Supplementary Information

Article title: Physical activity, sedentary time and breast cancer risk: A Mendelian randomization study

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Supplementary Methods

Mendelian randomization overview

Mendelian randomization (MR) is a form of instrumental variable analysis where exposures are measured indirectly using genotype. By measuring exposures using genetic proxies, which are randomised at meiosis (before conception) and are therefore less prone to bias such as selection bias, reverse causality, and confounding, MR may be able to provide estimates which more closely reflect underlying causal relationships. Since genotype is randomly allocated, MR studies simulate the design of a randomized controlled trial with groups defined by genotype analogous to trial arms, theoretically allowing MR to overcome key sources of bias in observational studies.

Defining genetic instruments: additional information

In defining instruments for our analysis, we selected genetic variants identified from GWAS models unadjusted for adiposity to avoid possible collider bias introduced by adjustment for a trait which is causally downstream.(1) We used the National Cancer Institute's LDpair or LDmatrix applications (2) to confirm that SNPs in each instrument were in linkage equilibrium (independent) (highest r^2=0.004). All SNPs were well-imputed (information score ≥0.90 for all but two SNPs; lowest score 0.84) (Table S2). We estimated the percent of variance explained in each trait (X) by the genetic instrument (Z) from data reported by the GWAS which identified the SNPs. We used the TwoSampleMR package function *get_r_from_pn* (3, 4), inputting the GWAS sample size and GWAS-reported p value for each SNP in the instrument to estimate r^2_{ZX} for each SNP, then summed r^2_{ZX} values to obtain a total r^2_{ZX} for the instrument.

Overall physical activity: additional information

Our primary physical activity instrument was derived from a recent GWAS which used UK Biobank data on movement measured by wrist-worn triaxial accelerometers.(5) Working with the UK Biobank Accelerometer Working Group, Doherty and colleagues derived a measure for overall activity, assessed as average vector magnitude (in milligravities) per 30-second period, recorded across an accelerometer wear period of three to seven days.(5, 6) They identified five SNPs associated with this phenotype at conventional genome-wide significance ($p<5x10^{-8}$).(5) A separate research group performed a GWAS of multiple physical activity measures using UK Biobank data,(7) including the overall activity (average accelerations) phenotype derived

by the UK Biobank Accelerometer Working Group.(6). Of the ten SNPs Klimentidis and colleagues identified as associated with overall activity at relaxed significance ($p<5x10^{-7}$), five signals overlapped with the Doherty-identified variants.(7, 8)

Vigorous physical activity: additional information

Klimentidis *et al* examined UK Biobank physical activity data from wrist-worn accelerometers (n~91,000) and self-report (n~377,000) to identify SNPs associated at stringent significance ($p<5x10^{-9}$) with vigorous activity.(7)

Outcomes: additional information

Ki-67 data to determine luminal A/B subtype was unavailable.

Statistical analysis: additional information

For the multi-SNP instruments, we used SNP-exposure and SNP-outcome beta coefficients and standard errors to estimate odds ratios and 95% confidence intervals of the effect of each trait on each outcome from inverse-variance weighted (IVW) MR, using a multiplicative random-effects model with simple weights (first-order term from delta expansion).(9) IVW-MR averages estimates of the causal effect across multiple SNPs, weighted by SNP-exposure beta coefficients, to derive a summary estimate.(9, 10) For the single-SNP instrument (accelerations >425 milligravities) we used the Wald (ratio) MR technique, dividing the SNP-outcome association (ZY) by the SNP-exposure association (ZX) to estimate the causal OR. The ratio estimate of the causal effect using a SNP 'k' is $\beta ZY_k/\beta ZX_k$. IVW-MR averages these Wald ratios across SNPs.

In sensitivity analyses, we applied weighted median MR(11) and MR-Egger(12), complementary methods which relax different MR assumptions. Weighted median MR allows up to half of the genetic instruments to be invalid; MR-Egger allows horizontal pleiotropy (although it has lower statistical power than IVW MR). We inspected causal estimates considering each SNP individually (inspecting scatter plots of SNP-exposure and SNP-outcome associations, and forest plots of SNP-specific causal effects). We also performed leave-one-out analyses (omitting one SNP each time) to further explore the robustness of our results to instrument composition.

Causal effects were estimated using the ‘MendelianRandomization’(13) package and outlier detection was performed using the ‘MR-PRESSO’ package.(14) Analyses were conducted and reported with reference to MR guidelines.(1, 15)

Supplementary Tables

Table S1. Acronyms and study names of Breast Cancer Association Consortium studies in the analysis

Study acronym	Study name	Reference(s)
2SISTER *	The Two Sister Study	(16)
ABCFS	Australian Breast Cancer Family Study	(17)
ABCS	Amsterdam Breast Cancer Study	(18)
ABCTB	Australian Breast Cancer Tissue Bank	(19)
AHS	Agricultural Health Study	(20, 21)
BBCC	Bavarian Breast Cancer Cases and Controls	(22, 23)
BBCS	British Breast Cancer Study	(24, 25)
BCEES	Breast Cancer Employment and Environment Study	(26)
BCFR-NY *	New York Breast Cancer Family Registry	(27-29)
BCFR-PA *	Philadelphia Breast Cancer Family Registry	(27, 30)
BCFR-UTAH *	Utah Breast Cancer Family Registry	(27, 30)
BCINIS	Breast Cancer In Northern Israel Study	(31, 32)
BREOGAN	Breast Oncology Galicia Network	(33-37)
BSUCH	Breast Cancer Study of the University Clinic Heidelberg	(38)
CBCS	Canadian Breast Cancer Study	(39-42)
CCGP	Crete Cancer Genetics Program	--
CECILE	CECILE Breast Cancer Study	(43)
CGPS	Copenhagen General Population Study	(44)
CPSII	Cancer Prevention Study-II Nutrition Cohort	(45)
CTS	California Teachers Study	(46)
DIETCOMPLYF	DietCompLyf Breast Cancer Survival Study	(47)
EPIC	European Prospective Investigation into Cancer and Nutrition	(48)
ESTHER	ESTHER Breast Cancer Study	(49)
FHRISK *	Family History Risk Study	(50, 51)
GC-HBOC *	German Consortium for Hereditary Breast and Ovarian Cancer	(52-55)
GENICA	Gene Environment Interaction & Breast Cancer in Germany	(56, 57)
GEPARSIXTO	A randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative and HER2-positive early breast cancer	(58-61)
GESBC	Genetic Epidemiologic Study of Breast Cancer by Age 50	(62)
HABCS	Hannover Breast Cancer Study	(63)
HCSC	Hospital Clinico San Carlos	(64, 65)
HEBCS *	Helsinki Breast Cancer Study	(66-68)
HMBCS	Hannover-Minsk Breast Cancer Study	(69)
HUBCS	Hannover-Ufa Breast Cancer Study	(69)
KARBAC *	Karolinska Breast Cancer Study	(70, 71)
KARMA	Karolinska Mammography Project for Risk Prediction of Breast Cancer – Cohort Study	(72)
KBCP	Kuopio Breast Cancer Project	(73, 74)
LMBC	Leuven Multidisciplinary Breast Centre	(75, 76)
MABCS	Macedonian Breast Cancer Study	--
MARIE	Mammary Carcinoma Risk Factor Investigation	(77)
MBCSG *	Milan Breast Cancer Study Group	(78, 79)
MCBCS	Mayo Clinic Breast Cancer Study	(80)
MCCS	Melbourne Collaborative Cohort Study	(81)
MEC	Multiethnic Cohort	(82)
MISS	Melanoma Inquiry of Southern Sweden	(83, 84)
MMHS	Mayo Mammography Health Study	(85)
MSKCC *	Memorial SloanKettering Cancer Center Study	(86)
MTLGEBCS	Montreal Gene-Environment Breast Cancer Study	--
NBCS	Norwegian Breast Cancer Study	(87-90)

Study acronym	Study name	Reference(s)
NBHS	Nashville Breast Health Study	(91)
NC-BCFR *	Northern California Breast Cancer Family Registry	(27, 30)
NCBCS	North Carolina Breast Cancer study	(92, 93)
NHS	Nurses' Health Study	(94, 95)
NHS2	Nurses' Health Study 2	(96)
OFBCR *	Ontario Familial Breast Cancer Registry	(27)
ORIGO	Leiden University Medical Centre Breast Cancer Study	(97, 98)
PBCS	NCI Polish Breast Cancer Study	(99)
pKARMA	Karolinska Mammography Project for Risk Prediction of Breast Cancer – Case-Control Study	--
PLCO	The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial	(100)
POSH	Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer	(101-106)
PREFACE	Evaluation of Predictive Factors regarding the Effectivity of Aromatase Inhibitor Therapy	(107)
PROCAS	Predicting the Risk Of Cancer At Screening Study	(50)
RBCS *	Rotterdam Breast Cancer Study	(108)
SBCS	Sheffield Breast Cancer Study	(109, 110)
SEARCH	Study of Epidemiology and Risk Factors in Cancer Heredity	(111)
SISTER *	The Sister Study	(112-114)
SKKDKFZS	Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study	(115)
SMC	Swedish Mammography Cohort	(116)
SUCCESSB	Simultaneous Study of Gemcitabine-Docetaxel Combination adjuvant treatment	(117-119)
SUCCESSC	Simultaneous Study of Docetaxel Based Anthracycline Free Adjuvant Treatment Evaluation	(120-123)
SZBCS	IHCC-Szczecin Breast Cancer Study	(124-127)
TNBCC	Triple Negative Breast Cancer Consortium Study	--
UBCS *	Utah Breast Cancer Study	(128, 129)
UCIBCS	UCI Breast Cancer Study	(130, 131)
UKBGS	UK Breakthrough Generations Study	(132)
UKOPS	UK Ovarian Cancer Population Study †	(133)
USRT	US Radiologic Technologists Study	(134-137)

-- No citation

* Included familial cases or controls (recruited on the basis of being at high risk for breast cancer).

† This study contributed controls only.

Table S2. Single nucleotide polymorphisms used as instruments for physical activity or sedentary time

SNP*	Chr	Position†	Function	Nearest gene	Effect‡ / Other allele	Beta for association with trait§	Standard error for association with trait§	UK Biobank effect allele‡ frequency	OncoArray effect allele‡ frequency	OncoArray imputation information score
Overall (average) activity: 5 SNPs associated at $p < 5 \times 10^{-8}$ (identified by Doherty *et al* (5))										
rs6775319	3	18,758,501	Intron	*SATB1-AS1*	A/T	0.027	0.005	0.27	0.30	0.99
rs6895232	5	152,039,421	--	--	T/A	0.027	0.005	0.66	0.69	0.99
rs564819152	10	21,820,650	Intron	*MLLT10*	A/G	0.028	0.005	0.68	0.65	0.99
rs2696625	17	44,326,864	Downstream	*MAPK8IP1P1*	G/A	0.037	0.005	0.23	0.21	0.97
rs59499656	18	40,768,309	Intergenic	*RIT2*	T/A	0.028	0.005	0.35	0.34	0.99
Overall (average) activity, secondary instrument: 10 SNPs associated at $p < 5 \times 10^{-7}$ (identified by Klimentidis *et al* (7, 8))**										
rs12045968	1	33,690,698	Intergenic	*ZNF362*	G/T	0.029	0.005	0.22	0.21	1.00
rs34517439	1	78,450,517	Intron	*DNAJB4*	C/A	0.038	0.007	0.91	0.92	1.00
rs6775319	3	18,758,501	Intron	*SATB1-AS1*	A/T	0.028	0.005	0.30	0.30	0.99
rs9293503	5	87,948,962	Intron	*LINC00461*	T/C	0.040	0.007	0.88	0.86	0.93
rs12522261	5	152,054,825	Intron	*LINC01470*	G/A	0.026	0.005	0.67	0.69	0.99
rs11012732	10	21,830,104	Intron	*MLLT10*	A/G	0.028	0.005	0.65	0.63	1.00
rs148193266	11	104,528,681	Intergenic	*RP11-681H10.1*	C/A	0.063	0.011	0.02	0.03	0.87
rs1550435	15	74,331,385	Intron	*PML*	T/C	0.025	0.005	0.53	0.54	0.99
rs55657917	17	43,844,560	--	--	G/T	0.036	0.005	0.22	0.20	1.00
rs59499656	18	40,768,309	Intergenic	*RIT2*	T/A	0.028	0.005	0.34	0.34	0.99
Fraction of time with accelerations >425 mg: 1 SNP associated at $p < 5 \times 10^{-9}$ (identified by Klimentidis *et al* (7))										
rs743580	15	74,328,116	Missense	*PML*	A/G ¶	0.025	0.00005	0.51	0.49	0.98
Self-reported vigorous physical activity: 5 SNPs associated at $p < 5 \times 10^{-9}$ (identified by Klimentidis *et al* (7))										
rs2764261	6	108,927,842	Intron	*FOXO3*	A/G	0.039	0.001	0.37	0.40	1.00
rs328902	7	35,020,843	Intron	*DPY19L1*	T/C	0.041	0.001	0.31	0.31	1.00
rs13243553	7	133,506,955	Intron	*EXOC4*	G/A	0.039	0.001	0.61	0.62	0.98
rs3781411	10	126,715,436	Missense	*CTBP2*	C/T	0.058	0.001	0.88	0.85	1.00
rs1248860	3	85,015,779	Intron	*CADM2*	A/G	0.041	0.001	0.52	0.51	0.99
Percent time spent sedentary: 6 SNPs associated at $p < 5 \times 10^{-8}$ (identified by Doherty *et al* (5))										
rs61776614	1	2,166,406	Intron	*SKI*	C/T	0.050	0.009	0.93	0.93	0.84
rs1858242	3	68,527,135	Intron	*FAM19A1*	A/G	0.031	0.005	0.26	0.25	0.99
rs26579	5	87,985,295	Intron	*LINC00461*	G/C	0.028	0.005	0.42	0.46	0.95
rs25981	5	106,822,908	Intron	*EFNA5*	G/C	0.028	0.005	0.53	0.53	0.99

SNP*	Chr	Position†	Function	Nearest gene	Effect‡ / Other allele	Beta for association with trait§	Standard error for association with trait§	UK Biobank effect allele‡ frequency	OncoArray effect allele‡ frequency	OncoArray imputation information score
rs6870096	5	151,945,811	Intergenic	*CTB-95D12.1*	G/C	0.028	0.005	0.68	0.69	0.98
rs34858520	7	71,723,883	Intron	*CALN1*	A/G	0.028	0.005	0.56	0.57	0.99

Abbreviations: Chr, chromosome; GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

* the National Cancer Institute's LDpair or LDmatrix (2) applications were used to confirm that SNPs on the same chromosome within each instrument are independent (highest r^2=0.004).

