Supplement for: A model and test for coordinated polygenic epistasis in complex traits

Brooke Sheppard, Nadav Rappoport, Po-Ru Loh, Stephan Sanders, Noah Zaitlen, Andy Dahl

March 4, 2021

Contents

Overview

- We first introduce our polygenic epistasis model and define Coordinated Interaction (CI).
- We then illustrate the case of 2 SNPs, where CI always exists if any epistasis exists, and the case of 3 SNPs, where CI can be seen in its general form as a correlation across SNP pairs.
- Section 2 connects CI to PRS-level interactions, leading to our Even/Odd test for CI.

- Section 3 lays out the interacting pathway model, where CI has a simple and interpretable form and the Even-Odd estimator has a simple, analytic distribution.
- Section 4 describes several plausible biological instances of the interacting pathways model, which thus exhibit CE and sensible EO estimates.
- Section 5 contains technical proofs, and Section 6 describes our main text simulations.

1 Coordinated polygenic interaction

We use the more general term Coordinated Interaction (CI) in the Supplement to emphasize that the results below here largely generalize to any high-dimensional features. We focus on Coordinated Epistasis (CE) in the main text because it deals with the case where the interacting features (G) are genotypes, whose interactions are called "epistasis" [1].

We assume a polygenic model with pairwise SNP interactions for a phenotype y measured on N samples. Let G be the $N \times S$ genotype matrix of S SNPs measured on the N samples. We write the saturated pairwise interaction model as:

$$y_i \overset{\text{ind}}{\sim} \sum_{s=1}^{S} G_{is}\beta_s + \sum_{s \geq s'} G_{is}G_{is'}\Omega_{ss'} + \epsilon_i$$

- $\beta \in \mathbb{R}^S$ is the vector of additive SNP effects.
- $\Omega \in \mathbb{R}^{S \times S}$ is a matrix of pairwise SNP interaction effects. $\Omega_{ss'}$ gives the interaction effect between SNPs s and s'. We assume Ω is lower triangular WLOG.
- ϵ is the noise, which we usually assume has i.i.d. Gaussian entries with mean zero.
- We scale columns of G to mean 0, variance 1 (WLOG, by rescaling β and Ω concomitantly).
- We have ignored all non-genetic effects for convenience, but including covariates (like genetic PCs) is straightforward and important and in practice.

The model can be written more succinctly using $*$, the column-wise Khatri-Rao product. For arbitrary matrices $A \in \mathbb{R}^{N \times p_A}$ and $B \in \mathbb{R}^{N \times p_B}$, each column of the matrix $A * B \in \mathbb{R}^{N \times (p_A \cdot p_B)}$ corresponds to the element-wise product of one column of A and one column of B. Though perhaps $*$ seems unfamiliar, it is a standard component of linear regression with interactions. For example, `R` uses $A * B$ as the design matrix in linear regressions on the interaction between $A * B$, or in other words $A * B =$ `model.matrix(~-1+A:B)`. Conceptually, the column-wise products capture the interactions between each column (or feature) in A and each column in B.

Using $*$, the pairwise interaction model simplifies to:

$$y \sim G\beta + (G * G)\,\omega + \epsilon \tag{1}$$

This defines $\omega := \text{vec}\,(\Omega) \in \mathbb{R}^{S^2}$, where $\text{vec}\,(\cdot)$ concatenates the columns of a matrix into a vector.

Previous analyses of pairwise SNP interaction have focused on one of two complementary strategies. First, each individual pairwise SNP interaction effect, $\Omega_{ss'}$, can be tested by fitting individual SNP pairs (or higher-order tuples) as fixed effects. Second, random effect models can be used to estimate the total magnitude of pairwise epistasis, $\|\Omega\|$, under the assumption that these effects are i.i.d. and also are independent of β. The former approach is particularly attractive for SNPs

with large effects or candidate SNPs, and genome-wide screens can also be useful for complex traits [2]. The latter approach generally has higher power in complex traits, but sacrifices resolution on causal SNPs and structure among the interactions [3–11]. Both approaches have been established for decades. One elegant approach to begin bridging this gap is to test the interaction between a single SNP and a polygenic random effect [12]: this compromise adds power to the SNP-by-SNP approach and adds resolution to the unstructured random effect approach, and conceptually homes in on slices of the pairwise interaction matrix, $\Omega_{s,}$.

In this work, we introduce a new parameter of polygenic interaction called coordination, which quantifies epistasis along a distinct dimension from these previous estimators. The Coordinated Interaction in a polygenic model is defined (roughly) as:

$$\gamma(\Omega, \beta) = \text{Cor}_{s \neq s'} \left(\Omega_{ss'}, \beta_s \beta_{s'} \right) \tag{2}$$

Intuitively, coordination measures the alignment between interactions and the product of main effects. When $\gamma > 0$, the interactions in Ω work in concert to amplify positive SNP effects; for $\gamma < 0$, however, Ω dampens positive SNP effects. The definition of coordination excludes the diagonal terms Ω_{ss} because we want to capture interactions between different SNPs, not nonlinear single-SNP effects like dominance.

We next illustrate CI in the simplest possible cases, where there are only two or three causal SNPs. With two SNPs, we can see how CI measures the synergy/dampening of main SNP effects. With three SNPs, we can see how CI measures the average synergy/dampening over all causal SNP pairs. We assume nonnegative phenotypes in these stylistic sections so that synergy/antagonism are equivalent to positive/negative epistasis [1]– although CI generally measures the latter, the former can be more intuitive. Later, in Section 4, we emphasize the breadth of the CI framework by proving that several plausible polygenic models fall under the CI umbrella:

- Master transcription factors governing gene expression phenotypes (Section 4.1)
- Polygenic buffers for complex traits (Section 4.2)
- Gene-environment interaction (GxE) with G-E dependence (Section 4.3)
- Randomly structured genome-wide epistasis (Section 4.4)

Example 1: Pairwise interaction between two SNPs

In these examples with 2 and 3 SNPs, it is important to use our exact definition of CI, which is:

$$\gamma(\Omega, \beta) := \frac{\sum_{s>s'} \Omega_{ss'} \beta_s \beta_{s'}}{\sqrt{\sum_{s>s'} \Omega_{ss'}^2} \sqrt{\sum_{s>s'} \beta_s^2 \beta_{s'}^2}} \tag{3}$$

Nonetheless, we usually think about CI using the correlation-based approximate definition in (2) because it is simple, interpretable, and accurate for polygenic models. Also in these two examples, we write $\Omega_{ss'} = \beta_s \beta_{s'} \tau_{ss'}$. This comes WLOG except in aberrant case where a SNP has zero main effect and nonzero interactions.

Our example imagines two haploid SNPs a/A and b/B with main effects β_A and β_B. We assume that the SNPs are coded such that $\beta_A, \beta_B > 0$ and that the mean phenotype for the ab genotype is 0. This ensures the phenotype is nonnegative.

We parameterize the pairwise interaction through τ_{AB}, which describes the gap between the true interaction model and the linear prediction for the mean AB phenotype (Table 1). In other words, the mean phenotype for samples with the AB genotype is $\beta_A + \beta_B$ under the linear model,

but under the true epistatic model the mean phenotype for AB samples is $\beta_A + \beta_B + \beta_A\beta_B\tau_{AB}$. Hence, $\tau_{AB} < 0$ means the genotypes act antagonistically, with the total effect of A and B being less that the sum of its parts. On the other hand, $\tau_{AB} > 0$ means the SNPs act synergistically.

For a single pair of SNPs, $\gamma \in \{-1, 1\}$ always, by the definition in (3) (unless $\tau_{AB} = 0$, in which case there is no interaction to coordinate and we formally set $\gamma = 0$). This emphasizes the difference between coordination and generic interaction: rather than measure the existence or size of interactions, CI assumes interactions exist and measures their alignment with main effects.

	a	A
b	0	β_A
B	β_B	$\beta_A + \beta_B + \beta_A\beta_B\tau_{AB}$

$$\implies \gamma = \frac{\beta_A^2\beta_B^2\tau_{AB}}{\sqrt{\beta_A^2\beta_B^2\tau_{AB}^2}\sqrt{\beta_A^2\beta_B^2}} = \text{sign}(\tau_{AB})$$

Table 1: Mean phenotype values with two interacting, haploid SNPs (a/A and b/B) with baseline effects $\beta_A, \beta_B > 0$. When $\tau < 0$, the AB genotype is buffered relative to the additive model; when $\tau > 0$, the effects of A and B are synergistic. γ is formally zero when the linear model holds.

Example 2: Pairwise interaction between three SNPs

In the case of two SNPs, there is only one interaction effect, hence the CI is simply sign of this interaction. More generally, if there are many SNPs, γ resembles a weighted average over the γ values for each SNP pair. Intuitively, γ estimates whether positive SNP effects are, on balance, synergistic or antagonistic with other positive SNP effects.

We illustrate this in the case of three SNPs in Table 2. First, we show γ decomposes into a weighted sum of the τ for each SNP pairs, which extends to the more general polygenic case used in subsequent sections (‡). Second, we show that γ^2 roughly describes the proportion of genetic interactions that is coordinated with main effects (†). Together, these results help bridge the intuition from these simple models with two or three SNPs to the polygenic models that are the focus of the main text and the rest of this document.

	a	A
b	0	β_A
B	β_B	$\beta_A + \beta_B + \beta_A\beta_B\tau_{AB}$

	a	A
c	0	β_A
C	β_C	$\beta_A + \beta_C + \beta_A\beta_C\tau_{AC}$

	c	C
b	0	β_C
B	β_B	$\beta_B + \beta_C + \beta_B\beta_C\tau_{BC}$

Define $w_{ll'} := \dfrac{\beta_l^2\beta_{l'}^2}{\sqrt{\sum_{s>s'}\tau_{ss'}^2\beta_s^2\beta_{s'}^2}\sqrt{\sum_{s>s'}\beta_s^2\beta_{s'}^2}}$

$$\begin{aligned}\implies \gamma &= w_{AB}\tau_{AB} + w_{BC}\tau_{BC} + w_{AC}\tau_{AC} \\ &\overset{‡}{=} \sum_{s>s'} w_{ss'}\tau_{ss'} \\ &\overset{†}{\approx} \frac{\text{sign}(\bar{\tau})}{\sqrt{1 + \text{Coeff. Variation}(\tau)^2}}\end{aligned}$$

Table 2: The equalities emphasize that γ is a type of weighted genome-wide average across all SNP pairs. The approximation works well for polygenic models.

To heuristically motivate the approximation †, assume τ is roughly independent of $\beta \otimes \beta$. Then:

$$\begin{aligned}
\gamma &= \frac{\sum_{s>s'} \tau_{ss'} \beta_s^2 \beta_{s'}^2}{\sqrt{\sum_{s>s'} \tau_{ss'}^2 \beta_s^2 \beta_{s'}^2} \sqrt{\sum_{s>s'} \beta_s^2 \beta_{s'}^2}} && (= \textstyle\sum_{s<s'} w_{ss'} \tau_{ss'} \text{ in Table 2}) \\
&\approx \frac{\bar{\tau} \sum_{s>s'} \beta_s^2 \beta_{s'}^2}{\sqrt{(\bar{\tau}^2 + \mathbb{V}(\tau)) \sum_{s>s'} \beta_s^2 \beta_{s'}^2} \sqrt{\sum_{s>s'} \beta_s^2 \beta_{s'}^2}} && \text{(by independence assumption)} \\
&= \frac{\bar{\tau}}{\sqrt{\bar{\tau}^2 + \mathbb{V}(\tau)}} && \text{(equivalent to † in Table 2)}
\end{aligned}$$

This illustrative approximation holds for large S or on average over random τ and β. This heuristic approximation is useful for building intuition: CI takes the relative buffering/synergy contribution from each SNP pair ($\tau_{ss'}$), and then averages over SNPs ($\bar{\tau}$), and then shrinks toward zero to penalize for variability amongst the $\tau_{ss'}$ (via the Coefficient of Determination, $\mathbb{V}(\tau)/\bar{\tau}^2$). This intuition will persist over later sections, where qualitatively similar results are obtained under more careful approximations analyzing polygenic models (Examples 3 and 4, and Sections 4.1, 4.4).

2 The even/odd estimator for coordination

Clearly, if we knew Ω and β we could just calculate the CI γ from equation (3). More generally, we could evaluate γ using estimates of Ω and β, which is likely to succeed when the SNP effect estimates are accurate. However, we are primarily interested in the domain where $S \gg N$ and β and Ω are dense, a setting where accurate effect estimates are hopeless.

A similar problem arises in the simpler setting of additive heritability estimation, where the goal is to estimate $\|\beta\|$ (and Ω is ignored). The simple plug-in estimator $\|\hat{\beta}\|$ will be highly inflated due to noise in $\hat{\beta}$[1]. The GREML approach to this problem is to instead directly estimate $\|\beta\|$ with a random effect model, without ever explicitly estimating β. Somewhat remarkably, GREML succeeds in practice even when the Gaussian random effect model for β is misspecified (so long as there are not too few causal SNPs) [13].

As in GREML, we do not attempt to directly calculate CI by plugging in estimates of β or Ω. Instead, we take an approach that averages signals over large genomic regions, which we name the Even-Odd estimate (or EO estimate, with a corresponding EO test). As in GREML, the EO estimate is unbiased and its significance test is powerful for sufficiently polygenic traits (Proposition 1). We formalize a plausible framework whre this holds in Section 3, where phenotypes are driven by interactions between polygenic, latent pathways.

Concretely, we are interested in the regression coefficients derived from fitting the following (misspecified) phenotypic model with ordinary linear regression, symbolically represented by:

$$y \sim \alpha_A P_A + \alpha_B P_B + \lambda P_A * P_B \tag{4}$$

$$P_{iA} := \sum_{s \in A} G_{is} \beta_s; \quad P_{iB} := \sum_{s \in B} G_{is} \beta_s \tag{5}$$

[1] Nonetheless, we expect that the plug-in estimator is less prone to bias for CI than for heritability, as CI measures correlation rather than absolute size. E.g. in preliminary simulations with $N \gg S$, the plug-in estimator works reasonably well, but we do not explore this in detail as our main practical interest is in the high-dimensional setting.

This defines P_A and P_B as the risk scores derived from the SNP sets A and B. We name the test Even-Odd for the case where A and B contain SNPs from even and odd chromosomes, respectively. Note that we have directly assumed that the estimated PRS, built from $\hat{\beta}$ in practice, are equal to the oracle PRS, built from β. Also, we have assumed that the pathways are independent, i.e. A and B are disjoint, but we lift this in Section 3.3.

We propose to estimate the coordination γ by rescaling the OLS estimate of λ:

$$\hat{\gamma}_{AB} := \sqrt{\frac{h_A^2 h_B^2}{h_{AB}^2}} \hat{\lambda}_{OLS} \tag{6}$$
$$h_A^2 := \|\beta_A\|^2; \quad h_B^2 := \|\beta_B\|^2; \quad h_{AB}^2 := \|\Omega_{AB}\|^2$$

This rescaling of the OLS coefficient $\hat{\lambda}_{OLS}$ is essential for unbiased estimates of γ. However, it has no effect on testing $\gamma = 0$ or the estimated sign of γ, which are the only quantities we study in the main text. (For these reasons, we refer to this regression coefficient as $\hat{\gamma}$ in the main text, for conceptual simplicity). In the future, it may be useful to scale λ_{OLS} with estimates of h_A^2, h_B^2 and h_{AB}^2 (e.g. from [3–11]) in order to quantify the absolute impact of CI on genetic architecture.

Our first significant theoretical result (Proposition 1) shows that this estimator is unbiased and consistent for the true Even-Odd CI, γ_{AB}:

$$\hat{\gamma}_{AB} = \gamma_{AB} + \mathcal{N}\left(0, \frac{1}{N h_{AB}^2}\right)$$

where γ_{AB} is defined as:

$$\gamma_{AB} = \frac{\beta_A^T \Omega_{AB} \beta_B}{\sqrt{h_A^2 h_B^2 h_{AB}^2}} \tag{7}$$

The precision of the EO estimate, $N h_{AB}^2$, is an intuitive measure of the effective sample size for the EO estimate. We note that the additive heritabilities do not affect this precision term because we assumed that $\hat{\beta} = \beta$, motivated by the assumption that additive heritability is significantly larger and easier to estimate than the pairwise-epistasis heritability. In future work, it may be interesting to precisely characterize the error from this approximation by expanding $\hat{\beta}$ around β; nonetheless, we speculate this more careful treatment would simply increase the calculated estimator variance and attenuate the expected estimate. In particular, we do not imagine these errors will induce false positives. These speculations are in line with the precisely characterized impact of genotyping or phenotyping errors in GREML [13].

Proposition 1 provides the link between our estimate of the EO CI, $\hat{\gamma}_{EO}$, and the true EO CI, γ_{AB}. In the next section, we will provide biologically plausible models that yield $\gamma_{AB} \approx \gamma$. Together, this will show that $\hat{\gamma}_{AB}$ is a reasonable estimator of the coordination γ.

3 Interacting pathways model

We now imagine a trait that is driven by pairwise interactions among K distinct pathways (or systems, or intermediate phenotypes). Our model is most sensible when these pathways are polygenic, with causal contributions spread along the genome. Hence, when we discuss pathways we are not primarily thinking of well-characterized molecular metabolic pathways in model organisms, i.e we

are not primarily imagining interactions among proteins in a complex, or other physical molecular interactions, or "biological epistasis" [14]. Rather, we refer to "statistical" interactions among biomedically distinct pathways that are themselves complex traits: for example, type 2 diabetes involves contributions from both insulin-producing and -sensing pathways; asthma involves contributions from both type 2 immune response and (heritable) environmental risk factors, like smoking; and many monogenic disorders have phenotypic presentation that depend both on the core gene and modifier genes. Broadly, our formal model stands on its own, and its test establishes statistical epistasis, but our EO test under interacting pathways will have greatest power when the pathways are complex polygenic traits. We discuss several biologically plausible mechanisms that instantiate this type of statistically-interacting pathway models in Section 4.

In this section, our focus is on the formal mathematical behavior of CI and the EO Estimate under latent, polygenic, statistically-interacting pathways. We derive the coordination, γ, and show the even/odd estimator, $\hat{\gamma}_{AB}$, is accurate for polygenic models.

We formalize the interacting pathways model as:

$$\begin{aligned} y &= \sum_{k} z_k + \sum_{k \leq k'} (z_k \circ z_{k'})\, \alpha_{kk'} + \epsilon \\ z_k &= \sum_{s \in S_k} G_{,s} \beta_s \end{aligned} \tag{8}$$

where z_k are the K discrete pathway main effects driven by the SNPs in the the set S_k. Note that z reflect causal biological pathways, while the A/B risk scores we construct in P are based on chosen, potentially arbitrary SNP sets. Here, we assume that the S_k are disjoint, but we lift this restriction in Section 3.3. Note that this interacting pathways model in (8) is an instance of the general polygenic pairwise interaction model in (1), with $\omega_{ss'} = \beta_s \beta_{s'} \alpha_{k(s)k(s')}$, where $k(s)$ indicates the pathway to which SNP s contributes.

