Table S6: Results of subgroup MVMR analyses by obesity, physical activity, menopausal status in females, and age (>50 years) in males.
Outlier SNPs and "weak" SNPs (F-statistic ≤10) excluded

A) Obesity

FVC

	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 difference	SE difference	Interaction P-value
	Not obese (BMI <30)								*Obese (BMI >=30)*								*Interaction*		
Testosterone (TT)																			
Males																			
MR F-IVW	74.03	62.17	-47.82	195.88	0.234	1.18E-12			204.38	99.50	9.36	399.39	**0.040**	2.11E-02			-130.35	117.33	0.267
MR R-IVW	74.03	87.48	-97.42	245.48	0.397	1.18E-12			204.38	111.12	-13.42	422.17	0.066	2.11E-02			-130.35	141.42	0.357
MR median	168.82	102.19	-31.47	369.12	0.099				157.67	139.91	-116.56	431.91	0.260				11.15	173.26	0.949
MR robust	102.83	91.76	-77.02	282.67	0.262				185.68	109.79	-29.50	400.86	0.091				-82.86	143.08	0.563
MR-Egger	71.14	88.02	-101.37	243.66	0.419		8.95E-13		208.76	113.86	-14.40	431.92	0.067		1.86E-02		-137.61	143.91	0.339
MR - 2SLS	39.87	65.57	-88.65	168.39	0.543			5.34E-10	342.55	97.63	151.19	533.91	**4.51E-04**			4.81E-01	-302.68	117.61	**0.010**
Females																			
MR F-IVW	38.85	14.69	10.06	67.64	**0.008**	2.09E-18			63.12	26.15	11.87	114.38	**0.016**	0.460			-24.27	29.99	0.418
MR R-IVW	38.85	22.24	-4.75	82.45	0.081	2.09E-18			63.12	26.24	11.69	114.56	**0.016**	0.460			-24.27	34.40	0.480
MR median	65.95	29.76	7.62	124.27	**0.027**				81.31	41.22	0.53	162.10	**0.049**				-15.37	50.84	0.762
MR robust	36.77	30.29	-22.59	96.13	0.225				58.56	50.55	-40.53	157.65	0.247				-21.79	58.93	0.712
MR-Egger	41.07	22.54	-3.10	85.25	0.068		1.82E-18		63.19	26.33	11.58	114.79	**0.016**		0.439		-22.11	34.66	0.523
MR - 2SLS	22.52	17.67	-12.10	57.15	0.202			5.18E-10	56.60	30.09	-2.37	115.57	0.060			0.520	-34.07	34.89	0.329
SHBG																			
Males																			
MR F-IVW	-19.37	33.55	-85.13	46.39	0.564	1.18E-12			-97.61	52.17	-199.86	4.64	0.061	2.11E-02			78.25	62.03	0.207
MR R-IVW	-19.37	47.21	-111.90	73.16	0.682	1.18E-12			-97.61	58.26	-211.81	16.59	0.094	2.11E-02			78.25	74.99	0.297
MR median	-93.89	55.07	-201.83	14.05	0.088				-100.29	72.18	-241.77	41.19	0.165				6.40	90.79	0.944
MR robust	-38.91	50.61	-138.11	60.29	0.442				-89.32	56.13	-199.32	20.69	0.112				50.41	75.58	0.505
MR-Egger	-24.52	49.16	-120.87	71.83	0.618		8.95E-13		-95.14	59.89	-212.53	22.24	0.112		1.86E-02		70.63	77.48	0.362
MR - 2SLS	0.51	35.56	-69.19	70.21	0.989			5.34E-10	-155.17	51.91	-256.91	-53.43	**0.003**			4.81E-01	155.67	62.92	**0.013**
Females																			
MR F-IVW	-2.64	8.41	-19.12	13.84	0.754	2.09E-18			-5.90	14.60	-34.51	22.72	0.686	0.460			3.26	16.85	0.847
MR R-IVW	-2.64	12.74	-27.60	22.32	0.836	2.09E-18			-5.90	14.65	-34.62	22.82	0.687	0.460			3.26	19.41	0.867
MR median	1.71	16.68	-30.97	34.40	0.918				6.89	23.97	-40.09	53.87	0.774				-5.18	29.20	0.859
MR robust	-4.58	16.60	-37.11	27.96	0.783				-3.08	18.89	-40.10	33.95	0.871				-1.50	25.15	0.952
MR-Egger	-9.91	16.88	-42.99	23.17	0.557		1.82E-18		-9.56	19.95	-48.67	29.55	0.632		0.439		-0.35	26.13	0.989
MR - 2SLS	-2.86	10.64	-23.72	18.00	0.788			5.18E-10	-17.27	17.96	-52.48	17.94	0.336			0.520	14.41	20.88	0.490

