

YOUNG ONSET COLORECTAL CANCER RISK AMONG INDIVIDUALS WITH IRON DEFICIENCY ANEMIA AND HEMATOCHEZIA

Joshua Demb, PhD MPH^{1,2}, Lin Liu PhD²⁻⁴, Caitlin C. Murphy PhD^{5,6}, Chyke A. Doubeni MD MPH⁷, Maria Elena Martinez PhD³, Samir Gupta MD MSCS¹⁻³

¹Division of Gastroenterology, Department of Internal Medicine, University of California San Diego, ²Veterans Affairs San Diego Healthcare System, ³University of California, San Diego Moores Cancer Center,

⁴Division of Biostatistics and Bioinformatics, Department of Family Medicine and Public Health, University of California, San Diego, ⁵Departments of Population & Data Sciences and Internal Medicine, University of Texas Southwestern Medical Center,

⁶Harold C. Simmons Comprehensive Cancer Center, ⁷Center for Health Equity and Community Engagement Research, and Department of Family Medicine, Mayo Clinic

BACKGROUND

- Proportion of colorectal cancer cases diagnosed before age 50, known as young-onset colorectal cancer (YCRC) has increased over time.¹
- Individuals with YCRC tend to be diagnosed at later stages, requiring more intense treatments.²
- 70% of YCRC cases detected due to signs/symptoms signaling presence of YCRC, such as iron deficiency anemia (IDA) or hematochezia (blood in stool).³
- The risks for YCRC after diagnosis of IDA or hematochezia have not been well established.

OBJECTIVES

- Examine association between iron deficiency anemia (IDA) and YCRC risk
- Examine association between hematochezia and YCRC risk

METHODS

Design:

- Cohort study of US Veterans ages 18-49 receiving care in the Veterans Health Administration (VHA) between 1999-2016.
- Matched cohorts (with replacement) used to perform analyses, matching on sex, birth year, first VHA visit date (± 180 days), and date of IDA/Hematochezia diagnosis date of exposed individual (start of follow-up).
 - Excluded individuals with YCRC or inflammatory bowel disease prior to start of follow-up.

Analytic Samples:

- 4:1 matching individuals without incident IDA to those with IDA (n = 239,000)
- 4:1 matching individuals without incident hematochezia to those with hematochezia (n = 653,740)

Measures

- IDA:** Defined using WHO criteria as:
 - Hemoglobin test identifying anemia (hemoglobin <13.0 mg/dL in males, <12.0 mg/dL in females), **AND**
 - Follow-up iron test within 3 months indicating iron deficiency (ferritin levels ≤ 15 ng/mL or transferrin saturation levels $\leq 16\%$)
- Hematochezia:** Identified by ICD-9 and ICD-10 diagnosis codes.
- Outcome:** YCRC diagnosed within five years of start of follow-up defined by:
 - Primary or secondary diagnoses identified in VA Central Cancer Registry or Oncology Raw database, **OR**
 - National Death Index-identified YCRC
- Covariates:** Race/ethnicity, body mass index (BMI), smoking status (current, former, never), diabetes prevalence, aspirin use.

Statistical Analysis

- Five-year cumulative YCRC risk estimates accounting for censoring (turning 50, non-YCRC-related death, five years of follow-up, December 31, 2016)
 - Used to calculate risk differences and number needed to scope to detect 1 YCRC (NNS)
 - 95% confidence intervals derived by boot-strapping with 1000 replications
- Cox proportional hazards models to estimate hazard ratio of YCRC and corresponding 95% confidence intervals.
 - Accounted for matching using cluster-specific random intercepts.

References:

¹Siegel RL et al. Colorectal Cancer Facts and Figures 2017-2019. Am Cancer Soc. 2017.
²Silla IO et al. Early-onset colorectal cancer: a separate subset of colorectal cancer. World J Gastroenterol. 2014;20(46):17288-17296.
³Patel SG, Ahnen DJ. Colorectal Cancer in the Young. Curr Gastroenterol Rep. 2018;20(4):15.
⁴Heitman SJ et al. Prevalence of Adenomas and Colorectal Cancer in Average Risk Individuals: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2009;7(12):1272-1278.



