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BIAS IN THE USE OF POLYGENIC SCORES TO EXPLORe GENETIC NURTURING EFFECTS IN BIOLOGICAL PARENT-OFFSPRING TRIOS

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Background: Research has begun to explore the effects of parental environments or behaviours (nurturing) on offspring outcomes using polygenic scores (PGSs) [1-4]. Findings suggest that the presence of genetic nurturing effects can be detected with PGSs. However, expanding these models by incorporating nurturing via parental phenotypes induces bias due to the PGSs lacking accuracy and only accounting for a fraction of the genetic variance in traits of interest.

Methods: The GS cohort is a family health based genetic epidemiology study with genetic and environmental data from 20,000+ individuals aged 18-98 across Scotland [5]. 2680 biological parent-offspring trios with genotyped data are available. Here, depression, educational attainment and height PGSs are generated for trios using the largest genome-wide association study (GWAS) meta-analyses available for each trait [6-8] and PRSice2 software [9].

Analyses consist of pathway models (Lavaan software [10]) incorporating trio PGSs to explore direct (offspring PGS) and genetic nurturing effects (parental PGS) in depression, educational attainment and height. Genetic nurturing via parental phenotypes (concordant with offspring phenotypes) are also incorporated into the models. To explore sources of bias within these models we conducted simulation analyses of 10,000 trios using combinations of PGS predictive accuracy and accounted variance.

Results: Models with only trio PGSs show highly significant genetic nurturing effects for educational attainment, but not for depression or height.

Inconsistencies were observed in genetic nurturing effects within models incorporating only trio PGSs versus models including parental phenotypes. E.g. Parental PGSs used to explore nurturing effects are non-significant in the former models. However, when additionally fitting parental phenotypes to explore mediated genetic nurturing effects, the parental PGSs (negative) and phenotypes (positive) were highly significant for height.

Simulation analyses of models including parental phenotypes show genetic nurturing effects are negative and significant, whereas, genetic nurturing via parental phenotype effects are positive and significant when PGSs lack accuracy as well as fail to capture the entirety of the trait genetic variance; despite the absence of simulated genetic nurturing effects. These biases are exacerbated as PGS accuracy and accounted variance decreases (e.g. from biased effect size estimates from the GWAS used for the PGS construction).

Discussion: Results suggest PGSs may be useful in detecting genetic nurturing effects in complex traits that are more heritable with relatively greater PGS accuracy and accounted variance, such as schizophrenia and as seen in educational attainment [11].

Exploring genetic nurturing via parental phenotypes can point to targets for interventions. However, here we demonstrate that in the absence of genuine genetic nurturing effects; limitations related to PGS accuracy and accounted trait phenotypic variance, coupled with parental phenotypes capturing larger proportions of trait genetic variance, result in false positive genetic nurturing effects when pathway models additionally incorporate parental phenotypes.

Findings point to the need for methods that can model mediating effects of parental behaviours to explore genetic nurturing effects, whilst also accounting for shared genetic variance between offspring and parental traits adequately.

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INDIVIDUAL DIFFERENCES IN DEPRESSIVE SYMPTOMS AFTER THE EARLY RESPONSES TO THE COVID-19 PANDEMIC IN AUSTRALIA

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Background: By the end of March 2020, Australia had initiated progressive lockdowns, international and national border control measures and social distancing rules in response to the COVID-19 pandemic. The steps taken to control the COVID-19 pandemic represent environmental and externally imposed stressors affecting all members of society, unlike the much more frequently studied self-reported and partially heritable “stressful life events”.

We hypothesised there would be individual differences in the impact of the response to the pandemic on changes in mental health. We hypothesize this impact to be more extreme in individuals with a history of depression than in those without this history and in those with a higher genetic risk for depression than in those with a lower genetic risk.

Methods: We used data from 6,686 genotyped participants with a history of depression from the Australian Genetics of Depression Study (AGDS) and without a history of depression from the QSkin Sun and Health Study (QSkin), matched by age, sex, and month of survey time (age 52, sd= 12.39, range 20 to 83; 64.5% women, survey responses from May to August).

We tested to what extent symptoms of depression and changes in symptoms compared with three months before the pandemic could be explained by a history of depression and genetic risk for depression (PRS computed from variants with p<0.1, the best predictor of history of depression). We used linear regression models and controlled for age, sex, and the first four principal components of genetic ancestry. Since the participants without a history of depression all lived in the state of Queensland and the participants with
a history of depression lived across all states in Australia, we also conducted sensitivity analyses with only Queensland residents (n = 1,588).