FEV1/FVC

	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 difference	SE difference	Interaction P-value
	Not obese (BMI <30)								*Obese (BMI >=30)*								*Interaction*		
Testosterone (TT)																			
Males																			
MR F-IVW	0.81	0.62	-0.40	2.02	0.190	5.38E-08			1.09	0.96	-0.80	2.98	0.257	0.012			-0.28	1.14	0.805
MR R-IVW	0.81	0.81	-0.77	2.39	0.315	5.38E-08			1.09	1.09	-1.04	3.23	0.315	0.012			-0.28	1.35	0.834
MR median	0.62	0.90	-1.15	2.39	0.492				1.60	1.45	-1.24	4.45	0.270				-0.98	1.71	0.566
MR robust	0.70	0.58	-0.43	1.84	0.223				1.16	1.02	-0.84	3.16	0.257				-0.45	1.17	0.699
MR-Egger	0.87	0.81	-0.71	2.46	0.280		0.355		1.07	1.11	-1.11	3.26	0.335		0.937		-0.20	1.38	0.883
MR - 2SLS	0.60	0.64	-0.66	1.87	0.348			1.52E-03	1.25	0.97	-0.65	3.15	0.198			0.423	-0.64	1.16	0.580
Females																			
MR F-IVW	0.23	0.18	-0.12	0.59	0.196	2.48E-08			-0.32	0.32	-0.94	0.31	0.321	0.106			0.55	0.37	0.133
MR R-IVW	0.23	0.24	-0.23	0.70	0.326	2.48E-08			-0.32	0.34	-0.98	0.35	0.355	0.106			0.55	0.42	0.186
MR median	0.43	0.30	-0.16	1.03	0.153				-1.41	0.51	-2.41	-0.40	**0.006**				1.84	0.59	**0.002**
MR robust	0.30	0.27	-0.23	0.84	0.263				-0.44	0.56	-1.54	0.65	0.429				0.75	0.62	0.230
MR-Egger	0.21	0.24	-0.26	0.68	0.384		0.511		-0.31	0.34	-0.98	0.36	0.358		0.751		0.52	0.42	0.210
MR - 2SLS	0.07	0.21	-0.34	0.49	0.733			1.43E-04	-0.23	0.36	-0.93	0.47	0.517			0.191	0.30	0.41	0.464
SHBG																			
Males																			
MR F-IVW	-0.85	0.33	-1.50	-0.20	**0.011**	5.38E-08			-0.91	0.51	-1.90	0.08	0.073	0.012			0.06	0.61	0.924
MR R-IVW	-0.85	0.43	-1.70	0.00	0.051	5.38E-08			-0.91	0.57	-2.02	0.21	0.112	0.012			0.06	0.72	0.936
MR median	-0.99	0.51	-1.99	0.01	0.052				-1.32	0.76	-2.81	0.17	0.082				0.33	0.92	0.720
MR robust	-0.85	0.35	-1.53	-0.17	**0.015**				-0.97	0.52	-1.98	0.05	0.062				0.12	0.62	0.846
MR-Egger	-0.74	0.45	-1.62	0.15	0.103		0.355		-0.92	0.59	-2.07	0.23	0.118		0.937		0.18	0.74	0.808
MR - 2SLS	-0.75	0.35	-1.44	-0.07	**0.031**			1.52E-03	-0.83	0.51	-1.84	0.17	0.102			0.423	0.08	0.62	0.897
Females																			
MR F-IVW	-0.08	0.10	-0.28	0.12	0.436	2.48E-08			-0.26	0.18	-0.61	0.09	0.141	0.106			0.18	0.21	0.378
MR R-IVW	-0.08	0.14	-0.35	0.19	0.554	2.48E-08			-0.26	0.19	-0.63	0.11	0.170	0.106			0.18	0.23	0.439
MR median	-0.04	0.16	-0.35	0.28	0.817				-0.18	0.27	-0.71	0.35	0.511				0.14	0.32	0.655
MR robust	-0.10	0.10	-0.29	0.09	0.316				-0.27	0.14	-0.55	0.01	0.062				0.17	0.17	0.325
MR-Egger	0.00	0.18	-0.36	0.35	0.987		0.511		-0.32	0.26	-0.82	0.19	0.221		0.751		0.31	0.32	0.320
MR - 2SLS	-0.01	0.13	-0.26	0.24	0.943			1.43E-04	-0.24	0.21	-0.67	0.18	0.254			0.191	0.24	0.25	0.346

