Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Top SNPs (n = 10) for Accelerometer-Based Activity ($P < 1 \times 10^{-7}$)

SNP ID	Proxy SNP	r^2 for proxy	Effect allele (alternative)	β (Standard Error) for PA	β (Standard Error) for MDD
rs59499656	-	-	A (T)†	-0.228 (0.038)	-0.003 (0.009)
rs11012732	-	-	A (G)	0.225 (0.039)	-0.008 (0.01)
rs12045968	-	-	T (G)	-0.239 (0.044)	0.01 (0.011)
rs12522261	-	-	G (A)	0.211 (0.038)	-0.004 (0.009)
rs148193266	-	-	A (C)	-0.51 (0.092)	0.035 (0.021)
rs56194509	rs113871181	1.0	G (A)	-0.291 (0.044)	-0.005 (0.011)
rs1550435	-	-	T (C)	0.2 (0.037)	-0.012 (0.009)
rs34517439	-	-	C (A)	0.308 (0.056)	-0.022 (0.015)
rs6775319	-	-	A (T)†	0.225 (0.041)	-0.018 (0.01)
rs9293503	-	-	T (C)	0.329 (0.059)	-0.019 (0.014)

PA = physical activity. MDD = major depressive disorder.
†Strand ambiguous SNP; forward strand inferred based on allele frequency information.
Note. All SNPs with $p < 1x10^{-7}$ (2,200) clumped at $r^2 < .001$ into 10 top SNPs. Proxy SNPs reported where the index SNP was not found in the outcome (MDD) summary statistics. Details about proxy SNP search strategy are reported in the manuscript. Alleles and betas reported for proxy SNPs.

eTable 2. Genome-Wide Reported SNPs (n = 2) for Accelerometer-Based Activity

SNP ID	Proxy SNP	r^2 for proxy	Effect allele (alternative)	β (Standard Error) for PA	β (Standard Error) for MDD
rs59499656	-	-	A (T)†	-0.228 (0.038)	-0.003 (0.009)
rs55657917	rs113871181	1.0	G (A)	-0.291 (0.044)	-0.005 (0.011)

PA = physical activity. MDD = major depressive disorder.
†Strand ambiguous SNP; forward strand inferred based on allele frequency information.

Note. Proxy SNPs and effects reported where the index SNP was not found in the outcome (MDD) summary statistics. Details about proxy SNP search strategy are reported in the manuscript. Alleles and betas reported for proxy SNPs.

eTable 3. Top SNPs (n = 25) for Self-Reported Activity ($P < 1 \times 10^{-7}$)

SNP ID	Proxy SNP	r^2 for proxy	Effect allele (alternative)	β (Standard Error) for PA	β (Standard Error) for MDD
rs10145335	-	-	G (A)	-0.014 (0.003)	-0.008 (0.01)
rs10157145	-	-	T (C)	-0.012 (0.002)	-0.012 (0.009)
rs1043595	-	-	G (A)	0.014 (0.002)	-0.003 (0.01)
rs114243593	-	-	A (G)	0.027 (0.005)	0.021 (0.024)
rs1186721	-	-	G (A)	-0.013 (0.002)	-0.008 (0.01)
rs12912808	-	-	C (T)	0.018 (0.003)	0.017 (0.013)
rs1921981	-	-	G (A)	0.013 (0.002)	-0.007 (0.01)
rs1972763	-	-	C (T)	0.013 (0.002)	0.009 (0.009)
rs1974771	-	-	G (A)	-0.021 (0.004)	0.008 (0.014)
rs2035562	-	-	A (G)	-0.014 (0.002)	0.016 (0.01)
rs2114286	-	-	A (G)	-0.012 (0.002)	-0.021 (0.009)
rs2494664	-	-	A (G)	-0.012 (0.002)	-0.017 (0.009)
rs2854277	-	-	C (T)	0.032 (0.005)	0.04 (0.014)
rs2942127	-	-	G (A)	0.016 (0.003)	0.006 (0.011)
rs2988004	-	-	T (G)	-0.013 (0.002)	0.013 (0.009)
rs429358	-	-	T (C)	-0.022 (0.003)	0.037 (0.015)
rs4886868	-	-	T (G)	-0.012 (0.002)	0.005 (0.01)
rs527737	-	-	C (T)	-0.012 (0.002)	-0.012 (0.009)
rs56293069	-	-	G (C)†	0.014 (0.003)	-0.022 (0.01)
rs67432617	-	-	A (C)	0.015 (0.003)	-0.006 (0.011)
rs7326482	-	-	G (T)	-0.013 (0.002)	0.028 (0.009)

rs77742115	-	-	T (C)	-0.018 (0.003)	0.002 (0.012)
rs7804463	-	-	T (C)	0.015 (0.002)	0.021 (0.009)
rs877483	-	-	T (C)	0.012 (0.002)	0.005 (0.009)
rs921915	-	-	T (C)	-0.014 (0.002)	0.002 (0.009)

