BIOMARKERS FOR PSYCHOSIS: ARE WE THERE YET?

UMBRELLA REVIEW OF 1478 BIOMARKERS

Paola Fuentes-Claramonte[1,2]†, Andrés Estradé[3]†, Aleix Solanes[4,5], Valentina Ramella[3], Maria Angeles Garcia-Leon[1,2], Javier de Diego Adeliño[2,5,6], Conrad Molins[7], Eric Fung[1], Marc Valentí[2,4,8], Gerard Anmella[2,4,8], Edith Pomarol-Clotet[1,2], Dominic Oliver[3,8-10], Eduard Vieta[2,4,11], Joaquim Radua[2,3,4,12,+], Paolo Fusar- Poli[3,13,+]

† Shared first authorship.

+ Shared senior authorship.

[1]FIDMAG Germanes Hospitalàries Research Foundation, Barcelona, Spain

[2]Biomedical Research Networking Centre Consortium on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Barcelona, Spain

[3]Early Psychosis: Interventions & Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry Psychology and Neuroscience, King's College London, London, United Kingdom

[4]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB), Barcelona, Spain

[5]Barcelona Autonomous University (UAB), Barcelona, Spain

[6]Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona, Spain

[7]Psychiatric Service, Hospital Universitari Santa Maria, Lleida, Catalonia, Spain

[8]Department of Psychiatry, University of Oxford, Oxford OX3 7JX, UK

[9]NIHR Oxford Health Biomedical Research Centre, Oxford OX3 7JX, UK

[10]OPEN early detection service, Oxford Health NHS Foundation Trust, Oxford OX3 7JX, UK[11]Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic de Barcelona, University of Barcelona, Barcelona, Spain

[12]Center for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

[13]OASIS service, South London and the Maudsley NHS Foundation Trust, London, United Kingdom

Corresponding author: Andrés Estradé, andres.estrade_vaz@kcl.ac.uk, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AF.

Running title: Umbrella review of 1478 psychosis biomarkers

Word count:

- Abstract: 248
- Body text (exc. CoI and Funding): 4,464
- Figures: 4
- Tables: 1

ABSTRACT

Background and Hypothesis: This umbrella review aims to comprehensively synthesize the evidence of association between peripheral, electrophysiological, neuroimaging, neuropathological, and other biomarkers and diagnosis of psychotic disorders.

Study Design: We selected systematic reviews and meta-analyses of observational studies on diagnostic biomarkers for psychotic disorders, published until February 1st, 2018. Data extraction was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Evidence of association between biomarkers and psychotic disorders was classified as convincing, highly suggestive, suggestive, weak, or non-significant, using a standardized classification. Quality analyses used the Assessment of Multiple Systematic Reviews (AMSTAR) tool.

Study Results: The umbrella review included 110 meta-analyses or systematic reviews corresponding to 3,892 individual studies, 1,478 biomarkers, and 392,210 participants. No factor showed a convincing level of evidence. Highly suggestive evidence was observed for transglutaminase autoantibodies levels (odds ratio [OR]=7.32; 95% CI: 3.36, 15.94), mismatch negativity in auditory event-related potentials (standardised mean difference [SMD]=0.73; 95% CI: 0.5, 0.96), P300 component latency (SMD=-0.6; 95% CI: -0.83, -0.38), ventricle brain ratio (SMD=0.61; 95% CI: 0.5, 0.71), and minor physical anomalies (SMD=0.99; 95% CI: 0.64, 1.34). Suggestive evidence was observed for folate, malondialdehyde, brain-derived neurotrophic factor, homocysteine, P50 sensory gating (P50 S2/S1 ratio), frontal N-acetyl-aspartate, and high-frequency heart rate variability. Among the remaining biomarkers, weak evidence was found for 626 and non-significant association for 833 factors.

Conclusions: While several biomarkers present highly suggestive or suggestive evidence of association with psychotic disorders, methodological biases and underpowered studies call for future higher-quality research.

Key words: schizophrenia, psychotic disorders, peripheral biomarkers, electrophysiological biomarkers, neuroimaging biomarkers, neuropathological biomarkers.

INTRODUCTION

Schizophrenia spectrum and other psychotic disorders have an estimated mean lifetime prevalence of 9.57 per 1000[1] and usually begin during youth and early adulthood (meta-analytic peak age of onset at 20.5 years[2]). The initial diagnosis of psychosis usually occurs at the time of the first episode of psychosis (FEP), occurring at a late stage in the neurodevelopmental trajectory of the disorder[3]. Following a FEP, standard care with antipsychotics is primarily symptom-focused and limited for altering the course of the disorder[4]. Psychotic disorders continue to be associated with poor clinical outcomes (one in seven recovery rate[5]) and a 3-fold excess mortality rate when compared to general population (standardized mortality rate of 3.08[6]) due to physical illness and increased suicide risk in the initial years following illness onset[7,8]. Schizophrenia is a global leading cause of health-related disability[9], with associated global economic costs of up to 1.65% of the gross domestic product[10]. Given the suboptimal results of current therapeutics, course altering preventive interventions during the early developmental stages, such as cannabidiol[11,12] or oxytocin[13,14], constitute promising future avenues for next-stage interventions[15]. Course-altering intereventions require a refined understanding of the pathophysiology and neurobiological substrates of psychosis[3]. After decades of research, however, the causes of psychotic disorders remain elusive. The etiological models that have received the strongest empirical support suggest a complex combination of direct and interactive effect of genetic, epigenetic and environmental factors across the developmental cycle that interfere with brain development and maturation[16,17].

Nonetheless, the past decades have witnessed an explosion of psychosis biomarker research. Biomarkers provide clues for understanding the pathophysiological basis of psychosis[18], and could become key tools in the real-world implementation of precision medicine[19,20] and individualised prediction modelling[21,22]. For example, biomarkers can aid in developing mechanism-driven preventive interventions[23], identifying illness subtypes via biological screening[24], or in the introduction of novel diagnostic frameworks based on pathophysiology of mental disorders[25]. As such, biomarkers could be helpful for ascertaining the presence of a disorder or specific illness subtypes (‘diagnostic’ biomarkers), predicting therapeutic response (‘predictive’ biomarkers) and course of the disorder (‘prognostic’ biomarkers), and for monitoring illness progression (‘monitoring’ biomarkers)[26,27]. However, the progress achieved in biomarker research has not been fully translated into real-world clinical practice[28], hence the current ‘translational gap’[29]. Over 100 years following Bleuler’s introduction of the term ‘schizophrenia’[30], diagnosis is still based on clinical examination in accordance with DSM (Diagnostic and Statistical Manual of Mental Disorders) or ICD (International Classification of Diseases) diagnostic criteria[31]. General psychopathological

knowledge, and evidence-interventions, are implemented following a trial-and-error approach according to a general clinical profile[23,32].

One obstacle for the translational potential of scientific findings is fragmentation of knowledge as primary biomedical studies proliferate and diversify[33]. This also affects secondary research due to the accumulation of overlapping, often contradictory, systematic reviews (SRs) and meta-analyses (MAs)[34,35]. Umbrella reviews help overcome this challenge by providing a synthesis and critical appraisal of SRs and MAs[36,37]. For example, umbrella reviews for schizophrenia and psychotic disorders have focused on sociodemographic, developmental and environmental risk factors[38], preventive treatments[15], or duration of untreated psychosis[39]. Regarding biomarker research, umbrella reviews on schizophrenia and FEP have been limited to peripheral biomarkers, while also incorporating environmental exposures[40] or other severe mental disorders[41]. As such, to the best of our knowledge, no comprehensive umbrella review of biomarkers for psychosis has been published to date. Our study aims to close this gap by providing a state-of-the-art comprehensive evidence synthesis on the association between peripheral, electrophysiological, neuroimaging, neuropathological and other biomarkers and psychotic disorders. We focus on observational studies of diagnostic biomarkers comparing individuals with psychosis *vs* healthy controls, as the analysis of prognostic markers would require a different design and evidence synthesis method which accounts for time-dependency of outcomes. To increase sampling power, we use an extended sampling approach by including a diagnosis of any non-organic psychotic spectrum disorder, rather than limiting our selection to the chronic and more symptomatic cases, such as schizophrenia.

In addition, biomarker research is often affected by underpowered samples, methodological biases, and inconsistent reporting practices[26,41]. To address this challenge, we provide a hierarchical classification of the robustness of the association for each factor. To achieve this, we conduct a systematic analysis of biases through a set of a priori criteria extensively validated in previous risk factors studies for physical[42–48], neurological[49–52], and mental disorders[38,53–56], as well as in clinical studies[57–60]. This classification into hierarchical levels of evidence is essential for reducing the ambiguities and contradictions often found in SRs and MAs[61].

METHODS

We pre-registered the umbrella review protocol with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42017084377).

Search strategy and eligibility criteria

Various researchers (PF-C and VR; plus JDA, EF, and CM for the neuroimaging part) systematically and independently searched *PubMed*, *Web of Science*, and *Scopus* through February 1st, 2018, using the search terms ("systematic review" OR "meta-analysis") and ("psychosis" OR "schizophrenia"), to identify SRs and MAs of studies examining potential diagnostic biomarkers for psychotic disorders. Reference lists of the SRs and MAs reaching full-text review were also carefully reviewed. Eligibility criteria included: 1) a SR or MA of individual observational studies examining associations between biological markers and psychotic disorders; 2) studies considering only established DSM or ICD diagnoses of non-organic psychotic spectrum disorders (e.g., schizophrenia, schizoaffective, schizophreniform, affective psychosis [mania, depression or bipolar disorder with psychosis], drug-induced psychosis, delusional disorder, brief psychotic disorder/acute and transient psychotic disorder, psychosis not otherwise specified); 3) inclusion of a healthy control comparison group, and 4) studies reporting sufficient data to perform the analyses (or where data were retrievable from the authors). No language restrictions were applied.