FEV1

	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 difference	SE difference	Interaction P-value
	Not obese (BMI <30)								*Obese (BMI >=30)*								*Interaction*		
Testosterone (TT)																			
Males																			
MR F-IVW	88.61	53.56	-16.36	193.58	0.098	9.73E-10			209.70	86.52	40.12	379.28	**0.015**	0.074			-121.09	101.76	0.234
MR R-IVW	88.61	72.08	-52.65	229.88	0.219	9.73E-10			209.70	93.63	26.19	393.21	**0.025**	0.074			-121.09	118.16	0.305
MR median	232.28	89.68	56.50	408.06	**0.010**				169.81	119.26	-63.94	403.56	0.154				62.47	149.22	0.675
MR robust	93.93	70.78	-44.81	232.67	0.185				181.56	84.74	15.48	347.64	**0.032**				-87.63	110.41	0.427
MR-Egger	89.53	72.55	-52.66	231.73	0.217		0.881		211.33	95.94	23.29	399.38	**0.028**		0.933		-121.80	120.29	0.311
MR - 2SLS	55.13	56.26	-55.13	165.40	0.327			2.64E-06	319.85	85.52	152.23	487.48	**1.84E-04**			0.671	-264.72	102.37	**0.010**
Females																			
MR F-IVW	35.44	12.41	11.13	59.76	**0.004**	8.74E-16			39.85	22.31	-3.88	83.57	0.074	0.710			-4.40	25.53	0.863
MR R-IVW	35.44	18.24	-0.30	71.18	0.052	8.74E-16			39.85	22.31	-3.88	83.57	0.074	0.710			-4.40	28.81	0.879
MR median	76.28	24.04	29.16	123.41	**0.002**				14.01	34.97	-54.53	82.55	0.689				62.28	42.44	0.142
MR robust	38.31	29.80	-20.10	96.72	0.199				25.04	41.17	-55.66	105.74	0.543				13.27	50.83	0.794
MR-Egger	35.92	18.50	-0.34	72.18	0.052		0.864		39.91	22.31	-3.82	83.63	0.074		0.758		-3.98	28.98	0.891
MR - 2SLS	18.91	14.76	-10.02	47.84	0.200			1.65E-09	35.91	25.54	-14.16	85.98	0.160			0.670	-17.00	29.50	0.564
SHBG																			
Males																			
MR F-IVW	-51.57	28.90	-108.23	5.08	0.074	9.73E-10			-113.74	45.37	-202.65	-24.82	**0.012**	0.074			62.16	53.79	0.248
MR R-IVW	-51.57	38.90	-127.81	24.66	0.185	9.73E-10			-113.74	49.09	-209.96	-17.52	**0.021**	0.074			62.16	62.64	0.321
MR median	-128.57	47.84	-222.34	-34.79	**0.007**				-91.28	62.07	-212.95	30.38	0.141				-37.28	78.37	0.634
MR robust	-56.29	37.84	-130.46	17.87	0.137				-100.45	43.94	-186.56	-14.33	**0.022**				44.15	57.98	0.446
MR-Egger	-49.93	40.52	-129.35	29.49	0.218		0.881		-112.82	50.47	-211.73	-13.90	**0.025**		0.933		62.88	64.72	0.331
MR - 2SLS	-33.03	30.56	-92.93	26.88	0.280			2.64E-06	-154.31	45.34	-243.17	-65.44	**6.66E-04**			0.671	121.28	54.68	**0.027**
Females																			
MR F-IVW	-3.94	7.10	-17.87	9.98	0.579	8.74E-16			-9.34	12.46	-33.75	15.08	0.454	0.710			5.39	14.34	0.707
MR R-IVW	-3.94	10.44	-24.41	16.52	0.706	8.74E-16			-9.34	12.46	-33.75	15.08	0.454	0.710			5.39	16.25	0.740
MR median	-13.83	13.29	-39.88	12.22	0.298				-11.84	19.38	-49.82	26.15	0.541				-1.99	23.50	0.932
MR robust	-5.48	13.21	-31.37	20.41	0.678				-7.30	16.65	-39.93	25.34	0.661				1.82	21.25	0.932
MR-Egger	-5.50	13.85	-32.66	21.65	0.691		0.864		-12.85	16.91	-45.99	20.28	0.447		0.758		7.35	21.86	0.737
MR - 2SLS	-1.68	8.95	-19.21	15.86	0.851			1.65E-09	-17.92	15.24	-47.79	11.94	0.240			0.670	16.25	17.67	0.358

N SNPs included (Outlier SNPs and SNPs with F<10 excluded)-->NOT obese: Males: Total = 165, TT = 64, SHBG = 128; Females: Total = 163, TT = 52, SHBG = 112 - Obese: Males: Total = 153, TT = 63, SHBG = 117; Females: Total = 143, TT = 45, SHBG = 99.
N in 2SLS: NOT obese : Males = 104,442; Females = 102,436 - Obese : Males = 34,890; Females = 31,121

