**Supplementary Results for "Increased depression genetic liability associates with an activated immune system through white blood cells"**

*Controlling for the impact of WBC genetics*

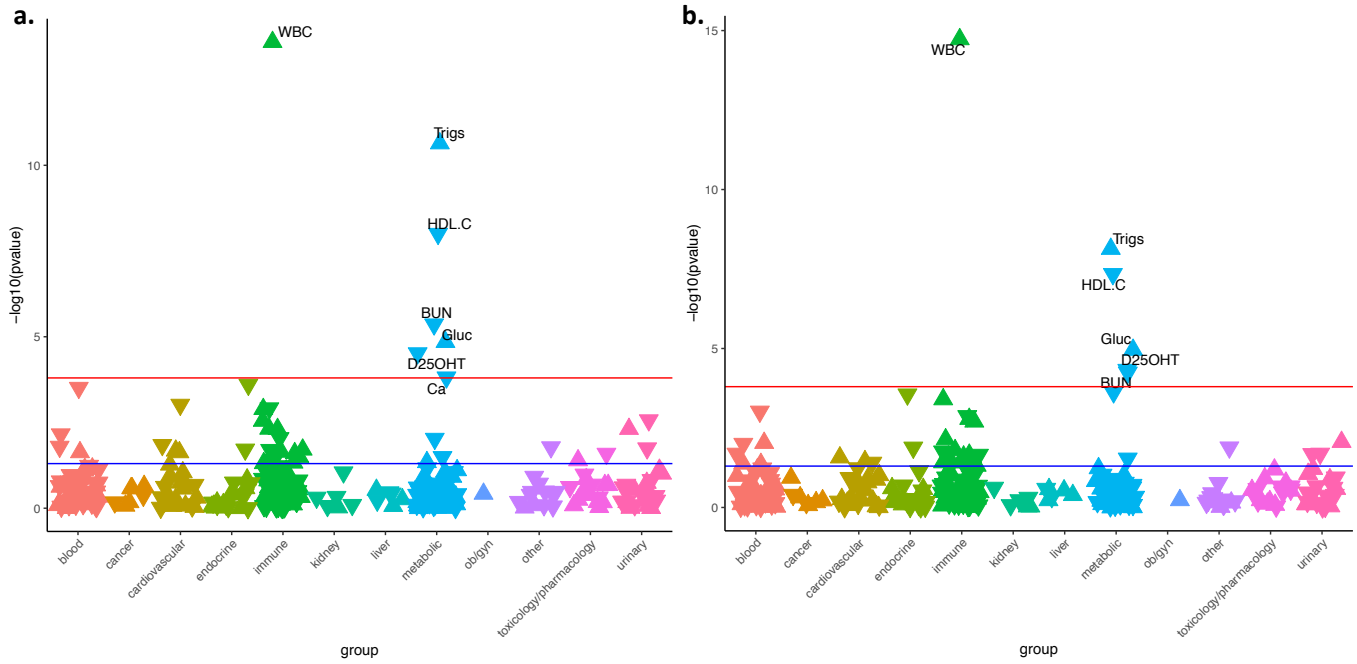
The LabWAS and phe-group conditional analyses confirmed a correlation between increased depression PGS and elevated WBC that is unlikely to be due to an underlying comorbid confounder. However, there remain multiple possible hypotheses to explain these results. First, increased depression PGS may lead to elevated WBC through mechanisms that directly (e.g., hematopoiesis) or indirectly (e.g., cortisol) activate the immune system. However, given that WBC itself is a highly heritable trait ($h^2$ = 14 – 40%[44]), it is also possible that the GWAS used to train the depression PGS includes WBC genetic associations due to either phenotypic hitchhiking in the original ascertainment of depression, or a real contribution from the heritable component of WBC acting as an independent risk factor for depression. In either circumstance, this would result in depression cases having higher WBC PGS than controls, which would also be reflected in the depression PGS and the subsequent genetic correlation between WBC and depression in independent samples.

