

**Association of Physical Activity and Sedentary Behavior with Type 2 Diabetes
and Glycemic Traits: a two-sample Mendelian randomization study**

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Supplement

Table 1 Exposure IV-association

SNP	Chr	Pos (hg38)	EA	O A	EAF	BETA	SE	P-value	R ²	F
Average accelerometer-based physical activity										
rs34517439	1	77984833	C	A	0.879	0.308	0.056	4.4x10 ⁻⁸	0.00033	29.972
rs336605	3	18614858	G	T	0.276	0.222	0.041	4.5x10 ⁻⁸	0.00033	29.913
rs10067451	5	88646688	G	A	0.887	0.326	0.058	2.5x10 ⁻⁸	0.00034	31.077
rs7084454	10	21532345	G	A	0.676	0.222	0.039	1.0x10 ⁻⁸	0.00036	32.753
rs148193266	11	104657953	A	C	0.957	-0.510	0.092	3.1x10 ⁻⁸	0.00034	30.670
rs79724577	17	45386127	A	C	0.818	-0.276	0.047	4.6x10 ⁻⁹	0.00038	34.369
rs1518139	18	43171267	G	T	0.662	-0.226	0.039	4.5x10 ⁻⁹	0.00038	34.415
accelerometer-based physical activity>425mg										
rs17006599	1	219763423	A	G	0.800	0.027	0.005	1.0x10 ⁻⁷	0.00031	28.350
rs6433478	2	174376754	T	C	0.457	-0.024	0.004	1.2x10 ⁻⁸	0.00036	32.465
rs62443625	7	39013531	T	C	0.767	-0.026	0.005	1.4x10 ⁻⁷	0.00031	27.683
rs72633364	8	34329370	G	A	0.711	-0.023	0.005	4.1x10 ⁻⁷	0.00028	25.635
rs4754194	11	107219461	C	T	0.773	-0.025	0.005	2.4x10 ⁻⁷	0.00029	26.642
rs743580	15	74035775	A	G	0.510	0.025	0.004	1.3x10 ⁻⁹	0.00041	36.764
rs56194509	17	45767193	T	G	0.780	-0.025	0.005	3.9x10 ⁻⁷	0.00028	25.743
rs1668835	18	24898988	T	A	0.688	-0.023	0.004	3.1x10 ⁻⁷	0.00029	26.184
Sedentary behaviour (MET ≤1.5)										
rs61776614	1	2234967	C	T	0.925	0.050	0.009	3.9x10 ⁻⁸	0.00033	30.182
rs6801032	3	68455263	A	G	0.261	0.031	0.005	5.6x10 ⁻⁹	0.00037	33.953
rs153685	5	88685213	C	T	0.381	0.028	0.005	6.5x10 ⁻⁹	0.00037	33.680
rs27853	5	107482386	C	G	0.520	0.027	0.005	1.3x10 ⁻⁸	0.00035	32.323
rs6870096	5	152566250	C	G	0.321	-0.028	0.005	2.4x10 ⁻⁸	0.00034	31.149
rs73143219	7	72221624	C	T	0.554	0.027	0.005	9.6x10 ⁻⁹	0.00036	32.917

Table 2 Association of genome wide significant SNPs used as instruments for accelerometer- average accelerations with T2D and glycemic traits

