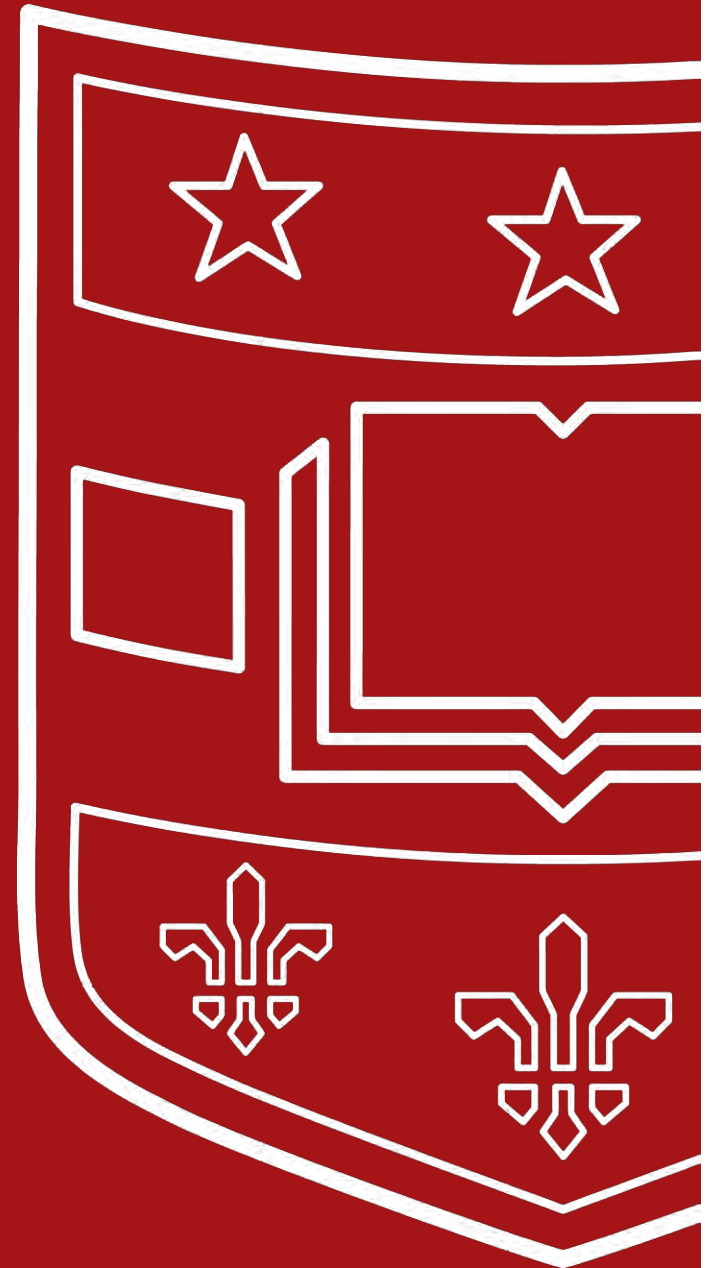


Why Young-Onset Colorectal Cancer: Modifiable risk factors

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Division of Public Health Sciences, Department of Surgery
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Alvin J. Siteman Cancer Center
Washington University School of Medicine in St. Louis

***MDACC Young-Onset Colorectal Cancer Virtual Patient Conference
May 20, 2023***



Disclosures

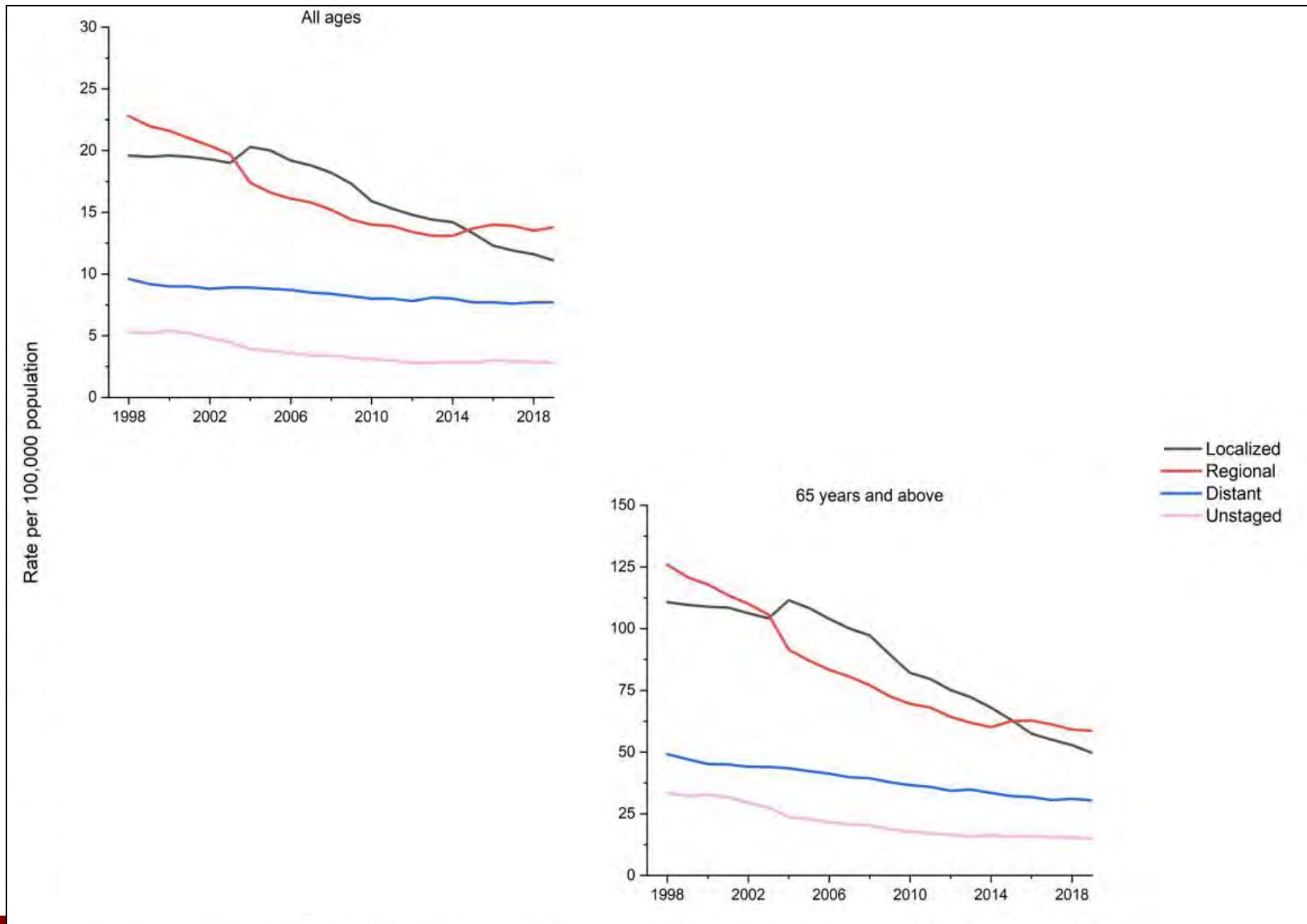
I have the following relevant financial relationships to disclose:

- Consultant for: Geneoscopy

Outline

- Evolving epidemiology of colorectal cancer (CRC)
- Modifiable risk factors of early-onset CRC

Trends in CRC incidence in the United States



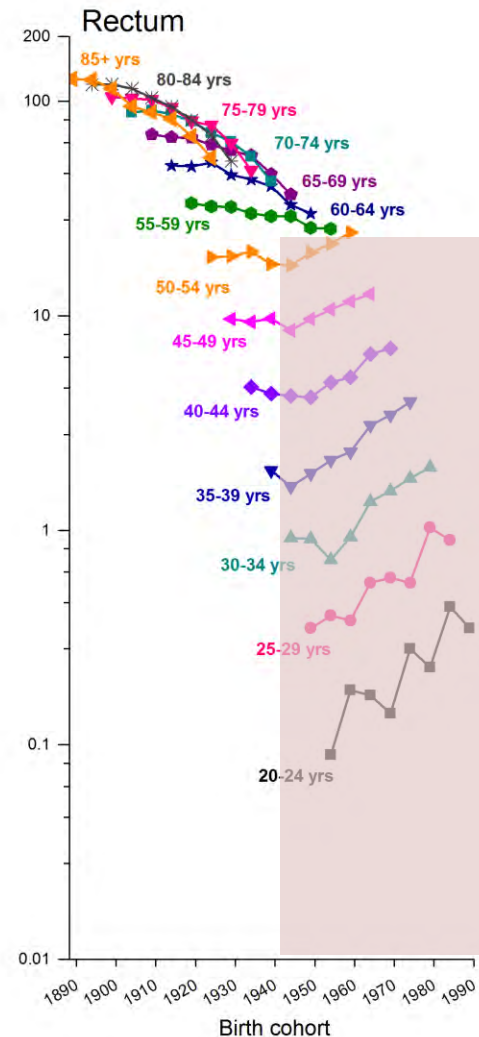
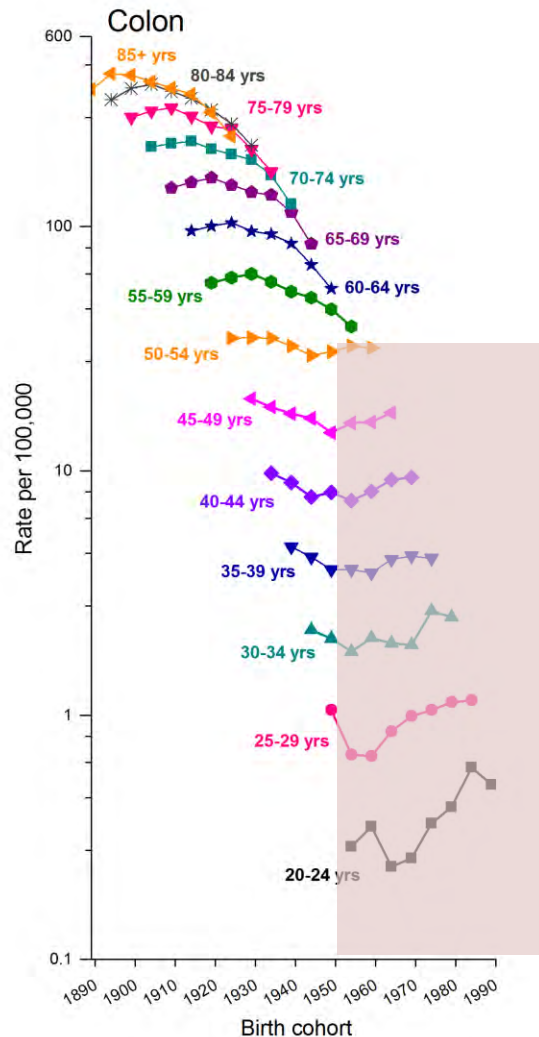
- The **decline** in CRC incidence slowed down from 3%-4% annually during the 2000s to **1%** annually during 2011–2019
- Driven partly by an increase in <55 y of 1%–2% annually since the mid-1990s.
- <55 y
 - 1995: **11%**
 - 2019: **20%**

Siegel et al. CA Cancer J Clin, 2023

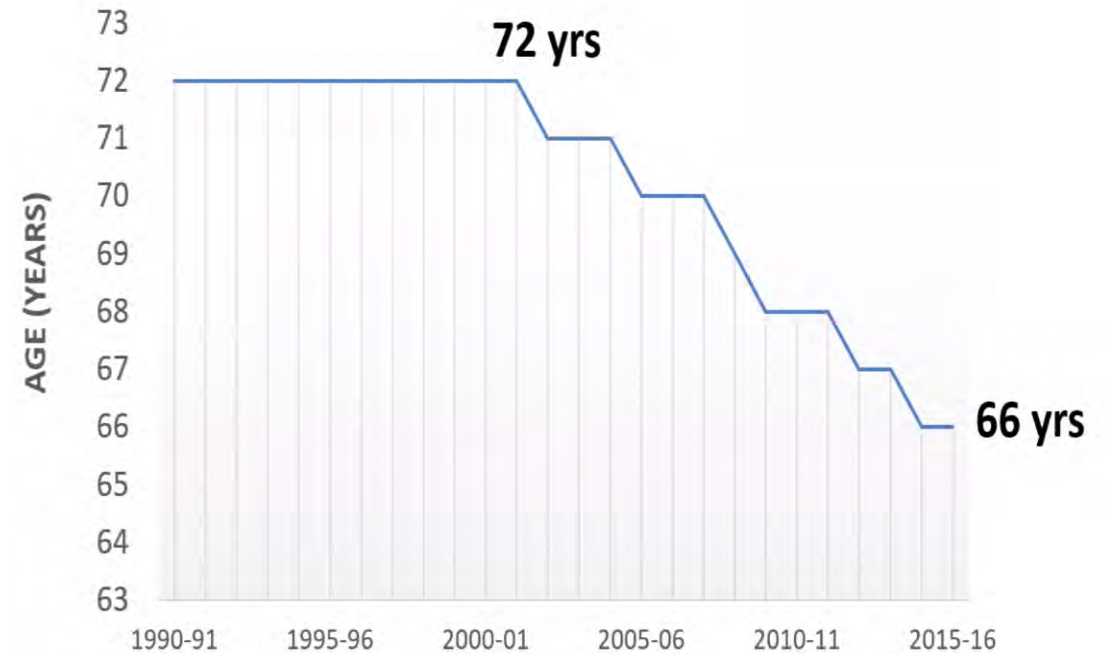
EO-CRC in the US

Higher incidence in successive birth cohorts

Birth cohort effects



Median age of CRC diagnosis



Siegel *et al*, J Natl Cancer Inst, 2017
Siegel *et al*, CA Cancer J Clin, 2020

Cao lab@Washington University in St Louis
EO-CRC/EO-adenoma, 2017+

Prospective cohorts Real-world evidence
Genetic consortium Microsimulation

2017-2023

Obesity (life course), *JAMA Oncology* 2018

Sedentary behavior

-*JNCI Cancer Spectrum* 2019

-*JAMA* 2019

Metabolic syndrome, *Gut* 2020

Diet quality, *JNCI* 2020

Diabetes, *Gastro Hep Advances*, 2021

Sugar-sweetened beverages (life course), *Gut* 2021

Sulfur microbial diet, *Gastroenterology* 2021

Vitamin D, *Gastroenterology* 2021

Cesarean delivery, *JAMA Network Open* 2023

Earlier signs and symptoms, *JNCI* 2023

Pregnancy and neonatal outcomes, *eClinicalMedicine* 2023

Circulating markers of microbial translocation, *eBioMedicine* 2023

Molecular landscape, submitted

Review, *Nature Rev Clinical Oncology*, 2020

Current focus

- **Emerging risk factors throughout the life course**
- **Novel biomarkers**
- **Preventive agents**
- **Microsimulation**

