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Supplemental information

Integration of rare expression outlier-associated variants improves polygenic risk prediction

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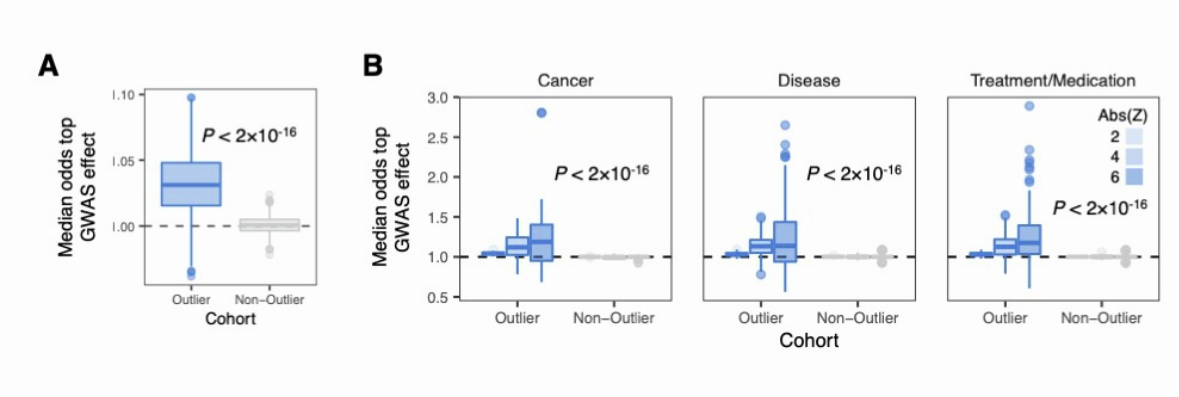
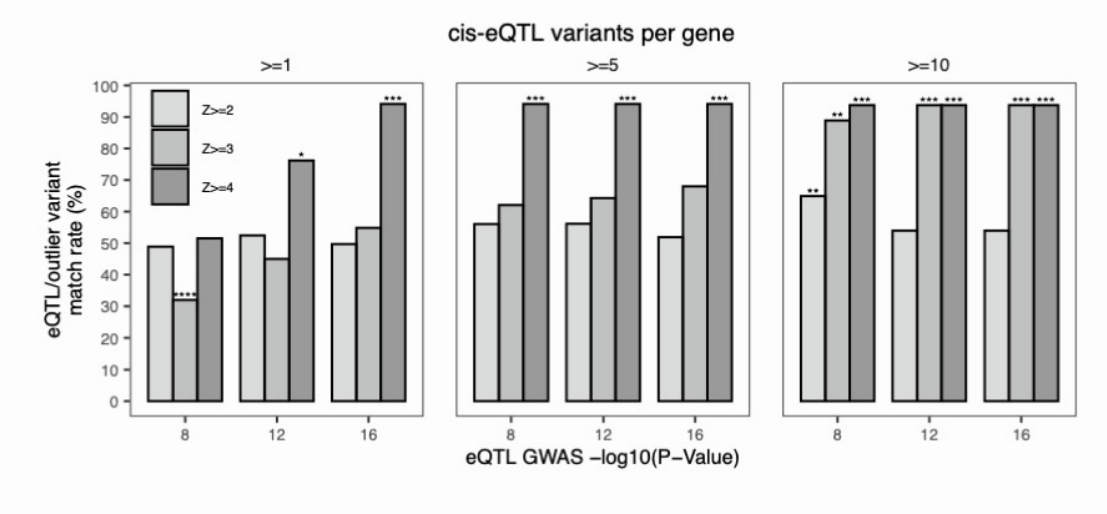
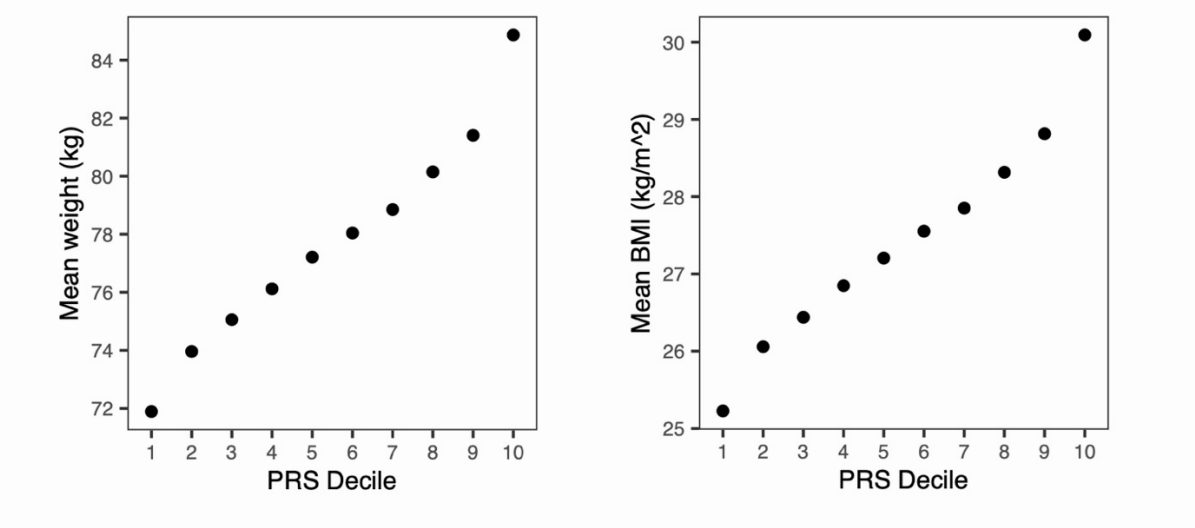


