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Examining the genetic links between clusters of immune-mediated diseases and psychiatric disorders

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Extant phenotypic and genetic literature has established consistent relationships between autoimmune, autoinflammatory, and psychiatric disorders. However, a comprehensive model investigating the association between a broad range of psychiatric disorders and immune-mediated disease in a multivariate framework is lacking. We utilized Genomic Structural Equation Modeling (Genomic SEM) to establish a factor structure across 11 immune-mediated diseases. Genetic correlations between these immune factors were examined with five established factors across 13 psychiatric disorders. We develop and validate a new heterogeneity metric, Q_{Factor}, that quantifies the degree to which factor correlations are driven by more specific pairwise associations, which were further investigated in the form of residual genetic correlations. A four-factor model of immune-mediated diseases fit the data well and described a continuum from autoimmune to autoinflammatory diseases, reflecting autoimmune, celiac, mixed pattern, and autoinflammatory diseases. Analyses revealed six significant factor correlations between the immune and psychiatric factors, including autoimmune and mixed pattern diseases with the substance use factors, autoinflammatory diseases and mixed pattern diseases with the internalizing factor, autoinflammatory diseases with the compulsive disorders factor, and autoinflammatory diseases with the schizophrenia/bipolar factor. Additionally, we find evidence of divergence in associations within factors as indicated by Q_{Factor} and 10 significant residual genetic correlations between individual psychiatric disorders and immune-mediated diseases. The results suggest that previously described relationships between specific psychiatric disorders and immune-mediated diseases often capture broader pathways of risk sharing indexed by our genomic factors yet are more specific than a general association across all psychiatric disorders and immune-mediated diseases.

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INTRODUCTION

Immune-mediated diseases are linked phenotypically to a range of psychiatric disorders, including eating [1], mood [2], psychotic [3, 4], stress-related [5], and neurodevelopmental disorders [6]. Recent genomic studies have mirrored phenotypic associations at a molecular genetic level. For example, an investigation of five psychiatric disorders and seven immune-mediated diseases found evidence of shared genetic signal for 24 out of 35 psychiatric-immune disorder pairs [7]. In addition, the human leukocyte antigen (*HLA*) region of the genome in the major histocompatibility complex (MHC) is critical for the adaptive immune response and is one of the most implicated regions in psychiatric genetics [8]. It has also been shown that immune-mediated diseases as a category are genetically related to psychiatric disorders, finding that these overall associations are bidirectional [9]. Widespread associations across psychiatric and immune-mediated outcomes suggests that overlap identified for pairs of psychiatric-immune disorders will often reflect shared etiology across a broader multivariate system of disorders. At the same time, meaningful biological distinctions within immune-mediated diseases caution against prematurely concluding that all immune-mediated diseases have equivalent associations with psychiatric traits [10].

Immune-mediated disease encompasses an overlapping continuum from autoimmune to autoinflammatory diseases [10]. Diseases falling between these ends share features of autoimmune and autoinflammatory disease and are classified as mixed-pattern diseases [11]. The commonality across these endpoints is a shared malfunction of the immune system that includes targeting self-tissue without an observable trigger, such as infection or injury, and subsequent systemic inflammation [12]. They are distinguished, however, by which part of the immune system is malfunctioning. Autoimmune diseases result from abnormal adaptive immune responses, whereas autoinflammatory diseases arise from a malfunctioning innate immune system [13, 14]. Though they work closely together, the adaptive and innate immune system also diverge with respect to the different types of cells and cell responses that form a complicated network

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Table 1. Sample Characteristics of Included Traits.

Phenotype	Cases	Controls	Liability Scale Heritability
Immune Mediated Diseases			
Addison's disease (AD) [57]	1 223	4 097	16%
Celiac disease (CEL) [39]	2 364	324 074	13%
Crohn's disease (CD) [58]	12 194	28 072	22%
Diabetes type 1 (T1D) [59]	18 942	501 638	14%
Juvenile idiopathic arthritis (JIA) [60]	3 305	9 196	13%
Myasthenia gravis (MG) [61]	1 873	36 370	11%
Psoriasis (PSO) [62]	15 967	28 194	15%
Psoriatic arthritis (PSA) [63]	5 065	21 286	13%
Rheumatoid arthritis (RA) [64]	14 361	43 923	9%
Systemic lupus erythematosus (SLE) [65]	4 036	6 959	10%
Ulcerative colitis (UC) [58]	12 366	33 609	15%
Psychiatric Disorders			
Alcohol use disorder (ALCH) [66]	8 485	20 272	14%
Anorexia nervosa (AN) [67]	16 992	55 525	16%
Anxiety disorder (ANX) [68]	31 977	82 114	23%
Attention-deficit/hyperactivity disorder (ADHD) [69]	38 691	186 843	18%
Autism spectrum disorder (ASD) [70]	18 381	27 969	12%
Bipolar disorder (BIP) [71]	41 917	371 549	19%
Cannabis use disorder (CUD) [72]	14 808	343 726	19%
Major depressive disorder (MDD) [73]	170 756	329 443	9%
Obsessive compulsive disorder (OCD) [74]	2 688	7 037	30%
Opioid use disorder (OUD) [75]	3 211	11 589	19%
Post traumatic stress disorder (PTSD) [76]	141 479	1 113 329	5%
Schizophrenia (SCZ) [77]	53 386	77 258	22%
Tourette's syndrome (TS) [78]	4 819	9 488	22%

This table describes all GWAS summary statistics of all external traits included in the analyses.

of interactions. Specifically, the adaptive immune system involves T lymphocyte subsets, B cells, and plasma cells, whereas the innate immune system encompasses cells such as macrophages, natural killer cells, and dendritic cells [11]. These divergent biological pathways suggest that autoimmune and autoinflammatory diseases may have similarly distinct associations with psychiatric disorders, which remains to be investigated in a systematic fashion.

Pervasive pairwise associations identified across immune-mediated and psychiatric diseases [15] necessitate a comprehensive multivariate approach to better characterize the shared etiological landscape across genomic factors of psychiatric and immune disorders. Genomic structural equation modeling (Genomic SEM) [16] is a recently introduced multivariate method that uses the shared features of genomic data to bring together even mutually exclusive datasets into a single statistical model and parse convergent and divergent genetic signal. In this study we apply Genomic SEM to (*i*) establish a genomic factor structure of immune-mediated diseases and (*ii*) investigate the degree to which these genomic factors of immune-mediated diseases are related to genomic factors of psychiatric disorders. The current study thereby clarifies the relationships between individual immune-mediated diseases and psychiatric disorders by investigating patterns of risk sharing between these two frequently linked classes of diseases on a factor and individual trait level. Follow-up analyses of gene expression in both classes of diseases shed light on potential shared underlying biological pathways between psychiatric and immune-mediated diseases.

