

Plasma Lipid Alterations and Polygenic Risk Track Multidimensional Psychosis Severity Across Classical Diagnostic Boundaries

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Article

Keywords:

Posted Date: July 9th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9605572/v1>

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Additional Declarations: The authors have declared there is **NO** conflict of interest to disclose

Abstract

Schizophrenia (SCZ) and bipolar disorder (BD) are characterised by pervasive clinical heterogeneity, compromising biological discovery and individualized treatment. Data-driven clustering has identified a transdiagnostic severe psychosis subtype marked by high psychotic symptom load, cognitive impairment, and poor functioning, yet its biological underpinnings remain to be understood. To address this, we examined associations among 14 PRS, plasma lipidomics (361 species across 16 classes), and a machine-learning-derived severe psychosis probability score in a sample spanning the psychosis spectrum (PRS $n=1,190$; lipid subset $n=428$) in the PsyCourse study. Genetic risk and lipid profiles were both associated with illness severity but appeared to act independently: SCZ-PRS was positively associated with severe psychosis subtype probability ($q=0.045$), while BD-PRS ($q=0.02$) and educational attainment PRS ($q=0.045$) showed negative associations. Eight lipid classes were enriched with severe subtype probability, including increased sphingolipids (dSM, dCer), glycerophospholipids (PC, PE-P, PE), TAG, and CE, alongside decreased PC-P. Enrichment patterns were robust to adjustment for diagnosis, medication, and symptom severity. PRS and lipid profiles each explained 7–8% of variance, jointly ~16%. No significant mediation or shared genetic-lipidomic covariation was detected. Together, these findings suggest that polygenic liability and lipidomic dysregulation contribute to disease severity through partly independent pathways, and their convergence on a symptom-derived severity score supports the premise that multidimensional phenotyping can reveal biological structure that diagnostic categories alone obscure. The lipidomic signal points toward pharmacologically tractable pathways, particularly ether-lipid remodelling and sphingolipid dysregulation, suggesting that lipidomics and polygenic risk are complementary dimensions for understanding and ultimately treating severe psychosis.

Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are among the most severe mental disorders, arising from a complex and largely shared genetic, environmental, and biopsychosocial interplay (1). SCZ is characterised by persistent psychosis, negative symptoms, and cognitive impairment, while BD is defined by recurrent affective episodes that can include psychotic features; both disorders share substantial symptomatic and etiological overlap (2). Yet illness trajectories and treatment responses vary enormously - both across and within diagnostic boundaries (3,4). This pervasive heterogeneity limits the utility of diagnostic categories as units of biological analysis and complicates the development of targeted treatments (5).

Heterogeneity can be reduced using unsupervised machine-learning techniques, enabling data-driven discovery of patient groupings that can enhance homogeneity and thus precision of downstream biological analyses (6–8). We previously used unsupervised learning in the PsyCourse study and identified five stable clinical psychosis subtypes (9), including a “severe psychosis” subtype characterized by predominantly SCZ diagnoses, lower educational achievement, male sex, low verbal intelligence, high psychotic symptom load (but not depressive or manic symptoms), and impaired functioning. Longitudinal validation indicated that despite a predominantly chronic illness course,

individuals showed remitting symptoms and relapsing-remitting functional trajectories, suggesting treatment-responsiveness but persistent risk of functional relapse — highlighting this group as both clinically burdened and in need of optimized, targeted intervention (9). While exact replication of data-driven subtypes across datasets is inherently challenging given differences in sample composition and clinical variables, independent transdiagnostic clustering studies converge on a similarly severe, high-symptom, low-functioning subgroup of patients across datasets and modalities (10–12). Yet the molecular underpinnings of this severe phenotype remain poorly understood, representing a critical knowledge gap for targeted treatment development.

Genetic and metabolic factors likely contribute to the molecular underpinnings of this severe phenotype. Both SCZ and BD are highly heritable and share substantial common-variant genetic liability, with genome-wide association studies (GWAS) identifying hundreds of risk loci - many pleiotropic across the psychosis spectrum (13–15). Both disorders also show characteristic plasma lipidomic alterations (16,17), making polygenic risk and lipid metabolism natural biological candidates for investigation (18). Polygenic risk scores (PRS) aggregate common-variant liability into a continuous individual-level measure, showing robust associations with psychiatric categorical diagnoses (19,20). SCZ-PRS associates with psychotic features across diagnostic boundaries, while BD-PRS captures both manic and psychotic symptomatology (21). Additionally, broader PRS batteries have revealed shared genetic architecture underlying diverse clinical presentations (15,22,23). However, while PRS show robust associations with categorical diagnoses in large population samples, they typically demonstrate weaker effects when predicting symptom severity, functional outcomes, or treatment response in diagnosed individuals (22,23) - consistent with the fact that they index liability to a diagnostic category rather than specific aspects of the clinical presentation within it (24,25). In Dwyer et al. (9), diagnostic PRS for SCZ, BD, and major depressive disorder (MDD) showed no specificity for severe subtype membership; instead, educational attainment PRS (EA-PRS) showed the strongest association - prompting a call for more comprehensive, transdiagnostic PRS batteries (9). Using an expanded, hypothesis-driven PRS set from recent, larger GWAS spanning psychiatric, cognitive, and personality phenotypes, we revisit this question as the first of two biological investigations in the current study.

Lipid metabolism is the second biological candidate described to be altered in psychotic disorders (26–28) with partially shared plasma lipidomic alterations in SCZ and BD (16,29,30). As key structural and signaling components of brain tissue (31–33), lipids influence synaptic plasticity, neuroinflammation, oxidative stress, and neurodevelopmental processes (32–36). Our previous large-scale plasma lipidomic work in this dataset identified changes in ceramides, triglycerides, glycerophospholipids, and plasmalogens as a core SCZ-associated signal, replicable across independent cohorts (16). Critically, lipid pathways are pharmacologically actionable: plasma lipid profiles are altered by antipsychotic treatment (37–40), and adjunctive agents targeting these pathways like statins (41–43) and omega-3 fatty acids (44–46), have shown mixed efficacy in psychotic disorders, suggesting that better patient stratification may be key to improving therapeutic translation. Notably, lipid metabolism genes are enriched among psychiatric GWAS loci in SCZ, BD, and MDD (16,47,48), raising the question whether

genetic liability and lipidomic dysregulation represent overlapping or truly independent biological dimensions of severe psychosis.

