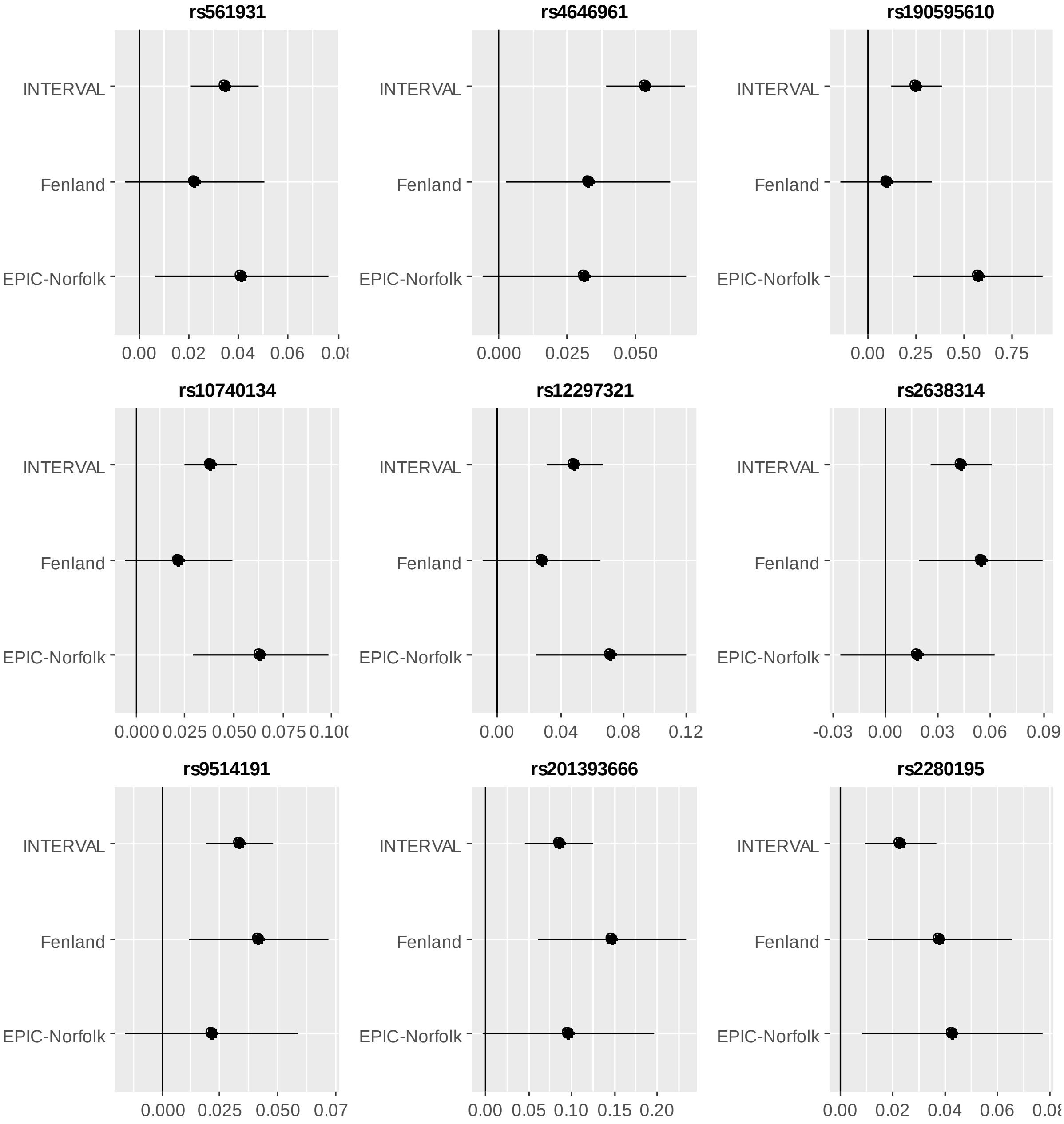
Assessing the causal association of glycine with risk of cardio-metabolic diseases

