Schizophrenia Research 252 (2023) 77–87

Contents lists available at ScienceDirect

Schizophrenia Research

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

Depression trajectories and cytokines in schizophrenia spectrum disorders - A longitudinal observational study

Gunnhild E. Hoprekstad [a,b,c,*], Eirik Kjelby [a,c], Rolf Gjestad [a,g], Farivar Fathian [a,c], Tor K. Larsen [b,k], Solveig K. Reitan [i,j], Maria Rettenbacher [h], Anja Torsvik [c,d,f], Silje Skrede [d,e], Erik Johnsen [a,b,c], Rune A. Kroken [a,b,c]

[a] Division of Psychiatry, Haukeland University Hospital, Box 1400, 5021 Bergen, Norway
[b] Department of Clinical Medicine, University of Bergen, P.O. Box 7804, 5020 Bergen, Norway
[c] Norwegian Centre for Mental Disorders Research (NORMENT), Haukeland University Hospital, Box 1400, 5021 Bergen, Norway
[d] Department of Clinical Science, University of Bergen, P.O. Box 7804, 5020 Bergen, Norway
[e] Section of Clinical Pharmacology, Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Box 1400, 5021 Bergen, Norway
[f] Dr. Einar Martens Research Group for Biological Psychiatry, Department of Medical Genetics, Haukeland University Hospital, Bergen, Norway
[g] Centre for Research and Education in Forensic Psychiatry, Haukeland University Hospital, Bergen, Norway
[h] Medizinische Universität Innsbruck, Austria
[i] St. Olav's University Hospital, Department of Mental Health, Trondheim, Norway
[j] Norwegian University of Science and Technology, Department of Mental Health, Trondheim, Norway
[k] The TIPS-center, Stavanger University Hospital, Stavanger, Norway

ARTICLE INFO

Keywords:
Psychosis
Inflammation
Interleukin
Depression
Trajectory
CRP

ABSTRACT

Depression occurs frequently in all phases of schizophrenia spectrum disorders. Altered activity in the immune system is seen in both depression and schizophrenia. We aimed to uncover depressive trajectories in a sample of 144 adult individuals with schizophrenia spectrum disorders followed for one year, in order to identify possible cytokine profile differences. Patients were assessed longitudinally with the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS), where a score above 6 predicts depression. The serum cytokine concentrations for tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, interleukin (IL)-1beta, IL-2, IL-4, IL-6, IL-10, IL-12p70 and IL-17A were measured using immunoassays. Latent growth curve models, multilevel models and latent class growth analysis (LCGA) were applied. The LCGA model supported three latent classes (trajectories) with differing CDSS profiles during the one-year follow-up: a high CDSS group (40.8 % of participants), a moderate CDSS group (43.9 %) and a low CDSS group (15.3 %). Five single PANSS items predicted affiliation to depressive trajectory: hallucinations, difficulty in abstract thinking, anxiety, guilt feelings and tension. In the high CDSS group, despite diminishing psychotic symptoms, depressive symptoms persisted throughout one year. The pro-inflammatory cytokines IFN-γ, IL-1β and TNF-α were differentially distributed between the depressive trajectories, although levels remained remarkably stable throughout 12 months. Significant changes were found for the anti-inflammatory cytokine IL-10 at baseline with an accompanying difference in change over time. More research is required to optimize future treatment stratification and investigate the contribution of inflammation in depressed patients with schizophrenia spectrum disorders.

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CDSS, Calgary Depression Scale; CRP, C-reactive protein; DE, Design effect; FIML, Full information maximization likelihood; GWAS, Genome Wide Association Studies; ICC, Intra class correlations; ICD-10, International Classification of Diseases −10; ICH-GCP, The International Council for Harmonisation of Techincal Requirements for Pharmaceuticals for Human Use (ICH). Good Clinical Practice (GCP); IFN, Interferon; IL, Interleukin; LCGA, Latent class growth analysis; LGC, Latent growth curve; LLOQ, Lower Limit of Quantification; LRT, Likelihood ratio test; ML, Multilevel; PANSS, the Positive and Negative Syndrome Scale; SCID-1, Structured Clinical Interview for DSM-IV Axis 1 Disorders; SCI-PANSS, Structured Clinical Interview for the Positive and Negative Syndrome Scale; SD, Standard deviation; SPSS, Statistical Package for Social Sciences; TNF, Tumor necrosis factor.

* Corresponding author at: Division of Psychiatry, Haukeland University Hospital, Box 1400, 5021 Bergen, Norway.
E-mail address: gunnhild.eldhuset.hoprekstad@helse-bergen.no (G.E. Hoprekstad).

https://doi.org/10.1016/j.schres.2022.12.049
Received 23 June 2022; Received in revised form 1 December 2022; Accepted 30 December 2022
Available online 10 January 2023

1. Introduction

Schizophrenia spectrum disorders, with a lifetime prevalence of up to 1 %, severely impact mental health through psychotic symptoms, cognitive dysfunction and loss of function (Charlson et al., 2018; Janoutova et al., 2016; Tandon et al., 2013) . Depressive symptoms are known to accompany schizophrenia, with prevalence estimates ranging from 25 to 80 % (Kjelby et al., 2018; McGinty et al., 2018; Siris et al., 1988; Upthegrove et al., 2010; Upthegrove et al., 2017) and a particularly high prevalence in females (Shimamoto and Rappeneau, 2017). Depression negatively contributes to all aspects of psychosis (Tollefson and Andersen, 1999; Vohringer et al., 2013), reduces quality of life and life expectancy (Knapp et al., 2004; Tollefson and Andersen, 1999), is associated with poor outcomes in first episode patients (Challis et al., 2013; Upthegrove et al., 2014) and increases the risk of relapse, (Upthegrove et al., 2014) self-harm and suicide (Drake et al., 1985; Kjelby et al., 2015). Depressive symptoms can occur in all stages of schizophrenia (Bressan et al., 2003): in the high risk syndromes (Salokangas and McGlashan, 2008) and acute phases (Schennach et al., 2015), as well as in the post-psychotic phase (Birchwood et al., 2000; Jeczmien et al., 2001; Upthegrove et al., 2010). Both psychological and biological factors may contribute to the increased risk of depression in patients with schizophrenia (Anderson et al., 2013). However, little is known about the underpinnings of depression in psychotic disorders, and current treatment leaves room for significant improvement (Donde et al., 2018; Gregory et al., 2017).

