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Exploring polygenic-environment and residual-environment interactions for depressive symptoms within the UK Biobank

Alexandra C. Gillett^{1,2}  | Bradley S. Jermy^{1,2}  | Sang Hong Lee^{3,4}  |
Oliver Pain^{1,2}  | David M. Howard^{1,5}  | Saskia P. Hagenaars¹  |
Ken B. Hanscombe¹  | Jonathan R. I. Coleman^{1,2}  | Cathryn M. Lewis^{1,2,6} 

¹Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

²NIHR Maudsley Biomedical Research Centre, South London and Maudsley NHS Trust, London, UK

³Australian Centre for Precision Health, University of South Australia, SA, Adelaide, Australia

⁴UniSA Allied Health and Human Performance, University of South Australia, Adelaide, SA, Australia

⁵Division of Psychiatry, Royal Edinburgh Hospital, University of Edinburgh, Edinburgh, UK

⁶Department of Medical and Molecular Genetics, Faculty of Life Sciences and Medicine, King's College London, London, UK

Correspondence

Alexandra Gillett, Social, Genetic and Developmental Psychiatry Centre Institute of Psychiatry, Psychology and Neuroscience, PO80, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.
Email: alexandra.a.gillett@kcl.ac.uk

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Abstract

Substantial advances have been made in identifying genetic contributions to depression, but little is known about how the effect of genes can be modulated by the environment, creating a gene–environment interaction. Using multivariate reaction norm models (MRNMs) within the UK Biobank ($N = 61294\text{--}91644$), we investigate whether the polygenic and residual variance components of depressive symptoms are modulated by 17 a priori selected covariate traits—12 environmental variables and 5 biomarkers. MRNMs, a mixed-effects modelling approach, provide unbiased polygenic–covariate interaction estimates for a quantitative trait by controlling for outcome–covariate correlations and residual–covariate interactions. A continuous depressive symptom variable was the outcome in 17 MRNMs—one for each covariate trait. Each MRNM had a fixed-effects model (fixed effects included the covariate trait, demographic variables, and principal components) and a random effects model (where polygenic–covariate and residual–covariate interactions are modelled). Of the 17 selected covariates, 11 significantly modulate deviations in depressive symptoms through the modelled interactions, but no single interaction explains a large proportion of phenotypic variation. Results are dominated by residual–covariate interactions, suggesting that covariate traits (including neuroticism, childhood trauma, and BMI) typically interact with unmodelled variables, rather than a genome-wide polygenic component,

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to influence depressive symptoms. Only average sleep duration has a polygenic–covariate interaction explaining a demonstrably nonzero proportion of the variability in depressive symptoms. This effect is small, accounting for only 1.22% (95% confidence interval: [0.54, 1.89]) of variation. The presence of an interaction highlights a specific focus for intervention, but the negative results here indicate a limited contribution from polygenic–environment interactions.

KEYWORDS

genotype–environment interaction, depressive symptoms, multivariate reaction norm model, residual–environment interaction

1 | INTRODUCTION

Major depressive disorder (MDD) is a common and debilitating mental disorder that is the second leading cause of years lived with disability worldwide (Vos et al., 2020). It has a lifetime prevalence of 17.8% in global populations (Vos et al., 2016). The core symptoms of depression are persistent low mood and anhedonia, with other diagnostic signs and symptoms including changes in cognition, appetite, or sleep, and feelings of fatigue and worthlessness. The heritability of MDD is lower than many other psychiatric disorders, estimated at between 30% and 40%, with higher values for severe cases (Kendall et al., 2021). This lower heritability suggests that a substantial proportion of liability to depression is due to environmental risk factors.

Genome-wide association studies (GWAS) have made progress in identifying variants associated with MDD, with 178 loci now identified and single nucleotide polymorphism (SNP)-heritability estimates ranging between 5.5% and 11.2%, depending on the depression definition used (Levey et al., 2021). The difference between pedigree and SNP-heritability estimates may indicate a role for additional sources of genetic-related variation, such as gene–environment (G–E) interactions. Identifying G–E interactions would provide insight into the biological mechanisms of depression, improve the accuracy of heritability estimates, and path the way to individualised preventative healthcare (Hunter, 2005). Genetic studies have used a wide range of definitions of MDD, from diagnosis in clinical studies, to self-report of a diagnosis with depression, to reported presence of depressive symptoms. These criteria show a strong common genetic overlap, with pairwise genetic correlations of at least 0.7 for most MDD definitions (Jermy et al., 2020; Levey et al., 2021). We have previously shown that a continuous measure of depression, based on factor analysis of questionnaire responses in the

general population effectively captures the polygenic component of depression (Jermy et al., 2020).

As noted above, a substantial component of the liability to depression arises from nongenetic factors. Stressful life events and exposure to trauma provide the strongest risks, with smoking, obesity, body mass index (BMI) and exercise also associated with depression (Coleman et al., 2020; Gianfredi, et al., 2020; Luppino et al., 2010). The interaction between these risk factors and the genetic predisposition to depression has been largely uninvestigated. Performing studies to disentangle the genetic and environmental contributions to complex traits such as depression is challenging. The environmental variables potentially have a genetic component, and these traits may also be genetically correlated with depression (Wray et al., 2018). Causation might be multidirectional, with depression risk increased as a consequence of a risk factor, or a risk factor being observed because a healthy lifestyle is more challenging to maintain during a depressive episode. Further, depression may influence the reporting of risk factor status, for example, retrospective reporting of trauma differs from prospective reporting (Baldwin et al., 2019). These complexities make testing for G–E interactions challenging, as highlighted by studies investigating an interaction between polygenic risk scores (PRSs) for depression and reported childhood trauma. Early investigations identified an interaction (Mullins et al., 2016; Peyrot et al., 2014), but a larger study in the Psychiatric Genomics Consortium (PGC) found no evidence for departure from additive contribution to risk of depression (Peyrot et al., 2018).

