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SUPPLEMENTARY INFORMATION

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Hidden heritability due to heterogeneity across seven populations

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Supplementary Tables

Supplementary Table 1. Heritability estimates of the full GREML model and gene-environment interaction models for education.

	Educational attainment							
Model	G		GxP		GxC		GxPxC	
	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]
$\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$	0.156381 (0.010166)	0[b]	0.135457 (0.010984)	0[b]	0.130677 (0.013603)	0[b]	0.124112 (0.014537)	0[b]
$\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$	--	--	0.111957 (0.023205)	0[b]	--	--	0.057223 (0.038299)	0.06452
$\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	0.049677 (0.017298)	0.000945	0.024439 (0.019309)	0.09781
$\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	--	--	0.076045 (0.047808)	0.05019
h^2_{SNP}	0.156381 (0.010166)		0.247414 (0.021533)		0.180353 (0.013095)		0.281819 (0.026164)	
N	32880							

Note: a = based on likelihood ratio tests comparing the full model with one constraining the respective variance component to 0. b= GCTA output when p-value was too small. $\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$ = proportion of observed variance in the outcome associated with genetic variance across all environments, $\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance in the outcomes associated with *additional* genetic variance within populations, $\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within demographic birth cohorts, $\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within populations and demographic birth cohorts, all analyses control for the first 20 Principal Components, sex, birth year and population.

Supplementary Table 2. Heritability estimates of the full GREML model and gene-environment interaction models for age at first birth.

	Age at first birth							
Model	G		GxP		GxC		GxPxC	
	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]
$\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$	0.077120 (0.018378)	4.0x10 $^{-6}$	0.055043 (0.021657)	0.004853	0.077367 (0.025351)	0.0001545	0.057442 (0.028232)	0.0001522
$\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$	--	--	0.071131 (0.038926)	0.02842	--	--	0.000001 (0.041981)	0.2097
$\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	0.000001 (0.034237)	0.5	0.069185 (0.065342)	0.04781
$\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	--	--	0.000001 (0.082471)	0.428
h^2_{SNP}	0.077120 (0.018378)		0.126174 (0.033126)		0.077367 (0.024951)		0.128115 (0.039575)	
N	16067							

N

Note: a = based on likelihood ratio tests comparing the full model with one constraining the respective variance component to 0. b= GCTA output when p-value was too small. $\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$ = proportion of observed variance in the outcome associated with genetic variance across all environments, $\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance in the outcomes associated with *additional* genetic variance within populations, $\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within demographic birth cohorts, $\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within populations and demographic birth cohorts, all analyses control for the first 20 Principal Components, sex, birth year and population.

Supplementary Table 3. Heritability estimates of the full GREML model and gene-environment interaction models for number of children ever born.

	Number of children ever born							
Model	G		GxP		GxC		GxPxC	
	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]
$\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$	0.030260 (0.009468)	0.0004095	0.007740 (0.010421)	0.2262	0.000001 (0.013265)	0.50	0.000001 (0.014717)	0.50
$\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$	--	--	0.115084 (0.024167)	$2.2\text{x}10^{-7}$	--	--	0.104507 (0.038526)	0.002827
$\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	0.091694 (0.016859)	$4.7\text{x}10^{-15}$	0.029537 (0.020536)	0.05901
$\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	--	--	0.000001 (0.049140)	0.402
h^2_{SNP}	0.030260 (0.009468)		0.122824	(0.021916)	0.091695	(0.012608)	0.134046	(0.027277)
N	31201							

Note: a = based on likelihood ratio tests comparing the full model with one constraining the respective variance component to 0. b= GCTA output when p-value was too small. $\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$ = proportion of observed variance in the outcome associated with genetic variance across all environments, $\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance in the outcomes associated with *additional* genetic variance within populations, $\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within demographic birth cohorts, $\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within populations and demographic birth cohorts, all analyses control for the first 20 Principal Components, sex, birth year and population.

Supplementary Table 4. Heritability estimates of the full GREML model and gene-environment interaction models for BMI.

