

Disclosure

I do not have any relationships to report within the last 24 months with ACCME defined ineligible companies.

I will not be discussing unlabeled/investigational uses of medical devices or pharmaceuticals during this presentation.

Pleiotropic heritability quantifies the shared genetic variance of common diseases

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Outline

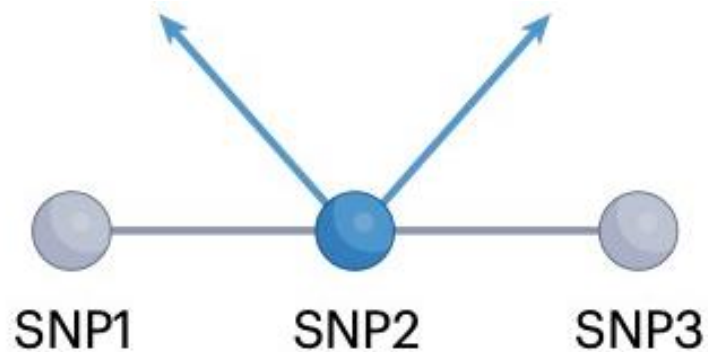
- **Background: Common diseases are highly pleiotropic**
- Defining and estimating pleiotropic heritability
- Results for 15 diseases from the UK Biobank
- Pleiotropic heritability vs. pleiotropic phenotypic variance

Common diseases are highly pleiotropic

- **Pleiotropy:** one genetic polymorphism affects multiple traits

Trait 1:
(e.g. depression)

Trait 2:
(e.g. hypertension)



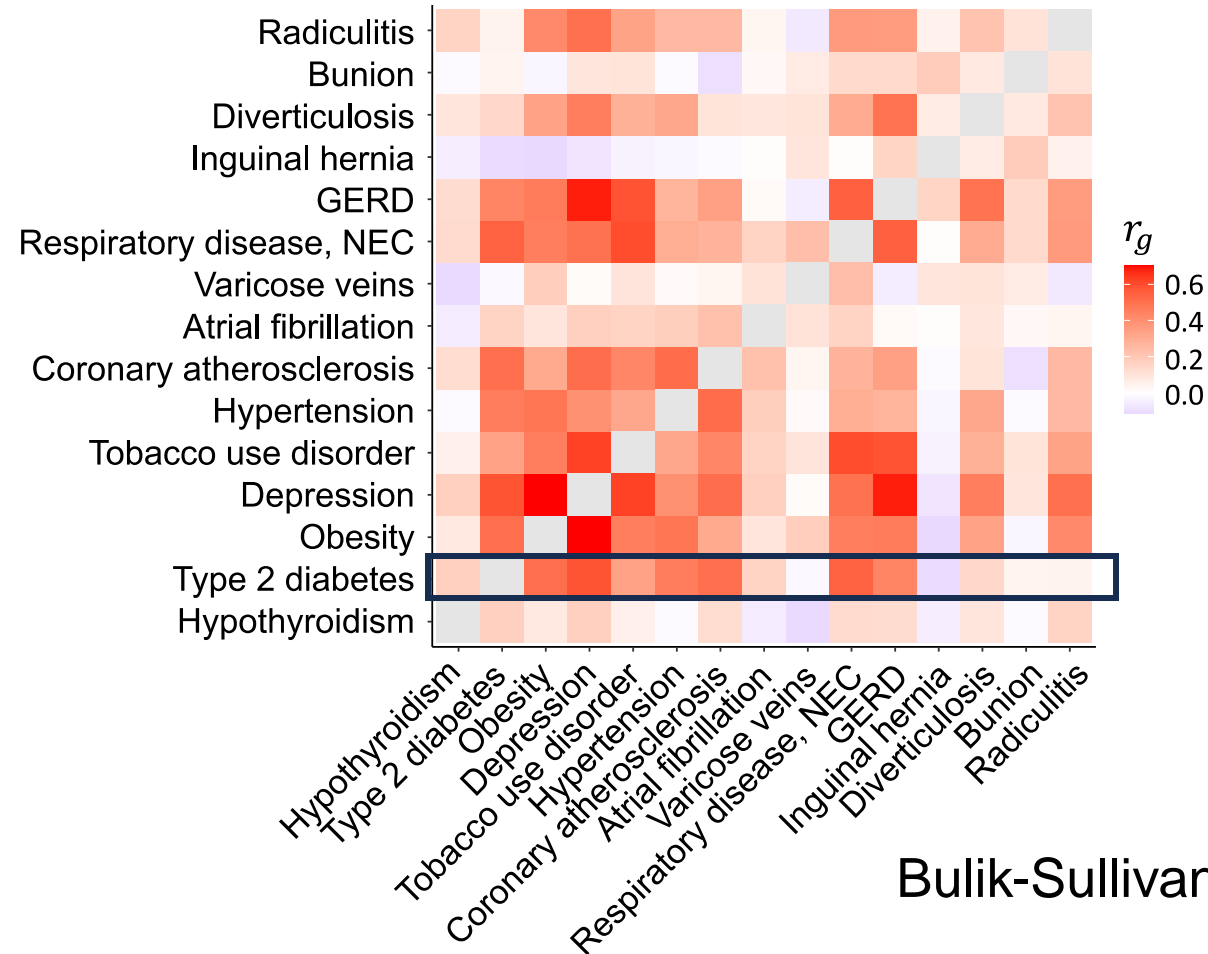
(Mackay et al. 2024 Nat Rev Genet)

- Most studies focus on genetic correlations with each auxiliary disease in turn.
- The overall contribution of pleiotropy to disease architectures is unknown.

(Watanabe et al. 2019 *Nat Genet*)