In this paper, we model a continuous measure of depressive symptoms and explore genome-wide genotype–covariate (G–C) and residual–covariate (R–C) interactions for 17 covariate traits, including environmental risk factors. A significant G–C interaction means that the additive genetic component for symptoms of

depression (G), which has been estimated internal to the data, varies with respect to a covariate trait (C) (Xuan et al., 2020). This can be thought of as a polygenic-covariate interaction (Dahl et al., 2020). A significant R-C interaction means that the variation observed in symptoms of depression is modulated by the covariate trait, but in a manner not specified by the model; hence it is a residual interaction. We analyse 17 measured traits in UK Biobank (UKB) including BMI and related body composition traits, exercise measures, smoking, neuroticism, sleep duration, childhood trauma, Townsend deprivation index (TDI) and biomarkers. The interactions are modelled in a reaction norm (RN) analysis using *mtg2* software (Lee & van der Werf, 2016) which tests whether individual differences in the genetic and residual effects are modulated by another risk factor. The multivariate reaction norm model (MRNM) uses covariance functions to model interactions between high-dimensional sets of genetic variants and an environmental covariate while controlling for trait correlations. It is useful when it is not feasible to investigate interactions variant by variant due to dimensionality (Jarquín et al., 2014), and has higher power compared to single variant interaction tests for polygenic traits (Dahl et al., 2020). This statistical framework allows us to robustly investigate the role of these factors in modulating the polygenic, and residual, effects on depression symptoms.

2 | METHODS

2.1 | UK Biobank (UKB)

Analysis was performed using the UKB, a health study of over 500,000 UK participants who were recruited in mid-life (40–69 years old) between 2006 and 2010 (Sudlow et al., 2015). Detailed information on health and lifestyle are available from self-report at baseline, when biological samples for genetic analysis and biomarker testing were also taken. A follow-up Mental Health Questionnaire (MHQ), completed online by 157,339 participants in 2016, collected information on a wide range of lifetime psychiatric diagnoses and current depression symptoms (Davis et al., 2020).

2.2 | Outcome trait

An outcome trait measuring depression symptoms was derived from the MHQ assessment of depressive symptoms over the last 2 weeks, which are drawn from the PHQ-9 and correspond to the Diagnostic and Statistical Manual of

Mental Disorders criteria for MDD. This trait, which we call *depSympt*, was constructed via a hierarchical model by Jermy et al. (2020) using MHQ depression-related symptom data. It summarises symptoms related to mood, anxiety, subjective well-being, psychomotor cognitive factors, and neuro-vegetative factors. A summary of *depSympt* and its construction can be found in the Supporting Information (Supplementary Materials (SM) section 1.1), with full information given in Jermy et al. (2020).

The SNP-based heritability of *depSympt* is 8.5% (95% confidence interval [CI]: [7.7, 9.2]), which is comparable to the SNP-based heritability of depression, where estimates range from 5.5% to 11.2% depending on the definition of depression used (Levey et al., 2021). Additionally, *depSympt* is strongly associated with lifetime MDD status, defined using the Composite International Diagnostic Interview Short Form, where it explains 11% of the variation in liability to MDD (Jermy et al., 2020). On average, prevalent MDD cases have higher *depSympt* values compared to controls, showing that ever having had depression is associated with increased current depressive symptoms compared to never having had depression (Figure S2). Permutation tests (used as *depSympt* is nonnormal) showed highly significant differences between both mean and median *depSympt* values in MDD cases and controls ($p < 1E - 315$).

2.3 | Covariate traits

Seventeen environmental and biomarker covariate traits were selected, based on previous associations with MDD phenotypes and availability in UKB. Body composition was represented by BMI, waist-to-hip ratio, and waist circumference. Exercise variables used the metabolic equivalent task (MET) scores based on the International Physical Activity Questionnaire, which assesses the frequency, intensity, and duration of exercise in three categories: walking, moderate exercise, and vigorous exercise. Four variables of summed MET minutes per week were analysed: all activities (MET total), and the separate categories of walking (MET walk), moderate exercise (MET mod), and vigorous exercise (MET vig). Other covariate traits from the baseline assessment were TDI, average sleep duration (sleep), neuroticism score, and pack years of smoking (smoking). Five biomarkers of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, C-reactive protein (CRP) and vitamin D were analysed. All biomarkers except for LDL were log-transformed (see SM section 1.2). From the MHQ, a continuous variable summarising reported childhood trauma was analysed (Pitharouli et al., 2021). All covariates were from the

baseline UKB assessment, except reported childhood trauma, which was collected in the MHQ.

2.4 | Genetic data

Autosomal genotype data underwent a centralised quality control procedure described by Bycroft et al. (2018) before imputation. We then selected HapMap3 SNPs from the imputed UKB genetic data (Ni et al., 2019; Xuan et al., 2020), and further removed variants with a minor allele frequency <0.01, an information score (used to index the quality of genotype imputation) <0.7 and completeness <95% (Coleman et al., 2016).

Quality control for participants followed procedures detailed by Coleman et al. (2020). Briefly, analysis was limited to unrelated individuals of European ancestry who had completed the online MHQ, had a call rate of >98% for genotyped SNPs and for whom genetic sex-matched self-reported sex. Additionally, individuals were removed for unusual levels of missingness or heterozygosity where recommended by the UKB core analysis team, or if they had withdrawn consent for analysis. After quality control, 126,522 participants were retained. This reduced to 119,692 after omitting individuals missing the outcome trait, depSympt (Jermy et al., 2020). From the 1,118,287 SNPs retained, genetic relationship matrices (GRMs) were created using Plink version 1.9 for use in the interaction models (Chang et al., 2015; Yang et al., 2011).

2.5 | Statistical analysis

Interaction analysis was performed using a mixed-effects model called the MRNM (Ni et al., 2019), which includes two interaction types (polygenic and residual) as random effects and adjusts for genetic and residual correlations between the outcome and covariate traits. In the sections that follow we provide a broad overview of the MRNM and detail its application in this study, with Figure 1 summarising our approach within the UKB. A detailed description of the MRNM is provided in SM section 1.3.

2.6 | Model overview

A RN is a genotype-specific function describing the relationship between an outcome and a covariate trait. Interactions are indicated by nonparallel RNs which produce a relationship between the variability of outcome and the covariate within a population. The MRNM looks for evidence of interactions by estimating the trend in outcome variability across the covariate trait

and decomposing this into an additive genetic variance component and a residual variance component using estimated genetic similarities from genome-wide SNP data within a random-effects model (Jarquín et al., 2014; Ni et al., 2019; Schaeffer, 2004). Genetic similarity here is defined using the GRM. We refer to the additive genetic variance component as the polygenic component.