PA = physical activity. MDD = major depressive disorder.
† Strand ambiguous SNP; forward strand inferred based on allele frequency information.
Note. All SNPs with $p < 1x10^{-7}$ (1,699) clumped at $r^2 < .001$ into 25 top SNPs.

eTable 4. Genome-Wide Reported SNPs (n = 8) for Self-Reported Physical Activity

SNP ID	Proxy SNP	r^2 for proxy	Effect allele (alternative)	β (Standard Error) for PA	β (Standard Error) for MDD
rs1043595	-	-	G (A)	0.014 (0.002)	-0.003 (0.01)
rs149943	-	-	G (A)	0.019 (0.003)	0.057 (0.014)
rs2035562	-	-	A (G)	-0.014 (0.002)	0.016 (0.01)
rs2854277	-	-	C (T)	0.032 (0.005)	0.04 (0.014)
rs2988004	-	-	T (G)	-0.013 (0.002)	0.013 (0.009)
rs429358	-	-	T (C)	-0.022 (0.003)	0.037 (0.015)
rs7791992	-	-	C (A)	-0.014 (0.002)	0.001 (0.009)
rs7804463	-	-	T (C)	0.015 (0.002)	0.021 (0.009)
rs3094622	N/A	N/A	-	-	-

PA = physical activity. MDD = major depressive disorder.
Note. Proxy SNPs and effects reported where the index SNP was not found in the outcome (MDD) summary statistics. Details about proxy SNP search strategy are reported in the manuscript. Alleles and betas reported for proxy SNPs.

eTable 5. Top SNPs (n = 17) for Depression ($P < 1 \times 10^{-6}$)

SNP ID	Proxy SNP	r^2 for proxy	Effect allele (alternative)	β (Standard Error) for MDD	β (Standard Error) for self-reported PA	β (Standard Error) for accelerometer-based PA
rs1025145	-	-	A (G)	-0.047 (0.009)	-0.005 (0.002)	0.054 (0.038)
rs1081458	-	-	A (T)†	0.06 (0.012)	-0.002 (0.003)	-0.023 (0.048)
rs1460943	-	-	T (C)	0.048 (0.009)	0.003 (0.002)	0.031 (0.037)
rs17499892	-	-	A (C)	-0.05 (0.009)	-0.001 (0.002)	-0.011 (0.037)
rs1936365	-	-	C (G)†	-0.068 (0.013)	-0.017 (0.003)	0.085 (0.049)
rs1950829	-	-	A (G)	0.054 (0.009)	-0.003 (0.002)	-0.023 (0.036)
rs2060886	-	-	T (C)	-0.045 (0.009)	-0.006 (0.002)	-0.056 (0.037)
rs2451828	-	-	T (C)	0.158 (0.031)	0.009 (0.007)	0.099 (0.123)
rs34382743	-	-	T (C)	0.045 (0.009)	0.0004 (0.002)	0.021 (0.037)
rs76025409	rs12658032	0.91	A (G)	0.054 (0.009)	-0.009 (0.002)	-0.034 (0.038)
rs4776768	-	-	T (C)	-0.05 (0.01)	-0.001 (0.002)	0.003 (0.04)
rs4811079	-	-	C (G)†	0.048 (0.009)	0.002 (0.002)	0.046 (0.038)
rs586275	-	-	A (G)	-0.06 (0.012)	0.001 (0.003)	0.006 (0.044)
rs6832890	-	-	C (G)†	-0.061 (0.011)	0.0004 (0.003)	-0.017 (0.046)
rs7546987	-	-	T (C)	-0.045 (0.009)	-0.001 (0.002)	0.06 (0.037)
rs78676209	-	-	C (G)†	-0.102 (0.02)	0.004 (0.005)	-0.242 0.086
rs10825942	N/A	N/A	-	-	-	-

MDD = major depressive disorder. PA = physical activity.