B) Physical activity

FVC

	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 difference	SE difference	Interaction P-value
	Not moderatly physical active								*Moderatly physical active*								*Interaction*		
Testosterone (TT)																			
Males																			
MR F-IVW	111.53	76.95	-39.28	262.35	0.147	3.19E-06			167.21	76.14	17.98	316.44	**0.028**	1.44E-06			-55.67	108.25	0.607
MR R-IVW	111.53	96.76	-78.12	301.18	0.249	3.19E-06			167.21	96.50	-21.92	356.33	0.083	1.44E-06			-55.67	136.65	0.684
MR median	209.25	120.60	-27.13	445.64	0.083				224.32	115.67	-2.38	451.03	0.052				-15.07	167.10	0.928
MR robust	82.39	119.41	-151.65	316.44	0.490				186.16	68.72	51.47	320.84	**0.007**				-103.76	137.77	0.451
MR-Egger	111.56	97.06	-78.67	301.80	0.250		2.50E-06		165.01	99.79	-30.57	360.60	0.098		1.12E-06		-53.45	139.21	0.701
MR - 2SLS	221.54	117.42	-8.60	451.67	0.059			5.56E-03	133.04	64.60	6.43	259.65	**0.039**			4.81E-11	88.49	134.01	0.509
Females																			
MR F-IVW	60.67	18.58	24.24	97.09	**0.001**	9.82E-09			21.43	18.92	-15.66	58.52	0.258	9.49E-07			39.24	26.52	0.139
MR R-IVW	60.67	24.60	12.46	108.87	**0.014**	9.82E-09			21.43	24.13	-25.86	68.72	0.375	9.49E-07			39.24	34.45	0.255
MR median	50.32	32.79	-13.95	114.59	0.125				49.15	32.67	-14.89	113.19	0.132				1.17	46.29	0.980
MR robust	61.04	30.81	0.66	121.42	**0.048**				24.40	34.51	-43.24	92.05	0.480				36.63	46.26	0.428
MR-Egger	61.82	24.71	13.40	110.25	**0.012**		8.60E-09		23.09	24.02	-23.99	70.17	0.336		1.78E-06		38.73	34.46	0.261
MR - 2SLS	68.66	33.30	3.40	133.92	**0.039**			0.908	35.15	17.86	0.15	70.15	**0.049**			2.82E-09	33.51	37.78	0.375
SHBG																			
Males																			
MR F-IVW	-44.86	41.09	-125.39	35.67	0.275	3.19E-06			-52.92	41.27	-133.80	27.96	0.200	1.44E-06			8.06	58.23	0.890
MR R-IVW	-44.86	51.67	-146.12	56.41	0.385	3.19E-06			-52.92	52.30	-155.42	49.59	0.312	1.44E-06			8.06	73.52	0.913
MR median	-110.91	61.81	-232.05	10.22	0.073				-100.97	63.54	-225.50	23.56	0.112				-9.94	88.64	0.911
MR robust	-32.72	60.78	-151.85	86.41	0.590				-64.13	40.33	-143.17	14.90	0.112				31.42	72.94	0.667
MR-Egger	-44.05	55.32	-152.47	64.37	0.426		2.50E-06		-53.61	53.02	-157.52	50.30	0.312		1.12E-06		9.56	76.62	0.901
MR - 2SLS	-94.24	63.57	-218.84	30.36	0.138			5.56E-03	-39.31	35.03	-107.96	29.35	0.262			4.81E-11	-54.93	72.58	0.449
Females																			
MR F-IVW	-14.99	10.59	-35.75	5.76	0.157	9.82E-09			8.70	10.72	-12.30	29.70	0.417	9.49E-07			-23.69	15.06	0.116
MR R-IVW	-14.99	14.01	-42.46	12.47	0.285	9.82E-09			8.70	13.66	-18.08	35.48	0.524	9.49E-07			-23.69	19.57	0.226
MR median	-0.82	18.97	-38.01	36.37	0.965				23.17	19.27	-14.60	60.95	0.229				-24.00	27.04	0.375
MR robust	-13.56	18.03	-48.89	21.77	0.452				5.13	17.10	-28.39	38.64	0.764				-18.69	24.85	0.452
MR-Egger	-22.96	18.79	-59.78	13.86	0.222		8.60E-09		-10.41	17.84	-45.38	24.55	0.559		1.78E-06		-12.54	25.91	0.628
MR - 2SLS	2.26	20.84	-38.58	43.10	0.914			0.908	-5.39	10.61	-26.18	15.41	0.612			2.82E-09	7.65	23.38	0.744

FEV1/FVC

	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 difference	SE difference	Interaction P-value
	Not moderatly physical active								*Moderatly physical active*								*Interaction*		
Testosterone (TT)																			
Males																			
MR F-IVW	0.46	0.74	-0.98	1.91	0.527	5.89E-04			1.71	0.75	0.24	3.17	**0.023**	3.30E-04			-1.24	1.05	0.237
MR R-IVW	0.46	0.87	-1.24	2.17	0.593	5.89E-04			1.71	0.89	-0.04	3.45	0.056	3.30E-04			-1.24	1.25	0.319
MR median	0.48	1.02	-1.52	2.48	0.638				1.71	1.04	-0.32	3.75	0.099				-1.23	1.46	0.398
MR robust	0.51	0.59	-0.65	1.67	0.392				1.70	0.50	0.73	2.67	**6.10E-04**				-1.19	0.77	0.123
MR-Egger	0.47	0.87	-1.23	2.17	0.586		0.218		1.70	0.92	-0.11	3.50	0.066		0.970		-1.22	1.27	0.334
MR - 2SLS	0.89	1.18	-1.42	3.20	0.449			0.200	0.98	0.62	-0.23	2.20	0.113			7.55E-04	-0.09	1.33	0.945
Females																			
MR F-IVW	0.14	0.22	-0.30	0.57	0.540	0.087			0.07	0.23	-0.39	0.52	0.771	3.05E-09			0.07	0.32	0.828
MR R-IVW	0.14	0.24	-0.33	0.61	0.568	0.087			0.07	0.31	-0.54	0.67	0.828	3.05E-09			0.07	0.39	0.858
MR median	0.14	0.32	-0.49	0.78	0.660				0.24	0.36	-0.46	0.94	0.501				-0.10	0.48	0.839
MR robust	0.14	0.20	-0.25	0.52	0.485				0.11	0.23	-0.35	0.57	0.654				0.03	0.31	0.919
MR-Egger	0.12	0.24	-0.35	0.59	0.620		0.319		0.07	0.31	-0.54	0.68	0.824		0.874		0.05	0.39	0.898
MR - 2SLS	-0.49	0.39	-1.26	0.28	0.212			0.585	0.06	0.21	-0.36	0.47	0.784			9.40E-06	-0.55	0.45	0.219
SHBG																			
Males																			
MR F-IVW	-0.66	0.39	-1.43	0.11	0.094	5.89E-04			-1.35	0.41	-2.14	-0.55	**8.74E-04**	3.30E-04			0.69	0.56	0.220
MR R-IVW	-0.66	0.46	-1.57	0.25	0.157	5.89E-04			-1.35	0.48	-2.30	-0.40	**5.24E-03**	3.30E-04			0.69	0.67	0.301
MR median	-0.65	0.57	-1.76	0.46	0.251				-1.76	0.58	-2.89	-0.63	**2.34E-03**				1.11	0.81	0.170
MR robust	-0.66	0.37	-1.38	0.06	0.073				-1.38	0.29	-1.95	-0.82	**1.61E-06**				0.72	0.47	0.122
MR-Egger	-0.44	0.49	-1.41	0.53	0.370		0.218		-1.35	0.49	-2.31	-0.39	**5.79E-03**		0.970		0.91	0.70	0.192
MR - 2SLS	-0.86	0.64	-2.11	0.40	0.181			0.200	-0.92	0.34	-1.58	-0.26	**6.52E-03**			7.55E-04	0.06	0.72	0.929
Females																			
MR F-IVW	-0.03	0.13	-0.28	0.22	0.828	0.087			-0.26	0.13	-0.52	-0.01	**0.043**	3.05E-09			0.24	0.18	0.194
MR R-IVW	-0.03	0.14	-0.30	0.24	0.840	0.087			-0.26	0.17	-0.61	0.08	0.130	3.05E-09			0.24	0.22	0.286
MR median	-0.13	0.18	-0.50	0.23	0.466				-0.18	0.21	-0.58	0.22	0.377				0.05	0.28	0.865
MR robust	-0.05	0.11	-0.26	0.16	0.668				-0.26	0.15	-0.55	0.03	0.079				0.21	0.18	0.243
MR-Egger	0.09	0.18	-0.27	0.45	0.609		0.319		-0.29	0.23	-0.74	0.16	0.211		0.874		0.38	0.29	0.194
MR - 2SLS	-0.53	0.25	-1.02	-0.04	**0.033**			0.585	0.01	0.13	-0.24	0.26	0.949			9.40E-06	-0.54	0.28	0.054

