Asian Journal of Psychiatry 114 (2025) 104749

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

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

Genetic signatures predict social-cognitive trajectories in ultra-high-risk psychosis: A 24-month longitudinal study

Zohreh Doborjeh [a,b,c,*], Alexander Sumich [d,e], Oleg N. Medvedev [c], Khan Buchwald [f], Maryam Doborjeh [a], Balkaran Singh [a], Sugam Budhraja [a], Alexander Merkin [g,h,i], Max Lam [j,k], Jie Yin Yee [k], Tih-Shih Lee [l], Wilson Goh [j,m,n,o,p], Jimmy Lee [j,k], Margaret Williams [q], Edmund M.-K. Lai [a,r], Nikola K. Kasabov [a,r,s,t]

[a] *Knowledge Engineering and Discovery Research Institute, School of Engineering, Computer, and Mathematical Sciences, Auckland University of Technology, New Zealand*
[b] *School of Population Health, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand*
[c] *School of Psychological and Social Sciences, The University of Waikato, New Zealand*
[d] *NTU Psychology, School of Social Sciences, Nottingham Trent University, United Kingdom*
[e] *Department of Psychology and Neuroscience, Auckland University of Technology, New Zealand*
[f] *School of Clinical Sciences, Auckland University of Technology, New Zealand*
[g] *Institute for Stroke and Applied Neurosciences, Auckland University of Technology, New Zealand*
[h] *Research Methods, Assessment & Science, Department of Psychology, University of Konstanz, Konstanz, Germany*
[i] *Center for Precise Psychiatry and Neurosciences, Germany*
[j] *Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore*
[k] *Institute of Mental Health, Singapore*
[l] *Neuroscience and Behavioural Disorders Programme, Duke-NUS Medical School, Singapore*
[m] *School of Biological Sciences, Nanyang Technological University, Singapore*
[n] *Center for Biomedical Informatics, Nanyang Technological University, Singapore*
[o] *Center of AI in Medicine, Nanyang Technological University, Singapore*
[p] *Division of Neurology, Department of Brain Sciences, Faculty of Medicine, Imperial College London, United Kingdom*
[q] *Department of Public Health and Psychosocial Studies, Auckland University of Technology, New Zealand*
[r] *School of Software Engineering, Dalian University, Dalian, China*
[s] *Institute for Information and Communication Technologies, Bulgarian Academy of Sciences, Sofia, Bulgaria*
[t] *Knowledge Engineering Cons. Ltd, Auckland, New Zealand*

ARTICLE INFO

Keywords:
Ultra-high Risk
Psychosis
Network analysis
Social-cognition
Genetics
Prediction
Longitudinal study

ABSTRACT

Background: Identifying biomarkers that predict social and cognitive outcomes in individuals at ultra-high risk (UHR) for psychosis remains a key challenge in preventive psychiatry. While genetic factors contribute to psychosis vulnerability, specific markers that predict individual trajectories of functional decline or resilience are still unclear.

Methods: In a 24-month longitudinal study involving UHR (n = 45) and healthy control participants (n = 54), we investigated for the first time the predictive causal relationship between key immunological genes (FABP5 family and immunoglobulins) and social-cognitive outcomes. Participants completed comprehensive assessments at baseline and four 6-month intervals. We used regression modelling and dynamic Bayesian network analysis to identify predictive relationships between gene expression and behavioral outcomes over time.

Results: FABP5 family genes (FABP5P1, FABP5P11, FABP5P9) significantly predicted verbal memory ($\beta = 0.233$, $p = 0.002$); working memory ($\beta = 0.225$, $p = 0.004$), and social skills ($\beta = -0{\cdot}190$, $p < 0.029$), respectively, at 24 months in the UHR group. Immunoglobulin-related genes showed distinct effects: FCGR2B predicted object recognition ability ($\beta = 0.233$, $p = 0.014$), while GOT2 inversely predicted planning ability ($\beta = -0.147$, $p = 0.067$). Network analysis revealed UHR-specific temporal dependencies absent in controls, with FCGRT emerging as a central node linking genetic markers to changes in processing speed and perceptual closure.

* Corresponding author at: Knowledge Engineering and Discovery Research Institute, School of Engineering, Computer, and Mathematical Sciences, Auckland University of Technology, New Zealand.
E-mail address: Zohreh.doborjeh@aut.ac.nz (Z. Doborjeh).

https://doi.org/10.1016/j.ajp.2025.104749
Received 23 July 2025; Received in revised form 22 October 2025; Accepted 23 October 2025
Available online 27 October 2025
1876-2018/© 2025 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Conclusions: This study provides the first evidence that FABP5 and immunoglobulin-related genetic markers can predict social-cognitive trajectories in individuals at risk for psychosis. These findings support the use of genetic profiling for early identification and highlight new opportunities for personalized preventive strategies in psychiatry.

1. Introduction

Psychosis, which can occur in disorders such as schizophrenia, encompasses a spectrum of experiences that disrupt an individual's cognition, emotions, perceptions, and behaviors (Orsolini et al., 2022). The construct of ultra-high risk (UHR) for psychosis was developed to characterize a potential prodromal phase, facilitating early detection and intervention of the condition (Fusar-Poli et al., 2013).The transition to psychosis from UHR states is estimated to be around 20–30 % within two years (Fusar-Poli et al., 2013; Gee and Cannon, 2011). This low specificity of UHR criteria poses a challenge to targeted prevention for individuals at-risk (Clark et al., 2015). Whilst prediction of conversion to psychosis has been a main point of interest in UHR studies, it is equally important to understand protective mechanisms present in UHR individuals who do not transition and the underlying physiologically protective mechanisms (Doborjeh et al., 2024; Simon et al., 2011; Studerus et al., 2017). Understanding interactions between genetic and environmental aetiological risk factors, and trajectories from UHR states, would allow early and accurate prediction of the emergence of psychosis and timely intervention at a critical juncture in illness progression (Clark et al., 2016). Therefore, identifying the mechanisms that underpin social and cognitive prodromal symptoms, which indicate impending illness onset, has become a critical focus in psychosis research (Bernardini et al., 2017; Doborjeh et al., 2023; Glenthøj et al., 2020; Luo et al., 2018).

The immune system and lipid metabolism are gaining prominence in understanding the biological basis of psychopathology, including schizophrenia and at-risk states (Frajerman et al., 2023). Genes regulating these systems are implicated in several biological processes associated with psychosis. In this study, we focus on genes regulating immune responses and lipid metabolism, particularly Immunoglobulin (Ig) and Fatty Acid-Binding Protein (FABP) genes. This focus is justified by evidence suggesting these gene families play essential roles in various physiological processes crucial for both social and cognitive functioning, which are key prodromal symptoms in UHR populations (Recio-Barbero et al., 2021; Tan et al., 2023).

According to immunology models of schizophrenia, abnormalities in the immune system can lead to chronic low-grade inflammation, which changes brain chemistry and precipitates neurotoxicity, increasing the risk for illness (Ermakov et al., 2022; Khandaker et al., 2015). Inflammation upregulates indoleamine 2,3-dioxygenase (IDO), an enzyme involved in the catabolism of the essential amino acid, tryptophan (Jenkins et al., 2016). Excessive tryptophan catabolism results in reduced synthesis of serotonin, and increased production of catabolites, such as kynurenic acid (KYNA) (Jenkins et al., 2016). Kynurenic acid is an endogenous, non-competitive antagonist of glutamate, (McCutcheon et al., 2020) particularly the N-methyl-D-aspartate (NMDA) receptor (Plitman et al., 2017). Thus, raised kynurenic acid in schizophrenia is in line with alternative models of schizophrenia that propose disruption to NMDA receptor (Plitman et al., 2017). More recent evidence suggests elevated production of KYNA in some genetic risk variants for schizophrenia may underpin excessive activity-dependent synaptic pruning, particularly in frontal and temporal regions (Orhan et al., 2023).

The FABP gene family embodies a group of diverse proteins which participate in a spectrum of tissue-specific pathways involved in lipid homeostasis (Gimeno, 2007). To date, nine putatively functional protein-coding FABP genes have been identified in humans, including FABP1 to FABP9, and FABP12 (Ke et al., 2021). In addition to protein coding FABPs, pseudogenes for FABP5 have been identified. For example, for FABP5, to date, 15 known pseudogenes have been identified in humans, and are classified as FABP5P1–15 (Smathers and Petersen, 2011), but delineation of specific functions is ongoing.

Studies showed that abnormal expression of FABPs transport can affect brain development, leading to cognitive impairment (Gimeno, 2007; Yehuda et al., 1999). FABP3 (along with FABP7) show various cognitive and behavioral changes, such as decreased social memory and novelty-seeking behavior, enhanced anxiety, and increased fear memory (Jang et al., 2022). FABP2, FABP5 and FABP6 have been investigated in relation to physical health, including Psoriasis and risk for cancers (Ke et al., 2021; Nowowiejska et al., 2022). FABP2 is involved in dietary lipid absorption and uptake, primarily in the small intestine, and may affect the gut-brain axis. However, very little is known about its role in behavior (Huang et al., 2022).

FABP5 has received the most attention in relation to behavior and is considered critical in the maintenance of cognitive function via regulating the brain uptake of the omega-3, docosahexaenoic acid (DHA; Pan et al., 2016). Downregulation of FABP5 is associated with cognitive deficits, particularly those associated with hippocampal function, such as memory (Penman et al., 2023). FABP5 has also been documented in the pathophysiology of schizophrenia and mood disorders (Iwayama et al., 2010).

Reduction in concentrations of peripheral polyunsaturated fatty acids (PUFAs), primarily omega-3, has been consistently found in schizophrenia, and is associated with symptom severity and illness progression (Amminger et al., 2010). Omega-3 supplementation may reduce the risk of transitioning to clinically relevant psychosis in UHR individuals (Amminger et al., 2007). However, not all studies support this (Hsu et al., 2020), and the precise proteins responsible remain elusive.

On the other hand, Igs genes have also emerged as potential contributors to schizophrenia's aetiology, particularly in the context of immunity against neurotropic viruses, such as cytomegalovirus (CMV) and herpes simplex virus type 1 (HSV1; Pandey et al., 2016). Exposure to these viruses has been postulated to contribute to cognitive impairments observed in schizophrenia and other neurodevelopmental disorders (Prasad et al., 2012). Igs family includes genes to encode Fc Fragment of IgG Binding Protein (FCGBP), Fc Gamma Receptor and Transporter (FCGRT), Fc fragment of IgG receptor IIb (FCG2B) and Glutamic-Oxaloacetic Transaminase 2 (GOT2).