METHODS

Phenotype selection and quality control

The list of immune-mediated diseases from the Mount Sinai Website (https://www.mountsinai.org/health-library/diseases-conditions/autoimmune-disorders), as well as recent studies in the immune-disease field, were referenced to make an initial list of disease traits that was cross-referenced with the CDC website (https://www.cdc.gov/index.html) to verify their status as an immune-mediated disease. This list was further restricted to immune-mediated diseases that are an immediate result of the immune system and perpetuate themselves without an ongoing external trigger. These true immune-mediated diseases are to be distinguished from other diseases that are a downstream effect of immune activation associated with a primary trigger such as infection or injury [17] (e.g., eczema). For each phenotype, we selected the most well-powered, publicly available GWAS of unrelated individuals of European genetic ancestry. We removed any traits with existing genome-wide association study (GWAS) summary statistics with low genomic coverage (<850 000 SNPs) or insufficient power, reflected by a SNP-based heritability (h^2_{SNP}) *Z*-statistic < 4 [18]. This resulted in a final list of 11 immune-mediated diseases (Table 1). For psychiatric traits, the same GWAS summary statistics of 13 disorders were used from a recently described psychiatric genomic model [19]. All GWAS summary statistics underwent a standardized quality control process using the *munge* function within the *GenomicSEM* R package. This function restricts the data to HapMap3 SNPs, aligns all GWAS summary statistics to the same reference allele, and filters at a minor allele frequency > 1% and an imputation quality > 0.9, when available.

LD-score regression

Multivariable Linkage Disequilibrium (LD)-score regression (LDSC) [18] was performed using LD scores calculated from the European subset of the 1000 Genomes Phase 3 project. The MHC region was excluded due to

complex LD structures in this region that can bias results. Multivariable LDSC produces two matrices as output: (*i*) the genetic covariance matrix with the SNP-based heritabilities and genetic covariances on the diagonal and off-diagonal, respectively, and (*ii*) a sampling covariance matrix with the squared standard errors of the estimates on the diagonal and the sampling dependencies on the off-diagonal representing participant sample overlap. Since all included traits were binary, the LDSC estimates were converted to a more interpretable liability scale, accounting for the continuous distribution of genetic risk (liability) and sample ascertainment. The liability scale conversion was calculated using the population prevalence specified in the corresponding GWAS paper or a prevalence reflective of the participant sample. Additionally, we used the sum of effective sample sizes across the contributing cohorts for the ascertainment correction, to produce the most accurate estimates of liability-scale heritability [20].

Genomic SEM

Genomic SEM takes as input the output from multivariable LDSC along with a user specified SEM [16]. We first modeled the genetic overlap across only immune-mediated diseases. Good model fit, which indexes how well the specified model captures the data, was established based on the comparative fit index (CFI ≥ 0.9) and the standardized root mean squared residual (SRMR ≤ 0.1). Our initial model reflected a theoretically motivated two-factor confirmatory factor analysis (CFA), with the two factors defined by either autoimmune or autoinflammatory diseases, with mixed presentation diseases being specified to cross-load on both factors. The two-factor solution had poor model fit (Table S1). We therefore ran a data-driven combination of exploratory analyses (EFA) followed by CFAs. The number of factors to include in the EFA for the immune-mediated disease phenotypes was determined based on the Kaiser rule [21], the acceleration factor, and the optimal coordinates [22]. To avoid model overfitting, we performed EFA and CFA on the odd and even chromosomes, respectively. Having finalized a four-factor model for immune-mediated diseases based on this approach, this model was integrated with a previously established five-factor model for 13 psychiatric disorders [19] with the updated PTSD summary statistics. The psychiatric factors in this model can be approximately described as reflecting compulsive, schizophrenia/bipolar, neurodevelopmental, internalizing, and substance use disorders. For disorders that define the same factor, we briefly consider some of their shared clinical characteristics. The compulsive disorders factor was defined by the shared genetic signal across disorders (e.g. obsessive-compulsive disorder or Tourette's syndrome) characterized by repetitive and ritualistic thoughts or behaviors. The schizophrenia/bipolar factor was defined by the shared signal across these two disorders, which can both include dysregulated thought processes that are inconsistent with reality. The neurodevelopmental disorders factor was defined primarily by conditions with childhood onset (e.g. ADHD and autism spectrum disorder). The internalizing disorders factor was defined by disorders that often present with symptoms of sadness, worry, and fear that are primarily directed towards the self (e.g. major depressive disorder or anxiety disorders). Finally, the substance use disorder factor (e.g. alcohol use and cannabis use disorder) represents disorders that are characterized by the abuse or dependence of the respective substance. The five psychiatric factors were specified to correlate with all immune-mediated disease factors and these inter-factor correlations were evaluated for significance to reflect patterns of risk sharing between overarching factors of psychiatric disorders and factors of immune-mediated diseases.

We also examined associations between specific pairwise combinations of psychiatric and immune diseases that were not captured by the factor model. This was achieved by adding residual genetic correlations between a psychiatric-immune disease pairs to the model. Which residual correlations to add was determined by first inspecting a matrix of model misfit, calculated as the difference between the model implied and observed covariance matrices. This matrix of misfit was then divided by the standard errors on those estimates to create a matrix of *Z*-statistics. Finally, residual genetic correlations between a psychiatric and immune disease were added to the model when there was a *Z*-statistic > 2 for that cell of the matrix and if the residual genetic variance of the indicator itself was significant to ensure that there is a meaningful amount of variance to examine a correlation for. Reported residual genetic correlations were standardized relative to the total SNP-based heritability, rather than the residual genetic variance in the disorders that is not explained by the factors. That is, we do not report partial genetic correlations, since partial genetic correlations can be exceedingly high when they are standardized relative to residual genetic variances that are small (e.g., only 12% of the genetic variance in juvenile idiopathic arthritis is left unexplained by the autoimmune factor). Residual genetic correlations, by contrast, have the added benefit of being more readily comparable to the genetic correlations estimated by LDSC, as both the residual genetic correlations and zero-order LDSC correlations are standardized relative to the same SNP-based heritabilities. Across all analyses, significance was determined after applying FDR multiple testing correction implemented using the *p.adjust* function in the *stats* R package.

