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Senescence-associated secretory phenotype proteins and inflammatory pathways are involved in psychosis: A transdiagnostic study using the Human Connectome Project for early psychosis (HCP-EP) data

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ABSTRACT

Biofluid proteins are promising transdiagnostic markers for delineating disease heterogeneity in psychosis. This study examined proteomic profiles in a transdiagnostic early psychosis sample to test the hypothesis that psychosis is associated with proteomic signatures of premature aging.

We analyzed proteomic data from 85 individuals with early psychosis and 35 healthy controls from the Human Connectome Project for Early Psychosis (HCP-EP), using the Olink platform across four validated panels (Cardiometabolic, Inflammation, Cardiovascular II, and III). Our dual analytic strategy included: (1) calculating an index based on senescence-associated secretory phenotype (SASP) proteins to assess cellular aging, and (2) analyzing 341 proteins using Gene Set Enrichment Analysis to identify whether predefined biological pathways are collectively enriched. We compared the SASP index and enriched pathways between groups and examined associations with sociodemographic, physical health, cognitive, psychological well-being, psychosocial functioning, symptom, and medication data.

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The SASP index was significantly elevated in the psychosis group. Pathway analyses revealed enrichment of two inflammation-related pathways in psychosis after multiple comparison correction: *Cellular Response to Tumor Necrosis Factor* and *Monocyte Chemotaxis*. The higher SASP index and the enriched inflammatory pathways were associated with increased body mass index (BMI) and reduced psychological well-being.

Our findings are consistent with prior research linking psychosis to premature aging and an increased inflammation response. They also underscore the value of examining multiple biomarkers and biological pathways simultaneously and highlight the importance of conceptualizing psychosis as a whole-body condition. However, given the sample size, results should be considered preliminary. Larger, longitudinal studies are needed to track proteomic changes over time and assess the predictive value of these biomarkers for identifying vulnerable individuals and clinical outcomes.

1. Introduction

Psychotic disorders represent a group of serious mental health conditions that significantly impact an individual's well-being (Crespo-Facorro et al., 2021) and include a range of diagnoses, such as schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder with psychotic features. However, these diagnostic categories fail to fully capture the shared phenomenological, biological, and genetic characteristics that span these disorders (Maj, 2018). Consequently, a key objective of contemporary psychiatry has been to identify transdiagnostic biomarkers for psychosis (Dalgleish et al., 2020). These biomarkers could elucidate common biological mechanisms across various disorders, deepen our understanding of the underlying pathophysiology, and facilitate personalized, effective treatments (Kotov et al., 2024; McGorry and Nelson, 2016).

Proteins in circulation indicate the physiological states of organ functions, and include proteins secreted, excreted or otherwise released from tissues for normal function and after injury, as well as immune response to those proteins and their metabolism (Elmas et al., 2024). They may reflect functional consequences of variations in the genome, epigenome, and transcriptome (Borgmann-Winter et al., 2020) in interaction with environmental and developmental factors (Guan et al., 2022). Blood-based protein biomarkers can be reliably identified and measured through minimally invasive and relatively cost-effective methods (Muneer, 2020). Consequently, they have been suggested as excellent biomarkers for preventive and therapeutic interventions (Elmas et al., 2024), as well as for detecting disease onset (Byrne et al., 2024), staging disease trajectories (Muneer, 2020), and monitoring disease progression (Smith et al., 2024) in psychiatric disorders.

Previous research has demonstrated changes in several proteins in psychosis, including proteins related to the complement and coagulation pathways (Byrne et al., 2024), the inflammatory response (Eren et al., 2023; Haroon et al., 2024), oxidative stress, lipid and energy metabolism (Guan et al., 2022), cell hemostasis (Santa Cruz et al., 2021), cell regulation (Elmas et al., 2024), cell communication (Shen et al., 2024), and the extracellular matrix (Seitz-Holland et al., 2024a; Seitz-Holland et al., 2021). These findings align with the notion that at least a subset of individuals with psychosis exhibit aberrant regulation of biological pathways, such as inflammatory response (Muller et al., 2015) and oxidative stress homeostasis (Yao and Keshavan, 2011), that might reflect a premature aging phenotype (Diniz et al., 2024; Kirkpatrick et al., 2008). Indeed, as highlighted in large-scale longitudinal analyses, a significant percentage of individuals with psychosis experience early cognitive impairments along with clinical (Kotov et al., 2017) and cognitive decline (Fett et al., 2020) throughout their lifespan. Individuals with psychosis present with increased rates of dementia (Stroup et al., 2021), more physical comorbidities, premature mortality (Liu et al., 2017), and structural brain changes related to aging (Seitz-Holland et al., 2024b). Furthermore, several studies have reported evidence of telomere shortening in psychosis, although findings remain mixed (Galletly et al., 2017; Polho et al., 2015; Russo et al., 2018; Wolkowitz et al., 2017).

While these findings suggest the potential of protein markers to identify a premature aging phenotype (Campeau et al., 2022; Chen et al., 2024; Diniz et al., 2024), several limitations persist. First, studies in transdiagnostic psychotic samples are sparse. In addition, many previously published studies focused on a few proteins, which may obscure dysfunctions in broader functional pathways (Westacott and Severance, 2024). Therefore, the present study aimed to examine proteomic profiles across individuals diagnosed with a psychotic disorder within the last five years. Specifically, we used the Human Connectome Project for Early Psychosis (HCP-EP) sample (Jacobs et al., 2025), which was established in the spirit of the Research Domain Criteria (RDoC) framework (Insel et al., 2010) to move beyond traditional diagnoses but focus on biologically informed dimensions and phenotypes.

To test our hypothesis that early psychosis would be associated with proteomic profiles indicative of premature aging, we leveraged novel technologies to examine numerous proteins simultaneously to delineate complex, multifactorial pathophysiological processes (Muneer, 2020) and followed a dual analytic strategy. First, we calculated a targeted index related to cellular aging based on senescence-associated secretory phenotype (SASP) proteins. Cellular senescence represents a multifaceted stress response (Hayflick and Moorhead, 1961) in which cells irreversibly cease division ("zombie cells") (Herranz and Gil, 2018) and adopt a complex secretory phenotype (Basisty et al., 2020). While the specific profile of SASP proteins may vary across cell types, a core set of proteins—integral to cell cycle control, communication, and immune-inflammatory responses (Gu and Kitamura, 2012)—is consistently expressed by all senescent cells, including brain cells (Salminen et al., 2011; Sierra et al., 2007). In healthy tissues, these proteins play a crucial role in preserving homeostasis (Neves et al., 2015; Storer et al., 2013); however, their proliferation with age and the build-up of senescent cells have been associated with tissue degradation (van Deursen, 2014). In 2017 Diniz et al. developed a SASP index to reflect whole-body senescence-related processes (Diniz et al., 2017). The authors selected 22 proteins based on preclinical work showing that senescent fibroblasts from different lineages secrete a shared set of proteins, including inflammatory and immune-modulatory cytokines and chemokines, growth factors, proteases, and cell-surface molecules (Coppe et al., 2008). They applied Principal Component Analysis (PCA) to the 22 proteins and labeled the first component the SASP index. The SASP index was associated with chronological age and cognitive functioning (Diniz et al., 2017), and subsequent studies showed associations with depression (Diniz et al., 2017; Diniz et al., 2019), bipolar disorder (Tessema et al., 2024), structural brain abnormalities (Mendes-Silva et al., 2019), cognitive impairment and poor physical health (Seitz-Holland et al., 2023). Here, in addition to analyzing the SASP index, we conducted an unbiased Gene Set Enrichment Analysis (GSEA) of all 341 proteins. GSEA does not test each protein independently; rather, it assesses whether predefined biological pathways are collectively enriched (Ashburner et al., 2000; Kanehisa and Goto, 2000; Milacic et al., 2024). This pathway-based approach substantially reduces the dimensionality of the data and provides biologically interpretable results. Last, in exploratory analyses, we examined correlations between the SASP/protein pathways and biopsychosocial variables.

2. Methods and materials

2.1. Participants

2.1.1. Recruitment

The HCP-EP study recruited participants between 2016 and 2022 at four institutions, including Massachusetts General Hospital (MGH), McLean Hospital, Beth Israel Deaconess Medical Center (BIDMC), and Indiana University (Jacobs et al., 2025). At MGH, participants were enrolled through the First Episode and Early Psychosis Program and inpatient referrals; McLean Hospital used its McLean OnTrack program as well as referrals from the McLean Psychotic Disorders inpatient, residential, and partial hospital programs; BIDMC recruited via its early psychosis program at the BIDMC-Massachusetts Mental Health Center; and Indiana University employed its Prevention and Recovery for Early Psychosis Program. All recruitment and informed consent processes were approved by the Partners Institutional Review Board Committee and the Indiana University Institutional Review Board.

2.1.2. Inclusion/exclusion

Eligible participants were between 16 to 35 years old, fluent in English, and capable of providing informed consent, directly or via an authorized legal representative, with the additional agreement to share de-identified data with the National Institute of Mental Health Data Archive (NDA).

Individuals were excluded if they met criteria for severe substance use disorder within the past 90 days as determined by the Structured Clinical Interview for DSM-5 Research version (SCID-5-RV (First, 2015)), had an IQ below 70 based on either medical history or the Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-II (McCrimmon and Smith, 2012)), or had a known history of Human Immunodeficiency Virus (HIV) positive status. Further exclusions applied to those with active medical conditions affecting brain or cognitive function, receipt of electroconvulsive therapy in the preceding 12 months, or contraindications for MRI (e.g., pregnancy, or the presence of implanted devices such as pacemakers, medication pumps, vagal stimulators, deep brain stimulators, transcutaneous electrical nerve stimulation units, or ventriculoperitoneal shunts). Individuals presenting with high risk for suicidal behavior or overly aggressive actions were also excluded.

Psychosis diagnoses were based on the DSM-5 criteria as defined by the SCID-5-RV (First, 2015). The transdiagnostic psychosis group comprised individuals who met DSM-5 criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder not otherwise specified, delusional disorder, brief psychotic disorder, major depressive disorder with psychosis (single or recurrent episodes), or bipolar disorder with psychosis (including most recent episodes of either depressed or manic type). Duration of illness was determined via the SCID interview, and duration of illness longer than five years was considered an exclusion criterion. Participants were excluded if the above diagnoses were determined to be substance-induced or due to a medical condition.

Healthy individuals were excluded if they met any of the previously listed psychiatric diagnoses, recurrent major depressive disorder, an anxiety disorder present in the last 12 months, or a lifetime history of anxiety that had a duration of illness of more than 12 months or required medication. Other exclusion criteria for the control group included a first-degree family member diagnosed with a schizophrenia spectrum disorder, use of psychiatric medications at the time of study entry, or a lifetime history of psychiatric hospitalization. Participants in the healthy control group were group-matched with participants in the psychosis group based on sex, age, handedness and parental socioeconomic status.

2.1.3. Data availability

In total, data for 303 individuals was uploaded to the National Institute of Mental Health Data Archive (NDA). Of the 223 individuals diagnosed with psychosis, 85 who underwent the blood draw procedure were included in the present study. Among the 80 healthy controls, 35 who participated in the blood draw were included. Relative to the total HCP-EP psychosis cohort, participants included in the present analyses were, among others, less likely from the Indiana site, had a higher proportion of males, showed lower global functioning and IQ, higher schizophrenia symptom burden on the negative and cognitive domains, and fewer manic symptoms. Healthy controls were less likely from the Indiana site, older, and had a lower body mass index (BMI). For the full comparison of biopsychosocial variables by proteomics data availability, see Supplementary Tables 1 and 2.

2.1.4. Sociodemographic and physical health data

Sociodemographic data included age, self-reported sex, self-reported race and ethnicity, highest level of completed education, and parental socioeconomic status (Hollingshead, 1975). Physical health measures included BMI, smoking (current status, lifetime status, and estimated pack years), as well as assessments of alcohol and drug use over the last month and lifetime.

2.1.5. Cognitive, psychological well-being, and psychosocial functioning data

We estimated cognitive abilities using the WASI-II (McCrimmon and Smith, 2012) for total IQ, and the NIH Toolbox (Hodes et al., 2013) summary scores for fluid composite, crystallized composite, and total cognition composite. We derived composite scores for emotional assessments from the NIH Toolbox, including positive affect, general satisfaction, meaning and purpose, and negative affect, based on previously described methods (Babakhanyan et al., 2018). Occupational and social functioning were evaluated using the Mental Illness Research, Education, and Clinical Center version of the Global Assessment of Functioning (MIRECC GAF) (Aas, 2011).

2.1.6. Symptom and medication data

Psychotic symptom severity was quantified by the Positive and Negative Syndrome Scale (PANSS (Kay et al., 1987)) and summarized via Marder PANSS factors (Marder et al., 1997). Depression and mania symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS (Montgomery and Asberg, 1979)) and the Young Mania Rating Scale (YMRS (Young et al., 1978)), respectively. We collected data on concomitant medications and calculated chlorpromazine equivalent dosage (CPZ) on the day of data collection. Given the approximative nature of CPZ, we employed a categorical CPZ approach (CPZ = 0 mg/day, CPZ < 300 mg/day, CPZ 300–1000 mg/day, CPZ > 1000 mg/day) (Sohler et al., 2003).