The MRNM is an extension of bivariate genome-wide genomic restricted maximum likelihood (bivariate-GREML) (Lee et al., 2012; Yang et al., 2011) that focuses on estimating a genome-wide G–E interaction. Bivariate-GREML estimates the genome-wide SNP heritability for two traits and their genetic correlation via a bivariate mixed model that includes polygenic random effects for each trait. The MRNM extends this such that the SNP heritability of one trait, which we call the outcome trait, can vary with respect to the second trait, which we call the covariate trait. The MRNM can therefore estimate the proportion of variability in outcome attributable to a genome-wide G–C interaction, while controlling for genetic correlation between the outcome and covariate traits.

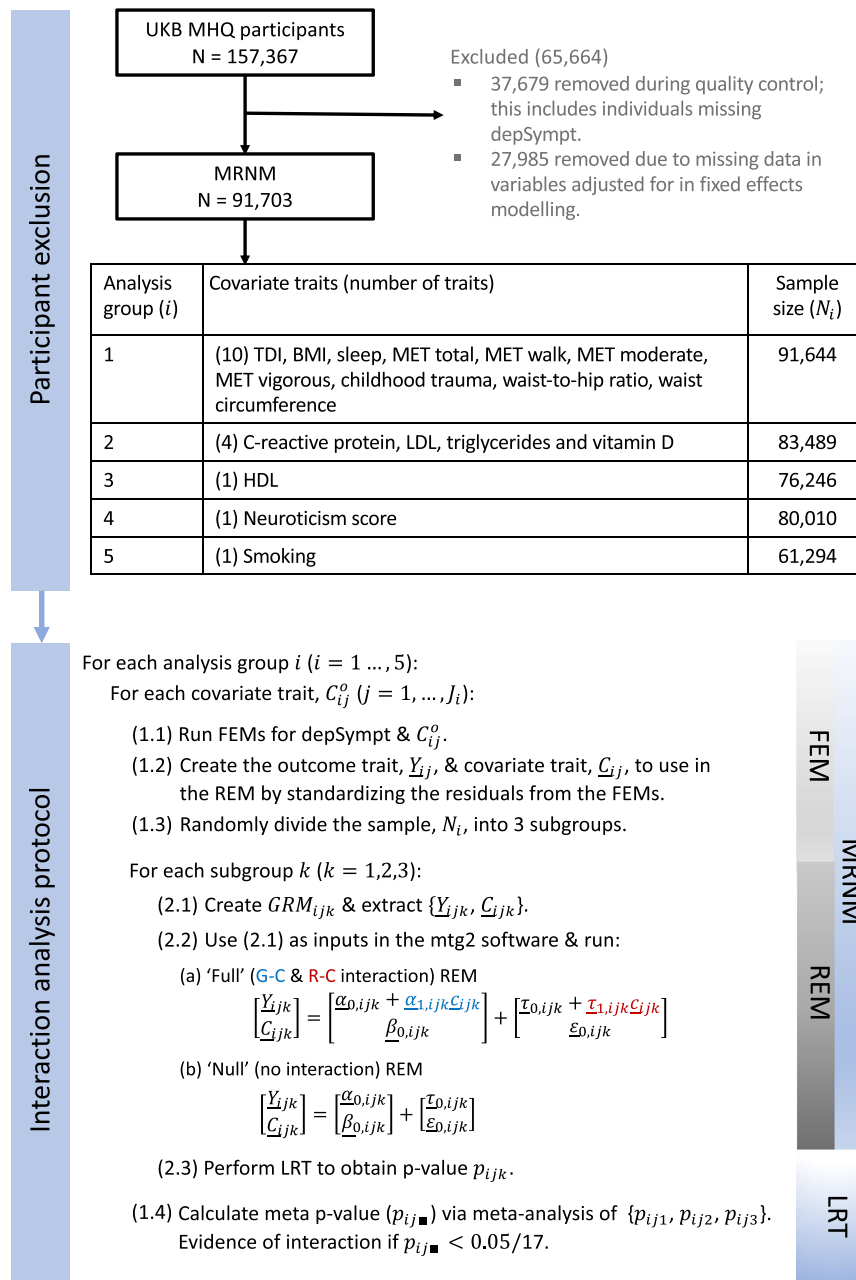
This bivariate mixed model approach (for investigating the modulation of the polygenic effects on the outcome trait from a covariate trait) is the simplest MRNM. In theory, the MRNM can incorporate multiple covariate traits, and so multiple G–C interactions, for the outcome trait via a multivariate mixed model. However, the computational burden increases with the number of covariates included (see Ni et al., 2019) and for this study, we only consider the bivariate case.

The MRNM used here has two modelling stages. First, in the fixed effects model, linear regression is used to estimate the expected value of a trait using a set of variables (fixed effects) selected for inclusion (e.g., genotype batch to adjust for possible confounding). This is done for both the outcome trait (here, depSympt) and the covariate traits (see SM section 1.2). Second, using a bivariate random effects model, the standardised residual variation in outcome (Y) and the covariate trait (C), not explained by their respective fixed effects models, is partitioned into polygenic and residual random components. For the outcome trait, these polygenic and residual random effects can be a function of C , allowing heterogeneity of the polygenic and residual variance components for Y across C , thereby incorporating G–C and R–C interactions into the model. This random effects model can be written as follows:

$$\begin{bmatrix} Y_i | C_i = c_i \\ C_i \end{bmatrix} = \begin{bmatrix} \alpha_{0i} + \alpha_{1i}c_i \\ \beta_{0i} \end{bmatrix} + \begin{bmatrix} \tau_{0i} + \tau_{1i}c_i \\ \varepsilon_{0i} \end{bmatrix} \quad (1)$$

where for an individual i : (1) α_{0i} (β_{0i}) is a random effect defining the random polygenic intercept for Y_i (C_i), (2) τ_{0i} (ε_{0i}) is a random effect defining the random