Common diseases are highly pleiotropic

- Shared genetic correlations of common diseases



Bulik-Sullivan et al. 2015b *Nat Genet*

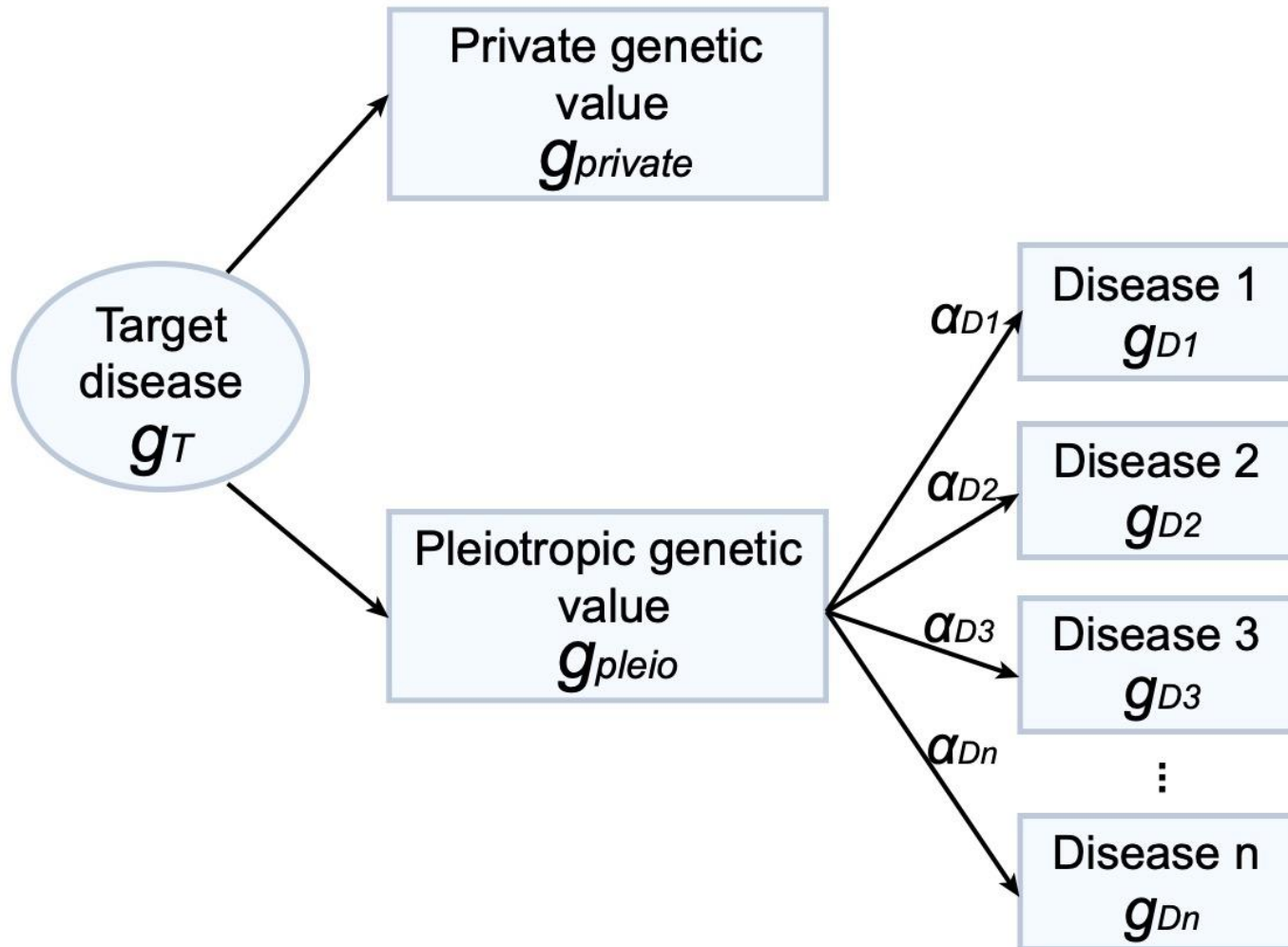
- Goal:** To quantify the genetic variance of a target disease that is shared with a specific set of auxiliary diseases

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- Background: Common diseases are highly pleiotropic
- **Defining and estimating pleiotropic heritability**
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Definition of pleiotropic heritability

- The proportion of target disease variance explained by any linear combination of the genetic values of the auxiliary diseases



$$g_T = g_{private} + \sum \alpha_D g_D$$

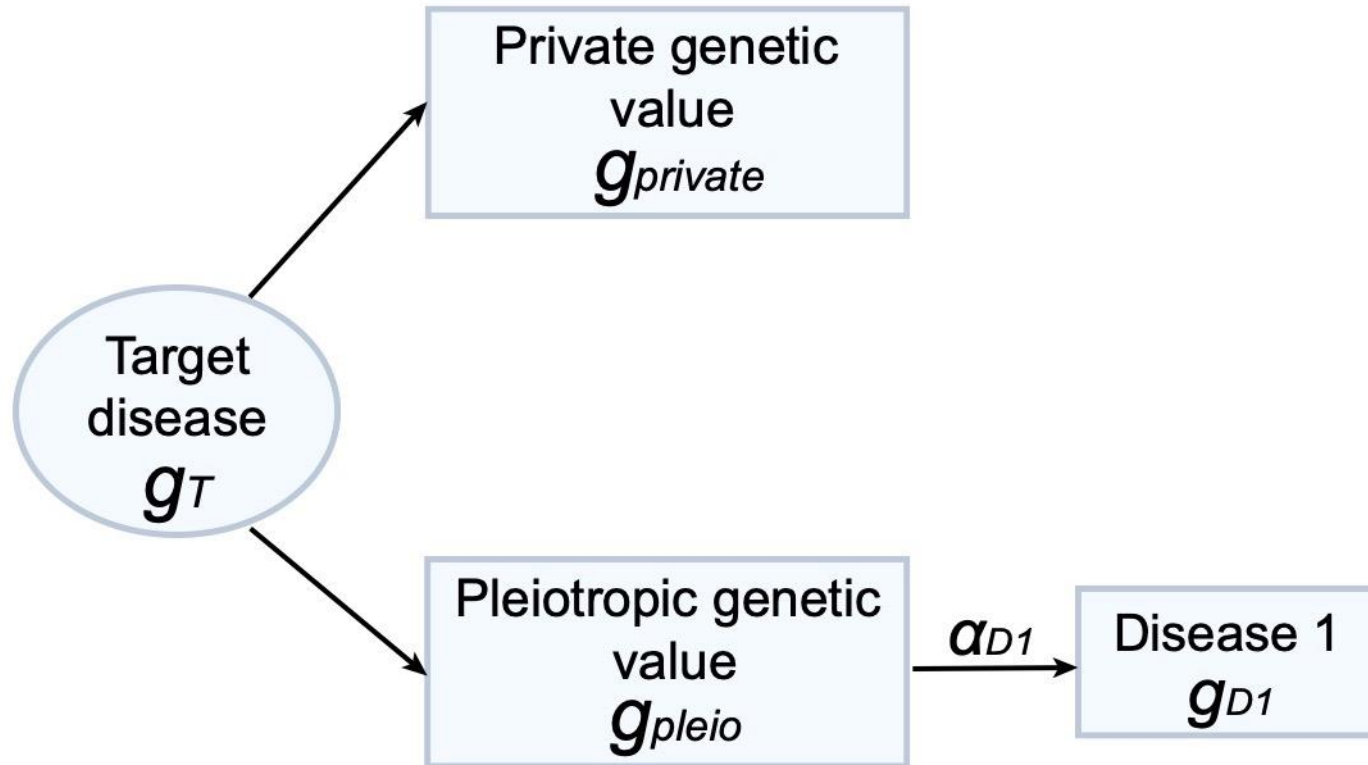
$$h^2_{pleio} = var(\sum \alpha_D g_D)$$

$(D = 1, 2, \dots, n)$

g : genetic value
 T : target disease
 D_1, \dots, D_n : auxiliary diseases
 $\alpha_{D1}, \dots, \alpha_{Dn}$: weights of diseases

Estimation of pleiotropic heritability

- One target disease – **one** auxiliary disease:



$$g_T = g_{private} + \alpha_{D1} g_{D1}$$

Objective function:

$$\alpha_{D1} = \min_{\alpha} E_g [(g_T - \alpha_{D1} g_{D1})^2]$$

$$\begin{aligned} h^2_{pleio} &= var(\alpha_{D1} g_{D1}) \\ &= r^2_{g_T, D1} * h^2_T \end{aligned}$$