Among Igs, GOT2 is thought to be involved in transamination of kynurenine into kynurenic acid. The involvement of Ig genes in schizophrenia suggests an intricate interplay between immune responses and neural functions, potentially influencing social and cognitive dimensions relevant to psychiatric illnesses (Plitman et al., 2017).

A link between immune-related genes and the social-cognitive dimensions of psychiatric disorders highlights their potential roles in shaping mental health outcomes. However, despite these insights, the specific implications of FABPs and Ig genes in individuals at high and ultra-risk for psychosis remain understudied.

Therefore, this study aimed to address this by utilizing a candidate gene approach focusing on both FABPs and Ig markers to delineate their potential influence on longitudinal social and cognitive changes, within a cohort comprising Control group and individuals at UHR for psychosis. This research has potential clinical implications for understanding the genetic basis of psychosis risk.

Statistical longitudinal correlation, regression and dynamic Bayesian network analysis methods were applied to:

1. Assess and estimate the predictive power of gene risk factors at baseline for social and cognitive variables at 24-months follow up.
2. Identify those key FABPs and Igs genes that are strong predictors of symptoms improvement or decline in social and cognitive functioning within UHR population.
3. Discover and compare the complex system of dynamic predictor and response relationships between genes, and social and cognitive functioning over time in both Control and UHR populations.

We hypothesize that the key biomarkers of FABPs and Igs will be useful for predicting social and cognitive outcomes. By examining these biomarkers, we aim to enhance the specificity of current UHR criteria, facilitating the development of personalized interventions for UHR population.

2. Methods and materials

All aspects of the study were completed in alignment with appropriate regulations and guidelines of the Asian Journal of Psychiatry publishing. Ethics approval was granted by the Singapore National Healthcare Group's Domain Specific Review Board. Informed consent was obtained from all participants. For those under 21 years of age, consent was obtained from a legal representative. The study protocol is shown in Fig. 1. includes the population, data collection, feature selection, and the designed methodology for association, interaction, and prediction.

2.1. Study populations and inclusion criteria

Participants are drawn from the Longitudinal Youth-at-Risk Study (LYRIKS), a prospective observational study on youths susceptible to psychosis (Lee et al., 2013) that includes n = 384 Control individuals (mean age = 21.7 years and SD = 3.4) and n = 173 UHR individuals (mean age = 21.3 years and SD = 3.5). All participants were between the ages of 14 and 29 years old. UHR status was determined using the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Lee et al., 2013). This approach identifies three subgroups of individuals at elevated risk: (i) attenuated psychotic symptoms (APS), (ii) brief limited intermittent psychotic symptoms (BLIPS), and (iii) genetic risk with functional decline (GRFD). These operational definitions are widely used in preventive psychiatry research and have been validated in multiple international studies, as identified by in the critical review by Fusar-Poli et al. (2013).

Current inclusion criteria: After imputation, individuals' data from all variables over two years were included in the current study. Thus, n = 99 (age mean = 21·94, SD = 3.50 individuals were selected (Control n = 54, age mean = 22.39, SD = 0.70; UHR n = 45, age mean = 21.53, SD = 3.23). The sample consisted of 63 males and 30 females. In terms of ethnicity, 66 participants identified as Chinese, 14 as Malay, 7 as Indian, and 6 as belonging to other ethnic backgrounds. Demographic information was not available for the remaining 7 participants.

2.2. Assessment

Multimodal data (social and cognitive functions) were collected every six months over two years: T0 = baseline assessment, T1 = 6-month, T2 = 12-month, T3 = 18-month and T4 = 24-month follow-ups. Genes data were collected at every 12 months over two years: T0 = baseline assessment, T2 = 12-month, T4 = 24-month follow-ups. In total, twenty-nine social, cognitive, and genetic features were identified as common features collected at baseline and at all available follow-up assessments. Table 1 presents all the data variables (social, cognitive, and genes), the subscales, and functions that were measured.

2.2.1. Social assessment

The performance-based social skills was measured on the High Risk Social Challenge Task (HiSoC; Gibson et al., 2010). Social skills are measured in terms of the display of affect, odd behavior and language, and social-interpersonal when evaluating the task. A 5-point Likert scale was used to rate the 16 items in the task (with higher scores indicating better social skills).

2.2.2. Cognitive assessment

The cognitive assessments are based on four cognitive neuropsychological batteries, including i) The Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) which comprises verbal memory (VM; verbal recall[1]), digit sequencing (DS; working memory[2]), token motor task (TMT; motor function[3]), semantic fluency (SF; semantic recall[4]), Tower of London (TOL; planning[5]), and symbol coding (SC; processing speed[6]) tests; ii) the snakes in the grass (SNK[7]; Jensen, 2019) test of fear-relevant attention (accuracy and reaction time of target stimuli); iii) the continuous performance test (CPT; sustained attention[8]; Kahn et al., 2012); and iv) perceptual closure test (PC; the ability to recognize objects or patterns and processing speed[9]; Snodgrass and Kinjo, 1998). On all BACs tasks, SNK accuracy and PC, higher scores refer to better performance. In SNK and PC reaction time, higher scores refer to slower performance.

2.2.3. Gene expression

Peripheral blood was drawn immediately following assessment into a Tempus Blood RNA tube (Applied Biosystems, Foster City, CA) and stored at − 80 °C until RNA extraction. Total blood RNA is extracted using a Tempus Spin RNA isolation kit (Applied Biosystems) and amplified using an Illumina Total Prep RNA amplification kit (Ambion, Austin, TX). To address multicollinearity, we estimated variance inflation factor (VIF) of 31 FABP and 12 Igs which were correlated with social and cognitive tests and removed 20 FABP and 5 Igs which critically contributed to VIF while exhibited lower correlation with the primary study outcomes. Therefore, seven FABPs including FABP6, FABP5P2, FABP5P7, FABP5P11, FABP3, FABP5P9, FABP5P1 and four Ig including FCGBP, FCGRT, FCGR2B, GOT2 were selected for analysis. The correlation matrix of all FABPs and Igs, are presented in Supplementary Fig. S1.

2.3. Statistics

A power analysis was conducted to ensure that the results were

[1] This test is designed to assess episodic memory functions and measure the number of words recalled per trial.

[2] This test is designed to assess working memory and measure the number of trials with all items in the correct order.

[3] This test is designed to assess motor functions and measure the number of tokens correctly dragged into the container.

[4] This is averaged score for 3 categories for animals, fruits, and vegetables. This test is designed to measure processing speed and the intactness of the semantic system and measure the number of words generated per trial.

[5] The test is designed to assess executive, problem solving, and planning abilities that measure the number of trials where the correct number of moves is the response.

[6] · This test is designed to assess attention and processing speed that measure the number of correct items.

[7] Accuracy in SNKs indicate the ability to correctly identify or discriminate between different stimuli· So, if SNK accuracy scores are higher, it suggests that participants are better at accurately detecting and responding to fear-relevant deviants (snake) among fear-irrelevant backgrounds (mushroom and flower). Larger reaction time to snakes, slower performance.

[8] This test measures a person's sustained and selective attention.

[9] The term, "perceptual closure," refers to a tendency to complete what is incompletely presented in the visual field. Subjects were required to indicate whether they detected a face or not via button press after each stimulus. The percentage of correct responses as well as reaction times in correct trials stimuli were measured.

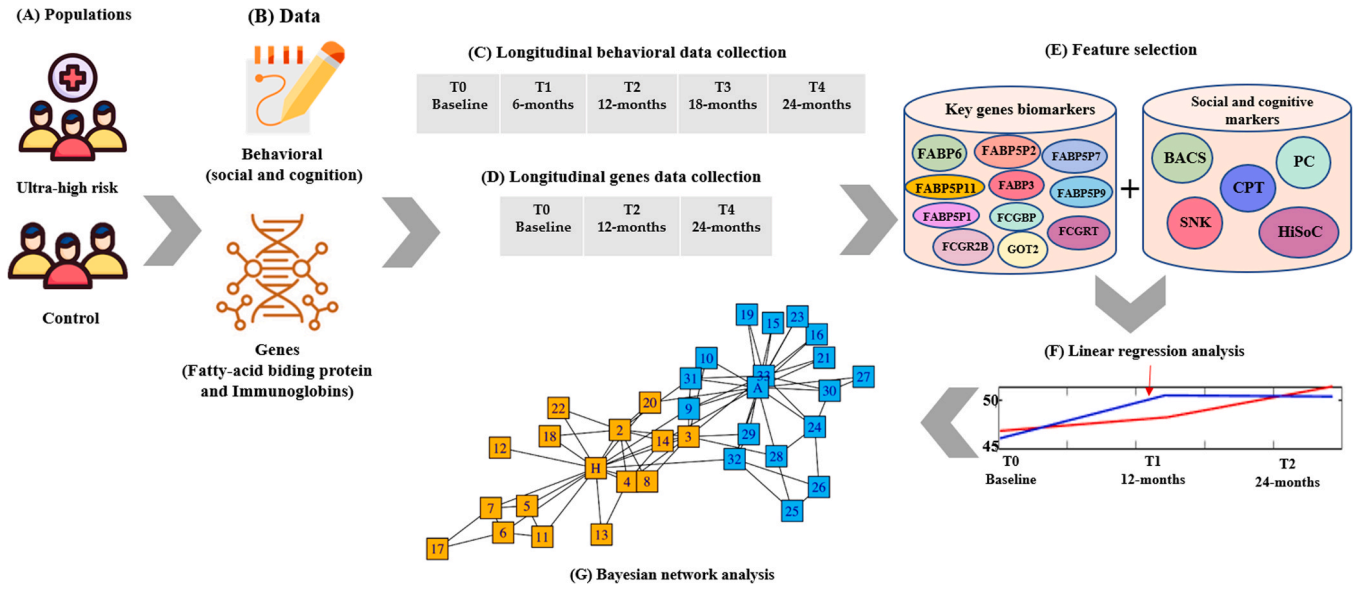

Fig. 1. The study protocol diagram includes the population, data collection, feature selection, and the designed methodology for association, interaction, and prediction. (A) Population: individuals at ultra-high risk (UHR) for psychosis and a Control group were included; (B) Multimodal data, including social, cognitive, and genetic data, were measured; (C) Longitudinal behavioral data were collected over a 2-year period, with assessments at T0 (baseline), T1 (6 months), T2 (12 months), T3 (18 months), and T4 (24 months); (D) Longitudinal genes data were measured three times at T0 (baseline), T2 (12-months), and T4 (24-months); (E) 11 key genes markers including Fatty Acid Binding Proteins and Immunoglobulin; and 18 behavioral variables including social and cognitive biomarkers were selected; (F) The designed methodology illustrates dynamic variable interactions for predicting social and cognitive data changes at 24 months based on the baseline genes data; (G) A Bayesian network method was designed to identify shared interactions between variables across groups.

adequately powered to detect significant differences between the control and UHR groups. According to research into youth at risk for psychosis, with an alpha level of 0.05 and a statistical power of 0.80, it was estimated that a total sample size of 128 participants (64 per group) would be required to detect medium-sized effects using independent samples *t*-tests. In our study, the sample size consists of n = 99 (Control: n = 54, UHR: n = 45), which is below the initially estimated target. However, given the longitudinal nature of the dataset and the inclusion of repeated measures over a two-year period, the power to detect medium-sized effects is expected to be sufficient. Longitudinal designs generally provide increased statistical power due to the repeated assessments, allowing for the detection of within-subject changes and reducing the influence of between-subject variability (Twisk, 2013).