†Strand ambiguous SNP; forward strand inferred based on allele frequency information.

Note. All SNPs with $p < 1x10^{-6}$ (584) clumped at $r^2 < .001$ into 17 top SNPs. At $p < 1x10^{-7}$, 79 SNPs clumped into only 5 top SNPs, hence we chose the former relaxed threshold of $p < 1x10^{-6}$. Proxy SNPs and effects reported where the index SNP was not found in the outcome (PA) summary statistics. Details about proxy SNP search strategy are reported in the manuscript. Alleles and betas reported for proxy SNPs.

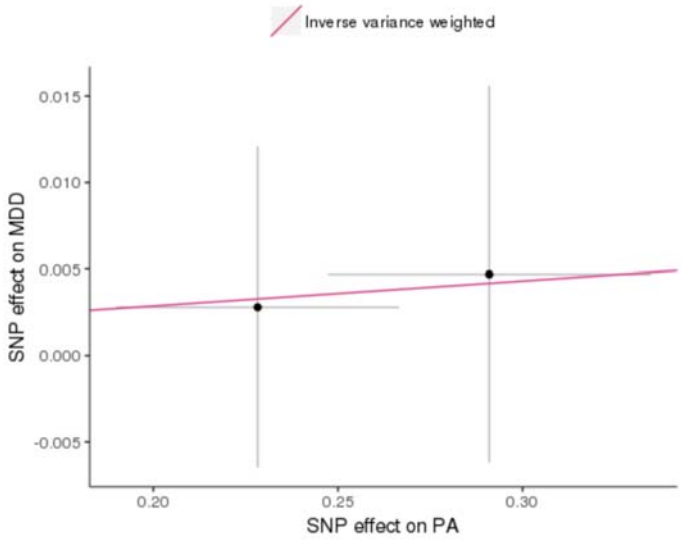
eTable 6. Mendelian Randomization Results of Accelerometer-Based Activity (Genome-Wide SNPs Only) → Depression

Method	Odds ratio	95% CI	*P* Value	SNPs
Inverse-variance weighted	1.12	0.72, 1.75	.60	2

Odds ratio = odds for MDD per 1 standard deviation increase in average acceleration. *Note.* No other analysis conducted due to limited SNPs.

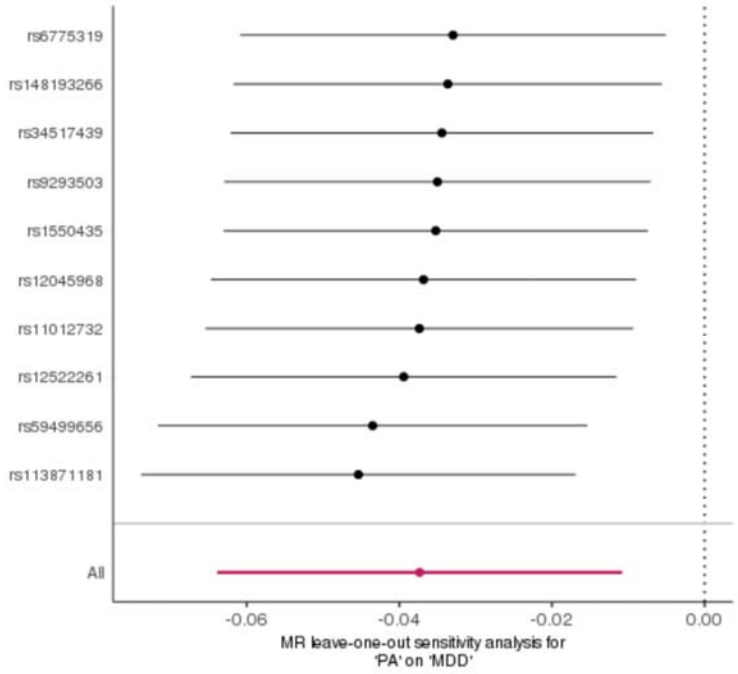
eFigure 1. Mendelian Randomization Plots for Accelerometer-Based Activity (Genome-Wide SNPs Only) → Depression

(a) Scatterplot of SNP effects on physical activity (PA) versus their effects on depression (MDD), with slope of line corresponding to the estimated MR effect.



eFigure 2. Leave-One-Out Analyses for SNPs Associated With Accelerometer-Based Activity (PA, Top SNPs $P < 1 \times 10^{-7}$) → Depression