Estimation of pleiotropic heritability

- One target disease – **multiple** auxiliary diseases:

genetic covariance matrix Σ_g :

h^2_T	$\text{Cov}(g_T, g_{D1})$	$\text{Cov}(g_T, g_{D2})$...	$\text{Cov}(g_T, g_{Dn})$
$\text{Cov}(g_T, g_{D1})$	h^2_{D1}	$\text{Cov}(g_{D1}, g_{D2})$...	$\text{Cov}(g_{D1}, g_{Dn})$
$\text{Cov}(g_T, g_{D2})$	$\text{Cov}(g_{D1}, g_{D2})$	h^2_{D2}	...	$\text{Cov}(g_{D2}, g_{Dn})$
\vdots	\vdots	\vdots	\ddots	\vdots
$\text{Cov}(g_T, g_{Dn})$	$\text{Cov}(g_{D1}, g_{Dn})$	$\text{Cov}(g_{D2}, g_{Dn})$...	h^2_{Dn}

Estimation of pleiotropic heritability

- One target disease – **multiple** auxiliary diseases:

genetic covariance matrix Σg :

$$g_T = \Sigma \alpha_D g_D + g_{private}$$

Objective function:

$$\alpha = \min_{\alpha} E_g [(g_T - \Sigma \alpha_D g_D)^2]$$

$$h^2_{pleio} = var(\Sigma \alpha_D g_D)$$

$$= E[g_D g_T]^T Cov[g_D]^{-1} E[g_D g_T]$$



h^2_T	Cov (g_T, g_{D1})	Cov (g_T, g_{D2})	...	Cov (g_T, g_{Dn})
Cov (g_T, g_{D1})	h^2_{D1}	Cov (g_{D1}, g_{D2})	...	Cov (g_{D1}, g_{Dn})
Cov (g_T, g_{D2})	Cov (g_{D1}, g_{D2})	h^2_{D2}	...	Cov (g_{D2}, g_{Dn})
\vdots	\vdots	\vdots	\ddots	\vdots
Cov (g_T, g_{Dn})	Cov (g_{D1}, g_{Dn})	Cov (g_{D2}, g_{Dn})	...	h^2_{Dn}

- Standard error was evaluated via genomic block-jackknife

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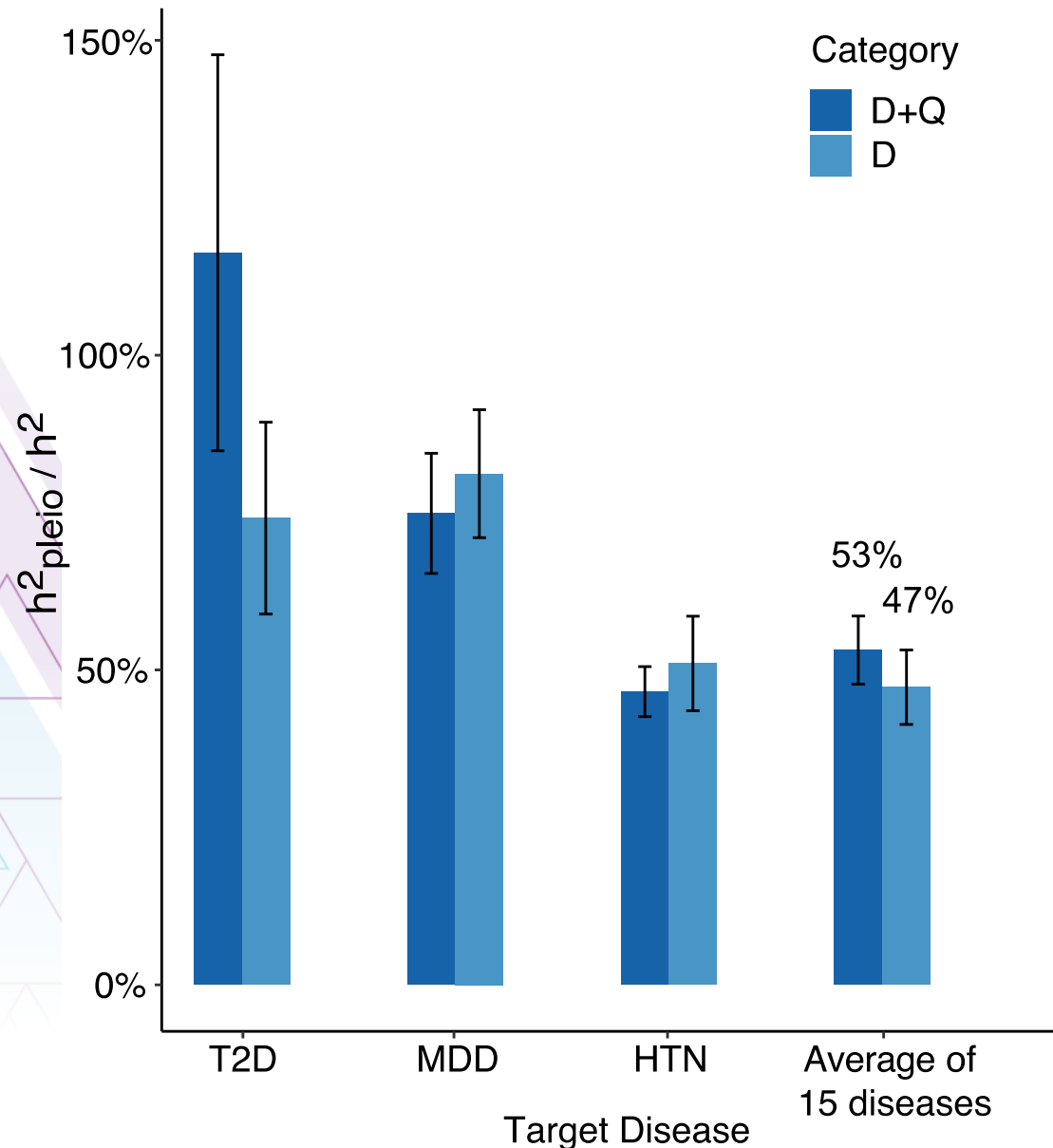
- Background: Common diseases are highly pleiotropic
- Defining and estimating pleiotropic heritability
- **Results for 15 diseases from the UK Biobank**
- Pleiotropic heritability vs. pleiotropic phenotypic variance

Target Disease Selection

- Select 15 highly heritable diseases with prevalence > 1% & heritability z-score > 6
 - Distributed across 7 disease systems defined by Phecode category
 - $r_g^2 < 0.5$

