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RESEARCH REPORT

Polygenic liability to C-reactive protein defines immunometabolic depression phenotypes and influences antidepressant therapeutic outcomes

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Inflammation has been implicated in the pathophysiology of major depressive disorder (MDD), with elevated serum C-reactive protein (CRP) and CRP polygenic scores (PGSs) previously associated with atypical symptoms and treatment outcomes. However, few studies have examined genetic CRP liability in relation to both depressive symptom profiles and pharmacological response within the same patient cohort. We investigated 1059 Caucasian patients with MDD from the European Group for the Study of Resistant Depression (GSRD) who received ≥ 4 weeks of antidepressant treatment. Depression severity was measured using Montgomery–Åsberg Depression Rating Scale (MADRS), with patients categorized as responders, nonresponders, or treatment-resistant cases. CRP-PGS were computed from individual-level genotypes using L1-penalized regression weights (snpnet) based on UK Biobank Genome-wide association studies (GWAS) training data (n = 223,327), and scores were standardized. Associations were tested through univariable and multivariable models controlling for population stratification and established prognostic variables. Higher CRP-PGS correlated with greater body mass index, lower employment status, and less weight and appetite loss following treatment. Notably, CRP-PGS demonstrated significant differences between treatment outcome groups ($F = 3.52$, $p = 0.03$), with highest values observed in treatment-resistant patients yet also elevated among responders compared to nonresponders, indicating a nonlinear relationship. When controlling for age, episode frequency, suicidal ideation, anxiety comorbidity, employment status, functional disability scores, antipsychotic comedication, illness duration, and previous antidepressant trials, CRP-PGS retained an independent and stronger association with treatment outcome ($F = 7.69$, $p < 0.001$), with CRP-PGS accounting for an additional 1.9% of outcome variance. CRP-related genetic liability may delineate an immunometabolic subtype of MDD characterized by metabolic dysregulation, which may modestly influence therapeutic efficacy. CRP-PGS captures independent prognostic information beyond conventional staging approaches and may facilitate inflammation-guided treatment selection.

Keywords: Major depression, inflammation, C-reactive protein (CRP), treatment-resistant depression (TRD), polygenic risk scores, immunometabolic depression.

Introduction

Major depressive disorder (MDD) is characterized by a variable clinical presentation, illness course, and response to treatment (1–5). A substantial proportion of patients fail to achieve adequate remission with first-line therapies (6, 7). This heterogeneity is linked, at least in part, to biological markers that could predict clinical variability and guide personalized treatment (8).

Genome-wide association studies (GWAS) implicated hundreds of common variants in disease susceptibility (9) but other biological factors modulate depression as well. Inflammatory aspects are in fact well known in depression (10), circulating C-reactive protein (CRP) levels are elevated in roughly one-quarter of depressed patients and track with greater overall symptom burden and cardiometabolic features (11). These observations suggest that pathways regulating CRP could help explain differential patterns of depressive psychopathology and suggest possible personalized therapeutic strategies. Twin and Single Nucleotide Polymorphism (SNP)-based heritability estimates (∼35–40%) indicate a substantial genetic contribution to basal CRP concentrations. The largest trans-ancestry GWAS to date (N ≈ 575 k) mapped 266 independent loci and provides highly powered summary statistics for building polygenic scores (PGS) that capture lifelong liability to higher CRP (12). Such CRP PGSs offer a stable instrument for interrogating inflammation–depression links without the confounding inherent in peripheral protein assays.

Emerging PGS work supports a symptom-specific signal. In three independent cohorts (UK Biobank, MARS, STAR*D), a higher CRP-PGS was associated with neurovegetative symptoms, especially appetite change, fatigue and (to a lesser extent) anhedonia, using network analytic methods (13). More recently, a population-scale Lifelines study showed that a CRP genetic risk score predicted higher negative affect and increased risk of anxiety disorders, extending inflammatory genetic influences beyond somatic symptoms (14). Together, these findings

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Table 1. Correlation of main clinical and sociodemographic variables with CRP-PGS

