Using EHR biomarker results to uncover pleiotropy between depression and the immune system

Julia M. Sealock[1], Heather Lee,[2] Arden Moscati[3], Sanan Venkatesh[3], Georgios Voloudakis[3], Panos Roussos[3], Jordan Smoller[2], Guanhua Chen[4], Lea K. Davis[1]

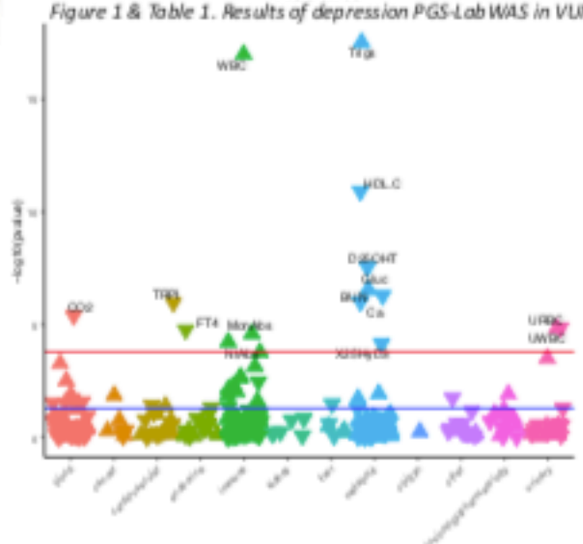
[1]Vanderbilt University, Nashville, TN, USA; [2]Massachusetts General Hospital, Boston, MA, USA; Mount Sinai School of Medicine, New York, NY, USA; University of Wisconsin-Madison, Madison, WI, USA

Abstract

Depression diagnosis has been consistently associated with increased pro-inflammatory biomarkers. We utilized four biobanks in the PsycheMERGE Network (n=340,149) to examine the effect of depression polygenic scores (PGS) on white blood cells (WBC). At VUMC, we used a lab-wide association scan (LabWAS) to find associations between depression PGS and 315 clinically measured labs and replicated in the PsycheMERGE Network. The top association from the LabWAS of depression PGS was with white blood cell count (WBC), which replicated across the PsycheMERGE Network, after controlling for depression and anxiety diagnoses, (p-value=2.48 x 10^{-100}, beta=0.04). In the mediation analysis, WBC mediated 1.2% of the association between depression PGS and depression diagnosis (p-value = 6.01 x 10^{-10}), while depression diagnosis mediated 2.8% of the association between depression PGS and WBC (p-value = 1.33 x 10^{-4}). Our results indicate that depression genetics contribute to a pro-inflammatory state through WBC. The effect size between depression PGS and WBC remained small across all sites, signaling depression PGS leads to an activated, but not abnormal immune system.

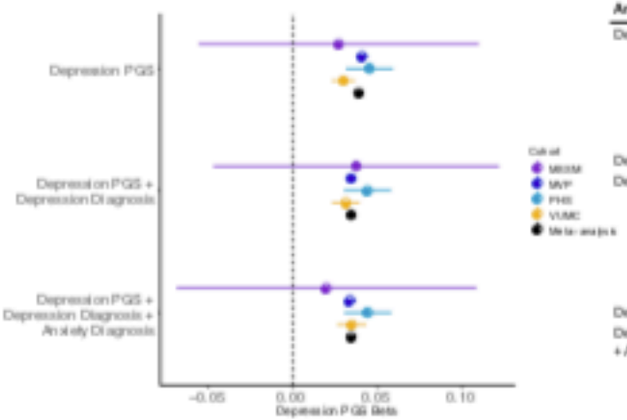
Results

Figure 1 & Table 1. Results of depression PGS-LabWAS in VUMC



Lab	Full Name	N	P-value	Beta	SE
Trigs	Triglycerides	30,703	3.14E-18	0.049	0.006
WBC	Leukocytes	65,120	1.07E-17	0.030	0.004
HDLC	Cholesterol in HDL	29,598	1.23E-11	-0.037	0.005
D25OHT	Calcitriol	18,325	2.83E-08	-0.039	0.007
Gluc	Glucose	62,555	2.84E-07	0.019	0.004
BUN	Urea nitrogen	62,617	5.19E-07	-0.020	0.004
Ca	Calcium	62,357	9.74E-07	-0.017	0.004
TRPI	Troponin I	10,443	1.09E-06	-0.045	0.009
CO2	Carbon dioxide	62,518	4.06E-06	-0.016	0.003
URBC	Erythrocytes in Urine	23,022	1.37E-05	-0.025	0.006

Figure 2 & Table 2. Replication of depression PGS and WBC association across the PsycheMERGE Network.