SNP	Chr	Pos (hg38)	EA	OA	N _{outcome}	EAF	BETA	SE	P-value
Type 2 diabetes									
rs34517439	1	77984833	C	A	898130	0.880	0.013	0.010	0.2000
rs336605	3	18614858	G	T	898130	0.280	-0.026	0.007	0.0003
rs10067451	5	88646688	G	A	898130	0.890	0.035	0.010	0.0008
rs7084454	10	21532345	G	A	898130	0.680	0.002	0.007	0.7700
rs148193266	11	104657953	A	C	898130	0.960	-0.006	0.016	0.7000
rs79724577	17	45386127	A	C	898130	0.820	-0.019	0.008	0.0250
rs1518139	18	43171267	G	T	898130	0.660	0.023	0.007	0.0008
HbA1c									
rs336605	3	18614858	G	T	123665	0.274	0.001	0.002	0.5419
rs10067451	5	88646688	G	A	123665	0.917	0.001	0.003	0.6993
rs7084454	10	21532345	G	A	123665	0.742	0.004	0.002	0.0665
rs79724577	17	45386127	A	C	123665	0.841	0.002	0.002	0.3589
rs1518139	18	43171267	G	T	123665	0.642	0.002	0.002	0.4209
Fasting glucose									
rs336605	3	18614858	G	T	58074	0.726	0.001	0.004	0.8112
rs10067451	5	88646688	G	A	58074	0.917	-0.002	0.006	0.7182
rs7084454	10	21532345	G	A	58074	0.742	0.003	0.004	0.4152
rs79724577	17	45386127	A	C	58074	0.841	0.005	0.005	0.2922
rs1518139	18	43171267	G	T	58074	0.642	0.000	0.004	0.9150
HOMA-B									
rs336605	3	18614858	G	T	36466	0.726	-0.002	0.004	0.5782
rs10067451	5	88646688	G	A	36466	0.917	0.009	0.006	0.1391
rs7084454	10	21532345	G	A	36466	0.742	-0.005	0.004	0.1411
rs79724577	17	45386127	A	C	36466	0.841	-0.006	0.005	0.2410
rs1518139	18	43171267	G	T	36466	0.642	0.004	0.003	0.3031
HOMA-IR									
rs336605	3	18614858	G	T	37037	0.726	-0.004	0.004	0.4127
rs10067451	5	88646688	G	A	37037	0.917	0.010	0.007	0.1499
rs7084454	10	21532345	G	A	37037	0.742	0.000	0.004	0.9406
rs79724577	17	45386127	A	C	37037	0.841	-0.001	0.006	0.8197
rs1518139	18	43171267	G	T	37037	0.642	0.004	0.004	0.3116

EA, effect allele. OA, other allele. EAF, effect allele frequency. SE, standard error

Supplementary Table 3 Association of genome wide significant SNPs used as instruments for accelerometer-based vigorous physical activity (>425 mg) with T2D and glycemic traits

SNP	Chr	Pos (hg38)	EA	OA	N _{outcome}	EAF	BETA	SE	P-value
Type 2 diabetes									
rs17006599	1	219763423	A	G	898130	0.790	0.012	0.008	0.1400
rs6433478	2	174376754	T	C	898130	0.470	0.017	0.006	0.0087
rs62443625	7	39013531	T	C	898130	0.770	0.010	0.008	0.1900
rs72633364	8	34329370	G	A	898130	0.710	-0.003	0.008	0.6600
rs4754194	11	107219461	C	T	898130	0.770	0.009	0.008	0.2500
rs743580	15	74035775	A	G	898130	0.500	-0.022	0.006	0.0006
rs56194509	17	45767193	T	G	898130	0.790	-0.018	0.008	0.0210
rs1668835	18	24898988	T	A	898130	0.680	-0.002	0.007	0.8200
HbA1c									
rs17006599	1	219763423	A	G	123665	0.779	0.001	0.002	0.5499
rs62443625	7	39013531	T	C	123665	0.758	-0.001	0.002	0.7475
rs4754194	11	107219461	C	T	123665	0.757	0.003	0.002	0.1764
rs743580	15	74035775	A	G	123665	0.518	0.001	0.002	0.5761
rs56194509	17	45767193	T	G	123665	0.800	0.003	0.002	0.1677
rs1668835	18	24898988	T	A	123665	0.678	0.000	0.002	0.9190
Fasting glucose									
rs17006599	1	219763423	A	G	58074	0.221	0.002	0.004	0.7401
rs62443625	7	39013531	T	C	58074	0.758	0.000	0.004	0.9649
rs4754194	11	107219461	C	T	58074	0.757	0.007	0.004	0.1327
rs743580	15	74035775	A	G	58074	0.518	0.002	0.006	0.7489
rs56194509	17	45767193	T	G	58074	0.800	-0.004	0.005	0.4420
rs1668835	18	24898988	T	A	58074	0.678	-0.009	0.004	0.0237
HOMA-B									
rs17006599	1	219763423	A	G	36466	0.221	0.005	0.004	0.1988
rs62443625	7	39013531	T	C	36466	0.758	0.000	0.004	0.9770
rs4754194	11	107219461	C	T	36466	0.757	0.000	0.004	0.9334
rs743580	15	74035775	A	G	36466	0.518	-0.002	0.006	0.8207
rs56194509	17	45767193	T	G	36466	0.800	0.005	0.004	0.2880
rs1668835	18	24898988	T	A	36466	0.678	-0.007	0.004	0.0473
HOMA-IR									
rs17006599	1	219763423	A	G	37037	0.221	0.004	0.005	0.3873
rs62443625	7	39013531	T	C	37037	0.758	0.002	0.005	0.6537
rs4754194	11	107219461	C	T	37037	0.757	0.002	0.005	0.7261
rs743580	15	74035775	A	G	37037	0.518	-0.002	0.007	0.7670
rs56194509	17	45767193	T	G	37037	0.800	0.001	0.005	0.8908
rs1668835	18	24898988	T	A	37037	0.678	-0.013	0.004	0.0016