Laura B. L. Wittemans *et al.*

Supplementary Information

Supplementary Figures

Supplementary Tables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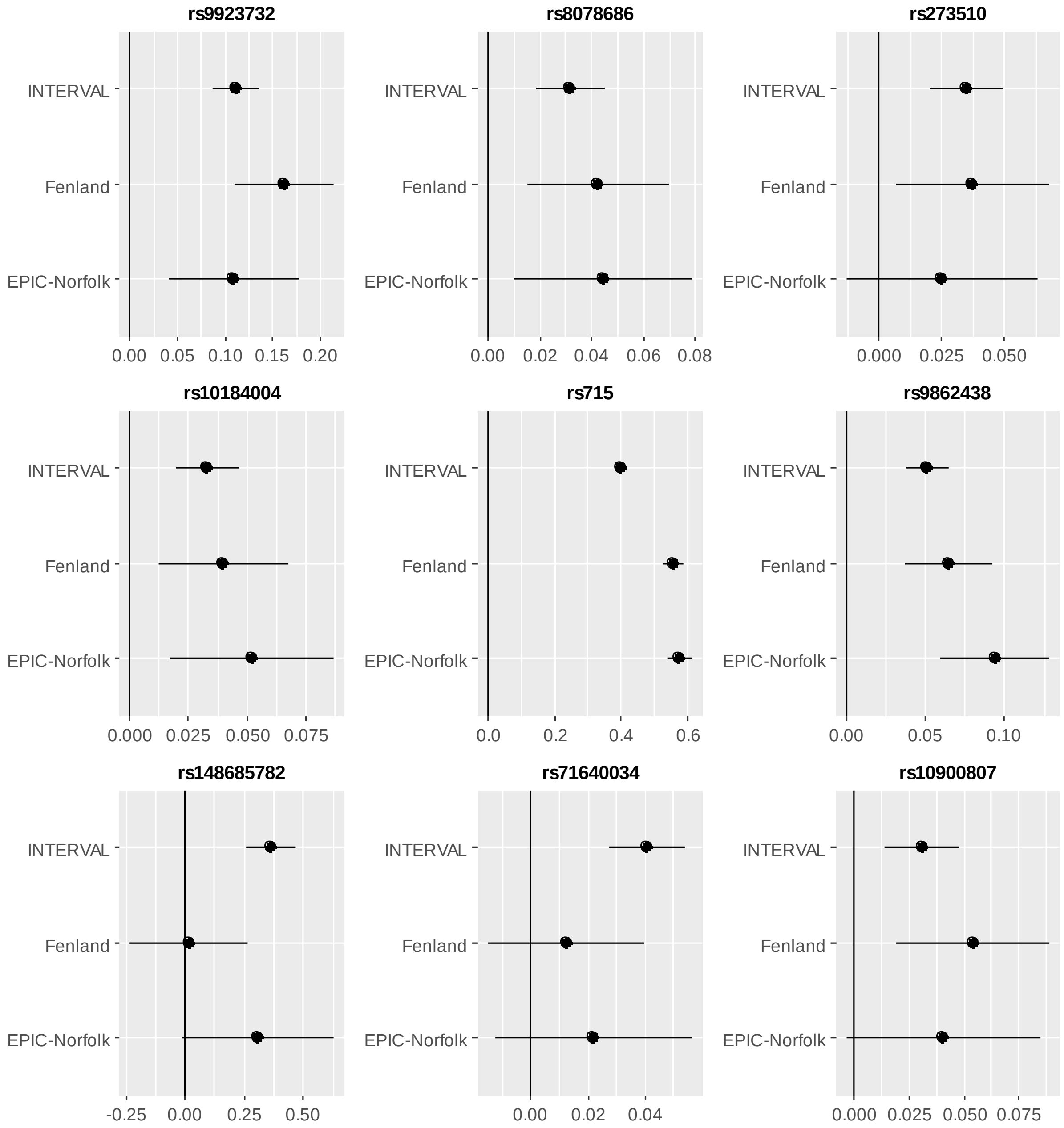
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INTERVAL
Fenland
EPIC-Norfolk
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INTERVAL
Fenland
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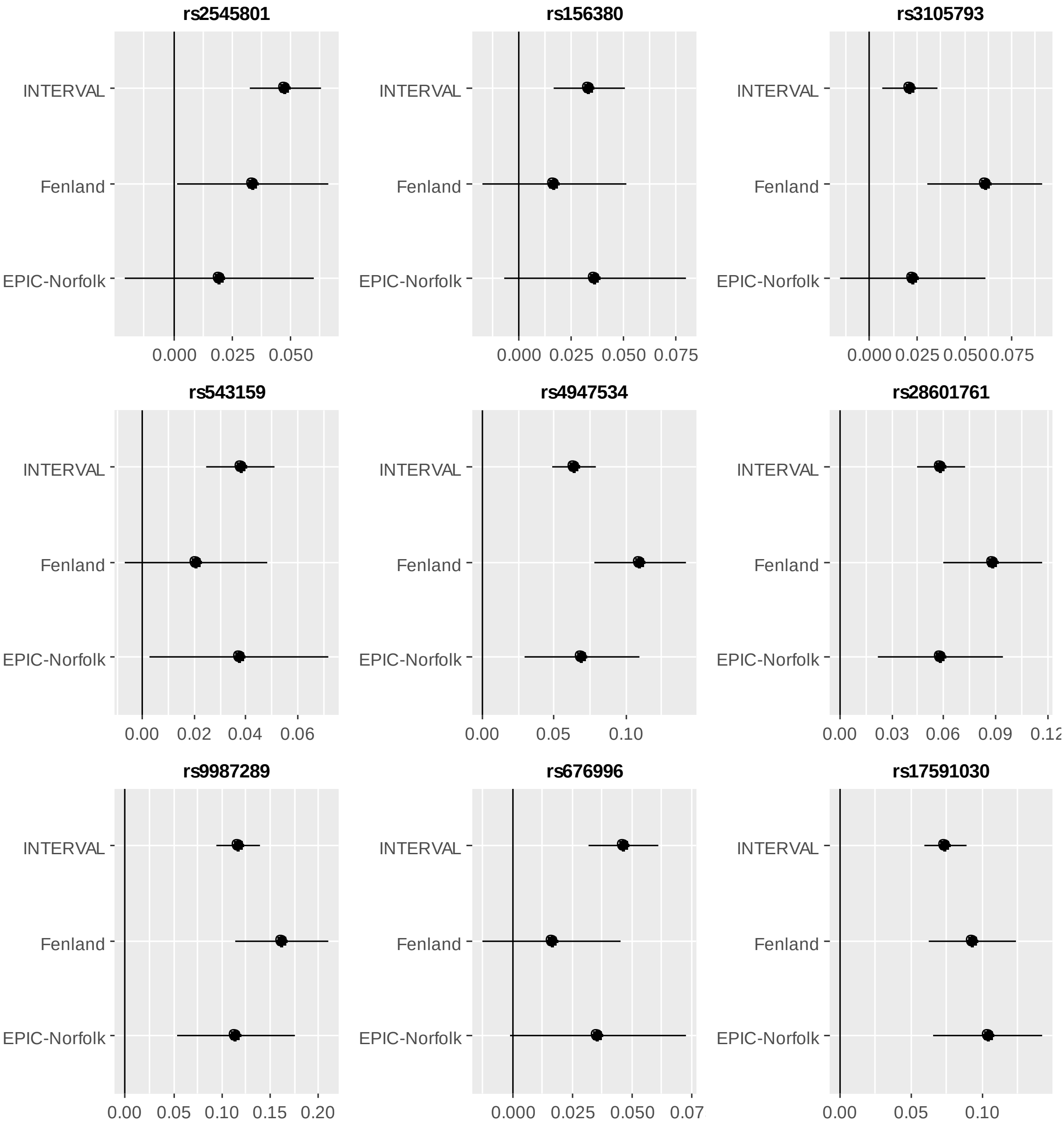
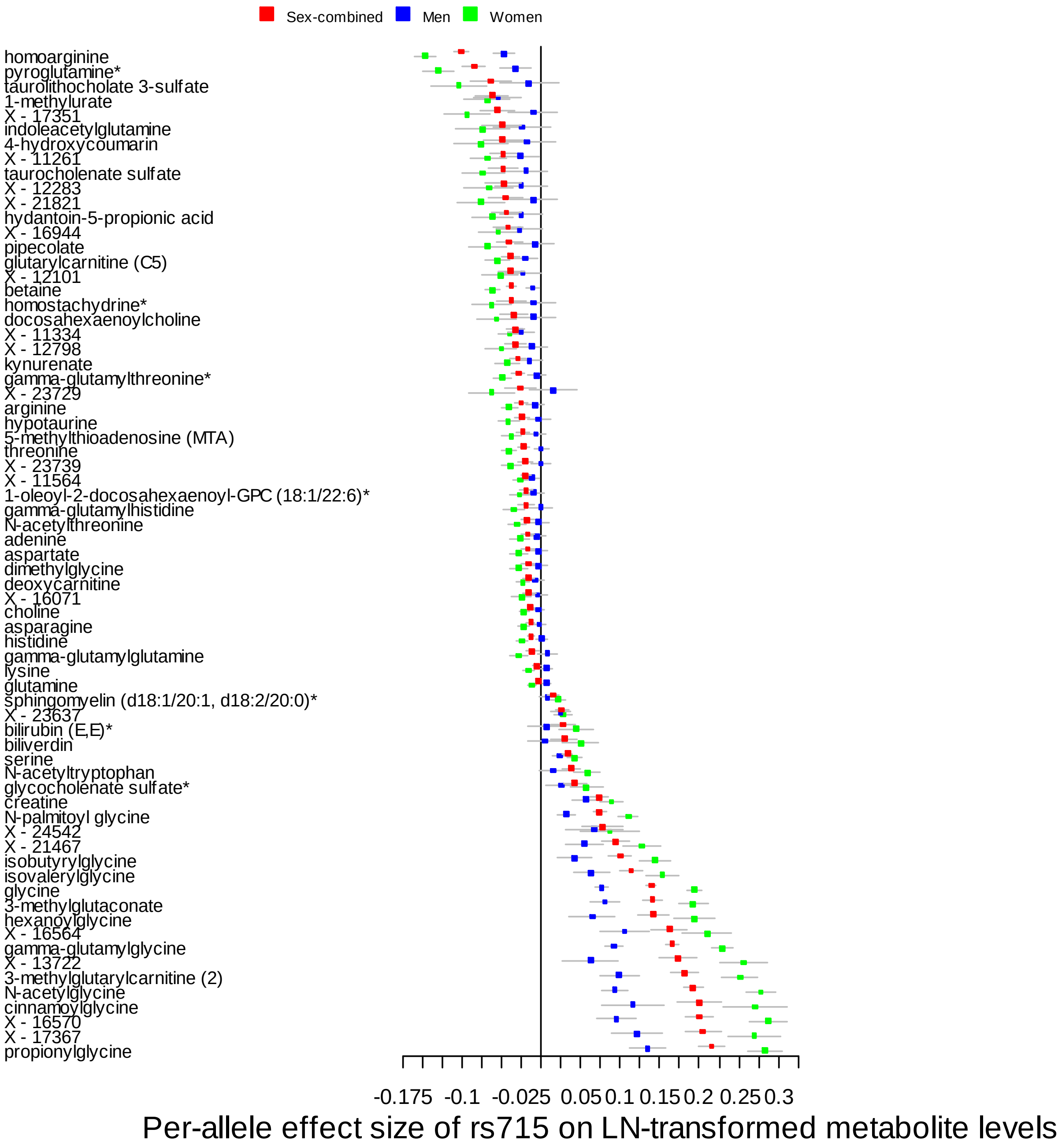
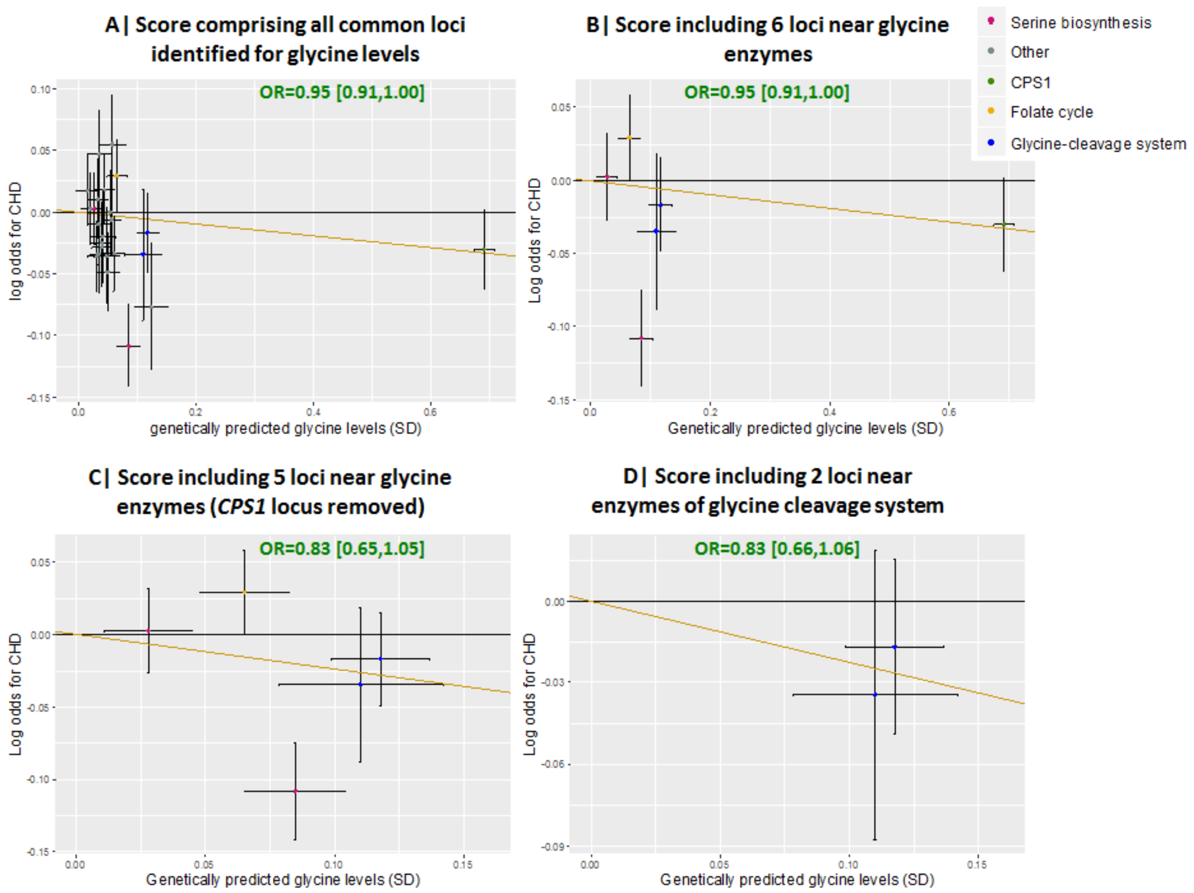