To address these complicating issues, we undertook a series of analyses. First, we calculated the genetic correlation between depression and WBC, which was non-significant (rg = 0.027, p-value = 0.268). Next, the weights for the depression PGS were conditioned on the weights from the WBC GWAS using mtCOJO to adjust for the effects of WBC on depression genetic risk. A conditional depression PGS built from the conditioned weights (MDD|WBC PGS) remained associated with WBC (p-value=3.60 x $10^{-108}$, beta=0.035), confirming the majority of the association between depression PGS and measured WBC arises not from the heritable component of WBC, but from the impact of genes that increase risk for depression (Supplementary Figure 4, Supplementary Table 9).

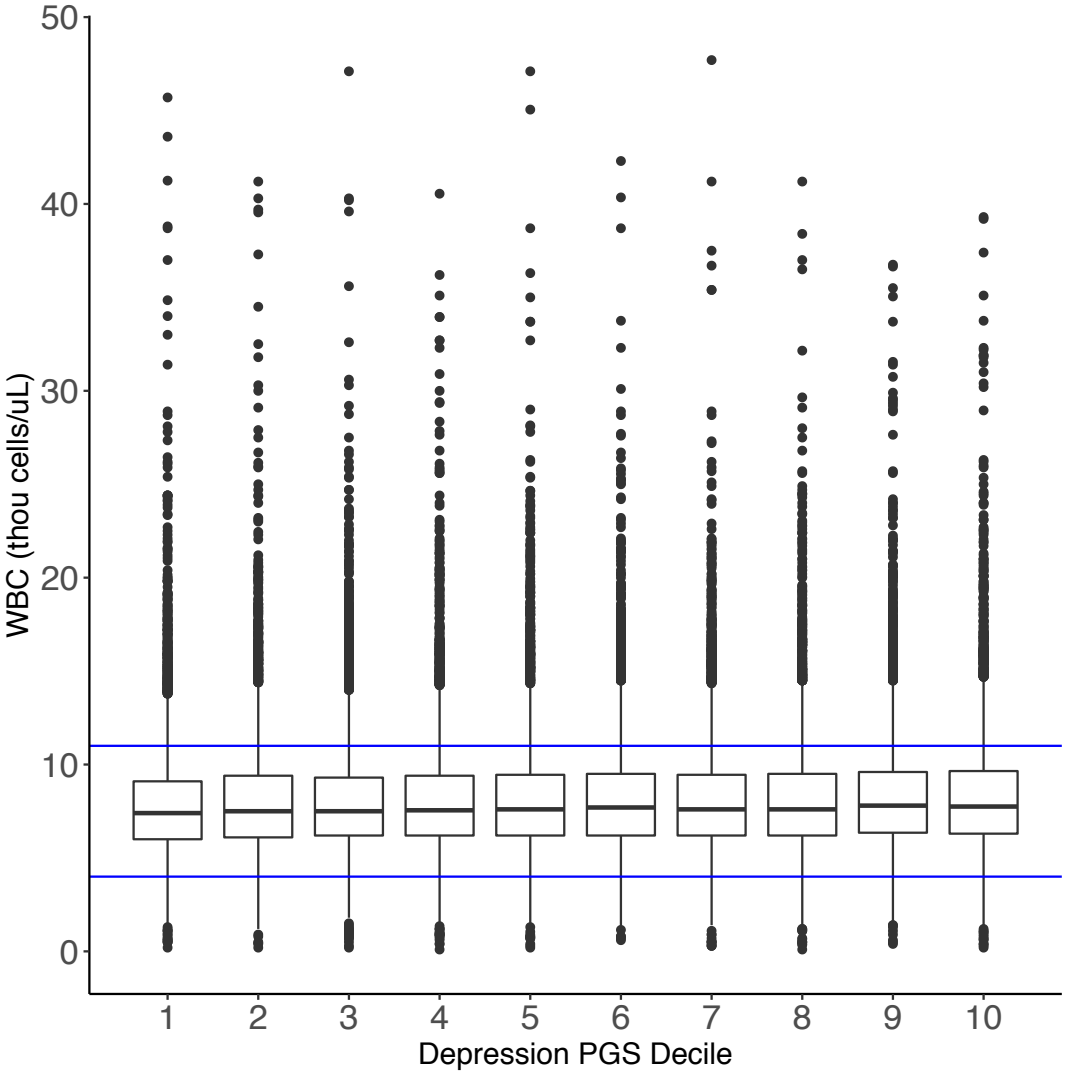
Next, we tested the association between WBC PGS and depression diagnosis in each biobank. The meta-analysis across the four sites suggested a small though significant association between WBC PGS and depression (p-value = $3.52 \times 10^{-5}$, beta=0.015), but this association was only observed in the MVP which contributed the largest sample size to the meta-analysis. In VUMC, depression status was not significantly associated with WBC levels (p-value = 0.062, beta = -0.084).

