Check for updates

Uncovering links between parental inflammatory bowel disease and autism in children

Findings from a nationwide cohort study in Sweden, polygenic risk score analyses in a general population-based cohort in the United Kingdom, Mendelian randomization analyses and genetic correlation (linkage disequilibrium) analyses suggest a link between parental diagnosis of and genetic liability to inflammatory bowel disease and autism in children.

This is a summary of:
Sadik, A. et al. Parental inflammatory bowel disease and autism in children. *Nat. Med.* https://doi.org/10.1038/s41591-022-01845-9 (2022).

Published online:
13 July 2022

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

The question

Inflammatory bowel disease (IBD) and its major subtypes, Crohn's disease and ulcerative colitis, are chronic autoimmune conditions associated with immune system dysregulation, intestinal microbiota alterations, micronutrient malabsorption and anemia[1,2]. Increasing evidence suggests that these features of IBD in parents may be associated with autism spectrum disorder (also known as autism, a neurodevelopmental condition of multifactorial etiology) in their children[3], although evidence on the links between a diagnosis of IBD in a parent and autism in their children is still inconclusive. Understanding these links may provide important insights into the origins of autism. We sought to triangulate evidence[4] by applying four complementary methodological approaches utilizing phenotype and genotype data. Triangulation refers to the application of more than two approaches with complementary strengths and different and unrelated sources of bias, in the context of the same underlying research question, to improve causal inference[4].

The discovery

We first assessed the links between parental diagnoses of IBD, including its subtypes, and autism in children using nationwide population-based registers from Sweden. The large total population sample of over 2 million parent–child pairs ensured sufficient statistical power and low likelihood of selection bias. However, the possibility of confounding, as well as misclassification of exposure (IBD diagnosis) and outcome (autism), in such observational data cannot be ruled out. We then investigated whether, regardless of a formal diagnosis of IBD, maternal genetic liability to IBD and its subtypes, as captured by polygenic risk scores (PRSs), might be associated with autistic traits in children, using individual-level genotype and phenotype data from the population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort in the United Kingdom. Of note, PRS analyses cannot detect or account for the potential influence of pleiotropy (common genetic variants that influence outcome via other independent pathways). To assess the influence of pleiotropic genetic variants, we applied the principles of Mendelian randomization and assessed the causal effects of genetic liability to IBD and its subtypes on autism, using genome-wide association study (GWAS) summary statistics. Using the same GWAS summary statistics, we assessed the genetic correlation between IBD and autism by applying linkage disequilibrium score regression.

In the Swedish population sample, we found evidence suggestive of associations between maternal and paternal diagnoses of IBD, Crohn's disease and ulcerative colitis and autism in the offspring (Fig. 1a). PRS analyses of 7,348 mothers from the ALSPAC birth cohort indicated associations between maternal genetic liability to Crohn's disease and ulcerative colitis and autistic traits in children (Fig. 1c). Mendelian randomization analyses provided further evidence of a causal effect of genetic liability to ulcerative colitis on autism (Fig. 1d). In linkage disequilibrium score regression analysis, there was no evidence to suggest a genetic correlation between IBD and its subtypes and autism (Fig. 1b).

By triangulating evidence across different methodological approaches, our findings suggest a potentially causal link between parental, particularly maternal, diagnosis of and genetic liability to IBD and its subtypes and autism in children.

The interpretation

This study extends previous investigations on the associations between parental diagnoses of IBD and autism in children. We found that not only a diagnosis of IBD but also maternal genetic liability to IBD is linked to autism in children, which suggests that sub-phenotypic manifestations of genetic liability to IBD (such as immunological alterations, micronutrient deficiencies or anemia) might influence the intrauterine environment and affect fetal development.

As for the limitations and generalizability of these findings, this study was conducted with samples and GWAS data from people of predominantly European ancestry. Research with ancestrally diverse samples is necessary to further understand these links. For example, a nationwide birth cohort study in Taiwan has suggested links between paternal IBD and autism in children[5].

Next we will focus on further understanding the potential etiological pathways that underlie the associations identified. We plan to investigate whether our findings reflect effects genetically transmitted from the parents to the children and/or in utero effects, using negative control designs (in this context, investigating the links between paternal versus maternal genetic liability to IBD and autism in children), polygenic transmission disequilibrium analyses and Mendelian randomization. Improved understanding of these mechanisms will help to enhance biological understanding of autism and contribute to improved care and quality of life of people with autism.

Christina Dardani and Dheeraj Rai, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.