Disease phenotype	Category	Prevalence	Observed-scale heritability (SE)
Hypothyroidism	Endocrine/metabolic	5%	0.089 (0.014)
Type 2 diabetes	Endocrine/metabolic	6%	0.043 (0.006)
Obesity	Endocrine/metabolic	14%	0.046 (0.005)
Depression	Mental disorders	14%	0.030 (0.004)
Tobacco use disorder	Mental disorders	5%	0.064 (0.008)
Hypertension	Circulatory system	37%	0.132 (0.008)
Coronary atherosclerosis	Circulatory system	8%	0.056 (0.006)
Atrial fibrillation	Circulatory system	5%	0.053 (0.008)
Varicose veins	Circulatory system	7%	0.051 (0.008)
Respiratory disease, NEC	Respiratory	24%	0.029 (0.004)
GERD	Digestive	17%	0.035 (0.004)
Inguinal hernia	Digestive	7%	0.042 (0.007)
Diverticulosis	Digestive	9%	0.026 (0.004)
Bunion	Musculoskeletal	5%	0.059 (0.009)
Radiculitis	Symptoms	10%	0.023 (0.004)

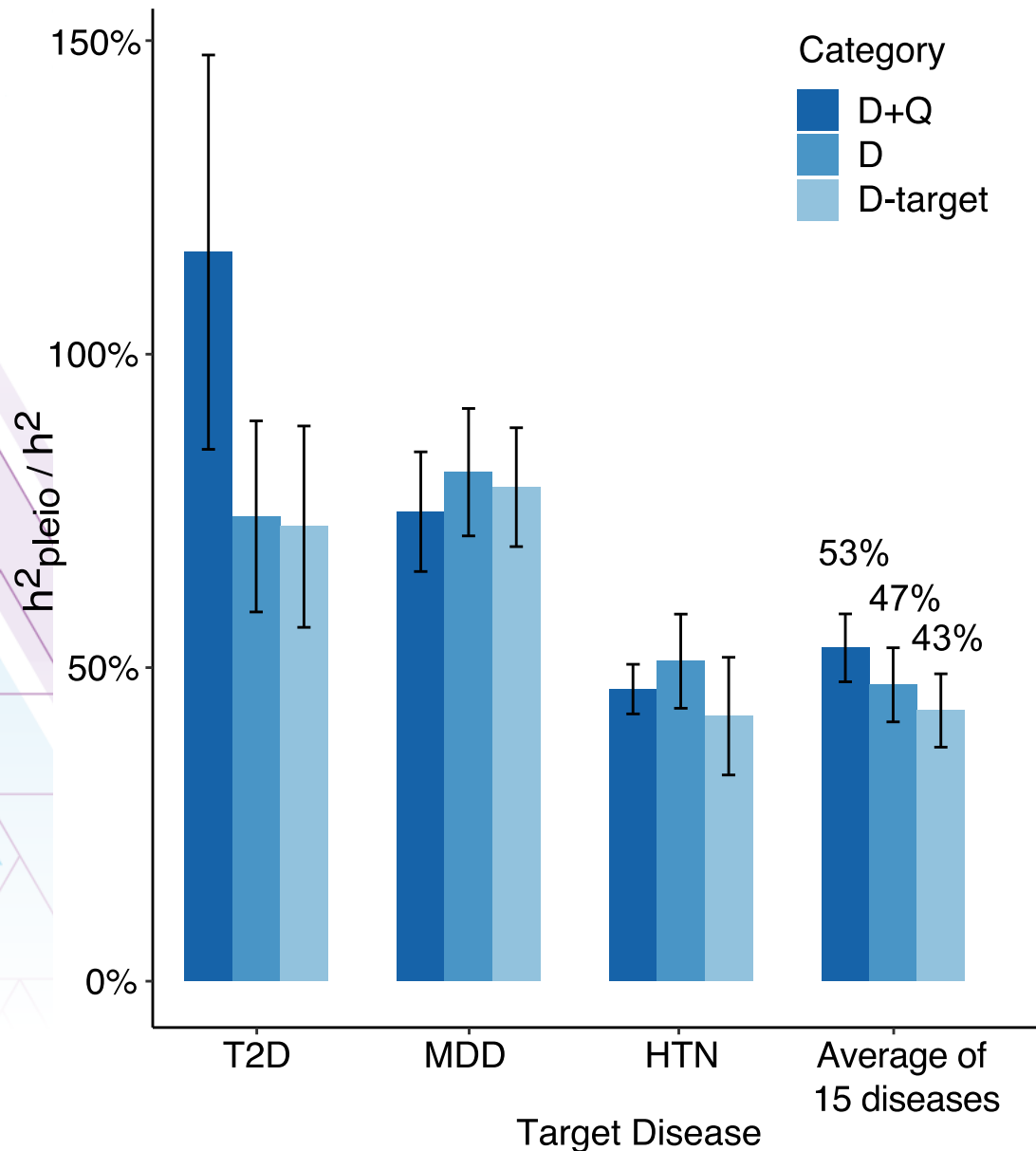
More than half of heritability is pleiotropic



Compare h^2_{pleio} to h^2 : h^2_{pleio} / h^2

- **D+Q:** (14 auxiliary diseases + 16 quantitative traits):
average = 53%, s.e. = 5.2%
- **D:** (14 auxiliary diseases):
average = 47%, s.e. = 5.9%

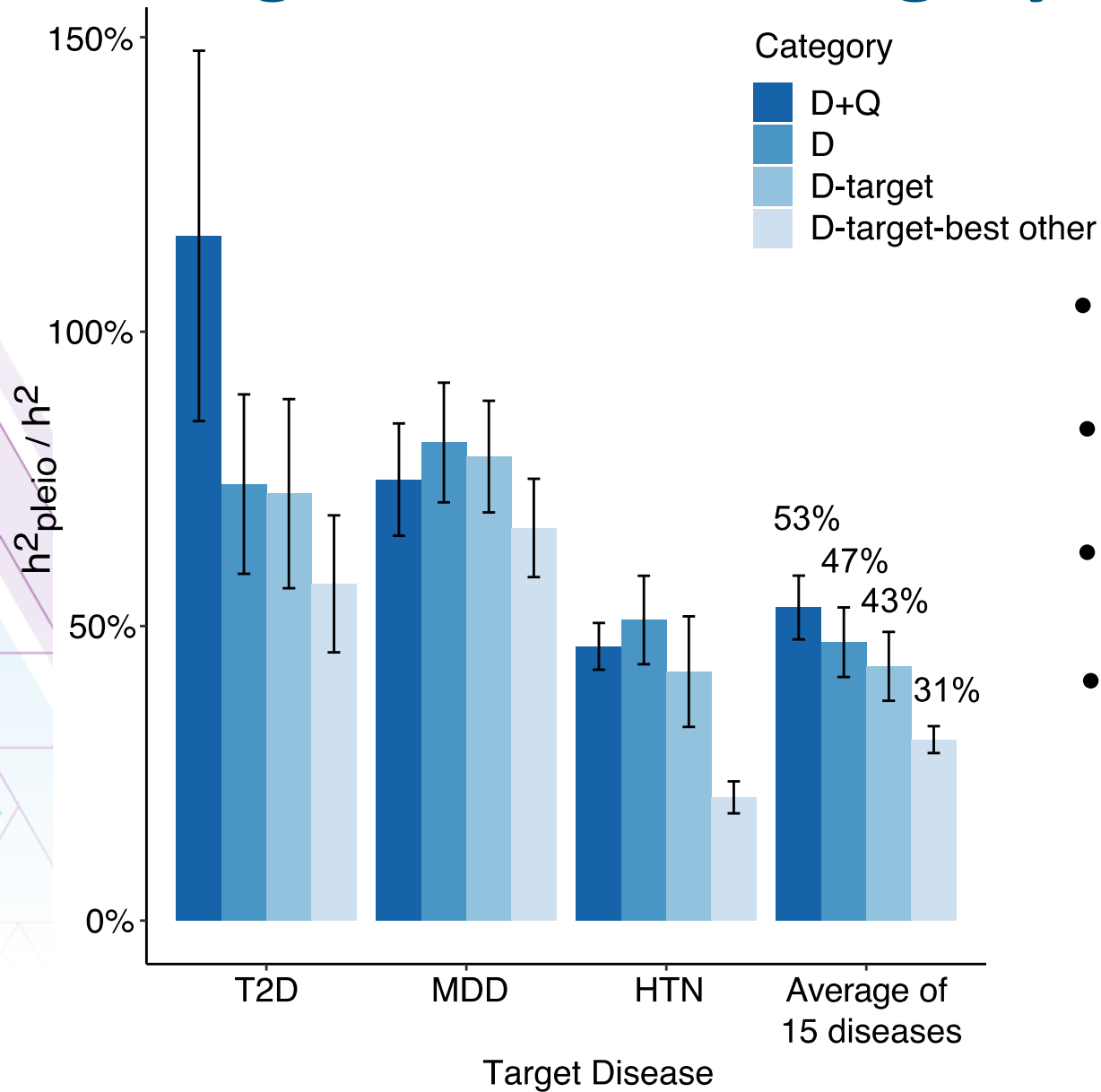
Most pleiotropic heritability remains even after removing target Phecode category



