Supplementary Table 1. Details of SNPs included in each of the models

SNP	Chromosome	Position	Abe 2017	Dunlop 2013	Frampton 2016	Hosono 2016	Hsu 2015	Huyghe 2019	Ibanez-Sanz 2017	Iwasaki 2017	Jenkins 2016	Jeon 2018	Smith 2018	Wang 2013	Xin 2018	Yarnall 2013
rs72647484	1	22,587,728			●			●			●	●				
rs4360494	1	38,455,891						●								
rs12144319	1	55,246,035						●								
rs10752881	1	182,973,491							●							
rs6678517	1	183,002,639						●								
rs10911251	1	183,081,194			●		●				●	●	●			
rs6691170	1	222,045,446			●		●		●			●				●
rs17011141	1	222,112,634						●								
rs6687758	1	222,164,948					●				●	●	●			
rs448513	2	159,964,552						●								
rs11903757	2	192,587,204					●				●	●	●			
rs11884596	2	199,612,407						●								
rs983402	2	199,781,586						●								
rs231775	2	204,732,714												●		
rs3731861	2	219,191,256						●								
rs3731055	3	14,220,439												●		
rs35470271	3	40,915,239						●								
rs35360328	3	40,924,962			●						●	●	●			
rs6781752	3	66,365,163						●								
rs812481	3	66,442,435			●						●	●	●			
rs13086367	3	112,903,888						●								
rs72942485	3	112,999,560						●								
rs10049390	3	133,701,119						●								
rs10936599	3	169,492,101	●		●	●	●		●		●	●	●			●
rs9876206	3	169,517,436						●								
rs13149359	4	94,938,618						●								
rs1391441	4	106,128,760						●								
rs3987	4	118,759,055									●					
rs11727676	4	145,659,064						●								
rs35509282	4	163,333,405			●						●					
rs11721827	4	186,991,137												●		
rs78368589	5	1,240,204						●								
rs2736100	5	1,286,516												●		
rs2735940	5	1,296,486						●								
rs7708610	5	40,102,443						●								
rs12514517	5	40,280,076						●								
rs160277	5	82,837,631												●		
rs186474654	5	96,137,458										●				
rs145364999	5	98,206,082						●								
rs755229494	5	112,097,351						●								
rs4976270	5	134,467,220						●								
rs647161	5	134,499,092	●		●		●				●	●	●			
rs116353863	6	31,010,185						●								
rs116685461	6	31,315,512						●								
rs2516420	6	31,449,620						●								
rs9271695	6	32,593,080						●								
rs16878812	6	35,569,562						●								
rs1321311	6	36,622,900			●		●		●		●	●	●			
rs9470361	6	36,623,379						●								
rs1983891	6	41,536,427												●		
rs4711689	6	41,692,812										●			●	
rs62396735	6	41,702,582						●								
rs13204733	6	55,566,108						●								
rs62404966	6	55,712,124						●								
rs712221	6	152,180,241												●		
rs7758229	6	160,840,252							●			●	●			
rs12672022	7	45,136,423						●								
rs80077929	7	46,094,089						●								
rs3214050	8	95,186,382												●		
rs2450115	8	117,624,093										●			●	
rs16892766	8	117,630,683		●	●		●	●	●		●	●	●			●
rs6469654	8	117,632,965						●								
rs6469656	8	117,647,788										●				

rs117079142	8	117,790,914	
rs10505477	8	128,407,443	
rs6983267	8	128,413,305	
rs7013278	8	128,414,892	
rs7014346	8	128,424,792	
rs4313119	8	128,571,855	
rs719725	9	6,365,683	
rs1412829	9	22,043,926	
rs1537372	9	22,103,183	
rs34405347	9	101,679,752	
rs10980628	9	113,671,403	
rs12217641	10	8,663,875	
rs10795668	10	8,701,219	
rs11255841	10	8,739,580	
rs10904849	10	16,997,266	
rs10821907	10	52,648,454	
rs4948317	10	60,571,435	
rs704017	10	80,819,132	
rs1250567	10	81,046,265	
rs10786560	10	101,315,166	
rs1035209	10	101,345,366	
rs11190164	10	101,351,704	
rs4919687	10	104,595,248	
rs12241008	10	114,280,702	
rs12246635	10	114,288,619	
rs10506868	10	114,319,380	
rs11196170	10	114,722,621	
rs11196172	10	114,726,843	
rs174533	11	61,549,025	
rs174537	11	61,552,680	
rs4246215	11	61,564,299	
rs174550	11	61,571,478	
rs1535	11	61,597,972	
rs869736	11	67,205,462	
rs7121958	11	74,280,012	
rs3824999	11	74,345,550	
rs7946853	11	74,409,077	
rs61389091	11	74,427,921	
rs55864876	11	100,717,136	
rs2186607	11	101,656,397	
rs3087967	11	111,156,836	
rs3802842	11	111,171,709	
rs12309274	12	975,948	
rs10774214	12	4,368,352	
rs35808169	12	4,368,607	
rs3217810	12	4,388,271	
rs3217874	12	4,400,808	
rs3217901	12	4,405,389	
rs10849432	12	6,385,727	
rs10849433	12	6,406,904	
rs2250430	12	6,421,174	
rs11064437	12	6,982,162	
rs2238126	12	12,009,741	
rs2710310	12	12,035,649	
rs11610543	12	43,134,191	
rs7136702	12	50,880,216	
rs11169552	12	51,155,663	
rs12372718	12	51,171,090	
rs4759277	12	57,533,690	
rs10879357	12	72,414,563	
rs3184504	12	111,884,608	
rs597808	12	111,973,358	
rs1427760	12	115,100,714	
rs59336	12	115,116,352	
rs7300312	12	115,890,922	
rs7315438	12	115,891,403	
rs73208120	12	117,747,590	

rs1572072	13	24,127,210												●		
rs10161980	13	34,092,164						●								
rs7333607	13	37,462,010						●								
rs45597035	13	73,649,152						●								
rs78341008	13	73,791,554						●								
rs1924816	13	73,997,961						●								
rs8000189	13	111,075,881						●								
rs1760944	14	20,923,149												●		
rs1951864	14	54,369,299						●								
rs4444235	14	54,410,919	●	●	●	●	●		●		●	●	●			●
rs35107139	14	54,419,106						●								
rs4901473	14	54,445,157						●								
rs1957636	14	54,560,018			●		●				●	●	●			
rs17094983	14	59,189,361						●								
rs8020436	14	59,208,437						●								
rs12708491	15	32,992,836						●								
rs16969681	15	32,993,111	●			●	●				●	●				
rs4779584	15	32,994,756	●	●	●	●	●					●	●		●	●
rs11632715	15	33,004,247					●				●	●				
rs2293581	15	33,010,736						●								
rs17816465	15	33,156,386						●								
rs12594720	15	67,007,018						●								
rs56324967	15	67,402,824						●								
rs745213	15	68,060,389						●								
rs79900961	16	9,297,812										●				
rs9924886	16	68,743,939						●								
rs9929218	16	68,820,946	●	●	●	●	●		●		●	●	●			●
rs9930005	16	80,043,258						●								
rs12447408	16	86,252,544						●								
rs12149163	16	86,339,315						●								
rs16941835	16	86,695,720			●						●	●				
rs62042090	16	86,703,949						●								
rs12603526	17	800,593										●	●		●	
rs4968127	17	809,643						●								
rs73975586	17	814,243						●								
rs1078643	17	10,707,241						●								
rs3135967	17	33,313,729												●		
rs744166	17	40,514,201									●					
rs983318	17	70,413,253						●								
rs373585858	17	80,394,556						●								
rs75954926	17	81,061,048						●								
rs7229639	18	46,450,976										●	●		●	
rs11874392	18	46,453,156						●								
rs4939827	18	46,453,463		●	●		●		●	●	●	●	●			●
rs34797592	19	16,417,198						●								
rs28840750	19	33,519,927						●								
rs10411210	19	33,532,300		●	●		●		●		●	●	●	●		●
rs1800469	19	41,860,296			●						●	●	●			
rs2241714	19	41,869,392									●	●				
rs1963413	19	41,871,573						●								
rs1799782	19	44,057,574												●		
rs73068325	19	59,079,096						●								
rs189583	20	6,376,457						●								
rs961253	20	6,404,281		●	●		●		●		●	●	●			●
rs994308	20	6,603,622						●								
rs4813802	20	6,699,595			●		●	●			●	●	●			
rs28488	20	6,762,221						●								
rs11087784	20	7,740,976						●								
rs2423279	20	7,812,350	●				●				●	●	●		●	
rs556532366	20	8,568,071						●								
rs6058093	20	33,213,196						●								
rs6031311	20	42,666,475						●								
rs6066825	20	47,340,117			●			●			●	●	●		●	
rs6067417	20	48,983,697						●								
rs6063514	20	49,055,318						●								
rs6091189	20	49,256,285						●								
rs4925386	20	60,921,044			●		●		●		●	●	●			●

rs1741640	20	60,932,414
rs6061231	20	60,956,917
rs2738783	20	62,308,612
rs5934683	23	9,751,474

