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Are ADRs at screening associated with CRC risk and death at 17 years?

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Background

- **Adenoma detection rate (ADR):** key endoscopy quality indicator
- Intuitive hypothesis: ↑ adenomas removed, ↑ CRC protection
- Evidence: ↑ ADR at screening endoscopy, ↓ CRC risk within a few years[1-5]
- Does this translate to long-term lower CRC incidence and mortality?

The UK Flexible Sigmoidoscopy Screening Trial (UKFSST):

- ADRs varied widely, reflecting differences in endoscopist performance

1) Corley DA, et al. *NEJM.* 2014. 2) Kaminski MF, et al. *Gastroenterology*. 2017. 3) Lam AY, et al. *Gastrointest Endosc*. 2020.
4) Kaminski MF, et al. *NEJM*. 2010. 5) Rogal SS, et al. *Clin Gastroenterol Hepatol. 2013.*

Relevance

How does an analysis of ADRs at screening FS relate to PCCRC?

- Important to maximise quality & efficacy of endoscopy procedures
- Potential disadvantages of higher ADRs:
  - ↑ burden of adenoma surveillance on endoscopy resources
  - ↑ adverse events (e.g. bowel perforation, GI bleeding)
- If our data show ↑ long-term benefits with ↑ ADRs → evidence of the importance of widespread ADR improvement

The UKFSST[1-3]

170,432
Eligible men and women
aged 55-64, 1994-1999

Randomised 2:1

113,195
Control

No further contact

57,237
Invited to screening

40,674
Screened using Flexible Sigmoidoscopy

29,406
No polyps

9,119
Low-risk polyps

2,149
High-risk polyps

38,525
Discharged

2,149
Colonoscopy

17yrs follow-up (2014)[3]

Incidence reductions: 26% all-site CRC
41% distal CRC

Mortality reductions: 30% all-site CRC
46% distal CRC

1) Atkin WS, et al. *Lancet*. 2002. 2) Atkin WS, et al. *Lancet*. 2010. 3) Atkin WS, et al. *Lancet*. 2017.

Standardised screening protocol

- Participants self-administered phosphate enema at home
- 60cm Olympus video-endoscope, carbon dioxide for insufflation
- Endoscopists instructed:
  - -Advance scope to at least SC-DC junction, avoiding undue pain
  - -No longer than 4-6 minutes
  - -Remove polyps ≤5mm on insertion, 6-9mm on withdrawal, ≥10mm intact
- Colonoscopy referral criteria:
  - -≥10mm polyp, 3+ adenomas, TVA or VA, HGD, malignancy, 20+ HPPs
- Colonoscopy surveillance: typically ≥2 at 3-year intervals

1) Atkin WS, et al. *Lancet*. 2002. 2) Atkin WS, et al. *Gastroenterology*. 2004.

Endoscopists

- Registrar-level gastroenterologist or surgeon
- Minimum JAG training, performed 50 supervised & 100 unsupervised prior FS
- Single endoscopist in each centre performed most FS exams:
  -96% screened by main endoscopist (range 84-99% by centre)
- Each performed ~3,000 FS (range 2,500-3,900 by centre)
- Knew that performance monitored

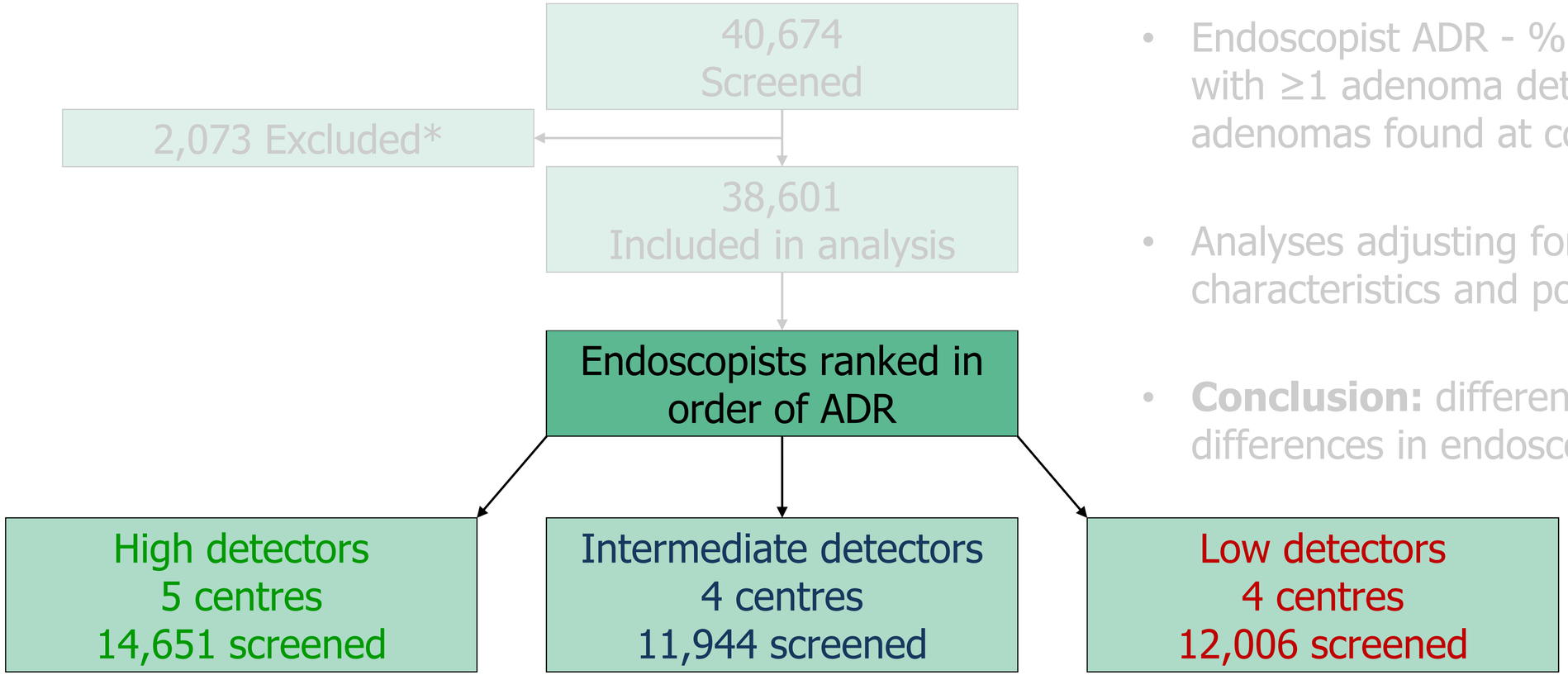
Centres

- Participants ~50% men and mean age of 60 years at each centre
- 71% uptake overall (range 62-77% by centre)

1) Atkin WS, et al. *Lancet*. 2002. 2) Atkin WS, et al. *Gastroenterology*. 2004.

