Supplementary Table 2: Descriptions of cohorts for simulations with population stratification

Abbreviation	Origin	Principal Investigator	Controls
clo3	Cardiff, UK	Walters, J	945
cou3	UK	O'Donovan, M	544
egcu	Estonia	Esko, T	1,177
swe5	Sweden	Sullivan, PF	2,617
swe6	Sweden	Sullivan, PF	1,219
umeb	Umeå, Sweden	Adolfsson, R	584
umes	Umeå, Sweden	Adolfsson, R	713

Supplementary table 1 describes the seven PGC Schizophrenia control cohorts used for simulation with population stratification. All cohorts were genotyped on the Illumina Omni Express array; only unaffected individuals (controls) and directly genotyped SNPs post-QC (between approximately 600,000 and 700,000 SNPs, depending on cohort) were retained for simulations. In total genotypes for 9,135 individuals were incorporated into the simulations with pure population stratification

Supplementary Table 3a: Performance of genomic control and LD Score regression intercept in simulations with continental-scale population stratification

Population 1	Population 2	λ_{GC}	Intercept	$(Intercept - 1)/(\lambda_{GC} - 1)$
cou3	clo3	1.093	1.07	0.748
egcu	clo3	9.413	8.508	0.892
egcu	cou3	6.604	6.045	0.900
swe5	clo3	3.582	3.445	0.947
swe5	cou3	2.767	2.635	0.925
swe5	egcu	9.384	8.767	0.926
swe6	clo3	3.744	3.600	0.947
swe6	cou3	3.267	4.238	1.428
swe6	egcu	6.880	6.413	0.920
swe6	swe5	1.712	1.703	0.987
umeb	clo3	3.635	3.614	0.992
umeb	cou3	2.633	2.879	1.151
umeb	egcu	4.603	4.764	1.045
umeb	swe5	2.145	2.313	1.147
umeb	swe6	1.278	1.880	3.162*
umes	clo3	7.316	7.389	1.012
umes	cou3	4.959	5.572	1.155
umes	egcu	9.304	9.742	1.053
umes	swe5	6.900	7.328	1.072
umes	swe6	4.172	4.443	1.085
umes	umeb	3.192	3.218	1.012
	Mean (SD)			**1.017 (0.14)***

This table compares the performance of λ_{GC} and the LD Score regression intercept in simulations with continental-scale population stratification. In each simulation, individuals from population 1 were labeled cases and N_2 individuals from population 2 were labeled controls. We then computed association statistics for variants in the intersection of the subset of HapMap 3 variants used for LD Score regressions on real data (Online Methods) and variants on the Illumina Omni Express array (approx. 450,000 variants in each simulation).

The conclusion is that the LD Score regression intercept gives approximately the same answer as $\boldsymbol{\lambda_{GC}}$ in simulations with pure population stratification, and so would be appropriately conservative if used as a correction factor.

* The mean and SD are computed with the umeb/swe6 outlier removed.

Supplementary Table 3b. Correlation between LD Score and FST in simulations with continental-scale population stratification

Population 1	Population 2	Signed R-squared
cou3	clo3	5.00e-05
egcu	clo3	8.28e-04
egcu	cou3	7.41e-04
swe5	clo3	1.61e-04
swe5	cou3	2.02e-04
swe5	egcu	4.29e-04
swe6	clo3	1.81e-04
swe6	cou3	-1.12e-05
swe6	egcu	4.32e-04
swe6	swe5	5.95e-05
umeb	clo3	1.07e-04
umeb	cou3	5.05e-05
umeb	egcu	2.55e-04
umeb	swe5	1.92e-06
umeb	swe6	-6.60e-05
umes	clo3	5.22e-06
umes	cou3	6.79e-09
umes	egcu	7.26e-05
umes	swe5	-2.19e-06
umes	swe6	-5.23e-06
umes	umeb	-7.52e-06
	Mean	**2.51e-4**

Column descriptions. Population 1 and population 2 are the two populations involved in the simulations. Signed R-squared is the squared Pearson correlation coefficient between F_{ST} (between the two populations in the simulation) and LD Score multiplied by the negative one if the (non-squared) correlation is negative.

