A proteogenomic analysis of the adiposity colorectal cancer relationship identifies GREM1 as a probable mediator

Matthew A Lee[1,2,*], Charlie A Hatcher[2,3], Emma Hazelwood[2,3], Lucy J Goudswaard[2,3], Konstantinos K Tsilidis[8,9], Emma E Vincent[2,3,10], Richard M Martin[2,3,11], Karl Smith-Byrne[12], Hermann Brenner[13,14,15], Iona Cheng[16], Sun-Seog Kweon[17,18], Loic Le Marchand[19], Polly A Newcomb[6,7], Robert E Schoen[20], Ulrike Peters[6,7], Marc J Gunter[1,8], Bethany Van Guelpen[4,5], Neil Murphy[1**]**

1 International Agency for Research on Cancer (IARC/WHO), Nutrition and Metabolism Branch, Lyon, France; 2 Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK; 3 Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, UK ; 4 Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden;5 Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden; 6 Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, WA, USA; 7 Department of Epidemiology, University of Washington, Seattle, WA, USA; 8 Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK; 9 Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; 10 School of Translational Health Sciences, University of Bristol, Bristol, UK; 11 National Institute for Health Research (NIHR) Bristol Biomedical Research Centre, University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol, Bristol, UK; 12 Cancer Epidemiology Unit, University of Oxford, Oxford, UK; 13 Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany; 14 Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany; 15 German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany; 16 Department of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco, California, United States of America; 17 Department of Preventive Medicine, Chonnam National University Medical School, Gwangju, Korea; 18 Jeonnam Regional Cancer Center, Chonnam National University Hwasun Hospital, Hwasun, Korea; 19 University of Hawaii Cancer Center, Honolulu, Hawaii, USA; 20 Department of Medicine and Epidemiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

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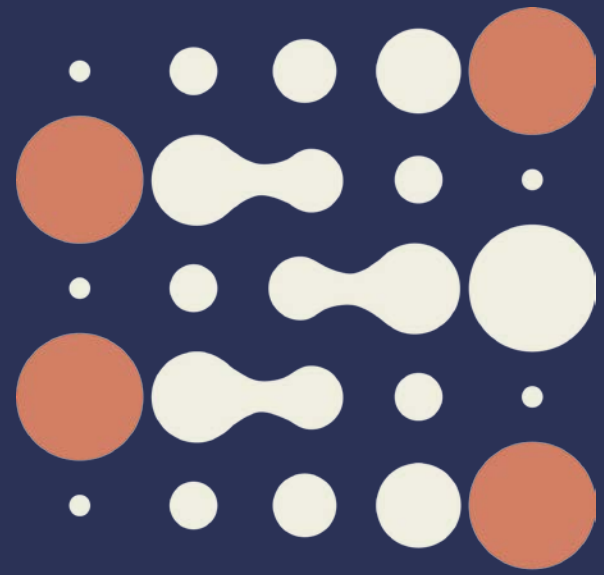
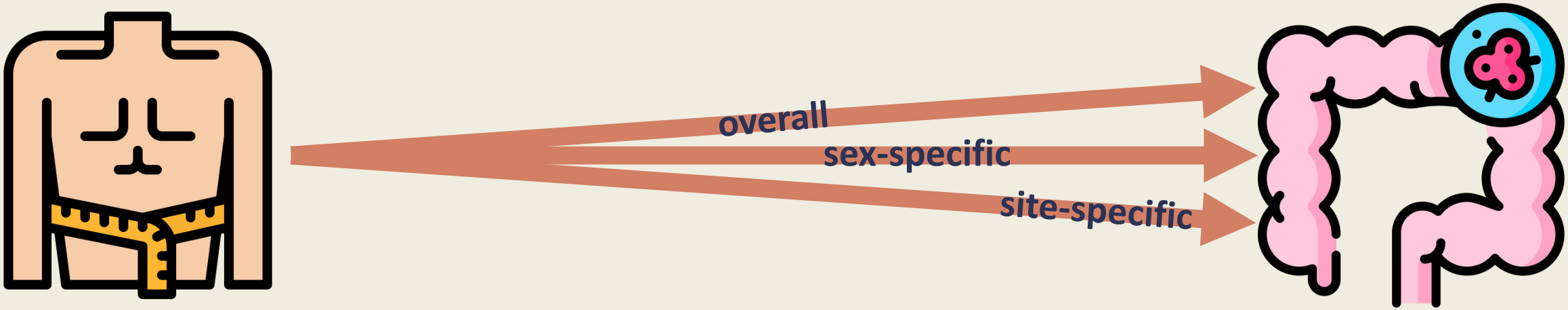
International Agency for Research on Cancer

