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Does environmental confounding mask pleiotropic effects of a multiple sclerosis susceptibility variant on vitamin D in psychosis?

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BACKGROUND: This work addresses the existing and emerging evidence of overlap within the environmental and genetic profiles of multiple sclerosis (MS) and schizophrenia. Aims: To investigate whether a genetic risk factor for MS (rs703842), whose variation is indicative of vitamin D status in the disorder, could also be a determinant of vitamin D status in chronic psychosis patients. Methods: A cohort of 224 chronic psychosis cases was phenotyped and biologically profiled. The relationship between rs703842 and physiological vitamin D status in the blood plasma was assessed by logistic regression. Deficiency was defined as a blood plasma concentration below 10 ng/µl. Potential environmental confounders of the vitamin D status were considered as part of the analysis. Results: We report suggestive evidence of an association with vitamin D status in established psychosis (βstandardized = 0.51, P = 0.04). The logistic model fit significantly benefited from controlling for body mass index, depression and ethnicity (χ² = 91.7; 2 degrees of freedom (df); P = 1.2 × 10⁻²⁰). Conclusions: The results suggest that, in addition to lifestyle changes that accompany the onset of illness, vitamin D dysregulation in psychosis has a genetic component that links into MS. Further, comprehensive studies are needed to evaluate this prospect.

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study is a single-nucleotide polymorphism (rs703842), located on the CYP27B1 gene (chromosome 12). Support for the contribution of the rs703842 locus to MS susceptibility is unequivocal. Furthermore, the encoded gene product, 25-hydroxyvitamin D-1-α-hydroxylase (or 1α(OH)ase), is responsible for converting the storage form of vitamin D, 25-hydroxyvitamin D (or 25(OH)D), into the biologically active vitamin D compound, 1,25(OH)₂D₃. The integral nature of the encoded enzyme to vitamin D biosynthesis would suggest that the true causal variant presumably tagged by rs703842 will influence vitamin D levels (and MS risk) through polymorphic variation in enzymic activation. But formal experiments that test this theory have not been reported. Current follow-up work has instead yielded insights into the consequences of rs703842 variation on gene expression. Expression profiles have been investigated using both diseased (MS) and non-diseased populations, there is a reassuring level of consistency between them. For instance, knock-on effects on metabolic measures and/or substance use habits, current pregnancy, mothers less than 6 months post partum and life-threatening or terminal medical conditions where intensive care is already provided.

### Materials and Methods

The Improving physical health and reducing substance use in psychosis (IMPACT)-randomized controlled trial is a clinical trial designed to evaluate the efficacy of a health intervention program in reducing the burden of heart disease, diabetes and stroke in patients with psychosis. The study is on the International Standard Randomized Controlled Trial Number (ISRCTN) online public registry (trial number: ISRCTN58667926; http://www.controlled-trials.com/ISRCTN58667926; IMPACT+RCT).

#### Recruitment

Recruited patients met the following inclusion criteria: 18–65 years old and an ICD-10 diagnosis of psychotic disorder (F20–29, F31.2, F31.5). Overall, 224 ethnically-representative subjects within The South London and Maudsley NHS Trust gave informed consent before their participation in the study. The exclusion criteria were as follows: a primary diagnosis of learning disability, a co-existing physical health problem that would, in the opinion of the medical investigators, independently have an impact on metabolic measures and/or substance use habits, current pregnancy, mothers less than 6 months post partum and life-threatening or terminal medical conditions where intensive care is already provided.

### Diagnoses

Diagnoses were based on ICD-10 diagnostic criteria and were extracted from the documented diagnosis made by the treating consultant psychiatrist in the clinical notes at the time of recruitment.

### Blood extraction and biological assays

Consented patients provided blood samples for DNA analysis and metabolic profiling. DNA was extracted using the phenol–chloroform method. Genotypic status at rs703842 was determined using a custom-designed Taqman assay. Design of the assay used an 800-base pair region downloaded from the ENSEMBL website (http://www.ensembl.org). The sequence incorporated the regions flanking the rs703842 locus. The sequence was subsequently uploaded to the assay design feature in the Applied Biosystems website (https://www5.appliedbiosystems.com/tools/cadt/). Reaction products were run on a 7900HT sequence detection system (Applied Biosystems, Paisley, UK).