Analysis of variation in ADRs[1]

Aim: examine extent to which differences in ADR between endoscopists are real and not attributable to population differences



- Endoscopist ADR - % screened individuals with ≥1 adenoma detected, including distal adenomas found at colonoscopy
- Analyses adjusting for endoscopist/centre characteristics and population characteristics
- **Conclusion:** differences in ADR reflect true differences in endoscopist performance

*828 screened by non-main endoscopist, 536 screened in pilot centre, 342 screened with colonoscopy, 367 where pathologist found to be over-diagnosing adenomas.

1) Atkin WS, et al. *Gastroenterology*. 2004.

ADRs by endoscopist and ranking group

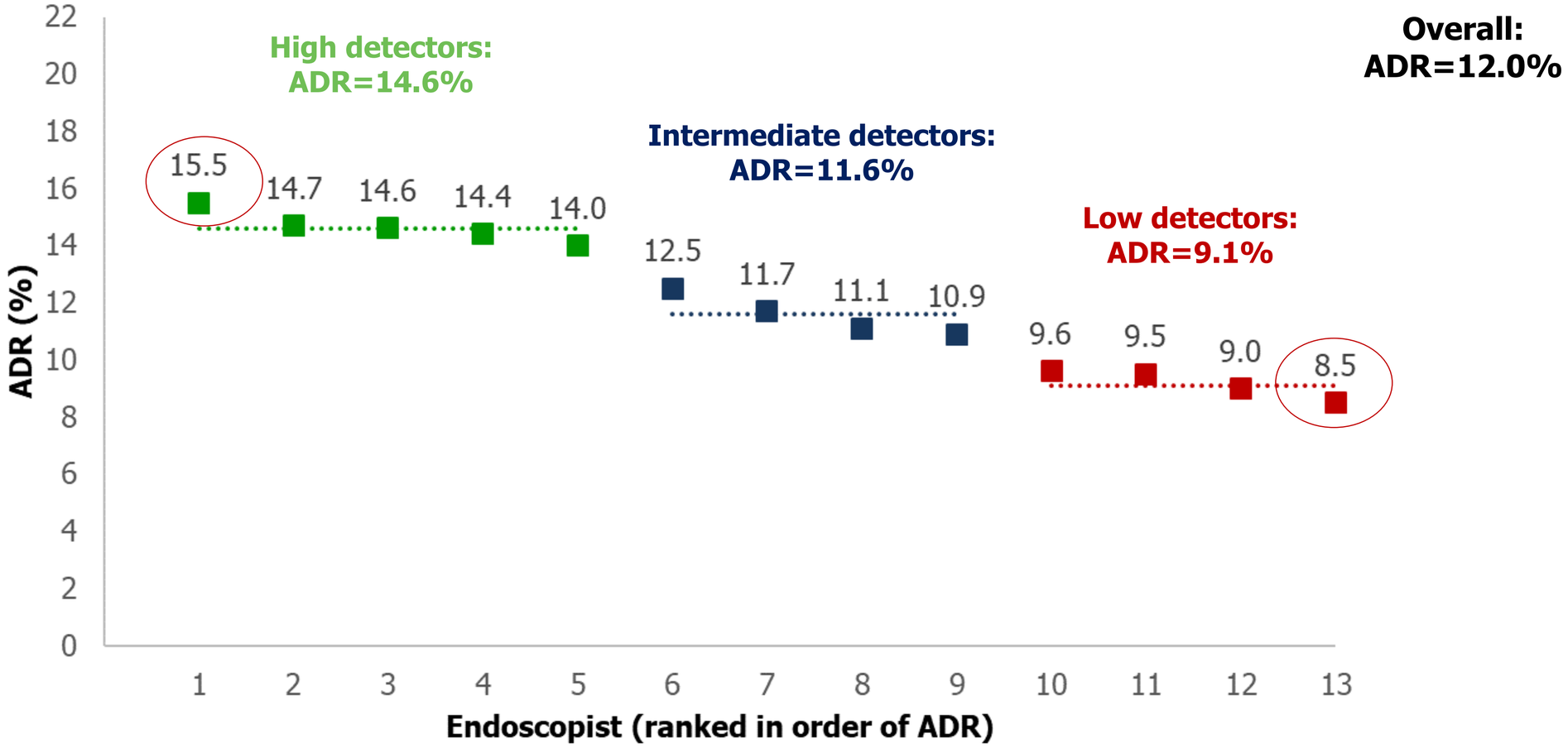


Figure prepared using data from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Adenoma detection rates by endoscopist