Reported in Table 1. Removal of any single instrument SNP does not appear to change the significance of the overall MR estimate.



eMethods 1. Further Sensitivity Analyses for Main Result With 10 Accelerometer-Based SNPs

In addition to looking up individual SNPs in GWAS databases for nominal associations with depression-relevant traits (see main manuscript), we mapped the 10 instrument SNPs for accelerometer-based physical activity to known genes (via the dbSNP database: https://www.ncbi.nlm.nih.gov/snp), as available, and examined if any of these genes have been associated with depression-relevant traits in the up-to-date online GWAS Catalog (https://www.ebi.ac.uk/gwas), as summarized in **eTable 7**. We conducted a more stringent sensitivity analysis in which we only included instrument SNPs that were not mapped to any genes that have been linked to potentially relevant traits such as IQ, neuroticism, or BMI. Importantly, we found the pattern of MR results remained substantively unchanged, as shown in **eTable 8** and **Figure 3**.

eTable 7. Instruments SNPs, dbSNP Genes, and GWAS-Linked Traits

SNP	dbSNP gene	GWAS catalog traits linked to this gene
rs59499656*	N/A	N/A, but was associated with BMI in PhenoScanner
rs11012732	MLLT10	Cancer
rs12045968	N/A	N/A
rs12522261*	LINC01470	Wellbeing; depression
rs148193266	N/A	N/A
rs113871181*	LINC02210-CRHR1	Neuroticism; IQ
rs1550435*	PML	BMI
rs34517439*	DNAJB4	BMI
rs6775319	LOC105376976	Autoimmune
rs9293503*	LINC00461	Neuroticism; IQ; education

*Instrument SNPs whose corresponding gene in dbSNP has known associations with depression-relevant traits in the GWAS Catalog as of 9/1/2018, regardless of pleiotropy type

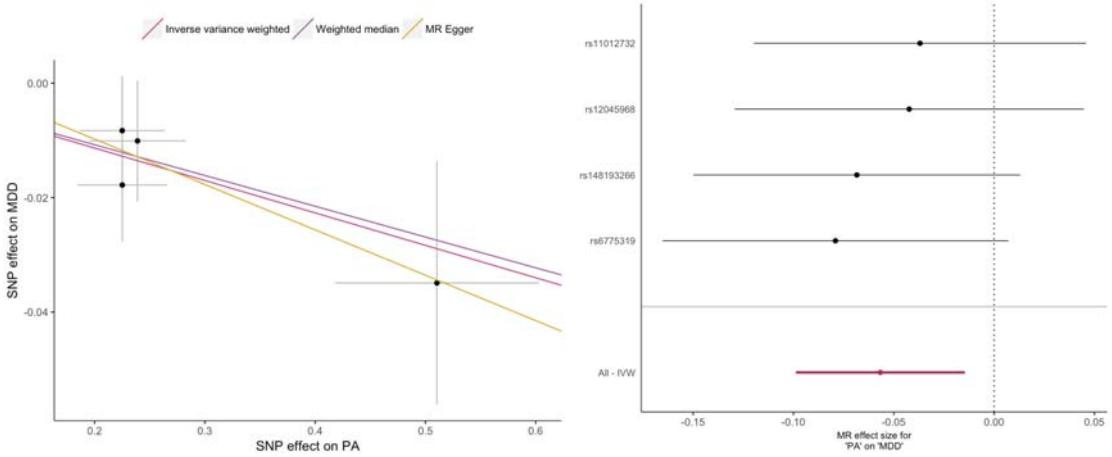
eTable 8. Mendelian Randomization Results for Sensitivity Analysis

Method	Odds ratio	95% CI	*P* Value	SNPs
Inverse-variance weighted	0.63	0.45, 0.89	0.008	4
Weighted median	0.65	0.43, 0.97	0.03	4
MR Egger	0.53	0.15, 1.82	0.42	4

Odds ratio = odds for MDD per 1 standard deviation increase in average acceleration.

eFigure 3. **Mendelian Randomization Plots for Accelerometer-Based Activity (Sensitivity Analysis) → Depression**

(a) Scatterplot of SNP effects on physical activity (PA) versus their effects on depression (MDD), with slope of line corresponding to the estimated MR effect.