FEV1

	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 difference	SE difference	Interaction P-value
	Not moderatly physical active								*Moderatly physical active*								*Interaction*		
Testosterone (TT)																			
Males																			
MR F-IVW	100.70	65.67	-28.02	229.42	0.125	6.02E-04			203.76	65.18	76.02	331.51	**1.77E-03**	5.46E-05			-103.06	92.53	0.265
MR R-IVW	100.70	77.65	-51.48	252.89	0.195	6.02E-04			203.76	79.47	48.00	359.53	**1.03E-02**	5.46E-05			-103.06	111.11	0.354
MR median	198.88	103.32	-3.64	401.39	0.054				193.27	93.99	9.04	377.49	**3.98E-02**				5.61	139.68	0.968
MR robust	98.28	94.76	-87.44	284.00	0.300				204.61	55.99	94.86	314.35	**2.58E-04**				-106.33	110.06	0.334
MR-Egger	101.11	77.77	-51.31	253.53	0.194		0.477		200.46	82.18	39.38	361.53	**1.47E-02**		0.869		-99.35	113.14	0.380
MR - 2SLS	208.64	101.37	9.95	407.33	**0.040**			0.036	142.29	55.20	34.09	250.49	**9.95E-03**			1.03E-07	66.35	115.43	0.565
Females																			
MR F-IVW	49.54	15.58	19.01	80.08	**1.47E-03**	2.25E-05			19.94	15.92	-11.26	51.13	0.210	3.68E-07			29.61	22.27	0.184
MR R-IVW	49.54	19.19	11.93	87.15	**0.010**	2.25E-05			19.94	20.47	-20.19	60.06	0.330	3.68E-07			29.61	28.06	0.291
MR median	59.45	26.60	7.30	111.59	**0.025**				47.87	27.86	-6.73	102.47	0.086				11.57	38.52	0.764
MR robust	49.54	22.68	5.08	94.00	**0.029**				21.87	28.00	-33.02	76.75	0.435				27.68	36.04	0.443
MR-Egger	49.66	19.30	11.84	87.49	**0.010**		0.931		21.24	20.41	-18.75	61.23	0.298		0.127		28.42	28.09	0.312
MR - 2SLS	37.34	27.75	-17.06	91.74	0.179			0.785	28.33	14.85	-0.77	57.43	0.056			5.46E-09	9.01	31.48	0.775
SHBG																			
Males																			
MR F-IVW	-60.70	35.07	-129.43	8.03	0.083	6.02E-04			-101.27	35.32	-170.51	-32.04	**0.004**	5.46E-05			40.57	49.77	0.415
MR R-IVW	-60.70	41.46	-141.96	20.56	0.143	6.02E-04			-101.27	43.07	-185.69	-16.85	**0.019**	5.46E-05			40.57	59.78	0.497
MR median	-106.66	54.12	-212.74	-0.58	**0.049**				-109.70	51.41	-210.46	-8.94	**0.033**				3.04	74.65	0.968
MR robust	-61.45	47.57	-154.69	31.80	0.196				-100.80	32.29	-164.10	-37.50	**0.002**				39.35	57.50	0.494
MR-Egger	-49.70	44.32	-136.56	37.17	0.262		0.477		-102.32	43.66	-187.89	-16.74	**0.019**		0.869		52.62	62.21	0.398
MR - 2SLS	-108.65	55.00	-216.46	-0.85	**0.048**			0.036	-70.45	30.01	-129.26	-11.64	**0.019**			1.03E-07	-38.20	62.65	0.542
Females																			
MR F-IVW	-11.43	8.88	-28.83	5.96	0.198	2.25E-05			0.17	9.01	-17.50	17.83	0.985	3.68E-07			-11.60	12.65	0.359
MR R-IVW	-11.43	10.93	-32.86	10.00	0.296	2.25E-05			0.17	11.59	-22.55	22.89	0.988	3.68E-07			-11.60	15.93	0.467
MR median	-9.72	15.41	-39.92	20.48	0.528				-7.88	15.31	-37.90	22.13	0.607				-1.83	21.72	0.933
MR robust	-10.70	13.94	-38.02	16.61	0.442				-1.87	13.06	-27.47	23.73	0.886				-8.83	19.10	0.644
MR-Egger	-12.28	14.68	-41.04	16.48	0.403		0.931		-14.83	15.16	-44.53	14.88	0.328		0.127		2.55	21.10	0.904
MR - 2SLS	-12.87	17.65	-47.47	21.73	0.466			0.785	-2.76	8.86	-20.13	14.61	0.755			5.46E-09	-10.11	19.75	0.609