Yet, lipidomic associations with psychosis *severity* specifically have yielded heterogeneous results (16,49,50). Two limitations of prior work may explain this. First, diagnostic categories conflate biologically distinct subgroups, potentially blurring within-disorder lipidomic signal (5). Second, unidimensional symptom scales capture only a fraction of illness complexity: Tkachev et al. (16) found the SCZ-associated lipidomic profile to be largely invariant across PANSS severity subgroups - consistent with it indexing diagnostic category rather than illness burden. Since psychosis severity is multidimensional and spans positive and negative symptoms, cognitive impairment, and functional disability, the full phenotype may not be appropriately captured by a single rating scale. The severe psychosis subtype offers an alternative: a clinically homogeneous group defined by this multidimensional complexity, against which broader phenotypic variation can be assessed, potentially revealing a lipidomic signal that category- and symptom-scale-based approaches might have missed.

Hence, in this study, we investigate PRS and plasma lipidomic associations with a machine-learning-derived multidimensional severe psychosis subtype probability score in the PsyCourse study, treating it as a continuous dimension of illness burden rather than a discrete category. We further test whether polygenic risk and lipidomic dysregulation operate through shared or independent biological pathways, and contextualize both signals against categorical and unidimensional approaches to establish what multidimensional transdiagnostic phenotyping adds to conventional approaches.

Materials and Methods

Participants

The PsyCourse Study (www.psycourse.de, (51)) is a longitudinal transdiagnostic deep-phenotyping study (52). We included 1,320 participants diagnosed with SCZ, brief psychotic disorder, schizoaffective disorder, recurrent depression or BD (DSM-IV), with genomic data available for $n=1,190$ and plasma lipidomic data for a subset of $n=428$, hereafter quality control. Participants with recurrent depression ($n=94$, 7.9% of the genomic sample) were retained to maintain consistency with the original PsyCourse clustering study (9); notably, no individuals with recurrent depression were present in the lipidomics subset, and the primary findings are therefore driven by SCZ and BD participants. Written informed consent was obtained from all participants. The study was approved by all relevant Ethics Committees (52) and was conducted in accordance with the Declaration of Helsinki.

Severe Psychosis Subtype Probability

The severe psychosis subtype probability score was derived in the current sample by applying a support vector machine (SVM) classifier trained on the 45 most discriminative features selected in the original sparse SVM solution (9). These features form a sparse representation of the 188-variable battery of

baseline symptom, functioning, demographic, and clinical history measures used to define the subtype (9), generating a probability score (0-1) for each participant. This approach treats severe psychosis not as a discrete category but as a continuous dimension of illness burden, capturing where each individual sits along a spectrum of psychotic severity. Full details about the SVM and probability score calculations are in Supplementary Methods, Supplementary Table 1 and Supplementary Figure S1.

Genotyping and Polygenic Risk Scores

Genotyping and quality control procedures have been described previously (53). We computed a hypothesis-driven battery of 14 PRS encompassing psychiatric liability (13,14,54–56), cognitive function (57,58), and traits relevant to psychosis pathophysiology (59,60) using PRS-CS (61). Additionally, lipid-pathway-enriched PRS for statistically significant PRS were constructed by restricting SNPs to regions within ± 50 kb of lipid metabolism genes (REACTOME_METABOLISM_OF_LIPIDS; MSigDB v2023.2 (62)). All PRS were standardized prior to analysis. Full details are in Supplementary Methods.

Lipidomics

Non-fasting plasma samples were quantified by untargeted LC-MS as previously described (16). After quality control which included the removal of fasting-status-affected lipid species (16), 361 annotated lipid species across 16 classes were retained, including triacylglycerides (TAG), acylcarnitines (CAR), phosphatidylcholines (PC), phosphatidylcholines plasmalogens (PC-P), ceramides (Cer), phosphatidylethanolamines (PE), phosphatidylethanolamine plasmalogens (PE-P), fatty acids (FA), sphingomyelins (SM), plasmanyolphosphatidylcholines (PC-O), cholesteryl esters (CE), diacylglycerols (DAG), lysophosphatidylcholines (LPC), lysophosphatidylcholine plasmalogens (LPC-P), lysoplasmanyolphosphatidylcholines (LPC-O), and lysophosphatidylethanolamines (LPE). Lipid intensities were log₂-transformed and z-score standardized; lipid class scores were computed as the mean of within-class z-scores. Full details are in Supplementary Methods.

Statistical Analysis

PRS and lipid species associations with severe psychosis subtype probability were tested using heteroskedasticity-robust (HC3) OLS regression, with age, sex, and the first five ancestry principal components as covariates for PRS models (n=1,190) and sex, age, Body Mass Index (BMI), duration of illness, and smoking status for lipid models (n=428). Sensitivity analyses were additionally adjusted for diagnosis, medication (number of drugs per medication class, e.g., mood stabilizers, tranquilizers, antidepressants and antipsychotics), and Positive and Negative Symptoms Scale (PANSS)-subscale scores (63). Results were FDR-corrected (Benjamini-Hochberg). Missing values in the covariates were imputed with a n=7 k-nearest-neighbours approach.

Lipid class enrichment was based on a gene-set-enrichment-analysis (GSEA) approach, ranking species

by signed regression coefficients and testing class-level enrichment via 5,000 permutations, yielding normalized enrichment scores (NES) and FDR-corrected q-values.

To quantify independent and joint contributions of both biological layers, we performed an incremental R^2 decomposition in the overlapping subsample, with each feature block residualized against its appropriate covariates. Statistical significance was assessed via permutation testing (20,000 permutations).