The pathophysiology of schizophrenia has not been fully mapped, however, the immune system seems to be involved (Kohler-Forsberg et al., 2020). Immune changes in pregnancy and fetal life are associated with increased risk of schizophrenia (Meyer et al., 2006; Spencer and Meyer, 2017). Genome wide association studies (GWAS) have identified genetic risk markers for schizophrenia in the immune coding parts of the genome (Ripke et al., 2013). Links between autoimmune diseases and schizophrenia are well established (Benros et al., 2014; Kalinkovich et al., 2020) and some anti-inflammatory drugs have been reported to reduce psychotic symptoms (Cho et al., 2019; Sommer et al., 2014). One potential level for interaction between inflammation and psychiatric symptoms are cytokines. Cytokines, including interleukins, interferons and some growth factors, are biochemical messengers and key mediators in the communication between immune cells, neurons and various stromal cells (Ransohoff and Benveniste, 2019). They have regulatory, pleiotropic and pro- and anti-inflammatory qualities, are potential clinical biomarkers (Mondelli et al., 2015) and may be targets of therapy. Cytokine alterations are reported in patients with schizophrenia (Momtazmanesh et al., 2019; Muller et al., 2015), in some studies with a pro-inflammatory profile in both blood and cerebrospinal fluid (Boerrigter et al., 2017; Goldsmith et al., 2018), but evidence is conflicting (Dunjic-Kostic et al., 2013; Meyer, 2011). Pro-inflammatory cytokines correlate with both symptoms of schizophrenia with depression, and depression per se (Goldstein et al., 2015; Khandaker et al., 2018; Lesh et al., 2018; Noto et al., 2016a). Elevated interleukin 6 (IL-6) has been shown (Almulla et al., 2021; Khandaker et al., 2014; Luo et al., 2019), and longitudinal studies have implied that higher levels of IL-6 in early life are linked to later development of both depression and psychosis (Khandaker et al., 2014). Correspondingly, decreasing levels of IL-6 have been reported to correlate with a decrease in depressive symptoms in schizophrenia (Ventura et al., 2020). Additionally, level of IL-10, an anti-inflammatory cytokine, has been shown elevated in individuals with schizophrenia when compared to healthy controls (Kunz et al., 2011), and IL-10 concentration has been shown to correlate with the severity of clinical symptoms (Xiu et al., 2014) and a chronic disease course (Rodrigues-Amorim et al., 2017). IL-10 has also been suggested to be a key cytokine in depression (Roque et al., 2009).

Moreover, various stages of psychosis, as well as the impact of treatment, are reflected in immune parameters: in a meta-analysis, Miller et al. found elevated levels of IL-1β, IL-6 and interferon- γ (IFN-γ) in both first episode psychosis and relapsing episodes, with declining immune markers after antipsychotic treatment (Miller et al., 2011). Higher levels of IL-3 (Xiu et al., 2015), IL-6 and tumor necrosis factor (TNF)-α are also evident in schizophrenia with comorbid depression (Lee et al., 2017). Low-grade elevation of C-reactive protein (CRP), a more well-established marker of inflammation (Marnell et al., 2005), has also been associated with schizophrenia (Dickerson et al., 2013), including in the context of comorbid depression (Faugere et al., 2018).

The immune system may also be involved in the pathophysiology of depression per se (Himmerich et al., 2019; Miller and Raison, 2016), supported by GWAS linking immune genes to an increased risk of depression (Barnes et al., 2017). Altered levels of cytokines, mainly those associated with a pro-inflammatory profile (Kim et al., 2016), are evident in affective disorders (Kiecolt-Glaser et al., 2015; Rosenblat et al., 2014; Rosenblat and McIntyre, 2016; Yuan et al., 2019). Increased inflammation in various parts of the human body is suspected to trigger depression (Sharma, 2016). In line with this, meta-analyses of clinical trials have indicated an anti-depressive effect of anti-inflammatory drugs (Kappelmann et al., 2018; Kohler et al., 2017). Accordingly, administration of the pro-inflammatory IL-2 and IFN-α cytokines as part of a medical treatment for hepatitis or cancer has been associated with a rapid development of depressive symptoms (Bonaccorso et al., 2002; Capuron et al., 2002).

A deeper understanding of depression in schizophrenia is of particular clinical importance, as the risk of suicidality in depression related to psychoses is high (Hawton et al., 2005; Popovic et al., 2014), and depressive symptoms may resemble negative symptoms and be overlooked. Hence, defined immunological state or trait markers of depression could be of clinical relevance in this group. Furthermore, insight into the role of inflammation in depression in this patient group may facilitate long-awaited progress in treatment. Many of the prior studies linking depression in schizophrenia to immunological parameters have been cross-sectional in nature, with few participants, leading to a call for larger longitudinal studies (Goldsmith et al., 2016). In this study, we investigated heterogeneity of depressive symptoms experienced throughout a 12-month follow-up period in patients with schizophrenia spectrum disorders treated with atypical antipsychotics. Our hypotheses were that cytokine profiles differ between depressive trajectories, and that patients with depression will show a more pro-inflammatory immune profile when compared to patients without depression. In this study, 9 cytokines (IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, IFN-γ and TNF-α) were measured by Luminex 200 at 8 time points during one year. Patients with psychosis were stratified into trajectories based on CDSS depression scores.

2. Methods

2.1. Study design and participating centers

The cohort includes data collected in the BeSt InTro randomized trial, in which the three antipsychotic drugs amisulpride, aripiprazole and olanzapine were compared (Johnsen et al., 2020). Participants were recruited from October 2011 to December 2016. Study visits were performed at baseline, followed by additional visits at week numbers 1, 3, 6, 12, 26, 39 and 52. Participating centers were Haukeland University Hospital, Bergen, St. Olavs University Hospital, Trondheim, and Stavanger University Hospital (all Norway) and the Medical University of Innsbruck (Austria). After inclusion, patients were randomly assigned to receive oral amisulpride, aripiprazole or olanzapine.

2.2. Ethics

The Norwegian Regional Committees for Medical Health and Research Ethics and the Norwegian Medicines Agency approved the study. For the study center in Innsbruck, the corresponding approval authorities were the Board for Ethical Issues at the University of

Innsbruck and the Austrian Federal Office for Safety in Health Care (BASG). All patients gave their written informed consent prior to inclusion in the study. The study was monitored according to the guidelines for Good Clinical Practice (ICH-GCP) supplied by the Department of Research and Development, Haukeland University Hospital in Norway, and by the Clinical Trial Centre at the Medical University of Innsbruck, Austria.

2.3. Participants

Eligible participants for the study were both in- and outpatients above 18 years of age, diagnosed within the schizophrenia spectrum according to the International Classification of Diseases (ICD-10), diagnoses F20-F29. The Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-1) confirmed the diagnoses (Spitzer et al., 1992); trained psychologists and physicians conducted the SCID-1- interview before converting the diagnoses to ICD-10 diagnoses.