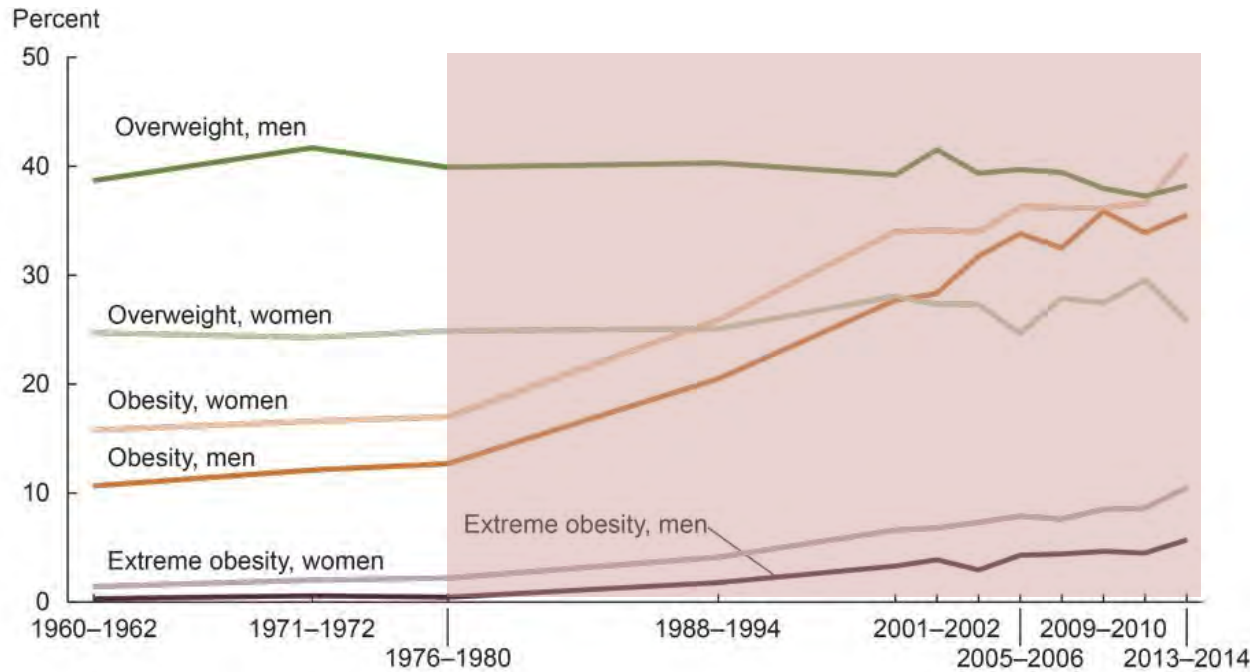


Outline

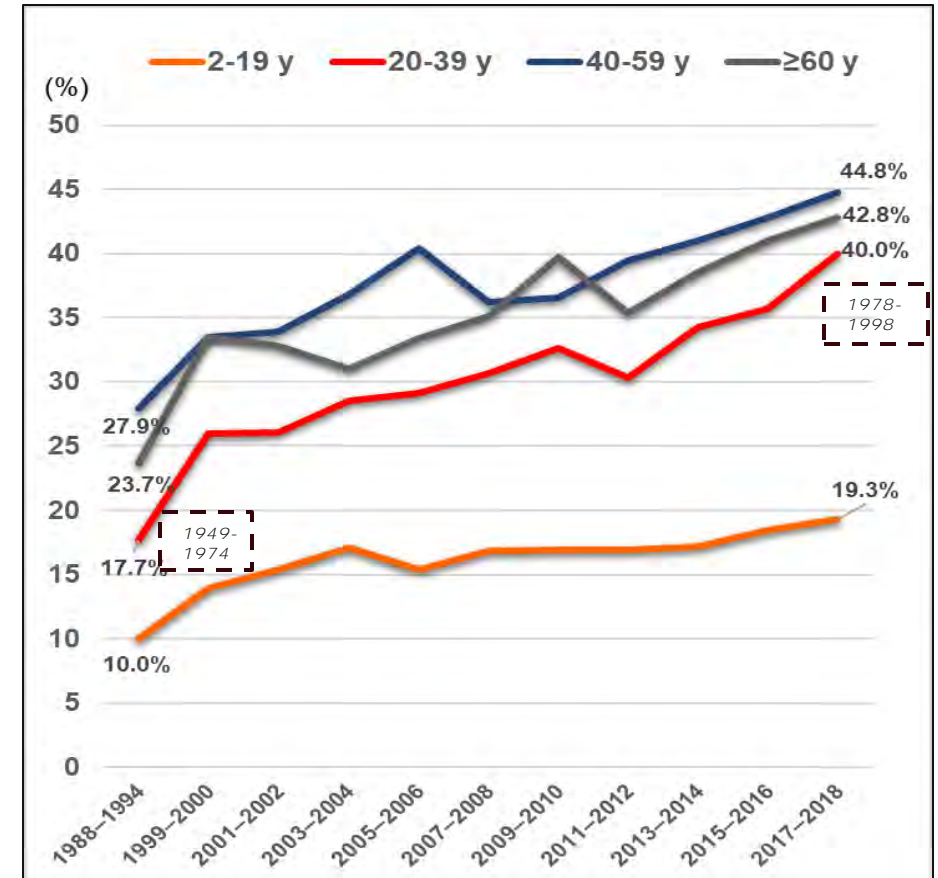
- Evolving epidemiology of CRC
- **Modifiable risk factors of early-onset CRC**
 - Obesity
 - Metabolic dysregulation
 - Sedentary behavior
 - Diet
 - Microbial dysbiosis related exposures

Trends in adult overweight, obesity, and severe obesity

National Health Examination Survey/National Health and Nutrition Examination Surveys, 1960–2018



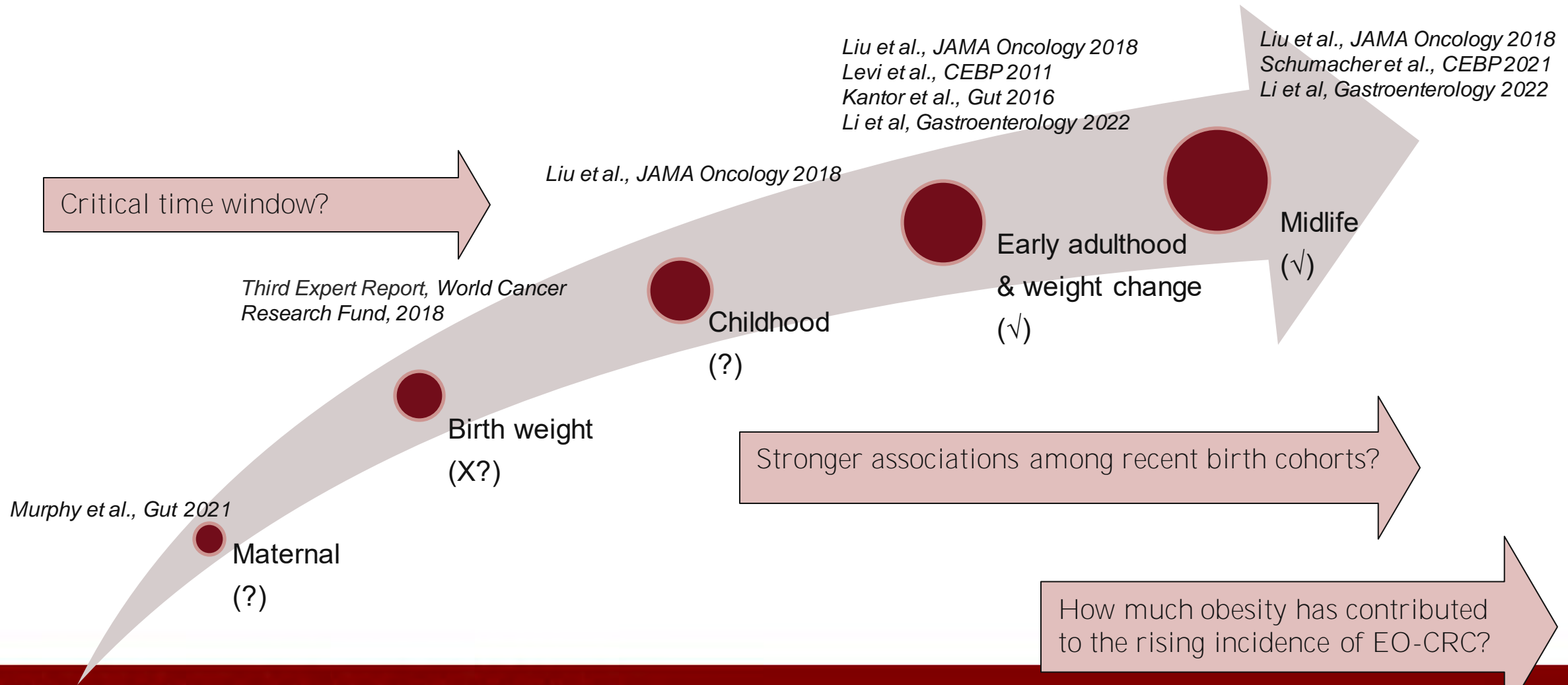
NOTES: Age-adjusted by the direct method to the year 2000 U.S. Census Bureau estimates using age groups 20–39, 40–59, and 60–74. Overweight is body mass index (BMI) of 25 kg/m² or greater but less than 30 kg/m²; obesity is BMI greater than or equal to 30; and extreme obesity is BMI greater than or equal to 40. Pregnant females were excluded from the analysis.
 SOURCES: NCHS, National Health Examination Survey and National Health and Nutrition Examination Surveys.



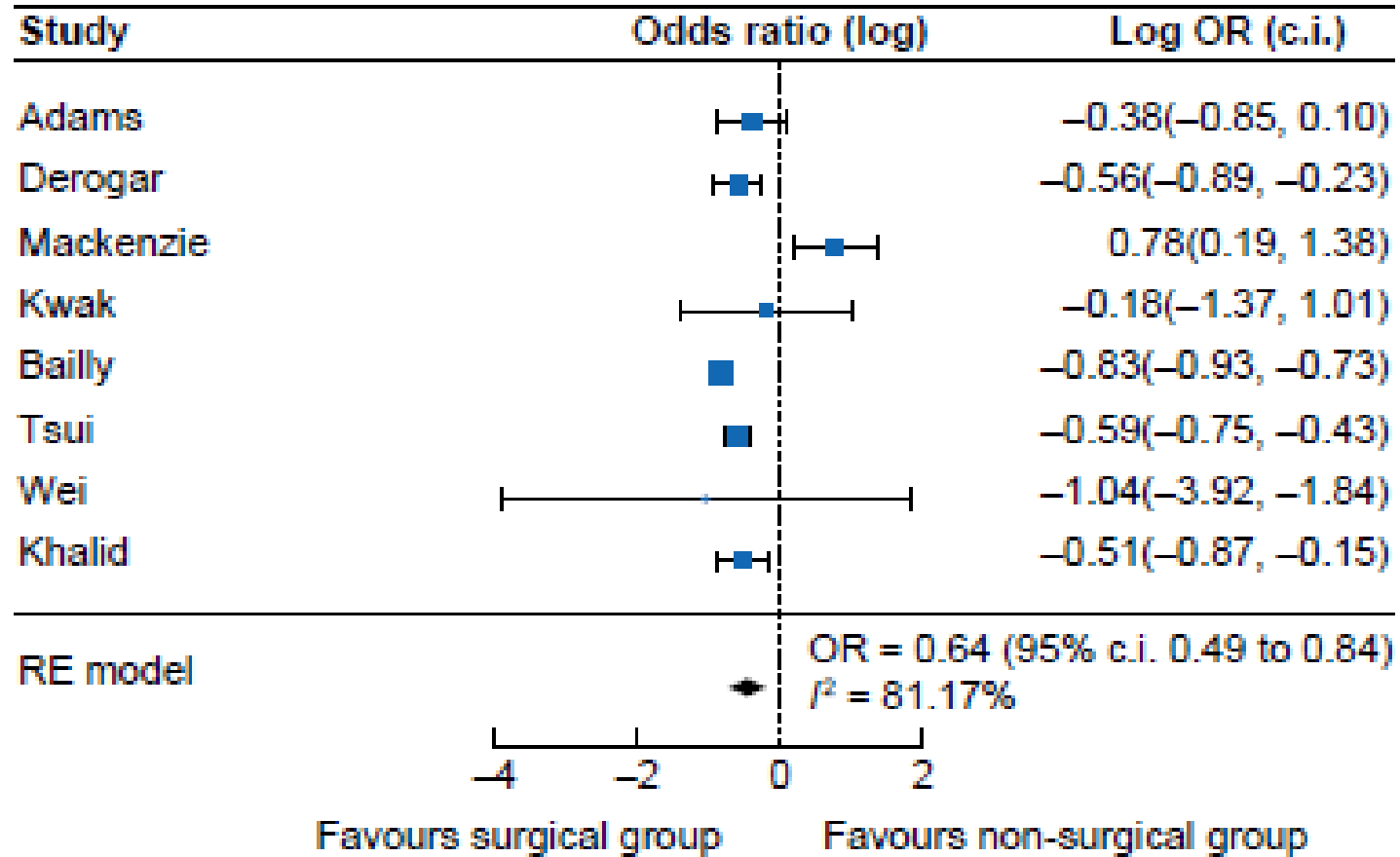
Recent birth cohorts of child/adolescent & younger adults:

- 1) Doubled obesity prevalence
- 2) Obese much earlier in life
- 3) Longer lifetime at risk

Obesity throughout life course vs. early-onset colorectal cancer



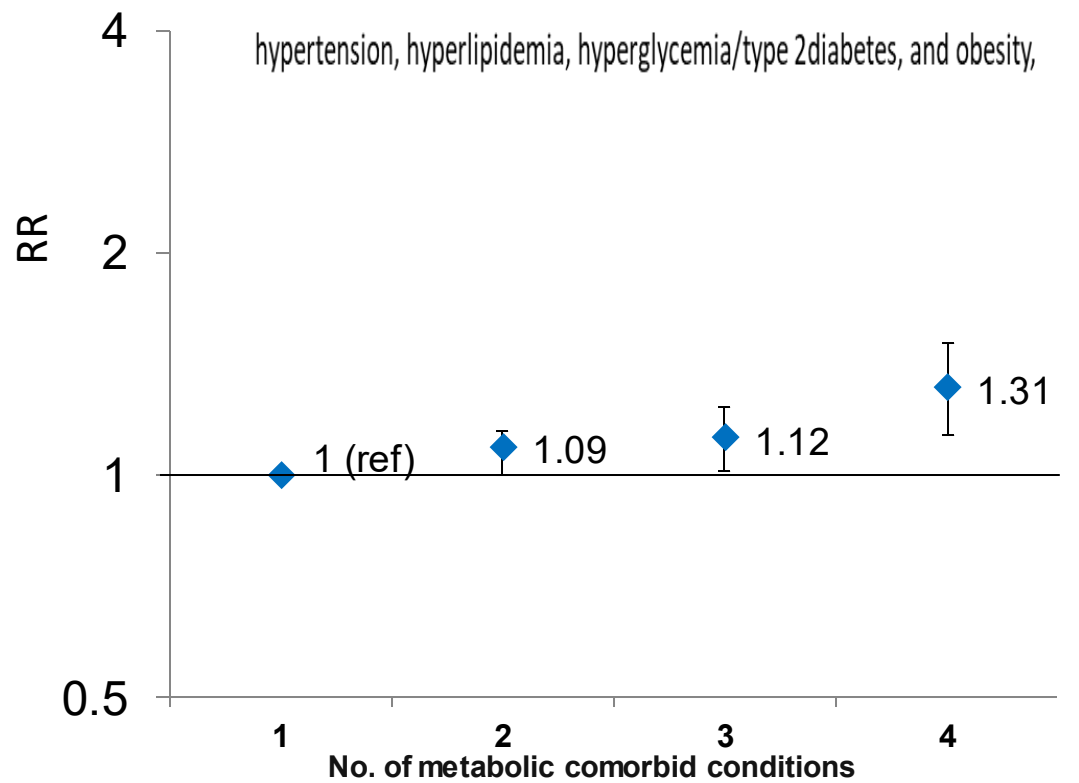
Bariatric surgery vs. CRC risk



Clapp *et al.*, BJS 2023

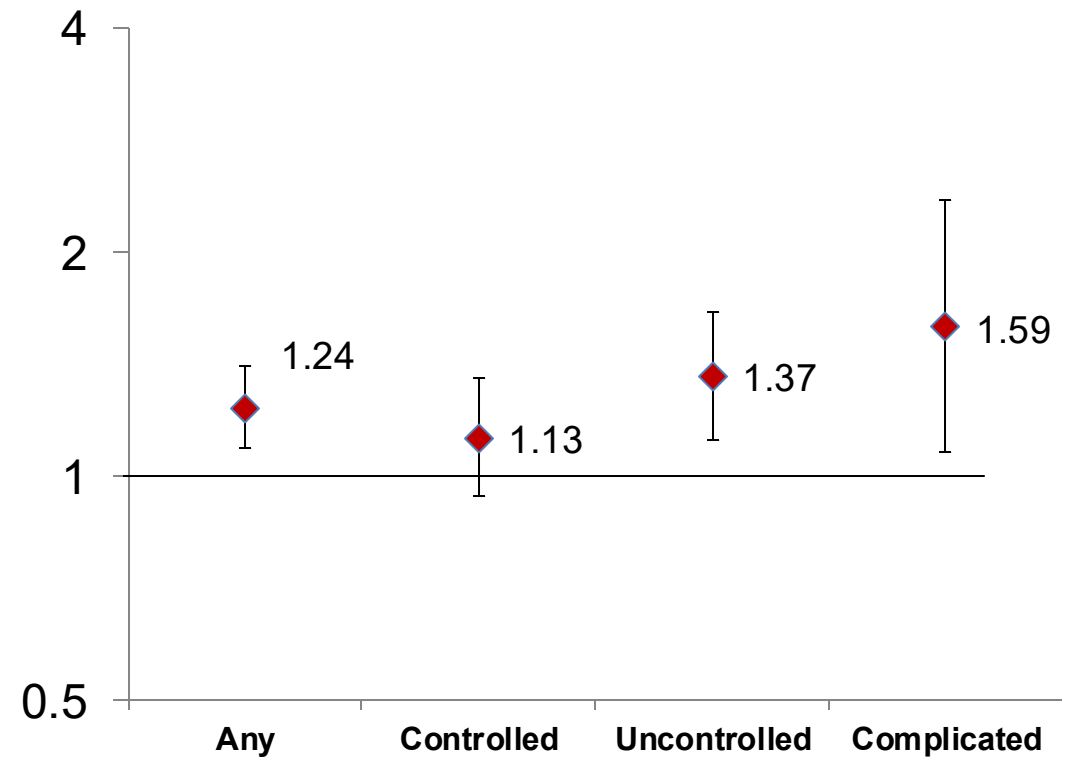
Metabolic dysregulation vs. EO-CRC

Metabolic comorbid conditions



Chen *et al.*, Gut 2021

Type 2 diabetes



Li *et al.*, Gastro Hep Advances 2022

Control of type 2 diabetes among adolescents and younger adults

| Characteristics | Individualized HbA _{1c} targets + BP <130/80 mm Hg + LDL-C <100 mg/dL | Individualized HbA _{1c} targets + BP <140/90 mm Hg + LDL-C <100 mg/dL |
|--------------------|--|--|
| | No. of adults with diagnosed diabetes ^c | 2368 |
| Overall prevalence | 18.0 (15.6-20.3) | 26.2 (23.4-29.1) |
| Age group, y | | |
| 18-44 | 7.4 (3.4-11.3) | 15.6 (10.2-21.0) |
| 45-64 | 18.0 (14.1-21.9) | 24.5 (19.5-29.4) |
| ≥65 | 21.7 (18.1-25.2) | 31.9 (28.0-35.7) |

Wang *et al.*, JAMA 2021

Table 2. Adjusted Odds Ratios for Glucose-Lowering, Blood-Pressure-Lowering, and Statin Treatment in Adult NHANES Participants with Diagnosed Diabetes, 1999–2018.*

| Variable | Use of Glucose-Lowering Medication in Persons with Glycated Hemoglobin Level of ≥7% | | Use of Blood-Pressure-Lowering Medication in Persons with Blood Pressure of ≥140/90 mm Hg | | Use of Statin Medication in Persons with Non-HDL Cholesterol Level of ≥130 mg/dl |
|----------|---|-----------------------------------|---|-----------------------------------|--|
| | 1 Medication (vs. No Treatment) | ≥2 Medications (vs. No Treatment) | 1 Medication (vs. No Treatment) | ≥2 Medications (vs. No Treatment) | Statin (vs. No Statin) |
| Age | | | | | |
| 20–44 yr | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) | 1 (reference) |
| 45–64 yr | 1.59 (1.00–2.55) | 2.59 (1.62–4.14) | 3.31 (1.50–7.34) | 3.21 (1.69–6.08) | 2.31 (1.58–3.36) |
| ≥65 yr | 1.85 (1.16–2.93) | 2.21 (1.38–3.53) | 5.60 (2.55–12.30) | 7.41 (3.89–14.11) | 2.14 (1.48–3.10) |

Fang *et al.*, NEJM 2021

Type 2 diabetes in adolescents and young adults

Nadia Lascar, James Brown, Helen Pattison, Anthony H Barnett, Clifford J Bailey, Srikanth Bellary

The prevalence of type 2 diabetes in adolescents and young adults is dramatically increasing. Similar to older-onset type 2 diabetes, the major predisposing risk factors are obesity, family history, and sedentary lifestyle. Onset of diabetes at a younger age (defined here as up to age 40 years) is associated with longer disease exposure and increased risk for chronic complications. Young-onset type 2 diabetes also affects more individuals of working age, accentuating the adverse societal effects of the disease. Furthermore, evidence is accumulating that young-onset type 2 diabetes has a more aggressive disease phenotype, leading to premature development of complications, with adverse effects on quality of life and unfavourable effects on long-term outcomes, raising the possibility of a future public health catastrophe. In this Review, we describe the epidemiology and existing knowledge regarding pathophysiology, risk factors, complications, and management of type 2 diabetes in adolescents and young adults.



CrossMark

Lancet Diabetes Endocrinol 2018; 6: 69–80

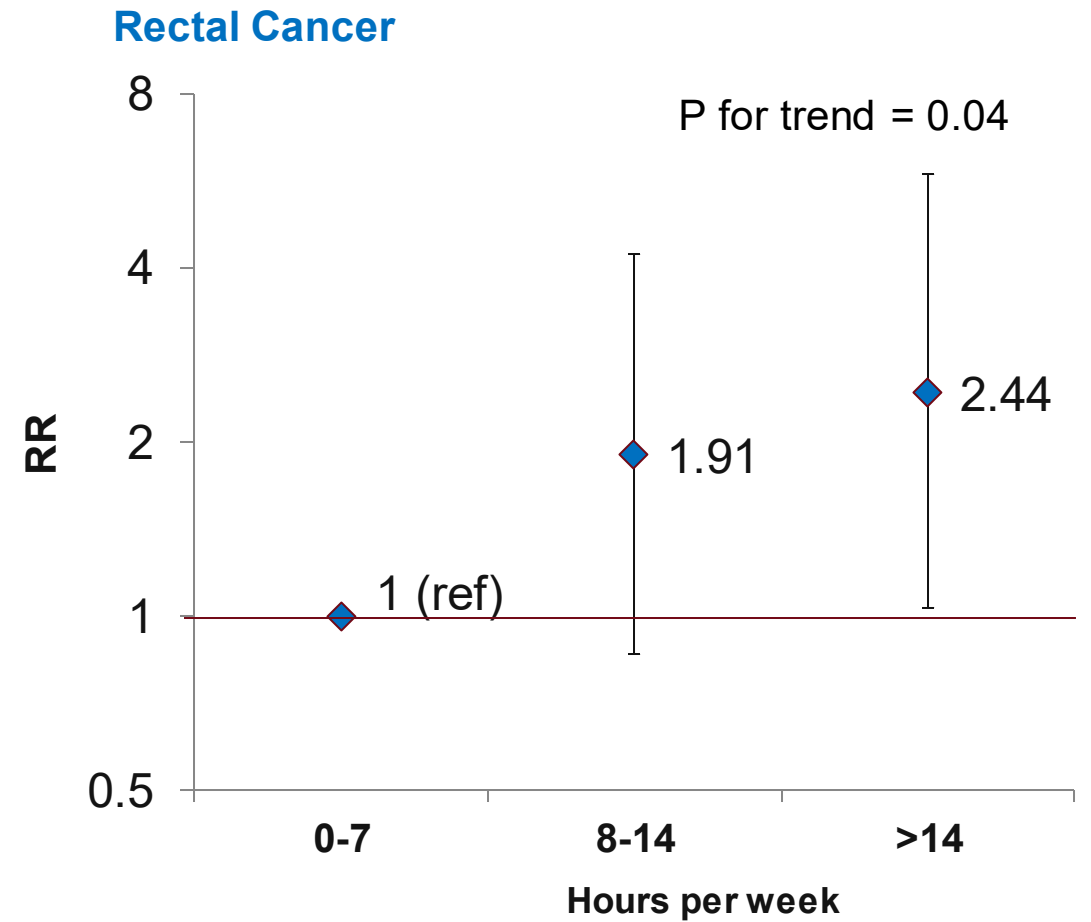
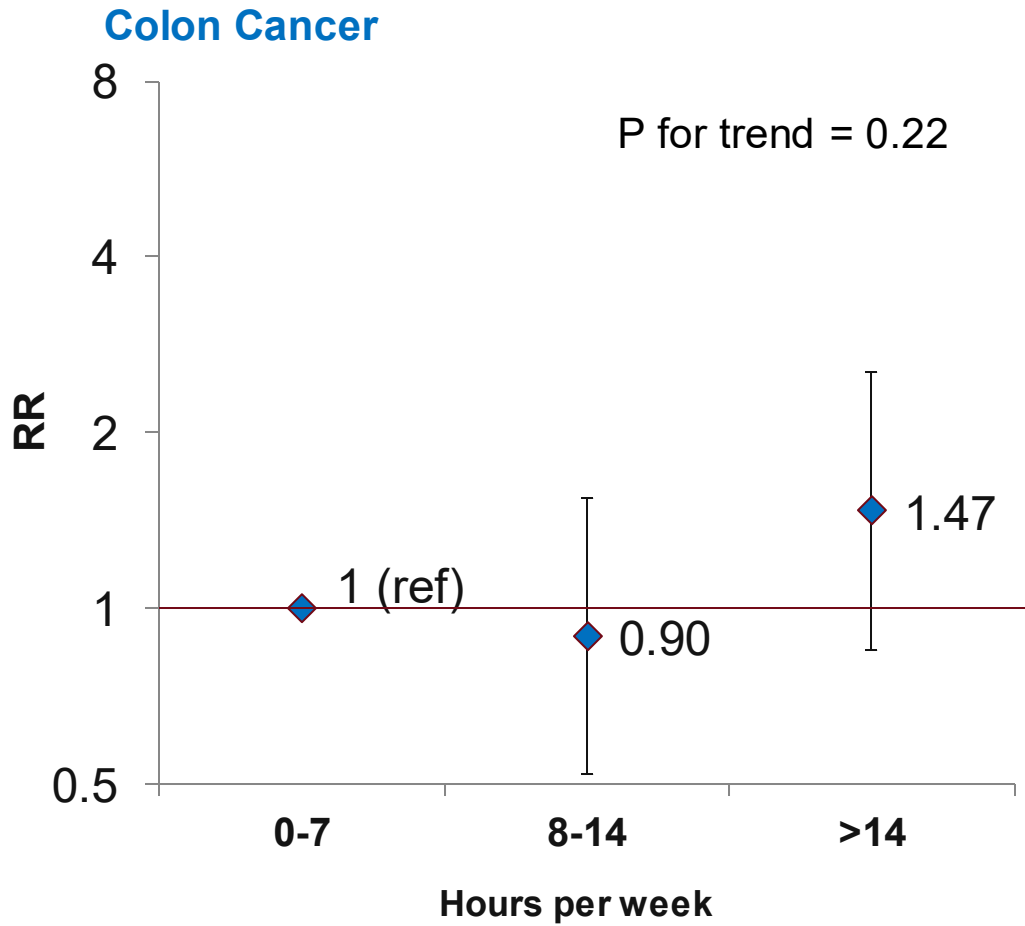
Published Online August 25, 2017 [http://dx.doi.org/10.1016/S2213-8587\(17\)30186-9](http://dx.doi.org/10.1016/S2213-8587(17)30186-9)