Supplementary Table 2. Derivation of phenotypic risk scores variables

Age: For all models including age either as a categorical or continuous variable the age of participants when they first attended the Biobank assessment centre was used.
Sex: For all models including sex, sex at baseline was used to categorise participants into male and female.
Ethnicity: The Smith (Wells) model for both men and women include a predictor with ethnicity defined as Hawaiian, Japanese, Latino or White Due to the predominantly white population in UK Biobank and the fact that the ethnicity data collected in the Biobank cohort did not include separate categories for many of these groups, we considered only White and Black ethnic groups in our analysis
BMI: The UK Biobank variable for BMI as constructed from height and weight measured during the initial assessment centre visit was used in all models including BMI as either a categorical or continuous variable.
Family history: The models which included family history did so with a categorical variable (yes/no). Biobank collected data on whether the participants' mother, father or (any of their) siblings have been affected by bowel cancer. A positive response was considered as a positive family history for this relative (father, mother, sibling). If the participant reported having been adopted or doesn't know if father or mother are still alive or number of siblings is unknown the corresponding value was set to missing. The FH variable was set to missing if the data for all the relatives was missing or set to 1 if at least one of the relatives had been affected by bowel cancer. For the Jenkins model FH was coded as 0, 1, or 2 or more first degree relatives.
Smoking: Pack years of smoking were included in the Abe and Hosono models as categorical variables (never, PY < 15, PY < 30, PY < 45, and PY ≧45). In the Jeon model smoking pack-years among ever smokers was harmonized across studies by sex- and study-specific quartiles and for never smokers it was assigned as "0." This variable was treated as a continuous variable in the analysis. The variables in UK Biobank used for this calculation are the age started smoking and (if relevant for ex-smokers) the age stopped smoking and the number of cigarettes smoked per day (in packs of 20). Pack years are estimated as the number of packs of cigarettes smoked per day multiplied by the number of years of smoking. A reduction of 6 months from the length of time smoking was applied for people who reported that they had previously quit smoking, but had then returned to smoking. People who reported smoking "less than 1" cigarette a day were coded as 0.5 cigarettes per day for this calculation. People who reported cigar or pipe smoking had pack years coded as missing; people who reported having smoked only "occasionally" or "once or twice" were coded with 0 pack years. For other models (Iwasaki, Jeon, Yarnall) smoking was incorporated as a binary or categorical variable using the baseline smoking status variable in Biobank (current, ex-smoker, never smoker).
Alcohol: Alcohol consumption was defined either as a categorical variable (never drinker, <5 g, <23 g, <46 g and ≧46 g ethanol/day in the Abe and Hosono models, <1 g/d, 1–28 g/d, >28 g/d in the Jeon[7] model, low-risk and high-risk consumption (> 4 units/day in men and > 2 units/day in women) between 30 and 40 years of age in the Ibanez-Sanz model, never/occasional/regular <300g per week/≥300g per week in the Iwasaki model and light/non drinkers, moderate drinkers and heavy drinkers (> 6.2 units) in the Yarnall model), or as a continuous variable as units/day (Smith (Wells) model). Consumption of alcohol was collected in Biobank using a screening question 'How often do you drink alcohol?' with responses 'Daily or almost daily', 'three or four times a week', 'once or twice a week', 'one to three times a month', 'special occasions only', 'never'. We defined rarely or occasional as 'one to three times a month' or 'special occasions only'. Where participants were asked about their weekly or monthly consumption of a range of different alcoholic drinks we calculated intake as units and grams per week. For this we converted the number of drinks within each category to units and then multiplied by 8 (the number of grams per unit in the UK). We then added up the available data so that the total amount is only missing when all information on beer, wine, spirit, etc consumption is missing. For the Ibanez_Sanz model we used the total number of units of alcohol and didn't take the age range into account as there is no information in UK Biobank on the alcohol consumption at a specific age. **References:** NHS Choices Livewell Alcohol Units. https://www.nhs.uk/live-well/alcohol-support/calculating-alcohol-units/ (accessed 18 Dec2018). Department of Health, Alcohol Units, page 10.

https://lx.iriss.org.uk/sites/default/files/resources/Alcohol%20Units%20a%20brief%20guide.pdf (accessed 18 Dec2018)
UK Parliament Alcohol Guidelines.
https://www.publications.parliament.uk/pa/cm201012/cmselect/cmsctech/1536/153605.htm (accessed 18 Dec2018).

Physical activity: Physical activity in the Ibanez_Sanz model is defined in terms of MET-hours and coded as a binary variable comparing people with zero and more than zero leisure time physical activity. In the Abe, Hosono, Smith (Wells) and Yarnall models physical activity was included as either a categorical or continuous variable calculated as average daily exercise hours in any intensity and categorized into the three levels of none, <0.5 h/day and ≧0.5 h/day (Abe, Hosono) and two levels of inactive/active in Yarnall. In the Jeon model physical activity was defined as "yes" if the total of vigorous and moderate physical activities is >=1 h/wk, and "no" otherwise. We used responses to questions about frequency (number of days per week of 10+ mins of type of activity) and duration of different types of physical activity (minutes of moderate/vigorous/ walking) to derive average hours spent on each type of activity. The average duration was set to 10 minutes if the frequency was given but the duration is missing or if the duration was less than 10 minutes. If the frequency for an activity was given as zero the duration was set to zero. The times spent on each type of activity were then added up to get the hours of physical activity per day and per week.

Reference:
Celis-Morales CA, Lyall DM, Anderson J, et al. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. Eur Heart J 2016;38:ehw249.

Red meat and processed meat consumption: We considered beef, pork and lamb as red meat. The Ibanez-Sanz model included a categorical variable, high intake of red and processed meat was considered eating ≥ 65 g/day (yes/no). Red meat and processed meat intake in the Jeon[7] model were harmonized across studies by sex and study-specific quartiles and then treated as continuous variables in the analysis. The Yarnall model included red and processed meat consumption as a continuous variable (per 100 g) and the Smith (Wells) model a continuous variable as ounces per day. For each of beef, lamb, pork and processed meat, participants in Biobank had indicated how often they ate them (Never, < once per week, once per week, 2-4 times per week, 5-6 times per week, once or more daily). We used the mid-point for each category to calculate red/processed meat consumption per day by adding up the amounts of different types of meat to get a continuous variable for each participant. This was then multiplied by a portion size of 70g to obtain grams per day.
We calculated quartiles of intake based on all non-missing responses in UK Biobank.

Reference:
World Health Organisation Q&A on the carcinogenicity of the consumption of red meat and processed meat. http://www.who.int/features/qa/cancer-red-meat/en/ (accessed 18 July 2019).
NHS Choices Livewell Meat. http://www.nhs.uk/Livewell/Goodfood/Pages/meat.aspx (accessed 18 July 2019).

Vegetables: In the Ibanez-Sanz model vegetable consumption was categorized into low or high intake using 200 g/day as cut-off. Vegetable intake in the Jeon model was harmonized across studies by sex and study-specific quartiles and then treated as continuous variable in the analysis.
Participants in UK Biobank were asked how many heaped tablespoons of salad and raw and cooked vegetables they were eating per day. If participants reported less than one we coded this as half a tablespoon. We then converted these numbers into number of portions, where one portion of vegetables was defined as 3 heaped tablespoons of cooked or raw vegetables[58]. We added up these numbers and multiplied by 80g to get the amount of vegetables eaten in grams per day.
We calculated quartiles of intake based on all non-missing responses in UK Biobank.

Fibre intake: Fibre intake in the Jeon model was harmonized across studies by sex and study-specific quartiles and then treated as a continuous variable in the analysis. In the Yarnall model the fibre intake was categorized in < 10 g/day, one 10 g serving of whole grains/day and three 10 g servings of whole grains/day.
As the Englyst dietary fibre variable in UK Biobank has lots of missing data we calculated the partial fibre score in the same way as Bradbury: We assigned pieces of fruit, tablespoons of vegetables, slices of bread and bowls of breakfast cereals an approximate non-starch polysaccharide content. To calculate the fibre score we multiplied the fibre content by the frequency of consumption for each food ('less than one' was coded as 0.5). For bread and breakfast cereal for which the touchscreen questionnaire asked about weekly consumption, the results were converted into a daily average. We

then summed the fibre intakes to get a daily estimated partial fibre intake. Participants who selected 'do not know' or 'prefer not to answer' for bread type or breakfast cereal type, but who reported their frequency of consumption of these food items, were assigned the average fibre content of these items. We calculated quartiles of intake based on all non-missing responses in UK Biobank.

Fruit Consumption: Fruit intake in the Jeon model was harmonized across studies by sex and study-specific quartiles and then treated as continuous variable in the analysis. Participants in UK Biobank were asked how many pieces of fresh and dried fruit they were eating per day. "Less than one" was coded as 0.5 and the portions for fresh and dried fruit were added up. We calculated quartiles of intake based on all non-missing responses in UK Biobank.

Reference:

NHS Choices Livewell Portion sizes. http://www.nhs.uk/Livewell/5ADAY/Pages/Portionsizes.aspx (accessed 18 July 2019).

Folate, Calcium and Total Energy intake: Folate consumption was used in the Abe and Hosono models as a variable derived from a food frequency questionnaire and then divided into three groups based on the distribution (tertiles) of folate consumption among controls. Folate, calcium and total energy intake in the Jeon model were harmonized across studies by sex and study-specific quartiles and then treated as continuous variables in the analysis. The corresponding variables in UK Biobank were derived from diet questionnaires, gathered during 5 'rounds', with the initial round carried out in the Assessment Centres and later rounds via an online questionnaire. The folate/calcium/total energy intake is an estimated value based on food and beverage consumption the previous day, excluding any supplements. We excluded dietary data when this was collected after CRC diagnosis. We also excluded data marked by UK Biobank as not credible, that is if the daily energy intake exceeded 20MJ for Males or 18MJ for Females. When more than one value per participant were available we used the mean folate/calcium/Total Energy of the different values. We calculated teriles/quartiles of intake based on all non-missing responses in UK Biobank.

Aspirin and NSAID use: The Jeon model includes a categorical variable for regular use of aspirin and one for regular nonsteroidal anti-inflammatory drug use (yes/no), the Smith (Wells) model includes three categories (no/yes, not currently/yes, currently) and the Ibanez-Sanz model included a categorical (yes/no) variable for regular use of NSAIDs/ASAs (consumed more than once per day for at least one year). As historic data is not available in Biobank, all participants who answered yes for aspirin to the question 'Do you regularly take any of the following? Aspirin, Ibuprofen, Paracetamol, Codeine' or had a code identified by a clinician on the team as indicating aspirin or NSAID use in the list of current regular treatments were coded as regular or current users. Previous users and non-users were collapsed into one category in the Smith (Wells) model.

Height: The Jeon model includes height as a continuous variable. We used the variable for standing height measured at the first assessment visit from the Biobank data for this.

Education: The Jeon model includes a categorical variable for education: Cat1 - less than high school graduate; Cat2 - high school graduate or completed General Educational Development; Cat3 - some college or technical school; Cat4 - college graduate or more. The equivalent variable in Biobank gives the different qualifications a participant has and we mapped the qualifications to the categories like this: Cat1: O levels/GCSEs, CSEs and Other professional qualifications; Cat2: A levels/AS levels; Cat3: NVQ or HND or HNC; Cat4: College or University degree. The Smith (Wells) model included a continuous variable for number of years spent in education. The equivalent variable in Biobank was the age at which participants completed their continuous full time education. The number of years spent in education was computed by subtracting 5 (the age children start UK primary education) from the age at which participants completed their full time education. All those who had a value of less than 0 were set to 0.