Variable	Mean ± SD (N)	CRP-PGS[a] correlation (r)	*p*-value	q-value
Age (years)	51.81 ± 13.78 (N = 1057)	0.03	0.354	0.547
MADRS[b] total (retrospective)	34.38 ± 7.53 (N = 1059)	0	0.918	0.918
MADRS total (current)	24.72 ± 11.36 (N = 1059)	0	0.916	0.918
Education	2.78 ± 0.95 (N = 1051)	− 0.04	0.151	0.321
Working status (low to high)	**2.24 ± 1.31 (N = 1054)**	**− 0.06**	**0.047**	**0.160**
BMI[c] (kg/m^2)	**25.69 ± 5.42 (N = 1057)**	**0.07**	**0.016**	**0.160**
SDS[d] Social	6.42 ± 2.66 (N = 1050)	− 0.01	0.78	0.918
Loss of weight (HAMD[e] current)	**0.38 ± 0.65 (N = 1059)**	**− 0.07**	**0.02**	**0.160**
Reduced appetite (MADRS current)	**1.39 ± 1.53 (N = 1059)**	**− 0.06**	**0.044**	**0.160**
Suicidal thoughts (MADRS current)	1.27 ± 1.43 (N = 1059)	0.05	0.084	0.238
Episode duration (days)	215.81 ± 189.43 (N = 918)	0.05	0.099	0.240
Number of depressive episodes	3.59 ± 2.59 (N = 824)	− 0.02	0.538	0.736
Age at onset (years)	**36.93 ± 15.07 (N = 1005)**	**0.06**	**0.046**	**0.160**
Duration of disease (years)	14.97 ± 12.94 (N = 996)	− 0.04	0.253	0.430
Number of hospitalizations	5.27 ± 17.06 (N = 1001)	0.04	0.187	0.353
Suicidal risk	0.89 ± 1.09 (N = 1058)	0.01	0.816	0.918
Side effects total	1.03 ± 0.29 (N = 1058)	− 0.02	0.563	0.736

Bold indicates associations significant at $p < 0.05$. *p*-values are uncorrected given the confirmatory nature of the analysis. Benjamini–Hochberg false discovery rate (FDR) q-values are reported. None survive $q < 0.05$, but the pattern of nominal associations (BMI, weight/appetite, age at onset, and working status) remains consistent with the immunometabolic profile.
[a]CRP-PGS: C-reactive protein polygenic score.
[b]MADRS: Montgomery–Åsberg Depression Rating Scale.
[c]BMI: body mass index.
[d]SDS: Sheehan Disability Scale.
[e]HAMD: Hamilton Depression Rating Scale.

suggest that inflammation-related genetic load may shape a specific immunometabolic depressive profile.

Inflammatory markers have also been linked to pharmacological outcomes. Baseline serum CRP levels differentially predicted response to the selective serotonin reuptake inhibitor (SSRI) escitalopram versus the norepinephrine reuptake Inhibitor (NRI) nortriptyline in the GENDEP trial, with higher CRP favoring noradrenergic therapy (15). Extending this to inherited risk, a higher CRP-PGS modestly interacted with the same two drugs in GENDEP, producing an opposite directional pattern compared with serum CRP and underscoring the importance of disentangling state versus trait inflammation (16). A systematic review of therapy-genetic studies further highlights CRP-PGS as one of the few nonpsychiatric scores repeatedly associated with antidepressant efficacy, although effect sizes remain small and replication limited (17).

Despite these advances, no study has jointly examined how CRP-PGS influences both depressive symptom architecture and treatment response within the same analytic framework. Addressing this gap could clarify whether genetic predisposition to higher CRP delineates a clinically actionable biotype that is prognostic of antidepressant treatment outcome and characterized by a specific constellation of symptoms. Here, we therefore (i) test associations between CRP-PGS and fine-grained depressive symptom dimensions, and (ii) evaluate whether CRP-PGS moderates acute antidepressant efficacy in a large, deeply phenotyped cohort (2). Elucidating these links may inform inflammation-stratified precision approaches in MDD and accelerate development of targeted immunomodulatory interventions.

Results

A total of 1059 Group for the Study of Resistant Depression (GSRD) patients with MDD had complete data and were included in the analysis. Table 1 reports the correlations of CRP-PGS with main clinical and sociodemographic variables.