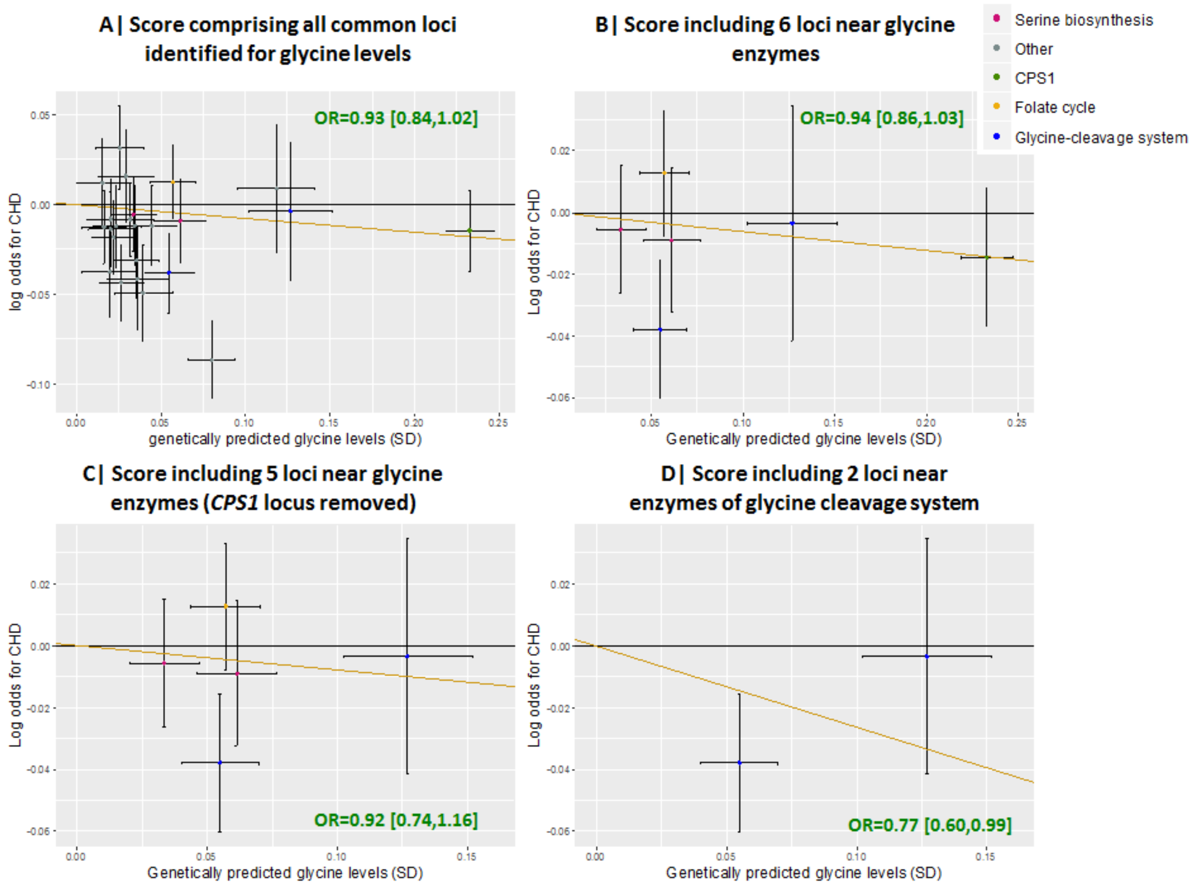
Supplementary Figure 1: Forest plots of study-specific effect sizes of the 27 significant loci on glycine in the Fenland, EPIC-Norfolk and INTERVAL studies. The x axes represent the per-allele effect size on standard deviations of glycine levels.



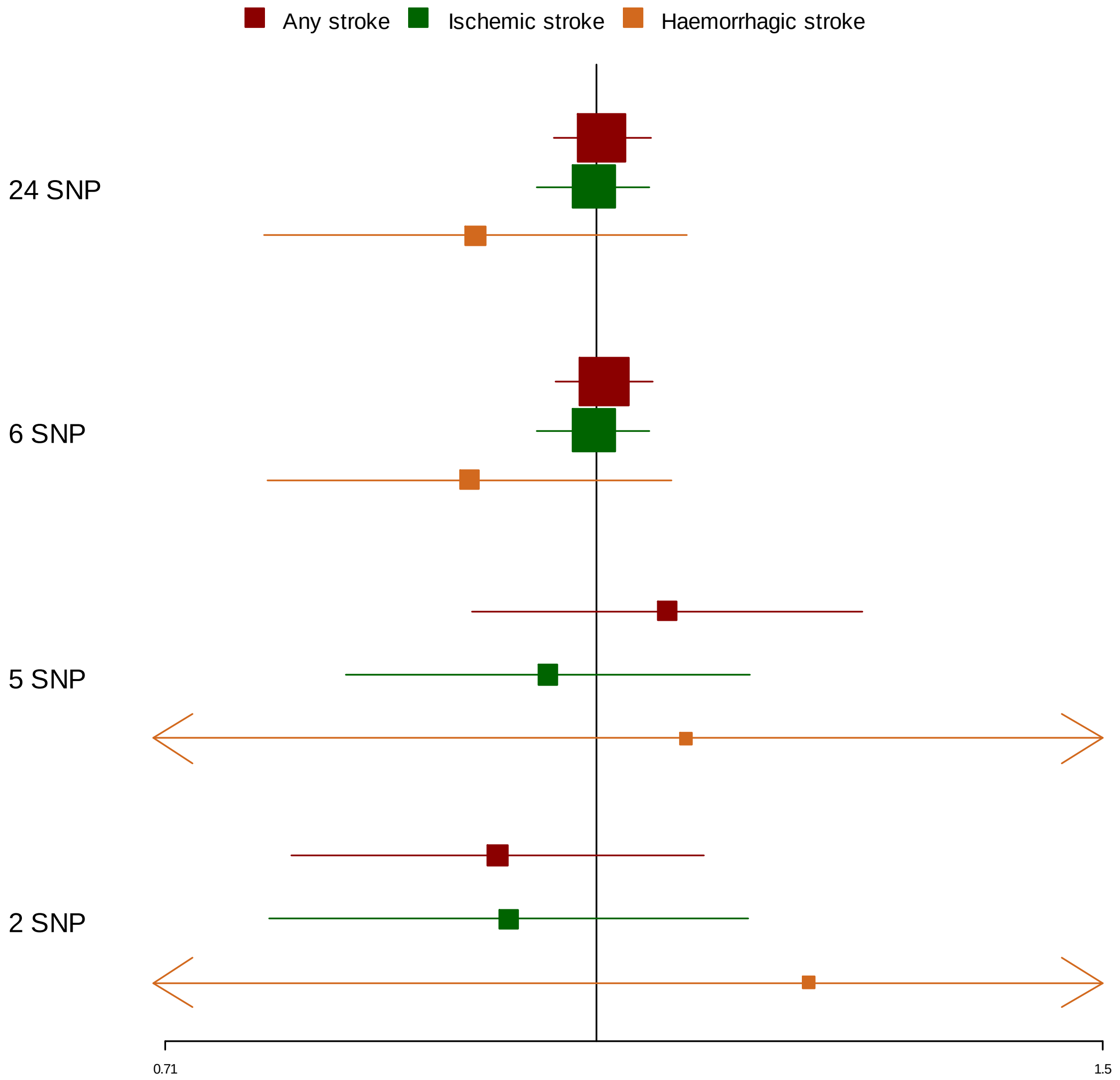
Supplementary Figure 2: Sex-combined and sex-specific per-allele effect sizes of rs715 (*CPS1*) on metabolite levels. Analyses based on 5,706 women and 5,086 men of the EPIC-Norfolk study. Metabolites were included in the plot if they were associated with rs715 at $p<5.6x10^{-4}$ in men or women, i.e., 69 out of 894 metabolites measured in random sub-cohorts A and B and at least 50% of the total sample size.



