Figure S1. Empirical pathways of pro-inflammatory SNPs, phenotypes, and CRC risk, interplaying with obesity status and obesity-lifestyle factors (Note: pathways in red and blue lines were tested in our previous GWA G×E and current post-GWA analyses; yellow lines reflect conceptual framework. BMI, body mass index; CRC, colorectal cancer; CRP, C-reactive protein; G×E, gene-environment interaction; GWA, genome-wide analysis; IL-6, interleukin-6; SNP, single-nucleotide polymorphism; WHR, waist-to-hip ratio; WST, waist circumference).

Table S1A. Allele frequencies (total n=10,798) of the 87 SNPs associated with pro-inflammatory phenotypes from our previous GWA analysis

Chr	Position¥	Gene	SNP	Allele		Alt Allele Frequency					
				Ref	Alt	AS264	GARNET	GECCOCYTO	GECCOINIT	HIPFX	WHIMS
						n=1,603	n=2,382	n=1,177	n=216	n=1,909	n=3,511
1	159652939	CRPP1	rs2592887	C	T	0.41	0.41	0.41	0.38	0.40	0.39
1	159653599	CRPP1	rs1470515	C	T	0.40	0.39	0.40	0.37	0.38	0.38
1	159655726	CRPP1	rs2592902	G	T	0.40	0.39	0.40	0.37	0.38	0.38
1	159665921	CRPP1	rs2808624	C	G	0.40	0.39	0.40	0.36	0.38	0.38
1	159668984	CRPP1	rs11265257	C	T	0.40	0.39	0.40	0.36	0.38	0.38
1	159674933	CRPP1	rs876537	C	T	0.40	0.39	0.40	0.36	0.38	0.38
1	159676011	CRPP1	rs2808628	G	A	0.34	0.34	0.34	0.32	0.33	0.33
1	159676796	CRPP1	rs2808629	G	A	0.34	0.34	0.35	0.32	0.33	0.33
1	159678816	CRPP1/CRP	rs2794520	C	T	0.34	0.34	0.34	0.32	0.33	0.33
1	159682233	CRP	rs1205	C	T	0.34	0.34	0.34	0.32	0.33	0.33
1	159684665	CRP	rs3091244	G	A	0.32	0.36	0.32	0.34	0.34	0.37
1	159689388	CRP	rs2027471	T	A	0.35	0.35	0.35	0.33	0.33	0.33
1	159691559	CRP	rs1341665	G	A	0.35	0.35	0.35	0.33	0.33	0.33
1	159693605	CRP	rs2211320	G	A	0.33	0.33	0.33	0.31	0.31	0.32
1	159694779	CRP	rs7551731	T	C	0.34	0.34	0.34	0.32	0.32	0.33
1	159698549	CRP	rs7553007	G	A	0.34	0.34	0.34	0.31	0.32	0.32
1	159699249	CRP	rs4546916	G	T	0.34	0.34	0.34	0.31	0.32	0.32
1	159703442	CRP	rs4287174	T	A	0.34	0.34	0.34	0.31	0.32	0.32
1	159703462	CRP	rs4428887	A	G	0.35	0.34	0.35	0.32	0.33	0.33
1	159706230	CRP	rs12037186	A	G	0.33	0.33	0.33	0.30	0.31	0.32
1	159708825	CRP/RP11-419N10.5	rs12042360	G	A	0.16	0.17	0.18	0.16	0.16	0.15
1	159713844	CRP/RP11-419N10.5	rs12049404	C	T	0.16	0.17	0.18	0.16	0.16	0.15
1	159717162	CRP/RP11-419N10.5	rs11588887	G	A	0.16	0.17	0.18	0.16	0.16	0.15
9	118330052	DEC1	rs149109490	T	C	0.99	0.99	0.99	0.99	0.99	0.99
12	121380544	HNF1A-AS1	rs2649999	T	C	NA	0.66	0.67	NA	0.68	0.65
12	121384495	HNF1A-AS1	rs11065358	T	C	NA	0.63	0.63	NA	0.64	0.62
12	121388559	HNF1A-AS1	rs1696359	T	C	NA	0.65	0.66	NA	0.67	0.64
12	121388962	HNF1A-AS1	rs2650000	A	C	0.66	0.65	0.66	NA	0.67	0.65
12	121390078	HNF1A-AS1	rs2701194	A	G	NA	0.63	0.65	NA	0.66	0.63
12	121391671	HNF1A-AS1	rs2701175	C	A	0.63	0.61	0.63	NA	0.64	0.61
12	121392040	HNF1A-AS1	rs11065365	G	A	NA	0.55	0.56	NA	0.57	0.54
12	121392341	HNF1A-AS1	rs1732391	C	T	0.66	0.65	0.66	NA	0.67	0.65

12	121397875	HNF1A-AS1	rs6489786	A	G	0.66	0.65	0.66	NA	0.67	0.65
12	121398654	HNF1A-AS1	rs7954039	A	C	0.66	0.65	0.66	NA	0.67	0.65
12	121398657	HNF1A-AS1	rs7954331	G	T	0.66	0.65	0.66	NA	0.67	0.65
12	121403724	HNF1A-AS1	rs7953249	G	A	0.59	0.58	0.59	NA	0.60	0.58
12	121404155	HNF1A-AS1	rs7135337	A	C	0.58	0.57	0.58	NA	0.58	0.57
12	121404584	HNF1A-AS1	rs1920792	C	T	0.51	0.53	0.53	NA	0.51	0.53
12	121405126	HNF1A-AS1	rs2251468	C	A	0.66	0.65	0.66	NA	0.67	0.65
12	121405210	HNF1A-AS1	rs10774579	C	T	0.51	0.53	0.52	NA	0.51	0.53
12	121406293	HNF1A-AS1	rs2393792	A	G	0.50	0.53	0.52	NA	0.51	0.53
12	121406370	HNF1A-AS1	rs2243616	G	T	0.65	0.64	0.65	NA	0.66	0.63
12	121413027	HNF1A-AS1	rs148608463	A	G	0.66	0.65	0.66	NA	0.67	0.65
12	121413345	HNF1A-AS1	rs142632970	G	A	0.68	0.67	0.68	NA	0.69	0.67
12	121414915	HNF1A-AS1	rs2255531	A	G	0.65	0.64	0.65	NA	0.67	0.64
12	121415293	HNF1A-AS1	rs7139079	G	A	0.59	0.58	0.60	NA	0.60	0.58
12	121415390	HNF1A-AS1	rs2464190	C	T	0.58	0.55	0.59	NA	0.58	0.56
12	121416622	HNF1A	rs1169289	G	C	0.57	0.54	0.58	NA	0.57	0.55
12	121416650	HNF1A	rs1169288	C	A	0.68	0.67	0.68	NA	0.69	0.67
12	121416988	HNF1A	rs2244608	G	A	0.68	0.67	0.68	NA	0.70	0.67
12	121419056	HNF1A	rs1169286	C	T	0.58	0.56	0.57	NA	0.59	0.57
12	121419926	HNF1A	rs1169284	C	T	0.68	0.68	0.69	NA	0.70	0.68
12	121420260	HNF1A	rs7979473	A	G	0.60	0.61	0.62	NA	0.61	0.61
12	121420263	HNF1A	rs7979478	A	G	0.60	0.60	0.61	NA	0.61	0.61
12	121420807	HNF1A	rs1183910	A	G	0.69	0.68	0.69	NA	0.70	0.68
12	121423285	HNF1A	rs11065384	T	C	0.68	0.68	0.69	NA	0.70	0.68
12	121423376	HNF1A	rs7970695	G	A	0.62	0.61	0.62	NA	0.63	0.61
12	121423386	HNF1A	rs11065385	A	G	0.69	0.68	0.69	NA	0.70	0.68
12	121423659	HNF1A	rs9738226	A	G	0.62	0.61	0.62	NA	0.63	0.61
12	121423956	HNF1A	rs2393791	C	T	0.62	0.61	0.62	NA	0.63	0.61
12	121424406	HNF1A	rs2393776	G	A	0.62	0.61	0.62	0.60	0.63	0.61
12	121424490	HNF1A	rs2243458	T	C	0.69	0.68	0.69	0.66	0.70	0.68
12	121424574	HNF1A	rs2393775	G	A	0.62	0.61	0.62	0.60	0.63	0.61
12	121424861	HNF1A	rs7310409	A	G	0.62	0.61	0.62	0.59	0.63	0.61
12	121426478	HNF1A	rs1169292	T	C	0.69	0.68	0.69	0.67	0.70	0.68
12	121426594	HNF1A	rs1169294	A	G	0.69	0.68	0.69	0.67	0.70	0.68
12	121431225	HNF1A	rs1169300	A	G	0.70	0.69	0.71	0.69	0.72	0.70
12	121431300	HNF1A	rs1169301	T	C	0.70	0.69	0.71	0.69	0.72	0.70

Chr	Position	Gene	SNP	Ref	Alt						
12	121432603	HNF1A	rs2264782	T	C	0.65	0.63	0.66	0.63	0.66	0.65
12	121434833	HNF1A	rs2259852	A	G	0.65	0.63	0.66	0.63	0.66	0.64
12	121435342	HNF1A	rs2259820	T	C	0.70	0.69	0.71	0.69	0.72	0.70
12	121435427	HNF1A	rs2464196	A	G	0.70	0.69	0.71	0.69	0.72	0.70
12	121435475	HNF1A	rs2464195	A	G	0.65	0.63	0.66	0.63	0.66	0.64
12	121435587	HNF1A	rs2259816	T	G	0.65	0.63	0.66	0.66	0.66	0.64
12	121438311	HNF1A	rs1169306	T	C	0.65	0.63	0.66	0.63	0.66	0.64
12	121438844	HNF1A	rs735396	C	T	0.65	0.63	0.66	0.63	0.66	0.64
12	121439192	HNF1A	rs1169309	T	G	0.65	0.63	0.66	0.66	0.66	0.64
12	121439433	HNF1A	rs1169310	A	G	0.65	0.63	0.66	0.63	0.66	0.64
12	121440731	C12orf43	rs1169311	T	C	0.65	0.63	0.66	0.63	0.66	0.64
12	121441461	C12orf43	rs1169312	T	G	0.65	0.63	0.66	0.63	0.66	0.64
12	121442670	C12orf43	rs1169313	C	T	0.65	0.63	0.65	0.63	0.66	0.64
12	121445808	C12orf43	rs2257962	C	T	0.65	0.63	0.65	0.63	0.66	0.64
12	121450384	C12orf43	rs2254971	C	C	0.63	0.61	0.64	0.60	0.63	0.62
12	121454622	C12orf43	rs1182933	T	C	0.70	0.69	0.71	0.69	0.72	0.70
19	45411941	APOE	rs429358	C	T	0.85	0.87	0.87	NA	0.87	0.86
22	22190785	MAPK1	rs56398890	A	T	0.58	0.56	0.56	0.53	0.57	0.56
22	22202164	MAPK1	rs9607320	T	C	0.59	0.58	0.57	0.53	0.58	0.57

Alt, alternative; Chr, chromosome; GWA, genome-wide association; Ref, reference; SNP, single-nucleotide polymorphism. ¥GRCh 37 coordinated.

Table S1B. Allele frequencies (total n=10,798) of the 65 SNPs associated with pro-inflammatory phenotypes from other GWA studies

Chr	Positions¥	Gene	SNP	Allele		Alt Allele Frequency					
				Ref	Alt	AS264 n=1,603	Garnet n=2,382	Geccocyto n=1,177	Geccoinit n=216	Hipfx n=1,909	Whims n=3,511
1	27180088	ZDHHC18	rs75460349	A	C	0.02	0.03	0.02	0.02	0.03	0.02
1	40036847	PABPC4	rs2293476	G	C	0.21	0.22	0.24	0.25	0.23	0.23
1	40064961	PABPC4/HEYL	rs12037222	G	A	NA	0.22	0.24	0.24	0.23	0.23
1	66085574	LEPR	rs3790439	A	T	0.63	0.63	0.62	0.67	0.63	0.63
1	66102257	LEPR	rs1805096	A	G	0.63	0.62	0.62	0.67	0.63	0.63
1	66161461	LEPR	rs4420065	T	C	0.63	0.62	0.62	0.68	0.63	0.63
1	91530305	ZNF644	rs469772	C	T	0.20	0.20	0.19	0.19	0.18	0.19
1	154426264	IL6R	rs4129267	C	T	0.41	0.40	0.41	0.40	0.40	0.41
1	154426970	IL6R	rs2228145	A	C	0.41	0.40	0.41	0.40	0.41	0.41
1	159683438	CRP	rs1800947	C	G	0.06	0.06	NA	0.06	0.06	0.05

Inflammatory genetic markers and CRC: post-GWAS RSF

1	159684186	CRP	rs1417938	T	A	0.30	0.31	0.31	0.32	0.32	0.32
1	247601595	NLRP3	rs12239046	C	T	0.37	0.37	0.38	0.36	0.37	0.37
1	247612562	NLRP3	rs10925027	C	T	0.40	0.40	NA	0.42	0.40	0.39
2	629881	TMEM18	rs12995480	C	T	0.17	0.18	0.18	0.17	0.17	0.18
2	27730940	GCKR	rs1260326	C	T	0.41	0.41	0.41	NA	0.41	0.40
2	88438050	FABP1	rs4246598	C	A	0.45	0.46	0.45	0.47	0.45	0.46
2	102744854	IL1R1	rs9284725	A	C	0.24	0.25	0.23	0.25	0.25	0.25
2	113838145	IL1F10	rs13409371	G	A	0.39	0.39	0.41	0.43	0.39	0.40
2	113841030	IL1F10	rs6734238	A	G	0.40	0.40	0.42	0.44	0.40	0.40
2	214033530	IKZF2	rs1441169	G	A	0.49	0.49	0.48	0.50	0.48	0.48
3	49891885	TRAIP	rs2352975	C	T	NA	0.69	NA	0.70	0.69	0.69
3	170705693	EIF5A2	rs1514895	A	G	0.30	0.30	0.30	0.27	0.28	0.29
5	131839618	IRF1	rs4705952	A	G	0.25	NA	0.27	0.24	0.25	0.24
5	172191052	DUSP1	rs17658229	T	C	0.04	NA	0.04	0.03	0.04	0.04
6	116314634	FRK	rs12202641	C	T	0.41	NA	0.41	0.41	0.40	0.41
6	117114025	GPRC6A	rs6901250	G	A	0.33	0.32	0.32	0.32	0.33	0.31
6	126851160	CENPW	rs1490384	T	C	0.49	0.51	0.51	0.54	0.47	0.49
6	130371227	L3MBTL3	rs9385532	C	T	0.33	0.31	0.31	0.33	0.32	0.33
7	22759469	IL6	rs1880241	G	A	0.52	0.52	0.50	0.52	0.51	0.51
7	22766645	IL6	rs1800795	G	C	0.43	0.43	0.41	0.40	0.43	0.44
7	36084529	EEPD1	rs2710804	T	C	0.37	0.36	0.39	0.38	0.38	0.38
7	72971231	BCL7B	rs13233571	C	T	0.11	0.13	0.11	0.13	0.12	0.12
8	9183358	PPP1R3B	rs9987289	G	A	0.09	0.09	0.08	0.08	0.09	0.09
8	9183596	PPP1R3B	rs4841132	G	A	0.09	0.09	0.08	0.08	0.09	0.09
8	117007850	TRPS1	rs2064009	T	C	0.42	0.43	0.40	0.39	0.41	0.41
8	126344208	NSMCE2	rs2891677	C	T	0.55	0.54	0.54	0.57	0.55	0.55
9	136142355	ABO	rs643434	G	A	0.36	0.37	0.35	0.31	0.35	0.35
10	91007360	LIPA	rs1051338	T	G	0.30	0.30	0.29	0.28	0.30	0.29
11	13357183	ARNTL	rs10832027	A	G	0.32	0.32	0.31	0.36	0.32	0.32
11	47312892	MADD	rs10838687	T	G	0.21	0.21	0.20	0.23	0.21	0.20
11	60021948	MS4A4A	rs1582763	G	A	0.36	0.38	0.35	0.39	0.36	0.38
11	72496148	STARD10	rs7121935	G	A	0.34	0.37	0.38	NA	0.38	0.38
12	95855385	METAP2	rs11108056	C	G	0.44	0.43	NA	0.44	0.46	0.43
12	103483094	ASCL1	rs10745954	G	A	0.52	0.52	0.50	0.55	0.51	0.52
12	103537266	C12orf42	rs10778215	A	T	0.53	0.53	0.53	0.58	0.52	0.53