To probe genetic-lipidomic integration, we performed bootstrap mediation analysis (5,000 resamples) testing whether enriched lipid classes mediated PRS-severity associations, and canonical correlation analysis (CCA; 1 component, 10,000 permutations) testing shared multivariate structure between PRS and lipid class profiles. Full methodological details are in Supplementary Methods.

All analyses were performed in Python 3.12 and the significance level was $\alpha=0.05$.; code is available at <https://github.com/anthano/psycourse>.

Results

Participant Characteristics

Demographic and clinical characteristics of the PRS sample (n=1,190) and the lipidomics subset (n=428) are presented in **Table 1**. The lipidomics subset differed from the PRS sample in containing a higher proportion of BD diagnoses (56.3% vs. 44.0%), male participants (61.2% vs. 55.4%), and mood stabilizer use (44.2% vs. 36.7%). Severe psychosis subtype probability was comparable across samples ($p=0.121$) and was right-skewed, consistent with the low base rate of the severe subtype in the sample (**Supplementary Figure S2**); HC3-robust regression was used throughout to account for potential heteroskedasticity.

Table 1. Demographic and Clinical Characteristics of the PRS Sample and Lipid Subset

Characteristic	PRS Sample (n = 1190)	Lipid Subset (n = 428)	Test
Demographics			
Age, mean (SD), years	42.9 (13.1)	42.1 (13.5)	$t = 1.05, p = 0.293$
Sex, n (%)			$\chi^2 = 4.14, p = 0.042$
Male	659 (55.4%)	262 (61.2%)	$\chi^2 = 4.14, p = 0.042$
Female	531 (44.6%)	166 (38.8%)	$\chi^2 = 4.14, p = 0.042$
BMI, mean (SD), kg/m ²	28.1 (6.1)	28.3 (6.2)	$t = -0.50, p = 0.620$
Diagnosis, n (%)			
Bipolar disorder	524 (44.0%)	241 (56.3%)	$\chi^2 = 18.54, p < 0.001$
Recurrent depression	94 (7.9%)	0 (0.0%)	$p < 0.001$
Schizophrenia spectrum	572 (48.1%)	187 (43.7%)	$\chi^2 = 2.25, p = 0.134$
Clinical Variables			
Duration of illness, mean (SD), years	12.6 (10.7)	11.9 (10.5)	$t = 1.09, p = 0.278$
Lifestyle Factors			
Smoking status, n (%)			$\chi^2 = 0.75, p = 0.686$
Current	640 (53.8%)	222 (51.9%)	$\chi^2 = 0.39, p = 0.533$
Former	220 (18.5%)	78 (18.2%)	$\chi^2 = 0.00, p = 0.962$
Never	330 (27.7%)	128 (29.9%)	$\chi^2 = 0.63, p = 0.427$
Medication			
Antipsychotic use, n (%)	951 (79.9%)	343 (80.1%)	$\chi^2 = 0.00, p = 0.977$
Mood stabilizer use, n (%)	437 (36.7%)	189 (44.2%)	$\chi^2 = 7.03, p = 0.008$

Antidepressant use, n (%)	476 (40.0%)	177 (41.4%)	$\chi^2 = 0.19$, $p = 0.665$
Total medications, mean (SD)	2.4 (1.3)	2.5 (1.2)	$t = -1.29$, $p = 0.198$
Severe Psychosis Subtype			
Severe psychosis subtype probability, mean (SD)	0.126 (0.237)	0.107 (0.209)	$t = 1.55$, $p = 0.121$

Note. BMI = body mass index; PRS = polygenic risk score. p-values reflect comparisons between the PRS sample and Lipid Subset. Significance level was $\alpha = 0.05$

PRS Associations

Three out of 14 tested PRS showed significant associations with severe psychosis subtype probability: higher SCZ-PRS ($\beta=0.02$, $q=0.045$), lower BD-PRS ($\beta=-0.02$, $q=0.02$), and lower educational attainment PRS ($\beta=-0.02$, $q=0.045$) (**Figure 1A**). Lipid-pathway-enriched versions of these three PRS showed no significant associations with severe subtype probability (all $q>0.05$; **Supplementary Table 5**). Further, lipid-pathway-enriched PRS showed modest correlations with their corresponding PRS (BD-PRS and Lipid-BD-PR: $r=0.3$, SCZ-PRS and Lipid-SCZ-PRS: $r=0.31$, and EA-PRS and Lipid-EA-PRS: $r=0.32$) (**Figure S3**).

Lipid Species Associations

Four lipid species were significantly associated with severe psychosis subtype probability after FDR correction: PE-P 42:5 ($\beta=0.05$, $q<0.001$), PE-P 40:4 ($\beta=0.03$, $q=0.006$), PE-P 40:5 ($\beta=0.04$, $q=0.039$), and PE 40:5 ($\beta=0.04$, $q=0.039$) (**Figure 1B**). Three of these belong to the PE-P class. After controlling for diagnosis and number of antipsychotics and mood stabilizers, respectively, no individual species remained significant (**Supplementary Figure S4**).

Lipid Class Enrichment

In the primary model, eight lipid classes showed significant enrichment ($q<0.05$) with the severe psychosis subtype probability (**Figure 2**). The sphingolipid classes dSM (NES=1.554, $q=0.001$) and dCer (NES=1.250, $q=0.015$), as well as the glycerophospholipid classes PC (NES=2.308, $q=0.001$), PE-P (NES=1.766, $q=0.002$) and PC-O (NES=1.636, $q=0.027$), the glycerolipid TAG (NES=1.042, $q=0.001$), and sterol lipid CE (NES=1.895, $q=0.012$) were positively enriched. PC-P (NES=-1.410, $q=0.002$) was negatively associated with severe psychosis probability. Enrichment patterns shifted after adjusting for diagnosis, with four classes remaining significant (dSM, dCer, PE, PC-O) and PC-O reversing direction

