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MENDELIAN RANDOMIZATION OF PHYSICAL ACTIVITY AND BODY COMPOSITION   2

Table S1. Participant Characteristics Included in the Genome-Wide Association Studies

Phenotype	Study	n	Women (%)	Age, Years (mean ± SD)	Trait Value (mean ± SD)
Self-report (hr./day)					
Sedentary Behavior	UKB / van de Vegte et al.	422,218	54.3	57.4 ± 8.0	4.7 ± 2.7
Moderate PA	UKB / Novel	360,912	53.4	56.7 ± 8.1	1.2 ± 1.3
MVPA	UKB / Klimentidis et al.	377,234	50.6	56.1 ± 8.2	1.9 ± 1.8
Vigorous PA (≥3 vs. 0 dys./wk.)[†]	UKB / Klimentidis et al.	98,060; 162,995	47.3; 58.1	55.4 ± 8.3; 57.4 ± 7.8	1.1 ± 0.9; 0.0 ± 0.0
SSOE (>2-3 vs 0 dys./wk.)[†]	UKB / Klimentidis et al.	124,842; 225,650	38.1; 35.3	52.7 ± 8.1; 52.6 ± 7.9	1.1 ± 0.7; 0.0 ± 0.0
Accelerometer					
Sedentary Behavior[§]	UKB / Doherty et al.	91,105	--	--	--
MVPA[‡]	UKB / Novel	97,737	56.1	56.2 ± 7.8	0.0799 ± 0.0384
Vigorous PA[‡]	UKB / Klimentidis et al.	90,667	56.1	56.2 ± 7.8	0.0026 ± 0.0033
Overall activity (milli-gravities)	UKB / Klimentidis et al.	91,105	56.1	56.2 ± 7.8	27.1 ± 27.0
Body Comp.					
BMI (kg/m^2)[††]	GIANT / Locke al.	249,796	--	--	--
WHR[††]	GIANT/ Shungin al.	224,459	--	--	--
WC (cm)[††]	GIANT/ Shungin al.	224,459	--	--	--
LBM (kg)[††]	GEFOS / Zillikens et al.	38,292	--	--	--
%TBF	Lu et al.	89,297	48.3	57.8 ± 9.4	31.6 ± 6.7
VAT (Self-Report PA; kg)	UKB / Karlsson et al.	56,908	56.7	57.1 ± 7.8	1.5 ± .86
VAT (Accel. PA; kg)	UKB / Karlsson et al.	323,769	53.8	56.9 ± 8.1	1.4 ± .83
Covariate					
Educational Attainment	UKB / Okbay et al.	293,723	55.1	57.5 ± 8.0	14.3 ± 3.6

Abbreviations: PA, Physical Activity, MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; LBM, lean body mass; %TBF, total body fat percent; VAT, visceral adipose tissue; UKB, UK Biobank, GIANT, Genetic Investigation of ANthropometric Traits consortium; GEFOS, GEnetic Factors for Osteoporosis consortium.

[†]Phenotype was evaluated as a binary variable.

[§]Phenotype was trained on 153 free-living individuals to predict metabolic equivalent of tasks.

[‡]Phenotype was derived from fraction accelerations based on metabolic equivalent of tasks.

[††]Consortium demographics unavailable.

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Table S2. F Statistics for Mendelian Randomization Analyses for Physical Activity to Body Composition

Phenotypes		Self-report MR			Accelerometer MR		
Activity	*Body Comp.*	*Mean F*	*Median F*	*Range F*	*Mean F*	*Median F*	*Range F*
Sedentary Behavior	LBM	45.75	38.97	30.41, 144.19	27.61	27.61	27.26, 27.95
	BMI	45.32	38.55	30.41-144.19	25.34	25.2	23.01, 27.95
	WHR	45.3	38.48	30.41-144.19	25.34	25.2	23.01, 27.95
	WC	45.23	38.62	30.41-144.19	25.34	25.2	23.01, 27.95
	%TBF	45.77	38.97	30.41-144.19	26.07	27.26	23.01, 27.95
	VAT	42.71	37.3	30.41-144.19	26.4	26.69	23.09, 30.18
Moderate PA	LBM	23.40	23.39	21.52, 26.05	--	--	--
	BMI	23.41	23.37	21.12-30.38	--	--	--
	WHR	23.39	23.13	21.12-30.38	--	--	--
	WC	23.39	23.13	21.12-30.38	--	--	--
	%TBF	23.51	23.37	21.12-30.38	--	--	--
	VAT	23.09	22.77	21.02-30.38	--	--	--
MVPA	LBM	25.85	24.16	20.97, 45.99	25.13	23.32	21.62, 33.12
	BMI	25.94	24.41	20.88-45.99	24.83	23.4	20.91, 34.67
	WHR	25.94	24.41	20.88-45.99	24.83	23.4	20.91, 34.67
	WC	25.9	24.39	20.88-45.99	24.83	23.4	20.91, 34.67
	%TBF	26.02	24.39	20.88-45.99	24.68	23.4	20.91, 34.67
	VAT	25.75	23.9	20.86-45.99	24.06	23.24	20.92, 34.72
Vigorous PA	LBM	27.78	23.05	21.18, 55.26	23.56	22.58	20.88, 26.64
	BMI	26.6	23.48	20.98-55.26	24.98	24.56	20.88, 36.07
	WHR	26.73	23.54	20.98-55.26	24.98	24.56	20.88, 36.07
	WC	26.47	23.42	20.98-55.26	24.98	24.56	20.88, 36.07
	%TBF	27.07	23.54	20.98-55.26	24.98	24.56	20.88, 36.07
	VAT	25.62	23.05	20.9-55.26	24.51	23.03	20.88, 36.76
SSOE	LBM	25.40	24.48	20.98, 37.34	--	--	--
	BMI	26.03	24.52	20.98-75.4	--	--	--
	WHR	25.99	24.65	20.98-75.4	--	--	--
	WC	26.09	24.59	20.98-75.4	--	--	--
	%TBF	26.17	24.65	20.98-75.4	--	--	--
	VAT	25.94	24.48	20.89-82.57	--	--	--
Overall Activity	LBM	--	--	--	25.16	24.84	22.66, 27.98
	BMI	--	--	--	24.54	23.76	22.66, 27.98
	WHR	--	--	--	24.54	23.76	22.66, 27.98
	WC	--	--	--	24.54	23.76	22.66, 27.98
	%TBF	--	--	--	24.54	23.76	22.66, 27.98
	VAT	--	--	--	24.45	24.84	21.28, 27.98

Abbreviations: MR, Mendelian randomization; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue.