All 224 subjects yielded unambiguous genotyping results (100% call rate). The distribution of genotypes at rs703842 was in Hardy–Weinberg equilibrium (P = 0.67). G (minor) allele frequency is consistent (0.33) across YRI and CEU Hapmap populations. Vitamin D levels (serum 25(OH)D) were determined with a chemiluminescence immunoassay (DiaSorin, S.P.A., Saluggia, Vercelli, Italy).

### Vitamin D status

In the analyses that follow, individuals with 25(OH)D levels below 10 ng/ml (< 25 nmol/l) were classified as vitamin D deficient. Individuals above this threshold were considered ‘non-deficient’. This stringent interpretation of the literature takes account of the fact that the median vitamin D levels in schizophrenia are much lower than those found in the general population. For example, our own analyses reveal that the median vitamin D level in the ‘non-deficiency’ subgroup only reaches 16.6 ng/ml (see Results; Table 1). Thus, a threshold of 10 ng/ml optimizes the distribution of cases between comparison groups. Moreover, the 10-ng/ml threshold is physiologically relevant, as calcium absorption is known to decline rapidly below this serum concentration.

#### Covariates

Information on the following factors was collected: age at sampling, season of sampling, gender and self-reported ethnicity. Body mass index (BMI) was calculated using height and weight data collected at the time of recruitment. Total scores were calculated for International Physical Activity Questionnaire and Montgomery Asberg Depression Rating Scale. Information on medication (chlorpromazine equivalence) was also collected. Conversion of antipsychotic medication dose to chlorpromazine equivalence values was performed according to the established protocols. Percentage of the maximum daily chlorpromazine equivalent dose (the maximum daily dose of chlorpromazine) is equivalent to 1000 mg daily, as defined by the British National Formulary-licenced maximum dose.
On the basis of a log-additive genetic model, a prevalence of vitamin D deficiency varies across the study cohort. The ratio of males to females in the analyzed cohort (n = 224) is almost 2:1. White British Caucasians represent the largest ethnic group, followed by individuals of African heritage. The remainder are of mixed White Caucasian/African heritage. The median age of the cohort is 45 (range in full sample: 23–66). As there were no significant differences in age or gender, the deficient and non-deficient groups are reasonably balanced in terms of demography (Table 2). Apart from the anticipated differences in plasma levels of 25(OH)D between deficient and non-deficient groups, patients with clinical vitamin D deficiency also tended to have a higher BMI, and score higher on the depressive symptom scale, compared with those who were non-deficient (Table 2). The direction of these differences is conventional in the sense that increasing depression symptoms, BMI and African heritage all correlate negatively with vitamin D at European geographical latitudes. Although these covariates have small effects, their aggregate effect on the vitamin D status in the logistic model is substantial (likelihood ratio statistics: χ² = 91.7 (2 degrees of freedom (df)); P = 1.2 × 10⁻¹⁹). Differences between the comparison groups in terms of age, medication, season of sampling, gender and ethnic makeup were not statistically meaningful (Table 2).