(NES=-1.528, $q=0.010$), suggesting diagnosis-related confounding for this class. After adjusting for medication, six classes were significant (dSM, TAG, PC, PC-P, PE-P, PC-O), with PC-O again reversing direction (NES=-1.373, $q=0.001$), consistent with treatment-related confounding. To control for each medication class individually, we performed an additional sensitivity analysis adjusting for each medication class in turn (**Supplementary Figure S8**). The core signal - PC, PC-P, dSM, TAG, and PE-P - remained significant across all four medication-adjusted models. The exception was PC-O, which reversed to negative enrichment specifically following mood stabilizer adjustment (NES=-1.65, $q=0.007$) but not after adjustment for antipsychotics, antidepressants, or tranquilizers, suggesting that the PC-O instability observed in the primary medication-adjusted model is driven predominantly by mood stabilizer use. After controlling for both diagnosis and medication, PC-O (NES=-2.095, $q=0.002$) and CAR (NES=-1.242, $q=0.01$) were negatively enriched, dSM (NES=1.592, $q=0.002$) and PE (NES=1.184, $q=0.031$) were positively enriched. The class showing the most consistent enrichment across all models was dSM, while PC-O was the least robust. Lipid class enrichment findings were broadly robust to additional adjustment for PANSS subscale scores, with the majority of enriched classes remaining significant across positive, negative, general, and total scale scores (**Supplementary Figure S7**). To further characterize the relationship between lipid class enrichment and symptom severity, we additionally ran enrichment analyses using PANSS positive, negative, general, and total scores as primary outcomes. PE-P and dSM showed robust enrichment across all four subscales. PC enrichment reversed direction between the severe psychosis probability (positive enrichment) and PANSS Positive (negative enrichment; NES=-1.53, $q=0.040$). CAR showed significant negative enrichment specific to PANSS Negative (NES=-1.22, $q=0.001$), absent from all other subscale and severe psychosis probability models. Full per-subscale enrichment statistics are reported in Supplementary Results.

Integrated Analysis

In our incremental R^2 decomposition analysis, results were consistent across block-specific residualized and raw covariate-adjusted model specifications (**Supplementary Tables 32-33**) and we report the residualized estimates below. The PRS battery explained 7.4% of variance in severe psychosis subtype probability beyond its respective covariates ($\Delta R^2=0.074$, $p=0.018$), and lipid class scores explained 8.6% beyond theirs ($\Delta R^2=0.086$, $p=0.012$). Both blocks retained their explanatory capacity when conditioned on the other: PRS explained 7.1% of variance beyond lipids ($\Delta R^2=0.071$, $p=0.025$) and lipids explained 8.4% beyond PRS ($\Delta R^2=0.084$, $p=0.016$). The joint model explained 15.7% of variance ($\Delta R^2=0.157$, $p=0.001$), indicating a shared variance component of less than 0.3% (**Figure 3**). Individually, SCZ-PRS and BD-PRS explained 1.7% ($\Delta R^2=0.017$, $p=0.010$) and 1.3% ($\Delta R^2=0.013$, $p=0.023$) of variance, respectively; EA-PRS showed a significant association in the primary regression but negligible individual variance explained ($\Delta R^2<0.001$, $p=0.890$). Individual lipid class scores each explained less than 1% of variance (all $p>0.05$), consistent with the enrichment signal being distributed across classes rather than driven by any single class.

To test whether lipid alterations mediate genetic associations with severe psychosis probability we performed bootstrap mediation analysis for the three significant PRS through eight enriched lipid classes. Although neither indirect effect reached statistical significance, both BD-PRS (indirect effect = 0.0014, SE = 0.0012, 95% CI [-0.0001, 0.0048], $p = 0.142$) and SCZ-PRS (indirect effect = 0.0010, SE = 0.0010, 95% CI [-0.0005, 0.0038], $p = 0.304$) showed small positive indirect effects through dihydroceramide (dCer), with confidence intervals marginally crossing zero which might be worth further investigation (**Supplementary Figure S11**). Further, we tested whether PRS and lipid profiles share common axes of multivariate variation independent of severity, we performed a post-hoc CCA, which yielded a non-significant first canonical correlation ($r=0.33$, $p=0.604$), with neither canonical score associating with severe psychosis probability; full results are reported in Supplementary Results.

Discussion

The convergence of independent genetic and lipidomic signals on a symptom-derived, transdiagnostic severity dimension suggests that multidimensional patient stratification can recover biologically meaningful structure that diagnostic categories alone may not capture. In this study, three PRS were associated with severe psychosis subtype probability, and eight lipid classes were robustly enriched, largely persisting after adjustment for diagnosis, medication, and PANSS subscale scores. Incremental R^2 decomposition indicated that polygenic risk and lipidomic profiles each independently explained approximately 7-8% of variance, together accounting for ~16%, suggesting these two biological layers capture distinct and complementary dimensions of severe psychosis.

The positive SCZ-PRS result extends prior evidence that SCZ-PRS associates with psychotic features across diagnostic boundaries (21,64). The negative BD-PRS association, which despite the substantial genetic correlation between SCZ and BD here, captures proportionally more affective than psychotic symptom dimensions (65), suggests that higher affective genetic loading shifts individuals toward less psychotically burdened presentations in the present study, which is consistent with other, more affectively defined subgroups identified in the original PsyCourse clustering (9), and with evidence that psychotic features in BD are linked to SCZ-PRS rather than BD-PRS (66). This pattern converges with a large-scale genetic decomposition of BD clinical heterogeneity study that identified a severe illness dimension characterized by psychosis and schizoaffective disorder showing the strongest SCZ genetic overlap and the highest SNP heritability among all BD subphenotypes, with a distinct neuro-immune signature, absent from affective BD dimensions (67). The negative EA-PRS association reflects that lower polygenic scores for educational attainment index greater neurodevelopmental burden and reduced cognitive reserve – consistent with cognitive impairment as a transdiagnostically replicated hallmark of severe psychotic illness (68) – and replicates the EA-PRS finding from the original PsyCourse clustering (9). Together, these findings suggest the higher severe psychosis subtype probability captures a genetically SCZ-enriched dimension of psychotic illness that transcends the SCZ-BD diagnostic boundary, and that cognitive impairment is an intrinsic rather than incidental feature of this illness dimension.