2.2. Blood proteins

2.2.1. Data Collection

Trained study staff at the Center for Clinical Investigation at BWH, McLean Hospital, or Indiana University collected blood samples. At the date of their other assessments, blood was collected in EDTA tubes for all individuals who consented to blood draw. Time of day varied based on when the individuals came in for their clinical assessment. Tubes were initially inverted gently 8 to 10 times to mix blood with additives and were kept at room temperature. On the same day, blood samples were packed on dry ice and shipped to the Rutgers University Cell & DNA Repository (RUCDR) Infinite Biologics Biorepository at Rutgers University via overnight courier. After accessioning, the tubes were centrifuged at 1,600 x g for 10 min and plasma isolated using a high throughput automated system from Hamilton (the Microlab STAR easyBlood instrument) which aspirated and dispensed the plasma into single-use (no freeze–thaw) aliquots. Vials of plasma were then placed into storage at −80°C.

Given their high-quality immunoassays, wide acceptance in the field (Sun et al., 2023), and high reproducibility and biological specificity, we

used Olink for proteomic analyses, which are based on the Proximity Extension Assay (PEA). Specifically, we selected four validated panels that included most of the previously studied SASP proteins: Target 96 Cardiometabolic, Target 96 Inflammation, Target 96 Cardiovascular II, and Target 96 Cardiovascular III, each containing 92 proteins (see Supplementary Table 3).

2.2.2. Pre-processing

Following previous practice (Deng et al., 2025) and suggestions from Olink manufacturer, the primary quantitative metric analyzed were Normalized Protein Expression (NPX) values. NPXs are proprietary units that reflect a relative abundance of a protein. They are derived from raw counts after normalizing to controls and log2 transformation. This procedure reduces the influence of technical variation and extreme measurements arising from assay performance rather than underlying biology. Higher NPX values always correspond to higher protein concentrations.

Across the four panels, there were 10 instances of duplicate proteins. To determine which duplicates to choose, we used the following strategy: 1) if we identified outliers in one of the duplicates by comparing the NPX-derived z-scores, we chose the one without outliers (z-score > 3; n $= 1$), 2) if the duplicates presented with a different number of data points below the limit of detection (LOD), we chose the one with fewer values below the LOD (n $= 1$), and 3) in all other cases, we opted for the first occurrence of the protein (n $= 8$).

Further data cleaning included four steps. First, we excluded proteins for which more than 50% of the expression values were below the LOD (n $= 17$, Supplementary Table 3). Next, samples that failed Olink quality control (1.7% of the data) were imputed using the mean expression value calculated from all other participants. The resulting dataset contained a total of 0.14% of values below the LOD. Following established conventions (Beal, 2001), values below 50% of the LOD—representing 0.09% of the data—were replaced with a value equal to 50% of the LOD. Since NPX values can be negative, we adapted this approach by subtracting half of the absolute LOD value when the original NPX value was negative. Please note that information about storage time was missing for three participants.

2.2.3. Processing

SASP-Index: To evaluate our primary hypothesis – that individuals with psychosis exhibit proteomic signatures of premature aging – we derived a previously published index of SASP proteins (Diniz et al., 2017). Diniz et al. selected 22 proteins based on preclinical work (Coppe et al., 2008). They measured the proteins in plasma, and applied data reduction strategies to derive a SASP index. They revealed an association of the SASP index with age and cognitive functioning (Diniz et al., 2017) and an elevated SASP index in individuals with depression relative to healthy controls (Diniz et al., 2017; Diniz et al., 2019). Additional studies showed that the elevation in the SASP index was associated with brain structure (Mendes-Silva et al., 2019) and various physical health measures (Seitz-Holland et al., 2023). In our study, we incorporated all 18 proteins available in the current data set from this original index (designated as SASP index, Supplementary Table 4). The 18 included proteins are: Interleukin-8 (IL8), C-C motif chemokine 2 (MCP-1), C-C motif chemokine 20 (CCL20), C-C motif chemokine 3 (CCL3), C-C motif chemokine 4 (CCL4), C-C motif chemokine 13 (MCP-4), Intercellular adhesion molecule 1 (ICAM1), Tumor necrosis factor receptor superfamily member 1A (TNF-R1), Interleukin-6 (IL6), Growth-regulated alpha protein (CXCL1), Insulin-like growth factor-binding protein 2 (IGFBP-2), Metalloproteinase inhibitor 1 (TIMP1), Urokinase plasminogen activator surface receptor (U-PAR), Tumor necrosis factor receptor superfamily member 11B (OPG), Tumor necrosis factor receptor superfamily member 1B (TNF-R2), Placenta growth factor (PGF), Insulin-like growth factor-binding protein 6 (IGFBP6), Angiogenin (ANG). As detailed below, in alignment with other proteomic research (Campeau et al., 2022), we employed PCAs to the expression values of these proteins and focused our analysis on the first component that explained the largest part of the variance in the SASP index.

All proteins: In addition to our hypothesis-driven analyses, we also examined all proteins simultaneously to identify biological pathways that exhibit differences in protein expression between groups. Therefore, we conducted Gene Set Enrichment analysis (GSEA) using the publicly available GSEA tool (https://www.gsea-msigdb.org/gsea/index.jsp) (Mootha et al., 2003; Subramanian et al., 2005). Unlike methods that focus on individual protein changes, GSEA evaluates whether predefined sets of proteins—representing biological pathways—are significantly enriched among those showing differential expression between phenotypes. First, all individual proteins are ranked according to the magnitude of their differential expression between groups. Then, the analysis determines whether any predefined pathways are enriched at the top or bottom of this ranked list, indicating coordinated and significant changes in expression across the pathway. This pathway-based approach substantially reduces the dimensionality of the data and provides biologically interpretable results.

2.3. Statistical analyses

Statistical analyses were conducted using R (version 4.3.2).

2.3.1. Group comparisons

SASP-Index: To examine how strongly the different proteins within the SASP index are related to each other, we performed Pearson correlation analyses in the transdiagnostic psychosis group and in healthy controls separately (*stats* 4.3.2 package). The intercorrelation within the index was visualized using Chord diagrams (*circlize* 0.4.16 package).

Following the approach introduced by Diniz et al. (2017), Diniz et al. (2019), Seitz-Holland et al. (2023), we applied PCAs (*FactoMineR* 2.10 package) to all proteins included in the SASP index. We extracted the individual scores on the first principal component for each participant for further analyses (SASP PC). Group difference comparing the transdiagnostic psychosis group to the healthy controls using the SASP PC were assessed with an Analyses of Covariance (ANCOVA, type III sum of squares, *car* 3.1–2 package) while controlling for age, self-reported sex, and sample storage time.

To further evaluate the observed SASP PC group difference, we conducted several sensitivity analyses. First, we employed rank-based Freedman-Lane permutation testing and robust regression using an MM estimator to test for the effects of outliers. Second, we examined the role of BMI in more detail. We did not include BMI in our primary analyses given that BMI may not simply represent an independent confounding variable but may lie, at least in part, on the causal pathway linking psychosis to aging. Individuals with psychosis experience a substantially greater burden of cardiometabolic abnormalities (Perry et al., 2021), which in turn have been linked to premature aging and cellular senescence. Therefore, adjusting for it could result in over-adjustment bias by removing variance that is directly relevant to psychosis (Schisterman et al., 2009). In our sensitivity analyses, we first created a BMI-matched subsample and repeated the group comparisons (*MatchIt* 4.7.2 package). Second, we conducted an exploratory mediation analysis, examining if BMI mediates the association between a diagnosis of psychosis and the SASP PC. We employed nonparametric bootstrapping with 10,000 simulations while controlling for age, self-reported sex, and storage time (*mediation* 4.5.1 package).

All proteins: We ran GSEA analyses introduced above. Following GSEA conventions, we included protein sets, which represent predefined biological pathways, that are part of the Gene Ontology Biological Processes (GOBP (Ashburner et al., 2000)), the Kyoto Encyclopedia of Genes and Genomes (KEGG (Kanehisa and Goto, 2000)), and the Reactome databases (Milacic et al., 2024). We first ranked proteins based on the Signal2Noise (S2N) metric, which calculates for each protein the mean difference between the two groups and then normalizes it by the sum of the respective standard deviations. This approach allowed us to

identify proteins differing most between the transdiagnostic psychosis group and healthy controls (***Supplementary Fig. 1***). Based on this ranking, we then ran GSEA to compute the enrichment score metric for each pathway encompassing at least five proteins (k = 515). The enrichment score iterates over each pathway individually and reflects the degree to which proteins of this pathway are concentrated at the top or bottom of the ranked protein list. To assess the statistical significance of these enrichment scores, we performed 1,000 permutations of the phenotype labels. This permutation-based approach generates a null distribution of enrichment scores expected by chance. By comparing the observed enrichment scores against this null distribution, we calculated p-values that reflect the likelihood of observing such enrichment scores by random chance, providing a robust assessment of the association between pathways and the diagnoses of psychosis.

To visualize our results, we used Cytoscape 3.10.2 (Shannon et al., 2003) and the Enrichment Map (version 3.4.10) (Merico et al., 2010) software. We plotted enriched pathways in a network where edges connected terms with a similarity score greater than 0.5.

After we determined significantly enriched pathways with GSEA, we applied PCAs to all proteins that were part of those pathways, extracting individual scores on the first PC for subsequent analysis (termed enriched PC). An ANCOVA was conducted on the enriched PC for all the significantly enriched pathways, comparing the transdiagnostic psychosis group and healthy controls while controlling for age, self-reported sex, and sample storage time.

In sensitivity analyses, group comparisons were repeated using non-parametric tests and in the BMI-matched subsample. We also ran complementary mediation analyses, testing if BMI mediates the association between a diagnosis of psychosis and the enriched PCs.

2.3.2. Associations with biopsychosocial variables

In preliminary analyses, we examined the association between the SASP PC and enriched PCs and sociodemographic, physical health, cognition, psychological well-being, psychosocial functioning, symptom, and medication data. We applied Pearson correlation to interval-scaled variables, and Kendall correlation for ordinal-scaled variables. We performed these analyses for the transdiagnostic psychosis group and the healthy controls separately. Given the explorative nature, we did not correct for multiple comparisons.

Again, in sensitivity analyses, we repeated all correlation analyses controlling for additional variables. Within the transdiagnostic psychosis group, associations were reexamined using partial correlations adjusted for BMI and chlorpromazine-equivalent dose (*ppcor* 1.1 package). In healthy controls, the corresponding analyses were adjusted for BMI only.

3. Results

3.1. Demographics

The transdiagnostic psychosis group was younger than the healthy control group (mean age: 22.44 vs. 25.29 years) and included a lower proportion of females (27% vs. 49%). Compared to healthy controls, individuals with transdiagnostic psychosis also presented with lower levels of completed education and a higher BMI (26.29 vs. 23.16). Cigarette use lifetime, and drug use lifetime were more prevalent in the transdiagnostic psychosis group. Whereas alcohol use in the past month was more prevalent in the healthy control group. Please refer to Table 1 for a detailed overview of biopsychosocial variables for the transdiagnostic psychosis group and healthy controls.

3.2. Group comparisons

3.2.1. SASP-Index

As displayed in Fig. 1, the proteins included in the SASP index were highly correlated with each other. To further reduce the dimensionality for statistical testing, we employed Principal Component Analysis (PCA) on the expression values of these proteins and focused our analysis on the first component that explained the largest part of the variance in the SASP index. This approach aligns with previous SASP research (Diniz et al., 2017) as well as recent proteomic research (Campeau et al., 2022). Detailed information on the principal component weights can be found in Supplementary Table 5. The loadings for all proteins on the SASP PC were positive, suggesting that increased protein expression levels correlated with higher PC scores.

The ANCOVA demonstrated a significant increase of the SASP PC in the transdiagnostic psychotic group compared to the healthy controls ($F(1,112) = 5.0$, $p = 0.027$, $\eta^2_p = 0.043$; Fig. 1***a***, Supplementary Table 6). Please note that while the Shapiro-Wilk test indicates a non-normal distribution of the ANCOVA residuals ($p < 0.001$), the Levene's test suggests homoskedasticity ($p = 0.774$) and the Freedman-Lane test indicates robust ANCOVA results concerning group differences ($p = 0.029$, 10,000 permutations).

To further evaluate whether the observed SASP PC group difference was driven by influential observations, we conducted several sensitivity analyses. First, we compared groups employing rank-based Freedman-Lane permutation testing and robust regression using an MM estimator. Second, we created a BMI-matched subsample and repeated the group comparisons using ANCOVAs. Third, we examined if BMI mediates the association between a diagnosis of psychosis and the SASP PC. The group difference in the SASP index remained statistically significant when using rank-based Freedman–Lane testing ($p = 0.041$, 10,000 permutations) and robust regression using an MM estimator ($\beta = -0.83$, $p = 0.042$, Supplementary Table 7). For the matched subsample, we achieved excellent BMI matching for all healthy control participants ($n = 34$; healthy controls BMI: 23.2 ± 3.51; transdiagnostic psychosis BMI: 23.5 ± 3.24, Supplementary Table 8). Age, self-reported sex, and storage time were secondary matching factors and residual differences in those variables were subsequently accounted for in matched-sample ANCOVA models. In the BMI-matched sample, the group difference in the SASP index was attenuated and only reached trend-level significance ($F(1,63) = 3.1$, $p = 0.083$, $\eta^2_p = 0.047$, Supplementary Table 9). In the mediation model, the total association between a psychosis diagnosis and the SASP index was significant ($\beta = 1.10$, 95% CI [0.27, 1.93], $p = 0.009$). The direct association between a psychosis diagnosis and the SASP index remained significant after accounting for BMI (ADE: $\beta = 0.77$, 95% CI [0.01, 1.52], $p = 0.046$). In addition, the indirect association through BMI was significant (ACME: $\beta = 0.33$, 95% CI [0.06, 0.69], $p = 0.012$). The estimated proportion mediated was 29.7% (95% CI [6.1%, 91.3%], $p = 0.020$), suggesting that BMI statistically accounted for approximately one-third of the psychosis–SASP association. Of note, as shown in ***Supplementary Fig. 2***, the wide confidence intervals for the different effects suggest that the results of the mediation analysis should be interpreted with caution.

