

**Table S4: Results of the MVMR analysis excluding “outlier” SNPs.**

**A) Excluding outliers detected using MVMR-PRESSO**

Removed SNPs that were detected by MVMR-PRESSO as outlier - Females (N=10): rs10778174,rs13108218,rs568088484,rs72681869,rs12950511,rs13220350,rs35447916,rs885683,rs974801,rs4804181 / Males (N=13): 6:26054177\_TA\_T,rs1129506,rs142798347,rs1800574,rs56196860,rs62062271,rs72827413,rs7923609,rs8066941,rs9288177,rs140584594,rs3768321,16:28704506\_ATT\_A

	FVC (mL)							FEV <sub>1</sub> /FVC (%)							FEV <sub>1</sub> (mL)										
	b	SE	LCI	UCI	p-value	Q test p-value	P-value intercept	Sargan P-value	b	SE	LCI	UCI	p-value	Q test p-value	P-value intercept	Sargan P-value	b	SE	LCI	UCI	p-value	Q test p-value	P-value intercept	Sargan P-value	
<b>Testosterone (TT)</b>																									
<b>Males</b>																									
MR F-IWV	163.27	49.70	65.86	260.67	<b>1.02E-03</b>	2.05E-17			1.18	0.48	0.24	2.11	<b>0.014</b>	4.62E-15			173.25	42.46	90.03	256.47	<b>4.49E-05</b>	7.24E-13			
MR R-IWV	163.27	74.29	17.67	308.87	<b>2.80E-02</b>	2.05E-17			1.18	0.69	-0.19	2.54	0.091	4.62E-15			173.25	59.97	55.70	290.80	<b>3.87E-03</b>	7.24E-13			
MR median	164.86	77.83	12.32	317.40	<b>3.42E-02</b>				1.22	0.69	-0.14	2.57	0.079				221.80	67.16	90.16	353.45	<b>9.59E-04</b>				
MR robust	171.49	76.35	21.85	321.12	<b>2.47E-02</b>				1.14	0.49	0.19	2.09	<b>0.019</b>				181.72	63.66	56.94	306.49	<b>4.31E-03</b>				
MR-Egger	163.04	74.53	16.97	309.12	<b>2.87E-02</b>		1.37E-17		1.17	0.70	-0.20	2.53	0.094		0.585		172.66	60.14	54.78	290.53	<b>4.09E-03</b>		0.669		
MR - 2SLS	149.26	57.53	36.50	262.01	<b>9.47E-03</b>		3.42E-15		0.77	0.56	-0.33	1.86	0.170		5.84E-06		144.34	49.22	47.87	240.81	<b>3.36E-03</b>			6.96E-10	
<b>Females</b>																									
MR F-IWV	40.58	12.37	16.33	64.83	<b>0.001</b>	5.94E-24			0.11	0.15	-0.18	0.41	0.457	3.88E-11			33.44	10.38	13.09	53.80	<b>0.001</b>	2.17E-19			
MR R-IWV	40.58	19.77	1.83	79.33	<b>0.040</b>	5.94E-24			0.11	0.21	-0.29	0.52	0.590	3.88E-11			33.44	15.88	2.33	64.56	<b>0.035</b>	2.17E-19			
MR median	27.67	24.61	-20.56	75.90	0.261				0.34	0.23	-0.12	0.80	0.145				38.34	20.05	-0.97	77.64	0.056				
MR robust	38.90	30.25	-20.40	98.19	0.199				0.21	0.16	-0.10	0.52	0.187				32.92	23.19	-12.54	78.38	0.156				
MR-Egger	43.44	19.88	4.48	82.40	<b>0.029</b>		1.20E-23		0.12	0.21	-0.29	0.53	0.576		0.834		35.64	15.97	4.34	66.93	<b>0.026</b>		0.241		
MR - 2SLS	41.72	15.69	10.97	72.47	<b>0.008</b>		1.82E-10		-0.04	0.19	-0.40	0.32	0.824		2.26E-05		30.29	13.04	4.74	55.84	<b>0.020</b>			2.28E-09	
<b>SHBG</b>																									
<b>Males</b>																									
MR F-IWV	-68.17	27.04	-121.17	-15.16	<b>0.012</b>	2.05E-17			-0.97	0.26	-1.48	-0.46	<b>1.79E-04</b>	4.62E-15			-93.52	23.11	-138.81	-48.24	<b>5.18E-05</b>	7.24E-13			
MR R-IWV	-68.17	40.43	-147.40	11.06	0.092	2.05E-17			-0.97	0.38	-1.72	-0.23	<b>9.96E-03</b>	4.62E-15			-93.52	32.64	-157.49	-29.55	<b>4.16E-03</b>	7.24E-13			
MR median	-88.16	42.00	-170.48	-5.84	<b>0.036</b>				-1.09	0.39	-1.85	-0.33	<b>4.80E-03</b>				-121.71	36.10	-192.47	-50.95	<b>7.48E-04</b>				
MR robust	-75.60	40.13	-154.25	3.04	0.060				-1.01	0.29	-1.59	-0.43	<b>6.26E-04</b>				-99.20	32.46	-162.83	-35.57	<b>2.25E-03</b>				
MR-Egger	-65.94	43.98	-152.13	20.25	0.134		1.37E-17		-0.89	0.41	-1.69	-0.08	<b>3.08E-02</b>		0.585		-87.66	35.49	-157.21	-18.10	<b>1.35E-02</b>		0.669		
MR - 2SLS	-54.61	30.96	-115.30	6.08	0.078		3.42E-15		-0.77	0.30	-1.36	-0.18	<b>1.08E-02</b>		5.84E-06		-74.31	26.54	-126.32	-22.29	<b>5.11E-03</b>			6.96E-10	
<b>Females</b>																									
MR F-IWV	-6.50	7.39	-20.98	7.97	0.379	5.94E-24			-0.09	0.09	-0.27	0.08	0.300	3.88E-11			-6.30	6.20	-18.45	5.84	0.309	2.17E-19			
MR R-IWV	-6.50	11.80	-29.63	16.63	0.582	5.94E-24			-0.09	0.12	-0.33	0.15	0.452	3.88E-11			-6.30	9.48	-24.88	12.27	0.506	2.17E-19			
MR median	1.30	14.64	-27.40	29.99	0.929				-0.17	0.15	-0.46	0.12	0.259				-16.22	12.26	-40.25	7.80	0.186				
MR robust	-8.69	15.31	-38.71	21.32	0.570				-0.12	0.10	-0.33	0.08	0.247				-9.17	12.73	-34.13	15.79	0.472				
MR-Egger	-18.92	15.53	-49.35	11.51	0.223		1.20E-23		-0.12	0.16	-0.43	0.20	0.481		0.834		-15.83	12.47	-40.27	8.61	0.204		0.241		
MR - 2SLS	-5.77	9.31	-24.02	12.47	0.535		1.82E-10		-0.07	0.11	-0.29	0.15	0.545		2.26E-05		-5.21	7.78	-20.46	10.04	0.503			2.28E-09	