Note: An F statistic of 10 indicates that the bias of the IV estimator is 10% of the bias of the observational estimator.

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MENDELIAN RANDOMIZATION OF PHYSICAL ACTIVITY AND BODY COMPOSITION   4

Table S3. MR-EGGER Intercept Estimates for Physical Activity to Body Composition

Phenotypes		Self-Report MR		Accelerometer MR	
Activity	*Body Comp.*	*MR-EGGER Intercept*	*p*	*MR-EGGER Intercept*	*p*
Sedentary Behavior	LBM	0.025031	0.2958	--	--
	BMI	-0.00449	0.3034	0.017358	0.64
	WHR	-0.00209	0.5284	0.00348	0.94
	WC	-0.00449	0.2279	0.002724	0.96
	%TBF	-0.01355	0.0073	0.052934	0.39
	VAT	-0.00168	0.586	0.005832	0.59
Moderate PA	LBM	0.037154	0.5654	--	--
	BMI	0.006266	0.3227	--	--
	WHR	0.001847	0.7752	--	--
	WC	0.0043	0.4634	--	--
	%TBF	-0.00217	0.7637	--	--
	VAT	-0.00245	0.6182	--	--
MVPA	LBM	0.035138	0.34	0.035717	0.513
	BMI	0.001909	0.5612	-0.00662	0.36
	WHR	-0.00197	0.5577	-0.00404	0.47
	WC	0.002466	0.496	-0.00533	0.44
	%TBF	0.000303	0.9364	-0.00891	0.18
	VAT	0.004179	0.2116	-0.00181	0.39
Vigorous PA	LBM	0.013209	0.753	-0.41894	0.047
	BMI	-0.0054	0.216	0.004192	0.74
	WHR	-0.00829	0.0331	0.004787	0.7
	WC	-0.0051	0.2259	-0.00019	0.99
	%TBF	-0.00134	0.7813	0.026992	0.13
	VAT	-0.00144	0.7043	-0.00095	0.8
SSOE	LBM	-0.00619	0.8902	--	--
	BMI	-0.00428	0.3557	--	--
	WHR	-0.00214	0.549	--	--
	WC	-0.00288	0.5143	--	--
	%TBF	-0.00267	0.5652	--	--
	VAT	-0.00182	0.5187	--	--
Overall Activity	LBM	--	--	-0.3933	0.631
	BMI	--	--	-0.1215	0.32
	WHR	--	--	-0.06486	0.29
	WC	--	--	-0.13557	0.23
	%TBF	--	--	-0.03473	0.64
	VAT	--	--	-0.00733	0.28

Abbreviations: MR, Mendelian randomization; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue.

Table S4. Heterogeneity estimates Mendelian Randomization Analyses for Physical Activity to Body Composition

Phenotypes		Self-report MR		Self-report MVMR		Accelerometer MR		Accelerometer MVMR	
Activity	*Body Comp.*	Q Stat.	*p*	Q Stat.	*p*	Q Stat.	*p*	Q Stat.	*p*
Sedentary Behavior	LBM	46.9	0.7435	--	--	22.2	0.035	--	--
	BMI	139.5	<0.001	--	--	18.9	<0.001	16.3	0.0121
	WHR	82.4	0.0098	253.7	<0.001	27	<0.001	17.5	0.0077
	WC	74	0.0766	145.1	<0.001	19.9	<0.001	18.2	0.0058
	%TBF	86.3	0.002	141.1	<0.001	11.8	0.0027	5.8	0.5654
	VAT	260.6	<0.001	315.8	<0.001	33.1	<0.001	160.8	<0.001
Moderate PA	LBM	4.2	0.8959	21.3	0.03	--	--	--	--
	BMI	33.2	0.0321	--	--	--	--	--	--
	WHR	18.4	0.4927	279.6	<0.001	--	--	--	--
	WC	24.8	0.1661	166.1	<0.001	--	--	--	--
	%TBF	13.9	0.788	150.8	<0.001	--	--	--	--
	VAT	52	0.0077	477.9	<0.001	--	--	--	--
MVPA	LBM	4.2	0.8959	21.3	0.03	18.9	<0.001	13.1	0.2867
	BMI	110.8	<0.001	--	--	96.9	<0.001	--	--
	WHR	91.2	0.0318	286.4	<0.001	66.6	<0.001	271.7	<0.001
	WC	94	0.0245	187	<0.001	44.8	0.0089	171.8	<0.001
	%TBF	59.1	0.6155	160.6	<0.001	34.3	0.0613	144.4	<0.001
	VAT	202.9	<0.001	554.2	<0.001	183.5	<0.001	1709.7	<0.001
Vigorous PA	LBM	21.7	0.2472	37.5	0.01	13.4	0.037	1.3	0.8616
	BMI	71.4	<0.001	--	--	20.4	0.119	--	--
	WHR	47.1	0.1242	279.8	<0.001	17.8	0.2154	278.4	<0.001
	WC	47.4	0.1685	153.3	<0.001	13.7	0.4738	165.1	<0.001
	%TBF	34.1	0.3687	165.8	<0.001	19	0.1666	162.6	<0.001
	VAT	148.8	<0.001	538.1	<0.001	90.8	<0.001	1308.6	<0.001
SSOE	LBM	25.5	0.8799	42.4	0.453	--	--	--	--
	BMI	190.7	<0.001	--	--	--	--	--	--
	WHR	132.2	<0.001	306.1	<0.001	--	--	--	--
	WC	98	0.0386	173.4	<0.001	--	--	--	--
	%TBF	51.1	0.9472	188.5	<0.001	--	--	--	--
	VAT	182.3	<0.001	458.4	<0.001	--	--	--	--
Overall Activity	LBM	--	--	--	--	4.1	0.1314	1.3	0.8616
	BMI	--	--	--	--	20.6	<0.001	38	<0.001
	WHR	--	--	--	--	14	0.0029	35.4	<0.001
	WC	--	--	--	--	2.6	0.4596	27	0.0046
	%TBF	--	--	--	--	2.5	0.4674	15.8	0.1986
	VAT	--	--	--	--	11.5	0.0211	214.7	<0.001

Abbreviations: MR, Mendelian randomization; MVMR, Multivariable Mendelian randomization; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue.

