



Dimou, N. L., Papadimitriou, N., Gill, D., Christakoudi, S., Murphy, N., Gunter, M. J., Travis, R. C., Key, T. J., Fortner, R. T., Haycock, P. C., Lewis, S. J., Muir, K., Martin, R. M., & Tsilidis, K. K. (2019). Sex hormone binding globulin and risk of breast cancer: A Mendelian randomization study. *International Journal of Epidemiology*, 48(3), 807-816. [dyz107]. <https://doi.org/10.1093/ije/dyz107>

Peer reviewed version

Link to published version (if available):
[10.1093/ije/dyz107](https://doi.org/10.1093/ije/dyz107)

[Link to publication record in Explore Bristol Research](#)
PDF-document

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Supplemental Table 1. Univariable Mendelian Randomization estimates between SHBG GWAS-identified genetic variants and breast cancer risk.

	Overall Breast Cancer				ER ^{+ve} Breast Cancer				ER ^{-ve} Breast Cancer			
	OR ^a	95% CI	P-value	Heterogeneity P-value ^b	OR ^a	95% CI	P-value	Heterogeneity P-value ^b	OR ^a	95% CI	P-value	Heterogeneity P-value ^b
IVW ^c	0.96	0.92 - 1.00	0.07	0.01	0.95	0.91 - 1.00	0.06	0.02	1.09	1.01 - 1.18	0.03	0.59
MR-Egger slope	1.00	0.86 - 1.15	0.95		0.99	0.83 - 1.18	0.88		1.03	0.87 - 1.21	0.74	
MR-Egger intercept			0.57				0.61				0.38	
Weighted median	0.98	0.92 - 1.04	0.44		0.99	0.92 - 1.06	0.74		1.05	0.95 - 1.16	0.33	
Weighted mode	0.98	0.92 - 1.04	0.41		0.98	0.91 - 1.05	0.52		1.06	0.95 - 1.18	0.31	
MR-PRESSO ^d	0.99	0.94 - 1.03	0.53	0.16	0.98	0.93 - 1.04	0.50	0.28	1.09	1.01 - 1.18	0.03	0.59
Sensitivity analysis 1 ^e	0.95	0.91 - 0.99	0.03	0.04	0.94	0.89 - 0.99	0.02	0.03	1.08	1.00 - 1.17	0.04	0.55
Sensitivity analysis 2 ^f	0.94	0.90 - 0.99	0.02	0.05	0.94	0.89 - 1.00	0.04	0.03	1.05	0.96 - 1.15	0.26	0.71
Sensitivity analysis 3 ^g	0.97	0.92 - 1.01	0.16	<0.01	0.96	0.90 - 1.02	0.17	<0.01	1.04	0.95 - 1.14	0.41	0.60
Sensitivity analysis 4 ^h	0.96	0.92 - 1.00	0.08	0.01	0.95	0.90 - 1.00	0.04	0.02	1.10	1.02 - 1.20	0.01	0.69
Sensitivity analysis 5 ⁱ	0.98	0.93 - 1.04	0.46	0.94	0.97	0.91 - 1.04	0.41	0.34	1.07	0.97 - 1.19	0.17	0.19
Sensitivity analysis 6 ^j	0.93	0.86 - 1.00	0.04	0.92	0.91	0.83 - 0.99	0.03	0.89	1.15	1.00 - 1.32	0.04	0.51

^a The odds ratios represent increase/decrease of risk per 25nmol/L increase in SHBG levels.

^b P-values of Chi-square Q test for heterogeneity are shown.

^c Results from the fixed-effects IVW MR analysis are shown (N=12 SNPs).

^d 11 SNPs were used for the overall and ER^{+ve} breast cancer analyses after excluding rs7910927. For ER^{-ve} breast cancer, we used 12 SNPs as no outliers were indicated.

^e Sensitivity analysis 1: We used 11 SNPs after excluding rs780093 due to potential pleiotropy with several other traits (1-4).

^f Sensitivity analysis 2: We used 9 SNPs after excluding rs1641537, rs1625895 and rs3779195 derived from conditional analyses in the GWAS of SHBG (5).