3.2.2. All proteins

Employing GSEA, after correcting for multiple comparisons we observed a significant enrichment of two pathways in the transdiagnostic psychosis group: the *Cellular Response to Tumor Necrosis Factor* (GOBP, $q_{FDR} = 0.032$, size = 27 proteins, Normalized Enrichment Score [NES] = 1.95) and the *Monocyte Chemotaxis* (GOBP, $q_{FDR} = 0.034$, size = 27 proteins, NES = 1.89) pathways (Fig. 2). To see all proteins included in the two upregulated pathways, please refer to Supplementary Table 10. We did not identify significantly upregulated pathways in the healthy controls. Please see Fig. 3 for additional pathways that showed a trend toward enrichment in either the psychosis or healthy control groups. Those pathways were associated with immune response, calcium-mediated signaling and cell proliferation (Fig. 4). For non-significant results, please see ***Supplementary Data 1 and 2***.

Given the significant findings, we applied PCAs to all proteins included in the *Cellular Response to Tumor Necrosis Factor* and *Monocyte Chemotaxis* pathways. For detailed information on the composition,

Table 1
Biopsychosocial variables comparing the transdiagnostic psychosis group and healthy controls.

		Transdiagnostic psychosis group (n = 85)	Healthy controls (n = 35)	Test statistic	P-values
Sociodemographic data					
Age (years)	n	85	35	t = -3.4	0.001
	mean ± std	22.44 (± 3.45)	25.29 (± 4.48)		
Self-reported Sex (n, %)	Female	23 (27%)	17 (49%)	$X^2 = 4.2$	0.040
	Male	62 (73%)	18 (51%)		
Self-reported Race (n, %)	American Indian or Alaskan Native	0 (0%)	0 (0%)	$X^2 = 10.0$	0.190
	Asian	3 (4%)	3 (9%)		
	Black or African American	25 (29%)	3 (9%)		
	More than one race	7 (8%)	1 (3%)		
	Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)		
	White	44 (52%)	23 (66%)		
	Other	3 (4%)	1 (3%)		
	Unknown or not reported	3 (4%)	4 (11%)		
Ethnicity (n, %)	Hispanic or Latino	6 (7%)	5 (14%)	$X^2 = 4.73$	0.094
	Not Hispanic or Latino	76 (89%)	26 (74%)		
	Unknown or not reported	3 (4%)	4 (11%)		
Highest Level of Completed Education (n, %)	Elementary school	0 (0%)	0 (0%)	$X^2 = 49.2$	< 0.001
	Middle/Junior High School	0 (0%)	0 (0%)		
	High School, no degree	15 (18%)	0 (0%)		
	General Educational Development program	2 (2%)	0 (0%)		
	High School, degree	14 (16%)	0 (0%)		
	Some University Courses	42 (49%)	11 (31%)		
	Associate's Degree	2 (2%)	1 (3%)		
	Bachelor's Degree	9 (11%)	9 (26%)		
	Some Graduate Level Courses	0 (0%)	5 (14%)		
	Master's Degree	1 (1%)	3 (9%)		
	Doctorate Level Courses	0 (0%)	2 (6%)		
	Doctorate Degree	0 (0%)	4 (11%)		
	Missing	0 (0%)	0 (0%)		
Parental Socioeconomic Status (n, %) (Hollingshead, 1975)	1	25 (29%)	8 (23%)	$X^2 = 2.5$	0.776
	2	32 (38%)	14 (40%)		
	3	10 (12%)	7 (20%)		
	4	10 (12%)	4 (11%)		
	5	6 (7%)	2 (6%)		
	Missing	2 (2%)	0 (0%)		
Physical health related data					
BMI	n	70	34	t = 3.6	< 0.001
	mean ± std	26.29 (± 5.37)	23.16 (± 3.51)		
Smoking Currently (n, %)	No	65 (76%)	33 (94%)	$X^2 = 5.3$	0.071
	Yes	19 (22%)	2 (6%)		
	Missing	1 (1%)	0 (0%)		
Smoking Lifetime (n, %)	No	39 (46%)	28 (80%)	$X^2 = 11.8$	0.003
	Yes	45 (53%)	7 (20%)		
	Missing	1 (1%)	0 (0%)		
Smoking Estimated Pack Years	n	84	35	t = 3.4	< 0.001
	mean ± std	0.80 (± 1.96)	0.06 (± 0.22)		
Alcohol Use Last Month (n, %)	Never / Occasional	59 (69%)	13 (37%)	$X^2 = 13.2$	0.004
	Recreational	22 (26%)	21 (60%)		
	Regular Use	2 (2%)	1 (3%)		
	Heavy Use	0 (0%)	0 (0%)		
	Very Heavy Use	0 (0%)	0 (0%)		
	Missing	2 (2%)	0 (0%)		
Alcohol Use Lifetime (n, %)	Never / Occasional	27 (32%)	10 (29%)	$X^2 = 2.8$	0.734
	Recreational	35 (41%)	18 (51%)		
	Regular Use	14 (16%)	6 (17%)		
	Heavy Use	5 (6%)	1 (3%)		
	Very Heavy Use	2 (2%)	0 (0%)		
	Missing	2 (2%)	0 (0%)		
Drug Use Last Month (n, %)	Never / Occasional	59 (69%)	33 (94%)	$X^2 = 9.1$	0.059
	Recreational	14 (16%)	2 (6%)		
	Regular Use	9 (11%)	0 (0%)		
	Heavy Use	1 (1%)	0 (0%)		
	Very Heavy Use	0 (0%)	0 (0%)		
	Missing	2 (2%)	0 (0%)		
Drug Use Lifetime (n, %)	Never / Occasional	25 (29%)	26 (74%)	$X^2 = 25.5$	< 0.001
	Recreational	16 (19%)	7 (20%)		
	Regular Use	18 (21%)	1 (3%)		
	Heavy Use	20 (24%)	1 (3%)		
	Very Heavy Use	4 (5%)	0 (0%)		
	Missing	2 (2%)	0 (0%)		

(*continued on next page*)

Table 1 (*continued*)

		Transdiagnostic psychosis group (n = 85)	Healthy controls (n = 35)	Test statistic	P-values
Cognition, psychological well-being, psychosocial functioning data					
WASI-II Full Scale IQ Score (McCrimmon and Smith, 2012)	n	84	35	t = -5.6	< 0.001
	mean ± std	101.07 (± 14.62)	114.89 (± 11.13)		
NIH Toolbox	n	79	34	t = -5.0	< 0.001
Cognition Fluid (Hodes et al., 2013)	mean ± std	38.57 (± 11.08)	48.88 (±9.72)		
NIH Toolbox	n	80	34	t = -1.0	0.342
Cognition Crystallized (Hodes et al., 2013)	mean ± std	57.04 (±12.41)	59.26 (±10.91)		
NIH Toolbox	n	79	34	t = -3.5	< 0.001
Cognition Total (Hodes et al., 2013)	mean ± std	47.41 (±11.13)	54.79 (±9.85)		
NIH Toolbox	n	84	34	t = -5.3	< 0.001
Positive Affect	mean ± std	42.94 (±8.39)	50.53 (±6.49)		
NIH Toolbox	n	84	34	t = -4.7	< 0.001
General Life Satisfaction (Babakhanyan et al., 2018)	mean ± std	44.3 (±10.84)	53.09 (±8.60)		
NIH Toolbox	n	81	34	t = -4.7	< 0.001
Meaning and Purpose (Babakhanyan et al., 2018)	mean ± std	42.73 (±10.68)	51.53 (±8.48)		
NIH Toolbox	n	73	30	t = -4.3	< 0.001
Negative Affect Summary (Babakhanyan et al., 2018)	mean ± std	42.25 (±9.82)	51.23 (±9.42)		
NIH Toolbox	n	67	30	t = -5.9	< 0.001
Social Satisfaction Summary (Babakhanyan et al., 2018)	mean ± std	40.87 (±9.45)	51.43 (±7.62)		
MIRECC GAF Symptom Scale (Aas, 2011)	n	83	35	t = -10.7	< 0.001
	mean ± std	57.95 (± 18.68)	86.43 (± 10.13)		
MIRECC GAF Occupational Functioning (Aas, 2011)	n	83	35	t = -10.8	< 0.001
	mean ± std	60.9 (± 23.47)	90.89 (± 5.96)		
MIRECC GAF Social Functioning (Aas, 2011)	n	83	35	t = -6.5	< 0.001
	mean ± std	67.98 (± 16.45)	86.11 (± 12.47)		
Symptom and medication data					
Age of Onset (years)	n	84			
	mean ± std	20.76 (± 3.49)			
Duration of Illness (years)	n	84			
	mean ± std	1.71 (± 1.32)			
Current CPZ category (n, %) (Sohler et al., 2003)	CPZ = 0 mg/day	3 (4%)			
	CPZ < 300 mg/day	27 (32%)			
	CPZ 300 – 1000 mg/day	42 (49%)			
	CPZ > 1000 mg/day	1 (1%)			
	Missing	12 (14%)			
PANSS Total Score (Kay et al., 1987; Marder et al., 1997)	n	78			
	mean ± std	49.79 (± 11.18)			
PANSS Negative Score (Kay et al., 1987; Marder et al., 1997)	n	80			
	mean ± std	13.23 (± 5.53)			
PANSS Positive Score (Kay et al., 1987; Marder et al., 1997)	n	82			
	mean ± std	13.84 (± 4.68)			
PANSS Cognitive Score (Kay et al., 1987; Marder et al., 1997)	n	81			
	mean ± std	11.06 (± 3.03)			
MADRS Score (Montgomery and Asberg, 1979)	n	83			
	mean ± std	7.78 (± 8.4)			
YMRS Score (Young et al., 1978)	n	81			
	mean ± std	4.50 (± 5.11)			

Abbreviations: Body mass index (BMI); Chlorpromazine equivalent dose (CPZ); Mental Illness Research, Education, and Clinical Center version of the Global Assessment of Functioning (MIRECC GAF); Montgomery–Åsberg Depression Rating Scale (MADRS); Positive and Negative Syndrome Scale (PANSS); standard deviation (std); Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II); Young Mania Rating Scale (YMRS).
Parental socioeconomic level was evaluated using the Hollingshead Four-Factor Parental Socioeconomic Status Scale, which weighted parental/guardian education and occupation scores to obtain a single score (1 = highest SES classification, 5 = lowest SES classification).

weights, and contributions to the first PC of the *Cellular Response to Tumor Necrosis Factor* (CRTNF PC) and the *Monocyte Chemotaxis* (MCT PC) analyses, please see Supplementary Table 11. Notably, the positive loadings of all but one protein suggest that higher protein expression levels correspond to increased PC scores. As expected, both PCs were significantly higher in the transdiagnostic psychosis group compared to the healthy controls (CRTNF PC: $F(1,112) = 7.4$, $p = 0.008$, $\eta_p^2 = 0.062$; MCT PC: $F(1,112) = 6.8$, $p = 0.011$, $\eta_p^2 = 0.057$; Supplementary Table 12). Please note that while the Shapiro-Wilk test indicates a non-normal distribution of the ANCOVA residuals (CRTNF PC: $p = 0.002$; MCT PC: $p = 0.024$), the Levene's test suggests homoskedasticity (CRTNF PC: $p = 0.571$; MCT PC: $p = 0.742$) and the Freedman-Lane test indicates robust ANCOVA results concerning group differences (CRTNF PC: $p = 0.007$, 10,000 permutations; MCT PC: $p = 0.009$, 10,000 permutations).

As sensitivity analyses, we compared the CRTNF PC and MCT PC between groups using rank-based Freedman-Lane permutation testing and robust regression using an MM estimator. In addition, we created a BMI-matched subsample and ran mediation analyses. For the CRTNF PC, the group difference remained significant when using rank-based Freedman–Lane testing ($p = 0.008$, 10,000 permutations) and robust regression ($\beta = -1.17$, $p = 0.013$, Supplementary Table 13). Similarly, for the MCT PC, the group difference remained significant when using rank-based Freedman–Lane testing ($p = 0.020$, 10,000 permutations) and robust regression ($\beta = -1.12$, $p = 0.023$, Supplementary Table 13). In the BMI-prioritized matched sensitivity analysis both pathway-derived inflammatory PCs also remained significantly elevated in the psychosis group (CRTNF PC: $F(1,63) = 4.3$, $p = 0.042$, $\eta_p^2 = 0.064$; MCT PC: $F(1,63) = 4.4$, $p = 0.039$, $\eta_p^2 = 0.066$, Supplementary Table 14). In the mediation analyses, the total effect between a diagnosis of psychosis and