World Health Organization



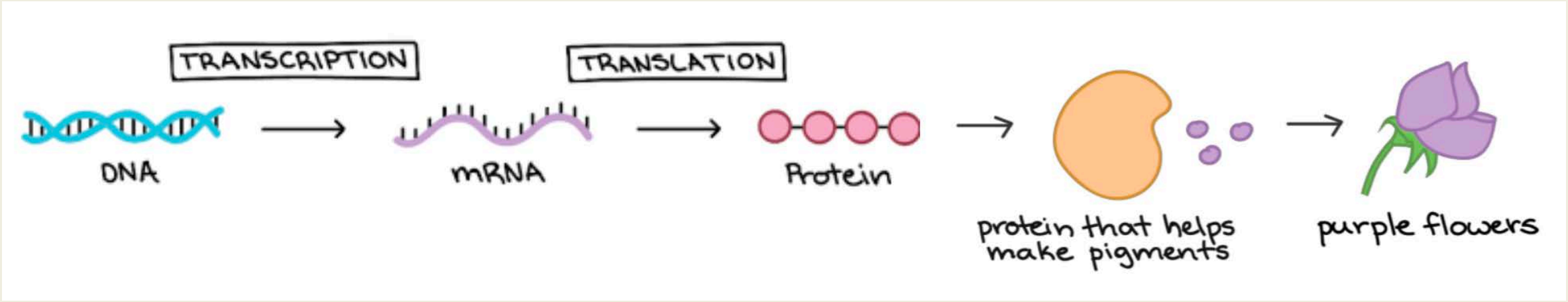


10.1186/s12916-020-01855-9

enzyme

structural elements

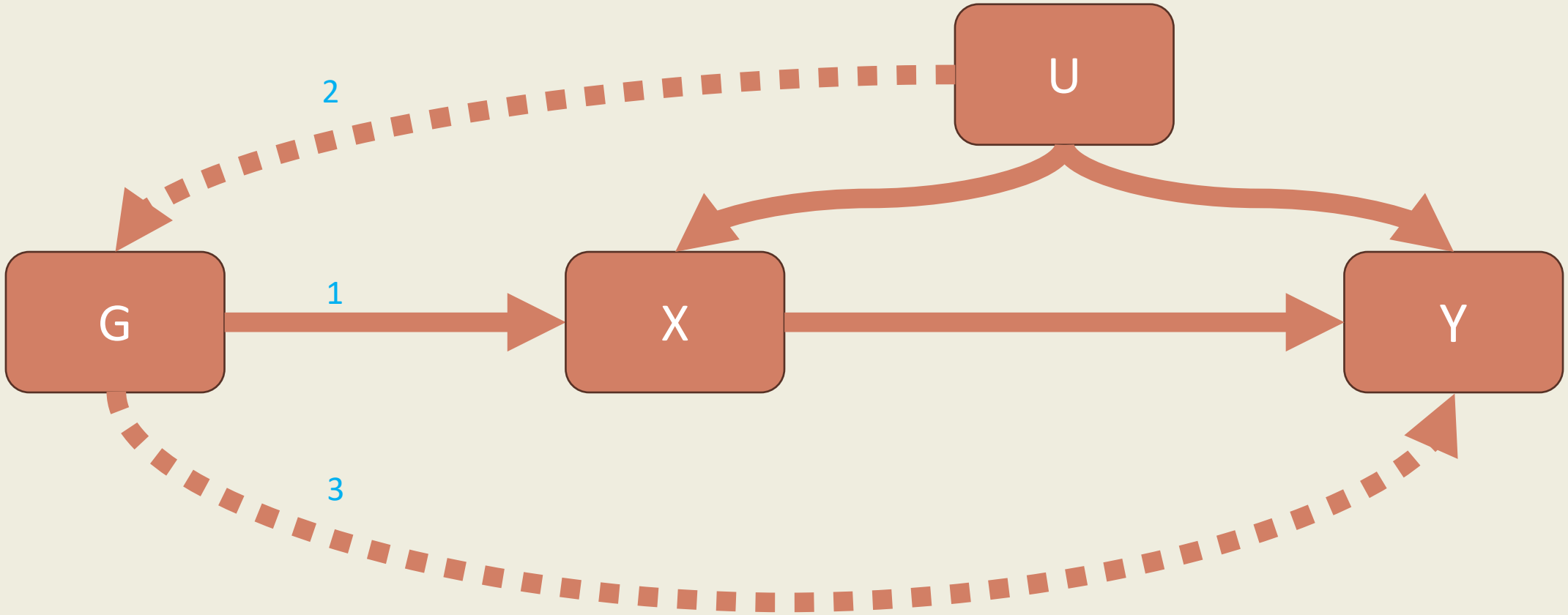
immune



messenger

regulator

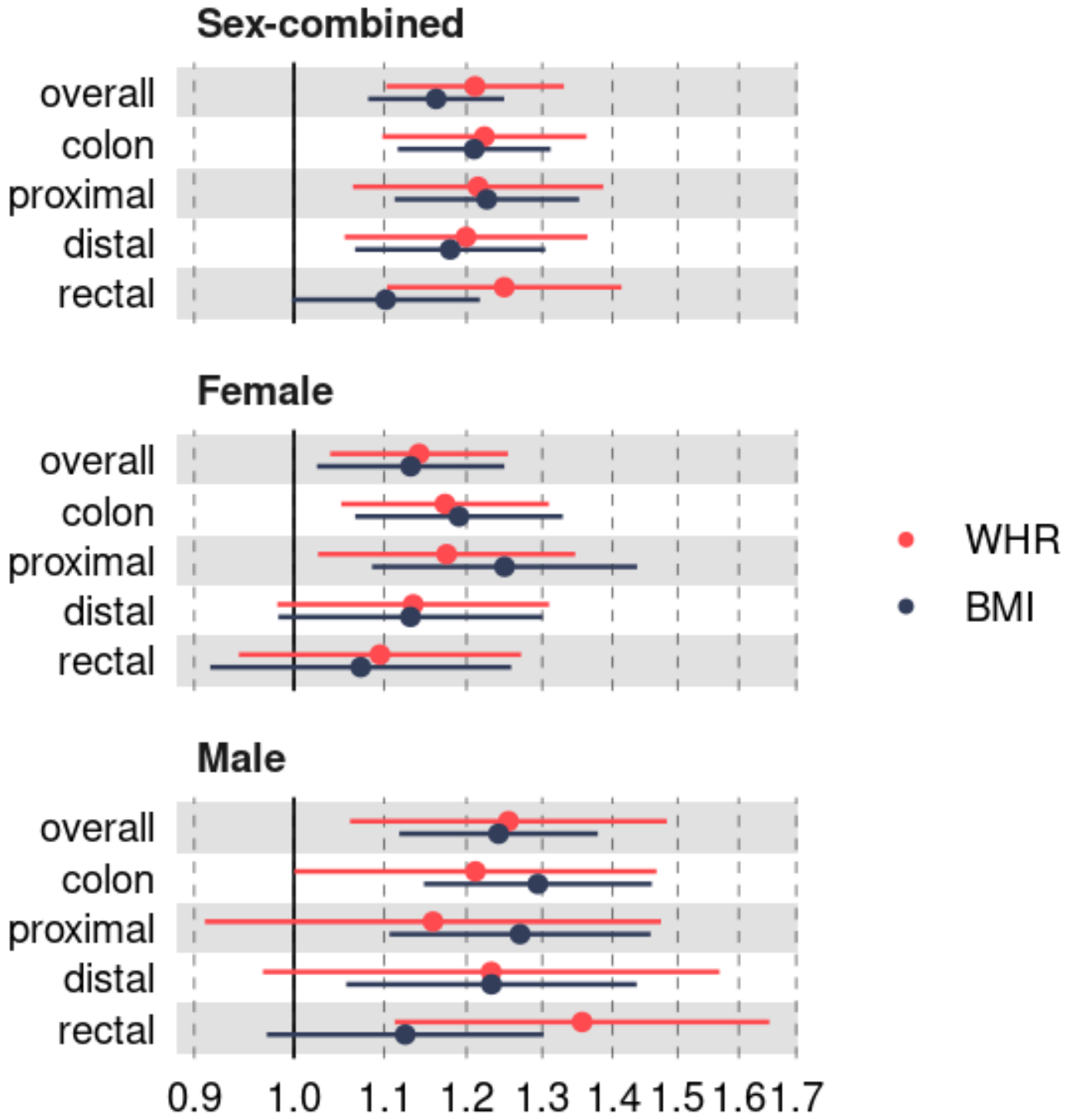
Mendelian randomization



adiposity -> cancer