Table 2 shows zero-order correlations for psychometric measures, FABPs and Ig. Pearson's zero-order correlations were initially computed to assess the relationship between the psychometrics (social and cognitive) at 24-months and their associations with genetic biomarkers (FABPs, Igs) at baseline T0. In addition to this, the descriptive statistics (means and standard deviations) of social and cognitive variables over time across UHR and Control groups are also provided in Supplementary materials as S2 and S3.

Hierarchical linear regression was used to test the predictive ability of identified gene biomarkers (FABPs and Igs) on social and cognitive functioning outcome variables, including BACS subscales, SNK's subscales, CPT scores, PC subscales and HiSoC subscales. In each case, to test whether there is a predictive relationship in the outcome variable, the baseline assessment of the outcome variable was included in the model. Baseline social and cognitive data variables were entered first (model 1), to control for prior functioning, which is expected to explain the largest proportion of variance in later outcomes. Gene variables were then entered (model 2) as predictors, to examine whether they accounted for additional variance beyond baseline performance. Inclusion of the binary variable 'Group' (Control, UHR) did not meaningfully alter the outcomes.

Bayesian networks were applied to identify dependence and independence structures between genes, social functioning, and cognitive functioning variables (He et al., 2024). In network nomenclature, nodes represent variables and edges represent relationships between variables. Bayesian networks encode directed acyclic graphs. In Bayesian networks, edges are directed, and these directed relationships provide dependence and conditional independence relationships in the network. The network is also a cyclical, does not contain feedback loops or cycles. Three types of connections serial, diverging, and converging may be used to identify if two variables are dependent or conditionally independent given third variables, and more information on this can be found in Briganti et al. (2023). Dynamic Bayesian networks introduce time into the model. We implemented two dynamic Bayesian networks using the hill-climbing algorithm to optimize the network. One dynamic Bayesian network was implemented on UHR individuals and the other on Controls. We implemented a network model with two time periods. T1 denotes baseline values, and T2 represents the follow-up values. There are two time segments (0–12 months, 12 months to 24 months). In the first segment, 0 months is the baseline (T1) and 12 months is the follow-up (T2). In the second segment, 12 months was the baseline (T1), and 24 months was the follow-up (T2). We compared T1 and T2 for each variable in the dynamic Bayesian network.

Furthermore, the hill climbing algorithms start with an empty graph and then adds, deletes, or reverse the direction of an edge until no further improvement can be made. We also introduced a blacklist. A blacklist is a list of edges not allowed in the network. Here we blacklisted all edges from parent nodes that are social and cognitive functioning variables to nodes that were genes variables. This means genes variables are predictor variables of social and cognitive functioning variables and not vice versa.

Once the network structure and parameters of the network have been reconstructed and estimated, inferences can be made about the network. Firstly, probabilistic queries between two or more variables can be made. Here, the query is the probability of an event occurring given evidence from some other variable (Briganti et al., 2023). A query to the network could be: Given that FCGBP in time period 1 is greater than the median of the sample, what is the probability that the continuous performance test result is also above the median response for the sample? In

Table 1
The social, cognitive, clinical, and genetic data variables used in the study and their domain·.

Cognitive Performance Tests	Cognitive Subscales	MATRIC Cognitive Domain
(1) The Brief Assessment of Cognition in Schizophrenia (BACS), (7 Subscales)	• Verbal Memory (VM) • Digit Sequencing (DS) • Token Motor Task (TMT) • Semantic Fluency (SF) • Verbal Fluency Total (fruit, vegetable, and animal) (VF) • Symbol Coding (SC) • Tower of London (TOL)	• Memory • Working memory • Motor function • Processing speed • Processing speed • Processing speed • Planning
(2) The Snakes in the Grass (SNK) (4 Subscales)	• Target Reaction Time (RT) • Target Accuracy • Distractor Accuracy • Total Score and Accuracy	• Processing speed and accuracy
(3) The Continuous Performance Test (CPT)	• The Total Score	• Sustained attention
(4) Perceptual Closure test (PC) (2 Subscales)	• Average Score (AVG) • Percentage of correctly identified items (PCT)	• Perceptual skills
Social Performance Test	Social Subscales	Social Domain
(5) The High-Risk Social Challenge (HiSoC) (4 Subscales)	• Affect • Odd Behaviour • Social Behaviour • Averaged Scores	• Facial and verbal affect • Speech • Social engagement
Genes Biomarkers	Selected Genes	
(7) Fatty Acid-Binding Proteins (FABPs) (7 Variables)	• FABP3 • FABP5P1 • FABP5P2 • FABP5P7 • FABP5P9 • FABP5P11 • FABP6	
(8) Immunoglobin G Genotypes (4 Variables)	• FCGBP • FCGRT • FCG2B • GOT2	

addition to probabilistic queries, centrality statistics can be estimated for the network. Centrality statistics are a measure of node importance within a network. Three centrality statistics are used in this study. Betweenness is the importance of a node in the average pathway between other nodes in the network; closeness refers to the relationship between one node and all other nodes in the network, taking the shortest distance; and degree is the number of incoming and outgoing edges to and from each node (Hevey, 2018).

Because Bayesian networks do not give an indication of severity or the magnitude of the change in the effect between time periods, pairwise *t*-tests were conducted on the sample to identify if there is a change at 24 months compared to baseline scores on the social and cognitive assessments of UHR individuals for psychosis. All longitudinal regressions and correlations were performed using Statistical Package for the Social Sciences (SPSS) version 25·0, IBM, and network analysis was carried out on R version 4·3·2 using the bnlearn package (Scutari, 2009) and dbnr package (Quesada, 2022).

3. Results

The results from the designed regression and Network study are presented in two phases.

- Correlation and regression analysis: Predictive role of FABP5 family Genes and Igs genes in cognitive and social outcomes in UHR and Control group.
- Bayesian network: Searches the space to identify optimal or suboptimal predictor and response relationships while controlling for third variables.

These steps are explained in the following Sections 3.1–3.3.

3.1. Correlations

Table 2 reports the longitudinal correlation results across UHR and Control group for social and cognitive tests performance at 24-months (T4) with genes biomarkers at baseline (T0). The social variables are from HiSoC test, including affect, odd behavior, social behavior, and total social averaged score. The cognitive variables are from BACS test including VM, DS, TMT, SF total score, SC, and TOL sub scores; the SNK test includes target reaction time, target/distractor accuracy, and total score accuracy; the PC test includes the average score and percentage of correctly identified items. We excluded hypothesis tests of correlations to avoid increases in type 1 error.

3.1.1. UHR group

Among the FABPs, the FABP5 family genes were identified as associated with cognitive outcomes in the UHR group. Small positive correlations were seen between FABP5P11 and DS ($r = 0{\cdot}219$), and FABP5P1 and VM ($r = 0{\cdot}317$), while FABP5P9 was negatively correlated with social skills ($r = -0.253$).

In Igs family, small positive correlations were seen between FCGR2B and PC ($r = 0{\cdot}267$) and DS ($r = 0{\cdot}2$), while GOT2 and TOL were inversely associated ($r = -0{\cdot}212$).

3.1.2. Control group

FABP5P1 was positively correlated with PC ($r = 0{\cdot}203$), VF ($r = 0{\cdot}196$), and VM ($r = 0{\cdot}196$), while FABP5P9 was negatively correlated with social skills (odd behavior) ($r = -0{\cdot}322$).

3.2. Linear regression

3.2.1. UHR group

Table 3 presents the hierarchical linear regression for gene risk factors at baseline (T0) predicting social and cognitive variables at 24-months (T4) while controlling for T0 outcome measures. After controlling for the baseline measures, FABP5 family genes significantly predicted the outcome variables as follows for UHR group: i) FABP5P1 predicted VM; ii) FABP5P11 predicted DS; and iii) FABP5P9 inversely predicted HiSoC (averaged score). In Igs family, FCGR2B predicted PC and GOT2 inversely predicted TOL.

3.2.2. Control group

As shown in Table 4, FABP5 family genes significantly predicted the following outcomes: i) FABP5P1 predicted several measures, including PC, SF, and VM; ii) FABP5P9 predicted HiSoC (odd behavior); and Igs family genes significantly predicted the following outcomes iii) FCGBP and FCGRT predicted VM.

Fig. 2 summarizes the main findings regarding FABP5 family and immunoglobulin-related genes as predictors of social and cognitive performance outcomes at 24 months.

3.3. Network analysis

3.3.1. Network analysis of UHR individuals

Fig. 3 shows the two-time-period dynamic Bayesian network model of genes, and social and cognitive variables across UHR individuals. Here, the genes were forced to be parents of social and cognitive variables, within and between time periods. This may have led to some clustering of gene variables in the network. However, there were some notable dependence and independence relationships. There were some dependencies between FABP5 family genes and social and cognitive

Table 2
Longitudinal correlations across ultra-high-risk group (UHR) and control for HiSoC, BACS, SNK, PC at 24 months and gene biomarkers (fatty acids and immunoglobulins) at baseline.