Table 2 provides a combined demographic, environmental and genetic overview of the study cohort. The diagnostic composition of the cohort varies with respect to the vitamin D status, and this is true regardless of whether the diagnosis are kept split or grouped according to affective/non-affective status (P ≥ 0.15). Table 2 provides a combined demographic, environmental and genetic overview of the study cohort. The ratio of males to females in the analyzed cohort (n = 224) is almost 2:1. White British Caucasians represent the largest ethnic group, followed by individuals of African heritage. The remainder are of mixed White Caucasian/African heritage. The median age of the cohort is 45 (range in full sample: 23–66). As there were no significant differences in age or gender, the deficient and non-deficient groups are reasonably balanced in terms of demography (Table 2). Apart from the anticipated differences in plasma levels of 25(OH)D between deficient and non-deficient groups, patients with clinical vitamin D deficiency also tended to have a higher BMI, and score higher on the depressive symptom scale, compared with those who were non-deficient (Table 2). The direction of these differences is conventional in the sense that increasing depression symptoms, BMI and African heritage all correlate negatively with vitamin D at European geographical latitudes. Although these covariates have small effects, their aggregate effect on the vitamin D status in the logistic model is substantial (likelihood ratio statistics: χ² = 91.7 (2 degrees of freedom (df)); P = 1.2 × 10⁻¹⁹). Differences between the comparison groups in terms of age, medication, season of sampling, gender and ethnic makeup were not statistically meaningful (Table 2).
research. A recent meta-analysis of vitamin D studies in schizophrenia revealed the genetic association to be resilient to the confounding of ethnicity, BMI and symptoms of depression (likelihood ratio statistics for the combined terms in the logistic model: $\chi^2 = 91.7 \ (2 df)$). Our subsequent analyses revealed the genetic association to be resilient to the addition of the remaining (unchosen) covariates in Table 2, namely International Physical Activity Questionnaire (outdoor physical activity), medication use and season of blood draw. This is to say that the genetic $P$ value remains significant at the $P < 0.05$ level when these covariates are added, individually or in combination, to the logistic model. The genetic effect can therefore be said to be additionally free of these potential confounders. It is important to note that such adjustment for environmental confounding is routine in vitamin D genetic research, e.g., Ahn et al.,59 Hiraki et al.60 and Ahn et al.41 but is rare in schizophrenia research. A recent meta-analysis of vitamin D studies in schizophrenia helps to highlight this pitfall for the field.42 For example, the research question posed here would be intractable in most other studies, the nature of the association found in psychosis research will inevitably involve using genetics to test the credentials of vitamin D as an underlying risk factor. It is not possible to explore this within the current study context, due to the absence of controls. The key objective of such studies will be to leverage as much of the available vitamin D genetic architecture as possible using a mendelian randomization framework.

The $P$ value for the genetic association is marginal and the corresponding explained variance only small ($P = 0.04$, Pseudo $R^2 = 0.049$); therefore, the failure to find methodologically compatible data sets for validation purposes is a limitation. Another issue is the failure to model all physiological confounders relevant to the research question posed. In particular, three hormones, calcitonin, parathyroid hormone (PTH) and prolactin, are known to stimulate increased levels of the bioactive $1,25$(OH)$_2$D molecule through the altered expression of the CYP27B1 gene (known also as 1αOHase).53,54 Drugs that affect the hypothalamic dopamine system and/or pituitary dopamine receptors can enhance prolactin levels. Antipsychotic drugs fit into this category and are associated with a 2–10-fold increase in prolactin levels.55 The question of whether calcitonin or parathyroid is regulating 1α(OH)ase gene expression at any given time-point depends on the physiological status of calcium. For example, hypocalcemia causes PTH to be elevated, and this initiates the renal synthesis of $1,24$(OH)$_2$D. However, at normal calcium levels PTH fails to stimulate the expression of 1α(OH)ase and is substituted in this role by calcitonin. Thus, the calcium status could potentially also be taken into account in conjunction with the three hormones. One final consideration relates to the assumption in our analysis that depression symptoms lead to low vitamin D, for it is also possible that muscular fatigue (and other symptoms associated with extreme deficiency) could provoke the onset of depression symptoms. We undertook post hoc analysis to understand the extent to which the main finding of the study is sensitive to uncertainty about this issue. The final logistic model was rerun, this time excluding Montgomery Asberg Depression Rating Scale scores.

We established that in the absence of depression symptoms the genetic association diminishes only slightly (odds ratio $= 1.62 \ (0.98–2.68) \ P = 0.061$; pseudo $R^2 = 0.053$); clearly not by enough to undermine our original diagnosis of a suggestive association (see Results). Thus, our preliminary findings suggest that the MS risk locus rs703842 may explain some of the variability of vitamin D status in established psychosis. The nature of the association found is consistent with the view that genetic variants linked with the vitamin D status can become obfuscated by confounding environmental factors; however, the conclusions reached by this study will require further validation in independent data sets.

**CONTRIBUTIONS**

FG, RMM, PG-S, SS and OH designed and supervised the collection of IMPACT study data. COI conceived the genetic study, supervised the genotyping/analysis, interpreted the results and wrote the manuscript. JL and PG-S collected and derived data on the confounders used. AA and LSS performed the genetic assays and analysis and co-wrote an earlier draft of the manuscript. FG, RMM, SS, PG-S, JL and OH critically reviewed the manuscript.