† human genome assembly GRCh37 (hg19)

‡ Allele associated with an increase in the trait (i.e., with increased physical activity [physical activity instruments], or with increased time spent sedentary [sedentary time instrument])

§ Betas and standard errors for associations between SNPs and exposure (physical activity or sedentary time) are from, or derived from, the GWAS which identified the SNPs.

** Five signals overlap with the Doherty-identified variants for overall activity.

¶ This SNP (rs743580, A/G) has an effect allele frequency near 50% and the minor allele in UK Biobank (G) differs from that in OncoArray (A) , but it is not palindromic so the trait-increasing allele was easily identifiable in OncoArray data. Additionally, we confirmed that the trait-increasing allele, A, was positively associated with strenuous activity in BCAC.

Table S3. Comparison of results from different Mendelian randomization methods: Association between the primary instrumental genetic variables for overall physical activity (per standard deviation) and risk of breast cancer

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
Invasive cancers			
All invasive	69,838		
IVW		0.48 (0.30-0.78)	0.016
Weighted median		0.59 (0.39-0.90)	
MR-Egger		0.14 (0.00-11.0)	0.569
Pre/perimenopausal	¶ 23,999		
IVW		0.51 (0.31-0.83)	0.419
Weighted median		0.56 (0.30-1.07)	
MR-Egger		0.03 (0.00-1.50)	0.148
Postmenopausal	**45,839		
IVW		0.48 (0.28-0.80)	0.054
Weighted median		0.58 (0.36-0.94)	
MR-Egger		0.36 (0.00-50.7)	0.911
By receptor status			
ER+	46,528		
IVW		0.45 (0.25-0.83)	0.004
Weighted median		0.58 (0.37-0.91)	
MR-Egger		0.17 (0.00-48.1)	0.726
ER-	11,246		
IVW		0.79 (0.37-1.66)	0.069
Weighted median		0.66 (0.32-1.37)	
MR-Egger		0.45 (0.00-546)	0.875
PR+	34,891		
IVW		0.43 (0.22-0.85)	0.003
Weighted median		0.56 (0.33-0.94)	
MR-Egger		0.08 (0.00-40.5)	0.601
PR-	16,432		
IVW		0.65 (0.38-1.13)	0.186
Weighted median		0.63 (0.34-1.14)	
MR-Egger		0.76 (0.00-140)	0.953
HER2+	6,945		
IVW		0.48 (0.26-0.89)	0.479
Weighted median		0.47 (0.21-1.05)	
MR-Egger		0.01 (0.00-1.91)	0.149
HER2-	33,214		
IVW		0.58 (0.35-0.98)	0.060
Weighted median		0.64 (0.39-1.04)	
MR-Egger		0.17 (0.00-20.4)	0.613
Combined hormone receptor- and/or HER2-defined subtypes			
ER+ or PR+; HER2+	4,816		
IVW		0.42 (0.20-0.88)	0.478
Weighted median		0.57 (0.22-1.46)	
MR-Egger		0.00 (0.00-0.94)	0.087
ER+ or PR+; HER2-	27,874		
IVW		0.57 (0.28-1.18)	0.004
Weighted median		0.64 (0.37-1.09)	
MR-Egger		0.13 (0.00-106)	0.667

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
ER-; PR-; HER2+	1,974		
IVW		0.53 (0.18-1.57)	0.700
Weighted median		0.42 (0.11-1.68)	
MR-Egger		0.09 (0.00-801)	0.701
ER-; PR-; HER2-	4,964		
IVW		0.60 (0.17-2.12)	0.015
Weighted median		0.56 (0.20-1.59)	
MR-Egger		0.32 (0.00-51,961)	0.917
ER- and PR- (all)	9,215		
IVW		0.65 (0.27-1.56)	0.036
Weighted median		0.47 (0.21-1.07)	
MR-Egger		0.20 (0.00-841)	0.783
By morphology			
Ductal	42,223		
IVW		0.52 (0.32-0.84)	0.053
Weighted median		0.64 (0.41-1.02)	
MR-Egger		0.10 (0.00-7.61)	0.463
Lobular	8,795		
IVW		0.32 (0.18-0.58)	0.500
Weighted median		0.31 (0.14-0.68)	
MR-Egger		4.01 (0.03-533)	0.310
By stage at diagnosis			
Stage I	17,583		
IVW		0.51 (0.32-0.82)	0.333
Weighted median		0.47 (0.26-0.85)	
MR-Egger		0.11 (0.00-7.18)	0.471
Stage II	15,992		
IVW		0.36 (0.22-0.58)	0.576
Weighted median		0.35 (0.18-0.66)	
MR-Egger		0.11 (0.00-5.81)	0.553
Stage III/IV	4,553		
IVW		0.37 (0.17-0.81)	0.499
Weighted median		0.34 (0.13-0.94)	
MR-Egger		0.10 (0.00-70.0)	0.687
By tumor grade			
Grade 1/2	34,647		
IVW		0.43 (0.23-0.81)	0.011
Weighted median		0.54 (0.33-0.89)	
MR-Egger		0.18 (0.00-63.2)	0.768
Grade 3	16,432		
IVW		0.46 (0.30-0.72)	0.552
Weighted median		0.42 (0.23-0.75)	
MR-Egger		0.28 (0.01-10.7)	0.786
In situ cancers			
All in situ	6,667		
IVW		0.63 (0.34-1.18)	0.390
Weighted median		0.71 (0.32-1.59)	
MR-Egger		0.01 (0.00-1.24)	0.087
Ductal carcinoma in situ	3,510		
IVW		0.92 (0.25-3.43)	0.039
Weighted median		1.01 (0.31-3.25)	
MR-Egger		0.00 (0.00-0.12)	0.011

Abbreviations: CI, confidence interval; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; IVW, inverse-variance weighted; MR, Mendelian Randomization; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* Causal odds ratios were estimated by three different Mendelian randomization methods, using five SNPs identified in a GWAS of accelerometer-measured movement traits by Doherty et al (5)

† Confidence intervals from weighted median MR were generated from 10,000 bootstrap samples (seed 314159265)

‡ Relating to IVW MR estimates: p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs

§ Relating to MR-Egger estimates: p-value for the intercept test (p-value for pleiotropy)

¶ vs pre/perimenopausal controls (n=17,686), assigned using age (<50 years) if menopause status was unknown

** vs postmenopausal controls (n=36,766), assigned using age (≥50 years) if menopause status was unknown

Table S4. Leave-one-out analyses: Association between the primary instrumental genetic variables for overall physical activity (per standard deviation) and risk of breast cancer, omitting one SNP at a time

	Full instrument (five SNPs)		Excluding rs6775319 *		Excluding rs6895232 **		Excluding rs564819152 †		Excluding rs2696625 ††		Excluding rs59499656 ‡	
Type of breast cancer	**Odds ratios (95% CI) §**	**P_{het}¶**	**Odds ratios (95% CI) §**	**P_{het}¶**	**Odds ratios (95% CI) §**	**P_{het}¶**	**Odds ratios (95% CI) §**	**P_{het}¶**	**Odds ratios (95% CI) §**	**P_{het}¶**	**Odds ratios (95% CI) §**	**P_{het}¶**
Invasive cancers												
All invasive	0.48 (0.30-0.78)	0.016	0.46 (0.25-0.82)	0.010	0.44 (0.25-0.79)	0.014	0.59 (0.42-0.83)	0.312	0.52 (0.28-0.97)	0.010	0.43 (0.25-0.72)	0.031
Pre/perimenopausal	0.51 (0.31-0.83)	0.419	0.46 (0.27-0.78)	0.402	0.48 (0.27-0.87)	0.306	0.57 (0.33-0.99)	0.383	0.63 (0.36-1.10)	0.565	0.45 (0.26-0.78)	0.404
Postmenopausal	0.48 (0.28-0.80)	0.054	0.45 (0.24-0.86)	0.030	0.44 (0.24-0.82)	0.040	0.61 (0.42-0.89)	0.816	0.48 (0.24-0.95)	0.025	0.42 (0.23-0.77)	0.058
By receptor status												
ER+	0.45 (0.25-0.83)	0.004	0.41 (0.20-0.84)	0.004	0.40 (0.20-0.80)	0.006	0.60 (0.43-0.85)	0.459	0.47 (0.21-1.05)	0.002	0.42 (0.20-0.88)	0.003
ER-	0.79 (0.37-1.66)	0.069	0.96 (0.44-2.06)	0.122	0.90 (0.38-2.18)	0.059	0.60 (0.31-1.17)	0.247	0.87 (0.33-2.31)	0.041	0.67 (0.28-1.60)	0.068
PR+	0.43 (0.22-0.85)	0.003	0.40 (0.18-0.92)	0.002	0.38 (0.17-0.85)	0.003	0.58 (0.37-0.91)	0.223	0.48 (0.20-1.14)	0.002	0.36 (0.17-0.76)	0.010
PR-	0.65 (0.38-1.13)	0.186	0.68 (0.35-1.34)	0.111	0.80 (0.49-1.30)	0.472	0.53 (0.33-0.87)	0.412	0.67 (0.33-1.39)	0.105	0.61 (0.31-1.19)	0.125
HER2+	0.48 (0.26-0.89)	0.479	0.41 (0.21-0.82)	0.475	0.47 (0.22-0.98)	0.323	0.52 (0.26-1.06)	0.364	0.62 (0.30-1.27)	0.685	0.40 (0.20-0.80)	0.502
HER2-	0.58 (0.35-0.98)	0.060	0.57 (0.30-1.09)	0.030	0.49 (0.30-0.81)	0.171	0.72 (0.49-1.07)	0.385	0.62 (0.31-1.23)	0.033	0.54 (0.29-1.03)	0.039
Combined hormone receptor- and/or HER2-defined subtypes												
ER+/PR+; HER2+	0.42 (0.20-0.88)	0.478	0.36 (0.16-0.81)	0.448	0.38 (0.17-0.85)	0.380	0.45 (0.19-1.07)	0.336	0.61 (0.26-1.41)	0.852	0.38 (0.17-0.86)	0.380
ER+/PR+; HER2-	0.57 (0.28-1.18)	0.004	0.52 (0.22-1.22)	0.003	0.47 (0.23-0.97)	0.020	0.79 (0.49-1.26)	0.254	0.61 (0.24-1.58)	0.002	0.55 (0.22-1.37)	0.002
ER-; PR-; HER2+	0.53 (0.18-1.57)	0.700	0.41 (0.13-1.36)	0.756	0.69 (0.21-2.30)	0.758	0.56 (0.16-1.87)	0.539	0.61 (0.17-2.14)	0.569	0.44 (0.13-1.48)	0.628
ER-; PR-; HER2-	0.60 (0.17-2.12)	0.015	0.95 (0.37-2.44)	0.224	0.61 (0.12-3.04)	0.007	0.39 (0.12-1.25)	0.094	0.69 (0.13-3.63)	0.008	0.51 (0.11-2.46)	0.009
ER- and PR- (all)	0.65 (0.27-1.56)	0.036	0.81 (0.32-2.03)	0.070	0.74 (0.26-2.15)	0.027	0.46 (0.22-0.96)	0.226	0.75 (0.24-2.33)	0.024	0.54 (0.19-1.54)	0.034
By morphology												
Ductal	0.52 (0.32-0.84)	0.053	0.47 (0.27-0.84)	0.045	0.48 (0.27-0.85)	0.041	0.63 (0.43-0.91)	0.346	0.57 (0.31-1.05)	0.039	0.46 (0.27-0.79)	0.067
Lobular	0.32 (0.18-0.58)	0.500	0.33 (0.17-0.65)	0.348	0.36 (0.19-0.69)	0.435	0.39 (0.20-0.74)	0.581	0.27 (0.14-0.54)	0.488	0.27 (0.14-0.53)	0.550
By stage at diagnosis												
Stage I	0.51 (0.32-0.82)	0.333	0.46 (0.28-0.75)	0.357	0.51 (0.28-0.94)	0.205	0.60 (0.37-0.98)	0.488	0.56 (0.31-1.01)	0.259	0.44 (0.27-0.72)	0.400
Stage II	0.36 (0.22-0.58)	0.576	0.36 (0.21-0.61)	0.408	0.31 (0.19-0.53)	0.693	0.42 (0.25-0.71)	0.718	0.39 (0.22-0.67)	0.446	0.33 (0.20-0.57)	0.473
Stage III/IV	0.37 (0.17-0.81)	0.499	0.46 (0.20-1.06)	0.570	0.28 (0.12-0.65)	0.854	0.38 (0.15-0.94)	0.340	0.41 (0.16-1.03)	0.360	0.37 (0.15-0.92)	0.339
By tumor grade												
Grade 1/2	0.43 (0.23-0.81)	0.011	0.38 (0.19-0.73)	0.023	0.40 (0.19-0.85)	0.007	0.58 (0.39-0.85)	0.514	0.45 (0.20-1.02)	0.005	0.40 (0.19-0.87)	0.007
Grade 3	0.46 (0.30-0.72)	0.552	0.51 (0.32-0.82)	0.546	0.43 (0.27-0.70)	0.466	0.50 (0.31-0.82)	0.477	0.48 (0.29-0.81)	0.402	0.40 (0.25-0.65)	0.722
In situ cancers												
All in situ	0.63 (0.34-1.18)	0.390	0.53 (0.27-1.04)	0.485	0.57 (0.27-1.22)	0.299	0.59 (0.27-1.28)	0.274	0.85 (0.42-1.74)	0.666	0.69 (0.32-1.50)	0.286
DCIS	0.92 (0.25-3.43)	0.039	0.69 (0.16-2.90)	0.055	0.65 (0.16-2.64)	0.071	0.82 (0.15-4.32)	0.021	1.69 (0.53-5.36)	0.228	1.16 (0.24-5.68)	0.031

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* This SNP was identified by MR-PRESSO as an outlier for analyses of triple negative cancers (ER-/PR-/HER2-). It was also associated with adiposity in a prior GWAS.

** This SNP is correlated with a SNP predicting sedentary behaviour, rs6870096 (r^2=0.25 using the National Cancer Institute's LDpair application(2)).

† This SNP was identified by pleiotropy investigations as an outlier for analyses of all invasive, ER+, PR+, HR+/HER2-, HR-, and well/moderately differentiated cancers. This SNP was associated with ovarian cancer risk in a prior GWAS.

†† This SNP was associated with ovarian cancer risk in a prior GWAS.

‡ This SNP was associated with adiposity in a prior GWAS.