Inflammatory genetic markers and CRC: post-GWAS RSF

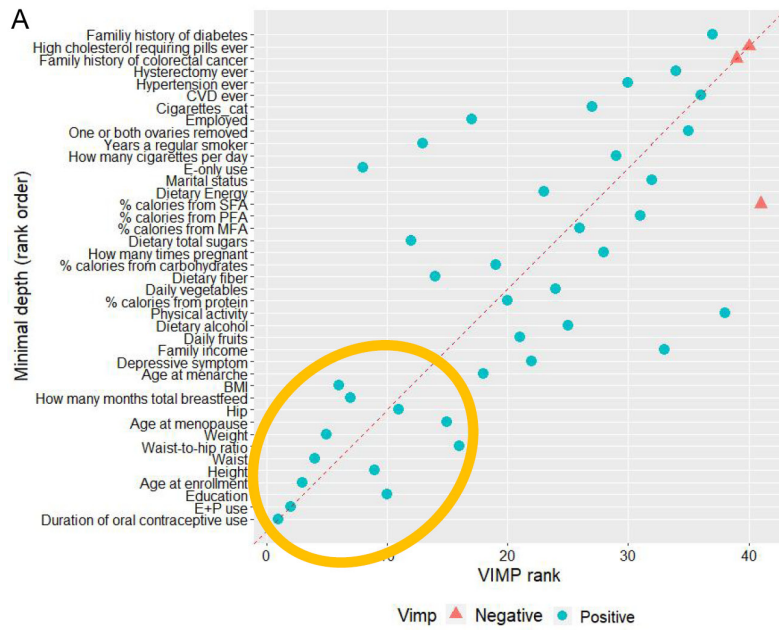| Chr	Position	Gene	SNP	Ref	Alt						
14	73011885	RGS6	rs2239222	A	G	0.36	0.36	0.34	NA	0.36	0.35
14	94838142	SERPINA1/SERPINA2P	rs112635299	G	T	0.02	0.02	0.02	0.03	0.02	0.02
15	51745277	DMXL2	rs4774590	G	A	0.38	0.37	0.39	0.35	0.38	0.39
15	53728154	WDR72	rs1189402	A	G	0.37	0.37	0.39	0.38	0.36	0.38
15	60878030	RORA	rs340005	A	G	0.38	0.37	0.37	0.38	0.39	0.38
15	60894965	RORA	rs340029	T	C	0.39	0.37	0.37	0.38	0.39	0.37
16	53803574	FTO	rs1558902	T	A	0.39	0.41	0.40	0.42	0.40	0.40
17	16097430	NCOR1	rs178810	C	T	NA	0.56	0.57	0.57	0.57	0.56
17	72699833	CD300LF/RAB37	rs10512597	C	T	0.19	0.19	0.18	0.16	0.18	0.19
18	12821593	PTPN2	rs2847281	A	G	0.39	0.39	0.38	0.39	0.40	0.40
18	12841176	PTPN2	rs2852151	G	A	0.39	0.39	0.38	0.39	0.40	0.40
18	55080437	ONECUT2	rs4092465	A	G	0.62	0.63	NA	NA	0.65	0.64
18	57897803	MC4R	rs12960928	T	C	0.26	0.26	0.26	0.26	0.27	0.27
19	45395714	TOMM40	rs157581	T	C	NA	0.21	0.21	NA	0.20	0.21
19	45396144	TOMM40	rs11556505	C	T	0.13	0.13	0.12	NA	0.12	0.14
19	45396219	TOMM40	rs157582	C	T	0.23	0.21	0.20	NA	0.20	0.21
20	43042364	HNF4A	rs1800961	C	T	0.03	0.03	NA	0.04	0.03	0.03
20	62343956	ZGPAT	rs2315008	G	T	0.31	0.32	0.32	0.30	0.31	0.33
21	40465534	PSMG1	rs2836878	G	A	0.27	0.27	0.25	0.28	0.27	0.27
22	39074737	TOMM22	rs6001193	A	G	NA	0.35	0.37	0.30	0.36	0.36

Alt, alternative; Chr, chromosome; GWA, genome-wide association; Ref, reference; SNP, single-nucleotide polymorphism. ¥GRCh 37 coordinated.
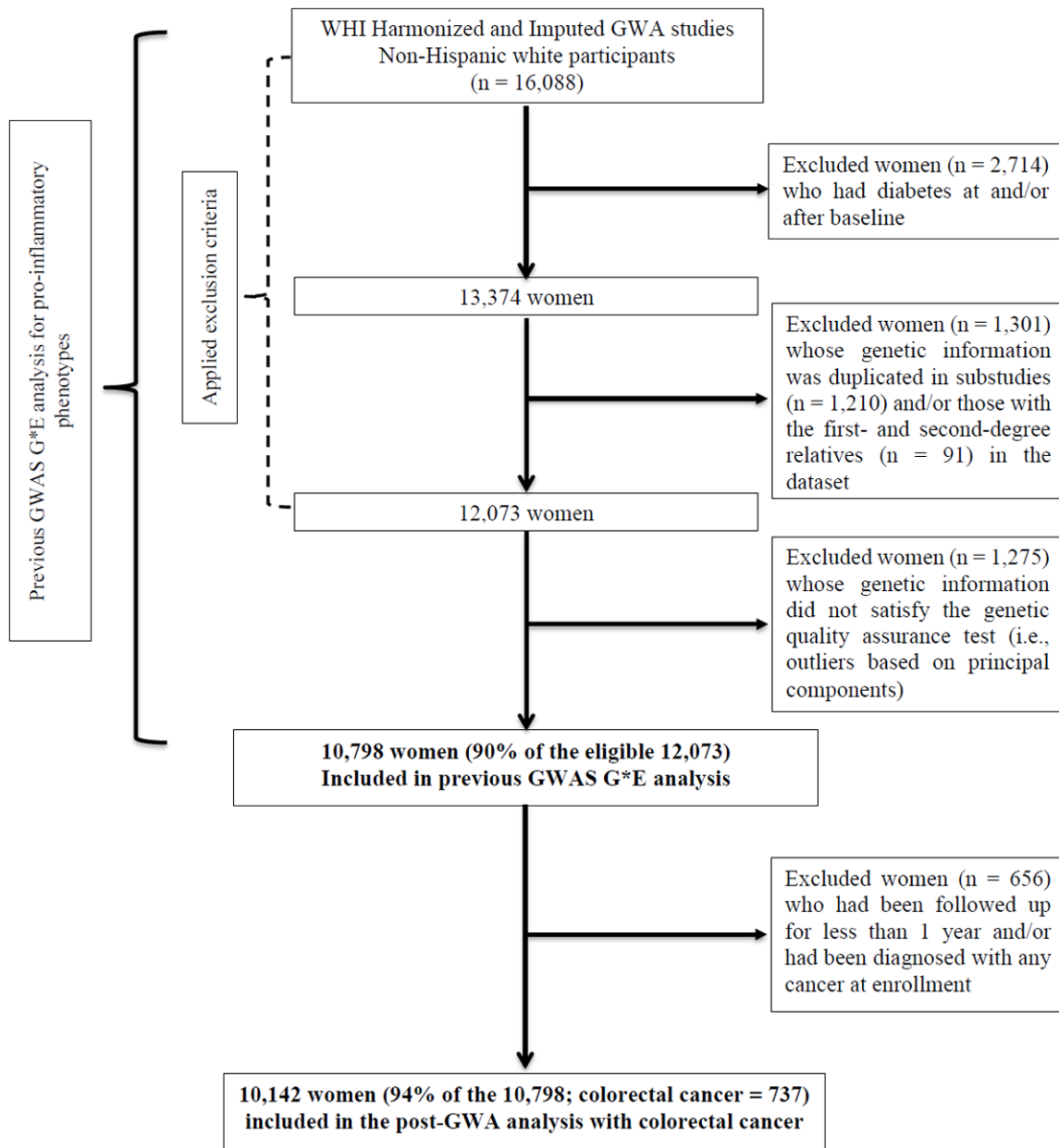
Figure S2. Flow diagram of analytic cohort derived from the previous GWA G×E interaction study. (G×E, gene-environment; GWAS, genome-wide association study; WHI, Women's Health Initiative).

Inflammatory genetic markers and CRC: post-GWAS RSF
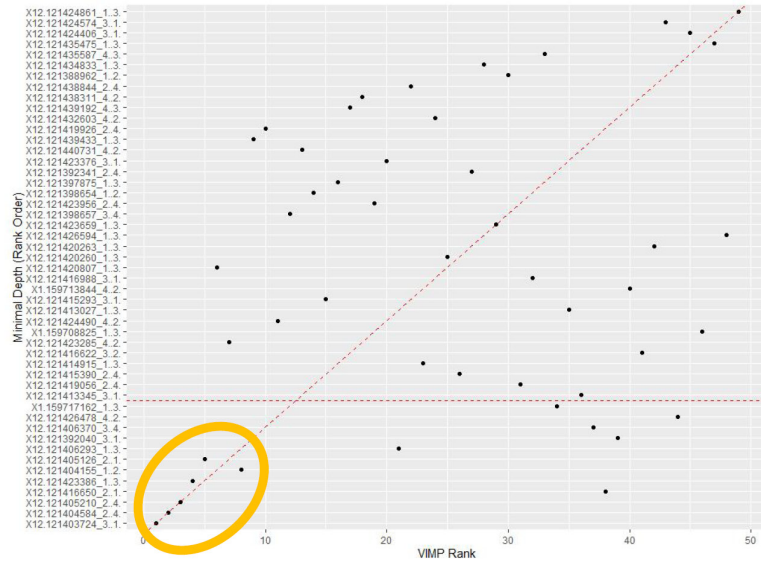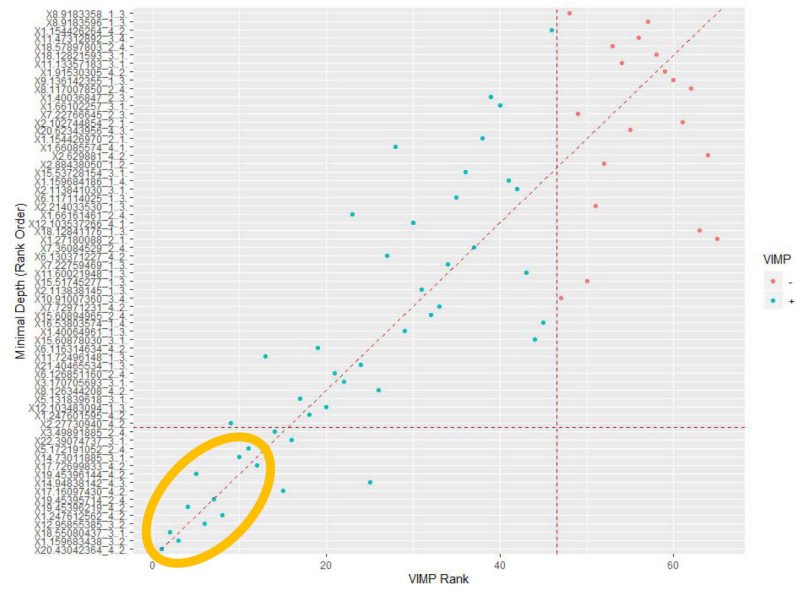
A