Q_{Factor} heterogeneity test

As part of the current manuscript, we introduce and validate a heterogeneity metric that we term Q_{Factor}. This metric is a χ^2 distributed measure of local model misfit that captures inter-factor correlations that fail to recapture the pairwise genetic relationships between the different disorders that define these factors. This could occur, for example, if two traits that define the same factor have directionally opposing relationships with the traits that define a second factor. Q_{Factor} is specific to a pair of factors in the model, such that multiple Q_{Factor} metrics can be calculated for a multifactorial model. This new addition to Genomic SEM was validated via simulations that are detailed in the Online Supplement and the mechanisms through which significant Q_{Factor} results can occur are illustrated in Figure S1. For our empirical results, a separate Q_{Factor} was calculated for each psychiatric with immune-mediated disease factor correlation. Q_{Factor} was used as a quality control check, where psychiatric-factor correlations are only reported as significant below when Q_{Factor} was not significant. This is because a non-significant Q_{Factor} result indicates the factor correlation appropriately describes broad pathways of risk sharing across these two clusters of disease traits. Second, Q_{Factor} was treated as a result in its own right to identify psychiatric-immune relationships that do not operate via the factors.

Transcriptome-wide SEM

We performed univariate transcriptome-wide association studies (TWAS) in FUSION for each of the individual psychiatric disorders and immune-meditated diseases, using the PsychEncode [23] prefrontal cortex gene expression weights to perform the transcriptomic imputations. We then performed transcriptome-wide structural equation modeling (T-SEM) [24], wherein the imputed gene expression for each gene was specified to predict all of the immune-mediated and psychiatric factors. Genes were only considered significant for the factors if they passed an FDR corrected significance threshold and were not significant for the Q_{Gene} heterogeneity metric. Q_{Gene} operates to identify genes that are unlikely to operate via the shared signal captured by the factors (e.g., genes with much larger effects on only one of the disorders that define the factor). Genes that were jointly associated with both a psychiatric and immune factor that were themselves significantly correlated were brought forward for follow-up models. These follow-up models were used to assess whether the effect of the gene is big enough to explain a significant proportion of the genetic correlation across the psychiatric-immune factors. Follow-up analyses are detailed in the Online Supplement.

Sensitivity analyses

To further characterize our findings, we additionally conducted two sets of sensitivity analyses. The first set of sensitivity analyses consisted of running a series of models for significantly correlated pairs of psychiatric and immune factors. These model included body-mass index (BMI [25]; $n = 683\,364.9$) or smoking (as measured by cigarettes per day [SMK] [26]; $n = 263\,954$) as predictors of the psychiatric-immune factors. These reflect two common correlates of both psychiatric and immune-mediated diseases [27–30]. The outcome of interest in these models was the residual genetic correlations between the psychiatric-immune factors when controlling for BMI or SMK. These analyses were run to seek insight into the larger constellation of traits that may underlie these psychiatric-immune relationships. Models were specified using unit variance identification, where the total genetic variance in the factors, including the variance explained by BMI or SMK, was set to 1. This ensured that the residual factor correlations were on a comparable scale to the zero-order factor correlations (i.e., those from the primary model used to estimate the collective set of psychiatric-immune correlations) as they were both standardized relative to a total factor variance of 1. Results are given in the Online Supplement (Figure S2).

The second set of sensitivity analyses consisted of including a GWAS of height ($N = 1\,452\,363$) [31] in the model to estimate genetic correlations with each of the psychiatric factors. Given pervasive genetic overlap

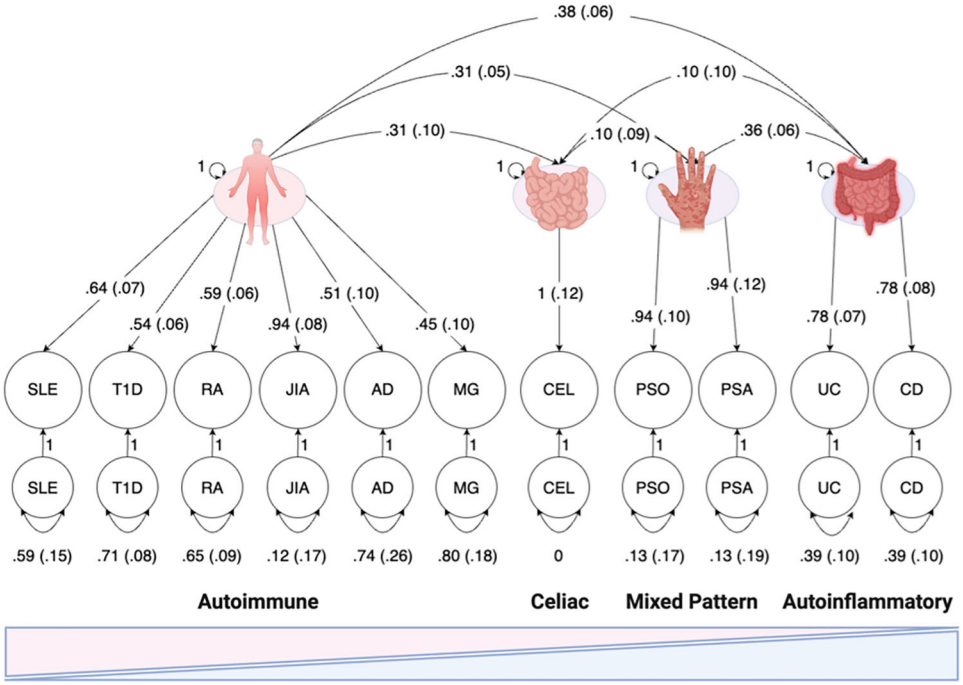

Fig. 1 Immune-mediated disease correlated factors model. Path diagram with standardized estimates for the correlated factors model used in genomic structural equation modelling (genomic SEM) with four factors of immune-mediated diseases. Latent variables are represented as circles. The genetic component of each phenotype is represented with a circle because the genetic component is a latent variable that is not directly measured but is inferred using linkage disequilibrium score regression (LDSC). Single-headed arrows are factor loadings; double-headed arrows connecting back to the same origin are variances; and double-headed arrows connecting two variables are correlations. Paths labeled 1 are fixed to 1; all estimates are given next to the path with standard errors in parentheses. Disease abbreviations are defined in Table 1.

reported across even seemingly disparate human complex traits [32], these analyses were performed to provide an empirical benchmark with which to compare the size of the psychiatric-immune factor correlations (Online Supplement; Figure S3).