N SNPs included --> Males: Total =165, TT = 64, SHBG = 128; Females: Total = 164, TT = 52, SHBG = 113.

N in 2SLS = Males=139,433; Females = 133,662.

SHBG = Sex Hormone Binding Globulin; TT = Total Testosterone.

MR = Mendelian Randomisation; F-IWV = Fixed effect Inverse variance weighted meta-analysis; R-IWV = Random effect Inverse variance weighted meta-analysis; 2SLS = Two-Stage least squares regression.

b = beta (regression estimate for a 1 unit increase in log TT or SHBG), SE = Standard Error of the mean, LCI/UCI = lower/upper confidence interval (95%)

The effect estimate for a 10% increase in TT or SHBG can be calculated by multiplying the beta (b) by ln(1.1)

**B) Excluding SNPs a priori considered potential sources of pleiotropy**

Removed 36 SNPs that were associated with smoking, weight-related traits, diabetes, insulin, leptin and adiponectin (rs1260326, rs6759145, rs13389219, rs2176040, rs645040, rs3936510, rs1635852, rs3740393, rs1042725, rs12824567, rs2925979, rs12454712, rs3729931, rs2307021, rs60775983, rs329124, rs506823, rs2090409, rs1935, rs8077638, rs1048317, rs4273712, rs8024515, rs6502629, rs7250869, rs174554, rs75616205, rs1800574, rs9986829, rs283811, rs738409, rs7529073, rs71304101, rs40270, rs974801, rs9987289)