§ Causal odds ratios were estimated by inverse-variance weighted Mendelian randomization, using SNPs identified in a GWAS of accelerometer-measured movement traits by Doherty et al (5)

¶ p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs

Table S5. Other phenotypes or gene expression differences associated with single nucleotide polymorphisms used in analysis as instruments for physical activity or sedentary time

			Characteristics associated with analysed (or correlated, $r^2 \geq 0.8$) SNPs in prior genome-wide association or gene expression studies (at $p < 5 \times 10^{-8}$), by direction of effect for allele predicting greater activity (PA instruments) or more sedentary time (sedentary time instrument) †				Relevance for our study
SNP	**Chr**	**Position***	**Traits: Conceivable confounders**	**Traits: Adiposity-related (conceivable mediators)**	**Traits: Cancer risk**	**Gene expression changes in breast tissue**	
Overall (average) activity: 5 SNPs associated at $p < 5 \times 10^{-8}$ (identified by Doherty *et al* (5))							
rs6775319	3	18,758,501	--	↓ Fat percentage (138)	--	--	Effect of PA on BC risk may be partially mediated through reduced adiposity
rs6895232	5	152,039,421	--	--	--	--	--
rs564819152	10	21,820,650	--	--	↓ Ovarian cancer (139)	--	Possible reflection of a confounding effect (away from null) along tumorigenic pathways; Reported results omitting this SNP
rs2696625	17	44,326,864	--	--	↑ Ovarian cancer (139)	--	Conceivable reflection of a confounding effect, but the association would likely bias toward the null; Reported results omitting this SNP
rs59499656	18	40,768,309	--	↓: Fat mass, Fat percentage, Waist circumference, Weight (138)	--	--	Effect of PA on BC risk may be partially mediated through reduced adiposity
Overall (average) activity, secondary instrument: 10 SNPs associated at $p < 5 \times 10^{-7}$ (identified by Klimentidis *et al* (7, 8))							
rs12045968	1	33,690,698	--	--	--	--	--
rs34517439	1	78,450,517	↓: Height (138); Psoriasis (140)	↓: Weight, Hip circumference, Fat mass, Basal metabolic rate, BMI, Waist circumference, Fat percentage (138)	↓ Lung cancer (141)	--	Any effect of PA on BC risk may be partially mediated through reduced adiposity; Possible confounding (height, psoriasis, unmeasured

			Characteristics associated with analysed (or correlated, $r^2 \geq 0.8$) SNPs in prior genome-wide association or gene expression studies (at $p<5x10^{-8}$), by direction of effect for allele predicting greater activity (PA instruments) or more sedentary time (sedentary time instrument) †				Relevance for our study
SNP	**Chr**	**Position***	**Traits: Conceivable confounders**	**Traits: Adiposity-related (conceivable mediators)**	**Traits: Cancer risk**	**Gene expression changes in breast tissue**	
							tumorigenic processes); Reported results omitting this SNP
rs6775319	3	18,758,501	--	↓ Fat percentage (138)	--	--	Effect of PA on BC risk may be partially mediated through reduced adiposity
rs9293503	5	87,948,962	--	--	--	--	--
rs12522261	5	152,054,825	--	--	--	--	--
rs11012732	10	21,830,104	--	↓: Fat percentage, Weight, Fat mass, Waist circumference, Hip circumference, BMI (138)	↑ Meningioma (142) ↓ Ovarian cancer (139)	--	Any effect of PA on BC risk may be partially mediated through reduced adiposity; Possible reflection of confounding effects along tumorigenic pathways; Reported results omitting this SNP
rs148193266	11	104,528,681	--	--	--	--	--
rs1550435	15	74,331,385	↑ Height (138, 143)	--	--	--	Possible confounding, but the association would likely bias toward the null; Reported results omitting this SNP
rs55657917	17	43,844,560	↑: Alcohol intake frequency, Medication for pain relief/ constipation/heartburn (138) ↓: Height, College qualifications, Daytime dozing or sleeping/ napping (138)	--	↑ Ovarian cancer (139)	↑ Expression of nearby genes *ARL17A*, *CRHR1*, *CRHR1-IT1*, *DND1P1*, *KANSL1-AS1*, *LRRC37A*, *LRRC37A2*, *RPS26P8*, collectively associated at $p<5x10^{-8}$ with >150 traits including alcohol intake frequency, bone mineral density, **breast cancer in BRCA1 and BRCA2**	Possible confounding (via influencing alcohol intake, medication use, height, education, unmeasured tumorigenic processes, or via altering gene expression levels of genes associated with confounders, or **directly with breast cancer**); Reported results omitting this SNP

SNP	Chr	Position*	Characteristics associated with analysed (or correlated, $r^2 \geq 0.8$) SNPs in prior genome-wide association or gene expression studies (at $p<5x10^{-8}$), by direction of effect for allele predicting greater activity (PA instruments) or more sedentary time (sedentary time instrument) †				Relevance for our study
			Traits: Conceivable confounders	**Traits: Adiposity-related (conceivable mediators)**	**Traits: Cancer risk**	**Gene expression changes in breast tissue**	
						carriers, education, fat mass/%, forced expiratory volume, height, and ovarian cancer ↓ Expression of nearby gene *LRRC37A4P* (associated at $p<5x10^{-8}$ with 18 traits, primarily red and white blood cell characteristics)	
rs59499656	18	40,768,309	--	↓: Fat mass, Fat percentage, Waist circumference, Weight (138)	--	--	Effect of PA on BC risk may be partially mediated through reduced adiposity
Fraction of time with accelerations >425 mg: 1 SNP associated at $p < 5 \times 10^{-9}$ (identified by Klimentidis *et al* (7))							
rs743580	15	74,328,116	↑ Height (138, 144)	↓: Fat percentage, BMI (138)	--	--	Any effect of PA on BC risk may be partially mediated through reduced adiposity; Conceivable confounding, but the association would likely bias toward the null; Reported results omitting this SNP
Self-reported vigorous physical activity: 5 SNPs associated at $p < 5 \times 10^{-9}$ (identified by Klimentidis *et al* (7))							
rs2764261	6	108,927,842	↑ Age at menarche (138) ↓ Height (138)	↓: Weight, Fat mass, Hip circumference, Basal metabolic rate, Waist circumference, BMI, Fat percentage (138)	--	--	Any effect of PA on BC risk may be partially mediated through reduced adiposity; Possible confounding (age at menarche, height); Reported results omitting this SNP
rs328902	7	35,020,843	--	--	--	--	--
rs13243553	7	133,506,955	--	--	--	--	--

			Characteristics associated with analysed (or correlated, $r^2 \geq 0.8$) SNPs in prior genome-wide association or gene expression studies (at $p < 5x10^{-8}$), by direction of effect for allele predicting greater activity (PA instruments) or more sedentary time (sedentary time instrument) †				Relevance for our study
SNP	**Chr**	**Position***	**Traits: Conceivable confounders**	**Traits: Adiposity-related (conceivable mediators)**	**Traits: Cancer risk**	**Gene expression changes in breast tissue**	
rs3781411	10	126,715,436	--	--	--	--	--
rs1248860	3	85,015,779	↑ Comparative body size age 10 (138) ↓ Past tobacco smoking (138)	--	--	--	Possible confounding (early-life body size, smoking); Reported results omitting this SNP
Percent time spent sedentary: 6 SNPs associated at $p < 5 \times 10^{-8}$ (identified by Doherty *et al* (5))							
rs61776614	1	2,166,406	--	--	--	--	--
rs1858242	3	68,527,135	--	--	--	--	--
rs26579	5	87,985,295	↑ Years of education (145); College Qualifications, High-school completion qualifications, Other professional qualifications (138)	↑ Trunk fat percentage (138)	--	--	Effect of sedentary behaviour on BC risk may be partially mediated through increased adiposity; Possible confounding (education); Reported results omitting this SNP
rs25981	5	106,822,908	--	--	--	--	--
rs6870096	5	151,945,811	--	--	--	--	--
rs34858520	7	71,723,883	--	--	--	--	--

Abbreviations: BC, breast cancer; BMI, body mass index; Chr, chromosome; DIY, do-it-yourself; GWAS, genome-wide association study; PA, physical activity; SNP, single nucleotide polymorphism; WHR, waist-hip ratio.

* human genome assembly GRCh37 (hg19)

† Data from the University of Cambridge PhenoScanner V2(146, 147) or NHGRI-EBI GWAS Catalog (148) (as of October 2020); arrows denote direction of effect (risk association or gene expression change) relating to the allele which is also associated with increased physical activity (activity instruments) or increased sedentary time (sedentary behaviour instrument). Expression data was from Genotype-Tissue Expression (GTEx) project.(149)

Table S6. Association between the secondary instrumental genetic variables for overall physical activity (per standard deviation) and risk of breast cancer

		Full instrument (ten SNPs)		Excluding one pleiotropic SNP for outcomes with detected pleiotropy *	
Type of breast cancer	**N cases (vs. 54,452 controls)**	**Odds ratios (95% CI) †**	**P for heterogeneity‡**	**Odds ratios (95% CI) †**	**P for heterogeneity‡**
Invasive cancers					
All invasive	69,838	0.61 (0.44-0.85)	0.010	0.71 (0.57-0.88)	0.596
Pre/perimenopausal	§ 23,999	0.65 (0.45-0.93)	0.494	--	
Postmenopausal	¶ 45,839	0.60 (0.43-0.84)	0.068	--	
By receptor status					
ER+	46,528	0.57 (0.39-0.83)	0.004	0.69 (0.54-0.88)	0.931
ER-	11,246	0.72 (0.45-1.17)	0.109	--	
PR+	34,891	0.55 (0.36-0.84)	0.003	0.67 (0.51-0.88)	0.647
PR-	16,432	0.66 (0.48-0.92)	0.443	--	
HER2+	6,945	0.58 (0.34-0.97)	0.254	--	
HER2-	33,214	0.70 (0.50-0.99)	0.072	--	
Combined hormone receptor- and/or HER2-defined subtypes					
ER+ or PR+; HER2+	4,816	0.49 (0.29-0.85)	0.458	--	
ER+ or PR+; HER2-	27,874	0.68 (0.45-1.04)	0.010	0.83 (0.62-1.12)	0.729
ER-; PR-; HER2+	1,974	0.74 (0.33-1.68)	0.468	--	
ER-; PR-; HER2-	4,964	0.73 (0.36-1.47)	0.088	--	
ER- and PR- (all)	9,215	0.70 (0.42-1.17)	0.126	--	
By morphology					
Ductal	42,223	0.63 (0.46-0.86)	0.067	--	
Lobular	8,795	0.45 (0.28-0.71)	0.358	--	
By stage at diagnosis					
Stage I	17,583	0.59 (0.43-0.82)	0.558	--	
Stage II	15,992	0.52 (0.35-0.78)	0.231	--	
Stage III/IV	4,553	0.51 (0.28-0.93)	0.385	--	
By tumor grade					
Grade 1/2	34,647	0.54 (0.37-0.80)	0.015	0.66 (0.50-0.86)	0.890
Grade 3	16,432	0.59 (0.42-0.83)	0.373	--	
In situ cancers					
All in situ	6,667	0.95 (0.55-1.67)	0.155	--	
Ductal carcinoma in situ	3,510	1.29 (0.51-3.25)	0.019	1.02 (0.44-2.37)	0.096

Abbreviations: CI, confidence interval; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* SNP rs11012732 was identified by MR-PRESSO as outlying (likely pleiotropic) for analyses of all invasive, ER+, PR+, HR+/HER2-, and low-grade tumors. For analyses of DCIS (for which MR-PRESSO detected pleiotropy, global test p=0.02) SNP rs34517439 (MR-PRESSO $p_{outlier}$=0.08) was identified as likely pleiotropic by inspecting genetic association scatter plots, comparing individual SNP causal effects, and inspecting leave-one-out analyses.

† Causal odds ratios were estimated by inverse-variance weighted Mendelian randomization, using SNPs identified for accelerometer-defined physical activity in a GWAS by Klimentidis et al (7, 8)

‡ p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs

§ vs pre/perimenopausal controls (n=17,686), assigned using age (<50 years) if menopause status was unknown

¶ vs postmenopausal controls (n=36,766), assigned using age (≥50 years) if menopause status was unknown

-- No outlying SNPs were identified.

Table S7. Comparison of results from different Mendelian randomization methods: Association between the secondary instrumental genetic variables for overall physical activity (per standard deviation) and risk of breast cancer

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
Invasive cancers			
All invasive	69,838		
IVW		0.61 (0.44-0.85)	0.010
Weighted median		0.70 (0.51-0.95)	
MR-Egger		1.28 (0.27-5.98)	0.342
Pre/perimenopausal	¶ 23,999		
IVW		0.65 (0.45-0.93)	0.494
Weighted median		0.77 (0.47-1.29)	
MR-Egger		1.39 (0.24-8.00)	0.378
Postmenopausal	**45,839		
IVW		0.60 (0.43-0.84)	0.068
Weighted median		0.65 (0.45-0.92)	
MR-Egger		1.30 (0.26-6.56)	0.343
By receptor status			
ER+	46,528		
IVW		0.57 (0.39-0.83)	0.004
Weighted median		0.73 (0.53-1.02)	
MR-Egger		0.95 (0.15-6.23)	0.584
ER-	11,246		
IVW		0.72 (0.45-1.17)	0.109
Weighted median		0.63 (0.37-1.08)	
MR-Egger		0.37 (0.03-4.10)	0.575
PR+	34,891		
IVW		0.55 (0.36-0.84)	0.003
Weighted median		0.67 (0.47-0.98)	
MR-Egger		0.83 (0.10-7.07)	0.695
PR-	16,432		
IVW		0.66 (0.48-0.92)	0.443
Weighted median		0.66 (0.42-1.03)	
MR-Egger		0.65 (0.12-3.47)	0.984
HER2+	6,945		
IVW		0.58 (0.34-0.97)	0.254
Weighted median		0.45 (0.23-0.85)	
MR-Egger		0.33 (0.02-4.64)	0.674
HER2-	33,214		
IVW		0.70 (0.50-0.99)	0.072
Weighted median		0.79 (0.54-1.14)	
MR-Egger		1.07 (0.19-5.93)	0.626
Combined hormone receptor- and/or HER2-defined subtypes			
ER+ or PR+; HER2+	4,816		
IVW		0.49 (0.29-0.85)	0.458
Weighted median		0.60 (0.29-1.28)	
MR-Egger		0.08 (0.01-1.16)	0.175
ER+ or PR+; HER2-	27,874		
IVW		0.68 (0.45-1.04)	0.010
Weighted median		0.81 (0.55-1.20)	
MR-Egger		1.15 (0.14-9.73)	0.622