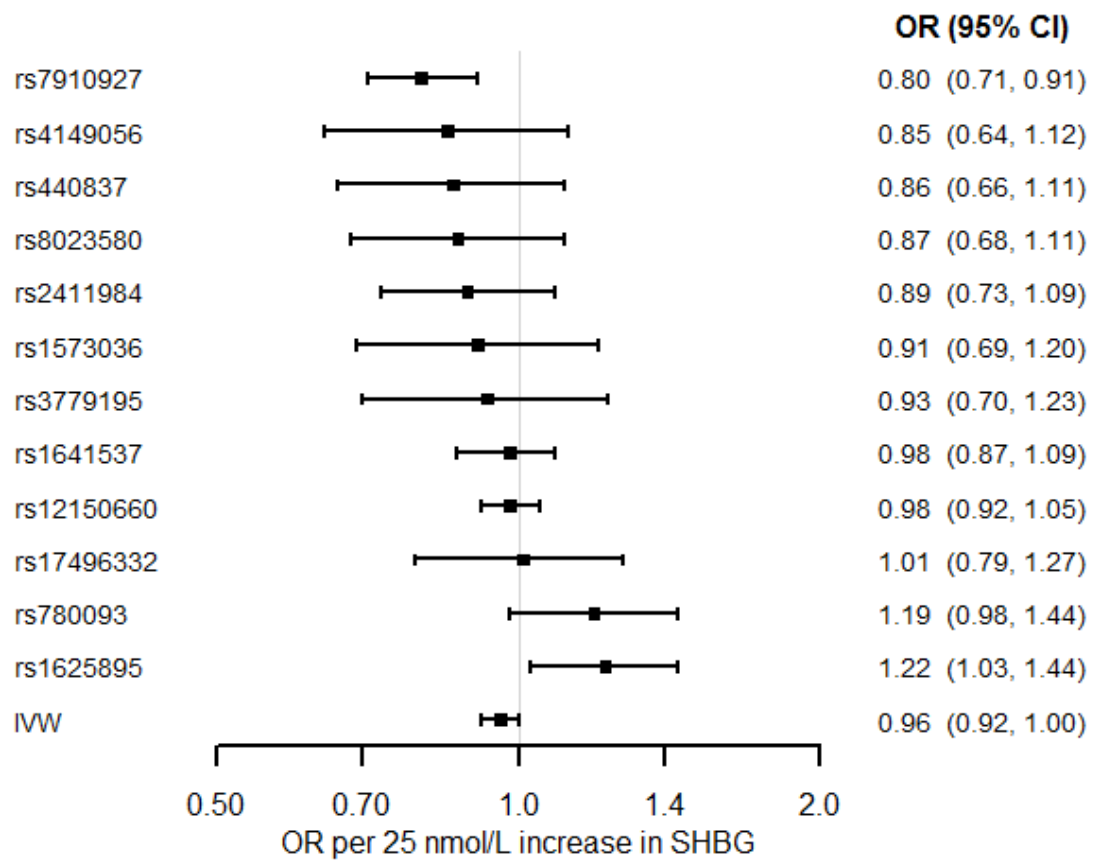
^g Sensitivity analysis 3: We used as instruments only the 3 SNPs (i.e. rs12150660, rs7910927, rs780093), which were significant in the GWAS analysis for SHBG only in women (5).

^h Sensitivity analysis 4: We used female-specific estimates for the SNP-SHBG associations (for 3 SNPs i.e. rs1641537, rs1625895 and rs3779195 estimates were only reported in males and females together) (5).