EXPERT OPINION

"This study combines four strategies to elucidate the connection between autism and gastrointestinal symptoms. The reported association between parental — mainly maternal — IBD and autism in the offspring is intriguing. Two aspects of this research stand out. First, the implication that maternal genetic factors, possibly involving the immune system, may influence fetal brain development in utero. Second, the elegant demonstration of the value of integrating independent strategies to address one question from different angles." **Jacob Vorstman, The Hospital for Sick Children, Toronto, Ontario, Canada.**

FIGURE

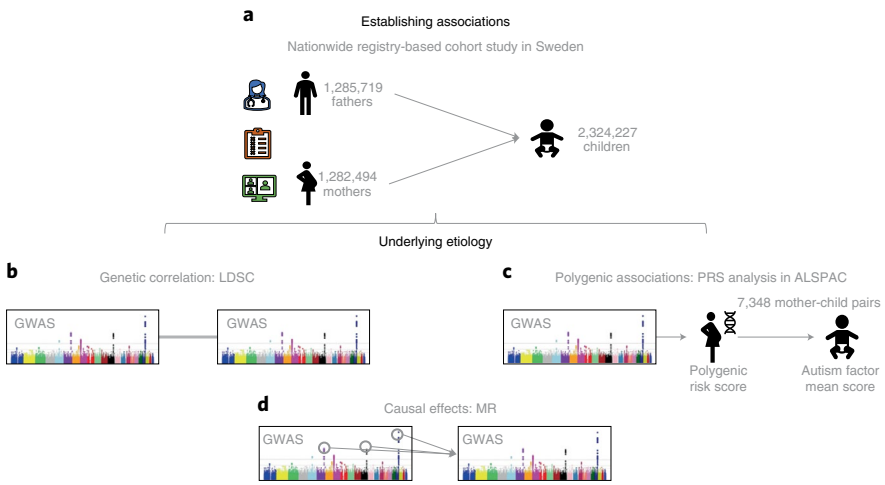

Fig. 1 | Summary of the studies conducted. Four methodological approaches were applied to investigate the potentially causal links between parental IBD and autism in children: population-based analysis (**a**), linkage disequilibrium score regression (LDSC) analysis (**b**), PRS analysis (**c**), and Mendelian randomization (MR) analysis (**d**). © 2022, Sadik, A. et al., CCBY 4.0.

BEHIND THE PAPER

The idea of this project arose when C.D. (then in her final year as PhD student) and I were brainstorming potential projects for an academic fellow (Aws Sadik) joining our research group. We are interested in the role of inflammation in autism and have increasingly used a triangulation framework to strengthen causal inference using epidemiological data. Our multidisciplinary collaborators in Sweden, Denmark, Norway and the United Kingdom enthusiastically supported our plans and helped to design and conduct the project during the COVID-19 pandemic. The use of multiple methods was an excellent training opportunity for Dr. Sadik, who is beginning his career as a clinical academic psychiatrist, and for C.D., whose submitted PhD thesis features this work. I am proud that these skilled future research leaders began the next steps of their careers having contributed to answering an important research question with an article in *Nature Medicine* as lead co-authors. **D.R.**

REFERENCES

1. Roda, G. et al. Crohn's disease. *Nat. Rev. Dis. Prim.* **6**, 1–19 (2020).
A Review on the pathophysiology and etiology of and treatment approaches for Crohn's diseas.

2. Taku, K. et al. Ulcerative colitis (primer). *Nat. Rev. Dis. Prim.* **6**, (2020).
A Review on the pathophysiology and etiology of and treatment approaches for ulcerative colitis.

3. Osokine, I. & Erlebacher, A. Inflammation and autism: from maternal gut to fetal brain. *Trends Mol. Med.* **23**, 1070–1071 (2017).
An article that synthesizes evidence from animal studies on the links between the maternal immune response and gut microbiota and autism in the offspring.

4. Lawlor, D. A., Tilling, K. & Davey Smith, G. Triangulation in aetiological epidemiology. *Int. J. Epidemiol.* **45**, 1866–1886 (2016).
An article that defines triangulation and highlights its importance in epidemiological research.

5. Lee, H. et al. Risk of attention deficit hyperactivity and autism spectrum disorders among the children of parents with autoimmune diseases: A nationwide birth cohort study. *Eur. Child Adolesc. Psychiatry* https://doi.org/10.1007/s00787-021-01860-0 (2021).
A recent study from Taiwan that identifies links between paternal IBD and autism in children.

FROM THE EDITOR

"This work by Sadik, Dardani and colleagues stood out to us because it combines four complementary genetic and epidemiological studies to provide new insights into the link between IBD in the parents and diagnoses of autism spectrum disorder in children, which is a debated topic in the field." **Editorial Team, *Nature Medicine***