

SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of 12 established SNPs for BF% in the NHS and HPFS

SNP	Chromosome	Nearest gene	BF% increasing allele/other allele	Effect size (β)		Frequency of Effect allele, %	
				Women	Men	NHS	HPFS
rs543874	1	<i>SEC16B</i>	G/A	0.037	0.028	0.21	0.19
rs2943652	2	<i>IRS1</i>	C/T	0.023	0.046	0.36	0.35
rs6755502	2	<i>TMEM18</i>	C/T	0.052	0.027	0.82	0.81
rs6738627	2	<i>COBLL1</i>	A/G	0.026	0.035	0.36	0.35
rs693839	13	<i>SPRY2</i>	C/T	0.021	0.034	0.31	0.32
rs1558902	16	<i>FTO</i>	A/T	0.050	0.051	0.42	0.44
rs4788099	16	<i>TUFM</i>	G/A	0.024	0.032	0.39	0.37
rs9906944	17	<i>IGF2BP1</i>	C/T	0.036	0.025	0.66	0.66
rs6567160	18	<i>MC4R</i>	C/T	0.029	0.042	0.24	0.24
rs6857	19	<i>TOMM40</i>	C/T	0.058	0.035	0.87	0.89
rs757318	19	<i>CRTC1</i>	C/A	0.037	-	0.52	-
rs3761445	22	<i>PLA2G6</i>	G/A	-	0.037	-	0.40

Allele coding based on the forward strand. Effect allele is the one associated with higher BF%; and other is the reference allele.

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Supplementary Table 2. Characteristics of 77 established SNPs for BMI in the NHS and HPFS

SNP	Chromosome	Nearest gene	BMI increasing allele/other allele	Effect size (β)	Frequency of Effect allele, %	
					NHS	HPFS
rs657452	1	<i>AGBL4</i>	A/G	0.023	0.38	0.37
rs2820292	1	<i>NAV1</i>	C/A	0.020	0.53	0.52
rs11583200	1	<i>ELAVL4</i>	C/T	0.018	0.39	0.37
rs543874	1	<i>SEC16B</i>	G/A	0.048	0.21	0.19
rs3101336	1	<i>NEGR1</i>	C/T	0.033	0.63	0.64
rs12566985	1	<i>FPGT-TNNI3K</i>	G/A	0.024	0.43	0.43
rs17024393	1	<i>GNAT2</i>	C/T	0.066	0.03	0.03
rs11165643	1	<i>PTBP2</i>	T/C	0.022	0.59	0.58
rs12401738	1	<i>FUBP1</i>	A/G	0.021	0.34	0.32
rs7599312	2	<i>ERBB4</i>	G/A	0.022	0.73	0.74
rs11126666	2	<i>KCNK3</i>	A/G	0.021	0.27	0.26
rs1528435	2	<i>UBE2E3</i>	T/C	0.018	0.63	0.62
rs11688816	2	<i>EHP1</i>	G/A	0.017	0.51	0.48
rs13021737	2	<i>TMEM18</i>	G/A	0.060	0.82	0.81
rs10182181	2	<i>ADCY3</i>	G/A	0.031	0.47	0.47
rs1016287	2	<i>FLJ30838</i>	T/C	0.023	0.29	0.30
rs2121279	2	<i>LRP1B</i>	T/C	0.025	0.13	0.14
rs2365389	3	<i>FHIT</i>	C/T	0.020	0.59	0.60
rs16851483	3	<i>RASA2</i>	T/G	0.048	0.06	0.07
rs6804842	3	<i>RARB</i>	G/A	0.019	0.57	0.59
rs3849570	3	<i>GBE1</i>	A/C	0.019	0.34	0.32
rs1516725	3	<i>ETV5</i>	C/T	0.045	0.87	0.86
rs13078960	3	<i>CADM2</i>	G/T	0.030	0.20	0.22
rs17001654	4	<i>SCARB2</i>	G/C	0.031	0.16	0.17
rs11727676	4	<i>HHIP</i>	T/C	0.036	0.92	0.91
rs10938397	4	<i>GNPDA2</i>	G/A	0.040	0.44	0.44
rs13107325	4	<i>SLC39A8</i>	T/C	0.048	0.07	0.08
rs2112347	5	<i>POC5</i>	T/G	0.026	0.64	0.63
rs13191362	6	<i>PARK2</i>	A/G	0.028	0.88	0.88
rs2033529	6	<i>TDRG1</i>	G/A	0.019	0.28	0.29
rs9400239	6	<i>FOXO3</i>	C/T	0.019	0.70	0.70
rs2207139	6	<i>TFAP2B</i>	G/A	0.045	0.17	0.17
rs205262	6	<i>C6orf106</i>	G/A	0.022	0.27	0.28
rs1167827	7	<i>HIP1</i>	G/A	0.020	0.57	0.57
rs2245368	7	<i>PMS2L11</i>	C/T	0.032	0.16	0.16