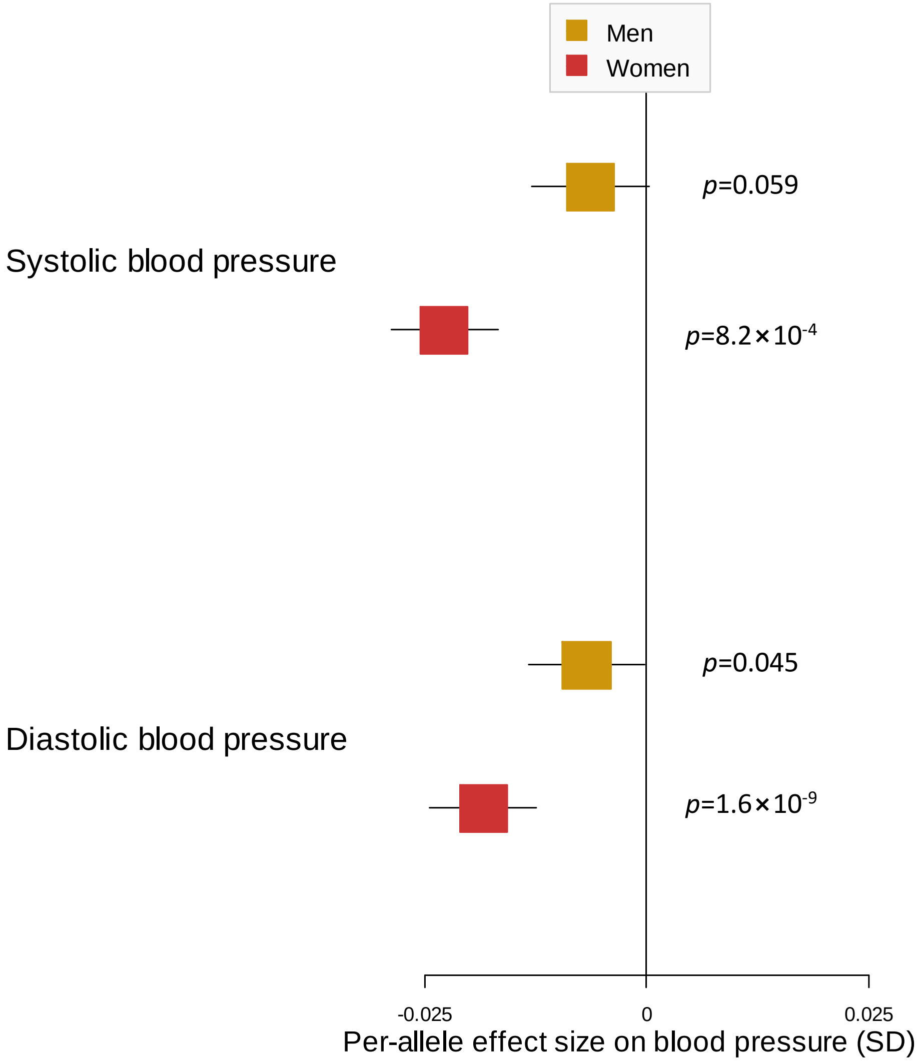
Supplementary Figure 3: Dosage plots of effect sizes of glycine variants on standard deviations of glycine levels versus the log odds for CHD in women: **A|** for the 24 SNP score, **B|** the 6 SNP score, **C|** the 5 SNP score and, **D|** the 2 SNP score. The orange line represents the slope estimated using the weighted median method. Associations with CHD were based on up to 9,853 cases and 202,124 controls from UK Biobank, EPIC-CVD and the GerMIF study.



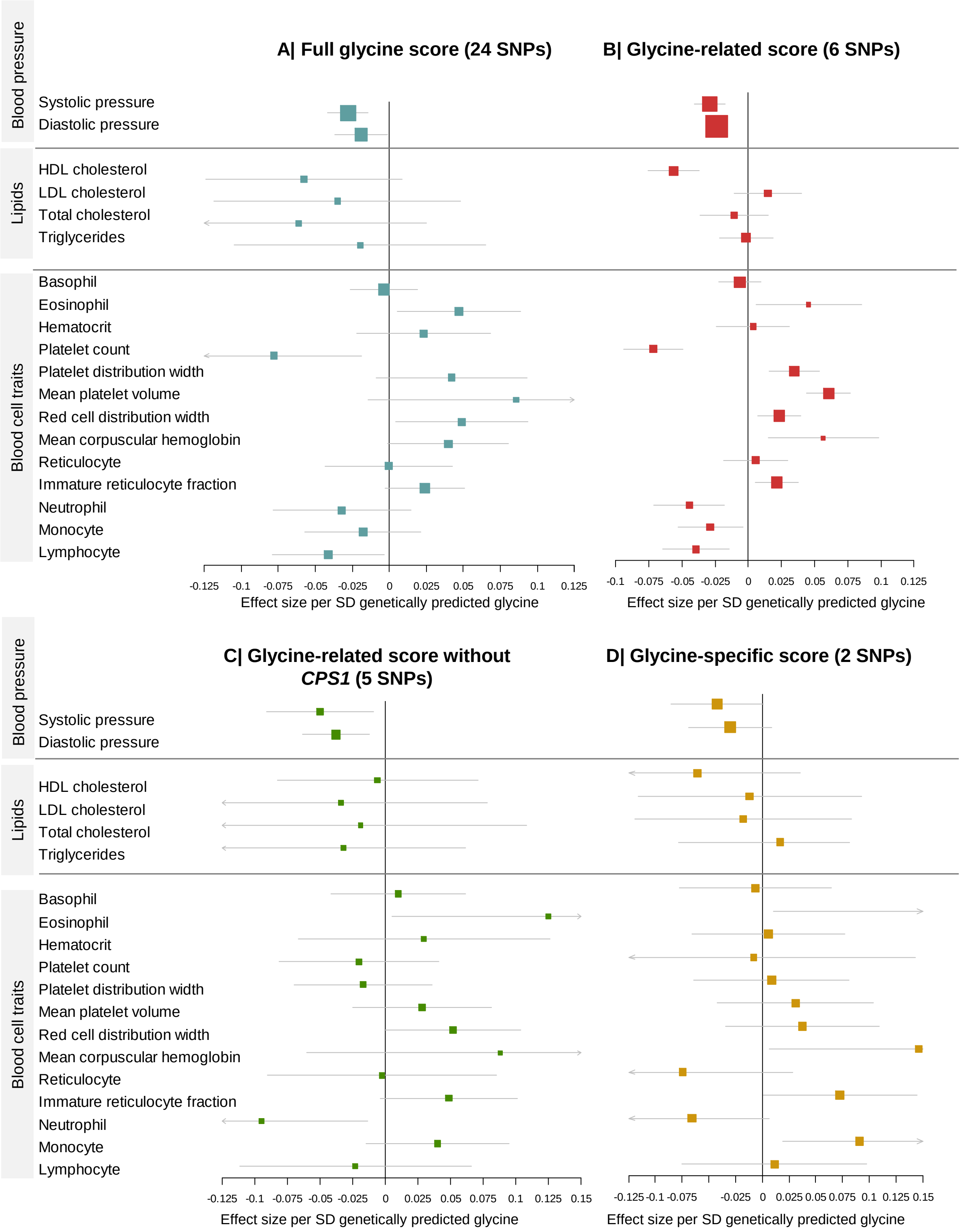
Supplementary Figure 4: Dosage plots of effect sizes of glycine variants on standard deviations of glycine levels versus the log odds for CHD in men: **A|** for the 24 SNP score, **B|** the 6 SNP score, **C|** the 5 SNP score and, **D|** the 2 SNP score. The orange line represents the slope estimated using the weighted median method. Associations with CHD were based on up to 21,944 cases and 194,944 controls from UK Biobank, EPIC-CVD and the GerMIF study.