Note: A large Q statistic and small p-value indicates instrument heterogeneity and potential violation of the MR assumptions. Where horizontal pleiotropy does not exist, observed values are expected to have smaller residuals, meaning that the variants do not deviate from the slope of the fitted regression. Inversely, variants deviating from the regression line suggest a pleiotropic effect.

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MENDELIAN RANDOMIZATION OF PHYSICAL ACTIVITY AND BODY COMPOSITION   6

Table S5. MR-PRESSO Estimates for Physical Activity to Body Composition

Phenotypes		Self-Report MR		Accelerometer MR	
Activity	*Body Comp.*	*Causal Estimate*	*p*	*Causal Estimate*	*p*
Sedentary Behavior	LBM	0.26	0.3437	0.19*	0.0646
	BMI	0.23	<0.001	0.19*	0.1228
	WHR	0.23	<0.001	0.46**	0.0068
	WC	0.24	<0.001	0.43*	0.1844
	%TBF	0.22	0.0011	0.02	0.8574
	VAT	0.3	<0.001	0.12*	0.1826
Moderate PA	LBM	-0.44	0.5124	--	--
	BMI	0.08	0.4447	--	--
	WHR	0.22	0.0426	--	--
	WC	0.16	0.09	--	--
	%TBF	0.01	0.8836	--	--
	VAT	0.13	0.2193	--	--
MVPA	LBM	0.23	0.5223	0.18	0.6794
	BMI	0.08	0.1298	-0.11*	0.014
	WHR	-0.05	0.3468	-0.06	0.2577
	WC	0	0.9948	-0.06*	0.2203
	%TBF	-0.11	0.0588	-0.17	0.0114
	VAT	-0.08	0.2327	0*	0.9618
Vigorous PA	LBM	0.03	0.9778	0.98	0.3291
	BMI	-0.11	0.3991	-0.08	0.1982
	WHR	-0.23	0.0379	-0.06	0.2683
	WC	-0.16	0.2133	-0.09	0.1648
	%TBF	-0.1	0.4995	-0.22	0.0195
	VAT	-0.12	0.3949	-0.09*	0.0106
SSOE	LBM	-0.4	0.6289	--	--
	BMI	-0.49*	<0.001	--	--
	WHR	-0.21	0.0261	--	--
	WC	-0.3*	0.0124	--	--
	%TBF	-0.41	<0.001	--	--
	VAT	-0.33**	0.003	--	--
Overall Activity	LBM	--	--	0.05	0.205
	BMI	--	--	-0.31	0.0638
	WHR	--	--	-0.16*	0.4411
	WC	--	--	-0.16	0.139
	%TBF	--	--	-0.28*	0.3675
	VAT	--	--	-0.05*	0.3327

Abbreviations: MR, Mendelian randomization; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue.

Note: MR-PRESSO evaluates for global pleiotropic effects by comparing the residual sum of squares with the expected distance under the null hypothesis for no horizontal pleiotropy. Individual pleiotropic outliers are identified by examining the observed and expected distributions of each variant; *Value was corrected for outliers; ** MR-PRESSO estimate reached significance after outlier correction.

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MENDELIAN RANDOMIZATION OF PHYSICAL ACTIVITY AND BODY COMPOSITION 7

Table S6. MR Median-based Estimates for Physical Activity to Body Composition

Phenotypes		Self-Report MR			Accelerometer MR		
Activity	*Body Comp.*	*SNPs (#)*	*beta*	*95% CI*	*SNPs (#)*	*beta*	*95% CI*
Sedentary Behavior	LBM	55	0.32	-0.54, 1.18	4	0.26	0.05, 0.46
	BMI	55	0.22	0.11, 0.33	4	0.35	0.07, 0.64
	WHR	56	0.24	0.12, 0.37	4	0.42	0.21, 0.63
	WC	59	0.22	0.11, 0.33	3	-0.13	-0.5, 0.24
	%TBF	53	0.34	0.18, 0.49	6	0.07	-0.08, 0.22
	VAT	128	0.24	0.2, 0.28	4	0.26	0.05, 0.46
Moderate PA	LBM	10	0.13	-2.26, 2.52	--	--	--
	BMI	21	0.11	-0.11, 0.32	--	--	--
	WHR	20	0.15	-0.1, 0.4	--	--	--
	WC	21	0.22	-0.02, 0.46	--	--	--
	%TBF	20	-0.05	-0.35, 0.25	--	--	--
	VAT	32	0.03	-0.05, 0.12	--	--	--
MVPA	LBM	39	0.57	-0.72, 1.86	14	0.25	-0.9, 1.4
	BMI	72	0.06	-0.06, 0.18	25	-0.1	-0.2, 0
	WHR	72	0.03	-0.11, 0.16	26	-0.03	-0.15, 0.09
	WC	72	-0.02	-0.15, 0.1	26	-0.06	-0.18, 0.06
	%TBF	66	-0.12	-0.28, 0.05	24	-0.15	-0.3, -0.01
	VAT	93	-0.07	-0.12, -0.01	46	-0.09	-0.16, -0.03
Vigorous PA	LBM	36	0.22	-2.43, 2.86	3	-1.07	-3.24, 1.09
	BMI	38	-0.05	-0.33, 0.23	15	-0.12	-0.25, 0.01
	WHR	38	0.09	-0.22, 0.39	15	-0.06	-0.23, 0.11
	WC	40	-0.2	-0.49, 0.1	15	-0.08	-0.23, 0.06
	%TBF	33	-0.07	-0.44, 0.3	15	-0.2	-0.4, 0
	VAT	61	-0.14	-0.24, -0.04	26	-0.19	-0.28, -0.1
SSOE	LBM	19	0.64	-2.57, 3.84	--	--	--
	BMI	74	-0.34	-0.59, -0.1	--	--	--
	WHR	74	-0.12	-0.38, 0.15	--	--	--
	WC	77	-0.06	-0.31, 0.19	--	--	--
	%TBF	72	-0.26	-0.59, 0.07	--	--	--
	VAT	98	-0.31	-0.41, -0.21	--	--	--
Overall Activity	LBM	--	--	--	7	1.12	-0.7, 2.93
	BMI	--	--	--	4	-0.18	-0.43, 0.07
	WHR	--	--	--	4	-0.16	-0.41, 0.1
	WC	--	--	--	4	-0.14	-0.35, 0.07
	%TBF	--	--	--	4	-0.29	-0.59, 0.02
	VAT	--	--	--	6	-0.21	-0.38, -0.03

Abbreviations: MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue.
Note: The weighted median causal estimates are based on the relationship between the strength of association between the SNP and exposure, and the SNP and outcome associations.