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rs2033732	8	<i>RALYL</i>	C/T	0.019	0.75	0.75
rs17405819	8	<i>HNF4G</i>	T/C	0.022	0.70	0.70
rs1928295	9	<i>TLR4</i>	T/C	0.019	0.56	0.54
rs4740619	9	<i>C9orf93</i>	T/C	0.018	0.44	0.46
rs10733682	9	<i>LMX1B</i>	A/G	0.017	0.49	0.49
rs6477694	9	<i>EPB41L4B</i>	C/T	0.017	0.34	0.33
rs10968576	9	<i>LINGO2</i>	G/A	0.025	0.31	0.31
rs7903146	10	<i>TCF7L2</i>	C/T	0.023	0.70	0.70
rs17094222	10	<i>HIF1AN</i>	C/T	0.025	0.21	0.22
rs11191560	10	<i>NT5C2</i>	C/T	0.031	0.09	0.09
rs7899106	10	<i>GRID1</i>	G/A	0.040	0.05	0.05
rs12286929	11	<i>CADM1</i>	G/A	0.022	0.47	0.47
rs2176598	11	<i>HSD17B12</i>	T/C	0.020	0.25	0.25
rs11030104	11	<i>BDNF</i>	A/G	0.041	0.79	0.78
rs3817334	11	<i>MTCH2</i>	T/C	0.026	0.41	0.41
rs4256980	11	<i>TRIM66</i>	G/C	0.021	0.64	0.63
rs11057405	12	<i>CLIP1</i>	G/A	0.031	0.90	0.92
rs7138803	12	<i>BCDIN3D</i>	A/G	0.032	0.38	0.40
rs12429545	13	<i>OLFM4</i>	A/G	0.033	0.13	0.13
rs12016871	13	<i>MTIF3</i>	T/C	0.030	0.19	0.18
rs10132280	14	<i>STXBP6</i>	C/A	0.023	0.69	0.67
rs12885454	14	<i>PRKD1</i>	C/A	0.021	0.66	0.59
rs7141420	14	<i>NRXN3</i>	T/C	0.024	0.53	0.48
rs11847697	14	<i>PRKD1</i>	T/C	0.021	0.05	0.04
rs3736485	15	<i>DMXL2</i>	A/G	0.018	0.46	0.45
rs16951275	15	<i>MAP2K5</i>	T/C	0.031	0.77	0.75
rs758747	16	<i>NLRC3</i>	T/C	0.023	0.27	0.29
rs9925964	16	<i>KAT8</i>	A/G	0.019	0.63	0.61
rs2650492	16	<i>SBK1</i>	A/G	0.021	0.32	0.32
rs1558902	16	<i>FTO</i>	A/T	0.082	0.42	0.44
rs3888190	16	<i>ATP2A1</i>	A/C	0.031	0.39	0.37
rs12446632	16	<i>GPRC5B</i>	G/A	0.040	0.86	0.86
rs1000940	17	<i>RABEP1</i>	G/A	0.019	0.28	0.28
rs12940622	17	<i>RPTOR</i>	G/A	0.018	0.57	0.58
rs7243357	18	<i>GRP</i>	T/G	0.022	0.83	0.83
rs6567160	18	<i>MC4R</i>	C/T	0.056	0.24	0.24
rs1808579	18	<i>C18orf8</i>	C/T	0.017	0.46	0.44
rs17724992	19	<i>PGPEP1</i>	A/G	0.019	0.74	0.73
rs2287019	19	<i>QPCTL</i>	C/T	0.036	0.82	0.82

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rs3810291	19	<i>ZC3H4</i>	A/G	0.028	0.32	0.33
rs2075650	19	<i>TOMM40</i>	A/G	0.026	0.88	0.90
rs29941	19	<i>KCTD15</i>	G/A	0.018	0.68	0.68

Allele coding based on the forward strand. Effect allele is the one associated with higher BMI; and other is the reference allele.