3.1 γ under interacting pathways

In the interacting pathways model, the coordination is:

$$\begin{aligned}
\gamma &:= \frac{\sum_{s<s'} \beta_s \beta_{s'} \omega_{ss'}}{\sqrt{\left(\sum_{s<s'} \beta_s^2 \beta_{s'}^2\right)\left(\sum_{s<s'} \omega_{ss'}^2\right)}} \\
&= \frac{\sum_{s<s'} \beta_s^2 \beta_{s'}^2 \alpha_{k(s)k(s')}}{\sqrt{\left(\sum_{s<s'} \beta_s^2 \beta_{s'}^2\right)\left(\sum_{s<s'} \beta_s^2 \beta_{s'}^2 \alpha_{k(s)k(s')}^2\right)}} \\
&= \frac{\sum_{k,k'} h_k^2 h_{k'}^2 \alpha_{kk'} - \sum_s \beta_s^4 \alpha_{k(s)k(s)}}{\sqrt{\left(\sum_{k,k'} h_k^2 h_{k'}^2 - \sum_k \sum_{s\in k} \beta_s^4\right)\left(\sum_{k,k'} h_k^2 h_{k'}^2 \alpha_{kk'}^2 - \sum_s \beta_s^4 \alpha_{k(s)k(s)}^2\right)}} \\
&=: \frac{\sum_{k,k'} h_k^2 h_{k'}^2 \alpha_{kk'} - s_1}{\sqrt{\left(h_\beta^4 - s_2\right)\left(h_\omega^2 - s_3\right)}} \\
&\approx \frac{\sum_{k,k'} h_k^2 h_{k'}^2 \alpha_{kk'}}{h_\beta^2 \sqrt{h_\omega^2}} \\
h_k^2 := \sum_{s\in k} \beta_s^2; \quad h_\beta^2 &:= \sum_s \beta_s^2 = \sum_k h_k^2; \quad h_\omega^2 := \sum_{k,k'} h_k^2 h_{k'}^2 \alpha_{kk'}^2 \approx 2 \sum_{s<s'} \omega_{ss'}^2
\end{aligned}$$

A few facts:

- γ is invariant to jointly multiplying all h_k^2 or all $\alpha_{kk'}$ by any positive number.
- $\gamma \neq 0$ implies that at least one heritable, interacting pathway exists–$\exists\, i, j$ s.t. $h_i^2, h_j^2, \alpha_{ij} \neq 0$.
- We have loosely assumed that the residual terms s_1, s_2, and s_3 are approximately zero. This will hold when the heritability is smoothly spread across many causal SNPs because these terms each sum over only L SNP pairs rather than L^2. This is particularly easy to see in the limit that $\beta_s^2 = b$ for all SNPs s. Taking s_1 as an example, and defining L_k as the number of SNPs contributing to pathway k:

$$\left|\frac{s_1}{\sum_{s,s'} \beta_s^2 \beta_{s'}^2 \alpha_{k(s)k(s')}}\right| = \left|\frac{2\sum_s b^2 \alpha_{k(s)k(s)}}{\sum_{s,s'} b^2 \alpha_{k(s)k(s')}}\right| = 2\left|\frac{\sum_k L_k \alpha_{kk}}{\sum_{k,k'} L_k L_{k'} \alpha_{kk'}}\right| \leq 2|\alpha_{(1)(1)}|/L_{(1)}$$

  where the inequality is over choices of α and (1) indicates the value of k that minimizes L_k. So, in the limit $L_j \to \infty\ \forall j$, then $s_1, s_2, s_3 \to 0$.

Example 3: Intra- and Inter-Pathway CI

First, assume there are only two pathways, i.e. $K = 2$. If there is no intra-pathway interaction, then $\alpha_{11} = \alpha_{22} = 0$, and the CI is:

$$\gamma \approx \frac{h_1^2 h_2^2 \alpha_{12}}{(h_1^2 + h_2^2)\sqrt{h_1^2 h_2^2 \alpha_{12}^2}} = \text{sign}(\alpha_{12}) \frac{\sqrt{h_1^2 h_2^2}}{h_1^2 + h_2^2} \tag{9}$$

This is proportional to the ratio of the geometric to arithmetic mean of the pathway-level heritabilities, which is always lies in $[0, 1]$. The CI is maximized in absolute value, at $\pm\frac{1}{2}$, when $h_1^2 = h_2^2$; conceptually, the factor of $\frac{1}{2}$ accounts for the loss of intra-pathway coordination from our assumption that $\alpha_{11} = \alpha_{22} = 0$. Conversely, the CI is zero when one pathway has no heritability, so $h_1^2 h_2^2 = 0$. Hence, a positive CI test demonstrates the existence of heritable and interacting pathways in this setting.

On the other hand, we can assume that all the interaction is intra-pathway, in the sense that $\alpha_{11} = \alpha_{22} = a$ and that $\alpha_{12} = \alpha_{21} = 0$. Then the CI is:

$$\gamma \approx \frac{a((h_1^2)^2 + (h_2^2)^2)}{(h_1^2 + h_2^2)\sqrt{a^2((h_1^2)^2 + (h_2^2)^2)}} = \text{sign}(a)\frac{\sqrt{(h_1^2)^2 + (h_2^2)^2}}{h_1^2 + h_2^2} \tag{10}$$

In this setting, a positive CI test does not guarantee the existence of multiple interacting pathways. In fact, the CI magnitude is maximized (at ± 1) when $h_1^2 h_2^2 = 0$. (As proof, the ratio in (10) compares the ℓ_2 and ℓ_1 norms of the vector (h_1^2, h_2^2).)

More generally, assume there are K pathways where both the intra-pathway nonlinearities and the inter-pathway interactions are evenly distributed, i.e. that $\alpha_{ij} = a$ if $i \neq j$ and $\alpha_{ii} = b$. Under this more general model, the CI is:

$$\begin{aligned}
\gamma &\approx \frac{\sum_{k,k'} h_k^2 h_{k'}^2 (a + (b-a) I\{k = k'\})}{h_\beta^2 \sqrt{\sum_{k,k'} h_k^2 h_{k'}^2 (a + (b-a) I\{k = k'\})^2}} \\
&= \frac{a(h_\beta^2)^2 + (b-a)\sum_k h_k^4}{h_\beta^2 \sqrt{a^2 (h_\beta^2)^2 + (b^2 - a^2)\sum_k h_k^4}} \\
&= \frac{a + (b-a)\xi^2}{\sqrt{a^2 + (b^2 - a^2)\xi^2}} \\
\xi &:= \frac{\sqrt{\sum_k h_k^4}}{h_\beta^2} \implies \xi^2 = \frac{1}{K}(1 + \text{Coeff. Variation}_k(h_k^2)^2)
\end{aligned}$$

The last equality implies that $\xi^2 \in [1/K, 1]$. ξ^2 is larger when heritability is concentrated in a few of the K pathways, and is smaller when heritability is diffusely distributed. Intuitively, when heritability is smoothly spread, interactions between pathways matter more, whereas when heritability is concentrated in a single pathway, only that pathway's nonlinearity matters for determining CI.

This last equation for γ can be rewritten to emphasize that it depends only on the relative inter- and intra-pathway interactions, b/a:

$$\gamma \approx \text{sign}(a)\frac{1 + (b/a - 1)\xi^2}{\sqrt{1 + (b^2/a^2 - 1)\xi^2}}$$

This is informative because it describes the interplay between inter- and intra-pathway interactions:

- When $b/a > 1$, increasing the relative strength of intra-pathway nonlinearity (b/a) mitigates CI toward 0.
- This effect weakens as ξ grows, since ξ upweights the impact of intra-pathway effects on CI.
- When $0 < b/a < 1$, increasing the relative strength of intra-pathway nonlinearity (b/a) increases CI toward 1. Further, increasing ξ now decreases the CI.

- When $b/a < 0$ is negative–so that inter- and intra-pathway CI contribute conflicting forms of sign epistasis–either source of effect may win out in determining the sign of γ, depending on the balance of $|a|$ and $\xi|b|$.

Broadly, when inter- and intra-pathway nonlinearities exist, the sign and magnitude of CI is a compromise bewtween these two contributions, with weights determined by the uniformity of the spread of heritability among pathways. This is visually described in Figure S2.

Example 4: Many Interacting Pathways

Assume K is large and h^2 and α are independent. Then:

$$\begin{aligned}
\gamma &\approx \frac{\sum_{k,k'} h_k^2 h_{k'}^2 \alpha_{kk'}}{h_\beta^2 \sqrt{h_\omega^2}} \\
&\approx \frac{K^2 \left(\frac{1}{K^2} \sum_{k,k'} h_k^2 h_{k'}^2\right) \left(\frac{1}{K^2} \sum_{k,k'} \alpha_{kk'}\right)}{h_\beta^2 \sqrt{K^2 \left(\frac{1}{K^2} \sum_{k,k'} h_k^2 h_{k'}^2\right) \left(\frac{1}{K^2} \sum_{k,k'} \alpha_{kk'}^2\right)}} \\
&= \frac{h_\beta^4 \bar{\alpha}}{h_\beta^2 \sqrt{h_\beta^4 \left(\bar{\alpha}^2 + \mathbb{V}\left(\alpha\right)\right)}} \\
&= \frac{\bar{\alpha}}{\sqrt{\bar{\alpha}^2 + \mathbb{V}\left(\alpha\right)}} \\
&= \frac{\text{sign}(\bar{\alpha})}{\sqrt{1 + \text{Coeff. Variation}(\alpha)^2}}
\end{aligned}$$

Hence, γ is the sign of the average level of positive/negative epistasis across pathways, shrunk toward zero to penalize variance between pairwise pathway-level interactions.

This qualitatively resembles the CI obtained with 3 interacting SNP pairs (Example 2, equation †), and provides a more rigorous context for that approximation. This also bears some resemblance to the CI obtained in Example 3 under K pathways with constant inter- and intra-pathway interactions, in that the coefficient of variation (in that case, across the pathway heritabilities) shrinks an average per-pathway-pair CI toward 0.

However, note that $\bar{\alpha}$ is a measure of the pathway-level coordination, analogous to the SNP-level coordination we seek to measure with γ. That is, SNP-level coordination persists for large K only when the pathways are themselves coordinated, which raises the question: When are pathways coordinated? The natural answer, as for SNP-level coordination, is that pathway coordination results when the pathways converge on lower-dimensional, parsimonious pathways–which is essentially a contradiction since we presumed the necessity of many pathways to explain the genetic architecture. In other words, the many-pathway limit is not expected to be biologically meaningful, which motivates our focus on traits driven by interactions between a small number of pathways. Nonetheless, we emphasize that, mathematically, the existence of parsimonious pathways is sufficient but not necessary for coordination.

3.2 γ_{AB} under interacting pathways

Above, we derived the behavior of the true, global coordination, γ. Here, we analyze γ_{AB}, the oracle estimator of γ we could create if we knew Ω (recall that we assume β is known). Starting from its definition,

$$\begin{aligned}
\gamma_{AB} &:= \frac{\beta_A^T \Omega_{AB} \beta_B}{\sqrt{h_A^2 h_B^2 h_{AB}^2}} \\
&= \frac{\sum_{s \in A, s' \in B} \beta_s (\beta_s \beta_{s'} \alpha_{k(s)k(s')}) \beta_{s'}}{\sqrt{h_A^2 h_B^2} \sqrt{\sum_{s \in A, s' \in B} \left(\alpha_{k(s)k(s')} \beta_s \beta_{s'}\right)^2}} \\
&= \frac{\sum_{k,k'} \alpha_{kk'} \sum_{s \in A \cap k, s' \in B \cap k'} \beta_s^2 \beta_{s'}^2}{\sqrt{h_A^2 h_B^2} \sqrt{\sum_{k,k'} \alpha_{kk'}^2 \sum_{s \in A \cap k, s' \in B \cap k'} \beta_s^2 \beta_{s'}^2}} \\
&= \frac{\sum_{k,k'} \alpha_{kk'} h_{A,k}^2 h_{B,k'}^2}{\sqrt{h_A^2 h_B^2} \sqrt{\sum_{k,k'} \alpha_{kk'}^2 h_{A,k}^2 h_{B,k'}^2}}
\end{aligned}$$

We have defined $h_{A,k}^2 = \sum_{s \in A \cap S_k} \beta_s^2$ as the pathway-k heritability that is captured by the SNPs in group A (and likewise for $h_{B,k}^2$). These parameters capture the overlap between the partition of SNPs by causal pathway and the partition of SNPs into A and B, which are arbitrarily chosen by the analyst subject to the condition that there is no LD between SNPs in A and B.

If only one pathway pair is active–$\alpha_{12} \neq 0$, say–then:

$$\gamma_{AB} = \text{sign}(\alpha_{12}) \sqrt{\frac{h_{A,1}^2}{\sum_k h_{A,k}^2}} \sqrt{\frac{h_{B,2}^2}{\sum_k h_{B,k}^2}} \tag{11}$$

In this simple case, γ_{AB}^2 measures the fraction heritability in group A (B) that tags pathway 1 (2). Hence γ_{AB} increases either when (a) superfluous main effects are excluded, so that $h_{A,k}^2$ ($h_{B,k'}^2$) decreases for $k \neq 1$ ($k' \neq 2$) or (b) meaningful main effects are added, so that $h_{A,1}^2$ or $h_{B,2}^2$ increases.

We note that for non-infinitesimal models, our assumption that $\alpha_{21} = 0$ is not trivial, as A and B may differ meaningfully. In this case, Ω must be symmetrized (i.e. we must set $\alpha_{21} = \alpha_{12}$ and then divide by 2). In this case,

$$\gamma_{AB}^2 = \frac{1}{2} \frac{h_{A,1}^2 h_{B,2}^2 + h_{A,2}^2 h_{B,1}^2}{h_A^2 h_B^2} \tag{12}$$

The is useful for the master transcription factor model in 4.1, because the master TF is assumed to derive all its heritability from a small, contiguous genomic region that must live entirely in either A or B. It is also clear that this exactly reduces to (11) under the infinitesimal model, as then $h_{A,2}^2 h_{B,1}^2 = h_{B,2}^2 h_{A,1}^2$.

Compared to γ in (9), the equation for γ_{AB} in (11) replaces the proportion of heritability tagged by group 1 (h_1^2/h_β^2) with the proportion of A-heritability tagged by group 1 ($h_{A,1}^2/h_A^2$), and makes the analogous change for the B group of SNPs. In other words, γ_{AB}/γ measures the enrichment of coordination between A and B SNPs compared to the average coordination across all SNP pairs. Intuitively, most choices for A and B will give γ_{AB} that reasonably approximates γ.

In the special case that the A/B split is purely random and the system is highly polygenic, then $h^2_{A,k} \approx \mathbb{E}_{A/B\ split}\left(h^2_{A,k}\right) = \frac{|A|}{S}h^2_k$ (and $h^2_{B,k} \approx \frac{|B|}{S}h^2_k$), which means that the AB estimator is approximately unbiased:

$$\mathbb{E}_{A/B\ split}\left(\gamma_{AB}\right) \approx \gamma$$

This informally establishes that random SNP partitions yield accurate estimates of polygenic coordination.

However, when A and B are chosen adversarially, arbitrarily large bias can arise. This is also true in GREML [13]. For example, when A perfectly captures pathway 1 heritability ($h^2_{A,1} = h^2_1$) and only pathway 1 heritability ($h^2_{A,1} = h^2_A$), and likewise B perfectly coincides with pathway 2, then $\gamma_{AB} = \text{sign}(\gamma)$ so long as γ is not exactly 0 (i.e., so long as epistasis exists). At the other extreme, $\gamma_{AB} \approx 0$ when A captures negligible pathway-1 heritability, because then $h^2_{A,1} \approx 0$.

More generally, increasing the concentration of A around pathway 1 (resp. B around 2) increases the AB coordination. In this sense, we can use the variation of γ_{AB} as a function of A and B to map the latent interacting pathways. This is the intuition supporting our tests for enrichment of CI in trait-relevant tissues, but can be generalized in many ways. For example, in the limit where $|A| \to 1$, a SNP-level model is obtained, giving a CI analogue of the SNP-by-Polygenic epistasis test in [12]. In the future, it may be interesting to systematically search for A and B to maximize γ_{AB}, which is essentially the CI analogue of searching for the optimal set of SNPs to include in an ordinary PRS.

3.3 Incorporating genetically correlated pathways

We now eliminate the assumption that the pathways z_k are each determined by disjoint sets of SNPs. Instead, we introduce pathway-specific effects $\beta^{(k)} \in \mathbb{R}^S$, which can have support on overlapping entries and/or correlation across k:

$$z_k = G\beta^{(k)}$$

When $K = 2$, and assuming no intra-pathway non-linearity ($\alpha_{11} = \alpha_{22} = 0$), the CI is:

$$\begin{aligned}
\gamma &:= \frac{\sum_{s<s'}(\sum_k \beta^{(k)}_s)(\sum_k \beta^{(k)}_{s'})\left(\alpha_{12}\beta^{(1)}_s\beta^{(2)}_{s'}\right)}{\sqrt{\left(\sum_{s<s'}(\sum_k \beta^{(k)}_s)^2(\sum_k \beta^{(k)}_{s'})^2\right)\left(\sum_{s<s'}\left(\alpha_{12}\beta^{(1)}_s\beta^{(2)}_{s'}\right)^2\right)}} \\
&\approx \frac{1/2\sum_{s,s'}(\sum_k \beta^{(k)}_s)(\sum_k \beta^{(k)}_{s'})\left(\alpha_{12}\beta^{(1)}_s\beta^{(2)}_{s'}\right)}{\sqrt{1/2\left(\sum_s(\sum_k \beta^{(k)}_s)^2\right)^2\left(1/2\sum_{s,s'}\left(\alpha_{12}\beta^{(1)}_s\beta^{(2)}_{s'}\right)^2\right)}} \\
&= \text{sign}(\alpha_{12})\frac{\left(\beta_1^T\beta_2 + \|\beta_1\|^2\right)\left(\beta_1^T\beta_2 + \|\beta_2\|^2\right)}{\left(\|\beta_1\|^2 + 2\beta_1^T\beta_2 + \|\beta_2\|^2\right)\|\beta_1\|\|\beta_2\|} \\
&= \text{sign}(\alpha_{12})\frac{(\rho h_2 + h_1)(\rho h_1 + h_2)}{h_1^2 + 2\rho h_1 h_2 + h_2^2} \\
&= \text{sign}(\alpha_{12})\left(\rho + (1-\rho^2)\frac{h_1 h_2}{h_1^2 + 2\rho h_1 h_2 + h_2^2}\right) \qquad (13)
\end{aligned}$$

We define $\rho = \widehat{\text{Cov}}(\beta^{(1)}, \beta^{(2)}) = \beta_1^T \beta_2$ (informally identifying β_i and $\beta^{(i)}$ where convenient, and under the standard assumption that these vectors have roughly mean 0). Because we assumed only $K = 2$ pathways, the space of inter-pathway correlation collapses to the scalar ρ. We assume $\rho \geq 0$ for simplicity and because this is usually biologically plausible, but could do similar calculations for $\rho < 0$; however, this doesn't come without loss of generality once the sign of α_{12} is chosen.

Intuitively, the deflation factor $(1-\rho)^2$ adjusts for double-counting the overlapping genetic signal between β_g and β_e–already counted in the first term, ρ–and this ensures that $|\gamma| \leq 1$, as expected.

This exactly agrees with the above equation (9) when $\rho = 0$, as it should because the former was derived in the independent-pathway setting. On the other hand, as $\rho \to 1$, $|\gamma| \to \rho$, and in particular $\rho = 1$ gives $\gamma = \pm 1$. On the other end, as $\rho \to -1$, the sign of γ and ρ can disagree; nonetheless, this holds only in a small range of the parameter space, and in this range both γ and ρ are nearly 0, anyways (Figure S1). In general, $\rho > 0$ serves to increase γ estimates, hence showing another source of coordination.