When the biomarker dataset of an article was part of a larger dataset in another article, we only retained the latter. When two articles presented minimally overlapping datasets on the same biomarker, we used both SR or MA conjointly counting the overlapping primary studies only once. We excluded articles with an outcome other than established psychotic disorder, such as those related to relapse, remission, or treatment response of psychosis or symptom severity, and those investigating genetic markers for psychosis. We used the same inclusion/exclusion criteria for each study included in every eligible SR or MA.

Definition of biomarker

We used the following accepted definition of biomarker: "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes or pathogenic processes"[62]. We did not include potential genetic biomarkers because umbrella reviews of genetic variables require different analytical methods and criteria[63]. Neither did we include potential biomarkers from whole-brain voxel-based neuroimaging studies (although we did include other types of neuroimaging data) because we would need to treat each voxel as a biomarker. Instead, we refer the reader to existing MAs of whole-brain imaging studies in psychosis[64].

We used the definition for each biomarker provided in the corresponding SR or MA. However, for reporting purposes, we classified biomarkers into the following categories: peripheral, electrophysiologic, neuropathological, neuroimaging, and other (e.g. minor physical

anomalies, high frequency heart rate variability). The clustering of different biomarkers was pragmatically operationalised following the definition presented by each individual study. These groups hold only descriptive value as the actual analyses were performed at the single marker level. There was no assumption of biological mechanisms underlying these categories, most of which are yet to be fully elucidated.

Data extraction and selection

Data extraction was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) guidelines[65]. Various investigators (PF-C and MAG-L; plus JDA, EF, CM, and AS for the neuroimaging part) conducted the following steps independently. First, we identified the potential biomarkers assessed in each selected SR or MA. Second, we confirmed that each article included in the SR or MA met our eligibility criteria for the umbrella review (i.e., ICD/DSM diagnosis, healthy control group, and sufficient data for analysis). Third, we extracted the following data (from the SR or MA or, otherwise, from the individual study): 1) first author and year of publication, 2) the number of cases and controls, 3) effect size (ES) measure (standardized mean difference [SMD] for continuous biomarkers, odds ratio [OR] for binary biomarkers) and corresponding 95% confidence interval (CI), 4) means and standard deviations for cases and controls for continuous biomarkers, and the number of cases and controls with and without the biomarker for binary biomarkers. An exception was neuroimaging biomarkers, for which we only relied on the information reported in the MAs unless this information showed that the biomarker's evidence could be stronger than class IV (see “Evidence stratification” below). An independent double extraction process was conducted for those biomarkers that presented unclear data. Fourth, for those biomarkers showing evidence of class I, II, or III, we rated the quality of the SRs or MAs that contributed studies for that biomarker using the Assessment of Multiple Systematic Reviews (AMSTAR) tool[66]. Our quality ratings obtained a high interrater agreement (intraclass correlation = 0.924). For further information on the quality analysis, see the Supplementary Material (**sTable 1**).

Statistical analyses

We conducted all analyses with the package "metaumbrella" for R (https://metaumbrella.org/)[67], that performs all the calculations necessary for stratifying evidence in umbrella reviews[36,38,68–70]. Specifically, it calculated, for each biomarker, the ES (Hedges' g for continuous variables, OR for binary variables) and its confidence and prediction intervals, the between-study heterogeneity (I^2 statistic), the Egger test to detect

potential publication/reporting bias, and the excess significance bias test. Hedges' g values represent SMDs between the patient and control groups and are interpreted as indicative of a 'small' (g=0.2), 'medium' (g=0.5) or 'large' effect (g=0.80)[71]. OR provides a measure of the likelihood of presenting any specific biomarker in cases *vs* healthy controls, with OR>1 indicating increased likelihood and OR<1 decreased likelihood. The I^2 statistic represents the percentage of total variance resulting from heterogeneity (i.e. real differences in the studies' ES), rather than chance. Egger's test quantifies the relationship between sample size and ES, with significant results indicating risk of publication bias[72]. Finally, the excess significance bias test evaluates the relative presence of studies with excessive significant findings, by comparing the observed *vs* the expected number of studies with significant results[73].

Evidence stratification

We classified the strength of the evidence according to previous criteria[38]: class I (convincing) when the number of patients >1000, $p < 10^{-6}$, $I^2 < 50\%$, the 95% prediction interval excludes the null, and no publication/reporting or excess significance biases are detected; class II (highly suggestive) when the evidence is weaker than convincing but the number of patients >1000, $p < 10^{-6}$, and the largest study is statistically significant; class III (suggestive) when the evidence is weaker than highly suggestive but the number of patients >1000 and $p < 10^{-3}$; and class IV (weak) when the evidence is lower than suggestive but $p < 0.05$.

RESULTS

We included 110 SRs and MAs (**sFigure 1**) covering 1,478 potential biomarkers with a cumulative sample size of 189,180 individuals with psychosis and 203,030 healthy controls. In **Table 1** we include the biomarkers that achieved highly suggestive (class II) or suggestive (class III) level of evidence. For the full list of biomarkers, see the Supplementary Material (**sTables 2-6**).

Peripheral biomarkers

We included 284 peripheral biomarkers from 63,390 patients and 79,410 controls (cumulated sample sizes; **sTable 2**). Transglutaminase (tTG) autoantibody levels achieved highly suggestive (class II) evidence with an OR = 7.32 (CI: 3.36, 15.94) (**Table 1; Figure 1**); we could not assess heterogeneity and potential biases because only one study was available for

this analysis. Blood levels of folate, malondialdehyde (MDA), brain-derived neurotrophic factor (BDNF), and homocysteine (Hcy) showed class III (suggestive) evidence of association, with effect sizes of -1.44 (CI: -2.18, -0.71), 1.38 (CI: 0.82, 1.94), -0.69 (CI: -1.05, -0.33) and 0.60 (CI: 0. 31, 0.89), respectively. These class III biomarkers showed very large heterogeneity and (except for folate) potential excess significance bias. One hundred sixty-three other peripheral biomarkers achieved class IV evidence.

Electrophysiologic biomarkers

We examined 79 electrophysiologic biomarkers in 18,151 patients vs 19,346 controls (cumulated sample sizes; **sTable 3**). Two biomarkers achieved class II evidence: mismatch negativity in auditory event-related potentials (g = 0.73, CI: 0.50, 0.96) and P300 component latency (g = -0.60, CI: -0.83, -0.38) (**Table 1; Figure 2**). However, they showed very large heterogeneity and potential excess significance bias. On the other hand, P50 sensory gating achieved class III evidence with an ES of g = 0.79 (CI: 0.43, 1.16), but showing very large heterogeneity. Forty-one other biomarkers achieved class IV evidence.

Neuroimaging biomarkers

We included 238 neuroimaging biomarkers in a cumulative sample size of 77,849 patients vs. 73,184 controls (**sTable 4**). Two of them showed class II or III evidence: ventricle-brain ratio (class II, g = 0.61, CI: 0.50, 0.71) and frontal N-acetylaspartate (NAA) levels (class III, g = -0.34, CI: -0.47, -0.20) (**Table 1; Figure 3**). The analyses suggested potential excess significance bias in both cases, and the heterogeneity was large (>50%). One hundred forty-nine other neuroimaging biomarkers achieved class IV evidence.

Neuropathological biomarkers

We studied a total of 406 neuropathological biomarkers in a cumulative sample size of 6,170 patients vs. 6,526 controls (**sTable 5**). One hundred thirteen biomarkers showed a statistically significant association with psychosis, all with class IV (weak) evidence.

Other biomarkers

The other biomarkers category enclosed 471 biomarkers in 23,620 patients vs. 24,564 controls (cumulated sample sizes; **sTable 6**). Minor physical anomalies achieved class II evidence (g = 0.99, CI: 0.64, 1.34) (**Table 1; Figure 4**), although with very large heterogeneity

and potential excess significance bias. High-frequency heart rate variability achieved class III evidence (*g* = -0.99, CI: -1.41, -0.58), although, beyond very large heterogeneity, it also showed potential publication and excess significance biases. One hundred sixty other biomarkers achieved class IV evidence.

DISCUSSION

To the best of our knowledge, this is the first comprehensive umbrella review of diagnostic biomarkers for psychosis that incorporates peripheral, electrophysiologic, neuroimaging, neuropathological, and other biomarkers, in addition to a robust hierarchical classification of evidence. Overall, 110 SRs and MAs, a total of 3,892 individual studies and 392,210 participants, and 1,478 potential biomarkers were included. None of the evaluated biomarkers presented convincing evidence (class I) of association. Nonetheless, there was highly suggestive evidence (class II) for five biomarkers (0.3% of all evaluated factors), and suggestive evidence (class III) for seven biomarkers (0.5%). Among the remaining biomarkers, 626 (42.6%) presented significant but weak (class IV) evidence. The remaining 833 (56.6%) presented non-significant associations.