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Supplementary Table 3. Relationships of the BF%-GRS, the BMI-GRS, and physical activity with body weight at the end of each 4-year interval and weight changes every 4 years in the two prospective cohorts

Variable	Attained weight at the end of each 4-year interval, kg*		Change in weight every 4 years, kg†	
	$\beta \pm SE$	P	$\beta \pm SE$	P
BF%-GRS per additional 10-risk allele				
NHS	4.85 ± 0.67	< 0.001	0.14 ± 0.09	0.13
HPFS	4.18 ± 0.77	< 0.001	0.17 ± 0.09	0.077
Pooled results‡	4.56 ± 0.51	< 0.001	0.16 ± 0.07	0.020
BMI-GRS per additional 10-risk allele				
NHS	3.30 ± 0.26	< 0.001	0.04 ± 0.04	0.22
HPFS	2.21 ± 0.32	< 0.001	0.07 ± 0.04	0.096
Pooled results‡	2.86 ± 0.20	< 0.001	0.06 ± 0.03	0.043
Physical activity per additional 10-MET-h/wk§				
NHS	-0.77 ± 0.06	< 0.001	-0.11 ± 0.01	< 0.001
HPFS	-0.20 ± 0.03	< 0.001	-0.07 ± 0.01	< 0.001
Pooled results‡	-0.34 ± 0.03	< 0.001	-0.08 ± 0.01	< 0.001

*Results were adjusted for age and genotyping source.

†Results were adjusted for age, genotyping source, and baseline BMI (quintile) at the beginning of each 4-year interval.

‡Results for the two cohorts were pooled by means of inverse-variance-weighted fixed effects meta-analysis.

§Results are attained weight at the end of each 4-year interval associated with baseline physical activity at the beginning of each 4-year interval; and change in weight associated with change in physical activity within each 4-year interval.

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Supplementary Table 4. Weight change per 10-risk allele increment of the BF%-GRS every 4 years, according to quartiles of change in physical activity*

Cohort	Change in physical activity, MET-h/wk				P for interaction
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
NHS	0.48 ± 0.19	-0.23 ± 0.22	0.31 ± 0.22	0.17 ± 0.20	0.030
HPFS	0.84 ± 0.23	0.11 ± 0.23	-0.06 ± 0.21	-0.21 ± 0.23	0.002
Pooled results†	0.63 ± 0.15	-0.08 ± 0.16	0.12 ± 0.15	0.01 ± 0.15	0.001

*Data are $\beta \pm SE$ (kg), based on 20 years of follow-up (1986-2006) in the NHS and HPFS. Results were adjusted for age, genotyping source, baseline BMI (quintiles) and lifestyle factors at the beginning of each 4-year interval: physical activity (quartiles), smoking status (never, former, current), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, ≥ 15 g/d), total energy intake (quintiles), and AHEI score (quintiles); and concurrent changes in lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current), alcohol intake (quintiles), total energy intake (quintiles), and AHEI score (quintiles).

†Results for the two cohorts were pooled by means of inverse-variance-weighted fixed effects meta-analysis.

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Supplementary Table 5. Weight change per 10-risk allele increment of the BMI-GRS every 4 years, according to quartiles of change in physical activity*

Cohort	Change in physical activity, MET-h/wk				P for interaction
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
NHS	0.04 ± 0.08	0.01 ± 0.09	0.04 ± 0.09	0.05 ± 0.08	0.24
HPFS	0.17 ± 0.10	0.11 ± 0.09	0.08 ± 0.09	-0.02 ± 0.09	0.048
Pooled results†	0.09 ± 0.06	0.06 ± 0.06	0.06 ± 0.06	0.02 ± 0.06	0.071

*Data are $\beta \pm SE$ (kg), based on 20 years of follow-up (1986-2006) in the NHS and HPFS. Results were adjusted for age, genotyping source, baseline BMI (quintiles) and lifestyle factors at the beginning of each 4-year interval: physical activity (quartiles), smoking status (never, former, current), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, ≥ 15 g/d), total energy intake (quintiles), and AHEI score (quintiles); and concurrent changes in lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current), alcohol intake (quintiles), total energy intake (quintiles), and AHEI score (quintiles).