- **results similar to previous**

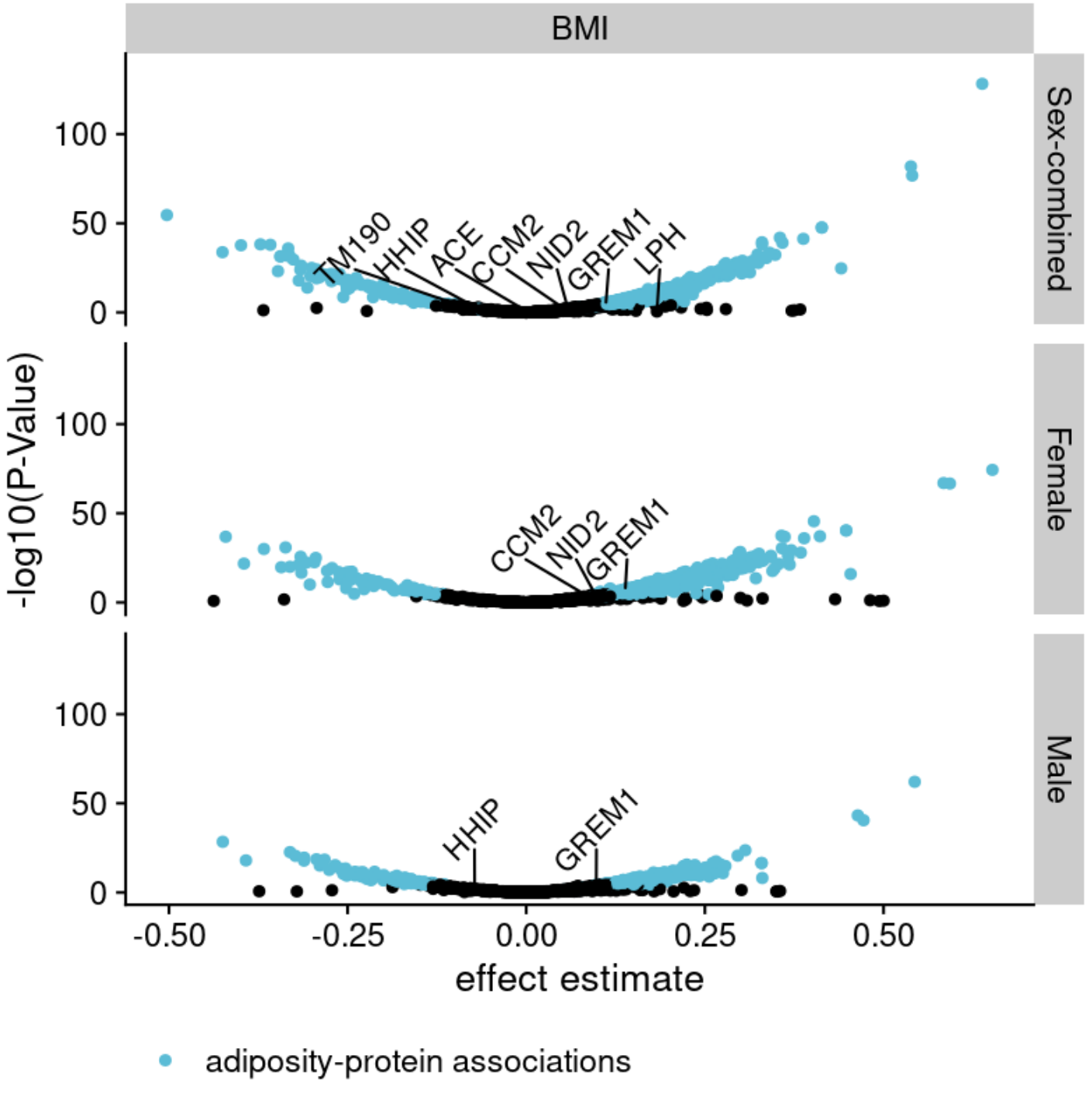
- **models = consistent; except:**
  - WHR-distal-male
  - WHR-rectal-female



adiposity -> proteins

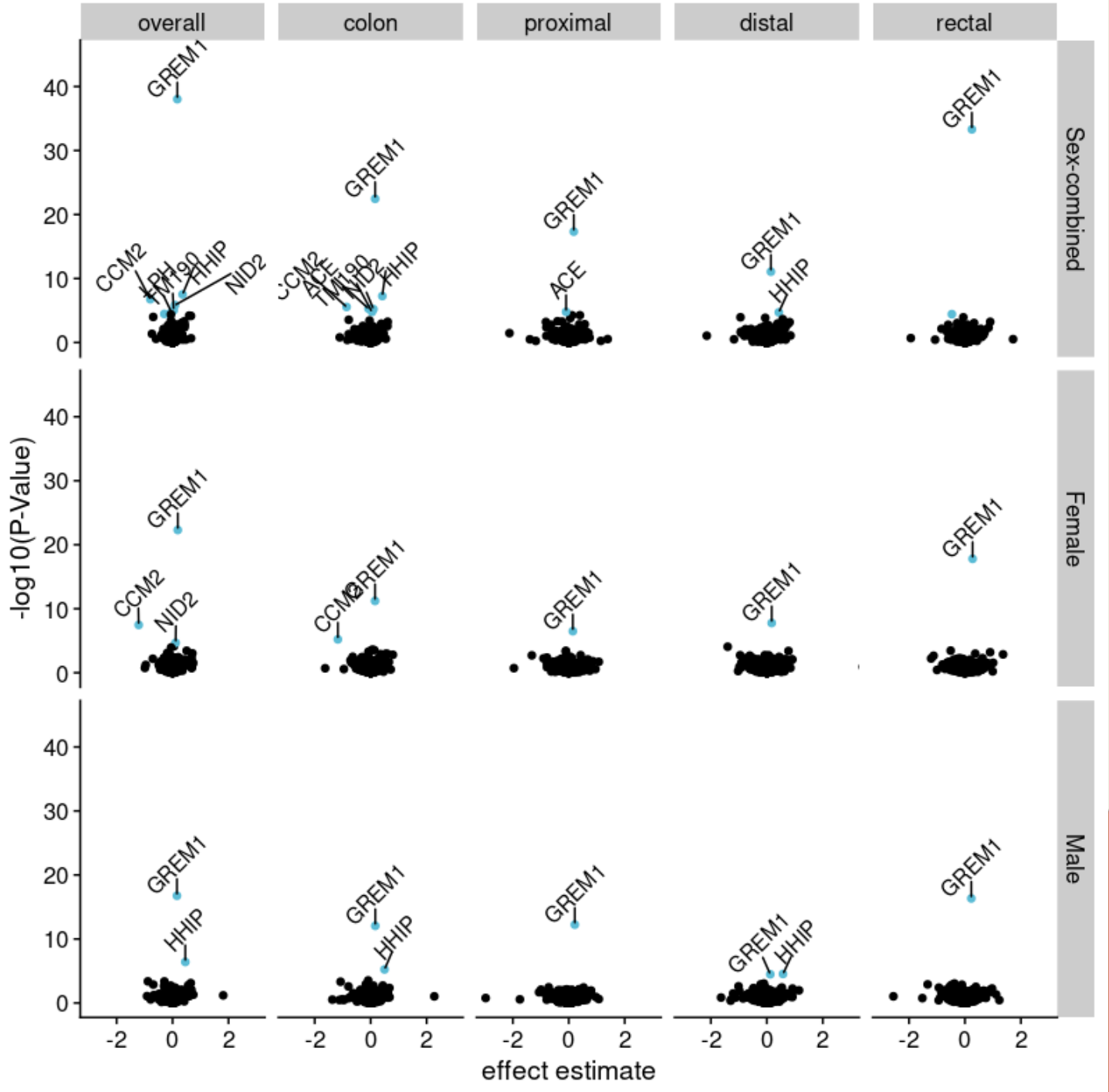
- **6,591 associations**
  - 2,628 (4,907) unique proteins
  - 2,395 BMI-female

