The vertical dotted line represents the time when the US Food and Drug Administration (FDA) boxed warning was announced. The y-axis reports percentage changes, calculated as $\Delta t = (n_t - n_1)/n_1$, where $n_t$ is the count in the first month (January 2016), and $n_1$ is the count in month $t$. Data are from IQVIA Rx. Patient counts were projected to reflect the overall US population.

Adjustments implemented with the following steps: (1) We estimated the annual percentage coverages of IQVIA Rx by the total number of opioid prescriptions reported by Centers for Disease Control and Prevention. The coverages for IQVIA were 86.3%, 86.8%, and 90.5% for 2015, 2016, and 2017, respectively. (2) We also calculated the number of patients with coprescriptions from IQVIA Rx. (3) We projected counts from IQVIA Rx to national estimates by dividing by the percentage coverages.

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COMMENT & RESPONSE

Factors Associated With Brain Heterogeneity in Schizophrenia

To the Editor The article by Alnæs et al,1 published in JAMA Psychiatry, addresses a topic of great interest. The study findings revealed higher heterogeneity of cortical thickness and area, cortical and ventricles volumes, and hippocampal subfields volume in individuals with schizophrenia. Moreover, higher polygenic risk score for schizophrenia was associated with thinner frontal and temporal cortices and smaller hippocampal subfields but not with structural brain variability.

After more than 40 years of neuroimaging research in schizophrenia, the issue of variability of brain volumes has been claimed to represent a promising tool to disentangle the biological phenotypic complexity of the disease. However, it is quite surprising to note that none of the well-known major confounders of brain volume abnormalities in schizophrenia (ie, antipsychotic medication and cannabis use) were taken into account in the data analysis in the study by Alnæs at al.1 In particular, a large number of cross-sectional and longitudinal studies showed that gray matter volume decrease in patients with schizophrenia is correlated with higher cumulative antipsychotic dosage over time and demonstrated a different and contrasting moderating role of first-generation vs second-generation antipsychotic medication intake on cortical gray matter changes.2 Thus, it could be pointed out that the variability of brain volumes observed by Alnæs et al may represent a consequence of the impact of antipsychotic medication rather than a primary effect of heterogeneous pathological processes of schizophrenia. A 2019 meta-analysis on the same topic showed that increased cumulative antipsychotic dosage correlated with increased variability in brain structures volumes in patients with schizophrenia.3


The current global picture deriving both from original studies or large database reviews of magnetic resonance imaging findings in individuals with schizophrenia seems to be somewhat unclear and often contradictory. In our opinion, there is the compelling need to set new methodological standards both for developing truly innovative neuroimaging research in schizophrenia and for reliably interpreting magnetic resonance imaging databases. Otherwise, the scientific community will continue to deal with redundant or weak findings with high-potential risk of confusing or dissipating already well-grounded notions about the pathophysiology of the disease.

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In Reply

We thank De Peri and Vita for their thoughtful comments on our recent study of brain structure heterogeneity in patients with schizophrenia.1 They point out some methodological aspects important for interpreting our results and discuss important challenges facing clinical neuroimaging as the field moves toward big data and large-scale integration of cohorts.

De Peri and Vita propose that medication and cannabis use might be important for explaining our observations of higher brain structure heterogeneity among patients with schizophrenia compared with controls. As they point out, we did not investigate the role of these variables, mainly owing to lack of harmonized protocols for clinical phenotyping across samples in our multisite approach. In addition to the putative heterogeneous primary disease processes acting on the brain, we concede that the large brain structure heterogeneity may also result from and interact with secondary factors related to lifestyle, education, work status, physical activity, social network and support, nutrition, smoking, drugs, and medication, all of which are expected to influence brain development and maintenance during the course of the lifespan. All these variables, and indeed most constituents of life itself, are likely to interact with myriad neurogenetic and neurodevelopmental processes and experiences to sculpt the brain into its current form and shape.

