Commentary

Early-Life Biomarkers for Psychosis Risk in Young People: Another Nail in the Coffin for Cartesian Dualism

Golam M. Khandaker

Disorders of the brain are not confined to this precious lump of fat that is typically thought to be shielded from rest of the body by the blood-brain barrier. Accumulating evidence now challenges Cartesian dualism by demonstrating that many brain disorders, including schizophrenia and depression, involve multiple systems (1). In this issue of *Biological Psychiatry*, Madrid-Gambin *et al.* (2) report a case-control study nested in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort on the association of psychotic experiences (PEs) in young adults assessed around 18 years of age with blood lipidomics, proteomics, and complement/coagulation protein biomarkers in childhood at 12 years of age. Based on 48 cases of definite PEs and 67 controls, Madrid-Gambin *et al.* (2) report that levels of a number of these biomarkers, including 12 phosphatidylcholines (PCs), four lysophosphatidylcholines (LPCs), and the coagulation protein plasminogen, are different at baseline between future cases and controls. Evidence for these associations remained after correction for multiple testing. PCs are a type of phospholipid and are a major component of cell membranes. LPCs are also phospholipids that originate from PCs and are present in cell membranes and blood plasma in relatively small quantities. Madrid-Gambin *et al.* (2) report that most of the lipids that are associated with PEs are also associated with plasminogen. Plasminogen is released from the liver in systemic circulation and is a zymogen or proenzyme (an inactive precursor of an enzyme) of plasmin that acts to dissolve fibrin blood clots. Finally, using a data-driven clustering approach, Madrid-Gambin *et al.* (2) identified four clusters based on these biomarkers, one of which was strongly associated with PEs—representing a so-called biological signature of psychosis risk in young people.

These findings are broadly in line with two previous studies from these investigators based on the same birth cohort. One of these studies reported a longitudinal association of childhood PCs and LPCs with psychotic disorder at 18 years of age, but there was no evidence for cross-sectional association between lipids and psychotic disorder at that age. The other study was based on proteomics analysis and reported a longitudinal association between disruptions in coagulation and complement pathways in childhood and psychotic disorder at 18 years of age. Taken together, these studies provide intriguing evidence for disruptions in lipid metabolism and coagulation/inflammation markers detectable at the group level in childhood in people who later present with PEs or psychotic disorder in early adulthood.

What do these findings mean? The increased risk of cardiometabolic illness in people with schizophrenia and related psychotic disorders, compared with the general population, is well known. There is evidence for altered glucose insulin homeostasis, such as insulin resistance, in drug-naïve first-episode psychosis and in young people with PEs (3). There is also evidence for low-grade inflammation as reflected by higher concentrations of C-reactive protein, interleukin-6, and other inflammatory markers in peripheral blood in schizophrenia cases compared with controls (4). Population-based longitudinal studies, including our own work from ALSPAC, Finland, and Sweden, suggest an association between higher levels of interleukin-6, C-reactive protein, and erythrocyte sedimentation rate in childhood/adolescence and risks for PEs and a diagnosis of schizophrenia subsequently in adulthood (5). The results of Madrid-Gambin *et al.* (2) are consistent with these previous studies, also suggesting that schizophrenia is a multisystem disorder. A key strength of this work is its longitudinal design, which is useful to tease out reverse causality (i.e., biomarker changes being a consequence of illness rather than its cause). However, whether these early biomarker changes are causal risk factors for PEs or psychotic disorder still remains an open question, because alternative explanations may include confounding.

Mendelian randomization (MR) analysis could be a useful tool to address residual confounding. The MR approach has been used successfully to identify evidence for potentially causal associations for interleukin-6, C-reactive protein, and triglycerides for depression in the UK Biobank cohort in a recent study (6), which suggests that inflammation and lipid metabolism could be shared mechanisms for coronary heart disease and depression. Findings from existing MR studies of metabolic alterations and schizophrenia are mixed. One study reported a potentially causal role for elevated fasting insulin in schizophrenia based on psychiatric genomics consortium data (7), but this finding has not been replicated. In the future, using the MR approach would be useful to test whether genetic variants regulating levels/activity of PC, LPC, and plasminogen are also associated with psychotic outcomes. If so, it would strongly suggest that the observational association for these biomarkers are unlikely to be fully explained by confounding.