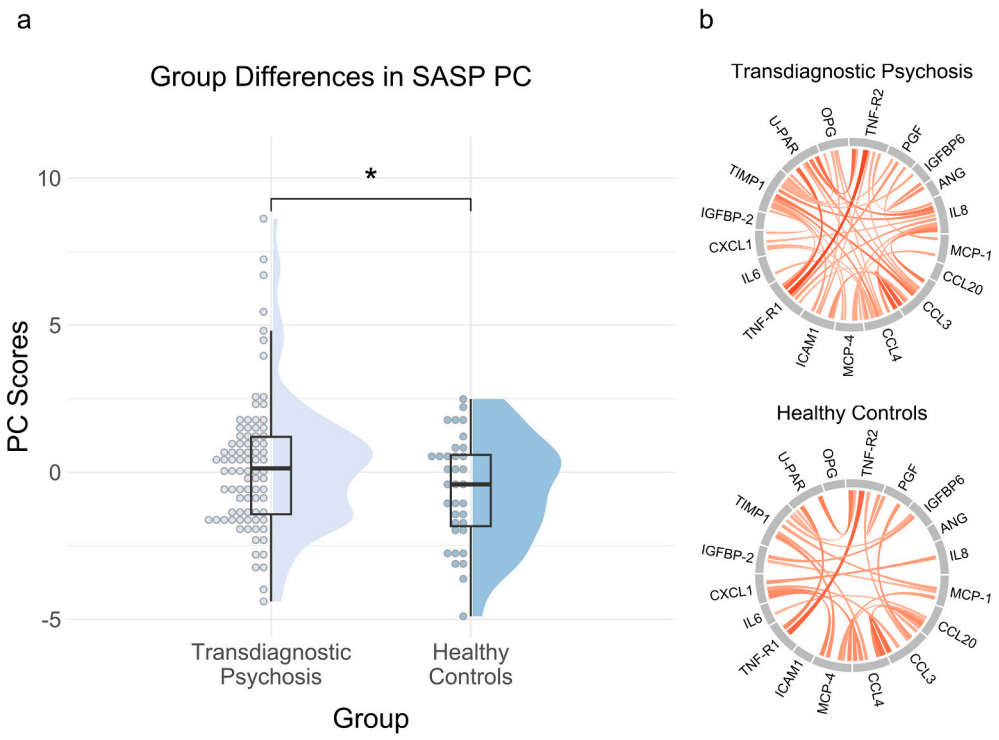


Fig. 1. Shows the analyses of the first principal component scores of the senescence-associated secretory phenotype (SASP PC) index. The left panel (a) displays the results of the group comparison (transdiagnostic psychosis group versus healthy controls) using Analysis of Covariance (ANCOVA) and controlling for age, self-reported sex, and storage time. Significant increases are shown for the SASP PC when comparing the transdiagnostic psychosis group to healthy controls. The top and bottom right panels (b) depict the pattern and strength of protein intercorrelations ($|r| > 0.4$) for the transdiagnostic psychosis group and healthy controls, respectively. The color of the links between two proteins indicates the direction of the association (red being positive). Abbreviations: Interleukin-8 (IL8); C-C motif chemokine 2 (MCP-1); C-C motif chemokine 20 (CCL20); C-C motif chemokine 3 (CCL3); C-C motif chemokine 4 (CCL4); C-C motif chemokine 13 (MCP-4); Intercellular adhesion molecule 1 (ICAM1); Tumor necrosis factor receptor superfamily member 1A (TNF-R1); Interleukin-6 (IL6); Growth-regulated alpha protein (CXCL1); Insulin-like growth factor-binding protein 2 (IGFBP-2); Metalloproteinase inhibitor 1 (TIMP1); Urokinase plasminogen activator surface receptor (U-PAR); Tumor necrosis factor receptor superfamily member 11B (OPG); Tumor necrosis factor receptor superfamily member 1B (TNF-R2); Placenta growth factor (PGF); Insulin-like growth factor-binding protein 6 (IGFBP6); Angiogenin (ANG).

CRTNF PC and MCT PC was significant (CRTNF PC: $\beta = 1.44$, 95% CI [0.42, 2.42], $p = 0.009$; MCT PC: $\beta = 1.45$, 95% CI [0.35, 2.50], $p = 0.011$). The direct association between a psychosis diagnosis and the PCs remained significant after accounting for BMI (CRTNF PC: $\beta = 1.10$, 95% CI [0.10, 2.06], $p = 0.03$; MCT PC: $\beta = 1.07$, 95% CI [0.01, 2.09], $p = 0.047$). Lastly, the indirect association through BMI was also significant for both pathway PCs (CRTNF PC: $\beta = 0.34$, 95% CI [0.06, 0.71], $p = 0.016$; MCT PC: $\beta = 0.38$, 95% CI [0.06, 0.78], $p = 0.015$). The estimated proportion mediated (CRTNF PC: 23.5%, 95% CI [3.7%, 73.3%], $p = 0.024$; MCT PC: 26.3%, 95% CI [4.4%, 87.9%], $p = 0.025$) suggests that BMI statistically accounted for approximately a quarter of the psychosis–pathway PC associations.

3.3. Associations with biopsychosocial variables

3.3.1. SASP-Index

Transdiagnostic psychosis group: A higher SASP PC was significantly associated with a higher BMI, less alcohol consumption over the past month, and lower self-reported meaning and purpose (Fig. 5, Supplementary Table 15).

Healthy controls: A higher SASP PC was significantly associated with worse fluid and total cognition, and more negative affect ***(Supplementary Fig. 3,*** Supplementary Table 16***).***

3.3.2. All proteins

Transdiagnostic psychosis group: In the transdiagnostic psychosis group, a higher CRTNF PC was significantly associated with a higher BMI and with lower general life satisfaction and meaning and purpose. A higher MCT PC was significantly associated with a higher BMI, less drug use lifetime, and lower general life satisfaction and meaning and purpose (Fig. 5, Supplementary Table 15).

Healthy controls: Higher CRTNF PC and MCT PC were significantly associated with worse fluid, crystallized and total cognition, and more negative affect. Higher MCT PC was also significantly associated with older age ***(Supplementary Fig. 3,*** Supplementary Table 16***).***

3.3.3. Sensitivity analyses

We performed partial correlations for all association analyses controlling for BMI and antipsychotic treatment (CPZ equivalents) in the transdiagnostic psychosis group and for BMI in the healthy control group. Controlling for these covariates did not significantly affect the overall pattern of the observed associations. Additionally, the partial correlation analysis indicated that higher scores for all PCs are associated with higher MADRS scores for individuals diagnosed with psychosis (Supplementary Tables 17 and 18).

4. Discussion

The present study examined proteomic profiles in a transdiagnostic early psychosis sample collected as part of the HCP-EP project. To test our hypothesis of premature aging, we analyzed the SASP index, a cell aging index previously studied in depression (Diniz et al., 2017; Diniz et al., 2019; Seitz-Holland et al., 2023). While we observed only a few group differences in individual proteins, the transdiagnostic psychosis group showed a significantly elevated SASP index. Complementary pathway analyses of 341 plasma proteins revealed significant

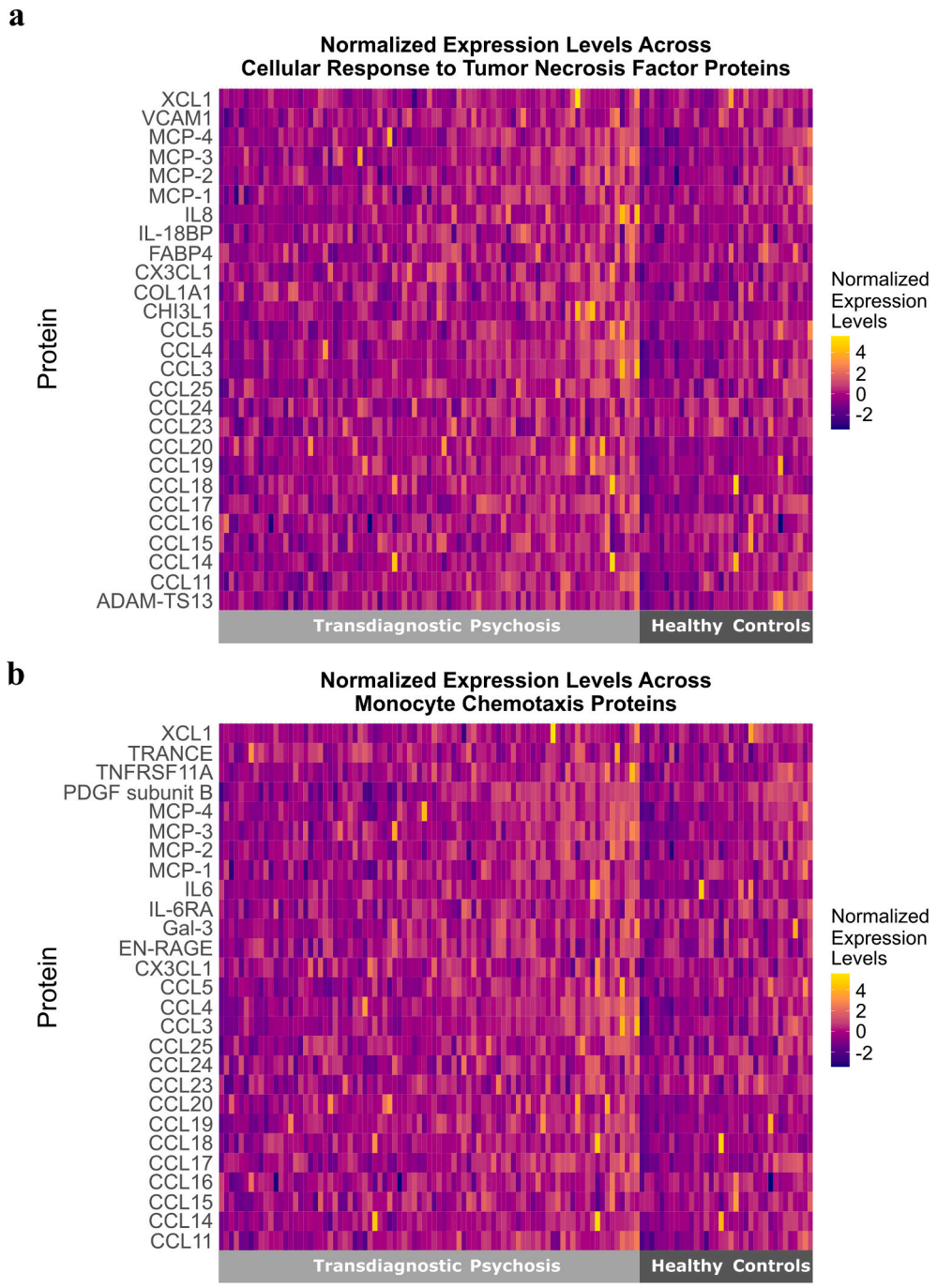


Fig. 2. Shows normalized expression levels of all proteins included in the (a) *Cellular Response to Tumor Necrosis Factor* (GOBP) and (b) *Monocyte Chemotaxis* pathways. Analyses were performed for each protein individually across all participants. Individuals were then split into the transdiagnostic psychosis group and healthy controls and sorted based on the sum of their normalized expression levels within their respective group. Abbreviations: C-C motif chemokine 20 (CCL20); Collagen alpha-1(I) chain (COL1A1); C-C motif chemokine 4 (CCL4); C-C motif chemokine 7 (MCP-3); C-C motif chemokine 18 (CCL18); Chitinase-3-like protein 1 (CHI3L1); C-C motif chemokine 19 (CCL19); Fractalkine (CX3CL1); C-C motif chemokine 3 (CCL3); C-C motif chemokine 17 (CCL17); IL8 (Interleukin-8); C-C motif chemokine 25 (CCL25); Interleukin-18-binding protein (IL-18BP); Eotaxin (CCL11); C-C motif chemokine 8 (MCP-2); C-C motif chemokine 13 (MCP-4); Vascular cell adhesion protein 1 (VCAM1); C-C motif chemokine 16 (CCL16); C-C motif chemokine 14 (CCL14); Fatty acid-binding protein, adipocyte (FABP4); A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAM-TS13); C-C motif chemokine 15 (CCL15); Lymphotactin (XCL1); C-C motif chemokine 2 (MCP-1); C-C motif chemokine 5 (CCL5); C-C motif chemokine 23 (CCL23); C-C motif chemokine 24 (CCL24); Interleukin-6 (IL6); Platelet-derived growth factor subunit B (PDGF subunit B); Protein S100-A12 (EN-RAGE); Galectin-3 (Gal-3); Tumor necrosis factor receptor superfamily member 11A (TNFRSF11A); Tumor necrosis factor ligand superfamily member 11 (TRANCE); Interleukin-6 receptor subunit alpha (IL-6RA).

enrichment of two inflammatory pathways in individuals with psychosis: the *Cellular Response to Tumor Necrosis Factor* and *Monocyte Chemotaxis* pathways. Together, these findings provide convergent evidence for aging and immune-related changes related to psychosis. The SASP index, *Cellular Response to Tumor Necrosis Factor,* and *Monocyte Chemotaxis* pathways were further associated with increased BMI and decreased sense of meaning and purpose in individuals with psychosis. The *Cellular Response to Tumor Necrosis Factor,* and *Monocyte Chemotaxis* pathways were also associated with decreased overall life satisfaction in individuals with psychosis.