As a function of $x := h_2/h_1 \geq 0$, γ varies over the interval $[\rho, \rho + \frac{(1-\rho)^2}{4}] = [\rho, \frac{(1+\rho)^2}{4}]$, because $4x \leq 1 + 2x + x^2$ for all $x \in \mathbb{R}$. We visualize these components as the upper/lower bounds in Figure S1, and illustrate how γ varies, especially for $\rho < 0$, as a function of the ratio of heritabilities h_1^2/h_2^2 (i.e. holding constant total heritability).

4 Biological models of coordinated interaction

4.1 Master transcription factor

eQTLs are SNPs that effect the expression of a gene. Here, we assume a phenotypic model where SNPs effect a complex trait–like type 2 diabetes or BMI–only through their impact on gene expression. We partition the eQTLs into S_0, governing the expression of a gene that is a master transcription factor (TF), and S_g, for all the genes g regulated by the master TF. We assume each gene is determined by additive SNP effects in a contiguous region. In other words, we assume an additive *cis*-eQTL architecture for the baseline expression of each gene:

$$\tilde{Z}_{ig} = \mu_g + G_{i(g)}\eta_{(g)} + \delta_{ig}$$
$$Z_{i0} = \mu_0 + G_{i(0)}\eta_{(0)} + \delta_{i0}$$

Each $\eta_{(g)}$ represents the effects of *cis* SNPs on some gene, and δ_{ig} indicates nongenetic determinants of gene expression.

Except for the master TF, we model each gene's expression as the product of its baseline, *cis*-driven expression and the expression of the master TF:

$$Z_{ig} = \tilde{Z}_{ig} Z_{i0}$$

Finally, we assume the phenotype is determined by linear gene effects plus some noise term ϵ:

$$y_i = \sum_{g>0} Z_{ig}\psi_g + \epsilon_i$$

Intuitively, the master TF scales the *cis*-genetic architecture of the genes it regulates, either amplifying or dampening the *cis*-signal depending on the expression of the master TF (Z_{i0}). In this way, the organism can control the phenotypic penetrance of entire genetic programs without altering

their *cis*-genetic architecture. This simplistic model resembles a *trans*-genetic regulation mechanism that was recently proposed as a biologically plausible mechanism for the omingenic model [15] and, more generally, is motivated by known *trans*-eQTLs with disease relevance, e.g. *KLF14* [16].

This master TF model can be recast as a pairwise SNP interaction model by expanding Z_{ig}:

$$\begin{aligned} y_i &= \sum_g \left(\left(\mu_g + G_{i(g)}\eta_{(g)} + \delta_{ig}\right) \cdot \left(\mu_0 + G_{i(0)}\eta_{(0)} + \delta_{i0}\right)\right)\psi_g + \epsilon_i \\ &= \mu_0 \sum_g \mu_g\psi_g + \mu_0 \sum_g \psi_g \sum_{s\in S_g} G_{is}\eta_s + \sum_g \mu_g\psi_g \sum_{s\in S_0} G_{is}\eta_s + \sum_{g,s\in S_g;s'\in S_0} G_{is}G_{is'}\eta_s\eta_{s'}\psi_g + \epsilon_i' \\ \implies y &= \mu' + G\beta + (G*G)\omega + \epsilon' \end{aligned}$$

This shows our stylized master TF model falls within the framework of the interacting pathway model in (8), where:

$$\beta_s := \eta_s \begin{cases} \mu_0\psi_g & \text{if } s \in S_g \\ \sum_g \mu_g\psi_g =: w_0 & \text{if } s \in S_0 \end{cases}$$

$$\omega_{ss'} := I\{s \in S_0, s' \in S_g\}\eta_s\eta_{s'}\psi_g = \frac{I\{s \in S_0\}}{\mu_0 w_0}\beta_s\beta_{s'}$$

These definitions assume, WLOG, that SNPs are indexed such that the smallest indices all correspond to S_0. We also define the new noise term ϵ' by combining the phenotypic noise ϵ and the phenotypic contribution of gene expression noise in δ.

Note that Ω is essentially proportional to $\beta\beta^T$, except that $\Omega_{ss'}$ is only nonzero when s corresponds to the master TF and s' corresponds to a regulated gene. Intuitively, then, we expect γ to be ± 1 divided by the fraction of the genome that contributes to the expression of the master Written in terms of block matrices, we want the block-wise correlations between the lower triangles of $\beta\beta^T$ and Ω:

$$\underbrace{\begin{pmatrix} \beta_{(1)}\beta_{(0)}^T & & & \\ \vdots & \ddots & & \\ \beta_{(S-1)}\beta_{(0)}^T & \beta_{(S-1)}\beta_{(1)}^T & \ddots & \\ \beta_{(S)}\beta_{(0)}^T & \beta_{(S)}\beta_{(1)}^T & \dots & \beta_{(S)}\beta_{(S-1)}^T \end{pmatrix}}_{\beta\beta^T} \quad \text{and} \quad \underbrace{\begin{pmatrix} \beta_{(1)}\beta_{(0)}^T & & & \\ \beta_{(2)}\beta_{(0)}^T & 0 & & \\ \vdots & \vdots & \ddots & \\ \beta_{(S)}\beta_{(0)}^T & 0 & \dots & 0 \end{pmatrix}}_{\mu_0 w_0 \Omega}$$

Let $h_{\neg 0}^2 := \sum_{g>0} h_g^2$ and $h_\beta^2 := h_0^2 + h_{\neg 0}^2$. Visually, the correlation decomposes into column-wise terms capturing the master TF ($\sqrt{h_0^2/h_\beta^2}$) and row-wise terms capturing its downstream genes ($\sqrt{h_{\neg 0}^2/h_\beta^2}$). Then γ can be derived directly from (9), because this model is a particular instance of the two-pathway interaction model:

$$\gamma = \frac{\sqrt{h_0^2 h_{\neg 0}^2}}{h_0^2 + h_{\neg 0}^2} \tag{14}$$

Because $(a+b)^2 > 4ab$ for all $a, b \in \mathbb{R}$, $\gamma \in [-1/2, 1/2]$, consistent with our interpretation of γ as a correlation. The factor of 2 accounts for the fact that there is no interaction between at least

half of all pairs of SNPs, because we assume no SNP is a *cis*-eQTL for both the master TF and a regulated gene.

(14) does not exactly agree with the approximation in (†) because the latter makes an independence assumption that does not hold for this model with a single TF, essentially because it is very sparse. Nonetheless, under the further assumption that each gene explains roughly equal heritability ($h_0^2 = h_g^2 = h_*^2$), then equation (14) becomes:

$$\gamma \approx \frac{\sqrt{h_*^2\left((G-1)h_*^2\right)}}{Gh_*^2} \approx \frac{1}{\sqrt{G}} = \frac{1/G}{\sqrt{(1/G)^2 + (1/G\cdot(G-1)/G)}} = \frac{\bar{\tau}}{\sqrt{\bar{\tau}^2 + \mathbb{V}(\tau)}} = (\dagger)$$

This uses the definition $\tau_{ss'} := \omega_{ss'}/(\beta_s\beta_{s'})$, as in Examples 1 and 2. It is not a coincidence that these equations agree under the assumption that each gene is roughly equally heritable–this assumption makes τ and $\beta \otimes \beta$ roughly uncorrelated, the main condition for the approximation in (†).

Finally, the AB coordination can be derived directly from (12). Because S_0 is assumed to be small and contiguous, we assume it lives entirely in either A or B–assume, WLOG, that $S_0 \subset A$. Also assume that $h_{\neg 0}^2$ is divided evenly across A and B, as expected if the split is chosen randomly. Then (12)–which respects the fact that this model is non-infinitesimal–gives:

$$\begin{aligned}
\gamma_{AB}^2 &= \frac{1}{2}\frac{(h_0^2)(h_{\neg 0}^2/2) + (h_{\neg 0}^2/2)(0)}{(h_0^2 + h_{\neg 0}^2/2)(h_{\neg 0}^2/2)} \\
&= \gamma^2 \frac{(h_0^2 + h_{\neg 0}^2)^2}{(2h_0^2 + h_{\neg 0}^2)h_{\neg 0}^2} \\
&= \gamma^2\left(1 + \frac{h_0^4}{2h_0^2h_{\neg 0}^2 + h_{\neg 0}^4}\right) \\
&\approx \gamma^2
\end{aligned} \tag{15}$$

where the approximation holds under the realistic assumption that h_0^2 is small, i.e. that the direct effect of the master TF is modest. For $h_0^2 > 0$, however, γ_{AB}^2 is slightly inflated due to the asymmetry between A and B that is induced by the single, strong master TF, which violates the infinitesimal model. This is a clear illustration, in one case, of the impact of violations to our assumption that effect sizes are uniformly distributed over the genome.

More broadly, we note that these calculations apply equally to any epistatic model where the phenotype results from interactions between a single core locus (S_0) and other loci distributed along the genome (S_g). Another example of such a model is Mendelian traits with modifier genes, where the core Mendelian gene, driven by S_0, has penetrance that is governed in part by other modifier genes.

4.2 Polygenic buffer

The polygenic buffer model is similar to the above master TF model in that two linear, fundamentally different systems interact. Above, each gene interacts with a single master TF; here, a polygenic buffer interacts with the individual effect of each SNP.

Partition the SNPs into S_0, for the polygenic buffer, and S_1, for the directly trait-relevant SNPs. We assume each pathway is linear and polygenic, as for the master TF, but now both pathways are

built from genome-wide SNPs:

$$\begin{aligned} Z_{i1} &= \mu_g + G_{i(1)}\eta_{(1)} + \delta_{i1} \\ Z_{i0} &= \mu_0 + G_{i(0)}\eta_{(0)} + \delta_{i0} \\ y_i &= Z_{i0} + Z_{i0} + \psi Z_{i0} Z_{i1} + \epsilon_i \end{aligned}$$

As for the master TF model, the polygenic buffer can be recast within the polygenic model with saturated pairwise SNP interactions (8). However, the pathways now potentially contain the same SNPs, as buffer SNPs may also have trait-specific effects. Because of this genetic correlation, we use the expression for γ derived in (13):

$$\gamma = \text{sign}(\psi)\left(\rho + (1-\rho)^2 \frac{\sqrt{h_0^2 h_1^2}}{h_0^2 + 2\rho h_0 h_1 + h_1^2}\right)$$

where $\rho := \text{Cor}(G\beta_0, G\beta_1)$ is the genetic correlation between the polygenic buffer and trait-specific genetic effects. In the case that the causal SNPs for each pathway are disjoint, or the SNP buffer effects and trait-specific effects are uncorrelated, then $\rho = 0$.

4.3 Gene-environment dependence and interaction

Gene-environment interaction (GxE) can be an important component of genetic architecture across diverse organisms and biological programs. Although GxE seems fundamentally distinct from epistasis (also called GxG), the two concepts come together when the environment E is heritable. In this case, E is essentially another latent pathway in our CI model–mathematically, there is no need for the pathway to live inside the organism.

In general, we expect that many useful choices for the environment in GxE will have some genetic basis, as is the case for most biologically meaningfully measurements. For example, smoking is an "environment" that significantly modifies the penetrance of BMI SNPs [17], and stress is another "environment" that significantly modifies the penetrance of major depression SNPs [18]. But smoking and stress are clearly heritable, and are themselves often treated as phenotypes of direct interest.

Mathematically, we assume a GxE model where the polygenic score $G\beta_g$ interacts with the continuous environment e':

$$y = G\beta_g + e' + \zeta(G\beta_g) \circ e' + \epsilon'$$

where $\circ$ indicates the Hadamard, or element-wise, product.

We also allow that the environment may have some genetic basis: $e' = G\beta_e + e$. This gives:

$$\begin{aligned} y &= G(\beta_g + \beta_e) + e + \zeta(G\beta_g) \circ (G\beta_e) + \zeta(G\beta_g) \circ e + \epsilon' \\ &=: G(\beta_g + \beta_e) + (G * G)(\zeta\beta_g \otimes \beta_e) + \epsilon \end{aligned}$$

This collapses e and $(G\beta_g) \circ e$ into ϵ. As e is independent of G, ϵ will be roughly Gaussian if ϵ' is roughly Gaussian.

This is now in the form of the interacting pathways model in (8). However, the pathways may now be correlated if there is genetic correlation ρ between the direct effect of G on the trait (β_g)

and the direct effect of G on the environment (β_e). We note, however, that $\rho \neq 0$ is not implied by $h_e^2 \neq 0$, i.e. G-E correlation is insufficient to cause $\rho \neq 0$.

Using the formula that allows inter-pathway correlation (13), the coordination is:

$$\gamma = \text{sign}(\zeta) \cdot \left(\rho + (1-\rho)^2 \frac{\sqrt{h_1^2 h_2^2}}{h_1^2 + 2\rho h_1 h_2 + h_2^2} \right)$$

This decomposes the coordination into two terms:

1. ρ, which captures the coordination from correlated pleiotropic effects of G on y and e'.
2. $(1-\rho)^2 \frac{\sqrt{h_1^2 h_2^2}}{h_1^2 + 2\rho h_1 h_2 + h_2^2}$, which captures the coordination from the interaction between the direct genetic pathway and the genetic pathway through the environment e'.

4.4 A random effect model for Ω

In this section, we assume that Ω has a random effect distribution.

$$\omega_{ss'} | \beta \overset{\text{ind}}{\sim} \mathcal{N}\left(\tau \beta_s \beta_{s'}, \sigma_\omega^2 \sigma_\beta^4\right) \tag{16}$$

This model on Ω is identical to previous work for genome-by-genome interactions when $\tau = 0$, as coordination drops out [3–11].

First, we assume that S is large enough so that the law of large numbers gives:

$$\gamma = \frac{\sum_{s>s'} \Omega_{ss'} \beta_s \beta_{s'}}{\sqrt{\sum_{s>s'} \Omega_{ss'}^2} \sqrt{\sum_{s>s'} \beta_s^2 \beta_{s'}^2}} \approx \frac{\tau}{\sqrt{\tau^2 + \sigma_\omega^2}}$$

Note the similarity to equation (†). Further, note that for small values of S, the coordination is itself a random variable with nontrivial variance.

Write $\Omega = \tau \beta \beta^T + \Omega'$, and define $h_A^2 := \frac{1}{|A|} \sum_{s \in A} \beta_s^2$ and $h_B^2 := \frac{1}{|B|} \sum_{s \in B} \beta_s^2$. The AB coordination is:

$$\begin{aligned}
\gamma_{AB} &= \frac{\beta_A^T \Omega_{AB} \beta_B}{\sqrt{h_A^2 h_B^2 h_{AB}^2}} \\
&= \frac{\tau \sum_{s \in A, s' \in B} \beta_s^2 \beta_{s'}^2 + \sum_{s \in A, s' \in B} \Omega'_{ss'} \beta_s \beta_{s'}}{\sqrt{\sum_{s \in A, s' \in B} \left(\tau^2 \beta_s^2 \beta_{s'}^2 + {\Omega'_{ss'}}^2\right)} \sqrt{\sum_{s \in A, s' \in B} \beta_s^2 \beta_{s'}^2}} \\
&\approx \frac{\tau h_A^2 h_B^2}{\sqrt{h_A^2 h_B^2 \left(\tau^2 h_A^2 h_B^2 + |A||B| \sigma_\omega^2 \sigma_\beta^4\right)}} + \delta_1 \\
&= \frac{\tau (\sigma_\beta^2 |A|)(\sigma_\beta^2 |B|)}{\sqrt{(\sigma_\beta^2 |A|)(\sigma_\beta^2 |B|) \left(\tau^2 (\sigma_\beta^2 |A|)(\sigma_\beta^2 |B|) + |A||B| \sigma_\omega^2 \sigma_\beta^4\right)}} + \delta_1 + \delta_2 \\
&= \frac{\tau}{\sqrt{\tau^2 + \sigma_\omega^2}} + \delta_1 + \delta_2 \\
&\approx \gamma
\end{aligned}$$

The first approximation assumes that S is large enough so that, for any A, B, it approximately holds that $\frac{1}{|A||B|}\sum_{s\in A,s'\in B}{\Omega'_{ss'}}^2 \approx \mathbb{V}(\Omega_{ss'}) = \sigma_\omega^2\sigma_\beta^4$. The second approximation assumes that δ_1 and δ_2 are negligible, which we motivate below.

The δ_1 term is just mean zero noise deriving from random uncoordinated fluctuations in Ω. This term vanishes as the number of captured interactions among SNPs, $|A||B|$, increases, as it averages out over the increasingly large number of comparisons. More formally:

$$\delta_1 := \frac{\sum_{s\in A,s'\in B}\Omega'_{ss'}\beta_s\beta_{s'}}{\sqrt{h_A^2h_B^2\left(\tau^2h_A^2h_B^2 + |A||B|\sigma_\omega^2\sigma_\beta^4\right)}} \implies \delta_1|A,B,\beta \sim \mathcal{N}\left(0, \frac{\sigma_\omega^2}{\tau^2h_A^2h_B^2 + |A||B|\sigma_\omega^2\sigma_\beta^4}\right)$$

In particular, this shows that for all A and B we have $\mathbb{V}(\delta_1|A,B,\beta) \leq \frac{1}{|A||B|\sigma_\beta^4}$, hence $\delta_1 \to 0$ deterministically as $|A||B|$ grows.

For δ_2, let $\varepsilon := \frac{h_A^2h_B^2}{|A||B|\sigma_\beta^4} - 1$. Then:

$$\begin{aligned}
\delta_2 &:= \frac{\tau\sqrt{h_A^2h_B^2}}{\sqrt{\tau^2h_A^2h_B^2 + |A||B|\sigma_\omega^2\sigma_\beta^4}} - \frac{\tau}{\sqrt{\tau^2+\sigma_\omega^2}} \\
&= \sqrt{\frac{\varepsilon+1}{\varepsilon+1+\sigma_\omega^2/\tau^2}} - \frac{\tau}{\sqrt{\tau^2+\sigma_\omega^2}} \\
&\approx \left(\left(\sqrt{\frac{1}{1+\sigma_\omega^2/\tau^2}}\right) + \varepsilon\left(-\frac{\sigma_\omega^2}{2(\tau^2+\sigma_\omega^2)}\right)\right) - \frac{\tau}{\sqrt{\tau^2+\sigma_\omega^2}} \\
&= -\frac{\sigma_\omega^2}{2(\tau^2+\sigma_\omega^2)}\varepsilon
\end{aligned}$$

The approximation is a first-order approximation of ε around 0, i.e. assuming $h_A^2h_B^2 \approx |A||B|\sigma_\beta^4$. Essentially, this approximation assumes that CI is stable over most random A/B splits, as expected for polygenic models.

We do not pursue formally characterizing the distribution of ε as a function of random A and B. But we list a few facts to demonstrate that the approximation $\varepsilon \approx 0$ is reasonable for polygenic models:

- By the LLN, as $|A|, |B| \to \infty$, then $h_A^2h_B^2 \to \sigma_\beta^4|A|B| \implies \varepsilon \to 0$.
- By the CLT, $h_A^2 \to \mathcal{N}\left(\sigma_\beta^2|A|, \frac{S}{|A|/S(1-|A|/S)}\sigma_\beta^2\right)$ in distribution as the number of (causal) SNPs in A grows. The variance calculation assumes S is large enough to approximate the probability of SNPs being in A or B as independent across SNPs.
- Assuming $h_A^2 \sim \mathcal{N}\left(\sigma_\beta^2|A|, \frac{S}{|A|/S(1-|A|/S)}\sigma_\beta^2\right)$, then:

  $$\mathbb{V}(\varepsilon) = \frac{1}{S-|A|}\left(\frac{S}{|A|} - 4\frac{|A|}{S} - 2\frac{1}{|A|S\sigma_\beta^4}\right) \to 0$$

  where the convergence is for $|A|, S \to \infty$.