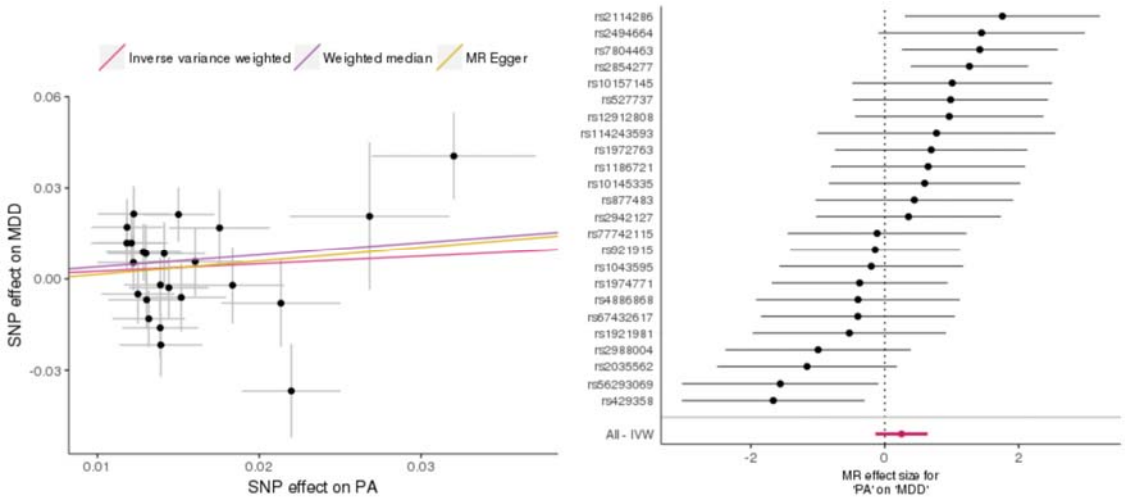
eTable 9. Mendelian Randomization Results of Self-Reported Activity (Top SNPs $P < 1 \times 10^{-7}$) → Depression

Method	Odds ratio	95% CI	*P* Value	SNPs
Inverse-variance weighted†	1.28	0.87, 1.90	.21	24
Weighted median†	1.49	0.94, 2.36	.08	24
MR Egger†	1.56	0.30, 8.03	.60	24
Inverse-variance weighted	1.17	0.77, 1.78	.46	25
Weighted median	1.44	0.90, 2.30	.13	25
MR Egger	1.86	0.31, 10.94	.50	25

†Main model, with MR-PRESSO outlier (rs7326482) removed.
Odds ratio = odds for depressive disorder per 1 standard deviation increase in standardized metabolic-equivalent minutes of moderate-to-vigorous physical activity.

eFigure 4. Mendelian Randomization Plots for Self-Reported Activity (Top SNPs $P < 1 \times 10^{-7}$) → Depression

(a) Scatterplot of SNP effects on physical activity (PA) versus their effects on depression (MDD), with slope of each line corresponding to estimated MR effect per method. (b) Forest plot of individual and combined SNP effects.



eTable 10. Mendelian Randomization Results of Self-Reported Activity (Top SNPs $P < 1 \times 10^{-7}$) → Depression, Further Excluding APOE SNP

Method	Odds ratio	95% CI	*P* Value	SNPs
Inverse-variance weighted*	1.40	0.96, 2.02	.08	23
Weighted median	1.56	0.97, 2.48	.06	23
MR Egger	2.67	0.56, 12.79	.23	23

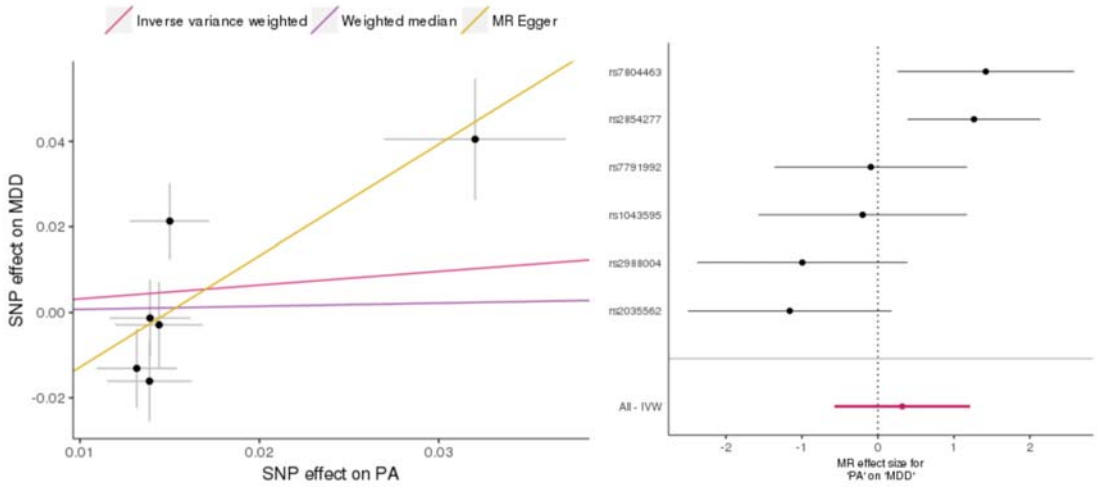
*With APOE SNP (rs429358) further removed.