EA, effect allele. OA, other allele. EAF, effect allele frequency. SE, standard error.

Table 4 Association of genome wide significant SNPs used as instruments for sedentary behavior with T2D and glycemic traits

SNP	Chr	Pos (hg38)	EA	OA	N _{outcome}	EAF	BETA	SE	P-value
Type 2 diabetes									
rs61776614	1	2234967	C	T	898130	0.921	0.008	0.013	0.5400
rs6801032	3	68455263	A	G	898130	0.260	-0.007	0.007	0.3700
rs153685	5	88685213	C	T	898130	0.380	-0.008	0.007	0.2300
rs27853	5	107482386	C	G	898130	0.520	0.007	0.006	0.2600
rs6870096	5	152566250	C	G	898130	0.320	-0.003	0.007	0.6700
rs73143219	7	72221624	C	T	898130	0.560	-0.012	0.006	0.0670
HbA1c									
rs6801032	3	68455263	A	G	123665	0.150	0.001	0.002	0.5623
rs153685	5	88685213	C	T	123665	0.376	-0.003	0.002	0.1547
rs27853	5	107482386	C	G	123665	0.500	0.002	0.004	0.5438
rs6870096	5	152566250	C	G	123665	0.292	0.001	0.004	0.7541
rs73143219	7	72221624	C	T	123665	0.544	0.002	0.002	0.1555
Fasting glucose									
rs6801032	3	68455263	A	G	58074	0.150	-0.003	0.004	0.5507
rs153685	5	88685213	C	T	58074	0.624	0.002	0.004	0.5560
rs27853	5	107482386	C	G	58074	0.518	0.001	0.004	0.8684
rs73143219	7	72221624	C	T	58074	0.544	0.001	0.004	0.7500
HOMA-B									
rs6801032	3	68455263	A	G	36466	0.150	-0.009	0.004	0.0310
rs153685	5	88685213	C	T	36466	0.624	0.004	0.004	0.3154
rs27853	5	107482386	C	G	36466	0.518	-0.001	0.003	0.8210
rs73143219	7	72221624	C	T	36466	0.544	0.004	0.003	0.2640
HOMA-IR									
rs6801032	3	68455263	A	G	37037	0.150	-0.011	0.005	0.0240
rs153685	5	88685213	C	T	37037	0.624	0.003	0.004	0.4684
rs27853	5	107482386	C	G	37037	0.518	-0.001	0.004	0.8293
rs73143219	7	72221624	C	T	37037	0.544	0.008	0.004	0.0384

EA, effect allele. OA, other allele. EAF, effect allele frequency. SE, standard error

Supplementary Table 5 Evidence of association ($p < 5 \times 10^{-8}$) of the SNPs used as genetic instruments from the GWAS by Klimentidis et al. for Mendelian randomization analyses of accelerometer-based physical activity and the GWAS by Doherty et al. for analyses of sedentary behavior with confounders (smoking) in PhenoScanner