RESULTS

Factor structure for immune-mediated diseases

The acceleration factor indicated one factor should be retained, the optimal coordinates rule two factors, and the Kaiser rule four factors. While a one- and two-factor model did not fit the data well (Table S1), a four-factor model of the immune-mediated diseases fit the data well in all autosomes (CFI = 0.96; SRMR = 0.08; Fig. 1; Table S1). The four factors that emerged from the confirmatory factor analysis can be classified as representing an autoimmune disease factor, a single indicator celiac disease factor, a mixed pattern disease factor, and an autoinflammatory disease factor. The autoimmune disease factor reflects shared genetic signal across systemic lupus erythematosus, diabetes type 1, rheumatoid arthritis, juvenile idiopathic arthritis, Addison's disease, and myasthenia gravis. The celiac disease factor reflects genetic signal of celiac disease and the mixed pattern disease factor reflects shared genetic signal between psoriasis and psoriatic arthritis. Finally, the autoinflammatory disease factor reflects shared genetic signal between ulcerative colitis and Crohn's disease. These factors reassuringly fall onto the theoretically overlapping spectrum described in the literature ranging from autoimmune to autoinflammatory diseases with mixed pattern diseases falling in between them.

Genetic associations between immune-mediated diseases and psychiatric disorders

A factor model that integrated the psychiatric and immune-mediated diseases initially yielded good model fit (CFI = 0.94; SRMR = 0.09; Table S1). Significant Q_{Factor} results for pairs of factors, which we consider in more detail below, indicated that part of the model misfit stemmed from inter-factor correlations that did not fit the data. Following the procedure outlined in the **Method**, residual genetic correlations between pairs of psychiatric and immune disease traits were then added to model where indicated. This combination of factor-factor and trait-trait genetic correlation tests reflects genetic risk sharing that is common for diseases on a factor vs. risk sharing that is specific to individual trait pairs. This updated model fit the data well (CFI = 0.94; SRMR = 0.08; Table S2 for full model output, Fig. 2 for significant residual correlations). Results are described separately below for each immune-mediated disease factor. Q_{Factor} results are given from the initial model, and significant inter-factor correlations, as well as residual correlations between pairs of disorders, are provided from the final model. We do not discuss the celiac disease factor below as it was not significantly genetically correlated with any of the psychiatric factors, though it was found to be Q_{Factor} significant with the neurodevelopmental disorders factor (p_{FDR} = 2.03e-11).

Autoimmune diseases correlate with the substance use disorders. Autoimmune diseases were positively genetically correlated with the substance use disorders factor (r_g = 0.17 [SE = 0.06], p_{FDR} = 6.02e-03; Fig. 3). Q_{Factor} analysis further revealed that there was divergent signal in terms of the genetic correlations between the individual indicators loading onto the autoimmune disease factor and the schizophrenia/bipolar (p_{FDR} = 2.03e-11), the neurodevelopmental disorders factors (p_{FDR} = 4.82e-07), and the internalizing disorders factor (p_{FDR} = 3.43e-02). The addition of 10 significant residual genetic correlations to the model clarified that these Q_{Factor} findings were driven by the fact that the disorders that defined the schizophrenia/bipolar and neurodevelopmental factors often showed divergent associations with the autoimmune diseases (Fig. 2). For example, while schizophrenia showed positive residual

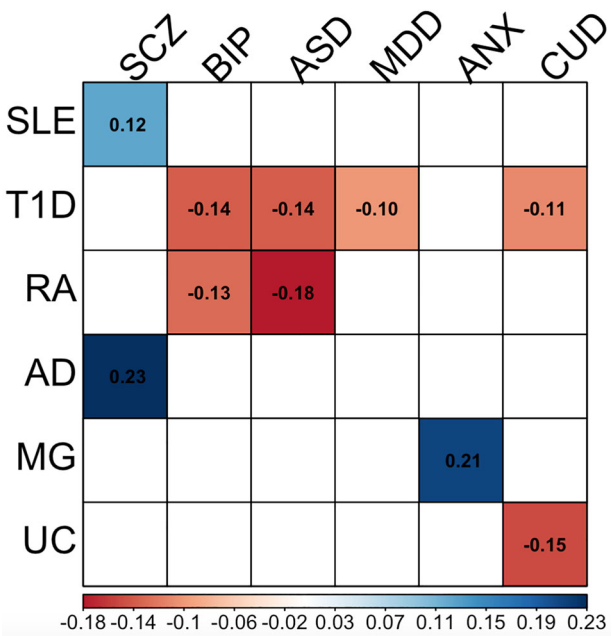

Fig. 2 Significant residual genetic correlations. Significant residual genetic correlations between immune-mediated diseases and psychiatric disorders. Disease abbreviations are defined in Table 1.

genetic correlations with Addison's disease ($r_{g\_resid} = 0.23$ [0.05], $p_{FDR} = 6.40e\text{-}05$) and systemic lupus ($r_{g\_resid} = 0.12$ [0.04], $p_{FDR} = 1.22e\text{-}02$), bipolar disorder was negatively correlated with type I diabetes ($r_{g\_resid} = -0.14$ [0.03], $p_{FDR} = 1.46e\text{-}05$) and rheumatoid arthritis ($r_{g\_resid} = -0.13$ [0.04], $p_{FDR} = 3.41e\text{-}03$).

Mixed pattern diseases correlate with internalizing and substance use disorders. The mixed pattern disease factor showed positive overlap with the internalizing ($r_g = 0.07$ [0.03], $p_{FDR} = 2.93e\text{-}02$) and substance use disorders factors ($r_g = 0.13$ [0.05], $p_{FDR} = 2.54e\text{-}02$; Fig. 4). The relationship between the mixed pattern diseases and the neurodevelopmental disorders was Q_{Factor} significant ($p_{FDR} = 3.13e\text{-}02$).