	FVC (mL)							FEV <sub>1</sub> /FVC (%)							FEV <sub>1</sub> (mL)									
	b	SE	LCI	UCI	p-value	Q test p-value	P-value intercept	Sargan P-value	b	SE	LCI	UCI	p-value	Q test p-value	P-value intercept	Sargan P-value	b	SE	LCI	UCI	p-value	Q test p-value	P-value intercept	Sargan P-value
<b>Testosterone (TT)</b>																								
<b>Males</b>																								
MR F-IVW	-75.86	46.03	-166.07	14.36	0.099	1.02E-32			0.37	0.44	-0.50	1.23	0.409	2.12E-16			-37.23	39.33	-114.31	39.86	0.344	1.03E-29		
MR R-IVW	-75.86	80.32	-233.28	81.56	0.345	1.02E-32			0.37	0.66	-0.94	1.67	0.582	2.12E-16			-37.23	67.06	-168.67	94.21	0.579	1.03E-29		
MR median	89.83	92.57	-91.62	271.27	0.332				0.71	0.82	-0.89	2.32	0.384				162.42	76.87	11.75	313.08	<b>0.035</b>			
MR robust	79.75	200.45	-313.14	472.64	0.691				0.43	0.66	-0.86	1.73	0.513				123.74	165.78	-201.18	448.66	0.455			
MR-Egger	-78.53	81.40	-238.07	81.01	0.335		6.13E-33		0.35	0.67	-0.97	1.67	0.603		0.867		-39.49	67.96	-172.70	93.72	0.561		0.815	
MR-2SLS	-90.89	53.42	-195.59	13.82	0.089		1.28E-24		0.10	0.52	-0.93	1.13	0.853		1.91E-06		-59.51	45.78	-149.25	30.22	0.194			2.84E-19
<b>Females</b>																								
MR F-IVW	46.45	12.72	21.51	71.38	<b>2.61E-04</b>	9.79E-32			0.14	0.15	-0.16	0.44	0.358	4.27E-15			38.71	10.68	17.78	59.63	<b>2.88E-04</b>	1.14E-25		
MR R-IVW	46.45	22.53	2.29	90.61	<b>0.039</b>	9.79E-32			0.14	0.23	-0.31	0.60	0.540	4.27E-15			38.71	17.97	3.49	73.92	<b>0.031</b>	1.14E-25		
MR median	37.51	26.47	-14.37	89.39	0.156				0.33	0.25	-0.15	0.81	0.176				47.96	21.12	6.56	89.36	<b>0.023</b>			
MR robust	46.83	32.51	-16.89	110.55	0.150				0.22	0.17	-0.11	0.55	0.192				39.95	26.28	-11.57	91.47	0.129			
MR-Egger	52.23	22.72	7.70	96.76	<b>0.022</b>		7.28E-31		0.16	0.24	-0.30	0.62	0.488		0.582		43.60	18.10	8.13	79.07	<b>0.016</b>		0.098	
MR-2SLS	52.55	16.14	20.91	84.19	<b>1.13E-03</b>		1.09E-14		-0.03	0.19	-0.41	0.34	0.864		2.74E-07		38.96	13.41	12.68	65.24	<b>3.67E-03</b>			7.90E-12
<b>SHBG</b>																								
<b>Males</b>																								
MR F-IVW	59.27	25.96	8.38	110.16	<b>0.022</b>	1.02E-32			-0.53	0.25	-1.02	-0.04	<b>0.033</b>	2.12E-16			18.92	22.18	-24.57	62.40	0.394	1.03E-29		
MR R-IVW	59.27	45.30	-29.52	148.06	0.191	1.02E-32			-0.53	0.37	-1.27	0.20	0.155	2.12E-16			18.92	37.83	-55.22	93.06	0.617	1.03E-29		
MR median	-51.41	49.07	-147.59	44.76	0.295				-0.83	0.46	-1.73	0.07	0.072				-92.63	41.37	-173.72	-11.53	<b>0.025</b>			
MR robust	-20.58	101.53	-219.58	178.42	0.839				-0.63	0.38	-1.38	0.11	0.097				-62.86	83.26	-226.04	100.33	0.450			
MR-Egger	56.16	47.40	-36.75	149.06	0.236		6.13E-33		-0.55	0.39	-1.32	0.22	0.160		0.867		16.28	39.58	-61.29	93.86	0.681		0.815	
MR-2SLS	77.80	30.05	18.91	136.70	<b>0.010</b>		1.28E-24		-0.39	0.29	-0.97	0.18	0.182		1.91E-06		38.18	25.74	-12.26	88.62	0.138			2.84E-19
<b>Females</b>																								
MR F-IVW	-27.98	8.57	-44.77	-11.19	<b>1.09E-03</b>	9.79E-32			-0.16	0.10	-0.36	0.04	0.126	4.27E-15			-24.89	7.19	-38.99	-10.80	<b>5.35E-04</b>	1.14E-25		
MR R-IVW	-27.98	15.17	-57.72	1.76	0.065	9.79E-32			-0.16	0.16	-0.46	0.15	0.308	4.27E-15			-24.89	12.10	-48.61	-1.18	<b>0.040</b>	1.14E-25		
MR median	-14.85	15.86	-45.93	16.23	0.349				-0.21	0.18	-0.57	0.14	0.234				-23.99	13.04	-49.56	1.58	0.066			
MR robust	-28.22	13.27	-54.22	-2.21	<b>0.033</b>				-0.15	0.15	-0.45	0.15	0.326				-22.01	10.77	-43.13	-0.89	<b>0.041</b>			
MR-Egger	-48.58	20.08	-87.93	-9.23	<b>0.016</b>		7.28E-31		-0.23	0.21	-0.64	0.17	0.259		0.582		-42.32	15.99	-73.66	-10.99	<b>8.12E-03</b>		0.098	
MR-2SLS	-12.96	10.43	-33.41	7.49	0.214		1.09E-14		-0.15	0.12	-0.40	0.09	0.222		2.74E-07		-13.25	8.67	-30.25	3.75	0.126			7.90E-12

NSNPs included -> Males: Total =152, TT =57, SHBG = 116; Females: Total = 138, TT =48, SHBG =90.

N in 2SLS = Males=139,433; Females = 133,662.