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Table S7. MR Mode-based Estimates for Physical Activity to Body Composition

Phenotypes		Self-Report MR			Accelerometer MR		
Activity	*Body Comp.*	*SNPs (#)*	*beta*	*95% CI*	*SNPs (#)*	*beta*	*95% CI*
Sedentary Behavior	LBM	55	0.38	-1.53, 2.29	4	0.24	0.02, 0.46
	BMI	55	0.21	-0.03, 0.44	4	0.37	-0.08, 0.82
	WHR	56	0.23	-0.01, 0.48	4	0.44	0.19, 0.69
	WC	59	0.16	-0.08, 0.39	3	-0.2	-0.58, 0.18
	%TBF	53	0.46	0.17, 0.75	6	0.03	-0.17, 0.24
	VAT	128	0.24	0.13, 0.36	4	0.24	0.02, 0.46
Moderate PA	LBM	10	0.4	-3.55, 4.35	--	--	--
	BMI	21	0.21	-0.21, 0.64	--	--	--
	WHR	20	0.14	-0.36, 0.63	--	--	--
	WC	21	0.2	-0.29, 0.69	--	--	--
	%TBF	20	-0.19	-0.75, 0.36	--	--	--
	VAT	32	0.04	-0.13, 0.21	--	--	--
MVPA	LBM	39	0.62	-2.2, 3.45	14	0.69	-1.56, 2.93
	BMI	72	-0.01	-0.32, 0.29	25	-0.1	-0.27, 0.07
	WHR	72	0.1	-0.24, 0.44	26	-0.06	-0.3, 0.18
	WC	72	0.05	-0.23, 0.32	26	-0.06	-0.34, 0.23
	%TBF	66	-0.2	-0.57, 0.17	24	-0.19	-0.44, 0.06
	VAT	93	-0.04	-0.17, 0.09	46	-0.03	-0.18, 0.11
Vigorous PA	LBM	36	3.5	-2.73, 9.74	3	-1.73	-4.91, 1.46
	BMI	38	-0.15	-0.86, 0.56	15	-0.17	-0.38, 0.03
	WHR	38	0.36	-0.17, 0.88	15	-0.05	-0.32, 0.22
	WC	40	0.4	-0.27, 1.07	15	-0.09	-0.35, 0.17
	%TBF	33	0.44	-0.44, 1.32	15	-0.27	-0.57, 0.03
	VAT	61	-0.09	-0.34, 0.15	26	-0.23	-0.39, -0.06
SSOE	LBM	19	4.44	-2.06, 10.93	--	--	--
	BMI	74	-0.51	-1.18, 0.16	--	--	--
	WHR	74	0.04	-0.85, 0.93	--	--	--
	WC	77	0.13	-0.48, 0.74	--	--	--
	%TBF	72	0.05	-0.67, 0.78	--	--	--
	VAT	98	-0.37	-0.73, 0	--	--	--
Overall Activity	LBM	--	--	--	7	2.56	-0.86, 5.98
	BMI	--	--	--	4	-0.04	-0.55, 0.46
	WHR	--	--	--	4	-0.04	-0.34, 0.26
	WC	--	--	--	4	-0.28	-0.61, 0.05
	%TBF	--	--	--	4	-0.26	-0.67, 0.15
	VAT	--	--	--	6	-0.17	-0.39, 0.06

Abbreviations: MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue.

Note: The weighted mode causal estimates are based on the relationship between the strength of association between the SNP and exposure, and the SNP and outcome associations. The weighted-mode estimate uses the property that valid instruments should provide the largest number of similar individual-instrument causal estimates even if the majority of instruments is invalid.

Supplemental material

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MENDELIAN RANDOMIZATION OF PHYSICAL ACTIVITY AND BODY COMPOSITION   9

