

**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

### B) Physical activity

P-Value	P-FIT												P-FOF												P-FV2																									
	b	SE	LCI	UCI	p-value	Intercept	P-value	Q-test	p-value	Sergant	b	SE	LCI	UCI	p-value	Intercept	P-value	Q-test	p-value	Sergant	b	SE	LCI	UCI	p-value	Intercept	P-value	Q-test	p-value	Sergant	b	SE	LCI	UCI	p-value	Intercept	P-value	Q-test	p-value	Sergant	b	SE	LCI	UCI	p-value	Intercept	P-value	Q-test	p-value	Sergant
<i>Not moderately physical activity</i>																																																		
<i>Moderately physical active</i>																																																		
<i>Intervention</i>																																																		
<i>Not moderately physical active</i>																																																		
111.53	76.95	-38.20	26.35	0.347	3.11E-06	109.21	76.54	138.44	10.28	0.025	144E-06	55.67	100.35	60.07	0.46	0.74	0.98	0.151	0.327	5.98E-04	1.71	0.75	0.24	0.37	0.233	3.0E-04	100.70	67.85	28.02	92.40	0.155	6.02E-04	203.76	65.18	76.02	131.51	1.78E-03	101.06	91.53	0.265										
111.53	96.76	-79.12	301.18	0.449	1.31E-06	109.22	96.40	21.92	356.33	0.081	1.44E-06	55.67	138.65	6.844	0.46	0.87	1.24	2.37	0.45	0.305	3.30E-04	1.71	0.89	0.08	0.45	0.236	3.0E-04	100.70	77.95	34.48	335.53	1.50E-03	101.06	113.11	0.354															
MR	20.29	120.60	-27.11	44.54	0.083	212.44	155.67	-24.45	451.03	0.052	-15.07	167.10	4.84	0.12	1.52	2.46	0.338	1.71	0.04	0.32	3.75	0.099	-1.23	188.88	102.22	3.64	401.39	0.058	191.27	93.99	0.34	377.49	3.86E-02	180.66	91.68	0.268														
MR-Elder	111.56	86.00	-8.67	301.80	0.250	2.50E-06	105.03	99.79	-30.57	360.60	0.098	1.12E-06	55.67	139.11	2.93	0.47	0.87	1.23	2.17	0.586	0.218	1.70	0.92	0.11	0.35	0.060	0.970	101.11	77.77	51.33	253.53	0.194	200.46	82.18	39.38	361.35	1.47E-02	89.69	-99.35	0.130										
MR-21Ls	21.54	117.42	-8.60	45.67	0.059	5.50E-06	113.04	64.60	63.45	295.05	0.059	4.81E-11	88.49	114.01	0.509	0.89	0.18	1.42	2.30	0.449	0.200	0.62	0.23	2.20	0.113	7.55E-04	206.64	104.71	0.007	39.05	0.040	0.477	1.03E-07	64.35	115.43	0.265														
<i>Females</i>																																																		
60.67	18.88	24.34	-0.20	15.66	58.52	0.258	4.90E-07	39.24	26.53	0.139	0.24	0.20	0.30	0.57	0.40	0.083	0.07	0.23	0.39	0.2	0.73	3.0E-09	0.07	0.32	0.838	49.54	15.58	19.01	80.88	1.49E-02	2.25E-05	19.94	15.93	11.26	51.33	0.230	3.68E-07	20.61	22.27	0.284										
60.67	24.67	12.60	14.66	0.87	0.014	8.20E-09	21.43	24.13	-26.05	44.37	0.90E-07	39.24	34.45	0.134	0.14	0.24	0.33	0.61	0.588	0.087	0.07	0.31	0.54	0.67	0.828	3.0E-09	49.54	15.19	19.93	80.65	0.010	2.35E-05	19.94	21.61	28.05	6.38E-07	19.94	20.47	-20.19	60.06	0.330	3.68E-07								
MR	50.22	32.79	-19.95	134.45	0.225	0.000	1.17	46.89	0.86	0.14	0.32	0.47	0.70	0.660	0.080	0.074	0.24	0.36	0.46	0.54	0.58	0.080	0.07	0.16	0.48	0.839	39.45	7.30	11.59	11.59	0.000	4.73E-05	47.47	27.86	-6.73	38.52	0.764	19.27	12.73	15.87	12.73	0.000	3.87E-05	24.87	27.86	0.745	38.52	0.000		
MR-Elder	61.82	24.71	13.40	11.05	12.05	0.012	8.62E-09	23.09	24.02	-29.29	70.17	0.336	1.78E-05	87.83	34.46	0.261	0.12	0.24	0.35	0.59	0.620	0.319	0.07	0.31	0.54	0.68	0.824	0.874	49.54	39.36	11.84	87.49	0.010	0.931	21.24	20.42	-18.75	61.23	0.298	0.127	24.82	29.09	0.012	39.36	0.000	5.46E-09	8.01	31.48	0.075	0.000
MR-21Ls	68.66	33.30	3.40	135.81	0.039	0.90E-06	55.15	27.66	-0.15	70.33	0.049	2.82E-09	35.51	37.78	0.075	0.49	0.39	-1.26	0.28	0.212	0.585	0.06	0.11	-0.36	0.47	0.784	9.40E-06	-0.55	0.45	0.219	37.34	27.75	-27.06	91.74	0.176	0.785	28.33	14.85	-0.77	57.43	0.056	5.46E-09	8.01	31.48	0.075	0.000				