Postmenopausal Hormones use: The Jeon model included a categorical variable for regular use of postmenopausal hormones (no/yes). We generated a variable for this based on the responses from participants in Biobank to four questions. To identify postmenopausal women we used the responses to "Had menopause" and treated "Not sure (other reason)" as not postmenopausal and for "Not sure (had hysterectomy)" we used the average age of the menopause in the UK (51) to define post-menopausal women. We used responses to "Have you ever used HRT?" and "When did you last use HRT?" and we also used the medication variable "Do you regularly take any medication – HRT" to identify current users of HRT. We then combined these variables to identify current postmenopausal users for HRT as all women who said they had their menopause and are either still using hormone-replacement therapy (HRT) or are still taking medication for HRT.

Oestrogen use: The Smith (Wells) model for females included categorical variables for oestrogen use (current user/past user). We generated proxy variables for these based on the responses from

participants in Biobank to six questions. First we used the responses to "Have you ever used HRT?" and "When did you last use HRT?" to identify current and past users for HRT. As participants were only asked when they last used HRT if they had responded 'yes' to the question "Have you ever used HRT?", those who answered "Do not know" or "Prefer not to answer" to that question were treated as past users. The two corresponding questions for oral contraceptive pill use were used in the same way to identify current and past users of oral contraceptive pills. It was not possible to distinguish between oestrogen-containing oral contraceptive pills and progesterone-only pills.

Referral Pattern: The Abe and Hosono models included categorical variables for referral pattern to the hospital (patient discretion, family or friend recommendation, referral from another clinic, secondary screening after primary screening and other). As this data was not available in UK Biobank this variable was removed from the models.

Diabetes: The Jeon model included a categorical variable for whether participants had a history of type 2 diabetes (yes/no) and the Smith (Wells) models a categorical variable for 'diabetes'. The corresponding variable in the Biobank cohort was self-report diagnosis of either 'Diabetes', 'Type 1 diabetes' 'gestational diabetes' or 'Type 2 diabetes' at the interview with a nurse at the baseline assessment. The majority were coded as 'Diabetes' without distinguishing between the various subtypes. Participants with either 'Type 2 diabetes' or 'Diabetes' were therefore included for the Jeon model.

Handling of missing data: There is variation across questions within the Biobank baseline assessment in how missing responses had been recorded. For example, for some questions a missing response is "truly missing" (i.e. we do not know whether the response means that a risk factor is present or not), while for others, such as medical history or current medication, the absence of an entry means that the risk factor is absent (i.e. it is appropriate to code these as zero, rather than missing). For each risk factor we checked the original question wording and response coding to ensure that we took the correct approach. Where the calculation of a risk factor variable for a model required the combination of multiple responses from across multiple Biobank baseline survey questions, consistent with other external validation approaches, we used a combination of practical choices with the over-arching approach to ensure missing values were coded where the missingness was truly uninformative, while minimising missing data by assigning values to missing data in some of the questions included in the combination of responses where appropriate. For example, in coding the physical activity as MET-hours per day the first relevant survey questions ask "In a typical week how many days do you do 10 minutes of moderate PA/vigorous PA/walking?" however some people who respond yes to this question then have a "missing" response to the question about the duration of activity. In this situation where the "In a typical week" question was non-missing and non-zero but the "Duration" question was zero or missing we assigned these people 10 minutes per day (for the number of days stated) in line with the response to the initial question. Doing this, however, meant that people with missing data had at least 10 minutes of exercise while some respondents who did reply to the "Duration" question reported <10 minutes. For consistency we also changed these individuals to 10 minutes. For questions around food and alcohol consumption, respondents were asked what they had eaten/drunk in the past week month. Unless there was a counter-indication we assumed that missing responses to these questions corresponded to zero intake.

Reference:

Dagan N, Cohen-Stavi C, Leventer-Roberts M, *et al.* External validation and comparison of three prediction tools for risk of osteoporotic fractures using data from population based electronic health records: retrospective cohort study. *BMJ* 2017;:i6755.

Supplementary Table 3. Validation cohort sample size and incident CRC cases, stratified by sex and risk score

Women

	GRS Genetic risk factors alone														GRS plus phenotypic risk factors								
	Abe 2017	Dunlop 2013	Frampton 2016	Hosono 2016	Hsu 2015	Huyghe 2019	Ibanez-Sanz 2017	Iwasaki 2017	Jenkins 2016	Jeon 2018	Smith 2018	Wang 2013	Xin 2018	Yarnall 2013	Abe 2017	Dunlop 2013	Hosono 2016	Ibanez-Sanz 2017	Iwasaki 2017	Jenkins 2019	Jeon 2018	Smith 2018	Yarnall 2013
Validation sample size	233604	233604	233604	233604	233604	255286	233604	233604	233604	233604	233604	213349	233604	233604	85210	228251	205231	204208	231602	197749	78476	213378	208226
Incident CRC	1116	1116	1116	1116	1116	345	1116	1116	1116	1116	1116	1042	1116	1116	265	1087	959	953	1104	943	241	1024	972

Men

	Abe 2017	Dunlop 2013	Frampton 2016	Hosono 2016	Hsu 2015	Huyghe 2019	Ibanez-Sanz 2017	Iwasaki 2017	Jenkins 2016	Jeon 2018	Smith 2018	Wang 2013	Xin 2018	Yarnall 2013	Abe 2017	Dunlop 2013	Hosono 2016	Ibanez-Sanz 2017	Iwasaki 2017	Jenkins 2019	Jeon 2018	Smith 2018	Yarnall 2013
Validation sample size	196907	196907	196907	196907	196907	211732	196907	196907	196907	196907	196907	179820	196907	196907	68539	189900	176848	174671	194918	157028	62677	159995	181087
Incident CRC	1487	1487	1487	1487	1487	457	1487	1487	1487	1487	1487	1380	1487	1487	380	1436	1317	1288	1466	1148	331	1168	1341

Supplementary Table 4. Characteristics of included participants from the UK Biobank cohort without a history of CRC, adenomas or IBD at baseline assessment, including distribution of variables between those with and without incident colorectal cancer in 6 years of follow up

	All	No incident CRC	Incident CRC
	n=443,888	n=441,209 (99.4%)	n=2,679 (0.6%)
Sex (n=443,888)			
Women	241,516	240,359 (99.5)	1,157 (0.5)
Men	202,372	200,850 (99.3)	1,522 (0.8)
Age at recruitment (n=443,888)			
Under 45	46,405	46,349 (99.9)	56 (0.1)
45-49	58,925	58,808 (99.8)	117 (0.2)
50-54	67,904	67,652 (99.6)	252 (0.4)
55-59	80,933	80,498 (99.5)	435 (0.5)
60-64	106,436	105,617 (99.2)	819 (0.8)
65-+	83,285	82,285 (98.8)	1,000 (1.2)
Ethnicity (n=441,141)			
White	419,579	416,992 (99.4)	2,587 (0.6)
Mixed	1,975	1,964 (99.4)	11 (0.6)
Asian	8,178	8,178 (99.7)	25 (0.3)
Black	6,312	6,294 (99.7)	18 (0.3)
Other/Chinese	5,097	6,058 (99.6)	19 (0.4)
Family history of CRC (n=431,013)			
No	383,186	380,992 (99.4)	2,194 (0.6)
Yes	47,827	47,423 (99.2)	404 (0.8)
Cancer diagnosis before recruitment (n=443,888)			
No	392,151	390,013 (99.5)	2,138 (0.5)
Yes	51,737	51,196 (99.0)	541 (1.1)
At least one relative in UK Biobank (n=443,888)			
No	369,938	367,710 (99.4)	2,228 (0.6)
Yes	73,950	73,499 (99.4)	451 (0.6)
Risk alleles (n=430,511)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Abe 2017	8 (7 - 10)	8 (7 - 10)	9 (7 - 10)
Dunlop 2013	9 (8 - 11)	9 (8 - 11)	10 (9 - 11)
Frampton 2016	34 (32 - 37)	34 (32 - 37)	35 (33 - 38)
Hosono 2016	4 (3 - 5)	4 (3 - 5)	5 (4 - 6)
Hsu 2015	27 (25 - 30)	27 (25 - 30)	28 (26 - 30)
Huyghe 2019	115 (111 - 120)	115 (111 - 120)	118 (114 - 122)
Ibanez-Sanz 2017	23 (20 - 25)	23 (20 - 25)	23 (21 - 25)
Iwasaki 2017	5 (4 - 6)	5 (4 - 6)	5 (4 - 6)
Jenkins 2016	39 (36 - 42)	39 (36 - 42)	40 (37 - 4)
Jeon 2018	58 (55 - 61)	58 (55 - 61)	59 (56 - 62)
Smith 2018	32 (30 - 35)	32 (30 - 35)	33 (31 - 36)
Wang 2013	Genotype based score		
Xin 2018	9 (8 - 10)	9 (8 - 10)	9 (8 - 11)
Yarnall 2013	15 (14 - 17)	15 (14 - 17)	16 (14 - 17)

Supplementary Table 5. Mean standardised GRS (standard deviation), stratified by ethnicity

	White (n=407,601)	Mixed (n=1,895)	Asian (n=7,800)	Black (n=6,013)	Other / Chinese (n=4,879)
Abe 2017	-0.04 (0.99)	0.33 (1.04)	0.55 (1.10)	0.67 (0.95)	0.62 (1.10)
Dunlop 2013	-0.00 (1.00)	-0.03 (1.00)	-0.43 (1.02)	0.50 (0.94)	-0.04 (1.02)
Frampton 2016	-0.00 (1.00)	0.02 (0.98)	0.04 (1.03)	-0.14 (0.86)	0.14 (1.06)
Hosono 2016	-0.03 (0.99)	0.33 (1.02)	0.50 (1.13)	0.59 (0.88)	0.75 (1.19)
Hsu 2015	-0.01 (1.00)	0.10 (0.97)	0.04 (1.05)	0.38 (0.88)	-0.04 (1.00)
Huyghe 2019	0.01 (1.00)	-0.10 (0.98)	-0.42 (1.00)	-0.02 (0.93)	-0.22 (0.97)
Ibanez-Sanz 2017	0.03 (0.99)	-0.31 (1.02)	-0.92 (1.01)	-0.11 (0.86)	-0.74 (1.15)
Iwasaki 2017	-0.01 (1.00)	0.02 (0.99)	-0.15 (0.93)	0.66 (0.77)	-0.14 (1.04)
Jenkins 2016	-0.03 (0.99)	0.23 (0.99)	0.31 (1.03)	1.04 (0.85)	0.22 (1.06)
Jeon 2018	0.01 (1.00)	-0.05 (0.99)	0.01 (1.00)	-0.27 (1.00)	-0.25 (1.01)
Smith 2018	-0.02 (0.99)	0.16 (0.99)	0.13 (1.03)	0.85 (0.93)	0.16 (1.03)
Wang 2013	0.03 (0.98)	-0.18 (1.02)	-0.20 (1.00)	-1.44 (1.09)	-0.53 (1.11)
Xin 2018	-0.03 (0.98)	0.30 (1.09)	0.38 (1.15)	0.45 (1.00)	0.84 (1.45)
Yarnall 2013	-0.00 (1.00)	-0.02 (0.98)	-0.21 (1.03)	0.35 (0.96)	-0.18 (1.04)

Supplementary Table 6. Discrimination (AUC ± 95% CI) for the risk models in men and women (Data for Figure 1).