2.4. Inclusion and exclusion criteria

The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) was applied to measure and distinguish any psychotic symptoms (Kay et al., 1987). All personnel assessing participants were trained and certified at the PANSS Institute, New York, USA in order to secure high inter-rater reliability. The ambition was to recruit representative samples of patients in a setting close to clinical practice. For inclusion, the patients had to score 4 or more on at least one of the following PANSS items: P1 delusions, P3 hallucinations, P5 grandiosity, P6 suspiciousness/persecution or G9 unusual thought content. These PANSS items evaluate core schizophrenia symptoms and a score of 4 or above on these items has been used for selecting participants in similar studies (C. et al., 2009; Melle et al., 2008). Exclusion criteria were pregnancy, breastfeeding, hypersensitivity to study medication, prolactin-dependent tumors, co-occurring treatment that would increase the risk of severe arrhythmia, known increased risk of narrow-angle glaucoma, pheochromocytoma or inability to understand the native language.

2.5. Serum collection and analysis of cytokine variables

Peripheral blood was collected in the fasting state between 8 and 10 a.m. at all study visits. Blood samples were drawn into serum tubes before centrifugation at 3300 rpm for 10 min. Serum was stored at 80 °C until analysis. Serum samples were thawed on ice and analyzed by multiplex immunoassay using the High Sensitivity 9-Plex Human ProcartaPlex™ Panel (ThermoFisher Scientific, Waltham, MA, USA). The kit included the following cytokines: IL-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, IFN-γ and TNF-α. The assay was prepared mostly according to the manufacturer's protocol, however, the universal assay buffer included in the kit was replaced with PBS/0.1 % Tween to reduce matrix effects. Samples were randomized with respect to antipsychotic drug and gender, but all samples from each individual (visits 1–8) were analyzed on the same plate. Data was acquired on a Luminex 200 instrument (Luminex, Austin, TX, USA). A standard curve was included on each plate to calibrate between-plate variability and to quantify the analyte concentrations. All samples were run in duplicates. Center-specific methods were employed for analysis of CRP on the following instruments: Roche Modular P (Bergen), Siemens Advia Chemistry XP (Innsbruck), Roche Modular $P < 2016$/Siemens Advia Chemistry XPT $>$ 2016 (Trondheim) and Abbott Architect c16000 (Stavanger).

2.6. Clinical variables

In addition to PANSS scoring at each visit, the Calgary Depression Scale for Schizophrenia (CDSS) was used to assess the level of depressive symptoms (Addington et al., 1996; Addington et al., 1993; The Calgary Depression Scale for Schizophrenia). A score above six on the CDSS predicts the presence of a major depressive episode with 85 % sensitivity and 82 % specificity. The assessment also included medical history and background information, including weight, height, blood pressure, smoking history, alcohol habits and usage of antipsychotic medications.

2.7. Statistical analyses

The Statistical Package for Social Sciences (SPSS) version 26 was used for estimating descriptive statistics (mean, standard deviation (SD), skewness, kurtosis and frequencies) (IBM, 2019). Mplus 8.8 was used for estimating latent growth curve (LGC) models (Supplementary fig. 2), multilevel (ML) models and latent class growth analysis (LCGA) (Muthén and Muthén, 2020; Wang and Wang, 2012). Out of the 144 patients, one participant had no blood sample observations or CDSS measures. All patients had been administered the PANSS in at least one study visit. All models used the full information maximization likelihood (FIML) estimator, which uses all available data under the "missing at random" assumption (Kline, 2016). Thus, the effect of missing data is minimized (Bollen and Curran, 2006). Skewness values for the outcome variables were close to normally distributed after accounting for plate differences in the ML analyses (Hox et al., 2018). In addition, non-normality in data was adjusted for with robust maximum likelihood (Wang and Wang, 2012). Therefore, no log-transformation of the outcome was necessary. The LGC models were analyzed within a multilevel framework in order to separate out variances due to plate differences. To investigate non-linear change over time, the LGC models were specified as latent contrast difference score models (Bollen and Curran, 2006; Newsom, 2015). LGC models capture levels and changes in intercept and slope factors, both at mean and individual levels, the last expressed as variances. In order to identify the model, the slope variances were constrained to zero. Thus, this model equals the random intercept fixed slope linear mixed effect model. Intra class correlations (ICC) and design effects (DE) indicated non-ignorable clustering (Heck and Thomas, 2015).

Then, CDSS was analyzed with LCGA in order to identify subgroups with different profiles of level and change in CDSS (depressive trajectories). In LCGA models, the intercept and slope factor variances are fixed to zero, in contrast to growth mixture models (GMM), which represent full LGC models in different sub-populations. Thus, heterogeneity in observed data is reflected by differences in unobserved groups or latent classes. Accordingly, LCGA represents a common pattern of level and change in CDSS. The models were evaluated with the entropy index and the model fit indices: Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), with lower fit and higher entropy values indicating improved model fit (Kline, 2016; Muthén and Muthén, 2015). Statistically significant improvement of adding classes was tested by Vuong-Lo-Mendell-Rubin and parametric bootstrapped likelihood ratio tests (LRT) (Muthén and Muthén, 2015). In addition, the smallest class should be above $N = 25$ or 5 % of the total sample (Wickrama et al., 2016). If entropy was found to be above 0.80 (Wang and Wang, 2012), the most likely latent class membership was saved for each patient and analyzed with baseline predictor variables (Supplementary table 1).

In the next step, multinomial regression analysis was used to regress these latent groups (classes) of depression on the baseline demographic and clinical variables. This analysis was explorative. First all predictors were entered, then non-significant predictors removed with a backward stepwise procedure (Cohen et al., 2003). The predictors were sex, age, ethnicity, cohabiting status (living alone), smoking, antipsychotic naivety, CRP and the PANSS sum scores (Positive, Negative and General). In another model, each PANSS item was tested with the exception of G6 depression. Finally, we analyzed LGC models of level and change in cytokines as outcome variables and latent CDSS classes as unadjusted predictors. The high CDSS group was the reference group.

3. Results

3.1. Demographic and clinical variables

Baseline information for the 144 patients included is presented in Table 1. Among the participants, 65 % were male and the average age was 31.7 years. The majority of participants were diagnosed with F20 schizophrenia (58 %), followed by F22 delusional disorder (15 %). The mean baseline PANSS total score was 78.4 (SD 15.9) and the mean CDSS score was 6.7 (SD 5.1). A CDSS score above 6 indicates the presence of depression (Addington et al., 1996).

3.2. Level and change in depression and cytokines

Table 2 shows the average baseline level and change in CDSS and cytokines in the entire patient population during the follow-up period. The ICC and DE results showed varying degrees of clustering over plates, which was additionally indicated by the between plate variance estimates. The CDSS score was significantly reduced from the first week and throughout the entire year of follow-up. There were large inter-individual differences (high SD), but overall, cytokine levels remained stable and consistent during follow-up, both at group level and at an individual level (see supplementary fig. 1). During the first week, the levels of IFN-γ increased. The mean IL-1β level decreased during the 3–6 week interval, while both IFN-γ and IL-12p70 decreased during the final interval, i.e. from 39 to 52 weeks. Still, these changes did not show any consistent trend over the 52 weeks. Analyzing the 0–52 week interval, only IL-17A and IL-4 showed statistically significant reductions. Furthermore, there was a trend for reduced TNF-α.