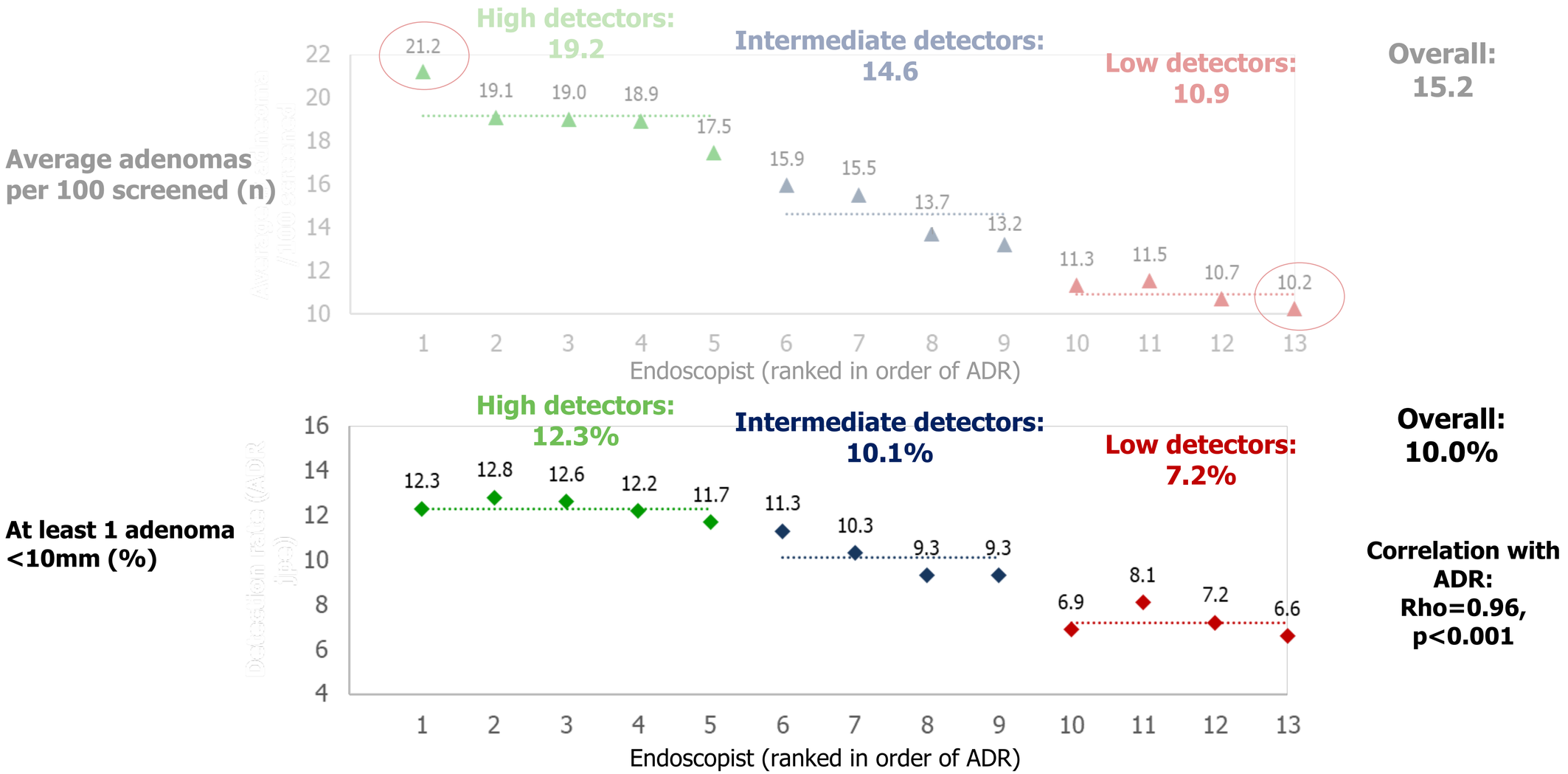
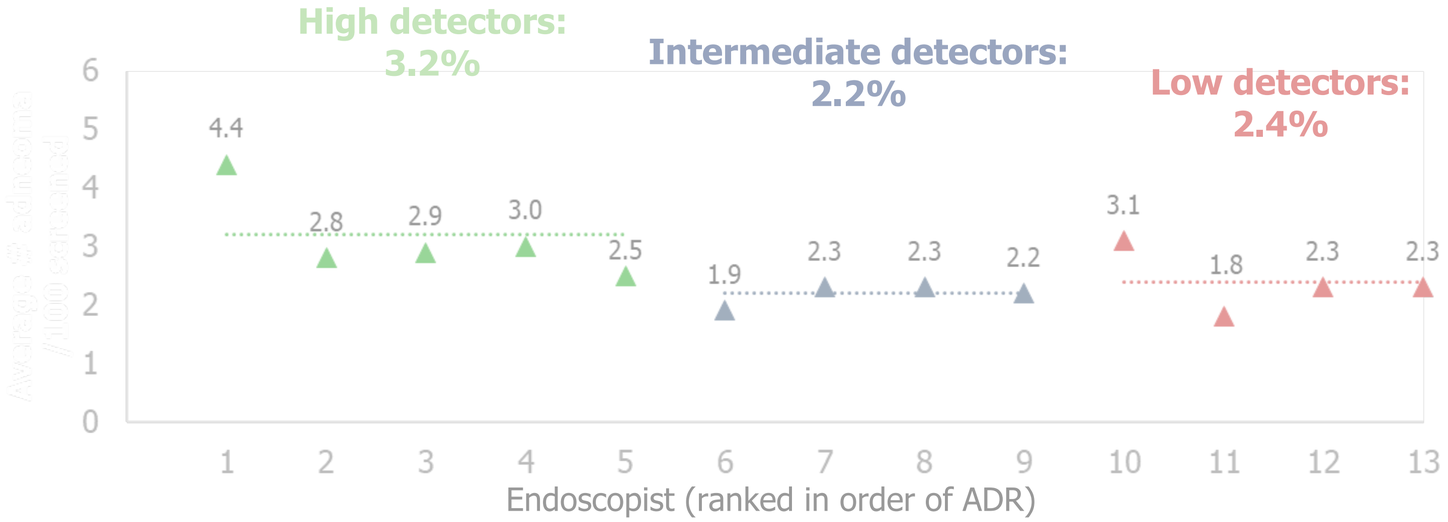


Figure prepared using data from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Adenoma detection rates by endoscopist

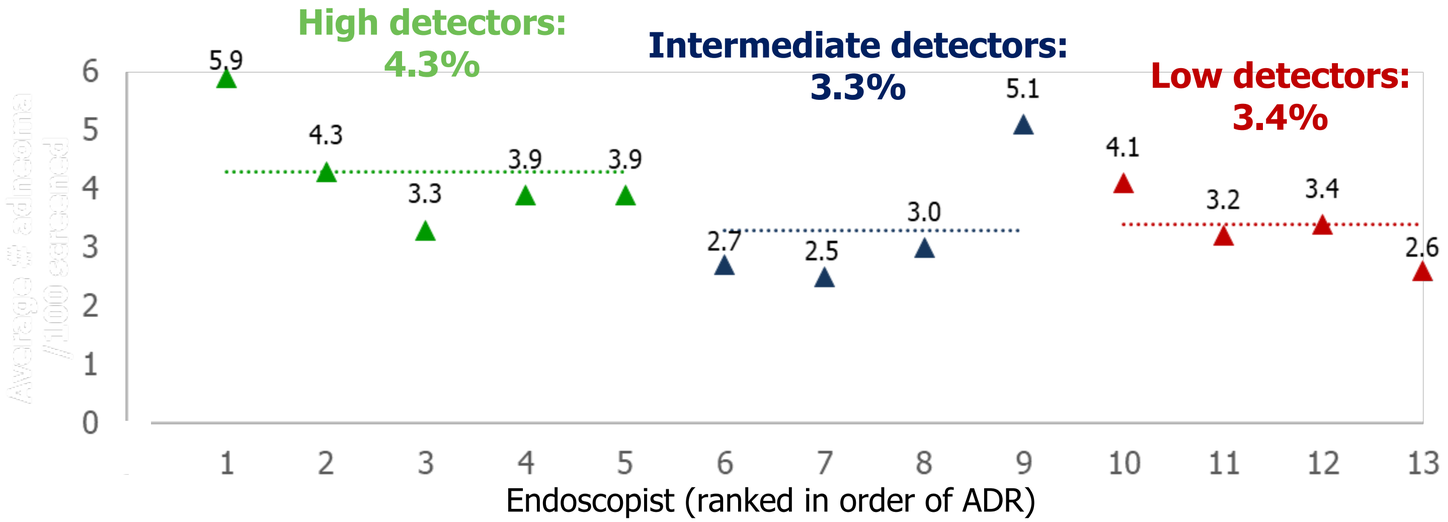
At least 1 adenoma ≥10mm (%)



Overall: 2.6%

Correlation with ADR: Rho=0.51, p=0.08

At least 1 advanced adenoma (%)



Overall: 3.7%

Correlation with ADR: Rho=0.42, p=0.15

Figure prepared using data from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Referral rates by endoscopist

