF-restricted OCBs	7	272	2.57 %
OCBs in CSF and serum	51	271	18.82 %
CSF Protein elevation	70	393	17.81 %

Cohort demographics and clinical characterization, whole sample.
Legend: N: number of observations, SD: standard deviation, PANSS: Positive and Negative Syndrome Scale, MoCA: Montreal Cognitive Assessment, TMT-A and –B: Trail-Making-Tests-A and –B, CSF: Cerebrospinal Fluid, WBC: white blood cells, APs: antipsychotic drugs, BMI: Body-Mass-Index, GAF: Global Assessment of Functioning, IgG: Immunoglobulin G, ICD-10: International Classification of Diseases Tenth Revision, CNS: Central Nervous System, OCBs: Oligoclonal Bands.

[a] Data only available from the Copenhagen cohort.

[b] Definition of any CSF alteration: Age-corrected CSF/serum Albumin ratio elevation or CSF WBC > 5 or CSF Protein elevation or OCBs in CSF or serum.

[c] since all individuals with CNS disorders had missing data regarding PANSS and cognitive outcomes, these individuals only appear in the overview table, the following CNS diseases were present: suspected, but not diagnosed NPH (1), meningoencephalitis at age 11 (2), past minor stroke (3), head trauma at age 4 (4), past head trauma III° (5), right frontotemporal defect after head trauma at age 5 (6), neuroborreliosis with ipsilateral facial paresis in year 2002 (7), meningitis at age 11 (8), suspected multiple sclerosis (9), suspected low-grade glioma of the right medulla oblongata (10), ICH diagnosed 2014 (11), infantile cerebral palsy (12); unclear epileptic seizures in childhood until age 14(13).

1.94 months (SD = 2.31) although only a subsample of the Copenhagen cohort (n = 70) had this information available.

Most individuals were assessed at the centers Munich/Augsburg (n = 316), followed by Copenhagen (n = 101), Mataró (n = 42), Magdeburg (n = 32), Muenster (n = 25), Goettingen (n = 11) and Oxford (n = 2). Individuals had a mean PANSS total score (n = 178) of 68.4 (SD = 19.9) and a mean PANSS positive score (n = 178) of 18.2 (SD = 6.4). Regarding the cognitive outcomes, individuals had a mean MoCA score (n = 93) of 26.6 (SD = 2.5) and mean TMT-A (n = 123) and TMT-B scores (n = 122) of 25.8 (SD = 10.3) and 69.8 (SD = 37.7) respectively.

3.2.2. CSF and blood – total sample

Regarding CSF data, only a subsample of the n = 531 individuals included had complete CSF data available. CSF and serum albumin levels were available for n = 455. In n = 271 patients OCBs were assessed in both CSF and serum. In a total of n = 393 subjects CSF protein levels were assessed.

Overall, n = 206/531 individuals showed any CSF alteration (38.8 %) and n = 111 showed an elevated age-adjusted albumin CSF/serum ratio (24.4 %). CSF-restricted OCBs were detected in n = 7/272 individuals (2.6 %) and OCBS in both CSF and blood were detected in n = 51/271 individuals (18.8 %). N = 70/393 showed study-specific CSF protein elevation (17.8 %). Mean CSF WBC (n = 531) was 1.6 cells (SD = 2.1) and mean IgG CSF/serum ratio (n = 320) was 2.8 (SD = 1.9). Mean albumin CSF/serum ratio (n = 455) was 5.5 (SD = 2.5). Serum WBC (n = 326) was 6.9 (SD = 2.2).

For details regarding the demographics and CSF outcomes of the male and female subgroups, please see Tables S2 and S3.