5 Technical results

5.1 $\hat{\gamma}_{AB}$ is consistent and unbiased for γ_{AB}

Proposition 1. *Assume the linear model in* (1)*, and that the S SNPs are partitioned into "independent" subsets A and B, i.e.:*

$$r^2(A,B) := \max_{s\in A, s'\in B} \frac{1}{N}\sum_{i=1}^{N} G_{is}G_{is'} = 0$$

Assume also that G has columns scaled to mean zero and variance one.

Define the A/B coordination as in (7)*:*

$$\gamma_{AB} = \frac{\beta_A^T \Omega_{AB} \beta_B}{\|\beta_A\|\|\beta_B\|\|\Omega_{AB}\|}$$

then the even/odd estimator of γ w.r.t. the partition A and B defined in (6) *is distributed:*

$$\hat{\gamma}_{AB} = \gamma_{AB} + \mathcal{N}\left(0, \frac{1}{N\|\Omega_{AB}\|^2}\right)$$

Proof

We are interested in the OLS estimate of γ. Letting $\Pi^{\perp}$ be the orthogonal projection onto $P := (P_A|P_B)$, the two stage least squares expression for the OLS estimate of $\hat{\gamma}$ is:

$$\hat{\gamma} := \frac{[P_A \circ P_B]^T \Pi^{\perp} y}{[P_A \circ P_B]^T \Pi^{\perp} [P_A \circ P_B]}$$

We assume that P_A and P_B are created from independent SNPs and that sample size is sufficiently large to replace empirical moments by their theoretical expectations. This implies that the PRS interaction terms $P_A \circ P_B$ orthogonal to both P_A and P_B, which in turn implies the OLS estimate of λ is:

$$\hat{\lambda}_{OLS} \approx \frac{[P_A \circ P_B]^T ([G * G]\,\omega + \epsilon)}{[P_A \circ P_B]^T [P_A \circ P_B]}$$

Expanding these product in the denominator gives:

$$\begin{aligned}
[P_A \circ P_B]^T [P_A \circ P_B] &= \sum_i \sum_{s,j\in A, s',j'\in B} (G_{is}G_{ij}G_{is'}G_{ij'})\,\beta_s\beta_j\beta_{s'}\beta_{j'} \\
&= \sum_{s,j\in A, s',j'\in B} \left(\sum_i G_{is}G_{ij}G_{is'}G_{ij'}\right)\beta_s\beta_j\beta_{s'}\beta_{j'} \\
&= \sum_{s,j\in A, s',j'\in B} \left(N\left[\sum_i G_{is}G_{is'}\right]\left[\sum_i G_{ij}G_{ij'}\right]\right)\beta_s\beta_j\beta_{s'}\beta_{j'} \qquad (\dagger) \\
&= N\beta_A^T R_A \beta_A \beta_B^T R_2 \beta_B \\
&= N\|\beta_A\|^2\|\beta_B\|^2 \qquad (\ddagger)
\end{aligned}$$

† uses the assumption of no LD between A and B, and ‡ uses the much stronger assumption that all causal SNPs are in linkage equilibrium. A similar expansion in the numerator gives:

$$\begin{aligned}
\hat{\lambda} &= \frac{\sum_{s\in A,s'\in B,j,j',i}\left(G_{is}G_{ij}G_{is'}G_{ij'}\right)\beta_s\beta_{s'}\omega_{jj'} + \sum_{s\in A,s'\in B}\left(G_{is}G_{is'}\beta_s\beta_{s'}\epsilon_i\right)}{N\|\beta_A\|^2\|\beta_B\|^2} \\
&\overset{d}{=} \frac{\beta_A^T\Omega_{AB}\beta_B}{\|\beta_A\|^2\|\beta_B\|^2} + \mathcal{N}\left(0, \frac{1}{N\|\beta_A\|^2\|\beta_B\|^2}\right) \\
&\overset{d}{=} \gamma_{AB}\frac{\|\Omega_{AB}\|}{\|\beta_A\|\|\beta_B\|} + \mathcal{N}\left(0, \frac{1}{Nh_A^2h_B^2}\right) \implies \\
\hat{\gamma}_{AB} &\sim \gamma_{AB} + \mathcal{N}\left(0, \frac{1}{N\|\Omega_{AB}\|^2}\right)
\end{aligned}$$

5.2 Monotone phenotype transformations

We consider the effect of nonlinear phenotype transformations on coordination. Assume that trait values are transformed by some twice-differentiable function $f : \mathbb{R} \mapsto \mathbb{R}$. We assume that f is monotone, which is equivalent to the notion of rescaling y because the order of the traits $f(y_i)$ is the same as the order of the traits y_i.

The coordination definition given in (3) assumes that the pairwise interaction model in (1) holds exactly for some true β and Ω. However, if f is applied to each phenotype value, then clearly (1) no longer holds for the transformed phenotype; moreover, unless f is linear, (1) does not hold for *any* values of β and Ω. Hence it is not clear how to define γ by (3).

Instead, we define the coordination under the transformation f as the coordination amongst the least-squares best fits for the linear and interaction parameters, $\tilde{\beta}$ and $\tilde{\Omega}$:

$$\gamma_f(\Omega, \beta) := \gamma(\tilde{\Omega}, \tilde{\beta}) \tag{17}$$

We assume that $\gamma = \pm 1$ on the original scale for ease, so $y := g\beta + \lambda\left(g \otimes g\right)\left(\beta \otimes \beta\right) + \epsilon$ for some reference genotype value $g \in \mathbb{R}^S$. Then the least-squares interaction estimate is:

$$\begin{aligned}
\nabla_{g_s} f(y) &= f'(y)\beta_s(1 + \lambda g\beta) \\
\nabla^2_{g_s,g_{s'}} f(y) &= f''(y)\beta_s\beta_{s'}(1 + \lambda g\beta)^2 + f'(y)(\lambda\beta_s\beta_{s'}) \\
&= \beta_s\beta_{s'}\left(f''(y)(1 + \lambda g\beta)^2 + \lambda f'(y)\right) \\
\implies \gamma_f(g) &:= \mathrm{Cor}\left((\nabla f)_g \otimes (\nabla f)_g, (\nabla^2 f)_g\right) \\
&= \mathrm{Cor}\left((f'(y)\beta(1 + \lambda g\beta)) \otimes (f'(y)\beta(1 + \lambda g\beta)), \beta \otimes \beta\left(f''(y)(1 + \lambda g\beta)^2 + \lambda f'(y)\right)\right) \\
&= \mathrm{sign}\left(f''(y)(1 + \lambda g\beta)^2 + \lambda f'(y)\right)
\end{aligned}$$

When $|f'\lambda|/|f''|$ is large, the second term dominates and

$$\gamma_f(g) = \mathrm{sign}(\lambda f'(y)) = \gamma\mathrm{sign}(f') \tag{18}$$

The last equality using the fact that $\gamma = \mathrm{sign}(\lambda)$ and emphasizes that $\mathrm{sign}(f')$ is constant for all y because f is monotone. (18) is the "right" answer, in the sense that γ is unchanged except, perhaps, a sign flip if f is decreasing.

On the other hand, if $|f'|/|f''|$ is small–meaning the function is quite non-linear–or if $|\lambda|$ is small–meaning the overall interaction signal is quite weak–then $\gamma_f(g)$ may have the incorrect sign.

On average over mean-zero genotypes g, the former force wins out, showing coordination is on balance preserved under relatively smooth, strictly monotone functions. To see this, assume that $\lambda > 0$ (a symmetric argument applies for $\lambda < 0$). Then:

$$\begin{aligned}\mathbb{E}\left(f''(y)(1+\lambda g\beta)^2 + \lambda f'(y)\right) &\geq \mathbb{E}\left(-\|f''\|_\infty(1+\lambda g\beta)^2\right) + \lambda\mathbb{E}\left(f'(y)\right) \\ &= -\|f''\|_\infty(1+\lambda^2\sigma_g^2) + \lambda\bar{f'} \geq 0 \iff \\ \text{sign}(f')\frac{\lambda}{(1+\lambda^2\sigma_g^2)} &\geq \frac{\|f''\|_\infty}{|\bar{f'}|}\end{aligned}$$

This has the same sign as λ so long as $|f''/\bar{f'}|$ never grows too large (over the support of g), i.e. the function never curves dramatically relative to its overall linear approximation. Large is defined in comparison to λ, which is basically (proportional to) the left hand side for realistic parameters.

6 Simulation details

For each sample $i \in \{1, \ldots, N\}$ and SNP $j \in \{1, \ldots, M\}$, genotypes G_{ij} was drawn independently from a Binomial(2,p_{ij}) distribution. In our baseline case, we draw $p_j \sim$ Uniform(.01, .99) and then take $p_{ij} = p_j$ for all samples i. To simulate population structure, we instead set $p_{ij} = \tilde{p}_{iz_i}$, where $z_i \in \{1, 2\}$ indicates the population for sample i and is drawn uniformly, and $\tilde{p}_{ik} \overset{\text{ind}}{\sim}$ Beta $\left(p_j\frac{F_{ST}}{1-F_{ST}}, 1-p_j\frac{F_{ST}}{1-F_{ST}}\right)$; we chose to set $F_{ST} = .1$. For the UKB-based simulations, we instead drew p_j independently from the observed allele frequency distribution at genotyped SNPs after excluding rarer variants with allele frequencies outside (.01, .99).

To generate genotypes under assortative mating, we performed the following steps:

- Simulate $2N$ unstructured genotypes under the above "baseline case"
- Draw phenotypes under the assumed generative model (as outlined below)
- Sort samples by phenotypes, and pair them by phenotype order statistic (e.g. 1+2, 3+4, ...)
- Generate one child genotype per parental pair by sampling one allele per parent at each SNP

We generated phenotypes under a model combining additive genetic effects (β_g), epistatic effects (u_x), a non-genetic contribution correlating with population (α), and pure noise (ϵ):

$$y = G\beta + u_x + \tilde{z}\alpha + \epsilon$$

$\tilde{z}$ is just the population indicator z scaled to mean 0, unit variance, i.e. $\tilde{z} = (z - 1.5)/.25$. In all cases, we draw the causal additive effects to be i.i.d. Gaussian with appropriate variance to give additive heritability h^2:

$$\beta \sim \mathcal{N}\left(0, \frac{h^2}{M}I_M\right)$$

We choose the population structure effect α to be either 0 or, in the case of confounding, .2. In all cases, we draw ϵ to be i.i.d. Gaussian with variance guaranteeing overall phenotypic variance of 1:

$$\epsilon \sim \mathcal{N}\left(0, (1 - h^2 - \|u_x\|^2/N - \alpha^2)I_N\right)$$

We assess a variety of models for the interaction term u_x:

1. Additive model: $u_x = 0$.
2. Isotropic pairwise interaction: we define $u_x = (G * G)\omega$, where 99% of the entries in ω are 0, and the remaining entries are drawn i.i.d. Gaussian with mean zero and variance equal to $.1 \cdot (.01 \cdot M)$. The number .1 is chosen so that pairwise interaction explain 10% of the overall phenotypic variance.
3. Isotropic triple-wise interaction: we define $u_x = (G * G * G)\omega$, where 99.99% of the entries in ω are 0, and the remaining entries are drawn i.i.d. Gaussian with mean zero and variance equal to $.1 \cdot (.0001 \cdot M)$.
4. Coordinate pairwise interaction: we define pathways by $P_k = G_{,S_k}\beta_{S_k}$ for $k \in \{1, 2\}$, where S_k is a random subset of the M SNPs with size $.3 \cdot M$ and $S_1 \cap S_2 = \emptyset$; then, define $u_x = v \cdot P_1 \circ P_2$, where $\circ$ is element-wise multiplication and v is chosen such that $\|u_x\|^2/N = .1$.
5. Coordinate triple-wise interaction: Same as Coordinate pairwise interaction, except for 3 pathways, and the third-way product $P_1 \circ P_2 \circ P_3$

Finally, when performing the EO test, we either randomly assign SNPs into "Even" and "Odd" chromosomes or, for the Oracle SNP partition, we use the subsets S_1 and S_2 (we only evaluate the Oracle under Coordinated pairwise interaction, the only case it is defined or sensible).

7 Supplementary Figures

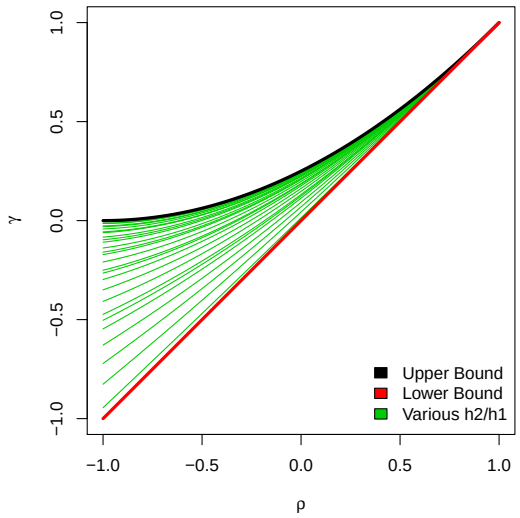

Figure S1: The γ values induced by a range of choices of ρ, h_1^2, and h_2^2. Upper Bound corresponds to $h_1^2 = h_2^2$; Lower Bound to $h_1^2 \approx 0$ or $h_2^2 \approx 0$; and green lines to intermediate values of h_1^2/h_2^2.

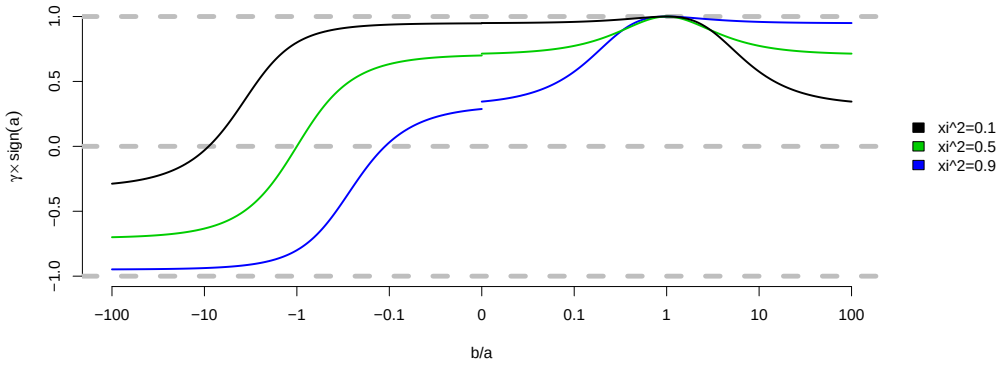

Figure S2: Coordinated Interaction under interacting pathways and nonlinear single-pathway effects. Inter-pathway interactions all have strength a; intra-pathway nonlinearities all have strength b. The x-axis is on the log scale, which causes an apparent discontinuity at 0.

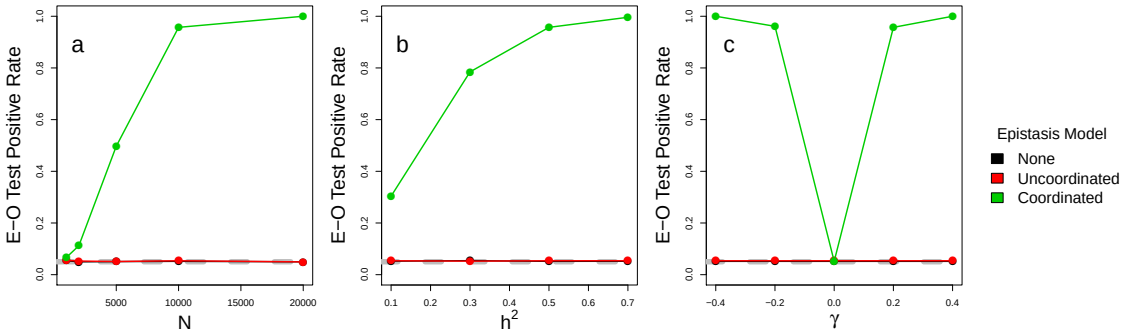

Figure S3: Simulation results under alternative parameter settings. We vary in turn: sample size, N (a); additive heritability h^2 (b); and Coordinated Epistasis strength, γ (c). Unless otherwise noted, simulations in this paper use N=10,000, h^2= 0.5, and γ= 0.2.

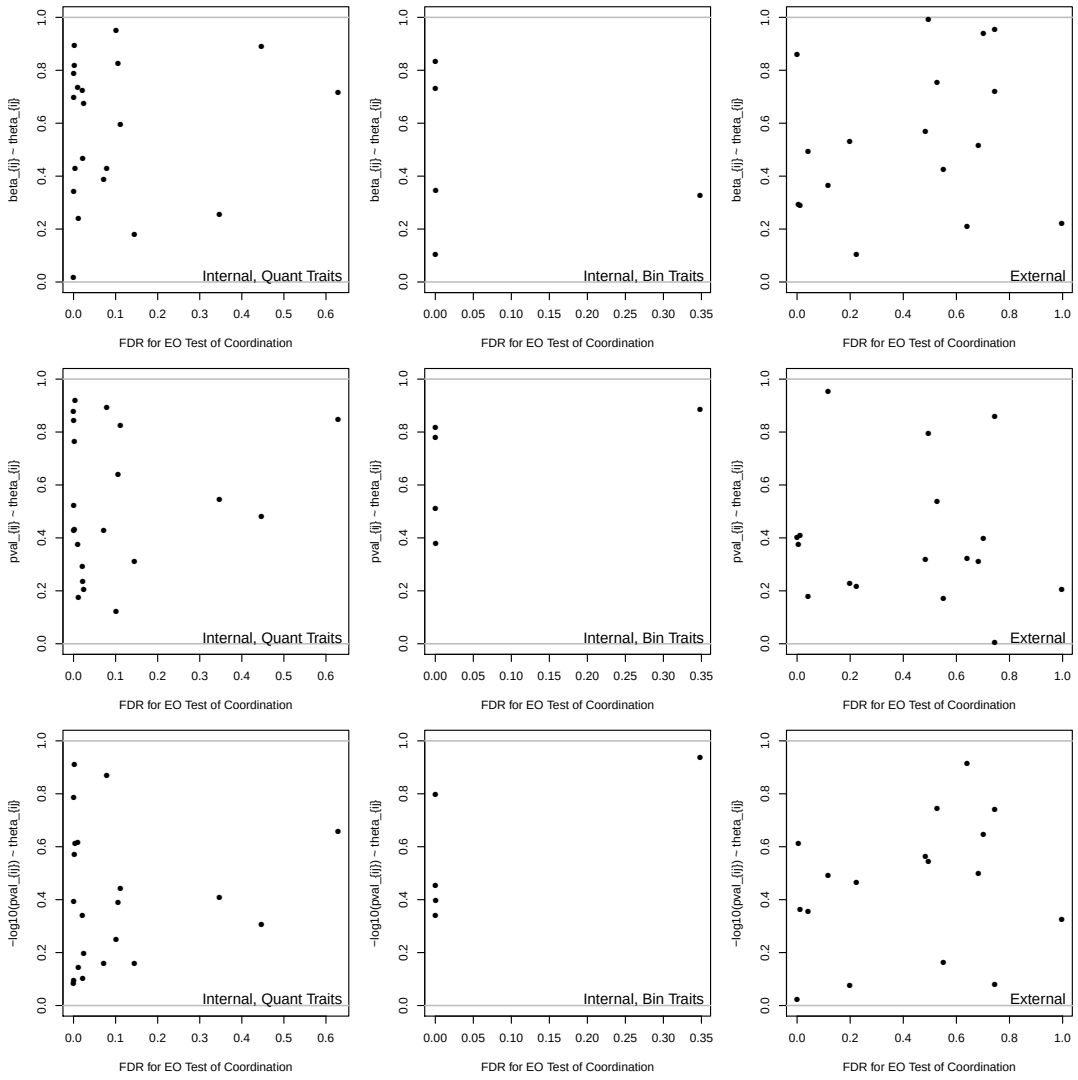

Figure S4: Comparing θ and characteristics of the Even-Odd test for Coordinated Epistasis in the UKBB. For each trait, the FDR-adjusted EO test for CE is plotted against correlation between θ_{ij} and the estimated value of γ (top), corresponding p-value (center), and corresponding $\log_{10}$ p-value (bottom). Results are shown for 21 quantitative traits using internal PRS (left), 5 binary traits using internal PRS (center) and 17 traits using external PRS (right).