FIGURE 1 Methods flowchart for UK Biobank: participant exclusion, analysis groupings and scheme for interaction analysis. FEM, fixed effects model; LRT, likelihood ratio test; REM, random effects model; G-C, genotype-covariate; MRNM, multivariate reaction norm model; R-C, residual-covariate; N_{ik} , sample size for analysis group i , subgroup k ; C_{ij} (C_{ijk}), vector of length N_i (N_{ijk}) containing the j th standardised residual covariate trait from analysis group i (and subgroup k); Y_{ij} (Y_{ijk}), vector of length N_i (N_{ijk}) containing the standardised residual outcome trait for interaction analysis with C_{ij} (C_{ijk}); $\alpha_{0,ijk}$ ($\beta_{0,ijk}$), random effects vector of length N_{ik} representing the contribution to the outcome (covariate) trait for each individual from the homogeneous polygenic component; $\tau_{0,ijk}$ ($\epsilon_{0,ijk}$), random effects vector of length N_{ik} representing the contribution to the outcome (covariate) trait for each individual from the homogeneous residual component; $\alpha_{1,ijk}$ ($\tau_{1,ijk}$), random effects vector of length N_{ik} representing the contribution to the outcome trait for each individual due to G-C (R-C) interaction



residual intercept for Y_i (C_i), (3) α_{1i} is a random effect capturing the interaction of the polygenic component for Y_i with C_i (the G-C interaction/polygenic-covariate interaction), and 4. τ_{1i} is a random effect capturing the trend in the phenotypic variability of Y_i across C_i that is not explained by the measured genetic variables (the R-C interaction, which can be thought of as covariate-specific noise). These random effects are random variables, characterised by a population multivariate normal distribution with mean zero, and a covariance matrix requiring estimation. The MRNM is therefore parameterised by estimating the covariance matrix between the random effects, which represent sources of (co)variation for Y and C within the population (see

SM equation 5). Genetic (residual) correlation between the two traits is included in the model by estimating the covariance parameters between the genetic (residual) random effects for Y and for C . This is an advantage of the MRNM because not accounting for trait correlations can lead to inflation in the strength of the interactions (Ni et al., 2019). Unlike bivariate-GREML, where estimation of the shared additive genetic variation between two traits is the primary motivation, here it is the G-C (R-C) interaction that is of interest, with correlations viewed as parameters to be controlled for. Within the MRNM, the effect of a G-C (R-C) interaction on the outcome trait is measured by the proportion of variability in outcome

explained by the G–C (R–C) interaction. Using Equation (1), the marginalised variance for Y_i is:

$$\text{Var}[Y_i] = \sigma_{\alpha_0}^2 + \sigma_{\alpha_1}^2 + \sigma_{\tau_0}^2 + \sigma_{\tau_1}^2 = 1 \quad (2)$$

for all individuals in the population, where the proportion of variability in outcome is attributable to four components: the polygenic components that are invariant to C , $\sigma_{\alpha_0}^2$, and that vary across C , $\sigma_{\alpha_1}^2$, then the residual components that are homogeneous across C , $\sigma_{\tau_0}^2$ and that vary across C , $\sigma_{\tau_1}^2$. When significant interactions are identified (see Section 2.8), $\sigma_{\alpha_1}^2$ and $\sigma_{\tau_1}^2$ are used as measures of the importance of the G–C and R–C interaction effects on the outcome trait within the study population.

2.7 | Phenotype adjustment

Interactions are assessed for each covariate trait in turn. In the first modelling stage of the MRNM, we adjust depSympt and the covariate trait for fixed effects, using a linear model. Fixed effects included demographic variables (such as year of birth, age, sex, and assessment centre) and population structure using the first 15 principal components. We also adjust for stressful and traumatic events in adulthood, due to their likely impact on depressive symptoms. SM section 1.2 details the complete list of fixed effects variables used for each depSympt-covariate trait combination.

Except for principal components, continuous fixed effects variables were allowed to have a nonlinear relationship with depSympt and the covariate traits by using fractional polynomials (FPs) (Royston & Altman, 1994). We used the `mfp` package (Benner & Ambler, 2015) within a generalised linear model `stats::glm` (R Core Team, 2020).

After fixed effects adjustment, all traits are standardised to allow comparison of their relative importance in explaining the variability in outcome across interaction models. For depSympt, we can recover the size of an interaction effect on the original, rather than residualised, scale and use the MRNMs to provide an estimate of the proportion of variability in depSympt explained by G–C and R–C interactions (see SM section 1.4.4).

Covariate traits were analysed in five groups, each with a different sample size based on the missingness of covariate traits (Figure 1). This addressed the trade-off between maximising sample size for each depSympt-covariate trait interaction analysis and the computational burden of constructing GRMs for each analysis. The fixed effects models are built using all available data within an

analysis group, with sample sizes ranging from 61,294 to 91,644.

2.8 | Identifying interactions

For each (fixed effects adjusted and standardised) covariate trait, we use MRNMs (Ni et al., 2019) to evaluate evidence of interactions explaining a nonzero proportion of the variability in depSympt. Following the approach of Xuan et al. (2020), we run a full MRNM, with both G–C and R–C interactions included as random effects, and a null MRNM with no interactions. A likelihood ratio test (LRT) is then used to compare these models, with a significant LRT Bonferroni-corrected p value ($p < 0.05/17 \approx 0.003$) providing evidence that interactions explain a nonzero proportion of outcome variance.

This approach assesses the evidence for an overall interaction effect. Simulation studies have shown there is low power to disentangle G–C and R–C interactions in nested MRNM comparisons (Xuan et al., 2020), with biased G–C interaction estimates to be expected if unmodelled R–C interactions are present (Dahl et al., 2020). In contrast, the full MRNM produced unbiased estimates of G–C and R–C variance components (Ni et al., 2019; Xuan et al., 2020). For significant covariate traits, we can therefore use variance component estimates from the full model (Equation 2), with 95% confidence intervals, to identify which interaction type, polygenic and/or residual, explain the variability in depSympt.

MRNMs are computationally demanding. Therefore, to perform interaction analysis for a given covariate trait at biobank scale we randomly divided the available UKB participants into three subgroups. MRNMs were run, using the `mtg2` package (Lee & van der Werf, 2016), and compared within each subgroup. Results were then meta-analysed using Fisher's method (Evangelou & Ioannidis, 2013), as described in SM section 1.4. Fixed effects adjustment and postmodelling analysis, including creating graphics, was performed using R version 4.0.4. A Bonferroni correction was applied to adjust for multiple testing (giving a significance threshold of $p = 0.05/17 \approx 0.003$). A sensitivity analysis was performed by refitting the MRNMs using a rank-based inverse normal transformation (RINT) of depSympt. Applying this transformation can control the type I error rate when the assumption of normality is violated (Ni et al., 2019) and loss of signal indicates spurious interaction effects in the untransformed model (Xuan et al., 2020). Simulations have shown that parameter estimates from the full model, without applying the

RINT, remain unbiased when the normality assumption is violated (Xuan et al., 2020). The MRNM without transforming depSympt was therefore used for variance component estimation.