- **labels = cancer-associated**



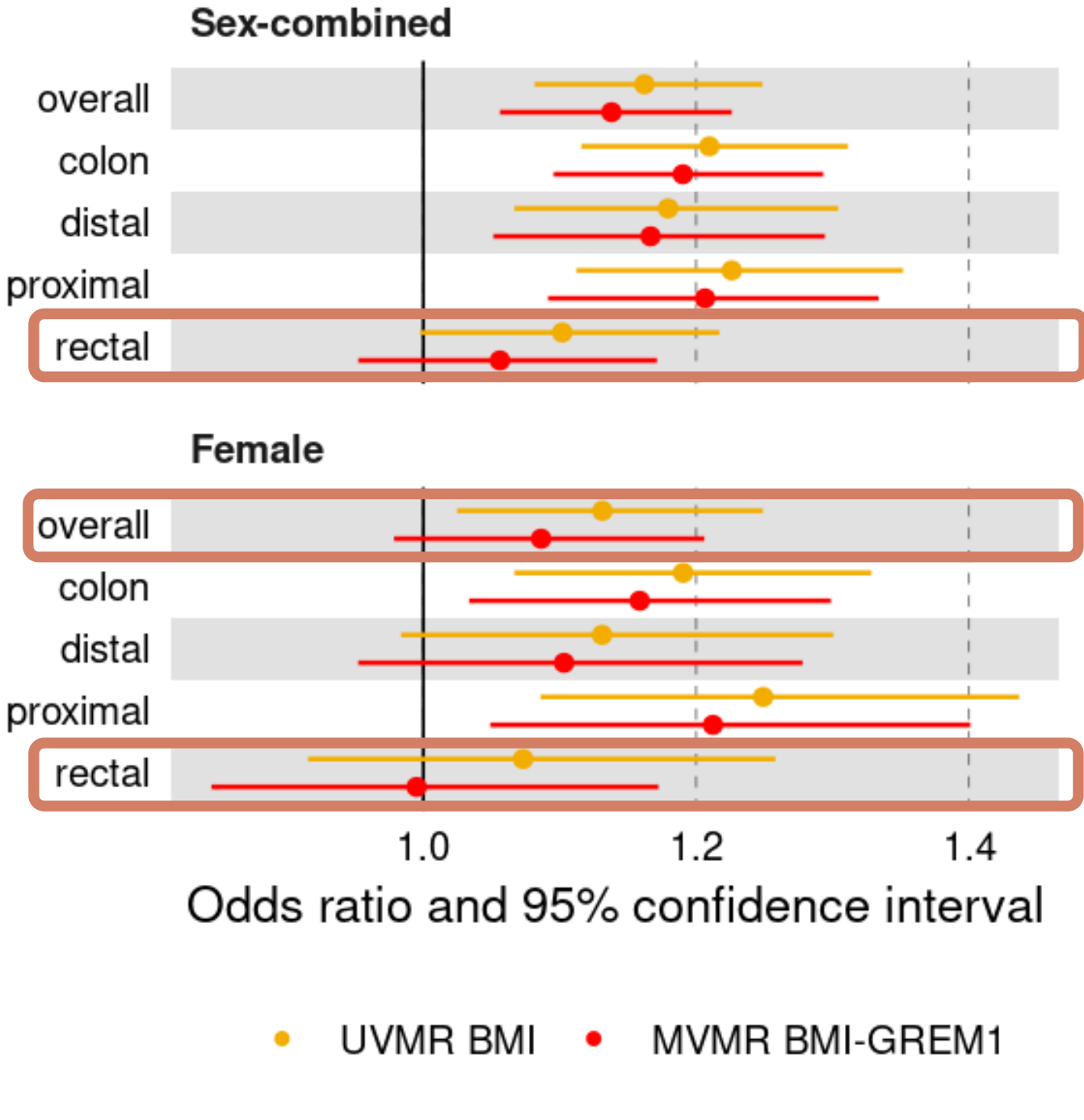
proteins -> cancer

- **962 proteins instrumentable**
- **33 protein-cancer associations**
  - 7 unique proteins
  - No bi-directional conflicts
- **Labels = adiposity-associations**



MVMR

- **1 protein directionally consistent**
  - GREM1
  - BMI -> GREM1 -> CRC
  - Sex-combined + female-specific
- **attenuation**
  - Compare UVMR estimate
  - Estimates + CIs towards the null
- **mediation?**
  - rectal-combined
  - overall-female
  - rectal-female



meaning…

- **GREM1 = adipokine**
  - bone morphogenic protein
  - embryonic development + morphogenesis
  - proliferation, angiogenesis, and epithelial-mesenchymal transition
- **GREM1 levels are dysregulated:**
  - CRC cases & tumour tissue
- **2 x phase II clinical trials:**
  - cancer, solid; unspecified