SNP	Chr	Position (hg38)	Trait	Excluded from sensitivity analysis
Average accelerations				
rs34517439	1	77984833	None	No
rs336605	3	18614858	Body fat %, whole body fat mass, Trunk fat mass	No
rs10067451	5	88646688	Trunk fat free mass, trunk predicted mass, arm fat free mass right and left	No
rs7084454	10	21532345	Waist circumference, body fat %, hip circumference, trunk fat mass, leg and arm fat mass left and right, weight, trunk fat mass	No
rs148193266	11	104657953	None	No
rs79724577	17	45386127	None	No
rs1518139	18	43171267	Body fat %, waist circumference, BMI, leg and arm fat mass left and right, trunk fat mass, weight	No

SNP	Chr	Position (hg38)	Trait	Excluded from sensitivity analysis
Vigorous activity (>425 mg)				
rs17006599	1	219763423	None	No
rs6433478	2	174376754	None	No
rs62443625	7	39013531	Body fat %, trunk fat %, Arm fat % left	No
rs72633364	8	34329370	None	No
rs4754194	11	107219461	None	No
rs743580	15	74035775	BMI, leg fat % left	No
rs56194509	17	45767193	none	No
rs1668835	18	24898988	none	No

SNP	Chr	Position (hg38)	Trait	Excluded from sensitivity analysis
Sedentary behavior				
rs61776614	1	2234967	None	No
rs6801032	3	68455263	None	No
rs153685	5	88685213	None	No
rs27853	5	107482386	None	No
rs6870096	5	152566250	None	No
rs73143219	7	72221624	None	No

Abbreviations: Chr, chromosome; SNP, single nucleotide polymorphism

Supplementary Table 6 Power-calculation

Power-calculation – accelerometer-based average accelerations physical activity

trait	N _{cases} / N _{controls}	OR=0.9	OR=0.85	OR=0.8	OR=0.75	OR=0.7
T2D	74,124/ 824,006	0.258	0.525	0.793	0.947	0.993
trait	N	$\beta = -0.15$	$\beta = -0.2$	$\beta = -0.25$	$\beta = -0.3$	$\beta = -0.5$
HbA1C	123,665	1.000	1.000	1.000	1.000	1.000
fasting glucose	58,074	1.000	1.000	1.000	1.000	1.000
HOMA-B	36,466	0.194	0.307	0.441	0.582	0.944
HOMA-IR	36,466	0.194	0.307	0.441	0.582	0.944

Power- calculation – accelerometer-based vigorous physical activity (>425 mg)

trait	N _{cases} / N _{controls}	OR=0.9	OR=0.85	OR=0.8	OR=0.75	OR=0.7
T2D	74,124/ 824,006	0.265	0.538	0.806	0.953	0.995
trait	N	$\beta = -0.15$	$\beta = -0.2$	$\beta = -0.25$	$\beta = -0.3$	$\beta = -0.5$
HbA1C	123,665	0.053	0.056	0.059	0.063	0.086
fasting glucose	58,074	0.052	0.053	0.054	0.056	0.068
HOMA-B	36,466	0.050	0.050	0.050	0.050	0.050
HOMA-IR	36,466	0.050	0.050	0.050	0.050	0.050

Power- calculation – sedentary behavior

trait	N _{cases} / N _{controls}	OR=1.1	OR=1.15	OR=1.2	OR=1.25	OR=1.3
T2D	74,124/ 824,006	0.197	0.368	0.562	0.736	0.861
trait	N	$\beta = 0.15$	$\beta = 0.2$	$\beta = 0.25$	$\beta = 0.3$	$\beta = 0.5$
HbA1C	123,665	1.000	1.000	1.000	1.000	1.000
fasting glucose	58,074	1.000	1.000	1.000	1.000	1.000
HOMA-B	36,466	0.158	0.245	0.352	0.472	0.873
HOMA-IR	36,466	0.158	0.245	0.352	0.472	0.873

Power calculation binary trait (Burgess PMID=24608958) continuous trait (Deng PMID=32048336)