	Women		Men	
Model	**Genes-only GRS**	**GRS plus phenotypic risk factors**	**Genes-only GRS**	**GRS plus phenotypic risk factors**
Abe 2017	0.55 (0.53-0.56)	0.67 (0.64-0.7)	0.55 (0.54-0.56)	0.71 (0.69-0.74)
Dunlop 2013	0.57 (0.55-0.59)	0.64 (0.62-0.66)	0.56 (0.55-0.57)	0.67 (0.66-0.69)
Frampton 2016	0.55 (0.54-0.57)		0.55 (0.53-0.56)	
Hosono 2016	0.53 (0.52-0.55)	0.66 (0.64-0.67)	0.54 (0.53-0.55)	0.7 (0.69-0.72)
Hsu 2015	0.58 (0.57-0.6)		0.57 (0.55-0.58)	
Huyghe 2019	0.62 (0.59-0.64)		0.64 (0.61-0.66)	
Ibanez-Sanz 2017	0.56 (0.54-0.58)	0.53 (0.52-0.55)	0.55 (0.54-0.57)	0.58 (0.56-0.59)
Iwasaki 2017	0.53 (0.52-0.55)	0.56 (0.54-0.58)	0.54 (0.53-0.55)	0.62 (0.6-0.63)
Jenkins 2016	0.57 (0.55-0.58)	0.56 (0.54-0.58)	0.57 (0.55-0.58)	0.58 (0.56-0.59)
Jeon 2018	0.58 (0.57-0.6)	0.59 (0.56-0.63)	0.58 (0.57-0.6)	0.6 (0.57-0.62)
Smith 2018	0.57 (0.56-0.59)	0.65 (0.63-0.66)	0.56 (0.55-0.58)	0.7 (0.68-0.71)
Wang 2013	0.5 (0.48-0.52)		0.51 (0.49-0.52)	
Xin 2018	0.53 (0.52-0.55)		0.54 (0.53-0.56)	
Yarnall 2013	0.56 (0.54-0.57)	0.54 (0.53-0.56)	0.55 (0.54-0.57)	0.59 (0.57-0.6)

Supplementary Table 7. Discrimination (AUC ± 95% CI) in white / ethnic minority groups

	All respondents with non-missing ethnicity	All participants with self-reported White/European ethnicity	All other non-White/European ethnic groups
Abe 2017	0.55 (0.54-0.56)	0.55 (0.54-0.56)	0.55 (0.49-0.62)
Dunlop 2013	0.56 (0.55-0.58)	0.56 (0.55-0.58)	0.57 (0.5-0.63)
Frampton 2016	0.55 (0.54-0.56)	0.55 (0.54-0.56)	0.58 (0.51-0.64)
Hosono 2016	0.54 (0.53-0.55)	0.54 (0.53-0.55)	0.53 (0.46-0.59)
Hsu 2015	0.57 (0.56-0.58)	0.57 (0.56-0.59)	0.56 (0.49-0.64)
Huyghe 2019	0.63 (0.61-0.64)	0.63 (0.61-0.65)	0.53 (0.41-0.64)
Ibanez-Sanz 2017	0.55 (0.54-0.57)	0.55 (0.54-0.56)	0.57 (0.51-0.64)
Iwasaki 2017	0.54 (0.53-0.55)	0.54 (0.53-0.55)	0.49 (0.42-0.56)
Jenkins 2016	0.57 (0.56-0.58)	0.57 (0.56-0.58)	0.52 (0.45-0.6)
Jeon 2018	0.58 (0.57-0.59)	0.58 (0.57-0.59)	0.59 (0.52-0.66)
Smith 2018	0.57 (0.56-0.58)	0.57 (0.56-0.58)	0.6 (0.53-0.66)
Wang 2013	0.51 (0.49-0.52)	0.5 (0.49-0.51)	0.54 (0.47-0.62)
Xin 2018	0.54 (0.53-0.55)	0.54 (0.53-0.55)	0.59 (0.53-0.66)
Yarnall 2013	0.55 (0.54-0.56)	0.55 (0.54-0.56)	0.56 (0.49-0.62)

Supplementary Table 8. Discrimination (AUC ± 95% CI) restricting the genes-only models to the samples with phenotype data available. P-value from test of whether there was any evidence of a difference in discriminative ability between genes and genes plus phenotypes versions using the algorithm of DeLong *et al*. implemented in Stata.

	Women			Men		
Model	**Genes-only GRS**	**GRS plus phenotypic risk factors**	**p-value**	**Genes-only GRS**	**GRS plus Phenotypic risk factors**	**p-value**
Abe 2017	0.55 (0.53-0.57)	0.67 (0.64-0.7)	<0.0001	0.55 (0.54-0.57)	0.71 (0.69-0.74)	<0.0001
Dunlop 2013	0.57 (0.56-0.59)	0.64 (0.62-0.66)	<0.0001	0.56 (0.54-0.57)	0.67 (0.66-0.69)	<0.0001
Frampton 2016						
Hosono 2016	0.54 (0.52-0.56)	0.66 (0.64-0.67)	<0.0001	0.54 (0.53-0.56)	0.7 (0.69-0.72)	<0.0001
Hsu 2015						
Huyghe 2019						
Ibanez-Sanz 2017	0.56 (0.54-0.57)	0.53 (0.52-0.55)	0.019	0.55 (0.53-0.57)	0.58 (0.56-0.59)	0.0033
Iwasaki 2017	0.53 (0.52-0.55)	0.56 (0.54-0.58)	0.046	0.54 (0.53-0.56)	0.62 (0.6-0.63)	<0.0001
Jenkins 2016	0.56 (0.54-0.58)	0.56 (0.54-0.58)	0.94	0.57 (0.55-0.58)	0.58 (0.56-0.59)	0.043
Jeon 2018	0.62 (0.58-0.65)	0.59 (0.56-0.63)	0.17	0.6 (0.58-0.63)	0.6 (0.57-0.62)	0.54
Smith 2018	0.57 (0.55-0.59)	0.65 (0.63-0.66)	<0.0001	0.57 (0.55-0.59)	0.7 (0.68-0.71)	<0.0001
Wang 2013						
Xin 2018						
Yarnall 2013	0.55 (0.54-0.57)	0.54 (0.53-0.56)	0.012	0.56 (0.54-0.57)	0.59 (0.57-0.6)	<0.0001

Supplementary Table 9. Discriminatory performance measures for each of the risk models for 6-year risk of developing colorectal cancer in women