Table 1
Patient characteristics ($N = 144$).

	N (%)
Men	93 (65.0)
Solitary living	61 (42.0)
Daily tobacco smoking	85 (59.0)
Alcohol abuse/dependence	13 (9.0)
Drug abuse/dependence*	27 (19.0)
Antipsychotic naive	56 (39.0)
CDSS total ≥ 7	67 (48.6)
Main diagnosis (ICD-10):	
F20 Schizophrenia	84 (58.0)
F21 Schizotypal disorder	2 (1.0)
F22 Persistent delusional disorder	21 (15.0)
F23 Acute and transient psychotic disorder	18 (12.0)
F25 Schizo-affective disorders	10 (7.0)
F28 Other non-organic psychotic disorders	1 (1.0)
F29 Unspecified non-organic psychosis	8 (6.0)
Medication	
Antidepressants	13 (9.0)
Mood stabilizers	6 (4.2)
Anti-inflammatory medication (NSAIDs)	5 (3.5)
Immune diseases**	8 (5.7)
	Mean (SD)
Age	31.7 (12.8)
PANSS total	78.4 (15.9)
PANSS Positive	21.2 (4.8)
PANSS Negative	17.8 (6.1)
PANSS General	39.4 (8.6)
CDSS total	6.7 (5.1)
BMI (kg/m^2)	25.6 (6)
CRP (mg/L)	2.7 (5.4)
Systolic blood pressure (mmHg)	121.3 (15.7)
Diastolic blood pressure (mmHg)	78.3 (9.6)

N: Total sample size. PANSS: Positive and Negative Syndrome Scales. CDSS: Calgary Depression Scale for Schizophrenia. BMI: Body Mass Index. CRP: C-reactive protein. *Drug abuse/dependence, mainly cannabis use (89 % in self-report, significantly lower percentage in urine samples). ** Relevant immune diseases (N): coeliac disease (1), Crohn's disease (1), psoriasis (3), unknown autoimmune disease (3).

Table 2
Multilevel latent growth curve models showing estimated level and change in CDSS and inflammation parameters ($N = 143$).

	Plate			Baseline		0–1 (weeks)		1–3		3–6		6–12		12–26		26–39		39–52		Overall change 0–52 weeks	
	ICC[a]	DE[b]	SD	Mean	SD	Mean	P	Mean	P	Mean	P	Mean	P	Mean	P	Mean	P	Mean	P	Mean	P
CDSS				6.70	3.50	−1.02	<0.01	−0.42	0.01	−0.22	0.06	0.06	0.47	−0.07	0.06	−0.06	0.12	0.06	0.09	−3.08	<0.01
IFN-γ	0.17(v3)	1.90	2.26	5.33	9.57	0.54	0.04	0.19	0.58	−0.24	0.40	0.05	0.64	−0.01	0.72	0.00	0.92	−0.06	0.03	−0.39	0.54
IL-1β	0.22(v8)	2.22	0.16	1.23	2.48	0.06	0.70	0.02	0.76	−0.09	0.03	0.02	0.42	−0.01	0.76	−0.01	0.70	0.01	0.55	−0.07	0.78
IL-10	0.33(v6)	2.89	0.53	1.21	2.05	0.14	0.50	0.03	0.82	−0.06	0.49	−0.02	0.47	0.02	0.37	−0.00	0.93	−0.02	0.31	−0.23	0.17
IL-12p70	0.05(v3)	1.28	0.65	3.11	7.51	0.01	0.93	0.08	0.50	−0.04	0.55	0.03	0.34	−0.01	0.85	−0.00	0.82	−0.03	0.04	−0.20	0.22
IL-17A	0.33(v3)	2.78	18.73	33.12	44.19	1.22	0.41	2.04	0.37	−2.91	0.25	0.68	0.37	0.04	0.55	−0.43	0.25	−0.08	0.53	−5.55	0.05
IL-2	0.33(v3)	2.89	15.16	26.12	28.06	1.16	0.20	1.53	0.25	−1.89	0.20	0.45	0.22	0.00	0.99	−0.15	0.42	−0.08	0.29	−1.67	0.38
IL-4	0.10(v3)	1.55	8.03	21.47	33.28	0.08	0.82	0.60	0.34	−0.37	0.33	0.01	0.91	0.02	0.81	−0.10	0.07	−0.07	0.19	−1.79	0.02
IL-6	0.11(v2)	1.63	0.74	2.16	2.97	0.19	0.15	0.06	0.64	−0.06	0.49	0.00	0.93	−0.00	0.95	0.02	0.45	−0.02	0.31	0.17	0.40
TNF-α	0.11(v2)	1.63	18.73	46.66	67.57	−3.35	0.34	3.34	0.09	−1.54	0.13	0.32	0.53	−0.15	0.56	−0.11	0.63	−0.10	0.41	−4.37	0.08

[a] ICC: Intra Class Correlation of individual blood measures within plates. Study visits (V1-V8) with highest values reported.
[b] DE: Design effect.

3.3. Depressive trajectories

The LCGA model showed improved fit for three latent classes (trajectories) with different CDSS profiles over time (see Fig. 1a and Supplementary table 1). The average probability for most likely latent class membership in these classes were 90 %, 95 % and 97 %. We identified three groups pertaining to high CDSS scores (40.8 % of participants), moderate CDSS scores (43.9 %) and low CDSS scores (15.3 %); hereafter referred to as the "high depression group", "moderate depression group" and "low depression group", respectively. The high depression group started at a CDSS score of 11.1 and underwent a statistically significant reduction during the first week, with a drop of −1.6 ($p = .018$). A further reduction occurred during the 1–3 week interval, with an average reduction of −0.7 units per week ($p = .039$). In the moderate depression group, the baseline CDSS started at 4.7 and was followed by reductions during the first and fifth intervals, pertaining to −0.8 and − 0.1 units, respectively, which trended towards statistical significance ($p = .062$ and $p = .064$). The low depression group started at CDSS 1.0 and showed no significant changes throughout the follow-up year.

3.4. Depressive trajectories predicted by demographic and clinical variables

We examined whether demographic and clinical variables could predict adherence to the different depression groups identified. In comparisons between the high and moderate depression groups, the age and sex of participants significantly differed; specifically, the high depression group was associated with lower age and female sex (see Table 3). In comparisons between the moderate and low depression groups, the PANSS Positive and PANSS General sub-scores significantly differed such that classification within the low depression group was more probable for patients with higher PANSS Positive scores, while lower for PANSS General scores. The variables of ethnicity, education, smoking, solitary living, antipsychotic naivety and PANSS negative subscore did not predict differences in depressive trajectory.