**Supplementary Material for "Increased depression genetic liability associates with an activated immune system through white blood cells"**

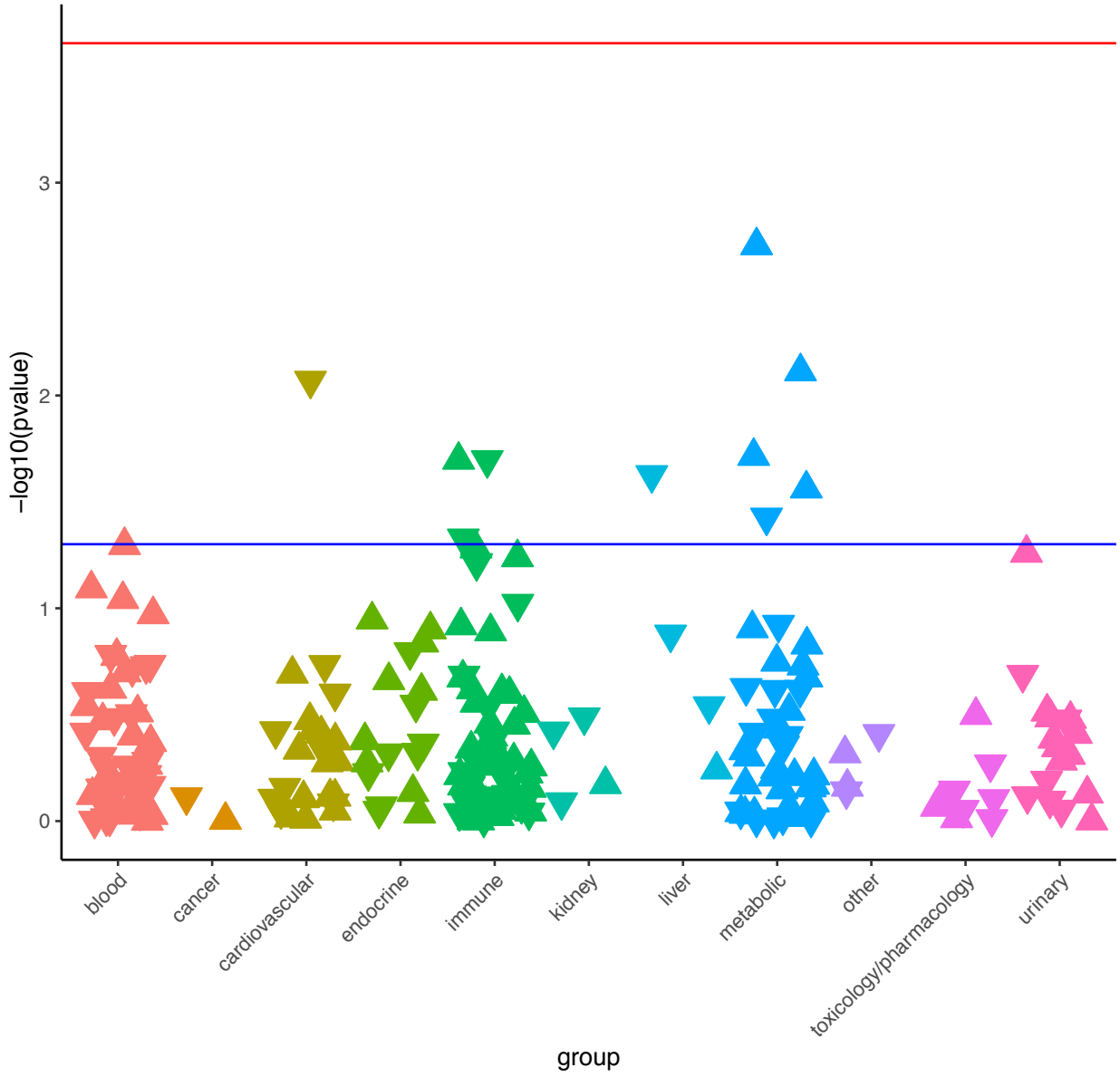
Supplementary Figure 1: LabWAS of depression PGS controlled for a) depression and b) depression and anxiety diagnoses in VUMC. Depression and anxiety diagnoses were defined as phecodes 296.2 and 300.1, respectively. The red line indicates the Bonferroni threshold for statistical significance ($p<1.58 \times 10^{-4}$) and the blue line indicates a p-value of 0.05. Upward triangles indicate that the PGS is associated with increased levels of the lab, while downward triangles indicate an association with reduced levels of the lab.