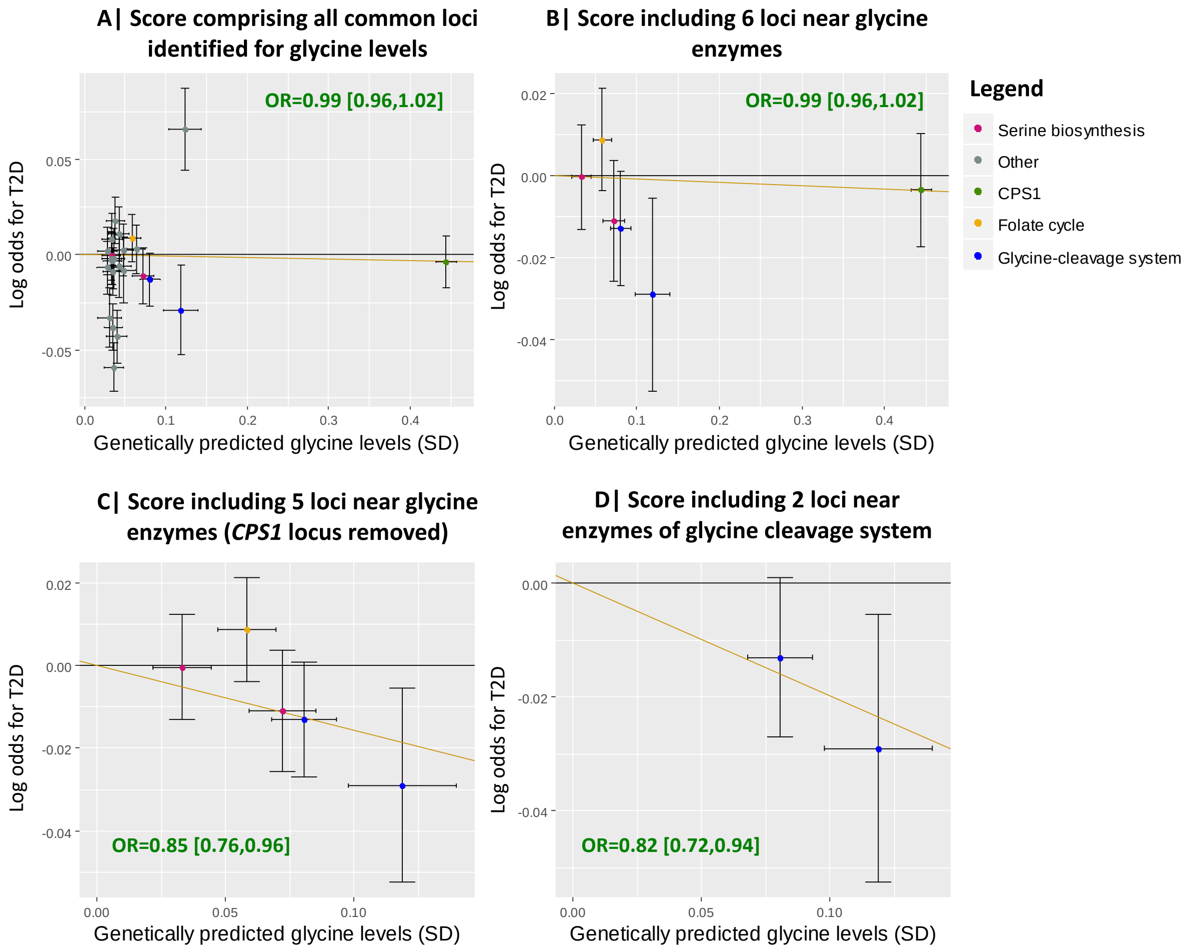
Supplementary Figure 5: **Forest plot of genetically predicted odds ratios on stroke and stroke sub-types per SD of genetically predicted glycine levels.** Results are based on 4 genetic scores for glycine and the weighted median MR method. Analyses were based on summary-level GWAS results from UK Biobank and MEGASTROKE for any and ischemic stroke (Any stroke: up to 48,916 cases and 765,017 non-cases; ischemic stroke: up to 37,771 cases and 764,290 non-cases), and from UK Biobank only for haemorrhagic stroke (1,655 cases and 365,988 non-cases).



Supplementary Figure 6: **Sex-specific associations of the glycine-increasing allele at rs715 with systolic and diastolic blood pressure.** Genetic associations based on 241,417 female and 203,943 male UK Biobank participants. P-values based on two-tailed t-test.



Supplementary Figure 7: Forest plots showing the effect sizes of genetically predicted glycine levels by 4 genetic scores on 19 risk factors of CHD. Genetic associations with blood pressure traits were based on 445,360 UK Biobank participants. Associations with blood lipids were based on look-ups in the summary-level GWAS results from the Global Lipids Genetics Consortium on up to 188,577 participants (Willer *et al*. Nature Genetics 45,1274-1283). Associations with blood cell traits were based on look-ups in the GWAS results on 173,480 participants by Astle *et al.* (Cell 167, 1415-1429).



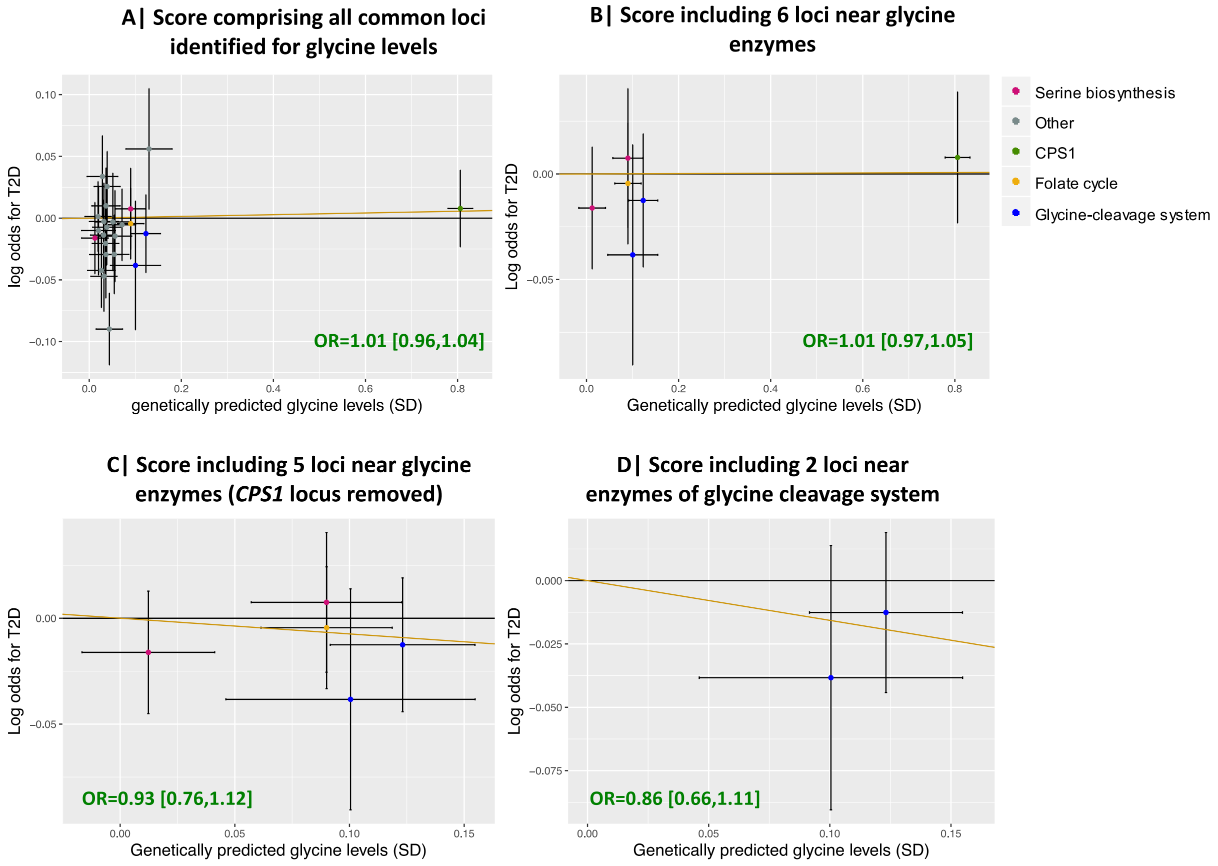
A| Score comprising all common loci identified for glycine levels