Supplementary Table 3c Heritability and intercept for a confounded GWAS with continental-scale population stratification

Population 1	Population2	Heritability	Intercept	Lambda
cou3	clo3	0.140	1.397	1.531
egcu	clo3	0.063	1.454	1.509
swe6	clo3	0.033	1.476	1.502
swe5	clo3	0.034	1.475	1.502
umeb	clo3	0.027	1.480	1.484
umes	clo3	0.009	1.493	1.487
swe5	cou3	0.044	1.468	1.506
umes	cou3	0.007	1.495	1.429
egcu	cou3	0.063	1.454	1.504
swe6	cou3	-0.096	1.570	1.399
umeb	cou3	0.026	1.481	1.418
swe5	egcu	0.048	1.465	1.502
umes	egcu	0.027	1.480	1.456
swe6	egcu	0.051	1.463	1.503
umeb	egcu	0.051	1.463	1.443
swe6	swe5	0.031	1.477	1.483
umes	swe5	0.002	1.498	1.465
umeb	swe5	0.007	1.495	1.431
umeb	swe6	-0.213	1.656	1.208
umes	swe6	-0.001	1.500	1.461
umes	umeb	-0.005	1.504	1.498
	Mean	**0.017**	**1.488**	**1.463**

This table puts the slopes from the simulations with continental-scale population stratification on an interpretable scale by transforming all parameters to the scale of a GWAS with 100,000 samples and mean chi-square of 1.5, where all inflation in the mean chi-square comes from population stratification. All estimates of h2(1kG) use M=15 million. For comparison, the aggregate LD Score estimator of h2(1kG), $\widehat{h^2} = \frac{M(\overline{\chi^2}-1)}{\overline{N\ell}}$, which is representative of heritability estimators that are highly susceptible to population stratification, would give a heritability estimate of **0.68** in all cases, assuming mean LD Score = 110. The reason why the LD Score regression slope is not equal to zero is likely because linked selection introduces a small correlation between LD Score and F_{ST}. The conclusion is that in a worst-case scenario (pure population stratification), LD Score regression misattributes on average a small proportion of stratification to heritability, but nevertheless performs many times better than existing estimators (upward bias of 0.017 for LD Score regression vs. approximately 0.68 for other methods).

Supplementary Table 4a: Performance of genomic control and LD Score regression intercept in simulations with national-scale population stratification

Population	PC	λ_{GC}	Intercept	$(Intercept - 1)/(\lambda_{GC} - 1)$
clo3	1	2.001	2.821	1.818
clo3	2	1.277	1.318	1.151
clo3	3	1.293	1.297	1.014
cou3	1	1.079	1.062	0.781
cou3	2	1.062	1.043	0.697
cou3	3	1.065	1.046	0.711
egcu	1	1.814	1.763	0.937
egcu	2	1.525	1.478	0.911
egcu	3	1.395	1.476	1.203
swe5	1	2.704	2.700	0.998
swe5	2	1.409	1.369	0.904
swe5	3	1.327	1.336	1.028
swe6	1	2.735	2.686	0.972
swe6	2	2.468	2.426	0.971
swe6	3	1.511	1.489	0.957
umeb	1	1.88	1.838	0.953
umeb	2	1.847	1.845	0.997
umeb	3	1.435	1.410	0.943
umes	1	2.039	1.958	0.922
umes	2	1.583	1.540	0.926
umes	3	1.328	1.294	0.896
Mean (SD)				**0.985 (0.224)**

This table compares the performance of λ_{GC} and the LD Score regression intercept in simulations with national-scale population stratification. We LD-pruned the SNPs so that no SNPs on the same chromosome had $R^2 > 0.02$, then computed the top three principal components. We then used these principal components as phenotypes and computed association statistics for the same set of variants as in the simulations described in supplementary table 2.