Associations supported by highly suggestive and suggestive evidence merit discussion. Regarding peripheral biomarkers, highly suggestive evidence was only found for elevated levels of tTG autoantibodies. This finding provides evidence, at for a subset of individuals, towards a link between psychosis and celiac disease[74,75]. The relationship between celiac disease or gluten sensitivity and neurologic and psychiatric disorders was initially reported almost 70 years ago[76,77], with celiac disease having since been linked to an increased risk of various neurological[78] and mental disorders[79]. In addition, it provides evidence for psychosis as a systemic disorder with potential autoimmune components[80,81]. While the specific nature of the association remains unknown, possible mechanisms include shared genetic susceptibility or immunological abnormalities[82]. However, the estimate is based on a single study. As a result, heterogeneity or publication bias could not be assessed. Nonetheless, the large sample of cases (n=2,301) grants this association a class II level of evidence. In addition, we found suggestive evidence for reduced blood levels of folate among individuals with psychosis, although this association was characterized by very large heterogeneity. This finding further indicates potential nutrition-related mechanisms in mental disorders[83–85]. For example, maternal exposure to nutritional deprivation during pregnancy[86] could result in deficits in micronutrients involved in 1-carbon metabolism, particularly folate (vitamin B9) and vitamin B12, leading to increased risk due to epigenetic changes via disruptions in DNA methylation[87–89]. Findings of decreased levels of vitamin B12 have been inconsistent[90,91] and

additional epidemiological and laboratory studies are required. We also acknowledge that there might be a bi-directional effect of psychosis on diet[92] and therefore no causal assumption is made when interpreting diet-related biomarkers. The scarcity of prospective studies is problematic, as folate and vitamin B12 levels could be confounded by use of antipsychotics[93]. We also observed suggestive evidence for increased plasma levels of Hcy, further indicating a potential role of 1-carbon metabolism. Hcy is a non-protein amino acid produced in 1-carbon methyl group-transfer metabolism with various functions in brain activity[94], and its regulation depends on dietary folate and other B vitamins[95]. In schizophrenia patients, plasma Hcy levels were found to correlate negatively with folate[96] and vitamin B12[97], and to be associated with symptom severity[94,98,99] and a progressive course of illness[100]. Elevated Hcy has been observed in FEP patients[101,102], although not in CHR-P individuals[103]. However, research in the CHR-P population is still in an emerging state. Potential mechanisms involved in the association between Hcy and psychosis include aberrant DNA methylation, altered NMDA receptor and glutamatergic transmission, toxic effects on dopaminergic neurons, premature apoptosis, oxidative stress, and placental vascular damage and fetal hypoxia[94,96,97,104,105]. Nonetheless, the question remains as to whether hyperhomocysteinemia is a contributor, a consequence or an epiphenomenon of psychosis[97]. Adjunct folate therapy has been found to improve symptoms of depressive and bipolar disorders, but not for schizophrenia[106]. However, emerging evidence suggests moderate effectiveness of pooled vitamin B (i.e. B6, B9, B12) supplementation on total schizophrenia symptoms[107]. It is still unclear what specific symptoms and clinical groups (e.g. FEP, chronic) would benefit the most from nutritional interventions, and an opportunity for clinical stratification might exist[4]. For example, folic acid appears to be more beneficial for the treatment of negative vs positive symptoms[108]. Likewise, a recent RCT study suggested that B-vitamin supplementation could have neuroprotective effects in FEP patients with elevated Hcy[109]. Also, it is unclear how nutritional deficiencies might interact with genetic variants[95,110]. For example, genetic variants linked to folate-metabolism can be associated with clinical response to adjunct folate therapy[111,112]. Overall, these findings call for further research into gene-environment interaction[17] and potential avenues for personalized medicine.

Finally, regarding peripheral biomarkers, elevated levels of MDA and reduced levels of BDNF also presented suggestive evidence which, despite large heterogeneity, was based on large samples (n=1,795 and n=4,955, respectively). Alongside increased Hcy, Elevated MDA and reduced BDNF levels suggest a role for oxidative stress and inflammation in psychosis pathophysiology, possibly linked to immune dysregulation[113]. Immune dysregulation in psychosis has been supported by genome-wide association[114,115] and postmortem studies[116,117]. Early-life adversity, including prenatal insults[86] and childhood trauma[38], can also

promote a proinflammatory state later in life, potentially via epigenetic changes[118,119]. We also observed weak evidence for other oxidative stress and inflammation biomarkers, such as docosahexaenoic acid (DHA), IL-6, TNF-alpha, and total antioxidant status. Overall, these findings are consistent with evidence suggestive of antioxidant status and pro-inflammatory imbalances among FEP patients[102] and CHR-P individuals[120]. However, these associations are often weakened by small samples, scarcity of prospective studies, and high heterogeneity potentially resulting from between-study sample differences (e.g. illness phase, developmental stage, antipsychotic status, and comorbid substance-user or other lifestyle factors)[102,121]. Heterogeneity and small effect sizes might further indicate that immune system involvement varies between individuals and across illness phases[122]. For example, anti-inflammatory agents have been found to be more effective for early-phase vs chronic schizophrenia[123]. Also, anti-inflammatory biomarkers can be associated with antipsychotic treatment response[124]. As such, an opportunity might also exist for personalized medicine approaches[22] via inflammatory biomarker-informed patient stratification.

In terms of electrophysiologic biomarkers, mismatch negativity (MMN) in auditory event-related potentials (ERP) achieved highly suggestive evidence. Reduced MMN is a well-replicated feature in first-episode and chronic psychosis[28,125–127], and might reflect N-methyl-d-aspartate (NMDA) receptor function[128,129]. MMN does not seem to always distinguish between early and chronic schizophrenia[130,131], and has been suggested to stabilize following deterioration during the first 1-2 years of diagnosis[125]. In addition, abnormal auditory MMN has also been observed to precede illness onset among CHR-P individuals[132–134], although not consistently[131], and with other studies reporting similar patterns in CHR-P and FEP individuals[135]. Overall, there is translational potential for MMN as a biomarker for monitoring illness progression and the identification of individuals at greater risk of transition[125,136]. In addition, we observed highly suggestive evidence for P300 component latency. Significant evidence, albeit weak, was also observed for P300 amplitude disturbances. Both P300 component latency and amplitude, a more direct biomarker of cognition than MMN[137–139], have been widely replicated in first-episode[140–142] and chronic psychosis patients[143,144], and first-degree relatives[145]. P300 anomalies have also been reported to respond to antipsychotic treatment in schizophrenia patients[146], and might be linked to grey matter volume reduction in both CHR-P[147,148] and psychosis samples[142]. As such, ERP deficits have potential as biomarkers for transition risk in clinical high-risk individuals[141,149–151] in whom both neurocognitive decline[152] and reduction in grey matter volume[153] precede illness onset. Finally, P50 sensory gating (P50 S2/S1 ratio) presented suggestive evidence, further supporting the existence of ERP deficits in psychosis[28]. All class II and class III electrophysiologic biomarkers were affected by large heterogeneity.

Among neuroimaging biomarkers, we observed highly suggestive evidence of increased ventricle-brain ratio among individuals with psychosis. Since the pioneer neuroimaging studies of the 1970-1980's[154–157], ventricular enlargement has remained one of the most replicated neuroanatomical correlated of schizophrenia, as reflected in the large number of participants in our summary (n=6,099). Ventricular enlargement has also been observed in unaffected first-degree relatives[158] and in transitioning CHR-P samples[159]. In addition, decreased frontal NAA achieved suggestive level of evidence. Weak evidence for reduced NAA was also present for other brain regions (e.g. temporal, cerebellum, thalamus), further supporting an association between psychosis and loss of neuronal integrity[3]. Deterioration in neuronal health might precede illness onset, as suggested by evidence for CHR-P individuals[160,161], although findings in this group have been inconsistent[162] and better-powered prospective studies are required. Overall, neuroimaging evidence is indicative of aberrant brain trajectories that seems to precede illness onset[163,164], suggesting a neurodevelopmental component to the disorder[16], and that have potential as markers for transition risk in high-risk individuals[165]. Following illness onset, comorbid substance use, antipsychotic medication, stress and lifestyle factors can contribute to progressive ventricular volume increases[166,167], in addition to underlying neurobiological factors. As such, high between-study heterogeneity observed in neuroimaging biomarkers might reflect methodological differences affecting selection of controls, diagnostic criteria, and clinical characteristics of included cases[168].

For neuropathological biomarkers, none of the 406 assessed factors obtained highly suggestive or suggestive evidence. While 113 biomarkers did present significant associations, the level of evidence was weak, with most (95.6%) estimates being based on a single study, and all of them employing small samples (range of n=9 to 176).

Regarding other biomarkers, minor physical abnormalities presented highly suggestive evidence, although very large heterogeneity and potential excess significance bias were observed. This finding is consistent with extensive evidence of early-life neurodevelopmental deviance in psychosis, including an excess of prenatal and perinatal insults[86], childhood motor[169] and cognitive[170] abnormalities, and structural brain alterations[164,171,172]. Originally, these observations led to the neurodevelopmental hypothesis of schizophrenia[173,174], later expanded to incorporate environmental adversity occurring during childhood and adolescence[16,175]. Finally, lower high-frequency heart rate variability achieved suggestive evidence. However, this association is affected by large heterogeneity and potential publication and excess significance bias. Nonetheless, this finding supports the hypothesis of reduced vagal activity among individuals with psychotic disorders as a potential endophenotype associated with executive function[176], emotional regulation[177,178], and threat inhibition[179]. This is also consistent with the evidence of increased risk of cardiovascular

disease among individuals with schizophrenia[180]. While it is unclear how autonomic function alterations manifest in CHR-P individuals[181,182], an increase in high-frequency heart rate variability has been observed in CHR-P men following intranasal oxytocin[14], suggesting possible novel disease-engagement psychopharmacological targets.