Higher CRP-PGS was significantly associated with increased body mass index (BMI; $p = 0.016$), lower employment status ($p = 0.047$), earlier age at onset ($p = 0.046$), less weight and appetite reduction after treatment ($p = 0.02$ and $p = 0.044$, respectively) (Table 1). No associations were observed with overall depressive severity [current or retrospective Montgomery-Åsberg Depression Rating Scale (MADRS) total], episode duration, or total side effect burden. Full correlation results are provided in Supplementary Table S1. Across individual symptom domains, CRP-PGS did not correlate with core affective symptoms (e.g., sadness, pessimism, and anhedonia), anxiety symptoms, or cognitive impairment. There was a trend toward higher CRP-PGS in patients with greater suicidal thoughts ($p = 0.084$), though this did not reach significance. Functional impairment and clinician-rated side effect domains showed no evidence of association with CRP-PGS.

CRP-PGS was associated with treatment outcome ($F = 3.52$, $p = 0.03$) with highest mean scores in treatment-resistant patients, followed by responders, and lowest in nonresponders (Figure 1; Supplementary

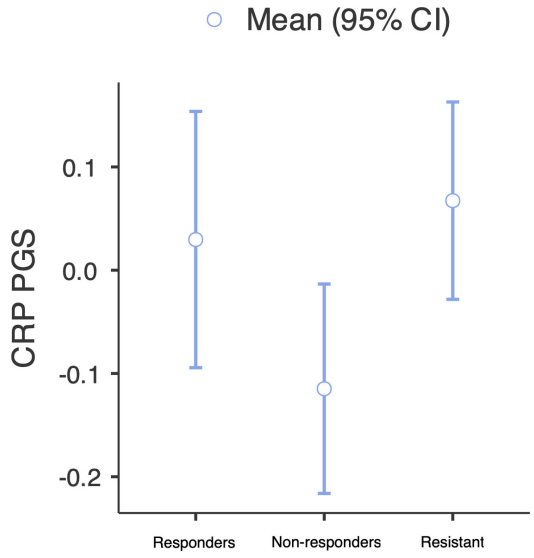

Figure 1. CRP-PGS and treatment outcome. Highest mean scores are observed in treatment-resistant patients, followed by responders, and lowest in non-responders.

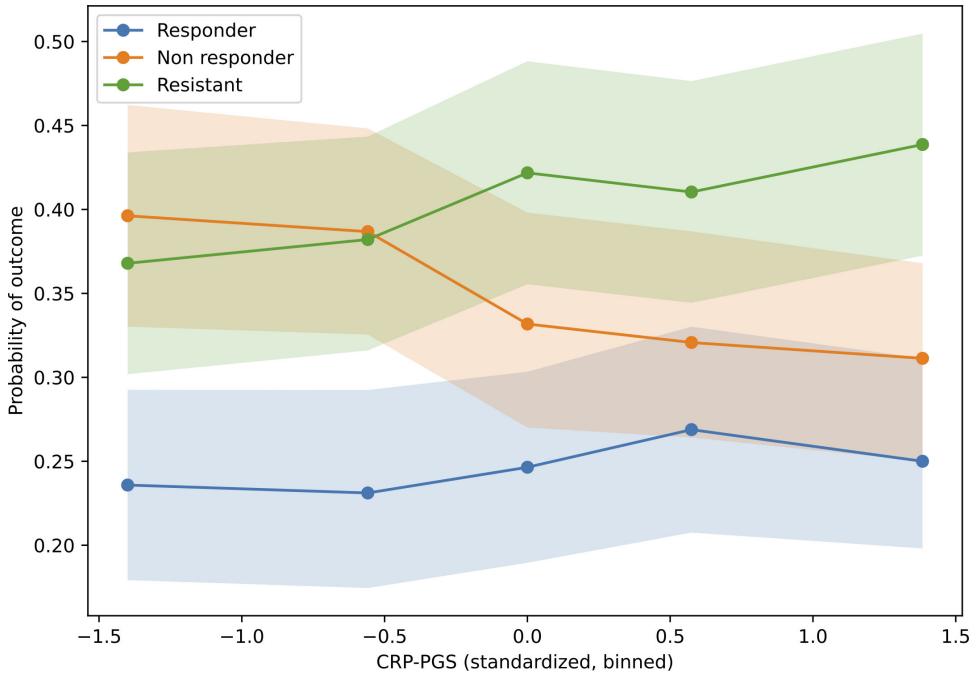

Figure 2. Observed outcome probabilities by CRP-PGS quintile with 95% bootstrap CI.

