

# Computationally efficient methods for estimating co-heritability of multivariate phenotypes using biobank data

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# Outline

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## Co-heritability in family data

- A fundamental question in precision medicine related to comorbidity is to what degree multiple phenotypes share the same genetic etiology.
- Using family history reports of disease in relatives from probands, existing studies (e.g., UK biobank, All of Us, Washington Heights-Inwood Community Aging Project) have shown substantial co-variation between traits.
- The phenotypic co-variation can be contributed by genetic co-inheritance and shared environmental factors.
- It is of interest to study the genetic co-heritability and environmental correlation for a large number of phenotypes.

## Existing literature to study single-trait heritability

- Shared frailty models with a random effect in each family (Chen et al. 2009, Graber-Naidich et al. 2011, Forfine et al. 2013).
- Copula models accounting for the correlation between family members (Hsu et al. 2018).
- Structural equation modeling accounting for multiple types of familial correlation (Munoz et al. 2016, Wang et al. 2020).
- A transformation model for time-to-event outcomes when the kinship is not completely known (Liang et al. 2019).

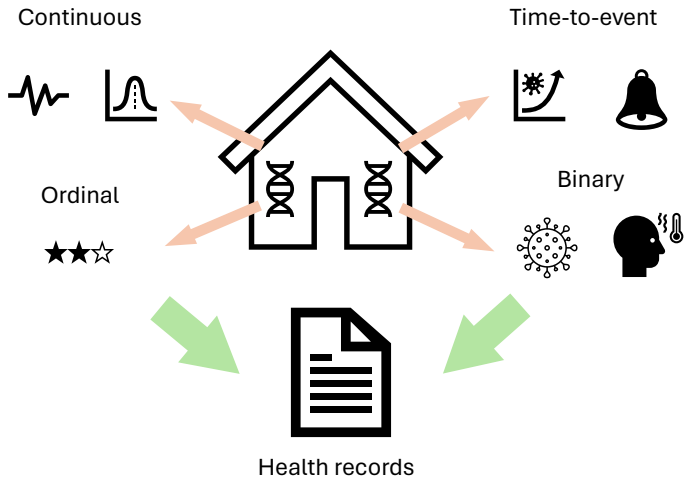
## Phenotypic co-variation

- Estimating co-heritability requires integrating multiple phenotypes.
- The co-variation of two phenotypes in two subjects are attributed to two sources:
  - (1) These two phenotypes share the same underlying genetic factors.
  - (2) These two subjects share the same environmental factors.

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- The co-variation of two phenotypes in two subjects are attributed to two sources:
  - (1) These two phenotypes share the same underlying genetic factors.
  - (2) These two subjects share the same environmental factors.
- Linear mixed models to estimate the polygenic effects for a pair of phenotypes (Lee et al. 2012).
- A Haseman-Elston estimator based on the regression residuals for a pair of phenotypes considering kinship correlation (Elgart et al. 2022).

# Phenotypic co-variation





## Challenges to study co-heritability

- Current statistical methods are designed to estimate heritability in a single data type (continuous). Phenotypes in different data types cannot be easily incorporated in a single model.
- The number of phenotypes and the sample size are both very large, resulting in high-dimensional covariance matrix.
- It is essential to account for the multi-level structure of dependence between phenotypes within a subject and the genetic/environmental correlation between subjects within a family.

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## Data structure

- In the biobank data, suppose there are  $n$  families and  $n_i$  members in the  $i$ th family.
- We measure  $K$  phenotypes which may be recorded in different data types (continuous, binary, ordinal, time-to-event).
- Let  $Y_{ijk}$  be the measurement for the  $k$ th phenotype on subject  $j$  in the  $i$ th family.
- Let  $\mathbf{X}_{ij}$  be the covariates,  
 $e_i$  be the environmental risk factor, and  
 $\epsilon_{ijk}$  be the genetic risk factor for the  $k$ th phenotype of subject  $j$  in the  $i$ th family.