	BMI							
Model	G		GxP		GxC		GxPxC	
	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]
$\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$	0.171099 (0.011238)	0[b]	0.160373 (0.012177)	0[b]	0.167345 (0.014816)	0[b]	0.161637 (0.015826)	0[b]
$\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$	--	--	0.053260 (0.024572)	0.01399	--	--	0.032544 (0.040927)	0.1709
$\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	0.006000 (0.018418)	0.3709	0.000001 (0.020717)	0.5
$\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	--	--	0.028135 (0.051338)	0.3155
h^2_{SNP}	0.171099 (0.011238)		0.213633 (0.022834)		0.173345 (0.014236)		0.222318 (0.027637)	
N	30496							

Note: a = based on likelihood ratio tests comparing the full model with one constraining the respective variance component to 0. b= GCTA output when p-value was too small. $\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$ = proportion of observed variance in the outcome associated with genetic variance across all environments, $\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance in the outcomes associated with *additional* genetic variance within populations, $\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within demographic birth cohorts, $\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within populations and demographic birth cohorts, all analyses control for the first 20 Principal Components, sex, birth year and population.

Supplementary Table 5. Heritability estimates of the full GREML model and gene-environment interaction models for Height.

	Height							
Model	G		GxP		GxC		GxPxC	
	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]
$\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$	0.394760 (0.011597)	0[b]	0.388266 (0.012367)	0[b]	0.389672 (0.014744)	0[b]	0.389469 (0.015791)	0[b]
$\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$	--	--	0.034265 (0.022808)	0.06305	--	--	0.000001 (0.038658)	0.5
$\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	0.010428 (0.017204)	0.266	0.000001 (0.019625)	0.5
$\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$	--	--	--	--	--	--	0.052960 (0.048074)	0.1345
h^2_{SNP}	0.394760 (0.011597)		0.422531 (0.021848)		0.400100 (0.014149)		0.442431 (0.026146)	
N	30497							

Note: a = based on likelihood ratio tests comparing the full model with one constraining the respective variance component to 0. b= GCTA output when p-value was too small. $\sigma^2_{\mathbf{G}}/\sigma^2_{\mathbf{Y}}$ = proportion of observed variance in the outcome associated with genetic variance across all environments, $\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance in the outcomes associated with *additional* genetic variance within populations, $\sigma^2_{\mathbf{G\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within demographic birth cohorts, $\sigma^2_{\mathbf{G\times P\times C}}/\sigma^2_{\mathbf{Y}}$= proportion of observed variance associated with *additional* genetic variance within populations and demographic birth cohorts, all analyses control for the first 20 Principal Components, sex, birth year and population.

Supplementary Table 6. Results of the model-fitting approach to test for significance of model specifications in reference to more parsimonious models (in bold better model from the versus comparison).

	Model	versus	LRT	DF	P-value
Height	GxPxC	GxC	3.043	2	0.1092
	GxPxC	GxP	0.762	2	0.3416
	GxC	G	0.391	1	0.266
	GxP	**G**	2.340	1	0.06305
BMI	GxPxC	GxC	4.865	2	0.0439
	GxPxC	**GxP**	0.230	2	0.4456
	GxC	G	0.109	1	0.3709
	GxP	G	4.830	1	0.01399
Education	**GxPxC**	GxC	25.045	2	$1.8x10^{-6}$
	GxPxC	GxP	7.512	2	0.01169
	GxC	G	9.653	1	0.000945
	GxP	G	25.551	1	$2.2x10^{-7}$
Age at first birth	GxPxC	GxC	4.960	2	0.04188
	GxPxC	**GxP**	0.000	2	0.5
	GxC	G	13.015	1	0.001545
	GxP	G	8.492	1	0.001783
Number of children	GxPxC	GxC	20.770	2	1.545e-05
	GxPxC	**GxP**	2.917	2	0.1163
	GxC	G	60.011	1	4.718e-15
	GxP	G	25.525	1	2.184e-07

Supplementary Table 7. Sample sizes of datasets divided by demographic birth cohorts born before and after the onset of fertility postponement

Country	Turning point mean age at first birth	Year of turning point	Data source
Netherlands	26.39	1944	HFD
United Kingdom	23.27	1944	Official Statistics
Sweden	26.39	1943	HFD
Australia	24.78	1939	QIMR
Estonia	25.05	1962	HFD/HFC
United States	24.63	1940	HFD

Note: For a description of the data sources see Text S3. HFD refers to Human Fertility Database (http://www.humanfertility.org/cgi-bin/main.php).