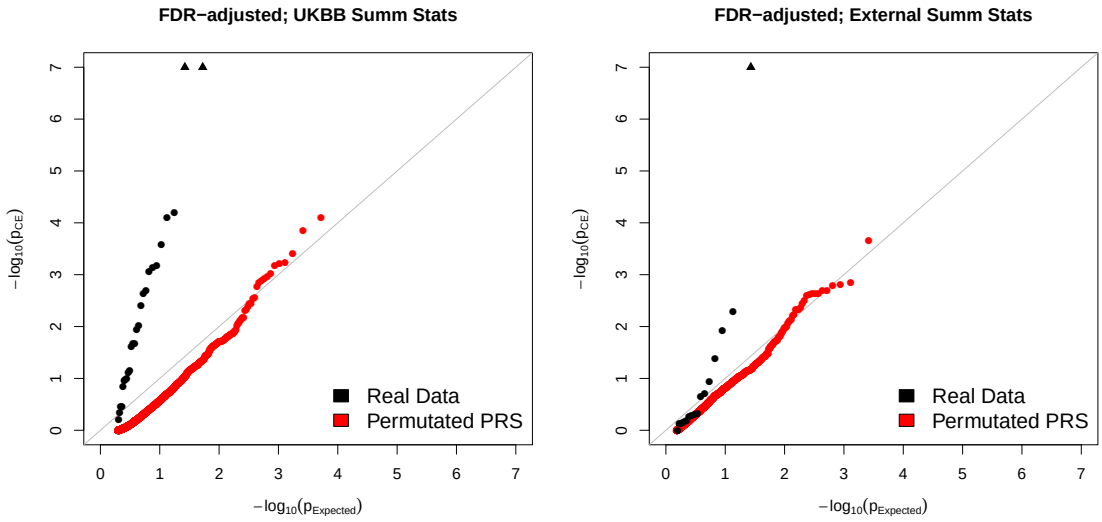

Figure S5: FDR-adjusted Even-Odd test for Coordinated Epistasis in the UKBB with randomly permuted PRS. The EO test was repeated for 100 random permutations of the PRS among samples (red). Results from real data (black) are also displayed for all 26 traits tested using internal UKBB PRS and 17 traits tested using PRS from external summary statistics. Left: QQ plot of observed vs expected FDR-adjusted EO test -$\log_{10}$ p-values for permutations using PRS from UKBB summary statistics. Right: QQ plot of observed vs expected EO test -$\log_{10}$ p-values for permutations using PRS calculated from external summary statistics.

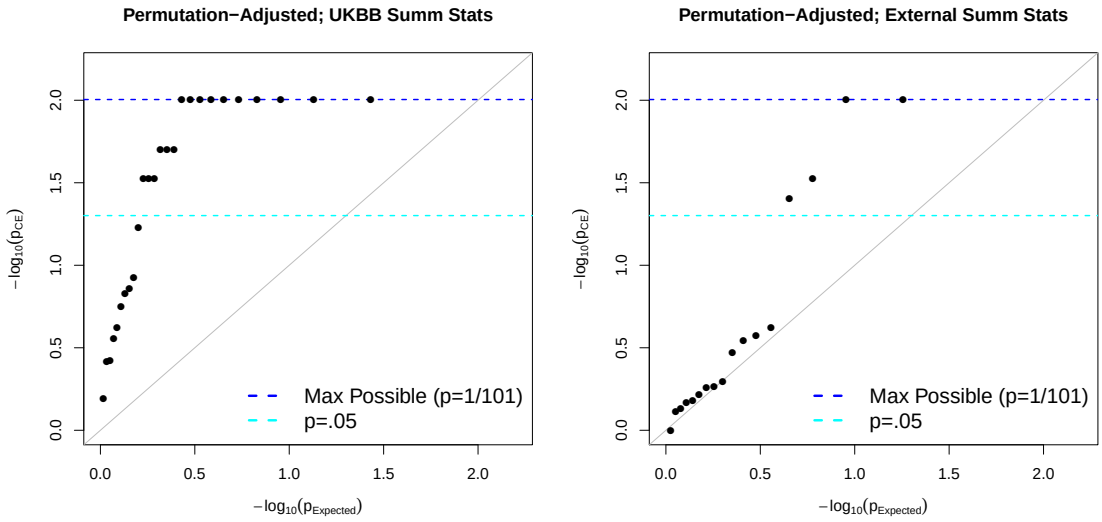

Figure S6: Permutation-adjusted Even-Odd test for Coordinated Epistasis in the UKBB. Empirical -$\log_{10}$ p-values for EO are plotted against expectation. Due to the number of permutations, the minimum empirical p-value is 1/101, indicated by the blue dashed line.

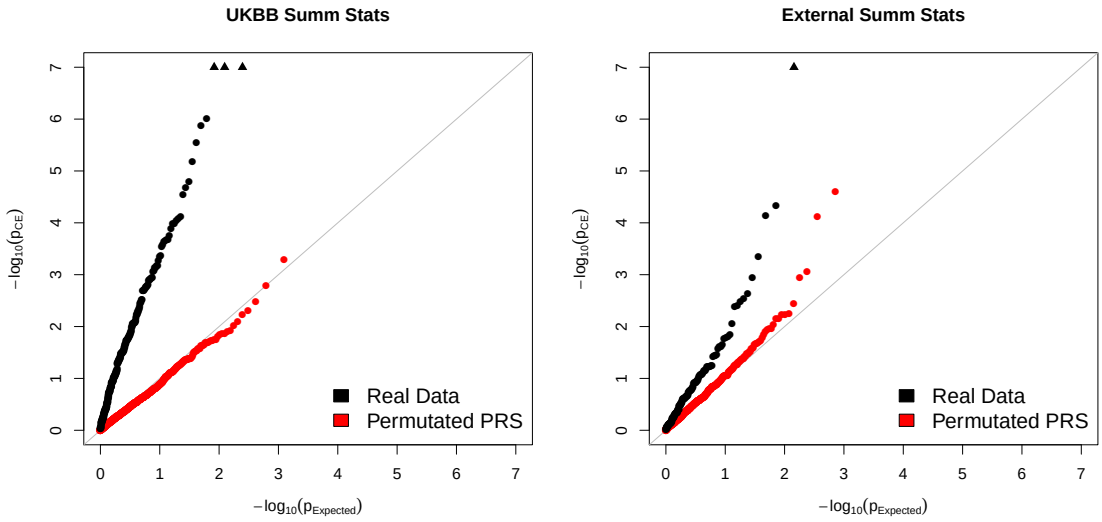

Figure S7: Tissue-specific Coordinated Epistasis in the UKBB. Five permutations of tissue-specific PRS (TPRS) across samples were tested. Results from real data are also displayed (black). Left: QQ plot of observed vs expected -$\log_{10}$ p-values for permutations using TPRS from UKBB summary statistics. Right: QQ plot of observed vs expected -$\log_{10}$ p-values for permutations using TPRS calculated from external summary statistics.

8 Supplementary Tables

	$\hat{\theta}_{eo}: \ PRS_E \sim PRS_O$		$\hat{\gamma}_{eo}: \ y \sim PRS_E * PRS_O$	
	χ^2 (sd)	PR ($\alpha = .05$)	χ^2 (sd)	PR ($\alpha = .05$)
Additive	1.0 (1.4)	0.05	1.0 (1.4)	0.05
Isotropic Epistasis	1.0 (1.4)	0.05	1.0 (1.4)	0.05
Coordinated Epistasis	1.0 (1.4)	0.05	15.4 (8.1)	0.96

Table S1: Simulations using UKBB minor allele frequency distribution. Mean, standard deviation (sd), and positive rate (PR) are shown for estimates of θ_{eo} and γ_{eo} for 10,000 simulations. For all models, SNPs were randomly assigned to either PRS_E or PRS_O. Baseline simulation parameters were used as in Table 1, except that MAFs for simulated genotypes were sampled from real UKBB minor allele frequencies. In these simulations, there is no assortative mating, population structure, or PC adjustment.

	$\hat{\theta}_{eo}: \ PRS_E \sim PRS_O$		$\hat{\gamma}_{eo}: \ y \sim PRS_E * PRS_O$	
	χ^2 (sd)	PR ($\alpha = .05$)	χ^2 (sd)	PR ($\alpha = .05$)
Additive	1.0 (1.4)	0.05	1.0 (1.4)	0.05
Isotropic Epistasis	1.0 (1.4)	0.05	1.0 (1.4)	0.05
Coordinated Epistasis	1.0 (1.4)	0.05	1.3 (1.8)	0.08

Table S2: Simulations using third-order epistatic interactions. Mean, standard deviation (sd), and positive rate (PR) are shown for estimates of θ_{eo} and γ_{eo} for 10,000 simulations. Phenotypes under isotropic and uncoordinated epistasis models were generated including third-order interactions between triples of SNPs and three pathways, respectively. For all models, SNPs were randomly assigned to either PRS_E or PRS_O. Baseline simulation parameters were used as in Table 1. In these simulations, there is no assortative mating, population structure, or PC adjustment.

Table S3: Even-odd test results for all traits in the UKBB. "Intern" indicates that the PRS was calculated using the cross-validation method with UKBB data (Methods). "Extern" indicates that the PRS was calculated using GWAS summary statistics from external datasets (Methods). τ is the p-value threshold for the PRS and is chosen to optimize cross-validated prediction. %VE is the percent of phenotype variance explained by the PRS. Min-p is the minimum p-value for the EO test obtained across all tested p-value thresholds for the PRS. Empirical p is the the empirical p-value determined by randomly permuting PRS across samples to correct for testing multiple p-value thresholds. FDR is the Benjamini-Hochberg adjusted FDR value. * indicates FDR <0.1; ** indicates FDR <0.01.

Phenotype	PRS Type	τ	%VE	Min-p	Empirical p	FDR	Sig Level
Basal Metabolic Rate	Intern Quant	1.00E-08	0.74%	2.70E-03	0.02	0.02	*
BMI	Intern Quant	0.0001	2.14%	0.02	0.15	0.1	
Bone Mineral Dens.	Intern Quant	0.001	3.39%	4.20E-04	9.90E-03	2.30E-03	**
Corp. Hemoglobin	Intern Quant	1	6.90%	0.09	0.28	0.63	
Edu Years	Intern Quant	1.00E-07	0.27%	0.04	0.24	0.14	
Eosinophil #	Intern Quant	1.00E-05	1.09%	0.05	0.18	0.11	
FEV/FVC	Intern Quant	1.00E-07	0.52%	2.40E-03	0.03	0.02	*
Glucose	Intern Quant	1.00E-05	2.28%	2.40E-03	0.06	0.02	*
Height	Intern Quant	1.00E-08	2.80%	4.40E-04	9.90E-03	4.00E-03	**
LDL	Intern Quant	1.00E-07	1.30%	1.40E-04	9.90E-03	7.30E-04	**
Lymphocyte #	Intern Quant	1.00E-05	1.05%	2.30E-04	0.02	2.00E-03	**
Monocyte #	Intern Quant	1.00E-08	0.95%	9.60E-05	9.90E-03	8.60E-04	**
Platelet #	Intern Quant	0.0001	5.81%	0.02	0.12	0.08	*
Platelet Distn Width	Intern Quant	1.00E-08	3.99%	2.90E-05	9.90E-03	2.60E-04	**
Platelet Vol.	Intern Quant	0.0001	9.06%	3.20E-12	9.90E-03	2.90E-11	**
RBC #	Intern Quant	1.00E-08	0.91%	0.1	0.39	0.35	
RBC Distn Width	Intern Quant	1.00E-06	2.04%	2.00E-03	0.02	0.01	*
Reticulocyte #	Intern Quant	1.00E-06	1.38%	0.1	0.38	0.45	
Sphered Cell Vol	Intern Quant	1.00E-06	1.73%	8.00E-03	0.03	0.07	*
Triglycerides	Intern Quant	0.0001	1.55%	1.10E-03	0.03	9.70E-03	**
WBC #	Intern Quant	0.0001	1.06%	0.03	0.14	0.11	
Asthma	Intern Bin	0.0001	2.79%	7.30E-05	9.90E-03	6.60E-04	**
Cardiovascular	Intern Bin	1.00E-08	3.90%	7.20E-06	9.90E-03	6.50E-05	**
Eczema	Intern Bin	1.00E-08	2.18%	9.00E-06	9.90E-03	8.10E-05	**
High Cholest.	Intern Bin	1.00E-08	6.44%	0.13	0.64	0.35	
T2D	Intern Bin	0.001	3.64%	1.00E-08	9.90E-03	9.40E-08	**
Asthma	Extern	0.0001	0.68%	0.02	0.27	0.12	
BMI	Extern	1.00E-05	1.05%	0.17	0.66	0.49	
Cardiovascular	Extern	0.001	0.54%	0.04	0.24	0.2	
Corp. Hemoglobin	Extern	—	19.17%	0.04	0.03	0.04	*
Edu Years	Extern	0.1	6.22%	0.18	0.6	0.74	
Eosinophil #	Extern	—	10.02%	0.48	0.55	0.48	
Height	Extern	1	7.29%	0.08	0.29	0.55	
LDL	Extern	1.00E-05	2.19%	1.80E-03	0.04	0.01	*
Lymphocyte #	Extern	—	8.08%	0.74	0.77	0.74	
Monocyte #	Extern	—	12.57%	1	1	1	
Platelet #	Extern	—	16.90%	5.20E-03	9.90E-03	5.20E-03	**
Platelet Vol.	Extern	—	29.41%	1.10E-25	9.90E-03	1.10E-25	**
RBC #	Extern	—	8.35%	0.53	0.54	0.53	
Reticulocyte #	Extern	—	11.16%	0.22	0.34	0.22	
T2D	Extern	0.001	11.72%	0.11	0.5	0.64	
Triglycerides	Extern	1.00E-05	3.24%	0.26	0.74	0.7	
WBC #	Extern	—	7.47%	0.68	0.68	0.68	

Table S4: Tissue-specific CE in the UKBB for 26 traits and 13 tissue-specific annotations. "Intern" indicates that the PRS was calculated using the cross-validation method with UKBB data (Methods). "Extern" indicates that the PRS was calculated using GWAS summary statistics from external datasets (Methods). TPRS %VE is the percent of phenotype variance explained by the tissue-specific PRS. These tests use the p-value threshold with strongest EO signal (Table S3). * indicates $p < .05$; ** indicates $p < .05/13$, which Bonferroni-adjusts for 13 tested tissues.

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
Basal Metabolic Rate	Franke.Blood.Cells	Intern Quant	0.002%	0.09		0.18
Basal Metabolic Rate	Franke.Adipocytes	Intern Quant	0.182%	4.1e-03	*	0.05
Basal Metabolic Rate	Franke.Brain	Intern Quant	0.089%	0.1		0.18
Basal Metabolic Rate	Franke.Hippocampus	Intern Quant	0.101%	0.03	*	0.18
Basal Metabolic Rate	Franke.Liver	Intern Quant	0.117%	0.11		0.18
Basal Metabolic Rate	Franke.Muscles	Intern Quant	0.045%	0.19		0.23
Basal Metabolic Rate	Franke.Pancreas	Intern Quant	0.084%	0.21		0.23
Basal Metabolic Rate	Adipose	Intern Quant	0.351%	0.09		0.18
Basal Metabolic Rate	Brain	Intern Quant	0.624%	0.19		0.23
Basal Metabolic Rate	Hippocampus	Intern Quant	0.445%	0.11		0.18
Basal Metabolic Rate	Liver	Intern Quant	0.527%	0.2		0.23
Basal Metabolic Rate	Pancreas	Intern Quant	0.665%	0.05		0.18
Basal Metabolic Rate	Skeletal_Muscle	Intern Quant	0.701%	0.41		0.41
Bone Mineral Dens.	Franke.Blood.Cells	Intern Quant	0.289%	0.18		0.23
Bone Mineral Dens.	Franke.Adipocytes	Intern Quant	1.464%	0.87		0.87
Bone Mineral Dens.	Franke.Brain	Intern Quant	2.075%	0.04	*	0.12
Bone Mineral Dens.	Franke.Hippocampus	Intern Quant	0.959%	0.11		0.21
Bone Mineral Dens.	Franke.Liver	Intern Quant	0.057%	0.04	*	0.12
Bone Mineral Dens.	Franke.Muscles	Intern Quant	0.738%	0.7		0.76
Bone Mineral Dens.	Franke.Pancreas	Intern Quant	0.53%	0.05	*	0.12
Bone Mineral Dens.	Adipose	Intern Quant	2.257%	0.17		0.23
Bone Mineral Dens.	Brain	Intern Quant	0.08%	0.15		0.23
Bone Mineral Dens.	Hippocampus	Intern Quant	0%	0.08		0.18
Bone Mineral Dens.	Liver	Intern Quant	1.072%	1.8e-03	**	0.02
Bone Mineral Dens.	Pancreas	Intern Quant	0.083%	0.02	*	0.12
Bone Mineral Dens.	Skeletal_Muscle	Intern Quant	1.685%	0.39		0.46
Corp. Hemoglobin	Franke.Blood.Cells	Intern Quant	0.033%	0.28		0.93
Corp. Hemoglobin	Franke.Adipocytes	Intern Quant	1.86%	0.66		0.93
Corp. Hemoglobin	Franke.Brain	Intern Quant	0.04%	0.3		0.93
Corp. Hemoglobin	Franke.Hippocampus	Intern Quant	0.13%	0.71		0.93
Corp. Hemoglobin	Franke.Liver	Intern Quant	1.448%	0.07		0.46
Corp. Hemoglobin	Franke.Muscles	Intern Quant	0.83%	0.88		0.94
Corp. Hemoglobin	Franke.Pancreas	Intern Quant	0.703%	0.05	*	0.46
Corp. Hemoglobin	Adipose	Intern Quant	6.072%	0.92		0.94
Corp. Hemoglobin	Brain	Intern Quant	3.931%	0.47		0.93
Corp. Hemoglobin	Hippocampus	Intern Quant	2.864%	0.44		0.93
Corp. Hemoglobin	Liver	Intern Quant	8.578%	0.61		0.93