Social and Cognitive variables (T4)	Group	Genes (T0)								
		FABP3	FABP5P11	FABP5P1	FABP5P9	FABP6	FCGBP	FCGR2B	FCGRT	GOT2
Perceptual closure (AVG)	UHR	− 0·059	0·026	0·127	0·002	0·102	− 0·051	**0·267**	0·075	− 0·094
	Control	− 0·092	0·314	**0·203**	− 0·025	− 0·009	0·135	0·244	− 0·05	0·127
Perceptual closure (PCT)	UHR	− 0·12	0·077	0·053	0·082	0·084	0·07	0·069	0·116	− 0·014
	Control	− 0·04	0·101	0·036	0·267	0·055	0·159	0·034	0·022	0·185
Digit sequencing	UHR	0·1	**0·219**	0·171	0·074	0·102	0·043	**0·212**	0·001	− 0·019
(DS)	Control	0·152	0·243	0·248	0·13	0·048	0·068	0·184	0·007	0·014
Semantic fluency	UHR	− 0·008	0·164	0·077	0·059	0·1	− 0·012	0·139	0·057	− 0·114
(SF)	Control	0·044	0·238	0·115	0·091	− 0·045	0·06	− 0·03	− 0·105	− 0·03
Token motor task	UHR	0·106	0·143	− 0·078	− 0·169	0·061	0·002	0·082	− 0·039	− 0·059
(TMT)	Control	0·157	0·043	− 0·057	− 0·036	− 0·039	0·033	0·132	− 0·107	− 0·043
Tower of London	UHR	0·152	− 0·121	0·055	− 0·058	0·101	− 0·026	− 0·004	0·087	**− 0·212**
(TOL)	Control	0·093	− 0·131	0·135	− 0·121	0·076	− 0·023	− 0·123	0·072	− 0·261
Verbal fluency	UHR	− 0·14	0·185	0·032	− 0·022	− 0·033	− 0·104	0·125	0·128	− 0·016
(VF)	Control	− 0·121	0·417	**0·196**	0·009	− 0·145	− 0·05	0·002	− 0·03	0·131
Verbal memory	UHR	− 0·021	0·104	**0·317**	0·162	0·037	0·178	0·149	0·052	0·169
(VM)	Control	− 0·105	0·407	**0·196**	0·258	0·035	**0·24**	0·079	**0·026**	0·206
Social skills	UHR	0·07	0·05	− 0·093	**− 0·253**	0·004	− 0·024	− 0·001	0·037	− 0·077
	Control	0·093	− 0·005	− 0·048	− 0·184	− 0·094	0·041	− 0·144	0·036	− 0·149
Odd behaviour	UHR	0	0·06	− 0·135	− 0·323	− 0·065	0·01	0·023	0·044	− 0·044
	Control	− 0·041	− 0·059	− 0·175	**− 0·322**	− 0·223	0·031	− 0·116	0·048	− 0·1
All snakes	UHR	0·036	0·143	0·124	− 0·057	− 0·099	0·173	− 0·149	− 0·069	0·092
	Control	− 0·173	0·163	0·211	− 0·075	− 0·105	0·168	− 0·212	0·048	0·095
All snakes accuracy	UHR	0·036	0·143	0·124	− 0·057	− 0·099	0·173	− 0·149	− 0·069	0·092
	Control	− 0·173	0·163	0·211	− 0·075	− 0·105	0·168	− 0·212	0·048	0·095
Distract stimuli accuracy	UHR	− 0·006	− 0·058	0·005	0·024	0·068	− 0·107	0·056	0·122	− 0·154
	Control	0·001	0·013	0·054	0·02	0	− 0·029	− 0·075	0·203	0·023
Target reaction time	UHR	0·116	− 0·121	− 0·208	0·125	0·123	0·016	0·028	0·114	0·021
	Control	0·209	0·023	− 0·151	0·26	0·252	0·009	− 0·035	0·165	− 0·052

Table 3
Hierarchical linear regression for estimating the predictive relationship between gene risk factors at baseline (T0) and social and cognitive variables at baseline (T0) on social and cognitive variables at 24-months follow up (T4) in the UHR group.

	B	*SE*	Std β	*t*	*p*	Tol	VIF
Verbal memory (T4) (Constant)	21·891	3·212		6·815	< 0·001		
Verbal memory (T0)	0·549	0·06	0·621	8·352	< 0·001	0·982	1·019
FABP5P1 (T0)	10·689	3·415	0·233	3·130	0·002	0·982	1·019
Model: [F (2,96) = 44·145 p < 0·0001, r2 = 0.479]							
Digit sequencing (T4) (Constant)	6·268	1·834		3·418	< 0·001		
Digit sequencing (T0)	0·602	0·077	0·598	7·818	< 0·001	0·984	1·017
FABP5P11 (T0)	8·123	2·765	0·225	2·938	0·004	0·983	1·018
FCGR2B (T0)	0·054	0·027	0·155	2·011	0·047	0·968	1·033
Model: [F (3,95) = 26.199, p < 0·0005, r2 = 0.453]							
Tower of London (T4) (Constant)	10·648	1·482		7·185	0·001		
Tower of London (T0)	0·509	0·067	0·600	7·541	0·001	0·988	1·012
GOT2 (T0)	− 0·40	0·021	− 0·147	1·852	0·067	0·988	1·012
Model: F (2,96) = 32.04, p < .0005, r2 = 0.388]							
Perceptual closure (T4) AVG (Constant)	2·135	0·387		5·517	0·005		
Perceptual closure AVG (T0)	0·340	0·101	0·315	3·367	0·001	0·989	1·012
FCGR2B (T0)	0·009	0·003	0·233	2·494	0·014	0·989	1·012
Model: [F (2,96) = 9·78, p < .0005, r2 = 0.169]							
High risk social challenge task (T4) (Constant)	1·899	0·316		6·017	0·005		
High-risk social challenge task (T0)	0·477	0·083	0·495	5·77	0·005	0·984	1·016
FABP5P9 (T0)	− 1·451	0·656	− 0·190	2·212	0·029	0·984	1·016
Model: [F (2,96) = 21.09, p < 0·.0005, r2 = 0.305]							

Note. B = betta coefficient; SE = Standard Error; Std β = Standardized betta coefficient; t = t-test statistics; Tol = Tolerance; and VIF = Variance Inflation Factor.

variables. For example, PC was dependent on FABP5P2 in time 1 and time 2, which means FABP5P2 was a predictor of PC. HiSoC was also dependent on PABP5P1 in T1 and T2. Cognitive performance variables were also associated with the Igs genes of FCGBP, FCGRT, GOT2.

CPT average variable was dependent on FCGBP in time one and time two, BACS (SC) and PC were dependent on FCGRT in time one and time two, and SNK Target Accuracy was dependent on GOT2 in time one and time 2. Interestingly, there was also some independence between genes and social and cognitive variables given a third variable. For example, BACS (SC) T2 and PC (PCT) T2 were dependent on FCGRT in T2. FCGRT was also dependent on the genes FCGR2B, FABP5P11, FABP5P9, FABP3, FCGBP in T2. This means that FCGR2B, FABP5P11, FABP5P9, FABP3, FCGBP in T2 are independent of BACS (SC) and PC (PCT) in T2, given the mediating association with FCGRT in T2. FCGRT is the mediating variable which results in these associations becoming conditionally independent.

Fig. 4 shows the dynamic Bayesian network model of genes, as well as social and cognitive variables across Control group. The network for Control had fewer edges than people with UHR of psychosis ($\Delta N = 14$). In addition to this, Control group had different edges than UHR

Table 4
Hierarchical linear regression for estimating the predictive relationship between gene risk factors at baseline (T0) and social and cognitive variables at baseline (T0) on social and cognitive variables at 24-months follow up (T4) in the Control group.

Social and Cognitive Subtests	*B*	*SE*	Std β	*t*	*P*	Tol	VIF
Verbal memory (T4) (Constant)	11·052	7·011		1·576	0·121		
Verbal memory (T0)	0·433	0·084	0·518	5·174	0·000	0·903	1·108
FABP5P1 T0)	14·695	4·186	0·366	3·511	0·001	0·834	1·200
FCGBP (T0)	0·235	0·083	0·307	2·822	0·007	0·762	1·313
FCGRT (T0)	0·035	0·019	0·207	1·822	0·075	0·697	1·434
Model FABP5P1 and VM: [F (4,49) = 15.413, p < ·001, r2 = .557]							
Model for FCGP and VM: [F (4,49) = 15.413, p < ·001, r2 = .557]							
Model: FCGRT and VM [F (4,49) = 15.413, p < ·001, r2 = .557]							
Semantic fluency (T4) (Constant)	5·536	4·094		1·352	0·182		
Semantic fluency (T0)	0·880	0·094	0·797	9·357	0·000	0·822	1·217
FABP5P1 (T0)	4·340	4·566	0·081	0·950	0·346	0·822	1·217
Model: [F (2,51) = 58.384, p < .001, r2 = .696],							
Odds behaviour (T4) (Constant)	16·830	2·048		8·216	0·000		
Odds behaviour (T0)	0·139	0·103	0·177	1·346	0·184	0·982	1·018
FABP5P9 (T0)	− 8·964	3·951	− 0·298	− 2·269	0·028	0·982	1·018
Model: [F (2,51) = 3.954, p < .025, r2 = .134]							
Perceptuel closure averaged (T4) (Constant)	2·149	0·496		4·333	0·000		
Perceptuel closure averaged (T0)	0·388	0·136	0·355	2·846	0·006	0·979	1·021
FABP5P1 (T0)	0·498	0·236	0·263	2·108	0·040	0·979	1·021
Model: [F (2,51) = 7·286, p < .002, r2 = .222]							

Note. *B* = betta coefficient; *SE* = Standard Error; Std β = Standardized betta coefficient; *t* = *t*-test statistics; Tol = Tolerance; and VIF = Variance Inflation Factor.

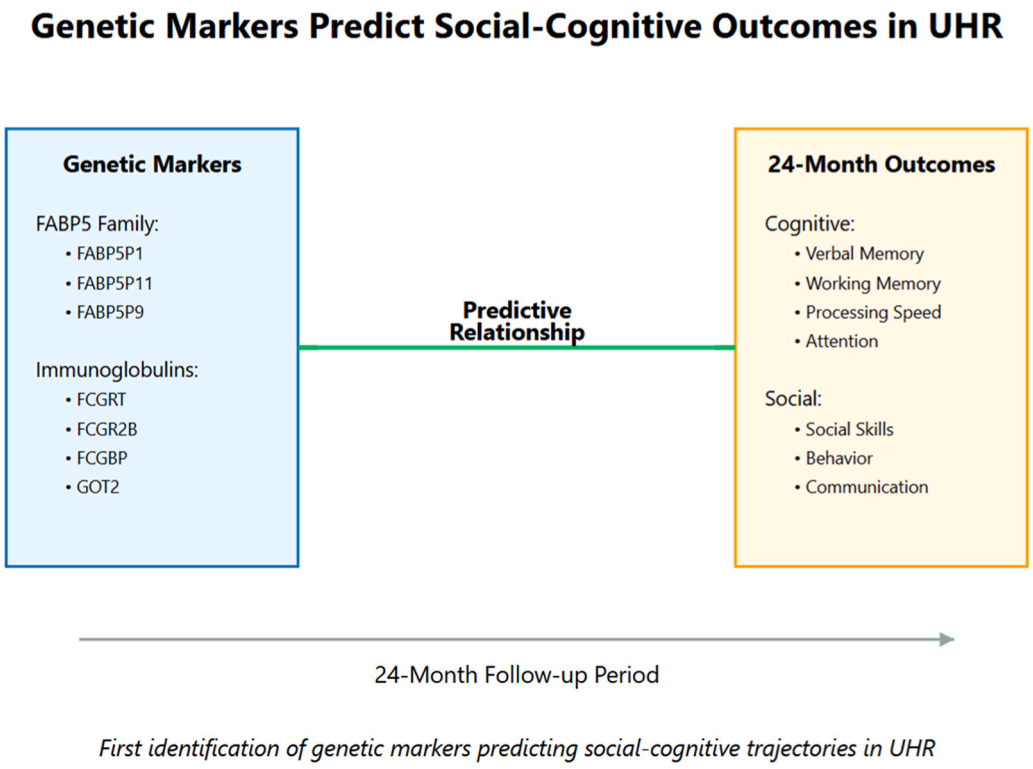

Fig. 2. The predictive relationship between FABP5 family genes and immunoglobulins (Igs) at baseline, and social and cognitive performance outcomes at 24 months.

individuals for psychosis. Only 38 edges were common to both UHR and Control, many of these were relationships between the same node over the two time periods. Hence, 78 edges in Control were not found in the network of UHR, and 92 edges in the network of UHR were not found in the network of Control. In all edges common to both the network of UHR and Control, none of these edges were between a gene (parent) and a social or cognitive variable (child). Hence, all gene associations with social and cognitive variables in the network of UHR were not found in the network of Control and vice versa.