# Model

- To address these challenges, we propose semiparametric joint modeling with latent polygenic effects governed by a copula model.
- For continuous, binary or ordinal outcomes, assume an exponential distribution family,

$$f(Y_{ijk} \mid \mathbf{X}_{ij}, e_i, \epsilon_{ijk}) = \exp\{\phi_{ijk}(\boldsymbol{\eta}_k)^\top \mathbf{T}(Y_{ijk}) - A(\phi_{ijk}) + c(Y_{ijk})\},$$

where  $\phi_{ijk}$  is a function of  $\mathbf{X}_{ij}$ ,  $e_i$  and  $\epsilon_{ijk}$  with unknown parameter  $\boldsymbol{\eta}_k$ .

- For time-to-event outcomes with right censoring, assume a proportional hazards model,

$$\Lambda_{ijk}(t \mid \mathbf{X}_{ij}, e_i, \epsilon_{ijk}) = \Lambda_k(t) \exp(\boldsymbol{\alpha}_k^\top \mathbf{X}_{ij} + \theta_k e_i + \epsilon_{ijk}),$$

where  $\Lambda_k(t)$  is the unknown baseline hazard function. We observe  $Y_{ijk} = (T_{ijk} \wedge C_{ijk}, I\{T_{ijk} \leq C_{ijk}\})$  with  $C_{ijk}$  being the censoring time.

## Model: examples

- Continuous  $Y_{ijk}$ ,

$$Y_{ijk} = \alpha_k^\top \mathbf{X}_{ij} + \theta_k e_i + \epsilon_{ijk} + u_{ijk}.$$

- Ordinal (including binary)  $Y_{ijk}$ , assuming a latent variable  $Z_{ijk}$  with

$$Z_{ijk} = \alpha_k^\top \mathbf{X}_{ij} + \theta_k e_i + \epsilon_{ijk} + u_{ijk},$$

where  $u_{ijk} \sim N(0, 1)$ , and  $Y_{ijk} = l$  if  $\delta_{k,l-1} < Z_{ijk} \leq \delta_{k,l}$ .

- Time-to-event  $T_{ijk}$ ,

$$H(T_{ijk}) = \alpha_k^\top \mathbf{X}_{ij} + \theta_k e_i + \epsilon_{ijk} + u_{ijk},$$

- There is a linear term dominating the distribution:

$$\alpha_k^\top \mathbf{X}_{ij} + \theta_k e_i + \epsilon_{ijk} + u_{ijk}.$$

## Structure of covariance

- Let  $\mathbf{\Gamma}$  be a  $K \times K$  matrix representing the co-heritability of  $K$  phenotypes.
- Let  $\mathbf{G}_i$  be the known  $n_i \times n_i$  kinship matrix of the  $i$ th family. For example,

$$\mathbf{G}_i = \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix}$$

in the family with a parent and a child.

- The environmental risk factor  $e_i \sim N(0, 1)$  independent across families.
- Let  $\boldsymbol{\epsilon}_{ik} = (\epsilon_{i1k}, \dots, \epsilon_{in_i k})^\top$  be the  $n_i \times 1$  vector of genetic risk factors in the  $i$ th family,

$$\boldsymbol{\epsilon}_i = (\boldsymbol{\epsilon}_{i1}^\top, \dots, \boldsymbol{\epsilon}_{ik}^\top)^\top \sim N(\mathbf{0}, \mathbf{\Gamma} \otimes \mathbf{G}_i).$$

- For two phenotypes  $(k, k')$  and two members  $(j, j')$  in the same family,

$$\text{cov}(\epsilon_{ijk}, \epsilon_{ij'k'}) = \gamma_{kk'} g_{jj'}.$$

## Parameter of interest: heritability

- Assuming additive genetic, environmental and error term, the total variation

$$\sigma_k^2 = \theta_k^2 + \gamma_{kk} + \text{var}(u_{ijk}).$$

- The (narrow-sense) heritability:  $h_k^2 = \gamma_{kk}/\sigma_k^2$ .
- The environmental effect:  $\xi_k^2 = \theta_k^2/\sigma_k^2$ .