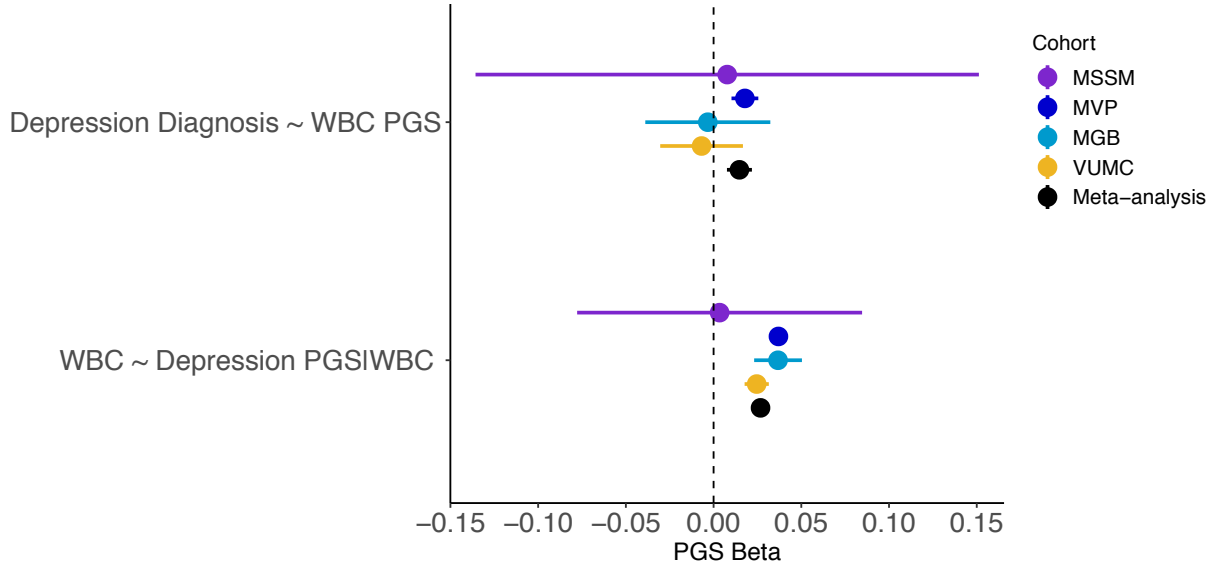
Supplementary Figure 2: Median WBC measurements stratified by depression PGS decile in VUMC. Individuals were divided into deciles based on their depression PGS. Each individual's median untransformed WBC measurement is plotted based on depression PGS decile. Blue lines indicate the normal clinical range for WBC (4-11thou cells/uL).