†Results for the two cohorts were pooled by means of inverse-variance-weighted fixed effects meta-analysis.

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Supplementary Table 6. Interaction effect of the BF%-GRS and BMI-GRS with physical activity on BMI change every 4 years*

Cohort	Physical activity in quartile scale		Physical activity in quantitative scale	
	$\beta \pm SE$	P for interaction	$\beta \pm SE$	P for interaction
BF%-GRS				
NHS	-0.005 \pm 0.002	0.025	-0.007 \pm 0.004	0.100
HPFS	-0.013 \pm 0.004	0.001	-0.003 \pm 0.001	0.008
Pooled results [†]	-0.007 \pm 0.002	< 0.001	-0.003 \pm 0.001	0.003
BMI-GRS				
NHS	-0.010 \pm 0.009	0.289	-0.011 \pm 0.009	0.229
HPFS	-0.036 \pm 0.016	0.027	-0.007 \pm 0.004	0.079
Pooled results [†]	-0.016 \pm 0.008	0.045	-0.008 \pm 0.004	0.037

*Data are $\beta \pm SE$ (kg/m²), based on 20 years of follow-up (1986-2006) in the NHS and HPFS. Results were adjusted for age, genotyping source, baseline BMI (quintiles) and lifestyle factors at the beginning of each 4-year interval: physical activity (quartiles), smoking status (never, former, current), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, ≥ 15 g/d), total energy intake (quintiles), and AHEI score (quintiles); and concurrent changes in lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current), alcohol intake (quintiles), total energy intake (quintiles), and AHEI score (quintiles).

[†]Results for the two cohorts were pooled by means of inverse-variance-weighted fixed effects meta-analysis.

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Supplementary Table 7. BMI change per 10-risk allele increment of the BMI-GRS (based on 42 BMI-SNPs with effect sizes comparable to that of the BF%-SNPs) every 4 years, according to quartiles of change in physical activity*

Cohort	Change in physical activity, MET-h/wk				P for interaction
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
NHS					
Model 1†	0.04 ± 0.04	-0.01 ± 0.05	0.01 ± 0.05	0.02 ± 0.05	0.145
Model 2‡	0.03 ± 0.04	-0.02 ± 0.05	0.01 ± 0.05	0.02 ± 0.05	0.158
HPFS					
Model 1†	0.13 ± 0.05	0.07 ± 0.05	0.02 ± 0.05	-0.01 ± 0.05	0.013
Model 2‡	0.13 ± 0.05	0.07 ± 0.05	0.02 ± 0.05	0.01 ± 0.04	0.019
Pooled results§					
Model 1†	0.08 ± 0.03	0.03 ± 0.03	0.02 ± 0.03	0.01 ± 0.03	0.031
Model 2‡	0.08 ± 0.03	0.03 ± 0.03	0.01 ± 0.03	0.01 ± 0.03	0.040

*Data are $\beta \pm SE$ (kg/m^2), based on 20 years of follow-up (1986-2006) in the NHS and HPFS. The BMI-GRS was calculated based on 42 BMI-SNPs with effect sizes comparable to that of the BF%-SNPs ($\beta \geq 0.023$).

†Model 1 was adjusted for age, genotyping source, and baseline BMI (quintiles) at the beginning of each 4-year interval.

‡Model 2 was further adjusted for baseline lifestyle factors at the beginning of each 4-year interval: physical activity (quartiles), smoking status (never, former, current), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, ≥ 15 g/d), total energy intake (quintiles), and AHEI score (quintiles); and concurrent changes in lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current), alcohol intake (quintiles), total energy intake (quintiles), and AHEI score (quintiles).

§Results for the two cohorts were pooled by means of inverse-variance-weighted fixed effects meta-analysis.