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- The environmental effect:  $\xi_k^2 = \theta_k^2/\sigma_k^2$ .
- The total variation contributed by genetic and environmental effects

$$\tilde{\sigma}_k^2 = \theta_k^2 + \gamma_{kk}.$$

- The fraction of genetic effect:  $\rho_k = \gamma_{kk}/\tilde{\sigma}_k^2$ .
- The fraction of environmental effect:  $\zeta_k = \theta_k^2/\tilde{\sigma}_k^2$ .



## Parameter of interest: co-heritability

- Genetic correlation for a pair of phenotypes  $\gamma_{kk'}$  (off-diagonal element of  $\mathbf{\Gamma}$ ).
- The genetic co-heritability:  $h_{kk'} = \gamma_{kk'} / \sigma_k \sigma_{k'}$ .
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## Estimation: maximizing the full likelihood

- Ideally, we can apply the maximum likelihood estimation to estimate parameters.
- The full likelihood function of all observed data  $\mathcal{O}$

$$L(\mathcal{O}) = \prod_{i=1}^n \int_{e_i} \int_{\epsilon_i} f(e_i) f(\epsilon_i; \Gamma) \prod_{j=1}^{n_i} \prod_{k=1}^K f(Y_{ijk} \mid \mathbf{X}_{ij}, e_i, \epsilon_{ijk}; \boldsymbol{\eta}_k) d\epsilon_i de_i.$$

- Note that the genetic risk factor  $\epsilon_i$  is an  $n_i K$ -dimensional vector.
- It is almost impossible to evaluate the likelihood by numerical integration.

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- Note that the genetic risk factor  $\epsilon_i$  is an  $n_i K$ -dimensional vector.
- It is almost impossible to evaluate the likelihood by numerical integration.
- To address this issue, we propose a two-stage procedure to estimate parameters.
- We first estimate  $\boldsymbol{\eta}_k$  and diagonal elements of  $\mathbf{\Gamma}$  by maximizing the marginal likelihood for phenotype  $k$ . Then we estimate off-diagonal elements of  $\mathbf{\Gamma}$  by solving estimating equations for each pair of phenotypes.

## Maximizing the marginal likelihood

- In the first stage, we maximize the marginal likelihood for phenotype  $k$ .
- The marginal likelihood for the  $k$ th phenotype

$$L_k(\mathcal{O}_k; \boldsymbol{\eta}_k) = \prod_{i=1}^n \int_{\mathbf{e}_i} \int_{\boldsymbol{\epsilon}_{ik}} f(\mathbf{e}_i) f(\boldsymbol{\epsilon}_{ik}; \boldsymbol{\gamma}_{kk}) \prod_{j=1}^{n_i} f(Y_{ijk} \mid \mathbf{X}_i, \mathbf{e}_i, \boldsymbol{\epsilon}_{ijk}; \boldsymbol{\eta}_k) d\boldsymbol{\epsilon}_{ik} d\mathbf{e}_i.$$

- The number of integration is reduced to  $n_i + 1$  from  $n_i K + 1$ .

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- The number of integration is reduced to  $n_i + 1$  from  $n_i K + 1$ .
- We apply the EM algorithm to estimate  $\boldsymbol{\eta}_k$  and  $\gamma_{kk}$  under the exponential distribution family.
- The complete-data likelihood

$$L_{k,\text{com}}(\mathcal{O}_k^*; \boldsymbol{\eta}_k) = \prod_{i=1}^n f(\mathbf{e}_i) f(\boldsymbol{\epsilon}_{ik}; \gamma_{kk}) \prod_{j=1}^{n_i} f(Y_{ijk} \mid \mathbf{X}_i, \mathbf{e}_i, \boldsymbol{\epsilon}_{ijk}; \boldsymbol{\eta}_k).$$