School of Life and Health Sciences (N Lascar MD, Prof H Pattison PhD, Prof C J Bailey PhD) and Aston Research Centre for Health

Lascar *et al.*, Lancet Diabetes Endocrinol 2018

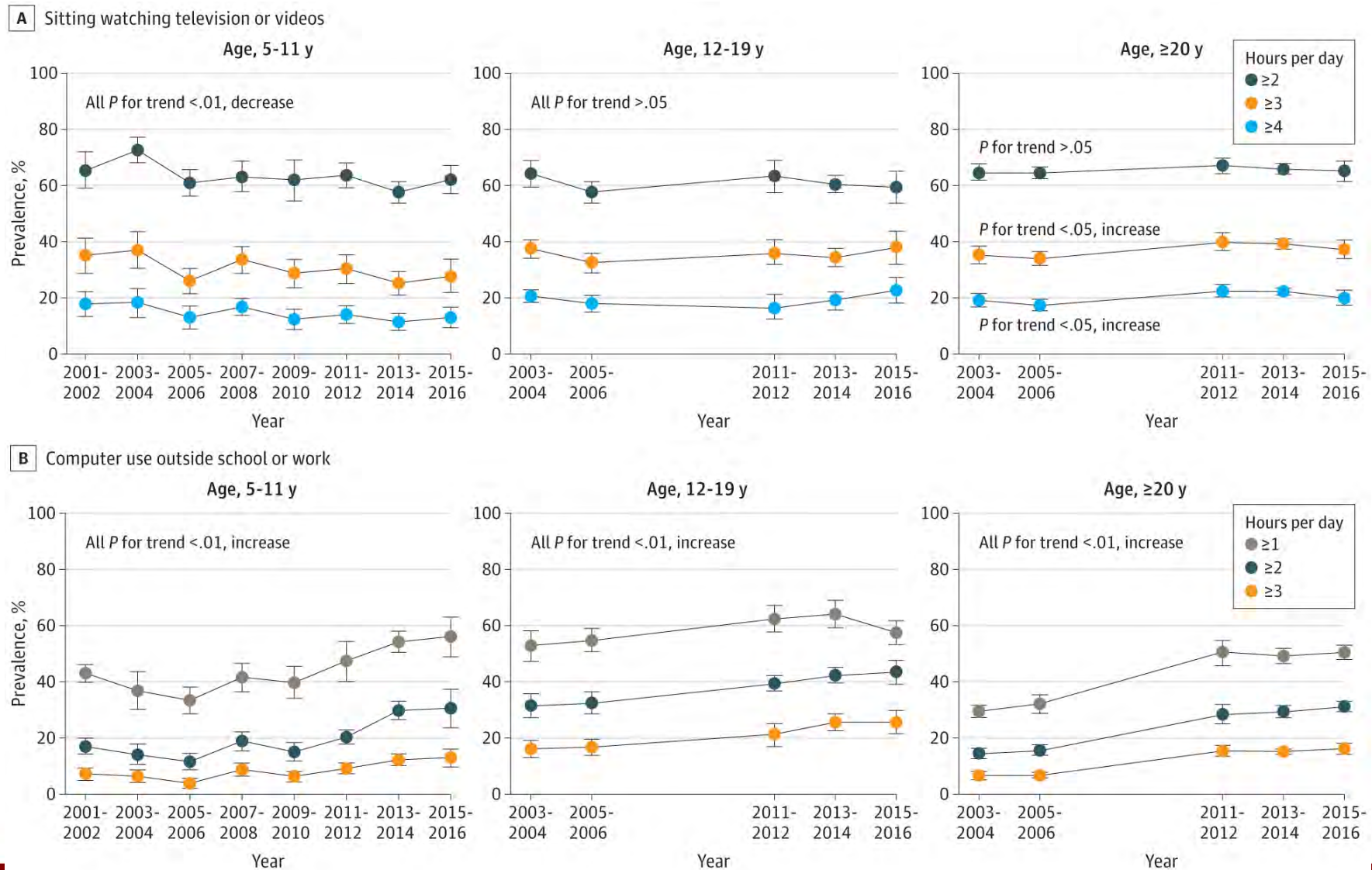
Sitting watching TV/videos vs. EO-CRC by anatomic site

Prospective cohort, NHSII 1991-2011



Nguyen *et al.*, JNCI Cancer Spectrum 2019

Trends of sedentary behaviors (TV/video watching & computer use) NHANES 2001-2016



Yang et al,
JAMA, 2019

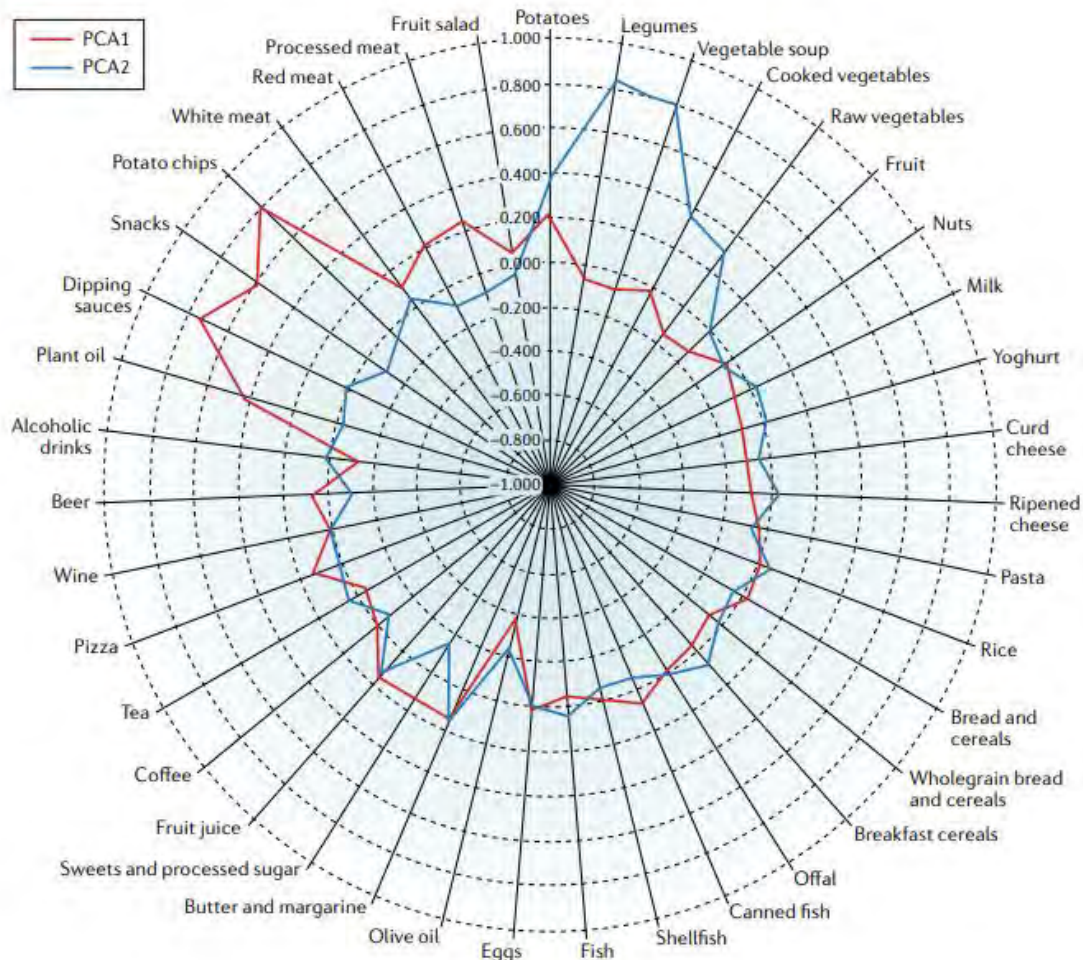
Measurement of diet quality: A priori dietary patterns

| Dietary Component | DASH ¹ |
|---------------------------------------|----------------------------|
| Fruits | Quintiles (1pt=Q1, 5pt=Q5) |
| Vegetables | Quintiles (1pt=Q1, 5pt=Q5) |
| Whole grains | Quintiles (1pt=Q1, 5pt=Q5) |
| Nuts ⁴ | Quintiles (1pt=Q1, 5pt=Q5) |
| Legumes ⁴ | Quintiles (1pt=Q1, 5pt=Q5) |
| Low-fat dairy | Quintiles (1pt=Q1, 5pt=Q5) |
| Red/processed meat | Quintiles (1pt=Q5, 5pt=Q1) |
| Sugar-sweetened beverage ⁵ | Quintiles (1pt=Q5, 5pt=Q1) |
| Sodium intake | Quintiles (1pt=Q5, 5pt=Q1) |
| Alcohol | -- |
| Fish | -- |
| MUFA: SFA ratio | -- |
| Polyunsaturated fat | -- |
| Omega-3 fatty acid | -- |
| Trans fat | -- |

DASH, Dietary Approaches to Stop Hypertension; AMED, Alternative Mediterranean Diet; AHEI-2010, Alternative Healthy Eating Index-2010; MUFA, monounsaturated fat; SFA, saturated fat

Measurement of diet quality: A posteriori (data-driven) dietary patterns

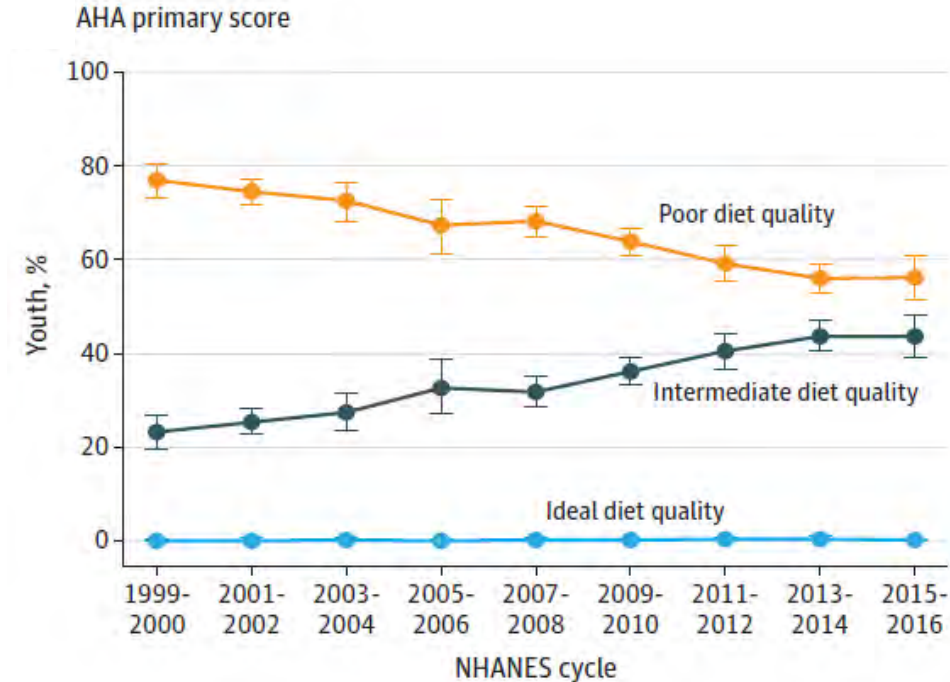
Western (red) vs Prudent (blue) diet



- Principal component analyses: a method of dimension reduction that identifies underlying patterns in dietary intake data based on maximizing the variance between the different dietary factors
- **Number of components, weighting, and labelling of dietary patterns can vary greatly across studies.**