3 | RESULTS

Before interaction analysis, linear regression models for the outcome trait, depSympt, with each covariate trait in turn were run (Table S7). With the exception of LDL, all covariate traits considered have a statistically significant main effect ($p < 0.05/17 \approx 0.003$), providing evidence that expected current symptoms of depression vary with these covariate traits. The effect sizes vary widely, ranging from 0.38% of the variability in depSympt explained by the HDL biomarker, to 21.55% of the variability in depSympt explained by neuroticism score. When FPs are considered, which allow covariate traits to have a nonlinear relationship with the expected value of depSympt, the effect of LDL on expected depSympt also becomes statistically significant, although the proportion of variability in depSympt explained is low (0.04%). The proportion of phenotypic variability in depSympt explained by each covariate trait does not greatly change between the main effects and the FP linear models, with average sleep duration having the largest absolute increase from 0.87% in the main effects model, to 2.24% in the FP model (Table S8).

Distribution plots of the outcome variable summarising depressive symptoms, depSympt, and each covariate trait (before and after fixed effects adjustment) can be found in Figures S3–S19, with Table S6 presenting the distribution characteristics for the unadjusted traits. Before fixed effects adjustment, the distribution of standardised depSympt is not normally distributed, with evidence of some positive skew (skewness = 0.47). Some deviations from normality are still present after fixed effects adjustment, with a median skewness of 0.34, however, we note that deviations from normality for depSympt after fixed effects adjustment does not mean that the normality assumption of the MRNM is violated since this applies to the distribution of outcome conditional on the fixed *and* the random effects models. Some covariate traits, for example, MET total, are highly skewed even after fixed effects adjustment, however, our primary focus is on the variance components for the outcome trait, for which we performed a sensitivity analysis, refitting the MRNMs using the RINT for depSympt to control the type I error rate if the assumption of normality is violated.

For each of the 17 covariate traits considered, MRNMs with and without interactions were run for

depSympt, and evidence of G–C and/or R–C interactions was assessed using LRTs. A total of 11 of the 17 covariate traits had p values below the Bonferroni-corrected significance level, which are presented in Table 1. These 11 traits remained significant in the RINT-based sensitivity analysis (Table S12), used to check significant results were not due to normality violations, providing evidence for an interaction effect between depSympt and the following variables: neuroticism, childhood trauma, average sleep duration, BMI, waist circumference, smoking, waist-to-hip ratio, TDI, and summed MET minutes for all activities, for walking and for moderate activities. These results show that, even after adjusting for fixed effects, individual-level differences in these covariate traits contribute to variation in depSympt.

To assess if these covariate traits modulate the polygenic component and/or the residual component of depression symptoms (the G–C and R–C interaction, respectively), we use a measure of interaction strength: the proportion of variability in depSympt explained by an interaction effect (see Equation 2). This measure is plotted as a %, with 95% CIs, for: (a) the G–C interaction and (b) the R–C interaction in Figure 2. When a 95% CI includes zero, we cannot be certain that the interaction term explains any of the variability in depSympt.

Nine of the eleven significant covariate traits had 95% CIs for the percentage of variability in depSympt attributable to R–C interactions that excluded zero, with point estimates ranging from 1.03% (95% CI: [0.34, 1.73]) for waist to hip ratio, to 2.98% (95% CI: [2.18, 3.77]) for childhood trauma. These results show that a small, but significant, proportion of the residual variability in depSympt is modulated by the following covariate traits: neuroticism, childhood trauma, average sleep duration, BMI, waist circumference, smoking, waist-to-hip ratio, summed MET minutes per week walking and TDI.

For the G–C interactions, only average sleep duration had a 95% CI that excluded zero (Figure 2). This polygenic–sleep interaction is estimated to explain 1.22% of the variability in depSympt (95% CI: [0.54, 1.89]). Figure 3 plots the relationship between the variance components (polygenic, residual, and total) for depSympt and fixed effects adjusted average sleep duration, as estimated by the full MRNM. It shows a U-shaped relationship between the polygenic variance component and sleep, suggesting a larger polygenic contribution to depression symptoms for individuals getting far more or less sleep than expected compared to those in central sleep duration percentiles (see Figure S38).

For the 11 covariates with significant interactions, R–C and G–C interactions account for only a small proportion of the variation in depSympt, and significant

TABLE 1 Percentage of variation in depSympt^a attributable to the genotype-covariate (G-C) interaction and the residual-covariate (R-C) interaction with 95% confidence intervals (CIs), for covariate traits with significant interaction effects, showing the *p* value for the comparison of the full model to null model, with significance set at $\alpha = 0.05/17 \approx 0.003$

Covariate	<i>p</i> value	Proportion of variability in depSympt ^a attributable to			
		G-C interaction (%)		R-C interaction (%)	
		Estimate	95% CI	Estimate	95% CI
Neuroticism	5.06E-139	-0.15	[-0.76, 0.46]	2.58	[1.86, 3.30]
Childhood trauma	2.59E-058	0.59	[-0.14, 1.32]	2.98	[2.18, 3.77]
Sleep	1.97E-041	1.22	[0.54, 1.89]	2.52	[1.78, 3.27]
BMI	6.36E-018	-0.23	[-0.86, 0.41]	1.39	[0.68, 2.09]
Waist circumference	6.15E-016	-0.15	[-0.78, 0.48]	1.48	[0.78, 2.19]
Smoking	2.49E-010	0.47	[-0.52, 1.46]	1.57	[0.51, 2.63]
Waist-to-hip ratio	4.49E-009	-0.33	[-0.95, 0.29]	1.03	[0.34, 1.73]
MET total	1.92E-007	0.23	[-0.42, 0.87]	0.53	[-0.17, 1.24]
MET walk	1.13E-005	0.10	[-0.55, 0.74]	1.18	[0.45, 1.92]
MET mod	5.73E-004	-0.26	[-0.87, 0.35]	-0.08	[-0.78, 0.61]
TDI	1.96E-003	-0.19	[-0.81, 0.42]	1.67	[0.97, 2.38]

Note: Polygenic and residual variance components for depSympt are functions of a covariate trait under the full MRNM. The percentage of variability in depSympt attributable to the G-C (R-C) interaction variance component relates to $\sigma_{\alpha_1}^2$ ($\sigma_{\tau_1}^2$) in Equation (2). For a G-C interaction, a 95% CI that excludes zero shows that the covariate trait modulates polygenic effects on depSympt. For an R-C interaction, a 95% CI that excludes zero indicates that the covariate trait has some unmodelled relationship with depSympt.