Supplementary Table 8. Gene-environment interaction model to test for sex-specific effects within populations ($\sigma^2_{gXpXsex}$) by phenotype.

Model	BMI		Height		Education		Age at first birth		Number of children	
	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]	Estimate (SE)	p-value[a]
$\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$	0.197711 (0.028231)	0[b]	0.453261 (0.031693)	0[b]	0.251800 (0.027964)	0[b]	0.146102 (0.047107)	0.0001225	0.116699 (0.032427)	0.0001759
$\sigma^2_{\mathbf{G\times P\times Sex}}/\sigma^2_{\mathbf{Y}}$	0.033757 (0.029247)	0.0461	0.000001 (0.041235)	0.5	0.003135 (0.032840)	0.458	0.000001 (0.062952)	0.5	0.010631 0.041610	0.407

Note: a = based on likelihood ratio tests comparing the full model with one constraining the respective variance component to 0. b= GCTA output when p-value too small. $\sigma^2_{\mathbf{G\times P}}/\sigma^2_{\mathbf{Y}}$ = proportion of observed variance in the outcomes associated with genetic variance within populations, $\sigma^2_{\mathbf{G\times P\times Sex}}/\sigma^2_{\mathbf{Y}}$ = proportion of observed variance associated with *additional* genetic variance within sexes.

Supplementary Notes

Supplementary Note 1. Human reproductive behaviour measure

The measures of human reproductive fertility – age at first birth (AFB) and number of children ever born (NEB) was virtually the same across all population. Only one aspect differed, which is the fact that HRS and ARIC explicitly excluded still-births (HRS, ARIC) while the others did not specifically isolate this aspect (TwinsUK asked in some waves: "How many children have you given birth to?"; EGCUT asked: "Do you have any biological children?", and subsequently: "Fill in their names, gender and date of birth). In STR, LifeLines, QIMR as well as most of the waves of the TwinsUK, information on both the date of birth and death of the child was asked.

An examination of this point suggests that it is not problematic for our analyses. In LifeLines and TwinsUK, we compared the live birth measure with number of children ever born and, as expected, given the diminishing mortality rate in both datasets, less than 0.2% of the children had not reached reproductive age and the correlation of number of children ever born and number of children reaching reproductive age was >0.98. We therefore do not expect a large bias from the exclusion of still-births in some of the countries. The questionnaires also slightly differed in the maximum number of children that could be listed. However, within each cohort, the maximum number of children has never been named more often than in 0.5 per cent of the cases and we do not anticipate that our results are influenced by this. Furthermore, in vitro fertilization (IVF) – often related to twinning and multiple births – can bias results if IVF compensates genetically based infertility. However, in our TwinsUK sample, only 60 women reported using IVF, of which we did not include in the final analyses.

Supplementary Note 2. Cohorts under study & data availability

a) Cohorts

ARIC

ARIC (Atherosclerosis Risk in Communities Study) is a community-based prospective cohort study of 15,792 adults aged 45–64. Participants were identified by probability sampling from four U.S. communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland) and were enrolled between 1987 and 1989. [1–3]

HRS

The Health and Retirement Study (HRS) is an ongoing cohort study of Americans, with interview data collected biennially on demographics, health behavior, health status, employment, income and wealth, and insurance status. The first cohort was interviewed in 1992 and subsequently every two years, with 5 additional cohorts added between 1994 and 2010. The full details of the study are described in. [4]

EGCUT

Estonian data come from of the Estonian Genome Center Biobank, University of Tartu (EGCUT, www.biobank.ee), a population-based database which consists of health, genealogical and genome data of currently more than 51,530 individuals.[5] Each participant filled out a Computer Assisted Personal Interview including personal data (place of birth, place(s) of living, nationality etc.), genealogical data (family history, three generations), educational and occupational history and lifestyle data (physical activity, dietary habits, smoking, alcohol consumption, and quality of life).