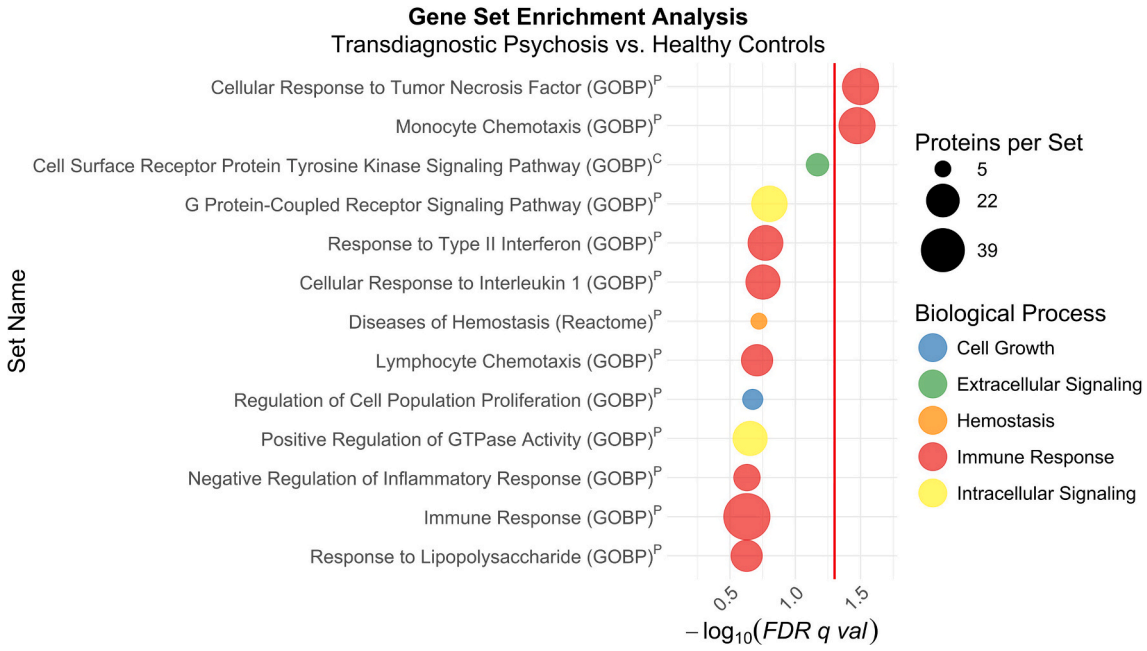


Fig. 3. Shows the Gene Set Enrichment Analysis (GSEA) results comparing the transdiagnostic psychosis group to healthy controls. Pathways are displayed sorted by statistical significance, with details on the number of proteins per pathway (size) and their associated biological processes (color). Superscript P and C trailing the set name indicate enrichment in the transdiagnostic psychosis group and healthy controls, respectively. The solid red line marks the significance threshold post-multiple comparison corrections. The pathways *Cellular Response to Tumor Necrosis Factor* and *Monocyte Chemotaxis* exceed this threshold, indicating significant enrichment after correcting for multiple comparisons in the transdiagnostic psychosis group. For the full GSEA output please see ***Supplementary Data 1–2***. Abbreviations: Gene Ontology Biological Processes (GOBP).

The elevated SASP levels observed in individuals with psychosis support the hypothesis of increased cellular senescence burden and premature aging even in this young population at an early stage of the disease. This interpretation is consistent with converging evidence across multiple levels of analysis, suggesting that a subset of individuals with psychosis may be particularly vulnerable to premature aging. Supporting evidence includes epidemiological studies reporting accelerated cognitive decline and increased rates of dementia in individuals with psychosis (Fett et al., 2020; Stroup et al., 2021). Clinical studies reported increased medical burden and elevated mortality rates in individuals with psychosis (Liu et al., 2017), as well as a declining clinical course (Kotov et al., 2017). While imaging studies reported signs of premature aging in psychosis (Seitz-Holland et al., 2024b), some biomarker studies showed shorter leukocyte telomere length in individuals with psychosis (Galletly et al., 2017; Wolkowitz et al., 2017). Furthermore, a recent study examining immunosenescence markers in schizophrenia linked those markers to behavioral and neuroimaging measures in schizophrenia (Li et al., 2025).

A closer examination of the cellular aging index reveals that many proteins comprising the SASP are involved in inflammatory processes, with a high proportion of pro-inflammatory markers. Key inflammatory proteins included in the SASP index include Interleukin-8 (IL-8) and Interleukin-6 (IL-6). IL-6, in particular, is among the most extensively studied peripheral inflammatory markers in psychosis. Elevated IL-6 levels have been reported in individuals at clinical high risk for psychosis (Misiak et al., 2021), during first-episode psychosis (Bocchio-Chiavetto et al., 2018; Dai et al., 2020), and in chronic schizophrenia (Frydecka et al., 2018), as well as in bipolar disorder (Coello et al., 2024; Xu et al., 2024) and major depressive disorder (Cakici et al., 2020). However, the contribution of individual markers, including IL-6, to the overall SASP index is relatively small and it is important to note that in addition to inflammatory markers the SASP includes growth factors, proteases, and cell-surface molecules that contribute to senescence signaling and propagation (Coppe et al., 2008). Consistent with this, we did not observe significant group differences for most single proteins in our study, highlighting the value of studying proteins in a combined index.

Consistent with the inflammatory composition of the SASP index, pathway analyses further underscored the role of immune activation in early psychosis. Specifically, we observed significant enrichment of inflammatory pathways related to the *Cellular Response to Tumor Necrosis Factor* and *Monocyte Chemotaxis*. These results align with prior research implicating soluble Tumor Necrosis Factor Receptors 1 and 2 in individuals with schizophrenia and affective disorders (Hope et al., 2009). Similarly, monocyte involvement has been reported in both schizophrenia and affective disorders (Dadouli et al., 2022; Mazza et al., 2020) and premature T-cell aging has been implicated in affective disorders (Schiweck et al., 2020; Simon et al., 2023). Indeed, a recent study in major depressive disorder suggests premature aging of monocytes, highlighting the mitochondrial apoptotic dysfunction and TNF inflammaging as potential core features of the disorder (Simon et al., 2021). Notably, elevated levels of monocyte chemoattractant protein-1 have been detected in the cerebrospinal fluid of individuals with bipolar disorder (Jakobsson et al., 2015), as well as peripherally in those with schizophrenia (Frydecka et al., 2018; Guo et al., 2024) and bipolar disorder (Coello et al., 2024). Finally, post-mortem evidence further implicates immune activation in the pathophysiology of schizophrenia (van Kesteren et al., 2017), and suggests that immune-related signals may be modulated by symptomatic state, including periods of active psychosis (De Picker et al., 2017). Such state-dependent effects may also help explain the heterogeneous and sometimes inconsistent post-mortem findings regarding immune involvement in bipolar disorder (Giridharan et al., 2020).

The SASP index correlated with an increased BMI, less alcohol consumption, and a decreased sense of meaning and purpose in individuals with psychosis. For our primary analyses, we decided against controlling for the effects of BMI or other clinical variables. Previous studies reported an elevated SASP across various health-related aging phenotypes, including cardiometabolic health, Alzheimer's Disease (Saez-Atienzar and Masliah, 2020) and depression (Diniz et al., 2017; Diniz et al.,

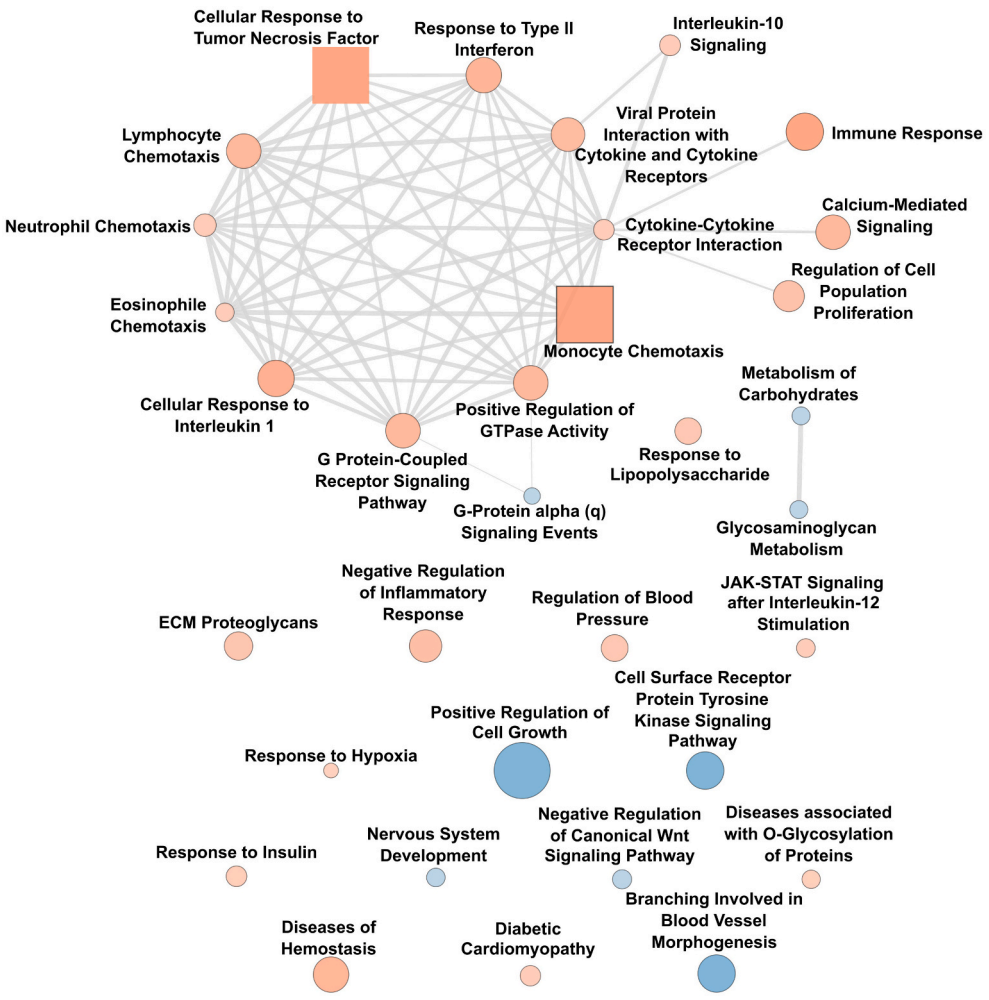


Fig. 4. Shows the results of the Gene Set Enrichment Analysis (GSEA) of pathways differing between the transdiagnostic psychosis group and healthy controls. The color of the nodes represents the group in which the pathway is enriched (red in the transdiagnostic psychosis group, blue in healthy controls) whereas the color intensity and the sizes of the nodes correspond to the p-value (larger nodes represent smaller p-values). Additionally, the shape of the nodes indicates significance after multiple comparison corrections (rectangles). The grey edges between nodes and their size represent overlapping proteins between the connected pathways.

2019; Mendes-Silva et al., 2019). Similar to our findings, previous studies also reported associations between the SASP and general health factors, including BMI (Seitz-Holland et al., 2023). Furthermore, adiposity has been linked to low-grade systemic inflammation and may contribute directly to elevations in cytokines and chemokines represented in the SASP and pathway-derived PCs (Zatterale et al., 2019). Consequently, we do not interpret our findings as being specific to psychosis pathology. Rather, we view the SASP index as a marker of an aging-related phenotype that may arise from the combined effects of psychosis, physical comorbidities, medication exposure, and lifestyle factors. This perspective is consistent with emerging models that conceptualize psychosis as a whole-body or multisystem condition in which disturbances extend beyond the brain to involve immune, metabolic, cardiovascular, and other physiological systems (Firth et al., 2019; Kirkpatrick et al., 2014). This whole-body perspective is particularly relevant given that a high proportion of individuals with psychosis experience physical comorbidities earlier than healthy individuals. Specifically, cardiometabolic dysfunction is related to dramatic reductions in both the quality and quantity of life in individuals with psychosis (Westman et al., 2018). While these outcomes could be partly related to the iatrogenic effects of antipsychotic medications, increasing evidence indicates that cardiometabolic deficits often predate medication exposure and contribute to the underlying pathophysiology of psychosis (Perry et al., 2021). From this perspective, BMI and other clinical variables (such as antipsychotic medication exposure) may not simply represent independent confounding factors but may lie, at least in part, on the causal pathway linking psychosis to aging. The results of our exploratory mediation analysis align with this interpretation and underscore a direct as well as an indirect, BMI-related association between psychosis and the SASP. However, we acknowledge the limitation that our cross-sectional design does not allow us to disentangle the relative contributions of psychosis, BMI, medication exposure, and other relevant factors to the observed elevations in the SASP index and inflammatory pathways.

4.1. *Strengths, limitations, and future directions*

Our findings suggest that psychosis is associated with cellular aging signatures, including widespread immune activation, which is best captured through the simultaneous assessment of multiple markers and pathways. Relative to the broader HCP-EP psychosis cohort, participants included in the present analyses showed lower global functioning and IQ, higher schizophrenia symptom burden on the negative and cognitive domains, and fewer manic symptoms. While the overall HCP-EP psychosis sample is comparatively healthy, our sub-sample more closely reflects the clinical profile typically observed in early-psychosis datasets. Therefore, findings from this subset may generalize more effectively to broader early-psychosis populations. Nonetheless, replication

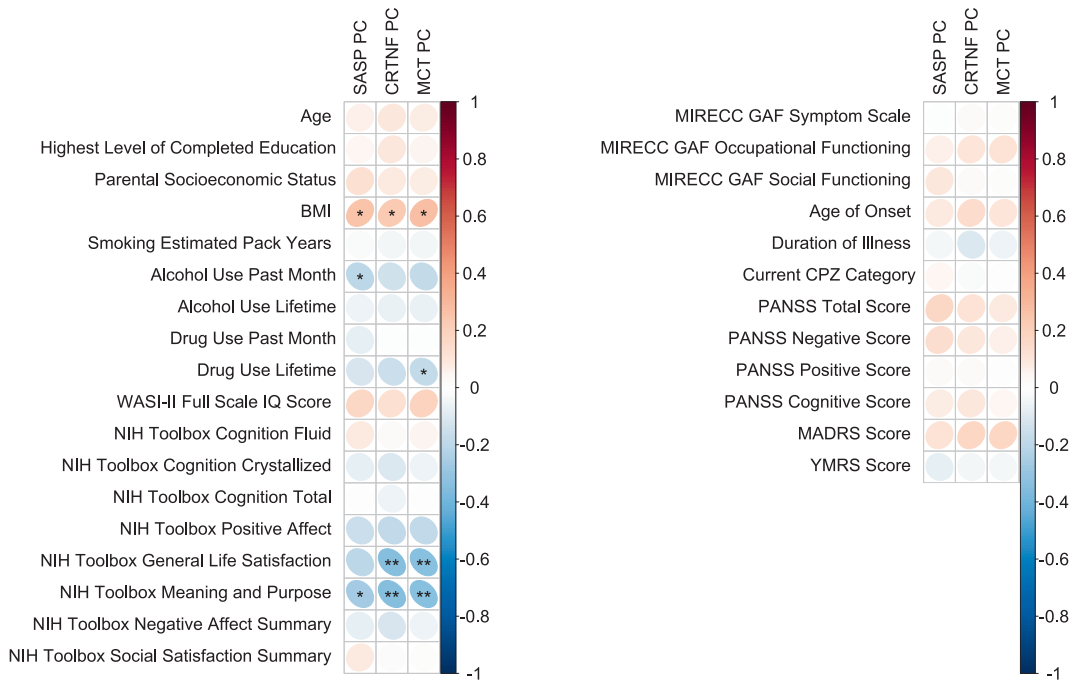


Fig. 5. Shows the correlations between the principal component scores of indices and biopsychosocial variables in the transdiagnostic psychosis group. Shape and color represent the strength and direction of the associations. Significance levels are marked as follows: *p < 0.05, **p < 0.01 (not corrected for multiple comparisons). Abbreviations: Body mass index (BMI); Cellular Response to Tumor Necrosis Factor (CRTNF); Chlorpromazine equivalent dose (CPZ); Mental Illness Research, Education, and Clinical Center version of the Global Assessment of Functioning (MIRECC GAF); Monocyte Chemotaxis (MCT); Montgomery–Åsberg Depression Rating Scale (MADRS); Positive and Negative Syndrome Scale (PANSS); First principal component scores (PC); Senescence-Associated Secretory Phenotype (SASP); Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II); Young Mania Rating Scale (YMRS).

across larger, more diverse datasets is essential to confirm and extend these results.