Five PANSS items predicted depressive trajectories: higher levels in G2 anxiety and G3 guilt feelings, as well as lower levels in G4 tension, predicted the high depression group membership in contrast to the low depression group. Lower levels in P3 hallucinations and G2 anxiety, as well as higher levels in N5 difficulty in abstract thinking, predicted classification in the moderate depression group in contrast to the high depression group. Sex was not related to group differences in the multinomial model (see Table 3).

3.5. Depressive trajectories and relation to cytokines and CRP

The only difference in cytokine levels identified between the depression groups was a significantly lower baseline level of IL-10 in the low depression group versus the high depression group (see Table 4 and Fig. 1b). Various longitudinal cytokine alterations were observed within the depressive trajectories: increased IL-10 was detected during the first week in the moderate depression group while IL-1 β showed a trend towards increased expression in the high depression group during the first week. Furthermore, significant reduction in IL-1β was present in the low depression group when compared to the high depression group. IL-1β was observed to be significantly increased during the 6–12 week interval in the moderate depression group. Analyzing the entire period (0–52 weeks), an increase in IL-1β was detected in the moderate depression group, while a decrease of this cytokine was identified in the low depression group. Regarding IFN-γ levels, a reduction occurred in the moderate depression group during the final interval (39–52 weeks). In the moderate depression group, IL-17A expression increased during the 12–26 week interval. An increase in IL-2 occurred during the first week in the moderate depression group. Additionally, analyses showed a reduction in IL-4 and TNF-α during the 26–39 week interval in the moderate depression group, however no significant changes of these cytokine levels were observed in the high depression group. Finally, a reduction in IL-6 was found in the low depression group for the whole study period (0–52 weeks). CRP was not related to any baseline predictor variables.

4. Discussion

The main finding of the current study is that individuals with schizophrenia spectrum disorders may be grouped into three different depressive trajectories, with a high, moderate or low symptom burden. The highest depression scores were identified at baseline, followed by rapid initial reduction in both the high and the moderate depression groups. None of the groups displayed increasing depression throughout the year. Hence, we found no support for the development of post-psychotic depression (Birchwood et al., 2000; Upthegrove et al., 2010). PANSS positive score was associated with increased initial

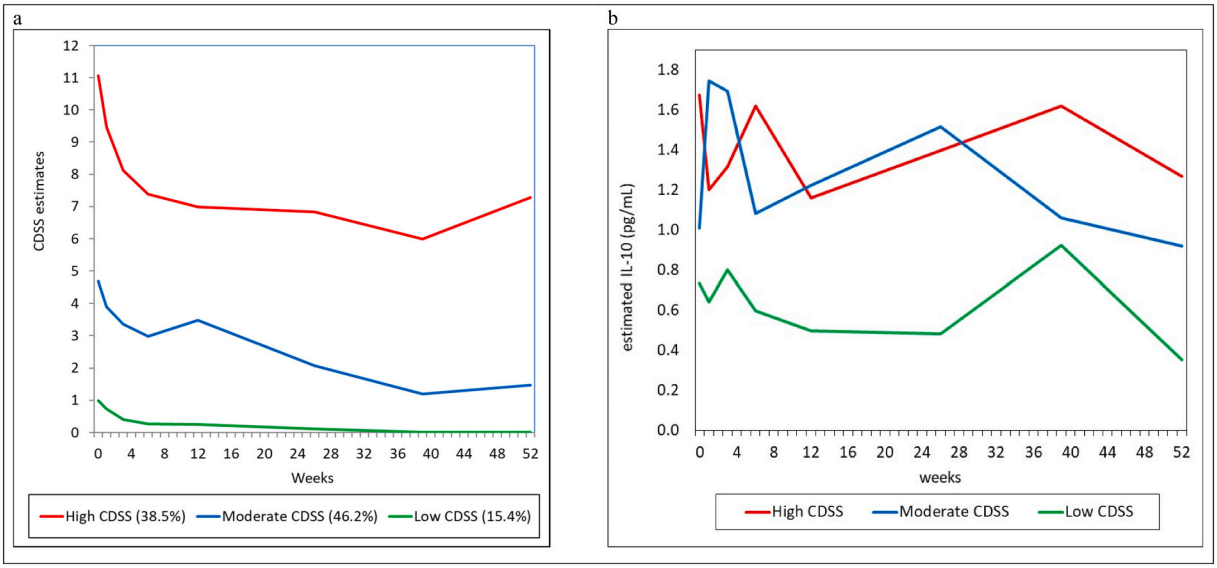

Fig. 1. 1a) Depression trajectories, expressed as various levels of the Calgary Depression Scale for Schizophrenia (CDSS), showing changes over time. 1b) Identified depression trajectories and their relationship with IL-10 levels (pg/mL).

Table 3
Multinomial regression analysis results of baseline predictors of most probable latent class.

	Low vs high depression group[a]				Moderate vs high depression group[b]			
	b	*p*	*OR*	$CI_{Low\text{-}High}$	*b*	*p*	*OR*	$CI_{Low\text{-}High}$
Model 1								
Intercept (b_0)	0.68	0.734			2.15	0.115		
Age	0.05	0.078	1.05	1.00–1.10	0.04	0.043	1.04	1.00–1.08
Sex	−0.59	0.410	0.55	0.14–2.26	−1.06	0.029	0.35	0.13–0.90
PANSS Positive	0.18	0.049	1.20	1.00–1.43	−0.05	0.456	0.95	0.84–1.08
PANSS General	−0.17	0.002	0.85	0.76–0.94	−0.05	0.145	0.95	0.89–1.02
CRP	−0.45	0.144	0.64	0.35–1.17	0.05	0.309	1.06	0.95–1.17
Model 2								
Intercept (b_0)	3.36	0.055			1.48	0.223		
Age	0.04	0.102	1.04	0.99–1.10	0.05	0.011	1.05	1.01–1.10
Hallucination (P3)	0.02	0.934	1.02	0.68–1.52	−0.40	0.005	0.67	0.51–0.88
Emotional social contact (N3)	−0.38	0.242	0.68	0.36–1.29	0.28	0.155	1.32	0.90–1.93
Abstract thinking (N5)	0.35	0.121	1.41	0.91–2.18	0.42	0.009	1.52	1.11–2.08
Anxiety (G2)	−1.73	<0.001	0.18	0.09–0.36	−0.73	0.002	0.48	0.31–0.76
Guilt (G3)	−0.66	0.013	0.52	0.31–0.87	−0.10	0.513	0.91	0.67–1.22
Tension (G4)	0.69	0.042	1.99	1.03–3.85	−0.06	0.767	0.94	0.63–1.41

OR: Odds ratio. $CI_{Low\text{-}High}$: 95 % confidence interval for the OR estimate.
[a] Low depression group versus high depression (reference) group.
[b] Moderate depression group versus high depression (reference) group.

depression, potentially indicating a masking of depressive symptoms in the most psychotic phase. However, as PANSS declined over the year (Johnsen et al., 2020), so did depressive symptoms. The notion that positive psychotic symptoms may mask symptoms of depression (Kjelby et al., 2018) was not confirmed. Although depressive symptoms declined throughout the year, the high symptom group never fell below the cut-off score for the presence of a major depressive episode (Addington et al., 1993). These findings support that clinical awareness of depression in schizophrenia, as well as more effective anti-depressive treatment, are called for.