The findings by Madrid-Gambin *et al.* (2) would be more valuable if they are seen as important clues for potential causes of psychosis, including common cause for psychotic and cardiometabolic disorders, rather than as tools for predicting development of PEs or transition of PEs to schizophrenia. PEs in young people are transient phenotypes that show both

homotypic and heterotypic continuity with, respectively, psychotic and nonpsychotic disorders, including depression and anxiety (8,9). Despite a strong association between childhood PEs and subsequent psychotic disorder, the positive predictive value for PEs in relation to future psychotic disorder is relatively low (5–23% according to findings from the ALSPAC cohort) (9). Similarly, the predictive utility of these lipidomic or proteomic biomarkers for outcomes of PEs or psychosis is likely to be low. The reported 71% occurrence of PEs associated with a certain biomarker profile needs to be replicated in other samples of PEs and in schizophrenia. If these findings are replicated, they would mark a notable advance for psychosis risk prediction. Reported early-life metabolic and immune changes may not be unique to PEs, because PEs are often comorbid with depression, including in the ALSPAC sample (2). Whether these biomarker changes are unique to PEs or are transdiagnostic markers of psychiatric risk is an important question for future studies.

It is possible that early-life metabolic and immune changes are related to genetic and environmental influences operating earlier in development, such as adversity during prenatal and childhood development. These changes may represent shared mechanisms for comorbid psychiatric and physical illness, such as schizophrenia, depression, and cardiometabolic disorders. This idea is consistent with Barker's developmental programming hypothesis, which proposes that exposure to risk factors during a critical developmental window can permanently alter physiologic systems, leading to increased risks for chronic diseases of adult life. (For a useful book, see *Fetal and Infant Origins of Adult Disease* by David Barker, published in 1993 by the British Medical Journal Press, London.) Longitudinal studies reporting an association of childhood maltreatment with increased circulating inflammatory marker levels, greater adiposity, and poorer lipid and hemoglobin profiles decades later in adulthood support this idea (10). This is not to say that childhood lipid and immune changes cannot be risk factors for psychiatric disorders. Biologically, it is plausible that they are both key mediators of genetic and environmental exposures operating earlier in development, and risk factors in their own right. Focusing efforts to identify risk factors for these childhood physiologic changes could provide useful targets for the prevention of a number of comorbid psychiatric and physical disorders, such as schizophrenia, depression, type 2 diabetes, and coronary heart disease, which are some of the leading contributors to health-related morbidity and mortality worldwide.

Acknowledgments and Disclosures

Article Information

From the Department of Psychiatry, University of Cambridge School of Clinical Medicine; Cambridgeshire and Peterborough National Health Service Foundation Trust; and the National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge, United Kingdom.

Address correspondence to Golam M. Khandaker, M.B.B.S., M.Phil., Ph.D., M.R.C.Psych., Department of Psychiatry, Level E4, Addenbrooke's Hospital, Cambridge Biomedical Campus, Cambridge CB2 2QQ, United Kingdom; E-mail: gmk24@medschl.cam.ac.uk.

References

1. Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB (2015): Inflammation and immunity in schizophrenia: Implications for pathophysiology and treatment. Lancet Psychiatry 2:258–270.

2. Madrid-Gambin F, Föcking M, Sabherwal S, Heurich M, English JA, O'Gorman A, *et al.* (2019): Integrated lipidomics and proteomics point to early blood-based changes in childhood preceding later development of psychotic experiences: Evidence from the Avon Longitudinal Study of Parents and Children. Biol Psychiatry 86:25–34.

3. Perry BI, McIntosh G, Weich S, Singh S, Rees K (2016): The association between first-episode psychosis and abnormal glycaemic control: Systematic review and meta-analysis. Lancet Psychiatry 3:1049–1058.

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

5. Khandaker GM, Dantzer R, Jones PB (2017): Immunopsychiatry: Important facts. Psychol Med 47:2229–2237.

6. Khandaker GM, Zuber V, Rees JMB, Carvalho L, Mason AM, Foley CN, *et al.* (2019): Shared mechanisms between coronary heart disease and depression: Findings from a large UK general population-based cohort [published online ahead of print Mar 19]. Mol Psychiatry.

7. Li Z, Chen P, Chen J, Xu Y, Wang Q, Li X, *et al.* (2018): Glucose and insulin-related traits, type 2 diabetes and risk of schizophrenia: A Mendelian randomization study. EBioMedicine 34:182–188.

8. McGrath JJ, Saha S, Al-Hamzawi A, Andrade L, Benjet C, Bromet EJ, *et al.* (2016): The bidirectional associations between psychotic experiences and DSM-IV mental disorders. Am J Psychiatry 173:997–1006.

9. Zammit S, Kounali D, Cannon M, David AS, Gunnell D, Heron J, *et al.* (2013): Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. Am J Psychiatry 170:742–750.

10. Li L, Pinto Pereira SM, Power C (2019): Childhood maltreatment and biomarkers for cardiometabolic disease in mid-adulthood in a prospective British birth cohort: Associations and potential explanations. BMJ Open 9:e024079.