B| Score including 6 loci near glycine enzymes

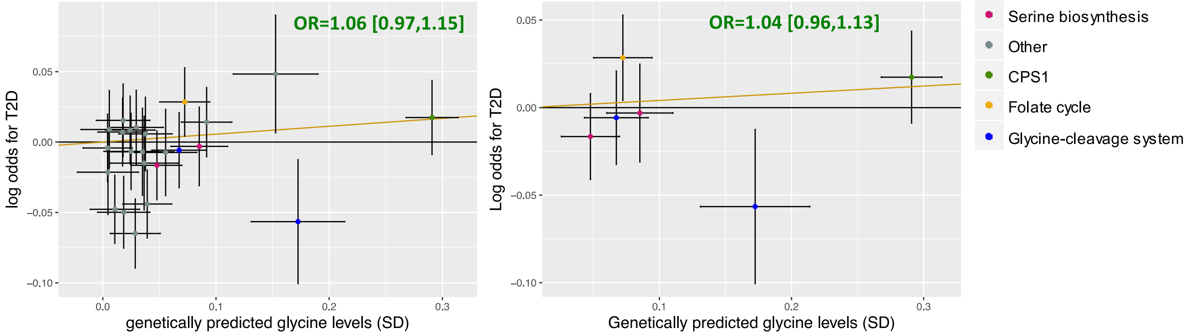
C| Score including 5 loci near glycine enzymes (*CPS1* locus removed)

D| Score including 2 loci near enzymes of glycine cleavage system

Supplementary Figure 8: Dosage plots of the effect sizes of genetic variants for glycine on standard deviations of glycine levels versus the log odds for type 2 diabetes for sex-combined analyses. A| For the 24 SNP score, **B|** 6 SNP score, **C|** 5 SNP score and, **D|** 2 SNP score. The orange line represents the slope estimated using the weighted median method. Genetic effect sizes on T2D were based on look-ups from the latest GWAS from the DIAGRAM consortium (Mahajan *et al.,* Nature Genetics 50, 1505-1513 (2018)), including 74,124 cases and 824,006 controls. The orange line represents the slope estimated using the weighted median method. SD: standard deviation, T2D: type 2 diabetes.

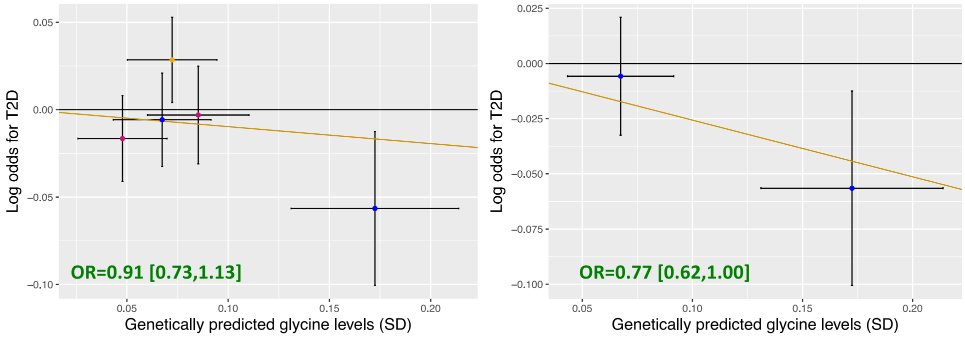


Supplementary Figure 9: Dosage plots of the effect sizes of genetic variants for glycine on standard deviations of glycine levels versus the log odds for type 2 diabetes for women-only analyses. A| For the 24 SNP score, **B|** 6 SNP score, **C|** 5 SNP score and, **D|** 2 SNP score. The orange line represents the slope estimated using the weighted median method. Genetic effect sizes on T2D were based on 12,013 cases and 188,632 controls from InterAct and UK Biobank studies. The orange line represents the slope estimated using the weighted median method. SD: standard deviation, T2D: type 2 diabetes.



A| Score comprising all common loci identified for glycine levels

B| Score including 6 loci near glycine enzymes



C| Score including 5 loci near glycine enzymes (*CPS1* locus removed)

D| Score including 2 loci near enzymes of glycine cleavage system

Supplementary Figure 10: Dosage plots of the effect sizes of genetic variants for glycine on standard deviations of glycine levels versus the log odds for type 2 diabetes for men-only analyses. A| For the 24 SNP score, **B|** 6 SNP score**, C|** 5 SNP score and, **D|** 2 SNP score. Genetic effect sizes on T2D were based on 16,914 cases and 153,582 controls from InterAct and UK Biobank studies. The orange line represents the slope estimated using the weighted median method. SD: standard deviation, T2D: type 2 diabetes.

Supplementary Table 1: Overview of samples, phenotype measurement and transformation, genotyping and imputation for the 5 studies included in the p-value and sample size-based meta-analysis of GWAS for glycine levels

Study	Sample size	Metabolomics platform	Sample type	Fasting status	Phenotype transformation	Genotyping array	Imputation reference panel	Number of variants
Fenland	(A) 949 + (B) 8,375	Biocrates p180	Plasma	Fasted	1) Natural log transformation, 2) Winsorise at 5 SDs, 3) transformation to Z score	(A) Affymetrix Genome-Wide Human SNP Array 5.0/(B) Affymetrix UK Biobank Axiom Array	(A) 1000G phase 1 / (B) 1000G phase 3	30,850,551
EPIC-Norfolk	5,840	Metabolon Discovery HD4	Plasma	Non-fasted	1) Natural log transformation, 2) Winsorise at 5 SDs, 3) transformation to Z score	Affymetrix UK Biobank Array	1000G phase 3	26,328,953
INTERVAL	40,509	High-throughput NMR platform	Serum	Non-fasted	1) Natural log transformation, 2) Winsorise at 5 SDs, 3) transformation to Z score	Affymetrix UK Biobank Arrary	UK10K and 1000G phase 3	34,244,352
Kettunen *et al.*	18,734	High-throughput NMR platform	Serum or plasma	Mostly fasted	Inverse rank-based normal transformation	illumina 610k; Illumina HumanOmniExpress; Illumina HumanCNV37 0; Illumina 318K; Illumina 370K; Affymetrix 250K; Illumina coreexome; Illumina 670k; Affymetrix 6.0; Illumina Human660W; Perlegen-Affymetrix 500K; Illumina 660K; Affymetrix 6.0 907K; Illumina Omni 1M	1000 Genomes Project March 2012	10,577,189
Shin *et al.* - TwinsUK only	5,596	Metabolon Discovery HD3	Plasma	Fasted	Log transformation	HumanHap300, HumanHap610Q, 1M-Duo and 1.2MDuo	HapMap2	2,230,893

Supplementary Table 2: Results of Mendelian randomisation analyses of glycine to CHD, sex-specific and combined, and using 4 different methods and 4 different genetic scores for glycine. IVW: inverse variance weighted; WM: weighted median; PWM: penalised weighted median

Full Score	**Sex-combined**				**Women**				**Men**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.904	0.977	0.948	0.881	0.928	0.957	0.953	0.954	0.817	0.954	0.926	0.937
LCI	0.836	0.897	0.919	0.793	0.848	0.864	0.910	0.912	0.692	0.763	0.842	0.816
UCI	0.978	1.064	0.978	0.979	1.014	1.060	0.997	0.998	0.964	1.193	1.019	1.076
p	0.012	0.587	0.001	0.019	0.100	0.401	0.039	0.041	0.017	0.677	0.118	0.360
CochQ *p*	0.507				0.174				0.092			
interEGGER		-0.013				-0.010				0.007		
EGGER *p*		0.003				0.226				0.057		

6 SNP score	**Sex-combined**				**Women**				**Men**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.945	0.967	0.953	0.958	0.942	0.975	0.954	0.954	0.926	0.972	0.941	0.942
LCI	0.887	0.885	0.924	0.929	0.826	0.816	0.911	0.913	0.814	0.777	0.860	0.857
UCI	1.006	1.056	0.984	0.988	1.075	1.165	0.998	0.998	1.054	1.216	1.029	1.036
p	0.076	0.452	0.003	0.006	0.375	0.779	0.039	0.040	0.245	0.804	0.181	0.218
CochQ *p*	0.845				0.127				0.800			
interEGGER		-0.007				-0.017				-0.007		
EGGER *p*		0.441				0.540				0.585		