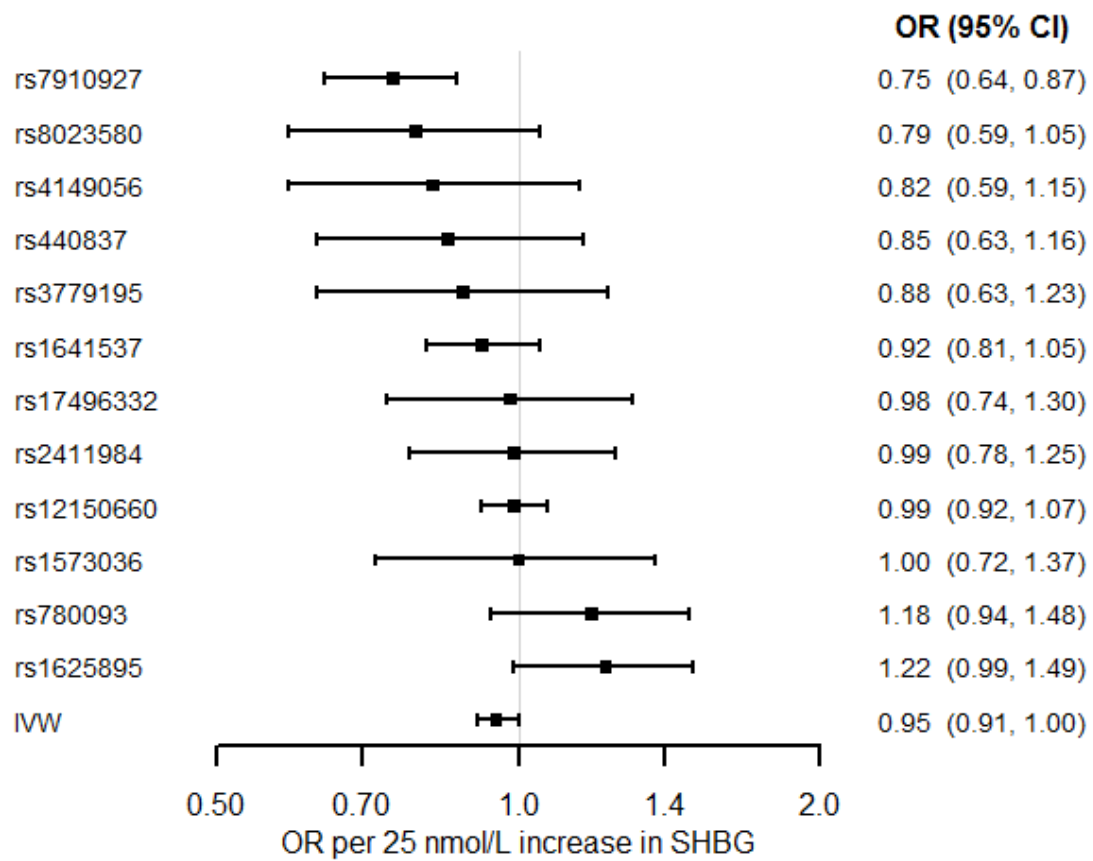
ⁱ Sensitivity analysis 5: We used 2 SNPs in the SHBG gene (rs12150660 and rs1641537) (5).

^j Sensitivity analysis 6: We used 7 SNPs after excluding rs12150660, rs1625895, rs7910927, rs780093 and rs17496332 due to association with BMI (6).