Compare h^2_{pleio} to h^2 : h^2_{pleio} / h^2

- **D+Q**: average = 53%, s.e. = 5.2%
- **D**: average = 47%, s.e. = 5.9%
- **D-target**: average = 43%, s.e. = 5.9%

Most pleiotropic heritability remains even after removing target Phecode category and best other category

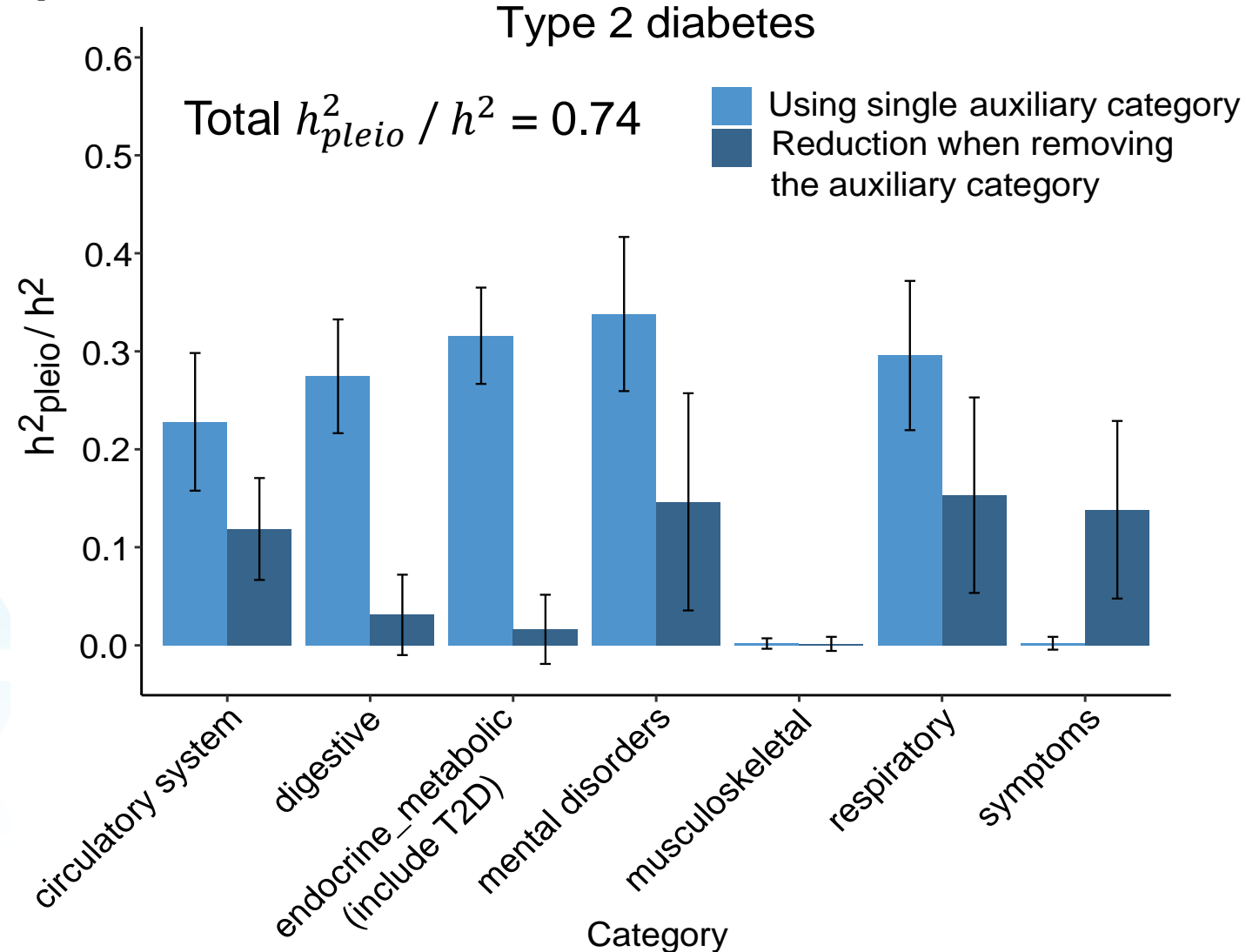


Compare h^2_{pleio} to h^2 : h^2_{pleio} / h^2

- **D+Q**: average = 53%, s.e. = 5.2%
- **D**: average = 47%, s.e. = 5.9%
- **D-target**: average = 43%, s.e. = 5.9%
- **D-target-best other**: average = 31%, s.e. = 2.2%