5 SNP score	**Sex-combined**				**Women**				**Men**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.836	0.657	0.803	0.767	0.735	0.590	0.827	0.840	0.885	1.043	0.924	0.957
LCI	0.699	0.389	0.710	0.677	0.424	0.128	0.649	0.658	0.663	0.432	0.736	0.756
UCI	0.999	1.110	0.908	0.870	1.273	2.727	1.054	1.072	1.182	2.518	1.161	1.212
p	0.049	0.116	4.8E-4	3.7E-5	0.272	0.500	0.124	0.162	0.408	0.926	0.498	0.716
CochQ *p*	0.789				0.104				0.686			
interEGGER		0.018				0.019				-0.011		
EGGER *p*		0.338				0.759				0.695		

2 SNP score	Sex-combined				Women				Men			
	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM
OR	0.798	NA	0.798	0.798	0.832	NA	0.832	0.832	0.769	NA	0.769	0.798
LCI	0.670	NA	0.693	0.701	0.656	NA	0.655	0.652	0.413	NA	0.595	0.615
UCI	0.950	NA	0.919	0.908	1.055	NA	1.056	1.062	1.433	NA	0.993	1.036
p	0.011	NA	0.002	0.001	0.130		0.131	0.139	0.408	NA	0.044	0.091
CochQ *p*	0.677				0.784				0.269			
interEGGER		NA				NA				NA		
EGGER *p*		NA				NA				NA		

Supplementary Table 3: Results of Mendelian randomisation analyses of glycine to stroke and stroke sub-types, using 4 different methods and 4 different genetic scores for glycine. IVW: inverse variance weighted; WM: weighted median; PWM: penalised weighted median

24 SNP score	**Any stroke**				**Ischemic stroke**				**Haemorrhagic stroke**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.997	1.008	1.004	1.004	0.994	0.999	0.997	0.997	0.972	0.883	0.907	0.907
LCI	0.950	0.948	0.965	0.966	0.933	0.921	0.953	0.954	0.837	0.733	0.766	0.767
UCI	1.046	1.071	1.044	1.045	1.059	1.083	1.043	1.041	1.129	1.064	1.074	1.072
p	0.910	0.802	0.847	0.824	0.863	0.977	0.896	0.892	0.711	0.192	0.258	0.251
CochQ *p*	0.995				0.899				0.922			
interEGGER		-0.002				-0.001				0.017		
EGGER *p*		0.572				0.858				0.040		

6 SNP score	**Any stroke**				**Ischemic stroke**				**Haemorrhagic stroke**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	1.005	0.984	1.006	1.006	0.995	0.980	0.997	0.997	0.924	0.868	0.903	0.903
LCI	0.958	0.923	0.968	0.968	0.946	0.912	0.953	0.954	0.788	0.700	0.768	0.767
UCI	1.054	1.050	1.045	1.045	1.046	1.054	1.043	1.043	1.085	1.076	1.061	1.063
p	0.844	0.624	0.776	0.759	0.848	0.587	0.899	0.897	0.335	0.195	0.215	0.220
CochQ *p*	0.942				0.916				0.878			
interEGGER		0.006				0.004				0.019		
EGGER *p*		0.340				0.539				0.285		

5 SNP score	**Any stroke**				**Ischemic stroke**				**Haemorrhagic stroke**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	1.019	0.686	1.058	1.058	0.981	0.631	0.961	0.961	1.153	1.039	1.074	1.074
LCI	0.860	0.485	0.905	0.907	0.820	0.423	0.817	0.808	0.689	0.236	0.574	0.579
UCI	1.207	0.968	1.237	1.246	1.173	0.941	1.131	1.143	1.931	4.574	2.008	1.991
p	0.829	0.032	0.480	0.449	0.830	0.024	0.633	0.654	0.587	0.959	0.824	0.822
CochQ *p*	0.877				0.832				0.818			
interEGGER		0.029				0.032				0.008		
EGGER *p*		0.006				0.001				0.874		

2 SNP score	**Any stroke**				**Ischemic stroke**				**Haemorrhagic stroke**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.923	NA	0.923	0.923	0.932	NA	0.932	0.932	1.185	NA	1.185	1.185
LCI	0.668	NA	0.782	0.785	0.742	NA	0.769	0.767	0.585	NA	0.586	0.574
UCI	1.276	NA	1.090	1.086	1.170	NA	1.129	1.133	2.401	NA	2.398	2.448
p	0.629	NA	0.346	0.334	0.543	NA	0.472	0.478	0.637	NA	0.636	0.646
CochQ *p*	0.494				0.655				0.566			
interEGGER		NA				NA				NA		
EGGER *p*		NA				NA				NA		

Supplementary Table 4: Results of Cox proportional hazards models for the association of glycine levels with coronary heart disease, myocardial infarction and stroke (including stroke subtypes)

Disease	Sex-combined		Women		Men	
	HR [95% CI]	***p***	**HR [95% CI]**	***p***	**HR [95% CI]**	***p***
Coronary heart disease	0.92 [0.87,0.96]	4.7E-04	0.94 [0.88,1.01]	0.083	0.88 [0.82,0.95]	7.2E-04
Myocardial infarction	0.89 [0.82,0.97]	5.5E-03	0.95 [0.85,1.07]	0.39	0.82 [0.73,0.93]	1.6E-03
Stroke (any)	0.99 [0.93,1.05]	0.70	0.98 [0.91,1.06]	0.68	1.00 [0.90,1.10]	0.92
Haemorrhagic stroke	1.11 [0.96,1.29]	0.15	1.07 [0.89,1.28]	0.49	1.20 [0.94,1.53]	0.13
Ischemic stroke	1.00 [0.92,1.10]	0.95	1.02 [0.91,1.14]	0.74	0.97 [0.84, 1.13]	0.73

Supplementary Table 5: results of inverse variance-weighted Mendelian randomisation analyses for the assessment of the effect of glycine levels on 19 CHD risk factors

CHD risk factors	24 SNP score			6 SNP score			5 SNP score			2 SNP score		
	beta	**SE**	**p-value**	**beta**	**SE**	**p-value**	**beta**	**SE**	**p-value**	**beta**	**SE**	**p-value**
Systolic blood pressure	-0.028	0.007	1.49E-05	-0.029	0.006	2.56E-06	-0.050	0.021	1.93E-02	-0.042	0.022	5.71E-02
Diastolic blood pressure	-0.019	0.009	3.87E-02	-0.024	0.004	4.32E-11	-0.038	0.013	3.09E-03	-0.030	0.020	1.28E-01
HDL cholesterol	-0.058	0.034	8.89E-02	-0.056	0.010	7.37E-09	-0.006	0.039	8.76E-01	-0.061	0.049	2.16E-01
LDL cholesterol	-0.035	0.043	4.11E-01	0.015	0.013	2.53E-01	-0.034	0.057	5.53E-01	-0.012	0.053	8.23E-01
Total cholesterol	-0.061	0.044	1.65E-01	-0.011	0.013	4.18E-01	-0.019	0.065	7.68E-01	-0.018	0.052	7.30E-01
Triglycerides	-0.020	0.043	6.48E-01	-0.002	0.010	8.69E-01	-0.032	0.048	4.98E-01	0.017	0.048	7.31E-01
Basophil	-0.004	0.012	7.52E-01	-0.006	0.008	4.25E-01	0.010	0.026	7.11E-01	-0.007	0.036	8.56E-01
Eosinophil	0.047	0.021	2.75E-02	0.046	0.020	2.52E-02	0.125	0.061	4.12E-02	0.213	0.103	3.92E-02
Haematocrit	0.023	0.023	3.14E-01	0.004	0.014	7.96E-01	0.030	0.049	5.49E-01	0.006	0.036	8.76E-01
Platelet count	-0.078	0.030	9.94E-03	-0.072	0.011	3.16E-10	-0.020	0.031	5.16E-01	-0.008	0.077	9.17E-01
Platelet distribution width	0.042	0.026	1.06E-01	0.035	0.010	2.88E-04	-0.017	0.027	5.25E-01	0.009	0.037	8.15E-01
Mean platelet volume	0.086	0.051	9.25E-02	0.061	0.008	5.35E-13	0.028	0.027	3.04E-01	0.031	0.037	4.06E-01
Red cell distribution width	0.049	0.023	3.15E-02	0.023	0.008	4.37E-03	0.052	0.027	5.29E-02	0.038	0.037	3.04E-01
Mean corpuscular haemoglobin	0.040	0.021	5.63E-02	0.057	0.021	7.78E-03	0.088	0.076	2.45E-01	0.146	0.071	4.00E-02
Reticulocyte	-0.001	0.022	9.80E-01	0.006	0.012	6.48E-01	-0.003	0.045	9.52E-01	-0.074	0.052	1.56E-01
Immature reticulocyte fraction	0.024	0.014	7.83E-02	0.021	0.008	9.42E-03	0.049	0.027	6.93E-02	0.072	0.037	4.79E-02

Neutrophil	-0.032	0.024	1.80E-01	-0.045	0.014	1.03E-03	-0.095	0.042	2.26E-02	-0.066	0.037	7.52E-02
Monocyte	-0.018	0.020	3.73E-01	-0.029	0.013	2.24E-02	0.040	0.028	1.52E-01	0.091	0.037	1.35E-02
Lymphocyte	-0.041	0.019	3.32E-02	-0.040	0.013	1.87E-03	-0.023	0.045	6.11E-01	0.012	0.044	7.93E-01

Supplementary Table 6: Results of Mendelian randomisation analyses of glycine to T2D, sex-specific and combined, and using 4 different methods and 4 different genetic scores for glycine. IVW: inverse variance weighted; WM: weighted median; PWM: penalised weighted median.