The most interpretively coherent lipidomic pattern was headgroup-specific ether-lipid remodeling: PE-P was positively enriched, and PC-P was negatively enriched across all sensitivity models. PE-P and PC-P are plasmalogen subclasses that are ether-linked glycerophospholipids enriched in neuronal membranes, where they contribute to membrane fluidity, myelination, and antioxidant defense (28,69,70). Critically, the same three PE-P species significantly enriched with severe psychosis probability here (PE-P 40:4, 40:5, 42:5) showed significant negative associations with processing speed in the same cohort (71), linking the plasma PE-P elevation to the cognitive impairment observed in this phenotype. PE-P upregulation may represent a compensatory antioxidant response under oxidative stress, whereas PC-P decreases may reflect preferential consumption or impaired synthesis (28,72). PC-O reversed direction after diagnosis and medication adjustment - individual medication class analyses indicate this reversal was driven specifically by mood stabilizer adjustment - consistent with medication-specific effects in the same dataset (38), and should not be interpreted as a severity marker; PC-P by contrast was the most robust glycerophospholipid across all sensitivity models.

We also observed enrichment of sphingolipid classes (dSM, dCer) associated with severe psychosis probability. Ceramide and sphingosine-1-phosphate (S1P) exert opposing effects on cell survival and neuroinflammation via the sphingolipid rheostat (73), and disrupted sphingolipid metabolism has been documented in *post mortem* SCZ brain tissue (74), with altered S1P levels linked to impaired oligodendrocyte differentiation and white matter abnormalities (66,75) and has been implicated with symptom severity in SCZ and first-episode psychosis patients (76,77). Critically, this pathway is directly targetable, as S1P receptor modulators and acid sphingomyelinase inhibitors are already in clinical use for other indications, raising the possibility of pharmacological repurposing (78–81). Sphingomyelin enrichment was the most robust sphingolipid finding, surviving both diagnosis and medication adjustment. Importantly, this finding does not seem to be a primary product of medication effects unique to severely affected individuals: clozapine was specifically associated with dSM decreases in matched analyses in the same dataset (38), and dSM enrichment survived adjustment for each medication class individually, together suggesting the positive dSM-severity association observed here is conservative. Ceramide enrichment attenuated after medication adjustment, consistent with antipsychotic-associated plasma ceramide changes (38,82), and TAG reversed direction after diagnosis adjustment, both likely reflecting SCZ-enrichment of the subtype rather than transdiagnostic severity biology (16,38).

Extending the prior categorical-diagnostic lipidomic work in this cohort (16), our multidimensional-severity-based approach recovers the core signal – PC increases, PC-P decreases, TAG and ceramide enrichment, and additionally identifies PE-P, PE, and CE as severity-associated classes, suggesting that a multidimensional severity phenotype captures a broader lipidomic signature than diagnostic category alone.

To contextualize the lipidomic signal, we compared enrichment patterns against unidimensional PANSS subscale scores, both as covariates and as alternative outcomes. CAR showed specific negative enrichment with PANSS negative scores as outcome, suggesting mitochondrial fatty acid oxidation deficits may track preferentially with negative symptom burden (83–86). This finding is absent from the

multidimensional severity model and potentially relevant to the well-documented treatment resistance of negative symptoms (87,88). The lipidomic signature was not fully reducible to any single symptom dimension, most strikingly demonstrated by PC enrichment reversing between the multidimensional score and PANSS positive as outcomes, likely reflecting the additional contribution of cognitive impairment and functional disability incorporated into the subtype probability score.

The near-perfect additivity of PRS and lipidomic contributions (~7% and ~8%, respectively, jointly ~16%) indicates that genetic predisposition and peripheral lipidomic dysregulation independently contribute to the probability of belonging to the severe psychosis subtype, and that measuring one does not substitute for the information provided by the other. Individually, SCZ- and BD-PRS explained 1.7% and 1.3% of variance in the observed scale, respectively, expectedly less than the 7–9% explained in population-level case-control GWAS for SCZ and BD (13,14) when predicting continuous clinical severity within already-diagnosed samples. The 7–8% explained by the full PRS battery and lipid class scores respectively, reflects cumulative block signal across multiple intercorrelated contributors (16,93) rather than the effect of any single PRS or lipid class predictor. The remaining ~84% of variance reflects the unmeasured environmental, epigenetic, and developmental factors (22–24), residual confounding by medication and lifestyle, and measurement error in both predictors and outcome. Mediation analyses found no significant indirect effects of PRS on severe psychosis probability through lipid class scores, and CCA identified no significant shared axes of covariation between the PRS battery and the lipidomic profile. Both null findings should be interpreted with caution: the mediation analyses were likely underpowered for small indirect effects (89), and the CCA operated on aggregate-level data, i.e. PRS scores and lipid class means, which may be too coarse to capture biologically meaningful genetic-lipidomic interactions.

Several limitations should be noted. First, we assessed plasma lipids, which may not fully reflect central nervous system processes. However, peripheral lipid alterations have been shown to partially mirror central dysregulation and remain biologically informative (90–92). Second, non-fasting sample collection introduces dietary confounding, though species strongly influenced by fasting status were excluded (16). Third, although we statistically adjusted for medication effects, residual confounding from specific drugs, dosages, and lifestyle factors cannot be excluded. Fourth, the lipidomics subsample differed from the full PRS sample in containing a higher proportion of BD diagnoses and greater mood stabilizer use, which may have influenced lipid profiles; notably however, the lipidomics subset showed a numerically lower severe psychosis subtype probability than the full sample, suggesting any bias is likely conservative with respect to the primary findings. Fifth, using our approach, we cannot rule out reverse causation, though existing Mendelian randomization studies support at least partial causal roles for specific lipid species in BD and MDD (30,93,94) with more mixed results in SCZ (95–98). Sixth, our exploration of integrated analysis of PRS and lipidomics via incremental R^2 decomposition, mediation and CCA share a common limitation: they operate at the block level and cannot speak to interactions between genetic liability and lipidomic dysregulation at the resolution of specific variants and lipid species. Resolving whether PRS and lipids are truly independent biological dimensions of severe psychosis, or whether their coupling is detectable only at finer resolution, will require larger samples and

approaches suited to high-dimensional multi-omic integration, such as Mendelian randomization at the lipid species level or sparse multi-block methods applied to well-powered cohorts (99). Additionally, our severity measure is a data-driven construct specific to the clinical variables assessed in the PsyCourse Study and may not fully generalize to other operationalizations of psychosis severity, warranting replication in independent cohorts with comparable phenotypic depth. To our knowledge, there are currently no other large transdiagnostic datasets, combining genotyping, lipidomics, and detailed psychosis-severity phenotyping that would permit direct replication of our clustering and mediation analyses, yet replication in larger, independent cohorts is needed.