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
ER-; PR-; HER2+	1,974		
IVW		0.74 (0.33-1.68)	0.468
Weighted median		0.75 (0.25-2.23)	
MR-Egger		2.37 (0.04-129)	0.560
ER-; PR-; HER2-	4,964		
IVW		0.73 (0.36-1.47)	0.088
Weighted median		0.74 (0.35-1.57)	
MR-Egger		0.63 (0.02-21.6)	0.934
ER- and PR- (all)	9,215		
IVW		0.70 (0.42-1.17)	0.126
Weighted median		0.68 (0.38-1.22)	
MR-Egger		0.44 (0.03-5.93)	0.724
By morphology			
Ductal	42,223		
IVW		0.63 (0.46-0.86)	0.067
Weighted median		0.70 (0.50-0.99)	
MR-Egger		0.89 (0.18-4.37)	0.654
Lobular	8,795		
IVW		0.45 (0.28-0.71)	0.358
Weighted median		0.59 (0.32-1.09)	
MR-Egger		1.55 (0.18-13.6)	0.256
By stage at diagnosis			
Stage I	17,583		
IVW		0.59 (0.43-0.82)	0.558
Weighted median		0.63 (0.41-0.99)	
MR-Egger		0.81 (0.17-3.87)	0.694
Stage II	15,992		
IVW		0.52 (0.35-0.78)	0.231
Weighted median		0.51 (0.30-0.87)	
MR-Egger		1.69 (0.26-11.0)	0.206
Stage III/IV	4,553		
IVW		0.51 (0.28-0.93)	0.385
Weighted median		0.41 (0.19-0.89)	
MR-Egger		0.42 (0.02-8.94)	0.891
By tumor grade			
Grade 1/2	34,647		
IVW		0.54 (0.37-0.80)	0.015
Weighted median		0.60 (0.42-0.86)	
MR-Egger		0.73 (0.10-5.21)	0.755
Grade 3	16,432		
IVW		0.59 (0.42-0.83)	0.373
Weighted median		0.55 (0.35-0.88)	
MR-Egger		2.14 (0.45-10.2)	0.099
In situ cancers			
All in situ	6,667		
IVW		0.95 (0.55-1.67)	0.155
Weighted median		0.94 (0.48-1.84)	
MR-Egger		2.38 (0.15-36.5)	0.503
Ductal carcinoma in situ	3,510		
IVW		1.29 (0.51-3.25)	0.019
Weighted median		1.51 (0.59-3.84)	
MR-Egger		0.27 (0.00-27.7)	0.499

Abbreviations: CI, confidence interval; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; IVW, inverse-variance weighted; MR, Mendelian Randomization; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* Causal odds ratios were estimated by three different Mendelian randomization methods, using ten SNPs identified for accelerometer-defined physical activity in a GWAS by Klimentidis et al (7, 8)

† Confidence intervals from weighted median MR were generated from 10,000 bootstrap samples (seed 314159265)

‡ Relating to IVW MR estimates: p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs

§ Relating to MR-Egger estimates: p-value for the intercept test (p-value for pleiotropy)

¶ vs pre/perimenopausal controls (n=17,686), assigned using age (<50 years) if menopause status was unknown

** vs postmenopausal controls (n=36,766), assigned using age (≥50 years) if menopause status was unknown

Table S8. Leave-one-out analyses: Association between the secondary instrumental genetic variables for overall physical activity (per standard deviation) and risk of breast cancer, omitting one SNP at a time

	Odds ratios (95% CI) *									
Type of cancer	**Excluding rs12045968**	**Excluding rs34517439 †**	**Excluding rs6775319 §**	**Excluding rs9293503**	**Excluding rs12522261**	**Excluding rs11012732 ¶**	**Excluding rs148193266 ****	**Excluding rs1550435 ††**	**Excluding rs55657917 §§**	**Excluding rs59499656 §**
Invasive cancers										
All invasive	‡0.60 (0.42-0.85)	‡0.58 (0.42-0.81)	‡0.61 (0.43-0.87)	‡0.60 (0.42-0.85)	‡0.61 (0.43-0.87)	0.71 (0.57-0.88)	‡0.59 (0.42-0.83)	‡0.61 (0.42-0.87)	‡0.65 (0.46-0.92)	‡0.59 (0.42-0.85)
Pre/perimenop.	0.68 (0.46-0.99)	0.59 (0.41-0.87)	0.62 (0.42-0.92)	0.61 (0.42-0.90)	0.65 (0.44-0.97)	0.71 (0.49-1.05)	0.62 (0.43-0.91)	0.63 (0.43-0.94)	0.72 (0.49-1.07)	0.62 (0.42-0.92)
Postmenop.	0.57 (0.40-0.82)	0.58 (0.40-0.83)	‡0.60 (0.41-0.88)	‡0.59 (0.41-0.87)	‡0.6 (0.41-0.87)	0.71 (0.54-0.93)	0.58 (0.40-0.83)	‡0.60 (0.41-0.87)	‡0.62 (0.42-0.91)	‡0.59 (0.40-0.85)
By receptor status										
ER+	‡0.56 (0.37-0.85)	‡0.55 (0.37-0.83)	‡0.56 (0.37-0.84)	‡0.55 (0.36-0.83)	‡0.56 (0.37-0.84)	0.69 (0.54-0.88)	‡0.55 (0.37-0.83)	‡0.55 (0.36-0.83)	‡0.60 (0.39-0.91)	‡0.56 (0.37-0.86)
ER-	0.73 (0.43-1.25)	0.65 (0.41-1.03)	0.79 (0.49-1.30)	0.74 (0.43-1.26)	0.77 (0.46-1.29)	0.63 (0.40-1.00)	0.79 (0.49-1.28)	0.73 (0.43-1.25)	0.76 (0.44-1.30)	0.66 (0.40-1.09)
PR+	‡0.53 (0.33-0.86)	‡0.52 (0.33-0.81)	‡0.54 (0.34-0.87)	‡0.54 (0.34-0.87)	‡0.54 (0.33-0.86)	0.67 (0.51-0.88)	‡0.53 (0.33-0.84)	‡0.53 (0.33-0.84)	‡0.59 (0.37-0.94)	‡0.52 (0.33-0.82)
PR-	0.66 (0.46-0.95)	0.63 (0.45-0.89)	0.68 (0.47-0.97)	0.64 (0.45-0.92)	0.74 (0.53-1.05)	0.60 (0.43-0.85)	0.70 (0.49-0.98)	0.67 (0.46-0.96)	0.68 (0.47-0.98)	0.64 (0.45-0.92)
HER2+	0.49 (0.30-0.79)	0.53 (0.31-0.90)	0.55 (0.31-0.97)	0.60 (0.33-1.07)	0.59 (0.33-1.06)	0.62 (0.36-1.10)	0.60 (0.34-1.06)	0.61 (0.35-1.08)	0.68 (0.41-1.13)	0.54 (0.31-0.96)
HER2-	0.72 (0.49-1.05)	0.65 (0.47-0.90)	‡0.70 (0.48-1.03)	0.68 (0.47-1.00)	0.67 (0.46-0.96)	0.81 (0.62-1.07)	‡0.69 (0.48-1.01)	0.68 (0.47-0.99)	0.74 (0.50-1.08)	‡0.69 (0.47-1.02)
Combined hormone receptor- and/or HER2-defined subtypes										
HR+; HER2+	0.42 (0.24-0.75)	0.46 (0.26-0.81)	0.46 (0.26-0.83)	0.52 (0.29-0.95)	0.48 (0.27-0.88)	0.53 (0.29-0.95)	0.53 (0.30-0.94)	0.49 (0.27-0.88)	0.60 (0.34-1.08)	0.47 (0.26-0.87)
HR+; HER2-	‡0.70 (0.43-1.12)	‡0.64 (0.41-0.99)	‡0.66 (0.41-1.05)	‡0.66 (0.41-1.06)	‡0.63 (0.41-0.98)	0.83 (0.62-1.12)	‡0.67 (0.42-1.06)	‡0.67 (0.42-1.07)	‡0.71 (0.44-1.15)	‡0.68 (0.42-1.10)
HR-; HER2+	0.56 (0.24-1.32)	0.67 (0.29-1.58)	0.67 (0.28-1.61)	0.74 (0.30-1.82)	0.88 (0.37-2.09)	0.79 (0.32-1.93)	0.74 (0.30-1.79)	0.88 (0.37-2.09)	0.84 (0.35-2.04)	0.70 (0.29-1.73)
HR-; HER2-	0.76 (0.35-1.64)	0.66 (0.32-1.39)	0.95 (0.54-1.67)	0.73 (0.33-1.60)	0.76 (0.35-1.64)	0.60 (0.31-1.17)	0.73 (0.34-1.57)	0.67 (0.32-1.42)	0.82 (0.38-1.76)	0.69 (0.32-1.50)
HR- (all)	0.69 (0.39-1.22)	0.63 (0.38-1.04)	0.79 (0.48-1.31)	0.71 (0.40-1.26)	0.76 (0.44-1.31)	0.60 (0.37-0.97)	0.74 (0.43-1.28)	0.70 (0.39-1.23)	0.76 (0.44-1.34)	0.65 (0.37-1.12)
By morphology										
Ductal	0.59 (0.43-0.82)	0.60 (0.43-0.84)	‡0.61 (0.43-0.86)	‡0.62 (0.44-0.88)	‡0.62 (0.44-0.88)	0.72 (0.56-0.93)	0.61 (0.43-0.86)	‡0.62 (0.44-0.89)	0.67 (0.48-0.94)	0.60 (0.43-0.85)
Lobular	0.44 (0.26-0.73)	0.41 (0.26-0.66)	0.47 (0.29-0.78)	0.43 (0.26-0.71)	0.51 (0.32-0.81)	0.53 (0.33-0.85)	0.45 (0.27-0.74)	0.42 (0.26-0.68)	0.43 (0.26-0.73)	0.43 (0.26-0.72)
By stage at diagnosis										
Stage I	0.56 (0.40-0.80)	0.59 (0.42-0.83)	0.57 (0.40-0.80)	0.61 (0.43-0.86)	0.61 (0.43-0.87)	0.67 (0.47-0.95)	0.57 (0.40-0.80)	0.58 (0.41-0.82)	0.63 (0.44-0.89)	0.56 (0.40-0.80)
Stage II	0.49 (0.32-0.75)	0.49 (0.32-0.74)	0.54 (0.34-0.84)	0.52 (0.33-0.82)	0.52 (0.33-0.82)	0.59 (0.40-0.86)	0.47 (0.32-0.68)	0.50 (0.32-0.78)	0.58 (0.38-0.88)	0.52 (0.33-0.83)
Stage III/IV	0.42 (0.23-0.77)	0.47 (0.25-0.87)	0.59 (0.32-1.09)	0.52 (0.26-1.01)	0.46 (0.25-0.86)	0.56 (0.29-1.07)	0.53 (0.27-1.02)	0.52 (0.27-1.01)	0.57 (0.30-1.10)	0.53 (0.27-1.04)
By tumor grade										
Grade 1/2	‡0.51 (0.34-0.76)	‡0.54 (0.35-0.83)	‡0.51 (0.34-0.78)	‡0.52 (0.34-0.80)	‡0.54 (0.35-0.83)	0.66 (0.50-0.86)	‡0.53 (0.35-0.82)	‡0.53 (0.34-0.81)	‡0.56 (0.36-0.87)	‡0.54 (0.35-0.83)
Grade 3	0.58 (0.40-0.84)	0.54 (0.38-0.76)	0.63 (0.45-0.90)	0.59 (0.40-0.87)	0.59 (0.4-0.86)	0.64 (0.45-0.91)	0.55 (0.39-0.77)	0.60 (0.41-0.87)	0.62 (0.42-0.90)	0.56 (0.39-0.82)
In situ cancers										
All in situ	0.81 (0.49-1.34)	0.88 (0.49-1.59)	0.91 (0.49-1.67)	0.95 (0.51-1.76)	0.96 (0.51-1.78)	0.97 (0.52-1.81)	0.89 (0.49-1.60)	1.03 (0.57-1.87)	1.17 (0.70-1.94)	1.05 (0.58-1.90)
DCIS	‡1.14 (0.42-3.07)	1.02 (0.44-2.37)	‡1.14 (0.42-3.09)	‡1.24 (0.44-3.50)	‡1.14 (0.42-3.07)	‡1.27 (0.45-3.61)	‡1.47 (0.56-3.84)	‡1.36 (0.49-3.79)	1.79 (0.76-4.23)	‡1.51 (0.56-4.06)

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* Causal odds ratios were estimated by inverse-variance weighted Mendelian randomization, using SNPs identified for accelerometer-defined physical activity in a GWAS by Klimentidis et al (7, 8)

† This SNP was identified by inspecting scatter plots and individual SNP causal effects as a likely outlier for analyses of DCIS, and was associated in prior GWAS with several possible confounders and with adiposity.

§ This SNP was associated with adiposity in prior GWAS.

¶ This SNP was identified by MR-PRESSO as an outlier for analyses of all invasive, ER+, PR+, HR+/HER2-, and well/moderately differentiated cancers, and was associated in prior GWAS with adiposity and risk of several cancers.

** This SNP had imputation quality score <0.9 and low minor allele frequency (3.1%)

†† This SNP was associated with a possible confounder (height) in prior GWAS.

§§ This SNP was associated with several possible confounders, risk of cancer (ovarian), and with expression of genes associated with multiple relevant traits, including breast cancer risk.