24 SNP score	**Sex-combined**				**Women**				**Men**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.975	1.025	0.992	0.992	0.994	1.032	1.007	1.007	1.009	1.135	1.058	1.063
LCI	0.892	0.921	0.962	0.961	0.928	0.96	0.969	0.969	0.875	0.954	0.970	0.973
UCI	1.064	1.140	1.022	1.024	1.065	1.109	1.046	1.046	1.163	1.349	1.154	1.162
p	0.566	0.651	0.593	0.611	0.871	0.391	0.731	0.729	0.902	0.152	0.203	0.178
CochQ *p*	0.028				0.139				2.00E-04			
interEGGER		-0.009				-0.014				-0.015		
EGGER *p*		0.121				0.026				0.038		

6 SNP score	**Sex-combined**				**Women**				**Men**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.982	0.996	0.992	0.992	1.005	1.025	1.008	1.008	1.022	1.051	1.042	1.049
LCI	0.939	0.933	0.961	0.962	0.968	0.978	0.971	0.972	0.894	0.823	0.957	0.963
UCI	1.028	1.063	1.023	1.023	1.043	1.074	1.046	1.045	1.169	1.342	1.134	1.142
p	0.566	0.651	0.593	0.611	0.801	0.310	0.683	0.675	0.752	0.689	0.342	0.271
CochQ *p*	0.955				0.846				0.807			
interEGGER		-0.004				-0.011				-0.005		
EGGER *p*		0.533				0.084				0.776		

5 SNP score	**Sex-combined**				**Women**				**Men**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	0.896	0.703	0.854	0.853	0.919	1.054	0.928	0.928	0.918	0.708	0.908	0.831
LCI	0.783	0.499	0.763	0.754	0.778	0.735	0.767	0.763	0.704	0.338	0.730	0.675
UCI	1.026	0.991	0.957	0.964	1.085	1.511	1.123	1.130	1.197	1.483	1.129	1.024
p	0.112	0.044	6.514E-03	1.090E-02	0.318	0.775	0.445	0.460	0.527	0.360	0.385	0.082
CochQ *p*	0.927				0.792				0.724			
interEGGER		0.018				-0.014				0.023		
EGGER *p*		0.140				0.354				0.458		

2 SNP score	**Sex-combined**				**Women**				**Men**			

	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM
OR	0.821	NA	0.821	0.821	0.919	NA	0.855	0.855	0.774	NA	0.774	0.774
LCI	0.721	NA	0.718	0.718	0.778	NA	0.661	0.664	0.623	NA	0.620	0.613
UCI	0.935	NA	0.939	0.938	1.085	NA	1.106	1.100	0.960	NA	0.966	0.976
p	2.99E-03	NA	4.00E-03	3.71E-03	0.318	NA	0.233	0.223	0.020	NA	0.024	0.031
CochQ *p*	0.849				0.657	NA			0.674			
interEGGER		NA				NA				NA		
EGGER *p*		NA				NA				NA		

Supplementary Table 7: Reverse Mendelian randomisation analyses to assess the causality of T2D risk factors on glycine levels. IVW: inverse variance weighted; WM: weighted median; PWM: penalised weighted median.

BMI	**IVW**	**MR-Egger**	**WM**	**PWM**
Beta	-0.041	-0.041	-0.009	-0.007
SE	0.030	0.074	0.041	0.040
pvalue	0.169	0.581	0.825	0.870
CochQp	1.000			
interEGGER		-1.34E-05		
interEGGER p		0.995		

Fasting insulin	**IVW**	**EGGER**	**WM**	**PWM**
beta	-0.960	-1.179	-0.863	-0.822
SE	0.212	1.253	0.211	0.211
P	5.98E-06	3.47E-01	4.29E-05	9.56E-05
CochQ *p*	0.393			
interEGGER		0.003		
interEGGER p		0.859		

Early-phase insulin secretion	**IVW**	**EGGER**	**MW**	**PMW**
Beta	0.022	-0.030	-0.011	-0.010
SE	0.033	0.087	0.038	0.037
pvalue	0.516	0.733	0.762	0.786
CochQ *p*	0.999			
interEGGER		-0.003		
EGGER *p*		0.524		

Supplementary Table 8: Results of Mendelian randomisation analyses of glycine to 3 site-specific cancers. IVW: inverse variance weighted; WM: weighted median; PWM: penalised weighted median.

24 SNP score	**Breast cancer**				**Ovarian cancer**				**Prostate cancer**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	1.014	1.016	1.018	1.018	0.989	1.011	1.006	1.007	0.985	1.085	1.045	1.046
LCI	0.987	0.984	0.998	0.998	0.929	0.942	0.966	0.967	0.862	0.900	0.973	0.976
UCI	1.042	1.049	1.038	1.038	1.052	1.085	1.049	1.048	1.127	1.308	1.123	1.120
pvalue	0.300	0.334	0.083	0.083	0.723	0.767	0.759	0.743	0.830	0.390	0.226	0.206
CochQp	0.998				0.591				0.046			
interEGGER		0.000			-0.007					-0.009		
interEGGER *p*		0.862			0.221					0.154		

6 SNP score	**Breast cancer**				**Ovarian cancer**				**Prostate cancer**			
	IVW	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**	**IVW**	**EGGER**	**WM**	**PWM**
OR	1.017	1.012	1.017	1.017	0.998	1.020	1.007	1.007	1.008	1.080	1.034	1.051
LCI	0.996	0.983	0.997	0.997	0.926	0.922	0.966	0.968	0.878	0.859	0.959	0.975
UCI	1.039	1.042	1.037	1.037	1.076	1.127	1.050	1.048	1.156	1.359	1.115	1.134
pvalue	0.119	0.409	0.092	0.091	0.964	0.705	0.749	0.720	0.914	0.511	0.386	0.193
CochQp	0.954				0.570				0.614			
interEGGER		0.002				-0.010				-0.010		
interEGGER *p*		0.609				0.501				0.447		

5 SNP score	Breast cancer				Ovarian cancer				Prostate cancer			
	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM
OR	0.999	0.820	0.986	0.986	0.845	0.699	0.922	0.962	0.898	0.905	0.842	0.825
LCI	0.909	0.676	0.900	0.900	0.624	0.306	0.746	0.778	0.676	0.381	0.674	0.669
UCI	1.098	0.995	1.081	1.080	1.144	1.600	1.140	1.191	1.191	2.148	1.052	1.017
pvalue	0.984	0.044	0.770	0.768	0.276	0.397	0.453	0.724	0.454	0.820	0.129	0.071
CochQp	0.894				0.511				0.531			
interEGGER		0.018				0.017				-0.001		
interEGGER *p*		1.52E-04				0.624				0.985		

2 SNP score	Breast cancer				Ovarian cancer				Prostate cancer			
	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM	IVW	EGGER	WM	PWM
OR	0.963	NA	0.963	0.963	0.789	NA	0.789	0.911	0.768	NA	0.768	0.768
LCI	0.869	NA	0.868	0.869	0.414	NA	0.629	0.715	0.636	NA	0.633	0.633
UCI	1.066	NA	1.067	1.066	1.505	NA	0.991	1.162	0.926	NA	0.931	0.932
pvalue	0.463	NA	0.466	0.463	0.473	NA	0.042	0.454	0.006	NA	0.007	0.007
CochQp	0.798				0.570				0.792			
interEGGER		NA				NA				NA		
interEGGER *p*		NA				NA				NA		

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