Autoinflammatory diseases show pervasive overlap with psychiatric factors. The autoinflammatory disease factor was genetically correlated with the compulsive ($r_g = 0.11$ [0.06], $p_{FDR} = 4.72e\text{-}02$), schizophrenia/bipolar ($r_g = 0.17$ [0.04], $p_{FDR} = 4.56e\text{-}05$), and internalizing disorders factors ($r_g = 0.16$ [0.03], $p_{FDR} = 1.05e\text{-}05$; Fig. 5). No psychiatric factor correlations were Q_{Factor} significant. One residual genetic correlation was added between psychiatric and autoinflammatory disease for ulcerative colitis and cannabis use disorder ($r_{g\_resid} = -0.15$ [0.05], $p_{FDR} = 9.03e\text{-}03$).

Transcriptome-wide SEM

T-SEM identified significant gene expression for all factors except the substance use disorders factor. Significantly associated genes for each of the psychiatric and immune-mediated factors are listed in Supplemental Tables S3–10. Four genes were significantly associated with both a psychiatric and immune factor that were themselves significantly correlated. These four genes each explained a significant proportion of the genetic correlation between the corresponding factors. *RP1-265C24.8* explained 2.2% (SE = 0.7; $p_{FDR} = 2.55e\text{-}3$) and *ZSCAN12P1* 7.8% (SE = 1.9; $p_{FDR} = 2.63e\text{-}4$) of the mixed-internalizing factor correlation. *C3orf62* explained 8.7% (SE = 3.8; $p_{FDR} = 1.72e\text{-}2$) of the autoinflammatory diseases and compulsive disorders relationship. Finally, *MED24* explained −1.3% (SE = 0.4; $p_{FDR} = 5.33e\text{-}4$) of the autoinflammatory diseases and internalizing disorders correlation. The negative effect explained by *MED24* reflects the fact that this gene was estimated to have antagonistic pleiotropy, with a negative and positive association identified for the autoinflammatory and internalizing factors, respectively.

Sensitivity analyses

Sensitivity analyses revealed that the residual genetic correlations between autoinflammatory diseases and the schizophrenia/bipolar and internalizing factors remained significant (FDR corrected) after removing genetic overlap with smoking or BMI (Figure S2; Table S11). The factor correlations between the SUD factor and the immune and mixed factors, and between the compulsive and inflammatory factors, became non-significant when controlling for SMK or BMI. Finally, the correlation was non-significant between the mixed and internalizing factors when controlling for SMK, but not BMI.

The inclusion of height in the model revealed two significant negative genetic correlations between height and the internalizing disorders factor ($r_g = -0.07$ [0.02], $p_{FDR} = 2.75e\text{-}05$), as well as the substance use disorders factor ($r_g = -0.07$ [0.03], $p_{FDR} = 1.78e\text{-}02$; Figure S3). While the genetic correlation between internalizing and the mixed pattern disease factors was similar in magnitude ($r_g = 0.07$), these point estimates are only roughly half as large as the estimated overlap between the internalizing and autoimmune factors ($r_g = 0.16$) and the substance use and mixed patterns factors ($r_g = 0.13$). In addition, there was no significant genetic correlation between height and the schizophrenia/bipolar factor and the point estimate for the correlation with height ($r_g = -0.03$ [0.02], $p_{FDR} = 1.31e\text{-}1$) was similarly smaller in magnitude relative to its correlation with the autoimmune factor ($r_g = 0.17$).

DISCUSSION

Extant literature at phenotypic and genetic levels has established a strong link between immune-mediated disease and psychiatric disorders. Here, we applied Genomic SEM to perform a multivariate genomic examination of immune-mediated and psychiatric disorders and shed light on genetic risk that is shared on a factor vs. individual immune-mediated disease and psychiatric disorder level. We began by establishing a factor structure for immune-mediated diseases. Although the genetic factor structure of immune-mediated diseases has previously been investigated, [33, 34] we build upon these findings by incorporating additional immune-mediated diseases. Moreover, this updated factor model that emerged from exploratory factor analysis captures the theoretical continuum of autoimmune and autoinflammatory diseases, which allowed us to examine differential genetic overlap between clusters of psychiatric disorders with diseases characterized by the adaptive versus innate immune system, as well as the mixed pattern diseases that are characterized by shared features of the two. We found that the internalizing and substance use disorders factors are each associated with two immune-mediated factors. In contract, the schizophrenia/bipolar and compulsive disorders factor are specifically associated with the autoinflammatory factor. Additionally, we identify five significant Q_{Factor} results that indexed psychiatric-immune relationships that do not operate via the factors, along with 10 significant residual genetic correlations between pairs of psychiatric-immune disorders. We consider these different levels of risk sharing, from broad associations across clusters of diseases to more specific risk sharing across pairs of psychiatric and immune diseases below.

Prior research has identified pervasive links between pairs of psychiatric and immune outcomes [35]. For example, etiological models of schizophrenia often include inflammatory elements and innate immunity [36], with a recent bibliometric analysis identifying over 3 000 articles examining the link between schizophrenia and inflammation [37]. In addition, phenotypic [38] and genetic studies [39] have linked depression to a host of immune-mediated

