



Effects of Screenings in Reducing Colorectal Cancer Incidence and Mortality Differ by Polygenic Risk Scores

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Study Highlight

- This prospective study investigated the effects of screenings in reducing colorectal cancer (CRC) incidence and mortality by CRC polygenic risk score (PRS), constructed using risk variants identified in genome-wide association studies.
- We found that individuals with a **high PRS of CRC benefited substantially more from a CRC screening than those with a low PRS.**
- Our findings could be useful in recommending **personalized strategies for CRC screening.**

Background

- Colorectal cancer (CRC) screening reduces CRC incidence and mortality.
- However, it is unclear whether the reduction in CRC risk may differ by genetic susceptibility.
- We constructed a polygenic risk score (PRS) of CRC using risk variants identified in genome-wide association studies and investigated the association of screening with reduced CRC incidence and mortality according to this PRS.

Methods

- We included 304,740 participants aged ≥ 50 years of European descent in the UK Biobank, a **population-based cohort study.**
- Participants who had received fecal occult-blood testing, colonoscopy, or sigmoidoscopy before enrollment constituted the **screening group** (N = 113,231); and others were in the **non-screening group** (N = 191,509).
- Cox models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) of CRC risk.

Results

- Median follow-up of 5.8 years, 2,261 incident CRC cases and 528 CRC deaths were identified.

Main outcome (Table 2)

- CRC screening was associated with a significantly reduced CRC incidence among individuals with a high (HR, 0.80; 95% CI, 0.71-0.92) and intermediate PRS (0.84, 0.71-0.98) but not among those with a low PRS (1.03, 0.86-1.25; $P_{interaction}$, 0.005).
- A similar, but more evident, difference was observed for mortality ($P_{interaction}$, 0.046), with more than 30% reduced mortality observed in the high PRS group (0.69, 0.52-0.91).

Stratified analyses by family history (Figure 1)

- We found a similar pattern of association regardless of a family history, although some estimates were unstable due to a smaller sample size.

Stratified analyses by age group (Figure 2)

- Among the younger group (age 50-60 years), CRC screenings were associated with a slightly, but non-significantly, elevated incidence and mortality in the low PRS group, but a reduced risk in the high PRS group ($P_{interaction}$, 0.043 [incidence]; 0.092 [mortality]).
- No significant interaction was observed in the older group (age > 60 years).

Table 1. Baseline characteristics

Characteristic	Screening	Non-screening	P value
No. of participants	113,231	191,509	–
Male sex, %	48.5	45.3	<0.0001
Age at enrollment (years)	63	59	<0.0001
> 60 years, %	69.0	38.5	
50 – 60 years, %	31.0	61.5	
Family history of CRC, %	15.7	09.9	<0.0001
Education, %			<0.0001
College or university degree	29.8	31.0	
Some professional qualifications	26.7	27.2	
Secondary education	20.3	21.7	
None of the above	22.1	19.0	
Living in the most deprived, %	21.3	21.9	<0.0001
Body mass index, %			<0.0001
< 18.5 kg/m ²	0.5	0.5	
18.5-24.9 kg/m ²	30.3	31.5	
25.0-29.9 kg/m ²	44.3	42.9	
≥ 30.0 kg/m ²	24.6	24.8	
Waist-to-hip ratio, Median	0.89	0.88	<0.0001
≥ 0.85 women, ≥ 0.90 men, %	54.9	50.6	<0.0001
Low physical activity, %	78.2	78.7	0.22
High processed/red meat intake, %	86.4	85.6	<0.0001
Low vegetable and fruit intake, %	66.2	68.2	<0.0001
High alcohol consumption, %	71.7	71.9	0.24
Smoking, %			<0.0001
Never	50.2	53.3	
Former	41.5	36.1	
Current	7.9	10.3	
PRS, %			0.0005
Low	33.0	33.5	
Intermediate	33.3	33.4	
High	33.7	33.1	

Figure 1. Associations of CRC risk with screenings, according to PRS and family history