‡ p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs was <0.05

¶

Table S9. Comparison of results from different Mendelian randomization methods: Association between instrumental genetic variables for self-reported vigorous physical activity (≥ 3 vs. 0 days/week) and risk of breast cancer

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
Invasive cancers			
All invasive	69,838		
IVW		0.83 (0.69-1.01)	0.650
Weighted median		0.80 (0.62-1.02)	
MR-Egger		0.71 (0.18-2.87)	0.821
Pre/perimenopausal	¶ 23,999		
IVW		0.62 (0.45-0.87)	0.788
Weighted median		0.59 (0.39-0.89)	
MR-Egger		0.45 (0.04-5.25)	0.790
Postmenopausal	**45,839		
IVW		0.95 (0.75-1.19)	0.630
Weighted median		0.95 (0.70-1.28)	
MR-Egger		0.95 (0.17-5.28)	0.997
By receptor status			
ER+	46,528		
IVW		0.86 (0.70-1.07)	0.917
Weighted median		0.88 (0.68-1.14)	
MR-Egger		0.90 (0.19-4.25)	0.962
ER-	11,246		
IVW		0.86 (0.61-1.21)	0.418
Weighted median		0.91 (0.58-1.44)	
MR-Egger		0.23 (0.02-2.96)	0.311
PR+	34,891		
IVW		0.77 (0.61-0.98)	0.544
Weighted median		0.81 (0.60-1.09)	
MR-Egger		0.88 (0.16-4.92)	0.886
PR-	16,432		
IVW		0.95 (0.70-1.28)	0.948
Weighted median		0.99 (0.68-1.42)	
MR-Egger		0.59 (0.06-5.35)	0.668
HER2+	6,945		
IVW		0.83 (0.53-1.31)	0.327
Weighted median		0.88 (0.50-1.55)	
MR-Egger		0.04 (0.00-0.88)	0.052
HER2-	33,214		
IVW		0.86 (0.68-1.10)	0.550
Weighted median		0.92 (0.67-1.25)	
MR-Egger		2.10 (0.37-12.1)	0.315
Combined hormone receptor- and/or HER2-defined subtypes			
ER+ or PR+; HER2+	4,816		
IVW		1.00 (0.58-1.70)	0.321
Weighted median		1.18 (0.60-2.31)	
MR-Egger		0.03 (0.00-1.33)	0.069
ER+ or PR+; HER2-	27,874		
IVW		0.82 (0.64-1.06)	0.560
Weighted median		0.87 (0.63-1.21)	
MR-Egger		2.47 (0.39-15.7)	0.241

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
ER-; PR-; HER2+	1,974		
IVW		0.57 (0.27-1.20)	0.727
Weighted median		0.55 (0.21-1.40)	
MR-Egger		0.05 (0.00-10.3)	0.356
ER-; PR-; HER2-	4,964		
IVW		1.30 (0.79-2.12)	0.593
Weighted median		1.28 (0.68-2.43)	
MR-Egger		1.33 (0.03-50.9)	0.987
ER- and PR- (all)	9,215		
IVW		0.95 (0.66-1.39)	0.559
Weighted median		1.02 (0.63-1.67)	
MR-Egger		0.23 (0.01-3.67)	0.311
By morphology			
Ductal	42,223		
IVW		0.81 (0.65-1.00)	0.932
Weighted median		0.79 (0.61-1.03)	
MR-Egger		0.80 (0.16-3.99)	0.991
Lobular	8,795		
IVW		0.78 (0.53-1.17)	0.809
Weighted median		0.81 (0.49-1.34)	
MR-Egger		0.17 (0.01-3.17)	0.300
By stage at diagnosis			
Stage I	17,583		
IVW		0.88 (0.65-1.19)	0.598
Weighted median		0.78 (0.53-1.15)	
MR-Egger		0.37 (0.04-3.36)	0.435
Stage II	15,992		
IVW		0.82 (0.59-1.14)	0.788
Weighted median		0.79 (0.53-1.19)	
MR-Egger		0.84 (0.08-9.25)	0.991
Stage III/IV	4,553		
IVW		0.75 (0.44-1.27)	0.910
Weighted median		0.85 (0.44-1.62)	
MR-Egger		0.22 (0.00-10.3)	0.528
By tumor grade			
Grade 1/2	34,647		
IVW		0.84 (0.66-1.06)	0.640
Weighted median		0.78 (0.58-1.06)	
MR-Egger		0.41 (0.07-2.32)	0.417
Grade 3	16,432		
IVW		0.99 (0.73-1.33)	0.557
Weighted median		1.13 (0.76-1.70)	
MR-Egger		1.38 (0.15-12.8)	0.767
In situ cancers			
All in situ	6,667		
IVW		0.94 (0.43-2.08)	0.007
Weighted median		1.03 (0.52-2.04)	
MR-Egger		0.39 (0.00-308)	0.795
Ductal carcinoma in situ	3,510		
IVW		0.85 (0.42-1.69)	0.204
Weighted median		0.63 (0.28-1.43)	
MR-Egger		0.06 (0.00-8.63)	0.291

Abbreviations: CI, confidence interval; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; IVW, inverse-variance weighted; MR, Mendelian Randomization; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* Causal odds ratios were estimated by three different Mendelian randomization methods, using five SNPs identified in a GWAS of physical activity by Klimentidis et al (7)

† Confidence intervals from weighted median MR were generated from 10,000 bootstrap samples (seed 314159265)

‡ Relating to IVW MR estimates: p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs

§ Relating to MR-Egger estimates: p-value for the intercept test (p-value for pleiotropy)

¶ vs pre/perimenopausal controls (n=17,686), assigned using age (<50 years) if menopause status was unknown

** vs postmenopausal controls (n=36,766), assigned using age (≥50 years) if menopause status was unknown

Table S10. Leave-one-out analyses: Association between instrumental genetic variables for self-reported vigorous physical activity (≥ 3 vs. 0 days/week) and risk of breast cancer, omitting one SNP at a time

	Full instrument (five SNPs)		Excluding rs2764261 *		Excluding rs328902		Excluding rs13243553		Excluding rs3781411		Excluding rs1248860 §	
Type of breast cancer	**Odds ratios (95% CI) †**	**P_{het}‡**	**Odds ratios (95% CI) †**	**P_{het}‡**	**Odds ratios (95% CI) †**	**P_{het}‡**	**Odds ratios (95% CI) †**	**P_{het}‡**	**Odds ratios (95% CI) †**	**P_{het}‡**	**Odds ratios (95% CI) †**	**P_{het}‡**
Invasive cancers												
All invasive	0.83 (0.69-1.01)	0.650	0.86 (0.70-1.06)	0.569	0.80 (0.65-0.99)	0.635	0.79 (0.64-0.98)	0.681	0.84 (0.68-1.04)	0.488	0.87 (0.70-1.08)	0.656
Pre/perimenopausal	0.62 (0.45-0.87)	0.788	0.61 (0.42-0.89)	0.644	0.57 (0.39-0.82)	0.933	0.63 (0.44-0.92)	0.640	0.64 (0.44-0.93)	0.651	0.67 (0.46-0.98)	0.800
Postmenopausal	0.95 (0.75-1.19)	0.630	1.00 (0.77-1.29)	0.607	0.92 (0.71-1.20)	0.490	0.88 (0.68-1.14)	0.809	0.94 (0.73-1.22)	0.461	1.00 (0.77-1.30)	0.596
By receptor status												
ER+	0.86 (0.70-1.07)	0.917	0.87 (0.69-1.11)	0.825	0.86 (0.68-1.08)	0.816	0.83 (0.66-1.05)	0.943	0.86 (0.68-1.09)	0.816	0.90 (0.71-1.14)	0.939
ER-	0.86 (0.61-1.21)	0.418	0.83 (0.54-1.29)	0.282	0.76 (0.52-1.11)	0.607	0.82 (0.54-1.25)	0.305	0.93 (0.63-1.38)	0.399	0.96 (0.65-1.42)	0.488
PR+	0.77 (0.61-0.98)	0.544	0.77 (0.59-0.99)	0.383	0.78 (0.60-1.01)	0.379	0.72 (0.56-0.94)	0.628	0.76 (0.59-0.98)	0.396	0.85 (0.66-1.11)	0.880
PR-	0.95 (0.70-1.28)	0.948	0.94 (0.67-1.31)	0.874	0.91 (0.65-1.27)	0.947	0.93 (0.67-1.30)	0.877	0.98 (0.70-1.37)	0.905	0.99 (0.71-1.39)	0.935
HER2+	0.83 (0.53-1.31)	0.327	0.73 (0.45-1.17)	0.380	0.77 (0.45-1.33)	0.255	0.82 (0.46-1.46)	0.203	1.03 (0.64-1.65)	0.797	0.85 (0.47-1.54)	0.204
HER2-	0.86 (0.68-1.10)	0.550	0.90 (0.69-1.17)	0.460	0.83 (0.64-1.08)	0.473	0.85 (0.65-1.11)	0.396	0.81 (0.62-1.06)	0.574	0.94 (0.72-1.23)	0.723
Combined hormone receptor- and/or HER2-defined subtypes												
ER+/PR+; HER2+	1.00 (0.58-1.70)	0.321	0.84 (0.48-1.45)	0.434	0.94 (0.48-1.83)	0.218	1.05 (0.53-2.06)	0.211	1.26 (0.72-2.21)	0.722	0.94 (0.47-1.88)	0.210
ER+/PR+; HER2-	0.82 (0.64-1.06)	0.560	0.87 (0.66-1.15)	0.540	0.81 (0.61-1.07)	0.404	0.80 (0.60-1.05)	0.438	0.76 (0.57-1.01)	0.679	0.88 (0.67-1.17)	0.602
ER-; PR-; HER2+	0.57 (0.27-1.20)	0.727	0.54 (0.24-1.24)	0.580	0.57 (0.25-1.30)	0.563	0.46 (0.20-1.05)	0.894	0.67 (0.29-1.55)	0.704	0.65 (0.28-1.50)	0.650
ER-; PR-; HER2-	1.30 (0.79-2.12)	0.593	1.23 (0.71-2.12)	0.455	1.11 (0.64-1.91)	0.771	1.37 (0.79-2.37)	0.462	1.29 (0.75-2.24)	0.424	1.52 (0.87-2.64)	0.715
ER- and PR- (all)	0.95 (0.66-1.39)	0.559	0.93 (0.61-1.41)	0.408	0.87 (0.57-1.31)	0.597	0.89 (0.59-1.35)	0.483	1.05 (0.69-1.60)	0.556	1.06 (0.69-1.62)	0.597
By morphology												
Ductal	0.81 (0.65-1.00)	0.932	0.82 (0.64-1.05)	0.861	0.81 (0.64-1.03)	0.840	0.77 (0.61-0.98)	0.987	0.81 (0.63-1.03)	0.840	0.83 (0.65-1.06)	0.896
Lobular	0.78 (0.53-1.17)	0.809	0.78 (0.50-1.22)	0.660	0.74 (0.47-1.15)	0.754	0.79 (0.51-1.24)	0.663	0.88 (0.56-1.39)	0.954	0.74 (0.47-1.16)	0.735
By stage at diagnosis												
Stage I	0.88 (0.65-1.19)	0.598	0.93 (0.66-1.29)	0.501	0.86 (0.62-1.20)	0.449	0.79 (0.57-1.10)	0.908	0.93 (0.67-1.31)	0.525	0.91 (0.65-1.28)	0.459
Stage II	0.82 (0.59-1.14)	0.788	0.75 (0.52-1.08)	0.926	0.83 (0.58-1.19)	0.636	0.84 (0.58-1.20)	0.642	0.81 (0.56-1.18)	0.638	0.89 (0.62-1.29)	0.830
Stage III/IV	0.75 (0.44-1.27)	0.910	0.80 (0.45-1.44)	0.862	0.73 (0.41-1.31)	0.812	0.71 (0.39-1.27)	0.846	0.83 (0.46-1.49)	0.914	0.69 (0.38-1.26)	0.874
By tumor grade												
Grade 1 and 2	0.84 (0.66-1.06)	0.640	0.85 (0.65-1.10)	0.480	0.79 (0.61-1.02)	0.689	0.80 (0.61-1.03)	0.622	0.88 (0.68-1.14)	0.592	0.88 (0.68-1.15)	0.604
Grade 3	0.99 (0.73-1.33)	0.557	0.93 (0.66-1.30)	0.502	1.07 (0.76-1.49)	0.587	0.93 (0.66-1.30)	0.496	0.95 (0.67-1.33)	0.436	1.08 (0.76-1.51)	0.599
In situ cancers												
All in situ	0.94 (0.43-2.08)	0.007	1.30 (0.72-2.34)	0.189	0.76 (0.32-1.78)	0.020	0.93 (0.33-2.56)	0.003	1.05 (0.39-2.83)	0.004	0.77 (0.31-1.93)	0.012
DCIS	0.85 (0.42-1.69)	0.204	0.94 (0.41-2.18)	0.146	0.74 (0.33-1.69)	0.165	0.91 (0.38-2.17)	0.129	1.06 (0.53-2.14)	0.310	0.64 (0.34-1.21)	0.483

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* This SNP was identified by MR-PRESSO as an outlier for analyses of in situ cancers. This SNP has also been identified in prior GWAS of several possible confounders (age at menarche, height), and of adiposity.

§ This SNP has been associated in prior GWAS with comparative body size (height) at age 10, and past tobacco smoking.

† Causal odds ratios were estimated by inverse-variance weighted Mendelian randomization, using SNPs identified in a GWAS of physical activity by Klimentidis et al (7)

‡ p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs

Table S11. Comparison of results from different Mendelian randomization methods: Association between instrumental genetic variables for sedentary time (per standard deviation) and risk of breast cancer

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
Invasive cancers			
All invasive	69,838		
IVW		1.20 (0.93-1.55)	0.962
Weighted median		1.23 (0.91-1.67)	
MR-Egger		0.99 (0.20-4.82)	0.806
Pre/perimenopausal	¶ 23,999		
IVW		1.22 (0.78-1.90)	0.589
Weighted median		1.15 (0.66-2.00)	
MR-Egger		1.22 (0.07-20.1)	0.998
Postmenopausal	**45,839		
IVW		1.21 (0.89-1.65)	0.983
Weighted median		1.17 (0.81-1.68)	
MR-Egger		0.75 (0.11-5.24)	0.630
By receptor status			
ER+	46,528		
IVW		1.19 (0.90-1.57)	0.992
Weighted median		1.23 (0.89-1.71)	
MR-Egger		0.75 (0.13-4.38)	0.604
ER-	11,246		
IVW		1.43 (0.90-2.26)	0.926
Weighted median		1.28 (0.73-2.22)	
MR-Egger		1.15 (0.06-21.3)	0.882
PR+	34,891		
IVW		1.19 (0.87-1.63)	0.386
Weighted median		1.29 (0.88-1.91)	
MR-Egger		0.17 (0.02-1.17)	0.046
PR-	16,432		
IVW		1.40 (0.94-2.09)	0.435
Weighted median		1.33 (0.80-2.21)	
MR-Egger		3.85 (0.28-52.7)	0.443
HER2+	6,945		
IVW		1.17 (0.67-2.06)	0.718
Weighted median		1.34 (0.67-2.67)	
MR-Egger		0.24 (0.01-8.33)	0.372
HER2-	33,214		
IVW		1.27 (0.93-1.74)	0.955
Weighted median		1.34 (0.92-1.95)	
MR-Egger		0.57 (0.08-4.15)	0.422
Combined hormone receptor- and/or HER2-defined subtypes			
ER+ or PR+; HER2+	4,816		
IVW		0.86 (0.44-1.67)	0.585
Weighted median		0.78 (0.34-1.79)	
MR-Egger		0.18 (0.00-11.4)	0.452
ER+ or PR+; HER2-	27,874		
IVW		1.12 (0.80-1.56)	0.801
Weighted median		1.12 (0.75-1.68)	
MR-Egger		0.50 (0.06-4.07)	0.444