The severe psychosis subtype represents one of the most clinically burdened and poorly understood phenotypes in psychiatry, yet prior biological characterization has relied largely on diagnostic categories and unidimensional symptom ratings that capture only a fraction of its complexity. Treating it as a continuous severity dimension in a transdiagnostic cohort, we identify independent polygenic and lipidomic correlates robust to adjustment for diagnosis, medication, and symptom subscales. Their convergence with this symptom-derived dimension suggests that psychosis severity, operationalized multidimensionally, indexes biological variation that categorical and single-scale approaches only partially capture, offering empirical support for the premise that richer phenotyping yields richer biology.

The lipidomic findings point toward pharmacologically tractable pathways — particularly ether-lipid remodeling and sphingolipid dysregulation — that may ultimately inform patient stratification and targeted treatment development for a group with significant unmet clinical need. Polygenic liability and lipidomic dysregulation operated largely independently, each contributing meaningfully to subtype probability and neither reducible to the other. Whether these dimensions converge at finer biological resolution remains an open question requiring larger samples, longitudinal designs, and fine-scale multi-omic integration to resolve.

Declarations

Acknowledgments

Non-author contributions:

We thank Dr. Friederike S. David for her support in PRS calculation.

Funding Sources:

AT receives a PhD fellowship from the University of Bonn. JM was supported by the Commonwealth through an Australian Government Research Training Program Scholarship [DOI: <https://doi.org/10.82133/C42F-K220>]. UD was funded by the German Research Foundation (DFG, grant FOR2107 DA1151/5-1, DA1151/5-2, DA1151/9-1, DA1151/10-1, DA1151/11-1 to UD; SFB/TRR 393, project grant no 521379614) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/016/26).

TGS is supported by the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG]) within the framework of the projects www.kfo241.de and www.PsyCourse.de (SCHU 1603/4-1, 5-1, 7-1; FA241/16-1). PF and TGS receive support via the German Center for Mental Health (BMBF 01EE2303F).

DBD and ECS received research funding via the Bonn-Melbourne Joint PhD Program. ECS was supported by the Munich Clinician Scientist Program and the DFG (SCHU 2419/6-1).

Data published:

Preliminary results of this study were presented as a poster at ECNP 2025 conference (<https://doi.org/10.1016/j.nsa.2025.105873>) and uploaded as a preprint to MedRxiv (<https://doi.org/10.64898/2026.02.24.26346956>).

Data Availability:

The data used can be obtained by making a proposal to the PsyCourse team at the IPPG of Munich (<http://www.psychcourse.de/proposals-en.php>). All analysis code of the present study is publicly available at <https://github.com/anthano/psychcourse>.

Author Contribution:

Conceptualization: A.T., A.C.W, J.M, D.B.D., E.C.S. **Data curation:** K.A., M.B., U.H., M.H., D.R.-E., F.S., A.N.F., J.W., E.Z.R., G.J., U.D., A.J.F., C.S., M.S., P.F., T.G.S. **Formal analysis:** A.T., J.M. **Funding acquisition:** P.F., P.K., T.G.S., D.B.D., E.C.S. **Investigation:** A.T.K., E.S., P.K, M.O.K, S.P **Methodology:** A.T., J.M., A.C.W., T.M., S.H., N.K., D.B.D., E.C.S. **Project administration:** E.C.S. **Resources:** N.K., T.G.S., P.F., E.C.S. **Supervision:** A.C.W, D.B.D., E.C.S. **Visualization:** A.T. **Writing – original draft:** A.T. **Writing – review & editing:** all authors.

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Competing Interests:

The authors declare no competing interests.