Tables S2 and S3), indicating a nonlinear pattern across treatment outcome categories. Given the nonlinear pattern, we tested a quadratic regression model (generalized linear model [GLM] with identity link), the quadratic term was statistically significant (β=0.16, $p = 0.013$), confirming a U-shaped relationship, with CRP-PGS levels lowest among nonresponders and higher among both responders and treatment-resistant patients. Residual diagnostics indicated no relevant violations of linear regression assumptions. When CRP-PGS was stratified into quintiles, the probability of being a nonresponder was highest in the lowest CRP-PGS quintile and declined thereafter, while both responder and treatment-resistant depression (TRD) probabilities showed a progressive increase at higher quintiles (Figure 2). Bootstrap 95% confidence intervals confirmed the robustness of these patterns. In the multivariable model, adding as covariates the factors previously associated with treatment resistance [age, number of depressive episodes, suicidal risk, anxiety disorders comorbidity, working status, Sheehan Disability Scale (SDS) social score, antipsychotic augmentation, duration of disease, and number of previous antidepressants], CRP-PGS remained independently associated with treatment outcome ($F = 7.69$, $p < 0.001$, PGS-pseudo-$R^2 = 1.9\%$).

Discussion

Our findings support the concept of an immunometabolic subtype of MDD that is partly modulated by common genetic variation influencing CRP. First, the CRP-PGS was positively associated with BMI and socioeconomic adversity and, in line with prior network-based work (13), selectively mapped onto weight-/appetite-related items rather than core mood or cognitive symptoms. Kappelmann *et al*. showed that a virtually identical CRP-PGS predicted increased appetite, fatigue, and anhedonia across three independent cohorts (UK Biobank, MARS, and STAR*D) (13), while the recent Lifelines mega-analysis extended genetic CRP effects to negative affect and anxiety disorders (14). The present replication in a pharmacologically treated sample strengthens the external validity of this symptom signature and supports the view that trait inflammation taps into energy-balance possibly related to reward-processing circuits that cut across traditional diagnostic boundaries. Polygenic scores, however, remain population-level probabilistic tools rather than deterministic tests for individuals, and should be interpreted as risk modifiers whose predictive utility always depends on the clinical context (18).

We also observed a small but significant association between higher CRP-PGS and antidepressant outcome: scores were highest in treatment-resistant patients yet, somewhat paradoxically, also among remitters relative to intermediate nonresponders. A V- or U-shaped pattern has been described before for state CRP, where both very low and very high serum concentrations predicted better outcomes than mid-range values in GENDEP (15). Our data suggest that a similar nonlinear relationship may exist at the level of inherited risk. One possibility is that very high CRP liability "pushes" patients toward more atypical, energy-rich symptom profiles that may respond better to dopaminergic or noradrenergic mechanisms, whereas modest CRP-PGS elevation may undermine serotonergic signaling and promote resistance. Consistent with this idea, Zwicker *et al*. found an interaction between CRP-PGS and drug class in GENDEP—higher scores favored escitalopram over nortriptyline despite the opposite effect for serum CRP (16). Importantly, the variance explained by CRP-PGS in our multivariable model was 1.9%, in line with earlier estimates (0.5–2%) from GENDEP and CAN-BIND (17). Although modest, this effect was independent of established clinical predictors embedded in the GSRD predictors algorithm (2), indicating that genetic inflammation captures information not already coded by chronicity, severity or comorbidity. However, this hypothesis should be tested in future studies.

The CRP-PGS applied in this study was derived from a single-cohort analysis of the UK Biobank using penalized regression (19), rather than from the larger trans-ancestry meta-GWAS of CRP levels (12). Nevertheless, the two GWASs are highly collinear and converge on hepatic endoplasmic reticulum stress, IL-6/JAK–STAT and lipid-metabolism pathways, lending plausibility to a mechanistic link between circulating CRP levels and systemic metabolic regulation. The genetic architecture of CRP is enriched for loci also implicated in cardiometabolic traits, consistent with epidemiological evidence that low-grade inflammation tracks both depressive symptoms and cardiovascular risk (11), suggesting pleiotropic effects that could underpin the excess cardiometabolic morbidity seen in TRD (20). This interpretation is further supported by recent work demonstrating local genetic correlations between insulin resistance-related conditions and neuropsychiatric disorders at immune-metabolic loci (21).