In addition to the difficulties in interpreting the results in the line of BMI group differences, a high proportion of individuals in the psychosis group took moderate to high doses of antipsychotics. Antipsychotic medications can influence metabolic and immune pathways, directly or indirectly, through weight gain, dyslipidemia, insulin resistance, and other cardiometabolic effects (Marcinowicz et al., 2021; Pillinger et al., 2020). Although we did not observe associations between medication use and our proteomic indices, it is impossible to rule out medication effects on immune and aging-related protein expression in a cross-sectional design. Future longitudinal studies, ideally including antipsychotic-naïve individuals before and after treatment initiation, are needed to determine whether the observed proteomic signatures reflect psychosis-related immune activation, BMI-related inflammation, medication-associated metabolic effects, or a combination of these processes.

We would also like to note several limitations related to aging assessment. In this young sample, we did not observe associations between age or illness duration and the SASP index. In addition, other established measures of biological aging, such as telomere length, DNA methylation, and markers of oxidative stress, were unavailable. While we see the circulating proteomic SASP index as a marker reflecting whole-body senescence-related processes, only direct cellular evidence can provide a definitive demonstration of cellular senescence. Furthermore, protein measurements are not cell-type specific and therefore do not allow conclusions regarding senescence in particular cell populations. Given the relatively small sample, we did not combine proteomic measures with e.g., aging related brain phenotypes. Nonetheless, we believe that our focus on proteins related to cellular senescence remains important. Circulating proteins reflect downstream biological processes that integrate signals across multiple systems and can therefore serve as accessible markers of whole-body processes. Furthermore, blood-based proteomic biomarkers are readily scalable, can be repeatedly assessed, and may be more easily translated into clinical applications. Moreover, we believe that SASP proteins are particularly relevant because they have emerged as potential promising therapeutic targets (Alharbi et al., 2022; Gonzales et al., 2022; Schafer et al., 2016; Tchkonia et al., 2013).

Finally, while our study is among the first to apply the novel and well-validated Olink proteomics platform in psychosis research, and our sample size is comparable to those of other recent proteomic studies in the field (Malmqvist et al., 2025; Yee et al., 2025), our findings should be considered preliminary due to the unbalanced groups. Given the limited sample size, we also solely focused on the first principal component as a summary score. We did not perform additional subgroup analyses within the transdiagnostic sample to compare diagnostic categories. Our findings are consistent with previous research suggesting that only a subset of individuals with psychosis may exhibit evidence of premature biological aging (Fries et al., 2026). Given the heterogeneous nature of schizophrenia (Keshavan et al., 2026), we would not expect molecular and cellular senescence markers to characterize all affected individuals. Furthermore, epidemiological and clinical studies have demonstrated substantial heterogeneity in long-term outcomes among individuals with psychosis, with at least one-third of individuals showing marked decline over time (Menezes et al., 2006; Kotov et al., 2017). However, due to sample size constraints, we did not further explore potential subgroups.

Larger studies are needed to replicate and extend our findings and incorporate broader proteomic panels to capture a more comprehensive range of biological processes. They should also test the association between the SASP and other relevant aging measures and test if the SASP index can be used to identify a subgroup of individuals with psychosis who are particularly vulnerable to the effects of aging.

5. Conclusion

This study offers novel insights into the proteomic landscape of early psychosis. By calculating a SASP index and analyzing a selected proteome of 341 plasma proteins through pathway analyses, we identified elevated SASP levels and significant enrichments of the *Cellular Response to Tumor Necrosis Factor* and *Monocyte Chemotaxis* pathways. These findings are consistent with prior research linking psychosis to premature aging and an increased inflammation response. Importantly, our results underscore the value of examining multiple biomarkers and biological pathways simultaneously to understand the complex pathophysiology of psychosis and highlight the importance of conceptualizing psychosis as a whole-body condition. Future research should replicate these findings in larger, more diverse, and longitudinal cohorts and further investigate the relationship between peripheral protein expression, other clinical variables, and central nervous system processes.

CRediT authorship contribution statement

Johanna Seitz-Holland: Writing – original draft, Visualization, Validation, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Moritz Haaf:** Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Ana Paula Mendes-Silva:** Writing – review & editing, Visualization, Validation, Methodology. **Nora Penzel:** Writing – review & editing, Visualization, Software, Methodology. **Cornelius Berberich:** Writing – review & editing, Data curation. **Sylvain Bouix:** Writing – review & editing, Investigation, Data curation. **Michael J. Coleman:** Writing – review & editing, Investigation, Data curation. **Elana Kotler:** Writing – review & editing, Data curation. **Nicholas Kim:** Writing – review & editing, Data curation. **Katherine E. Burdick:** Writing – review & editing, Supervision, Methodology. **Roman Kotov:** Writing – review & editing, Supervision, Methodology. **Peter Falkai:** Writing – review & editing, Supervision, Methodology. **Mark Vangel:** Writing – review & editing, Supervision, Methodology. **Gregor Leicht:** Writing – review & editing, Resources. **Christoph Mulert:** Writing – review & editing, Resources. **Tilo Kircher:** Writing – review & editing, Methodology. **Kathryn E. Lewandowski:** Writing – review & editing, Investigation, Funding acquisition. **Daphne Holt:** Writing – review & editing, Investigation, Funding acquisition. **Matcheri S. Keshavan:** Writing – review & editing, Investigation, Funding acquisition. **Dost Öngür:** Writing – review & editing, Investigation, Funding acquisition. **Alan Breier:** Writing – review & editing, Resources, Investigation, Funding acquisition. **Martha E. Shenton:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition. **Steven E. Arnold:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Breno S. Diniz:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Marek Kubicki:** Writing – review & editing, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dost Öngür received honoraria from Boehringer-Ingelheim in the past 12 months. The other authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2026.107023.

Data availability

Biopsychosocial data is available through the HCP-EP NDA upload (https://nda.nih.gov/edit_collection.html?id=2914). Proteomics data is available upon reasonable request to the corresponding author.

References

Aas, I.H., 2011. Guidelines for rating Global Assessment of Functioning (GAF). Ann. Gen. Psychiatry 10, 2.
Alharbi, K.S., Afzal, O., Altamimi, A.S.A., Almalki, W.H., Kazmi, I., Al-Abbasi, F.A., Alzarea, S.I., Makeen, H.A., Albratty, M., 2022. A study of the molecular mechanism of quercetin and dasatinib combination as senolytic in alleviating age-related and kidney diseases. J. Food Biochem. 46, e14471.
Ashburner, M., Ball, C.A., Blake, J.A., Botstein, D., Butler, H., Cherry, J.M., Davis, A.P., Dolinski, K., Dwight, S.S., Eppig, J.T., Harris, M.A., Hill, D.P., Issel-Tarver, L., Kasarskis, A., Lewis, S., Matese, J.C., Richardson, J.E., Ringwald, M., Rubin, G.M., Sherlock, G., 2000. Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat. Genet. 25, 25–29.
Babakhanyan, I., McKenna, B.S., Casaletto, K.B., Nowinski, C.J., Heaton, R.K., 2018. National institutes of health toolbox emotion battery for english- and spanish-speaking adults: normative data and factor-based summary scores. Patient Relat Outcome Meas. 9, 115–127.
Basisty, N., Kale, A., Jeon, O.H., Kuehnemann, C., Payne, T., Rao, C., Holtz, A., Shah, S., Sharma, V., Ferrucci, L., Campisi, J., Schilling, B., 2020. A proteomic atlas of senescence-associated secretomes for aging biomarker development. PLoS Biol. 18, e3000599.
Beal, S.L., 2001. Ways to fit a PK model with some data below the quantification limit. J. Pharmacokinet Pharmacodyn. 28, 481–504.
Bocchio-Chiavetto, L., Zanardini, R., Tosato, S., Ventriglia, M., Ferrari, C., Bonetto, C., Lasalvia, A., Giubilini, F., Fioritti, A., Pileggi, F., Pratelli, M., Pavanati, M., Favaro, A., De Girolamo, G., Frisoni, G.B., Ruggeri, M., Gennarelli, M., GET UP Group, 2018. Immune and metabolic alterations in first episode psychosis (FEP) patients. Brain Behav. Immun. 70, 315–324.
Borgmann-Winter, K.E., Wang, K., Bandyopadhyay, S., Torshizi, A.D., Blair, I.A., Hahn, C.G., 2020. The proteome and its dynamics: a missing piece for integrative multi-omics in schizophrenia. Schizophr. Res. 217, 148–161.
Byrne, J.F., Healy, C., Focking, M., Susai, S.R., Mongan, D., Wynne, K., Kodosaki, E., Heurich, M., de Haan, L., Hickie, I.B., Smesny, S., Thompson, A., Markulev, C., Young, A.R., Schafer, M.R., Riecher-Rossler, A., Mossaheb, N., Berger, G., Schlogelhofer, M., Nordentoft, M., Chen, E.Y.H., Verma, S., Nieman, D.H., Woods, S. W., Cornblatt, B.A., Stone, W.S., Mathalon, D.H., Bearden, C.E., Cadenhead, K.S., Addington, J., Walker, E.F., Cannon, T.D., Cannon, M., McGorry, P., Amminger, P., Cagney, G., Nelson, B., Jeffries, C., Perkins, D., Cotter, D.R., 2024. Proteomic Biomarkers for the Prediction of transition to Psychosis in individuals at Clinical High Risk: a Multi-cohort Model Development Study. Schizophr. Bull. 50, 579–588.
Cakici, N., Sutterland, A.L., Penninx, B., Dalm, V.A., de Haan, L., van Beveren, N.J.M., 2020. Altered peripheral blood compounds in drug-naive first-episode patients with either schizophrenia or major depressive disorder: a meta-analysis. Brain Behav. Immun. 88, 547–558.
Campeau, A., Mills, R.H., Stevens, T., Rossitto, L.A., Meehan, M., Dorrestein, P., Daly, R., Nguyen, T.T., Gonzalez, D.J., Jeste, D.V., Hook, V., 2022. Multi-omics of human plasma reveals molecular features of dysregulated inflammation and accelerated aging in schizophrenia. Mol. Psychiatry 27, 1217–1225.
Chen, S., Tan, Y., Tian, L., 2024. Immunophenotypes in psychosis: is it a premature inflamm-aging disorder? Mol. Psychiatry 29, 2834–2848.
Coello, K., Holstad Pedersen, H., Munkholm, K., Lie Kjaerstad, H., Stanislaus, S., Rye Ostrowski, S., Faurholt-Jepsen, M., Miskowiak, K.W., Frikke-Schmidt, R., Vinberg, M., Thorn Ekstrom, C., Lyng Forman, J., Vedel Kessing, L., 2024. A composite immune and vascular stress marker in patients newly diagnosed with bipolar disorder and their unaffected first-degree relatives. Brain Behav. Immun. 118, 449–458.
Coppe, J.P., Patil, C.K., Rodier, F., Sun, Y., Munoz, D.P., Goldstein, J., Nelson, P.S., Desprez, P.Y., Campisi, J., 2008. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 6, 2853–2868.
Crespo-Facorro, B., Such, P., Nylander, A.G., Madera, J., Resemann, H.K., Worthington, E., O'Connor, M., Drane, E., Steeves, S., Newton, R., 2021. The burden of disease in early schizophrenia - a systematic literature review. Curr. Med. Res. Opin. 37, 109–121.
Dadouli, K., Janho, M.B., Hatziefthimiou, A., Voulgaridi, I., Piaha, K., Anagnostopoulos, L., Ntellas, P., Mouchtouri, V.A., Bonotis, K., Christodoulou, N., Speletas, M., Hadjichristodoulou, C., 2022. Neutrophil-to-lymphocyte, monocyte-to-