3.3.2. *Queries to the network in UHR*

Table 5 presents all the dependencies between genes, and social and cognitive variables for UHR's individuals. The values columns represent the median value and the direction of the association (lower than the median, greater than the median). The closer the value is to 1 or 0, the stronger the dependence is when conditioning on these variables to be above or below the median value. The relationships found in this table indicate a negative relationship, for the most part. For example, if FABP3 in time one is above the median value, there is a 0·797 probability that PC in time two is below the median. Likewise, if GOT2 is above the median, then there is a 0·707 probability that SNK response to target

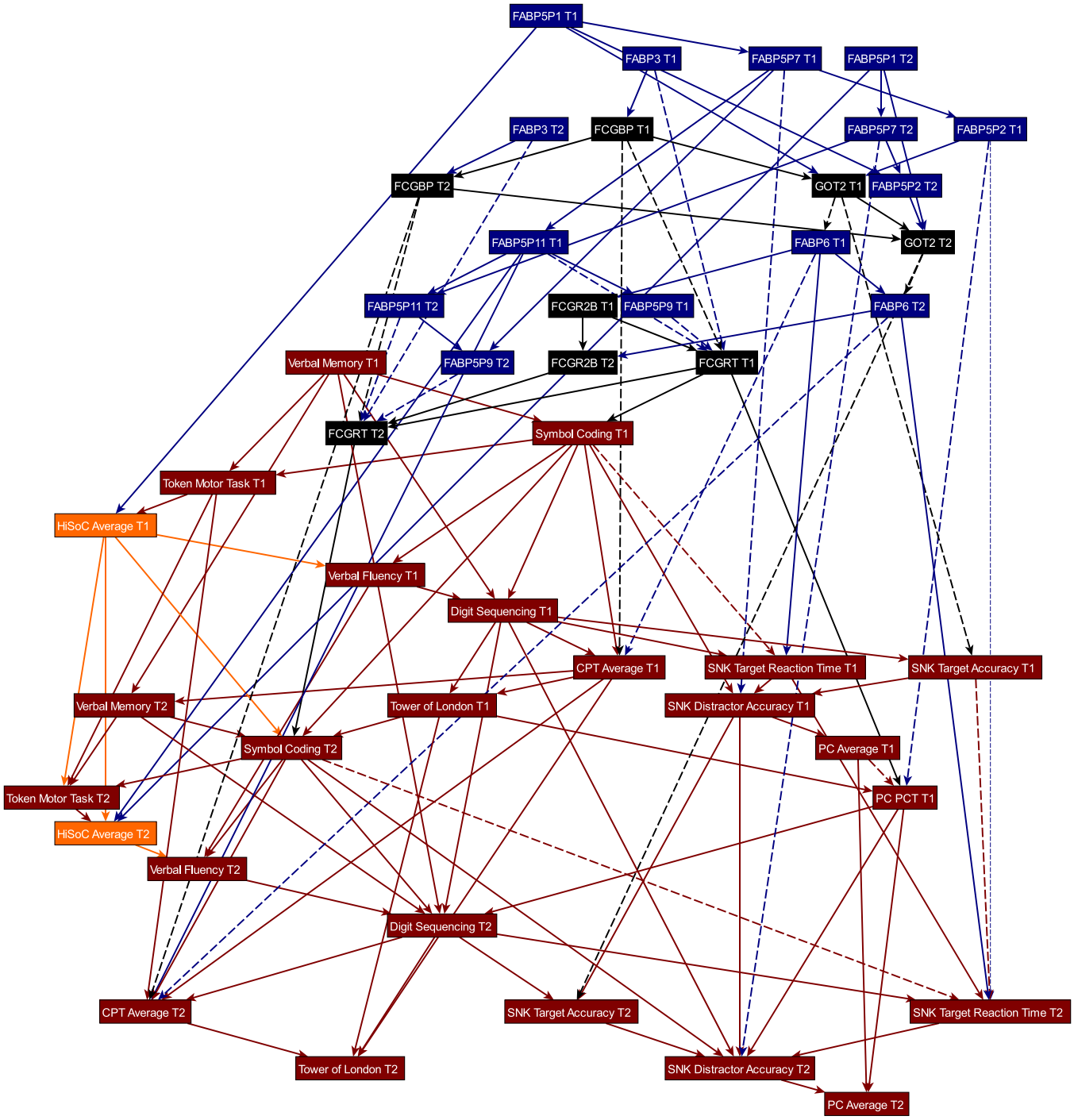

Fig. 3. Longitudinal dynamic Bayesian network illustrating the interactions and causal associations among gene risk factors, social and cognitive functioning in individuals at ultra-high risk (UHR) of psychosis at baseline (T1) and after 12 months (T2). The blue nodes indicate fatty acid genes (FABPs), black nodes signify immunoglobulin genes (Igs), orange nodes represent social functioning, and red nodes denote cognitive functioning. Dashed edges correspond to negative coefficients, while solid edges indicate positive coefficients, with line thickness reflecting normalised coefficient values.

stimuli (accuracy) in time one is above the median value. There are also some inverse relationships. When looking at reaction time variables, if FABP6 is above the median value in time 2, there is a 0·646 probability that the reaction time to target stimuli in SNK is also above the median value. Probabilities were lower than 0·5 between FCGRT and BACs (SC) in time two, which indicates that if FCGRT is above the median, there is a lower probability that BACs (SC) are below the median value. This is also true for FABP5P1 in time 1 and HiSoC average in time 1.

4. Discussion

This longitudinal study examined whether FABPs and immunoglobulin-related genes predict changes in social and cognitive functioning over a two-years period in individuals at UHR for psychosis and healthy control. Using regression and dynamic Bayesian network analysis, this study provides the first evidence that specific genetic markers are linked to long-term trajectories in memory, processing speed, and social skills. These findings highlight new possibilities for early identification of UHR individuals and the development of

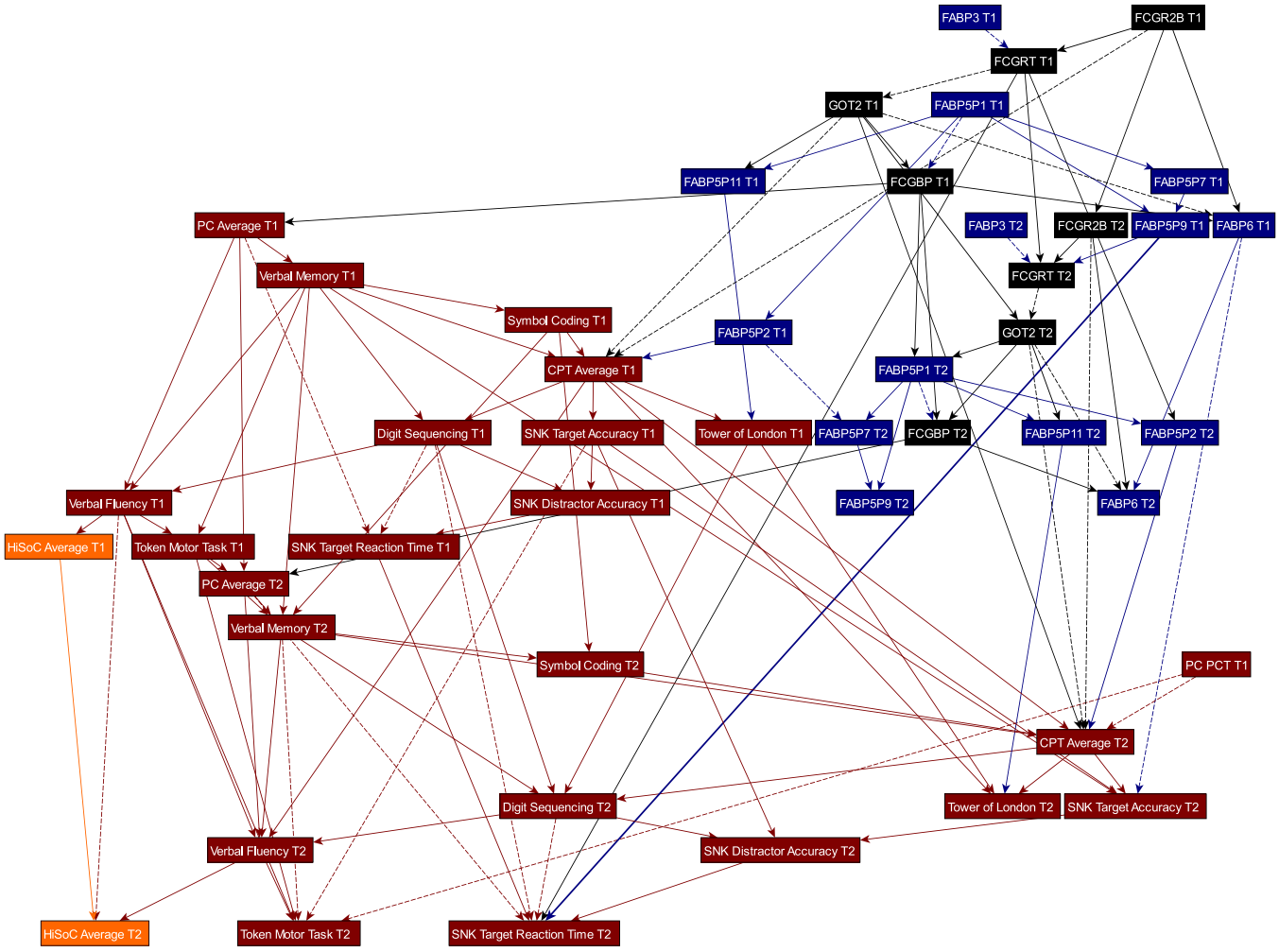

Fig. 4. Longitudinal dynamic Bayesian network illustrating the interactions the causal relationships among gene risk factors, social functioning, and cognitive functioning in control individuals at baseline (T1) and after 12 months (T2). The blue nodes indicate fatty acid genes, black nodes signify immunoglobulin genes, orange nodes represent social functioning, and red nodes denote cognitive functioning. Dashed edges correspond to negative coefficients, while solid edges indicate positive coefficients, with line thickness reflecting normalised coefficient values.

personalized interventions.