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Figures

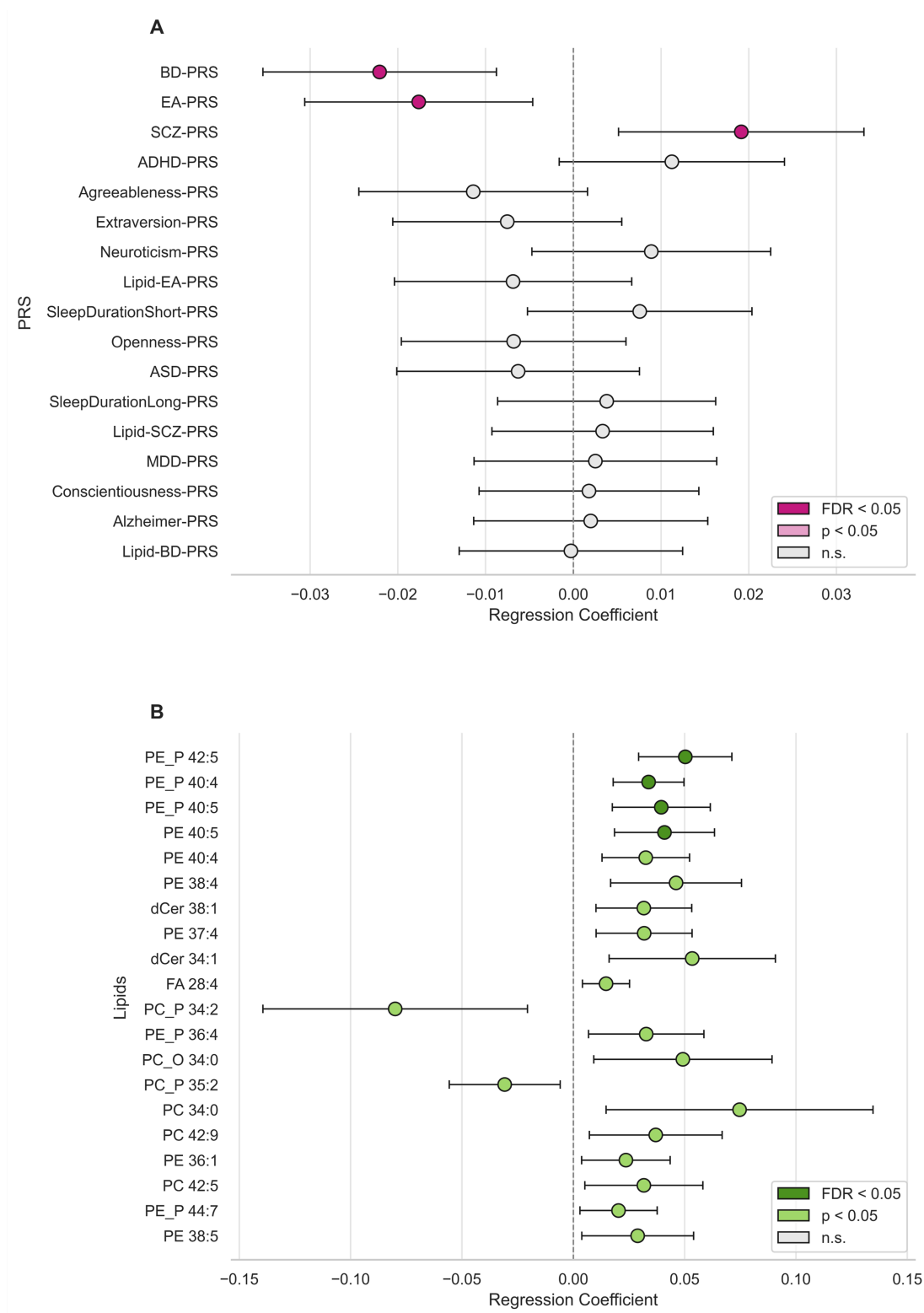


Figure 1

Associations of polygenic risk scores and plasma lipid species with severe psychosis subtype probability. Regression coefficients (β) with 95% confidence intervals from HC3-robust ordinary least squares regression. (A) Associations between polygenic risk scores (PRS), lipid-pathway-enriched PRS (prefixed “Lipid-”), and severe psychosis subtype probability. (B) Associations between individual plasma lipid species and severe psychosis subtype probability. Top 20 species by FDR are shown; full results in

Supplementary Table 6. Color indicates significance: dark fill, FDR <0.05; light fill, p <0.05; open, not significant. BD, bipolar disorder; EA, educational attainment; SCZ, schizophrenia; ADHD, attention-deficit-hyperactivity disorder; PE-P, phosphatidylethanolamine plasmalogen; PC-P, phosphatidylcholine plasmalogen; PC-O, plasmanyolphosphatidylcholine; dCer, dihydroceramide.