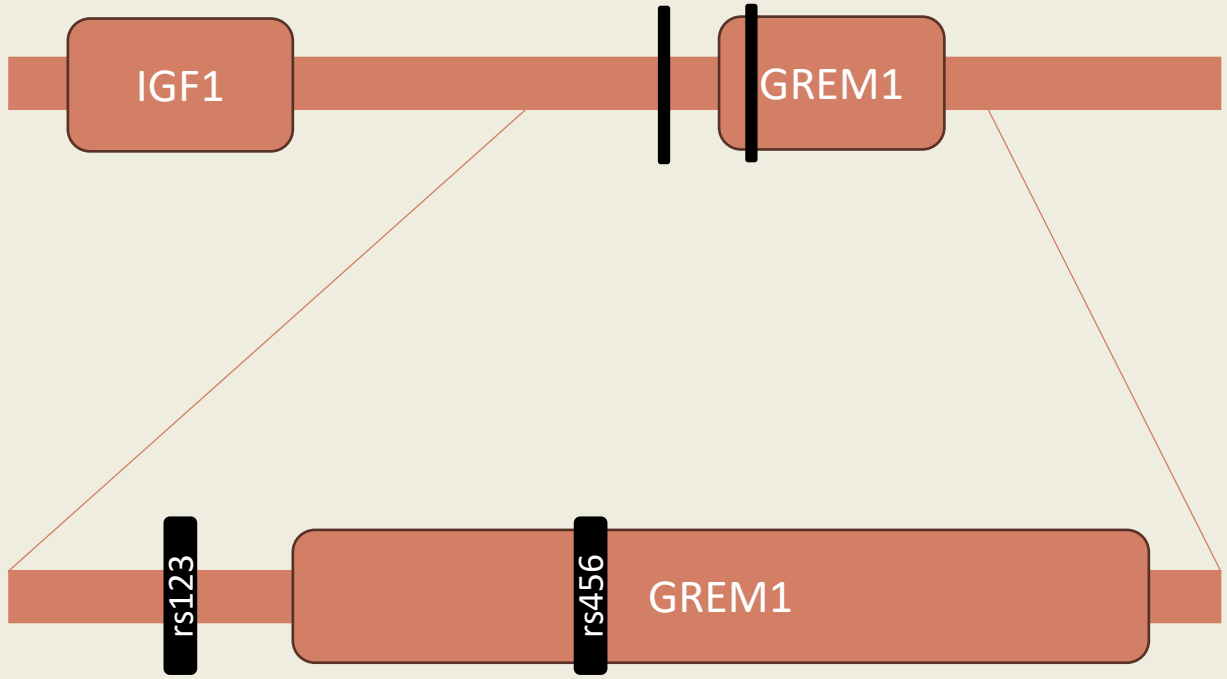
next…

- **MR**
  - ~3000 more proteins – UK biobank
  - adiposity imaging data
- **Individual level data**
  - EPIC nested case control: 400 matched – 96 proteins
  - EPIC cohort: 938 cases; 8,574 non-case - 7500 proteins

Bonus slides…

data

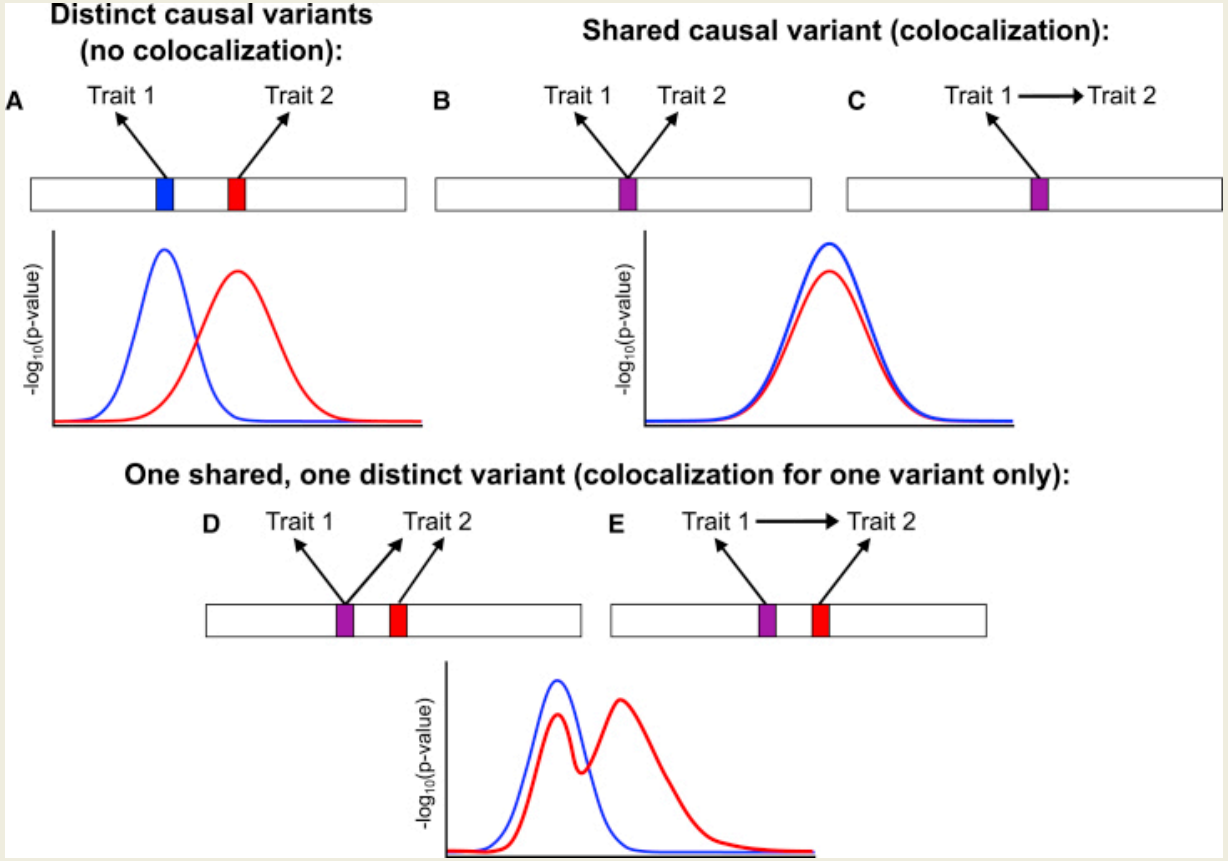
- **BMI & WHR**
  - N up-to = 806,834
  - combined, male, female
- **plasma proteins: 4,907**
  - N up-to = 35,559
  - combined
- **cancer**
  - N case/control up-to = 58,131 / 67,347
  - overall, colon, distal, proximal, rectal
  - combined, male, female
- **instruments**
  - adiposity: 5E-9; LD r2 0.001, 10kb window
  - Proteins: 1.8E-9; <1Mb TSS; 1Mb window, LD r2 0.8
  - CRC: 5E-8; LD r2 0.001, 10kb window
- **units = essentially meaningless**