3.3. Clinical characteristics of patients with vs. Without CSF/serum albumin ratio elevation

No significant difference between individuals with increased vs. non-increased CSF/serum albumin ratio regarding PANSS total scores (n = 135, SMD = -0.12, 95 %CI −0.61 to 0.37, p = 0.5498) and PANSS positive scores (n = 135, SMD = 0.30, 95 %CI −0.09 to 0.69, p = 0.1092). Nevertheless, male individuals with an elevated CSF/serum albumin ratio showed significantly higher PANSS positive scores than males with CSF/serum albumin ratio within normal range (n = 82, SMD = 0.34, 95 %CI 0.05 to 0.64, p = 0.0368, I^2 = 0 %). Female individuals with an elevated CSF/serum albumin ratio did not show significantly higher PANSS total (n = 53, SMD = -0.48, 95 %CI −1.74 to 0.78, p = 0.50) or PANSS positive scores (n = 53, SMD = 0.22, 95 %CI −1.62 to 2.05, p = 0.25) compared to female individuals without elevated CSF/serum albumin ratio.

There was no significant difference regarding PANSS negative scores (n = 135, SMD = -0.20, 95 %CI −0.65 to 0.26, p = 0.3234), but a significant subgroup difference in PANSS negative scores between sexes (p = 0.0181).

Regarding cognitive outcomes, there was no significant difference in TMT-A and TMT-B scores between groups (n = 122, SMD = -0.33, 95 % CI −0.92 to 0.25, p = 0.1677 and n = 121, SMD = -0.16, 95 %CI −0.67 to 0.34, p = 0.3797). There was also no significant difference in MoCA scores between groups (n = 92, SMD = 0.25, 95 %CI −0.49 to 0.98, p = 0.3655). For more details, please see Fig. 2 and supplement Tables S5a-n.

3.4. Additional analyses

The mixed-effects and simple regression models examining the relationship between CSF parameters (CSF WBC and IgG CSF/Serum ratio) and symptomatic outcomes showed no significant associations (p > 0.1). Furthermore, a non-significant interaction between sex and CSF parameters (p > 0.1) indicated no modulatory role for sex in the association between CSF outcomes and symptoms (please see Table S4 for further details).