Overall, the evidence summarized in this study presents some limitations. First, we provide estimates of association and do not assume a cause-effect relationship between psychotic disorders and the reported biomarkers. Reverse causality[183] is an important component in biomarker research, as the temporality of the exposure cannot always be ascertained. Furthermore, we found common methodological limitations in psychosis biomarker research. On one hand, large statistical heterogeneity (I^2 >50%) was observed in 12.1% of all 1,478 factors, and in 91.7% of factors with class II or III evidence. In addition, between-study heterogeneity could not be evaluated for 74.5% of biomarkers, and for one factor with class II evidence. This could indicate between-study methodological differences related to data collection and reporting, or sampling criteria, which can limit the reproducibility and real-world translation of findings. High heterogeneity can also be indicative of real difference between clinical or biological subtypes, meriting further exploration[24,184]. In addition to high heterogeneity, excess significance bias (affecting 75% of class II and III biomarkers) and limited number of cases of <1,000 (affecting 92.4% of all 1,478 factors) were frequently observed. Inflated effect sizes have been suggested to particularly affect newly discovered associations due to suboptimal power[185]. In our sample, 38.8% of all factors based on a single study reported statistically significant associations. Among 865 estimates based on a single study (affecting 58.5% of all factors), all but one had a sample of cases of <1,000 participants. High heterogeneity, excess significance bias and small samples are methodological limitations not restrictive of psychosis research, and have also been observed in biomarker research for other mental disorders[41,68,186,187]. Furthermore, reporting bias via Egger test could not be assessed for 87.5% of all factors due to insufficient data or due to only one study being included, and was significant for 1.1% and non-significant for 11.4% of biomarkers. Overall, these results highlight the need for better-powered replication studies with representative samples that will allow us to assess whether these biomarkers are generalisable to other settings with different sociodemographics and service configurations. Without this understanding, the prospects of implementing these biomarkers in real-world clinical care and benefitting patients is severely limited[188]. Moreover, implementing a biomarker that is only useful in certain (usually majority) sub-populations or settings can lead to harm and perpetuation of existing health inequities[189,190]. Ongoing large multisite research networks are being cunducted to address these limitations[191,192]. In addition, compliance with common guidelines and practices for evaluating and reporting biomarkers[193] is needed to increase the

replicability of finding and minimize missing data. Another limitation is that the current literature search is not fully updated. This is due to the high complexity of data extraction, data quality check procedures and synthesis that are needed for this type of analyses. However, our robust method could be leveraged by subsequent evidence syntheses in this field to mainstream updated summaries. As a final limitation of our report, we did not assess the quality of individual primary studies included in the evidence synthesis as this was outside the scope of our review. In the same lines, In the same lines, the scope of this review was limited to diagnostic biomarkers and we did not assess prognostic biomarkers or those useful to forecast drug response[194].

CONCLUSION

Several biomarkers presented a highly suggestive or suggestive evidence of association with psychotic disorders, indicating various translational opportunities for personalized medicine. However, the widespread presence of methodological biases and underpowered studies in biomarker research highlight the need for future higher-quality research.

CONFLICT OF INTEREST

GA has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Lundbeck/Otsuka, and Angelini, with no financial or other relationship relevant to the subject of this article. EV has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, AbbVie, Angelini, Biogen, Boehringer-Ingelheim, Celon Pharma, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Glaxo-Smith Kline, Janssen, Lundbeck, Novartis, Orion Corporation, Organon, Otsuka, Sage, Sanofi-Aventis, Sunovion, Takeda, and Viatris, outside the submitted work. JR has received CME honoraria from Inspira Networks for a machine learning course promoted by Adamed, outside the submitted work. PFP has received research funds or personal fees from Lundbeck, Angelini, Menarini, Sunovion, Boehringer Ingelheim, Mindstrong, Proxymm Science, outside the current study.

FUNDING

The study was funded by a Wellcome Trust grant to PFP (Early DetectioN of menTal disorERs, ENTER: 215793/Z/19/Z) and the Catalonian Government (2017SGR01271 and 2021SGR01475 to EP-C), CIBERSAM and Instituto de Salud Carlos III, co-funded by European Union (FEDER/FSE, “Investing in your future”): Sara Borrell contract (CD22/00106

to MAG-L), Research Project Grant (PI21/00416 to EP-C). PF-C is funded by a fellowship from “la Caixa” Foundation (ID 100010434, fellowship LCB/BQ/PR22/11920017). MAG-L was also funded by a Júlia Gil Pineda Research Fellowship. GA is supported by a Rio Hortega 2021 grant (CM21/00017) financed by the Instituto de Salud Carlos III (ISCIII) and cofinanced by the Fondo Social Europeo Plus (FSE+). JR work is supported by the Spanish Ministry of Science and Innovation (PI19/00394 and PI22/00261), integrated into the Plan Nacional de I+D+I and co-financed by ERDF Funds from the European Commission ("A Way of Making Europe") and the CERCA Program / Generalitat de Catalunya and Secretaria d’Universitats i Recerca del Departament d’Economia I Coneixement (2021 SGR 01128).

REFERENCES

1. Moreno-Küstner B, Martín C, Pastor L. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. *PLoS One*. 2018;13(4):1-25.
2. Solmi M, Radua J, Miriam O, et al. Age at onset of mental disorders worldwide: a large-scale meta-analysis of 192 epidemiological studies. *Mol Psychiatry*. 2022;27:281–295.
3. Millan MJ, Andrieux A, Bartzokis G, et al. Altering the course of schizophrenia: progress and perspectives. *Nat Rev Drug Discov*. 2016;15(7):485-515.
4. Fusar-Poli P, McGorry PD, Kane JM. Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*. 2017;16(3):251-265.
5. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull*. 2013;39(6):1296-1306.
6. Oakley P, Kisely S, Baxter A, et al. Increased mortality among people with schizophrenia and other non-affective psychotic disorders in the community: a systematic review and meta-analysis. *J Psychiatr Res*. 2018;102(November 2017):245-253.
7. De Hert M, Correll C, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10(1):52-77.
8. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *The Lancet Psychiatry*. 2017;4(4):295-301.
9. Global Burden of Disease 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990 – 2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1211-1259.
10. Chong HY, Teoh SL, Wu DBC, Kotirum S, Chiou CF, Chaiyakunapruk N. Global economic burden of schizophrenia: a systematic review. *Neuropsychiatr Dis Treat*. 2016;12:357-373.
11. Amminger GP, Lin A, Kerr M, et al. Cannabidiol for at risk for psychosis youth: A randomized controlled trial. *Early Interv Psychiatry*. 2022;16(4):419-432.

12. Chesney E, Oliver D, McGuire P. Cannabidiol (CBD) as a novel treatment in the early phases of psychosis. *Psychopharmacology (Berl)*. 2022;239(5):1179-1190.

13. Davies C, Paloyelis Y, Rutigliano G, et al. Oxytocin modulates hippocampal perfusion in people at clinical high risk for psychosis. *Neuropsychopharmacology*. 2019;44(7):1300-1309.

14. Martins D, Davies C, Micheli A De, Oliver D, Fusar-Poli P, Paloyelis Y. Intranasal oxytocin increases heart-rate variability in men at clinical high risk for psychosis: a proof-of-concept study. *Transl Psychiatry*. 2020;10(227):1-12.

15. Fusar-Poli P, Davies C, Solmi M, et al. Preventive treatments for psychosis: umbrella review (just the evidence). *Front Psychiatry*. 2019;10:1-21.

16. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet*. 2014;383:1677-1687.

17. Van Os J, Rutten BPF, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr Bull*. 2008;34(6):1066-1082.

18. Chana G, Bousman CA, Money TT, et al. Biomarker investigations related to pathophysiological pathways in schizophrenia and psychosis. *Front Cell Neurosci*. 2013;7:1-18.

19. Vieta E. La medicina personalizada aplicada a la salud mental: la psiquiatría de precisión. *Rev Psiquiatr Salud Ment*. 2015;8(2):117-118.

20. Salagre E, Vieta E. Precision psychiatry: complex problems require complex solutions. *Eur Neuropsychopharmacol*. 2021;52:94-95.

21. Fusar-Poli P, Correll CU, Arango C, Berk M, Patel V, Ioannidis J. Preventive psychiatry: a blueprint for improving the mental health of young people. *World Psychiatry*. 2021;20(2):200-221.

22. Fraguas D, State MW, Gur RE, et al. Mental disorders of known aetiology and precision medicine in psychiatry: a promising but neglected alliance. *Psychol Med*. 2017;47(2):193-197.

23. Arango C, Kapur S, Kahn RS. Going beyond “trial-and-error” in psychiatric treatments: OPTiMiSE-ing the treatment of first episode of schizophrenia. *Schizophr Bull*. 2015;41(3):546-548.

24. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry*. 2012;17:1174-1179.

25. Insel TR, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748-751.

26. Prata D, Mechelli A, Kapur S. Clinically meaningful biomarkers for psychosis: a systematic and quantitative review. *Neurosci Biobehav Rev*. 2014;45:134-141.