Recent study emphasizes the need to refine current conceptual models of schizophrenia, highlighting the importance of integrating biological and dimensional frameworks into early identification strategies (Tandon, 2024). This aligns with our findings, which underscore the utility of genetic biomarkers in understanding the pathways that shape social and cognitive outcomes in individuals at UHR.

4.1. *FABP5 genes, social and cognitive outcomes*

The FABP5 family emerged as strong predictors of memory and social outcomes in the UHR group. FABP5 proteins help the brain transport and use healthy fats (e.g., omega-3 DHA) that are vital for memory and learning. When this process is disrupted, memory and problem-solving can decline. In our study, FABP5P1 predicted verbal memory, FABP5P11 predicted working memory and processing speed, while FABP5P9 was linked to poorer social functioning.

These results align with prior evidence showing FABP5's role in hippocampal-dependent memory and short-term memory (Pan et al., 2016; Yu et al., 2014). Reduced FABP5 expression has also been linked to lower DHA availability and smaller hippocampal volume in high-risk individuals (McHugo et al., 2024). Together, these findings suggest FABP5 as a promising target for future therapies.

4.2. *Immune-related genes, social and cognitive outcomes*

Immunoglobulin-related genes also showed distinct effects. In UHR individuals, FCGR2B predicted perceptual skills and GOT2 was linked to impaired planning ability. In controls, FCGBP and FCGRT predicted verbal memory.

These genes likely affect the brain through inflammatory and immune pathways. For example, GOT2 is involved in the kynurenine pathway and may increase neurotoxic metabolites, disrupting executive function. FCGR2B, an anti-inflammatory receptor, was linked to better working memory and perceptual skills, consistent with its protective role. FCGBP, though less studied, has been implicated in inflammation and neurodegeneration (Gómez-Garre et al., 2022). Our findings suggest it may also influence cognition.

4.3. *Temporal dynamics in UHR vs controls*

The dynamic Bayesian model extended these findings by revealing temporal dependencies and indirect gene-behavior pathways, particularly within the UHR group. FCGRT emerged as a key mediator between genetic predictors and behavioral outcomes, highlighting potential gene-gene interactions that influence cognitive performance. Our findings suggest that when some genes are overexpressed, UHR individuals tend to perform worse on certain cognitive or social tasks. There were

Table 5
Probability queries for UHR.

Variable 1 (Genes)	Value	Variable 2 (social and cognitive)	Value	Probability
FABP3 at T1	> 0·613	Perceptual Closure (PCT) at T2	< 100	0·797
FABP5P11 at T1	> 0·140	CPT at T2	< 3·13	0·565
FABP5P2 at T2	> 0·080	Perceptual Closure Averaged (PCT) at T2	< 100	0·771
FABP5P2 at T1	> 0·083	Perceptual Closure Averaged (PCT) at T1	< 95	0·658
FABP5P2 at T1	> 0·083	SNK Target stimuli RT at T2	> 856·025	0·534
FABP5P7 at T2	> 0·153	SNK Distractor stimuli Accuracy at T2	< 88·89	0·618
FABP5P7 at T1	> 0·175	SNK Distractor stimuli Accuracy at T1	< 86·11	0·65
FABP6 at T2	> 0·331	CPT at T2	< 3·13	0·619
FABP6 at T2	> 0·331	SNK Target stimuli RT at T2	> 856·025	0·646
FABP6 at T1	> 0·281	CPT at T1	< 2·855	0·541
FABP6 at T1	> 0·281	SNK Target stimuli RT at T1	> 889·75	0·672
FCGBP at T2	> 25·919	CPT at T2	< 3·13	0·629
FCGBP at T1	> 27·219	CPT at T1	< 2·855	0·565
FCGRT at T2	> 244·925	Symbol Coding at T2	< 63·5	0·418
FCGRT at T2	> 244·925	Perceptual Closure (PCT) at T2	< 100	0·683
FCGRT at T1	> 237·746	Symbol Coding at T1	< 61·5	0·445
FCGRT at T1	> 237·746	Perceptual Closure (PCT) at T1	< 95	0·565
GOT2 at T2	> 32·349	SNK Target stimuli Accuracy at T2	< 94·44	0·707
GOT2 at T1	> 33·483	SNK Target stimuli Accuracy at T1	< 91·67	0·677
FABP5P1 at T2	> 0·347	HiSoC at T2	< 3·497	0·553
FABP5P1 at T1	> 0·329	HiSoC at T1	< 3·55	0·49
FABP5P11 at T1	> 0·140	HiSoC at T2	< 3·497	0·544

also a few positive associations, but the overall pattern points toward gene overactivity disrupting function. That means, in UHR individuals, genes and behavior became more tightly linked over time, whereas in controls these relationships were weaker and more independent

4.4. Genetic predictors of social and cognitive impairments in UHR

Consistent with previous research, UHR individuals often show subtle yet clinically significant cognitive and social impairments, even before the onset of psychotic symptoms. While only 16 % of UHR individuals transition to full psychosis within two years, many experience persistent functional difficulties (Yung et al., 1996). Studies show mild to moderate cognitive impairments in UHR individuals (Anda et al., 2019), which become more pronounced in those who transition schizophrenia (Trotta et al., 2015). In terms of social functioning, UHR individuals demonstrate moderate to large differences compared to controls, reaching levels comparable to first-episode schizophrenia (Buchwald et al., 2024; Kahn and Keefe, 2013).

From this study, it is unclear whether an increase or decrease in gene expression is a cause of cognitive decline in UHR individuals, although we found that social and cognitive functioning assessment scores are dependent on specific genetic markers within and between time periods over 24 months. The current study may, therefore, identify genetic markers of social and cognitive impairments, using Bayesian networks and regression to elucidate these relationships. Therefore, this study's findings lay the groundwork for precision psychiatry in UHR populations, potentially enabling genetic-based stratification for targeted interventions. Complementing these findings, recent Genome-wide association exploratory research in UHR populations in China identified several risk loci including NRXN1, DRD1, DRD2, CHI3L1, and ARVCF that were associated with transition to schizophrenia over two years (Wang et al., 2024). These results support the broader evidence that genetic vulnerability influences functional and clinical outcomes early in the disease trajectory. By examining FABP5 and immune-related genes in a longitudinal design, our study contributes to this growing body of work by identifying complementary biological pathways that may drive cognitive and social functioning in UHR individuals.

Our findings show that FABP5P11 and FABP5P1 in time T1 of the Bayesian model were positively associated with social skills in time T2, for the UHR group. Some studies have implicated inflammation in impaired cognitive empathy and theory of mind, suggesting potential contributions of inflammation-related pathways to social functioning (Heym et al., 2019). Thus, it is possible that associations between FABP5 (FABP5P11 and FABP5P1) and social skills reflect a role in immune regulation. However, the current study did not reveal a significant association between Igs genes and social skills in UHR group.

Beyond FABP5, we identified additional immune-related genes with important roles. Of these, FCGBP, FCGRT, FCGR2B, and GOT2 emerged as novel predictors of cognitive function.

Network analysis indicated that the association between FCGRT and cognitive function was independent of processing speed when FCGRT was included as a mediating variable. Given that poor perceptual skills performance in schizophrenia is associated with lower intrinsic connectivity of the visual cortex, future studies should investigate this in relation to FCGRT and FCGR2B (van de Ven et al., 2017).

FCGBP was associated with verbal memory performance in Control group. The function of FCGBP is poorly understood; however, its characterization in differential expression analyses has revealed that this gene is involved in several disorders in which immune and inflammation processes are important in the onset and development of the disease (Gómez-Garre et al., 2022). It may play a role in mediating the link between gut microbiota and intestinal inflammatory processes, as well as contributing to neuroinflammation and neurodegeneration. Although no prior studies have reported FCGBP as a biomarker for psychosis, an exome sequencing study describes a genetic variant in the FCGBP gene in patients with neurodegenerative disorders that could lead to the major cause of cognitive and motor dysfunction (Gómez-Garre et al., 2022). For example, increased FCGBP expression was observed in patients with advanced Parkinson's disease, indicating its potential significance in the interaction between the gut and the brain in Parkinson's (Gómez-Garre et al., 2022). Thus, our findings, for the first time, demonstrate a link between FCGBP and cognitive function, suggesting its potential significance as a novel biomarker in this context.

GOT2, previously associated with neurodegenerative and psychiatric conditions (Tsai et al., 2007; Wingo et al., 2022), was linked to poorer planning ability in our study. Prior work has shown reduced GOT2 expression in the hippocampus of Alzheimer's patients and suggested its role in glutamate regulation and synaptic pruning. These mechanisms are relevant to schizophrenia, especially in frontal brain regions responsible for executive function. Our findings may thus reflect early-stage frontal dysfunction in UHR individuals (He et al., 2024; Tsai et al., 2007). Li et al. (2023) found subcutaneous injection of GOT improved neurological function and associated protein expression in mice with AD. This finding suggests that GOT therapy can decrease the concentration of glutamate in the brain, enhance memory and cognition. Our study is the first to show similar associations in UHR populations. Future studies should confirm whether the inverse associations between GOT2 and cognition reflect increased kynurenic acid production and excessive synaptic pruning (Orhan et al., 2023). These processes may particularly disrupt frontal and temporal brain regions in schizophrenia. Thus, underpinning brain networks should also be investigated. This association holds particular relevance in the context of psychosis, where commonly observed impairments in executive control are likely the

consequence of perturbations in frontal regions.

