Supplemental Material

- **Supplemental Material 1. Manhattan plots for moderate and vigorous physical activity**
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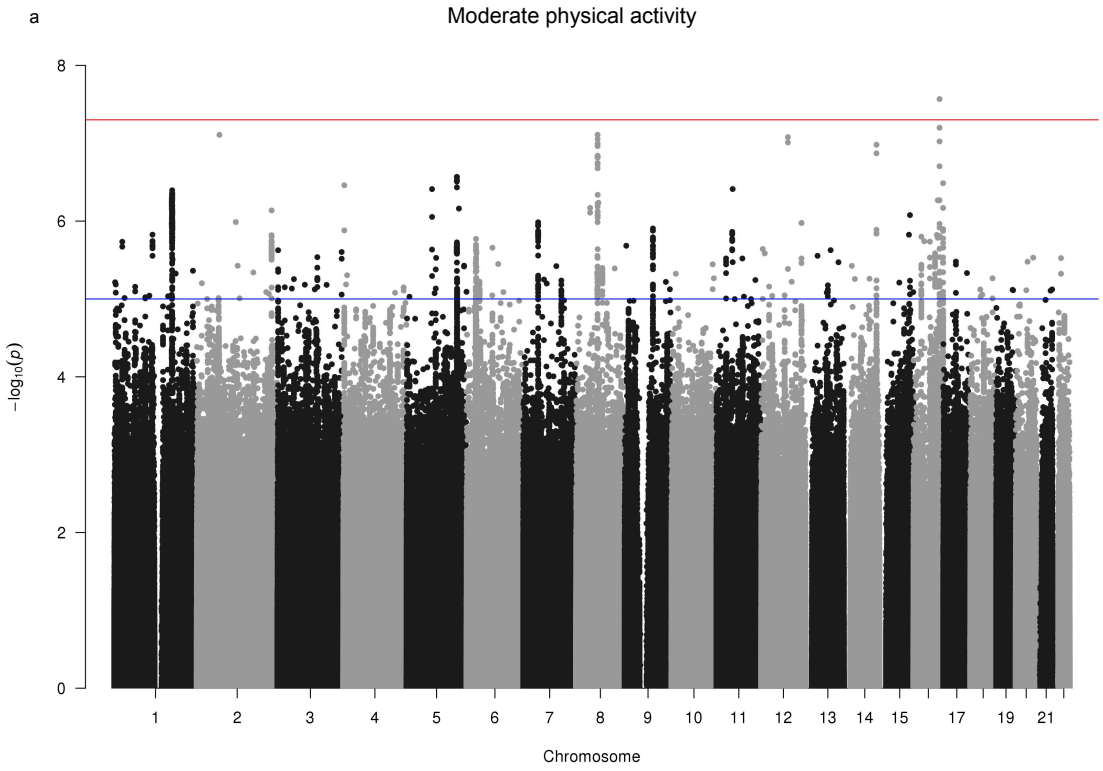