27. Peterson BS. Editorial: Biomarkers in precision medicine for mental illnesses. *J Child Psychol Psychiatry*. 2020;61(12):1279-1281.

28. Lawrie SM, Olabi B, Hall J, Mcintosh AM. Do we have any solid evidence of clinical utility about the pathophysiology of schizophrenia? *World Psychiatry*. 2011;10(1):19-31.

29. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M. The new field of “precision psychiatry.” *BMC Med*. 2017;15(1):1-7.

30. Berrios GE. Eugen Bleuler’s place in the history of psychiatry. *Schizophr Bull*. 2011;37(6):1095-1098.

31. Stein DJ, Szatmari P, Gaebel W, Berk M. Mental, behavioral and neurodevelopmental disorders in the ICD-11: an international perspective on key changes and controversies. *BMC Med*. 2020;18(21):1-24.

32. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. *Br J Psychiatry*. 2012;200(2):97-106.

33. Ioannidis JPA. Evolution and translation of research findings: from bench to where? *PLoS Clin Trials*. 2006;e36:1-5.

34. Siontis KC, Hernandez-Boussard T, Ioannidis JPA. Overlapping meta-analyses on the same topic: survey of published studies. *BMJ*. 2013;347:f4501.

35. Ioannidis JPA. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. *Milbank Q*. 2016;94(3):485-514.

36. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. *Evid Based Ment Health*. 2018;21(3):95-100.

37. Ioannidis JPA. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ*. 2009;181(8):488-493.

38. Radua J, Ramella-Cravaro V, Ioannidis JPA, et al. What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*. 2018;17(1):49-66.

39. Howes OD, Whitehurst T, Shatalina E, et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. *World Psychiatry*. 2021;20(1):75-95.

40. Belbasis L, Köhler CA, Stefanis N, et al. Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: an umbrella review of meta-analyses. *Acta Psychiatr Scand*. 2018;137(2):88-97.

41. Carvalho AF, Solmi M, Sanches M, et al. Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Transl Psychiatry*. 2020;10(1).

42. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr*. 2018;72(1):30-43.

43. Markozannes G, Tzoulaki I, Karli D, et al. Diet, body size, physical activity and risk of prostate cancer: an umbrella review of the evidence. *Eur J Cancer*. 2016;69:61-69.

44. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Med*. 2016;14(1).

45. Belbasis L, Stefanaki I, Stratigos AJ, Evangelou E. Non-genetic risk factors for cutaneous melanoma and keratinocyte skin cancers: an umbrella review of meta-analyses. *J Dermatol Sci*. 2016;84(3):330-339.

46. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ*. 2017;356:1-10.

47. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JPA. Type 2 diabetes and cancer: umbrella review of meta-analyses of observationlal studies. *BMJ*. 2015;350(January):1-11.

48. Ioannidis JPA, Zhou Y, Chang CQ, Schully SD, Khoury MJ, Freedman AN. Potential increased risk of cancer from commonly used medications: an umbrella review of meta-analyses. *Ann Oncol*. 2014;25(1):16-23.

49. Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JPA, Evangelou E. Systematic evaluation of the associations between environmental risk factors and dementia: an umbrella review of systematic reviews and meta-analyses. *Alzheimer's Dement*. 2017;13(4):406-418.

50. Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JPA. Environmental risk factors and Parkinson's disease: an umbrella review of meta-analyses. *Park Relat*

Disord. 2016;23:1-9.

51. Belbasis L, Bellou V, Evangelou E. Environmental risk factors and amyotrophic lateral sclerosis: an umbrella review and critical assessment of current evidence from systematic reviews and meta-analyses of observational studies. *Neuroepidemiology*. 2016;46(2):96-105.

52. Belbasis L, Bellou V, Evangelou E, Ioannidis JPA, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol*. 2015;14(3):263-273.

53. Solmi M, Dragioti E, Arango C, et al. Risk and protective factors for mental disorders with onset in childhood/adolescence: an umbrella review of published meta-analyses of observational longitudinal studies. *Neurosci Biobehav Rev*. 2021;120(September 2020):565-573.

54. Arango C, Dragioti E, Solmi M, et al. Risk and protective factors for mental disorders beyond genetics: an evidence-based atlas. *World Psychiatry*. 2021;20(3):417-436.

55. Bortolato B, Köhler CA, Evangelou E, et al. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. *Bipolar Disord*. 2017;19(2):84-96.

56. Kim JH, Kim JY, Lee J, et al. Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review. *The Lancet Psychiatry*. 2020;7(11):955-970.

57. Dragioti E, Karathanos V, Gerdle B, Evangelou E. Does psychotherapy work? An umbrella review of meta-analyses of randomized controlled trials. *Acta Psychiatr Scand*. 2017;136(3):236-246.

58. Papageorgiou P, Deschner J, Papageorgiou S. Effectiveness and adverse effects of deep brain stimulation: umbrella review of meta-analyses. *J Neurol Surg*. 2016;78(2):180-190.

59. Tonelli A, Zein J, Adams J, Ioannidis J. Effects of interventions on survival in acute respiratory distress syndrome: an umbrella review of 159 published randomized trials and 29 meta-analyses. *Intensive Care Med*. 2014;40(6):769–787.

60. Barbui C, Purgato M, Abdulmalik J, et al. Efficacy of psychosocial interventions for mental health outcomes in low-income and middle-income countries: an umbrella review. *The Lancet Psychiatry*. 2020;7(2):162-172.

61. Fleischhacker WW. A meta view on meta-analyses. *JAMA Psychiatry*.

2017;74(7):684-685.

62. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89-95.

63. Ioannidis JPA, Boffetta P, Little J, et al. Assessment of cumulative evidence on genetic associations: interim guidelines. *Int J Epidemiol*. 2008;37:120-132.

64. Picó-Pérez M, Vieira R, Fernández-rodríguez M, et al. Multimodal meta-analysis of structural gray matter, neurocognitive and social cognitive fMRI findings in schizophrenia patients. *Psychol Med*. 2022;52:614-624.

65. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372(71):1-9.

66. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7.

67. Gosling CJ, Solanes A, Fusar-Poli P, Radua J. Metaumbrella: the first comprehensive suite to perform data analysis in umbrella reviews with stratification of the evidence. *BMJ Ment Heal*. 2023;26(1):1-8.

68. Fullana MA, Abramovitch A, Via E, et al. Diagnostic biomarkers for obsessive-compulsive disorder: a reasonable quest or ignis fatuus? *Neurosci Biobehav Rev*. 2020;118(June):504-513.

69. Solanes A, Albajes-Eizagirre A, Fullana MA, et al. Can we increase the subjective well-being of the general population? An umbrella review of the evidence. *Rev Psiquiatr Salud Ment*. 2021;14(1):50-64.

70. Fullana MA, Tortella-Feliu M, Fernández De La Cruz L, et al. Risk and protective factors for anxiety and obsessive-compulsive disorders: an umbrella review of systematic reviews and meta-analyses. *Psychol Med*. 2020;50(8):1300-1315.

71. Hedges L V. Effect Sizes in Cluster-Randomized Designs. *J Educ Behav Stat*. 2007;32(4):341–370.

72. Egger M, Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

73. Ioannidis JPA. Clarifications on the application and interpretation of the test for excess significance and its extensions. *J Math Psychol*. 2013;57(5):184–187.

74. Di Sabatino A, Vanoli A, Giuffrida P, Luinetti O, Solcia E, Corazza GR. The function of

tissue transglutaminase in celiac disease. *Autoimmun Rev*. 2012;11(10):746-753.

75. Wijarnpreecha K, Jaruvongvanich V, Cheungpasitporn W, Ungprasert P. Association between celiac disease and schizophrenia: a meta-analysis. *Eur J Gastroenterol Hepatol*. 2018;7:442-446.

76. Bender L. Childhood schizophrenia. *Psychiatr Q*. 1953;27:663–681.

77. Dohan FC. Wheat '"consumption"' and hospital admissions for schizophrenia during World War II. A preliminary report. *Am J Clin Nutr*. 1966;18:7-10.

78. Casella G, Bordo BM, Schalling R, et al. Neurological disorders and celiac disease. *Minerva Gastroenterol Dietol*. 2015;61:1-2.

79. Zingone F, Swift GL, Card TR, Sanders DS, Ludvigsson JF, Bai JC. Psychological morbidity of celiac disease: a review of the literature. *United Eur Gastroenterol J*. 2015;3(2):136–145.

80. Al-diwani AAJ, Pollak A, Irani SR, Lennox BR. Psychosis: an autoimmune disease? *Immunology*. 2017;152:388-401.

81. Pollak TA, Lennox BR, Müller S, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. *The Lancet Psychiatry*. 2020;7:19-22.

82. Kalaydjian AE, Eaton W, Cascella N, The FA. The gluten connection: the association between schizophrenia and celiac disease. *Acta Psychiatr Scand*. 2006;113:82-90.

83. Stevens AJ, Rucklidge JJ, Kennedy MA. Epigenetics, nutrition and mental health. Is there a relationship ? *Nutr Neurosci*. 2018;21(9):602-613.

84. Bottiglieri T. Homocysteine and folate metabolism in depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:1103-1112.

85. Hsieh Y chi, Chou L shiu, Lin C hua, Wu H chi, Li D jeng, tseng PT. Serum folate levels in bipolar disorder: a systematic review and meta-analysis. *BMC Psychiatry*. 2019;19(305):1-9.

86. Davies C, Segre G, Estradé A, et al. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *The Lancet Psychiatry*. 2020;7(5):399-410.