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Supplementary Table 8. BMI change per 1-risk allele increment of the GRS (based on 5 BMI-SNPs overlapping with the BF%-SNPs) every 4 years, according to quartiles of change in physical activity*

Cohort	Change in physical activity, MET-h/wk				P for interaction
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
NHS					
Model 1†	0.02 ± 0.01	-0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.425
Model 2‡	0.02 ± 0.01	-0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.431
HPFS					
Model 1†	0.03 ± 0.01	0.01 ± 0.01	-0.01 ± 0.01	0.01 ± 0.01	0.027
Model 2‡	0.03 ± 0.01	0.02 ± 0.01	-0.02 ± 0.01	0.01 ± 0.01	0.039
Pooled results§					
Model 1†	0.03 ± 0.01	0.001 ± 0.01	0.00 ± 0.01	0.01 ± 0.01	0.034
Model 2‡	0.03 ± 0.01	0.003 ± 0.01	0.001 ± 0.01	0.01 ± 0.01	0.045

*Data are $\beta \pm SE$ (kg/m^2), based on 20 years of follow-up (1986-2006) in the NHS and HPFS. The GRS was calculated based on 5 BMI-SNPs overlapping with the BF% SNPs (*TOMM40* rs2075650, *SEC16B* rs543874, *MC4R* rs6567160, *TMEM18* rs13021737, and *FTO* rs1558902).

†Model 1 was adjusted for age, genotyping source, and baseline BMI (quintiles) at the beginning of each 4-year interval.

‡Model 2 was further adjusted for baseline lifestyle factors at the beginning of each 4-year interval: physical activity (quartiles), smoking status (never, former, current), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, ≥ 15 g/d), total energy intake (quintiles), and AHEI score (quintiles); and concurrent changes in lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current), alcohol intake (quintiles), total energy intake (quintiles), and AHEI score (quintiles).

§Results for the two cohorts were pooled by means of inverse-variance-weighted fixed effects meta-analysis.

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Supplementary Table 9. Main associations of the two GRSs and their interactions with change in physical activity on 4-year BMI change in participants younger than 65 years or in participants who had never smoked

Subgroup	Sample size	Main effect on BMI change, kg/m ² *			Interaction on BMI change, kg/m ² †		
		β	SE	P	β	SE	P
Participants younger than 65 years							
BF%-GRS							
NHS	9210	0.05	0.04	0.27	-0.07	0.03	0.023
HPFS	4546	0.10	0.04	0.027	-0.06	0.02	< 0.001
Pooled results‡		0.07	0.03	0.019	-0.06	0.02	< 0.001
BMI-GRS							
NHS	9210	0.03	0.02	0.15	-0.01	0.01	0.51
HPFS	4546	0.03	0.01	0.080	-0.01	0.002	0.029
Pooled results‡		0.03	0.01	0.024	-0.01	0.002	0.024
Participants who had never smoked							
BF%-GRS							
NHS	4131	0.06	0.05	0.23	-0.05	0.03	0.13
HPFS	2502	0.07	0.04	0.094	-0.02	0.01	0.047
Pooled results‡		0.07	0.03	0.040	-0.02	0.01	0.022
BMI-GRS							
NHS	4131	-0.01	0.02	0.46	-0.01	0.01	0.17
HPFS	2502	0.04	0.02	0.069	0.003	0.003	0.33
Pooled results‡		0.01	0.01	0.42	-0.001	0.003	0.80

Data are based on 20 years of follow-up (1986-2006) in the NHS and HPFS.