Table S8. MR-EGGER Estimates for Physical Activity to Body Composition

Phenotypes		Self-Report MR			Accelerometer MR		
Activity	*Body Comp.*	*SNPs (#)*	*beta*	*95% CI*	*SNPs (#)*	*beta*	*95% CI*
Sedentary Behavior	LBM	55	0	-0.24, 0.24	4	-0.25	-1.24, 0.74
	BMI	55	0.53	0, 1.06	4	-0.32	-2.81, 2.17
	WHR	56	0.54	0.1, 0.99	4	0.33	-3.35, 4.02
	WC	59	0.37	-0.03, 0.77	3	0.14	-3.02, 3.29
	%TBF	53	1.03	0.45, 1.62	6	-1.87	-4.7, 0.95
	VAT	128	0.34	0.13, 0.56	4	0	-0.69, 0.69
Moderate PA	LBM	10	-0.05	-0.26, 0.15	--	--	--
	BMI	21	-0.36	-1.23, 0.51	--	--	--
	WHR	20	-0.14	-0.95, 0.67	--	--	--
	WC	21	0.09	-0.81, 0.99	--	--	--
	%TBF	20	0.18	-0.82, 1.18	--	--	--
	VAT	32	0.08	-0.21, 0.38	--	--	--
MVPA	LBM	39	-0.15	-0.35, 0.05	14	0.03	-0.08, 0.15
	BMI	72	-0.08	-0.57, 0.41	25	0.11	-0.44, 0.66
	WHR	72	-0.2	-0.74, 0.35	26	0.1	-0.44, 0.63
	WC	72	0.11	-0.4, 0.61	26	0.1	-0.33, 0.54
	%TBF	66	-0.12	-0.7, 0.46	24	0.18	-0.32, 0.68
	VAT	93	-0.18	-0.4, 0.03	46	-0.09	-0.24, 0.06
Vigorous PA	LBM	36	0.35	-0.05, 0.75	3	0.18	-0.39, 0.75
	BMI	38	0.62	-0.41, 1.65	15	-0.26	-1.31, 0.8
	WHR	38	0.55	-0.44, 1.53	15	-0.09	-1.26, 1.09
	WC	40	0.81	-0.08, 1.71	15	-0.27	-1.27, 0.74
	%TBF	33	0.05	-1.07, 1.17	15	-1.37	-2.76, 0.03
	VAT	61	0.05	-0.2, 0.3	26	-0.24	-0.51, 0.02
SSOE	LBM	19	0.01	-0.3, 0.31	--	--	--
	BMI	74	0.32	-1.08, 1.72	--	--	--
	WHR	74	0.2	-1.13, 1.54	--	--	--
	WC	77	0.1	-0.98, 1.18	--	--	--
	%TBF	72	0.01	-1.41, 1.42	--	--	--
	VAT	98	-0.09	-0.45, 0.26	--	--	--
Overall Activity	LBM	--	--	--	7	0.14	-0.07, 0.35
	BMI	--	--	--	4	4.15	-2.54, 10.84
	WHR	--	--	--	4	4.58	-1.08, 10.24
	WC	--	--	--	4	2.19	-1.08, 5.46
	%TBF	--	--	--	4	0.95	-3.56, 5.47
	VAT	--	--	--	6	-0.25	-1.08, 0.57

Abbreviations: MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue.

Note: MR-Egger regression assumes linearity and homogeneity in the associations between the genetic variants, risk factor, and outcome. Egger regression provides an estimate of the causal effect that is consistent asymptotically even if all the genetic variants have pleiotropic effects on the outcome.

Table S9. CAUSE estimates for Physical Activity to Body Composition

Phenotypes		Self-Report MR		Accelerometer MR	
Activity	*Body Comp.*	*Effect*	*95% CI*	*Effect*	*95% CI*
Sedentary Behavior	LBM	0.00	-0.36, 0.40	0.42	-1.04, 1.85
	BMI	0.14	0.10, 0.18**	0.05	-0.06, 0.17
	WHR	0.13	0.08, 0.17**	0.02	-0.12, 0.17
	WC	0.16	0.11, 0.20**	0.03	-0.15, 0.20
	%TBF	0.17	0.11, 0.24	0.12	-0.08, 0.33
	VAT	0.23	0.19, 0.28***	0.10	-0.01, 0.21
Moderate PA	LBM	-0.69	-2.18, 0.81	--	--
	BMI	0.07	-0.11, 0.26	--	--
	WHR	0.20	0.02, 0.39	--	--
	WC	0.13	-0.10, 0.36	--	--
	%TBF	0.04	-0.24, 0.32	--	--
	VAT	0.25	0.02, 0.47	--	--
MVPA	LBM	0.51	-0.15, 1.24	0.00	-0.47, 0.47
	BMI	-0.02	-0.11, 0.07	-0.13	-0.19, -0.07
	WHR	-0.03	-0.11, 0.06	-0.08	-0.15, -0.02
	WC	-0.03	-0.12, 0.07	-0.12	-0.19, -0.05
	%TBF	-0.08	-0.20, 0.03	-0.11	-0.19, -0.03
	VAT	-0.06	-0.16, 0.04	-0.11	-0.15, -0.07***
Vigorous PA	LBM	0.59	-0.84, 2.05	0.15	-0.42, 0.75
	BMI	0.00	-0.18, 0.19	-0.08	-0.16, 0.01
	WHR	-0.03	-0.20, 0.14	-0.02	-0.10, 0.06
	WC	0.02	-0.16, 0.21	-0.07	-0.16, 0.02
	%TBF	-0.11	-0.34, 0.12	-0.07	-0.19, 0.05
	VAT	-0.13	-0.33, 0.06	-0.14	-0.19, -0.08***
SSOE	LBM	1.36	-0.19, 2.82	--	--
	BMI	-0.19	-0.36, -0.02	--	--
	WHR	-0.22	-0.37, -0.08	--	--
	WC	-0.22	-0.39, -0.05	--	--
	%TBF	-0.34	-0.56, -0.11	--	--
	VAT	-0.28	-0.46, -0.11	--	--
Overall Activity	LBM	--	--	0.18	-0.98, 1.31
	BMI	--	--	-0.12	-0.28, 0.04
	WHR	--	--	-0.09	-0.25, 0.08
	WC	--	--	-0.11	-0.30, 0.07
	%TBF	--	--	-0.17	-0.35, 0.02
	VAT	--	--	-0.08	-0.19, 0.03

Abbreviations: MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises; LBM, lean body mass; BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; %TBF, total body fat percent; VAT, visceral adipose tissue. Note: ***$p<.001$, **$p<.01$

Table S10. Bidirectional MR IVW Estimates for Body Composition to Physical Activity