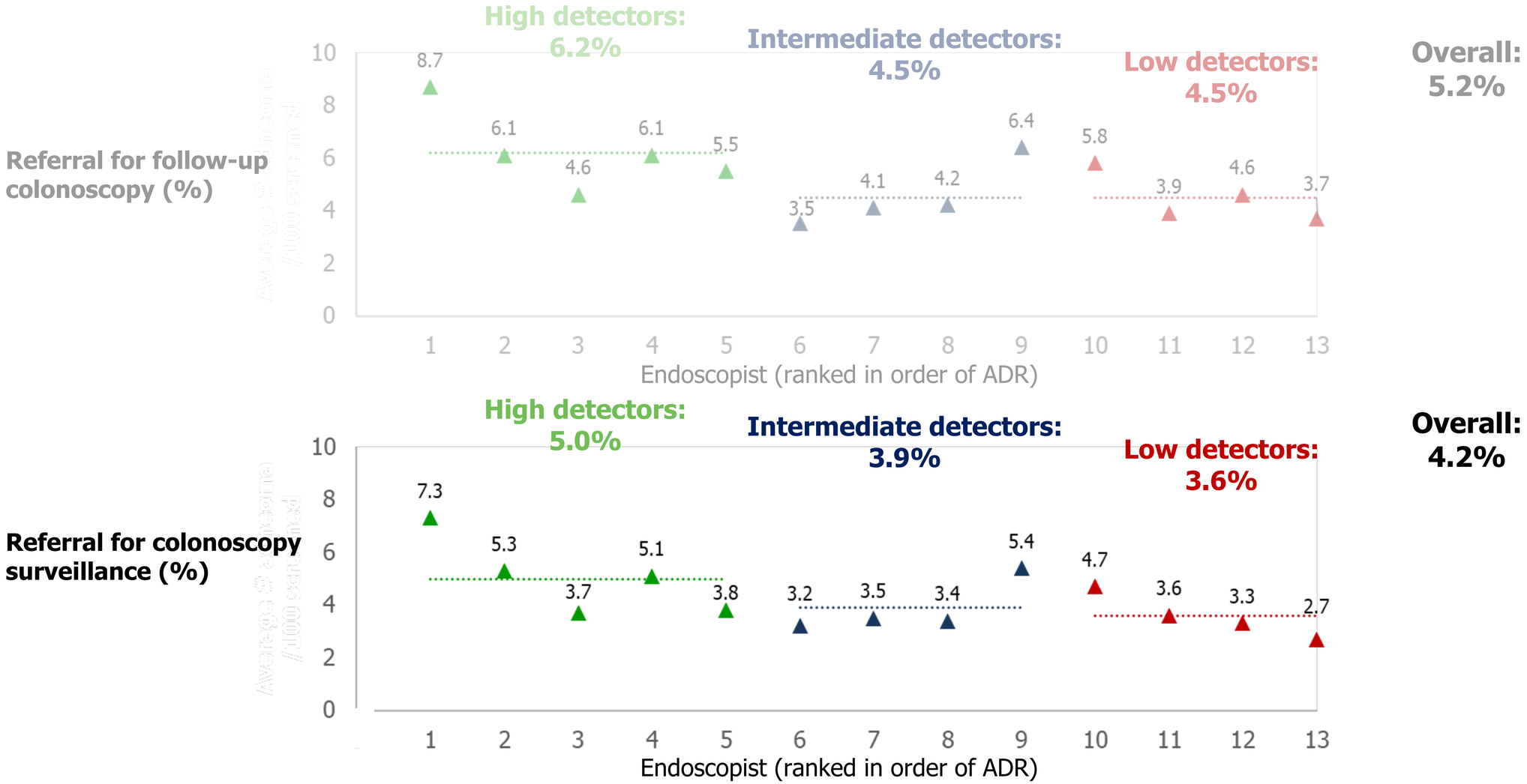


Figure prepared using data from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Analysis of ADRs and long-term outcomes[1]

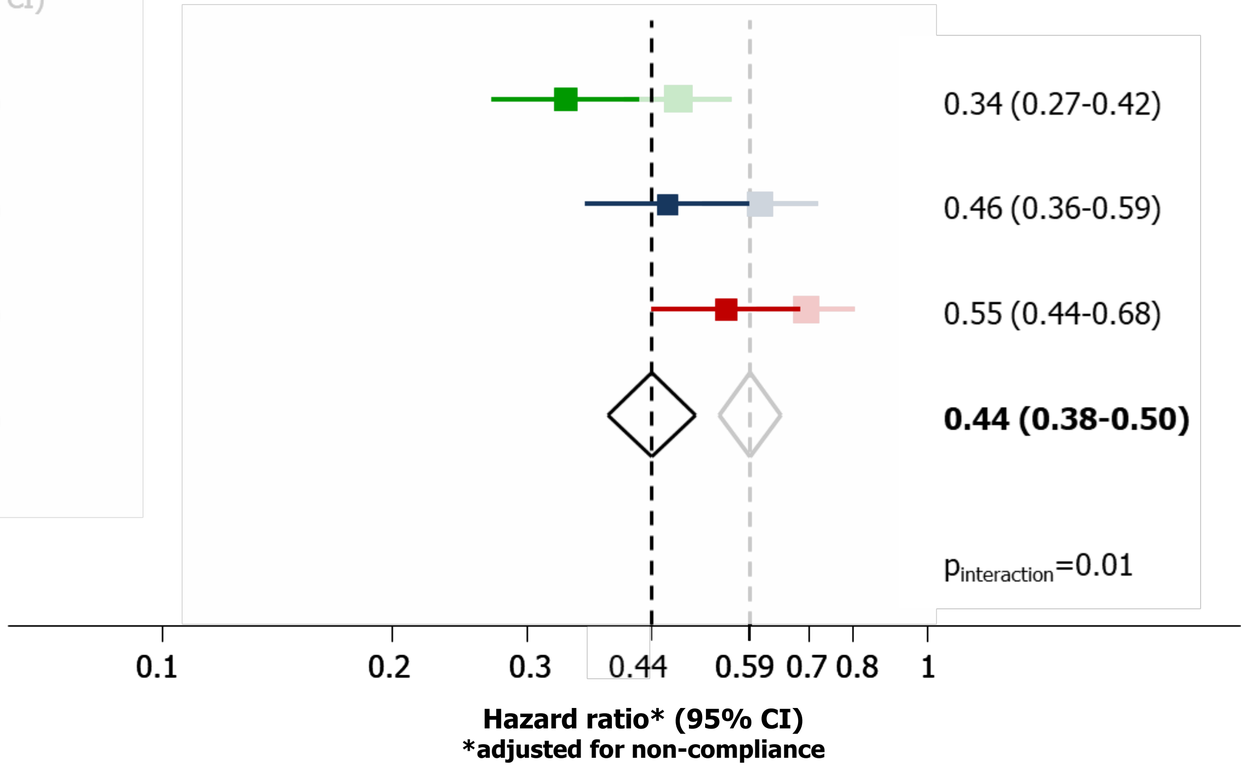
Aim: examine if effectiveness of FS screening after 17yrs varied by detector ranking group

- For each detector ranking group
  - -Compared CRC incidence and mortality among invited-to-screening and control arms
  - -Outcomes: distal CRC and all-site CRC
  - -Estimated hazard ratios using Cox regression
- Examined heterogeneity of effect by detector ranking using tests of interaction
- Also conducted per-protocol analyses, adjusted for non-compliance with screening[2]
- Estimated the number needed to screen[3] to prevent one CRC diagnosis or death
- Calculated 3-year average rate ratios for first 16yrs of follow-up

1) Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022. 2) Cuzick J et al. *Stat Med.* 1997.
3) Tabar L et al. *J Med Screen.* 2004.