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**Abbreviations:** Adj, adjusted; BMI, body mass index; CI, confidence interval; CO Iyegbe et al., AA and LSS performed the genetic assays and analysis and co-wrote an earlier draft of the manuscript. FG, RMM, SS, PG-S, JL and OH critically reviewed the manuscript.

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**Table 3.** The effect of covariate control on the rs703842 regression coefficient

| Covariate model (based on $N = 224$) | Logistic regression | Genetic P value |
|--------------------------------------|---------------------|----------------|
| 1. Null (unadjusted)                 | 0.20 (−0.19–0.60)   | 0.31           |
| 2. Adj. age                          | 0.20 (−0.19–0.60)   | 0.30           |
| 3. Adj. gender                       | 0.20 (−0.21–0.58)   | 0.36           |
| 4. Adj. ethnicity                    | 0.40 (0.07–0.87)    | 0.09           |
| 5. Adj. BMI                          | 0.27 (−0.13–0.68)   | 0.19           |
| 6. Adj. depression symptoms          | 0.21 (−0.18–0.61)   | 0.29           |
| 7. Full adjusted                     | 0.51 (0.02–1.02)    | 0.04           |

The effect of covariate control on the rs703842 regression coefficient. Standardized coefficient (95% CI) is reported at the clinical stages of illness.18

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References:

1. Ahn et al.,59 Hiraki et al.60 and Ahn et al.41 but is rare in schizophrenia research. A recent meta-analysis of vitamin D studies in schizophrenia helps to highlight this pitfall for the field.42

2. The variance attributable to rs703842 (0.049) represents 62% of the total variance explained in the final model (Pseudo $R^2 = 0.080$). See Supplementary Table S1 for full logistic regression data.

3. The relationship between rs703842 genotype and vitamin D status, under the logistic model: $\chi^2 = 91.7 \ (2 df)$ $P = 1.2 \times 10^{-10}$.

4. The directional concordance between SNPs jointly associated with both traits does not reflect the directional relationship anticipated from prior observational work.51,52

5. Independent validation of our findings would suggest that shared genetics may help to explain convergence between the environmental risk profiles of psychosis and MS, based on season, geography and migration.6,14 Sustaining progress in this niche area of psychosis research will inevitably involve using genetics to test the credentials of vitamin D as an underlying risk factor. It is not possible to explore this within the current study context, due to the absence of controls. The key objective of such studies will be to leverage as much of the available vitamin D genetic architecture as possible using a mendelian randomization framework.

6. The $P$ value for the genetic association is marginal and the corresponding explained variance only small ($P = 0.04$, Pseudo $R^2 = 0.049$); therefore, the failure to find methodologically compatible data sets for validation purposes is a limitation.

7. Another issue is the failure to model all physiological confounders relevant to the research question posed. In particular, three hormones, calcitonin, parathyroid hormone (PTH) and prolactin, are known to stimulate increased levels of the bioactive $1,25$(OH)$_2$D molecule through the altered expression of the CYP27B1 gene (known also as 1αOHase).53,54

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9. We established that in the absence of depression symptoms the genetic association diminishes only slightly (odds ratio $= 1.62 \ (0.98–2.68) \ P = 0.061$; pseudo $R^2 = 0.053$); clearly not by enough to undermine our original diagnosis of a suggestive association (see Results).

10. Thus, our preliminary findings suggest that the MS risk locus rs703842 may explain some of the variability of vitamin D status in established psychosis. The nature of the association found is consistent with the view that genetic variants linked with the vitamin D status can become obfuscated by confounding environmental factors; however, the conclusions reached by this study will require further validation in independent data sets.

11. FG, RMM, PG-S, SS and OH designed and supervised the collection of IMPACT study data. COI conceived the genetic study, supervised the genotyping/analysis, interpreted the results and wrote the manuscript. JL and PG-S collected and derived data on the confounders used. AA and LSS performed the genetic assays and analysis and co-wrote an earlier draft of the manuscript. FG, RMM, SS, PG-S, JL and OH critically reviewed the manuscript.

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COMPETING INTERESTS
Dr Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organized by Astra-Zeneca, Autifony, BMS, Eli Lilly, Janssen, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion and Roche. Neither Dr Howes nor his family have been employed by or have holdings/a financial stake in any biomedical company.

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Supplementary Information accompanies the paper on the npj *Schizophrenia* website (http://www.nature.com/npjschz)