	Genetic risk factors alone														Genetic plus phenotypic risk factors								
	Abe 2017	Dunlop 2013	Frampton 2016	Hosono 2016	Hsu 2015	Huyghe 2019	Ibanez-Sanz 2017	Iwasaki 2017	Jenkins 2016	Jeon 2018	Smith 2018	Wang 2013	Xin 2018	Yarnall 2013	Abe 2017	Dunlop 2013	Hosono 2016	*Ibanez-Sanz* 2017*	Iwasaki 2017	*Jenkins* 2019*	*Jeon* 2018*	Smith 2018	*Yarnall* 2013*
Top 10%																							
Sensitivity	12	12.3	13.2	11.6	13.7	18.6	13.2	12.4	13.3	14.2	13.1	8.3	12.2	13.8	20.4	19.7	21.1	*12.6*	14.4	*13.4*	*14.5*	20.7	*12.8*
Specificity	90.1	90	90	90.1	90.1	90.1	90	90.1	90.1	90	90.1	90	90.1	90	90.4	90.2	89.9	*90*	90	*90.1*	*90.1*	90.2	*90*
LR+	1.2	1.2	1.3	1.2	1.4	1.9	1.3	1.2	1.3	1.4	1.3	0.8	1.2	1.4	2.1	2	2.1	*1.3*	1.4	*1.4*	*1.5*	2.1	*1.3*
LR-	1	1	1	1	1	.9	1	1	1	1	1	1	1	1	0.9	0.9	0.9	*1*	1	*1*	*0.9*	0.9	*1*
PPV (%)	0.6	0.6	0.6	0.6	0.7	.3	0.6	0.6	0.6	0.7	0.6	0.4	0.6	0.7	0.7	1	1	*0.6*	0.7	*0.6*	*0.4*	1	*0.6*
NPV (%)	99.5	99.5	99.5	99.5	99.5	99.9	99.5	99.5	99.5	99.5	99.5	99.5	99.5	99.5	99.7	99.6	99.6	*99.5*	99.5	*99.5*	*99.7*	99.6	*99.5*
Top 20%																							
Sensitivity	22.6	25	25.7	23	28.8	30.7	26.8	24.6	26.4	27.6	27	19.2	22.8	25.4	36.2	33.8	36.7	*22.4*	27.4	*26.5*	*28.6*	38.1	*24.8*
Specificity	80.1	80.1	80	80.1	80.1	80.2	80	80.1	80.2	80.1	80.1	79.9	80.1	80.1	80.7	80.2	80	*80*	80.1	*80.1*	*80.1*	80.3	*80*
LR+	1.1	1.3	1.3	1.2	1.4	1.5	1.3	1.2	1.3	1.4	1.4	1	1.1	1.3	1.9	1.7	1.8	*1.1*	1.4	*1.3*	*1.4*	1.9	*1.2*
LR-	1	0.9	0.9	1	0.9	.9	0.9	0.9	0.9	0.9	0.9	1	1	0.9	0.8	0.8	0.8	*1*	0.9	*0.9*	*0.9*	0.8	*0.9*
PPV (%)	0.5	0.6	0.6	0.6	0.7	.2	0.6	0.6	0.6	0.7	0.6	0.5	0.5	0.6	0.6	0.8	0.9	*0.5*	0.7	*0.6*	*0.4*	0.9	*0.6*
NPV (%)	99.5	99.6	99.6	99.5	99.6	99.9	99.6	99.5	99.6	99.6	99.6	99.5	99.5	99.6	99.8	99.6	99.6	*99.5*	99.6	*99.6*	*99.7*	99.6	*99.6*
Top 80%																							
Sensitivity	85.1	87.1	84.9	84.5	88	91.3	84.9	84.4	86.6	89.5	87.6	81.9	83.5	84.9	94.7	92.1	93.8	*82.3*	84.8	*86.9*	*88.4*	92.7	*85*
Specificity	20.2	20.1	20.1	20.1	20.1	20.1	20	20.1	20.1	20	20.1	19.9	20.1	20.1	20.4	20.2	19.9	*19.9*	20	*20.1*	*20.1*	20.3	*20*
LR+	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1	1	1.1	1.2	1.2	1.2	*1*	1.1	*1.1*	*1.1*	1.2	*1.1*
LR-	0.7	0.6	0.8	0.8	0.6	.4	0.8	0.8	0.7	0.5	0.6	0.9	0.8	0.7	0.3	0.4	0.3	*0.9*	0.8	*0.7*	*0.6*	0.4	*0.8*
PPV (%)	0.5	0.5	0.5	0.5	0.5	.2	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.4	0.5	0.5	*0.5*	0.5	*0.5*	*0.3*	0.6	*0.5*
NPV (%)	99.6	99.7	99.6	99.6	99.7	99.9	99.6	99.6	99.7	99.7	99.7	99.6	99.6	99.6	99.9	99.8	99.9	*99.6*	99.6	*99.7*	*99.8*	99.8	*99.6*
Top 90%																							
Sensitivity	93	93.5	93	92.3	95.8	97.4	93.7	91.9	94.5	95.7	94.4	90.6	93.2	93.6	98.5	96.9	97.3	*91.7*	94.2	*94.6*	*95.4*	96.8	*92.8*
Specificity	10.1	10	10	10	10.1	10.1	10	10	10.1	10	10.1	9.9	10.1	10.1	10.3	10.1	9.9	*10*	10	*10.1*	*10*	10.1	*10*
LR+	1	1	1	1	1.1	1.1	1	1	1.1	1.1	1.1	1	1	1	1.1	1.1	1.1	*1*	1	*1.1*	*1.1*	1.1	*1*
LR-	0.7	0.7	0.7	0.8	0.4	.3	0.6	0.8	0.5	0.4	0.6	0.9	0.7	0.6	0.1	0.3	0.3	*0.8*	0.6	*0.5*	*0.5*	0.3	*0.7*
PPV (%)	0.5	0.5	0.5	0.5	0.5	.1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.3	0.5	0.5	*0.5*	0.5	*0.5*	*0.3*	0.5	*0.5*
NPV (%)	99.7	99.7	99.7	99.6	99.8	100	99.7	99.6	99.7	99.8	99.7	99.5	99.7	99.7	100	99.9	99.9	*99.6*	99.7	*99.7*	*99.9*	99.8	*99.7*

* Genes plus phenotypes models in italics do not include age as part of the phenotypic risk score

LR+ can be calculated as sensitivity divided by one minus specificity, LR- is calculated by one minus sensitivity divided by specificity.

Supplementary table 10. Discriminatory performance measures for each of the risk models for 6-year risk of developing colorectal cancer in men

	Genetic risk factors alone														Genetic plus phenotypic risk factors								
	Abe 2017	Dunlop 2013	Frampton 2016	Hosono 2016	Hsu 2015	Huyghe 2019	Ibanez-Sanz 2017	Iwasaki 2017	Jenkins 2016	Jeon 2018	Smith 2018	Wang 2013	Xin 2018	Yarnall 2013	Abe 2017	Dunlop 2013	Hosono 2016	*Ibanez-Sanz* 2017*	Iwasaki 2017	*Jenkins* 2019*	*Jeon* 2018*	Smith 2018	*Yarnall* 2013*
Top 10%																							
Sensitivity	12.3	13.7	12.2	11.8	14.1	22.3	15.1	11.3	14.4	14.7	13.4	10.8	12.4	13.4	22.9	21.1	26.9	*15.1*	19.6	*16.3*	*13*	23.4	*17.7*
Specificity	90.1	90.1	90.1	90.1	90.1	90.2	90.1	90.1	90.1	90.1	90.1	90	90.1	90.1	90.4	90.3	90.1	*90.1*	90.2	*90.2*	*90.2*	90.4	*90.1*
LR+	1.2	1.4	1.2	1.2	1.4	2.3	1.5	1.1	1.5	1.5	1.4	1.1	1.2	1.4	2.4	2.2	2.7	*1.5*	2	*1.7*	*1.3*	2.4	*1.8*
LR-	1	1	1	1	1	.9	0.9	1	0.9	0.9	1	1	1	1	0.9	0.9	0.8	*0.9*	0.9	*.9*	*1*	0.8	*0.9*
PPV (%)	0.9	1	0.9	0.9	1.1	.5	1.1	0.9	1.1	1.1	1	0.8	0.9	1	1.3	1.6	2	*1.1*	1.5	*1.2*	*0.7*	1.8	*1.3*
NPV (%)	99.3	99.3	99.3	99.3	99.3	99.8	99.3	99.3	99.3	99.3	99.3	99.2	99.3	99.3	99.5	99.3	99.4	*99.3*	99.3	*99.3*	*99.5*	99.4	*99.3*
Top 20%																							
Sensitivity	23.9	26	24.6	23.7	26	35.7	27	23.6	25.7	27.9	24.5	20.6	23.6	26.7	47.9	38.2	44	*28.5*	34.4	*28.4*	*26.9*	43	*29.8*
Specificity	80.1	80.2	80.1	80.1	80.2	80.3	80.1	80.1	80.2	80.1	80.2	80	80.2	80.2	80.7	80.4	80.1	*80.1*	80.3	*80.2*	*80.3*	80.6	*80.1*
LR+	1.2	1.3	1.2	1.2	1.3	1.8	1.4	1.2	1.3	1.4	1.2	1	1.2	1.3	2.5	2	2.2	*1.4*	1.7	*1.4*	*1.4*	2.2	*1.5*
LR-	0.9	0.9	0.9	1	0.9	.8	0.9	1	0.9	0.9	0.9	1	1	0.9	0.6	0.8	0.7	*0.9*	0.8	*.9*	*0.9*	0.7	*0.9*
PPV (%)	0.9	1	0.9	0.9	1	.4	1	0.9	1	1.1	0.9	0.8	0.9	1	1.4	1.5	1.6	*1.1*	1.3	*1*	*0.7*	1.6	*1.1*
NPV (%)	99.3	99.3	99.3	99.3	99.3	99.8	99.3	99.3	99.3	99.3	99.3	99.2	99.3	99.3	99.6	99.4	99.5	*99.3*	99.4	*99.3*	*99.5*	99.5	*99.4*
Top 80%																							
Sensitivity	84.3	85.9	84.5	85.7	86.6	92.1	84.3	83.3	85.5	87	86.8	81.5	83.7	84.4	96.3	95.7	96.7	*86.2*	90.1	*86*	*89.7*	96.1	*87.2*
Specificity	20.2	20.1	20.1	20.2	20.1	20.2	20	20.1	20.2	20.1	20.2	19.9	20.1	20.1	20.5	20.4	20.1	*20.1*	20.2	*20.2*	*20.2*	20.5	*20*
LR+	1.1	1.1	1.1	1.1	1.1	1.2	1.1	1	1.1	1.1	1.1	1	1	1.1	1.2	1.2	1.2	*1.1*	1.1	*1.1*	*1.1*	1.2	*1.1*
LR-	0.8	0.7	0.8	0.7	0.7	.4	0.8	0.8	0.7	0.6	0.7	0.9	0.8	0.8	0.2	0.2	0.2	*0.7*	0.5	*.7*	*0.5*	0.2	*0.6*
PPV (%)	0.8	0.8	0.8	0.8	0.8	.2	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.7	0.9	0.9	*0.8*	0.8	*.8*	*0.6*	0.9	*0.8*
NPV (%)	99.4	99.5	99.4	99.5	99.5	99.9	99.4	99.4	99.5	99.5	99.5	99.3	99.4	99.4	99.9	99.8	99.9	*99.5*	99.6	*99.5*	*99.7*	99.9	*99.5*
Top 90%																							
Sensitivity	92.6	93.7	92.3	94	93.9	97.2	92.5	92.9	94.1	94.1	93.7	91.3	91.7	92.5	98.4	98.7	98.9	*93*	95.4	*94.8*	*97.6*	98.7	*94.2*
Specificity	10.1	10.1	10	10	10.1	10.1	10	10	10.1	10.1	10.1	9.9	10	10.1	10.2	10.2	10	*10*	10.1	*10.1*	*10.1*	10.3	*10*
LR+	1	1	1	1	1	1.1	1	1	1	1	1	1	1	1	1.1	1.1	1.1	*1*	1.1	*1.1*	*1.1*	1.1	*1*
LR-	0.7	0.6	0.8	0.6	0.6	.3	0.7	0.7	0.6	0.6	0.6	0.9	0.8	0.7	0.2	0.1	0.1	*0.7*	0.5	*.5*	*0.2*	0.1	*0.6*
PPV (%)	0.8	0.8	0.8	0.8	0.8	.2	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.6	0.8	0.8	*0.8*	0.8	*.8*	*0.6*	0.8	*0.8*
NPV (%)	99.4	99.5	99.4	99.5	99.5	99.9	99.4	99.5	99.6	99.6	99.5	99.3	99.4	99.4	99.9	99.9	99.9	*99.5*	99.7	*99.6*	*99.9*	99.9	*99.6*

* Genes plus phenotypes models in italics do not include age as part of the phenotypic risk score

Supplementary Table 11. Relative risk calibration in women (data for Figure 3)

