



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/>

Table 1. Characteristics of genetic variants associated with sex hormone-binding globulin (SHBG) and breast cancer in published GWAS.

SNPs	Chr: pos (hg19)	Locus	Effect/ Ref allele	Circulating SHBG		Body Mass Index		Overall Breast Cancer		ER ^{+ve} Breast Cancer		ER ^{-ve} Breast Cancer	
				Beta ^a (SE)	P-value	Beta ^b (SE)	P-value	Beta ^c (SE)	P-value	Beta ^c (SE)	P-value	Beta ^c (SE)	P-value
rs17496332	1:107546375	PRMT6	G/A	0.028 (0.0041)	1.40E-11	0.0124 (0.0032)	1.01E-04	0.0003 (0.0068)	9.61E-01	-0.0009 (0.0081)	9.13E-01	0.0169 (0.0123)	1.68E-01
rs780093	2:27742603	GCKR	C/T	0.032 (0.0039)	2.20E-16	0.012 (0.0030)	7.64E-05	0.0113 (0.0064)	7.55E-02	0.0106 (0.0076)	1.61E-01	0.0136 (0.0115)	2.39E-01
rs3779195	7:97993362	BAIAP2L1	T/A	0.028 (0.0051)	2.70E-08	-0.001 (0.0047)	8.32E-01	-0.0040 (0.0081)	6.23E-01	-0.0072 (0.0096)	4.50E-01	0.0253 (0.0148)	8.76E-02
rs440837	8:81461974	ZBTB10	G/A	0.028 (0.0047)	3.40E-09	-0.0058 (0.0045)	1.97E-01	-0.0088 (0.0075)	2.46E-01	-0.0090 (0.0090)	3.18E-01	0.0183 (0.0136)	1.78E-01
rs7910927	10:65138910	JMJD1C	G/T	0.048 (0.0039)	6.10E-35	-0.0124 (0.0036)	5.72E-04	-0.0217 (0.0062)	5.24E-04	-0.0286 (0.0075)	1.32E-04	-0.0018 (0.0115)	8.73E-01
rs4149056	12:21331549	SLCO1B1	T/C	0.029 (0.0052)	1.90E-08	-0.0002 (0.004)	9.51E-01	-0.0098 (0.0084)	2.45E-01	-0.0115 (0.0100)	2.49E-01	-0.0130 (0.0153)	3.93E-01
rs8023580	15:96708291	NR2F2	C/T	0.030 (0.0044)	8.30E-12	-0.0008 (0.0042)	8.49E-01	-0.0085 (0.0076)	2.61E-01	-0.0144 (0.0090)	1.09E-01	0.0067 (0.0135)	6.20E-01
rs2411984	17:47445751	ZNF652	A/G	0.033 (0.0044)	3.50E-14	0.0001 (0.004)	9.80E-01	-0.0078 (0.0068)	2.49E-01	-0.0009 (0.0081)	9.11E-01	0.0044 (0.0123)	7.23E-01
rs12150660	17:7521915	SHBG	T/G	0.103 (0.0047)	1.80E-106	0.0091 (0.0043)	3.43E-02	-0.0043 (0.0072)	5.51E-01	-0.0018 (0.0086)	8.35E-01	0.0068 (0.0131)	6.05E-01
rs1641537	17:7545721	SHBG	C/T	0.0814 (0.0062)	8.19E-39	-0.0014 (0.0054)	7.95E-01	-0.0042 (0.0094)	6.52E-01	-0.0139 (0.0111)	2.11E-01	0.0317 (0.0173)	6.67E-02
rs1625895	17:7578115	TP53	C/T	0.052 (0.0067)	1.17E-14	0.0134 (0.0059)	2.31E-02	0.0209 (0.0093)	2.42E-02	0.0209 (0.0111)	6.00E-02	0.0191 (0.0170)	2.61E-01
rs1573036	X:109820068	TDGF3	T/C	0.028 (0.0037)	4.10E-14	NA	NA	-0.0053 (0.0081)	5.16E-01	-0.0002 (0.0093)	9.81E-01	-0.0066 (0.0145)	6.49E-01

^a Beta units are per-allele effect estimates in natural logarithm transformed SHBG concentrations (nmol/L) (1). To enable better comparison with results from observational studies, we run MR analyses after transforming these beta coefficients into the natural scale (nmol/L) using a formula suggested by Rodriguez-Barranco and colleagues (2).

^b Beta units are per standard deviation increase of body mass index (kg/m²) (3).

^c Per-allele logarithm of the odds ratios between breast cancer cases and controls (4).

Abbreviations: GWAS, genome-wide association studies; SNPs, single nucleotide polymorphisms; Chr, Chromosome; pos, position; SHBG, sex hormone-binding globulin; ER, oestrogen receptor; SE, standard error; NA, non available;

Table 2. Number of cancer cases and controls and statistical power in Mendelian randomization study of SHBG and breast cancer risk.

Cancer type	Cases	Controls	Total	Proportion of cases	Minimum detectable odds ratio ^a		
					R ² =0.06 / F-statistic=153.3	R ² =0.08 / F-statistic=208.9	R ² =0.10 / F-statistic=266.9
Overall	122,977	105,974	228,951	0.54	0.953/1.049	0.960/1.042	0.963/1.038
ER ^{+ve}	69,501	95,042	164,543	0.42	0.945/1.058	0.952/1.050	0.957/1.045
ER ^{-ve}	21,468	100,594	122,062	0.18	0.922/1.085	0.930/1.075	0.937/1.067

Abbreviations: ER: estrogen receptor.

^aMinimum detectable odds ratio per 25nmol/L increase/decrease in SHBG levels: assume 80% power, 5% alpha level, and that 6% to 10% of SHBG variance is explained by the twelve SNPs used in the MR analysis.

References

1. 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.
2. Rodriguez-Barranco M, Tobias A, Redondo D, Molina-Portillo E, Sanchez MJ. Standardizing effect size from linear regression models with log-transformed variables for meta-analysis. *BMC Med Res Methodol.* 2017;17(1):44.
3. 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.
4. Michailidou K, Lindstrom S, Dennis J, Beesley J, Hui S, Kar S, et al. Association analysis identifies 65 new breast cancer risk loci. *Nature.* 2017;551(7678):92-4.