87. Kirkbride JB, Susser E, Kundakovic M, Kresovich JK, Davey Smith G, Relton CL. Prenatal nutrition, epigenetics and schizophrenia risk: can we test causal effects? *Epigenomics*. 2012;4(3):303-315.

88. Wolff GL, Kodell RL, Moore SR, Cooney CA. Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. *FASEB J*. 1998;12(11):949-957.

89. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci*. 2008;105(44):17046-17049.

90. Cao B, Wang DF, Xu MY, et al. Vitamin B12 and the risk of schizophrenia: a meta-analysis. *Schizophr Res*. 2016;172(1-3):216-217.

91. Zhang Y, Hodgson NW, Trivedi MS, et al. Decreased brain levels of vitamin B12 in aging, autism and schizophrenia. *PLoS One*. 2016;11(1):1-19.

92. Aucoin M, Lachance L, Cooley K, Kidd S. Diet and psychosis: a scoping review. *Neuropsychobiology*. 2020;79(1):20-42.

93. Misiak B, Frydecka D, Łaczmański Ł, Ślęzak R, Kiejna A. Effects of second-generation antipsychotics on selected markers of one-carbon metabolism and metabolic syndrome components in first-episode schizophrenia patients. *Eur J Clin Pharmacol*. 2014;70(12):1433-1441.

94. Moustafa AA, Hewedi DH, Eissa AM, Frydecka D, Misiak B. Homocysteine levels in schizophrenia and affective disorders - focus on cognition. *Front Behav Neurosci*. 2014;8(October):1-10.

95. Nishi A, Numata S, Tajima A, et al. Meta-analyses of blood homocysteine levels for gender and genetic association studies of the MTHFR C677T polymorphism in schizophrenia. *Schizophr Bull*. 2014;40(5):1154-1163.

96. Brown AS, Bottiglieri T, Schaefer CA, et al. Elevated prenatal homocysteine levels as a risk factor for schizophrenia. *Arch Gen Psychiatry*. 2007;64(1):31-39.

97. Bouaziz N, Ayedi I, Sidhom O, et al. Plasma homocysteine in schizophrenia: determinants and clinical correlations in Tunisian patients free from antipsychotics. *Psychiatry Res*. 2010;179(1):24-29.

98. Petronijević ND, Radonjić N V., Ivković MD, et al. Plasma homocysteine levels in young male patients in the exacerbation and remission phase of schizophrenia. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2008;32(8):1921-1926.

99. Goff DC, Bottiglieri T, Arning E, et al. Folate, homocysteine, and negative symptoms in schizophrenia. *Am J Psychiatry*. 2004;161:1705-1708.

100. Di Lorenzo R, Amoretti A, Baldini S, et al. Homocysteine levels in schizophrenia

patients newly admitted to an acute psychiatric ward. *Acta Neuropsychiatr*. 2015;27(6):336-344.

101. Applebaum J, Shimon H, Sela BA, Belmaker RH, Levine J. Homocysteine levels in newly admitted schizophrenic patients. *J Psychiatr Res*. 2004;38(4):413-416.

102. Fraguas D, Díaz-caneja CM, Ayora M, et al. Oxidative stress and inflammation in first-episode psychosis: a systematic review and meta-analysis. *Schizophr Bull*. 2019;45(4):742-751.

103. Onozato M, Uta A, Magarida A, et al. Alterations in methionine to homocysteine ratio in individuals with first-episode psychosis and those with at-risk mental state. *Clin Biochem*. 2020;77(September 2019):48-53.

104. Kinoshita M, Numata S, Tajima A, Shimodera S, Imoto I, Ohmori T. Plasma total homocysteine is associated with DNA methylation in patients with schizophrenia. *Epigenetics*. 2013;8(6):584-590.

105. Tyagi N, Sedoris KC, Steed M, et al. Mechanisms of homocysteine-induced oxidative stress. *Am J Physiol Hear Circ Physiol*. 2005;289:2649-2656.

106. Zheng W, Li W, Qi H, et al. Adjunctive folate for major mental disorders: a systematic review. *J Affect Disord*. 2020;267(December 2019):123-130.

107. Firth J, Stubbs B, Sarris J, et al. The effects of vitamin and mineral supplementation on symptoms of schizophrenia: a systematic review and meta-analysis. *Psychol Med*. 2017;47(9):1515-1527.

108. Sakuma K, Matsunaga S, Nomura I, Okuya M, Kishi T, Iwata N. Folic acid/methylfolate for the treatment of psychopathology in schizophrenia: a systematic review and meta-analysis. *Psychopharmacology (Berl)*. 2018;235:2303-2314.

109. Allott K, McGorry PD, Yuen HP, et al. The vitamins in psychosis study: a randomized, double-blind, placebo-controlled trial of the effects of vitamins B12, B6, and folic acid on symptoms and neurocognition in first-episode psychosis. *Biol Psychiatry*. 2019;86(1):35-44.

110. Johnson WG. DNA polymorphism-diet-cofactor-development hypothesis and the gene-teratogen model for schizophrenia and other developmental disorders. *Am J Med Genet*. 1999;88:311-323.

111. Hill M, Shannahan K, Jasinski S, et al. Folate supplementation in schizophrenia: a possible role for MTHFR genotype. *Schizophr Res*. 2011;127(1-3):41-45.

112. Roffman JL, Brohawn DG, Nitenson AZ, MacKlin EA, Smoller JW, Goff DC. Genetic

variation throughout the folate metabolic pathway influences negative symptom severity in schizophrenia. *Schizophr Bull*. 2013;39(2):330-338.

113. Landek-salgado MA, Faust TE, Sawa A. Molecular substrates of schizophrenia: homeostatic signaling to connectivity. *Mol Psychiatry*. 2016;21:10-28.

114. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;24(511):421-427.

115. Pouget JG, Gonçalves VF, Schizophrenia Working Group of the Psychiatric Genomics Consortium, et al. Genome-wide association studies suggest limited immune gene enrichment in schizophrenia compared to 5 autoimmune diseases. *Schizophr Bull*. 2016;42(5):1176-1184.

116. Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP. Postmortem evidence of cerebral in flammation in schizophrenia: a systematic review. *Mol Psychiatry*. 2016;21:1009-1026.

117. Trépanier MO, Hopperton KE, Mizrahi R, Mechawar N, Bazinet RP. Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Mol Psychiatry*. 2016;21:1009-1026.

118. Rodrigues-Amorim D, Rivera-baltanás T, Spuch C, et al. Cytokines dysregulation in schizophrenia: a systematic review of psychoneuroimmune relationship. *Schizophr Res*. 2018;197:19-33.

119. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood in fl ammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol Psychiatry*. 2016;21:642-649.

120. Khoury R, Nasrallah HA. Inflammatory biomarkers in individuals at clinical high risk for psychosis (CHR-P): state or trait? *Schizophr Res*. 2018;199:31-38.

121. Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. *Biol Psychiatry*. 2013;74(6):400-409.

122. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol Psychiatry*. 2016;21(12):1696-1709.

123. Çakici N, van Beveren NJM, Judge-Hundal G, Koola MM, Sommer IE. An update on the efficacy of anti-inflammatory agents for patients with schizophrenia: a meta-analysis. *Psychol Med*. 2019;49:2307-2319.

124. Martinez-Cengotitabengoa M, MacDowell K, Alberich S, et al. BDNF and NGF signalling in early phases of psychosis: relationship with inflammation and response to antipsychotics after 1 year. *Schizophr Bull*. 2016;42(1):142-151.

125. Erickson MA, Ruf A, Gold JM. A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease specificity and progression. *Biol Psychiatry*. 2016;79:980-987.

126. Haigh SM, Coffman BA, Salisbury DF. Mismatch negativity in first-episode schizophrenia: a meta-analysis. *Clin EEG Neurosci*. 2017;48(1):3-10.

127. Avissar M, Xie S, Vail B, Lopez-Calderon J, Wang Y, Javitt DC. Meta-analysis of mismatch negativity to simple versus complex deviants in schizophrenia. *Schizophr Res*. 2018;191:25-34.

128. Umbricht D, Koller R, Vollenweider FX, Schmid L. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biol Psychiatry*. 2002;51(5):400-406.

129. Javitt DC, Steinschneidertt M, Schroedertt CE, Arezzott JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc Natl Acad Sci*. 1996;93(October):11962-11967.

130. Hay RA, Roach BJ, Srihari VH, Woods SW, Ford JM, Mathalon DH. Equivalent mismatch negativity deficits across deviant types in early illness schizophrenia-spectrum patients. *Biol Psychol*. 2015;105:130-137.

131. Hirt V, Schubring D, Schalinski I, Rockstroh B. Mismatch negativity and cognitive performance in the course of schizophrenia. *Int J Psychophysiol*. 2019;145(June 2018):30-39.

132. Bodatsch M, Ruhrmann S, Wagner M, et al. Prediction of psychosis by mismatch negativity. *Biol Psychiatry*. 2010;69(10):959-966.

133. Shaikh M, Valmaggia L, Broome MR, et al. Reduced mismatch negativity predates the onset of psychosis. *Schizophr Res*. 2012;134(1):42-48.

134. Higuchi Y, Sumiyoshi T, Seo T, Miyanishi T, Kawasaki Y. Mismatch negativity and cognitive performance for the prediction of psychosis in subjects with at-risk mental state. *PLoS One*. 2013;8(1):1-10.