QIMR

Data for Australia uses the Queensland Institute for Medical Research (QIMR). The participants were drawn from cohorts of adult twin families that have taken part in a wide range of studies of health and well-being via questionnaire and telephone interview studies, and recruitment was extended to their relatives (parents, siblings, adult children and spouses).

LifeLines Cohort Study

The LifeLines Cohort Study[6] is a multi-disciplinary prospective population-based cohort study from the Netherlands, using a three-generation design to study the health and health-related behaviours of 167,729 persons living in the North of The Netherlands including genotype information from more than 13,000 unrelated individuals. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics.

TwinsUK

For the UK, we use data from TwinsUK, the largest adult twin registry in the country with more than 12,000 respondents.[7] The TwinsUK Study recruited white monozygotic (MZ) and dizygotic (DZ) twin pairs from the TwinsUK adult twin registry, a group designed to study the heritability and genetics of age-related diseases (www.twinsuk.ac.uk). These twins were recruited from the general population through national media campaigns in the UK and shown to be comparable to age-matched population singletons in terms of clinical phenotype and lifestyle characteristics.

STR

The Swedish Twin Registry (STR) was first established in the late 1950s to study the importance of smoking and alcohol consumption on cancer and cardiovascular diseases whilst controlling for genetic propensity to disease. Between 1998 and 2002, the STR conducted telephone interview screening of all twins born in 1958 or earlier regardless of

gender composition or vital status of the pair. This effort is known as Screening Across the Lifespan Twin study (SALT). A subsample of SALT (≈10,000) was genotyped as part of the TwinGene project [8,9] and we use this information in the current study.

b) Data availability

Data were collected and maintained by third parties. For ethical and legal reasons we are not allowed to distribute them. However, it is possible to contact the studies directly to request access to data as specified on their respective websites: The TwinsUK data is available on request by contacting the Twin Research Unit at www.twinsuk.ac.uk/data-access/submission-procedure. The LifeLines data is available by contacting the LifeLines Research Office (LLscience@umcg.nl)(https://www.lifelines.nl/lifelines-research/access-tolifelines/application-process). Researchers interested in using STR data can contact Patrik Magnusson (Patrik.magnusson@ki.se). Researchers interested in using QIMR data can contact Nick Martin (Nick.Martin@qimrberghofer.edu.au) and Sarah Medland (medlandse@gmail.com). For the HRS, phenotypic data are publicly available. Researchers who wish to link genetic data with other HRS measures can apply for access from HRS (http://hrsonline.isr.umich.edu/gwas). Data from the Atherosclerosis Risk in Communities (ARIC) Study can be accessed through the NHLBI BioLINCC repository (https://biolincc.nhlbi.nih.gov/home/) or by contacting the ARIC Coordinating Center (http://www2.cscc.unc.edu/aric/distribution-agreements). The raw microarray data for the EGCUT cohort are freely available for researchers through managed access control via the Estonian Genome Center's DAC (Scientific Committee of the Estonian Genome Center), as defined by the cohort's consent. All respective requests should be submitted by email to biobank@ut.ee. Data can typically not be released without assessment by a local steering

committee with transfer agreements and ethical approval, as the phenotypic data can be sensitive.