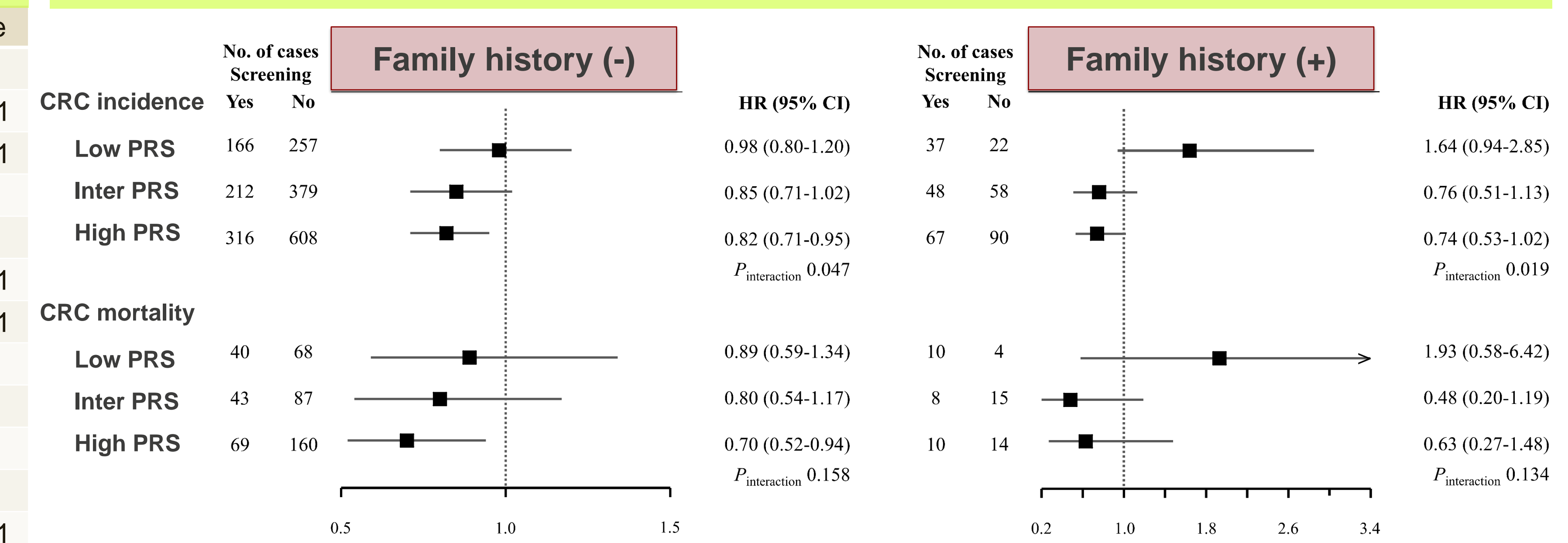
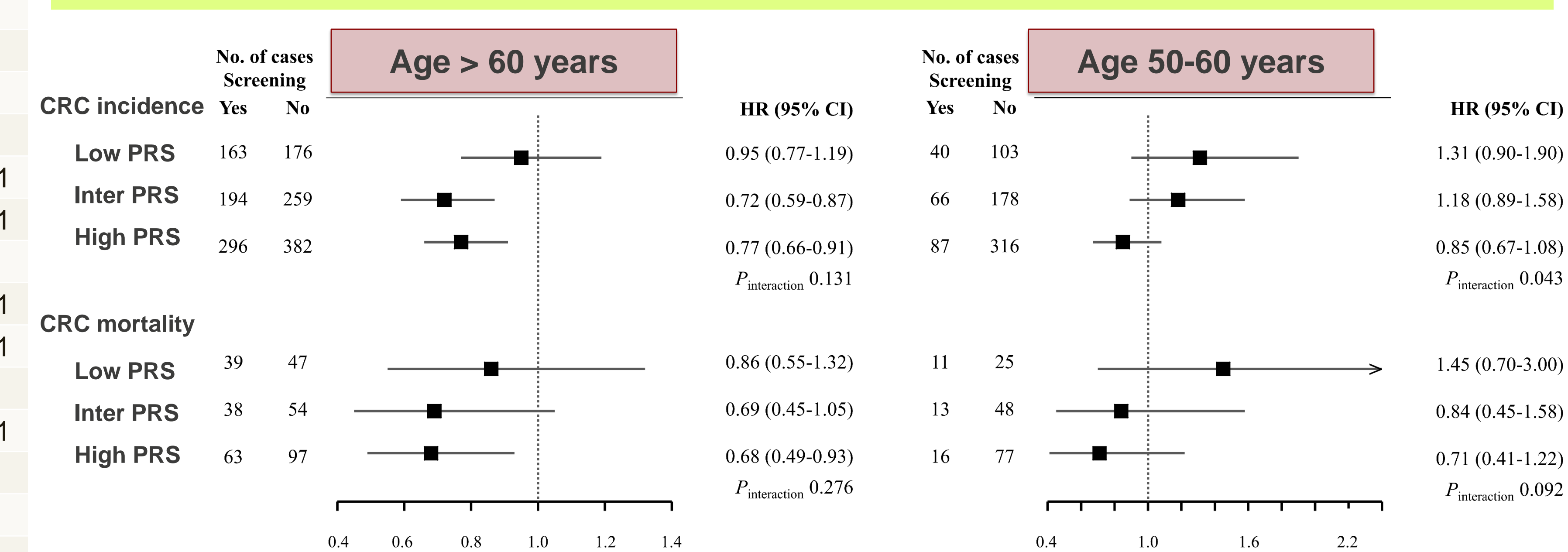