In line with earlier studies of sex differences (Shimamoto and Rappeneau, 2017), we found that females were more likely to belong to the high depression group. Additionally, younger individuals were more likely to be in the high depression group. This is an important clinical aspect, as a young age with co-morbid depression significantly increases the risk of suicide (Nordentoft, 2007).

To our knowledge, this is the first study to link trajectories of depressive symptoms in schizophrenia spectrum disorders with long-term cytokine observations. Several processes co-occurred in the same time interval, including initiation or change of antipsychotic drug treatment and decline of psychotic symptoms (Johnsen et al., 2020). The alteration in levels of the pro-inflammatory IL-1β and TNF-α differed between the moderate and high depression groups. As no such changes were observed for individuals without depression, our findings support the idea that subpopulations among patients with schizophrenia differ with respect to immune activation, and that different clinical and biochemical phenotypes coexist (Noto et al., 2016a; Roomruangwong et al., 2020). IL-1β and TNF-α are among the pro-inflammatory cytokines previously found to be elevated in subpopulations of individuals with schizophrenia (Lee et al., 2017; Luo et al., 2019) as well as in subgroups of individuals with major depressive disorder (Brunoni et al., 2020). Regarding IL-6, significantly lower levels were found in the low depression group compared to the high depression group, consistent with earlier studies (Ventura et al., 2020). However, we did not find any association between baseline CRP and CDSS, also in line with earlier findings (Johnsen et al., 2016). Altogether, these results indicate that pro-inflammatory cytokine changes are less prominent in patients with depression associated with schizophrenia spectrum disorders. This might indicate that depression in schizophrenia spectrum disorders has different biological correlates than depression in affective disorders (Goldsmith et al., 2016; Upthegrove et al., 2017).

At baseline, the high depression group had higher levels of IL-10 than the moderate and low depression groups. As IL-10 often is grouped as an anti-inflammatory cytokine (Iyer and Cheng, 2012), this is not in line with our hypotheses that high depression scores are associated with a pro-inflammatory profile. However, both decrease (Miller et al., 2011) and increase (Kim et al., 2009; Maes et al., 1994) of IL-10 have been seen in patients with schizophrenia, correlated with severity (Xiu et al., 2014) and duration of illness (Roque et al., 2009). Furthermore, there are reviews and meta-analyses indicating increased IL-10 levels in depression (Kohler et al., 2017) and a role for IL-10 in depression has been suggested (Brunoni et al., 2020). Interestingly, IL-10 has been linked to inflammation in neurodegenerative diseases, as well as many of the autoimmune diseases patients with schizophrenia are prone to suffer from (Jeppesen and Benros, 2019; Noto et al., 2016b). The role of IL-10 in depression in different populations needs further exploration.

The summarized results from our sample support the notion that, when patients are grouped according to depressive trajectories, serum levels of various cytokines differ among subpopulations within the schizophrenia spectrum. However, our findings from repeated measures throughout a year indicate that cytokine levels are quite stable. Our most pronounced finding involves the level of IL-10: the low depression group, which displayed no depressive symptoms at baseline or throughout the follow-up period, showed continuously lower levels of IL-10 compared to the high depression group when analyzed from baseline throughout the entire follow-up. These results indicate that lower levels of inflammation exist in the low depression group compared to the high depression group. Additionally, we found that female and younger patients had a higher level of depressive symptoms.

5. Strengths and limitations

Major assets of the study are the follow-up duration of 12 months, and the sample size of 144. Cohorts linking repeated assessments of both clinical symptoms and immune signatures, are highly relevant when trying to understand schizophrenia and its comorbid psychiatric diseases. The BeSt InTro cohort was systematically mapped clinically and biochemically, with 8 study visits all including a wide range of psychometric tools and fasting state blood samples drawn in the morning. Clinical scores were performed by trained raters and cytokine analyses were performed concomitantly for all patients, analyzing all samples from the same patient on the same plate. Serum samples were stored at

Table 4
Estimated level and change in inflammation parameters predicted by three latent classes describing depressive trajectories: low depression and moderate depression groups compared to the high depression group.