Steck & Murphy, Nature Reviews Cancer 2020

Diet quality is poorer in the young & recent generations

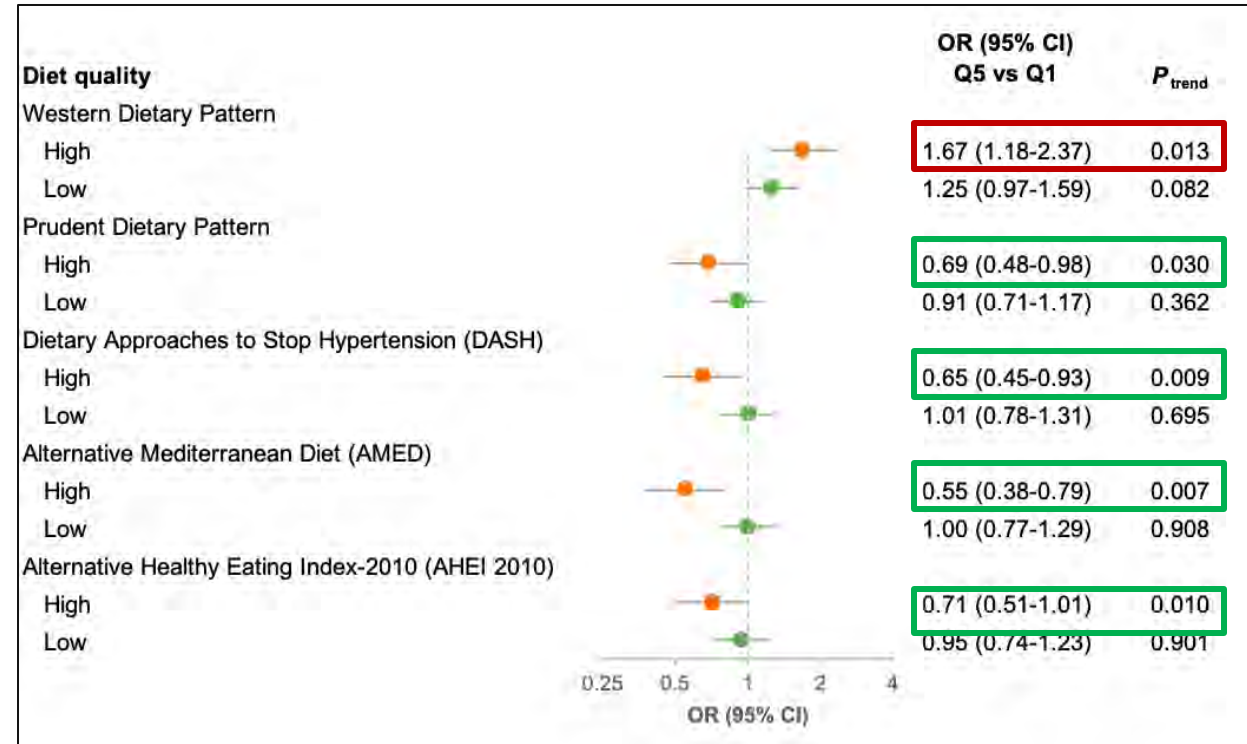
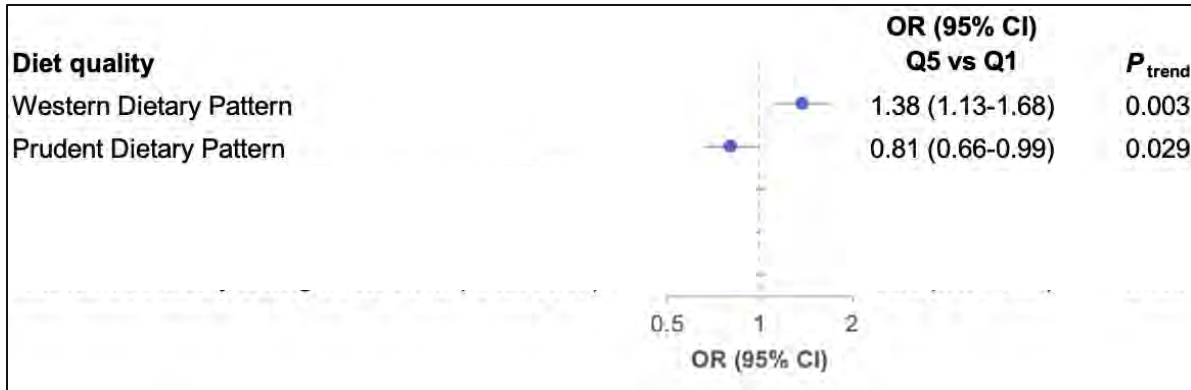


The primary score is based on total fruits and vegetables, whole grains, fish and shellfish, sugar-sweetened beverages, and sodium.

Sijtsma et al. Am J Clin Nutr 2012; Liu *et al.* JAMA 2020

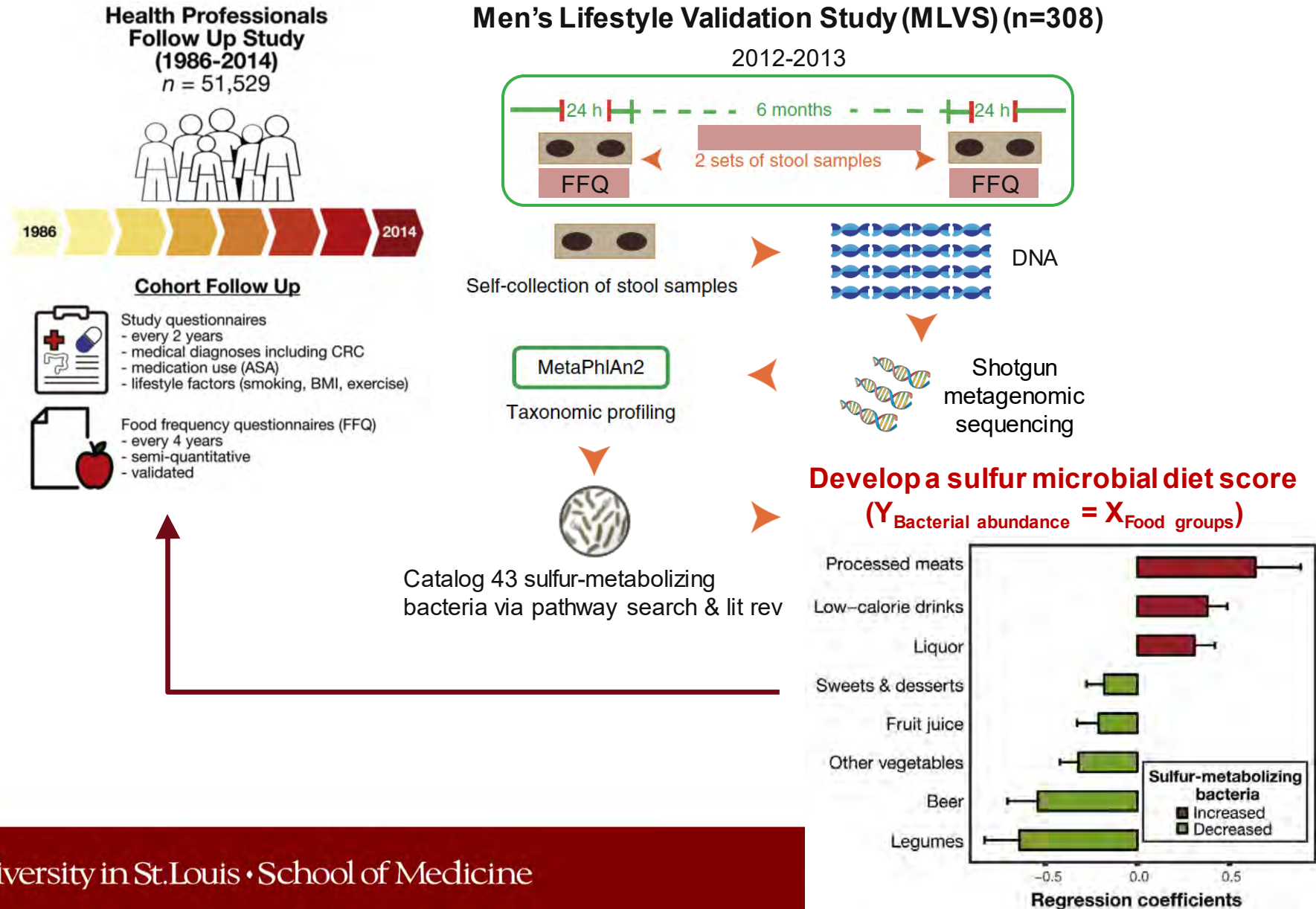
Diet quality vs. early-onset colorectal adenoma