B

(1) 87 SNPs from our previous GWAS in overall analysis

(2) 65 SNPs from outside GWASs in overall analysis
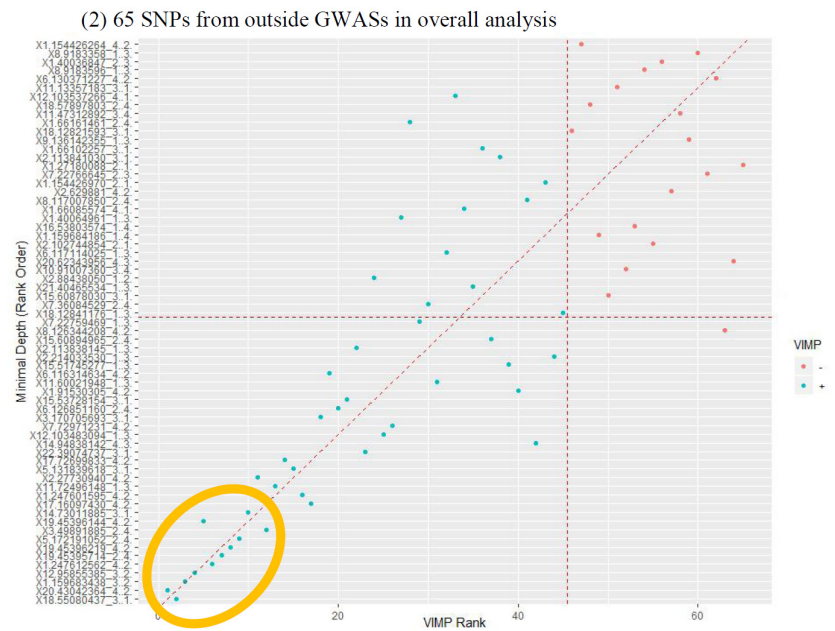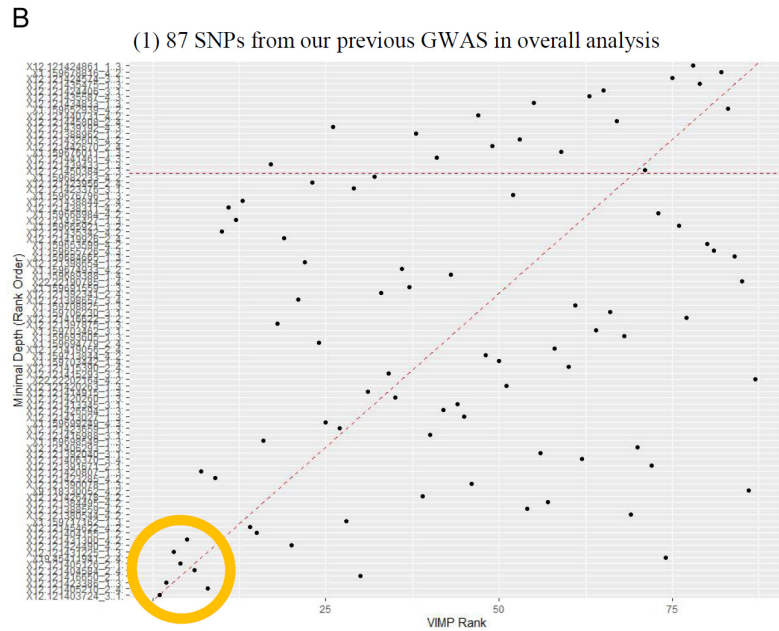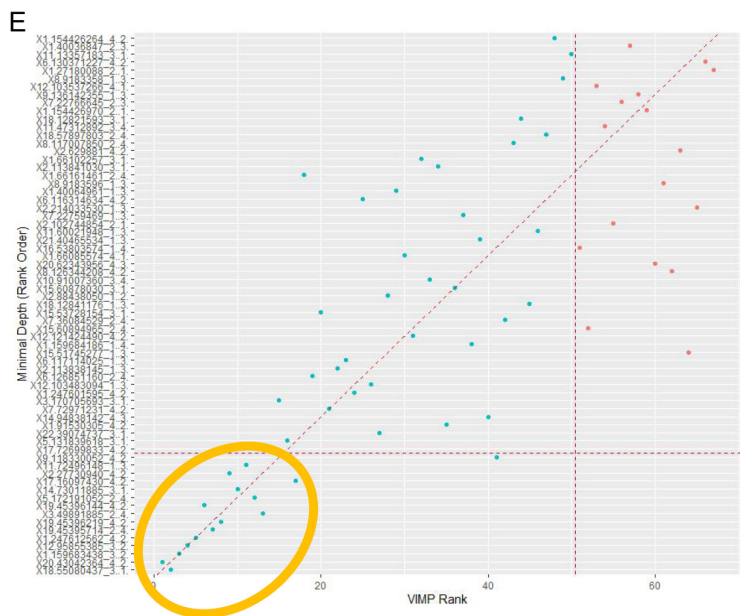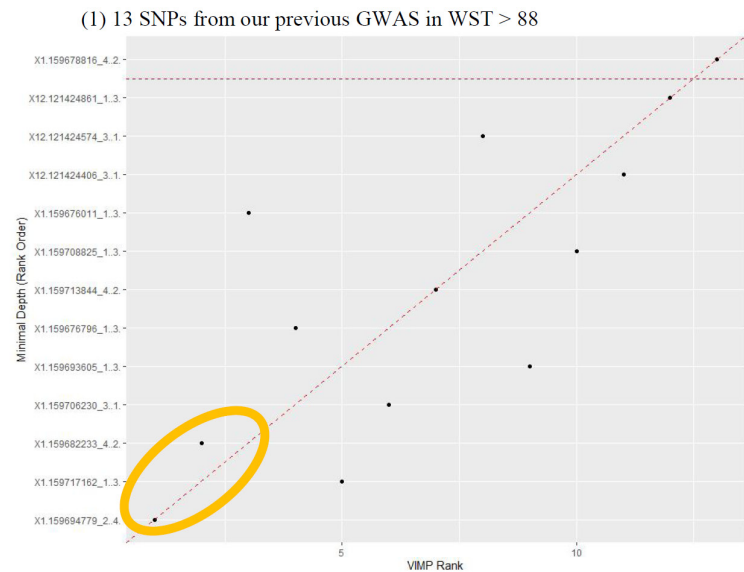
Inflammatory genetic markers and CRC: post-GWAS RSF
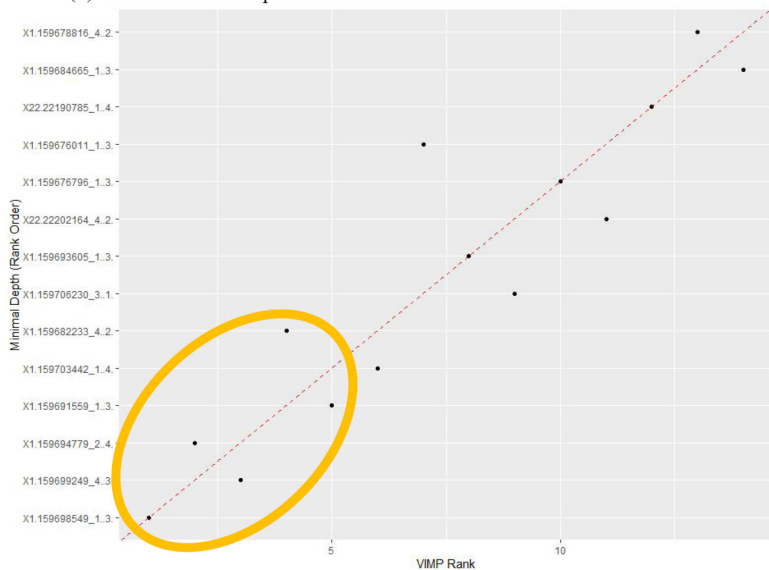
C

(1) 49 SNPs from our previous GWAS in BMI < 30
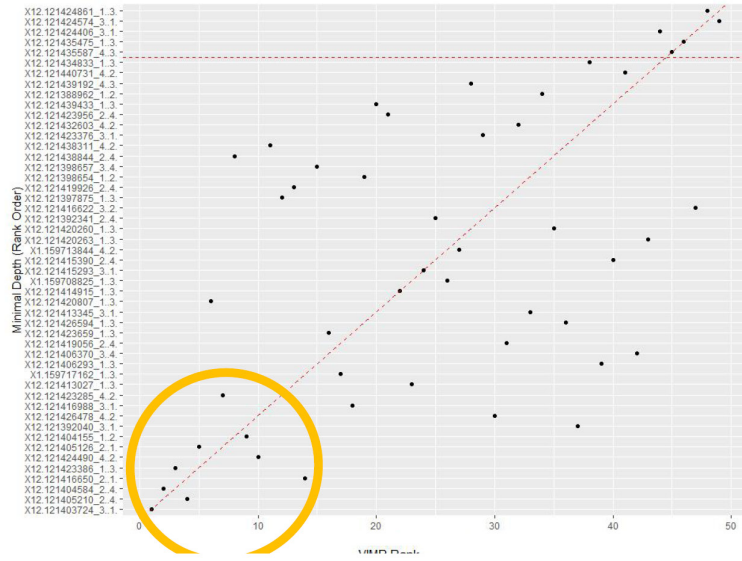
(2) 65 SNPs from outside GWASs in BMI < 30
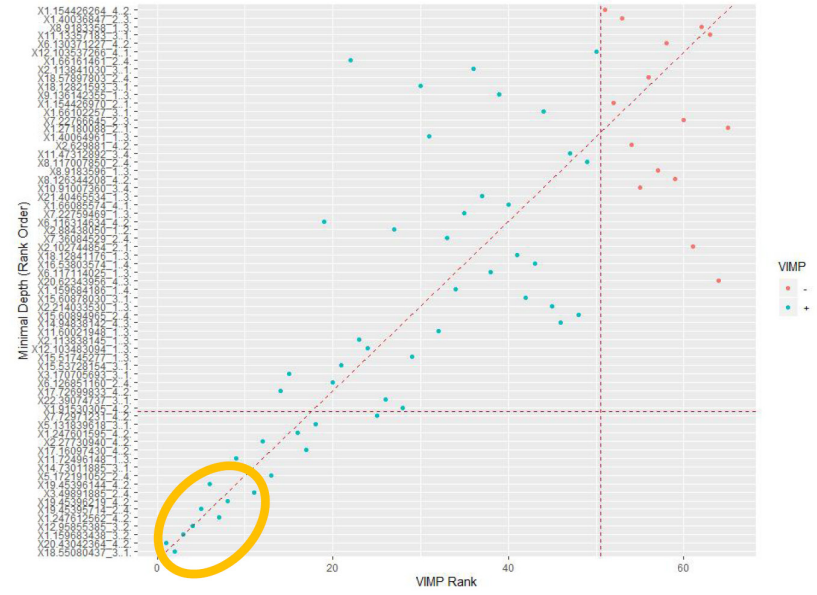
D

(1) 49 SNPs from our previous GWAS in BMI < 30

(2) 65 SNPs from outside GWASs in BMI ≥ 30

Inflammatory genetic markers and CRC: post-GWAS RSF

E

F

G

(1) 13 SNPs from our previous GWAS in WST $\leq$ 88
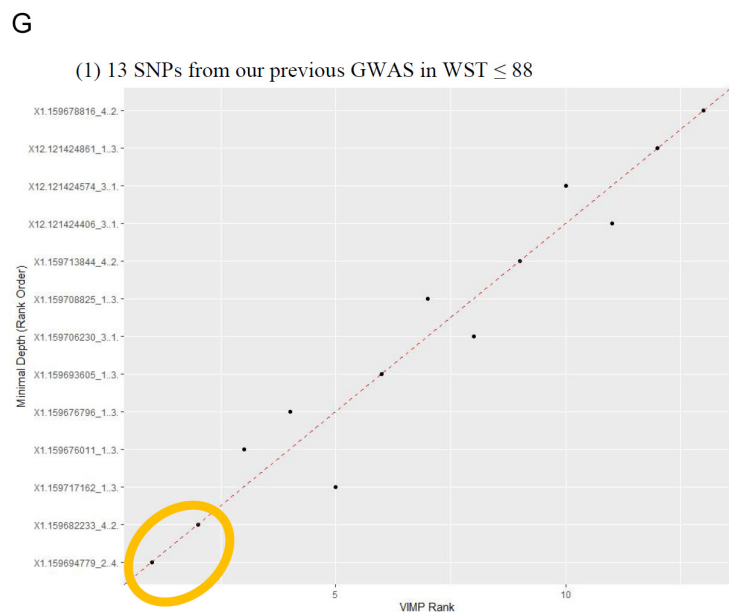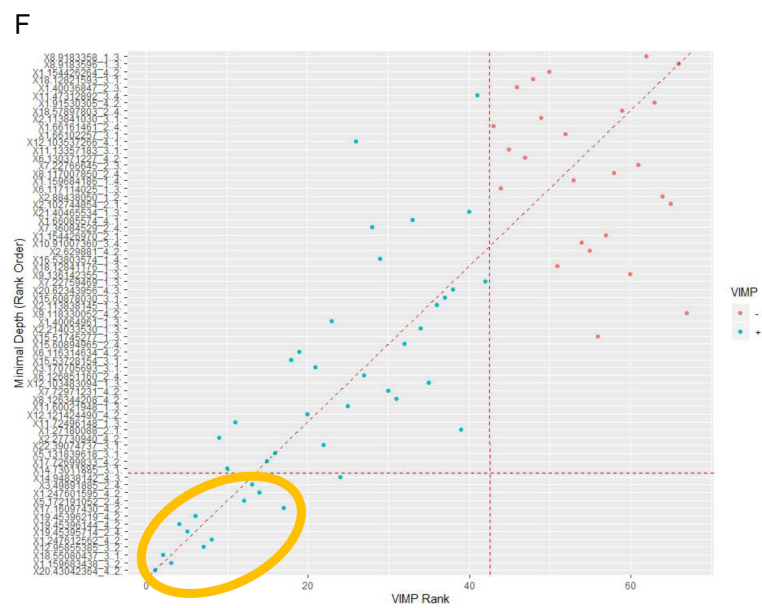
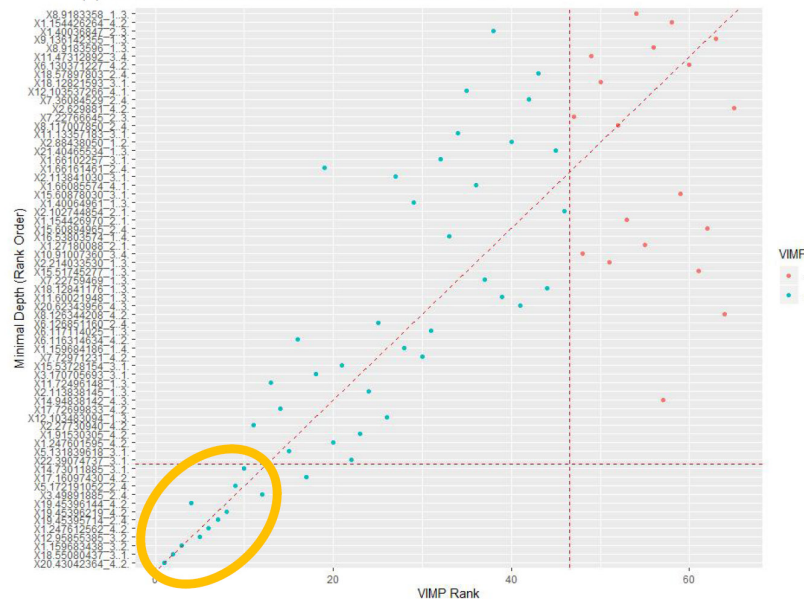(2) 65 SNPs from outside GWASs in WST $\leq$ 88