Distal CRC incidence

Detector ranking group	Control arm		Invited to screening arm	
	Cases	Rate (95% CI)	Cases	Rate (95% CI)
High	748	113 (105-121)	179	53 (46-62)
Intermediate	548	107 (98-116)	168	65 (56-75)
Low	673	118 (109-127)	239	82 (72-93)
Overall	1,969	113 (108-118)	586	66 (61-72)

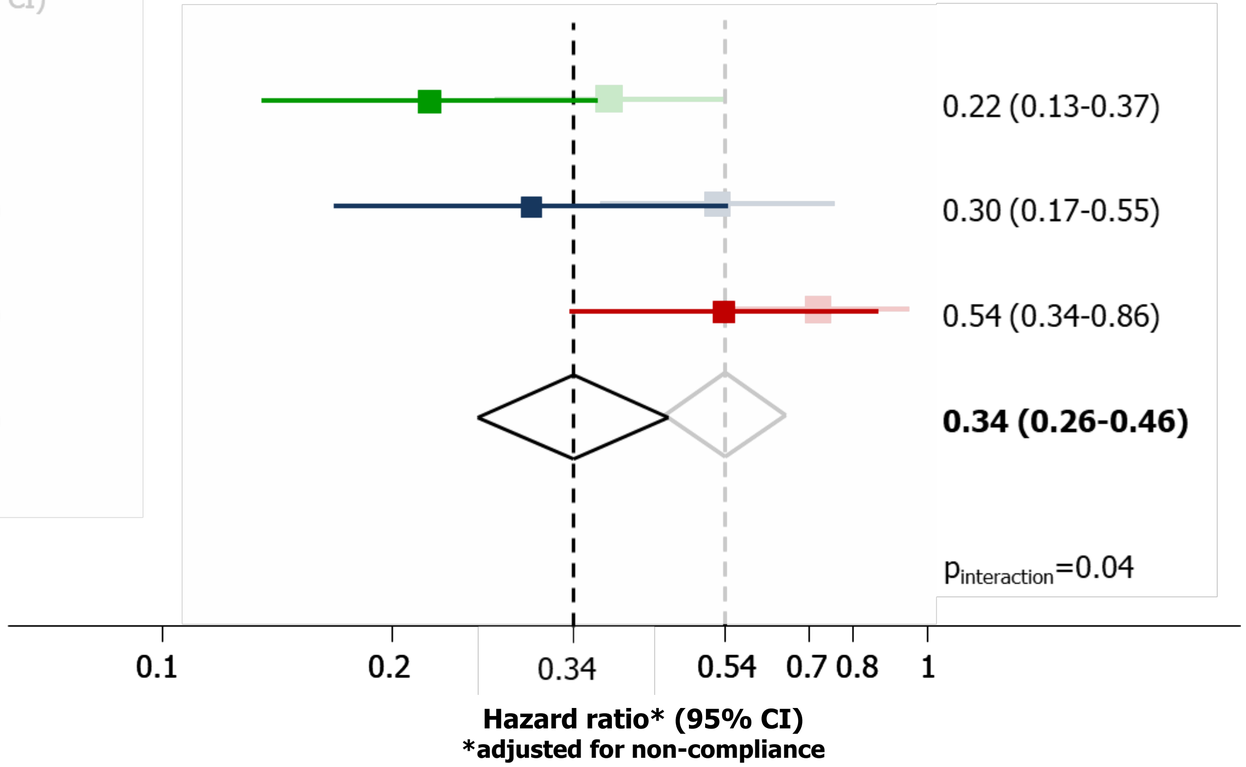


Rates are per 100,000 person-years.

Figure taken from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Distal CRC mortality

Detector ranking group	Control arm		Invited to screening arm	
	Cases	Rate (95% CI)	Cases	Rate (95% CI)
High	201	30 (26-35)	39	12 (8-16)
Intermediate	145	28 (24-33)	39	15 (11-20)
Low	190	33 (29-38)	70	24 (19-30)
Overall	536	31 (28-33)	148	17 (14-20)

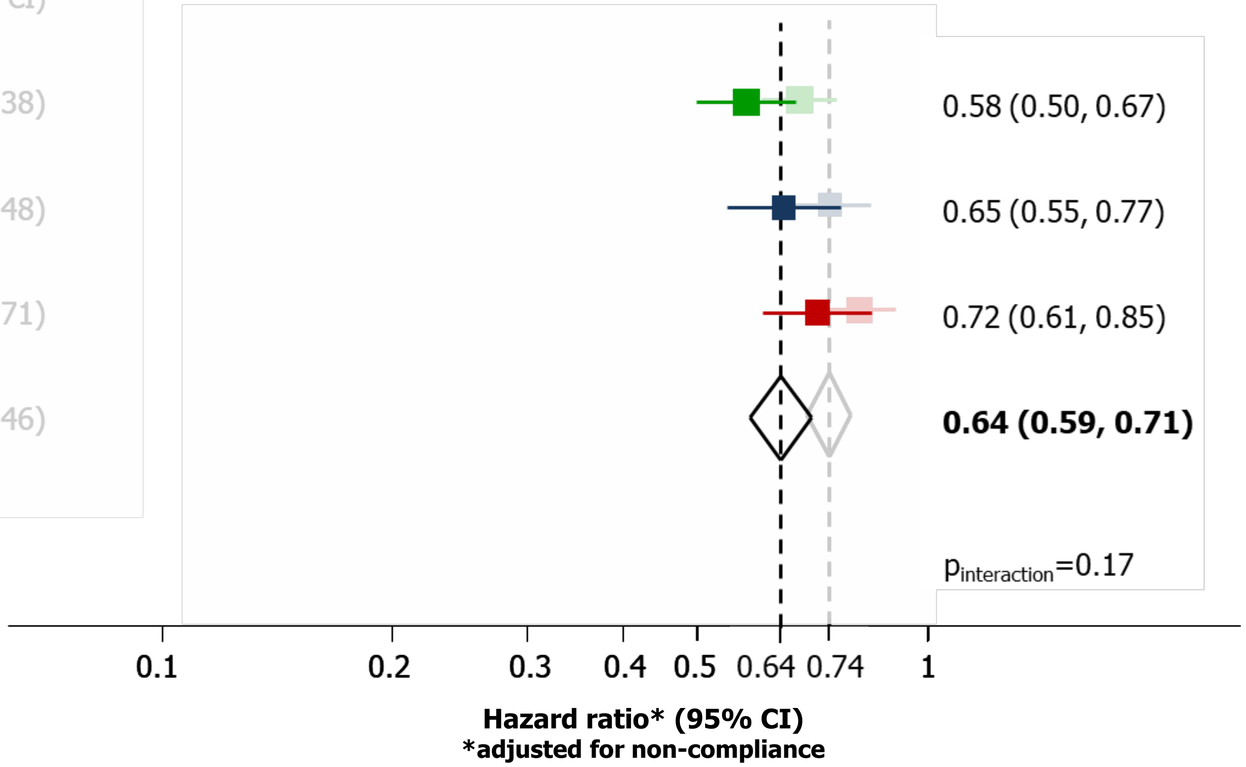


Rates are per 100,000 person-years.