	Decile of predicted risk Average expected risk in decile, Observed RR(95%CI)									
Model	1	2	3	4	5	6	7	8	9	10
GRS genes-only										
Abe 2017										
Dunlop 2013	0.6482 0.7 (0.6-0.9)	0.7795 0.7 (0.5-0.9)	0.8606 0.8 (0.6-1.0)	0.9330 0.9 (0.8-1.2)	1,1	1.0694 1.3 (1.1-1.5)	1.1500 1.3 (1.1-1.6)	1.2469 1.5 (1.3-1.8)	1.3789 1.4 (1.2-1.7)	1.6772 1.4 (1.1-1.6)
Frampton 2016	0.4606 0.7 (0.5-0.9)	0.6416 0.8 (0.6-1.0)	0.7658 0.8 (0.6-1.0)	0.8805 0.9 (0.7-1.1)	1,1	1.1322 1.2 (1.0-1.4)	1.2904 1.0 (0.8-1.2)	1.4935 1.1 (0.9-1.3)	1.7995 1.3 (1.0-1.5)	2.6107 1.3 (1.1-1.5)
Hosono 2016										
Hsu 2015	0.7740 0.4 (0.3-0.5)	0.8729 0.8 (0.6-1.0)	0.9232 0.8 (0.7-1.0)	0.9637 0.8 (0.6-1.0)	1,1	1.0355 1.0 (0.8-1.2)	1.0723 1.0 (0.9-1.3)	1.1134 1.3 (1.0-1.5)	1.1664 1.5 (1.3-1.8)	1.2676 1.4 (1.2-1.6)
Huyghe 2019	0.4952 0.2 (0.1-0.4)	0.6721 0.5 (0.3-0.8)	0.7876 0.6 (0.4-0.9)	0.8929 0.7 (0.4-1.0)	1,1	1.1162 0.7 (0.4-1.0)	1.2508 1 (0.7-1.3)	1.4202 1.0 (0.7-1.4)	1.6729 1.0 (0.7-1.4)	2.3083 1.5 (1.1-1.9)
Ibanez-Sanz 2017										
Iwasaki 2017	0.4130 0.8 (0.7-1.0)	0.5997 0.8 (0.6-1.0)	0.7420 1.1 (0.9-1.3)	0.8799 1.1 (0.9-1.3)	1,1	1.1657 1.0 (0.8-1.2)	1.3330 1.2 (1.0-1.4)	1.5763 1.0 (0.8-1.2)	1.9373 1.3 (1.0-1.5)	2.8541 1.3 (1.1-1.6)
Jenkins 2016	0.3964 0.5 (0.4-0.7)	0.5913 0.8 (0.6-0.9)	0.7283 0.7 (0.6-0.9)	0.8607 0.9 (0.7-1.1)	1,1	1.1570 1.1 (0.9-1.3)	1.3458 1.1 (0.9-1.4)	1.5966 1.0 (0.8-1.2)	1.9834 1.3 (1.1-1.6)	3.0241 1.3 (1.1-1.6)
Jeon 2018	0.6060 0.4 (0.3-0.6)	0.7507 0.6 (0.5-0.8)	0.8403 0.8 (0.6-1.0)	0.9210 1.0 (0.8-1.2)	1,1	1.0847 1.1 (0.9-1.3)	1.1810 1.2 (1.0-1.4)	1.2988 1.2 (1.0-1.4)	1.4682 1.4 (1.1-1.6)	1.8711 1.5 (1.2-1.7)
Smith 2018	0.4641 0.5 (0.4-0.7)	0.6424 0.6 (0.5-0.8)	0.7650 0.7 (0.6-0.9)	0.8804 0.9 (0.7-1.1)	1,1	1.1320 1.1 (1.0-1.4)	1.2889 1.0 (0.8-1.2)	1.4919 1.1 (0.9-1.4)	1.8015 1.3 (1.1-1.6)	2.6036 1.3 (1.1-1.5)
Wang 2013	0.1702 1.0 (0.8-1.3)	0.3702 0.9 (0.7-1.2)	0.5532 1.1 (0.9-1.4)	0.7583 1.2 (1.0-1.5)	1,1	1.3075 1.0 (0.8-1.3)	1.7150 1.2 (1.0-1.4)	2.3152 1.2 (1.0-1.4)	3.3627 1.2 (0.9-1.4)	6.8624 0.9 (0.7-1.1)
Xin 2018	0.7198 0.6 (0.4-0.7)	0.8245 0.8 (0.7-1.0)	0.8888 0.8 (0.6-1.0)	0.9450 0.9 (0.8-1.1)	1,1	1.0582 0.7 (0.6-0.9)	1.1240 0.9 (0.7-1.0)	1.2056 1.0 (0.8-1.1)	1.3216 0.9 (0.8-1.1)	1.6018 1.1 (0.9-1.3)
Yarnall 2013	0.6080 0.6 (0.4-0.7)	0.7532 0.8 (0.6-1.0)	0.8431 0.6 (0.5-0.8)	0.9222 0.8 (0.6-1.0)	1,1	1.0817 1.0 (0.9-1.3)	1.1731 1.0 (0.8-1.2)	1.2842 1.0 (0.8-1.2)	1.4426 1.1 (0.9-1.3)	1.8074 1.3 (1.1-1.5)
GRS plus phenotypes										
Abe 2017	0.2138 0.3 (0.2-0.5)	0.3686 0.5 (0.4-0.8)	0.5358 0.7 (0.5-0.9)	0.7439 0.8 (0.6-1.1)	1,1	1.3038 1.2 (1.0-1.5)	1.6734 1.8 (1.5-2.1)	2.1457 1.6 (1.3-2.0)	2.8502 1.9 (1.5-2.2)	4.6291 2.9 (2.5-3.3)
Dunlop 2013	0.2326 0.3 (0.2-0.4)	0.4159 0.6 (0.5-0.8)	0.6005 0.7 (0.6-0.9)		1,1		1.4053 1.5 (1.3-1.7)	1.7380 1.2 (0.8-1.7)	2.0535 1.6 (1.3-1.8)	3.6349 2.2 (1.9-2.6)
Hosono 2016	0.2036 0.3 (0.1-0.4)	0.3546 0.3 (0.2-0.5)	0.5222 0.5 (0.4-0.7)	0.7361 0.6 (0.4-0.8)	1,1	1.3218 1.1 (0.9-1.4)	1.7162 1.2 (1.0-1.5)	2.2371 1.4 (1.2-1.7)	3.0043 1.7 (1.4-1.9)	4.8731 2.2 (1.9-2.5)
Ibanez-Sanz 2017	0.5665 0.8 (0.7-1.0)	0.7224 1.0 (0.8-1.3)	0.8226 0.8 (0.7-1.0)	0.9176 0.9 (0.7-1.1)	1,1	1.0911 1.1 (0.9-1.3)	1.2138 1.1 (0.9-1.3)	1.3841 1.3 (1.0-1.5)	1.6821 1.0 (0.8-1.2)	2.5956 1.3 (1.1-1.6)
Iwasaki 2017	0.2966 0.5 (0.4-0.7)	0.4956 0.9 (0.7-1.0)	0.6540 0.7 (0.5-0.8)	0.8181 0.8 (0.6-0.9)	1,1	1.2120 0.9 (0.7-1.1)	1.4735 0.9 (0.8-1.1)	1.8213 0.9 (0.8-1.1)	2.3511 1.2 (1.0-1.4)	3.7284 1.3 (1.1-1.6)
Jenkins 2019	0.3813 0.5 (0.4-0.7)	0.5750 0.7 (0.6-0.9)	0.7150 0.8 (0.6-1.0)	0.8519 0.8 (0.7-1.0)	1,1	1.1707 1.2 (1.0-1.5)	1.3849 1.0 (0.8-1.2)	1.6781 1.0 (0.8-1.2)	2.1637 1.3 (1.0-1.5)	3.6802 1.3 (1.1-1.6)
Jeon 2018	0.4853 0.3 (0.1-0.5)	0.6586 0.4 (0.2-0.7)	0.7841 0.6 (0.3-1.0)	0.8802 0.4 (0.3-0.7)	1,1	1.0742 0.6 (0.3-1.0)	1.1436 0.6 (0.3-0.9)	1.3861 1.0 (0.8-1.3)	1.7539 0.8 (0.6-1.2)	2.2349 1.2 (0.6-2.1)
Smith 2018	0.2310 0.4 (0.2-0.5)	0.4237 0.5 (0.3-0.6)	0.6010 0.6 (0.5-0.8)	0.7908 0.9 (0.7-1.1)	1,1	1.2411 1.3 (1.1-1.6)	1.5319 1.3 (1.1-1.6)	1.9110 1.5 (1.2-1.8)	2.5003 2.2 (1.8-2.5)	4.1002 2.6 (2.2-3.0)
Yarnall 2013	0.5359 0.6 (0.5-0.8)	0.7001 0.7 (0.5-0.9)	0.8075 0.8 (0.6-1.0)	0.9033 0.8 (0.7-1.0)	1,1	1.1044 0.9 (0.7-1.1)	1.2241 0.9 (0.8-1.2)	1.3756 0.9 (0.7-1.1)	1.5927 1.1 (0.9-1.3)	2.1143 1.1 (0.9-1.4)

Supplementary Table 12. Relative risk calibration in men (data for Figure 4).