Inflammatory genetic markers and CRC: post-GWAS RSF

H

(1) 13 SNPs from our previous GWAS in WST > 88

(2) 65 SNPs from outside GWASs in WST > 88

I

(1) 14 SNPs from our previous GWAS in MET ≥ 10
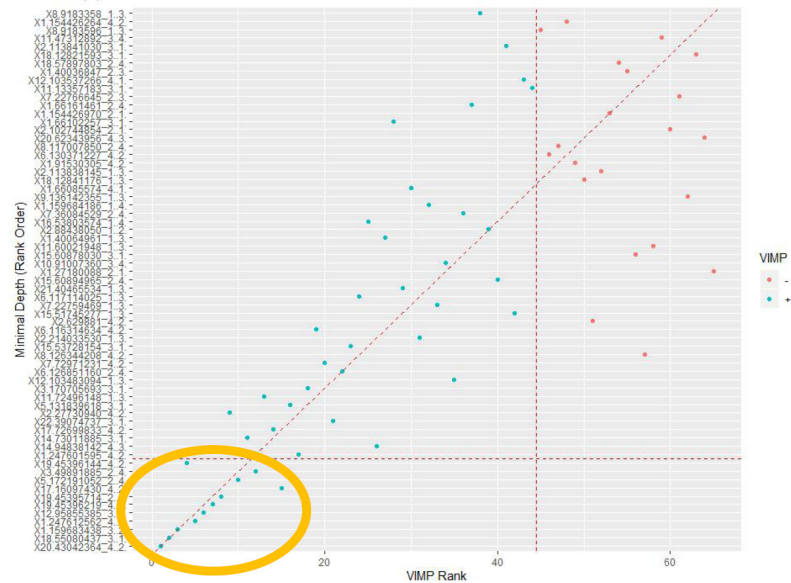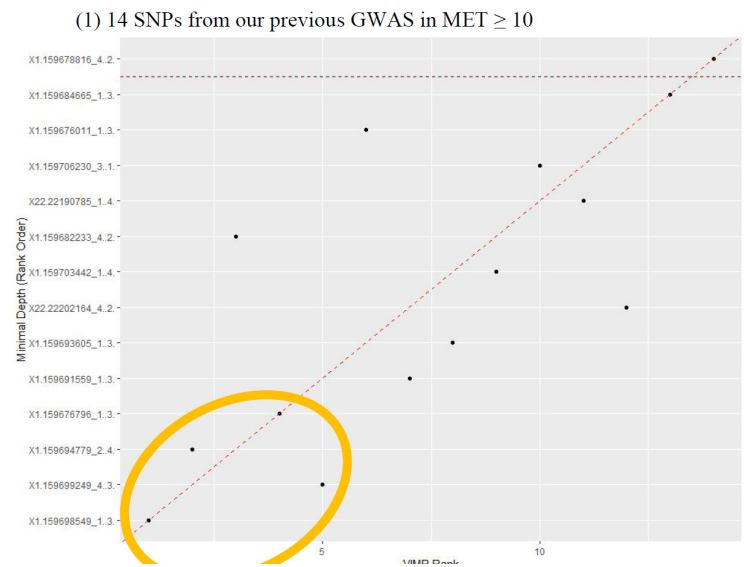
(2) 65 SNPs from outside GWASs in MET ≥ 10
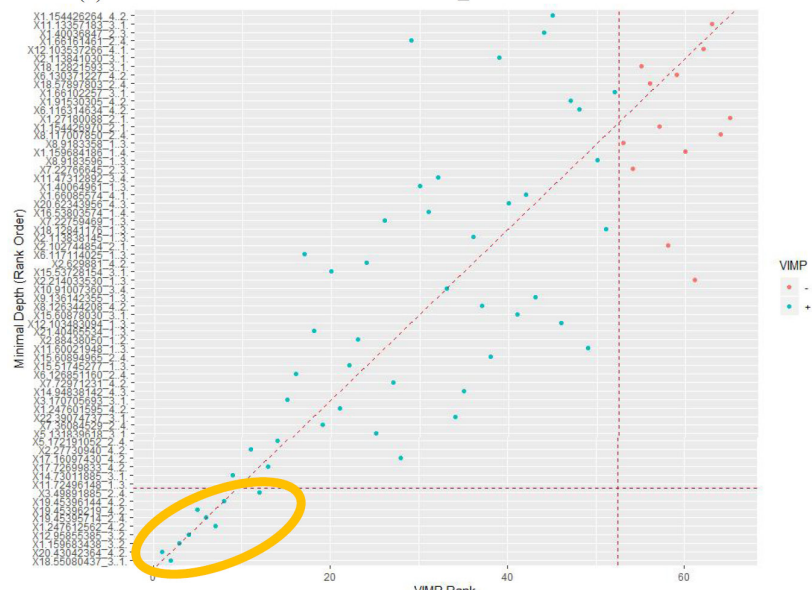
Inflammatory genetic markers and CRC: post-GWAS RSF

J
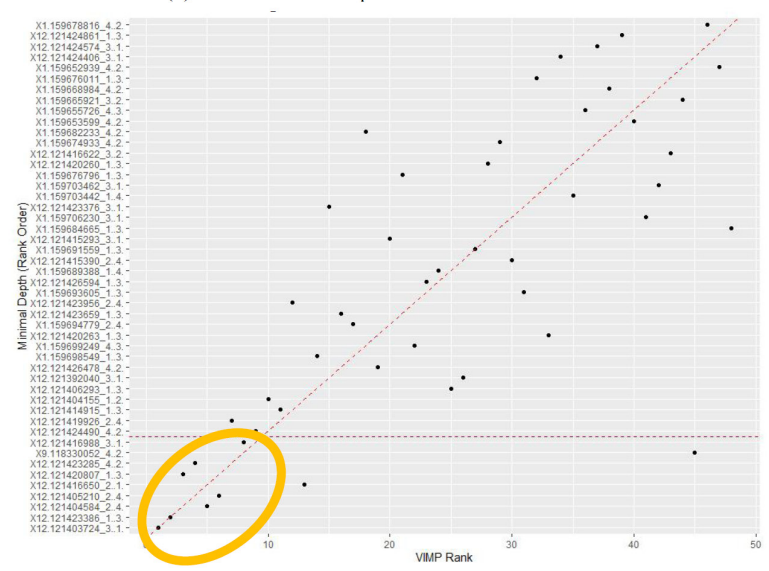
(1) 14 SNPs from our previous GWAS in MET < 10

(2) 65 SNPs from outside GWASs in MET < 10
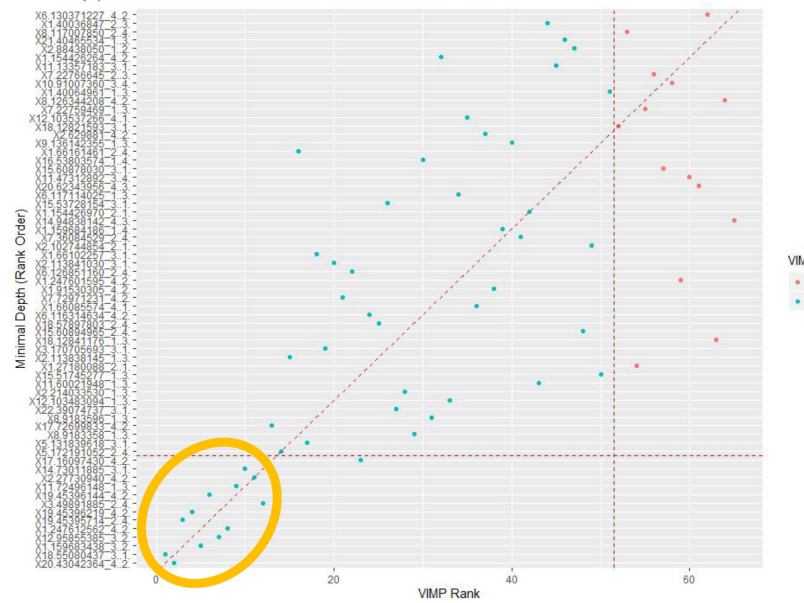
K

(1) 48 SNPs from our previous GWAS in SFA < 9.0

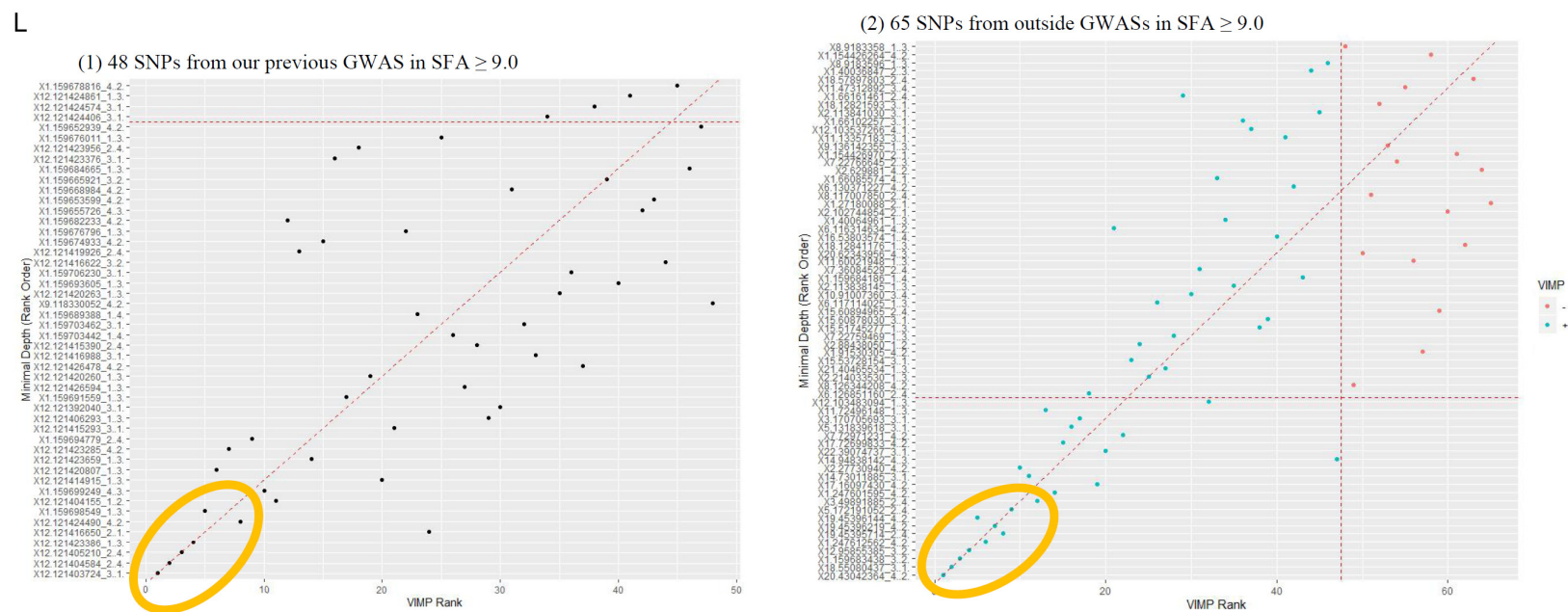### (2) 65 SNPs from outside GWASs in SFA < 9.0

Figure S3. The first stage of random survival forest analysis, comparing minimal depth and VIMP rankings. A. Behavioral factors (BMI, body mass index; CVD, cardiovascular disease; E-only, exogenous estrogen; E+P, E + progestin; MFA, monounsaturated fatty acids; PFA, polyunsaturated fatty acids; SFA, saturated fatty acids; VIMP, variable of importance. Note: The 12 variables within the gold ellipse were identified as the most influential predictors). B. 152 (=87 + 65) SNPs in overall analysis (SNPs, single-nucleotide polymorphisms. Note: The 18 (=7 + 11) SNPs within the gold ellipses were identified as the most influential predictors). C. 114 (=49 + 65) SNPs in BMI-stratified analysis-non-overall obese group (BMI < 30) (BMI, body mass index. Note: The 18 (=9 + 9) SNPs within the gold ellipses were identified as the most influential predictors). D. 114 (=49 + 65) SNPs in BMI-stratified analysis - overall obese group (BMI ≥ 30) (Note: The 17 (=6 + 11) SNPs within the gold ellipses were identified as the most influential predictors). E. 67 SNPs (combining our 2 GWA SNPs and 65 SNPs from outside GWASs) in WHR-stratified analysis - non-viscerally obese group (WHR ≤ 0.85) (WHR, waist-to-hip ratio. Note: The 14 SNPs within the gold ellipse were identified as the most influential predictors). F. 67 SNPs (combining our 2 GWA SNPs and 65 SNPs from outside GWASs) in WHR-stratified analysis - viscerally obese group (WHR > 0.85) (Note: The 12 SNPs within the gold ellipse were identified as the most influential predictors). G. 78 (=13 + 65) SNPs in WST-stratified analysis - non-viscerally obese group (WST ≤ 88) (WST, waist circumference. Note: The 13 (=2 + 11) SNPs within the gold ellipses were identified as the most influential predictors). H. 78 (=13 + 65) SNPs in WST-stratified analysis-non-viscerally obese group (WST > 88) (Note: The 13 (=2 + 11) SNPs within the gold ellipses were identified as the most influential predictors). I. 79 (=14 + 65) SNPs in physical activity-stratified analysis - active group (MET ≥ 10) (MET, metabolic equivalent. Note: The 13 (=4 + 9) SNPs within the gold ellipses were identified as the most influential predictors). J. 79 (=14 + 65) SNPs in physical activity-stratified analysis-inactive group (MET < 10) (Note: The 16 (=5 + 11) SNPs within the gold ellipses were identified as the most influential predictors). K. 113 (=48 + 65) SNPs in SFA-stratified analysis- < 9.0% calories from SFA (SFA, saturated fatty acids. Note: The 19 (=7 + 12) SNPs within the gold ellipses were identified as the most influential predictors). L. 113 (=48 + 65) in SFA-stratified analysis - ≥ 9.0% calories from SFA (Note: The 16 (=6 + 10) SNPs within the gold ellipse were identified as the most influential predictors).

Table S2. GMDR-based model for high-order gene-gene interactions in relation to CRC risk

n	Model	TBA	P Value	CVC
	<Overall>			
1	*ONECUT2* rs4092465	0.6954	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7019**	**0.0010**	**10/10**
	<Non-overall obese group, BMI < 30 kg/m^2>			
1	*ONECUT2* rs4092465	0.6933	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.6993**	**0.0010**	**10/10**
	<Overall obese group, BMI ≥ 30 kg/m^2>			
1	*ONECUT2* rs4092465	0.7006	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7084**	**0.0010**	**10/10**
	<Non-viscerally obese group, WHR ≤ 0.85>			
1	*ONECUT2* rs4092465	0.7010	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7106**	**0.0010**	**10/10**
	<Viscerally obese group, WHR > 0.85>			
1	*ONECUT2* rs4092465	**0.6819**	**0.0010**	**10/10**
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	0.6769	0.0010	10/10
	<Non-viscerally obese group, WST ≤ 88 cm>			
1	*ONECUT2* rs4092465	0.6943	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7014**	**0.0010**	**10/10**
	<Viscerally obese group, WST > 88 cm>			
1	*ONECUT2* rs4092465	0.6970	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7029**	**0.0010**	**10/10**
	<Active group, MET ≥ 10.0>			
1	*ONECUT2* rs4092465	0.6925	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7014**	**0.0010**	**10/10**
	<Inactive group, MET < 10.0>			
1	*ONECUT2* rs4092465	0.6973	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7009**	**0.0010**	**10/10**
	<Low-fat diet group, % cal. from SFA < 9.0>			
1	*ONECUT2* rs4092465	0.7061	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.7135**	**0.0010**	**10/10**
3	*ONECUT2* rs4092465 *HNF4A* rs1800961 *CRP* rs1800947	0.7094	0.0010	10/10
	<High-fat diet group, % cal. from SFA ≥ 9.0>			
1	*ONECUT2* rs4092465	0.6922	0.0010	10/10
2	*ONECUT2* rs4092465 *HNF4A* rs1800961	**0.6984**	**0.0010**	**10/10**

BMI, body mass index; CRC, colorectal cancer; CVC, cross-validation consistency; GMDR, generalized multifactor dimensionality reduction; MET, metabolic equivalent; SFA, saturated fatty acids; TBA, testing balance accuracy; WHR, waist-to-hip ratio; WST, waist circumference. Models in bold face are considered the best, with the highest TBA, 10/10 CVC, and p < 0.05.