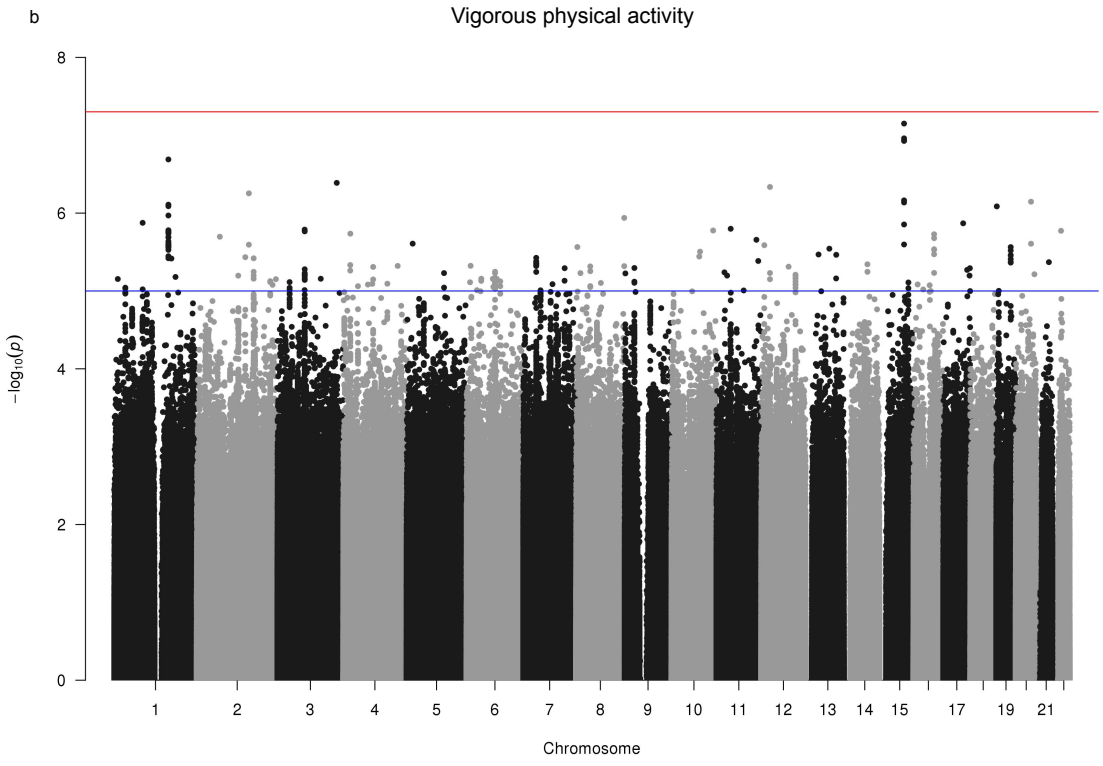
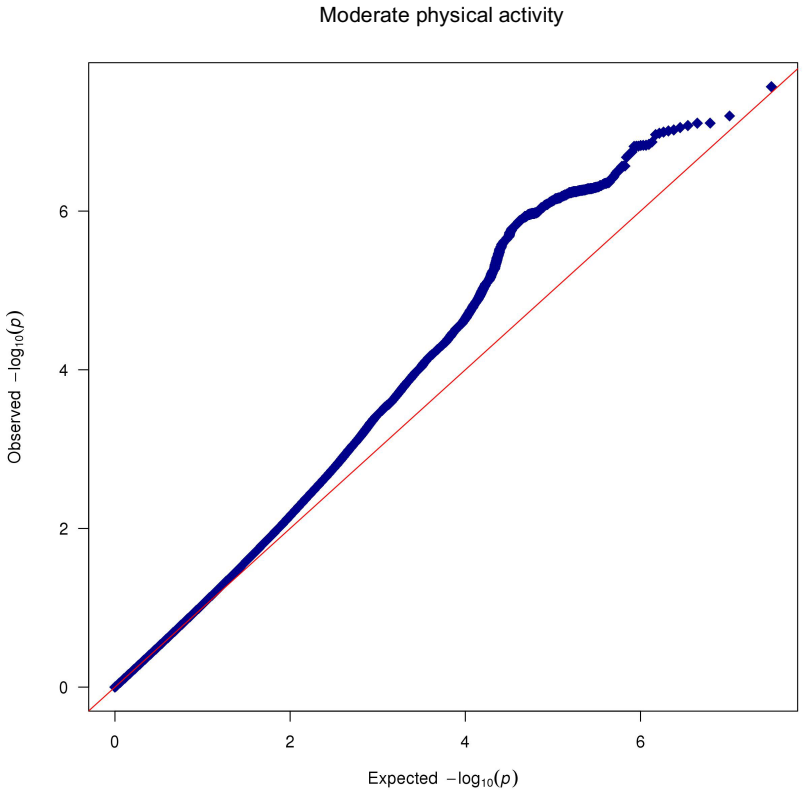
Supplemental Material 1. Manhattan plots for moderate and vigorous physical activity