4.5. Implications for personalized interventions

These findings suggest that both over and under-expression of key genes may disrupt homeostatic balance: reduced FABP5 expression can limit DHA transport and impair hippocampal function, while excessive immune-related gene activity (e.g., GOT2) may drive neuroinflammation and excitotoxicity. Thus, deviations in either direction may increase dependence between genes and social-cognitive outcomes in UHR individuals, with most relationships between genes and social-cognitive outcomes not observed in controls. Together, these results contribute new insight into the genetic mechanisms underlying social and cognitive outcomes in UHR individuals. They support a model in which fatty acid–binding and immune-regulatory genes interact to shape long-term neurobehavioral trajectories. These findings highlight the potential for biomarker-guided personalized interventions. For example, FABP5-related markers associated with memory and working memory trajectories could inform the use of cognitive remediation or memory strategy training programs. Given FABP5's role in lipid transport, individuals carrying this vulnerability may also benefit from nutritional interventions such as omega-3 fatty acid supplementation, which has shown some efficacy in reducing transition risk (Nelson et al., 2018; Susai et al., 2022). In contrast, Ig-related markers such as FCGR2B and GOT2 implicate immune dysregulation, suggesting that anti-inflammatory approaches, including adjunctive pharmacological agents, exercise, or diet-based anti-inflammatory strategies may hold promise. More broadly, these findings support a stratified prevention model, in which biological markers are used to match UHR individuals to the most relevant treatment pathway, thereby moving closer toward precision psychiatry (Budhraja et al., 2023; Singh et al., 2023).

Limitations and Future Work: The sample primarily consisted of individuals from Singapore and other Asian backgrounds, which may limit generalizability to other populations. Furthermore, although networks identify a locally optimal arrangement of predictors and response variables, the exact causal relationships and underlying mechanisms between immune dysregulation, neuroinflammation, and the development of psychosis are not yet fully analyzed. Hence, unaccounted third variables or latent variables could be the cause of the results. Future research is needed to elucidate the complex and causal interactions between the immune system and the brain in UHR individuals and to determine the clinical implications for predictions and possible preventions, as well as early detection and personalized treatment approaches. Future studies will need to further test the relationships presently shown in a larger cohort of participants who go on to development of acute phase of psychosis when the typical psychotic symptoms occur.

5. Conclusions

This study is the first to examine relationships between immunological gene markers specifically FABP5 and immunoglobulin-related genes and long-term social and cognitive outcomes in individuals at UHR for psychosis. Key findings highlight FABP5P1, FABP5P11, and FABP5P9, as well as FCGBP, FCGR2B, and GOT2, as significant predictors of functional trajectories over a 24-month period. The distinct roles these genes play in the UHR and control groups underscore their relevance as potential biomarkers of vulnerability and resilience. By bridging genetic risk with behavioral outcomes, these findings provide a critical step toward precision psychiatry in early psychosis. They support the development of targeted, biologically informed strategies for early detection and personalized intervention, offering the potential to shift clinical practice from reactive treatment to proactive prevention.

CRediT authorship contribution statement

Wilson Goh: Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Zohreh Doborjeh:** Writing – original draft, Visualization, Methodology, Funding acquisition, Formal analysis. **Jimmy Lee:** Writing – review & editing, Validation, Supervision, Resources, Investigation, Funding acquisition, Conceptualization. **Alexander Sumich:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Margaret Williams:** Writing – review & editing, Validation, Supervision, Project administration. **Oleg N. Medvedev:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis. **Edmund M-K Lai:** Writing – review & editing, Supervision, Software, Project administration, Funding acquisition, Conceptualization. **Khan Buchwald:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis. **Alexander Merkin:** Writing – review & editing, Validation, Supervision, Project administration. **Max Lam:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Jie Yin Yee:** Writing – review & editing, Resources, Funding acquisition, Data curation, Conceptualization. **Tih-Shih Lee:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Data curation, Conceptualization. **Nikola K. Kasabov:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Maryam Doborjeh:** Writing – review & editing, Supervision, Software, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Balkaran Singh:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Sugam Budhraja:** Writing – review & editing, Visualization, Software, Methodology.

Financial Disclosure

This research was supported by the National Research Foundation, Singapore under its Industry Alignment Fund – Pre-positioning (IAF-PP) Funding Initiative, and the Ministry of Business, Innovation and Employment (MBIE), New Zealand, through the Data Science Research Program. The LYRIKS dataset was supported by the National Research Foundation Singapore under the National Medical Research Council Translational and Clinical Research Flagship Program (NMRC/TCR/003/2008).

The funding bodies had no role in the study design, data collection, analysis or interpretation, writing of the manuscript, or the decision to submit this article for publication. The views expressed are those of the author(s) and do not necessarily reflect those of the National Research Foundation, Singapore or MBIE.

Data Sharing

Dataset is not publicly available due to participant consent statement but could be available from the corresponding author upon reasonable request and with permission of NTU and IMH, Singapore, considering a data sharing agreement procedure.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

Acknowledgements

This research is supported by the National Research Foundation, Singapore under its Industry Alignment Fund - Pre-positioning (IAF-PP) Funding Initiative and the Ministry of Business, Innovation and Employment (MBIE), New Zealand, under the Data Science Research

Program. Any opinions, findings and conclusions or recommendations expressed in this material are those of the author(s) and do not reflect the views of National Research Foundation, Singapore. The LYRIKS was supported by the National Research Foundation Singapore under the National Medical Research Council Translational and Clinical Research Flagship Program (NMRC/TCR/003/2008). This support did not influence any part of the research process or preparation of this manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2025.104749.

References

Amminger, G., Schaefer, M.R., Papageorgiou, K., Becker, J., Mossaheb, N., Harrigan, S. M., Berger, G.E., 2007. Omega-3 fatty acids reduce the risk of early transition to psychosis in ultra-high risk individuals: a doubleblind randomized, placebocontrolled treatment study. Schizophr. Bull. 33 (2), 418–419.

Amminger, G.P., Schäfer, M.R., Papageorgiou, K., Klier, C.M., Cotton, S.M., Harrigan, S. M., Mackinnon, A., McGorry, P.D., Berger, G.E., 2010. Long-chain ω-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch. Gen. Psychiatry 67 (2), 146–154.

Anda, L., Brønnick, K.K., Johannessen, J.O., Joa, I., Kroken, R.A., Johnsen, E., Løberg, E. M., 2019. Cognitive profile in ultra high risk for psychosis and schizophrenia: a comparison using coordinated norms. Front. Psychiatry 10, 695.

Bernardini, F., Attademo, L., Cleary, S.D., Luther, C., Shim, R.S., Quartesan, R., Compton, M.T., 2017. Risk prediction models in psychiatry: toward a new frontier for the prevention of mental illnesses. J. Clin. Psychiatry 78 (5), 18451.

Briganti, G., Scutari, M., McNally, R.J., 2023. A tutorial on Bayesian networks for psychopathology researchers. Psychol. Methods 28 (4), 947.

Buchwald, K., Narayanan, A., Siegert, R.J., Vignes, M., Arrowsmith, K., Sandham, M., 2024. Centrality statistics of symptom networks of schizophrenia: a systematic review. Psychol. Med. 54 (6), 1061–1073.

Budhraja, S., Doborjeh, M., Singh, B., Tan, S., Doborjeh, Z., Lai, E., Merkin, A., Lee, J., Goh, W., Kasabov, N., 2023. Filter and wrapper stacking ensemble (FWSE): a robust approach for reliable biomarker discovery in high-dimensional omics data. Brief. Bioinform. 24 (6) bbad382.

Clark, S., Baune, B., Schubert, K., Lavoie, S., Smesny, S., Rice, S., Schäfer, M., Benninger, F., Feucht, M., Klier, C., 2016. Prediction of transition from ultra-high risk to first-episode psychosis using a probabilistic model combining history, clinical assessment and fatty-acid biomarkers. Transl. Psychiatry 6 (9) (e897-e897.

Clark, S.R., Schubert, K.O., Baune, B.T., 2015. Towards indicated prevention of psychosis: using probabilistic assessments of transition risk in psychosis prodrome. J. Neural Transm. 122, 155–169.

Doborjeh, Z., Doborjeh, M., Sumich, A., Singh, B., Merkin, A., Budhraja, S., Goh, W., Lai, E.M., Williams, M., Tan, S., 2023. Investigation of social and cognitive predictors in non-transition ultra-high-risk' individuals for psychosis using spiking neural networks. Schizophrenia 9 (1), 10.

Doborjeh, Z., N., Medvedev, O., Doborjeh, M., Singh, B., Sumich, A., Budhraja, S., Goh, W.W.B., Lee, J., Williams, M., Lai, E, M.K., 2024. A generalisability theory approach to quantifying changes in psychopathology among ultra-high-risk individuals for psychosis. Schizophrenia 10 (1), 87.

Ermakov, E.A., Melamud, M.M., Buneva, V.N., Ivanova, S.A., 2022. Immune system abnormalities in schizophrenia: an integrative view and translational perspectives. Front. Psychiatry 13, 880568.

Frajerman, A., Chaumette, B., Farabos, D., Despres, G., Simonard, C., Lamazière, A., Krebs, M.-O., Kebir, O., 2023. Membrane lipids in ultra-high-risk patients: potential predictive biomarkers of conversion to psychosis. Nutrients 15 (9), 2215.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L.J., 2013. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70 (1), 107–120.

Gee, D.G., Cannon, T.D., 2011. Prediction of conversion to psychosis: review and future directions. Braz. J. Psychiatry 33, s129–s142.

Gibson, C.M., Penn, D.L., Prinstein, M.J., Perkins, D.O., Belger, A.J.S.r., 2010. Social skill and social cognition in adolescents at genetic risk for psychosis. Schizophr. Res. 122 (1–3), 179–184.

Gimeno, R.E., 2007. Fatty acid transport proteins. Curr. Opin. Lipidol. 18 (3), 271–276.

Glenthøj, L.B., Mariegaard, L., Kristensen, T.D., Wenneberg, C., Medalia, A., Nordentoft, M., 2020. Self-perceived cognitive impairments in psychosis ultra-high risk individuals: associations with objective cognitive deficits and functioning. npj Schizophr. 6 (1), 31.

Gómez-Garre, P., Periñán, M.T., Jesús, S., Bacalini, M.G., Garagnani, P., Mollenhauer, B., Pirazzini, C., Provini, F., Trenkwalder, C., Franceschi, C., 2022. Transcriptomic analysis reveals an association of FCGBP with Parkinson's disease. npj Park.'s Dis. 8 (1), 157.

He, D., Li, L., Zhang, H., Liu, F., Li, S., Xiu, X., Fan, C., Qi, M., Meng, M., Ye, J., 2024. Accurate identification of genes associated with brain disorders by integrating heterogeneous genomic data into a Bayesian framework. Ebiomedicine 107.

Hevey, D., 2018. Network analysis: a brief overview and tutorial. Health Psychol. Behav. Med. 6 (1), 301–328.

Heym, N., Heasman, B., Hunter, K., Blanco, S., Wang, G., Siegert, R., Cleare, A., Gibson, G., Kumari, V., Sumich, A., 2019. The role of microbiota and inflammation in self-judgement and empathy: implications for understanding the brain-gut-microbiome axis in depression. Psychopharmacology 236, 1459–1470.