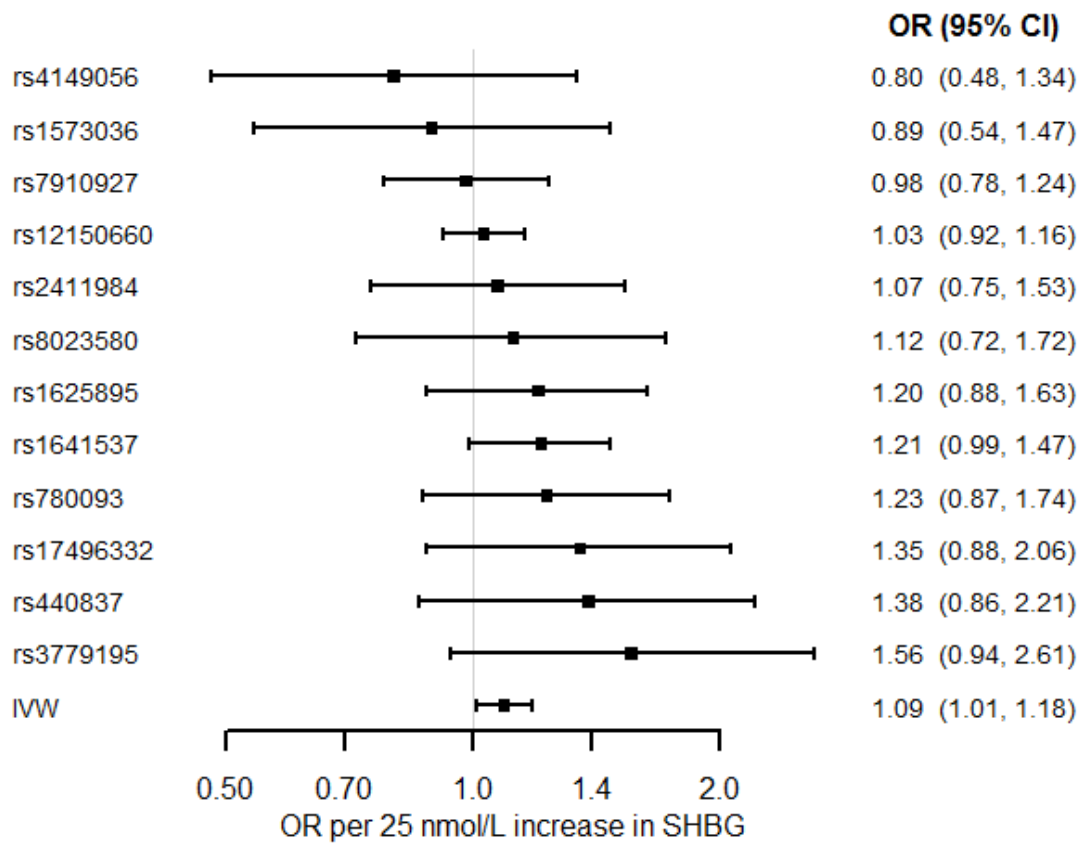
Abbreviations: OR, odds ratio; 95% CI, 95% confidence Interval; IVW, inverse-variance weighted; GWAS, genome-wide association studies; ER, oestrogen receptor; SHBG, sex hormone-binding globulin; N, number of SNPs used in the analysis; BMI, Body Mass Index



Supplemental Figure 1. Forest plot showing MR analysis by each separate SNP and the pooled univariable MR result between sex hormone-binding globulin (SHBG) concentrations and risk of overall breast cancer (Cochran's Q P: 0.01).



Supplemental Figure 2. Forest plot showing MR analysis by each separate SNP and the pooled univariable MR result between sex hormone-binding globulin (SHBG) concentrations and risk of ER⁺ve breast cancer (Cochran's Q P: 0.02).



Supplemental Figure 3. Forest plot showing MR analysis by each separate SNP and the pooled univariable MR result between sex hormone-binding globulin (SHBG) concentrations and risk of ER-ve breast cancer (Cochran's Q P: 0.59).

References

1. Below JE, Parra EJ, Gamazon ER, Torres J, Krithika S, Candille S, et al. Meta-analysis of lipid-traits in Hispanics identifies novel loci, population-specific effects, and tissue-specific enrichment of eQTLs. *Sci Rep.* 2016;6:19429.
2. Eriksson N, Benton GM, Do CB, Kiefer AK, Mountain JL, Hinds DA, et al. Genetic variants associated with breast size also influence breast cancer risk. *BMC Med Genet.* 2012;13:53.
3. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet.* 2010;42(12):1118-25.
4. Yang Q, Kottgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet.* 2010;3(6):523-30.
5. Coviello AD, Haring R, Wellons M, Vaidya D, Lehtimaki T, Keildson S, et al. A genome-wide association meta-analysis of circulating sex hormone-binding globulin reveals multiple Loci implicated in sex steroid hormone regulation. *PLoS Genet.* 2012;8(7):e1002805.
6. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature.* 2015;518(7538):197-206.