RESULTS

IDA Analytic Cohort:

- Cohort population was predominantly female (53%), ages 40-49 and overweight or obese (**Table 1**).
- Individuals with IDA were more likely to be Black (43% vs. 27%), never smokers (32% vs. 40%), have prevalent diabetes (13% vs. 7%), and be aspirin users (13% vs. 6%) compared to individuals without IDA.

Hematochezia Analytic Cohort:

- Cohort population was mostly male (87%), ages 40-49, non-Hispanic White, and overweight or obese (**Table 1**).
- Individuals with hematochezia were more likely to be current smokers (33% vs. 26%), overweight or obese (72% vs. 49%) and aspirin users (10% vs. 6%) compared to individuals without hematochezia.

Summary of Findings:

- YCRC five-year cumulative incidence markedly higher among individuals diagnosed with IDA or hematochezia (**Figure 1**).
- YCRC risk elevated among men with IDA diagnosis and individuals ages ≥ 30 with IDA or hematochezia diagnosis (**Figure 2**).
- NNS is at or below 333 cut-off for IDA and hematochezia diagnosis overall, and for men diagnosed with IDA or hematochezia and individuals ages 40-49 diagnosed with IDA or hematochezia (**Figure 3**).

Figure 1. Cumulative incidence curves for YCRC risk by IDA and hematochezia exposure.