Type of breast cancer	N cases (vs. 54,452 controls)	Odds ratios (95% CI) *†	P for heterogeneity‡ or pleiotropy§
ER-; PR-; HER2+	1,974		
IVW		1.94 (0.71-5.25)	0.646
Weighted median		1.56 (0.46-5.35)	
MR-Egger		0.06 (0.00-32.0)	0.272
ER-; PR-; HER2-	4,964		
IVW		2.04 (1.06-3.93)	0.500
Weighted median		2.52 (1.10-5.79)	
MR-Egger		0.31 (0.00-19.6)	0.367
ER- and PR- (all)	9,215		
IVW		1.77 (1.07-2.92)	0.819
Weighted median		1.72 (0.93-3.17)	
MR-Egger		1.15 (0.05-27.6)	0.788
By morphology			
Ductal	42,223		
IVW		1.21 (0.91-1.62)	0.992
Weighted median		1.21 (0.86-1.70)	
MR-Egger		1.07 (0.17-6.66)	0.894
Lobular	8,795		
IVW		1.12 (0.66-1.91)	0.695
Weighted median		1.02 (0.53-1.98)	
MR-Egger		0.17 (0.01-4.89)	0.266
By stage at diagnosis			
Stage I	17,583		
IVW		1.62 (0.99-2.65)	0.187
Weighted median		1.33 (0.79-2.23)	
MR-Egger		0.45 (0.02-11.2)	0.428
Stage II	15,992		
IVW		1.23 (0.79-1.90)	0.820
Weighted median		1.36 (0.80-2.31)	
MR-Egger		0.29 (0.02-4.47)	0.294
Stage III/IV	4,553		
IVW		0.91 (0.45-1.84)	0.640
Weighted median		1.02 (0.43-2.43)	
MR-Egger		1.17 (0.01-105)	0.912
By tumor grade			
Grade 1/2	34,647		
IVW		1.15 (0.84-1.57)	0.901
Weighted median		1.15 (0.79-1.67)	
MR-Egger		0.65 (0.09-4.68)	0.568
Grade 3	16,432		
IVW		1.32 (0.88-1.97)	0.967
Weighted median		1.24 (0.77-1.98)	
MR-Egger		0.94 (0.07-11.8)	0.788
In situ cancers			
All in situ	6,667		
IVW		1.75 (1.00-3.07)	0.933
Weighted median		1.79 (0.92-3.50)	
MR-Egger		0.75 (0.02-26.1)	0.637
Ductal carcinoma in situ	3,510		
IVW		2.11 (0.99-4.49)	0.487
Weighted median		2.49 (0.96-6.43)	
MR-Egger		0.23 (0.00-27.0)	0.357

Abbreviations: CI, confidence interval; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; IVW, inverse-variance weighted; MR, Mendelian Randomization; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* Causal odds ratios were estimated by three different Mendelian randomization methods, using six SNPs identified in a GWAS of accelerometer-measured movement traits by Doherty et al (5)

† Confidence intervals from weighted median MR were generated from 10,000 bootstrap samples (seed 314159265)

‡ Relating to IVW MR estimates: p-value associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs

§ Relating to MR-Egger estimates: p-value for the intercept test (p-value for pleiotropy)

¶ vs pre/perimenopausal controls (n=17,686), assigned using age (<50 years) if menopause status was unknown

** vs postmenopausal controls (n=36,766), assigned using age (≥50 years) if menopause status was unknown

Table S12. Leave-one-out analyses: Association between instrumental genetic variables for sedentary time (per standard deviation) and risk of breast cancer, omitting one SNP at a time

	Odds ratios (95% CI) * †						
Type of cancer	**Full instrument (six SNPs)**	**Excluding rs61776614 ‡**	**Excluding rs1858242**	**Excluding rs26579 §**	**Excluding rs25981 ****	**Excluding rs6870096 ¶**	**Excluding rs34858520**
Invasive cancers							
All invasive	1.20 (0.93-1.55)	1.22 (0.93-1.60)	1.21 (0.92-1.60)	1.18 (0.89-1.55)	1.26 (0.96-1.67)	1.19 (0.90-1.56)	1.16 (0.88-1.54)
Pre/perimenopausal	1.22 (0.78-1.90)	1.20 (0.74-1.94)	1.30 (0.80-2.11)	1.26 (0.77-2.05)	1.40 (0.86-2.29)	1.10 (0.68-1.78)	1.08 (0.66-1.77)
Postmenopausal	1.21 (0.89-1.65)	1.25 (0.90-1.74)	1.19 (0.84-1.67)	1.15 (0.82-1.62)	1.22 (0.87-1.71)	1.22 (0.87-1.72)	1.22 (0.86-1.71)
By receptor status							
ER+	1.19 (0.90-1.57)	1.21 (0.90-1.64)	1.23 (0.90-1.67)	1.16 (0.85-1.58)	1.17 (0.86-1.60)	1.18 (0.87-1.61)	1.16 (0.85-1.59)
ER-	1.43 (0.90-2.26)	1.47 (0.90-2.42)	1.31 (0.79-2.18)	1.47 (0.89-2.45)	1.53 (0.92-2.55)	1.33 (0.81-2.21)	1.45 (0.87-2.41)
PR+	1.19 (0.87-1.63)	1.33 (0.95-1.85)	1.25 (0.86-1.81)	1.16 (0.79-1.70)	1.17 (0.80-1.73)	1.16 (0.79-1.70)	1.06 (0.76-1.49)
PR-	1.40 (0.94-2.09)	1.30 (0.85-2.01)	1.46 (0.91-2.34)	1.49 (0.94-2.37)	1.33 (0.83-2.12)	1.24 (0.80-1.92)	1.62 (1.04-2.52)
HER2+	1.17 (0.67-2.06)	1.29 (0.70-2.38)	1.18 (0.64-2.20)	1.12 (0.60-2.09)	1.01 (0.54-1.88)	1.34 (0.72-2.48)	1.11 (0.60-2.08)
HER2-	1.27 (0.93-1.74)	1.33 (0.94-1.86)	1.33 (0.94-1.88)	1.25 (0.88-1.77)	1.24 (0.87-1.76)	1.27 (0.90-1.80)	1.21 (0.86-1.72)
Combined hormone receptor- and/or HER2-defined subtypes							
HR+; HER2+	0.86 (0.44-1.67)	0.95 (0.47-1.94)	0.85 (0.41-1.77)	0.74 (0.36-1.53)	0.71 (0.34-1.48)	1.02 (0.49-2.09)	0.93 (0.45-1.93)
HR+; HER2-	1.12 (0.80-1.56)	1.16 (0.81-1.66)	1.20 (0.83-1.73)	1.10 (0.76-1.59)	1.08 (0.74-1.56)	1.15 (0.80-1.65)	1.02 (0.70-1.47)
HR-; HER2+	1.94 (0.71-5.25)	2.38 (0.81-6.95)	2.05 (0.69-6.15)	2.14 (0.71-6.40)	2.01 (0.67-6.05)	1.90 (0.64-5.63)	1.31 (0.43-3.93)
HR-; HER2-	2.04 (1.06-3.93)	2.35 (1.16-4.75)	1.82 (0.88-3.73)	1.99 (0.94-4.20)	1.92 (0.92-4.02)	1.74 (0.85-3.54)	2.55 (1.24-5.26)
HR- (all)	1.77 (1.07-2.92)	1.84 (1.07-3.15)	1.66 (0.96-2.89)	1.83 (1.05-3.17)	1.74 (1.00-3.02)	1.58 (0.91-2.72)	2.00 (1.15-3.48)
By morphology							
Ductal	1.21 (0.91-1.62)	1.22 (0.89-1.66)	1.24 (0.90-1.70)	1.17 (0.85-1.62)	1.25 (0.91-1.72)	1.21 (0.88-1.66)	1.19 (0.86-1.63)
Lobular	1.12 (0.66-1.91)	1.26 (0.71-2.25)	1.11 (0.62-1.99)	0.96 (0.53-1.72)	1.19 (0.66-2.15)	1.04 (0.58-1.87)	1.18 (0.65-2.13)
By stage at diagnosis							
Stage I	1.62 (0.99-2.65)	1.73 (0.98-3.04)	1.76 (0.99-3.12)	1.66 (0.91-3.03)	1.69 (0.93-3.08)	1.70 (0.94-3.05)	1.25 (0.81-1.95)
Stage II	1.23 (0.79-1.90)	1.32 (0.83-2.11)	1.34 (0.83-2.17)	1.16 (0.72-1.87)	1.13 (0.70-1.82)	1.18 (0.73-1.89)	1.25 (0.77-2.02)
Stage III/IV	0.91 (0.45-1.84)	0.90 (0.42-1.92)	0.88 (0.41-1.91)	1.07 (0.49-2.32)	0.81 (0.37-1.77)	0.76 (0.35-1.63)	1.10 (0.51-2.40)
By tumor grade							
Grade 1/2	1.15 (0.84-1.57)	1.18 (0.84-1.65)	1.22 (0.86-1.72)	1.12 (0.79-1.58)	1.19 (0.84-1.69)	1.11 (0.79-1.56)	1.09 (0.77-1.54)
Grade 3	1.32 (0.88-1.97)	1.37 (0.89-2.10)	1.25 (0.80-1.94)	1.25 (0.81-1.95)	1.34 (0.86-2.08)	1.38 (0.89-2.13)	1.35 (0.87-2.10)
In situ cancers							
All in situ	1.75 (1.00-3.07)	1.84 (1.01-3.38)	1.76 (0.95-3.26)	1.74 (0.93-3.22)	1.56 (0.84-2.91)	1.93 (1.04-3.55)	1.69 (0.91-3.15)
DCIS	2.11 (0.99-4.49)	2.55 (1.13-5.73)	1.67 (0.73-3.83)	2.33 (1.00-5.41)	1.91 (0.82-4.45)	2.48 (1.09-5.64)	1.86 (0.81-4.28)

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; ER+/-, estrogen receptor positive/negative; GWAS, genome wide association study; HER2+/-, human epidermal growth factor receptor 2 positive/negative; PR+/-, progesterone receptor positive/negative; SNP, single nucleotide polymorphism.

* Causal odds ratios were estimated by inverse-variance weighted Mendelian randomization using SNPs identified in a GWAS of accelerometer-measured movement traits by Doherty et al (5)

† All p-values associated with the heterogeneity test statistic (Cochran's Q statistic) measuring heterogeneity of causal effects between SNPs were >0.10

‡ This SNP had imputation quality score <0.9 and low minor allele frequency (6.6%), and was suggested by scatter plots and per-SNP forest plots to be a possible outlier for PR+ analyses.

§ This SNP has been associated with a possible confounder (education) and with adiposity in prior GWAS.

** This is a strand-ambiguous SNP with minor allele frequency near 0.50.

¶ This SNP is correlated with a SNP predicting overall activity, rs6895232 (r^2=0.25 using the National Cancer Institute's LDpair application (2)).

Table S13. Power to detect expected associations* and instrument strength by exposure trait and outcome analysed

	Sample size (% cases)	Power (F-statistic)			
		Overall physical activity instrument †	Vigorous physical activity instrument (accelerometer) ‡	Vigorous physical activity instrument (self-reported) §	Sedentary time instrument **
Type of breast cancer					
Invasive cancers					
All invasive	124,290 (56%)	52% (124.31)	15% (26.05)	37% (81.62)	34% (144.20)
Pre/perimenopausal	41,685 (58%)	22% (42.36)	8% (9.40)	16% (28.04)	14% (49.03)
Postmenopausal	82,605 (55%)	38% (82.96)	12% (17.65)	26% (54.58)	24% (96.17)
By receptor status					
ER+	100,980 (46%)	42% (101.19)	12% (21.35)	30% (66.50)	30% (117.35)
ER-	65,698 (17%)	16% (66.18)	7% (14.24)	12% (43.61)	16% (76.69)
PR+	89,343 (39%)	35% (89.64)	11% (19.00)	25% (58.95)	27% (103.94)
PR-	70,884 (23%)	21% (71.33)	8% (15.28)	15% (46.98)	19% (82.67)
HER2+	61,397 (11%)	12% (61.91)	6% (13.37)	10% (40.82)	12% (71.74)
HER2-	87,666 (38%)	34% (87.98)	11% (18.67)	24% (57.86)	26% (102.01)
Combined hormone receptor- and/or HER2-defined subtypes					
ER+/PR+; HER2+	59,268 (8%)	10% (59.80)	6% (12.94)	8% (39.44)	10% (69.29)
ER+/PR+; HER2-	82,326 (34%)	30% (82.68)	10% (17.59)	22% (54.40)	24% (95.85)
ER-; PR-; HER2+	56,426 (3%)	7% (56.98)	5% (12.37)	6% (37.60)	7% (66.01)
ER-; PR-; HER2-	59,416 (8%)	10% (59.95)	6% (12.97)	8% (39.54)	10% (69.46)
ER- and PR- (all)	63,667 (14%)	14% (64.17)	7% (13.83)	11% (42.30)	14% (74.35)
By morphology					
Ductal	96,675 (44%)	40% (96.92)	12% (20.48)	28% (63.71)	29% (112.9)
Lobular	63,247 (14%)	14% (63.75)	7% (13.75)	11% (42.02)	14% (73.87)
By stage at diagnosis					
Stage I	72,035 (24%)	22% (72.47)	8% (15.52)	16% (47.72)	20% (84.00)
Stage II	70,444 (23%)	21% (70.89)	8% (15.20)	15% (46.69)	19% (82.16)
Stage III/IV	59,005 (8%)	10% (59.54)	6% (12.89)	8% (39.27)	10% (68.98)
By tumor grade					
Grade 1/2	89,099 (39%)	35% (89.40)	11% (18.96)	25% (58.79)	27% (103.66)
Grade 3	70,884 (23%)	21% (71.33)	8% (15.28)	15% (46.98)	19% (82.67)
In situ cancers					
All in situ	61,119 (11%)	12% (61.64)	6% (13.32)	9% (40.64)	12% (71.42)
DCIS	57,962 (6%)	9% (58.51)	6% (12.68)	7% (38.60)	9% (67.78)

* Calculating estimated power requires five parameters: sample size, proportion of cases, R^2_{xz} (proportion of variance in the exposure explained by the instrument), assumed 'true' odds ratios, and type I error rate. The first

three parameters were determined by our data. Possible expected associations (assumed approximate 'true' odds ratio of the outcome variable per standard deviation in the exposure, based on evidence from the literature) for these power calculations were considered to be odds ratios of 0.70 (for physical activity variables) and 1.30 (for sedentary behaviour); for simplicity the same odds ratio was chosen across breast cancer subtypes/outcomes and categories of exposure. The alpha level was set at the typical level of 0.05. Power varied according to the sample size in each analysis (determined by outcome examined) and the proportion of variance explained for the association between each instrument and exposure (R^2_{xz}), detailed below. Power was estimated using the mRnd Mendelian randomization power calculation tool, https://shiny.cnsgenomics.com/mRnd/ (150)

† Calculations based on R^2_{xz} = 0.00099 (0.099% of variance in the exposure explained).