Hsu, M.-C., Huang, Y.-S., Ouyang, W.-C., 2020. Beneficial effects of omega-3 fatty acid supplementation in schizophrenia: possible mechanisms. Lipids Health Dis. 19, 1–17.

Huang, X., Zhou, Y., Sun, Y., Wang, Q., 2022. Intestinal fatty acid binding protein: a rising therapeutic target in lipid metabolism. Prog. Lipid Res. 87, 101178.

Iwayama, Y., Hattori, E., Maekawa, M., Yamada, K., Toyota, T., Ohnishi, T., Iwata, Y., Tsuchiya, K.J., Sugihara, G., Kikuchi, M., 2010. Association analyses between brain-expressed fatty-acid binding protein (FABP) genes and schizophrenia and bipolar disorder. Am. J. Med. Genet. Part B: Neuropsychiatr. Genet. 153 (2), 484–493.

Jang, S., Choi, B., Lim, C., Lee, B., Cho, K.S., 2022. Roles of Drosophila fatty acid-binding protein in development and behavior. Biochem. Biophys. Res. Commun. 599, 87–92.

Jenkins, T.A., Nguyen, J.C., Polglaze, K.E., Bertrand, P.P., 2016. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. Nutrients 8 (1), 56.

Jensen, C., 2019. Examining Snake Detection Theory: Conscious and Unconscious Responses to Snakes.

Kahn, R.S., Keefe, R.S., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70 (10).

Kahn, P.V., Walker, T.M., Williams, T.S., Cornblatt, B.A., Mohs, R.C., Keefe, R.S., 2012. Standardizing the use of the Continuous Performance Test in schizophrenia research: a validation study. Schizophr. Res. 142 (1–3), 153–158.

Ke, Y., Jin, X., Al-Bayati, A., He, G., Zhang, J., Wei, Q., 2021. Fatty acid-binding proteins and their roles in disease and cancer. Open Access J. Oncol. Med.

Keefe, R.S., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L.J.S.r., 2004. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 68 (2–3), 283–297.

Khandaker, G.M., Cousins, L., Deakin, J., Lennox, B.R., Yolken, R., Jones, P.B., 2015. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2 (3), 258–270.

Lee, J., Rekhi, G., Mitter, N., Bong, Y.L., Kraus, M.S., Lam, M., Rapisarda, A., Lee, T.-S., Subramaniam, M., Chong, S.A., 2013. The longitudinal youth at risk study (LYRIKS)—an Asian UHR perspective. Schizophr. Res. 151 (1-3), 279–283.

Li, H., Zhang, D., Wang, X., Wang, S., Xiao, M., 2023. Protective effect of glutamic-oxaloacetic transaminase on hippocampal neurons in Alzheimer's disease using model mice. Neurosci. Lett. 803, 137194.

Luo, N., Sui, J., Chen, J., Zhang, F., Tian, L., Lin, D., Song, M., Calhoun, V.D., Cui, Y., Vergara, V.M., 2018. A schizophrenia-related genetic-brain-cognition pathway revealed in a large Chinese population. Ebiomedicine 37, 471–482.

McCutcheon, R.A., Krystal, J.H., Howes, O.D., 2020. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. World Psychiatry 19 (1), 15–33.

McHugo, M., Roeske, M.J., Vandekar, S.N., Armstrong, K., Avery, S.N., Heckers, S., 2024. Smaller anterior hippocampal subfields in the early stage of psychosis. Transl. Psychiatry 14 (1), 1–8.

Nelson, B., Amminger, G., Yuen, H., Markulev, C., Lavoie, S., Schäfer, M., Hartmann, J., Mossaheb, N., Schlögelhofer, M., Smesny, S., 2018. NEURAPRO: a multi-centre RCT of omega-3 polyunsaturated fatty acids versus placebo in young people at ultra-high risk of psychotic disorders—medium-term follow-up and clinical course. NPJ Schizophr. 4 (1), 11.

Nowowiejska, J., Baran, A., Flisiak, I., 2022. Fatty acid-binding proteins in psoriasis–a review. Metabolites 12 (9), 833.

Orhan, F., Malwade, S., Khanlarkhani, N., Gkoga, A., Jungholm, O., Koskuvi, M., Sellgren, C.M., 2023. Kynurenic acid promotes activity-dependent synaptic pruning in schizophrenia. bioRxiv, 2023-10.

Orsolini, L., Pompili, S., Volpe, U., 2022. Schizophrenia: a narrative review of etiopathogenetic, diagnostic and treatment aspects. J. Clin. Med. 11 (17), 5040.

Pan, Y., Short, J.L., Choy, K.H., Zeng, A.X., Marriott, P.J., Owada, Y., Scanlon, M.J., Porter, C.J., Nicolazzo, J.A., 2016. Fatty acid-binding protein 5 at the blood–brain barrier regulates endogenous brain docosahexaenoic acid levels and cognitive function. J. Neurosci. 36 (46), 11755–11767.

Pandey, J.P., Namboodiri, A.M., Elston, R.C., 2016. Immunoglobulin G genotypes and the risk of schizophrenia. Hum. Genet. 135, 1175–1179.

Penman, S.L., Roeder, N.M., Berthold, E.C., Senetra, A.S., Marion, M., Richardson, B.J., White, O., Fearby, N.L., McCurdy, C.R., Hamilton, J., 2023. FABP5 is important for cognitive function and is an important regulator of the physiological effects and pharmacokinetics of acute Δ9 tetrahydrocannabinol inhalation in mice. Pharmacol. Biochem. Behav. 231, 173633.

Plitman, E., Iwata, Y., Caravaggio, F., Nakajima, S., Chung, J.K., Gerretsen, P., Kim, J., Takeuchi, H., Chakravarty, M.M., Remington, G., 2017. Kynurenic acid in schizophrenia: a systematic review and meta-analysis. Schizophr. Bull. 43 (4), 764–777.

Prasad, K.M., Watson, A.M., Dickerson, F.B., Yolken, R.H., Nimgaonkar, V.L., 2012. Exposure to herpes simplex virus type 1 and cognitive impairments in individuals with schizophrenia. Schizophr. Bull. 38 (6), 1137–1148.

Quesada, D., 2022. DbnR: Dynamic Bayesian Network Learning and Inference (In).

Recio-Barbero, M., Segarra, R., Zabala, A., Gonzalez-Fraile, E., Gonzalez-Pinto, A., Ballesteros, J., 2021. Cognitive enhancers in schizophrenia: a systematic review and meta-analysis of alpha-7 nicotinic acetylcholine receptor agonists for cognitive deficits and negative symptoms. Front. Psychiatry 12, 631589.

Scutari, M., 2009. Learning Bayesian networks with the bnlearn R package. arXiv Prepr. arXiv:0908.3817.

Simon, A.E., Velthorst, E., Nieman, D.H., Linszen, D., Umbricht, D., de Haan, L.J.S.r., 2011. Ultra high-risk state for psychosis and non-transition: a systematic review. Schizophr. Res. 132 (1), 8–17.
Singh, B., Doborjeh, M., Doborjeh, Z., Budhraja, S., Tan, S., Sumich, A., Goh, W., Lee, J., Lai, E., Kasabov, N., 2023. Constrained neuro fuzzy inference methodology for explainable personalised modelling with applications on gene expression data. Sci. Rep. 13 (1), 456.
Smathers, R.L., Petersen, D.R., 2011. The human fatty acid-binding protein family: evolutionary divergences and functions. Hum. Genom. 5 (3), 1–22.
Snodgrass, J.G., Kinjo, H., 1998. On the generality of the perceptual closure effect. J. Exp. Psychol. Learn. Mem. Cogn. 24 (3), 645.
Studerus, E., Ramyead, A., Riecher-Rössler, A., 2017. Prediction of transition to psychosis in patients with a clinical high risk for psychosis: a systematic review of methodology and reporting. Psychol. Med. 47 (7), 1163–1178.
Susai, S.R., Sabherwal, S., Mongan, D., Föcking, M., Cotter, D.R., 2022. Omega-3 fatty acid in ultra-high-risk psychosis: A systematic review based on functional outcome. Early Interv. Psychiatry 16 (1), 3–16.
Tan, S.M.X., Yee, J.Y., Budhraja, S., Singh, B., Doborjeh, Z., Doborjeh, M., Kasabov, N., Lai, E., Sumich, A., Lee, J., 2023. RNA-sequencing of peripheral whole blood of individuals at ultra-high-risk for psychosis–A longitudinal perspective. Asian J. Psychiatry 89, 103796.
Tandon, R., 2024. Reinventing schizophrenia. Updating the construct a three-year international project. Asian J. Psychiatry 97, 104107.
Trotta, A., Murray, R., MacCabe, J., 2015. Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. Psychol. Med. 45 (2), 381–394.
Tsai, S.-J., Hong, C.-J., Liou, Y.-J., Liao, D.-L., 2007. Association study of got2 genetic polymorphisms and schizophrenia. Psychiatr. Genet. 17 (5), 314.
Twisk, J.W., 2013. Applied Longitudinal Data Analysis for Epidemiology: A Practical Guide. cambridge university press.
van de Ven, V., Jagiela, A.R., Oertel-Knöchel, V., Linden, D.E., 2017. Reduced intrinsic visual cortical connectivity is associated with impaired perceptual closure in schizophrenia. NeuroImage Clin. 15, 45–52.
Wang, F., Huang, Z.-h, Ye, Y., He, X.-Y., Wang, S.-B., Jia, F.-J., Hou, C.-L., 2024. Genome-wide association exploratory studies in individuals with ultra-high risk for schizophrenia in Chinese Han nationality in two years follow-up: a subpopulation study. Asian J. Psychiatry 97, 104071.
Wingo, T.S., Liu, Y., Gerasimov, E.S., Vattathil, S.M., Wynne, M.E., Liu, J., Lori, A., Faundez, V., Bennett, D.A., Seyfried, N.T., 2022. Shared mechanisms across the major psychiatric and neurodegenerative diseases. Nat. Commun. 13 (1), 4314.
Yehuda, S., Rabinovitz, S., Mostofsky, D.I., 1999. Essential fatty acids are mediators of brain biochemistry and cognitive functions. J. Neurosci. Res. 56 (6), 565–570.
Yu, S., Levi, L., Casadesus, G., Kunos, G., Noy, N., 2014. Fatty acid-binding protein 5 (FABP5) regulates cognitive function both by decreasing anandamide levels and by activating the nuclear receptor peroxisome proliferator-activated receptor β/δ (PPARβ/δ) in the brain*◆. J. Biol. Chem. 289 (18), 12748–12758.
Yung, A.R., McGorry, P.D., McFarlane, C.A., Jackson, H.J., Patton, G.C., Rakkar, A., 1996. Monitoring and care of young people at incipient risk of psychosis. Schizophr. Bull. 22 (2), 283–303.