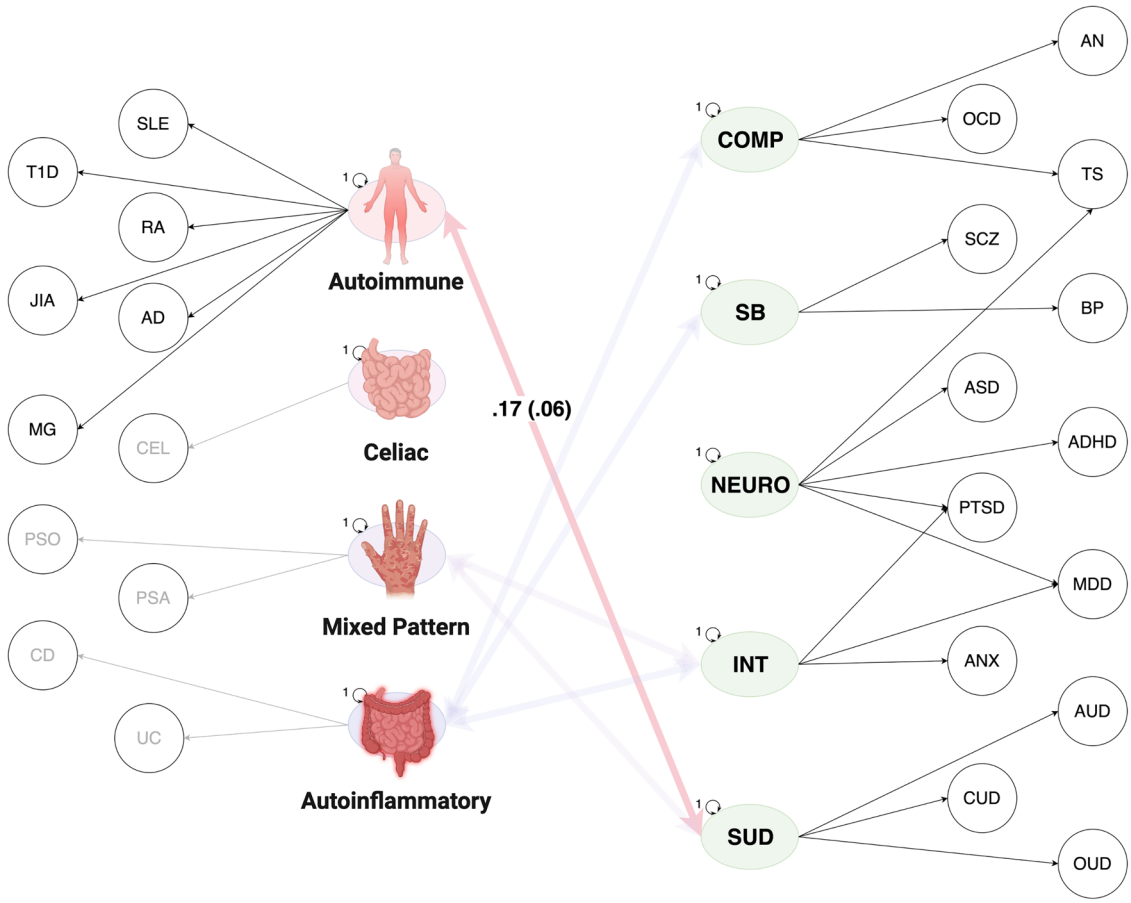

Fig. 3 Autoimmune diseases correlate with psychiatric disorders. Path diagram with standardized estimates for the correlated factors model used in genomic structural equation modelling with four factors of immune-mediated disease and five factors of psychiatric disorders. Latent variables are represented as circles. The genetic component of each phenotype is represented with a circle because the genetic component is a latent variable that is not directly measured but is inferred using linkage disequilibrium score regression. Single-headed arrows are factor loadings; double-headed arrows connecting back to the same origin are variances; and double-headed arrows connecting two variables are correlations. All residual variances, factor loadings, non-significant correlations, as well as significant correlations with factors other than the autoimmune factor are left out for simplicity, but all factors are allowed to correlate in this model. Disease abbreviations are defined in Table 1.

diseases. The pervasive nature of these comorbidities and associations indicates that reported risk sharing may be operating at a much broader level that is shared across multiple disorders. In support of this, previous research [40] has found common upstream pathways for stress related disorders (i.e. PTSD) and autoimmune diseases. While this supports the findings of the current study, the research collapses across multiple autoimmune diseases. We build on this work by utilizing Genomic SEM, alongside the unique ability of genetics to bring together data from even mutually exclusive participant samples into a unified statistical model, to formally test the multivariate system of relationships across a comprehensive set of psychiatric disorders and immune-mediated diseases. Identified inter-factor genetic correlations capture overlapping signal across clusters of psychiatric and immune-mediated diseases and recharacterize prior bivariate findings as indexing broader patterns of risk-sharing that is shared across multiple psychiatric and immune disorders. For example, we find that previously described pairwise genetic associations between schizophrenia [41, 42] and bipolar disorder [43] and ulcerative colitis and Crohn's disease likely reflect shared pathways across this broader set of four disorders. Further support for the idea that pairwise associations between two disorders often reflect broad pathways shared among multiple disorders comes from previous research that has identified 11 genes that were co-expressed between schizophrenia, ulcerative colitis and Crohn's disease and mainly enriched in immune-related signal transduction [42]. In addition, recent research utilizing Mendelian randomization has found a causal effect of schizophrenia on irritable bowel syndrome which is and umbrella term for both ulcerative colitis and Crohn's disease [44]. Given the sheer volume of research conducted in this area, our findings provide a critical context for interpreting these autoinflammatory risk pathways as operating at the level of shared signal across schizophrenia and bipolar disorder.

For three out of six significant immune–psychiatric relationships, specific genes explained a significant proportion of the genetic correlation between the factors. This included *RP1-265C24.8* and *ZSCAN12P1* for the genetic association between the mixed pattern disease factor and the internalizing disorders factor and *C3orf62* for the autoinflammatory diseases and compulsive disorders relationship. In addition, *MED24* was found to have antagonistic pleiotropy for the autoinflammatory diseases and internalizing disorders relationship. One way to conceptualize this is that the positive genetic correlation between the autoinflammatory and internalizing factors at the genome-wide level may be an underestimate of total shared signal given more localized, opposite direction (antagonistic) effects, like we observed for *MED24*. All identified genes have previously been associated with immune function, with *MED24* linked to eosinophil [45] and neutrophil [46] counts, which are types of white blood