Figure taken from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

All-site CRC incidence

Detector ranking group	Control arm		Invited to screening arm	
	Cases	Rate (95% CI)	Cases	Rate (95% CI)
High	1,216	184 (174-195)	417	125 (114-138)
Intermediate	917	179 (168-191)	345	133 (120-148)
Low	1,092	192 (181-204)	453	156 (142-171)
Overall	3,225	185 (179-192)	1,215	138 (130-146)

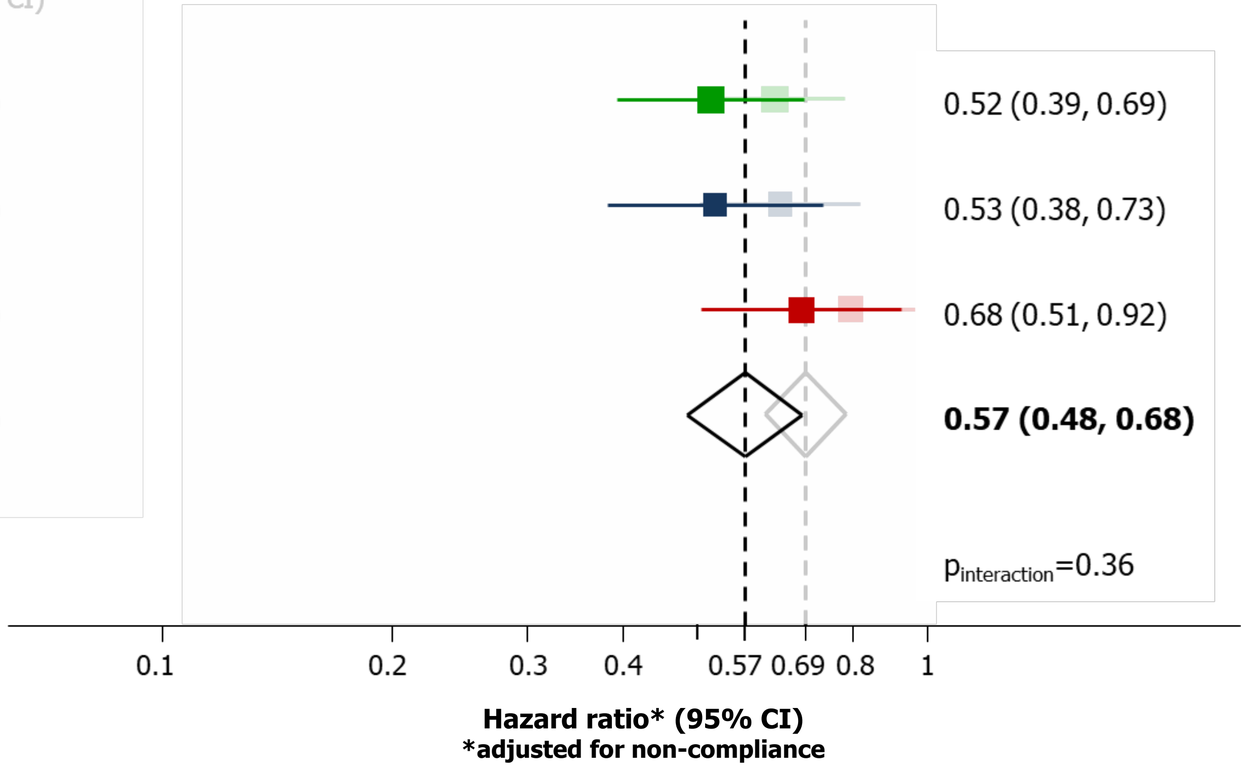


Rates are per 100,000 person-years.

Figure taken from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

All-site CRC mortality

Detector ranking group	Control arm		Invited to screening arm	
	Cases	Rate (95% CI)	Cases	Rate (95% CI)
High	362	54 (49-60)	115	34 (29-41)
Intermediate	272	53 (47-59)	88	34 (27-42)
Low	351	61 (55-68)	142	49 (41-57)
Overall	985	56 (53-60)	345	39 (35-43)

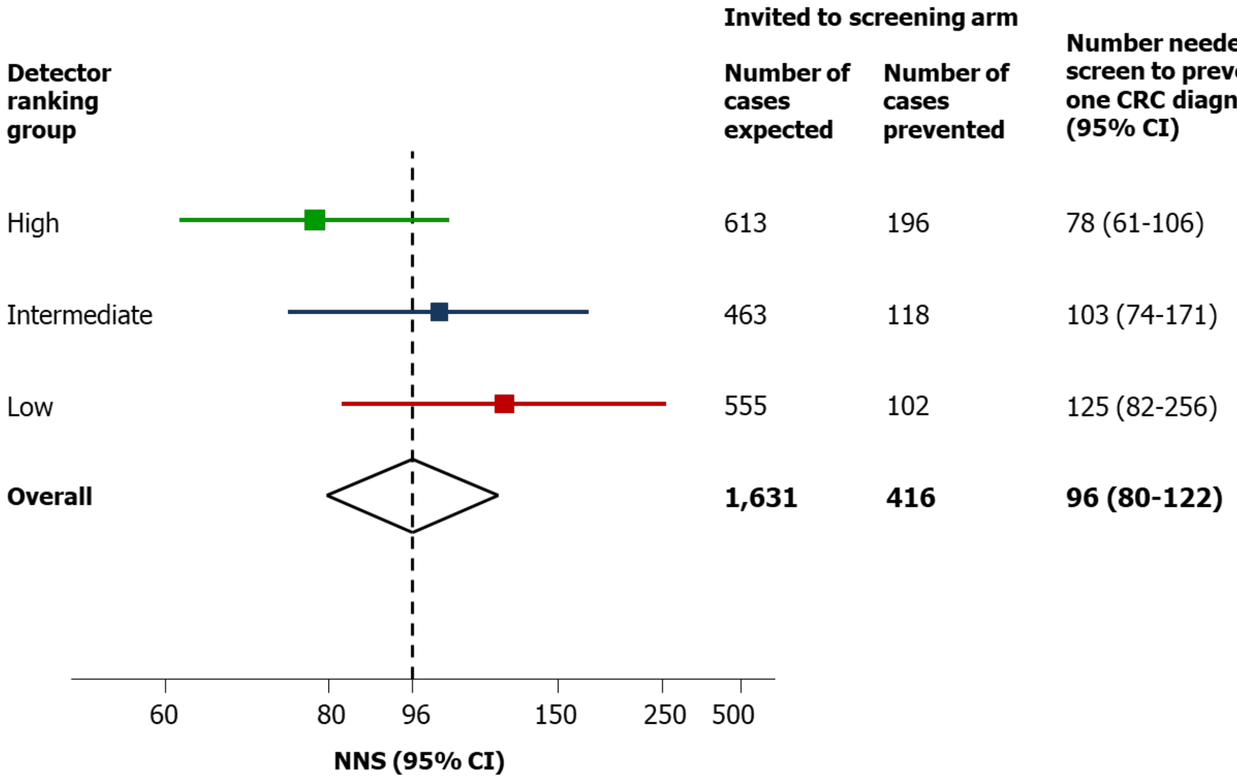


Rates are per 100,000 person-years.