eTable 11. Mendelian Randomization Results of Self-Reported Activity (Genome-Wide SNPs Only) → Depression

Method	Odds ratio	95% CI	*P* Value	SNPs
Inverse-variance weighted†	1.38	0.57, 3.37	.48	6
Weighted median†	1.08	0.47, 2.49	.86	6
MR Egger†	13.55	1.28, 143.74	.10	6
Inverse-variance weighted	1.45	0.52, 4.04	.48	8
Weighted median	0.95	0.39, 2.29	.91	8
MR Egger	8.71	0.25, 304.52	.28	8

†Main model, with MR-PRESSO outliers (rs149943, rs429358) removed.
Odds ratio = odds for depressive disorder per 1 standard deviation increase in standardized metabolic-equivalent minutes of moderate-to-vigorous physical activity.

eFigure 5. Mendelian Randomization Plots for Self-Reported Activity (Genome-Wide SNPs Only) → Depression
(a) Scatterplot of SNP effects on physical activity (PA) versus their effects on depression (MDD), with slope of each line corresponding to estimated MR effect per method. (b) Forest plot of individual and combined SNP effects.



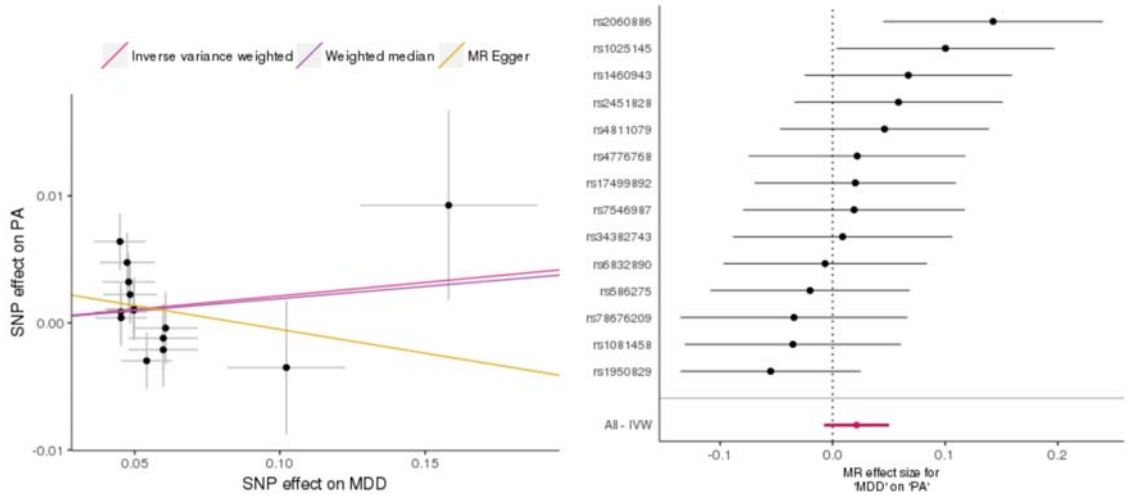
eTable 12. Mendelian Randomization Results of Depression (Top SNPs $P < 1 \times 10^{-6}$) → Self-Reported Activity

Method	Beta	95% CI	*P* Value	SNPs
Inverse-variance weighted†	0.02	-0.008, 0.05	.15	14
Weighted median†	0.02	-0.02, 0.06	.32	14
MR Egger†	-0.04	-0.16, 0.08	.55	14
Inverse-variance weighted	0.02	-0.03, 0.04	.96	16
Weighted median	0.02	-0.02, 0.06	.30	16
MR Egger	0.05	-0.17, 0.27	.65	16