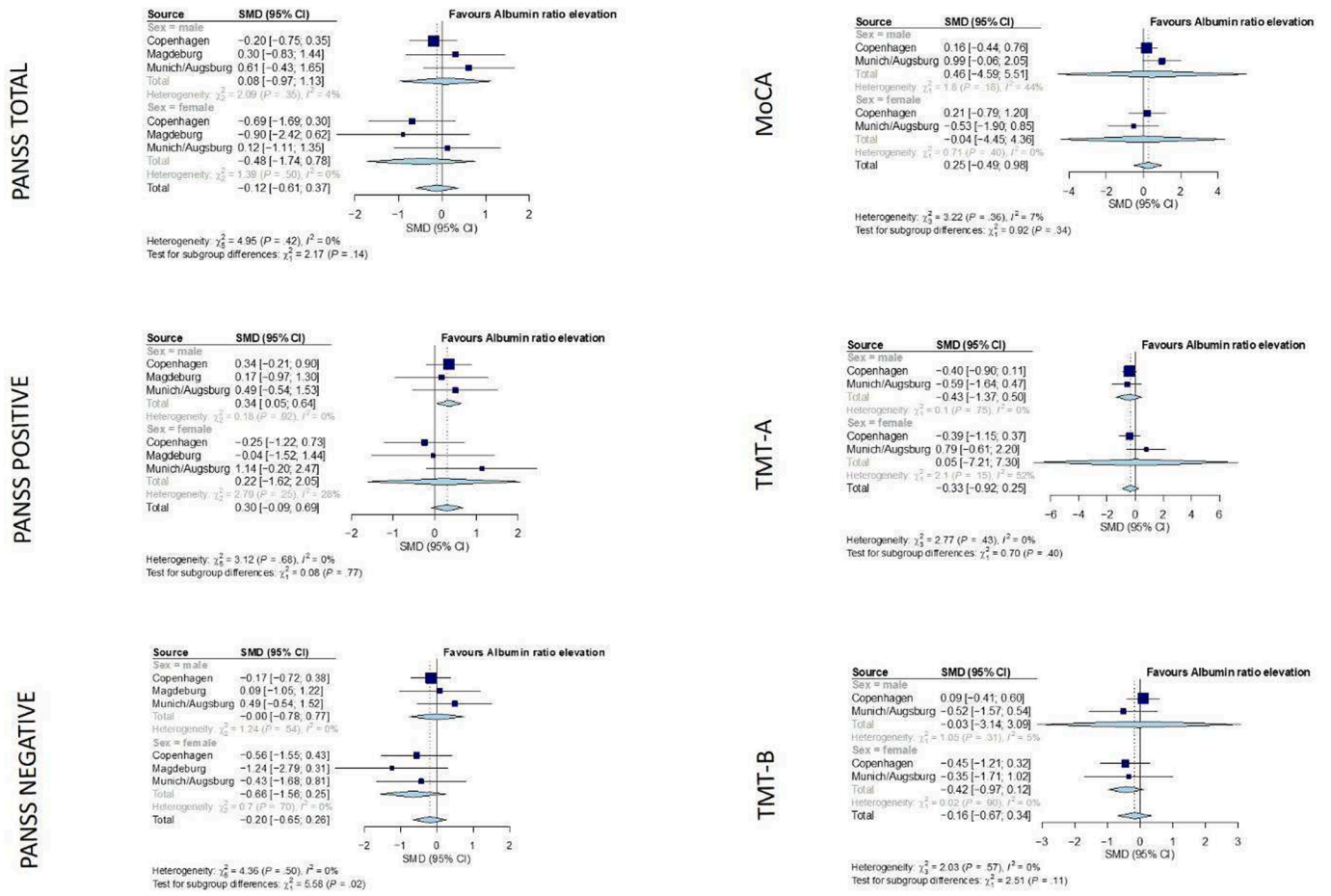

Fig. 2. Meta-analyses graphic results of albumin CSF/serum ratio vs. continuous clinical outcomes. Legend: SMD: Standardized mean difference, CI: confidence interval, χ^2, I^2 heterogeneity measures, PANSS: Positive and Negative Syndrome Scale, MoCA: Montreal Cognitive Assessment, TMT-A and –B: Trail-Making-Tests-A and –B, CSF: Cerebrospinal Fluid.

3.5. Clinical characteristics of patients with vs. Without any CSF alteration

There was no significant difference regarding PANSS total (n = 178, SMD = -0.17, 95 %CI −0.55 to 0.22, p = 0.3413) and PANSS positive scores (n = 178, SMD = 0.20, 95 %CI −0.13 to 0.54, p = 0.1952). Nevertheless, male individuals with any CSF alteration showed significantly higher PANSS positive scores than individuals without any CSF alteration (n = 107, SMD = 0.29, 95 %CI 0.17 to 0.41, p = 0.0047, I^2 = 0 %). Female individuals with any CSF alteration did not show significantly higher PANSS total (n = 71, SMD = -0,52, 95 %CI −1.37 to 0.34, p = 0.50) or PANSS positive scores (n = 71, SMD = 0.07. −1.05 to 1.20, p = 0.26) than female individuals without any CSF alteration. There was no significant difference regarding PANSS negative scores (n = 178, SMD = -0.18, 95 %CI −0.58 to 0.23, p = 0.3407).

Regarding cognitive outcomes, there was no significant difference in TMT-A and TMT-B scores between groups (n = 123, SMD = -0.35, 95 % CI −0.96 to 0.26, p = 0.1637 and n = 122, SMD = -0.13, 95 %CI −0.60 to 0.34, p = 0.4418). There was also no significant difference in MoCA scores between groups (n = 93, SMD = 0.28, 95 %CI −0.46 to 1.02, p = 0.3140). For more details, please see Fig. 3 and supplement Tables S5a-n.