Prospective cohort, NHSII 1991-2011



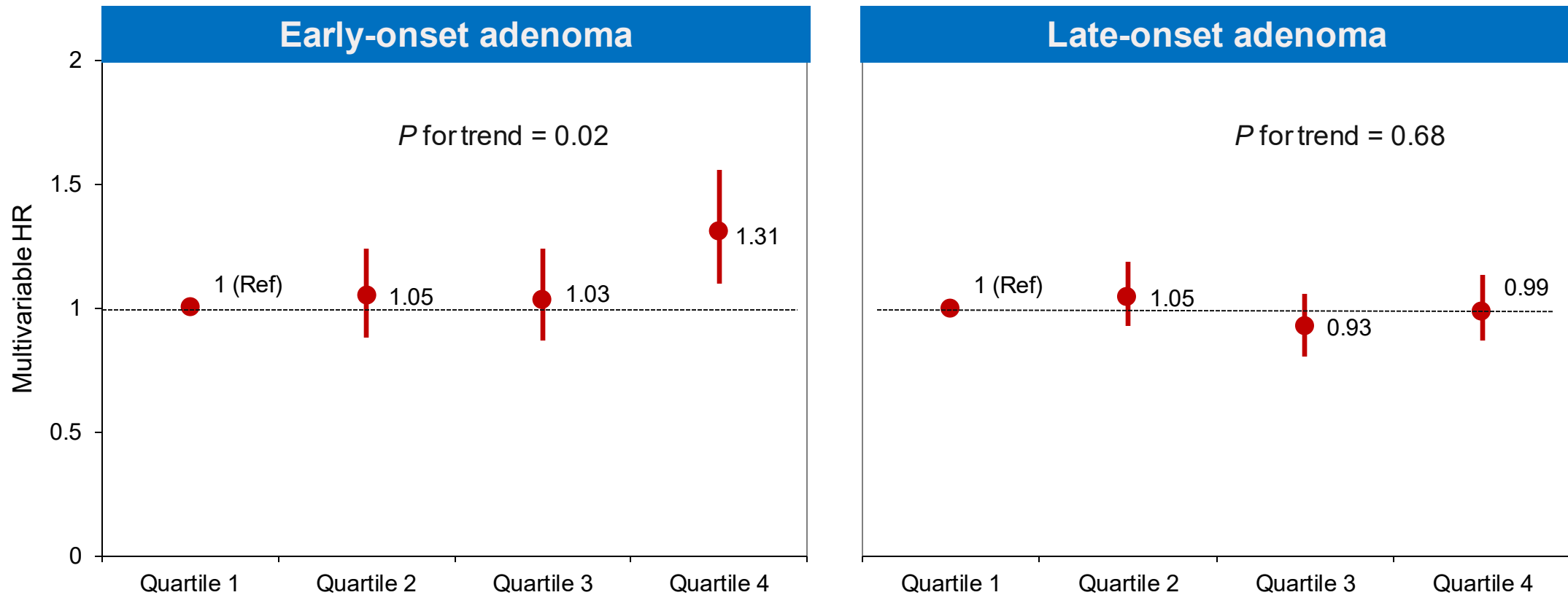
Zheng* and Hur* *et al*, JNCI 2021

Deriving a sulfur microbial diet for CRC prevention



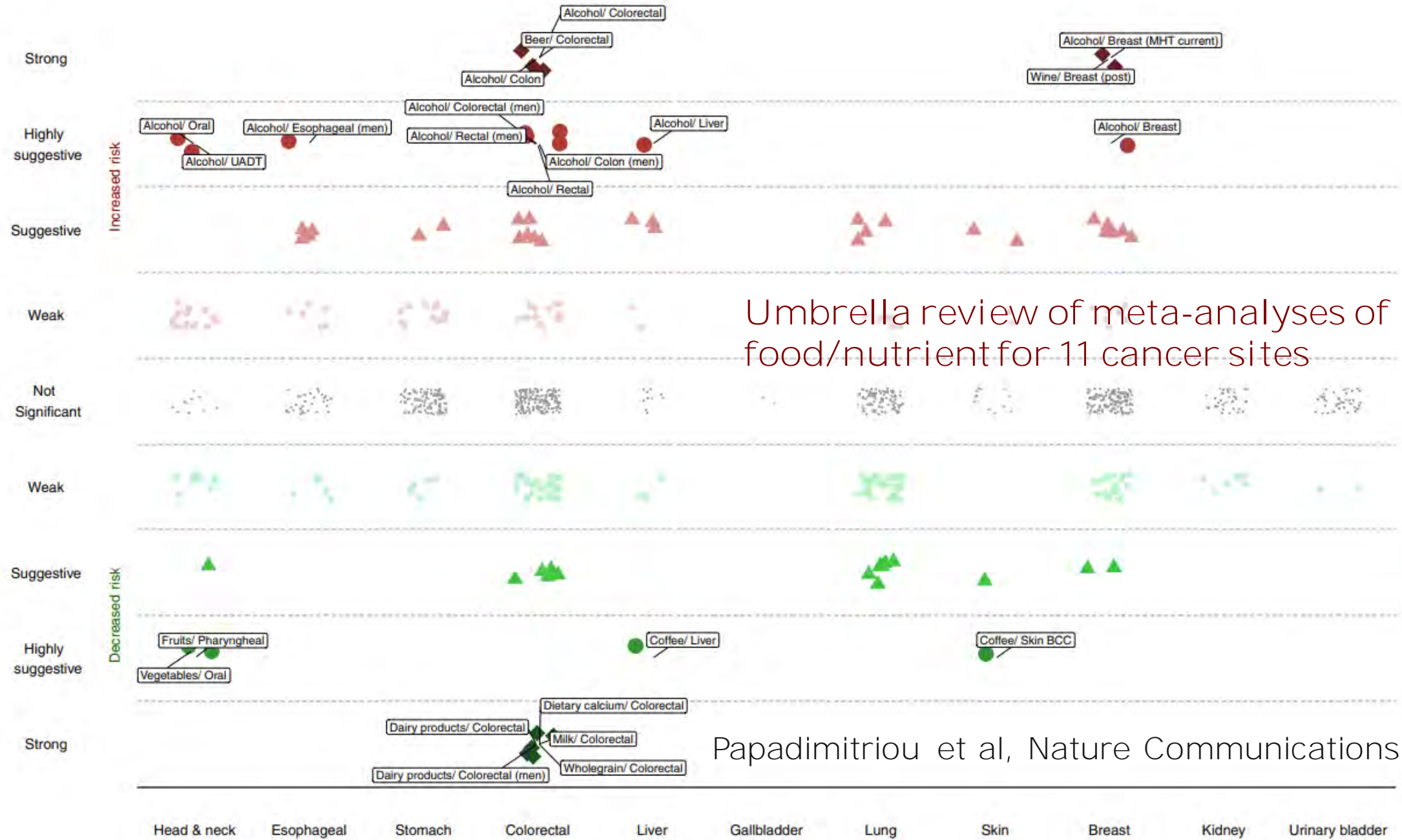
Nguyen et al.
 Gastroenterology.
 2020

Sulfur microbial diet associated with early but not late-onset adenomas (age < 50 years)