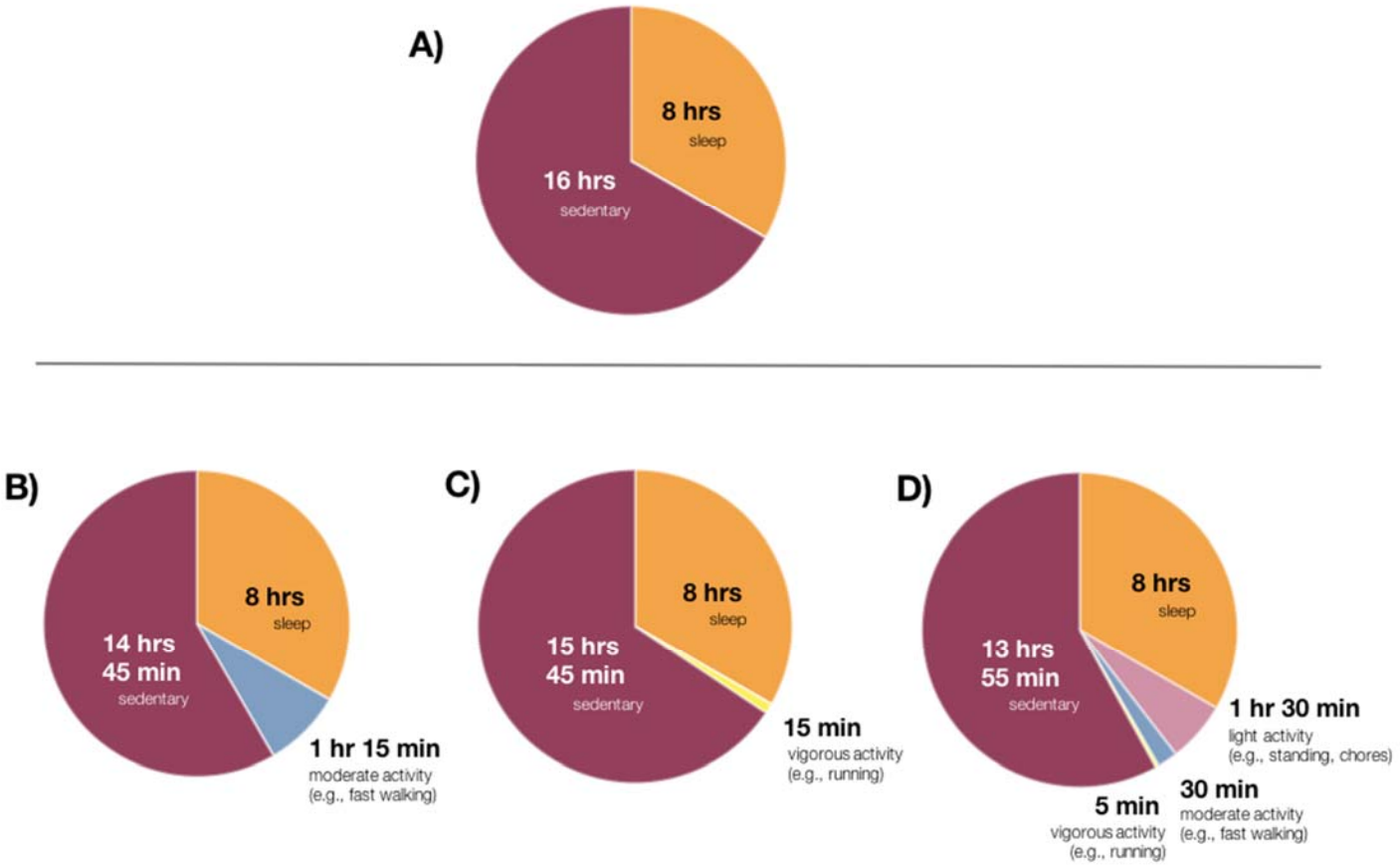
†Main model, with MR-PRESSO outliers (rs1936365, rs12658032) removed.
Beta = change in standardized metabolic-equivalent minutes of moderate-to-vigorous physical activity per depressive disorder caseness.

eFigure 6. Mendelian Randomization Plots for Depression (Top SNPs $P < 1 \times 10^{-6}$) → Self-Reported Activity