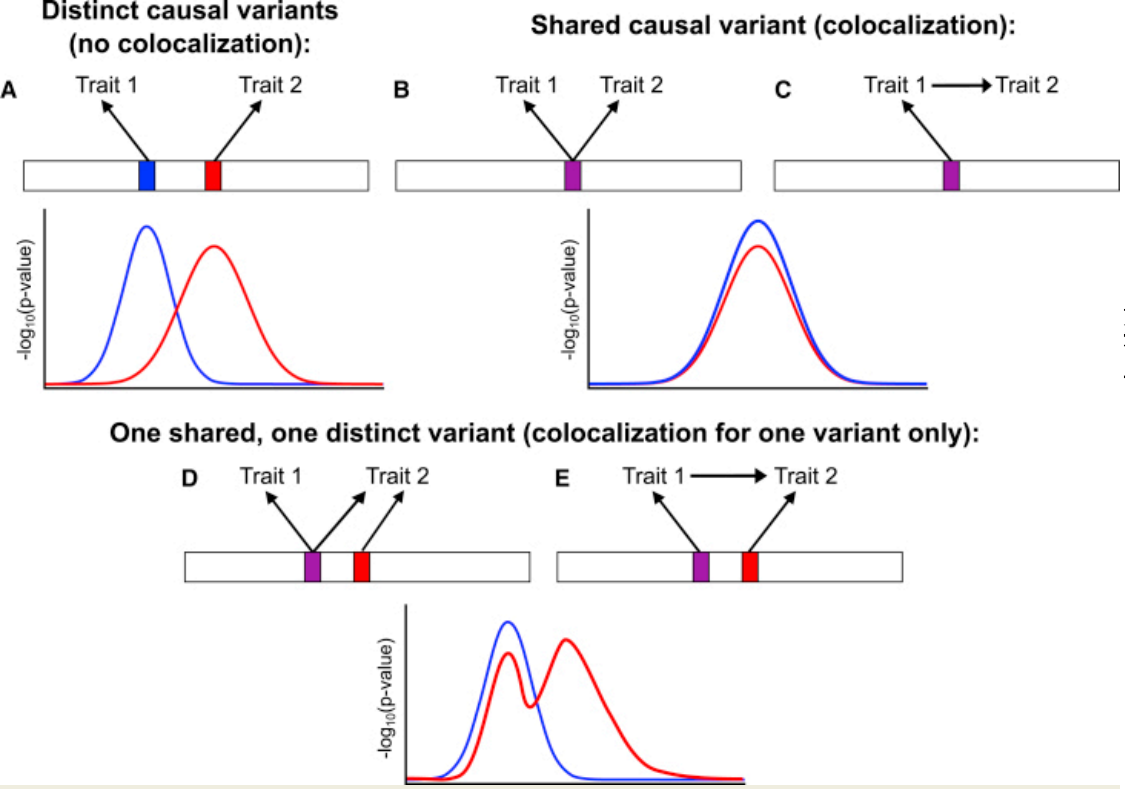
colocalization

- **Linkage disequilibrium**
  - Non-random association of alleles at DIFFERENT loci
  - i.e., SNPs can be correlated just because of location

- **Traits can be “causal” because of:**
  - Distinct causal variants = possibly LD
  - Shared causal variants = colocalization



10.1016/j.ajhg.2022.04.001



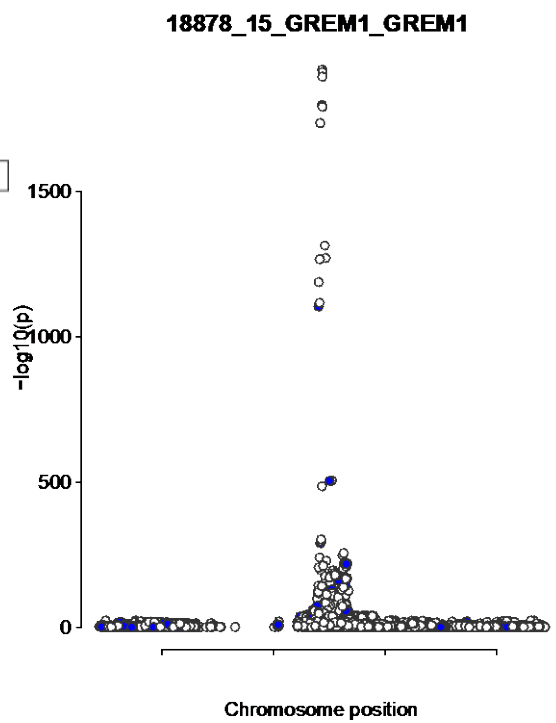
A. 2 traits with distinct causal variants

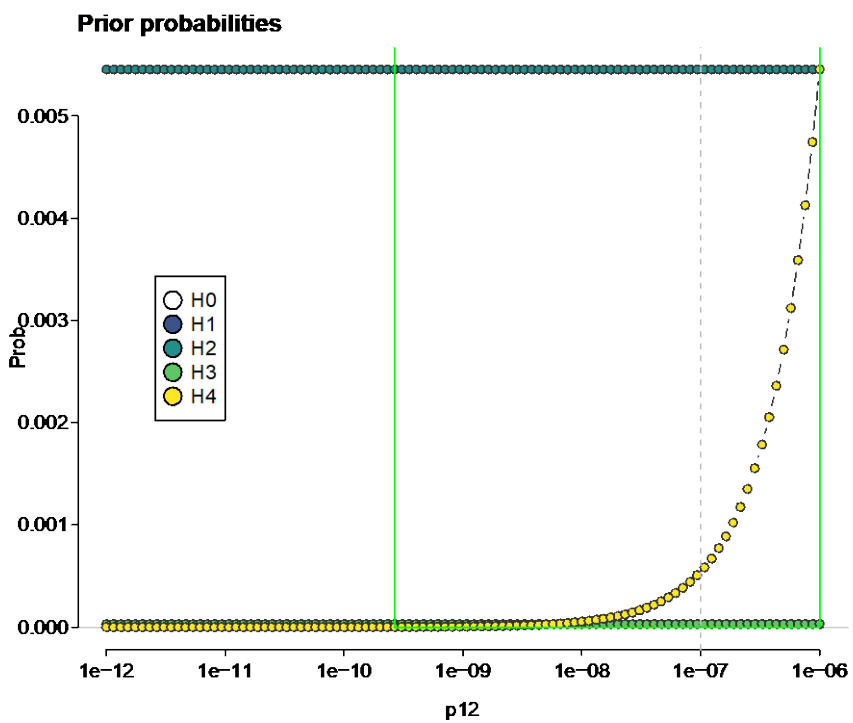
B. 2 unrelated traits with shared causal variant

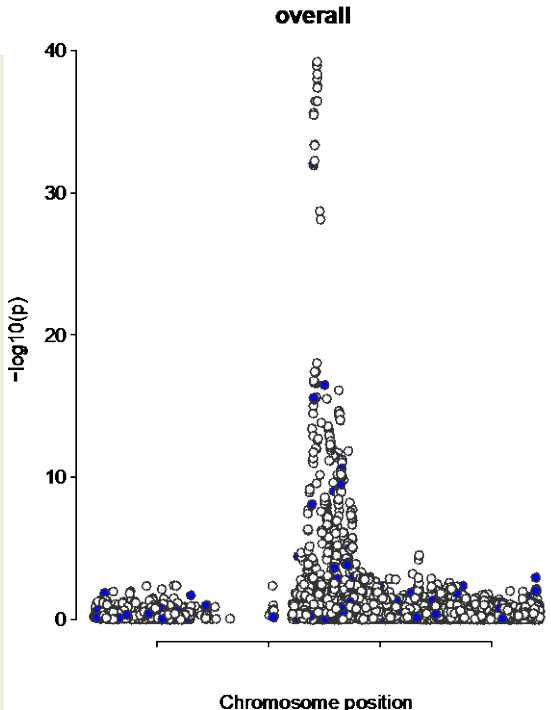
C. 2 traits with a shared causal variant where the first trait influences the second trait

