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LETTER TO THE EDITOR

Replicating G × E: The Devil and the Details

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Vassos et al[1] "failed to confirm the findings of Ursini et al.[2]" There are a number of critical issues in comparing the 2 studies and in potentially explaining the inconsistencies. Here, we will stress only our concerns about the validity of their documentation of Early Life Complications (ELCs), overlooking other issues related to the broader definition of psychosis of Vassos et al[1] and their inclusion of a sample with only 17 controls. In their largest sample, the UK Biobank (UKB), birth weight was their sole proxy for ELCs. Many ELCs associated with schizophrenia risk do not affect birth weight. In the Cardiff sample, the ELC data came from patient interviews, a questionable source.

But the more incisive issue is the limited survey of ELCs represented in the Lewis-Murray scale. This scale includes only 15 complications, and it does not include many ELCs that we detected in our samples and that may be associated with schizophrenia risk, such as abortion attempt, substance use, severe illnesses during pregnancies, amniotic fluid infection, oligohydramnios, cotwin death, pelvic disproportion, maternal anesthesia, cyanosis, low Apgar score, neonatal severe distress, hyperbilirubinemia, and neonatal brain damage. Ursini et al used the McNeil-Sjostrom Scale, assessing over 100 complications.[2] Further, based on their Supplementary Material, it seems that Vassos et al[1] defined a positive history of ELCs based on the presence of at least one definite or even one "equivocal" ELC. Ursini et al[2] defined a positive history of ELCs based on the presence of only *certain* ELCs, and only those considered potentially harmful for the fetal brain (severity level equal or higher than 4 as assessed with the McNeil-Sjostrom Scale). The supplemantary table represents a detailed comparison of the 2 assessments.

We would not have been able to detect ELCs present in our discovery sample in ~31% of controls and in ~38% of patients using the Lewis-Murray scale. Thus, when we rerun the analysis in our discovery sample based on this scale, the interaction was undetected ($t = 1.048$, $P = .295$). While Vassos et al[1] acknowledge the possibility that the inconsistencies may reflect differences in approaches, the fact is that had both studies used their limited approach, the results would be negative and not inconsistent!

We caution that research aimed at assessing the contribution of the environment to complex disorders needs to be appropriately detailed and precise. Our meta-analysis of 3 case-control samples,[2] each of which showed independent significant interactions of polygenic risk score (PRS) × ELCs, had an overall interaction P value of 10^{-5}, and the meta-analysis P value of 5 case samples of PRS in ELCs+ vs ELCs− cases was 10^{-4}. While these are not weak statistical values, further replication is needed. We anticipate that results from The Norwegian Thematically Organized Psychosis (TOP) Study based on prospective birth registry data and the comprehensive assessments of the McNeil-Sjostrom Scale will be a critical test of replication. The study by Vassos et al[1] is not an adequate effort at replication.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin* online.

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