**Results:** All participants reported an increase in depressive symptoms in the last two weeks compared with the three months before the pandemic. A history of depression was associated with a larger magnitude of this change for feeling fidgety, fatigued, irritable, lonely, with difficulties concentrating and with negative thoughts. People without a history of depression reported more differences in how sad vs happy they felt. In the analyses conducted in the Queensland participants, the results largely replicated, although no differences were observed in the worsening of feeling fidgety, irritable or having negative thoughts according to the history of depression. Genetic risk for depression did not predict the magnitude of the change in symptoms (some nominal associations were observed but they did not survive multiple testing correction).

**Discussion:** During the first months of restrictions in place to control the COVID-19 pandemic, the participants of this study reported an increase in their depressive symptoms. We observed this change was larger in participants with a history of depression for most symptoms, except for sadness, where participants without a history of depression reported a larger change. Genetic risk for depression did not seem to play a role in the worsening of the symptoms over and above the effect of history of depression. This suggests that in this situation, the role of external stressors was not moderated by a genetic predisposition to the disorder.

**Disclosure:** Nothing to disclose.

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**W36. INTEGRATING FUNCTIONAL NEUROIMAGING AND SERUM PROTEINS CAN IMPROVE THE DIAGNOSTIC ACCURACY OF MAJOR DEPRESSIVE DISORDER: A PILOT STUDY**

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**Background:** Major depressive disorder (MDD) is a disabling disease with high misdiagnosis; however, correct/accurate diagnosis is important for the effective treatment. Abnormal brain functions and peripheral protein levels are often observed in MDD and even considered to be involved in the pathogenesis of MDD. This study explored whether integrating functional neuroimaging and serum proteins can improve the diagnostic accuracy of MDD.

**Methods:** A total of 50 MDD patients and 48 healthy controls (HC) underwent resting-state functional magnetic resonance imaging to examine amplitudes of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo) of spontaneous activity. Blood samples of 30 MDD and 30 HC subjects among them were drawn for detecting serum levels of brain-derived neurotrophic factor (BDNF), cortisol, interferon (IFN)-γ and C-reactive protein (CRP). Correlation analyses was employed to determine the correlation among brain functions, clinical variables, and serum protein levels. Receiver operating characteristic curve analysis and Fisher stepwise discriminant analysis were applied to evaluate the classification powers of single and combined index in discriminating between the MDD and HC subjects.

**Results:** Compared with HC, higher ALFF and lower ReHo in right precentral gyrus (ReHo_rPrCG), higher ReHo in right superior frontal gyrus (ReHo_rSFG), higher cortisol and IFN-γ, and lower BDNF were observed in MDD patients, while CRP was not significantly different. Both IFN-γ levels and ReHo_rSFG were positively correlated with baseline HAMD-17 scores, and CRP levels negatively related to both ReHo_rPrCG and reduction rate of HAMD-17 scores. Integrating BDNF, cortisol, IFN-γ and ReHo_rPrCG displayed a better discrimination ability (AUC=0.924, sensitivity= 87.2%, specificity=87.5%) with a leave-one-out cross validation accuracy of 85.1%.

**Discussion:** These results demonstrated that regional spontaneous activities and serum protein levels changed in MDD patients, and integrated functional neuroimaging and proteins can improve the accuracy of the diagnosis.

**Disclosure:** Nothing to disclose.

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**W37. GENETIC INVESTIGATION OF THE METABOLIC CONTRIBUTION TO ANOREXIA NERVOSA IN AN EHR SETTING**

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**Background:** Anorexia nervosa (AN) is a psychiatric disorder defined by low body weight, accompanied by a fear of weight gain and disturbed body image. Recent genetic studies have identified an association between AN and metabolic conditions, reconceptualizing AN as a metabo-psychiatric disorder. Under the earlier diagnostic criteria of the DSM-IV, in order to receive an AN diagnosis, patients had to present as clinically underweight. Since the implementation of the DSM-5 in 2013, that criteria have expanded to “a significantly low body weight in the context of age, sex, developmental trajectory, and physical health,” but low body weight continues to remain a hallmark of the disease. One hypothesis arising from these observations is that genetically predicted BMI may determine the BMI “set point” of an individual thus influencing their likelihood of receiving an AN diagnosis even in the presence of all other clinical criteria.

**Methods:** For the 66,914 individuals in the Vanderbilt Medical Center Biobank with genotype data available, we calculated polygenic risk scores for AN and BMI using the largest GWAS of AN (N=72,517) and GWAS of BMI (N~700,000) to date. We then performed multivariable regression analyses with a subset of 123 cases and 615 age-matched controls to test the association between AN and BMI polygenic risk scores (PRS) and corresponding phenotypes in our EHR.