lymphocyte, platelet-to-lymphocyte ratio and systemic immune-inflammatory index in different states of bipolar disorder. Brain Sci. 12, 1034.
Dai, N., Jie, H., Duan, Y., Xiong, P., Xu, X., Chen, P., Kang, M., Li, M., Li, T., Huang, Z., Chen, H., 2020. Different serum protein factor levels in first-episode drug-naive patients with schizophrenia characterized by positive and negative symptoms. Psychiatry Clin. Neurosci. 74, 472–479.
Dalgleish, T., Black, M., Johnston, D., Bevan, A., 2020. Transdiagnostic approaches to mental health problems: current status and future directions. J. Consult. Clin. Psychol. 88, 179–195.
De Picker, L.J., Morrens, M., Chance, S.A., Boche, D., 2017. Microglia and Brain Plasticity in Acute Psychosis and Schizophrenia Illness Course: a Meta-Review. Front. Psych. 8, 238.
Deng, Y.T., You, J., He, Y., et al., 2025. Atlas of the plasma proteome in health and disease in 53,026 adults. Cell 188, 253–271.e7.
Diniz, B.S., Reynolds 3rd, C.F., Sibille, E., Lin, C.W., Tseng, G., Lotrich, F., Aizenstein, H. J., Butters, M.A., 2017. Enhanced Molecular Aging in Late-Life Depression: the Senescent-Associated Secretory Phenotype. Am. J. Geriatr. Psychiatry 25, 64–72.
Diniz, B.S., Reynolds Iii, C.F., Sibille, E., Bot, M., Penninx, B., 2019. Major depression and enhanced molecular senescence abnormalities in young and middle-aged adults. Transl. Psychiatry 9, 198.
Diniz, B.S., Seitz-Holland, J., Sehgal, R., Kasamoto, J., Higgins-Chen, A.T., Lenze, E., 2024. Geroscience-Centric Perspective for Geriatric Psychiatry: Integrating Aging Biology with Geriatric Mental Health Research. Am. J. Geriatr. Psychiatry 32, 1–16.
Elmas, A., Spehar, K., Do, R., Castellano, J.M., Huang, K.L., 2024. Associations of Circulating Biomarkers with Disease risks: a Two-Sample Mendelian Randomization Study. Int. J. Mol. Sci. 25, 7376.
Eren, F., Schwieler, L., Orhan, F., Malmqvist, A., Piehl, F., Cervenka, S., Sellgren, C.M., Fatouros-Bergman, H., Engberg, G., Erhardt, S., 2023. Immunological protein profiling of first-episode psychosis patients identifies CSF and blood biomarkers correlating with disease severity. Brain Behav. Immun. 111, 376–385.
Fett, A.J., Velthorst, E., Reichenberg, A., Ruggero, C.J., Callahan, J.L., Fochtmann, L.J., Carlson, G.A., Perlman, G., Bromet, E.J., Kotov, R., 2020. Long-term changes in Cognitive Functioning in individuals with Psychotic Disorders: Findings from the Suffolk County Mental Health Project. JAMA Psychiat. 77, 387–396.
First, M.B., 2015. Structured Clinical Interview for the DSM (SCID). The Encyclopedia of Clinical Psychology. John Wiley & Sons, Hoboken, NJ, USA, pp. 1–6.
Firth, J., Siddiqi, N., Koyanagi, A., Siskind, D., Rosenbaum, S., Galletly, C., Allan, S., Caneo, C., Carney, R., Carvalho, A.F., Chatterton, M.L., Correll, C.U., Curtis, J., Gaughran, F., Heald, A., Hoare, E., Jackson, S.E., Kisely, S., Lovell, K., Maj, M., McGorry, P.D., Mihalopoulos, C., Myles, H., O'Donoghue, B., Pillinger, T., Sarris, J., Schuch, F.B., Shiers, D., Smith, L., Solmi, M., Suetani, S., Taylor, J., Teasdale, S.B., Thornicroft, G., Torous, J., Usherwood, T., Vancampfort, D., Veronese, N., Ward, P. B., Yung, A.R., Killackey, E., Stubbs, B., 2019. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry 6, 675–712.
Fries, G.R., De La Garza, S., Zhao, N.O., Bass, A.W., Lima, C.N.C., Kobori, N., Barichello, T., Turecki, G., Schulz, P.E., Diniz, B.S., Soares, J.C., 2026. Preliminary Investigation of the Association between Epigenetic Aging Acceleration and Amyloid Biomarkers in Bipolar Disorder. Am. J. Geriatr. Psychiatry 34, 210–221.
Frydecka, D., Krzystek-Korpacka, M., Lubeiro, A., Stramecki, F., Stanczykiewicz, B., Beszlej, J.A., Piotrowski, P., Kotowicz, K., Szewczuk-Boguslawska, M., Pawlak-Adamska, E., Misiak, B., 2018. Profiling inflammatory signatures of schizophrenia: a cross-sectional and meta-analysis study. Brain Behav. Immun. 71, 28–36.
Galletly, C., Dhillon, V.S., Liu, D., Balzan, R.P., Hahn, L.A., Fenech, M.F., 2017. Shorter telomere length in people with schizophrenia: a preliminary study from Australia. Schizophr. Res. 190, 46–51.
Giridharan, V.V., Sayana, P., Pinjari, O.F., Ahmad, N., da Rosa, M.I., Quevedo, J., Barichello, T., 2020. Postmortem evidence of brain inflammatory markers in bipolar disorder: a systematic review. Mol. Psychiatry 25, 94–113.
Gonzales, M.M., Garbarino, V.R., Marques Zilli, E., Petersen, R.C., Kirkland, J.L., Tchkonia, T., Musi, N., Seshadri, S., Craft, S., Orr, M.E., 2022. Senolytic Therapy to Modulate the Progression of Alzheimer's Disease (SToMP-AD): a pilot Clinical Trial. J. Prev Alzheimers Dis. 9, 22–29.
Gu, L., Kitamura, M., 2012. Sensitive detection and monitoring of senescence-associated secretory phenotype by SASP-RAP assay. PLoS One 7, e52305.
Guan, F., Ni, T., Zhu, W., Williams, L.K., Cui, L.B., Li, M., Tubbs, J., Sham, P.C., Gui, H., 2022. Integrative omics of schizophrenia: from genetic determinants to clinical classification and risk prediction. Mol. Psychiatry 27, 113–126.
Guo, T., Chen, L., Luan, L., Yang, M., Zhang, X., Yang, H., 2024. Variations in inflammatory regulators in male patients with chronic schizophrenia associated with psychopathology and cognitive deficits. BMC Psychiatry 24, 811.
Haroon, H., Ho, A.M., Gupta, V.K., Dasari, S., Sellgren, C.M., Cervenka, S., Engberg, G., Eren, F., Erhardt, S., Sung, J., Choi, D.S., 2024. Cerebrospinal fluid proteomic signatures are associated with symptom severity of first-episode psychosis. J. Psychiatr. Res. 171, 306–315.
Hayflick, L., Moorhead, P.S., 1961. The serial cultivation of human diploid cell strains. Exp. Cell Res. 25, 585–621.
Herranz, N., Gil, J., 2018. Mechanisms and functions of cellular senescence. J. Clin. Invest. 128, 1238–1246.
Hodes, R.J., Insel, T.R., Landis, S.C., NIH Blueprint for Neuroscience Research, 2013. The NIH toolbox: setting a standard for biomedical research. Neurology 80, S1.
Hollingshead, A.B., 1975. Four Factor Index of Social Status. Unpublished working paper. Department of Sociology, Yale University, New Haven, CT.
Hope, S., Melle, I., Aukrust, P., Steen, N.E., Birkenaes, A.B., Lorentzen, S., Agartz, I., Ueland, T., Andreassen, O.A., 2009. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord. 11, 726–734.
Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167, 748–751.
Jacobs, G.R., Coleman, M.J., Lewandowski, K.E., Pasternak, O., Cetin-Karayumak, S., Mesholam-Gately, R.I., Wojcik, J., Kennedy, L., Knyazhanskaya, E., Reid, B., Swago, S., Lyons, M.G., Rizzoni, E., John, O., Carrington, H., Kim, N., Kotler, E., Veale, S., Haidar, A., Prunier, N., Haaf, M., Levitt, J.J., Seitz-Holland, J., Rathi, Y., Kubicki, M., Keshavan, M.S., Holt, D.J., Seidman, L.J., Ongur, D., Breier, A., Bouix, S., Shenton, M.E., 2025. An Introduction to the Human Connectome Project for Early Psychosis. Schizophr. Bull. 51, 658–671.
Jakobsson, J., Bjerke, M., Sahebi, S., Isgren, A., Ekman, C.J., Sellgren, C., Olsson, B., Zetterberg, H., Blennow, K., Palsson, E., Landen, M., 2015. Monocyte and microglial activation in patients with mood-stabilized bipolar disorder. J. Psychiatry Neurosci. 40, 250–258.
Kanehisa, M., Goto, S., 2000. KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res. 28, 27–30.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Keshavan, M.S., Nasrallah, H.A., Abi-Dargham, A., Grace, A.A., Javitt, D.C., Lewis, D.A., Marder, S.R., Meyer, J.M., Murray, R.M., Ongur, D., Stahl, S.M., Tandon, R., 2026. Toward a Pluralistic Model for the Schizophrenia Spectrum-Dopamine and beyond. JAMA Psychiat.
Kirkpatrick, B., Messias, E., Harvey, P.D., Fernandez-Egea, E., Bowie, C.R., 2008. Is schizophrenia a syndrome of accelerated aging? Schizophr. Bull. 34, 1024–1032.
Kirkpatrick, B., Miller, B., Garcia-Rizo, C., Fernandez-Egea, E., 2014. Schizophrenia: a systemic disorder. Clin. Schizophr. Relat. Psychoses 8, 73–79.
Kotov, R., Carpenter, W.T., Cicero, D.C., Correll, C.U., Martin, E.A., Young, J.W., Zald, D. H., Jonas, K.G., 2024. Psychosis superspectrum II: neurobiology, treatment, and implications. Mol. Psychiatry 29, 1293–1309.
Kotov, R., Fochtmann, L., Li, K., Tanenberg-Karant, M., Constantino, E.A., Rubinstein, J., Perlman, G., Velthorst, E., Fett, A.J., Carlson, G., Bromet, E.J., 2017. Declining Clinical Course of Psychotic Disorders over the two decades following first Hospitalization: evidence from the Suffolk County Mental Health Project. Am. J. Psychiatry 174, 1064–1074.
Li, N., Li, Y., Yu, T., Chen, W., Gou, M., Zheng, W., Liu, Z., Wang, X., Fang, J., Tong, J., Chen, S., Tian, B., Li, C.R., Tian, L., Tan, Y., 2025. Immunosenescence-related T cell phenotypes, structural brain imaging, and cognitive impairment in patients with schizophrenia: a moderated mediation analysis. Schizophrenia (heidelb) 11, 101.
Liu, N.H., Daumit, G.L., Dua, T., Aquila, R., Charlson, F., Cuijpers, P., Druss, B., Dudek, K., Freeman, M., Fujii, C., Gaebel, W., Hegerl, U., Levav, I., Munk Laursen, T., Ma, H., Maj, M., Elena Medina-Mora, M., Nordentoft, M., Prabhakaran, D., Pratt, K., Prince, M., Rangaswamy, T., Shiers, D., Susser, E., Thornicroft, G., Wahlbeck, K., Fekadu Wassie, A., Whiteford, H., Saxena, S., 2017. Excess mortality in persons with severe mental disorders: a multilevel intervention framework and priorities for clinical practice, policy and research agendas. World Psychiatry 16, 30–40.
Maj, M., 2018. Why the clinical utility of diagnostic categories in psychiatry is intrinsically limited and how we can use new approaches to complement them. World Psychiatry 17, 121–122.
Malmqvist, A., Eren, F., Schwieler, L., Orhan, F., Fatouros-Bergman, H., Flyckt, L., Piehl, F., Cervenka, S., Back, M., Sellgren, C.M., Engberg, G., Erhardt, S., 2025. Cardiovascular protein profiling in patients with first-episode psychosis. Schizophrenia (heidelb) 11, 88.
Marcinowicz, P., Wiedlocha, M., Zborowska, N., Debowska, W., Podwalski, P., Misiak, B., Tyburski, E., Szulc, A., 2021. A Meta-Analysis of the Influence of Antipsychotics on Cytokines Levels in first Episode Psychosis. J. Clin. Med. 10, 2488.
Marder, S.R., Davis, J.M., Chouinard, G., 1997. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the north American trials. J. Clin. Psychiatry 58, 538–546.
Mazza, M.G., Capellazzi, M., Lucchi, S., Tagliabue, I., Rossetti, A., Clerici, M., 2020. Monocyte count in schizophrenia and related disorders: a systematic review and meta-analysis. Acta Neuropsychiatr 32, 229–236.
McCrimmon, A.W., Smith, A.D., 2012. Review of the Wechsler abbreviated scale of intelligence, Second Edition (WASI-II). J. Psychoeducat. Assess. 31, 337–341.
McGorry, P., Nelson, B., 2016. Why we need a transdiagnostic staging approach to emerging psychopathology, early diagnosis, and treatment. JAMA Psychiat. 73, 191–192.
Mendes-Silva, A.P., Mwangi, B., Aizenstein, H., Reynolds 3rd, C.F., Butters, M.A., Diniz, B.S., 2019. molecular senescence is associated with white matter microstructural damage in late-life depression. Am. J. Geriatr. Psychiatry 27, 1414–1418.
Menezes, N.M., Arenovich, T., Zipursky, R.B., 2006. A systematic review of longitudinal outcome studies of first-episode psychosis. Psychol. Med. 36, 1349–1362.
Merico, D., Isserlin, R., Stueker, O., Emili, A., Bader, G.D., 2010. Enrichment map: a network-based method for gene-set enrichment visualization and interpretation. PLoS One 5, e13984.