Model	Decile of predicted risk Average expected risk in decile, Observed RR(95%CI) 1	2	3	4	5	6	7	8	9	10
Genes-only										
Abe 2017										
Dunlop 2013	0.6481 0.5 (0.4-0.6)	0.7792 0.7 (0.5-0.8)	0.8604 0.7 (0.6-0.9)	0.9310 0.8 (0.6-0.9)	1,1	1.0722 0.8 (0.7-1.0)	1.1529 0.9 (0.8-1.1)	1.2494 0.9 (0.8-1.1)	1.3825 1.1 (0.9-1.2)	1.6830 1.2 (1.0-1.4)
Frampton 2016	0.4613 0.7 (0.6-0.8)	0.6405 0.7 (0.6-0.9)	0.7645 0.8 (0.7-1.0)	0.8802 0.8 (0.6-0.9)	1,1	1.1325 1 (0.8-1.1)	1.2903 1.0 (0.8-1.2)	1.4937 1.0 (0.9-1.2)	1.8003 1.2 (1.0-1.4)	2.6145 1.1 (1.0-1.3)
Hosono 2016										
Hsu 2015	0.7719 0.6 (0.4-0.7)	0.8724 0.7 (0.5-0.8)	0.9231 0.8 (0.6-0.9)	0.9636 0.8 (0.6-0.9)	1,1	1.0355 1.0 (0.8-1.1)	1.0728 1.1 (0.9-1.3)	1.1136 1.2 (1.0-1.3)	1.1657 1.1 (1.0-1.3)	1.2672 1.4 (1.2-1.6)
Huyghe 2019	0.4939 0.3 (0.1-0.6)	0.6705 0.6 (0.3-0.9)	0.7865 0.5 (0.3-0.8)	0.8926 1.4 (1.0-1.8)	1,1	1.1154 1.4 (1.0-1.8)	1.2505 1.2 (0.9-1.7)	1.4202 1.4 (1.0-1.8)	1.6695 1.6 (1.2-2.1)	2.2951 2.8 (2.3-3.4)
Ibanez-Sanz 2017										
Iwasaki 2017	0.4110 0.8 (0.7-1.0)	0.5973 1.1 (0.9-1.3)	0.7396 1.2 (1.0-1.4)	0.8796 0.9 (0.8-1.1)	1,1	1.1650 1.2 (1.0-1.4)	1.3316 1.4 (1.2-1.7)	1.5741 1.3 (1.1-1.5)	1.9337 1.5 (1.3-1.7)	2.8306 1.3 (1.1-1.6)
Jenkins 2016	0.3963 0.6 (0.5-0.8)	0.5898 0.9 (0.8-1.1)	0.7272 0.8 (0.7-1.0)	0.8609 0.9 (0.7-1.1)	1,1	1.1565 1.1 (0.9-1.3)	1.3472 1.3 (1.1-1.5)	1.5976 1.4 (1.2-1.6)	1.9852 1.2 (1.1-1.5)	3.0303 1.6 (1.4-1.8)
Jeon 2018	0.6046 0.6 (0.5-0.8)	0.7494 0.7 (0.6-0.9)	0.8405 0.8 (0.7-1.0)	0.9209 0.9 (0.7-1.1)	1,1	1.0838 1.1 (0.9-1.3)	1.1792 1.2 (1.0-1.4)	1.2978 1.4 (1.2-1.6)	1.4674 1.4 (1.2-1.7)	1.8690 1.6 (1.4-1.9)
Smith 2018	0.4645 0.6 (0.5-0.8)	0.6438 0.7 (0.6-0.9)	0.7649 1.0 (0.8-1.2)	0.8794 0.9 (0.8-1.1)	1,1	1.1315 1.2 (1.0-1.4)	1.2878 1.3 (1.1-1.5)	1.4926 1.3 (1.1-1.5)	1.8021 1.2 (1.0-1.4)	2.6014 1.5 (1.3-1.7)
Wang 2013	0.1699 0.9 (0.8-1.1)	0.3728 1.0 (0.9-1.2)	0.5572 1.0 (0.9-1.2)	0.7607 1.3 (1.1-1.5)	1,1	1.3043 1.1 (0.9-1.3)	1.7077 1.1 (0.9-1.3)	2.3018 1.1 (0.9-1.3)	3.3500 1.0 (0.9-1.2)	6.8709 1.1 (1.0-1.4)
Xin 2018	0.7200 0.8 (0.6-0.9)	0.8248 0.7 (0.6-0.9)	0.8888 0.8 (0.6-0.9)	0.9453 0.9 (0.7-1.1)	1,1	1.0587 1.0 (0.8-1.2)	1.1246 1.0 (0.8-1.1)	1.2050 1.1 (0.9-1.3)	1.3186 1.0 (0.9-1.2)	1.5954 1.2 (1.0-1.4)
Yarnall 2013	0.6083 0.7 (0.6-0.9)	0.7537 0.8 (0.7-1.0)	0.8429 0.9 (0.8-1.1)	0.9223 0.9 (0.7-1.0)	1,1	1.0819 1.1 (0.9-1.3)	1.1730 1.0 (0.8-1.1)	1.2846 1.0 (0.9-1.2)	1.4413 1.4 (1.2-1.6)	1.8049 1.4 (1.2-1.6)
Genes plus phenotypes										
Abe 2017	0.1962 0.1 (0.0-0.2)	0.3421 0.2 (0.1-0.3)	0.5095 0.4 (0.3-0.6)	0.7277 0.8 (0.6-1.0)	1,1	1.3231 0.9 (0.7-1.1)	1.7105 1.3 (1.1-1.6)	2.2085 1.5 (1.2-1.7)	2.9445 2.4 (2.1-2.7)	4.8387 2.8 (2.5-3.2)
Dunlop 2013	0.1520 0.1 (0.0-0.1)	0.3431 0.3 (0.2-0.4)	0.6254 0.7 (0.5-0.8)	(-)	1,1	1.0387 0.5 (0.2-0.8)	1.4854 1.5 (1.3-1.6)	1.7038 0.8 (0.5-1.1)	2.2322 1.7 (1.5-1.9)	4.0625 2.2 (2.0-2.5)
Hosono 2016	0.1811 0.1 (0.0-0.2)	0.3291 0.2 (0.1-0.4)	0.5029 0.6 (0.4-0.7)	0.7263 0.7 (0.5-0.9)	1,1	1.3264 1.3 (1.1-1.6)	1.7287 1.6 (1.3-1.8)	2.2589 1.7 (1.5-2.0)	3.0596 2.3 (2.0-2.6)	5.0661 3.6 (3.2-4.0)
Ibanez-Sanz 2017	0.5566 0.7 (0.5-0.8)	0.7091 0.7 (0.5-0.9)	0.8138 0.8 (0.6-0.9)	0.9033 0.8 (0.6-1.0)	1,1	1.1158 1.1 (0.9-1.3)	1.2379 1.1 (0.9-1.3)	1.4142 1.2 (1.0-1.4)	1.7398 1.4 (1.2-1.6)	2.6972 1.6 (1.3-1.8)
Iwasaki 2017	0.2928 0.4 (0.3-0.6)	0.4972 0.5 (0.4-0.7)	0.6576 0.7 (0.6-0.9)	0.8197 0.9 (0.8-1.1)	1,1	1.2131 1.0 (0.8-1.1)	1.4748 1.0 (0.8-1.2)	1.8165 1.2 (1.0-1.4)	2.3218 1.6 (1.4-1.8)	3.5881 2.1 (1.9-2.4)
Jeon 2018	0.5058 0.3 (0.1-0.5)	0.7043 1.0 (0.7-1.4)	0.7653 0.9 (0.5-1.4)	0.9177 0.9 (0.6-1.3)	1,1	1.1930 1.4 (1.0-1.9)	1.2671 0.9 (0.6-1.4)	1.5419 1.8 (1.3-2.4)	1.9152 1.5 (1.1-2.0)	2.8422 1.5 (1.0-2.1)
Jenkins 2019	0.3800 0.5 (0.4-0.7)	0.5721 0.9 (0.7-1.1)	0.7128 0.8 (0.6-1.0)	0.8517 0.9 (0.7-1.1)	1,1	1.1719 1.1 (0.9-1.4)	1.3860 1.2 (1.0-1.4)	1.6846 1.2 (1.0-1.5)	2.1702 1.3 (1.1-1.5)	3.7199 1.8 (1.6-2.1)
Smith 2018	0.2206 0.1 (0.0-0.2)	0.4094 0.3 (0.2-0.4)	0.5879 0.5 (0.4-0.7)	0.7841 0.7 (0.5-0.9)	1,1	1.2503 1.1 (0.9-1.4)	1.5481 1.4 (1.1-1.6)	1.9415 1.8 (1.5-2.1)	2.5656 2.5 (2.2-2.9)	4.3126 3.0 (2.7-3.4)
Yarnall 2013	0.5264 0.6 (0.4-0.7)	0.6929 0.7 (0.5-0.8)	0.8026 0.8 (0.6-0.9)	0.9015 0.8 (0.7-1.0)	1,1	1.1064 0.9 (0.7-1.1)	1.2290 1.1 (0.9-1.3)	1.3809 1.2 (1.0-1.4)	1.6046 1.2 (1.0-1.4)	2.1469 1.8 (1.6-2.1)

Supplementary Table 13. Comparison of discrimination (AUC ± 95% CI) of genes-only GRS models with models additionally including age and family history.

Model	Women		Men	
Age (above and below 60)	0.61 (0.59-0.62)		0.64 (0.63-0.65)	
Family history	0.52 (0.51-0.53)		0.53 (0.52-0.54)	
Age and family history	0.62 (0.60-0.63)		0.65 (0.64-0.66)	
	Genes-only GRS (main analysis)	**Genes-only GRS plus Age (above and below 60) plus FH**	**Genes-only GRS (main analysis)**	**Genes-only GRS plus Age (above and below 60) plus FH**
Abe 2017	0.55 (0.53-0.56)	0.63 (0.62-0.65)	0.55 (0.54-0.56)	0.67 (0.65-0.68)
Dunlop 2013	0.57 (0.55-0.59)	0.64 (0.63-0.66)	0.56 (0.55-0.57)	0.67 (0.65-0.68)
Frampton 2016	0.55 (0.54-0.57)	0.64 (0.62-0.65)	0.55 (0.53-0.56)	0.66 (0.65-0.68)
Hosono 2016	0.53 (0.52-0.55)	0.63 (0.62-0.65)	0.54 (0.53-0.55)	0.66 (0.65-0.68)
Hsu 2015	0.58 (0.57-0.6)	0.65 (0.63-0.67)	0.57 (0.55-0.58)	0.67 (0.66-0.69)
Huyghe 2019	0.62 (0.59-0.64)	0.65 (0.62-0.68)	0.64 (0.61-0.66)	0.68 (0.66-0.71)
Ibanez-Sanz 2017	0.56 (0.54-0.58)	0.64 (0.62-0.65)	0.55 (0.54-0.57)	0.67 (0.65-0.68)
Iwasaki 2017	0.53 (0.52-0.55)	0.63 (0.61-0.64)	0.54 (0.53-0.55)	0.66 (0.65-0.67)
Jenkins 2016	0.57 (0.55-0.58)	0.64 (0.62-0.65)	0.57 (0.55-0.58)	0.66 (0.65-0.68)
Jeon 2018	0.58 (0.57-0.6)	0.65 (0.63-0.67)	0.58 (0.57-0.6)	0.68 (0.67-0.69)
Smith 2018	0.57 (0.56-0.59)	0.63 (0.61-0.65)	0.56 (0.55-0.58)	0.67 (0.65-0.68)
Wang 2013	0.5 (0.48-0.52)	0.61 (0.59-0.63)	0.51 (0.49-0.52)	0.65 (0.63-0.66)
Xin 2018	0.53 (0.52-0.55)	0.63 (0.61-0.64)	0.54 (0.53-0.56)	0.66 (0.65-0.67)
Yarnall 2013	0.56 (0.54-0.57)	0.64 (0.62-0.65)	0.55 (0.54-0.57)	0.67 (0.65-0.68)