## Maximizing the marginal likelihood

- In the E step, we evaluate the conditional expectation of any function  $Q(\mathcal{O}_{ik}^*)$  given observed data and current estimates,

$$\hat{E}(Q(\mathcal{O}_{ik}^*) \mid \mathcal{O}_{ik}; \boldsymbol{\eta}_k^{(m)}) = \frac{\int_{\mathbf{e}_i} \int_{\boldsymbol{\epsilon}_{ik}} f(\mathbf{e}_i) f(\boldsymbol{\epsilon}_{ik}; \hat{\boldsymbol{\gamma}}_{kk}^{(m)}) f(Y_{ijk} \mid \mathbf{X}_{ij}, \mathbf{e}_i, \boldsymbol{\epsilon}_{ijk}; \boldsymbol{\eta}_k^{(m)}) Q(\mathcal{O}_{ik}^*) d\boldsymbol{\epsilon}_{ik} d\mathbf{e}_i}{\int_{\mathbf{e}_i} \int_{\boldsymbol{\epsilon}_{ik}} f(\mathbf{e}_i) f(\boldsymbol{\epsilon}_{ik}; \hat{\boldsymbol{\gamma}}_{kk}^{(m)}) f(Y_{ijk} \mid \mathbf{X}_{ij}, \mathbf{e}_i, \boldsymbol{\epsilon}_{ijk}; \boldsymbol{\eta}_k^{(m)}) d\boldsymbol{\epsilon}_{ik} d\mathbf{e}_i}.$$

- In the M step, we maximize the complete-data log-likelihood. Specifically,

$$\begin{aligned} (\theta_k^{(m+1)})^2 &= \frac{1}{n} \sum_{i=1}^n \hat{E}(e_i^2 \mid \mathcal{O}_{ik}; \boldsymbol{\eta}_k^{(m)}), \\ \gamma_{kk}^{(m+1)} &= \frac{1}{\sum_{i=1}^n n_i} \sum_{i=1}^n \hat{E}(\boldsymbol{\epsilon}_{ik}^\top \mathbf{G}_i^{-1} \boldsymbol{\epsilon}_{ik} \mid \mathcal{O}_{ik}; \boldsymbol{\eta}_k^{(m)}). \end{aligned}$$

## Likelihood for a pair of phenotypes

- In the second stage, we estimate the off-diagonal elements of  $\mathbf{\Gamma}$ .
- The observed-data likelihood for the  $(k, k')$  pair of phenotypes

$$L_{k,k'}(\mathcal{O}_k, \mathcal{O}_{k'}) = \prod_{i=1}^n \int_{\mathbf{e}_i} \int_{(\boldsymbol{\epsilon}_{ik}, \boldsymbol{\epsilon}_{ik'})} f(\mathbf{e}_i) f(\boldsymbol{\epsilon}_{ik}, \boldsymbol{\epsilon}_{ik'}; \gamma_{kk}, \gamma_{k'k'}, \gamma_{kk'}) \\ \prod_{j=1}^{n_i} f(Y_{ijk} \mid \mathbf{X}_{ij}, \mathbf{e}_i, \boldsymbol{\epsilon}_{ijk}; \boldsymbol{\eta}_k) f(Y_{ijk'} \mid \mathbf{X}_{ij}, \mathbf{e}_i, \boldsymbol{\epsilon}_{ijk'}; \boldsymbol{\eta}_{k'}) d(\boldsymbol{\epsilon}_{ik}, \boldsymbol{\epsilon}_{ik'}) d\mathbf{e}_i.$$

- There is only one known parameter  $\gamma_{kk'}$  in the likelihood if plugging in the first-stage estimates.
- The number of integration is  $2n_i + 1$ , which can be further reduced.