Phenotypes		Self-Report MR			Accelerometer MR		
Body Comp.	*Activity*	*SNPs (#)*	*beta*	*95% CI*	*SNPs (#)*	*beta*	*95% CI*
LBM[†]	Sedentary Behavior	15	0.00	-0.00, 0.00	--	--	--
	Moderate PA	16	0.00	-0.01, 0.00	--	--	--
	MVPA	16	0.00	-0.00, 0.01	16	0.00	0.00, 0.01
	Vigorous PA	16	0.00	-0.00, 0.00	16	0.01	0.00, 0.02
	SSOE	16	0.00	-0.00, 0.00	--	--	--
	Overall Activity	--	--	--	--	--	--
BMI	Sedentary Behavior	67	0.09	0.08, 0.10	11	0.12	-0.03, 0.26
	Moderate PA	78	0.01	-0.02, 0.03	12	-0.04	-0.16, 0.07
	MVPA	78	-0.01	-0.04, 0.03	71	-0.03	-0.08, 0.02
	Vigorous PA	78	0.01	-0.01, 0.03	71	-0.08	-0.13, -0.04
	SSOE	78	0.00	-0.02, 0.02	--	--	--
	Overall Activity	--	--	--	11	-0.03	-0.17, 0.11
%TBF	Sedentary Behavior	6	0.12	-0.04, 0.29	2	0.11	-0.18, 0.40
	Moderate PA	9	-0.05	-0.10, 0.00	2	0.07	-0.16, 0.31
	MVPA	9	-0.05	-0.17, 0.05	9	-0.02	-0.14, 0.10
	Vigorous PA	9	-0.00	-0.06, 0.05	9	-0.00	-0.11, 0.10
	SSOE	9	0.01	-0.03, 0.04	--	--	--
	Overall Activity	--	--	--	2	0.07	-0.3, 0.45
VAT	Sedentary Behavior	18	0.05	-0.01, 0.11	28	0.23	0.10, 0.36
	Moderate PA	19	-0.01	-0.05, 0.03	29	-0.12	-0.25, 0.01
	MVPA	17	0.02	-0.03, 0.07	236	-0.17	-0.22, -0.12
	Vigorous PA	17	0.03	0.00, 0.06	211	-0.19	-0.23, -0.14
	SSOE	17	0.03	0.02, 0.05	--	--	--
	Overall Activity	--	--	--	27	-0.10	-0.25, 0.05

Abbreviations: MR, Mendelian randomization; SNPs, single nucleotide polymorphisms; LBM, lean body mass; BMI, body mass index; %TBF, total body fat percent; VAT, visceral adipose tissue; PA, physical activity; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises.

[†]LBM contained one SNPs at the genome-wide significance level; a reduced IV threshold ($p < 5 \times 10^{-6}$) was used for analyses. Outcome SNPs could not be identified in GWAS of sedentary behavior, moderate PA, or overall activity.

SNP ID	Chromosome	Position	Gene	Allele	EAF	B	SE	*p*
rs6545389	2	54386901	ACYP2	A / G	0.4997	-0.0127	0.0023	3.5e-08
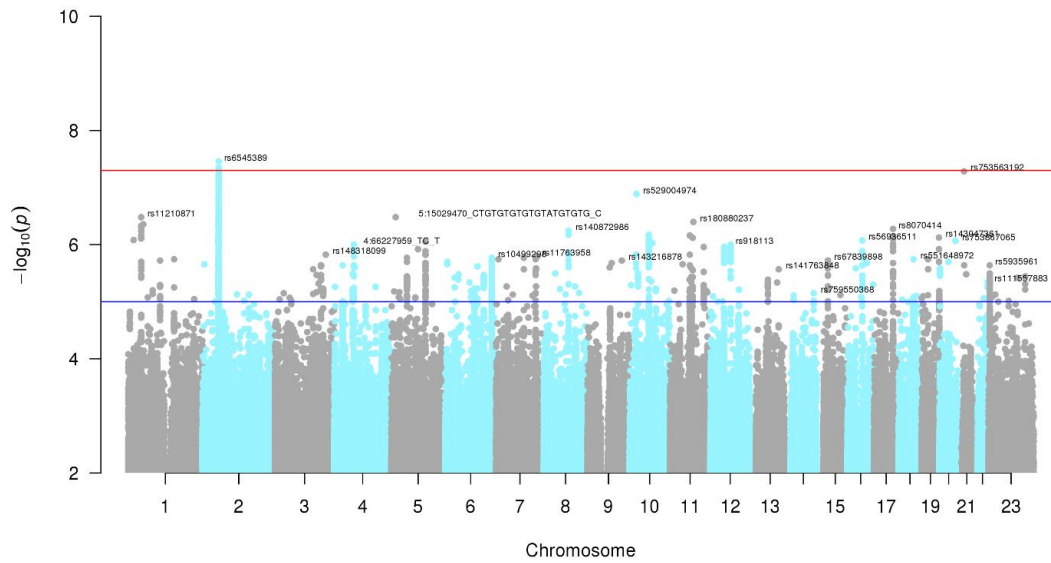
Figure S1. Manhattan Plot and genome-wide significant SNPs for self-reported moderate PA

SNP ID	Chromosome	Position	Gene	Allele	EAF	B	SE	*p*
rs4480415	1	174800121	RABGAP1L	G / A	0.7248	-0.012	0.0023	4.6e-08
rs17443704	5	151668231	--	G / A	0.8231	-0.013	0.0023	3.5e-08
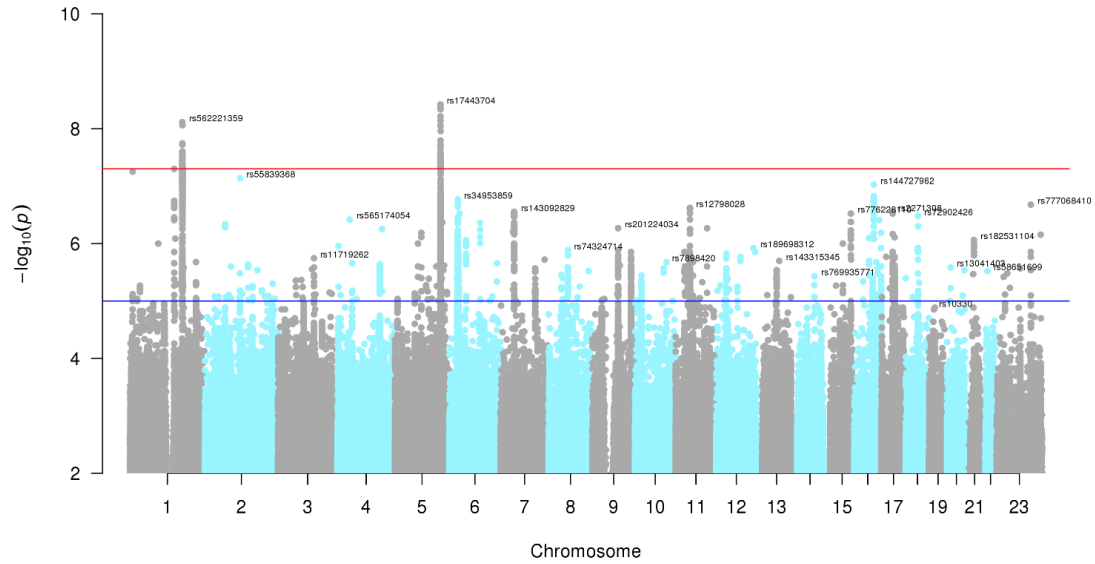
Figure S2. Manhattan Plot and genome-wide significant SNPs for accelerometer-measured MVPA