^aAdjusted for age, sex, genetic batch and PCs 1 to 15 (SM section 1.4.4 provides details for producing interaction variance component estimates and standard errors on this scale).

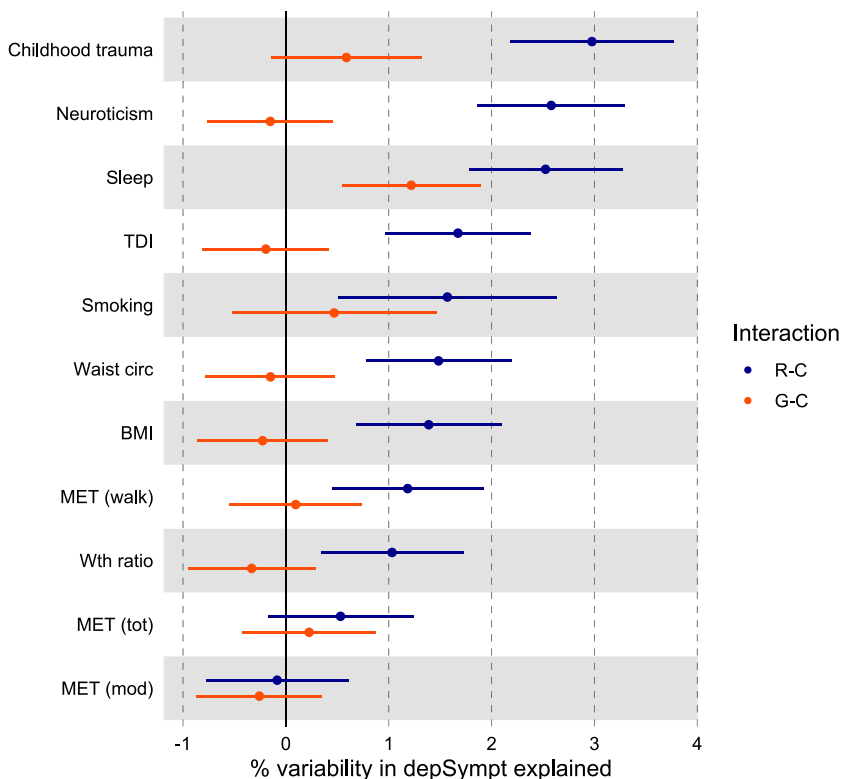


FIGURE 2 The percentage of variation in depSympt^a attributable to the G-C (genotype-covariate) interaction (red) and the R-C (residual-covariate) interaction (blue) with 95% confidence intervals^b. ^aAdjusted for age, sex, genetic batch and PCs 1 to 15 (SM section 1.4.4 provides details for producing interaction variance component estimates and standard errors on this scale). ^bWhen the 95% CI for a G-C interaction variance component excludes zero, there is evidence that the covariate trait modulates polygenic effects on depSympt. When the 95% CI for an R-C interaction variance component excludes zero, there is evidence that the covariate trait can explain further variability in depSympt, in addition to that specified by the full MRNM

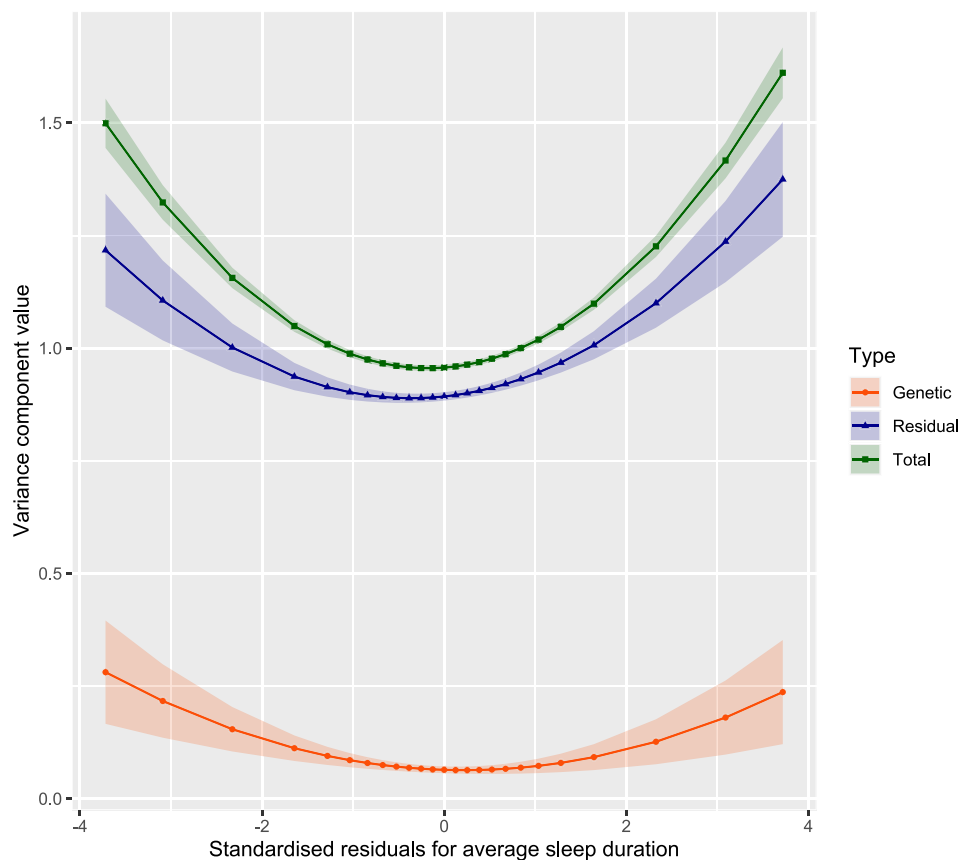


FIGURE 3 Variance components for standardised residual depSympt by standardised residual average sleep duration, with 95% confidence intervals (presented as coloured bands). See SM section 1.4.3 for variance component and standard error equations

results are primarily driven by R–C interactions, not G–C interactions. These results imply that covariate traits exert more influence on depressive symptoms through the modulation of residual (unmodelled) effects compared to polygenic effects.