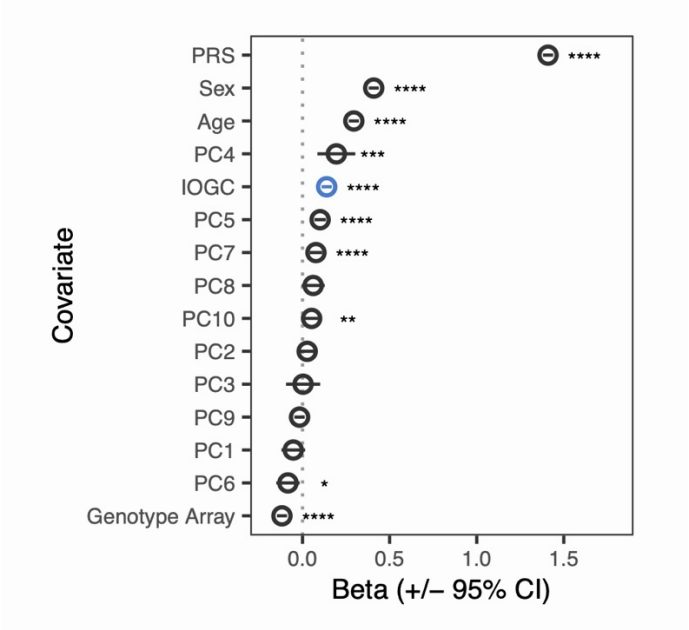
Supplementary Figure 1. A. Distribution of median odds across permutations for selected UKB phenotypes comparing GWAS effect estimates for outlier-associated variants compared with non-outlier variants (blue) and non-outlier variants only (gray). P-value from Wilcoxon test. **B.** Distribution of median odds across permutations for selected UKB GWAS phenotypes subdivided in to meta-categories (cancer; disease (non-cancer); treatment/medication) comparing GWAS effect estimates for outlier-associated variants compared with non-outlier variants (blue) and non-outlier variants only (gray). The analysis was repeated at more extreme thresholds of outlier gene expression abs(Z-score). P-values from Wilcoxon test.



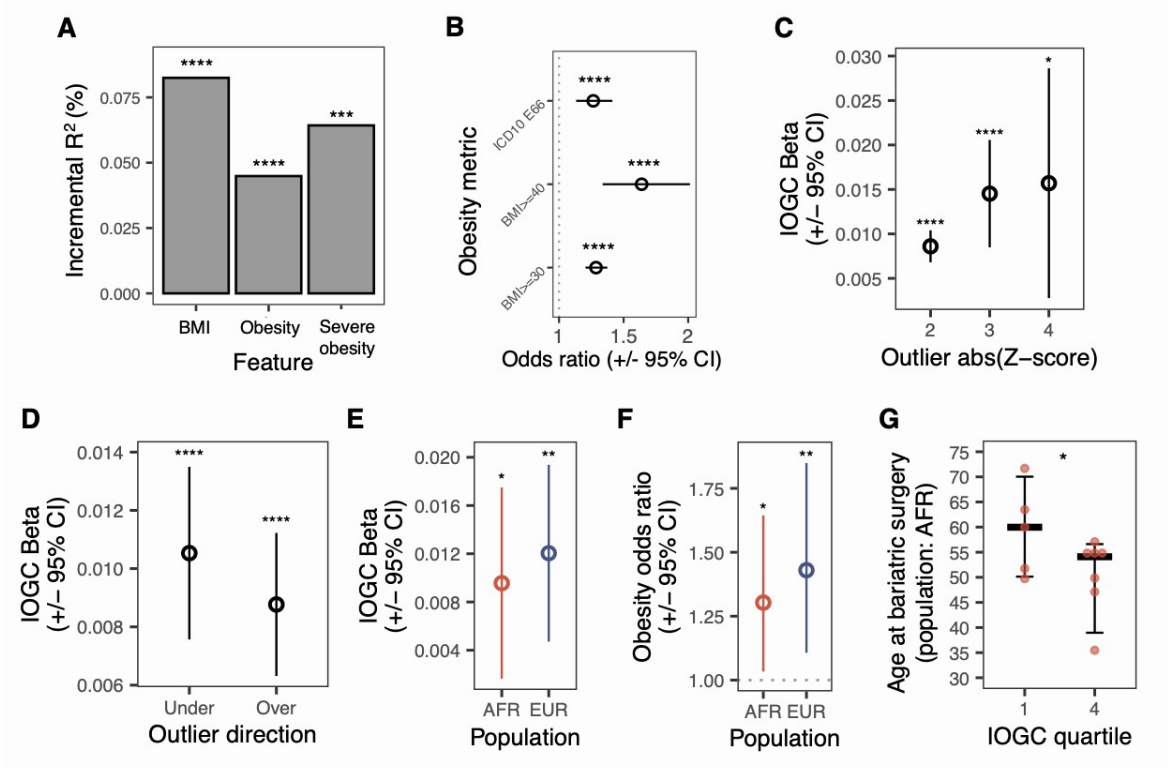
Supplementary Figure 2. Rate of concordance between cis-eQTL and outlier-associated variants per gene, matched on cis-eQTL slope/outlier direction and GWAS effect direction (risk/protective) and stratified by cis-eQTL GWAS P-Value, number of cis-eQTL variants per gene, and outlier gene expression abs(Z-score). P-values obtained from Binomial test.