Table S3A. The second stage of random survival forest analysis: predictive value of variables in non-overall obese group (BMI < 30 kg/m^2)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	1.8458	0.0472	0.8617	0.1383	0.3617
HNF4A rs1800961	2.7410	0.0259	0.9332	0.0668	0.0715
ONECUT2 rs4092465	2.8580	0.0171	0.9532	0.0468	0.0201
CRP rs1800947	3.0740	0.0117	0.9523	0.0477	-0.0010
METAP2 rs11108056	3.3444	0.0107	0.9556	0.0444	0.0034
NLRP3 rs10925027	3.6380	0.0076	0.9585	0.0415	0.0029
TOMM40 rs157581	4.0532	0.0120	0.9569	0.0431	-0.0016
TOMM40 rs157582	4.2028	0.0091	0.9572	0.0428	0.0004
TRAIP s2352975	4.4012	0.0027	0.9585	0.0415	0.0013
Age at enrollment	4.6002	0.0017	0.9597	0.0403	0.0011
TOMM40 rs11556505	4.8112	0.0113	0.9598	0.0402	0.0001
Waist circumference	5.2336	0.0001	0.9597	0.0403	-0.0001
Hip circumference	5.2418	-0.0001	0.9592	0.0408	-0.0005
Waist-to-hip ratio	5.3210	0.0001	0.9593	0.0407	0.0001
Age at menopause	5.3436	0.0003	0.9598	0.0402	0.0005
HNF1A rs1169288	5.3498	0.0018	0.9587	0.0413	-0.0012
Duration of E+P use	5.4476	0.0007	0.9606	0.0394	0.0019
HNF1A rs11065385	5.5488	0.0056	0.9602	0.0398	-0.0004
Total months of breastfeeding	5.6758	0.0003	0.9589	0.0411	-0.0012
Height	5.6878	-0.0002	0.9585	0.0415	-0.0004
HNF1A rs11065384	5.7466	0.0057	0.9583	0.0417	-0.0002
HNF1A-AS1 rs7135337	5.7714	0.0030	0.9575	0.0425	-0.0007
Weight	5.9938	-0.0001	0.9571	0.0429	-0.0004
HNF1A rs2243458	6.1380	0.0030	0.9565	0.0435	-0.0006
HNF1A-AS1 rs2251468	6.1412	0.0058	0.9558	0.0442	-0.0007
Education	6.3760	-0.0001	0.9572	0.0428	0.0014
HNF1A-AS1 rs7953249	6.9202	0.0065	0.9570	0.0430	-0.0002
HNF1A-AS1 rs10774579	7.2118	0.0032	0.9566	0.0434	-0.0004
HNF1A-AS1 rs1920792	7.2578	0.0035	0.9555	0.0445	-0.0011

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3617) from 0.5.

Table S3B. The second stage of random survival forest analysis: predictive value of variables in overall obese group (BMI ≥ 30 kg/m^2)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	2.4382	0.0344	0.8249	0.1751	0.3249
HNF4A rs1800961	2.9428	0.0334	0.9024	0.0976	0.0775
CRP rs1800947	3.7300	0.0155	0.9022	0.0978	-0.0002
ONECUT2 rs4092465	3.8762	0.0181	0.9373	0.0627	0.0351
METAP2 rs11108056	4.1160	0.0093	0.9383	0.0617	0.0010
NLRP3 rs10925027	4.4502	0.0068	0.9409	0.0591	0.0026
TOMM40 rs157582	5.2110	0.0125	0.9408	0.0592	-0.0001
RGS6 rs2239222	5.3524	0.0035	0.9416	0.0584	0.0008
TOMM40 rs157581	5.3750	0.0103	0.9424	0.0576	0.0008
Education	5.5236	-0.0005	0.9431	0.0569	0.0007
TOMM40 rs11556505	5.5752	0.0136	0.9471	0.0529	0.0040
DUSP1 rs17658229	5.6148	0.0038	0.9513	0.0487	0.0042
CD300LF/RAB37 rs10512597	5.7284	0.0015	0.9514	0.0486	0.0001
Height	5.8142	-0.0001	0.9496	0.0504	-0.0019
Age at enrollment	6.0544	0.0002	0.9466	0.0534	-0.0030
Age at menopause	6.0706	0.0000	0.9456	0.0544	-0.0010
Hip circumference	6.0802	0.0006	0.9479	0.0521	0.0023
HNF1A rs11065385	6.2498	0.0033	0.9469	0.0531	-0.0010
Waist circumference	6.3752	-0.0003	0.9462	0.0538	-0.0008
HNF1A-AS1 rs7135337	6.3972	0.0030	0.9447	0.0553	-0.0014
Waist-to-hip ratio	6.4432	-0.0001	0.9427	0.0573	-0.0021
HNF1A-AS1 rs7953249	6.4710	0.0080	0.9417	0.0583	-0.0009
HNF1A-AS1 rs2251468	6.5062	0.0061	0.9391	0.0609	-0.0027
Weight	6.7850	-0.0006	0.9381	0.0619	-0.0010
Duration of E+P use	6.9146	0.0000	0.9381	0.0619	0.0000
HNF1A-AS1 rs1920792	7.8064	0.0026	0.9394	0.0606	0.0013
HNF1A-AS1 rs10774579	7.9144	0.0026	0.9402	0.0598	0.0008
Total months of breastfeeding	8.0044	0.0000	0.9392	0.0608	-0.0010

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3249) from 0.5.

Table S3C. The second stage of random survival forest analysis: predictive value of variables in non-viscerally obese group (waist-to-hip ratio ≤ 0.85)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	1.9340	0.0409	0.8510	0.1490	0.3510
HNF4A rs1800961	2.6618	0.0267	0.9326	0.0674	0.0817
ONECUT2 rs4092465	2.7684	0.0185	0.9540	0.0460	0.0214
CRP rs1800947	3.1084	0.0124	0.9519	0.0481	-0.0022
METAP2 rs11108056	3.3028	0.0101	0.9520	0.0480	0.0001
NLRP3 rs10925027	3.5750	0.0075	0.9551	0.0449	0.0032
TOMM40 rs157581	3.7964	0.0120	0.9556	0.0444	0.0005
TOMM40 rs157582	3.9188	0.0107	0.9562	0.0438	0.0006
TOMM40 rs11556505	4.3290	0.0132	0.9568	0.0432	0.0006
TRAIP rs2352975	4.3390	0.0029	0.9597	0.0403	0.0030
DUSP1 rs17658229	4.4170	0.0038	0.9646	0.0354	0.0049
Age at enrollment	4.6750	0.0010	0.9649	0.0351	0.0003
NCOR1 rs178810	4.8928	0.0003	0.9640	0.0360	-0.0010
RGS6 rs2239222	4.9694	0.0020	0.9627	0.0373	-0.0013
Duration of E+P use	5.0122	0.0011	0.9640	0.0360	0.0013
Hip circumference	5.0998	-0.0002	0.9639	0.0361	-0.0002
GCKR rs1260326	5.1030	0.0029	0.9649	0.0351	0.0011
Age at menopause	5.1118	0.0004	0.9641	0.0359	-0.0008
Waist circumference	5.1856	0.0000	0.9642	0.0358	0.0002
STARD10 rs7121935	5.2054	0.0025	0.9629	0.0371	-0.0014
Height	5.5332	-0.0002	0.9629	0.0371	0.0000
BMI	5.5796	-0.0002	0.9627	0.0373	-0.0002
Weight	5.6600	0.0001	0.9614	0.0386	-0.0013
Education	5.9200	-0.0003	0.9605	0.0395	-0.0009
Total months of breastfeeding	6.6006	0.0000	0.9602	0.0398	-0.0004

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3510) from 0.5.

Table S3D. The second stage of random survival forest analysis: predictive value of variables in viscerally obese group (waist-to-hip ratio > 0.85)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	2.1058	0.0563	0.8342	0.1658	0.3342
HNF4A rs1800961	2.9236	0.0282	0.9160	0.0840	0.0818
CRP rs1800947	3.0800	0.0157	0.9134	0.0866	-0.0026
ONECUT2 rs4092465	3.4690	0.0226	0.9385	0.0615	0.0251
METAP2 rs11108056	4.0050	0.0085	0.9387	0.0613	0.0001
NLRP3 rs10925027	4.1224	0.0082	0.9379	0.0621	-0.0008
TOMM40 rs157581	4.4910	0.0216	0.9361	0.0639	-0.0018
TOMM40 rs11556505	4.5374	0.0255	0.9411	0.0589	0.0050
TOMM40 rs157582	4.8506	0.0176	0.9399	0.0601	-0.0012
Age at enrollment	4.9918	0.0030	0.9435	0.0565	0.0037
DUSP1 rs17658229	5.0486	0.0038	0.9486	0.0514	0.0051
TRAIP rs2352975	5.1480	0.0017	0.9493	0.0507	0.0007
NLRP3 rs12239046	5.2114	0.0036	0.9497	0.0503	0.0004
NCOR1 rs178810	5.3192	0.0009	0.9482	0.0518	-0.0015
Education	5.6916	-0.0006	0.9466	0.0534	-0.0017
Height	5.8588	-0.0001	0.9447	0.0553	-0.0019
Weight	6.0178	-0.0003	0.9455	0.0545	0.0008
Total months of breastfeeding	6.0396	0.0007	0.9456	0.0544	0.0001
BMI	6.0644	-0.0002	0.9441	0.0559	-0.0015
Hip circumference	6.2248	0.0002	0.9432	0.0568	-0.0010
Age at menopause	6.2702	-0.0005	0.9439	0.0561	0.0007
Waist circumference	6.3782	0.0004	0.9418	0.0582	-0.0021
Duration of E+P use	7.3304	-0.0001	0.9408	0.0592	-0.0010

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.4251) from 0.5.

Table S3E. The second stage of random survival forest analysis: predictive value of variables in non-viscerally obese group (waist circumference ≤ 88 cm)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	1.8380	0.0508	0.8749	0.1251	0.3749
ONECUT2 rs4092465	2.7844	0.0209	0.9479	0.0521	0.0730
HNF4A rs1800961	2.8618	0.0234	0.9534	0.0466	0.0055
CRP rs1800947	3.1218	0.0164	0.9534	0.0466	-0.0001
METAP2 rs11108056	3.2872	0.0094	0.9537	0.0463	0.0004
NLRP3 rs10925027	3.5948	0.0069	0.9560	0.0440	0.0022
TOMM40 rs157581	3.8174	0.0162	0.9554	0.0446	-0.0006
TOMM40 rs157582	3.9572	0.0136	0.9569	0.0431	0.0015
TOMM40 rs11556505	4.2854	0.0178	0.9568	0.0432	-0.0001
Age at enrollment	4.4032	0.0015	0.9580	0.0420	0.0012
TRAIP rs2352975	4.6390	0.0025	0.9592	0.0408	0.0013
RGS6 rs2239222	4.8606	0.0033	0.9592	0.0408	-0.0001
DUSP1 rs17658229	4.8922	0.0034	0.9623	0.0377	0.0031
Hip circumference	5.3536	-0.0002	0.9612	0.0388	-0.0011
Duration of E+P use	5.3606	0.0008	0.9617	0.0383	0.0005
Age at menopause	5.3786	0.0001	0.9614	0.0386	-0.0004
Waist-to-hip ratio	5.5536	-0.0002	0.9620	0.0380	0.0006
Height	5.5628	-0.0003	0.9616	0.0384	-0.0004
CRP rs7551731	5.6326	0.0013	0.9611	0.0389	-0.0005
Education	5.7548	-0.0002	0.9602	0.0398	-0.0008
BMI	5.8016	-0.0001	0.9600	0.0400	-0.0003
Weight	5.8430	0.0000	0.9588	0.0412	-0.0011
Total months of breastfeeding	5.9848	0.0001	0.9581	0.0419	-0.0007
CRP rs1205	6.4662	0.0012	0.9576	0.0424	-0.0005

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3749) from 0.5.

Table S3F. The second stage of random survival forest analysis: predictive value of variables in viscerally obese group (waist circumference > 88 cm)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	2.1864	0.0392	0.8140	0.1860	0.3140
HNF4A rs1800961	2.5850	0.0300	0.9117	0.0883	0.0977
ONECUT2 rs4092465	3.1096	0.0206	0.9442	0.0558	0.0325
CRP rs1800947	3.1376	0.0203	0.9410	0.0590	-0.0032
METAP2 rs11108056	3.7004	0.0090	0.9425	0.0575	0.0015
NLRP3 rs10925027	3.7572	0.0086	0.9442	0.0558	0.0017
TOMM40 rs157581	4.2294	0.0170	0.9423	0.0577	-0.0019
TOMM40 rs11556505	4.3040	0.0207	0.9483	0.0517	0.0061
TOMM40 rs157582	4.3952	0.0149	0.9473	0.0527	-0.0010
TRAIP rs2352975	4.5670	0.0029	0.9500	0.0500	0.0027
DUSP1 rs17658229	4.5686	0.0048	0.9560	0.0440	0.0060
NCOR1 rs178810	4.7188	0.0010	0.9551	0.0449	-0.0009
Waist-to-hip ratio	5.2952	0.0008	0.9541	0.0459	-0.0010
Age at enrollment	5.3224	0.0011	0.9525	0.0475	-0.0016
Hip circumference	5.4536	0.0000	0.9512	0.0488	-0.0013
Weight	5.4926	-0.0001	0.9489	0.0511	-0.0023
CRP rs7551731	5.4994	0.0030	0.9506	0.0494	0.0017
BMI	5.5298	0.0001	0.9492	0.0508	-0.0014
Height	5.6658	0.0003	0.9483	0.0517	-0.0009
Age at menopause	5.6948	0.0003	0.9481	0.0519	-0.0003
Education	5.8200	-0.0003	0.9469	0.0531	-0.0012
Duration of E+P use	6.0930	0.0004	0.9473	0.0527	0.0004
CRP rs1205	6.5412	0.0022	0.9465	0.0535	-0.0009
Total months of breastfeeding	6.7822	-0.0001	0.9452	0.0548	-0.0013

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3140) from 0.5.