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
Corp. Hemoglobin	Pancreas	Intern Quant	7.902%	0.62		0.93
Corp. Hemoglobin	Skeletal_Muscle	Intern Quant	5.335%	0.94		0.94
FEV/FVC	Franke.Blood.Cells	Intern Quant	0.128%	2.9e-06	**	1.9e-05
FEV/FVC	Franke.Adipocytes	Intern Quant	0.218%	0.01	*	0.01
FEV/FVC	Franke.Brain	Intern Quant	0.185%	2.1e-05	**	9.2e-05
FEV/FVC	Franke.Hippocampus	Intern Quant	0.406%	8.4e-03	*	9.9e-03
FEV/FVC	Franke.Liver	Intern Quant	0.28%	1.3e-06	**	1.8e-05
FEV/FVC	Franke.Muscles	Intern Quant	0.025%	9e-05	**	2.3e-04
FEV/FVC	Franke.Pancreas	Intern Quant	0.463%	3e-03	**	3.9e-03
FEV/FVC	Adipose	Intern Quant	0.53%	2.9e-05	**	9.3e-05
FEV/FVC	Brain	Intern Quant	0.992%	0.02	*	0.02
FEV/FVC	Hippocampus	Intern Quant	0.393%	2.2e-04	**	4.8e-04
FEV/FVC	Liver	Intern Quant	1.795%	8.9e-04	**	1.4e-03
FEV/FVC	Pancreas	Intern Quant	0.965%	4.4e-04	**	8.2e-04
FEV/FVC	Skeletal_Muscle	Intern Quant	1.806%	1.1e-03	**	1.6e-03
Glucose	Franke.Blood.Cells	Intern Quant	0.011%	6.7e-03	*	0.02
Glucose	Franke.Adipocytes	Intern Quant	0.001%	0.04	*	0.05
Glucose	Franke.Brain	Intern Quant	0.015%	1.9e-03	**	8.4e-03
Glucose	Franke.Hippocampus	Intern Quant	0.005%	0.1		0.11
Glucose	Franke.Liver	Intern Quant	0.126%	0.02	*	0.03
Glucose	Franke.Muscles	Intern Quant	0.065%	2.4e-04	**	3.1e-03
Glucose	Franke.Pancreas	Intern Quant	0.152%	0.04	*	0.05
Glucose	Adipose	Intern Quant	0.039%	0.02	*	0.03
Glucose	Brain	Intern Quant	0.021%	0.02	*	0.03
Glucose	Hippocampus	Intern Quant	0.006%	0.03	*	0.05
Glucose	Liver	Intern Quant	0%	1.6e-03	**	8.4e-03
Glucose	Pancreas	Intern Quant	0.111%	0.3		0.3
Glucose	Skeletal_Muscle	Intern Quant	0.084%	0.02	*	0.03
Height	Franke.Blood.Cells	Intern Quant	0.027%	4e-12	**	5.2e-11
Height	Franke.Adipocytes	Intern Quant	0.525%	0.53		0.68
Height	Franke.Brain	Intern Quant	0.052%	0.03	*	0.13
Height	Franke.Hippocampus	Intern Quant	0.094%	8.6e-03	*	0.06
Height	Franke.Liver	Intern Quant	0.318%	0.46		0.68
Height	Franke.Muscles	Intern Quant	0.086%	0.63		0.68
Height	Franke.Pancreas	Intern Quant	0.203%	0.12		0.4
Height	Adipose	Intern Quant	0.857%	0.59		0.68
Height	Brain	Intern Quant	1.511%	0.63		0.68
Height	Hippocampus	Intern Quant	0.966%	0.86		0.86
Height	Liver	Intern Quant	1.475%	0.28		0.62
Height	Pancreas	Intern Quant	1.928%	0.29		0.62
Height	Skeletal_Muscle	Intern Quant	2.046%	0.61		0.68
LDL	Franke.Blood.Cells	Intern Quant	0.098%	1.1e-04	**	4.6e-04

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
LDL	Franke.Adipocytes	Intern Quant	1.77%	2.6e-04	**	7.6e-04
LDL	Franke.Brain	Intern Quant	1.1%	6.6e-04	**	1.4e-03
LDL	Franke.Hippocampus	Intern Quant	0.381%	6.5e-06	**	8.4e-05
LDL	Franke.Liver	Intern Quant	3.021%	1.6e-03	**	2.6e-03
LDL	Franke.Muscles	Intern Quant	0.257%	1.3e-03	**	2.3e-03
LDL	Franke.Pancreas	Intern Quant	1.952%	2e-03	**	2.9e-03
LDL	Adipose	Intern Quant	5.802%	5.1e-03	*	6.6e-03
LDL	Brain	Intern Quant	4.714%	2.9e-04	**	7.6e-04
LDL	Hippocampus	Intern Quant	4.244%	1.6e-05	**	1e-04
LDL	Liver	Intern Quant	9.212%	8e-03	*	9.5e-03
LDL	Pancreas	Intern Quant	4.074%	0.01	*	0.01
LDL	Skeletal_Muscle	Intern Quant	3.131%	0.02	*	0.02
Lymphocyte #	Franke.Blood.Cells	Intern Quant	0.426%	0.12		0.19
Lymphocyte #	Franke.Adipocytes	Intern Quant	0.942%	0.07		0.14
Lymphocyte #	Franke.Brain	Intern Quant	0.301%	8.4e-03	*	0.02
Lymphocyte #	Franke.Hippocampus	Intern Quant	0.896%	2.1e-03	**	0.02
Lymphocyte #	Franke.Liver	Intern Quant	0.611%	9.6e-03	*	0.02
Lymphocyte #	Franke.Muscles	Intern Quant	0.13%	3.3e-03	**	0.02
Lymphocyte #	Franke.Pancreas	Intern Quant	0.231%	5.8e-03	*	0.02
Lymphocyte #	Adipose	Intern Quant	8.763%	0.15		0.2
Lymphocyte #	Brain	Intern Quant	5.293%	0.18		0.2
Lymphocyte #	Hippocampus	Intern Quant	3.805%	0.18		0.2
Lymphocyte #	Liver	Intern Quant	7.12%	0.08		0.14
Lymphocyte #	Pancreas	Intern Quant	4.866%	0.15		0.2
Lymphocyte #	Skeletal_Muscle	Intern Quant	7.215%	0.23		0.23
Monocyte #	Franke.Blood.Cells	Intern Quant	0.21%	0.41		0.59
Monocyte #	Franke.Adipocytes	Intern Quant	0.432%	0.03	*	0.14
Monocyte #	Franke.Brain	Intern Quant	0.009%	0.34		0.59
Monocyte #	Franke.Hippocampus	Intern Quant	0.146%	4.3e-04	**	5.6e-03
Monocyte #	Franke.Liver	Intern Quant	0.245%	0.22		0.56
Monocyte #	Franke.Muscles	Intern Quant	0.01%	5.8e-03	*	0.04
Monocyte #	Franke.Pancreas	Intern Quant	0.262%	0.46		0.6
Monocyte #	Adipose	Intern Quant	3.191%	0.09		0.29
Monocyte #	Brain	Intern Quant	1.722%	0.68		0.68
Monocyte #	Hippocampus	Intern Quant	1.032%	0.55		0.66
Monocyte #	Liver	Intern Quant	5.678%	0.4		0.59
Monocyte #	Pancreas	Intern Quant	2.834%	0.3		0.59
Monocyte #	Skeletal_Muscle	Intern Quant	2.484%	0.66		0.68
Platelet #	Franke.Blood.Cells	Intern Quant	0.003%	0.08		0.11
Platelet #	Franke.Adipocytes	Intern Quant	1.031%	1.1e-03	**	5.2e-03
Platelet #	Franke.Brain	Intern Quant	0.203%	0.02	*	0.04
Platelet #	Franke.Hippocampus	Intern Quant	0.388%	7.6e-05	**	9.9e-04

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
Platelet #	Franke.Liver	Intern Quant	0.571%	0.04	*	0.07
Platelet #	Franke.Muscles	Intern Quant	0.17%	1.2e-03	**	5.2e-03
Platelet #	Franke.Pancreas	Intern Quant	0.169%	7.5e-03	*	0.02
Platelet #	Adipose	Intern Quant	2.537%	0.37		0.37
Platelet #	Brain	Intern Quant	3.076%	0.09		0.11
Platelet #	Hippocampus	Intern Quant	1.587%	0.12		0.13
Platelet #	Liver	Intern Quant	4.377%	0.02	*	0.04
Platelet #	Pancreas	Intern Quant	3.773%	0.05	*	0.07
Platelet #	Skeletal_Muscle	Intern Quant	2.92%	1.8e-03	**	5.8e-03
Platelet Distn Width	Franke.Blood.Cells	Intern Quant	1.121%	0.38		0.38
Platelet Distn Width	Franke.Adipocytes	Intern Quant	0.702%	0.01	*	0.04
Platelet Distn Width	Franke.Brain	Intern Quant	0.041%	5.3e-04	**	6.9e-03
Platelet Distn Width	Franke.Hippocampus	Intern Quant	0.183%	2e-03	**	0.01
Platelet Distn Width	Franke.Liver	Intern Quant	0.093%	0.12		0.14
Platelet Distn Width	Franke.Muscles	Intern Quant	0.089%	0.25		0.27
Platelet Distn Width	Franke.Pancreas	Intern Quant	0.022%	0.03	*	0.05
Platelet Distn Width	Adipose	Intern Quant	2.991%	0.02	*	0.05
Platelet Distn Width	Brain	Intern Quant	3.703%	0.05		0.07
Platelet Distn Width	Hippocampus	Intern Quant	2.556%	8.7e-03	*	0.04
Platelet Distn Width	Liver	Intern Quant	2.601%	0.02	*	0.05
Platelet Distn Width	Pancreas	Intern Quant	0.69%	0.03	*	0.05
Platelet Distn Width	Skeletal_Muscle	Intern Quant	2.015%	0.02	*	0.05
Platelet Vol.	Franke.Blood.Cells	Intern Quant	0.361%	1.8e-04	**	4.6e-04
Platelet Vol.	Franke.Adipocytes	Intern Quant	1.829%	9.6e-07	**	4.2e-06
Platelet Vol.	Franke.Brain	Intern Quant	0.001%	1.4e-09	**	9.2e-09
Platelet Vol.	Franke.Hippocampus	Intern Quant	0.016%	6.8e-13	**	8.8e-12
Platelet Vol.	Franke.Liver	Intern Quant	1.273%	1.3e-03	**	2.8e-03
Platelet Vol.	Franke.Muscles	Intern Quant	0.077%	0.14		0.14
Platelet Vol.	Franke.Pancreas	Intern Quant	0.624%	1.3e-04	**	4.2e-04
Platelet Vol.	Adipose	Intern Quant	4.827%	0.03	*	0.03
Platelet Vol.	Brain	Intern Quant	0.007%	8.8e-03	*	0.01
Platelet Vol.	Hippocampus	Intern Quant	0.045%	5.1e-03	*	7.4e-03
Platelet Vol.	Liver	Intern Quant	6.96%	0.09		0.1
Platelet Vol.	Pancreas	Intern Quant	2.788%	4.7e-03	*	7.4e-03
Platelet Vol.	Skeletal_Muscle	Intern Quant	0.615%	3.6e-03	**	6.6e-03
RBC Distn Width	Franke.Blood.Cells	Intern Quant	1.565%	0.05		0.44
RBC Distn Width	Franke.Adipocytes	Intern Quant	2.042%	0.09		0.44
RBC Distn Width	Franke.Brain	Intern Quant	0.133%	0.13		0.44
RBC Distn Width	Franke.Hippocampus	Intern Quant	0.108%	0.17		0.44
RBC Distn Width	Franke.Liver	Intern Quant	1.683%	0.4		0.66
RBC Distn Width	Franke.Muscles	Intern Quant	0.103%	0.44		0.66
RBC Distn Width	Franke.Pancreas	Intern Quant	0.986%	0.15		0.44

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
RBC Distn Width	Adipose	Intern Quant	9.167%	0.67		0.7
RBC Distn Width	Brain	Intern Quant	0.27%	0.5		0.66
RBC Distn Width	Hippocampus	Intern Quant	0.175%	0.31		0.66
RBC Distn Width	Liver	Intern Quant	14.787%	0.56		0.66
RBC Distn Width	Pancreas	Intern Quant	7.547%	0.7		0.7
RBC Distn Width	Skeletal_Muscle	Intern Quant	2.086%	0.54		0.66
Sphered Cell Vol	Franke.Blood.Cells	Intern Quant	0.509%	3e-03	**	0.04
Sphered Cell Vol	Franke.Adipocytes	Intern Quant	1.856%	0.16		0.34
Sphered Cell Vol	Franke.Brain	Intern Quant	0.661%	0.04	*	0.12
Sphered Cell Vol	Franke.Hippocampus	Intern Quant	0.342%	0.05	*	0.12
Sphered Cell Vol	Franke.Liver	Intern Quant	1.233%	0.02	*	0.07
Sphered Cell Vol	Franke.Muscles	Intern Quant	0.852%	0.18		0.34
Sphered Cell Vol	Franke.Pancreas	Intern Quant	1.069%	0.01	*	0.07
Sphered Cell Vol	Adipose	Intern Quant	2.045%	0.72		0.78
Sphered Cell Vol	Brain	Intern Quant	0.609%	0.47		0.61
Sphered Cell Vol	Hippocampus	Intern Quant	0.94%	0.35		0.51
Sphered Cell Vol	Liver	Intern Quant	2.856%	0.89		0.89
Sphered Cell Vol	Pancreas	Intern Quant	0.295%	0.52		0.61
Sphered Cell Vol	Skeletal_Muscle	Intern Quant	0.002%	0.36		0.51
Triglycerides	Franke.Blood.Cells	Intern Quant	0.014%	1.3e-03	**	3.3e-03
Triglycerides	Franke.Adipocytes	Intern Quant	1.981%	0.11		0.12
Triglycerides	Franke.Brain	Intern Quant	0.307%	0.1		0.12
Triglycerides	Franke.Hippocampus	Intern Quant	0.225%	0.38		0.38
Triglycerides	Franke.Liver	Intern Quant	2.108%	8.4e-04	**	2.7e-03
Triglycerides	Franke.Muscles	Intern Quant	0.354%	7.3e-04	**	2.7e-03
Triglycerides	Franke.Pancreas	Intern Quant	0.486%	6.6e-04	**	2.7e-03
Triglycerides	Adipose	Intern Quant	11.408%	0.08		0.1
Triglycerides	Brain	Intern Quant	4.385%	0.05	*	0.07
Triglycerides	Hippocampus	Intern Quant	3.163%	7.3e-04	**	2.7e-03
Triglycerides	Liver	Intern Quant	6.516%	3.4e-03	**	7.4e-03
Triglycerides	Pancreas	Intern Quant	4.168%	0.02	*	0.03
Triglycerides	Skeletal_Muscle	Intern Quant	7.901%	0.03	*	0.05
Asthma	Franke.Blood.Cells	Intern Bin	1.151%	0.15		0.66
Asthma	Franke.Adipocytes	Intern Bin	1.379%	0.14		0.66
Asthma	Franke.Brain	Intern Bin	0.578%	0.68		0.74
Asthma	Franke.Hippocampus	Intern Bin	0.978%	0.41		0.71
Asthma	Franke.Liver	Intern Bin	2.018%	0.6		0.71
Asthma	Franke.Muscles	Intern Bin	0.686%	0.57		0.71
Asthma	Franke.Pancreas	Intern Bin	1.374%	0.24		0.71
Asthma	Adipose	Intern Bin	6.706%	0.48		0.71
Asthma	Brain	Intern Bin	7.585%	0.82		0.82
Asthma	Hippocampus	Intern Bin	6.169%	0.54		0.71

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
Asthma	Liver	Intern Bin	20.291%	0.07		0.66
Asthma	Pancreas	Intern Bin	7.074%	0.39		0.71
Asthma	Skeletal_Muscle	Intern Bin	12.612%	0.42		0.71
Cardiovascular	Franke.Blood.Cells	Intern Bin	0.027%	0.18		0.2
Cardiovascular	Franke.Adipocytes	Intern Bin	0.212%	0.02	*	0.04
Cardiovascular	Franke.Brain	Intern Bin	0.006%	8.2e-05	**	6.7e-04
Cardiovascular	Franke.Hippocampus	Intern Bin	0.019%	0.03	*	0.05
Cardiovascular	Franke.Liver	Intern Bin	0.242%	1e-04	**	6.7e-04
Cardiovascular	Franke.Muscles	Intern Bin	0.044%	2.1e-04	**	9.1e-04
Cardiovascular	Franke.Pancreas	Intern Bin	0.359%	0.01	*	0.04
Cardiovascular	Adipose	Intern Bin	0.259%	1.7e-03	**	5.6e-03
Cardiovascular	Brain	Intern Bin	0.181%	0.13		0.15
Cardiovascular	Hippocampus	Intern Bin	0.092%	0.36		0.36
Cardiovascular	Liver	Intern Bin	0.228%	0.03	*	0.05
Cardiovascular	Pancreas	Intern Bin	0.334%	0.07		0.11
Cardiovascular	Skeletal_Muscle	Intern Bin	0.116%	0.11		0.15
Eczema	Franke.Blood.Cells	Intern Bin	0.942%	8.9e-03	*	0.02
Eczema	Franke.Adipocytes	Intern Bin	0.842%	5.6e-03	*	0.02
Eczema	Franke.Brain	Intern Bin	0.09%	0.78		0.78
Eczema	Franke.Hippocampus	Intern Bin	0.208%	0.03	*	0.05
Eczema	Franke.Liver	Intern Bin	0.929%	1.7e-03	**	0.01
Eczema	Franke.Muscles	Intern Bin	0.067%	2.1e-04	**	2.7e-03
Eczema	Franke.Pancreas	Intern Bin	0.41%	8.2e-03	*	0.02
Eczema	Adipose	Intern Bin	2.842%	0.03	*	0.05
Eczema	Brain	Intern Bin	2.427%	0.12		0.15
Eczema	Hippocampus	Intern Bin	1.664%	0.23		0.25
Eczema	Liver	Intern Bin	4.641%	0.03	*	0.05
Eczema	Pancreas	Intern Bin	2.222%	0.09		0.11
Eczema	Skeletal_Muscle	Intern Bin	2.157%	0.01	*	0.03
T2D	Franke.Blood.Cells	Intern Bin	0.063%	0.01	*	0.05
T2D	Franke.Adipocytes	Intern Bin	6.969%	0.01	*	0.05
T2D	Franke.Brain	Intern Bin	1.962%	0.08		0.09
T2D	Franke.Hippocampus	Intern Bin	1.792%	0.1		0.11
T2D	Franke.Liver	Intern Bin	2.129%	0.41		0.41
T2D	Franke.Muscles	Intern Bin	1.159%	0.02	*	0.06
T2D	Franke.Pancreas	Intern Bin	6.5%	0.07		0.09
T2D	Adipose	Intern Bin	43.945%	4.4e-03	*	0.05
T2D	Brain	Intern Bin	26.729%	0.04	*	0.06
T2D	Hippocampus	Intern Bin	21.983%	0.03	*	0.06
T2D	Liver	Intern Bin	30.987%	0.04	*	0.06
T2D	Pancreas	Intern Bin	25.498%	0.01	*	0.05
T2D	Skeletal_Muscle	Intern Bin	28.326%	0.03	*	0.06