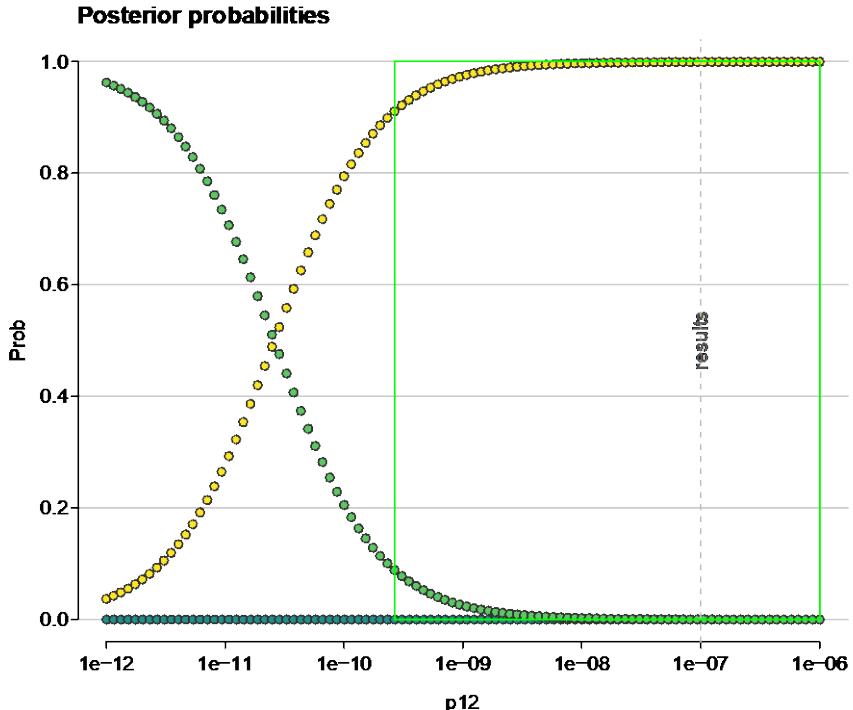
D. 1 shared causal variant and 1 distinct causal variant for trait 2