N SNPs included (Outlier SNPs and SNPs with F<10 excluded) --> NOT active: Males: Total = 165, TT = 63, SHBG = 128; Females: Total = 165, TT = 52, SHBG = 114 - Active: Males: Total = 165, TT = 64, SHBG = 128; Females: Total = 162, TT = 52, SHBG = 111.
N in 2SLS: NOT active: Males = 28,637; Females = 25,289 - Active : Males = 106,207; Females = 101,526

C) Menopause (females only)

FVC

	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 difference	SE difference	Interaction P-value
	Pre-menopausal								*Post-menopausal*								*Interaction*		
Testosterone (TT)																			
MR F-IVW	40.35	24.18	-7.03	87.73	0.095	8.95E-03			35.06	17.79	0.19	69.92	**0.049**	5.17E-08			5.29	30.02	0.860
MR R-IVW	40.35	27.69	-13.92	94.63	0.145	8.95E-03			35.06	23.24	-10.50	80.62	0.132	5.17E-08			5.29	36.15	0.884
MR median	28.02	40.12	-50.61	106.65	0.485				14.50	29.93	-44.15	73.16	0.628				13.52	50.05	0.787
MR robust	42.67	30.47	-17.05	102.40	0.161				28.69	33.48	-36.93	94.31	0.391				13.98	45.27	0.757
MR-Egger	44.23	28.34	-11.32	99.77	0.119		8.29E-03		39.93	23.33	-5.80	85.66	0.087		9.91E-08		4.30	36.71	0.907
MR - 2SLS	38.80	28.55	-17.15	94.75	0.174			0.057	23.73	20.95	-17.33	64.79	0.257			2.27E-04	15.07	35.41	0.670
SHBG																			
MR F-IVW	1.50	15.22	-28.33	31.34	0.921	8.95E-03			4.12	9.73	-14.95	23.18	0.672	5.17E-08			-2.61	18.06	0.885
MR R-IVW	1.50	17.43	-32.67	35.67	0.931	8.95E-03			4.12	12.71	-20.80	29.03	0.746	5.17E-08			-2.61	21.58	0.904
MR median	-5.51	29.34	-63.02	52.00	0.851				11.56	16.52	-20.81	43.94	0.484				-17.07	33.67	0.612
MR robust	-7.34	33.04	-72.09	57.42	0.824				3.86	13.32	-22.24	29.96	0.772				-11.20	35.62	0.753
MR-Egger	-9.52	23.94	-56.44	37.40	0.691		8.29E-03		-13.67	16.84	-46.67	19.33	0.417		9.91E-08		4.15	29.27	0.887
MR - 2SLS	22.73	18.24	-13.02	58.49	0.213			0.057	-5.23	12.43	-29.60	19.14	0.674			2.27E-04	27.97	22.08	0.205

FEV1/FVC

	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 difference	SE difference	Interaction P-value
	Pre-menopausal								*Post-menopausal*								*Interaction*		
Testosterone (TT)																			
MR F-IVW	-0.04	0.26	-0.54	0.46	0.868	4.76E-02			0.03	0.23	-0.41	0.48	0.885	1.23E-08			-0.08	0.34	0.826
MR R-IVW	-0.04	0.28	-0.59	0.51	0.880	4.76E-02			0.03	0.30	-0.56	0.62	0.913	1.23E-08			-0.08	0.41	0.855
MR median	-0.04	0.40	-0.83	0.74	0.919				0.09	0.36	-0.62	0.81	0.803				-0.13	0.54	0.808
MR robust	-0.01	0.25	-0.49	0.48	0.982				0.11	0.26	-0.41	0.62	0.682				-0.11	0.36	0.754
MR-Egger	-0.20	0.28	-0.75	0.35	0.476		0.006		0.04	0.30	-0.56	0.63	0.906		0.941		-0.24	0.41	0.569
MR - 2SLS	-0.02	0.29	-0.59	0.55	0.938			0.327	-0.11	0.26	-0.63	0.40	0.662			1.17E-03	0.09	0.39	0.814
SHBG																			
MR F-IVW	0.03	0.16	-0.29	0.34	0.861	0.048			-0.11	0.12	-0.35	0.14	0.387	1.23E-08			0.14	0.20	0.504
MR R-IVW	0.03	0.18	-0.32	0.37	0.874	0.048			-0.11	0.16	-0.43	0.21	0.513	1.23E-08			0.14	0.24	0.574
MR median	0.05	0.25	-0.44	0.54	0.840				0.01	0.20	-0.38	0.39	0.978				0.04	0.32	0.887
MR robust	0.00	0.15	-0.29	0.30	0.990				-0.08	0.13	-0.32	0.17	0.539				0.08	0.20	0.687
MR-Egger	0.47	0.24	0.01	0.94	**0.045**		0.006		-0.12	0.22	-0.55	0.31	0.590		0.941		0.59	0.32	0.066
MR - 2SLS	-0.06	0.19	-0.43	0.32	0.767			0.327	-0.07	0.16	-0.37	0.24	0.674			1.17E-03	0.01	0.25	0.970