As such, we agree with De Peri and Vita that a profound understanding of the sources of brain heterogeneity requires detailed mapping of a range of clinical and lifestyle factors, including use of psychoactive substances. We also concur with the need for new methodological standards to develop innovative and interpretable clinical neuroimaging research. Recent large-scale case–control studies have demonstrated remarkable consistency with respect to the regional patterns of mean differences between groups of patients and controls.2 However, novel approaches have demonstrated that the consistency in brain aberrations between patients is far less impressive,3 and the value of increasing precision in estimating the average patient’s brain aberrations rest on a debatable assumption that the current clinical diagnostic nosology complies with the underlying pathophysiology. As the field now moves into the era of big data and our capabilities of integrating and dissecting complex data sets keep improving, we are starting to uncover a multitude of associations, each with a low effect size, between clinical, genetic, behavioral, demographic, and brain variables.4 Likewise, psychiatric genomics have revealed that mental disorders are complex traits associated with multiple common genetic variants with small effect sizes, with substantial overlap between disorders as well as with normal traits.5

After more than 40 years of clinical neuroimaging, a reasonable conclusion is that detecting a single or a small number of causal brain aberrations in any mental illness is highly unlikely. This is supported by our findings of substantial brain structure dispersion1 and evidence of largely nonoverlapping brain aberrations among individual patients with schizophrenia.3 We would argue that instead of understanding the substantial heterogeneity as noise or confounds hampering the precise delineation of the average patient brain, we need to incorporate models that embrace and parse heterogeneity across diagnostic boundaries and allow for inference at the individual level.6

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Reconsidering the Association Between Infection-Related Health Care Use and Occurrence of Eating Disorders: Chicken or Egg?

To the Editor

Breithaupt and colleagues published epidemiological data from a population-based female Danish cohort and concluded that infections that require hospitalization and treatment with anti-infective agents in childhood are associated with an increased risk for an eating disorder. This risk was greatest in the first 3 months after hospitalization. Such epidemiological cohort studies may contribute important evidence to the identification of risk factors for mental disorders.

However, in this case, we would like to challenge the contiguous interpretation of the data and propose that the putative association may at least in parts be vice versa: individuals who have (or are about to develop) an eating disorder often present with symptoms that may be misclassified as inflammation-associated symptoms in an early stage of the eating disorder. We believe that this hypothesis is supported by several aspects of the study design and data. First and most importantly, inflammatory processes in the cohort patients were not validated, but the exposure to inflammation was defined only based on hospitalization and antibiotics prescription data. Both can only be considered an indirect proxy for actual infections, especially given the well-known overprescription of antibiotics. Therefore, we believe that it would be more precise to talk about putative infections.

Second, the authors specifically performed secondary analyses on gastrointestinal infections. It has recently been emphasized that clinical symptoms of an eating disorder can mimic those of gastrointestinal disorders; this makes it additionally hard to disentangle what was then first. Third, incidence of anorexia nervosa in the Danish cohort was nearly 3 times as high as the incidence of bulimia nervosa, which is surprising as anorexia nervosa generally is rarer than bulimia nervosa. Anorexia nervosa is often ego-syntonic in nature, and mental disorders are associated with (self-)stigmatization; hence, it is often not the patient, but significant others, who consider eating disorder symptoms as alarming. Therefore, patients who are just about to develop anorexia nervosa and their families might rather present with somatic (eg, gastrointestinal symptoms) pre-dominantly caused by rapid weight loss, undernutrition, and inadequate compensatory behaviors.

Taken together, we argue that the data might at least in parts mirror a misclassification of (gastrointestinal) symptoms as being caused by inflammation, while these symptoms evolved in an early eating disorder stage, resulting in an overdiagnosis of infections and an underdiagnosis of eating disorder. This emphasizes the necessity for a consistent psychosomatic approach in medicine that differentiates psychological and somatic contributions and their interactions to symptoms and their underlying processes.

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In Reply

We thank Giel et al for reviewing our work1 and sharing their concerns about possible misclassification of infections as eating disorder symptoms. We fully acknowledge that register-based data cannot confirm nor deny the presence of inflammation/infections, that hospitalizations and prescriptions for antibiotics in the current study are used as a proxy for the presence of inflammation, and unmeasured confounding cannot be eliminated in observational studies. However, routine hospitalization protocols in Denmark include measurement of C-reactive protein levels in blood or urine to confirm infection diagnosis. Furthermore, it is also unlikely that anti-infective agents are prescribed without the presence of infection symptoms, although we cannot determine the type or severity of the infection nor the compliance to the anti-infective treatment.

Giel et al suggest that early clinical symptoms of an eating disorder may mimic those of gastrointestinal (GI) infections. Although some overlap in symptoms can occur between eating disorder and GI infection (eg, loss of appetite, early satiety, weight loss) several lines of evidence argue against their...