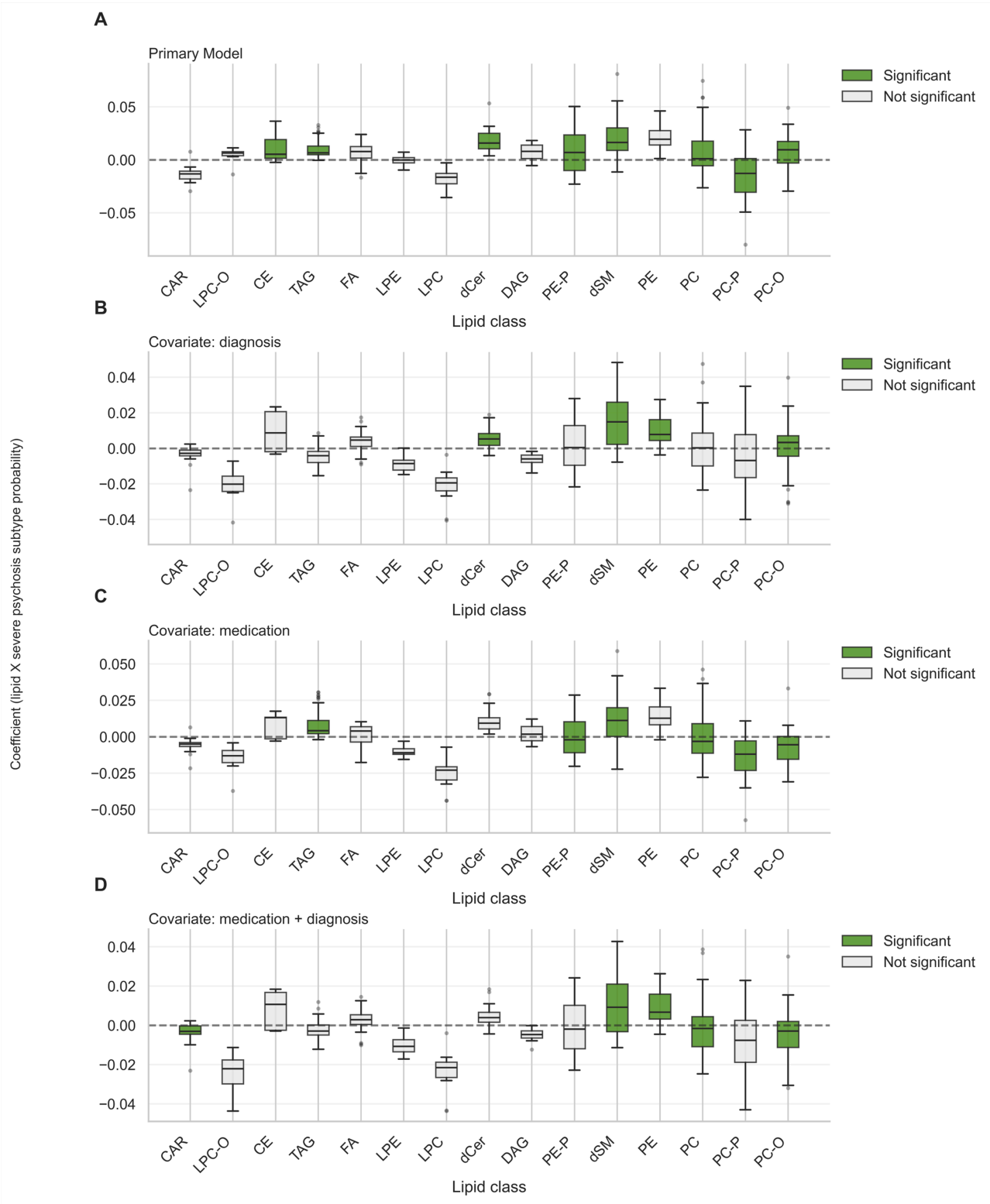


Figure 2

Lipid-class based enrichment analysis for severe psychosis subtype probability. Boxplots of ordinary least squares regression coefficients (β) for individual lipid species, grouped by lipid class. Each box represents the distribution of species-level coefficients within a class. Blue boxes indicate lipid classes with FDR-significant enrichment ($q < 0.05$) from permutation-based gene set enrichment analysis (5,000 permutations); grey boxes indicate non-significant classes. The dashed horizontal line indicates $\beta = 0$. (A) Primary model, adjusted for age, sex, BMI, smoking status, and duration of illness; (B) additionally adjusted for diagnosis; (C) additionally adjusted for number of drugs from each medication class; D) additionally adjusted for diagnosis and number of medications.

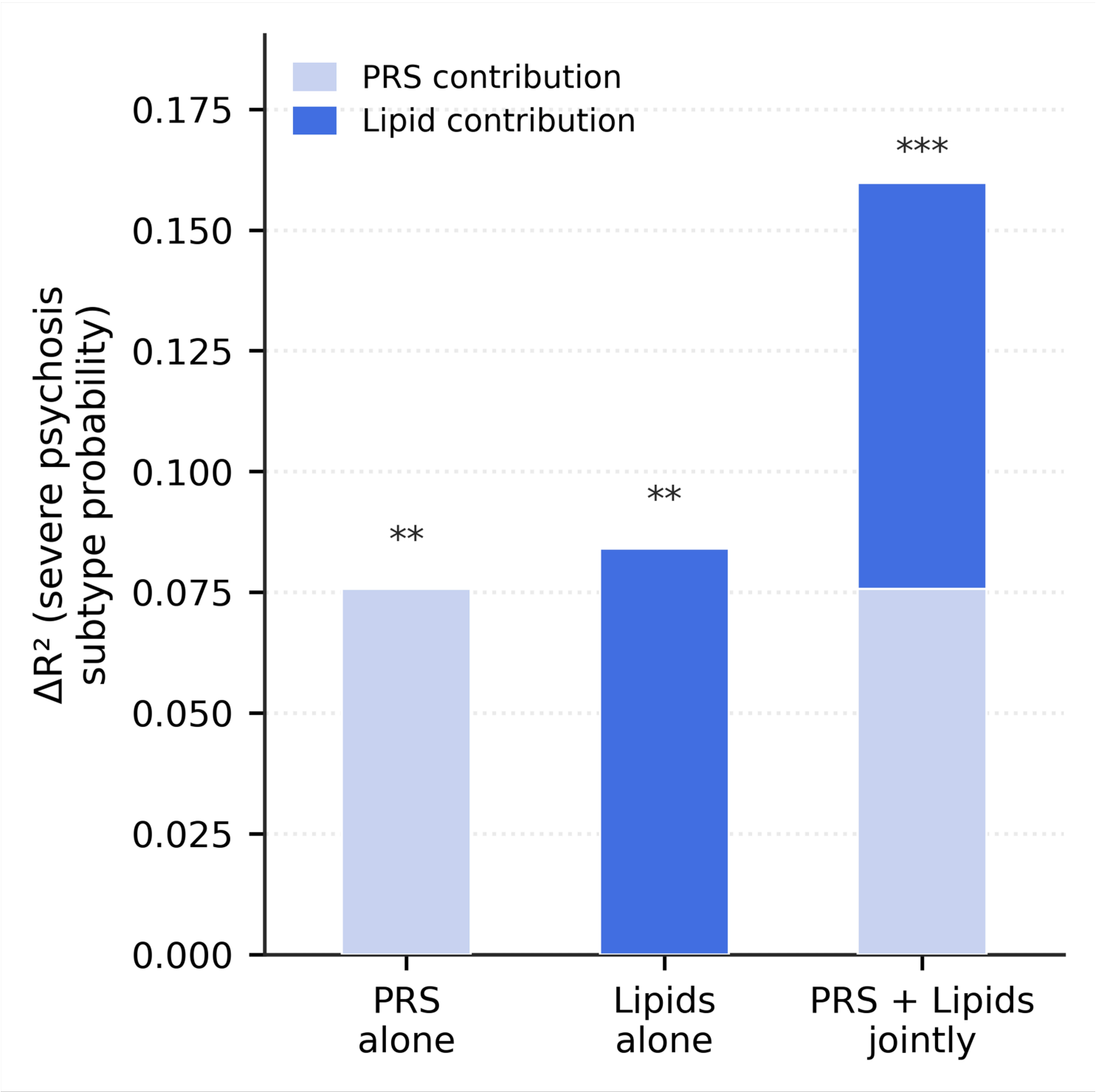


Figure 3

Incremental R^2 decomposition of polygenic risk and plasma lipidomic contributions to severe psychosis subtype probability. Bars show the incremental variance explained (ΔR^2) by the PRS battery alone, lipid class scores alone, and both blocks jointly. The joint bar is stacked to show the relative contributions of each block. The shared variance of 0.3% in the joint model (bar 3) could not be visualized to scale and is therefore not depicted. Statistical significance was assessed via permutation testing (20,000 permutations); * $p < 0.05$, ** $p < 0.01$.

Supplementary Files

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