Supplementary Figure 3: Lab-wide association scan of depression PGS in individuals of African ancestry in VUMC.



Supplementary Figure 4: Controlling for the impact of WBC genetics on the association between depression PGS and WBC levels. The pathway between WBC genetics and depression diagnosis was assessed by regressing a WBC polygenic score on depression diagnosis defined as phecode 296.2. The effect of WBC genetics in depression genetics was assessed by conditioning depression PGS on WBC genetics and finding the association with WBC measurements.



Supplementary Table 3: Phenotypes associated with depression PGS and median WBC measurements using PheWAS in VUMC. Common phenotypes passing Bonferroni significance in each scan were binned into categories based on similarity.

| Phecode | Phenotype | Groupz | WBC p-value | WBC beta | Depression PGS p-value | Depression PGS beta |
|---|---|---|---|---|---|---|
| 411.3 | Angina pectoris | Cardiovascular | 5.14E-20 | 0.0265 | 1.54E-06 | 0.0244 |
| 433 | Cerebrovascular disease | Cardiovascular | 1.09E-29 | 0.0176 | 6.37E-06 | 0.0157 |
| 428.1 | Congestive heart failure (CHF) NOS | Cardiovascular | 3.90E-69 | 0.017 | 2.38E-05 | 0.0152 |
| 411.4 | Coronary atherosclerosis | Cardiovascular | 2.34E-98 | 0.0151 | 1.12E-08 | 0.0131 |
| 401.1 | Essential hypertension | Cardiovascular | 3.26E-143 | 0.0115 | 4.90E-06 | 0.0099 |
| 401 | Hypertension | Cardiovascular | 6.38E-142 | 0.0114 | 9.73E-07 | 0.0098 |
| 411 | Ischemic Heart Disease | Cardiovascular | 5.21E-104 | 0.0144 | 7.38E-09 | 0.0125 |
| 411.2 | Myocardial infarction | Cardiovascular | 1.17E-78 | 0.0213 | 1.22E-05 | 0.0192 |
| 418 | Nonspecific chest pain | Cardiovascular | 5.14E-18 | 0.0116 | 1.97E-14 | 0.0105 |
| 411.1 | Unstable angina (intermediate coronary syndrome) | Cardiovascular | 9.82E-21 | 0.0274 | 1.95E-08 | 0.0252 |
| 292.4 | Altered mental status | Psychiatric | 1.29E-14 | 0.0194 | 1.91E-05 | 0.0176 |
| 313.1 | Attention deficit hyperactivity disorder | Psychiatric | 1.22E-12 | 0.0316 | 2.27E-07 | 0.0324 |
| 296.1 | Bipolar | Psychiatric | 9.90E-06 | 0.0263 | 3.91E-23 | 0.0261 |
| 313 | Pervasive developmental disorders | Psychiatric | 2.63E-15 | 0.0265 | 2.40E-08 | 0.0274 |
| 300.9 | Posttraumatic stress disorder | Psychiatric | 1.96E-06 | 0.0324 | 2.76E-25 | 0.0327 |
| 318 | Tobacco use disorder | Psychiatric | 4.77E-175 | 0.0152 | 1.89E-25 | 0.0137 |
| 250 | Diabetes mellitus | Obesity | 3.02E-100 | 0.013 | 1.62E-06 | 0.0116 |
| 278.11 | Morbid obesity | Obesity | 5.06E-90 | 0.021 | 5.71E-09 | 0.0197 |
| 278.1 | Obesity | Obesity | 4.41E-94 | 0.0151 | 9.65E-09 | 0.0139 |
| 278 | Overweight, obesity and other hyperalimentation | Obesity | 1.11E-81 | 0.0141 | 9.54E-08 | 0.013 |
| 250.2 | Type 2 diabetes | Obesity | 7.15E-110 | 0.0134 | 7.60E-08 | 0.0119 |
| 327.3 | Sleep apnea | Respiratory | 1.36E-14 | 0.0161 | 9.64E-06 | 0.0149 |
| 495 | Asthma | Respiratory | 9.18E-25 | 0.0181 | 3.86E-06 | 0.0171 |
| 496 | Chronic airway obstruction | Respiratory | 5.69E-144 | 0.018 | 1.68E-08 | 0.016 |
| 496.2 | Chronic bronchitis | Respiratory | 6.60E-55 | 0.0325 | 1.02E-05 | 0.03 |
| 512.7 | Shortness of breath | Respiratory | 1.59E-91 | 0.0132 | 6.99E-07 | 0.0117 |
| 70 | Viral hepatitis | Hepatic | 7.14E-53 | 0.0301 | 4.40E-07 | 0.0279 |
| 70.3 | Viral hepatitis C | Hepatic | 6.85E-52 | 0.0319 | 1.35E-06 | 0.0296 |
| 338.1 | Acute pain | Pain | 8.70E-23 | 0.0151 | 2.38E-06 | 0.0138 |
| 338 | Pain | Pain | 1.20E-20 | 0.0133 | 4.09E-09 | 0.0121 |
| 798 | Malaise and fatigue | Pain | 1.45E-63 | 0.0108 | 3.49E-07 | 0.0098 |
| 557.1 | Celiac disease | Autoimmune | 1.52E-15 | 0.0568 | 1.78E-09 | 0.0545 |