Figure 2. Associations of CRC risk with screenings, according to PRS and age groups



Conclusion

- Individuals with a **higher genetic risk benefited more substantially from CRC screenings** than those with a lower risk.
- Our findings suggest that PRS may be used to develop **personalized CRC screening to maximize its effect on CRC prevention.**

Future direction

- In our study, there is a lack of information on the type and frequency of screening interventions.
- Thus, future studies can be carried out to quantify the size of this modifying effect by screening modalities.

✧ This research was conducted using the UK Biobank Resource under Application Number 40685.

Table 2. Association of CRC incidence or mortality with receiving CRC screenings according to PRS in the UK Biobank

PRS category	Screening		Non-screening		HR (95% CI) ^a		Non-screening within each PRS category	$P_{interaction}$
	Cases (N)	Non-cases (N)	Cases (N)	Non-cases (N)	By screening and PRS jointly Screening	Non-screening		
CRC incidence								
Low	203	37,147	279	63,942	Reference	0.97 (0.80-1.17)	1.03 (0.86-1.25)	0.005
Intermediate	260	37,420	437	63,464	1.27 (1.06-1.52)	1.53 (1.29-1.83)	0.84 (0.71-0.98)	
High	383	37,818	698	62,689	1.86 (1.56-2.20)	2.32 (1.98-2.73)	0.80 (0.71-0.92)	
Overall	846	112,385	1,414	190,095	–	–	0.86 (0.79-0.95)	
CRC mortality								
Low	50	37,300	72	64,149	Reference	1.02 (0.70-1.49)	0.98 (0.67-1.43)	0.046
Intermediate	51	37,629	102	63,799	1.02 (0.69-1.50)	1.44 (1.01-2.05)	0.74 (0.52-1.05)	
High	79	38,122	174	63,213	1.58 (1.11-2.25)	2.29 (1.65-3.18)	0.69 (0.52-0.91)	
Overall	180	113,051	348	191,161	–	–	0.77 (0.64-0.93)	

^aAdjusted for age at enrollment, sex, family history of CRC, education, Townsend deprivation index, body mass index, waist-to-hip ratio, physical activity, processed and red meat intake, vegetable and fruit intake, alcohol consumption, tobacco smoking, top 5 PCs for ancestry, and genotyping batch, and stratified by birth cohort.