Analysis	Cohort	P-value	Beta	SE
Depression PGS	MSSM	0.519	0.027	0.042
	MVP	3.84E-114	0.041	0.002
	PHS	1.63E-10	0.045	0.007
	VUMC	1.07E-17	0.03	0.004
	Meta-analysis	2.52E-137	0.039	0.002
Depression PGS + Depression Diagnosis	MSSM	0.384	0.038	0.043
	MVP	2.12E-81	0.035	0.002
	PHS	5.3E-10	0.044	0.007
	VUMC	2.54E-14	0.031	0.004
	Meta-analysis	3.93E-102	0.035	0.002
Depression PGS + Depression Diagnosis + Anxiety Diagnosis	MSSM	0.658	0.02	0.045
	MVP	1.71E-78	0.034	0.002
	PHS	4.77E-10	0.044	0.007
	VUMC	1.88E-15	0.035	0.004
	Meta-analysis	2.48E-100	0.035	0.002

Methods

LabWAS of Depression PGS

Depression polygenic scores were generated using PRS-CS[1] using SNP weights from the latest depression meta-analysis[2]. At VUMC, lab results were extracted from the EHRs of 70,704 individuals and cleaned as previously described[3]. The median observation for each individual in each lab was selected and adjusted for cubic splines of age at measurement. The age-adjusted value was inverse normalized to ensure a normal distribution for downstream analyses, generating age-adjusted INT lab values. Depression PGS were screened for associations with 308 clinical lab measurements using a lab-wide association scan (LabWAS)[3] in VUMC's biobank. The LabWAS of depression PGS was controlled for sex and top 10 genetic principal components. In conditional analyses, the LabWAS of depression PGS was covaried for depression and anxiety diagnoses, defined by phecodes 296.2 and 300.1, respectively.

Replication in the PsycheMERGE Network

Using the PsycheMERGE network, the analyses between depression PGS and WBC was replicated in three external biobanks, the Million Veterans Program (MVP), Mount Sinai Icahn School of Medicine (MSSM), and Partner's Healthcare System (PHS)

Mediation Analyses

Two potential pathways between depression PGS, WBC, and depression diagnosis were assessed using mediation analyses. In the first analysis, measured WBC was modeled to mediate the relationship between depression PGS as the exposure and depression diagnosis as the outcome. In the second analysis, depression diagnosis was modeled to mediate the association between the depression PGS as the exposure and measured WBC as the outcome. The mediation analyses were conducted using bootstrapping simulations until a stable p-value was achieved using the mediation[6] R package.

Table 3. Results of mediation analyses across the PsycheMERGE Network.

Exposure	Mediator	Outcome	Site	Proportion mediated	P-value	Lower 95% CI	Upper 95% CI
MDD PGS	WBC	MDD diagnosis	VUMC	0.003	0.16	-0.001	0.01
			MSSM	-0.016	0.871	-0.25	0.11
			MVP	0.035	<2e-16	0.031	0.04
			PHS	0.008	0.024	0.001	0.02
			Meta	0.011	6.01E-10	0.008	0.015
MDD PGS	Depression diagnosis	WBC	VUMC	0.011	0.18	-0.005	0.03
			MSSM	-0.086	0.74	-0.919	0.79
			MVP	0.165	<2e-16	0.142	0.18
			PHS	0.033	0.026	0.004	0.07
			Meta	0.028	1.33E-4	0.014	0.043

Conclusions

- Increased genetic liability associates with several clinical labs, including altered metabolic and immune biomarkers
- Depression genetics are robustly associated with increased WBC across several biobanks
- Mediation analyses suggest a feedback loop between depression genetics, increased WBC, and increased risk of depression diagnosis

References

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