## Pairwise estimating equations

- We collapse eligible member pairs. Notice that

$$\frac{\partial}{\partial \gamma_{kk'}} E \left\{ \log \int_{e_i} \int_{(\epsilon_{ijk}, \epsilon_{ij'k'})} f(e_i) f(\epsilon_{ijk}, \epsilon_{ij'k'}; \gamma_{kk}, \gamma_{k'k'}, \gamma_{kk'}) \right. \\ \left. f(Y_{ijk} \mid \mathbf{X}_{ij}, e_i, \epsilon_{ijk}; \alpha_k, \theta_k) f(Y_{ij'k'} \mid \mathbf{X}_{ij'}, e_i, \epsilon_{ij'k'}; \alpha_{k'}, \theta_{k'}) d(\epsilon_{ijk}, \epsilon_{ij'k'}) de_i \right\} = 0.$$

- So we can estimate  $\gamma_{kk'}$  solve the estimating equation  $\sum_{i=1}^n U_{i,kk'}(\gamma_{kk'}; \hat{\eta}_k, \hat{\eta}_{k'}) = 0$ , where

$$U_{i,kk'}(\gamma_{kk'}; \hat{\eta}_k, \hat{\eta}_{k'}) = \frac{\partial}{\partial \gamma_{kk'}} \sum_{(j,j') \in \mathcal{J}_i} \log \int_{e_i} \int_{(\epsilon_{ijk}, \epsilon_{ij'k'})} f(e_i) f(\epsilon_{ijk}, \epsilon_{ij'k'}; \hat{\gamma}_{kk}, \hat{\gamma}_{k'k'}, \gamma_{kk'}) \\ f(Y_{ijk} \mid \mathbf{X}_{ij}, e_i, \epsilon_{ijk}; \hat{\eta}_k) f(Y_{ij'k'} \mid \mathbf{X}_{ij'}, e_i, \epsilon_{ij'k'}; \hat{\eta}_{k'}) d(\epsilon_{ijk}, \epsilon_{ij'k'}) de_i.$$

- We only need to perform 3 times of integration in each family.

## Variance estimation

- For  $k$  in the exponential distribution family, estimating the variance by plugging in influence function is straightforward.
- For time-to-event  $k$ , we use the profile likelihood to estimate the variance.
- The profile log-likelihood for phenotype  $k$

$$pl(\mathcal{O}_k; \beta_k) = \max_{\Lambda_k \in \mathcal{S}_k} \sum_{i=1}^n \ell_{ik}(\mathcal{O}_{ik}; \beta_k, \Lambda_k).$$

- The score function of the parametric part can be evaluated by

$$\hat{\mathbf{S}}_k(\mathcal{O}_{ik}; \hat{\beta}_k) = \frac{1}{h_n} \begin{pmatrix} pl_i(\mathcal{O}_{ik}; \hat{\beta}_k + h_n \mathbf{e}_1) - pl_i(\mathcal{O}_{ik}; \hat{\beta}_k) \\ \vdots \\ pl_i(\mathcal{O}_{ik}; \hat{\beta}_k + h_n \mathbf{e}_{p_k}) - pl_i(\mathcal{O}_{ik}; \hat{\beta}_k) \end{pmatrix},$$

## Scale up to large data

- In biobank scale data, both the family size  $n_i$  and the number of families  $n$  are very large.
- To deal with the large family size  $n_i$ , we can select nuclear families from the whole sample (Gao et al. 2023).
- To deal with the large number of families  $n$ , we apply the “divide-and-conquer” strategy.
- We estimate the parameters in each block, and then aggregate them by inverse variance weighting (IVW).

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# UK biobank data



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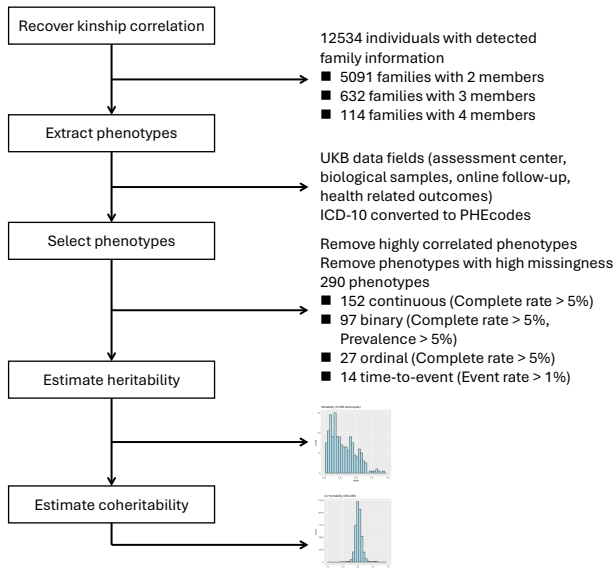
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+ Touchscreen	396	<a href="#">Level 2</a>
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# Data processing