Table S3G. The second stage of random survival forest analysis: predictive value of variables in active group (MET ≥ 10.0)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	1.9696	0.0472	0.8663	0.1337	0.3664
ONECUT2 rs4092465	2.8608	0.0232	0.9467	0.0533	0.0803
HNF4A rs1800961	3.0362	0.0250	0.9509	0.0491	0.0042
CRP rs1800947	3.3198	0.0181	0.9534	0.0466	0.0025
TOMM40 rs157581	3.6268	0.0192	0.9550	0.0450	0.0017
METAP2 rs11108056	3.6452	0.0099	0.9551	0.0449	0.0001
TOMM40 rs157582	3.6524	0.0182	0.9547	0.0453	-0.0004
NLRP3 rs10925027	3.9368	0.0073	0.9538	0.0462	-0.0009
TOMM40 rs11556505	4.1794	0.0188	0.9531	0.0469	-0.0007
Age at enrollment	4.6828	0.0020	0.9546	0.0454	0.0015
TRAIP rs2352975	4.7204	0.0021	0.9546	0.0454	0.0000
Waist-to-hip ratio	5.3104	0.0002	0.9542	0.0458	-0.0004
Hip circumference	5.5046	-0.0001	0.9530	0.0470	-0.0012
CRP rs4546916	5.6138	0.0018	0.9523	0.0477	-0.0006
CRP rs7553007	5.6618	0.0030	0.9516	0.0484	-0.0008
Duration of E+P use	5.7384	0.0005	0.9522	0.0478	0.0006
Age at menopause	5.8254	0.0005	0.9549	0.0451	0.0027
CRP rs7551731	5.8472	0.0024	0.9544	0.0456	-0.0005
Height	5.9668	0.0001	0.9539	0.0461	-0.0005
Waist circumference	6.0430	-0.0002	0.9531	0.0469	-0.0008
Weight	6.0468	0.0000	0.9520	0.0480	-0.0012
BMI	6.0648	0.0000	0.9515	0.0485	-0.0005
Education	6.3488	0.0002	0.9508	0.0492	-0.0007
Total months of breastfeeding	6.6838	0.0000	0.9507	0.0493	-0.0001
CRPP1 rs2808629	6.6970	0.0015	0.9497	0.0503	-0.0010

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3664) from 0.5.

Table S3H. The second stage of random survival forest analysis: predictive value of variables in inactive group (MET < 10.0)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	1.9854	0.0442	0.8406	0.1594	0.3406
HNF4A rs1800961	2.6084	0.0284	0.9229	0.0771	0.0823
CRP rs1800947	2.9872	0.0218	0.9222	0.0778	-0.0007
ONECUT2 rs4092465	3.0140	0.0195	0.9514	0.0486	0.0292
METAP2 rs11108056	3.5080	0.0085	0.9487	0.0513	-0.0026
NLRP3 rs10925027	3.8052	0.0073	0.9510	0.0490	0.0023
TOMM40 rs11556505	4.2900	0.0202	0.9531	0.0469	0.0021
TOMM40 rs157581	4.3890	0.0164	0.9549	0.0451	0.0018
TOMM40 rs157582	4.4968	0.0126	0.9552	0.0448	0.0004
TRAIP rs2352975	4.7224	0.0024	0.9581	0.0419	0.0029
DUSP1 rs17658229	4.7960	0.0041	0.9640	0.0360	0.0059
Age at enrollment	4.8076	0.0012	0.9640	0.0360	0.0000
Age at menopause	5.3608	0.0000	0.9637	0.0363	-0.0003
RGS6 rs2239222	5.4870	0.0031	0.9622	0.0378	-0.0015
Height	5.5214	0.0002	0.9612	0.0388	-0.0010
Waist-to-hip ratio	5.5884	0.0000	0.9604	0.0396	-0.0009
Education	5.6460	-0.0003	0.9614	0.0386	0.0010
Hip circumference	5.7232	0.0001	0.9607	0.0393	-0.0007
Waist circumference	5.7434	0.0001	0.9603	0.0397	-0.0004
Weight	6.1228	0.0000	0.9594	0.0406	-0.0009
Duration of E+P use	6.1626	0.0006	0.9599	0.0401	0.0005
CRP rs4546916	6.1910	0.0017	0.9587	0.0413	-0.0012
BMI	6.1978	0.0000	0.9581	0.0419	-0.0006
Total months of breastfeeding	6.2060	0.0002	0.9574	0.0426	-0.0007
CRP rs7553007	6.2664	0.0023	0.9562	0.0438	-0.0012
CRP rs7551731	6.4542	0.0021	0.9574	0.0426	0.0013
CRP rs1341665	6.8222	0.0016	0.9570	0.0430	-0.0004
CRP rs1205	8.0524	0.0012	0.9564	0.0436	-0.0007

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; MET metabolic equivalent; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top **variable, fol**lowed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3406) from 0.5.

Table S3I. The second stage of random survival forest analysis: predictive value of variables in low fat-diet group (< 9.0% calories from SFA)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	2.3760	0.0380	0.8533	0.1467	0.3533
HNF4A rs1800961	3.4392	0.0255	0.9087	0.0913	0.0554
CRP rs1800947	3.7850	0.0138	0.9173	0.0827	0.0085
ONECUT2 rs4092465	3.9060	0.0224	0.9458	0.0542	0.0285
METAP2 rs11108056	4.4608	0.0085	0.9440	0.0560	-0.0019
NLRP3 rs10925027	4.5676	0.0059	0.9476	0.0524	0.0036
TOMM40 rs157581	4.8704	0.0147	0.9482	0.0518	0.0006
TOMM40 rs157582	4.9000	0.0127	0.9459	0.0541	-0.0023
Age at enrollment	5.2120	0.0030	0.9475	0.0525	0.0017
TRAIP rs2352975	5.2532	0.0036	0.9498	0.0502	0.0023
TOMM40 rs11556505	5.7586	0.0102	0.9513	0.0487	0.0015
GCKR rs1260326	5.8828	0.0034	0.9528	0.0472	0.0015
Total months of breastfeeding	5.9300	0.0004	0.9524	0.0476	-0.0004
STARD10 rs7121935	6.0306	0.0045	0.9509	0.0491	-0.0015
Waist-to-hip ratio	6.0872	0.0007	0.9508	0.0492	-0.0001
Duration of E+P use	6.4696	0.0008	0.9526	0.0474	0.0018
Height	6.6032	-0.0001	0.9552	0.0448	0.0026
RGS6 rs2239222	6.6070	0.0028	0.9539	0.0461	-0.0012
HNF1A rs11065385	6.6214	0.0065	0.9530	0.0470	-0.0009
HNF1A rs11065384	6.7248	0.0059	0.9517	0.0483	-0.0013
HNF1A rs1183910	6.7818	0.0062	0.9514	0.0486	-0.0003
Age at menopause	6.7838	0.0002	0.9513	0.0487	-0.0001
Hip circumference	6.8202	0.0002	0.9503	0.0497	-0.0010
BMI	6.8798	0.0003	0.9511	0.0489	0.0009
HNF1A rs2244608	6.9668	0.0038	0.9490	0.0510	-0.0021
Waist circumference	7.0358	-0.0001	0.9502	0.0498	0.0012
HNF1A-AS1 rs7953249	7.0712	0.0036	0.9507	0.0493	0.0005
Weight	7.1228	0.0002	0.9505	0.0495	-0.0002
Education	7.2266	-0.0003	0.9494	0.0506	-0.0010
HNF1A-AS1 rs10774579	7.3834	0.0023	0.9479	0.0521	-0.0015
HNF1A-AS1 rs1920792	7.4540	0.0023	0.9480	0.0520	0.0000

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; SFA, saturated fatty acids; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3533) from 0.5.

Table S3J. The second stage of random survival forest analysis: predictive value of variables in high fat-diet group (≥ 9.0% calories from SFA)

Variable*	Minimal Depth†	VIMP	C-index	Error¶	Drop Error§
Duration of oral contraceptive use	1.9438	0.0480	0.8444	0.1556	0.3444
HNF4A rs1800961	2.4968	0.0297	0.9318	0.0682	0.0874
ONECUT2 rs4092465	2.8286	0.0169	0.9561	0.0439	0.0243
CRP rs1800947	3.0134	0.0153	0.9552	0.0448	-0.0009
METAP2 rs11108056	3.2954	0.0102	0.9561	0.0439	0.0009
NLRP3 rs10925027	3.4476	0.0082	0.9572	0.0428	0.0011
TOMM40 rs157581	4.0982	0.0127	0.9559	0.0441	-0.0013
TOMM40 rs157582	4.1014	0.0115	0.9570	0.0430	0.0011
TOMM40 rs11556505	4.3028	0.0148	0.9579	0.0421	0.0009
TRAIP rs2352975	4.3790	0.0028	0.9604	0.0396	0.0025
DUSP1 rs17658229	4.4004	0.0053	0.9659	0.0341	0.0055
Age at enrollment	4.7984	0.0011	0.9656	0.0344	-0.0003
Waist-to-hip ratio	5.3352	0.0000	0.9653	0.0347	-0.0004
HNF1A rs11065385	5.3556	0.0055	0.9650	0.0350	-0.0003
Hip circumference	5.3852	0.0000	0.9640	0.0360	-0.0010
Age at menopause	5.3868	0.0001	0.9634	0.0366	-0.0006
Duration of E+P use	5.5778	0.0006	0.9649	0.0351	0.0015
CRP rs7553007	5.5802	0.0014	0.9647	0.0353	-0.0002
Education	5.6508	-0.0003	0.9643	0.0357	-0.0004
Height	5.6578	-0.0001	0.9631	0.0369	-0.0012
Waist circumference	5.7086	-0.0001	0.9624	0.0376	-0.0006
BMI	5.9430	-0.0003	0.9616	0.0384	-0.0008
HNF1A-AS1 rs7953249	5.9834	0.0045	0.9615	0.0385	-0.0001
HNF1A rs2243458	6.0142	0.0027	0.9604	0.0396	-0.0011
Weight	6.0170	-0.0001	0.9597	0.0403	-0.0008
Total months of breastfeeding	6.5938	0.0001	0.9615	0.0385	0.0019
HNF1A-AS1 rs10774579	6.9126	0.0043	0.9608	0.0392	-0.0007
HNF1A-AS1 rs1920792	6.9468	0.0044	0.9603	0.0397	-0.0005