135. Solís-vivanco R, Mondragón-maya A, León-ortiz P, Rodríguez-agudelo Y, Cadenhead KS, Fuente-sandoval C De. Mismatch Negativity reduction in the left cortical regions

in fi rst-episode psychosis and in individuals at ultra high-risk for psychosis. *Schizophr Res*. 2014;158(1-3):58-63.

136. Nagai T, Tada M, Kirihara K, Araki T, Jinde S, Kasai K. Mismatch negativity as a “translatable” brain marker toward early intervention for psychosis: a review. *Front Psychiatry*. 2013;4:1-10.

137. McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency and reaction time. *Science (80-)*. 1981;211:77-80.

138. Duncan-Johnson CC, Donchin E. The relation of P300 latency to reaction time as a function of expectancy. *Prog Brain Res*. 1980;54:717-722.

139. Polich J, Kokb A. Cognitive and biological determinants of P300: an integrative review. 1995;41:103-146.

140. Wang J, Tang Y, Li C, et al. Decreased P300 current source density in drug-naive first episode schizophrenics revealed by high density recording. *Int J Psychophysiol*. 2010;75:249-257.

141. del Re EC, Spencer KM, Oribe N, et al. Clinical high risk and first episode schizophrenia: auditory event-related potentials. *Psychiatry Res*. 2015;231(2):126-133.

142. McCarley RW, Salisbury DF, Hirayasu Y, et al. Association between smaller left posterior superior temporal gyrus volume on magnetic resonance imaging and smaller left temporal P300 amplitude in first-episode schizophrenia. *Arch Gen Psychiatry*. 2002;59:321-331.

143. Jeon YW, Polich J. Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. *Psychophysiology*. 2003;40:684-701.

144. Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S. Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophr Res*. 2004;70:315-329.

145. Kim M, Lee TH, Kim JH, et al. Decomposing P300 into correlates of genetic risk and current symptoms in schizophrenia: an inter-trial variability analysis. *Schizophr Res*. 2018;192:232-239.

146. Park E jin, Han S ick, Jeon Y whan. Auditory and visual P300 reflecting cognitive improvement in patients with schizophrenia with quetiapine: a pilot study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:674-680.

147. Fusar-poli P, Crossley N, Woolley J, et al. Gray matter alterations related to P300 abnormalities in subjects at high risk for psychosis: longitudinal MRI-EEG study.

Neuroimage. 2011;55(1):320-328.

148. Fusar-poli P, Crossley N, Woolley J, et al. White matter alterations related to P300 abnormalities in individuals at high risk for psychosis: an MRI – EEG study. *J Psychiatry Neurosci*. 2011;36(4):239-248.

149. Tang Y, Wang J, Zhang T, et al. P300 as an index of transition to psychosis and of remission: data from a clinical high risk for psychosis study and review of literature. *Schizophr Res*. 2020;226:74-83.

150. Hamilton HK, Roach BJ, Bachman PM, et al. Association between P300 responses to auditory oddball stimuli and clinical outcomes in the psychosis risk syndrome. *JAMA Psychiatry*. 2019;94121(11):1187-1197.

151. Bodatsch M, Brockhaus-Dumke A, Klosterkötter J, Ruhrmann S. Forecasting psychosis by event-related potentials — Systematic review and specific meta-analysis. *Biol Psychiatry*. 2015;77(11):951-958.

152. Catalan A, Salazar de Pablo G, Aymerich C, et al. Neurocognitive functioning in individuals at clinical high risk for psychosis: systematic review and meta-analysis. *JAMA Psychiatry*. 2021;In press:e211290.

153. Fortea A, Batalla A, Radua J, et al. Cortical gray matter reduction precedes transition to psychosis in individuals at clinical high-risk for psychosis: a voxel-based meta-analysis. *Schizophr Res*. 2021;232:98-106.

154. Johnstone E, Frith CD, Crow TJ, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;308(7992):924-926.

155. Reveley A, Clifford CA, Reveley MA, Murray RM. Cerebral ventricular size in twins discordant for schizophrenia. *Lancet*. 1982;319(8271):540-541.

156. Pfefferbaum A, Zipursky RB, Lim KO, Zatz LM, Stahl SM, Jernigan TL. Computed tomographic evidence for generalized sulcal and ventricular enlargement in schizophrenia. *Arch Gen Psychiatry*. 1988;45:633-640.

157. Weinberger DR, Fuller Torrey E, Neophytides AN, Wyatt RJ. Structural abnormalities in the cerebral cortex of chronic schizophrenic patients. *Arch Gen Psychiatry*. 1979;36:935-939.

158. McDonald C, Marshall N, Sham PC, et al. Regional brain morphometry in patients with unaffected relatives. *Am J Psychiatry*. 2006;163:478-487.

159. Chung Y, Haut KM, He G, et al. Ventricular enlargement and progressive reduction of cortical gray matter are linked in prodromal youth who develop psychosis. *Schizophr*

Res. 2017;189:169-174.

160. Brugger S, Davis JM, Leucht S, Stone JM. Proton Magnetic Resonance Spectroscopy and Illness Stage in Schizophrenia—A Systematic Review and Meta-Analysis. *Biol Psychiatry*. 2011;69(5):495-503.

161. Mondino M, Brunelin J, Saoud M. N-acetyl-aspartate level is decreased in the prefrontal cortex in subjects at-risk for schizophrenia. *Front Psychiatry*. 2013;4:1-6.

162. Natsubori T, Inoue H, Abe O, et al. Reduced frontal glutamate + glutamine and N-Acetylaspartate levels in patients with chronic schizophrenia but not in those at clinical high risk for psychosis or with first-episode schizophrenia. *Schizophr Bull*. 2014;40(5):1128-1139.

163. Smieskova R, Fusar-Poli P, Allen P, et al. Neuroscience and biobehavioral reviews neuroimaging predictors of transition to psychosis — A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2010;34(8):1207-1222.

164. Mechelli A, Riecher-Rössler A, Meisenzahl EM, et al. Neuroanatomical abnormalities that predate the onset of psychosis. *Arch Gen Psychiatry*. 2011;68(5):489-495.

165. Fusar-Poli P, Salazar De Pablo G, Correll CU, et al. Prevention of psychosis: advances in detection, prognosis, and intervention. *JAMA Psychiatry*. 2020;77(7):755-765.

166. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull*. 2013;39(6):1363-1372.

167. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev*. 2013;37(8):1680-1691.

168. Sayo A, Jennings RG, Van Horn JD. Study factors in fluencing ventricular enlargement in schizophrenia: a 20 year follow-up meta-analysis. *Neuroimage*. 2012;59:154-167.

169. Walther S, Strik W. Motor symptoms and schizophrenia. *Neuropsychobiology*. 2012;66:77-92.

170. Reichenberg A, Caspi A, Harrington H, et al. Static and dynamic cognitive deficits in childhood preciding adult schizophrenia: a 30-year study. *Am J Psychiatry*. 2010;167:160-169.

171. Fusar-poli P, Borgwardt S, Crescini A, et al. Neuroanatomy of vulnerability to

psychosis: a voxel-based meta-analysis. *Neurosci Biobehav Rev*. 2011;35:1175-1185.

172. Koutsouleris N, Riecher-Rössler A, Meisenzahl EM, et al. Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. *Schizophr Bull*. 2015;41(2):471-482.

173. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *J R Army Med Corps*. 1987;156(3):150-153.

174. Weinberger DR. Implications of normal brain development for the pathogenesis of schizphrenia. *Arch Gen Psychiatry*. 1987;44(7):660-669.

175. Murray RM, Bhavsar V, Tripoli G, Howes O. 30 years on: how the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. *Schizophr Bull*. 2017;43(6):1190-1196.

176. Lill A, Helge B, Thayer JF. Vagal influence on working memory and attention. *Int J Psychophysiol*. 2003;48:263-274.

177. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Adv Nurs*. 2000;61:201-216.

178. Williams DP, Cash C, Rankin C, Bernardi A, Thayer JF. Resting heart rate variability predicts self-reported difficulties in emotion regulation: a focus on different facets of emotion regulation. *Front Psychol*. 2015;6:1-8.

179. Thayer JF, Hansen AL, Saus-Rose E, Johnsen BH. Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. *ann behav med*. 2009;37:141-153.

180. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Curric Cardiol*. 2005;150:1115-1121.

181. Clamor A, Sundag J, Lincoln TM. Specificity of resting-state heart rate variability in psychosis: a comparison with clinical high risk, anxiety, and healthy controls. *Schizophr Res*. 2019;206:89-95.

182. Kocsis A, Gajwani R, Gross J, et al. Altered autonomic function in individuals at clinical high risk for psychosis. *Front Psychiatry*. 2020;11:1-11.

183. Van Os J, Kenis G, Rutten BPF. The environment and schizophrenia. *Nature*. 2010;468(7321):203-212.

184. Feczko E, Miranda-Dominguez O, Marr M, Graham AM, Nigg JT, Fair, Damien A. The Heterogeneity problem: approaches to identify psychiatric subtypes. *Trends Cogn Sci*.

2019;23(7):584–601.

185. Ioannidis JPA. Why most discovered true associations are inflated. *Epidemiology*. 2008;19(5):640-648.

186. Carvalho AF, Köhler CA, Brunoni AR, et al. Bias in peripheral depression biomarkers. *Psychother Psychosom*. 2016;85(2):81-90.