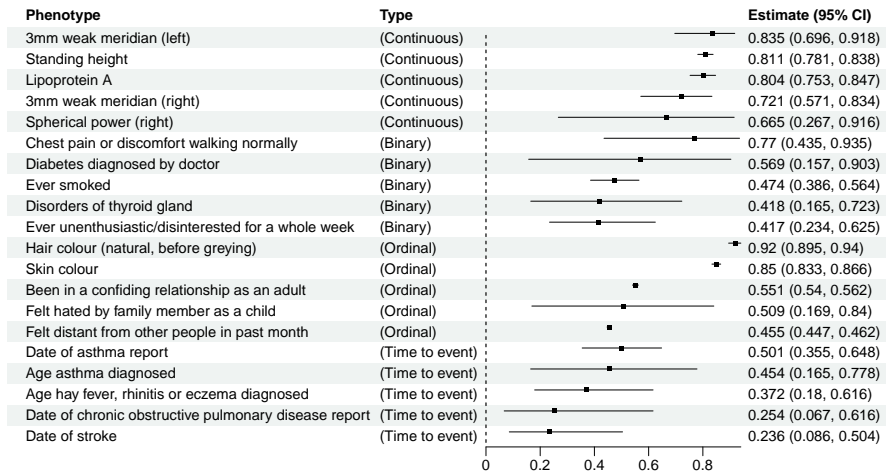
## Continuous phenotypes: single-trait heritability

- Our estimates are consistent with existing findings.

Table: Estimated heritability (%) for continuous phenotypes

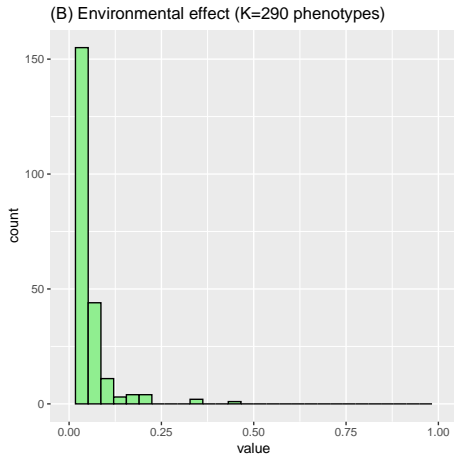
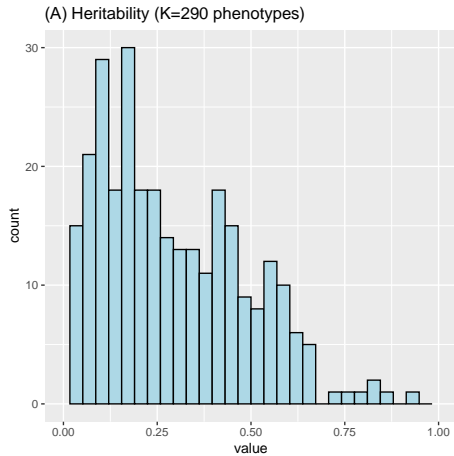
Phenotype	Estimate (CI)	Estimates in literature
Height	81.4 (74.3–89.0)	20–80
BMI	55.6 (49.3–61.8)	31–90
Diastolic blood pressure	32.7 (27.1–38.8)	17–40
Systolic blood pressure	33.7 (28.0–40.0)	17–62
Red blood cells count	44.8 (39.1–50.8)	30–70
White blood cells count	35.0 (29.0–41.6)	14–49