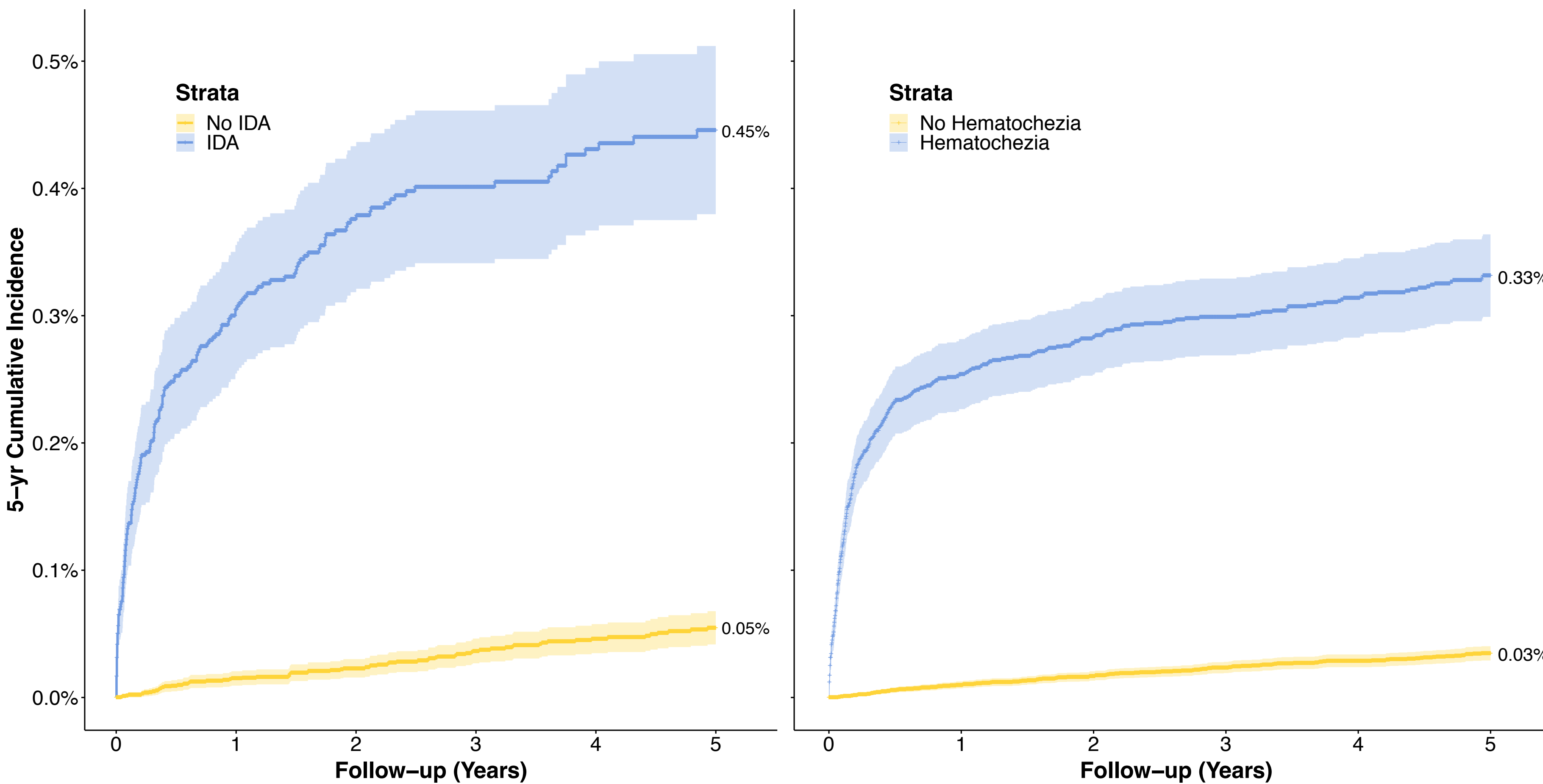
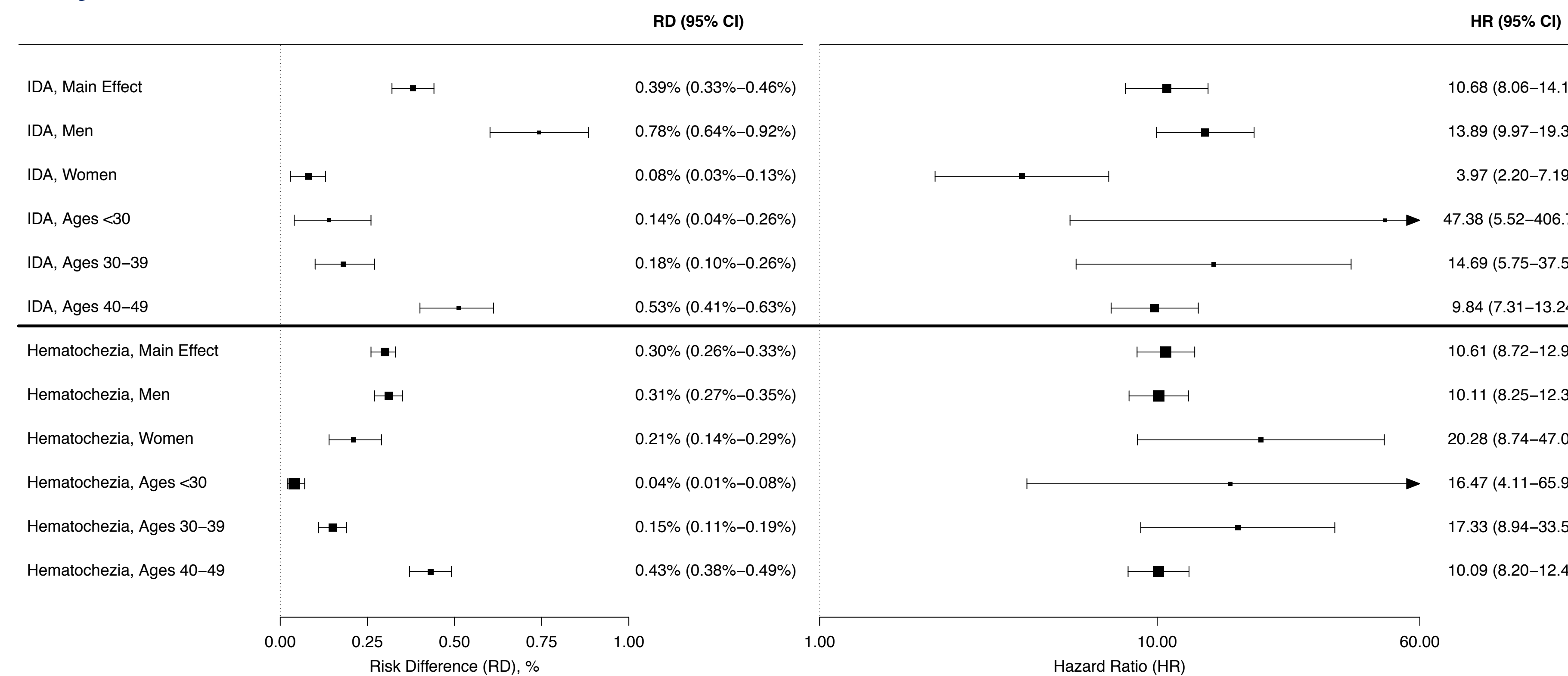