Supplemental material

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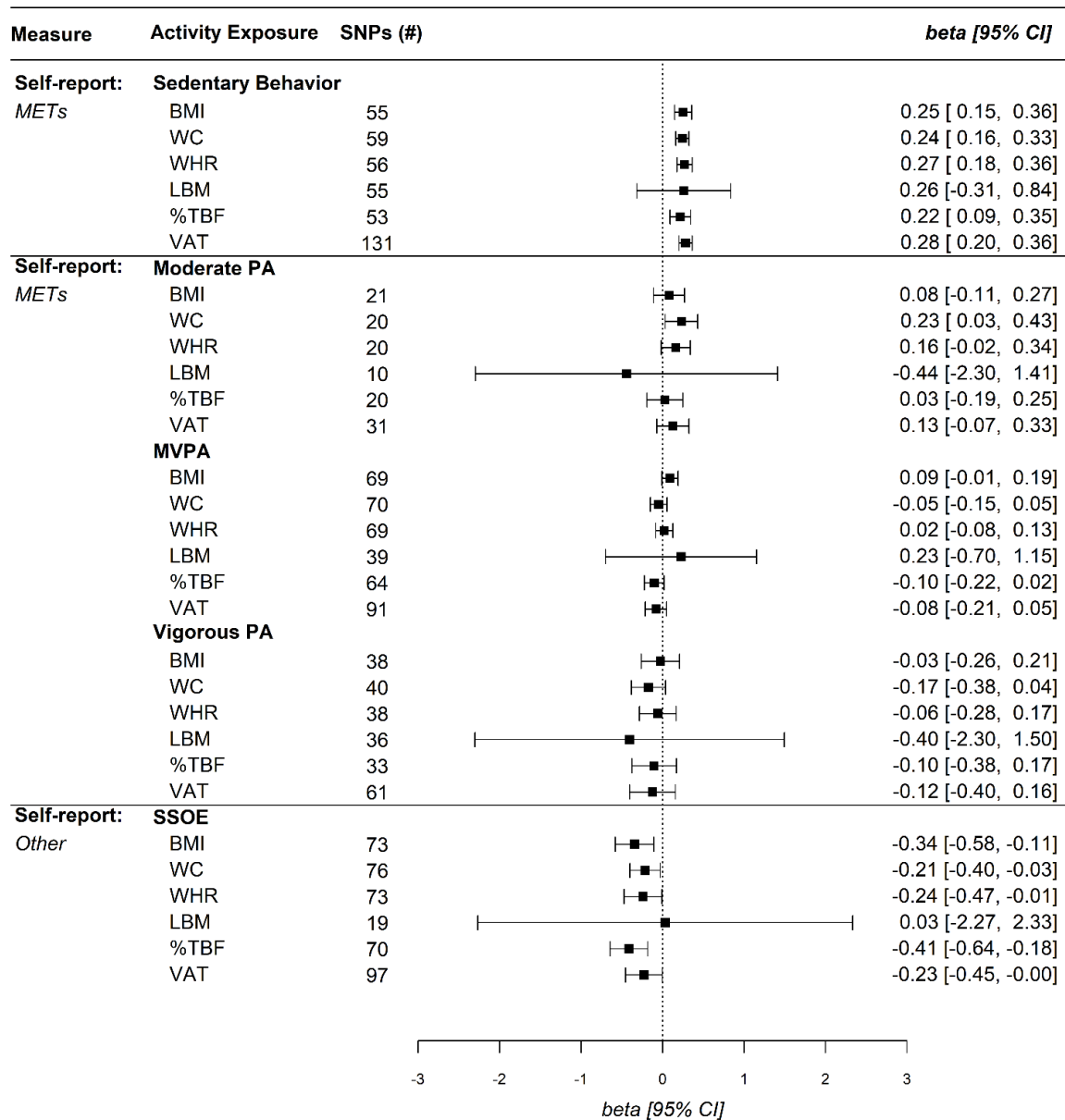| Measure	Activity Exposure	SNPs (#)		beta [95% CI]
Self-report:	**Sedentary Behavior**			
METs	BMI	55		0.25 [0.15, 0.36]
	WC	59		0.24 [0.16, 0.33]
	WHR	56		0.27 [0.18, 0.36]
	LBM	55		0.26 [-0.31, 0.84]
	%TBF	53		0.22 [0.09, 0.35]
	VAT	131		0.28 [0.20, 0.36]
Self-report:	**Moderate PA**			
METs	BMI	21		0.08 [-0.11, 0.27]
	WC	20		0.23 [0.03, 0.43]
	WHR	20		0.16 [-0.02, 0.34]
	LBM	10		-0.44 [-2.30, 1.41]
	%TBF	20		0.03 [-0.19, 0.25]
	VAT	31		0.13 [-0.07, 0.33]
	MVPA			
	BMI	69		0.09 [-0.01, 0.19]
	WC	70		-0.05 [-0.15, 0.05]
	WHR	69		0.02 [-0.08, 0.13]
	LBM	39		0.23 [-0.70, 1.15]
	%TBF	64		-0.10 [-0.22, 0.02]
	VAT	91		-0.08 [-0.21, 0.05]
	Vigorous PA			
	BMI	38		-0.03 [-0.26, 0.21]
	WC	40		-0.17 [-0.38, 0.04]
	WHR	38		-0.06 [-0.28, 0.17]
	LBM	36		-0.40 [-2.30, 1.50]
	%TBF	33		-0.10 [-0.38, 0.17]
	VAT	61		-0.12 [-0.40, 0.16]
Self-report:	**SSOE**			
Other	BMI	73		-0.34 [-0.58, -0.11]
	WC	76		-0.21 [-0.40, -0.03]
	WHR	73		-0.24 [-0.47, -0.01]
	LBM	19		0.03 [-2.27, 2.33]
	%TBF	70		-0.41 [-0.64, -0.18]
	VAT	97		-0.23 [-0.45, -0.00]

beta [95% CI]

Figure S3. Univariable Mendelian Randomization IVW Sensitivity Analysis for Self-Reported Physical Activity Levels and Body Composition removing the *APOE* rs429358 variant. Abbreviations: SNPs, single nucleotide polymorphisms; CI, confidence interval; METs, metabolic equivalent of tasks; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; LBM, lean body mass; %TBF, total body fat percent; VAT, visceral adipose tissue; MVPA, moderate-to-vigorous PA; SSOE, strenuous sports or other exercises.