Supplementary Table 7 Between SNP-heterogeneity

accelerometer-based average accelerations

outcome	Q	df	P-value
T2D	44.726	6	5.3x10 ⁻⁸
HbA1C	5.114	4	0.2758
fasting glucose	1.998	4	0.7361
HOMA-B	6.995	4	0.1362
HOMA-IR	3.739	4	0.4425

accelerometer-based vigorous physical activity (>425 mg)

outcome	Q	df	P-value
T2D	26.752	7	0.0004
HbA1C	4.135	5	0.5302
fasting glucose	7.435	5	0.1903
HOMA-B	5.681	5	0.3385
HOMA-IR	9.131	5	0.1040

sedentary behavior (MET ≤1.5)

outcome	Q	df	P-value
T2D	4.428	4	0.3512
HbA1C	4.240	3	0.2366
fasting glucose	0.786	2	0.6751
HOMA-B	6.871	2	0.0322
HOMA-IR	10.151	2	0.0062

df: degree of freedom

Supplementary Table 8 Leave-one-out – accelerometer-based average accelerations

SNP	N _{outcome}	OR/ beta	95% CI	P-value
type 2 diabetes				
rs10067451	898130	0.984	0.925; 1.047	0.6149
rs148193266	898130	1.000	0.929; 1.077	0.9907
rs1518139	898130	1.022	0.961; 1.086	0.4966
rs336605	898130	1.021	0.963; 1.083	0.4791
rs34517439	898130	0.996	0.927; 1.071	0.9157
rs7084454	898130	1.001	0.929; 1.078	0.9807
rs79724577	898130	0.991	0.924; 1.062	0.7958
HbA1c				
rs10067451	123665	0.001	-0.010; 0.012	0.8815
rs1518139	123665	0.003	-0.006; 0.013	0.4928
rs336605	123665	0.000	-0.010; 0.011	0.9476
rs7084454	123665	-0.002	-0.010; 0.006	0.6524
rs79724577	123665	0.004	-0.005; 0.014	0.3932
fasting glucose				
rs10067451	58074	0.000	-0.017; 0.018	0.9585
rs1518139	58074	-0.002	-0.019; 0.016	0.8609
rs336605	58074	-0.002	-0.020; 0.015	0.8070
rs7084454	58074	-0.005	-0.022; 0.013	0.5958
rs79724577	58074	0.004	-0.014; 0.021	0.6769
HOMA-B				
rs10067451	36466	-0.008	-0.026; 0.010	0.3677
rs1518139	36466	0.002	-0.022; 0.025	0.8800
rs336605	36466	-0.001	-0.025; 0.024	0.9613
rs7084454	36466	0.003	-0.017; 0.024	0.7547
rs79724577	36466	-0.007	-0.028; 0.013	0.4858
HOMA-IR				
rs10067451	37037	-0.008	-0.027; 0.011	0.3979
rs1518139	37037	0.004	-0.016; 0.023	0.7213
rs336605	37037	0.002	-0.017; 0.022	0.8215
rs7084454	37037	-0.001	-0.023; 0.020	0.8956
rs79724577	37037	-0.003	-0.024; 0.018	0.7868

Supplementary Table 9 Leave-one-out – accelerometer-based vigorous physical activity (>425 mg)