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Menopausal (Females only)																											
FVC																											
Parameter	b	SE	LCI	UCI	p-value		Q-test		p-value		Surgen																
					b	SE	LCI	UCI	p-value	difference	b	SE															
Postmenopausal	Pre-menopausal		Pre-menopausal		p-value		p-value		p-value		Interaction																
MR + FVC	40.35	24.18	-7.03	87.73	0.095	8.951-03	35.06	17.79	0.19	69.92	0.049	5.176-08															
MR - FVC	40.37	27.59	-15.92	86.94	0.145	8.951-03	35.06	23.24	-0.50	80.62	0.031	5.176-08															
MR + BVE	28.62	17.05	-1.05	56.27	0.001	8.951-03	28.62	17.05	-1.05	56.27	0.001	8.951-03															
MR robust	42.67	30.47	-17.05	120.40	0.161	0.391	28.69	33.68	-9.63	94.31	0.031	19.45	27.77	0.26	0.006	0.006											
MR - BVE	42.67	30.47	-17.05	120.40	0.161	0.391	28.69	33.68	-9.63	94.31	0.031	19.45	27.77	0.26	0.006	0.006											
MR + 2SLs	38.80	28.55	-17.15	94.75	0.174	8.796-03	0.057	23.70	20.95	-17.33	64.79	0.257	2.276-04	15.07	35.41	0.670	0.02	0.29	0.39	0.55	0.938	0.327	1.176-03	0.09	0.39	0.814	0.209
MR - 2SLs	38.80	28.55	-17.15	94.75	0.174	8.796-03	0.057	23.70	20.95	-17.33	64.79	0.257	2.276-04	15.07	35.41	0.670	0.02	0.29	0.39	0.55	0.938	0.327	1.176-03	0.09	0.39	0.814	0.209
FEV5/FVC																											
Parameter	b	SE	LCI	UCI	p-value		Q-test		p-value		Surgen																
Postmenopausal	Pre-menopausal		Pre-menopausal		p-value		p-value		p-value		Interaction																
MR + FEV5	29.41	19.40	-0.03	58.79	0.050	5.110-07	28.07	20.16	11.45	67.59	0.164	1.021-03															
MR - FEV5	29.41	19.40	-0.03	58.79	0.050	5.110-07	28.07	20.42	-19.01	55.71	0.243	1.021-03															
MR + BVE	28.43	18.82	-1.05	50.05	0.001	8.951-03	28.43	18.82	-1.05	50.05	0.001	8.951-03															
MR robust	20.85	25.21	-28.65	70.26	0.408	0.066	20.85	25.21	-28.65	70.26	0.408	0.066															
MR - BVE	20.85	25.21	-28.65	70.26	0.408	0.066	20.85	25.21	-28.65	70.26	0.408	0.066															
MR + 2SLs	26.54	23.48	-19.47	72.56	0.242	9.116-05	17.99	17.47	-16.55	52.24	0.303	8.55	29.27	0.27	0.019	0.019											
MR - 2SLs	26.54	23.48	-19.47	72.56	0.242	9.116-05	17.99	17.47	-16.55	52.24	0.303	8.55	29.27	0.27	0.019	0.019											
FEV1																											
Parameter	b	SE	LCI	UCI	p-value		Q-test		p-value		Surgen																
Postmenopausal	Pre-menopausal		Pre-menopausal		p-value		p-value		p-value		Interaction																
MR + FEV1	22.73	18.44	-13.02	58.60	0.213	8.796-03	22.73	18.44	-13.02	58.60	0.213	8.796-03															
MR - FEV1	22.73	18.44	-13.02	58.60	0.213	8.796-03	22.73	18.44	-13.02	58.60	0.213	8.796-03															
MR + BVE	22.73	18.44	-13.02	58.60	0.213	8.796-03	22.73	18.44	-13.02	58.60	0.213	8.796-03															
MR robust	11.30	22.40	-33.67	44.27	0.001	8.951-03	11.30	22.40	-33.67	44.27	0.001	8.951-03															
MR - BVE	11.30	22.40	-33.67	44.27	0.001	8.951-03	11.30	22.40	-33.67	44.27	0.001	8.951-03															
MR + 2SLs	11.30	22.40	-33.67	44.27	0.001	8.951-03	11.30	22.40	-33.67	44.27	0.001	8.951-03															
MR - 2SLs	11.30	22.40	-33.67	44.27	0.001	8.951-03	11.30	22.40	-33.67	44.27	0.001	8.951-03															

D) Age 50 (males only)