187. Carvalho AF, Köhler CA, Fernandes BS, et al. Bias in emerging biomarkers for bipolar disorder. *Psychol Med*. 2016;46(11):2287-2297.

188. Oliver D. The importance of external validation to advance precision psychiatry. *Lancet Reg Heal - Eur*. 2022;22:100498.

189. Fusar-poli P, Manchia M, Koutsouleris N, et al. Ethical considerations for precision psychiatry: A roadmap for research and clinical practice. *Eur Neuropsychopharmacol*. 2022;63:17-34.

190. Kéri P, White LA, Oliver D, Fusar-Poli P. Empowering experts by experience to guide ethical precision psychiatry. *Biol Psychiatry2*. 2023;In press.

191. Addington J, Liu L, Brummitt K, et al. North American Prodrome Longitudinal Study (NAPLS 3): Methods and baseline description. *Schizophr Res*. 2022;243:262-267.

192. Brady LS, Larrauri CA. Accelerating Medicines Partnership® Schizophrenia (AMP®SCZ): developing tools to enable early intervention in the psychosis high risk state. *World Psychiatry*. 2023;22(1):42-43.

193. Andreazza AC, Laksono I, Fernandes BS, et al. Guidelines for the standardized collection of blood-based biomarkers in psychiatry: steps for laboratory validity – a consensus of the Biomarkers Task Force from the WFSBP. *World J Biol Psychiatry*. 2019;20(5):340-351.

194. Pisanu C, Severino G, De Toma I, et al. Transcriptional biomarkers of response to pharmacological treatments in severe mental disorders: a systematic review. *Eur Neuropsychopharmacol*. 2022;55:112-157.

195. Ezeoke A, Mellor A, Buckley A, Miller B. A systematic, quantitative review of blood autoantibodies in schizophrenia. *Schizophr Bull*. 2013;150(1):245-251.

196. Wang D, Zhai J xia, Liu D wu. Serum folate levels in schizophrenia: a meta-analysis. *Psychiatry Res*. 2016;235:83-89.

197. Davison J, Gorman AO, Brennan L, Cotter DR. A systematic review of metabolite biomarkers of schizophrenia. *Schizophr Res*. 2018;195:32-50.

198. Grignon S, Marc J. Assessment of malondialdehyde levels in schizophrenia: a meta-analysis and some methodological considerations. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:365-369.

199. Cui H, Jin Y, Wang J, Weng X, Li C. Serum brain-derived neurotrophic factor (BDNF) levels in schizophrenia: a systematic review. *Shanghai Arch Psychiatry*. 2012;24(5):250-261.

200. Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. *Mol Psychiatry*. 2011;16:960-972.

201. Rowbotham IM, Orsucci FF, Mansour MF, Chamberlain SR, Raja HY. Relevance of brain-derived neurotrophic factor levels in schizophrenia: a systematic review and meta-analysis. *AIMS Neurosci*. 2015;2(4):280-293.

202. Toll A, Mané A. Brain-derived neurotrophic factor levels in first episode of psychosis: a systematic review. *World J Psychiatry*. 2015;5(1):154-159.

203. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr Res*. 2005;76:1-23.

204. Xiong Y, Li X, Zhao L, Wang C. Mismatch negativity in Han Chinese patients with schizophrenia: a meta-analysis. *Shanghai Arch Psychiatry*. 2017;29(5):259-267.

205. Qiu Y qin, Tang Y xiang, Chan RCK, Sun X yang, He J. P300 aberration in first-episode schizophrenia patients: a meta-analysis. *PLoS One*. 2014;9(6):1-8.

206. Buoli M, Caldiroli A, Melter CC, Serati M, de Nijs J, Altamura AC. Biological aspects and candidate biomarkers for psychotic bipolar disorder: a systematic review. *Psychiatry Clin Neurosci*. 2016;70:227-244.

207. Cheng C hsiung, Chan P ying S, Liu C yih, Hsu S chieh. Auditory sensory gating in patients with bipolar disorders: a meta-analysis. *J Affect Disord*. 2016;203:199-203.

208. de Wilde OM, Bour LJ, Dingemans PM, Koelman JHTM, Linszen DH. A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups. *Schizophr Res*. 2007;97(1-3):137-151.

209. Patterson J V, Hetrick WP, Boutros NN, et al. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. *Psychiatry Res*. 2008;158:226-247.

210. Sayo A, Jennings RG, van Horn JD. Study factors influencing ventricular enlargement in schizophrenia: a 20 year follow-up meta-analysis. *Neuroimage*. 2012;59(1):154-

167.

211. Xu T, Chan RCK, Compton MT. Minor physical anomalies in patients with schizophrenia, unaffected first-degree relatives, and healthy controls: a meta-analysis. *PLoS One*. 2011;6(9):2-7.

212. Clamor A, Lincoln TM, Thayer JF, Koenig J. Resting vagal activity in schizophrenia: meta-analysis of heart rate variability as a potential endophenotype. *Br J Psychiatry*. 2016;208:9-16.

Table 1. Biomarkers with highly suggestive or suggestive evidence of association with psychotic disorders

Factor	k	Diagnosis	ES (95% CI)	Features used for classification of level of evidence									eOR	CE
				N	Cases	Controls	p	I^2	PI 95% CI	Egger	ESB	LS		
Peripheral biomarkers														
tTG autoantibodies[195]	1	SZ	OR, 7.32 (3.36, 15.94)	2301	1401	900	1×10^{-6}	NA	NA	NA	No	Yes	7.32	II
Folate[196]	16	SZ	SMD, -1.44 (-2.18, -0.71)	2599	1260	1339	1.20×10^{-4}	98%	-4.71, 1.83	No	No	Yes	0.07	III
Malondialdehyde[121,197,198]	26	SZ	SMD, 1.38 (0.82, 1.94)	1795	1077	718	1×10^{-6}	94%	-1.56, 4.32	No	Yes	Yes	12.22	III
BDNF[199–202]	47	FEP, SZ	SMD, -0.69 (-1.05, -0.33)	4955	2756	2199	2.00×10^{-4}	91%	-3.2, 1.82	No	Yes	Yes	0.29	III
Homocysteine[95]	19	SZ	SMD, 0.6 (0.31, 0.89)	3320	1303	2017	5.1×10^{-5}	89%	-0.7, 1.91	No	Yes	Yes	2.98	III
Electrophysiologic biomarkers														
Mismatch negativity in auditory event-related potentials[126,127,203,204]	47	SZ	SMD, 0.73 (0.5, 0.96)	5649	2871	2778	$<1 \times 10^{-6}$	86%	-0.81, 2.28	No	Yes	Yes	3.77	II
P300 component latency[144,205]	56	SZ	SMD, -0.6 (-0.83, -0.38)	3502	1735	1767	$<1 \times 10^{-6}$	90%	-2.22, 1.01	No	Yes	Yes	0.33	II
P50 sensory gating (P50 S2/S1 ratio)[144,206–209]	80	AP, SZ	SMD, 0.79 (0.43, 1.16)	4999	2107	2892	2.0×10^{-5}	93%	-2.43, 4.02	No	No	Yes	4.22	III
Neuroimaging biomarkers														
Ventricle brain ratio[210]	72	SZ	SMD, 0.61 (0.5, 0.71)	6099	3463	2636	$<1 \times 10^{-6}$	68%	(-0.14, 1.35)	No	Yes	Yes	3.00	II
Frontal NAA[160]	68	SZ	SMD, -0.34 (-0.47, -0.2)	2868	1444	1424	1×10^{-6}	63%	(-1.22, 0.55)	No	Yes	No	0.54	III
Other biomarkers														
Minor physical anomalies[211]	14	SZ	SMD, 0.99 (0.64, 1.34)	2160	1153	1007	$<1 \times 10^{-6}$	93%	-0.45, 2.42	No	Yes	Yes	5.99	II
High frequency heart rate variability[212]	28	SZ	SMD, -0.99 (-1.41, -0.58)	3008	1330	1678	2×10^{-6}	98%	-3.24, 1.25	Yes	Yes	Yes	0.16	III

AP – affective psychosis, BDNF - brain-derived neurotrophic factor, CI – confidence interval, CE – class of evidence, eOR – equivalent odds ratio, Egger – significant Egger test, ES – effect size, ESB – excess significance bias, FEP – first episode of psychosis, k – number of studies for each factor, LS - largest study with significant effect, N – total number of participants, NA – not assessable, NAA - N-acetylaspartate, OR – odds ratio, PI – prediction interval, SMD – standardized mean difference, SZ – schizophrenia, tTG transglutaminase.

Figure 1. Standardized mean differences for peripheral biomarkers and psychotic disorders

[add Figure 1 here]

OR for tTG autoantibodies have been converted to equivalent Hedges' g (eG) to allow for a comparison across risk factors. BDNF - brain-derived neurotrophic factor, CI - confidence interval, eG – equivalent Hedges' g, SMD – standardized mean difference, tTG - transglutaminase.

Figure 2. Standardized mean differences for electrophysiological biomarkers and psychotic disorders

[add Figure 2 here]

CI - confidence interval, SMD – standardized mean difference.

Figure 3. Standardized mean differences for neuroimaging biomarkers and psychotic disorders

[add Figure 3 here]

CI - confidence interval, NAA - N-acetylaspartate, SMD – standardized mean difference.

Figure 4. Standardized mean differences for other biomarkers and psychotic disorders

[add Figure 4 here]

CI - confidence interval, SMD – standardized mean difference.