Figure taken from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

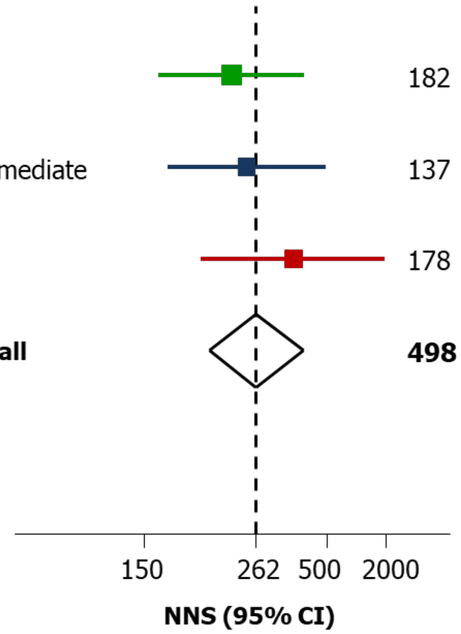
Number needed to screen

NNS to prevent one CRC diagnosis



Detector ranking group	Invited to screening arm: Number of cases expected	Invited to screening arm: Number of cases prevented	Number needed to screen to prevent one CRC diagnosis (95% CI)
High	613	196	78 (61-106)
Intermediate	463	118	103 (74-171)
Low	555	102	125 (82-256)
Overall	**1,631**	**416**	**96 (80-122)**