BMI, body mass index; C-index, concordance index; E+P, exogenous estrogen + progestin; SFA, saturated fatty acids; VIMP, variable of importance. *Variables are ordered by minimal depth. †Predictive value of variable was assessed via minimal depth in the nested random survival forest models. A lower value is likely to have a greater impact on prediction. ¶The incremental error rate of each variable was estimated in the nested sequence of models starting with the top variable, followed by the model with the top 2 variables, then the model with the top 3 variables, and so on. For example, the 3rd error rate was estimated from the 3rd nested model (including the 1st, 2nd, and 3rd variables). §The drop error rate was estimated by the difference between the error rates from the nested models with a prior and the corresponding variable. For example, the drop error rate of the 2nd variable was estimated by the difference between the error rates from the 1nd and 2rd nested models. The error rate for the null model is set at 0.5; thus, the drop error rate for the 1st variable was obtained by subtracting the error rate (0.3444) from 0.5.
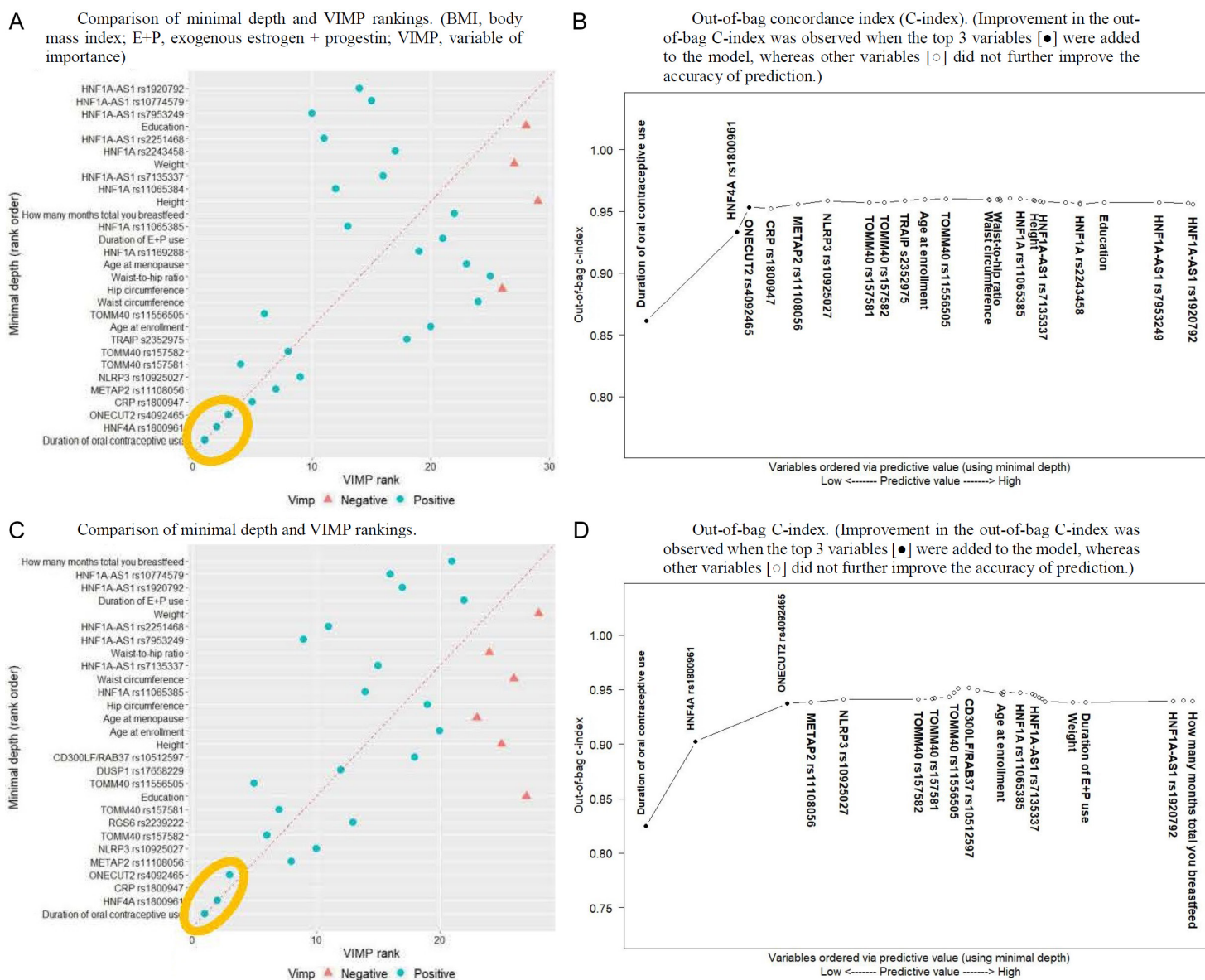
Figure S4. BMI-stratified analysis: the second stage of random survival forest (RSF) with 18 single-nucleotide polymorphisms (SNPs) and 12 behavioral factors selected from the first stage of RSF in non-overall obese group (BMI < 30, A and B); and with 17 SNPs and 12 behavioral factors selected in overall obese group (BMI ≥ 30, C and D). The variables within the gold ellipses in (A and C) were identified as the most influential predictors.
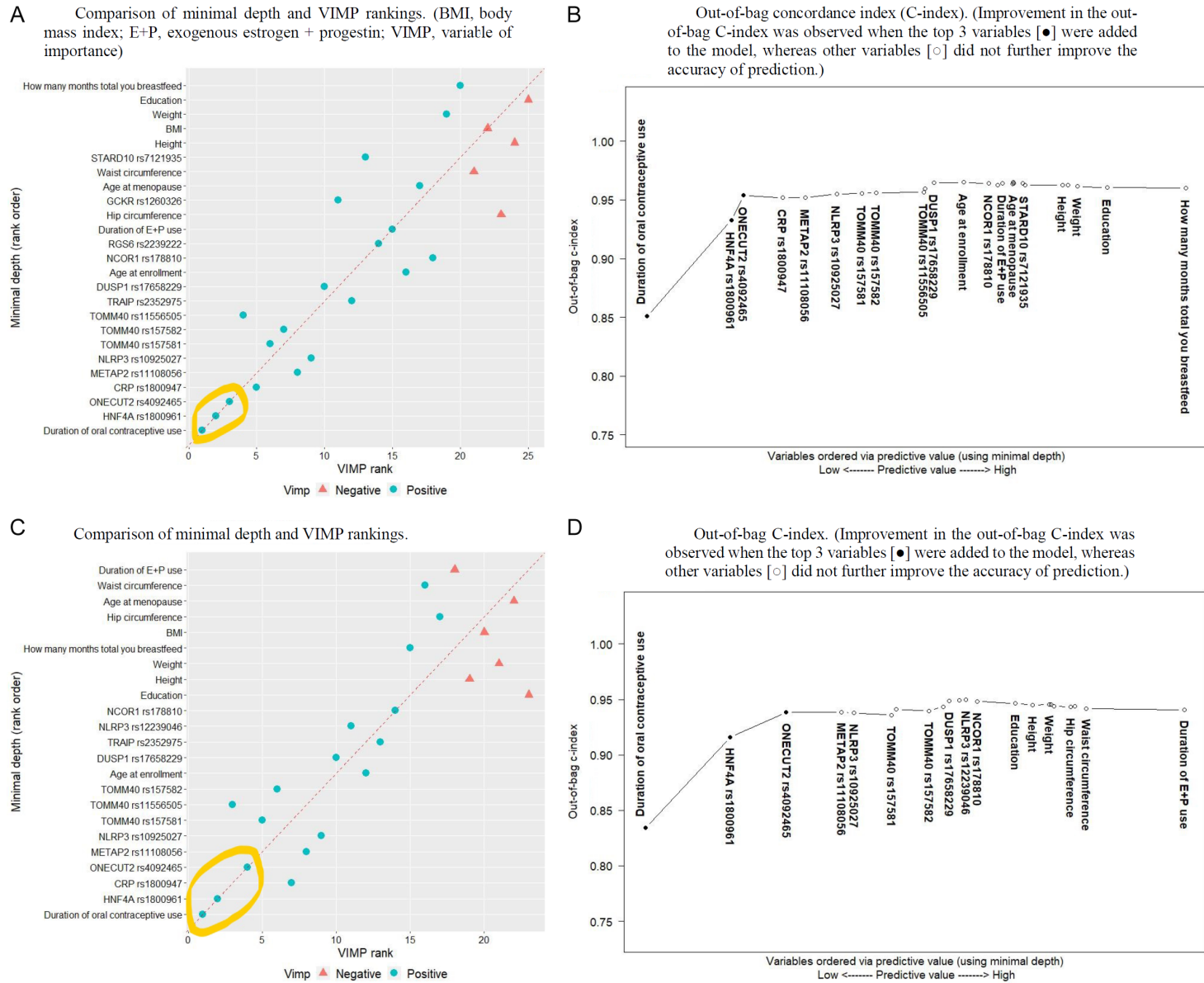
Figure S5. WHR-stratified analysis: the second stage of random survival forest (RSF) with 14 single-nucleotide polymorphisms (SNPs) and 12 behavioral factors selected from the first stage of RSF in non-viscerally obese group (WHR ≤ 0.85, A and B); and with 12 SNPs and 12 behavioral factors selected in viscerally obese group (WHR > 0.85, C and D). The variables within the gold ellipses in (A and C) were identified as the most influential predictors. (WHR, waist-to-hip ratio).
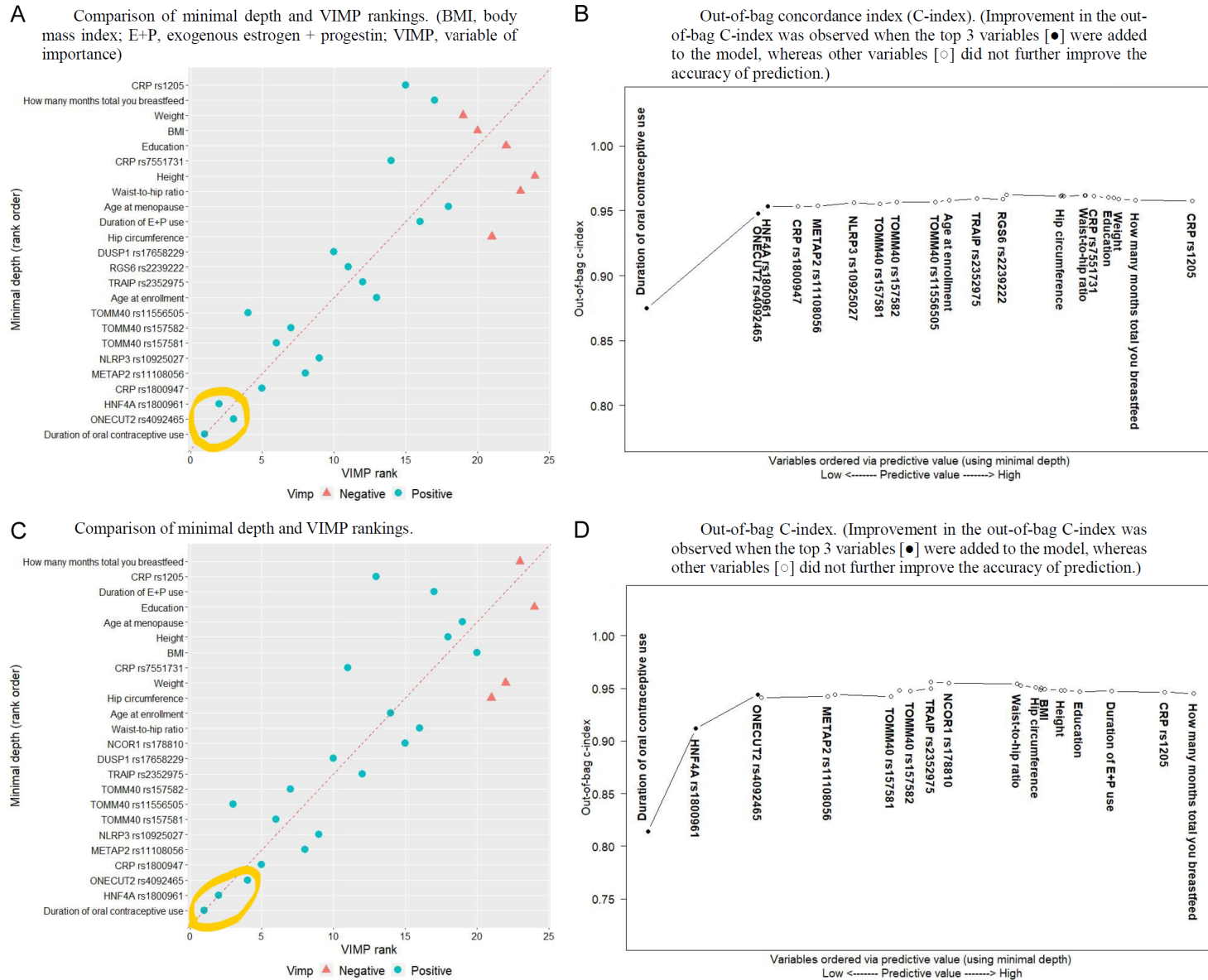
Figure S6. WST-stratified analysis: the second stage of random survival forest (RSF) with 13 single-nucleotide polymorphisms (SNPs) and 12 behavioral factors selected from the first stage of RSF in non-viscerally obese group (WST ≤ 88, A and B); and with 13 SNPs and 12 behavioral factors in viscerally obese group (WST > 88, C and D). The variables within the gold ellipses in (A and C) were identified as the most influential predictors. (WST, waist circumference.).

Figure S7. Physical activity-stratified analysis: the second stage of random survival forest (RSF) with 13 single-nucleotide polymorphisms (SNPs) and 12 behavioral factors selected from the first stage of RSF in active group (metabolic equivalent [MET] ≥ 10, A and B); and with 16 SNPs and 12 behavioral factors in inactive group (MET < 10, C and D). The variables within the gold ellipses in (A and C) were identified as the most influential predictors.
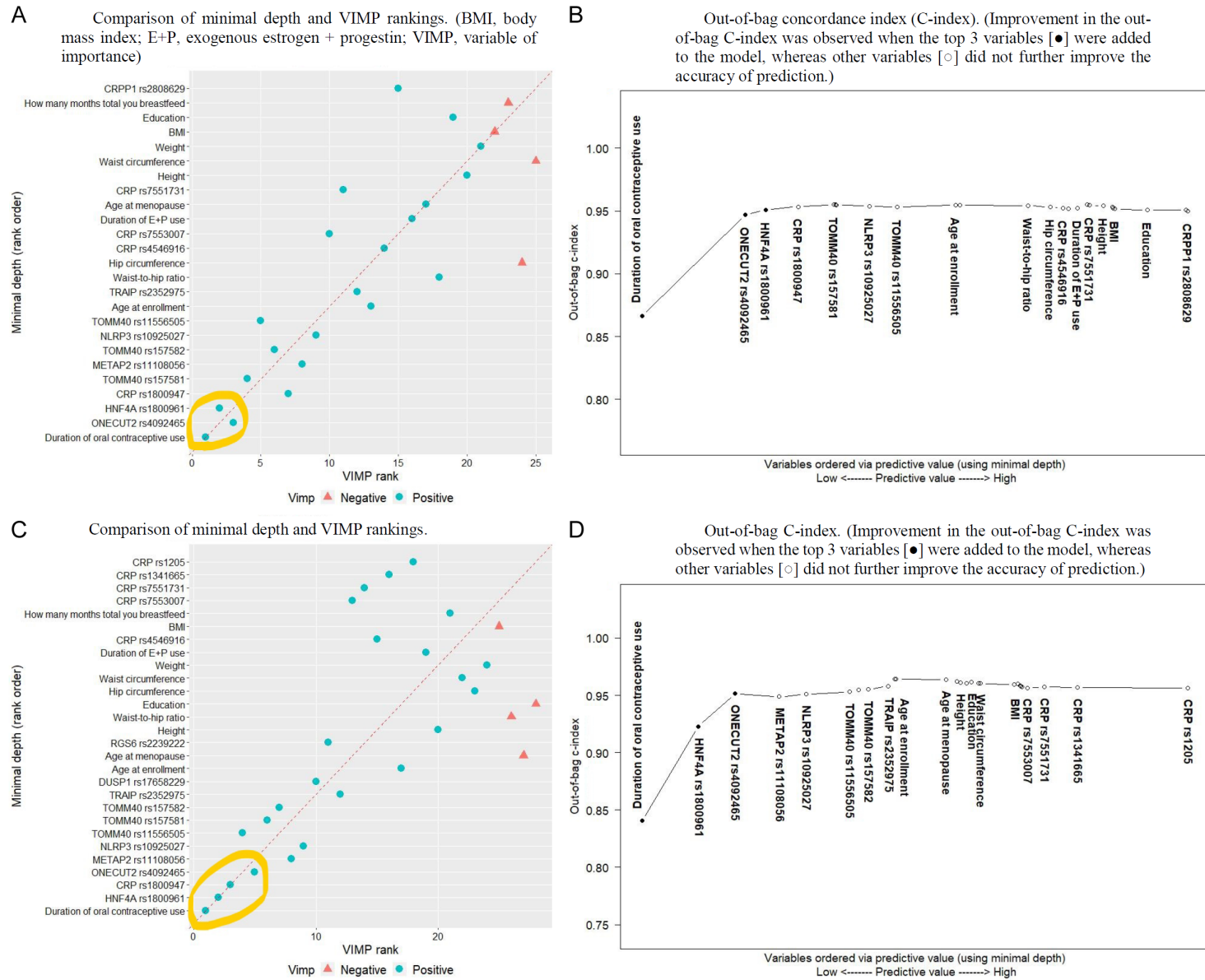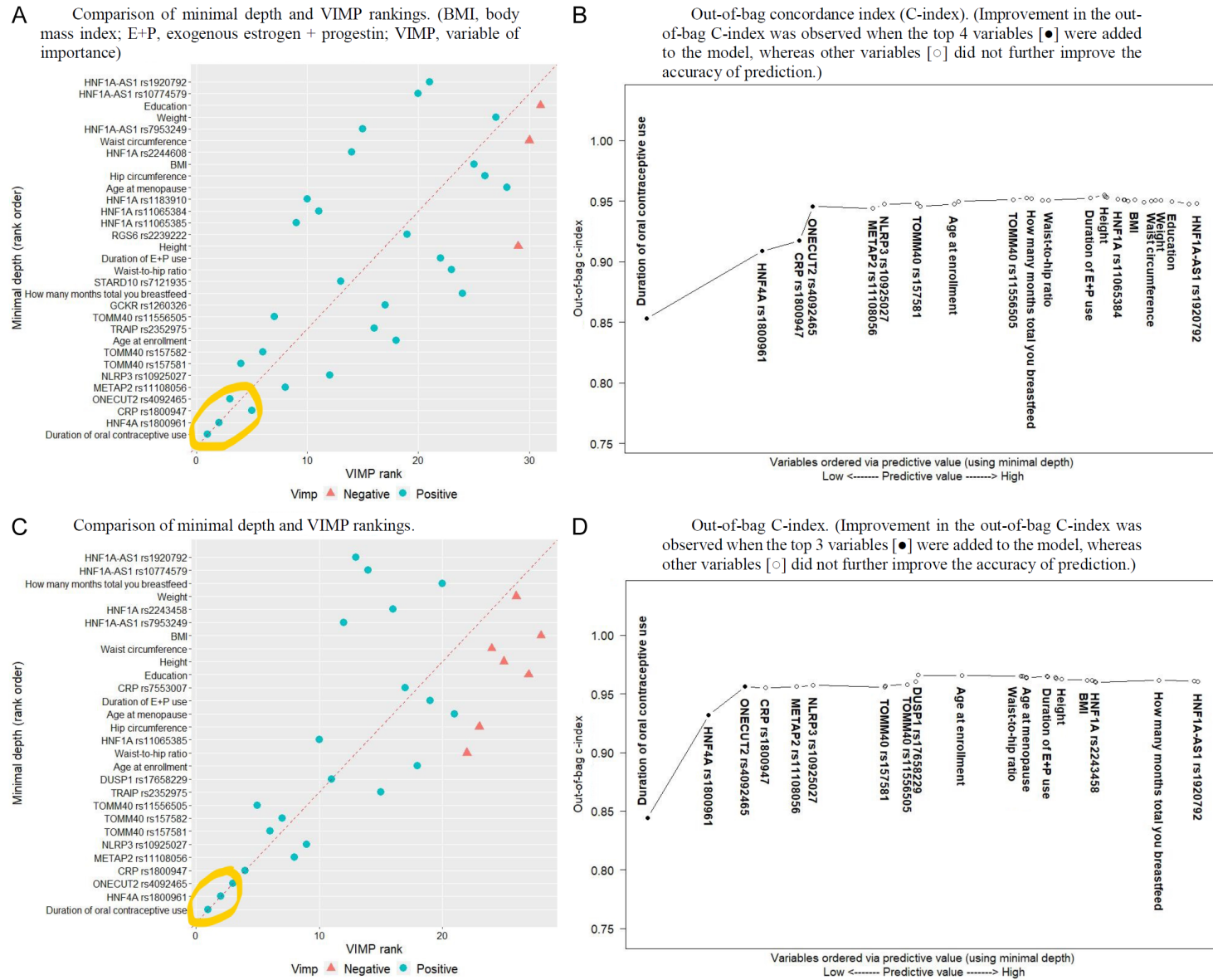
Figure S8. SFA-stratified analysis: the second stage of random survival forest (RSF) with 19 single-nucleotide polymorphisms (SNPs) and 12 behavioral factors selected from the first stage of RSF in low fat-diet group (< 9.0% calories from SFA, A and B); and with 16 SNPs and 12 behavioral factors in high fat-diet group (≥ 9.0% calories from SFA, C and D). The variables within the gold ellipses in (A and C) were identified as the most influential predictors. (SFA, saturated fatty acids.)