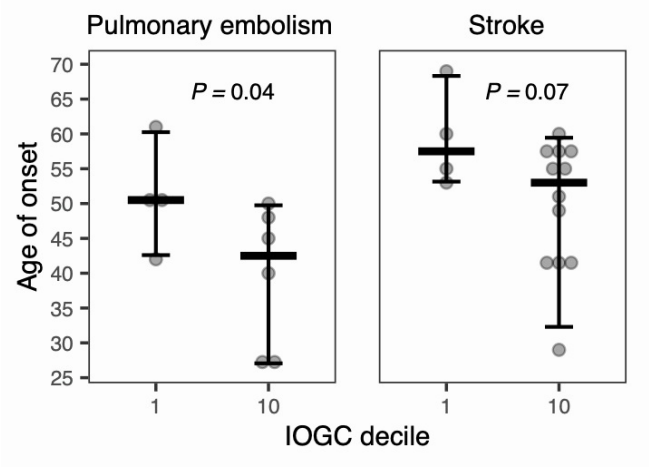
Supplementary Figure 3. Mean weight (left) and BMI (right) observed in UKB validation cohort across deciles of a polygenic risk score for BMI.



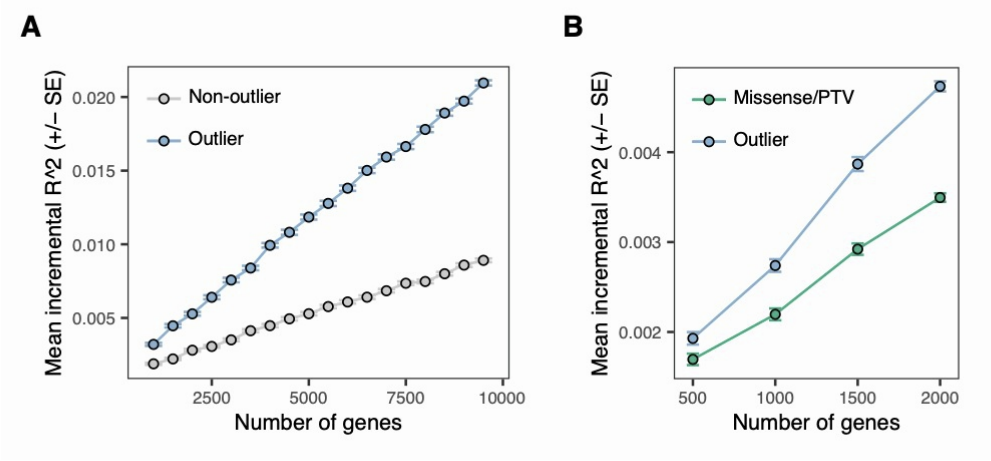
Supplementary Figure 4. Linear regression coefficients from a model testing the effect of IOGC score (blue circle) on BMI in UKB, adjusting for the effects of PRS, sex, age, genotype array, and first 10 principal components of ancestry (black circles). All predictors were scaled (mean=0 and variance=1) and ordered by their regression coefficient estimate to aid visual comparison. P-values obtained from linear regression.