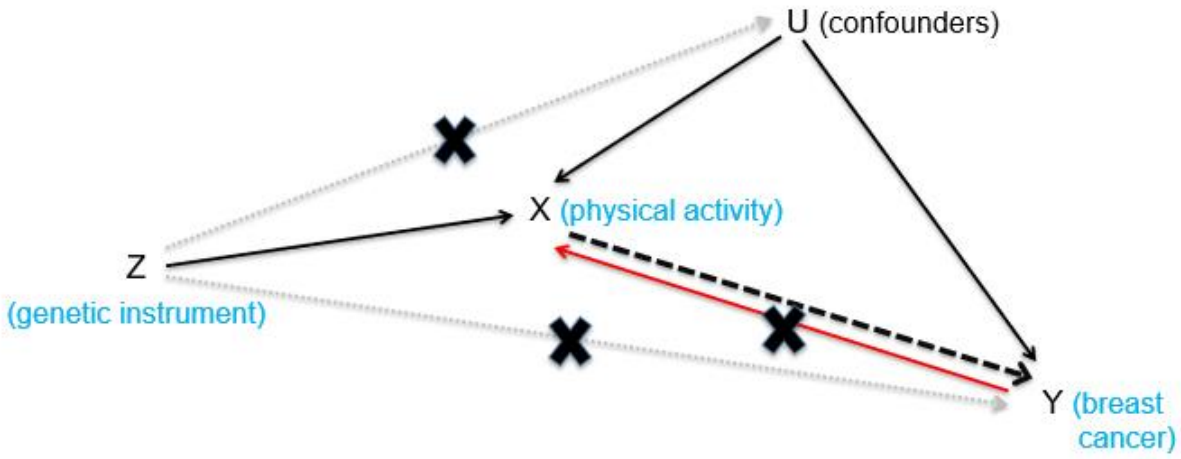
‡ Calculations based on R^2_{xz} = 0.00020 (0.02% of variance in the exposure explained).

§ Calculations based on R^2_{xz} = 0.00065 (0.065% of variance in the exposure explained).

** Calculations based on R^2_{xz} = 0.00115 (0.115% of variance in the exposure explained).

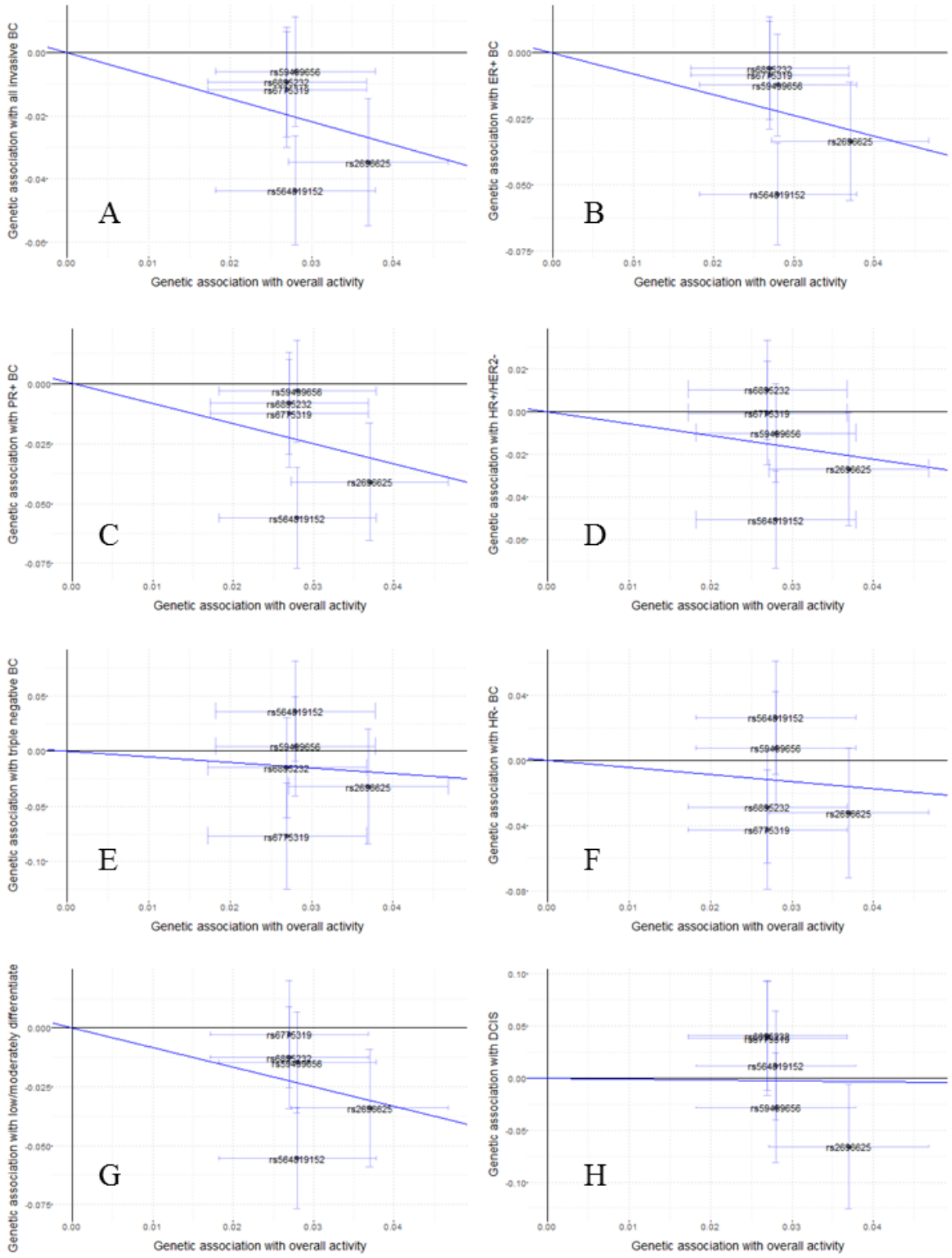
Supplementary Figures

Figure S1. Causal graph of the relationships investigated in this study, illustrating the Mendelian randomization approach and assumptions



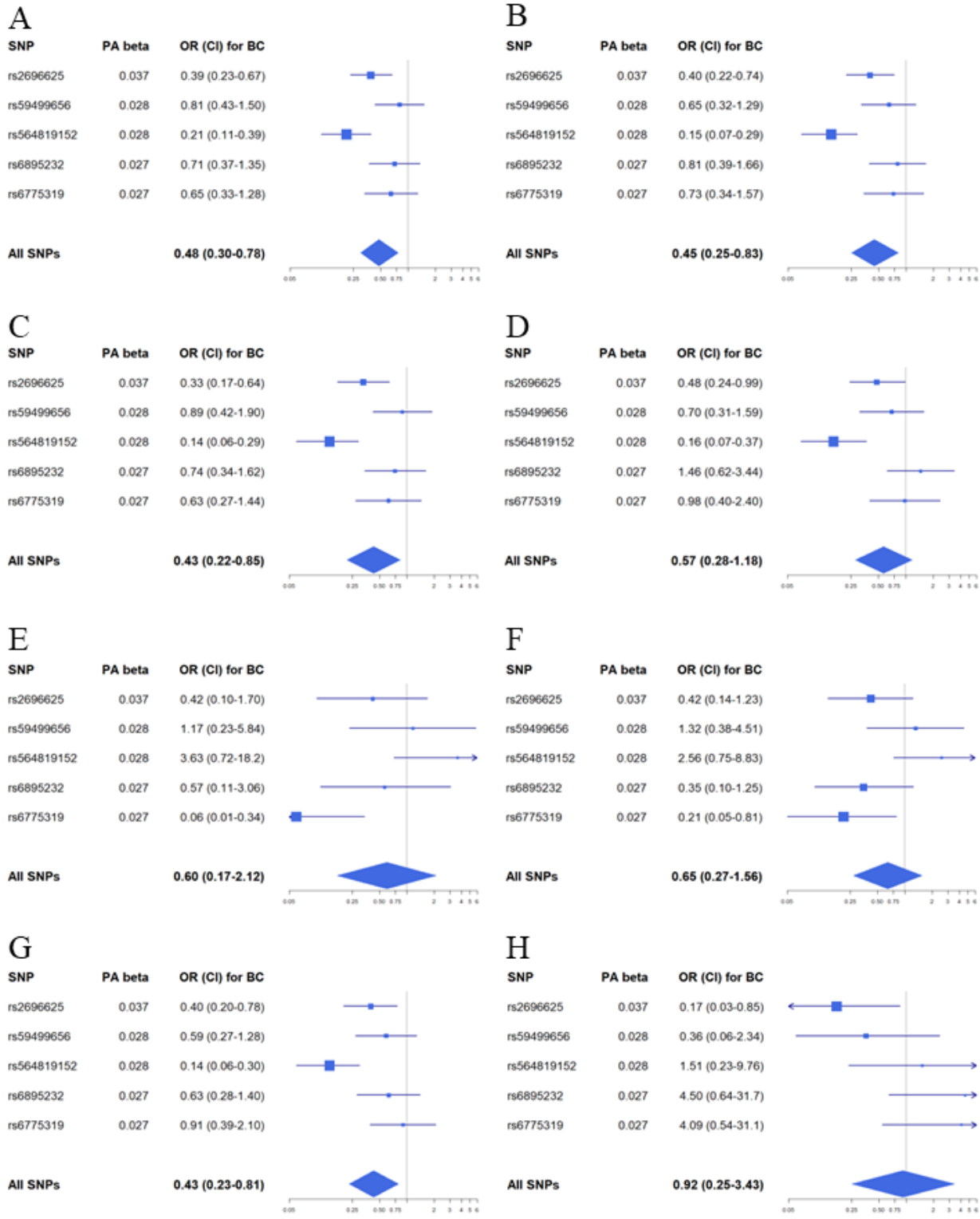
Legend: Crosses indicate an assumption that this causal path does not operate.

Figure S2. Scatter plots of SNP associations with exposure (overall activity; SNPs associated at $p<5x10^{-8}$ (5)) and outcome, for analyses with suspected pleiotropy



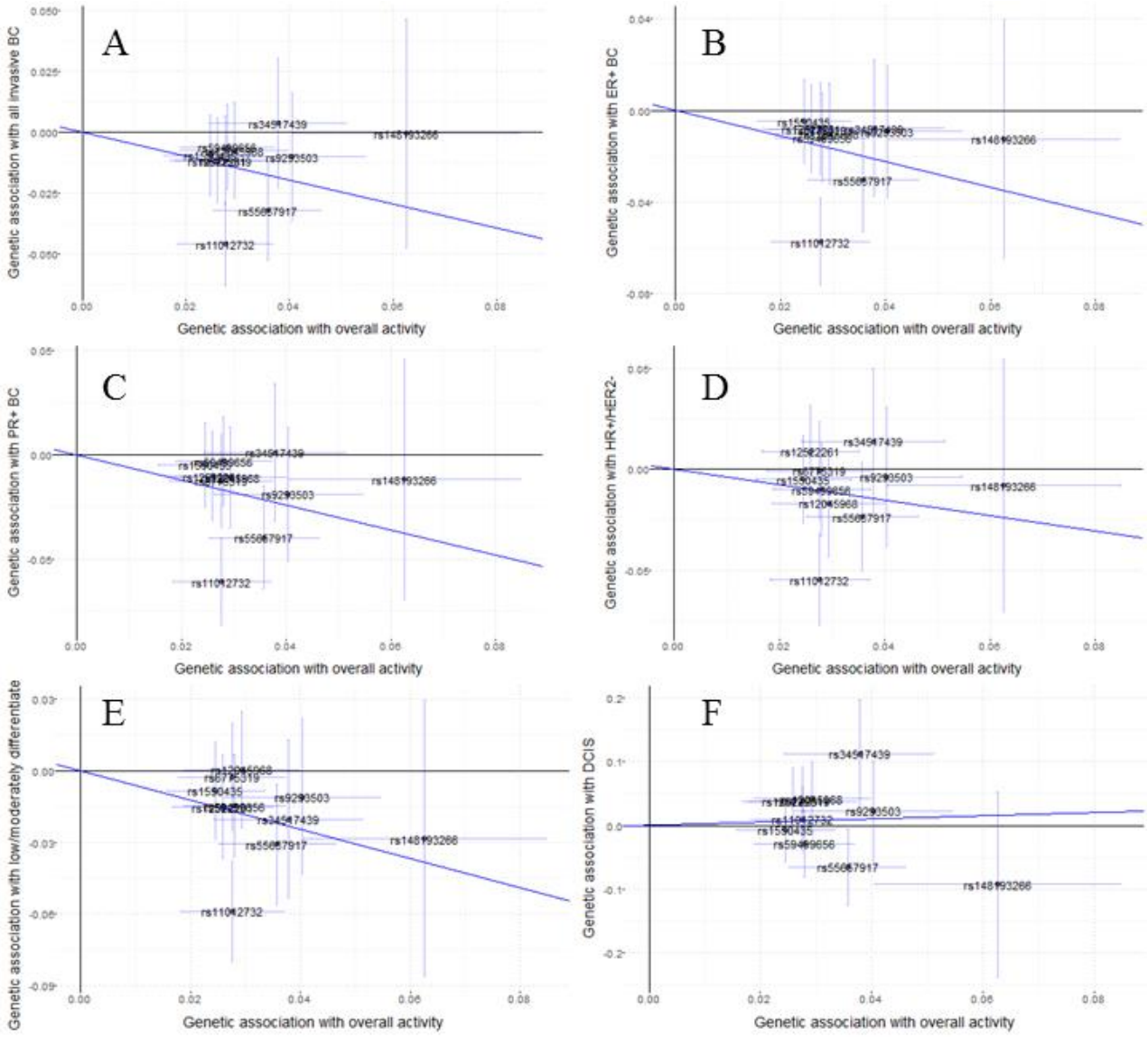
Legend: (A) all invasive breast cancers; (B) ER+; (C) PR+; (D) HR+/HER2-; (E) triple negative; (F) HR-; (G) well/moderately differentiated cancers; (H) DCIS.