Table S4A. Overall analysis: results from multivariate regression predicting CRC risk

Variable	HR† (95% CI)	p
SNP (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**7.49 (5.95-9.42)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**2.68 (1.61-4.48)**	**0.000158**
Behavioral factor*		
Duration of oral contraceptive use	**2.88 (2.48-3.35)**	**< 2e-16**

Alt, alternative allele; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; Ref, reference allele; SNP, single-nucleotide polymorphism. Numbers in bold face are statistically significant. †Multivariate regression was adjusted by age at enrollment, education, body mass index, waist-to-hip ratio, age at menopause, total months of breastfeeding, and exogenous estrogen plus progestin. *A behavioral factor was analyzed as a binary variable via a cutoff value, where the cutoff level and/or higher reflects a greater risk for CRC on the basis of random survival forest analysis. The cutoff for oral contraceptive use was 5.1 years.

Table S4B. Stratified analysis: results from multivariate regression predicting CRC risk

Variable	HR† (95% CI)	p
<Non-overall obese group (BMI < 30 kg/m^2) (n=7,151)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**7.25 (5.56-9.47)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**2.63 (1.45-4.78)**	**0.00153**
Behavioral factor*		
Duration of oral contraceptive use	**3.01 (2.52-3.58)**	**< 2e-16**
<Overall obese group (BMI ≥ 30 kg/m^2) (n=2,991)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**8.27 (5.26-13.01)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**2.90 (1.08-7.85)**	**0.03549**
Behavioral factor*		
Duration of oral contraceptive use	**2.76 (2.06-3.70)**	**8.91E-12**
<Non-viscerally obese group, WHR ≤ 0.85 (n=7,222)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**8.27 (6.21-11.02)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**4.38 (1.96-9.81)**	**0.000321**
Behavioral factor*		
Duration of oral contraceptive use	**3.08 (2.57-3.68)**	**< 2e-16**
<Viscerally obese group, WHR > 0.85 (n=2,920)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**6.04 (4.11-8.88)**	**< 2e-16**
Behavioral factor*		
Duration of oral contraceptive use	**2.44 (1.85-3.21)**	**1.88E-10**
<Non-viscerally obese group, WST ≤ 88 cm (n=5,998)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**7.53 (5.55-10.23)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**4.50 (1.86-10.88)**	**0.000835**
Behavioral factor*		
Duration of oral contraceptive use	**3.46 (2.84-4.21)**	**< 2e-16**
<Viscerally obese group, WST > 88 cm (n=4,144)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**7.42 (5.24-10.50)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	1.79 (0.95-3.37)	0.06981

Behavioral factor*		
Duration of oral contraceptive use	**2.38 (1.89-3.00)**	**1.28E-13**
<Active group, MET ≥ 10.0 (n=4,203)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**7.42 (5.23-10.55)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**3.28 (1.35-7.95)**	**0.00850**
Behavioral factor*		
Duration of oral contraceptive use	**2.57 (2.04-3.22)**	**3.96E-16**
<Inactive group, MET < 10.0 (n=5,939)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**7.49 (5.53-10.16)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**2.34 (1.25-4.39)**	**0.00792**
Behavioral factor*		
Duration of oral contraceptive use	**3.15 (2.58-3.86)**	**< 2e-16**
<Low fat-diet group, < 9.0% cal. from SFA (n=2,290)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**9.91 (5.92-16.62)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**5.99 (1.48-24.26)**	**0.012135**
Behavioral factor*		
Duration of oral contraceptive use	**3.60 (2.63-4.93)**	**1.21E-15**
<High fat-diet group, ≥ 9.0% cal. from SFA (n=7,852)>		
SNPs (Ref/Alt)		
ONECUT2 rs4092465 (GG + AA/GA)	**7.01 (5.42-9.06)**	**< 2e-16**
HNF4A rs1800961 (CC + CT/TT)	**2.26 (1.30-3.92)**	**0.00368**
Behavioral factor*		
Duration of oral contraceptive use	**2.70 (2.27-3.20)**	**< 2e-16**

Alt, alternative allele; BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MET, metabolic equivalent; Ref, reference allele; SFA, saturated fatty acids; SNP, single-nucleotide polymorphism; WHR, waist-to-hip ratio; WST, waist circumference. Numbers in bold face are statistically significant. †Multivariate regression was adjusted by age at enrollment, education, BMI, WHR, age at menopause, total months of breastfeeding, and exogenous estrogen plus progestin; variables used to stratify were not included as covariates in the multivariate analysis; additional variables were adjusted in specific strata (height and weight were adjusted in BMI strata; waist and hip circumferences, in WHR strata; and hip circumference instead of WHR, in WST strata). *A behavioral factor was analyzed as a binary variable via a cutoff value, where the cutoff level and/or higher reflects a greater risk for CRC on the basis of random survival forest analysis. The cutoff for oral contraceptive use was 5.1 years.

Table S5. Combined effect of past OC use and risk genotypes (ONECUT2 rs4092465 GA; HNF4A rs1800961 TT) on CRC risk in obesity strata

n£	n total	HR† (95% CI)	p*
<Non-viscerally obese group, WHR ≤ 0.85 (n=7,222)>			
0	2,590	reference	
1	3,525	**5.45 (3.78-7.85)**	**< 2e-16**
2	1,107	**22.63 (15.68-32.66)**	**< 2e-16**
p_{trend}			**< 2e-16**
<Viscerally obese group, WHR > 0.85 (n=2,920)>§			
0	908	reference	
1	1,456	**3.01 (1.88-4.83)**	**4.98E-06**
2	556	**11.00 (6.84-17.69)**	**< 2e-16**
p_{trend}			**< 2e-16**
<Non-viscerally obese group, WST ≤ 88 cm (n=5,998)>			
0	2,206	reference	
1	2,953	**4.95 (3.39-7.24)**	**< 2e-16**
2	839	**22.06 (15.04-32.35)**	**< 2e-16**
p_{trend}			**< 2e-16**
<Viscerally obese group, WST > 88 cm (n=4,144)>			
0	1,353	reference	
1	1,996	**3.78 (2.49-5.76)**	**5.35E-10**
2	795	**13.64 (8.96-20.76)**	**< 2e-16**
p_{trend}			**< 2e-16**
<Active group, MET ≥ 10.0 (n=4,203)>			
0	1,481	reference	
1	2,105	**4.71 (3.09-7.19)**	**6.12E-13**
2	617	**16.80 (10.92-25.85)**	**< 2e-16**
p_{trend}			**< 2e-16**
<Inactive group, MET < 10.0 (n=5,939)>			
0	2,078	reference	
1	2,844	**4.16 (2.85-6.07)**	**1.42E-13**
2	1,017	**18.03 (12.38-26.27)**	**< 2e-16**
p_{trend}			**< 2e-16**
<Low fat-diet group, < 9.0% cal. from SFA (n=2,290)>			
0	788	reference	
1	1,137	**3.36 (1.88-5.99)**	**4.05E-05**
2	365	**19.93 (11.28-35.21)**	**< 2e-16**
p_{trend}			**< 2e-16**
<High fat-diet group, ≥ 9.0% cal. from SFA (n=7,852)>			
0	2,771	reference	
1	3,812	**4.75 (3.44-6.56)**	**< 2e-16**
2	1,269	**16.94 (12.22-23.49)**	**< 2e-16**
p_{trend}			**< 2e-16**

CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MET, metabolic equivalent; OC, oral contraceptive; SFA, saturated fatty acids; WHR, waist-to-hip ratio; WST, waist circumference. Numbers in bold face are statistically significant. £The combined number of risk genotypes and behavioral factors was based on 1) risk genotypes defined as 0 (low risk: none or 1 risk allele) and 1 (high risk: 2 risk alleles) and 2) behavioral factors defined as 0 (low risk: past OC use ≥ 5.1 years) and 1 (high risk: past OC use < 5.1 years). The ultimate number of combined risk genotypes and behavioral factors was defined as 0 (low risk for genotypes and behaviors), 1 (high risk for either genotypes or behaviors), and 2 (high risk for both genotypes and behaviors). §In the viscerally obese group (WHR), only the *ONECUT2* rs4092465 GA genotype was analyzed. †Multivariate regression was adjusted by age at enrollment, education, body mass index, hip and waist circumferences (both in WHR strata; hip only in WST strata), waist-to-hip ratio (in MET and SFA strata), age at menopause, total months of breastfeeding, and exogenous estrogen plus progestin. *p values were adjusted to correct for multiple testing via the Benjamini-Hochberg approach.

Table S6. Joint effect of past OC use with risk genotypes (ONECUT2 rs4092465 GA; HNF4A rs1800961 TT) on CRC risk in obesity strata

n£	Total		Past OC use ≥ 5.1 years			Past OC use < 5.1 years		
	HR† (95% CI)	p*	n	HR† (95% CI)	p*	n	HR† (95% CI)	p*
<Non-viscerally obese group, WHR ≤ 0.85 (n=7,222)>								
Risk genotypes								
0	reference		2,590	reference		984	**1.80 (1.04-3.11)**	**0.036327**
1	**8.76 (6.61-11.61)**	**< 2e-16**	2,541	**6.72 (4.66-9.70)**	**< 2e-16**	1,107	**22.05 (15.28-31.83)**	**< 2e-16**
p_{trend}					**< 2e-16**			
<Viscerally obese group, WHR > 0.85 (n=2,920)>								
Risk genotypes§								
0	reference		908	reference		479	0.96 (0.44-2.11)	0.928426
1	**6.02 (4.09 - 8.85)**	**< 2e-16**	977	**3.85 (2.39-6.20)**	**3.19e-08**	556	**10.82 (6.73-17.40)**	**< 2e-16**
p_{trend}					**< 2e-16**			
<Non-viscerally obese group, WST ≤ 88 cm (n=5,998)>								
Risk genotypes								
0	reference		2,206	reference		747	**2.02 (1.14-3.58)**	**0.01653**
1	**7.60 (5.65-10.21)**	**< 2e-16**	2,206	**5.82 (3.98-8.53)**	**< 2e-16**	839	**21.66 (14.76-31.77)**	**< 2e-16**
p_{trend}					**< 2e-16**			
<Viscerally obese group, WST > 88 cm (n=4,144)>								
Risk genotypes								
0	reference		1,353	reference		745	1.23 (0.65-2.32)	0.52740
1	**7.15 (5.15-9.93)**	**< 2e-16**	1,251	**5.06 (3.31-7.74)**	**6.47e-14**	795	**13.35 (8.77-20.32)**	**< 2e-16**
p_{trend}					**< 2e-16**			
<Active group, MET ≥ 10.0 (n=4,203)>								
Risk genotypes								
0	reference		1,481	reference		563	1.25 (0.62-2.55)	0.53390
1	**7.97 (5.64-11.28)**	**< 2e-16**	1,542	**5.85 (3.83-8.93)**	**3.13e-16**	617	**16.39 (10.65-25.22)**	**< 2e-16**
p_{trend}					**< 2e-16**			
<Inactive group, MET < 10.0 (n=5,939)>								
Risk genotypes								
0	reference		2,078	reference		929	**1.83 (1.07-3.13)**	**0.02792**
1	**6.97 (5.25-9.26)**	**< 2e-16**	1,915	**5.13 (3.50-7.52)**	**< 2e-16**	1,017	**17.67 (12.13-25.74)**	**< 2e-16**
p_{trend}					**< 2e-16**			
<Low fat-diet group, < 9.0% cal. from SFA (n=2,290)>								
Risk genotypes								
0	reference		788	reference		362	0.67 (0.22-2.06)	0.488644
1	**9.73 (5.96-15.90)**	**< 2e-16**	775	**4.50 (2.52-8.05)**	**3.99e-07**	365	**19.59 (11.09-34.60)**	**< 2e-16**
p_{trend}					**< 2e-16**			
<High fat-diet group, ≥ 9.0% cal. from SFA (n=7,852)>								
Risk genotypes								
0	reference		2,771	reference		1,130	**1.90 (1.19-3.04)**	**0.00715**
1	**6.92 (5.42-8.85)**	**< 2e-16**	2,682	**5.80 (4.19-8.03)**	**< 2e-16**	1,269	**16.50 (11.90-22.89)**	**< 2e-16**
p_{trend}					**< 2e-16**			

CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MET, metabolic equivalent; OC, oral contraceptive; SFA, saturated fatty acids; WHR, waist-to-hip ratio; WST, waist circumference. Numbers in bold face are statistically significant. £The number of risk genotypes was defined on the basis of Kaplan-Meier's analysis as follows: 0 (none or 1 risk allele) and 1 (2 risk alleles). †Multivariate regression was adjusted by age at enrollment, education, body mass index, hip and waist circumferences (both in WHR strata; hip only in WST strata), waist-to-hip ratio (in MET and SFA strata), age at menopause, total months of breastfeeding, OC use (in total analysis), and exogenous estrogen plus progestin. *p values were adjusted to correct for multiple testing via the Benjamini-Hochberg approach. §In the viscerally obese group (WHR), only the ONECUT2 rs4092465 GA genotype was analyzed.