3.6. CSF alterations in male vs. Female patients

When comparing male vs. female patients with regard to the frequency of any CSF alteration (140/298 events in males vs. 66/233 events in females) and CSF/serum albumin ratios (83/257 events in males vs. 28/198 events in females), there was no significant sex-related differences in both CSF conditions (RR = 1.36, 95 %CI 0.64 to 2.90, p = 0.3394; RR = 1.53, 95 %CI 0.28 to 8.34, p = 0.4842 respectively, both with substantial heterogeneity with I^2 = 55 %). Please see Fig. 4 and supplement Tables S5a-n for more details.

4. Discussion

We report the first individual patient data *meta*-analysis investigating the association between CSF alterations and symptom severity in early psychosis. Our sample constitutes the largest available cohort of ROP and FEP individuals having received CSF diagnostics to date.

We observed CSF alterations in 39 % of individuals. This is in line with previous monocentric cohorts from Munich, Germany (Campana et al., 2022) and slightly lower than the 49 % prevalence reported in another large, although not exclusively FEP, cohort (Endres et al., 2020).

To contextualize these findings, a study on patients with recent-onset depression reported abnormal CSF/serum albumin ratios in around 18 % of cases (Sorensen, 2022). A similar prevalence (21 %) was found in a age and sex matched healthy control population (Sorensen, 2022). In multiple sclerosis, as chronic inflammatory disease of the central nervous system, OCBs are positive in up to 95 % of patients (Deisenhammer et al., 2019), while CSF/serum albumin ratios are presumed to be elevated in approximately 12–23 % of cases (LeVine, 2016).

Looking at the respective alterations separately, around 24 % of individuals showed an increased CSF/serum albumin ratio, which is higher than previously reported in the literature (e.g. only 16 % of FEP individuals in Endres et al. (Endres et al., 2020). The presence of OCBs in