Supplementary Table 14. Discrimination (AUC ± 95% CI) excluding people with cancer at baseline

	Women		Men	
Model	**Genes-only GRS**	**GRS plus phenotypic risk factors**	**Genes-only GRS**	**GRS plus phenotypic risk factors**
Abe 2017	0.55 (0.53-0.57)	0.67 (0.63-0.7)	0.54 (0.53-0.56)	0.7 (0.68-0.73)
Dunlop 2013	0.57 (0.55-0.59)	0.64 (0.62-0.65)	0.56 (0.54-0.58)	0.67 (0.66-0.69)
Frampton 2016	0.56 (0.54-0.57)		0.55 (0.53-0.56)	
Hosono 2016	0.54 (0.52-0.55)	0.65 (0.63-0.67)	0.54 (0.52-0.55)	0.7 (0.69-0.72)
Hsu 2015	0.58 (0.56-0.6)		0.57 (0.55-0.58)	
Huyghe 2019	0.62 (0.59-0.66)		0.65 (0.62-0.67)	
Ibanez-Sanz 2017	0.56 (0.54-0.57)	0.52 (0.5-0.54)	0.55 (0.54-0.57)	0.57 (0.56-0.59)
Iwasaki 2017	0.53 (0.51-0.55)	0.56 (0.54-0.58)	0.54 (0.53-0.56)	0.62 (0.6-0.63)
Jenkins 2016	0.57 (0.55-0.59)	0.56 (0.54-0.58)	0.57 (0.55-0.59)	0.58 (0.56-0.59)
Jeon 2018	0.59 (0.57-0.6)	0.59 (0.55-0.62)	0.58 (0.56-0.6)	0.6 (0.57-0.63)
Smith 2018	0.58 (0.56-0.59)	0.65 (0.63-0.66)	0.56 (0.55-0.58)	0.7 (0.68-0.71)
Wang 2013	0.5 (0.48-0.52)		0.51 (0.49-0.52)	
Xin 2018	0.54 (0.52-0.56)		0.54 (0.53-0.56)	
Yarnall 2013	0.55 (0.54-0.57)	0.55 (0.53-0.57)	0.55 (0.54-0.57)	0.59 (0.57-0.6)

Supplementary Table 15. Discrimination (AUC ± 95% CI) excluding all relatives in UK Biobank

	Women		Men	
Model	**Genes-only GRS**	**GRS plus phenotypic risk factors**	**Genes-only GRS**	**GRS plus phenotypic risk factors**
Abe 2017	0.54 (0.53-0.56)	0.67 (0.64-0.7)	0.56 (0.54-0.57)	0.71 (0.69-0.74)
Dunlop 2013	0.57 (0.55-0.59)	0.64 (0.63-0.66)	0.57 (0.55-0.58)	0.68 (0.66-0.69)
Frampton 2016	0.56 (0.54-0.57)		0.54 (0.53-0.56)	
Hosono 2016	0.53 (0.51-0.55)	0.66 (0.64-0.67)	0.55 (0.53-0.56)	0.71 (0.69-0.72)
Hsu 2015	0.58 (0.56-0.6)		0.57 (0.55-0.58)	
Huyghe 2019	0.61 (0.58-0.64)		0.64 (0.61-0.67)	
Ibanez-Sanz 2017	0.57 (0.55-0.58)	0.54 (0.52-0.56)	0.55 (0.54-0.57)	0.58 (0.57-0.6)
Iwasaki 2017	0.54 (0.52-0.56)	0.56 (0.54-0.58)	0.54 (0.52-0.55)	0.62 (0.6-0.63)
Jenkins 2016	0.57 (0.55-0.59)	0.56 (0.55-0.58)	0.57 (0.55-0.58)	0.58 (0.56-0.6)
Jeon 2018	0.59 (0.57-0.6)	0.58 (0.54-0.62)	0.58 (0.57-0.6)	0.6 (0.57-0.63)
Smith 2018	0.57 (0.56-0.59)	0.65 (0.63-0.66)	0.56 (0.55-0.58)	0.7 (0.68-0.71)
Wang 2013	0.51 (0.49-0.53)		0.51 (0.49-0.53)	
Xin 2018	0.54 (0.52-0.55)		0.54 (0.53-0.56)	
Yarnall 2013	0.56 (0.54-0.58)	0.55 (0.53-0.57)	0.55 (0.54-0.57)	0.59 (0.57-0.6)

Supplementary Table 16. Discrimination (AUC ± 95% CI) excluding all people with a history of colonoscopy at baseline

	Women		Men	
Model	**Genes-only GRS**	**GRS plus phenotypic risk factors**	**Genes-only GRS**	**GRS plus phenotypic risk factors**
Abe 2017	0.55 (0.53-0.56)	0.67 (0.64-0.7)	0.55 (0.53-0.56)	0.71 (0.69-0.74)
Dunlop 2013	0.57 (0.55-0.59)	0.64 (0.62-0.66)	0.56 (0.54-0.57)	0.67 (0.66-0.69)
Frampton 2016	0.55 (0.54-0.57)		0.54 (0.53-0.56)	
Hosono 2016	0.53 (0.52-0.55)	0.66 (0.64-0.67)	0.54 (0.53-0.55)	0.7 (0.69-0.72)
Hsu 2015	0.58 (0.57-0.6)		0.57 (0.55-0.58)	
Huyghe 2019	0.62 (0.59-0.65)		0.64 (0.61-0.66)	
Ibanez-Sanz 2017	0.56 (0.54-0.58)	0.53 (0.52-0.55)	0.55 (0.54-0.57)	0.58 (0.56-0.59)
Iwasaki 2017	0.53 (0.52-0.55)	0.56 (0.54-0.58)	0.54 (0.53-0.55)	0.62 (0.6-0.63)
Jenkins 2016	0.57 (0.55-0.58)	0.56 (0.54-0.58)	0.57 (0.55-0.58)	0.58 (0.56-0.59)
Jeon 2018	0.59 (0.57-0.6)	0.59 (0.56-0.63)	0.58 (0.57-0.59)	0.59 (0.56-0.62)
Smith 2018	0.57 (0.56-0.59)	0.65 (0.63-0.66)	0.56 (0.55-0.58)	0.7 (0.68-0.71)
Wang 2013	0.5 (0.48-0.52)		0.51 (0.49-0.52)	
Xin 2018	0.53 (0.51-0.55)		0.54 (0.53-0.56)	
Yarnall 2013	0.56 (0.54-0.57)	0.55 (0.53-0.56)	0.55 (0.54-0.57)	0.59 (0.57-0.6)

Supplementary Table 17. Discrimination (AUC ± 95% CI) for the risk models in women and men aged above and below 60

Model	Women		Men	
	Genes-only GRS (60 and under)	Genes-only GRS (over 60)	Genes-only GRS (60 and under)	Genes-only GRS (over 60)
Abe 2017	0.55 (0.53-0.58)	0.54 (0.52-0.56)	0.56 (0.53-0.58)	0.55 (0.53-0.57)
Dunlop 2013	0.56 (0.54-0.59)	0.56 (0.55-0.59)	0.56 (0.54-0.59)	0.56 (0.54-0.58)
Frampton 2016	0.56 (0.54-0.59)	0.54 (0.52-0.56)	0.55 (0.52-0.57)	0.55 (0.53-0.56)
Hosono 2016	0.55 (0.52-0.57)	0.52 (0.51-0.55)	0.54 (0.51-0.56)	0.55 (0.53-0.56)
Hsu 2015	0.56 (0.55-0.60)	0.58 (0.57-0.61)	0.56 (0.55-0.6)	0.56 (0.55-0.59)
Huyghe 2019	0.64 (0.61-0.66)	0.61 (0.59-0.64)	0.64 (0.62-0.67)	0.62 (0.60-0.63)
Ibanez-Sanz 2017	0.55 (0.53-0.58)	0.56 (0.54-0.59)	0.56 (0.54-0.59)	0.54 (0.52-0.56)
Iwasaki 2017	0.52 (0.50-0.55)	0.54 (0.52-0.56)	0.54 (0.51-0.56)	0.54 (0.53-0.56)
Jenkins 2016	0.56 (0.53-0.58)	0.56 (0.55-0.60)	0.57 (0.55-0.60)	0.56 (0.55-0.59)
Jeon 2018	0.58 (0.56-0.61)	0.57 (0.56-0.60)	0.58 (0.57-0.62)	0.57 (0.56-0.59)
Smith 2018	0.56 (0.54-0.59)	0.57 (0.56-0.60)	0.57 (0.55-0.60)	0.56 (0.54-0.58)
Wang 2013	0.49 (0.46-0.51)	0.50 (0.49-0.53)	0.50 (0.48-0.53)	0.50 (0.49-0.52)
Xin 2018	0.55 (0.52-0.57)	0.52 (0.50-0.55)	0.52 (0.51-0.56)	0.55 (0.53-0.57)
Yarnall 2013	0.55 (0.52-0.58)	0.56 (0.54-0.58)	0.56 (0.54-0.59)	0.54 (0.53-0.56)

Supplementary Table 18. Discrimination (AUC ± 95% CI) for the Abe model excluding folate

	Women		Men	
Model	Genes-only GRS	GRS plus phenotypic risk factors	Genes-only GRS	GRS plus phenotypic risk factors
Abe	0.55 (0.53-0.56)	0.67 (0.64-0.7)	0.55 (0.54-0.56)	0.71 (0.69-0.74)
Abe (excluding folate)	0.55 (0.53-0.56)	0.65 (0.64-0.67)	0.55 (0.54-0.56)	0.7 (0.68-0.71)

Supplementary Table 19. Discrimination (AUC ± 95% CI) for the Huyghe model only including incident CRC post 30th September 2014 (main analysis) and the full 6 years of follow up (sensitivity analysis)

Model	Women	Men
Huyghe model (full 6 years of follow up)	0.62 (0.61-0.64)	0.62 (0.61-0.64)
Huyghe model only including new incident CRC	0.62 (0.59-0.64)	0.64 (0.61-0.66)