Figure 2. Risk difference and hazard ratio findings, main effect and stratified, for IDA and hematochezia analytic cohorts.

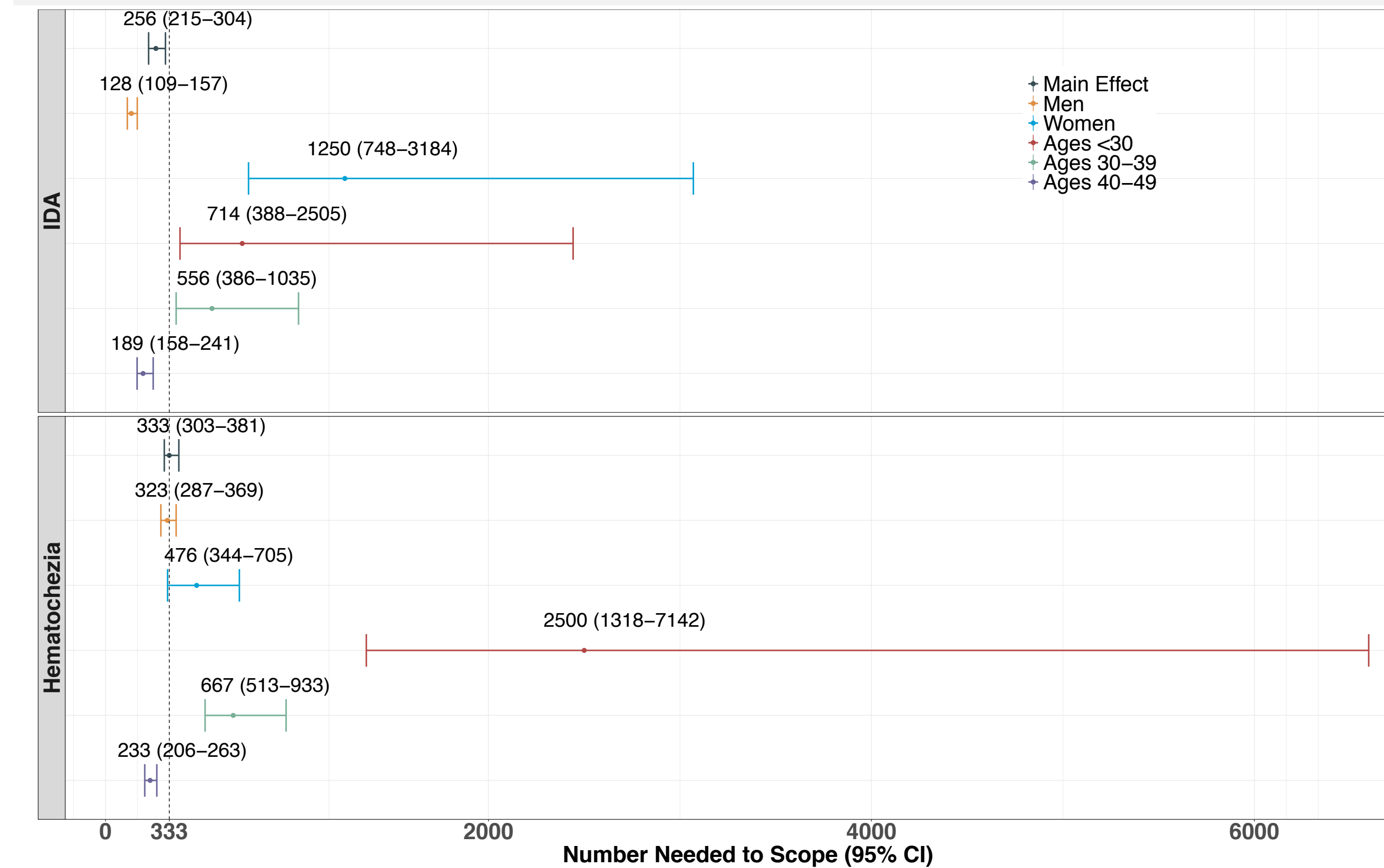


Hazard ratio models include matching strata variable as random intercept and adjusts for race/ethnicity, BMI and aspirin use

Table 1. Characteristics of IDA and hematochezia analytic cohorts.

| | IDA Cohort | Hematochezia Cohort |
|-------------------------------------|-------------------|---------------------|
| | Overall | Overall |
| | N=239,000 | N=653,740 |
| Follow-up in Years, Median [Q1, Q3] | 3.8 [1.7, 5.0] | 5.0 [3.1, 5.0] |
| Age, Median [Q1, Q3] | 42 [36, 46] | 42 [34, 46] |
| Ages <30 | 25,430 (10.6%) | 98,575 (15.0%) |
| Ages 30-39 | 62,407 (26.1%) | 162,800 (24.9%) |
| Ages 40-49 | 151,163 (63.2%) | 392,365 (60.0%) |
| Sex: | | |
| Male | 112,225 (47.0%) | 571,295 (87.4%) |
| Female | 126,775 (53.0%) | 82,445 (12.6%) |
| Race/Ethnicity: | | |
| White | 116,577 (48.8%) | 349,040 (53.4%) |
| Black | 72,569 (30.4%) | 153,210 (23.4%) |
| Hispanic | 16,849 (7.1%) | 49,902 (7.6%) |
| Asian/Pacific Islander | 4,435 (1.9%) | 4,542 (0.7%) |
| American Indian | 1,880 (0.8%) | 10,348 (1.6%) |
| Multiracial/Other | 4,124 (1.7%) | 12,830 (2.0%) |
| Missing | 22,566 (9.4%) | 73,868 (11.3%) |
| Smoking Status: | | |