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
Asthma	Franke.Blood.Cells	Extern	0.336%	0.07		0.39
Asthma	Franke.Adipocytes	Extern	0.187%	0.58		0.62
Asthma	Franke.Brain	Extern	0.079%	0.2		0.44
Asthma	Franke.Hippocampus	Extern	0.079%	0.4		0.51
Asthma	Franke.Liver	Extern	0.364%	0.45		0.53
Asthma	Franke.Muscles	Extern	0.281%	0.29		0.47
Asthma	Franke.Pancreas	Extern	0.448%	0.24		0.45
Asthma	Adipose	Extern	0.394%	0.17		0.44
Asthma	Brain	Extern	0.036%	0.02	*	0.29
Asthma	Hippocampus	Extern	0%	0.09		0.39
Asthma	Liver	Extern	0.912%	0.18		0.44
Asthma	Pancreas	Extern	0.024%	0.34		0.49
Asthma	Skeletal_Muscle	Extern	0.209%	0.78		0.78
Cardiovascular	Franke.Blood.Cells	Extern	0.02%	0.75		0.98
Cardiovascular	Franke.Adipocytes	Extern	0.046%	0.93		0.98
Cardiovascular	Franke.Brain	Extern	0.006%	0.47		0.98
Cardiovascular	Franke.Hippocampus	Extern	0%	0.94		0.98
Cardiovascular	Franke.Liver	Extern	0.039%	0.54		0.98
Cardiovascular	Franke.Muscles	Extern	0%	0.79		0.98
Cardiovascular	Franke.Pancreas	Extern	0.008%	0.79		0.98
Cardiovascular	Adipose	Extern	0.417%	0.98		0.98
Cardiovascular	Brain	Extern	0.115%	0.84		0.98
Cardiovascular	Hippocampus	Extern	0.224%	0.79		0.98
Cardiovascular	Liver	Extern	0.463%	0.76		0.98
Cardiovascular	Pancreas	Extern	0.201%	0.74		0.98
Cardiovascular	Skeletal_Muscle	Extern	0.06%	0.8		0.98
Corp. Hemoglobin	Franke.Blood.Cells	Extern	0.034%	0.24		0.79
Corp. Hemoglobin	Franke.Adipocytes	Extern	0.003%	0.06		0.37
Corp. Hemoglobin	Franke.Brain	Extern	0.002%	0.56		0.79
Corp. Hemoglobin	Franke.Hippocampus	Extern	0%	0.79		0.79
Corp. Hemoglobin	Franke.Liver	Extern	0.005%	0.02	*	0.32
Corp. Hemoglobin	Franke.Muscles	Extern	0%	0.73		0.79
Corp. Hemoglobin	Franke.Pancreas	Extern	0.021%	0.56		0.79
Corp. Hemoglobin	Adipose	Extern	0.178%	0.25		0.79
Corp. Hemoglobin	Brain	Extern	0.221%	0.7		0.79
Corp. Hemoglobin	Hippocampus	Extern	0.114%	0.46		0.79
Corp. Hemoglobin	Liver	Extern	0.205%	0.75		0.79
Corp. Hemoglobin	Pancreas	Extern	0.424%	0.33		0.79
Corp. Hemoglobin	Skeletal_Muscle	Extern	0.373%	0.52		0.79
Height	Franke.Blood.Cells	Extern	0%	0.22		0.27
Height	Franke.Adipocytes	Extern	0.165%	0.06		0.14
Height	Franke.Brain	Extern	0.003%	0.06		0.14

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
Height	Franke.Hippocampus	Extern	0.002%	0.03	*	0.14
Height	Franke.Liver	Extern	0.072%	0.47		0.47
Height	Franke.Muscles	Extern	0.05%	0.11		0.16
Height	Franke.Pancreas	Extern	0.031%	0.3		0.33
Height	Adipose	Extern	1.049%	0.07		0.14
Height	Brain	Extern	1.027%	0.08		0.14
Height	Hippocampus	Extern	0.8%	0.04	*	0.14
Height	Liver	Extern	1.033%	0.08		0.14
Height	Pancreas	Extern	1.31%	0.17		0.21
Height	Skeletal_Muscle	Extern	1.281%	0.09		0.14
LDL	Franke.Blood.Cells	Extern	0.083%	0.31		0.4
LDL	Franke.Adipocytes	Extern	0.439%	2.3e-03	**	0.03
LDL	Franke.Brain	Extern	0.115%	0.15		0.27
LDL	Franke.Hippocampus	Extern	0.096%	0.23		0.33
LDL	Franke.Liver	Extern	1.184%	0.06		0.19
LDL	Franke.Muscles	Extern	0.083%	0.12		0.26
LDL	Franke.Pancreas	Extern	0.721%	8.8e-03	*	0.06
LDL	Adipose	Extern	0.882%	0.36		0.42
LDL	Brain	Extern	0.922%	0.18		0.29
LDL	Hippocampus	Extern	0.878%	0.12		0.26
LDL	Liver	Extern	3.3%	0.06		0.19
LDL	Pancreas	Extern	0.847%	0.48		0.52
LDL	Skeletal_Muscle	Extern	0.507%	0.56		0.56
Lymphocyte #	Franke.Blood.Cells	Extern	0.027%	0.24		0.49
Lymphocyte #	Franke.Adipocytes	Extern	0.073%	0.34		0.49
Lymphocyte #	Franke.Brain	Extern	0.006%	0.04	*	0.25
Lymphocyte #	Franke.Hippocampus	Extern	0.015%	0.02	*	0.25
Lymphocyte #	Franke.Liver	Extern	0.05%	0.23		0.49
Lymphocyte #	Franke.Muscles	Extern	0.032%	0.87		0.87
Lymphocyte #	Franke.Pancreas	Extern	0.053%	0.22		0.49
Lymphocyte #	Adipose	Extern	0%	0.75		0.87
Lymphocyte #	Brain	Extern	0.09%	0.27		0.49
Lymphocyte #	Hippocampus	Extern	0.033%	0.86		0.87
Lymphocyte #	Liver	Extern	0.01%	0.39		0.51
Lymphocyte #	Pancreas	Extern	0.019%	0.29		0.49
Lymphocyte #	Skeletal_Muscle	Extern	0.191%	0.34		0.49
Monocyte #	Franke.Blood.Cells	Extern	0.225%	0.4		0.6
Monocyte #	Franke.Adipocytes	Extern	0.058%	0.16		0.6
Monocyte #	Franke.Brain	Extern	0.022%	0.42		0.6
Monocyte #	Franke.Hippocampus	Extern	0.022%	0.22		0.6
Monocyte #	Franke.Liver	Extern	0.058%	0.65		0.71
Monocyte #	Franke.Muscles	Extern	0.015%	0.71		0.71

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
Monocyte #	Franke.Pancreas	Extern	0.059%	0.24		0.6
Monocyte #	Adipose	Extern	0.021%	0.51		0.6
Monocyte #	Brain	Extern	0.027%	0.47		0.6
Monocyte #	Hippocampus	Extern	0.004%	0.19		0.6
Monocyte #	Liver	Extern	0.054%	0.08		0.6
Monocyte #	Pancreas	Extern	0.001%	0.3		0.6
Monocyte #	Skeletal_Muscle	Extern	0.203%	0.45		0.6
Platelet #	Franke.Blood.Cells	Extern	0.052%	0.15		0.19
Platelet #	Franke.Adipocytes	Extern	0.051%	0.12		0.18
Platelet #	Franke.Brain	Extern	0.002%	0.22		0.22
Platelet #	Franke.Hippocampus	Extern	0.001%	0.17		0.2
Platelet #	Franke.Liver	Extern	0.031%	0.03	*	0.15
Platelet #	Franke.Muscles	Extern	0.009%	0.09		0.18
Platelet #	Franke.Pancreas	Extern	0.007%	0.02	*	0.15
Platelet #	Adipose	Extern	0%	0.18		0.2
Platelet #	Brain	Extern	0.139%	0.12		0.18
Platelet #	Hippocampus	Extern	0.016%	0.12		0.18
Platelet #	Liver	Extern	0.001%	0.11		0.18
Platelet #	Pancreas	Extern	0.002%	0.06		0.18
Platelet #	Skeletal_Muscle	Extern	0%	0.04	*	0.15
Platelet Vol.	Franke.Blood.Cells	Extern	0.059%	0.01	*	0.02
Platelet Vol.	Franke.Adipocytes	Extern	0.076%	1.6e-08	**	2e-07
Platelet Vol.	Franke.Brain	Extern	0.016%	2.9e-03	**	5.9e-03
Platelet Vol.	Franke.Hippocampus	Extern	0.019%	4.1e-03	*	5.9e-03
Platelet Vol.	Franke.Liver	Extern	0.051%	0.45		0.45
Platelet Vol.	Franke.Muscles	Extern	0.064%	4.7e-05	**	3.1e-04
Platelet Vol.	Franke.Pancreas	Extern	0.002%	7.4e-05	**	3.2e-04
Platelet Vol.	Adipose	Extern	0.131%	1.1e-03	**	3e-03
Platelet Vol.	Brain	Extern	0.022%	3.3e-03	**	5.9e-03
Platelet Vol.	Hippocampus	Extern	0.01%	0.02	*	0.02
Platelet Vol.	Liver	Extern	0%	4.6e-04	**	1.5e-03
Platelet Vol.	Pancreas	Extern	0.01%	0.02	*	0.02
Platelet Vol.	Skeletal_Muscle	Extern	0.306%	4e-03	*	5.9e-03
T2D	Franke.Blood.Cells	Extern	0.168%	0.24		0.91
T2D	Franke.Adipocytes	Extern	0.243%	0.51		0.91
T2D	Franke.Brain	Extern	0.099%	0.45		0.91
T2D	Franke.Hippocampus	Extern	0.062%	0.12		0.79
T2D	Franke.Liver	Extern	0.989%	0.6		0.91
T2D	Franke.Muscles	Extern	1.005%	0.08		0.79
T2D	Franke.Pancreas	Extern	2.311%	0.84		0.91
T2D	Adipose	Extern	0.792%	0.91		0.91
T2D	Brain	Extern	0.104%	0.63		0.91

Table S4 continued from previous page

Phenotype	Tissue	PRS Type	TPRS %VE	p-value	Sig Level	FDR
T2D	Hippocampus	Extern	0.366%	0.49		0.91
T2D	Liver	Extern	0.985%	0.69		0.91
T2D	Pancreas	Extern	0.181%	0.88		0.91
T2D	Skeletal_Muscle	Extern	1.281%	0.87		0.91
Triglycerides	Franke.Blood.Cells	Extern	0%	0.07		0.44
Triglycerides	Franke.Adipocytes	Extern	0.001%	0.26		0.56
Triglycerides	Franke.Brain	Extern	0.07%	0.56		0.8
Triglycerides	Franke.Hippocampus	Extern	0.01%	0.85		0.85
Triglycerides	Franke.Liver	Extern	0.669%	0.1		0.44
Triglycerides	Franke.Muscles	Extern	0%	0.16		0.53
Triglycerides	Franke.Pancreas	Extern	0.329%	0.07		0.44
Triglycerides	Adipose	Extern	2.126%	0.74		0.8
Triglycerides	Brain	Extern	0.164%	0.59		0.8
Triglycerides	Hippocampus	Extern	0.308%	0.39		0.73
Triglycerides	Liver	Extern	0.61%	0.24		0.56
Triglycerides	Pancreas	Extern	0.197%	0.7		0.8
Triglycerides	Skeletal_Muscle	Extern	0.44%	0.69		0.8

Table S5: Tissue-pair CE in the UKBB for all tested trait-tissue-tissue triples. Only trait-tissue pairs with significant tissue-specific CE were tested (Table 3). "Intern" indicates that the PRS was calculated using the cross-validation method with UKBB data (Methods). "Extern" indicates that the PRS was calculated using GWAS summary statistics from external datasets (Methods). p-values for tissue-tissue CE estimates are Bonferroni adjusted for testing across multiple phenotype and tissue-tissue pairs.

Phenotype	Tissue 1	Tissue 2	PRS Type	p-value
FEV/FVC	Franke.Blood.Cells	Franke.Brain	Intern Quant	0.06
FEV/FVC	Franke.Blood.Cells	Franke.Liver	Intern Quant	0.02
FEV/FVC	Franke.Blood.Cells	Franke.Muscles	Intern Quant	8e-03
FEV/FVC	Franke.Blood.Cells	Franke.Pancreas	Intern Quant	0.07
FEV/FVC	Franke.Blood.Cells	Adipose	Intern Quant	0.42
FEV/FVC	Franke.Blood.Cells	Hippocampus	Intern Quant	0.21
FEV/FVC	Franke.Blood.Cells	Liver	Intern Quant	0.05
FEV/FVC	Franke.Blood.Cells	Pancreas	Intern Quant	0.12
FEV/FVC	Franke.Blood.Cells	Skeletal_Muscle	Intern Quant	0.23
FEV/FVC	Franke.Brain	Franke.Liver	Intern Quant	1.3e-03
FEV/FVC	Franke.Brain	Franke.Muscles	Intern Quant	1.1e-03
FEV/FVC	Franke.Brain	Franke.Pancreas	Intern Quant	0.05
FEV/FVC	Franke.Brain	Adipose	Intern Quant	0.02
FEV/FVC	Franke.Brain	Hippocampus	Intern Quant	6e-03
FEV/FVC	Franke.Brain	Liver	Intern Quant	0.03
FEV/FVC	Franke.Brain	Pancreas	Intern Quant	8.5e-03
FEV/FVC	Franke.Brain	Skeletal_Muscle	Intern Quant	0.13
FEV/FVC	Franke.Liver	Franke.Muscles	Intern Quant	4.8e-03
FEV/FVC	Franke.Liver	Franke.Pancreas	Intern Quant	2.2e-05
FEV/FVC	Franke.Liver	Adipose	Intern Quant	1.4e-03
FEV/FVC	Franke.Liver	Hippocampus	Intern Quant	4e-03
FEV/FVC	Franke.Liver	Liver	Intern Quant	2.3e-03
FEV/FVC	Franke.Liver	Pancreas	Intern Quant	0.06
FEV/FVC	Franke.Liver	Skeletal_Muscle	Intern Quant	0.06
FEV/FVC	Franke.Muscles	Franke.Pancreas	Intern Quant	0.04
FEV/FVC	Franke.Muscles	Adipose	Intern Quant	9e-03
FEV/FVC	Franke.Muscles	Hippocampus	Intern Quant	0.02
FEV/FVC	Franke.Muscles	Liver	Intern Quant	2.4e-03
FEV/FVC	Franke.Muscles	Pancreas	Intern Quant	0.01
FEV/FVC	Franke.Muscles	Skeletal_Muscle	Intern Quant	0.02
FEV/FVC	Franke.Pancreas	Adipose	Intern Quant	0.05
FEV/FVC	Franke.Pancreas	Hippocampus	Intern Quant	0.01
FEV/FVC	Franke.Pancreas	Liver	Intern Quant	8.3e-03
FEV/FVC	Franke.Pancreas	Pancreas	Intern Quant	0.05
FEV/FVC	Franke.Pancreas	Skeletal_Muscle	Intern Quant	0.17
FEV/FVC	Adipose	Hippocampus	Intern Quant	0.22
FEV/FVC	Adipose	Liver	Intern Quant	0.02

Table S5 continued from previous page

Phenotype	Tissue 1	Tissue 2	PRS Type	p-value
FEV/FVC	Adipose	Pancreas	Intern Quant	2.3e-03
FEV/FVC	Adipose	Skeletal_Muscle	Intern Quant	0.39
FEV/FVC	Hippocampus	Liver	Intern Quant	0.1
FEV/FVC	Hippocampus	Pancreas	Intern Quant	0.26
FEV/FVC	Hippocampus	Skeletal_Muscle	Intern Quant	0.43
FEV/FVC	Liver	Pancreas	Intern Quant	0.04
FEV/FVC	Liver	Skeletal_Muscle	Intern Quant	0.31
FEV/FVC	Pancreas	Skeletal_Muscle	Intern Quant	0.13
Glucose	Franke.Brain	Franke.Muscles	Intern Quant	0.03
Glucose	Franke.Brain	Liver	Intern Quant	0.03
Glucose	Franke.Muscles	Liver	Intern Quant	1.1e-03
LDL	Franke.Blood.Cells	Franke.Adipocytes	Intern Quant	5.6e-03
LDL	Franke.Blood.Cells	Franke.Brain	Intern Quant	0.47
LDL	Franke.Blood.Cells	Franke.Hippocampus	Intern Quant	0.12
LDL	Franke.Blood.Cells	Franke.Liver	Intern Quant	1.4e-03
LDL	Franke.Blood.Cells	Franke.Muscles	Intern Quant	0.01
LDL	Franke.Blood.Cells	Franke.Pancreas	Intern Quant	0.03
LDL	Franke.Blood.Cells	Brain	Intern Quant	5.5e-03
LDL	Franke.Blood.Cells	Hippocampus	Intern Quant	8.6e-03
LDL	Franke.Adipocytes	Franke.Brain	Intern Quant	0.1
LDL	Franke.Adipocytes	Franke.Hippocampus	Intern Quant	0.18
LDL	Franke.Adipocytes	Franke.Liver	Intern Quant	0.01
LDL	Franke.Adipocytes	Franke.Muscles	Intern Quant	0.31
LDL	Franke.Adipocytes	Franke.Pancreas	Intern Quant	0.12
LDL	Franke.Adipocytes	Brain	Intern Quant	6.5e-03
LDL	Franke.Adipocytes	Hippocampus	Intern Quant	0.02
LDL	Franke.Brain	Franke.Hippocampus	Intern Quant	0.55
LDL	Franke.Brain	Franke.Liver	Intern Quant	0.04
LDL	Franke.Brain	Franke.Muscles	Intern Quant	0.07
LDL	Franke.Brain	Franke.Pancreas	Intern Quant	0.17
LDL	Franke.Brain	Brain	Intern Quant	0.17
LDL	Franke.Brain	Hippocampus	Intern Quant	0.09
LDL	Franke.Hippocampus	Franke.Liver	Intern Quant	0.23
LDL	Franke.Hippocampus	Franke.Muscles	Intern Quant	0.16
LDL	Franke.Hippocampus	Franke.Pancreas	Intern Quant	0.19
LDL	Franke.Hippocampus	Brain	Intern Quant	0.36
LDL	Franke.Hippocampus	Hippocampus	Intern Quant	0.53
LDL	Franke.Liver	Franke.Muscles	Intern Quant	0.16
LDL	Franke.Liver	Franke.Pancreas	Intern Quant	0.02
LDL	Franke.Liver	Brain	Intern Quant	5.5e-04
LDL	Franke.Liver	Hippocampus	Intern Quant	0.01
LDL	Franke.Muscles	Franke.Pancreas	Intern Quant	0.14