Supplementary Note 3. Data sources for human reproduction trends

Aggregate data to describe country specific human reproduction or what is known in demography as fertility trends have been obtained from the Human Fertility Database (HFD, http://www.humanfertility.org/cgi-bin/main.php) and the Human Fertility Collection (HFC, http://www.fertilitydata.org/cgi-bin/index.php) if available. Both data collections are joint projects of the Max Planck Institute for Demographic Research (MPIDR) in Rostock, Germany and the Vienna Institute of Demography (VID) in Vienna, Austria. The projects provide access to detailed and high-quality data on period and cohort fertility. The HFD is entirely based on official vital statistics. The HFC incorporates a variety of valuable fertility data from diverse, not necessarily official, data sources. All data are freely available after registration. We focused on fertility information for cohorts that was aggregated for individuals older than 45.

For the UK, official data on birth order have only been collected within marriages, and may therefore be slightly biased, particularly for younger birth cohorts. We therefore relied on estimates from the Office for National Statistics, Cohort fertility, Table 2. Available at: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77–2631333. For Estonia, data on completed reproduction by age 45 and over was only available until the year 1962. For subsequent cohorts, however, there was an estimate of AFB available based on official statistics at the age of 40. For Australia, no official data on a time series of cohort specific AFB was available and the trends are based on the data used for analysis in this study.

Supplementary Note 4. Simulation studies

We conducted 50 simulation replications. In each simulation replication, we randomly selected 5000 SNPs that were in approximate linkage equilibrium (pairwise r^2 between SNPs below 0.05). Four separate simulations were conducted.

Simulation 1 (Sim 1)

We first simulated a phenotype across all individuals from these loci as: $y_j = \sum_{i=1}^{k} w_{ij} b_i + e_j$, where $w_{ij} = \frac{(x_{ij} - 2p_i)}{\sqrt{2p_i(1-p_i)}}$, with b_i representing the allelic effect of the i^{th} standardized SNP and e_j the residual (environmental effect). b_i was simulated from $N(0, h^2_{\text{SNP}}/m)$, with m being the number of causal variants, and e_j simulated from $N(0, 1 - h^2_{\text{SNP}})$, where h^2_{SNP} is the SNP heritability of the trait, which we set as 0.50. This produces a single trait with a genetic basis that is constant across countries.

Simulation 2 (Sim 2)

We again simulated a phenotype with no genotype-population interaction with the SNP effects being the same within each population. However, in this second simulation the residual variance and thus the phenotypic variance changes across populations. This is an example of variance heterogeneity. These same effects would also occur under measurement error - some countries have better measurement, so the residual variance is lower, whereas other countries have poorer measurements making the residual variance higher. We used the same SNP loci and same SNP effects as in Sim 1, resulting in the genetic correlation across populations = 1. In this instance rather than keeping the residual variance at 0.5, we allowed it to vary across populations with the phenotypic variance of 2, 1.8, 1.6, 1.4, 1.2, 1.0, 0.8, which is split into genetic variance of 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5, and residual variance of

1.5, 1.3, 1.1, 0.9, 0.7, 0.5, 0.3, giving a heritability of 0.25, 0.278, 0.3125, 0.357, 0.417, 0.5, 0.625.

Simulation 3 (Sim 3)

We simulated a phenotype where the genetic basis differed across the seven countries. To do this we simulated the effects $b_{i,k}$ for each causal variant i in each country k from a multivariate normal $MVN(0,\mathbf{G})$, where $\mathbf{G}$ is a matrix with diagonal h^2_{SNP}/m and off diagonal elements $\rho\sqrt{(h^2_{\mathrm{SNP}}/m) * (h^2_{\mathrm{SNP}}/m)}$, with ρ the genetic correlation for the phenotype among countries. We set h^2_{SNP} for each country as 0.5 and ρ among countries as 0.8. e_j was simulated from $MVN(0, \mathbf{E})$, where $\mathbf{E}$ is $\mathrm{diag}(1 - h^2_{\mathrm{SNP}})$, with the 0 off-diagonal elements representing independent residual errors for individuals across countries. This generates phenotypes with a genetic correlation of 0.8 across data sets.

Simulation 4 (Sim 4)

This is the same genotype-environment simulation as Sim 3, but the genetic correlation across populations is lower at 0.5.

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