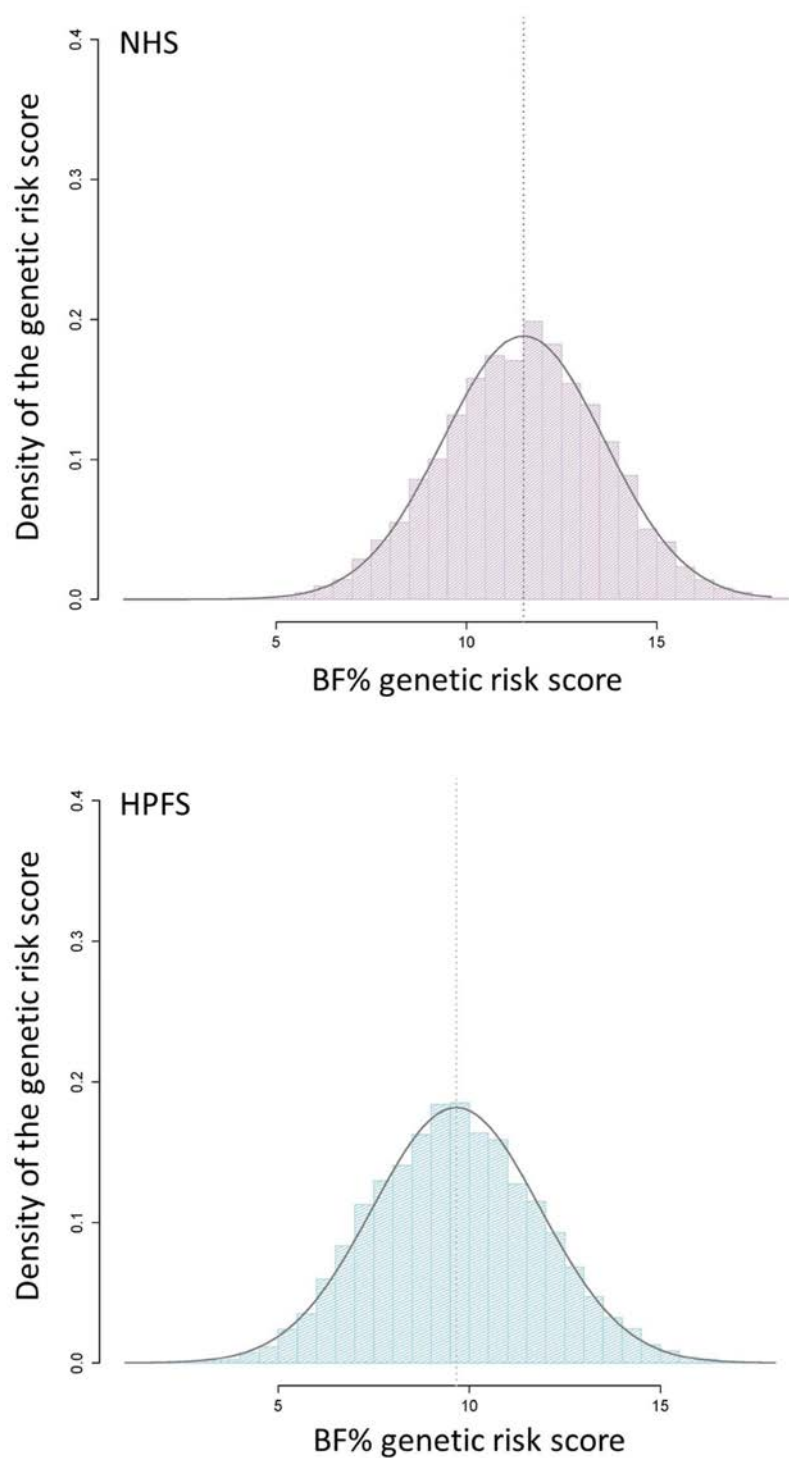
*Results are change in BMI per 10-risk allele increment of the GRS, with adjustment for age, genotyping source, and baseline BMI (quintile) at the beginning of each 4-year interval.

†Results are differences in genetic effect (each additional 10-risk allele of the GRS) on change in BMI associated with each increment of 10-MET-h/wk physical activity, with adjustment for age, genotyping source, baseline BMI (quintiles) and lifestyle factors at the beginning of each 4-year interval: physical activity (quartiles), smoking status (never, former, current), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, ≥15 g/d), total energy intake (quintiles), and AHEI score (quintiles); and concurrent changes in lifestyle factors: smoking status (never to never, never to current, past to past, past to current, current to past, current to current), alcohol intake (quintiles), total energy intake (quintiles), and AHEI score (quintiles).

‡Results for the two cohorts were pooled by means of inverse-variance-weighted fixed effects meta-analysis.

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Supplementary Figure 1. Distribution of the BF%-GRS in the NHS and HPFS



The mean scores differed among the two cohorts, due to the sex-specific effect sizes (β coefficients) used to weight each SNP in score calculation.

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Supplementary Figure 2. Distribution of the BMI-GRS in the NHS and HPFS