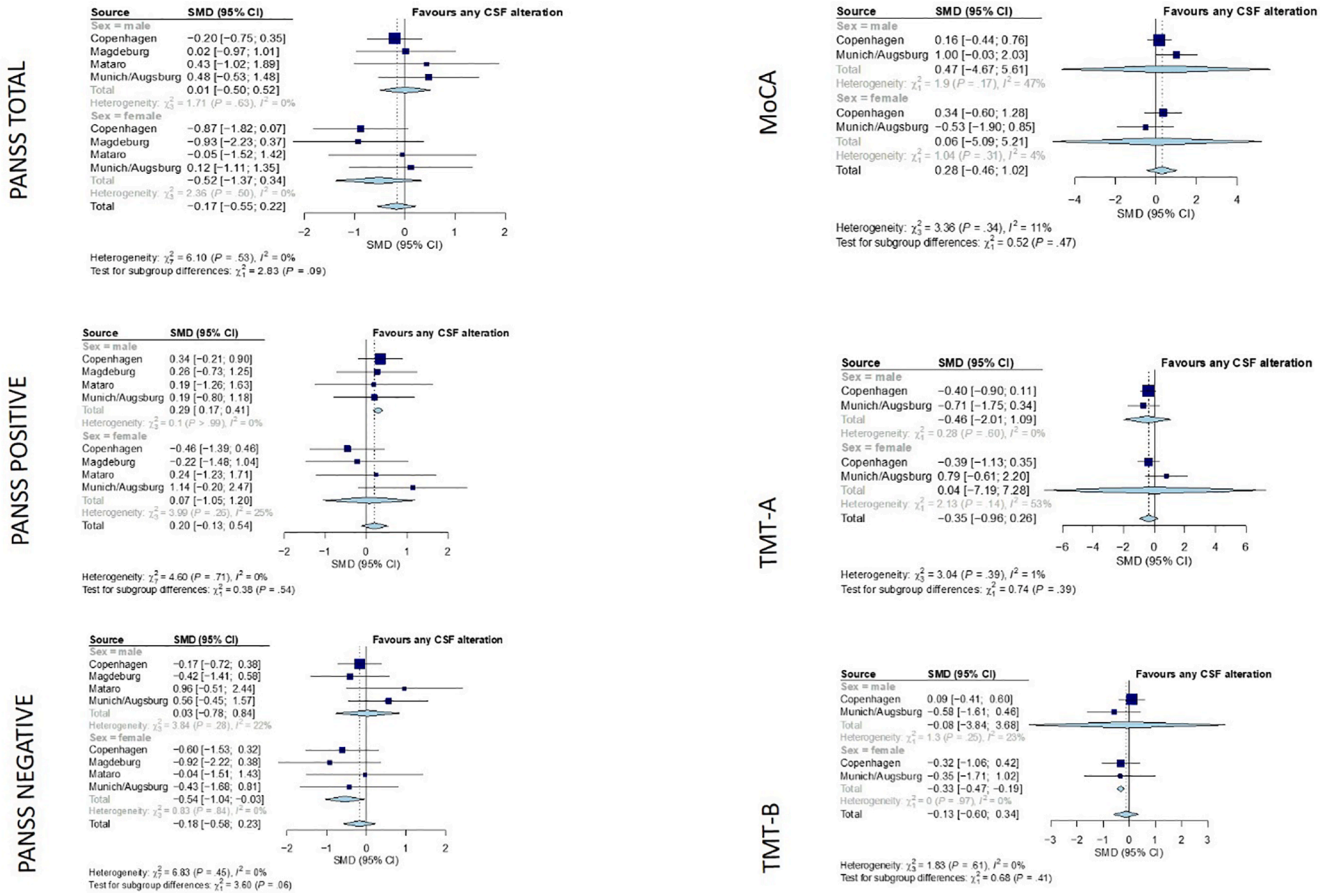

Fig. 3. Meta-analyses graphic results of any CSF alteration vs. continuous clinical outcomes. Legend: SMD: Standardized mean difference, CI: confidence interval, χ^2, I^2 heterogeneity measures, PANSS: Positive and Negative Syndrome Scale, MoCA: Montreal Cognitive Assessment, TMT-A and –B: Trail-Making-Tests-A and –B, CSF: Cerebrospinal Fluid. Definition of any CSF alteration: Age-corrected CSF/serum albumin ratio elevation or CSF WBC > 5 or CSF Protein elevation or OCBs in CSF or serum.

CSF and blood was the next most common CSF alteration assessed in our sample. This is also a pathognomonic sign of a disrupted BCB, as a highly permeable BCB allows the transfer of OCBs between the bloodstream and the CNS. Overall, our data solidify the evidence for a substantial subgroup of FEP individuals showing measurable CSF alterations early in the illness.

Regarding symptom severity, our sample was mildly to moderately ill (Leucht et al., 2005) with an average PANSS total score of 68.4 (SD = 19.9). This is in line with data from other large FEP cohort samples (Abdin et al., 2017). We found no statistically significant differences when comparing symptom severity between individuals with and without CSF alterations or with and without age-adjusted CSF/serum albumin ratio elevation. Similarly, our mixed-effects models for continuous CSF outcomes showed non-significant results.

Interestingly, in our IPD *meta*-analysis, males with any CSF alteration as well as males with increased CSF/serum albumin ratio were characterized by a significantly higher PANSS positive subscale than individuals without the aforementioned alterations with small effect sizes (SMDs > 0.29). These differences could not be observed in the respective PANSS subscales in women (p-values ≥ 0.25).

It is worth mentioning that no significant differences in any CSF alterations or elevated CSF/serum albumin ratio frequency were detected in our IPD *meta*-analyses when groups of male and female individuals were taken into account. Similarly, we did not find any significant differences in PANSS scores between sexes. It can be speculated that biological sex-determined factors might enhance positive symptom severity when CSF is altered and promote early-onset treatment-resistance. It is well known that sex-hormones have a complex modulatory action on the immune system (Klein and Flanagan, 2016). Given that BCB impairment in SSDs might be associated with immune dysregulation and inflammation, it could be speculated that increased estrogen levels in females might be protective regarding the detrimental effect of BCB impairment on symptom load which is in line with evidence from animal models which indicate that sex hormones modulate BCB permeability in a sex-specific manner (Dion-Albert et al., 2022; Shin et al., 2011).