At the therapeutic level, accumulating trial data indicate that patients with high inflammatory burden may benefit from immune-targeted augmentation, for example, the infliximab proof-of-concept study where baseline hs-CRP > 5 mg/L predicted a ~4-point MADRS advantage over

placebo (22), or similar more recent studies (23). On the other hand, a consistent literature showed that higher CRP predicted better than placebo and low CRP predicted worse than placebo, antidepressant effects with add-on anti-inflammatory substances (24): given that most antidepressants share anti-inflammatory effects (10), which are well evident also in severe, nonpsychiatric inflammatory conditions (25), it is possible that nonlinear dynamics in the relationship between CRP and antidepressant response might arise from the individual sensitivity to these mechanisms, and the possible anti-inflammatory effects of the administered drugs. In indirect agreement with this hypothesis, the observation that: (i) PGS for CRP and CRP plasma levels can have opposite effects on antidepressant response (16); (ii) PGS000675 and many other PGS for CRP share a protective effect against the development of postpartum depression (PPD) in patients with MDD (26), despite PPD being associated with immune-inflammatory mechanisms (27) and higher circulating CRP levels (28); suggest that many factors associated with this biomarker and/or its PGS, might have an effect on the antidepressant phenotype. Interestingly, while some studies described a reduction of CRP before/after antidepressant treatment, although unrelated with its antidepressant effect in meta-regression analyses (29), other recent studies measuring CRP with high-sensitivity methods described an increase in high-sensitivity C-reactive protein (hsCRP) proportional to the antidepressant effects of both, escitalopram (30), paroxetine (31), and the immunomodulatory interleukin 2 (23). These latter observations again suggest individual effects and a nonlinear association of CRP with depressive psychopathology. Assuming linearity for the CRP association with depression may be even less appropriate when considering treatment nonresponse and treatment resistance, given that failing one, or two or more treatments, predicts very different future outcomes and clinical phenotypes. While a germline CRP-PGS cannot substitute for real-time protein assays in such trials, it could help prescreen individuals more likely to have persistently elevated inflammation even in clinical remission, thereby reducing misclassification when serial blood sampling is impractical. Specifying inflammation as a subtype of MDD in future diagnostic systems such as DSM-6 has recently been proposed (32), and tools such as CRP-PGS could play a supporting role in stratified care models. Accordingly, future prognostic work could integrate CRP-PGS with serum-CRP measurements so that both lifelong and current inflammatory burden are modelled together, a strategy that has already improved risk discrimination when genetic scores are combined with circulating biomarkers in cardiometabolic disease (33).

The present study comes with some strengths and limitations. Key strengths include (i) the use of a large, well-phenotyped, multicenter cohort (GSRD), (ii) the use of a validated, penalized-regression PGS with no discovery–target sample overlap, and (iii) comprehensive adjustment for known clinical moderators of TRD. Limitations include the cross-sectional design that limits causal inference, the naturalistic treatment that introduces heterogeneity in drug choice, dose and adherence, though this mirrors real-world care. The sample composition is exclusively of European ancestry, limiting generalizability of our findings across ancestries and warranting dedicated replication. Multiple testing was not formally corrected, any multiple testing correction would reduce observed findings to nonsignificant and for the association between CRP-PGS and substance abuse only 5 patients contributed to the significance; replication in an independent prospective cohort is essential.

Taken together, our results support a multilevel inflammation framework in which CRP genetics shape a distinct symptom cluster and partly predict pharmacological outcome. Integrating CRP-PGS with circulating biomarkers, other immune-related PGSs (e.g., for IL-6) and environmental exposures (smoking and adiposity) may boost predictive utility beyond the 2% ceiling reached by single scores. Future work should test for gene $\times$ serum CRP and gene $\times$ drug-class interactions in randomized designs, explore multi-omic signatures (methylation, proteomics, and metabolomics) of high CRP-PGS carriers, evaluate whether combining CRP-PGS with cardiometabolic PGSs improves risk stratification for the cardiometabolic sequelae of MDD, a major source of excess mortality.