# Single trait: heritability for different data types

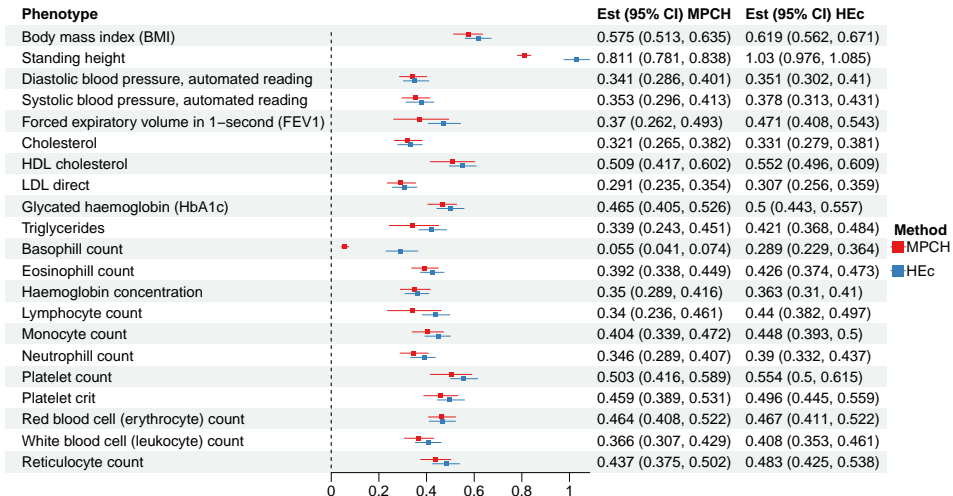




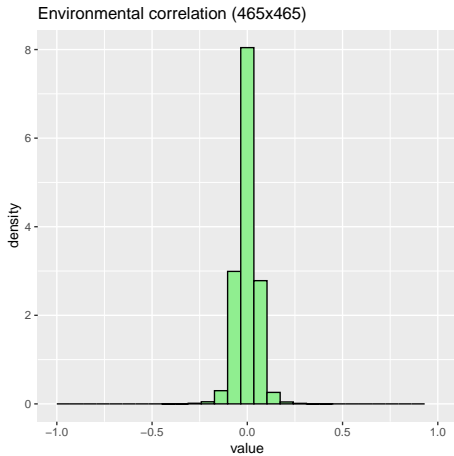
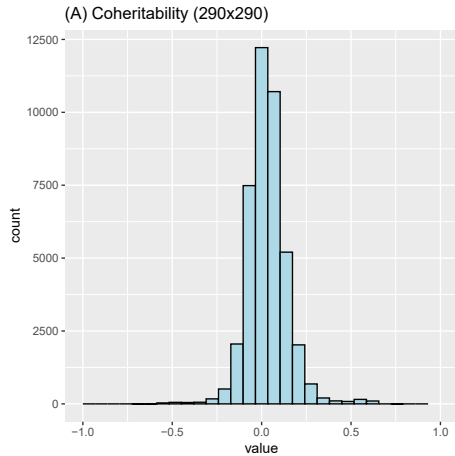
# Single trait: heritability and environmental effect



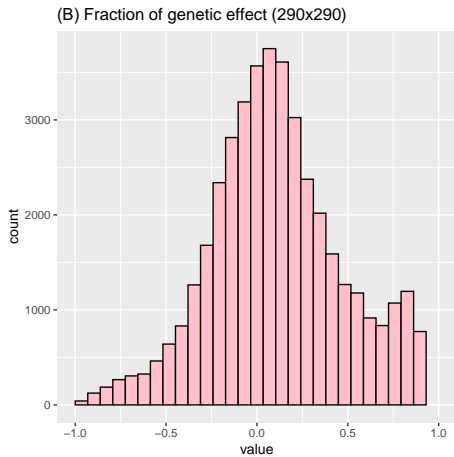
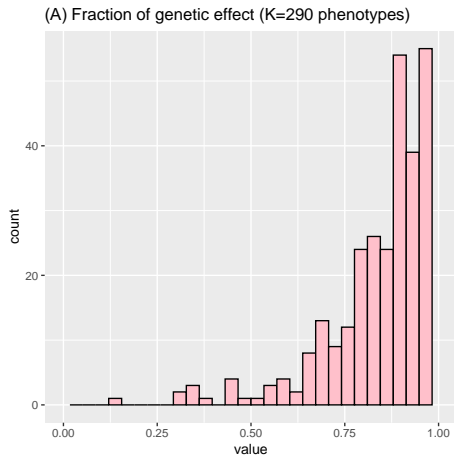
# Single trait: heritability compared with HEc