Milacic, M., Beavers, D., Conley, P., Gong, C., Gillespie, M., Griss, J., Haw, R., Jassal, B., Matthews, L., May, B., Petryszak, R., Ragueneau, E., Rothfels, K., Sevilla, C., Shamovsky, V., Stephan, R., Tiwari, K., Varusai, T., Weiser, J., Wright, A., Wu, G., Stein, L., Hermjakob, H., D'Eustachio, P., 2024. The reactome pathway knowledgebase 2024. Nucleic Acids Res. 52, D672–D678.
Misiak, B., Bartoli, F., Carra, G., Stanczykiewicz, B., Gladka, A., Frydecka, D., Samochowiec, J., Jarosz, K., Hadrys, T., Miller, B.J., 2021. Immune-inflammatory markers and psychosis risk: a systematic review and meta-analysis. Psychoneuroendocrinology 127, 105200.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Mootha, V.K., Lindgren, C.M., Eriksson, K.F., Subramanian, A., Sihag, S., Lehar, J., Puigserver, P., Carlsson, E., Ridderstrale, M., Laurila, E., Houstis, N., Daly, M.J., Patterson, N., Mesirov, J.P., Golub, T.R., Tamayo, P., Spiegelman, B., Lander, E.S., Hirschhorn, J.N., Altshuler, D., Groop, L.C., 2003. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat. Genet. 34, 267–273.
Muller, N., Weidinger, E., Leitner, B., Schwarz, M.J., 2015. The role of inflammation in schizophrenia. Front. Neurosci. 9, 372.
Muneer, A., 2020. The discovery of clinically applicable biomarkers for bipolar disorder: a review of candidate and proteomic approaches. Chonnam Med. J. 56, 166–179.
Neves, J., Demaria, M., Campisi, J., Jasper, H., 2015. Of flies, mice, and men: evolutionarily conserved tissue damage responses and aging. Dev. Cell 32, 9–18.
Perry, B.I., Burgess, S., Jones, H.J., Zammit, S., Upthegrove, R., Mason, A.M., Day, F.R., Langenberg, C., Wareham, N.J., Jones, P.B., Khandaker, G.M., 2021. The potential shared role of inflammation in insulin resistance and schizophrenia: a bidirectional two-sample mendelian randomization study. PLoS Med. 18, e1003455.
Pillinger, T., McCutcheon, R.A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., Howes, O.D., 2020. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 7, 64–77.
Polho, G.B., De-Paula, V.J., Cardillo, G., dos Santos, B., Kerr, D.S., 2015. Leukocyte telomere length in patients with schizophrenia: a meta-analysis. Schizophr. Res. 165, 195–200.
Russo, P., Prinzi, G., Proietti, S., Lamonaca, P., Frustaci, A., Boccia, S., Amore, R., Lorenzi, M., Onder, G., Marzetti, E., Valdiglesias, V., Guadagni, F., Valente, M.G., Cascio, G.L., Fraietta, S., Ducci, G., Bonassi, S., 2018. Shorter telomere length in schizophrenia: evidence from a real-world population and meta-analysis of most recent literature. Schizophr. Res. 202, 37–45.
Saez-Atienzar, S., Masliah, E., 2020. Cellular senescence and Alzheimer disease: the egg and the chicken scenario. Nat. Rev. Neurosci. 21, 433–444.
Salminen, A., Ojala, J., Kaarniranta, K., Haapasalo, A., Hiltunen, M., Soininen, H., 2011. Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. Eur. J. Neurosci. 34, 3–11.
Santa Cruz, E.C., Zandonadi, F.D.S., Fontes, W., Sussulini, A., 2021. A pilot study indicating the dysregulation of the complement and coagulation cascades in treated schizophrenia and bipolar disorder patients. Biochim Biophys Acta Proteins Proteom 1869, 140657.
Schafer, M.J., White, T.A., Evans, G., Tonne, J.M., Verzosa, G.C., Stout, M.B., Mazula, D. L., Palmer, A.K., Baker, D.J., Jensen, M.D., Torbenson, M.S., Miller, J.D., Ikeda, Y., Tchkonia, T., van Deursen, J.M., Kirkland, J.L., LeBrasseur, N.K., 2016. Exercise Prevents Diet-Induced Cellular Senescence in Adipose Tissue. Diabetes 65, 1606–1615.
Schisterman, E.F., Cole, S.R., Platt, R.W., 2009. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology 20, 488–495.
Schiweck, C., Valles-Colomer, M., Arolt, V., Muller, N., Raes, J., Wijkhuijs, A., Claes, S., Drexhage, H., Vrieze, E., 2020. Depression and suicidality: a link to premature T helper cell aging and increased Th17 cells. Brain Behav. Immun. 87, 603–609.
Seitz-Holland, J., Aleman-Gomez, Y., Cho, K.I.K., Pasternak, O., Cleusix, M., Jenni, R., Baumann, P.S., Klauser, P., Conus, P., Hagmann, P., Do, K.Q., Kubicki, M., Dwir, D., 2024a. Matrix metalloproteinase 9 (MMP-9) activity, hippocampal extracellular free water, and cognitive deficits are associated with each other in early phase psychosis. Neuropsychopharmacology 49, 1140–1150.
Seitz-Holland, J., Cetin-Karayumak, S., Wojcik, J.D., Lyall, A., Levitt, J., Shenton, M.E., Pasternak, O., Westin, C.F., Baxi, M., Kelly, S., Mesholam-Gately, R., Vangel, M., Pearlson, G., Tamminga, C.A., Sweeney, J.A., Clementz, B.A., Schretlen, D., Viher, P. V., Stegmayer, K., Walther, S., Lee, J., Crow, T., James, A., Voineskos, A., Buchanan, R.W., Szeszko, P.R., Malhotra, A.K., Rathi, Y., Keshavan, M., Kubicki, M., 2021. Elucidating the relationship between white matter structure, demographic, and clinical variables in schizophrenia-a multicenter harmonized diffusion tensor imaging study. Mol. Psychiatry 26, 5357–5370.
Seitz-Holland, J., Haas, S.S., Penzel, N., Reichenberg, A., Pasternak, O., 2024b. BrainAGE, brain health, and mental disorders: a systematic review. Neurosci. Biobehav. Rev. 159, 105581.
Seitz-Holland, J., Mulsant, B.H., Reynolds 3rd, C.F., Blumberger, D.M., Karp, J.F., Butters, M.A., Mendes-Silva, A.P., Vieira, E.L., Tseng, G., Lenze, E.J., Diniz, B.S., 2023. Major depression, physical health and molecular senescence markers abnormalities. Nat. Ment. Health 1, 200–209.
Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T., Ramage, D., Amin, N., Schwikowski, B., Ideker, T., 2003. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 13, 2498–2504.
Shen, H.P., Dong, X., Li, Z.B., Wu, J.Z., Zheng, C.M., Hu, X.J., Qian, C., Wang, S.P., Zhao, Y.L., Li, J.C., 2024. Protein Profiles and Novel Molecular Biomarkers of Schizophrenia based on 4D-DIA Proteomics. J. Proteome Res. 23, 2376–2385.
Sierra, A., Gottfried-Blackmore, A.C., McEwen, B.S., Bulloch, K., 2007. Microglia derived from aging mice exhibit an altered inflammatory profile. Glia 55, 412–424.
Simon, M.S., Ioannou, M., Arteaga-Henriquez, G., Wijkhuijs, A., Berghmans, R., Musil, R., Muller, N., Drexhage, H.A., 2023. Premature T cell aging in major depression: a double hit by the state of disease and cytomegalovirus infection. Brain Behav Immun Health 29, 100608.
Simon, M.S., Schiweck, C., Arteaga-Henriquez, G., Poletti, S., Haarman, B.C.M., Dik, W. A., Schwarz, M., Vrieze, E., Mikova, O., Joergens, S., Musil, R., Claes, S., Baune, B.T., Leboyer, M., Benedetti, F., Furlan, R., Berghmans, R., de Wit, H., Wijkhuijs, A., Arolt, V., Muller, N., Drexhage, H.A., 2021. Monocyte mitochondrial dysfunction, inflammaging, and inflammatory pyroptosis in major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 111, 110391.
Smith, B.J., Guest, P.C., Martins-de-Souza, D., 2024. Maximizing Analytical Performance in Biomolecular Discovery with LC-MS: Focus on Psychiatric Disorders. Annu Rev Anal Chem (Palo Alto, Calif) 17, 25–46.
Sohler, N.L., Walkup, J., McAlpine, D., Boyer, C., Olfson, M., 2003. Antipsychotic dosage at hospital discharge and outcomes among persons with schizophrenia. Psychiatr. Serv. 54, 1258–1263.
Storer, M., Mas, A., Robert-Moreno, A., Pecoraro, M., Ortells, M.C., Di Giacomo, V., Yosef, R., Pilpel, N., Krizhanovsky, V., Sharpe, J., Keyes, W.M., 2013. Senescence is a developmental mechanism that contributes to embryonic growth and patterning. Cell 155, 1119–1130.
Stroup, T.S., Olfson, M., Huang, C., Wall, M.M., Goldberg, T., Devanand, D.P., Gerhard, T., 2021. Age-specific Prevalence and Incidence of Dementia Diagnoses among older US adults with Schizophrenia. JAMA Psychiat. 78, 632–641.
Subramanian, A., Tamayo, P., Mootha, V.K., Mukherjee, S., Ebert, B.L., Gillette, M.A., Paulovich, A., Pomeroy, S.L., Golub, T.R., Lander, E.S., Mesirov, J.P., 2005. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. PNAS 102, 15545–15550.
Sun, B.B., Chiou, J., Traylor, M., Benner, C., Hsu, Y.H., Richardson, T.G., Surendran, P., Mahajan, A., Robins, C., Vasquez-Grinnell, S.G., Hou, L., Kvikstad, E.M., Burren, O. S., Davitte, J., Ferber, K.L., Gillies, C.E., Hedman, A.K., Hu, S., Lin, T., Mikkilineni, R., Pendergrass, R.K., Pickering, C., Prins, B., Baird, D., Chen, C.Y., Ward, L.D., Deaton, A.M., Welsh, S., Willis, C.M., Lehner, N., Arnold, M., Worheide, M.A., Suhre, K., Kastenmuller, G., Sethi, A., Cule, M., Raj, A., Alnylam Human Genetics, AstraZeneca Genomics Initiative, Biogen Biobank Team, Bristol Myers Squibb, Genentech Human Genetics, GlaxoSmithKline Genomic Sciences, Pfizer Integrative Biology, Population Analytics of Janssen Data Sciences, Regeneron Genetics Center, Burkitt-Gray, L., Melamud, E., Black, M.H., Fauman, E.B., Howson, J.M.M., Kang, H.M., McCarthy, M.I., Nioi, P., Petrovski, S., Scott, R.A., Smith, E.N., Szalma, S., Waterworth, D.M., Mitnaul, L.J., Szustakowski, J.D., Gibson, B.W., Miller, M.R., Whelan, C.D., 2023. Plasma proteomic associations with genetics and health in the UK Biobank. Nature 622, 329–338.
Tchkonia, T., Zhu, Y., van Deursen, J., Campisi, J., Kirkland, J.L., 2013. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J. Clin. Invest. 123, 966–972.
Tessema, T., Diniz, B.S., Vieira, E.M., Mendes-Silva, A.P., Voineskos, A.N., Gildengers, A. G., Husain, M.I., Ortiz, A., Blumberger, D.M., Rajji, T.K., Mulsant, B.H., 2024. Elevated senescence-associated secretory phenotype index in late-life bipolar disorder. J. Affect. Disord. 360, 163–168.
van Deursen, J.M., 2014. The role of senescent cells in ageing. Nature 509, 439–446.
van Kesteren, C.F., Gremmels, H., de Witte, L.D., Hol, E.M., Van Gool, A.R., Falkai, P.G., Kahn, R.S., Sommer, I.E., 2017. Immune involvement in the pathogenesis of schizophrenia: a meta-analysis on postmortem brain studies. Transl. Psychiatry 7, e1075.
Westacott, L.J., Severance, E.G., 2024. The plasma proteome and prognosis for psychiatric symptoms in psychosis: a focus on function, not factors. Brain Behav. Immun. 121, 26–27.
Westman, J., Eriksson, S.V., Gissler, M., Hallgren, J., Prieto, M.L., Bobo, W.V., Frye, M.A., Erlinge, D., Alfredsson, L., Osby, U., 2018. Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. Epidemiol. Psychiatr. Sci. 27, 519–527.
Wolkowitz, O.M., Jeste, D.V., Martin, A.S., Lin, J., Daly, R.E., Reuter, C., Kraemer, H., 2017. Leukocyte telomere length: Effects of schizophrenia, age, and gender. J. Psychiatr. Res. 85, 42–48.
Xu, F., Su, Y., Wang, X., Zhang, T., Xie, T., Wang, Y., 2024. Olink proteomics analysis uncovers inflammatory proteins in patients with different states of bipolar disorder. Int. Immunopharmacol. 131, 111816.
Yao, J.K., Keshavan, M.S., 2011. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxid. Redox Signal. 15, 2011–2035.
Yee, J.Y., Phua, S.X., See, Y.M., Andiappan, A.K., Goh, W.W.B., Lee, J., 2025. Predicting antipsychotic responsiveness using a machine learning classifier trained on plasma levels of inflammatory markers in schizophrenia. Transl. Psychiatry 15, 51.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.
Zatterale, F., Longo, M., Naderi, J., Raciti, G.A., Desiderio, A., Miele, C., Beguinot, F., 2019. Chronic Adipose Tissue Inflammation linking Obesity to Insulin Resistance and Type 2 Diabetes. Front. Physiol. 10, 1607.