Figure S3. Forest plots of individual SNP causal effects on outcomes with suspected pleiotropy: Association between single genetic variants predicting (at $p<5x10^{-8}$) overall physical activity (per standard deviation) and risk of breast cancer



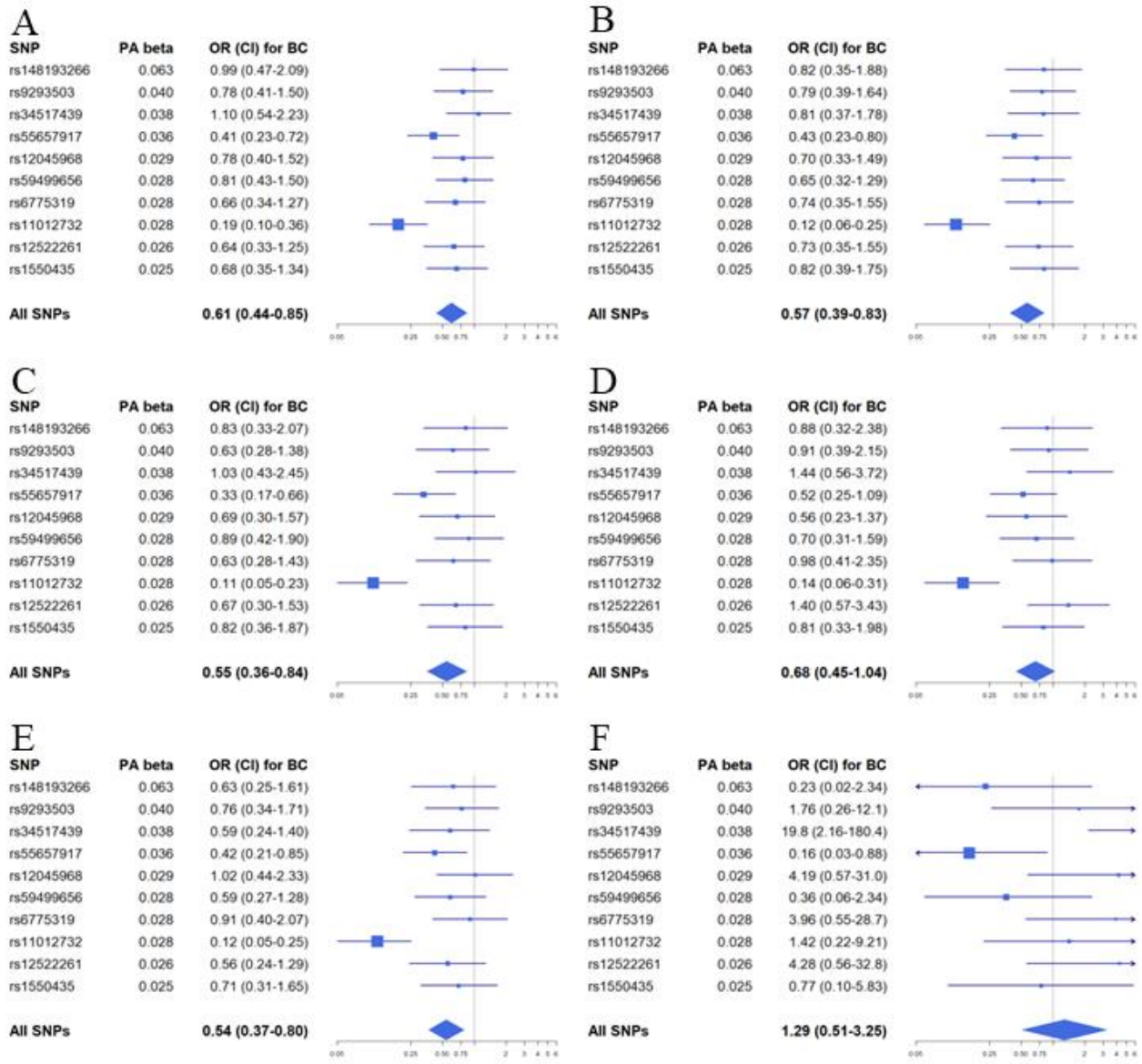
Legend: (A) all invasive breast cancers; (B) ER+; (C) PR+; (D) HR+/HER2-; (E) triple negative; (F) HR-; (G) well/moderately differentiated cancers; (H) DCIS. BC = breast cancer; CI = 95% confidence interval; OR = odds ratio; PA beta = effect on physical activity in prior GWAS. Associations for each SNP were estimated by Mendelian randomization (Wald ratio technique). Box size represents precision.

Figure S4. Scatter plots of SNP associations with exposure (overall activity; SNPs associated at $p<5x10^{-7}$ (7, 8)) and outcome, for analyses with suspected pleiotropy



Legend: (A) all invasive breast cancers; (B) ER+; (C) PR+; (D) HR+/HER2-; (E) well/moderately differentiated cancers; (F) DCIS.

Figure S5. Forest plots of individual SNP causal effects on outcomes with suspected pleiotropy: Association between single genetic variants predicting (at $p<5x10^{-7}$) overall physical activity (per standard deviation) and risk of breast cancer



Legend: (A) all invasive breast cancers; (B) ER+; (C) PR+; (D) HR+/HER2-; (E) well/moderately differentiated cancers; (F) DCIS. BC = breast cancer; CI = 95% confidence interval; OR = odds ratio; PA beta = effect on physical activity in prior GWAS. Associations for each SNP were estimated by Mendelian randomization (Wald ratio technique). Box size represents precision.

Figure S6. Scatter plot of SNP associations with exposure (self-reported vigorous activity (7)) and in situ cancers (analysis with suspected pleiotropy)

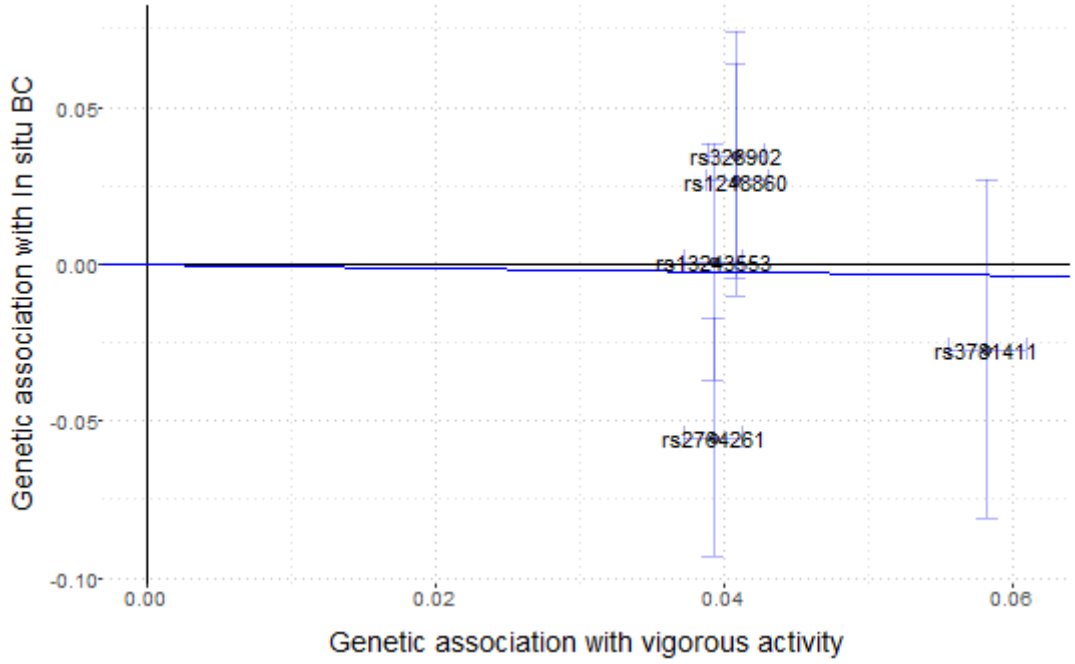
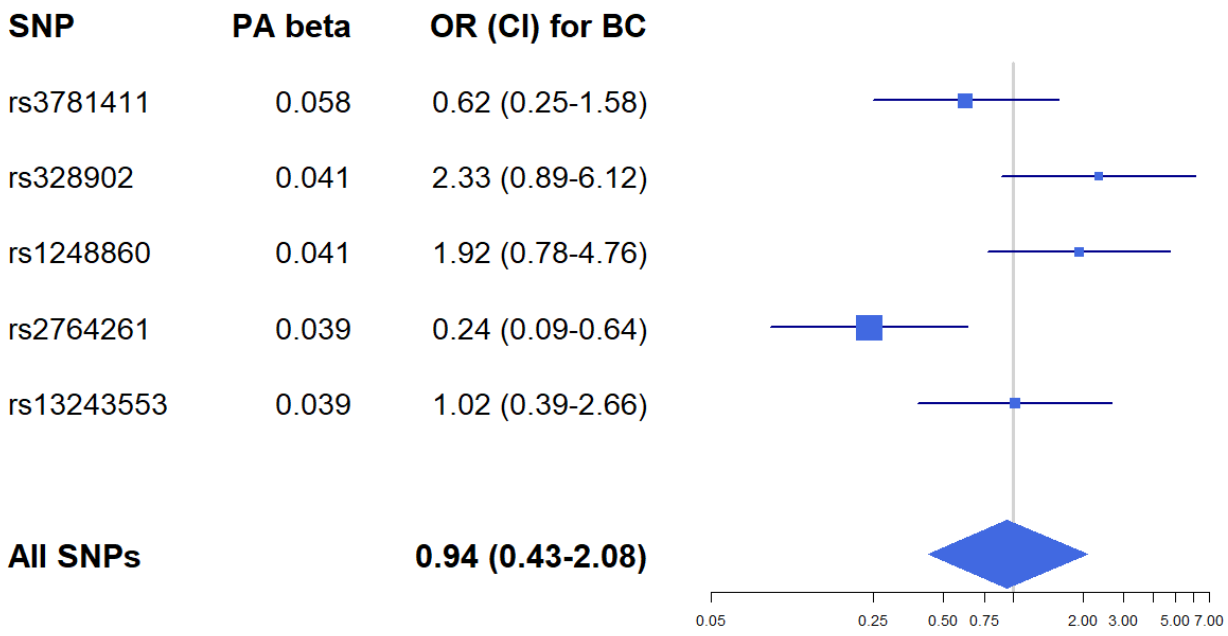


Figure S7. Forest plot of individual SNP causal effects on risk of in situ cancers (suspected pleiotropy): Association between single genetic variants predicting self-reported vigorous physical activity (≥ 3 vs. 0 days/week) and risk of in situ cancers



Note: BC = breast cancer; CI = 95% confidence interval; OR = odds ratio; PA beta = effect on vigorous physical activity in prior GWAS. Associations for each SNP were estimated by Mendelian randomization (Wald ratio technique). Box size represents precision.

Figure S8. Scatter plot of SNP associations with exposure (sedentary time (5)) and PR+ cancers (analysis with possible pleiotropy)

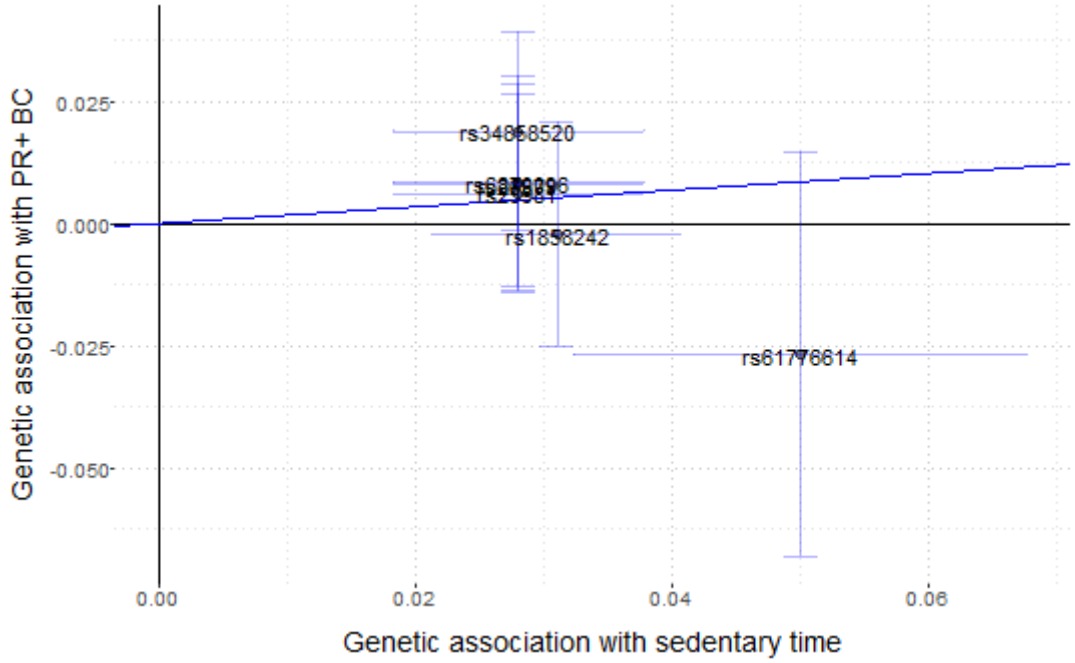
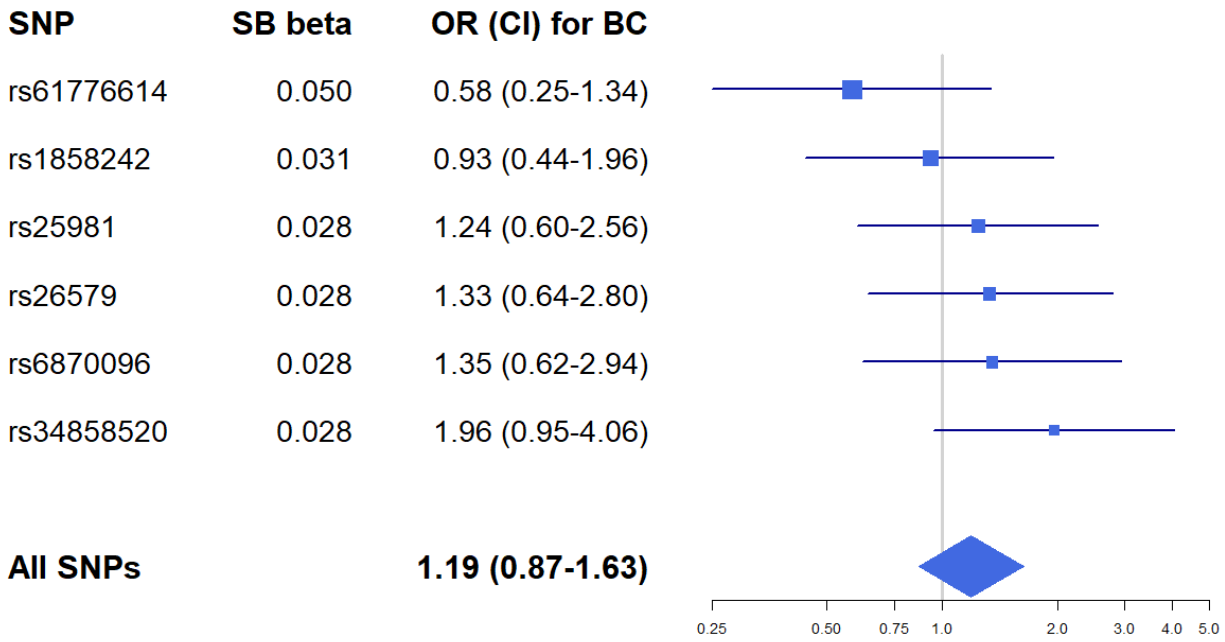


Figure S9. Forest plot of individual SNP causal effects: Association between single genetic variants predicting sedentary time (per standard deviation) and risk of PR+ cancers (possible pleiotropy)



Note: BC = breast cancer; CI = 95% confidence interval; OR = odds ratio; SB beta = effect on sedentary time in prior GWAS. Associations for each SNP were estimated by Mendelian randomization (Wald ratio technique). Box size represents precision.

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