Supplementary Table 4: Association between depression PGS and WBC levels controlled for common phenotype groups in VUMC. The association was controlled for each phenotype group separately and all groups in one analysis in the "All" phenotype. Associations were found using a linear regression controlling for sex and top 10 principal components of ancestry.

| Phenotype | Depression PGS P-value | Depression PGS beta | SE | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|
| Original | 4.5E-20 | 0.0322 | 0.0035 | 0.0253 | 0.0391 |
| Cardiovascular | 8.1E-17 | 0.0313 | 0.0038 | 0.0239 | 0.0386 |
| Psychiatric | 2.1E-13 | 0.0326 | 0.0044 | 0.0239 | 0.0413 |
| Obesity | 8.4E-16 | 0.0306 | 0.0038 | 0.0232 | 0.0381 |
| Respiratory | 9.7E-11 | 0.0274 | 0.0042 | 0.0191 | 0.0356 |
| Hepatic | 1.2E-18 | 0.034 | 0.0039 | 0.0265 | 0.0416 |
| Pain | 1.9E-17 | 0.0332 | 0.0039 | 0.0255 | 0.0408 |
| Autoimmune | 5.5E-12 | 0.029 | 0.0042 | 0.0208 | 0.0373 |
| All | 0.0082 | 0.0209 | 0.0079 | 0.0053 | 0.0365 |

Supplementary Table 5: Characteristics of PsychEMERGE Network sites.

| Site | Group | N genotyped (European) | N WBC | N genotyped + WBC | % Female | Average age in years, (SD) | Average Length of record in years, (SD) |
|---|---|---|---|---|---|---|---|
| MSSM | All | 9,255 | 3,668 | 823 | 52.10% | 59.7 (16.0) | 11.2 (4.4) |
| | Depression or Anxiety Controls | 6,722 | 2,499 | 578 | 51.4% | 59.3 (16.4) | 10.7 (4.4) |
| | Depression or Anxiety Cases | 1,622 | 1,169 | 245 | 53.9% | 60.5 (15.0) | 12.5 (3.9) |
| VUMC | All | 72,828 | 948,590 | 70,921 | 55.9% | 48.1 (22.3) | 8.7 (6.3) |
| | Depression or Anxiety Controls | 59,520 | 301,982 | 57,161 | 52.6% | 46.8 (23.7) | 7.6 (6.1) |
| | Depression or Anxiety Cases | 15,985 | 71,692 | 15,951 | 64.4% | 50.9 (18.8) | 11.3 (6.1) |
| MVP | All | 289,880 | 289,880 | 289,880 | 7.2% | 64.3 (12.0) | 12.0 |
| | Depression or Anxiety Controls | 150,328 | 150,328 | 150,328 | 4.1% | 67.7 (11.2) | 11.2 |
| | Depression or Anxiety Cases | 129,552 | 129,552 | 129,552 | 10.9% | 61.6 (11.9) | 12.9 |
| MGB | All | 25,331 | 72,329 | 20,828 | 51.5% | 56.1 | 13.8 (8.3) |
| | Depression or Anxiety Controls | 17,879 | 51,612 | 17,098 | 52.0% | 59.8 (16.7) | 11.3 (7.1) |
| | Depression or Anxiety Cases | 7,452 | 20,717 | 3,730 | 64.2% | 56.7 (16.9) | 14.0 (6.7) |