Table S5 continued from previous page

Phenotype	Tissue 1	Tissue 2	PRS Type	p-value
LDL	Franke.Muscles	Brain	Intern Quant	0.18
LDL	Franke.Muscles	Hippocampus	Intern Quant	8.8e-03
LDL	Franke.Pancreas	Brain	Intern Quant	0.23
LDL	Franke.Pancreas	Hippocampus	Intern Quant	0.14
LDL	Brain	Hippocampus	Intern Quant	7.4e-04
Lymphocyte #	Franke.Hippocampus	Franke.Muscles	Intern Quant	3e-03
Platelet #	Franke.Adipocytes	Franke.Hippocampus	Intern Quant	0.01
Platelet #	Franke.Adipocytes	Franke.Muscles	Intern Quant	1.5e-04
Platelet #	Franke.Adipocytes	Skeletal_Muscle	Intern Quant	8.8e-03
Platelet #	Franke.Hippocampus	Franke.Muscles	Intern Quant	0.01
Platelet #	Franke.Hippocampus	Skeletal_Muscle	Intern Quant	0.74
Platelet #	Franke.Muscles	Skeletal_Muscle	Intern Quant	0.12
Platelet Distn Width	Franke.Brain	Franke.Hippocampus	Intern Quant	0.69
Platelet Vol.	Franke.Blood.Cells	Franke.Adipocytes	Intern Quant	0.03
Platelet Vol.	Franke.Blood.Cells	Franke.Brain	Intern Quant	1.8e-05
Platelet Vol.	Franke.Blood.Cells	Franke.Hippocampus	Intern Quant	3e-03
Platelet Vol.	Franke.Blood.Cells	Franke.Liver	Intern Quant	4.4e-03
Platelet Vol.	Franke.Blood.Cells	Franke.Muscles	Intern Quant	0.06
Platelet Vol.	Franke.Blood.Cells	Franke.Pancreas	Intern Quant	0.68
Platelet Vol.	Franke.Blood.Cells	Adipose	Intern Quant	0.17
Platelet Vol.	Franke.Blood.Cells	Brain	Intern Quant	0.03
Platelet Vol.	Franke.Blood.Cells	Liver	Intern Quant	0.02
Platelet Vol.	Franke.Blood.Cells	Skeletal_Muscle	Intern Quant	0.04
Platelet Vol.	Franke.Adipocytes	Franke.Brain	Intern Quant	0.56
Platelet Vol.	Franke.Adipocytes	Franke.Hippocampus	Intern Quant	0.02
Platelet Vol.	Franke.Adipocytes	Franke.Liver	Intern Quant	0.02
Platelet Vol.	Franke.Adipocytes	Franke.Muscles	Intern Quant	0.17
Platelet Vol.	Franke.Adipocytes	Franke.Pancreas	Intern Quant	0.59
Platelet Vol.	Franke.Adipocytes	Adipose	Intern Quant	0.75
Platelet Vol.	Franke.Adipocytes	Brain	Intern Quant	0.86
Platelet Vol.	Franke.Adipocytes	Liver	Intern Quant	0.4
Platelet Vol.	Franke.Adipocytes	Skeletal_Muscle	Intern Quant	0.51
Platelet Vol.	Franke.Brain	Franke.Hippocampus	Intern Quant	0.02
Platelet Vol.	Franke.Brain	Franke.Liver	Intern Quant	7.6e-03
Platelet Vol.	Franke.Brain	Franke.Muscles	Intern Quant	0.01
Platelet Vol.	Franke.Brain	Franke.Pancreas	Intern Quant	0.13
Platelet Vol.	Franke.Brain	Adipose	Intern Quant	0.19
Platelet Vol.	Franke.Brain	Brain	Intern Quant	0.49
Platelet Vol.	Franke.Brain	Liver	Intern Quant	0.2
Platelet Vol.	Franke.Brain	Skeletal_Muscle	Intern Quant	0.1
Platelet Vol.	Franke.Hippocampus	Franke.Liver	Intern Quant	2.3e-04
Platelet Vol.	Franke.Hippocampus	Franke.Muscles	Intern Quant	0.01

Table S5 continued from previous page

Phenotype	Tissue 1	Tissue 2	PRS Type	p-value
Platelet Vol.	Franke.Hippocampus	Franke.Pancreas	Intern Quant	0.09
Platelet Vol.	Franke.Hippocampus	Adipose	Intern Quant	0.5
Platelet Vol.	Franke.Hippocampus	Brain	Intern Quant	0.76
Platelet Vol.	Franke.Hippocampus	Liver	Intern Quant	0.24
Platelet Vol.	Franke.Hippocampus	Skeletal_Muscle	Intern Quant	0.15
Platelet Vol.	Franke.Liver	Franke.Muscles	Intern Quant	0.32
Platelet Vol.	Franke.Liver	Franke.Pancreas	Intern Quant	0.01
Platelet Vol.	Franke.Liver	Adipose	Intern Quant	0.02
Platelet Vol.	Franke.Liver	Brain	Intern Quant	0.18
Platelet Vol.	Franke.Liver	Liver	Intern Quant	0.05
Platelet Vol.	Franke.Liver	Skeletal_Muscle	Intern Quant	8.8e-03
Platelet Vol.	Franke.Muscles	Franke.Pancreas	Intern Quant	0.02
Platelet Vol.	Franke.Muscles	Adipose	Intern Quant	0.05
Platelet Vol.	Franke.Muscles	Brain	Intern Quant	0.45
Platelet Vol.	Franke.Muscles	Liver	Intern Quant	0.16
Platelet Vol.	Franke.Muscles	Skeletal_Muscle	Intern Quant	0.01
Platelet Vol.	Franke.Pancreas	Adipose	Intern Quant	0.78
Platelet Vol.	Franke.Pancreas	Brain	Intern Quant	0.72
Platelet Vol.	Franke.Pancreas	Liver	Intern Quant	0.72
Platelet Vol.	Franke.Pancreas	Skeletal_Muscle	Intern Quant	0.06
Platelet Vol.	Adipose	Brain	Intern Quant	0.2
Platelet Vol.	Adipose	Liver	Intern Quant	0.25
Platelet Vol.	Adipose	Skeletal_Muscle	Intern Quant	0.32
Platelet Vol.	Brain	Liver	Intern Quant	0.05
Platelet Vol.	Brain	Skeletal_Muscle	Intern Quant	0.18
Platelet Vol.	Liver	Skeletal_Muscle	Intern Quant	5.2e-03
Triglycerides	Franke.Blood.Cells	Franke.Liver	Intern Quant	0.6
Triglycerides	Franke.Blood.Cells	Franke.Muscles	Intern Quant	1.1e-03
Triglycerides	Franke.Blood.Cells	Franke.Pancreas	Intern Quant	4.5e-03
Triglycerides	Franke.Blood.Cells	Hippocampus	Intern Quant	0.02
Triglycerides	Franke.Blood.Cells	Liver	Intern Quant	0.13
Triglycerides	Franke.Liver	Franke.Muscles	Intern Quant	0.04
Triglycerides	Franke.Liver	Franke.Pancreas	Intern Quant	0.11
Triglycerides	Franke.Liver	Hippocampus	Intern Quant	0.04
Triglycerides	Franke.Liver	Liver	Intern Quant	8.7e-03
Triglycerides	Franke.Muscles	Franke.Pancreas	Intern Quant	0.01
Triglycerides	Franke.Muscles	Hippocampus	Intern Quant	0.13
Triglycerides	Franke.Muscles	Liver	Intern Quant	0.05
Triglycerides	Franke.Pancreas	Hippocampus	Intern Quant	0.03
Triglycerides	Franke.Pancreas	Liver	Intern Quant	0.04
Triglycerides	Hippocampus	Liver	Intern Quant	0.01
Cardiovascular	Franke.Brain	Franke.Liver	Intern Bin	0.16

Table S5 continued from previous page

Phenotype	Tissue 1	Tissue 2	PRS Type	p-value
Cardiovascular	Franke.Brain	Franke.Muscles	Intern Bin	0.49
Cardiovascular	Franke.Brain	Adipose	Intern Bin	0.28
Cardiovascular	Franke.Liver	Franke.Muscles	Intern Bin	0.41
Cardiovascular	Franke.Liver	Adipose	Intern Bin	0.07
Cardiovascular	Franke.Muscles	Adipose	Intern Bin	0.02
Eczema	Franke.Liver	Franke.Muscles	Intern Bin	8.7e-04
Cardiovascular	Franke.Brain	Franke.Liver	Extern	0.3
Cardiovascular	Franke.Brain	Franke.Muscles	Extern	0.83
Cardiovascular	Franke.Brain	Adipose	Extern	0.04
Cardiovascular	Franke.Liver	Franke.Muscles	Extern	0.26
Cardiovascular	Franke.Liver	Adipose	Extern	0.31
Cardiovascular	Franke.Muscles	Adipose	Extern	0.94
LDL	Franke.Blood.Cells	Franke.Adipocytes	Extern	0.03
LDL	Franke.Blood.Cells	Franke.Brain	Extern	0.54
LDL	Franke.Blood.Cells	Franke.Hippocampus	Extern	0.51
LDL	Franke.Blood.Cells	Franke.Liver	Extern	5.6e-03
LDL	Franke.Blood.Cells	Franke.Muscles	Extern	0.07
LDL	Franke.Blood.Cells	Franke.Pancreas	Extern	0.02
LDL	Franke.Blood.Cells	Brain	Extern	0.01
LDL	Franke.Blood.Cells	Hippocampus	Extern	0.01
LDL	Franke.Adipocytes	Franke.Brain	Extern	0.02
LDL	Franke.Adipocytes	Franke.Hippocampus	Extern	0.12
LDL	Franke.Adipocytes	Franke.Liver	Extern	0.03
LDL	Franke.Adipocytes	Franke.Muscles	Extern	0.33
LDL	Franke.Adipocytes	Franke.Pancreas	Extern	0.16
LDL	Franke.Adipocytes	Brain	Extern	0.07
LDL	Franke.Adipocytes	Hippocampus	Extern	0.11
LDL	Franke.Brain	Franke.Hippocampus	Extern	0.91
LDL	Franke.Brain	Franke.Liver	Extern	0.06
LDL	Franke.Brain	Franke.Muscles	Extern	0.52
LDL	Franke.Brain	Franke.Pancreas	Extern	0.07
LDL	Franke.Brain	Brain	Extern	0.12
LDL	Franke.Brain	Hippocampus	Extern	0.11
LDL	Franke.Hippocampus	Franke.Liver	Extern	0.56
LDL	Franke.Hippocampus	Franke.Muscles	Extern	0.36
LDL	Franke.Hippocampus	Franke.Pancreas	Extern	0.13
LDL	Franke.Hippocampus	Brain	Extern	0.35
LDL	Franke.Hippocampus	Hippocampus	Extern	0.28
LDL	Franke.Liver	Franke.Muscles	Extern	2.9e-03
LDL	Franke.Liver	Franke.Pancreas	Extern	5.5e-04
LDL	Franke.Liver	Brain	Extern	0.02
LDL	Franke.Liver	Hippocampus	Extern	4.2e-03

Table S5 continued from previous page

Phenotype	Tissue 1	Tissue 2	PRS Type	p-value
LDL	Franke.Muscles	Franke.Pancreas	Extern	0.08
LDL	Franke.Muscles	Brain	Extern	3.9e-03
LDL	Franke.Muscles	Hippocampus	Extern	0.08
LDL	Franke.Pancreas	Brain	Extern	9.1e-03
LDL	Franke.Pancreas	Hippocampus	Extern	0.04
LDL	Brain	Hippocampus	Extern	0.13
Lymphocyte #	Franke.Hippocampus	Franke.Muscles	Extern	1
Platelet #	Franke.Adipocytes	Franke.Hippocampus	Extern	0.34
Platelet #	Franke.Adipocytes	Franke.Muscles	Extern	0.02
Platelet #	Franke.Adipocytes	Skeletal_Muscle	Extern	0.6
Platelet #	Franke.Hippocampus	Franke.Muscles	Extern	2e-04
Platelet #	Franke.Hippocampus	Skeletal_Muscle	Extern	0.2
Platelet #	Franke.Muscles	Skeletal_Muscle	Extern	0.12
Platelet Vol.	Franke.Blood.Cells	Franke.Adipocytes	Extern	0.63
Platelet Vol.	Franke.Blood.Cells	Franke.Brain	Extern	0.27
Platelet Vol.	Franke.Blood.Cells	Franke.Hippocampus	Extern	0.03
Platelet Vol.	Franke.Blood.Cells	Franke.Liver	Extern	0.45
Platelet Vol.	Franke.Blood.Cells	Franke.Muscles	Extern	0.14
Platelet Vol.	Franke.Blood.Cells	Franke.Pancreas	Extern	2.2e-03
Platelet Vol.	Franke.Blood.Cells	Adipose	Extern	0.03
Platelet Vol.	Franke.Blood.Cells	Brain	Extern	0.88
Platelet Vol.	Franke.Blood.Cells	Liver	Extern	0.02
Platelet Vol.	Franke.Blood.Cells	Skeletal_Muscle	Extern	0.03
Platelet Vol.	Franke.Adipocytes	Franke.Brain	Extern	0.26
Platelet Vol.	Franke.Adipocytes	Franke.Hippocampus	Extern	0.21
Platelet Vol.	Franke.Adipocytes	Franke.Liver	Extern	0.8
Platelet Vol.	Franke.Adipocytes	Franke.Muscles	Extern	0.45
Platelet Vol.	Franke.Adipocytes	Franke.Pancreas	Extern	0.21
Platelet Vol.	Franke.Adipocytes	Adipose	Extern	0.81
Platelet Vol.	Franke.Adipocytes	Brain	Extern	0.07
Platelet Vol.	Franke.Adipocytes	Liver	Extern	0.05
Platelet Vol.	Franke.Adipocytes	Skeletal_Muscle	Extern	0.61
Platelet Vol.	Franke.Brain	Franke.Hippocampus	Extern	0.04
Platelet Vol.	Franke.Brain	Franke.Liver	Extern	0.15
Platelet Vol.	Franke.Brain	Franke.Muscles	Extern	7.4e-03
Platelet Vol.	Franke.Brain	Franke.Pancreas	Extern	0.4
Platelet Vol.	Franke.Brain	Adipose	Extern	0.8
Platelet Vol.	Franke.Brain	Brain	Extern	0.31
Platelet Vol.	Franke.Brain	Liver	Extern	0.63
Platelet Vol.	Franke.Brain	Skeletal_Muscle	Extern	0.31
Platelet Vol.	Franke.Hippocampus	Franke.Liver	Extern	0.78
Platelet Vol.	Franke.Hippocampus	Franke.Muscles	Extern	0.18

Table S5 continued from previous page

Phenotype	Tissue 1	Tissue 2	PRS Type	p-value
Platelet Vol.	Franke.Hippocampus	Franke.Pancreas	Extern	0.64
Platelet Vol.	Franke.Hippocampus	Adipose	Extern	0.83
Platelet Vol.	Franke.Hippocampus	Brain	Extern	0.42
Platelet Vol.	Franke.Hippocampus	Liver	Extern	0.11
Platelet Vol.	Franke.Hippocampus	Skeletal_Muscle	Extern	0.55
Platelet Vol.	Franke.Liver	Franke.Muscles	Extern	0.21
Platelet Vol.	Franke.Liver	Franke.Pancreas	Extern	0.95
Platelet Vol.	Franke.Liver	Adipose	Extern	0.89
Platelet Vol.	Franke.Liver	Brain	Extern	0.43
Platelet Vol.	Franke.Liver	Liver	Extern	0.64
Platelet Vol.	Franke.Liver	Skeletal_Muscle	Extern	0.9
Platelet Vol.	Franke.Muscles	Franke.Pancreas	Extern	0.02
Platelet Vol.	Franke.Muscles	Adipose	Extern	0.38
Platelet Vol.	Franke.Muscles	Brain	Extern	0.03
Platelet Vol.	Franke.Muscles	Liver	Extern	0.67
Platelet Vol.	Franke.Muscles	Skeletal_Muscle	Extern	0.66
Platelet Vol.	Franke.Pancreas	Adipose	Extern	0.27
Platelet Vol.	Franke.Pancreas	Brain	Extern	0.27
Platelet Vol.	Franke.Pancreas	Liver	Extern	0.35
Platelet Vol.	Franke.Pancreas	Skeletal_Muscle	Extern	2.3e-03
Platelet Vol.	Adipose	Brain	Extern	0.41
Platelet Vol.	Adipose	Liver	Extern	0.42
Platelet Vol.	Adipose	Skeletal_Muscle	Extern	0.07
Platelet Vol.	Brain	Liver	Extern	0.28
Platelet Vol.	Brain	Skeletal_Muscle	Extern	0.08
Platelet Vol.	Liver	Skeletal_Muscle	Extern	0.34
Triglycerides	Franke.Blood.Cells	Franke.Liver	Extern	0.84
Triglycerides	Franke.Blood.Cells	Franke.Muscles	Extern	0.6
Triglycerides	Franke.Blood.Cells	Franke.Pancreas	Extern	0.19
Triglycerides	Franke.Blood.Cells	Hippocampus	Extern	0.51
Triglycerides	Franke.Blood.Cells	Liver	Extern	0.3
Triglycerides	Franke.Liver	Franke.Muscles	Extern	0.84
Triglycerides	Franke.Liver	Franke.Pancreas	Extern	0.34
Triglycerides	Franke.Liver	Hippocampus	Extern	0.73
Triglycerides	Franke.Liver	Liver	Extern	0.53
Triglycerides	Franke.Muscles	Franke.Pancreas	Extern	0.9
Triglycerides	Franke.Muscles	Hippocampus	Extern	0.17
Triglycerides	Franke.Muscles	Liver	Extern	0.4
Triglycerides	Franke.Pancreas	Hippocampus	Extern	0.16
Triglycerides	Franke.Pancreas	Liver	Extern	0.21
Triglycerides	Hippocampus	Liver	Extern	0.4

References

[1] P. C. Phillips. "Epistasis — the essential role of gene interactions in the structure and evolution of genetic systems". *Nature Reviews Genetics* 9.11 (2008), pp. 855–867.

[2] J. Marchini, P. Donnelly, and L. R. Cardon. "Genome-wide strategies for detecting multiple loci that influence complex diseases". *Nature Genetics* 37.4 (2005), pp. 413–417.

[3] C. C. Cockerham. "An Extension of the Concept of Partitioning Hereditary Variance for Analysis of Covariances among Relatives When Epistasis Is Present". *Genetics* 39.6 (1954), p. 859.

[4] C. R. Henderson. "Best linear unbiased prediction of nonadditive genetic merits in noninbred populations". *Journal of Animal Science* (1985).

[5] J.-L. Jannink. "Identifying Quantitative Trait Locus by Genetic Background Interactions in Association Studies". *Genetics* 176.1 (2007), pp. 553–561.

[6] Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium 2 et al. "A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1." *Nature Genetics* 42.11 (2010), pp. 985–990.

[7] A. A. Brown et al. "Genetic interactions affecting human gene expression identified by variance association mapping." *eLife* 3 (2014), e01381.

[8] G. Hemani et al. "Detection and replication of epistasis influencing transcription in humans." *Nature* 508.7495 (2014), pp. 249–253.

[9] A. I. Young and R. Durbin. "Estimation of Epistatic Variance Components and Heritability in Founder Populations and Crosses". *Genetics* 198.4 (2014), pp. 1405–1416.

[10] J. S. Bloom et al. "Genetic interactions contribute less than additive effects to quantitative trait variation in yeast." *Nature communications* 6.1 (2015), p. 8712.

[11] Y. Jiang and J. C. Reif. "Modeling Epistasis in Genomic Selection". *Genetics* 201.2 (2015), pp. 759–768.

[12] L. Crawford, P. Zeng, S. Mukherjee, and X. Zhou. "Detecting epistasis with the marginal epistasis test in genetic mapping studies of quantitative traits." *PLoS Genetics* 13.7 (2017), e1006869.

[13] D. Steinsaltz, A. Dahl, and K. W. Wachter. "Statistical properties of simple random-effects models for genetic heritability". *Electronic Journal of Statistics* 12.1 (2018), pp. 321–358.

[14] J. H. Moore and S. M. Williams. "Traversing the conceptual divide between biological and statistical epistasis: systems biology and a more modern synthesis". *Bioessays* 27.6 (2005), pp. 637–646.

[15] X. Liu, Y. I. Li, and J. K. Pritchard. "Trans Effects on Gene Expression Can Drive Omnigenic Inheritance". *Cell* 177.4 (2019), 1022–1034.e6.

[16] K. S. Small et al. "Regulatory variants at KLF14 influence type 2 diabetes risk via a female-specific effect on adipocyte size and body composition". *Nature Genetics* 50.4 (2018), pp. 572–580.

[17] M. R. Robinson et al. "Genotype-covariate interaction effects and the heritability of adult body mass index." *Nature Genetics* 49.8 (2017), pp. 1174–1181.

[18] R. E. Peterson et al. “Molecular Genetic Analysis Subdivided by Adversity Exposure Suggests Etiologic Heterogeneity in Major Depression.” *The American journal of psychiatry* 175.6 (2018), pp. 545–554.