	Depression	Baseline		0–1 (weeks)		1–3		3–6		6–12		12–26		26–39		39–52		0–52	
	group	*b*	*P*	*b*	*P*	*b*	*P*	*b*	*P*	*b*	*P*	*b*	*P*	*b*	*P*	*b*	*P*	*b*	*P*
IFN-γ	High (b_0)	4.69		0.54	0.18	0.04	0.87	0.04	0.82	−0.00	0.94	−0.01	0.81	0.03	0.36	−0.01	0.89	0.89	0.52
	Moderate (b_1)	1.15	0.47	0.02	0.95	0.33	0.53	−0.53	0.37	0.14	0.55	−0.02	0.79	−0.03	0.46	−0.09	0.01	−2.13	0.25
	Low (b_2)	0.85	0.69	−0.12	0.80	−0.25	0.54	−0.10	0.69	−0.07	0.21	−0.01	0.59	−0.01	0.64	−0.12	0.12	−3.23	0.15
IL1-β	High (b_0)	0.83		0.44	0.06	−0.09	0.30	−0.09	0.24	−0.01	0.56	0.01	0.12	0.02	0.14	0.03	0.34	0.65	0.09
	Moderate (b_1)	0.14	0.65	−0.42	0.13	0.14	0.24	0.03	0.75	0.07	0.04	−0.04	0.08	−0.03	0.25	−0.03	0.41	1.01	0.04
	Low (b_2)	2.36	0.09	−1.39	0.01	0.37	0.17	−0.15	0.53	−0.02	0.51	0.06	0.42	−0.11	0.18	−0.03	0.36	−1.87	0.03
IL-10	High (b_0)	1.68		−0.48	0.14	0.06	0.61	0.10	0.39	−0.08	0.24	0.02	0.34	0.02	0.58	−0.03	0.43	−0.41	0.09
	Moderate (b_1)	−0.67	0.15	1.21	0.02	−0.08	0.79	−0.31	0.10	0.10	0.20	0.00	0.90	−0.05	0.18	0.02	0.71	0.32	0.52
	Low (b_2)	−0.94	0.03	0.38	0.18	0.02	0.86	−0.17	0.17	0.06	0.28	−0.02	0.20	0.02	0.69	−0.02	0.68	0.02	0.95
IL-12p70	High (b_0)	2.33		−0.08	0.34	−0.03	0.67	0.03	0.50	0.01	0.77	−0.01	0.32	0.00	0.96	−0.02	0.22	−0.31	0.22
	Moderate (b_1)	0.15	0.82	0.30	0.06	0.28	0.20	−0.15	0.19	0.06	0.41	0.01	0.90	−0.01	0.66	−0.04	0.19	0.25	0.47
	Low (b_2)	5.10	0.28	−0.45	0.37	−0.11	0.62	0.06	0.71	−0.01	0.82	0.00	0.69	−0.01	0.56	0.03	0.09	−0.16	0.77
IL-17A	High (b_0)	3.10		0.03	0.69	−0.10	0.38	0.05	0.46	−0.01	0.81	−0.00	0.75	0.00	0.99	−0.02	0.06	−0.39	0.04
	Moderate (b_1)	0.53	0.54	0.23	0.34	0.52	0.20	−0.63	0.21	0.14	0.39	0.02	0.03	−0.12	0.19	0.01	0.66	−0.86	0.22
	Low (b_2)	0.16	0.90	−0.10	0.73	−0.07	0.52	−0.11	0.32	0.07	0.10	−0.02	0.18	0.00	0.83	0.05	0.27	0.28	0.75
IL-2	High (b_0)	2.53		−0.12	0.24	0.02	0.66	0.02	0.35	0.00	0.93	0.00	0.42	−0.01	0.07	0.00	0.61	−0.03	0.75
	Moderate (b_1)	0.12	0.80	0.37	0.02	0.28	0.23	−0.40	0.17	0.10	0.20	0.01	0.44	−0.05	0.25	−0.02	0.34	−0.48	0.37
	Low (b_2)	0.33	0.58	0.09	0.57	−0.01	0.90	−0.06	0.25	−0.00	0.71	−0.04	0.34	0.05	0.33	−0.01	0.43	−0.28	0.27
IL-4	High (b_0)	1.99		0.04	0.49	−0.04	0.30	0.00	0.86	−0.01	0.56	0.00	0.56	0.00	0.80	−0.01	0.10	−0.14	0.27
	Moderate (b_1)	0.13	0.75	0.06	0.48	0.15	0.18	−0.08	0.28	0.01	0.55	0.00	0.95	−0.03	0.01	−0.01	0.51	−0.17	0.46
	Low (b_2)	0.67	0.61	−0.11	0.28	0.01	0.80	0.02	0.49	−0.01	0.32	−0.00	0.90	−0.00	0.32	0.01	0.55	0.08	0.76
IL-6	High (b_0) [a]	2.24		0.00	0.999	0.00	0.999	0.00	0.999	0.00	0.999	0.00	0.999	0.00	0.999	0.00	0.999	0.65	0.12
	Moderate (b_1)	2.21	0.19	0.03	0.85	1.81	0.24	−1.12	0.27	−0.00	0.96	−0.01	0.91	−0.03	0.16	0.01	0.88	−0.78	0.11
	Low (b_2)	2.51	0.14	0.25	0.30	−0.08	0.53	−0.22	0.21	0.03	0.57	−0.01	0.61	−0.02	0.55	0.00	0.99	−1.16	0.04
TNF-α	High (b_0)	41.86		0.42	0.66	−0.07	0.90	0.04	0.94	−0.22	0.53	−0.30	0.42	0.33	0.38	−0.05	0.73	−1.25	0.49
	Moderate (b_1)	5.13	0.64	−0.13	0.89	3.88	0.12	−2.54	0.23	1.02	0.35	0.02	0.98	−0.72	0.01	−0.25	0.37	−5.14	0.31
	Low (b_2)	18.71	0.49	−24.04	0.28	10.84	0.31	−2.74	0.29	−0.31	0.35	0.12	0.39	0.01	0.86	0.04	0.82	−8.72	0.34

The regression coefficients b_1 and b_2 represent group differences compared to the high group (reference group: b_0).

[a] Due to estimation problems, the intercept values were constrained to zero for some intervals. This is also indicated with *p*-values 0.999.

-80° C to minimize degradation during the storage period. As the inclusion period spanned several years, blood sample storage time did vary, and stability issues could thus have influenced results. A common challenge in cohort studies, dropouts, may also have influenced results. Attrition rate for CDSS was 57 % at 52 weeks. This problem was minimized as we employed statistical analyses using all available data (FIML). Due to our pragmatic study design involving a patient sample representative for clinical everyday practice, 18 patients in our sample were diagnosed with acute and transient psychotic disorder (F23).

BMI, sex and smoking are confounders when analyzing immune markers (Ain et al., 2021), and were adjusted for in the models. The potential effects of antipsychotic medication were not scrutinized through our analyses. Due to the exploratory nature of the study and the risk of masking important links and associations (type II errors), we did not adjust for multiple comparisons (Rothman, 1990), leading to vulnerability to false positive findings (type I error). Not controlling for multiple comparisons may lead to spurious findings, while Bonferroni corrections may conceal significant findings in smaller samples (Althouse, 2016).

6. Conclusion

Depression is an important, potentially underdiagnosed and undertreated aspect of schizophrenia. It would be clinically relevant to know whether the immune system is dysregulated in some patients, thereby sustaining depressive symptoms. We found significant differences between the levels of depressive symptoms between subgroups of patients with schizophrenia. Levels of cytokines were stable over repeated measures, indicating biological and internal consistency. Throughout the year of testing, differences were most prominent during the first week of follow-up. However, despite diminishing psychotic symptoms, individuals with high levels of depressive symptoms at baseline did not achieve satisfactory relief from depressive symptoms during the one-year period of follow-up. The pro-inflammatory cytokines IFN-γ, IL-1β and TNF-α were associated with some variations between the three examined depressive trajectories, although the cytokine levels overall were stable throughout a year, both individually and at group level. A significant difference was found for the anti-inflammatory cytokine IL-10, suggesting a potential aim for further research into elaborating depression in schizophrenia. This might pave the way for immune-modulatory add-on therapy.

Twitter suggestion

Study finds significant differences between depressive symptoms in schizophrenia. Distinct patterns were detected for the anti-inflammatory cytokine IL-10, a potential target for further research, diagnostics and add-on treatment.