The conclusion is that the LD Score regression intercept gives approximately the same answer as $\boldsymbol{\lambda_{GC}}$ in simulations with pure population stratification, and so would be appropriately conservative if used as a correction factor.

Supplementary Table 4b. Correlation between LD Score and FST in simulations with national-scale population stratification

Population	PC	Signed R-Squared
clo3	1	-2.96e-04
clo3	2	1.85e-05
clo3	3	5.03e-06
cou3	1	2.71e-05
cou3	2	4.75e-05
cou3	3	4.73e-05
egcu	1	3.74e-05
egcu	2	1.17e-04
egcu	3	3.23e-05
swe5	1	1.94e-04
swe5	2	8.46e-05
swe5	3	8.79e-08
swe6	1	3.37e-05
swe6	2	1.30e-04
swe6	3	4.49e-05
umeb	1	4.49e-05
umeb	2	1.44e-05
umeb	3	2.25e-05
umes	1	1.44e-04
umes	2	2.18e-05
umes	3	9.09e-05
	Mean:	**4.10e-05**

Column descriptions. Population is the population and PC is the principal component used to simulate population stratification in the simulations and population 2. Signed R-squared is the squared Pearson correlation coefficient between F_{ST} (between the two populations in the simulation) and LD Score multiplied by the negative one if the (non-squared) correlation is negative.

Supplementary Table 4c: Heritability and intercept for a confounded GWAS with national-scale population stratification

Population	PC	Heritability	Intercept	Lambda
clo3	1	-0.178	1.630	1.347
clo3	2	0.048	1.465	1.404
clo3	3	0.031	1.477	1.471
cou3	1	0.144	1.395	1.505
cou3	2	0.254	1.313	1.450
cou3	3	0.229	1.332	1.467
egcu	1	0.035	1.474	1.506
egcu	2	0.068	1.450	1.494
egcu	3	0.043	1.468	1.389
swe5	1	0.039	1.472	1.473
swe5	2	0.076	1.444	1.491
swe5	3	0.024	1.483	1.469
swe6	1	0.017	1.488	1.502
swe6	2	0.036	1.474	1.488
swe6	3	0.047	1.466	1.487
umeb	1	0.031	1.477	1.501
umeb	2	0.014	1.490	1.491
umeb	3	0.042	1.469	1.498
umes	1	0.047	1.466	1.505
umes	2	0.037	1.473	1.510
umes	3	0.082	1.440	1.490
	Mean	**0.056**	**1.459**	**1.473**

This table is similar to supplementary table 2c it puts the slopes from the simulations with national-scale population stratification on an interpretable scale by transforming all parameters to the scale of a GWAS with 100,000 samples and mean chi-square of 1.5 where all inflation in the mean chi-square comes from population stratification along the relevant principal component. As in supplementary table 4, the aggregate estimator would give a h2(1kG) estimate of 0.68, which is similar to the result that one would obtain with Haseman-Elston regression or linear mixed models (using M=15 million). The conclusions are similar to supplementary table 4.

Supplementary Table 5: Simulations with both bias and polygenicity

Bias	Intercept (SD)	Null $\bar{\chi}^2$ (SD)	Null $\bar{\chi}^2$/Intercept (SD)
Relatedness	1.46 (0.02)	1.45 (0.02)	1.00 (0.00)
Stratification	1.53 (0.17)	1.48 (0.15)	0.97 (0.01)

Column descriptions. The column labeled bias identifies the source of bias, either cryptic relatedness (from the Framingham Heart Study) or population stratification (from introducing an environmental stratification term correlated with the first PC of the WTCCC2 data). Intercept is LD Score regression intercept, with the standard deviation (SD) across five simulations in parentheses. Null $\bar{\chi}^2$ is the mean χ^2 among SNPs on the opposite halves of chromosomes from causal SNPs, with SD across five simulations in parentheses. Since null SNPs are not in LD with causal SNPs, the mean χ^2 among null SNPs precisely quantifies the mean inflation in χ^2-statistics that results from bias. Null $\bar{\chi}^2$/Intercept is equal to the mean χ^2 among null SNPs divided by the LD Score regression intercept, with the SD across five simulations in parentheses. Null $\bar{\chi}^2$/Intercept should be approximately equal to one if the LD Score regression intercept is accurately estimating the mean inflation in test statistics that results from bias.