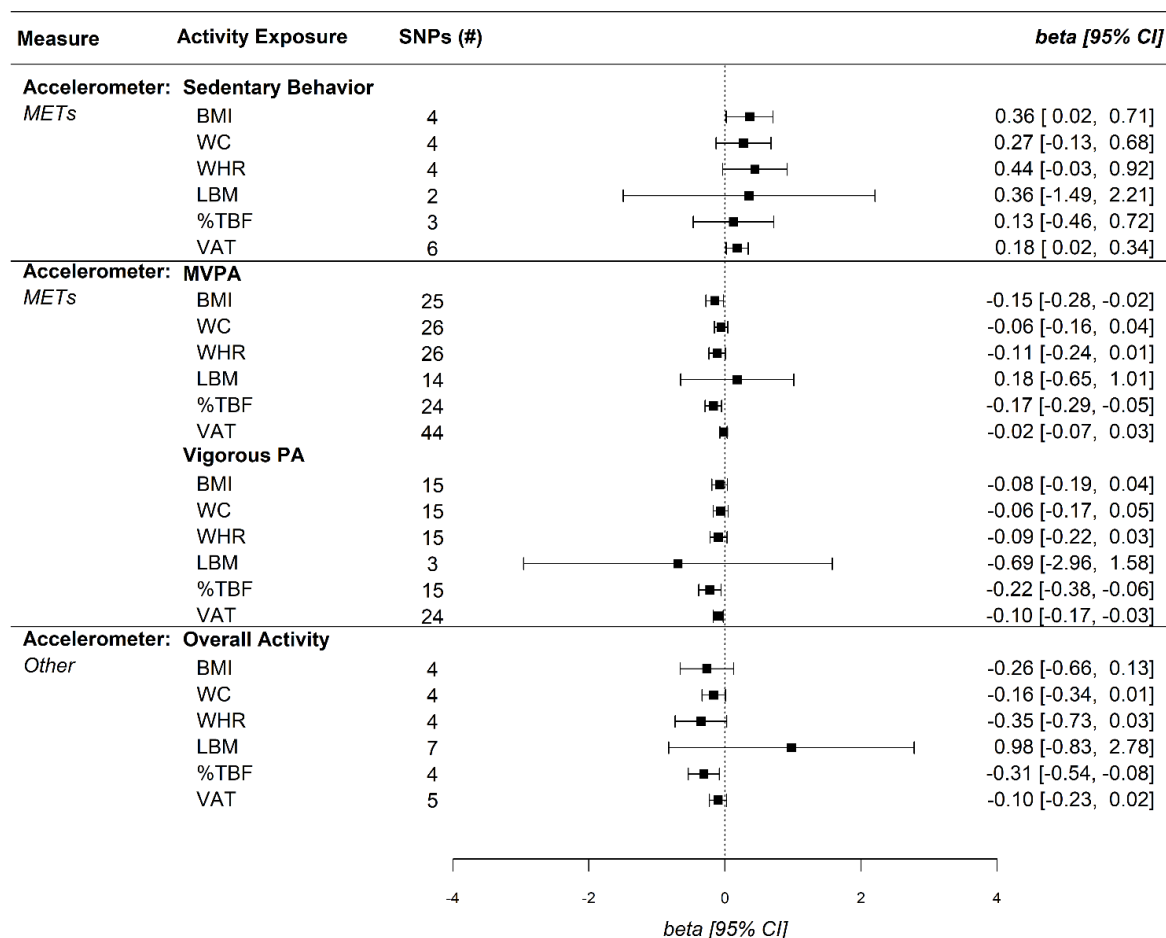| Measure	Activity Exposure	SNPs (#)	beta [95% CI]
Accelerometer:	**Sedentary Behavior**		
METs	BMI	4	0.36 [0.02, 0.71]
	WC	4	0.27 [-0.13, 0.68]
	WHR	4	0.44 [-0.03, 0.92]
	LBM	2	0.36 [-1.49, 2.21]
	%TBF	3	0.13 [-0.46, 0.72]
	VAT	6	0.18 [0.02, 0.34]
Accelerometer:	**MVPA**		
METs	BMI	25	-0.15 [-0.28, -0.02]
	WC	26	-0.06 [-0.16, 0.04]
	WHR	26	-0.11 [-0.24, 0.01]
	LBM	14	0.18 [-0.65, 1.01]
	%TBF	24	-0.17 [-0.29, -0.05]
	VAT	44	-0.02 [-0.07, 0.03]
	Vigorous PA		
	BMI	15	-0.08 [-0.19, 0.04]
	WC	15	-0.06 [-0.17, 0.05]
	WHR	15	-0.09 [-0.22, 0.03]
	LBM	3	-0.69 [-2.96, 1.58]
	%TBF	15	-0.22 [-0.38, -0.06]
	VAT	24	-0.10 [-0.17, -0.03]
Accelerometer:	**Overall Activity**		
Other	BMI	4	-0.26 [-0.66, 0.13]
	WC	4	-0.16 [-0.34, 0.01]
	WHR	4	-0.35 [-0.73, 0.03]
	LBM	7	0.98 [-0.83, 2.78]
	%TBF	4	-0.31 [-0.54, -0.08]
	VAT	5	-0.10 [-0.23, 0.02]

beta [95% CI]

Figure S4. Univariable Mendelian Randomization IVW Sensitivity Analysis for Accelerometer-Measured Physical Activity Levels and Body Composition removing the *APOE* rs429358 variant. Abbreviations: SNPs, single nucleotide polymorphisms; CI, confidence interval; METs, metabolic equivalent of tasks; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; LBM, lean body mass; %TBF, total body fat percent; VAT, visceral adipose tissue; MVPA, moderate-to-vigorous PA.