Commentary: CRP and schizophrenia: cause, consequence or confounding?

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Schizophrenia is a debilitating psychiatric disorder affecting millions of people worldwide. Both genetic and environmental factors contribute to disease development, but the pathophysiology of schizophrenia is poorly understood and treatment mainly consists of psychosocial interventions and antipsychotic medication. Mendelian randomization (MR) analysis has the potential to identify causal factors for an outcome of interest, providing insights into the biological pathways that cause disease, and can aid in detecting novel therapeutic targets. Genome-wide association studies (GWAS) have identified more than 100 loci for schizophrenia that can be used in MR analysis for the identification of causal factors for the disease.

In 2016, Prins et al. described for the first time an association between genetically determined C-reactive protein (CRP) and schizophrenia in an MR study. In contrast to prior published observational association studies, in which higher CRP levels were observed in schizophrenia patients compared with controls, Prins et al. found a protective causal effect of CRP on schizophrenia. Using similar CRP and schizophrenia GWAS data, this finding was confirmed in a subsequent MR study that incorporated robust MR sensitivity analyses. Additionally, Hartwig et al. investigated the role of IL-6, which is the major upstream regulator of CRP, and findings in the MR of IL-6 were in agreement with the protective effect of CRP. Recently, in a novel CRP GWAS effort, up to 52 genetic variants were included in MR analyses of CRP and schizophrenia, and a similar protective effect of CRP on schizophrenia risk was found. Furthermore, the MR analysis that included only the genetic variant
within the CRP gene, which reduces the chance of horizontal pleiotropy in which the genetic variant is independently associated with multiple phenotypes, showed similar results.

The study by Lin et al., 1930, published in this issue, examined the causal association between CRP and several blood metabolites with schizophrenia in an MR study applying different MR methods. The study is important and novel for several reasons. First, the authors used the most recent GWAS datasets available for both CRP and schizophrenia to perform the first bidirectional MR analysis. Second, they are the first to apply generalized summary data-based Mendelian randomization (GSMR) analysis, which has the advantage of more statistical power compared with MR Egger and includes the possibility to detect putative pleiotropic effects through the heterogeneity in dependent instruments (HEIDI) test. Third, extensive MR sensitivity analyses were applied to exclude weak instrument bias, horizontal pleiotropy and heterogeneity in the instrumental variables. Finally, with regard to blood metabolites, a novel MR technique developed to handle high-throughput data performing multiple multivariable MR models was applied. The authors observed in all MR analyses a protective effect of CRP on schizophrenia, and no effect of genetic liability to schizophrenia on CRP levels, confirming published MR work. In sensitivity analyses, no evidence was found for weak instrument bias or horizontal pleiotropy, and selection or survivor bias is unlikely to explain the association between CRP and schizophrenia.

Although robust MR analyses suggest a causal protective effect of CRP on schizophrenia, could the results still be confounded? MR analyses rely on several assumptions, one of them being that the instrument affects the outcome only through the risk factor. This assumption may be violated in the CRP–schizophrenia association when the CRP variants affect schizophrenia directly, not through CRP. Even the single risk variant at the CRP gene or a variant in high linkage disequilibrium may have an effect on schizophrenia that is not through serum CRP levels. Another assumption of MR analysis is that the genetic variants are not associated with confounders of the association between the exposure and the outcome. We may be unaware of confounding factors of the CRP–schizophrenia association, and the association of genetic variants with these confounding factors.

If we assume that CRP truly does have a causal effect on schizophrenia, what is the biological explanation? CRP is a pentameric protein first discovered by William Tillet and Thomas Francis in 1930 and named after the C-polysaccharide of the Pneumococcus bacterium. 6 CRP has a notable role in the immune system as an activator of the classic complement cascade, among other things. Therefore, CRP is important for antimicrobial defence. Prior research has indeed shown that CRP may protect against bacterial infections, 7 and infections have been hypothesized as a cause for schizophrenia. 8 Considering the role of CRP in antimicrobial defence, CRP may thus lower schizophrenia risk by reducing infection risk. However, there is no strong evidence yet to support this hypothesis. Furthermore, CRP may have a biological effect on neurocognitive function that is yet unknown. Since MR studies estimate the lifetime effect of the exposure on the outcome, Lin et al. speculate that other CRP risk variants affect CRP levels in children and that possibly childhood infections attributable to environmental factors increase schizophrenia risk. This hypothesis does not explain the protective effect of CRP observed in the MR analyses, and there are no data to support the hypothesis that the genetic background of CRP levels in children is different from adults.

To get a better understanding of the association between CRP and schizophrenia, it would be of interest to examine the association between CRP and infection risk in well-powered MR studies. Genetic data on infection risk is scarce, but GWAS have been published for specific pathogens. 9 Also, an assessment of the causal association between infections with specific pathogens and schizophrenia may elucidate if, and which, pathogens may contribute to the risk of schizophrenia. Furthermore, thinking outside the field of epidemiology, it is possible that wet lab experiments designed to assess the effect of CRP on neural cells may identify an effect of CRP on the brain. The results of Lin et al.’s study provide further evidence for a causal protective effect of CRP on schizophrenia, and future studies will hopefully shed light on the biological mechanism behind this remarkable observation.

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