Supplementary Table 6: Results of PsycheMERGE replication between depression PGS and WBC levels. Associations were controlled for sex and top 10 principal components. Beta estimates were combined for meta-analysis using a fixed-effects inverse weighted method.

| Analysis | Cohort | P-value | Beta | SE | Lower 95% CI | Upper 95% CI |
|---|---|---|---|---|---|---|
| Depression PGS | MSSM | 0.519 | 0.027 | 0.042 | -0.055 | 0.11 |
| | MVP | 3.84E-114 | 0.041 | 0.002 | 0.037 | 0.044 |
| | MGB | 9.11E-10 | 0.043 | 0.007 | 0.029 | 0.056 |
| | VUMC | 1.07E-17 | 0.03 | 0.004 | 0.023 | 0.037 |
| | Meta-analysis | 1.03E-136 | 0.034 | 0.002 | 0.031 | 0.038 |
| Depression PGS + Depression Diagnosis | MSSM | 0.384 | 0.038 | 0.043 | -0.047 | 0.122 |
| | MVP | 2.12E-81 | 0.035 | 0.002 | 0.031 | 0.038 |
| | MGB | 1.92E-9 | 0.042 | 0.007 | 0.028 | 0.056 |
| | VUMC | 2.54E-14 | 0.031 | 0.004 | 0.023 | 0.039 |
| | Meta-analysis | 9.52E-102 | 0.034 | 0.002 | 0.031 | 0.038 |
| Depression PGS + Depression Diagnosis + Anxiety Diagnosis | MSSM | 0.658 | 0.02 | 0.045 | -0.069 | 0.109 |
| | MVP | 1.71E-78 | 0.034 | 0.002 | 0.03 | 0.037 |
| | MGB | 2.55E-9 | 0.042 | 0.007 | 0.028 | 0.055 |
| | VUMC | 1.88E-15 | 0.035 | 0.004 | 0.026 | 0.044 |
| | Meta-analysis | 8.23E-100 | 0.034 | 0.002 | 0.031 | 0.038 |

Supplementary Table 7. Mediation results with WBC as the mediator across PsycheMERGE sites. Proportion mediated estimates were estimated using three different treatment percentiles of depression PGS (85%, 90%, and 95%) compared to the 50% percentile of PGS for controls.

| Cohort | MDD PGS Percentile | P.value | Proportion Mediated (SE) | 95% Confidence Interval |
|---|---|---|---|---|
| MGB | 85% | 0.25 | 0.003 (0.004) | -0.003 - 0.011 |
| | 90% | 0.25 | 0.003 (0.004) | -0.003 - 0.011 |
| | 95% | 0.25 | 0.003 (0.004) | -0.003 - 0.011 |
| MVP | 85% | <2e-16 | 0.035 (0.002) | 0.031 - 0.039 |
| | 90% | <2e-16 | 0.035 (0.002) | 0.031 - 0.039 |
| | 95% | <2e-16 | 0.035 (0.002) | 0.031 - 0.039 |
| MSSM | 85% | 0.871 | -0.016 (0.062) | -0.255 - 0.104 |
| | 90% | 0.871 | -0.016 (0.062) | -0.255 - 0.106 |
| | 95% | 0.871 | -0.016 (0.062) | -0.255 - 0.105 |
| VUMC | 85% | 0.16 | 0.003 (0.002) | -0.001 - 0.008 |
| | 90% | 0.16 | 0.003 (0.002) | -0.001 - 0.008 |
| | 85% | 0.16 | 0.003 (0.002) | -0.001 - 0.008 |
| Meta-analysis | 85% | 3.32E-36 | 0.015 (0.001) | 0.013 - 0.018 |
| | 90% | 5.05E-43 | 0.02 (0.001) | 0.017 - 0.022 |
| | 95% | 5.42E-57 | 0.028 (0.002) | 0.024 - 0.031 |