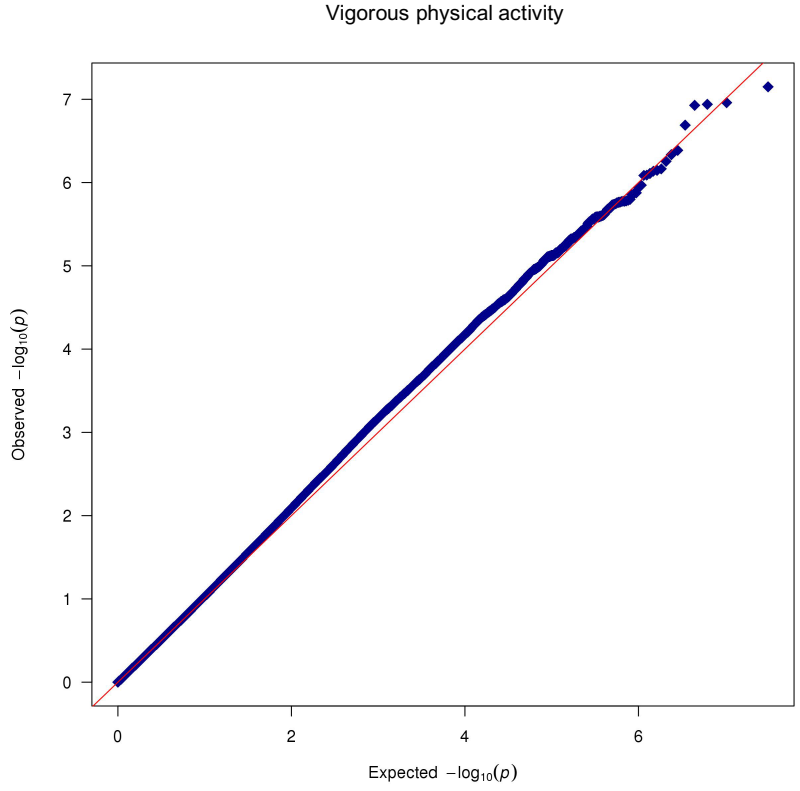


Supplemental Material 2. Q-Q plots for moderate and vigorous physical activity

a



b



Supplemental Material 3. Parameters estimates corresponding to the top 10 competing LHC-MR optimized models with the maximum likelihood

Minimum log likelihood	h2X	h2Y	tX	tY	Y->X
-412147.3671	0.06281798	0.05972831	0.55586295	0.21994846	-1.1194312
-412147.3637	0.06660269	0.05920051	0.55615452	0.22445207	-1.1208508
-412147.324	0.06539105	0.06254814	0.54331899	0.21695751	-1.0782648
-412147.3004	0.06183298	0.05200991	0.59744722	-0.2364826	1.33060451
-412147.2961	0.06497437	0.06463484	0.53530224	0.21185777	-1.0356249
-412147.2948	0.06419906	0.06317745	0.54240102	0.21519858	-1.0422385
-412147.2623	0.06488136	0.04864499	0.61077951	-0.2430935	1.40694142
-412147.2596	0.06188799	0.04512306	0.63443065	-0.245956	1.50326793
-412147.2513	0.06760578	0.06494738	0.53304795	0.21439371	-1.0055237
-412147.2475	0.06226536	0.05414764	0.58597942	-0.233136	1.28782801

Notes. Heritability on exposure (X) and outcome (Y) shown as h2X and h2Y respectively. The effect of the confounder on X and Y shown as tX and tY respectively. Causal effect from Y to X (Y→X) is also reported, whereas causal effect from X to Y (X→Y) is non-significant.