FEV1

	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 difference	SE difference	Interaction P-value
	Pre-menopausal								*Post-menopausal*								*Interaction*		
Testosterone (TT)																			
MR F-IVW	28.07	20.16	-11.45	67.59	0.164	1.02E-03			29.41	14.99	0.03	58.79	**0.050**	5.11E-07			-1.34	25.12	0.957
MR R-IVW	28.07	24.02	-19.01	75.15	0.243	1.02E-03			29.41	19.20	-8.21	67.04	0.126	5.11E-07			-1.34	30.75	0.965
MR median	26.04	32.18	-37.04	89.11	0.419				3.69	26.45	-48.16	55.53	0.889				22.35	41.66	0.592
MR robust	28.81	23.88	-18.00	75.62	0.228				20.85	25.21	-28.56	70.26	0.408				7.96	34.72	0.819
MR-Egger	24.91	24.59	-23.28	73.10	0.311		0.527		32.90	19.31	-4.94	70.75	0.088		0.166		-7.99	31.26	0.798
MR - 2SLS	26.54	23.48	-19.47	72.56	0.258			0.019	17.99	17.47	-16.25	52.24	0.303			9.11E-05	8.55	29.27	0.770
SHBG																			
MR F-IVW	2.24	12.69	-22.64	27.12	0.860	1.02E-03			1.20	8.20	-14.86	17.27	0.883	5.11E-07			1.04	15.11	0.945
MR R-IVW	2.24	15.12	-27.40	31.88	0.882	1.02E-03			1.20	10.50	-19.37	21.78	0.909	5.11E-07			1.04	18.41	0.955
MR median	-23.15	23.32	-68.87	22.56	0.321				0.81	14.52	-27.65	29.26	0.956				-23.96	27.47	0.383
MR robust	-10.34	27.16	-63.57	42.89	0.703				-0.15	11.02	-21.75	21.44	0.989				-10.19	29.31	0.728
MR-Egger	11.21	20.77	-29.49	51.92	0.589		0.527		-11.55	13.93	-38.86	15.76	0.407		0.166		22.76	25.01	0.363
MR - 2SLS	16.49	15.18	-13.26	46.24	0.277			0.019	-4.32	10.41	-24.74	16.09	0.678			9.11E-05	20.81	18.41	0.258

N SNPs included (Outlier SNPs and SNPs with F<10 excluded) --> Pre-menopause: Total = 136, TT = 47, SHBG = 90; Post-menopause: Total = 164, TT = 52, SHBG =113.
N in 2SLS: Pre-menopause = 33,539; Post-menopause = 74,703

D) Age 50 (males only)

FVC

	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 difference	SE difference	Interaction P-value
	Age <= 50 years								*Age > 50 years*								*Interaction*		
Testosterone (TT)																			
MR F-IVW	139.76	108.32	-72.55	352.06	0.197	6.63E-05			155.81	61.19	35.88	275.74	**0.011**	2.27E-11			-16.05	124.41	0.897
MR R-IVW	139.76	132.62	-120.18	399.69	0.292	6.63E-05			155.81	84.51	-9.82	321.44	0.065	2.27E-11			-16.05	157.26	0.919
MR median	133.55	157.23	-174.62	441.73	0.396				261.93	97.40	71.02	452.83	**0.007**				-128.37	184.96	0.488
MR robust	112.11	118.72	-120.57	344.79	0.345				152.79	87.13	-17.97	323.56	0.079				-40.68	147.26	0.782
MR-Egger	173.30	135.91	-93.08	439.68	0.202		7.42E-05		150.76	85.33	-16.49	318.01	0.077		1.82E-11		22.54	160.48	0.888
MR - 2SLS	217.12	117.05	-12.30	446.54	0.064			2.01E-02	146.32	63.47	21.92	270.72	**0.021**			5.79E-09	70.79	133.15	0.595
SHBG																			
MR F-IVW	-77.81	54.03	-183.71	28.09	0.150	6.63E-05			-52.89	33.72	-118.98	13.20	0.117	2.27E-11			-24.92	63.69	0.696
MR R-IVW	-77.81	66.15	-207.47	51.85	0.240	6.63E-05			-52.89	46.57	-144.17	38.39	0.256	2.27E-11			-24.92	80.90	0.758
MR median	-98.27	78.46	-252.05	55.52	0.210				-119.07	53.62	-224.17	-13.98	**0.026**				20.81	95.03	0.827
MR robust	-66.69	59.69	-183.67	50.30	0.264				-51.29	47.57	-144.53	41.95	0.281				-15.40	76.33	0.840
MR-Egger	-61.89	67.64	-194.45	70.67	0.360		7.42E-05		-58.62	48.13	-152.96	35.71	0.223		1.82E-11		-3.27	83.01	0.969
MR - 2SLS	-99.78	58.72	-214.86	15.31	0.089			0.020	-46.57	35.14	-115.45	22.31	0.185			5.79E-09	-53.21	68.43	0.437