The cross-sectional design of this study cannot elucidate whether a BCB disruption or CSF alterations are cause or consequence of a more pronounced disease manifestation in a subgroup of individuals. Nevertheless, it is worth discussing such findings. A large *meta*-analysis showed that most FEP patients respond to antipsychotic medications, with up to 81 % of individuals achieving a 20 % PANSS score reduction and 52 % of individuals reaching a 50 % PANSS score reduction after antipsychotic treatment (Zhu et al., 2017). Meanwhile, up to 30 % of FEP patients meet the criteria for TRS (Chan et al., 2021; Siskind et al., 2022). TRS is defined as persistence of symptoms despite ≥ 2 adequate antipsychotic trials (Lehman et al., 2004; Howes et al., 2017). Although symptoms might be negative or cognitive, positive symptoms are generally a central feature in TRS (Potkin et al., 2020; Farooq et al., 2013). As shown in a recent *meta*-analysis, men with FEP are 1.57 times more likely to develop TRS than women (Siskind et al., 2022). Moreover, it is well documented that antipsychotic treatment is associated with better response in women than in men with schizophrenia (Rabinowitz et al., 2014; Storosum et al., 2023). In this light, the presence of more severe positive symptoms in men with CSF alterations or BCB disruption is of central relevance, as such alterations might play a role in antipsychotic response and in TRS development. Overall, this data suggests that

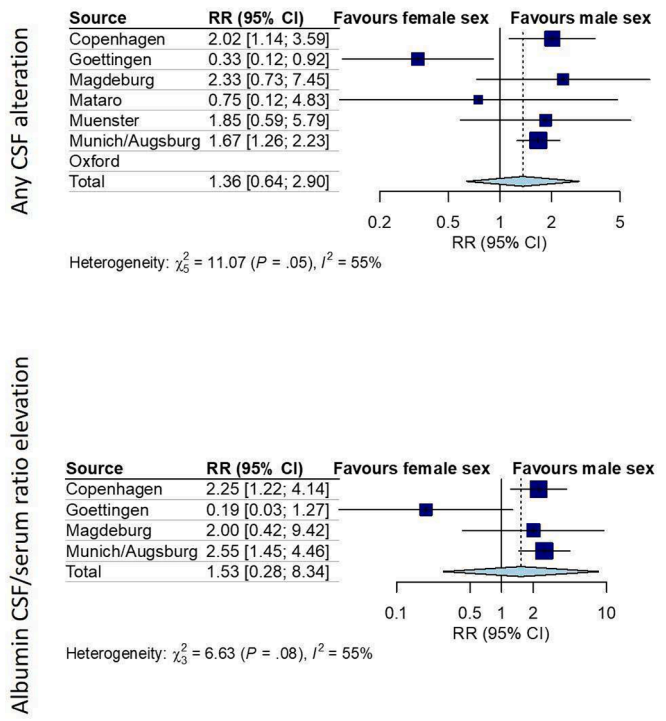

Fig. 4. Relative risks for any CSF alteration and elevated albumin CSF serum ratio in males and females. Legend: RR: relative risks, CI: confidence interval, χ^2, I^2 heterogeneity measures, CSF: Cerebrospinal Fluid. Definition of any CSF alteration: Age-corrected CSF/serum albumin ratio elevation or CSF WBC > 5 or CSF Protein elevation or OCBs in CSF or serum.

CSF alterations, and more specifically BCB disruption, could be key in determining sex-differences in antipsychotic response and treatment trajectories. Males with such alterations could be more at risk for developing TRS. These findings could inform prospective studies assessing the predictive power of such alterations for the development of TRS. If more evidence regarding this notion emerges, stratified clinical trials could investigate whether an earlier commencement of the antipsychotic clozapine in males with CSF alterations could reduce TRS rate.