SNP	N _{outcome}	OR/ beta	95% CI	P-value
Type 2 diabetes				
rs1668835	898130	0.803	0.515; 1.254	0.3355
rs17006599	898130	0.760	0.506; 1.141	0.1860
rs4754194	898130	0.849	0.542; 1.332	0.4769
rs56194509	898130	0.748	0.519; 1.079	0.1206
rs62443625	898130	0.856	0.546; 1.340	0.4960
rs6433478	898130	0.910	0.598; 1.382	0.6569
rs72633364	898130	0.801	0.516; 1.242	0.3215
rs743580	898130	0.954	0.654; 1.391	0.8072
HbA1c				
rs1668835	123665	-0.019	-0.093; 0.055	0.6104
rs17006599	123665	-0.032	-0.106; 0.042	0.3972
rs4754194	123665	0.002	-0.072; 0.075	0.9678
rs56194509	123665	0.001	-0.072; 0.074	0.9814
rs62443625	123665	-0.026	-0.099; 0.047	0.4839
rs743580	123665	-0.031	-0.106; 0.043	0.4070
Fasting glucose				
rs1668835	58074	-0.007	-0.166; 0.151	0.9277
rs17006599	58074	0.067	-0.152; 0.287	0.5490
rs4754194	58074	0.133	-0.025; 0.290	0.0983
rs56194509	58074	0.050	-0.161; 0.260	0.6443
rs62443625	58074	0.083	-0.132; 0.298	0.4516
rs743580	58074	0.063	-0.141; 0.267	0.5459
HOMA-B				
rs1668835	36466	0.014	-0.133; 0.160	0.8548
rs17006599	36466	0.036	-0.128; 0.201	0.6632
rs4754194	36466	0.079	-0.090; 0.249	0.3598
rs56194509	36466	0.112	-0.030; 0.254	0.1234
rs62443625	36466	0.089	-0.083; 0.261	0.3115
rs743580	36466	0.078	-0.080; 0.237	0.3331
HOMA-IR				
rs1668835	37037	-0.009	-0.184; 0.167	0.9235
rs17006599	37037	0.089	-0.178; 0.356	0.5124
rs4754194	37037	0.135	-0.112; 0.383	0.2845
rs56194509	37037	0.126	-0.127; 0.378	0.3299
rs62443625	37037	0.147	-0.101; 0.395	0.2441
rs743580	37037	0.119	-0.123; 0.362	0.3352

Supplementary Table 10 Leave-one-out – sedentary behavior (MET \leq 1.5)

SNP	N _{outcome}	OR/ beta	95% CI	P-value
Type 2 diabetes				
rs153685	898130	0.892	0.675; 1.179	0.4213
rs61776614	898130	0.806	0.638; 1.019	0.0719
rs6801032	898130	0.875	0.656; 1.168	0.3662
rs6870096	898130	0.809	0.636; 1.030	0.0850
rs73143219	898130	0.931	0.732; 1.183	0.5564
HbA1c				
rs153685	123665	0.054	-0.034; 0.143	0.2266
rs6801032	123665	-0.003	-0.130; 0.124	0.9686
rs6870096	123665	0.015	-0.096; 0.126	0.7919
rs73143219	123665	-0.029	-0.120; 0.062	0.5300
Fasting glucose				
rs153685	58074	-0.019	-0.211; 0.173	0.8462
rs6801032	58074	0.063	-0.128; 0.255	0.5187
rs73143219	58074	-0.001	-0.194; 0.192	0.9926
HOMA-B				
rs153685	36466	-0.063	-0.475; 0.348	0.7625
rs6801032	36466	0.133	-0.041; 0.307	0.1344
rs73143219	36466	-0.069	-0.464; 0.326	0.7315
HOMA-IR				
rs153685	37037	-0.022	-0.677; 0.633	0.9466
rs6801032	37037	0.209	0.000; 0.419	0.0498
rs73143219	37037	-0.119	-0.576; 0.338	0.6106

Supplementary Table 11 MR-Egger Test on Intercept

accelerometer-based average accelerations			
outcome	intercept	std. error	P-value
T2D	-0.0513	0.0327	0.1775
HbA1C	0.0046	0.0087	0.6327
fasting glucose	0.01450	0.0140	0.3777
HOMA-B	-0.0329	0.0131	0.0870
HOMA-IR	-0.0273	0.0156	0.1778

accelerometer-based vigorous PA (>425 mg)			
outcome	intercept	std. error	P-value
T2D	-0.0538	0.0981	0.6030
HbA1C	-0.0051	0.0163	0.7696
fasting glucose	0.0529	0.0347	0.2016
HOMA-B	0.0224	0.0322	0.5258
HOMA-IR	0.0683	0.0396	0.1598

sedentary behavior (MET ≤1.5)			
outcome	intercept	std. error	P-value
T2D	-0.0245	0.0183	0.2716
HbA1C	0.0031	0.0283	0.9239
fasting glucose	0.0305	0.0402	0.5870
HOMA-B	0.0933	0.0372	0.2417
HOMA-IR	0.1408	0.0442	0.1937