FEV1/FVC

	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 difference	SE difference	Interaction P-value
	Age <= 50 years								*Age > 50 years*								*Interaction*		
Testosterone (TT)																			
MR F-IVW	-0.10	0.92	-1.90	1.69	0.909	3.45E-01			1.27	0.62	0.05	2.49	**0.041**	2.61E-10			-1.37	1.11	0.215
MR R-IVW	-0.10	0.93	-1.94	1.73	0.911	3.45E-01			1.27	0.84	-0.39	2.92	0.133	2.61E-10			-1.37	1.26	0.276
MR median	-0.37	1.23	-2.78	2.03	0.761				1.30	0.91	-0.47	3.08	0.150				-1.68	1.53	0.272
MR robust	-0.13	0.56	-1.23	0.97	0.814				1.20	0.56	0.11	2.29	**0.031**				-1.33	0.79	0.092
MR-Egger	-0.04	0.96	-1.92	1.85	0.968		0.757		1.31	0.85	-0.36	2.99	0.124		0.663		-1.35	1.29	0.293
MR - 2SLS	-0.62	0.99	-2.56	1.32	0.529			0.957	1.20	0.65	-0.06	2.47	0.063			8.66E-05	-1.82	1.18	0.123
SHBG																			
MR F-IVW	-0.17	0.46	-1.06	0.73	0.716	0.345			-1.13	0.34	-1.81	-0.46	**9.38E-04**	2.61E-10			0.97	0.57	0.090
MR R-IVW	-0.17	0.47	-1.08	0.75	0.722	0.345			-1.13	0.47	-2.05	-0.22	**1.49E-02**	2.61E-10			0.97	0.66	0.142
MR median	0.09	0.60	-1.09	1.28	0.876				-1.24	0.51	-2.24	-0.24	**1.53E-02**				1.33	0.79	0.092
MR robust	-0.14	0.29	-0.72	0.44	0.628				-1.12	0.34	-1.78	-0.46	**8.47E-04**				0.98	0.45	**0.029**
MR-Egger	-0.13	0.48	-1.07	0.80	0.779		0.757		-1.08	0.48	-2.03	-0.14	**2.44E-02**		0.663		0.95	0.68	0.162
MR - 2SLS	0.09	0.50	-0.89	1.06	0.862			0.957	-1.05	0.36	-1.75	-0.35	**3.33E-03**			8.66E-05	1.14	0.61	0.063

FEV1

	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 difference	SE difference	Interaction P-value
	Age <= 50 years								*Age > 50 years*								*Interaction*		
Testosterone (TT)																			
MR F-IVW	109.91	91.38	-69.19	289.01	0.229	1.25E-02			168.11	52.55	65.10	271.11	**1.38E-03**	2.56E-10			-58.20	105.41	0.581
MR R-IVW	109.91	103.16	-92.28	312.09	0.287	1.25E-02			168.11	71.40	28.16	308.05	**1.86E-02**	2.56E-10			-58.20	125.46	0.643
MR median	143.65	134.62	-120.20	407.50	0.286				294.16	87.21	123.22	465.10	**7.44E-04**				-150.51	160.40	0.348
MR robust	83.76	102.20	-116.56	284.07	0.412				159.52	74.33	13.84	305.20	**3.19E-02**				-75.76	126.37	0.549
MR-Egger	138.29	105.64	-68.76	345.33	0.191		0.226		166.16	72.14	24.77	307.56	**2.13E-02**		0.824		-27.88	127.92	0.827
MR - 2SLS	141.56	98.29	-51.09	334.21	0.150			0.351	161.39	54.64	54.30	268.48	**3.14E-03**			5.38E-07	-19.83	112.45	0.860
SHBG																			
MR F-IVW	-74.24	45.58	-163.57	15.10	0.103	1.25E-02			-85.74	28.96	-142.50	-28.98	**3.07E-03**	2.56E-10			11.50	54.00	0.831
MR R-IVW	-74.24	51.46	-175.09	26.62	0.149	1.25E-02			-85.74	39.35	-162.86	-8.62	**2.93E-02**	2.56E-10			11.50	64.78	0.859
MR median	-93.51	67.46	-225.73	38.71	0.166				-146.71	47.58	-239.97	-53.45	**2.05E-03**				53.20	82.55	0.519
MR robust	-57.47	50.63	-156.70	41.75	0.256				-79.76	39.02	-156.24	-3.27	**4.10E-02**				22.28	63.92	0.727
MR-Egger	-60.77	52.57	-163.80	42.27	0.248		0.226		-87.94	40.69	-167.70	-8.19	**3.07E-02**		0.824		27.17	66.48	0.683
MR - 2SLS	-78.03	49.42	-174.89	18.83	0.114			0.351	-79.44	30.28	-138.79	-20.10	**8.70E-03**			5.38E-07	1.41	57.96	0.981

N SNPs included (Outlier SNPs and SNPs with F<10 excluded)-->Age <= 50 years: Total =154, TT = 60, SHBG = 121; Age > 50 years: Total = 165, TT = 64, SHBG = 128.
N in 2SLS: Age <= 50 years = 36,088; Age > 50 years = 103,345

-0.10736 0.120044

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)