Supplementary Table 8. Mediation results with MDD diagnosis as the mediator across PsycheMERGE sites. Proportion mediated estimates were estimated using three different treatment percentiles of depression PGS (85%, 90%, and 95%) compared to the 50% percentile of PGS for controls.

| Cohort | MDD PGS Percentile | P.value | Proportion Mediated (SE) | 95% Confidenc Interval |
|---|---|---|---|---|
| MGB | 85% | 0.24 | 0.018 (0.017) | -0.014 - 0.052 |
| | 90% | 0.24 | 0.018 (0.017) | -0.014 - 0.05 |
| | 95% | 0.24 | 0.017 (0.017) | -0.014 - 0.05 |
| MVP | 85% | <2e-16 | 0.17 (0.009) | 0.133 - 0.188 |
| | 90% | <2e-16 | 0.169 (0.009) | 0.136 - 0.186 |
| | 95% | <2e-16 | 0.169 (0.008) | 0.137 - 0.185 |
| MSSM | 85% | 0.74 | 0 (0.745) | -1.462 - 1.46 |
| | 90% | 0.74 | -0.006 (0.674) | -1.322 - 1.314 |
| | 95% | 0.74 | -0.006 (0.624) | -1.284 - 1.217 |
| VUMC | 85% | 0.18 | 0.003 (0.002) | 0 - 0.007 |
| | 90% | 0.18 | 0.003 (0.002) | 0 - 0.007 |
| | 85% | 0.18 | 0.003 (0.002) | 0 - 0.007 |
| Meta-analysis | 85% | 2.10E-08 | 0.012 (0.002) | 0.008 - 0.016 |
| | 90% | 2.78E-10 | 0.013 (0.002) | 0.009 - 0.017 |
| | 95% | 1.14E-10 | 0.013 (0.002) | 0.009 - 0.018 |

Supplementary Table 9: Results of direction of association analysis across PsycheMERGE sites. Beta estimates were combined using a fixed-effects inverse weighted method.

| Outcome | Predictor | Cohort | PGS P-value | PGS Beta | PGS SE | PGS Lower 95% CI | PGS Upper 95% CI |
|---|---|---|---|---|---|---|---|
| Depression diagnosis | WBC PGS | MSSM | 0.915 | 0.008 | 0.073 | -0.136 | 0.151 |
| | | MVP | 4.71E-6 | 0.018 | 0.004 | 0.01 | 0.025 |
| | | MGB | 0.856 | -0.003 | 0.018 | -0.039 | 0.032 |
| | | VUMC | 0.57 | -0.007 | 0.012 | -0.03 | 0.017 |
| | | Meta-analysis | 4.94E-5 | 0.015 | 0.004 | 0.008 | 0.022 |
| WBC measurement | Depression PGS conditioned on WBC genetics | MSSM | 0.934 | 0.003 | 0.041 | -0.078 | 0.085 |
| | | MVP | 2.26E-93 | 0.037 | 0.002 | 0.033 | 0.041 |
| | | MGB | 1.26E-7 | 0.037 | 0.007 | 0.023 | 0.050 |
| | | VUMC | 2.80E-12 | 0.025 | 0.004 | 0.018 | 0.031 |
| | | Meta-analysis | 1.83E-28 | 0.027 | 0.002 | 0.022 | 0.032 |