E. 1 shared causal variant and 1 distinct causal variant for trait 2

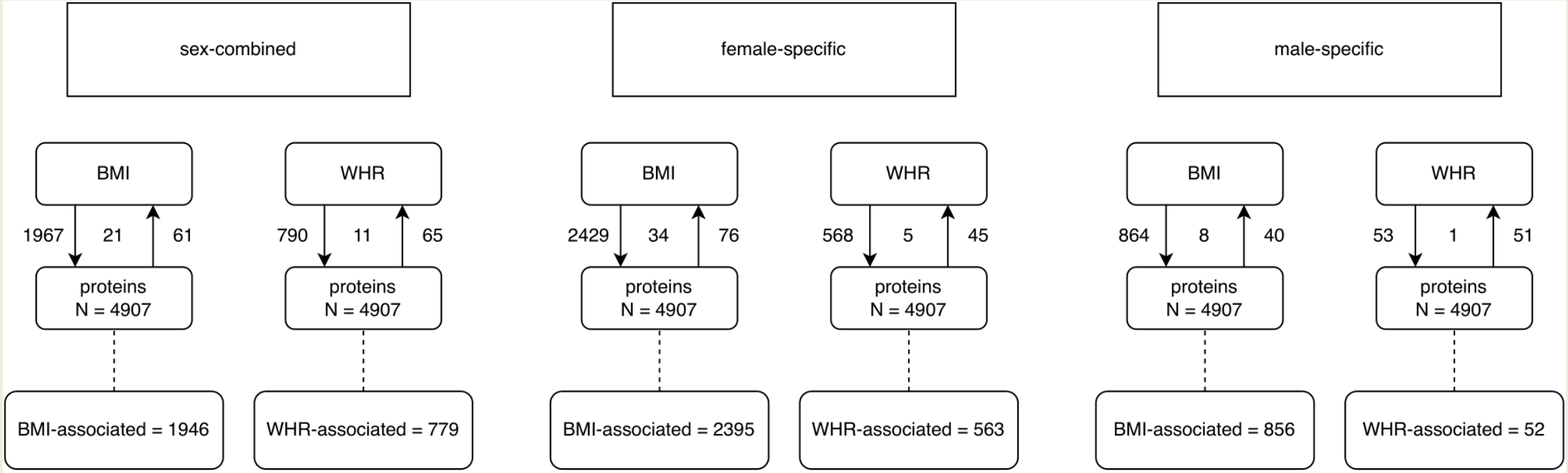






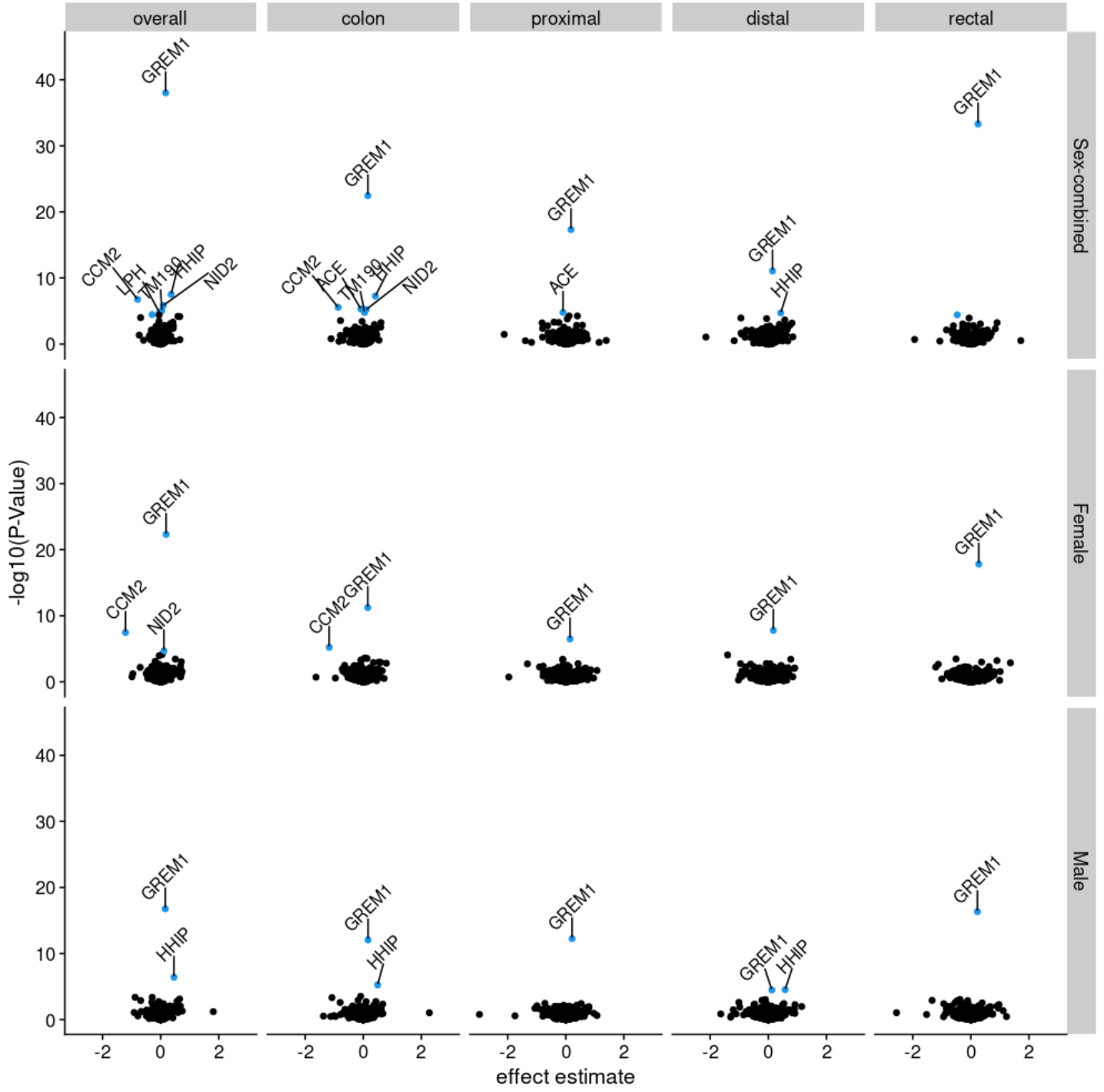


adiposity -> proteins

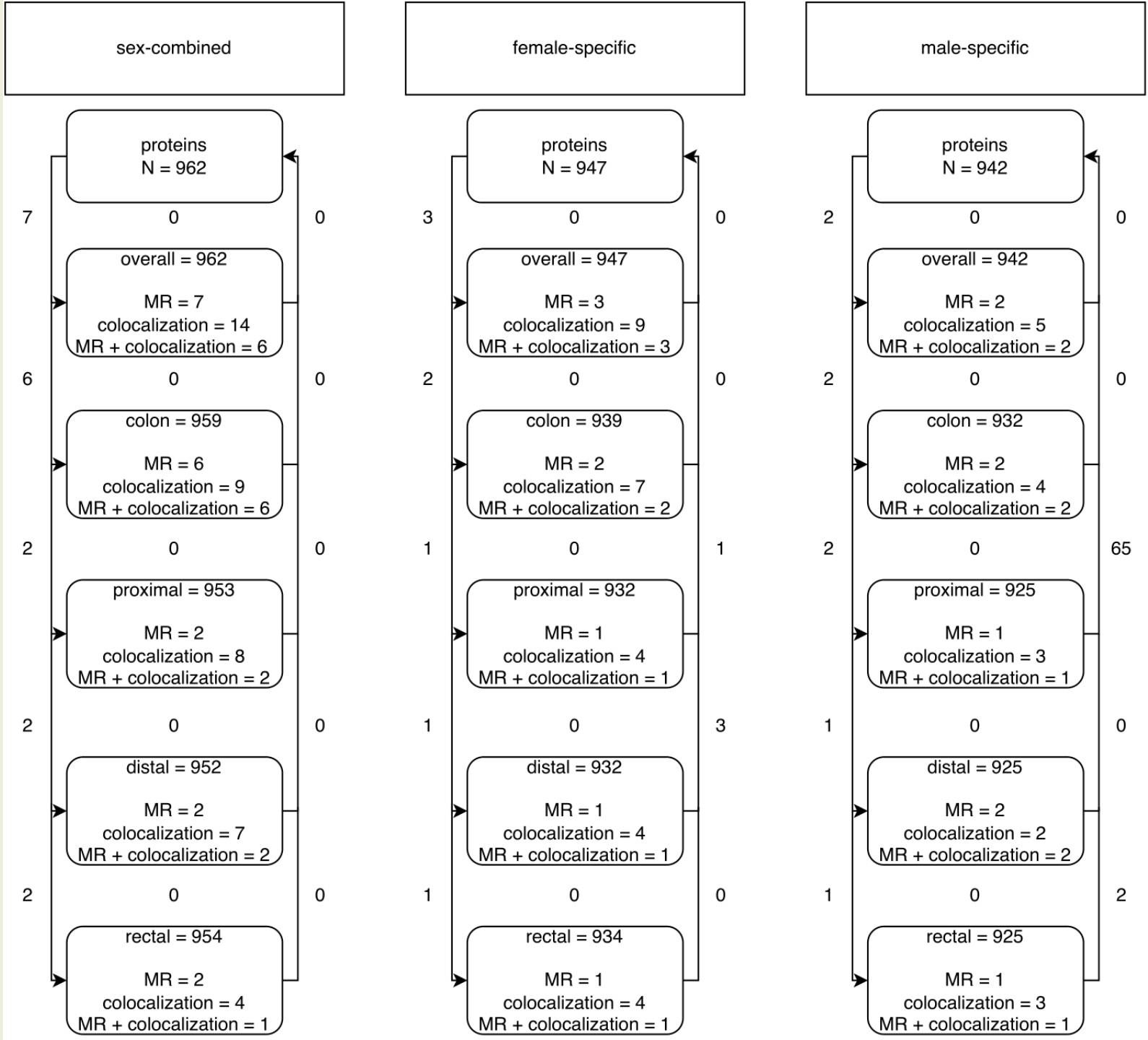


proteins -> cancer

- **962 proteins instrumentable**
- **35 protein-cancer associations**
  - 8 unique proteins
  - No bi-directional conflicts
- **Labels = adiposity-associations**
- **Colocalization**
  - 87 protein-cancer pairs
  - 25 unique proteins
- **MR + colocalization**
  - 33 protein-cancer associations
  - 7 unique proteins



proteins -> cancer



tissue expression

- **differentially expressed in most tissues compared to whole blood**
  - Wilcoxon rank sum test
  - p-value 0.05/53
- **some of the highest levels in colon & adipose tissue**