Nguyen LH* & Cao Y*, et al. Gastroenterology. 2021

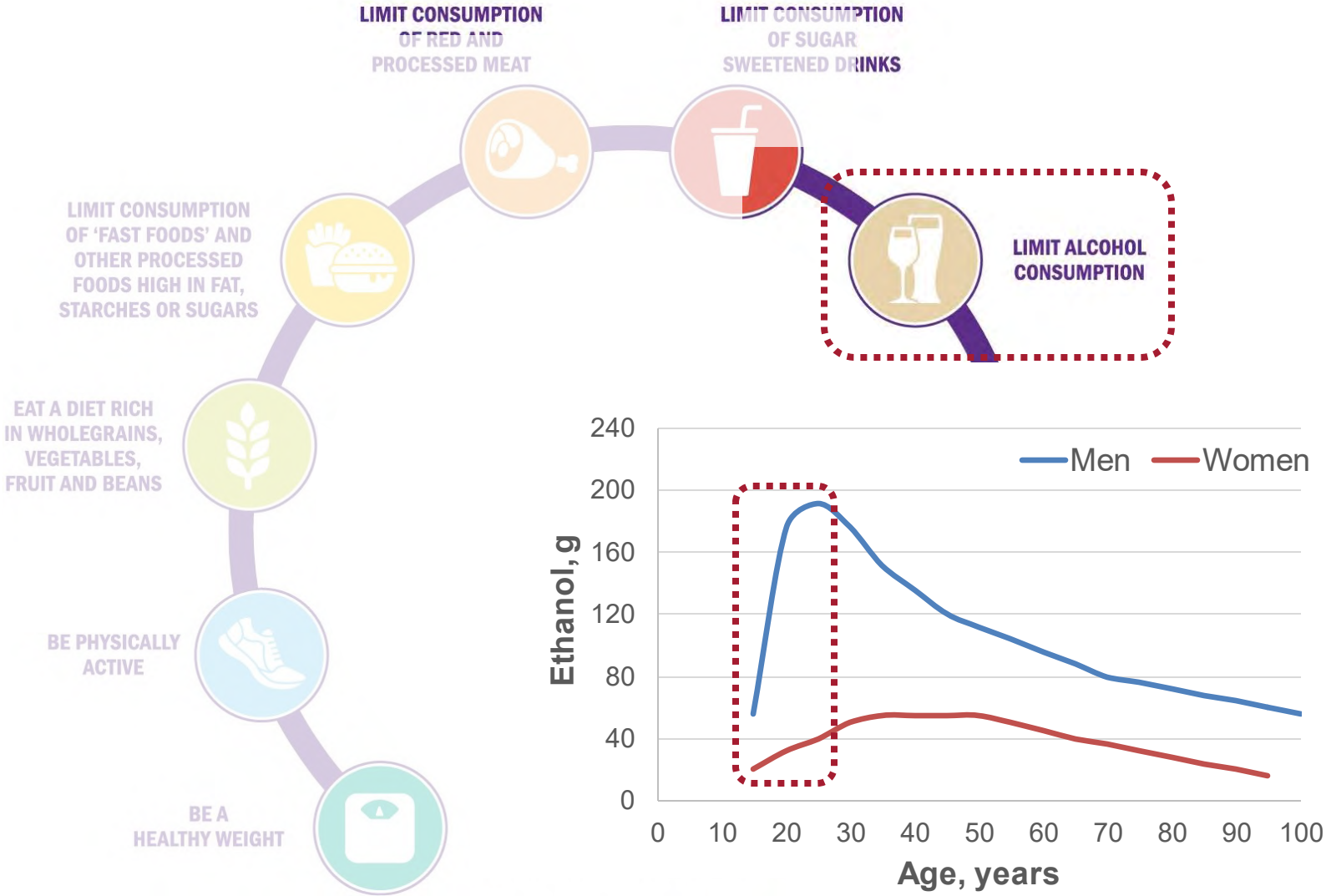
Evidence Grade



Umbrella review of meta-analyses of food/nutrient for 11 cancer sites

Papadimitriou et al, Nature Communications, 2021

Alcohol intakes peaks in early adulthood



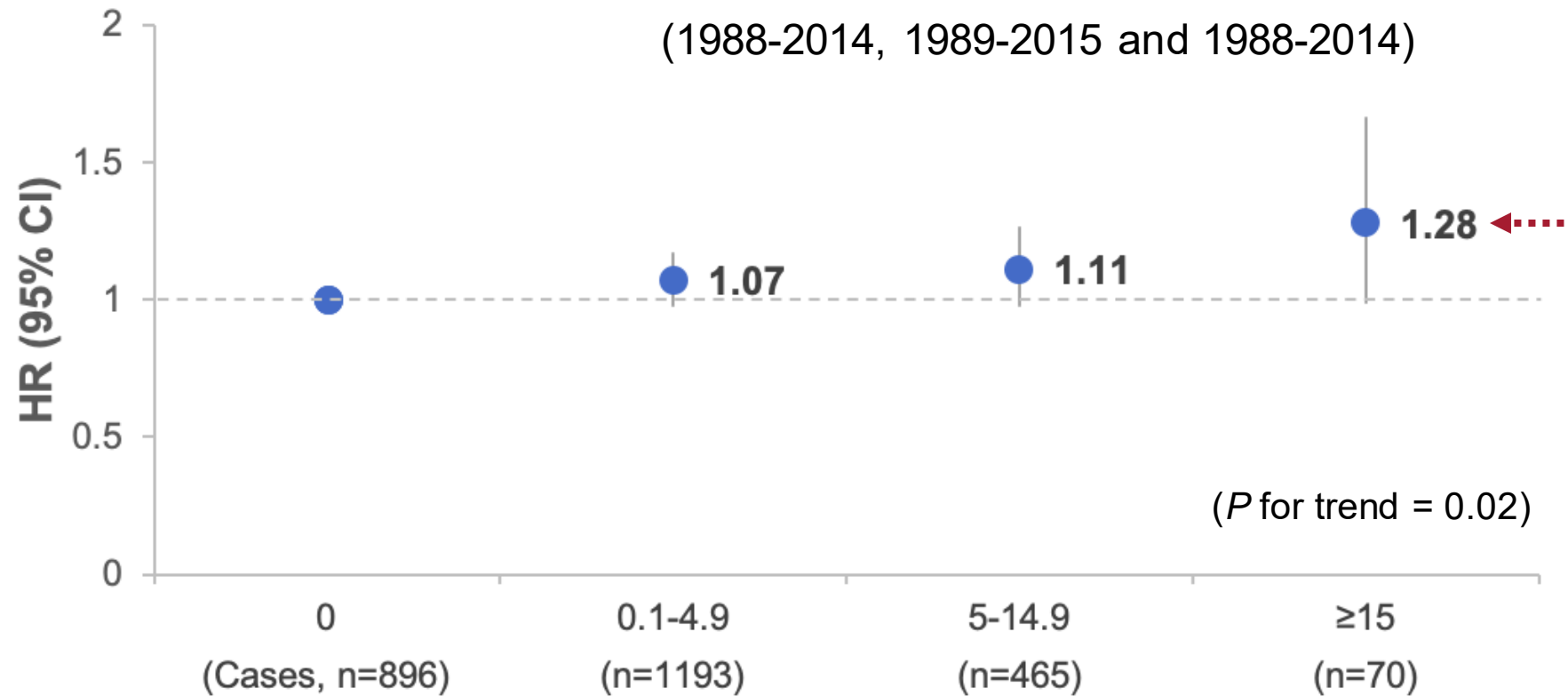
Adolescence & early adulthood

- Lifetime peak in alcohol consumption
- High-risk drinking behaviors

Britton et al. *BMC Medicine* 2015

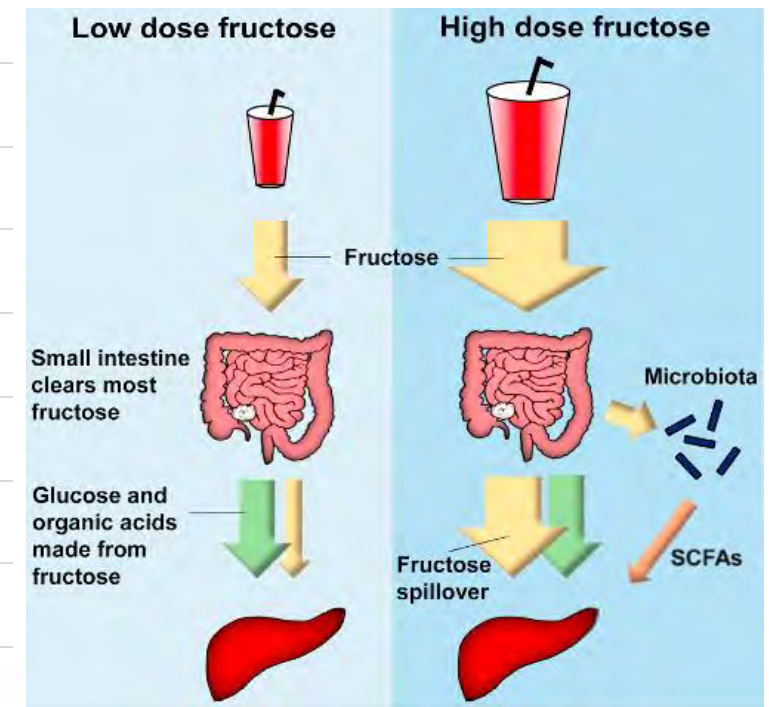
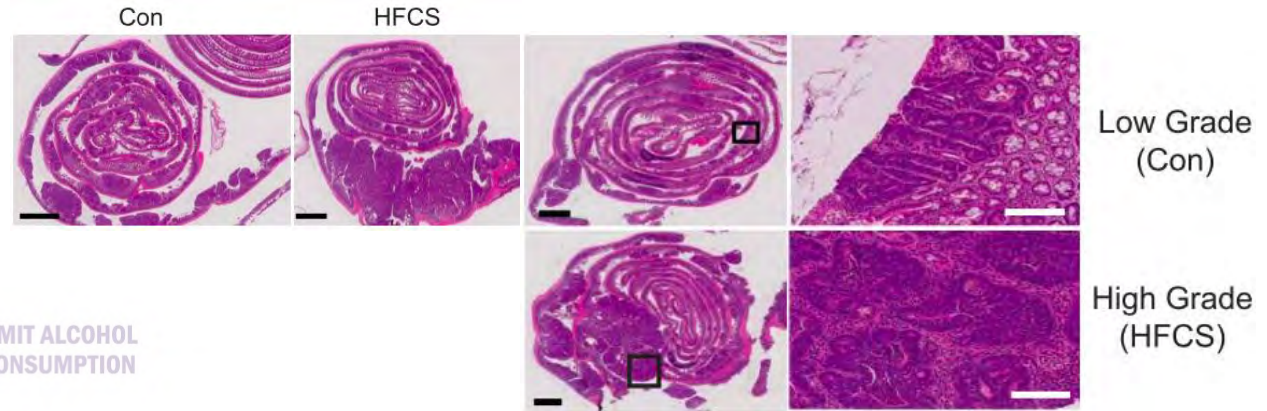
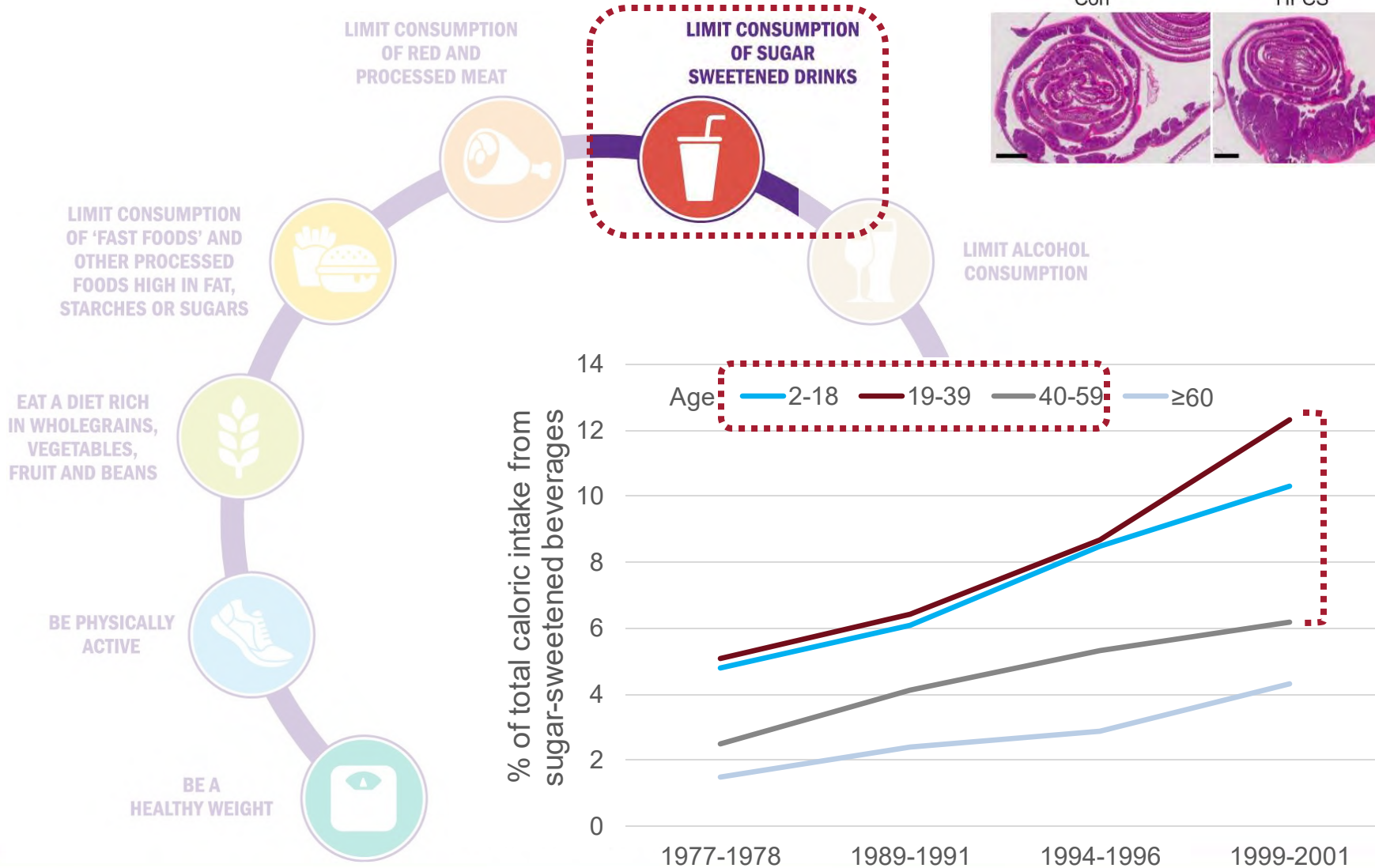
Alcohol intake in early adulthood vs. CRC later in life

Pooled multivariable hazard ratios (HRs) from the NHS, NHSII and HPFS



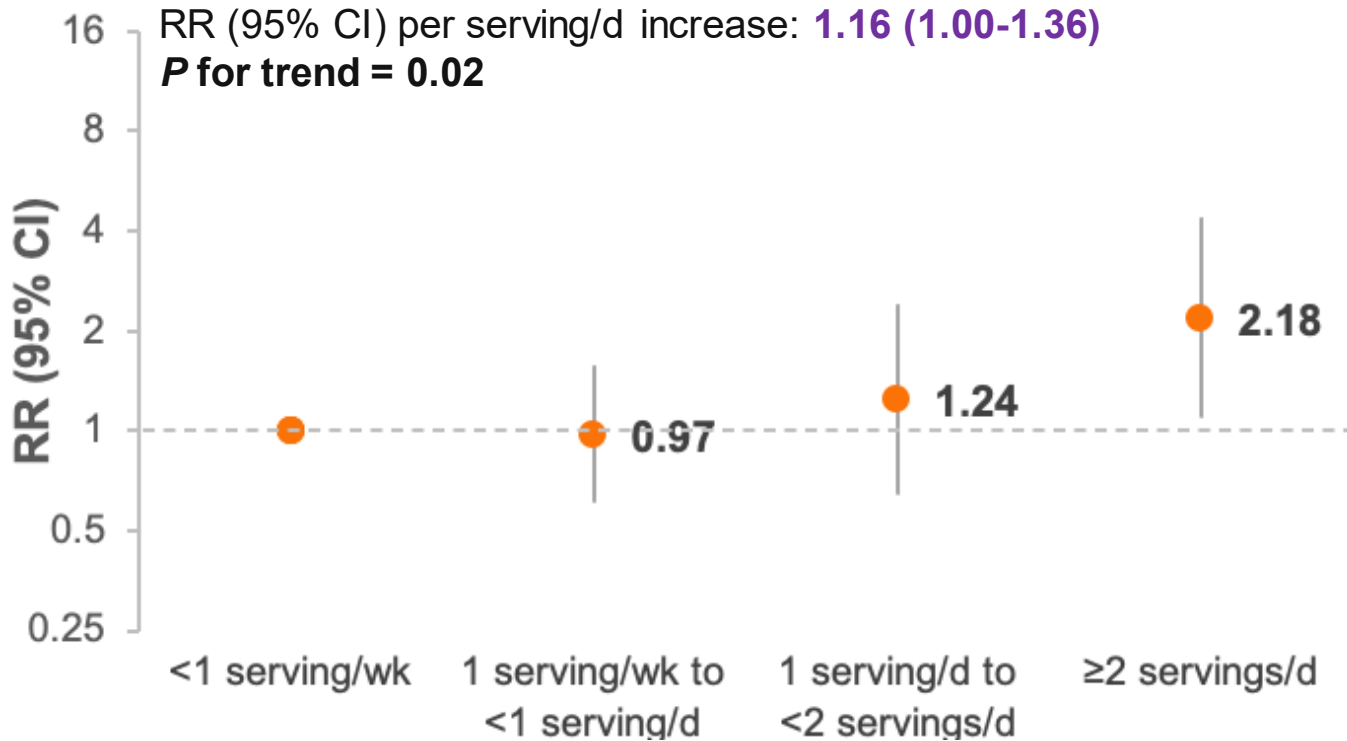
Alcohol intake in early adulthood, g/day Hur et al. *Eur J Epidemiol* 2021

Sugar-sweetened beverages intake the highest in aged <40

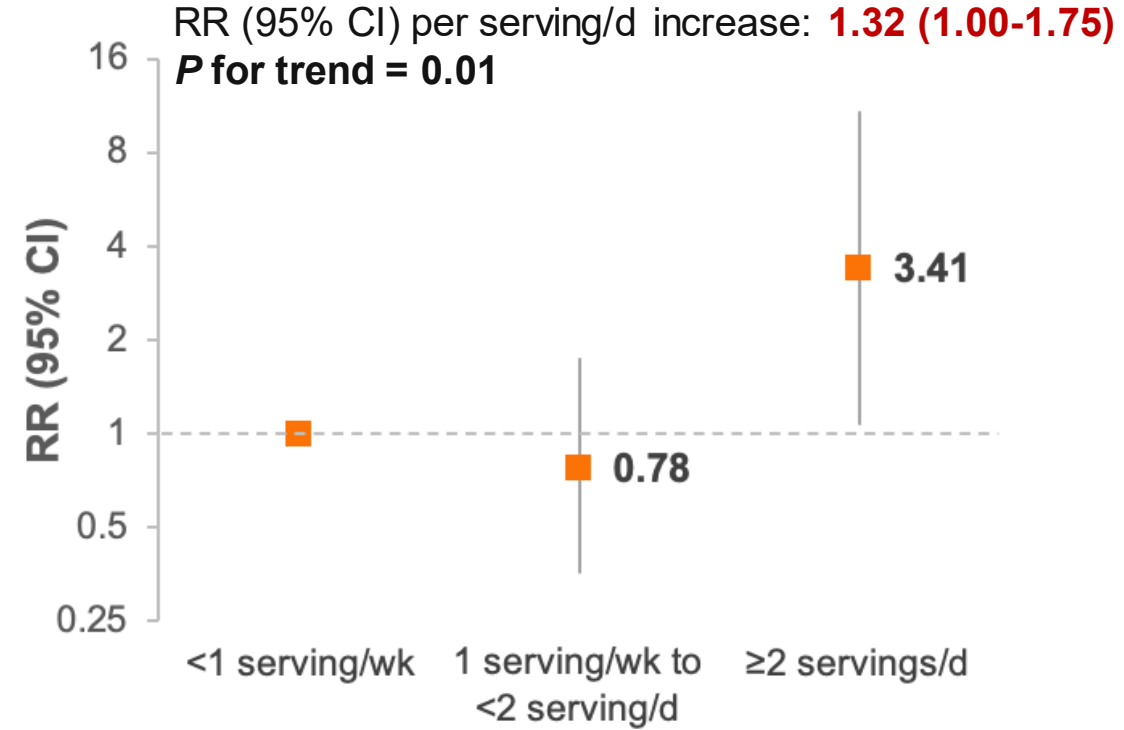


SSB intake throughout the life course vs. EO-CRC NHSII 1991-2015

Mid-adulthood

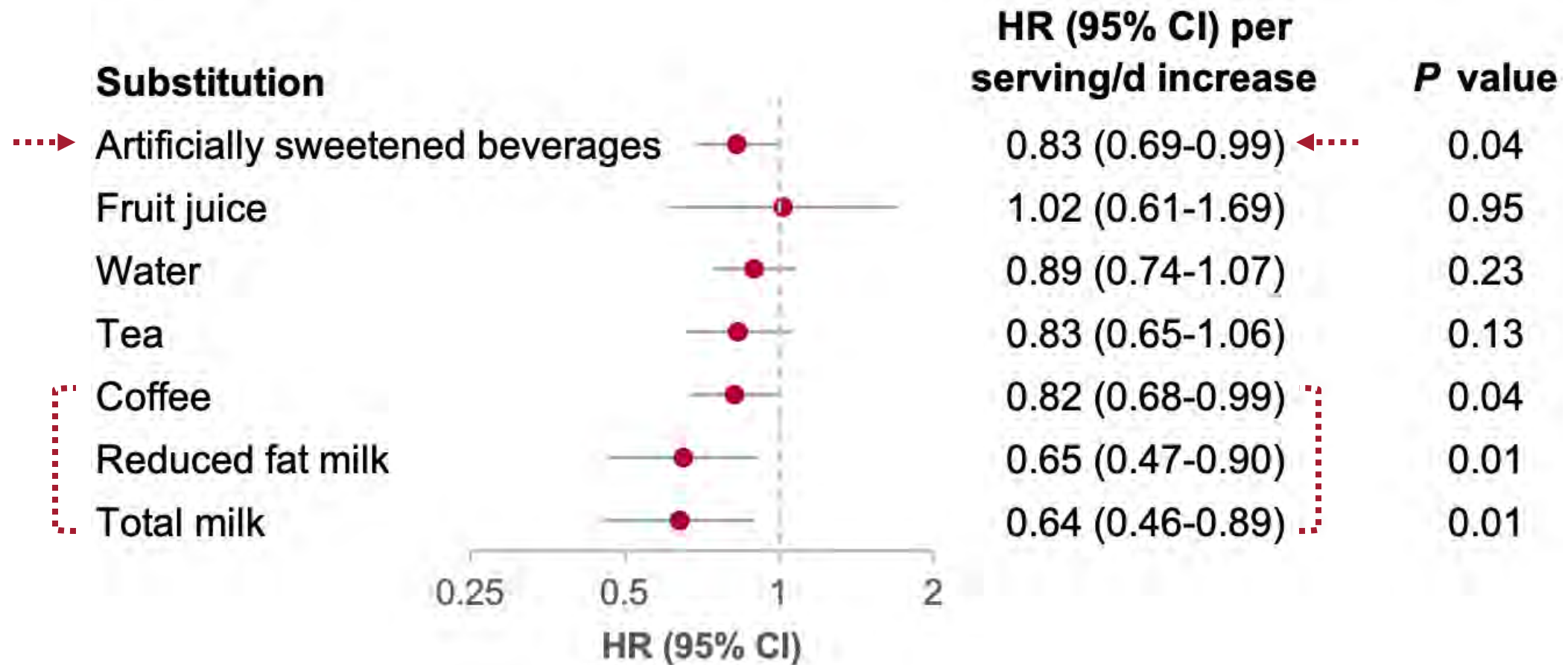


Adolescence



Hur *et al.*, Gut 2021

Replacement of SSBs with other beverages and risk of EO-CRC NHSII 1991-2015



Hur *et al.*, Gut 2021

Antibiotics vs. adenoma/CRC/EO-CRC

Modest associations that likely vary by tumor location/antibiotic class
Swedish registers 2005-2016