Supplemental Material 4. Standard MR analysis on potential confounders

Exposure	Outcome	MR method	Valid SNPs	Causal estimate	SE	P-value
Educational attainment and general cognitive functioning						
Edu	**CF**	**MR Egger**	**33**	**0.845**	**0.609**	**0.175**
		Weighted median	**33**	**0.647**	**0.056**	**1.35e-30**
		Inverse variance weighted	**33**	**0.674**	**0.055**	**4.46e-34**
		Simple mode	**33**	**0.759**	**0.134**	**2.95e-06**
		Weighted mode	**33**	**0.671**	**0.112**	**1.20e-06**
CF	Edu	MR Egger	131	0.478	0.113	4.52e-05
		Weighted median	131	0.405	0.023	8.77e-67
		Inverse variance weighted	131	0.417	0.0199	7.44e-98
		Simple mode	131	0.457	0.071	2.30e-09
		Weighted mode	131	0.443	0.076	3.56e-08
Educational attainment and Average accelerometer-based physical activity – model 1						
Edu	**PA**	**MR Egger**	**34**	**0.560**	**0.755**	**0.463**
		Weighted median	**34**	**-0.008**	**0.072**	**0.907**
		Inverse variance weighted	**34**	**-0.012**	**0.069**	**0.862**
		Simple mode	**34**	**0.100**	**0.162**	**0.543**
		Weighted mode	**34**	**0.0100**	**0.141**	**0.485**
PA	Edu	MR Egger	6	-1.801	1.045	0.159
		Weighted median	6	0.013	0.086	0.878
		Inverse variance weighted	6	0.032	0.107	0.766
		Simple mode	6	-0.068	00.199	0.747
		Weighted mode	6	-0.143	0.136	0.341
Body mass index and general cognitive functioning						
BMI	**CF**	**MR Egger**	**306**	**-0.099**	**0.067**	**0.143**
		Weighted median	**306**	**-0.064**	**0.018**	**3.08e-04**
		Inverse variance weighted	**306**	**-0.122**	**0.0213**	**1.01e-08**
		Simple mode	**306**	**0.038**	**0.071**	**0.594**
		Weighted mode	**306**	**0.019**	**0.037**	**0.607**
CF	BMI	MR Egger	131	-0.324	0.220	0.144
		Weighted median	131	-0.116	0.022	2.04e-07
		Inverse variance weighted	131	-0.179	0.039	3.54e-06
		Simple mode	131	-0.142	0.056	0.012
		Weighted mode	131	-0.130	0.050	0.011
Body mass index and Average accelerometer-based physical activity – model 1						
BMI	**PA**	**MR Egger**	**306**	**0.102**	**0.069**	**0.140**
		Weighted median	**306**	**-0.126**	**0.027**	**4.11e-06**
		Inverse variance weighted	**306**	**-0.207**	**0.023**	**4.11e-20**
		Simple mode	**306**	**-0.438**	**0.134**	**0.001**
		Weighted mode	**306**	**-0.008**	**0.053**	**0.886**
PA	BMI	MR Egger	6	1.188	1.100	0.584
		Weighted median	6	-0.233	0.063	2.3e-04
		Inverse variance weighted	6	-0.277	0.163	0.089

		Simple mode	6	-0.466	0.099	0.005
		Weighted mode	6	0.140	0.106	0.245

Body mass index and Moderate accelerometer-based physical activity (fraction of acceleration > 100 mg and < 425 mg)

BMI	**PA**	**MR Egger**	**306**	**0.057**	**0.068**	**0.407**
		Weighted median	**306**	**-0.122**	**0.028**	**1.16e-05**
		Inverse variance weighted	**306**	**-0.186**	**0.022**	**4.15e-17**
		Simple mode	**306**	**-0.150**	**0.119**	**0.210**
		Weighted mode	**306**	**-0.025**	**0.051**	**0.622**
PA	BMI	MR Egger	33	-0.607	0.941	0.523
		Weighted median	33	-0.058	0.030	0.053
		Inverse variance weighted	33	-0.096	0.046	0.037
		Simple mode	33	-0.142	0.062	0.028
		Weighted mode	33	-0.107	0.060	0.082

Educational attainment and Moderate accelerometer-based physical activity (fraction of acceleration > 100 mg and < 425 mg)

Edu	**PA**	**MR Egger**	**34**	**0.409**	**0.601**	**0.505**
		Weighted median	**34**	**-0.070**	**0.075**	**0.351**
		Inverse variance weighted	**34**	**-0.024**	**0.055**	**0.672**
		Simple mode	**34**	**-0.153**	**0.162**	**0.352**
		Weighted mode	**34**	**-0.127**	**0.149**	**0.401**
PA	Edu	MR Egger	33	-0.668	0.531	0.218
		Weighted median	33	0.033	0.033	0.317
		Inverse variance weighted	33	0.027	0.026	0.308
		Simple mode	33	0.058	0.075	0.444
		Weighted mode	33	0.058	0.074	0.438

Notes. CF = general cognitive functioning; Edu = educational attainment; PA = accelerometer-based physical activity; BMI = body mass index; Causal estimates from 5 standard MR methods on alternating exposure and outcome traits. For moderate physical activity as exposure, the cutoff was decreased to 10e-5 because of the low number of genome wide significant SNPs to use as instruments. The tables required for the investigation of the potential confounders are highlighted in bold.