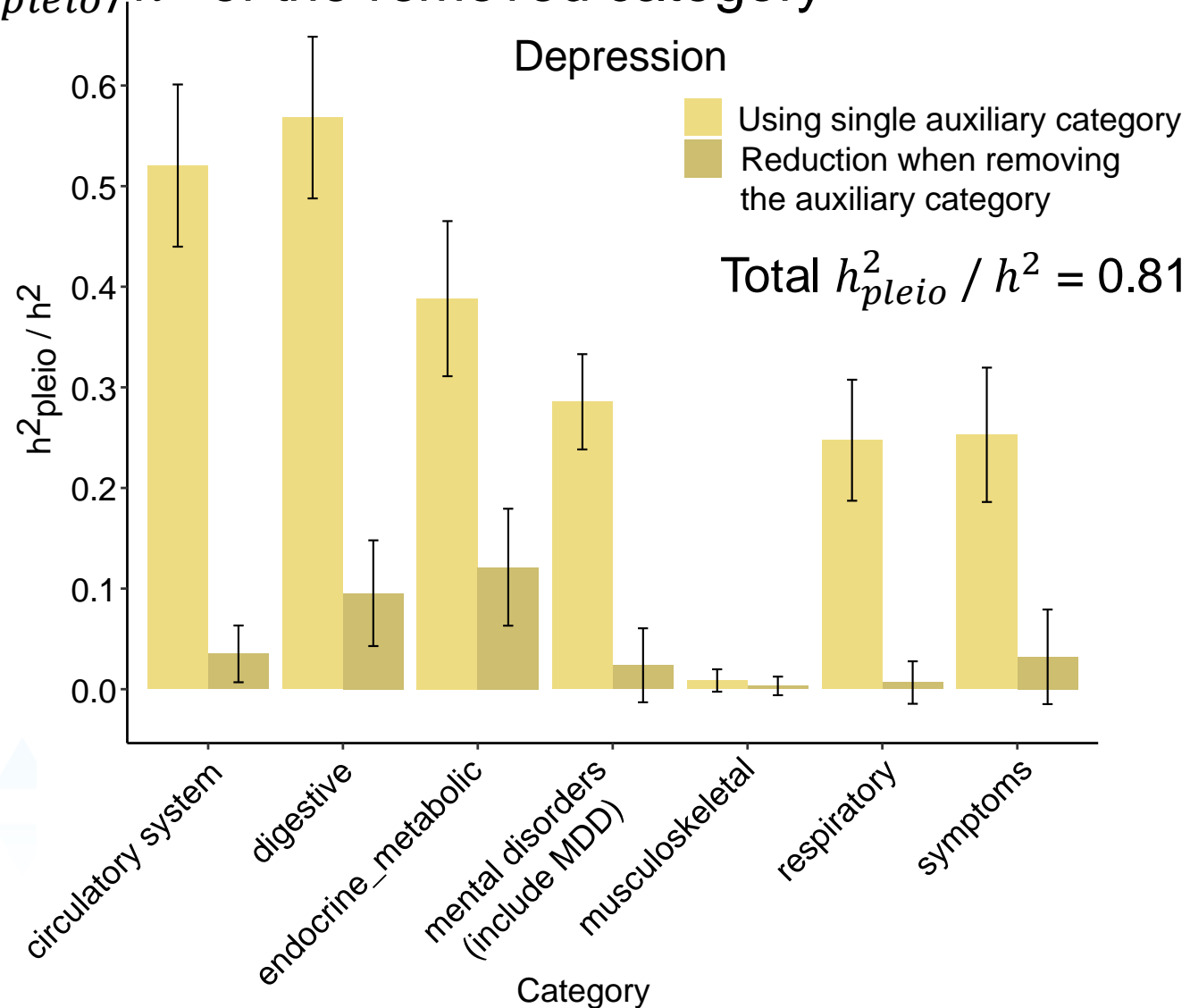
Pleiotropic heritability is broadly distributed across disease systems

- Reduction $\ll h^2_{pleio}/h^2$ of the removed category



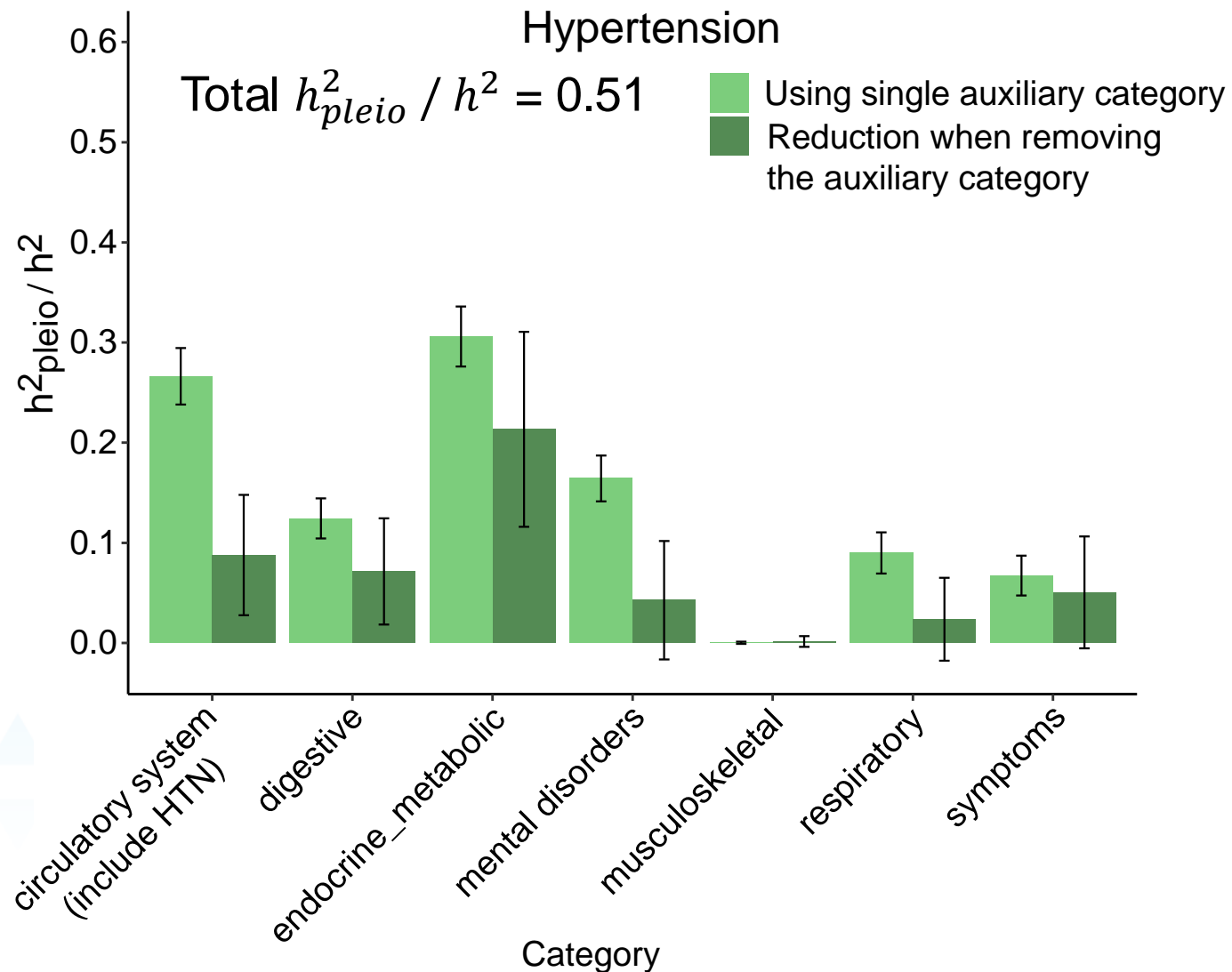
Pleiotropic heritability is broadly distributed across disease systems