| Age at diagnosis | Antibiotics use ^a | Proximal Colon | | Distal Colon | | Rectum | |
|---|---------------------------------|------------------------|-----------------------------------|------------------------|-----------------------------------|------------------------|-----------------------------------|
| | | Case (n) / Control (n) | Adjusted OR ^b (95% CI) | Case (n) / Control (n) | Adjusted OR ^b (95% CI) | Case (n) / Control (n) | Adjusted OR ^b (95% CI) |
| Age < 50 years (early onset) (n= 1 905) | No use | 205 / 1 028 | 1 (Reference) | 259 / 1 259 | 1 (Reference) | 309 / 1 547 | 1 (Reference) |
| | Low | 58 / 327 | 0.87 (0.62-1.21) | 70 / 368 | 0.86 (0.64-1.17) | 92 / 427 | 0.98 (0.75-1.29) |
| | Moderate | 219 / 1 039 | 0.99 (0.79-1.25) | 236 / 1 203 | 0.90 (0.72-1.11) | 268 / 1 417 | 0.89 (0.74-1.08) |
| | High | 37 / 245 | 0.60 (0.39-0.92) | 47 / 254 | 0.76 (0.52-1.10) | 61 / 276 | 1.00 (0.71-1.39) |
| | Very high | 16 / 36 | 1.53 (0.77-3.07) | 12 / 36 | 1.38 (0.66-2.92) | 16 / 63 | 1.15 (0.62-2.15) |
| | P _{trend} ^c | | 0.51 | | 0.27 | | 0.48 |
| Age ≥ 50 years (n= 38 095) | No use | 4 287 / 23 529 | 1 (Reference) | 3 792 / 19 423 | 1 (Reference) | 4 666 / 22 443 | 1 (Reference) |
| | Low | 1 649 / 8 311 | 1.08 (1.01-1.15) | 1 315 / 6 534 | 1.01 (0.94-1.08) | 1 515 / 7 167 | 1.01 (0.95-1.08) |
| | Moderate | 5 999 / 29 152 | 1.10 (1.05-1.15) | 4 689 / 22 610 | 1.03 (0.98-1.08) | 4 912 / 25 389 | 0.92 (0.88-0.97) |
| | High | 1 803 / 8 207 | 1.11 (1.04-1.19) | 1 165 / 6 211 | 0.93 (0.86-1.01) | 1 225 / 6 476 | 0.90 (0.84-0.97) |
| | Very high | 492 / 1 951 | 1.16 (1.04-1.30) | 279 / 1 422 | 0.95 (0.83-1.10) | 307 / 1 645 | 0.91 (0.79-1.03) |
| | P _{trend} ^c | | <.001 | | 0.70 | | <.001 |

Low (1-10 days), moderate (11-60 days), high (61-180 days), and very high (> 180 days) use

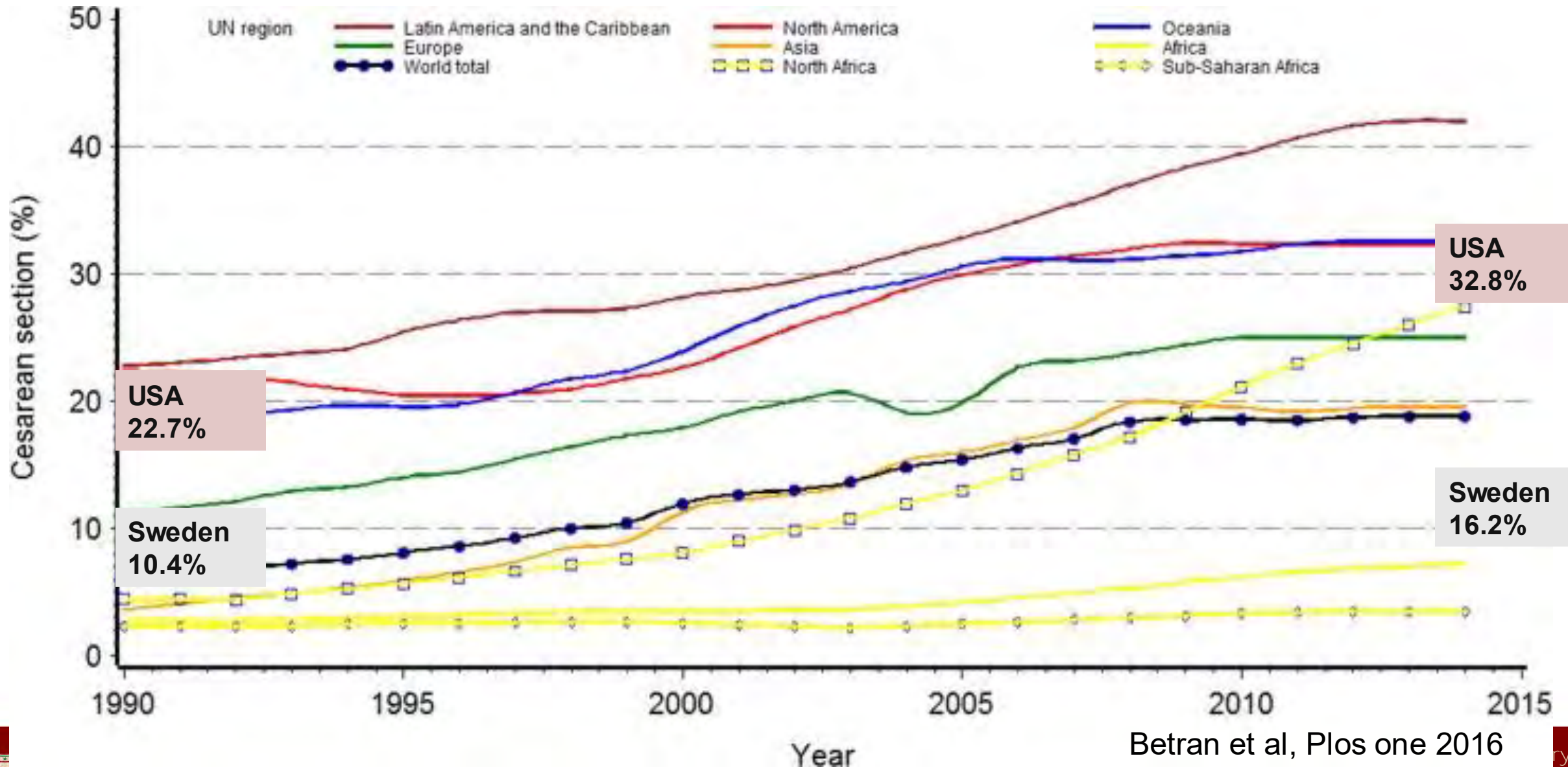
Cao *et al.*, Gut 2017

Lu *et al.*, JNCI 2021

Nguyen*, Cao* *et al.*, CTG 2022

Later-onset (UK Clinical Practice Research Datalink): Zheng *et al.*, Gut 2019

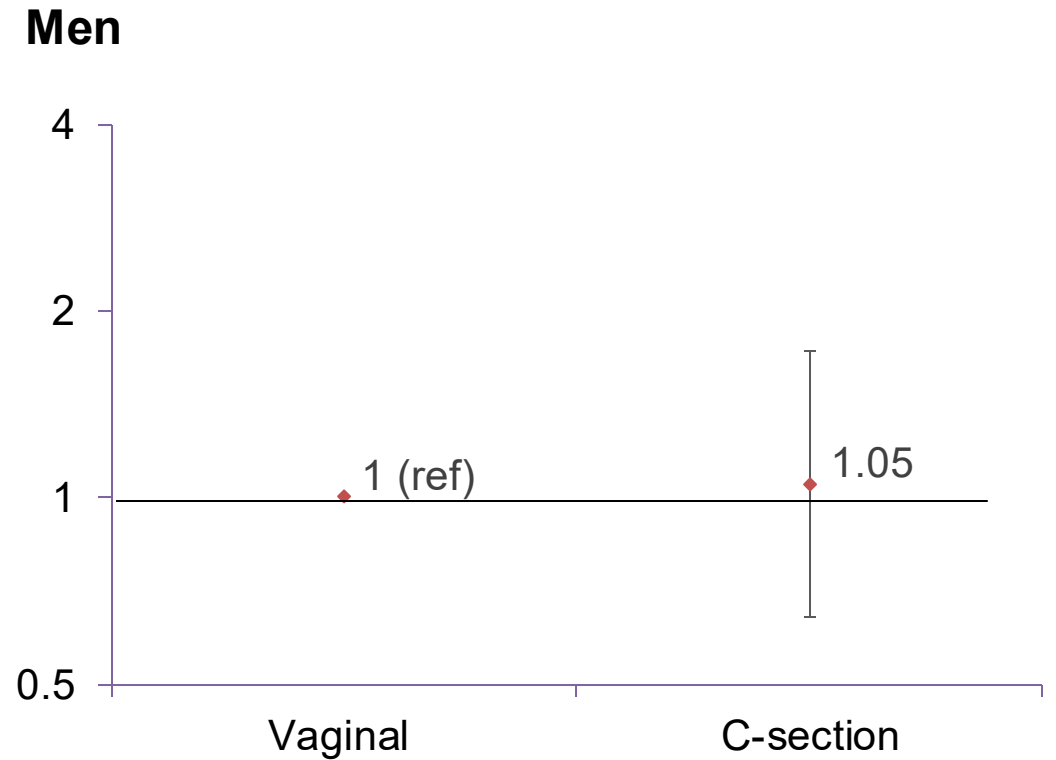
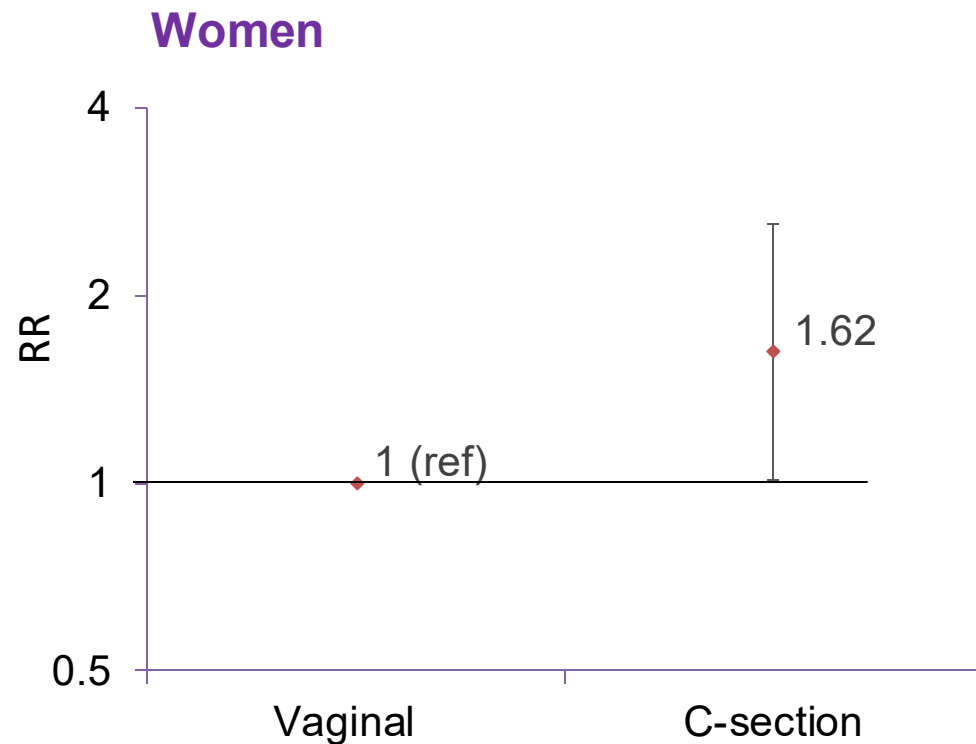
Cesarean delivery rates increased substantially globally



Betran et al, Plos one 2016

Birth via C section vs. EO-CRC

Population-based case-control, Sweden 1973-2017



Cao *et al.*, JAMA Network Open 2023

Conclusions

- The decline of CRC is slowing down due to the rising incidence of early-onset CRC
- EO-CRC risk factors are multifactorial
 - Emerging data support the role of metabolic/behavioral/diet/microbial related exposures throughout the life course in EO-CRC
- Calling for a comprehensive understanding of behavioral & environmental factors throughout the life course for recent generations
- Challenges and opportunities
 - Research infrastructure development
 - Cross-disciplinary collaborations
 - Imperative need for implementation studies to improve CRC prevention
 - Patient advocacy and engagement



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Memorial Sloan Kettering Cancer Center

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Erasmus Medical Cancer
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