Supplementary Table 6: Simulations with Ascertained Binary Phenotypes

Sample Size	Prevalence	$\widehat{h}_l^2$ (SD)	Intercept (SD)	λ_{GC} (SD)	$\overline{\chi}^2$ (SD)
10000	0.01	0.804 (0.027)	0.995 (0.048)	2.253 (0.063)	2.452 (0.025)
10000	0.1	0.793 (0.041)	1.006 (0.04)	1.688 (0.031)	1.761 (0.015)
1000	0.01	0.772 (0.121)	1.005 (0.019)	1.139 (0.014)	1.145 (0.015)
1000	0.1	0.729 (0.226)	1.007 (0.027)	1.083 (0.03)	1.076 (0.013)

This table displays results from simulations with ascertained binary phenotypes following the liability threshold model. In all simulation replicates, the true heritability (of liability, in the population) was 0.8, the effective number of independent SNPs (defined as $M_{eff} := M/\bar{\ell}$) was 10,000 and the proportion of cases in the sample was 0.5. All SNPs were causal, with effect sizes (precisely, per-normalized genotype effects on liability) drawn *i.i.d.* from a normal distribution. Each entry in the table represents 20 simulation replicates. The column labeled $\widehat{h}_l^2$ lists the estimated heritability of liability in the population from the LD Score regression slope. The column labeled intercept lists LD Score regression intercepts. There was no population stratification in these simulations, so the intercept should be close to one. The columns λ_{GC} and $\overline{\chi}^2$ list the genomic control inflation factor and mean χ^2 computed from a perfectly LD-pruned set of variants.

Supplementary Table 7: Simulations with frequency-dependent genetic architecture

Exponent	Intercept (SD)	$\overline{\chi}^2$ (SD)
-3	1.007 (0.013)	1.011 (0.008)
-2	1.006 (0.014)	1.013 (0.008)
-1	1.003 (0.014)	1.023 (0.009)
-0.5	1.001 (0.013)	1.037 (0.009)
-0.25	1.000 (0.012)	1.048 (0.008)
0	0.998 (0.011)	1.059 (0.007)
0.25	0.997 (0.011)	1.070 (0.006)
0.5	0.996 (0.011)	1.079 (0.006)
1	0.994 (0.012)	1.091 (0.007)
2	0.991 (0.013)	1.101 (0.009)
3	0.989 (0.013)	1.105 (0.010)

Supplementary table 5 describes simulations in which per-normalized genotype effects (precisely, if X denotes a matrix of genotypes normalized to mean zero and variance one, the per-normalized genotype effects are a vector β such that $X\beta$ is equal to the additive genetic component of the phenotype) for 10,000 randomly chosen causal variants were drawn from $N(0, (p(1-p))^x)$, where *p* is MAF and *x* is the entry in the column labeled exponent. To prevent singleton and doubleton variants from having extreme effects for large negative values of *x*, we drew the effect sizes for variants with MAF < 1% from $N(0, 0.0099^x)$. Our model holds when *x=0*, which corresponds to moderate negative selection on the phenotype in question, similar to a typical disease phenotype. *x=1* is an appropriate model for a selectively neutral phenotype. Values of *x* outside the range [0,1] represent extreme genetic architectures. Standard errors are empirical standard errors across 10 replicates with randomly chosen causal variants and effect sizes.