We note the presence of negative variance component estimates, which are possible within random-effects models including the MRNM (Ni et al., 2019; Xuan et al., 2020). These values arise as the algorithm estimates this parameter freely, without any constraint that the variance must be positive. All negative variance component estimates have 95% CIs that cross 0, indicating that they are under-estimates of a null interaction effect.

For 2 of the 11 covariate traits, MET total and MET moderate, where the interaction model provided a better fit to the data compared to the null model, the 95% CIs for the proportion of variance explained overlap with 0 for both the R–C and the G–C interactions. These results imply that while there is evidence for a trend in the variability of depSympt across these covariate traits, we are unable to confidently disentangle the source of this interaction into genetic or residual components.

4 | DISCUSSION

G–E interactions in depression may give insights into its aetiology, highlighting both the biological mechanism and identifying environmental risk factors whose role in depression is moderated by genetics. The low heritability for depression compared to many other psychiatric disorders, and the prominent role of environmental risk factors through trauma and stress, make depression a natural target for exploring G–E interactions. Previous G–E interaction studies in depression using genome-wide data, performing SNP-by-environment tests, have identified few significant and replicated results either in European ancestries (Arnau-Soler et al., 2019) or in Hispanic, African American and Hans Chinese populations (Dunn et al., 2016; Peterson et al., 2018). Increasing sample sizes may yield more significant SNP-by-environment interactions, but the highly polygenic nature of depression makes searching for polygenic-environment interactions appealing. Investigations of G–E interactions using depression PRSs have demonstrated null or conflicting results (Kendall et al., 2021), and these PRS-environment interaction analyses have not modelled a residual trend in the variability of

outcome, which can bias G–E interaction estimates (Dahl et al., 2020). Additionally, the SNP effects used to construct a PRS are estimated assuming an additive genetic model. PRSs are therefore currently designed with the expectation that they do not vary across an environmental gradient. To assess whether the polygenic component for a trait is modified by the environment, a model which can create a polygenic score allowing for this possibility should be employed.

Furthermore, for a complex trait like depression, we would expect the genetic space to map to the phenotypic space through the environment, making the outcome a complex interplay between genes and environment (Assary et al., 2020). Since environmental traits are often complex traits themselves, part of this interplay may include a genetic correlation between environment and depression, that is, BMI, smoking and exercise measures have a positive genetic correlation with depression (Wray et al., 2018). Not accounting for G–E correlation while investigating G–E interaction can lead to biased variance component estimates (Purcell, 2002), and have been shown to inflate the significance of interaction results (Ni et al., 2019). Interaction analyses using PRSs do adjust for correlation through a main effect, however, they do not allow for residual correlations between traits nor offer the opportunity to investigate G–E interactions in the presence of G–E correlation. In this paper, we have used MRNMs (Ni et al., 2019) within the UKB to identify genome-wide G–C and R–C interactions for depressive symptoms whilst controlling for residual trait correlations, including genetic correlation. The G–C and R–C interactions allow the polygenic variance component and the residual variance component for depressive symptoms, respectively to vary across a continuous covariate trait. The MRNM extends existing polygenic–environment interaction approaches from categorical environmental traits to continuous ones, providing a route to avoid the pitfalls associated with the arbitrary categorising of continuous traits (Altman & Royston, 2006; Naggara et al., 2011).

We included 17 continuous covariate traits, which covered childhood trauma, body composition, physical activity and smoking. For each covariate in turn, MRNMs with and without interactions were run and compared using LRTs. These models jointly test the presence of G–C and/or R–C interaction effects. The contribution of each interaction is then extracted from the variance component estimates, summarised as the proportion of the outcome variability an interaction effect explains.

MRNMs for 11 of the 17 covariates found evidence for some interaction effect. Across these 11 covariates, the variability in depressive symptoms attributable to the R–C interaction effect tended to be substantially larger than that attributable to the G–C effect. Only one

covariate, average sleep duration, had a G–C variance component estimate where the confidence interval excluded zero. The significant p values observed in the LRTs between the null and interaction models are therefore likely to be driven by the R–C interactions. For nine covariate traits, the proportion of variability in depressive symptoms attributable to the R–C interaction had a confidence interval which did not include zero, but the proportion of variance accounted for was small, with the residual–‘childhood trauma’ interaction explaining the largest percentage of phenotypic variation at 3.0%, decreasing to 1.0% for the residual–‘waist-to-hip ratio’ interaction.

These R–C interactions can be interpreted as non-random noise, where the covariate traits explain additional variation in depSympt not captured explicitly in the model. Several possible extensions to the model may better explain the role of these covariate traits in depressive symptoms. First, these variables may have a nonlinear relationship with symptoms of depression not captured by FPs; refinement of the nonlinear fixed effects model would resolve this, for example, fitting splines. Second, the covariates may interact with each other, or with additionally unmodelled environmental variables, to influence depressive symptoms. Finally, the covariates may interact with genetic variants not captured by genome-wide genotyping and imputation (such as rare variants, repeats, or structural variation), or with other omics-type data (such as the transcriptome).

Individually these R–C interactions are small, but cumulatively they could explain a large proportion of the variability in depressive symptoms. Random noise is not useful for prediction and further research to explain the residual heteroscedasticity is warranted. A potential route could be incorporating an environmental similarity matrix into the MRNM and looking for ‘exposome’ effects by utilising shared environmental information (Xuan et al., 2020).

A further consideration is that the R–C interaction effect can capture deviations from normality in the conditional outcome trait; an effect not necessarily indicative of an interaction, rather driven by the mean–variance relationship of nonnormal distributions (Young et al., 2018). If this were true, then exploring the significant R–C interactions may not yield useful results. However, possible explanations for the significant R–C interactions, such as environment–environment interactions, have been reported in the depression literature (Hullam et al., 2019; Morrissey & Kinderman, 2020), indicating that further exploration via multivariate approaches will improve the accuracy of depression models and reveal sets of relevant risk factors unlikely to be identified via univariate methods.

Our primary interest in these models was to assess evidence for G–C interactions for depressive symptoms. Only average sleep duration had an estimate of the proportion of phenotypic variability explained by a G–C interaction with a 95% confidence interval not overlapping with zero. A small, but statistically significant, proportion of the variability in current depressive symptoms is therefore attributable to a genome-wide G–E interaction with average sleep duration measured at the UKB baseline assessment, 5–10 years earlier than the assessment of depSympt. Our results imply that the optimal sleep duration to minimise depressive symptoms can vary by genetic profile, but this modification of the polygenic variation for depSympt using historic sleep patterns is limited, with the estimate of variation attributable to this interaction being low at 1.2%. Other covariate traits that had nonzero estimates for the R–C interaction variance component, had much lower G–C interaction variance components, ranging from 0.59% (for childhood trauma), to estimates that were below zero (indicating no interaction).