- Reduction $\ll h^2_{pleio} / h^2$ of the removed category



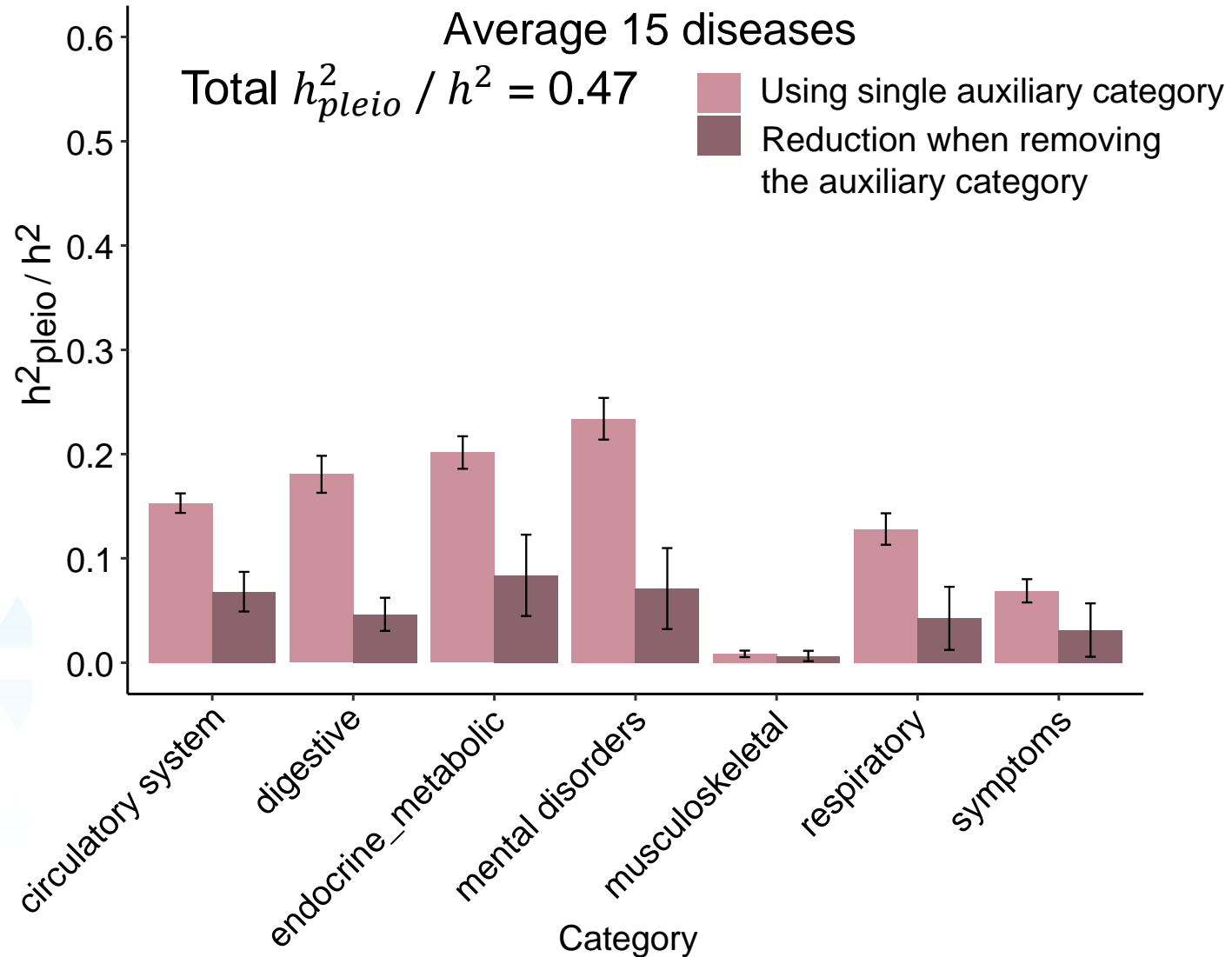
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Pleiotropic phenotypic variance

- **Definition:** The proportion of phenotypic variance of target disease **liability** (σ_T) that can be explained by any linear combination of **liabilities** of auxiliary disease (σ_D)
- Liability-scale covariance matrix \rightarrow pleiotropic phenotypic variance V^2_{pleio}

(Loh et al. 2015b *Nat Genet*)

1	Cov (σ_T, σ_{D1})	Cov (σ_T, σ_{D2})	...	Cov (σ_T, σ_{Dn})
Cov (σ_T, σ_{D1})	1	Cov (σ_{D1}, σ_{D2})	...	Cov (σ_{D1}, σ_{Dn})
Cov (σ_T, σ_{D2})	Cov (σ_{D1}, σ_{D2})	1	...	Cov (σ_{D2}, σ_{Dn})
⋮	⋮	⋮	⋱	⋮
Cov (σ_T, σ_{Dn})	Cov (σ_{D1}, σ_{Dn})	Cov (σ_{D2}, σ_{Dn})	...	1



$$\sigma_T = \sum \beta_D \sigma_D + \sigma_{private} \quad (D = 1, 2, \dots, n)$$