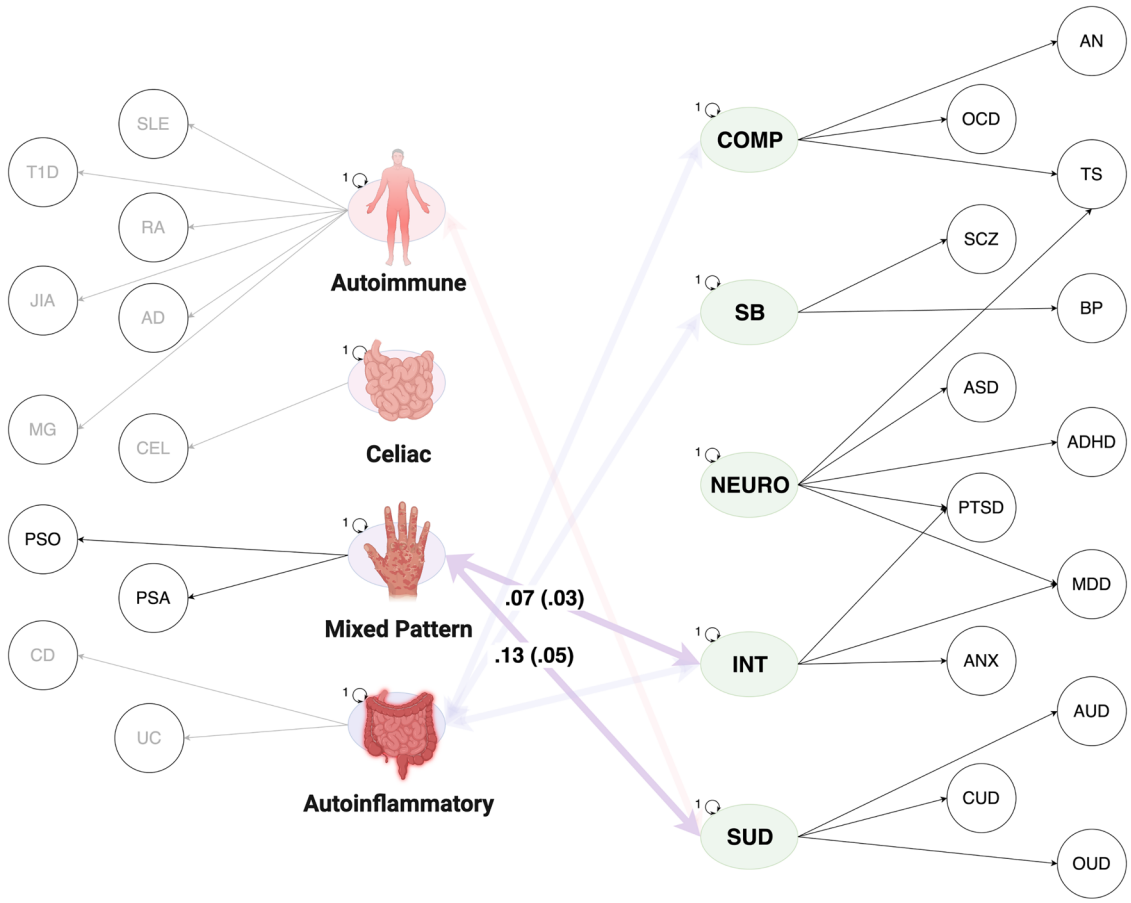

Fig. 4 Mixed pattern diseases correlate with psychiatric disorders. Path diagram with standardized estimates for the correlated factors model used in genomic structural equation modelling with four factors of immune-mediated disease and five factors of psychiatric disorders. Latent variables are represented as circles. The genetic component of each phenotype is represented with a circle because the genetic component is a latent variable that is not directly measured but is inferred using linkage disequilibrium score regression. Single-headed arrows are factor loadings; double-headed arrows connecting back to the same origin are variances; and double-headed arrows connecting two variables are correlations. All residual variances, factor loadings, non-significant correlations, as well as significant correlations with factors other than the mixed pattern factor are left out for simplicity, but all factors are allowed to correlate in this model. Disease abbreviations are defined in Table 1.

cells and important immune markers. These genes index potential biological pathways underlying the genetic relationship of the immune-mediated disease and psychiatric disorder association, that should be further investigated and followed up on regarding potential drug repurposing.

Initially significant genetic associations between the substance use disorders factor and the autoimmune and mixed factors, as well as the autoinflammatory and compulsive disorders factors, became non-significant after adjusting for genetic overlap with BMI or smoking. The mixed pattern and internalizing disorders relationship also became non-significant after accounting for smoking, but not BMI. Attenuation of these factor-factor relationships by accounting for genetic effects of BMI and smoking should further be investigated and could potentially reflect systematic effects of these phenotypes on overall mental and physical health, including the immune system.

Significant residual genetic correlations between specific pairs of psychiatric and immune-mediated diseases, indexing genetic signal specific to individual disease-disorder pairs, rather than operating via the factors that capture broader risk sharing across multiple diseases and disorders, pointed towards more circumscribed relationships across psychiatric and immune disorders. In addition, these residual genetic correlations revealed associations that were not apparent in the zero-order genetic correlations. For example, it was only when parsing out shared signal across bipolar and schizophrenia that divergent autoimmune associations emerged, with schizophrenia and bipolar showing positive (risk conferring) and negative (protective) residual associations, respectively. In particular, schizophrenia showed a high level of residual overlap with Addison's disease. In combination with the factor level results highlighted above, autoinflammatory conditions then appear to index a component of what is shared across schizophrenia and bipolar disorder, while autoimmune conditions capture a source of genetic divergence.

Out of five total Q_{Factor} results in our model, three were identified for the neurodevelopmental disorders factor alone, indicating that this specific psychiatric factor does not index shared pathways with immune-mediated disease. This result was driven by largely positive associations for ADHD relative to ASD's unique pattern of negative associations with immune-mediated diseases. This finding is inconsistent with prior results linking ASD to increased risk for immune-mediated conditions [47]. However, review articles have noted inconsistencies in this association [48] or highlighted that these links may stem from the prenatal environment (e.g., maternal infection) [49].

Limitations and future directions

Due to differences in the correlational structure in the genome, the analyses presented here must be conducted within a particular genetic ancestry. GWAS data was of sufficient sample size only in