In conclusion, a higher genetic propensity for elevated CRP delineates a small but clinically relevant component of depression heterogeneity that may modulate symptom expression and treatment response. Leveraging this information, if confirmed, in precision-psychiatry pipelines could help move beyond "one-size-fits-all" antidepressant prescribing toward inflammation-stratified care (34–36).

Methods

Sample and phenotypic characterization

Patients included in the present research were collected as part of the cross-sectional, naturalistic, multicenter European GSRD study. As detailed elsewhere (2, 37), adults with current MDD were diagnosed according to DSM IV-TR criteria; participants were naturalistically treated with at least one antidepressant drug at a sufficient dose for at least 4 weeks. Demographic and clinical data were collected as previously reported (37, 38). The MADRS (39) was administered at inclusion and to assess retrospectively symptoms at the beginning of the current episode (considering patients' interview and medical records). Patients were classified as responders if a reduction in total MADRS score $\geq$ 50% from baseline was obtained after $\geq$ 4 weeks of treatment; otherwise, they were considered as nonresponders. In case of nonresponse after two or more trials, patients were defined as TRD. Additional assessments included the SDS (40), Mini-International Neuropsychiatric Interview (MINI) (41), Hamilton Depression Rating Scale (HAMD) (42), and the Committee of Clinical Investigations side effect scale (43). All procedures of this study comply with the Helsinki Declaration and were approved by the local ethics committees of each research center involved in the study (coordinating center approval number: B406201213479). Written informed consent was provided by all patients included in this study.

Genotyping and quality control of the target dataset Genome-wide genotyping in GSRD was performed using the Illumina Infinium PsychArray 24 BeadChip (Illumina, Inc., San Diego) as previously reported (44). Briefly, SNPs and subjects were removed with a missing genotype rate $\geq$ 5%, genotyping rate $<$ 97%, sex discrepancies, abnormal heterozygosity, population outliers or high relatedness (identity by descent $>$ 0.1875) (45, 46). Minimac3 and reference data from the Haplotype Reference Consortium (HRC) r1.1 2016 were used for imputation. Variants with minor allele frequency $<$ 0.01, poor imputation quality ($r^2 < 0.30$), and genotype probability $<$ 0.90 were eliminated (47).

Statistical analyses CRP-PGS were computed using publicly available penalized regression weights derived from UK Biobank, as described by Sinnott-Armstrong *et al.* (19). Specifically, the PGS coefficients were obtained from the BASIL algorithm implemented in the snpnet R package, which applies L1-penalized multivariate regression (lasso) on high-dimensional genotype data. A UK Biobank subcohort including Europeans individuals only (N = 319,074; 70% training, 10% validation, 20% test split) was used to train and validate the prediction models for 35 biomarkers, including log-transformed CRP levels (19). The CRP-PGS used in this study is based on the optimal lasso model trained on 223,327 individuals and validated in an independent test set of 63,818 individuals. The model achieved an R^2 of 0.1215 for log-transformed CRP in the test set, indicating a robust predictive capacity for genetic liability to elevated CRP levels. Coefficients (BETA) for approximately 1.08 million variants were released through PGS Catalog entry PGS000675, and CRP-PGS were calculated in the target GSRD sample using the PLINK2 –score function (48). CRP-PGS were standardized and then were used as independent variables in univariable (correlations, *t* test, and analysis of variance) and multivariable analyses (general linear models and quadratic term) including previously reported predictors (2), adjusting for two population principal components (49). All analyses were performed using Python version 3 for MacOS (pandas, numpy, scipy.stats, statsmodels, and matplotlib) (50) and PLINK2 (48). The statistical significance level was set at $p = 0.05$, uncorrected because of the confirmative nature of the analysis given the previously reported studies on CRP-PGS and depression (51).

Data availability

The data are not publicly available due to privacy and ethical restrictions.

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Author contributions

AS oversaw the entire work, conducted and designed all analyses and wrote the manuscript. DS, SK, LB, JZ, SM, PF, DR, RF, GF, CF, RZ, FB, BB, and JM collected data, oversaw stages of the project and revised the manuscript. The manuscript has been read and approved by all authors. All authors take full responsibility for all data, figures, and text and approve the content and submission of the study. No related work is under consideration elsewhere. All authors state that all unprocessed data are available, and all figures provide accurate presentations of the original data. Corresponding authors: Professor AS for any aspect of the work and data analyses. The corresponding author takes full responsibility for the submission process.

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