CRediT authorship contribution statement

G.E.H drafted the manuscript and contributed to extraction of the data, statistical analysis and interpretation of the results. E.K. revised the manuscript and contributed to data collection and interpretation of the results. R.G. performed statistical analysis, contributed to study design and interpretation of the results. F.F. contributed to data collection and revised the manuscript. T.K.L. revised the manuscript and contributed to interpretation of the data. S.K.R. revised the manuscript, contributed to data collection, interpretation and contextualization of the data. M.R. contributed to data collection and revised the manuscript. A.T. contributed to the study design, extraction of the data and data collection and revised the manuscript. S. S. contributed to the study design, data management and interpretation, and revision of the manuscript. E. J. revised the manuscript and contributed to study design and interpretation of the results. R.A.K. contributed to the study design and revised the manuscript. All authors have approved the final version of this work.

Funding

This work was supported by the Western Norway Regional Health Authority (#911679, #911820, #F-11490) and by the Research Council of Norway (#213727).

Declaration of competing interest

Nothing to declare.

Acknowledgement

We thank Kristin Paulsen Rye and Jorunn Bringsli for technical assistance. All authors have declared that there are no conflicts of interest nor financial conflicts in relation to the subject of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.12.049.

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Gunnhild E. Hoprekstad MD from 2007, studied at the University of Bergen, Norway. Specialist of psychiatry in 2017. Worked with oncology before entering psychysomatic medicine. Currently working as senior consultant in the psychosis department. PhD Candidate in University of Bergen, investigating immunology and psychosis.

Eirik Kjelby (born 1978) is a medical doctor (University of Bergen, Norway, 2003), specialist in psychiatry (2011) and PhD (2020). Since 2011 he has worked as senior consultant at the Department of Old Age Psychiatry at Haukeland University Hospital in Bergen, Norway. Research interests are depressive illness and suicidality within psychotic disorders, antipsychotics and old age psychiatry.

Rolf Gjestad, PhD, works as a statistician at the Research Department and Centre for Research and Education in Forensic Psychiatry, Division of Mental Health, Haukeland University Hospital, Bergen, Norway. He is also now in a part time position at the University of Bergen. He is clinical psychologist, and has worked with trauma, grief, stress, depression, and anxiety at the Centre for Crisis Psychology. In 2007 he started as a researcher at the Faculty of Medicine, University of Bergen, where he defended his PhD thesis in 2012: "Modelling Comorbidity Change and Long-term Mortality. A Treatment Study of Women with Alcohol Addiction." Special interests are multivariate models, factor models (EFA and CFA), and structural equation modelling, multilevel and different longitudinal models.

Farivar Fathian, born 1965, Norwegian citizen. M.D. Tehran University Medical Sciences 1991, and University of Oslo 1997. Specialty in Psychiatry 2010. PhD from University of Bergen 2019. Member of Bergen Psychosis Research Group and NORMENT (Norwegian Centre for Mental Disorders). Senior consulting psychiatrist since 2010, with experiences from psychosis field at Haukeland University Hospital, and gerontopsychiatry at NKS Olaviken Gerontopsychiatric Hospital in Bergen, Norway. She conducted a research project 2014-2019 studying the association between the inflammatory marker CRP and cognitive functions in acute phase of psychosis, and effects of antipsychotics on CRP level in schizophrenia spectrum disorders.

Tor Ketil Larsen: MD from 1989, specialist of psychiatry in 2003. Worked with oncology and studies of philosophy before entering psychiatry. Dissertation in 1999 (dr med) was over the theme of early intervention in psychosis. He has been working in clinical psychiatry with focus of detection and treatment of psychosis. Leader of the "schizophrenia-competence centre" in Stavanger, Norway during 1992-95. Larsen has had three periods with scholarship at the University of Oslo during 1996 to 2007. He was in charge of the early detection sector in the TIPS-study during 1996 to 2007. He was head of Research at Stavanger University Hospital, psychiatric division during 2010 to 2014. He is currently professor (II) of psychiatry at the University of Bergen. His research has been on early detection of psychosis, detection of prepsychotic conditions, drug abuse in psychosis, ADHD and epilepsia, follow-up studies of psychosis (1,2,5 and 10 years) and OCD and psychosis. He has a special interest in conceptual and ethical aspects of psychiatry in general and also the use of involuntary hospitalizations / treatment.

Solveig Klæbo Reitan (born 1970) finished medical school at University of Tromsø (UIT), Norway in 1995. In 2002 she defended her PhD degree in medicine (on immunology) at UIT. She specialised in psychiatry in 2006 and is working as senior psychiatrist/consultant at St Olavs University Hospital in Trondheim. She is also professor in psychiatry at NTNU (Norwegian University of Science and Technology), Trondheim. Reitan is also working as a forensic psychiatrist and she has had various positions in the Norwegian Medical Association. She is member of the Board of the Norwegian Psychiatric Association.

Maria Anna Rettenbacher (born 1971), MD, PhD. She is professor in psychiatry and leading consultant on the acute and crisis intervention ward at the Department of Psychiatry Psychotherapy and psychosomatics, Medical University Innsbruck in Austria.

Anja Torsvik is a researcher at the Department of Clinical Science at the University of Bergen, Norway. She has a master's degree in molecular biology (2002), and a PhD in biomedicine (2012), both from the University of Bergen, Norway. After her PhD, she worked as a researcher at SINTEF before she returned to the University of Bergen in 2017. Since then, Torsvik has been associated with the Norwegian Centre for Mental Disorders Research, NORMENT CoE. Her research interest is within blood markers and biological mechanisms associated with antipsychotic use and comorbidities of schizophrenia and bipolar disorder.

Silje Skrede (born 1979) is a medical doctor (University of Bergen, Norway, 2006), PhD (2012) and specialist in clinical pharmacology (2021). She is professor of pharmacology at the University of Bergen, and a senior consultant of clinical pharmacology at Haukeland University Hospital. Research interests include psychopharmacology and pharmacokinetics/ therapeutic drug monitoring of biologic drugs.

Erik Johnsen MD PhD is psychiatrist and head of the Bergen Psychosis Research Group and in the leader group of the Norwegian Centre for Mental Disorders Research (NORMENT) Centre of Excellence. He is head consultant at Haukeland University Hospital, professor at the University of Bergen, and is the principal investigator of several researcher initiated clinical drug trials in schizophrenia and related disorders. Fields of interest include translational psychosis research and clinical psychopharmacology.

Rune A. Kroken, MD at the University of Bergen in 1989, worked as a general practitioner before entering psychiatry, specialist of psychiatry in 1998. As specialist worked as consultant at in-patient units, from 2012 as head of the Psychosis Department at Haukeland University Hospital in parallel with conducting research. Completed PhD in 2013, currently engaged in several clinical research projects with themes including effects of antipsychotic treatment, effect of prednisolon on psychosis/schizophrenia and more broadly psychosis and inflammation/immunity.