In our sample, more than 90 % of individuals were treated with antipsychotics, with 17.5 % being treated with two or three antipsychotic agents. There was no difference in the number of antipsychotic agents between sexes. It might be speculated that the subsample being treated with ≥ 2 antipsychotics represents a specific ROP subsample at higher risk for developing early-onset treatment resistance.

Since antipsychotics must cross the BCB or BBB to exert their pharmacological action, BCB influence on antipsychotic pharmacodynamics is relevant (Pollak et al., 2018). BCB as well as blood–brain barrier endothelial cells express several key molecules such as P-glycoprotein that act as an efflux transporter and modulate CNS drugs concentrations (Qosa et al., 2015). Modulation of P-glycoprotein functionality could lead to variable drugs concentration, therefore contributing to the variability in therapeutic response (Pollak et al., 2018). Various antipsychotics are substrates for P-glycoprotein (Moons et al., 2011) and P-glycoprotein function is increased in individuals with chronic schizophrenia (de Klerk et al., 2010). One could speculate, that a reduced efflux as a consequence of neuroinflammatory processes promotes the accumulation of neurotoxic substances which favors more severe or persistent symptoms. The lack of such an effect in female individuals could be explained by steroid hormoneś modulatory effects on P-glycoprotein (Bebawy and Chetty, 2009; van Assema et al., 2012). Interestingly, clozapine does not seem to be a substrate for P-glycoprotein, which might explain its efficacy in TRS (Pollak et al., 2018; Moons et al., 2011).

5. Limitations

Several limitations hinder a further interpretation of the data. The cross-sectional design of this analysis prevents the assessment of CSF parameterś dynamic during the course of the illness. Longitudinal CSF data, on the other hand, is uncommon because it is infrequently clinically indicated and difficult to obtain. Moreover, scarcity on medication data impedes a thorough assessment on the role of APs and their dosage in BCB alterations. Nevertheless, the majority of the sample (n = 485) had data available on the number of individuals medicated with APs. The vast majority (73.6 %) was in treatment with one AP, with almost 16 % receiving two APs. Although formally not precise, the number of APs used could be taken as a proxy for difficult-to-treat states. Having only duration of treatment data from the Copenhagen cohort (n = 70), no *meta*-regression was undertaken for this variable. Similarly, a lack of other clinical information such as substance abuse, duration of untreated psychosis or medical comorbidities does not allow for adequate confounders correction. In general, availability of CSF data was inhomogeneous between the various sub-cohorts. For example, in Jeppesen et al. (n = 101) and Giné-Servén et al. (n = 42) OCBs data was lacking (Jeppesen et al., 2022; Gine-Serven et al., 2022). In Raeuber et al. (n = 25) as well as in Giné-Servén et al. (n = 42) data on CSF albumin levels was missing (Guasp et al., 2021; Rauber et al., 2021). Similarly, CSF protein levels were missing in n = 141 individuals. More complete data might have led to a more accurate assessment of CSF alterations in SSDs individuals early in their illness. It is worth mentioning that no data on neuronal antibodies, such as antibodies to the NR1 subunit of the N-methyl-D-aspartate-receptor (NMDAR) or the anti-Contactin-associated protein-2 (CASPR2) and anti-Leucine-rich glioma inactivated 1 protein (LGI1) antibodies, was available. The assessment of such antibodies, which have been linked to psychotic syndromes (Lennox et al., 2017; Kayser et al., 2013; Oviedo-Salcedo et al., 2018), could have further refined the etiological and clinical interpretation of the reported CSF alterations.

Furthermore, we performed a power analysis (Faul, 2007) to evaluate the sample size required to confidently detect group differences in further routine CSF investigations among people with FEP. When assessing key variables such as the difference between individuals with increased vs. non-increased CSF/serum albumin ratio regarding PANSS positive score, our sample size (n = 135) covers about a third of the required sample size (n = 396) when assuming a power level of 0.8 and a significance level (2-sided) of α = 0.05. Thus, although we report results from the largest available cohort of ROP and FEP individuals having received CSF diagnostics to date, these results require careful interpretation.