Supplementary Table 8a: Summary Statistic Metadata, Quantitative Trait

Citation	Trait	N	Public	Ref
Heid, *et. al.*, Nat Genet, 2010	Waist-Hip Ratio	113,636	Yes	7
Lango Allen, *et. al.*, Nature, 2010	Height	183,727	Yes	8
Speliotes, *et. al.*, Nat Genet, 2010	Body Mass Index	249,796	Yes	9
TAG Consortium, Nat Genet, 2010	Smoking	74,053	Yes	10
International Consortium for Blood Pressure GWAS, Nature, 2011	Diastolic / Systolic Blood Pressure	69,395	Yes	11
Estrada *et. al.*, Nat Genet, 2011	Bone Mineral Density	32,961	Yes	12
Manning *et. al.*, Nat Genet, 2012	Fasting Insulin	51,750	Yes	13
Rietveld, *et. al.*, Science, 2013	Years of Education	126,559	Yes	14

Column descriptions. All columns are self-explanatory, except the column labeled N counts the number of individuals in the discovery phase of the GWAS, not including replication samples. The column labeled public indicates whether the summary statistics are publicly available for download (see URLs).

Supplementary Table 8b: Summary Statistic Metadata, Case/Control

Citation	Trait	Cases	Controls	Public	Ref
Neale, *et. al.*, J Am Acad Adolesc Psychiatry, 2010	ADHD	896	2455	Yes	15
Stahl, *et. al.*, Nat Genet, 2010	Rheumatoid Arthritis	5,539	20,169	Yes	16
PGC Bipolar Working Group, Nat Genet, 2011	Bipolar Disorder	7,481	9,250	Yes	17
Schunkert *et. al.*, Nat Genet, 2011	Coronary Artery Disease	22,233	64,762	Yes	18
Jostins, *et. al.*, Nature, 2012	Inflammatory Bowel Disease	12,882	21,770	No	19
Jostins, *et. al.*, Nature, 2012	Crohn's Disease	5,956	14,927	Yes*	19
Jostins, *et. al.,* Nature, 2012	Ulcerative Colitis	6,968	20,464	Yes*	19
Morris, *et. al.*, Nat Genet, 2012	Type 2 Diabetes	12,171	56,862	Yes	20
Cross-Disorder Group, Lancet, 2013	PGC Cross-Disorder	33,332	27,888	Yes	21
Ripke, *et. al.*, Mol Psych, 2013	Major Depression	9,240	9,519	Yes	22
O'Donovan, *et. al.*, in preparation	Schizophrenia	31,335**	38,765**	Yes	23
Rietveld, *et. al.*, Science, 2013	College	22,044***	73,383	Yes	14

Column descriptions. All columns are self-explanatory, except the columns labeled cases and controls note the number of cases and controls in the discovery phase of the GWAS, not including replication samples. The column labeled public indicates whether the summary statistics are publicly available for download (see URLs)

* These summary statistics may be meta-analyzed with Immunochip data, which is not appropriate for LD Score regression.

** This figure counts only European samples. The full GWAS includes several thousand Asian samples, which were excluded from the LD Score regression, because the 1000 Genomes European LD Score is not representative of LD patterns in Asian populations.

*** Here cases are individuals with college education, controls those without.

Supplementary Table 9: Simulation with intergenic GC correction

Annotation	Mean χ^2	Lambda
Null (chromosome 2)	1.0098	1.0082
Within 100 kB of a coding exon on chromosome 1	1.4592	1.2511
More than 100 kB from a coding exon on chromosome 1	1.2505	**1.0817**

This table describes a simulation with 1000 Swedish samples and ~700,000 best-guess imputed genotypes on chromosome 1. We simulated phenotypes by assigning causal effects to only SNPs within coding exons on chromosome 1. We then computed association statistics for variants within 100 kB of a gene, more than 100 kB from a gene and for null SNPs on chromosome 2. Because of long-range linkage disequilibrium, lambda (*i.e.,* λ_{GC}) is significantly elevated for intergenic SNPs even though there is no bias in the test statistics, as can be seen from the fact that the test statistics of null SNPs are not inflated.