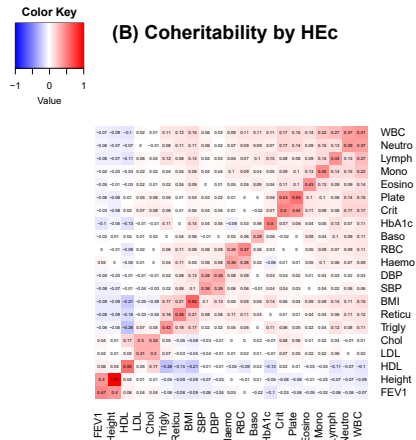
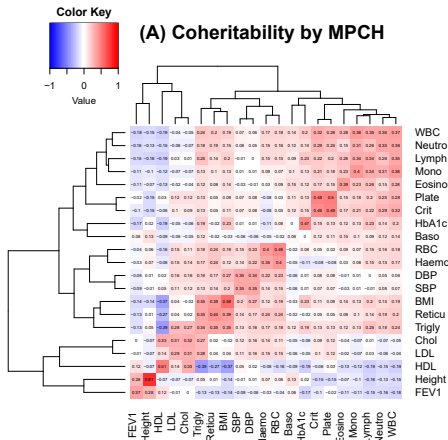
# Co-heritability and environmental correlation



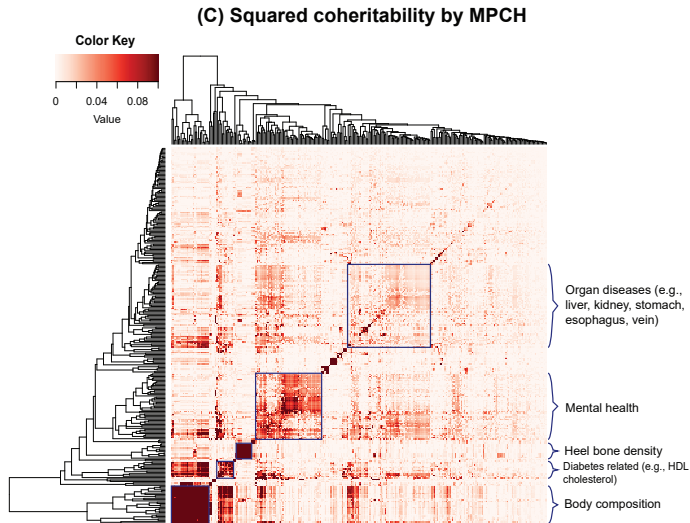
# Fraction of genetic effect in phenotypic correlation



# Co-heritability compared with HEc



# Co-heritability for all phenotypes



## Summary of UK biobank data analysis

- We find that some phenotypes share very high genetic co-heritability (which can be seen from clusters).
- The environmental correlation is generally small compared to the genetic co-heritability.
- This may be because that the family relation in the UK biobank data is “derived”.
- Some binary and time-to-event phenotypes have very low incidences, rendering the high variance of the estimated co-heritability.

## Summary of the methods

- Through modeling with random effects, phenotypes in different data types are unified to the same scale.
- We propose a computational efficient method to estimate the co-heritability of phenotypes using biobank data.
- The first stage estimates the single-trait parameters by likelihood methods, which maintains as much efficiency as possible.
- The second stage estimation only involves a single parameter, so it is computational efficient.
- The asymptotic properties are established based on influence functions.
- Utilizing modern parallel computation devices, the framework is useful to handle a huge number of phenotypes.



## Acknowledgements

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