

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 ₁ /FVC (%)					FEV ₁ (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	
Testosterone (TT)																									
Males																									
MR F-IVW	163.27	49.70	65.86	260.67	1.02E-03	2.05E-17			1.18	0.48	0.24	2.11	0.014	4.62E-15			173.25	42.46	90.03	256.47	4.49E-05	7.24E-13			
MR R-IVW	163.27	74.29	17.67	308.87	2.80E-02	2.05E-17			1.18	0.69	-0.19	2.54	0.091	4.62E-15			173.25	59.97	55.70	290.80	3.87E-03	7.24E-13			
MR median	164.86	77.83	12.32	317.40	3.42E-02				1.22	0.69	-0.14	2.57	0.079				221.80	67.16	90.16	353.45	9.59E-04				
MR robust	171.49	76.35	21.85	321.12	2.47E-02				1.14	0.49	0.19	2.09	0.019				181.72	63.66	56.94	306.49	4.31E-03				
MR-Egger	163.04	74.53	16.97	309.12	2.87E-02		1.37E-17		1.17	0.70	-0.20	2.53	0.094		0.585		172.66	60.14	54.78	290.53	4.09E-03		0.669		
MR - 2SLS	149.26	57.53	36.50	262.01	9.47E-03		3.42E-15		0.77	0.56	-0.33	1.86	0.170			5.84E-06	144.34	49.22	47.87	240.81	3.36E-03			6.96E-10	
Females																									
MR F-IVW	40.58	12.37	16.33	64.83	0.001	5.94E-24			0.11	0.15	-0.18	0.41	0.457	3.88E-11			33.44	10.38	13.09	53.80	0.001	2.17E-19			
MR R-IVW	40.58	19.77	1.83	79.33	0.040	5.94E-24			0.11	0.21	-0.29	0.52	0.590	3.88E-11			33.44	15.88	2.33	64.56	0.035	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	0.029		1.20E-23		0.12	0.21	-0.29	0.53	0.576		0.834		35.64	15.97	4.34	66.93	0.026		0.241		
MR - 2SLS	41.72	15.69	10.97	72.47	0.008		1.82E-10		-0.04	0.19	-0.40	0.32	0.824			2.26E-05	30.29	13.04	4.74	55.84	0.020			2.28E-09	
SHBG																									
Males																									
MR F-IVW	-68.17	27.04	-121.17	-15.16	0.012	2.05E-17			-0.97	0.26	-1.48	-0.46	1.79E-04	4.62E-15			-93.52	23.11	-138.81	-48.24	5.18E-05	7.24E-13			
MR R-IVW	-68.17	40.43	-147.40	11.06	0.092	2.05E-17			-0.97	0.38	-1.72	-0.23	9.96E-03	4.62E-15			-93.52	32.64	-157.49	-29.55	4.16E-03	7.24E-13			
MR median	-88.16	42.00	-170.48	-5.84	0.036				-1.09	0.39	-1.85	-0.33	4.80E-03				-121.71	36.10	-192.47	-50.95	7.48E-04				
MR robust	-75.60	40.13	-154.25	3.04	0.060				-1.01	0.29	-1.59	-0.43	6.26E-04				-99.20	32.46	-162.83	-35.57	2.25E-03				
MR-Egger	-65.94	43.98	-152.13	20.25	0.134		1.37E-17		-0.89	0.41	-1.69	-0.08	3.08E-02		0.585		-87.66	35.49	-157.21	-18.10	1.35E-02		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	1.08E-02			5.84E-06	-74.31	26.54	-126.32	-22.29	5.11E-03			6.96E-10	
Females																									
MR F-IVW	-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-IVW	-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-IVW = Fixed effect Inverse variance weighted meta-analysis; R-IVW = 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 ₁ /FVC (%)					FEV ₁ (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
Testosterone (TT)																								
Males																								
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	0.035			
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
Females																								
MR F-IVW	46.45	12.72	21.51	71.38	2.61E-04	9.79E-32			0.14	0.15	-0.16	0.44	0.358	4.27E-15			38.71	10.68	17.78	59.63	2.88E-04	1.14E-25		
MR R-IVW	46.45	22.53	2.29	90.61	0.039	9.79E-32			0.14	0.23	-0.31	0.60	0.540	4.27E-15			38.71	17.97	3.49	73.92	0.031	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	0.023			
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	0.022		7.28E-31		0.16	0.24	-0.30	0.62	0.488		0.582		43.60	18.10	8.13	79.07	0.016		0.098	
MR - 2SLS	52.55	16.14	20.91	84.19	1.13E-03		1.09E-14		-0.03	0.19	-0.41	0.34	0.864		2.74E-07		38.96	13.41	12.68	65.24	3.67E-03			7.90E-12
SHBG																								
Males																								
MR F-IVW	59.27	25.96	8.38	110.16	0.022	1.02E-32			-0.53	0.25	-1.02	-0.04	0.033	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	0.025			
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	0.010		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
Females																								
MR F-IVW	-27.98	8.57	-44.77	-11.19	1.09E-03	9.79E-32			-0.16	0.10	-0.36	0.04	0.126	4.27E-15			-24.89	7.19	-38.99	-10.80	5.35E-04	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	0.040	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	0.033				-0.15	0.15	-0.45	0.15	0.326				-22.01	10.77	-43.13	-0.89	0.041			
MR-Egger	-48.58	20.08	-87.93	-9.23	0.016		7.28E-31		-0.23	0.21	-0.64	0.17	0.259		0.582		-42.32	15.99	-73.66	-10.99	8.12E-03		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

N SNPs included → Males: Total =152, TT =57, SHBG = 116; Females: Total = 138, TT =48, SHBG =90.

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