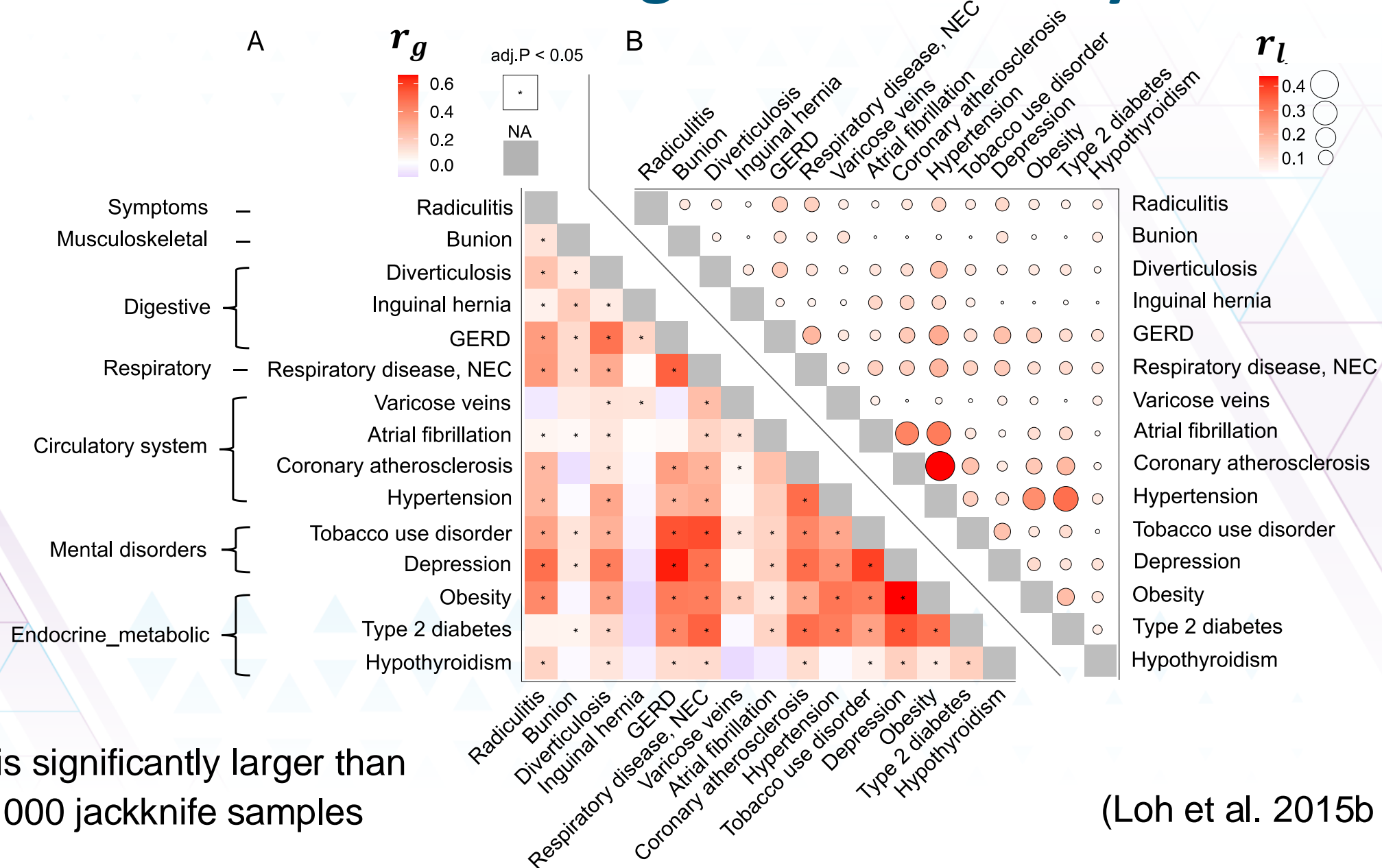
$$\beta_D = \min_{\beta} E_p [(\sigma_T - \sum \beta_D \sigma_D)^2]$$

$$V^2_{pleio} = \text{var}(\sum \beta_D \sigma_D) \quad (D = 1, 2, \dots, n)$$

Jackknife individuals to estimate V^2_{pleio} and its standard error

Liability-scale covariance matrix

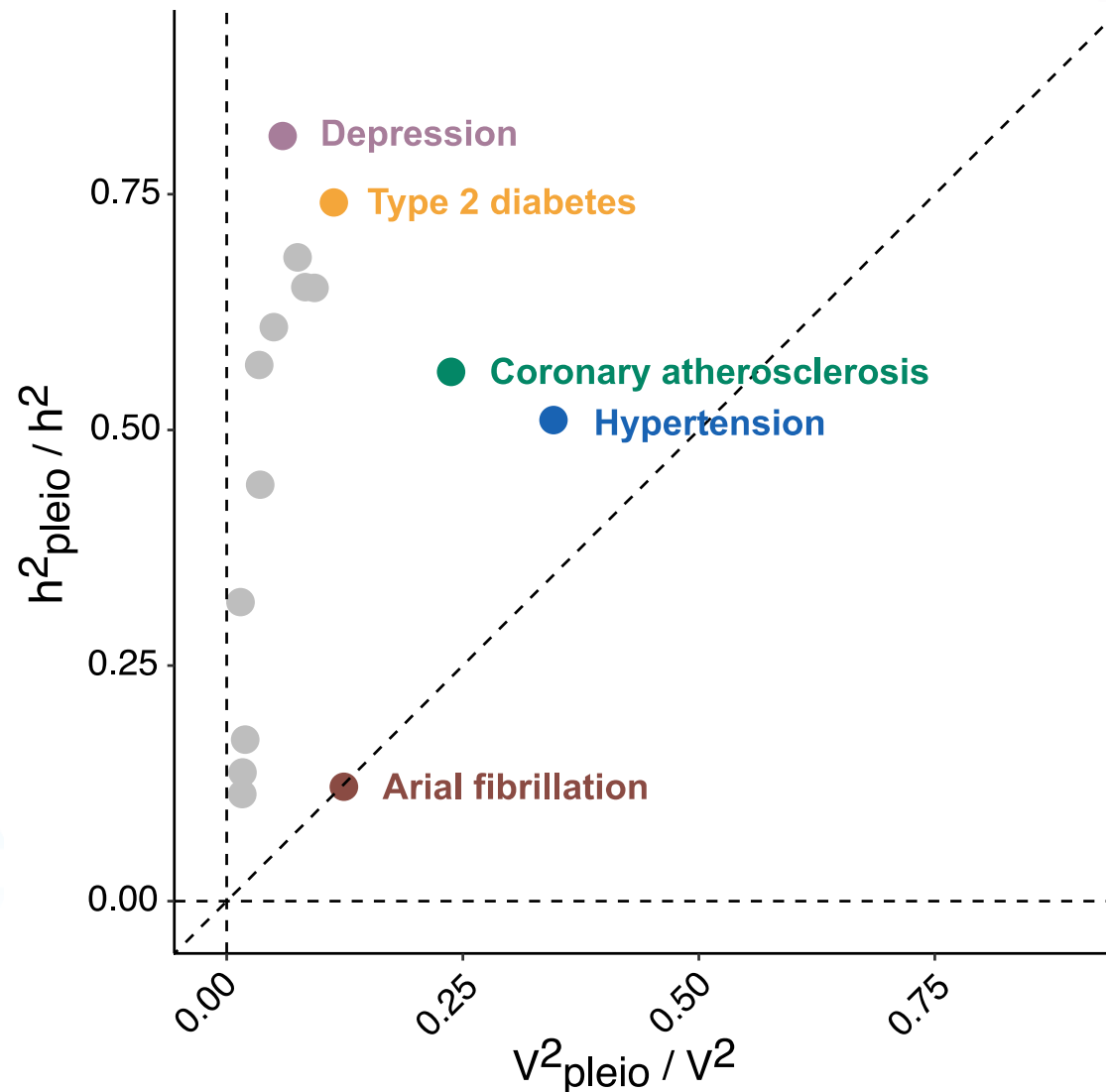
Genetic correlation is larger than liability correlation



(Loh et al. 2015b *Nat Genet*)

Pleiotropic heritability is much higher than pleiotropic phenotypic variance

- V^2_{pleio}/V^2 (phenotypic variance) (8.8%, s.e. = 0.1%) \ll h^2_{pleio}/h^2 (47.3%, s.e. = 5.9%)



Conclusions

- More than half of heritability is pleiotropic in common diseases.
- Pleiotropic heritability is substantially explained by a broad range of unrelated disease across different disease systems.
- Pleiotropic heritability is much higher than pleiotropic phenotypic variance.

Acknowledgements

- Xilin Jiang and Alkes Price