| Never | 79,949 (33.5%) | 169,458 (25.9%) |
| Former | 22,569 (9.4%) | 58,781 (9.0%) |
| Current | 60,234 (25.2%) | 180,728 (27.6%) |
| Missing | 76,248 (31.9%) | 244,773 (37.4%) |
| Prevalent Diabetes | 18,847 (7.9%) | 44,390 (6.8%) |
| BMI, Median [Q1, Q3] | 28.8 [25.0, 33.0] | 29.0 [25.7, 32.9] |
| Underweight | 1,695 (0.7%) | 2,503 (0.4%) |
| Normal | 41,900 (17.5%) | 88,345 (13.5%) |
| Overweight | 58,852 (24.6%) | 161,697 (24.7%) |
| Obese | 73,541 (30.8%) | 189,632 (29.0%) |
| Missing | 63,012 (26.4%) | 211,563 (32.4%) |
| Aspirin Use | 17,605 (7.4%) | 42,446 (6.5%) |

Figure 3. Number needed to scope findings for IDA and hematochezia analytic cohorts.



Note: NNS of 333 corresponds to number of individuals undergoing asymptomatic screening colonoscopy needed to scope to detect 1 person with CRC.⁴

CONCLUSIONS

- Individuals between ages 18-49 diagnosed with IDA or hematochezia of undetermined origin are at increased YCRC risk.
- YCRC risk associated with IDA is highest among men.
- YCRC risk associated with hematochezia or IDA is highest among individuals ages ≥ 30 .
- Colonoscopy should be strongly considered in adults <50 with IDA or hematochezia without a clinically confirmed source.

FUNDING: NIH/NCI 1F32CA239360-01 (Demb, PI); VA HSR&D 5I01HX001574-04 (Gupta, PI); NIH/NCI 5R37CA 222866-02 (Gupta, PI)