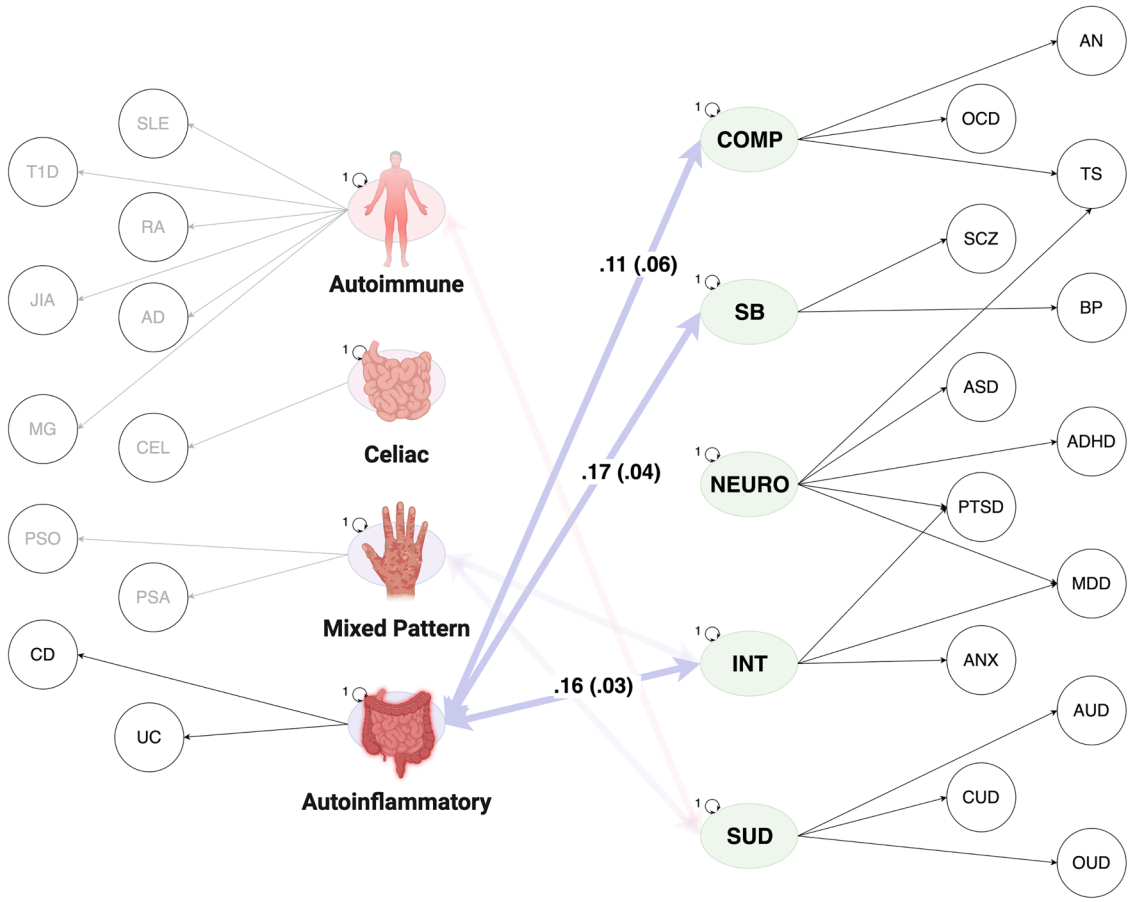

Fig. 5 Autoinflammatory diseases correlate with psychiatric disorders. Path diagram with standardized estimates for the correlated factors model used in genomic structural equation modelling with four factors of immune-mediated disease and five factors of psychiatric disorders. Latent variables are represented as circles. The genetic component of each phenotype is represented with a circle because the genetic component is a latent variable that is not directly measured but is inferred using linkage disequilibrium score regression. Single-headed arrows are factor loadings; double-headed arrows connecting back to the same origin are variances; and double-headed arrows connecting two variables are correlations. All residual variances, factor loadings, non-significant correlations, as well as significant correlations with factors other than the autoinflammatory factor are left out for simplicity, but all factors are allowed to correlate in this model. Disease abbreviations are defined in Table 1.

individuals of European ancestry, but future work extending these analyses to other ancestral groups is of vital importance. The Major Histone Complex (MHC) has a highly complex LD structure [50] and was excluded from the current analyses as this can bias results from LDSC [18]. Yet, this genomic region is highly relevant for both innate and adaptive immune pathways, with the MHC region coding for the human leukocyte antigen (*HLA*) gene [51]. In addition, the MHC region is often significantly associated with psychiatric GWAS for a wide range of disorders [8]. It is important to note that genetic associations between immune-mediated diseases and psychiatric disorders reported here solely reflect shared genetic effects and potential immune-mechanisms outside of this genomic region. Future research, along with methods developed to estimate genetic overlap in this LD complex region, should investigate the role of the MHC region in the link between immune-mediated diseases and psychiatric disorders. The present study clarifies that the psychiatric-immune link exists beyond just the MHC region and contributes to the significant genetic association between the two classes of diseases. In addition, certain autoimmune diseases, but not autoinflammatory diseases, are more predominant in females [52, 53]. Further, the prevalence of certain psychiatric disorders also differs by biological sex [54], indicating that future analyses would benefit from considering sex-specific genetic links between autoimmune disease and psychiatric disorders. Sensitivity analyses, benchmarking the strength of the significant associations we find against height, showed that height was also significantly genetically correlated with the internalizing and substance use disorders factors. The genetic correlation between the internalizing factor and both the mixed pattern disease factor and height were similar in magnitude, indicating that this may not reflect a particularly specific level of risk sharing. However, the remaining immune-psychiatric genetic correlations were approximately twice as large as for height. Finally, while we found different genetic associations of autoimmune and autoinflammatory diseases with psychiatric disorders, it is not clear from this study alone whether differences in the underlying biological mechanisms between the adaptive and innate immune system are responsible for divergent association patterns of these two ends of the spectrum of immune-mediated diseases. Given known biological systems and immune markers (e.g., C-reactive protein [55, 56]) associated with immune-mediated disease, future work should gain a more complete, mechanistic understanding of this psychiatric-immune link by examining the potential role of these intermediate biological processes.

Conclusion

The phenotypic literature describes widespread associations across pairs of immune-mediated and psychiatric disorders. The current study leveraged the unique ability of genomics to bring together different participant samples in the same statistical model to perform a multivariate examination of these two illness

domains. In doing so, our findings revealed varying levels of risk sharing, from pervasive associations between psychiatric disorders identified for the autoinflammatory disease factor, to more specific relationships between certain psychiatric clusters and either the autoimmune or autoinflammatory diseases. Additionally, we observed genetic signal specific to individual immune-mediated diseases and psychiatric disorders, as highlighted by significant residual genetic correlations. Collectively, these results add to our understanding of the different levels of risk sharing across immune-mediated diseases and psychiatric disorders.

CODE AVAILABILITY

All results were produced using *GenomicSEM* version v0.0.5 (https://github.com/GenomicSEM/GenomicSEM) and *FUSION* (https://github.com/gusevlab/fusion_twas).

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AUTHOR CONTRIBUTIONS

SB and ADG conceived and designed the study. SB, JML, LSS and ADG analyzed the data and SB, YHL, EWK, AK, JML, LSS, and ADG interpreted the outcomes. SB drafted the manuscript. ADG supervised the study. All authors contributed to the writing and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. The data utilized in this study were obtained from publicly available databases. This study did not involve direct research on human participants, animals, or identifiable images; therefore, no additional ethical approval was required. All original studies obtained the necessary ethical approval and informed consent from participants.

ADDITIONAL INFORMATION

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