Finally, we were only able to collect data from large clinical centers in European cities, thus our sample might not be representative of FEP individuals in other environments. Nevertheless, as mentioned above, only two cohorts with available IPD were not included in our analyses.

Overall, this data substantially enriches the limited knowledge available on CSF alterations in early psychosis. We consolidate the evidence for a large subgroup of individuals early in the disease presenting CSF alterations and signs of BCB disruption. Notably, we found a significant difference in positive symptom severity between male individuals with and without BCB disruption, which might play an important role in the lower rate of antipsychotic response seen in males and their higher likelihood to develop TRS (Siskind et al., 2022).

Since the CSF/serum albumin ratio is an indirect marker of blood–CSF permeability, and cannot localize leaks, approaches that can directly quantify blood–brain barrier impairment, such as dynamic contrast-enhanced MRI (DCE-MRI) are needed for SSDs where prevalence of unspecific CSF alterations and especially BCB breakdown is evident. Finally, considering sex-related differences in future clinical trials might prove to be a valuable step towards a more individualized treatment approach.

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financial interests or potential conflicts of interest regarding the content of this report. AH received paid speakership by Janssen, Otsuka, Lundbeck, and Recordati and was member of advisory boards of these companies and Rovi. PF received paid speakership by Boehringer-Ingelheim, Janssen, Otsuka, Lundbeck, Recordati, and Richter and was member of advisory boards of these companies and Rovi. G.M.z.H. received compensation for serving on scientific advisory boards (Alexion, Roche, LFB) and speaker honoraria (Alexion). D.S. is supported by an NHMRC Investigator Fellowship GNT 1194635. S.H. is supported by an Australian Research Training Program scholarship. N.W. has received speaker fees from Otsuka, Lundbeck and Janssen. All other authors report no biomedical financial interests or potential conflicts of interest.

CRediT authorship contribution statement

Mattia Campana: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Vladislav Yakimov:** Writing – review & editing, Writing – original draft, Data curation. **Joanna Moussiopoulou:** Writing – review & editing, Writing – original draft. **Isabel Maurus:** Writing – review & editing, Writing – original draft, Conceptualization. **Lisa Löhrs:** Writing – review & editing, Investigation. **Florian Raabe:** Writing – review & editing, Resources. **Iris Jäger:** Investigation, Data curation. **Matin Mortazavi:** Writing – review & editing, Formal analysis, Data curation. **Michael E. Benros:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Rose Jeppesen:** Writing – review & editing, Investigation, Data curation. **Gerd Meyer zu Hörste:** Writing – review & editing, Investigation, Data curation. **Michael Heming:** Writing – review & editing, Investigation, Data curation. **Eloi Giné-Servén:** Writing – review & editing, Investigation, Data curation. **Javier Labad:** Writing – review & editing, Investigation, Data curation. **Ester Boix:** Writing – review & editing, Investigation, Data curation. **Belinda Lennox:** Writing – review & editing, Investigation, Data curation. **Ksenija Yeeles:** Writing – review & editing, Investigation, Data curation. **Johann Steiner:** Writing – review & editing, Investigation, Data curation. **Gabriela Meyer-Lotz:** Writing – review & editing, Investigation, Data curation. **Henrik Dobrowolny:** Writing – review & editing, Investigation, Data curation. **Berend Malchow:** Writing – review & editing, Investigation, Data curation. **Niels Hansen:** Writing – review & editing, Investigation, Data curation. **Peter Falkai:** Writing – review & editing, Supervision. **Spyridon Siafis:** Writing – review & editing, Formal analysis. **Stefan Leucht:** Writing – review & editing, Formal analysis. **Sean Halstead:** Writing – review & editing, Methodology. **Nicola Warren:** Writing – review & editing. **Dan Siskind:** Writing – review & editing, Supervision. **Wolfgang Strube:** Writing – review & editing, Supervision. **Alkomiet Hasan:** Writing – review & editing, Supervision, Conceptualization. **Elias Wagner:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available upon request, given approval of the local ethical committee

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.04.011.

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