This is not the first study to identify a significant gene–sleep interaction for depression. A twin study by Watson et al. (2014) found that the genetic contribution to depressive symptoms was significantly higher for both short (<7 h per night) and long (≥ 9 h per night) sleep durations compared to the average (7–8.9 h per night)—a trend that we also observed (Figure S38). Additionally, there is evidence for a complex bidirectional relationship between sleep and depression involving variables/biomarkers such as circadian rhythms (Khan et al., 2018; Kronfeld-Schor & Einat, 2012), stress (Leggett et al., 2016; Palagini et al., 2019), melatonin (Rahman et al., 2010), serotonin (van Dalen & Markus, 2019), dopamine (Boland et al., 2020; Finan & Smith, 2013), and their respective genes. Future work investigating gene–sleep interactions for depression could utilise these previously highlighted genes within genomic partitioning analysis.

An initially surprising result is that this MRNM analysis does not support a nonzero G–C interaction effect for childhood trauma, despite G–C interactions of childhood trauma with depression previously having been identified (Mullins et al., 2016; Peyrot et al., 2014; Shen et al., 2020). In addition to methodological and data set differences, this study used a recently developed, composite measure of childhood trauma (Pitharouli et al., 2021). The null G–C interaction result here, in contrast with previous significant results for other measures of childhood trauma, may suggest that G–C interactions for differing types of childhood trauma should be investigated as separate covariates and not as a continuous weighted aggregate.

Although estimated interaction effects for symptoms of depression are small, the MRNM has been able to identify strong lifestyle modulation effects on cardiovascular traits. Xuan et al. (2020) used the MRNM and 22 lifestyle traits to explore interactions for 23 cardiovascular traits, finding evidence of lifestyle modulation for 42% of the outcome-covariate trait pairings. Sizeable G–C and R–C interactions were observed suggesting the need for personalised lifestyle interventions to reduce the risk of cardiovascular disease. The largest G–C interaction explained $\sim 10\%$ of (fixed effects adjusted) phenotypic variability and was for the modulation of the polygenic effect on HDL cholesterol level by physical activity. The largest R–C interaction effect, explaining $\sim 20\%$ of phenotypic variability, was for the modulation of the nongenetic component for white blood cell count by smoking.

Our study has limitations. The environmental risk factors analysed here were selected based on a literature review, but no systematic review or meta-analysis was performed and other variables with equally compelling rationale for inclusion may not have been considered. Similarly, biomarkers were included that have been widely tested for association with depression (CRP, vitamin D) but we cannot exclude interactions with other biomarkers. Additionally, the modifying effect of covariate traits on depressive symptoms were considered in separate models. A joint model for interactions may provide a better fit, however, the computational burden and the required sample size for robust parameter estimation will increase. All statistical models require assumptions about variables to be analysed. We analysed a continuous measure of depression, as required by the MRNM, and chose to use a composite measure previously constructed and validated as highly correlated with MDD diagnosis. Other options would have been to take raw scores for numbers of depression symptoms reported, or the ordinal measure of presence/absence of the two core depression symptoms (each scored 0, 1, 2), as analysed in other genome-wide association studies (Levey et al., 2021; Turley et al., 2018). The outcome trait depSympt, extracted from a hierarchical model, was chosen as it accounts for correlation between reported depression symptoms, and is continuous. The UKB depressive symptoms, from which the depSympt variable was constructed, represents a snapshot of participants mental health over the 2 weeks before completing the MHQ. This does not account for historical mental health, or capture trends of mental health, and the potential dynamic nature of G–E interactions, over time. Our study analysed only European ancestries in UKB and findings may not extend beyond this sample. The MRNM provides a flexible and broad modelling framework, but

model fitting is computationally intensive, particularly given the large sample sizes available in UKB. Meta-analysis across three subgroups was required to make this computational feasible. Ni et al. (2019) showed that using meta-analysis across subgroups reduced the power to identify nonzero interaction variance components compared to using the complete sample, and analysis with the full available UKB sample might yield more significant G-C/R-C interactions. The MRNM used here estimates the polygenic-covariate interaction and, as an aggregate genome-wide measure, does not provide accessible information about the contribution from individual variants, genes, or pathways (Assary et al., 2020), although the model could be extended for use within genomic partitioning.

In summary, the MRNM provides a flexible, if computationally intensive, a framework to comprehensively model genetic and environmental contributions to complex traits. For depression, these models show significant R-C interactions, potentially highlighting unmodelled relationships between nongenetic contributions to depressive symptoms. Evidence for a G-C interaction was only found at one covariate (average sleep duration), suggesting that any modulation of the polygenic effects on depressive symptoms by the explored environmental variables is limited. Genome-wide G-C interactions do not play a major role in the aetiology of depressive symptoms, and therefore, personalised lifestyle interventions using SNP profiles are not required.

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CONFLICTS OF INTEREST

Cathryn Lewis sits on the Myriad Neuroscience Scientific Advisory Board. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The individual-level data that support the findings of this study are available with the permission of the UK Biobank (<http://www.ukbiobank.ac.uk>). We conducted this study using the UK Biobank resource under an approved data application (ref: 18177).

WEB RESOURCES

LDSC HapMap 3 SNP-list: https://data.broadinstitute.org/alkesgroup/LDSCORE/w_hm3.snplist.bz2
mtg2 software: <https://sites.google.com/site/honglee0707/mtg2>

ORCID

Alexandra C. Gillett  <http://orcid.org/0000-0002-5069-3197>

Bradley S. Jermy  <http://orcid.org/0000-0002-3188-9581>

Sang Hong Lee  <http://orcid.org/0000-0001-9701-2718>

Oliver Pain  <http://orcid.org/0000-0001-5680-3281>

David M. Howard  <http://orcid.org/0000-0002-6005-1972>

Saskia P. Hagenaars  <http://orcid.org/0000-0001-9697-8596>

Ken B. Hanscombe  <http://orcid.org/0000-0002-3715-6805>

Jonathan R. I. Coleman  <http://orcid.org/0000-0002-6759-0944>

Cathryn M. Lewis  <http://orcid.org/0000-0002-8249-8476>

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