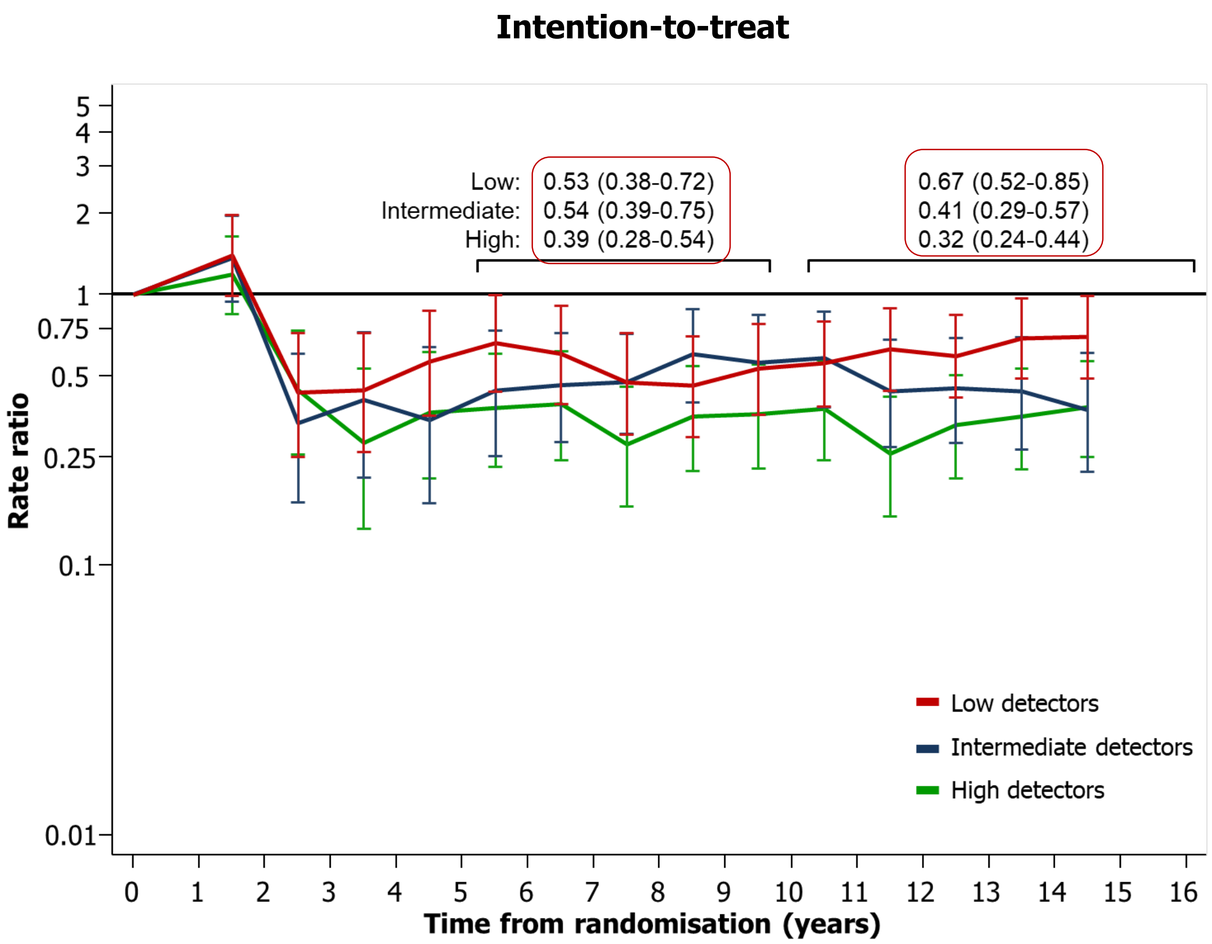
NNS to prevent one CRC death

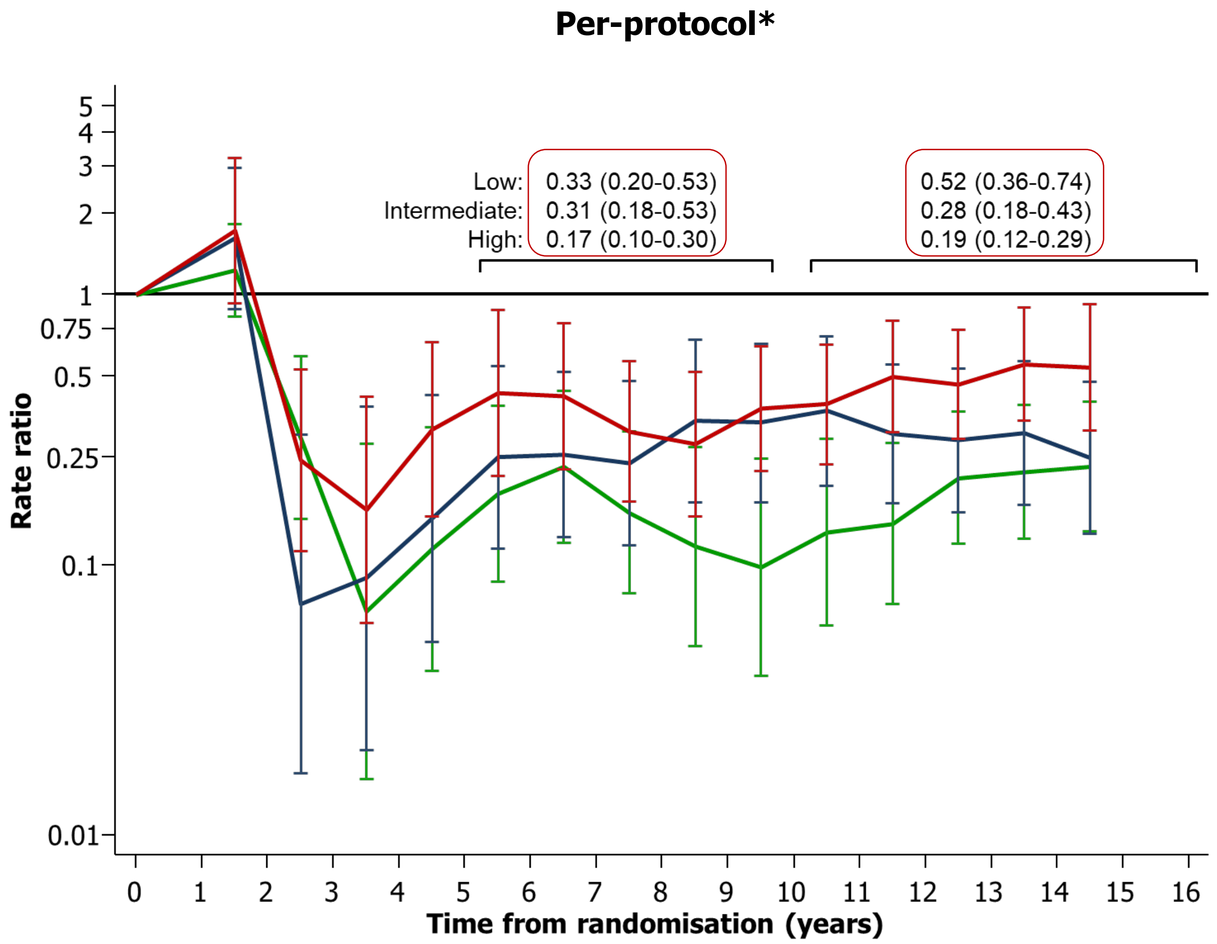


Detector ranking group	Invited to screening arm: Number of cases expected	Invited to screening arm: Number of cases prevented	Number needed to screen to prevent one CRC death (95% CI)
High	182	67	226 (159-387)
Intermediate	137	49	247 (165-490)
Low	178	36	349 (192-1,904)
Overall	**498**	**153**	**262 (200-381)**

Figure taken from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Distal CRC incidence - rate ratios over time

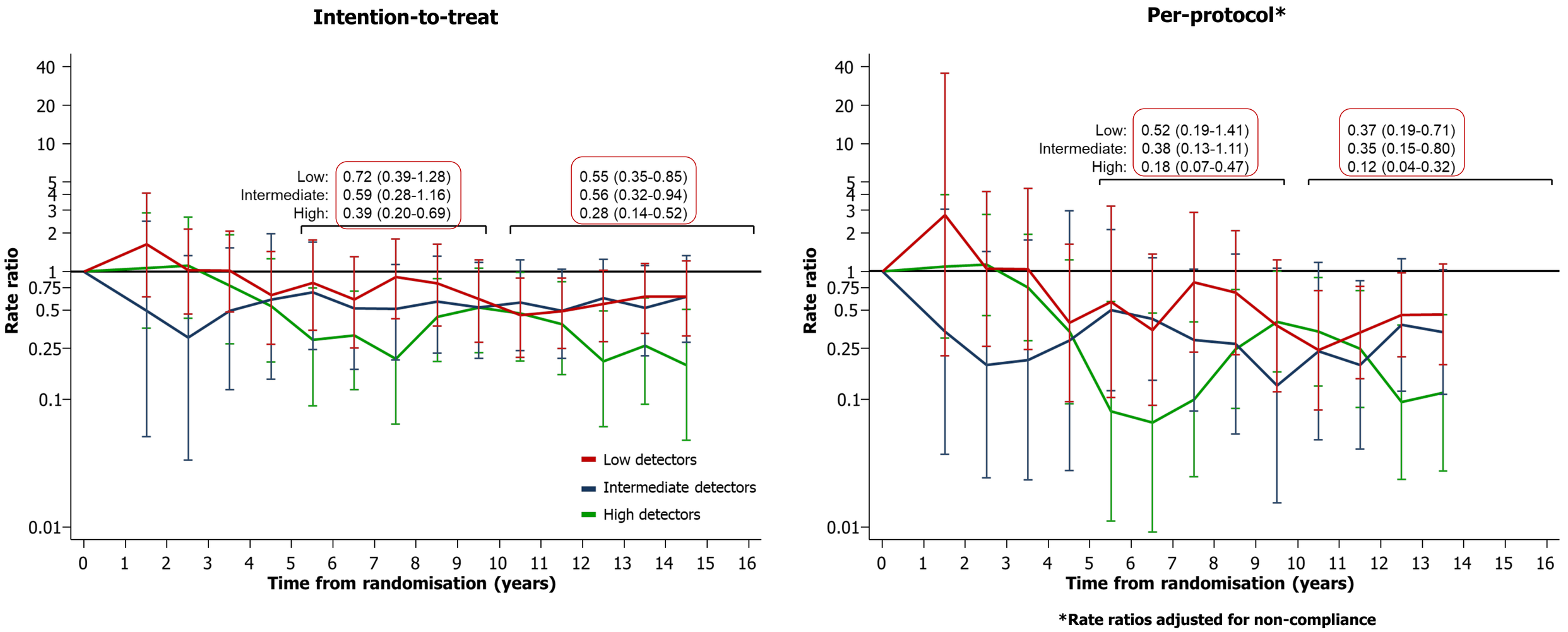




*Rate ratios adjusted for non-compliance

Figure taken from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Distal CRC mortality - rate ratios over time



*Rate ratios adjusted for non-compliance

Figure taken from: Cross AJ et al. *Clin Gastroenterol Hepatol*. 2022.

Strengths and limitations

Strengths:

- Large, high-quality dataset, minimal loss to follow-up
- Variation in ADRs and long follow-up period
- Low variation in outcome rates among controls → not confounded by differences in baseline CRC risk

Limitations:

- Screening performed in late 90's, advances in endoscopy technology since
- UKFSST recruited those interested in screening: ↓ risk of colorectal neoplasia?

  However, have shown CRC risk in controls similar to general population

Summary

- Striking differences for distal CRC by endoscopist ADR ranking group
- No significant heterogeneity for all-site CRC: proximal cancers diluted effect
- Higher ADRs driven by better small adenoma detection

Conclusion: higher ADRs at screening FS provide greater long-term protection against CRC incidence and mortality → distal CRC incidence ↓66% and mortality ↓78% if screened by high detector

Highlights the importance of quality assurance and careful monitoring of ADRs to realise the full public health benefits of endoscopic screening, involving either FS or colonoscopy

Future directions

- Funding to follow cohort for further 10yrs:
  -Are differences in effect by detector ranking group maintained for >25yrs?
  -If there is attenuation in effect, does it vary by detector ranking group?
  -Is high protection against CRC maintained in high detectors for further 10yrs?

- Examine CRC incidence by baseline polyp groups and anatomic subsite

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