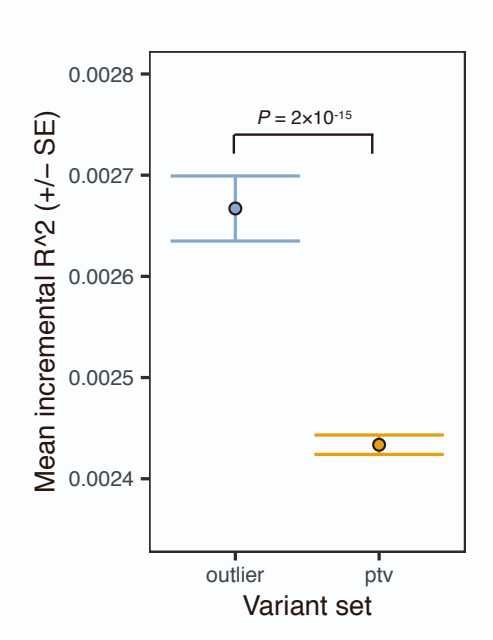
Supplementary Figure 5. A. Incremental R^2 for BMI, obesity (BMI>=30 kg/m^2) and severe obesity (BMI>=40 kg/m^2) observed when adding IOGC to a regression model controlling for PRS, age, sex, principal components of ancestry 1-10, and genotyping array in UKB validation cohort. P-values obtained from ANOVA tests. **B.** Odds ratios for obesity (BMI>=30 kg/m^2), diagnostic history of obesity (ICD-10 code E66), and severe obesity (BMI>=40 kg/m^2) comparing individuals in top and bottom 10% of IOGC score. P-values obtained from Fisher's Exact Test. **C.** IOGC regression coefficients across more extreme gene expression outlier Z-scores. P-values obtained from linear regression. **D.** IOGC regression coefficients for under-expression and over-expression outlier-associated variants. P-values obtained from linear regression. **E.** Regression coefficients across two distinct ancestry groups in UKB, directly modeling the effect of IOGC on BMI in UKB individuals with self-reported African ancestry (N=6,459) (AFR, red) compared with a matched number of randomly sampled UKB non-British White individuals (EUR, blue). P-values obtained from linear regression. **F.** Odds ratios for obesity (BMI>=30 kg/m^2) comparing individuals in top and bottom 10% of IOGC score for same cohorts described in (**E.**). P-values obtained from Fisher's Exact Test. **G.** Age at bariatric surgery for top and bottom 25% of IOGC score among AFR cohort individuals described in (**E.**). Crossbars indicate median, error bars indicate 90% of data range. P-value obtained from T-test.



Supplemental Figure 6. Age at time pulmonary embolism (left) or stroke (right) was diagnosed for individuals classified as severely obese (BMI>=40 kg/m^2) and in the top or bottom 10% of IOGC score. Crossbars indicate median, error bars indicate 90% of data range.



Supplementary Figure 7. A. Mean Incremental R^2 (%) resulting from adding IOGC to a regression model predicting BMI and controlling for PRS, age, sex, principal components of ancestry 1-10, and genotyping array. IOGC was calculated using outlier-associated (blue) or non-outlier (gray) variants across permutations of progressively larger gene sets. **B.** Following the same procedure as in (**A.**) for missense variants or PTVs matched on minor allele frequency of outlier-associated variants in intersecting genes.



Supplementary Figure 8. Mean Incremental R^2 (%) resulting from adding IOGC to a regression model predicting BMI and controlling for PRS, age, sex, principal components of ancestry 1-10, and genotyping array. IOGC was calculated separately for outlier-associated variants (blue) and PTVs (yellow) across permutations in the intersecting gene set containing at least one variant from both categories. P-value obtained from Wilcoxon test.

Table 1. Area under receiver operator curve (AUROC) and area under prediction recall curve (AUPRC) across covariates-only, covariates+PRS and covariates+PRS+IOGC logistic regression models predicting obesity, severe obesity and age of onset for bariatric surgery

Phenotype	AUROC			AUPRC		
	Baseline[1]	+PRS	+PRS+IOGC	Baseline[1]	+PRS	+PRS+IOGC
Obesity (BMI>=30 kg/m^2)	**0.5423** (NA)	**0.6575** (+21.2%)	**0.6581** (+0.09%)	**0.2717** (NA)	**0.3769** (+38.7%)	**0.3781** (+0.28%)
Severe Obesity (BMI>=40 kg/m^2)	**0.5870** (NA)	**0.7340** (+25.1%)	**0.7356** (+0.09%)	**0.0269** (NA)	**0.0603** (+224.0%)	**0.0610** (+1.06%)
Early onset bariatric surgery[2]	**0.6937** (NA)	**0.6951** (+0.21%)	**0.7415** (+6.68%)	**0.6976** (NA)	**0.7002** (+0.37%)	**0.7135** (+1.90%)

[1] Baseline model: obesity = age + sex + PC1…PC10 + genotyping array; bariatric surgery = sex + PC1…PC10 + genotyping array
[2] Binary outcome: age at bariatric surgery <= cohort mean

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