(a) Scatterplot of SNP effects on depression (MDD) versus their effects on physical activity (PA), with slope of each line corresponding to estimated MR effect per method. (b) Forest plot of individual and combined SNP effects.



eFigure 7. Contextualizing 1-SD Increase in Objectively Measured Physical Activity
Based on different hypothetical patterns of physical activity in a 24-hour period, Persons B, C and D may each show an increase of approximately 8 milligravities of average acceleration compared to Person A (see **Table S8**).



eTable 13. Contextualizing 1-SD Increase in Objectively Measured Physical Activity

		# of epochs (hours)			
Activity	**mg/epoch**	**A) "Sedentary only"**	**B) "Moderate only"**	**C) "Vigorous only"**	**D) "Mixed"**
Sleep	7	5760 (8)	5760 (8)	5760 (8)	5760 (8)
Light activity	65	0	0	0	1080 (1.5)
Moderate activity	180	0	900 (1.25)	0	360 (0.5)
Vigorous activity	750	0	0	180 (0.25)	60 (0.083)
Sedentary behavior	25	11520 (16)	10620 (14.75)	11340 (15.75)	10020 (13.92)
Total mg		328320	467820	458820	470820
Average acceleration		19	27.1	26.6	27.2
Difference from A)			**8.1**	**7.6**	**8.2**

Based on different hypothetical patterns of physical activity in a 24-hour period, Persons B, C and D may each show an increase of approximately 8 milligravities of average acceleration compared to Person A (see e**Figure 7**).
mg = milligravities; *epoch* = 5-second window of accelerometer data. *mg/epoch* values for illustrative purposes are based on plausible ranges from the literature.[1–3] *Total mg* = # of epochs x estimated mg/epoch per activity, summed across activities per person. *Average acceleration* = total mg divided by the number of possible 5-second epochs in 24 hours, i.e., 17,280.

References

1. Bakrania K, Yates T, Rowlands AV, et al. Intensity Thresholds on Raw Acceleration Data: Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) Approaches. *PLoS ONE*. 2016;11(10):e0164045. doi:10.1371/journal.pone.0164045

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eMethods 2. MR Power Calculations

We estimated statistical power for our MR analyses at a standard alpha level of 0.05, using an online calculator based on the Burgess (2014) approach to MR power calculations[4] for binary and continuous outcomes (https://sb452.shinyapps.io/power). Statistical power for MR given a specific (outcome) sample size relies on several parameters[2], including the proportion of variance (R^2) in the exposure explained by genetic instruments; the "true" causal effect of the exposure on the outcome, which can be projected across plausible values to investigate impact on statistical power; and the ratio of cases to controls (for binary outcomes). R^2 estimates were obtained as part of the MR Steiger directionality test[6] implemented in the *TwoSampleMR* package, which computes variance explained by the genetic instruments.

Physical activity (accelerometer-based) → MDD (binary). Using the MDD GWAS sample size (N = 143,265) and ratio of cases to control (1 to 2.14), and an estimated R^2 of 0.004 for 10 genetic instruments on accelerometer-based physical activity, we calculated sufficient power (>80%) to detect effects of physical activity on MDD if the true causal effect of physical activity on MDD had an OR of 0.77 or less. We had 89% power to detect a causal OR of 0.75.

MDD → physical activity (accelerometer-based; continuous). Using the accelerometer-based activity GWAS sample size (N = 91,084) and an estimated R^2 of 0.003 for 16 genetic instruments on MDD, we calculated sufficient (>80%) power to detect effects of MDD on accelerometer-based activity if the true causal effect was a decreasing effect of 0.17 standardized units of accelerometer-based activity per 1 SD change in MDD.

Physical activity (self-reported) → MDD (binary). Using the MDD GWAS sample size (N = 143,265) and ratio of cases to control (1 to 2.14), and an estimated R^2 of 0.002 for 24 genetic instruments on self-reported physical activity, we calculated sufficient power

(>80%) to detect effects of physical activity on MDD if the true causal effect of self-reported physical activity on MDD had an OR of less than 0.70. **MDD → physical activity (self-reported; continuous).** Using the self-reported activity GWAS sample size (N = 377,234) and an estimated R^2 of 0.003 for 16 genetic instruments on MDD, we calculated sufficient (>80%) power to detect effects of MDD on self-reported activity if the true causal effect was a decreasing effect of 0.09 standardized units of self-reported activity per 1 SD change in MDD.

References

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