Family history (+)
Age 50-60 years

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Our findings could be useful in recommending personalized strategies for CRC screening.

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; Pinteraction, 0.005).

A similar, but more evident, difference was observed for mortality (Pinteraction, 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 (Pinteraction, 0.043 [incidence]; 0.092 [mortality]).

No significant interaction was observed in the older group (age > 60 years).

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 40665.