Does it matter what we eat and whether we exercise?

Jeffrey Meyerhardt, MD, MPH
Dana-Farber Cancer Institute
Boston, MA

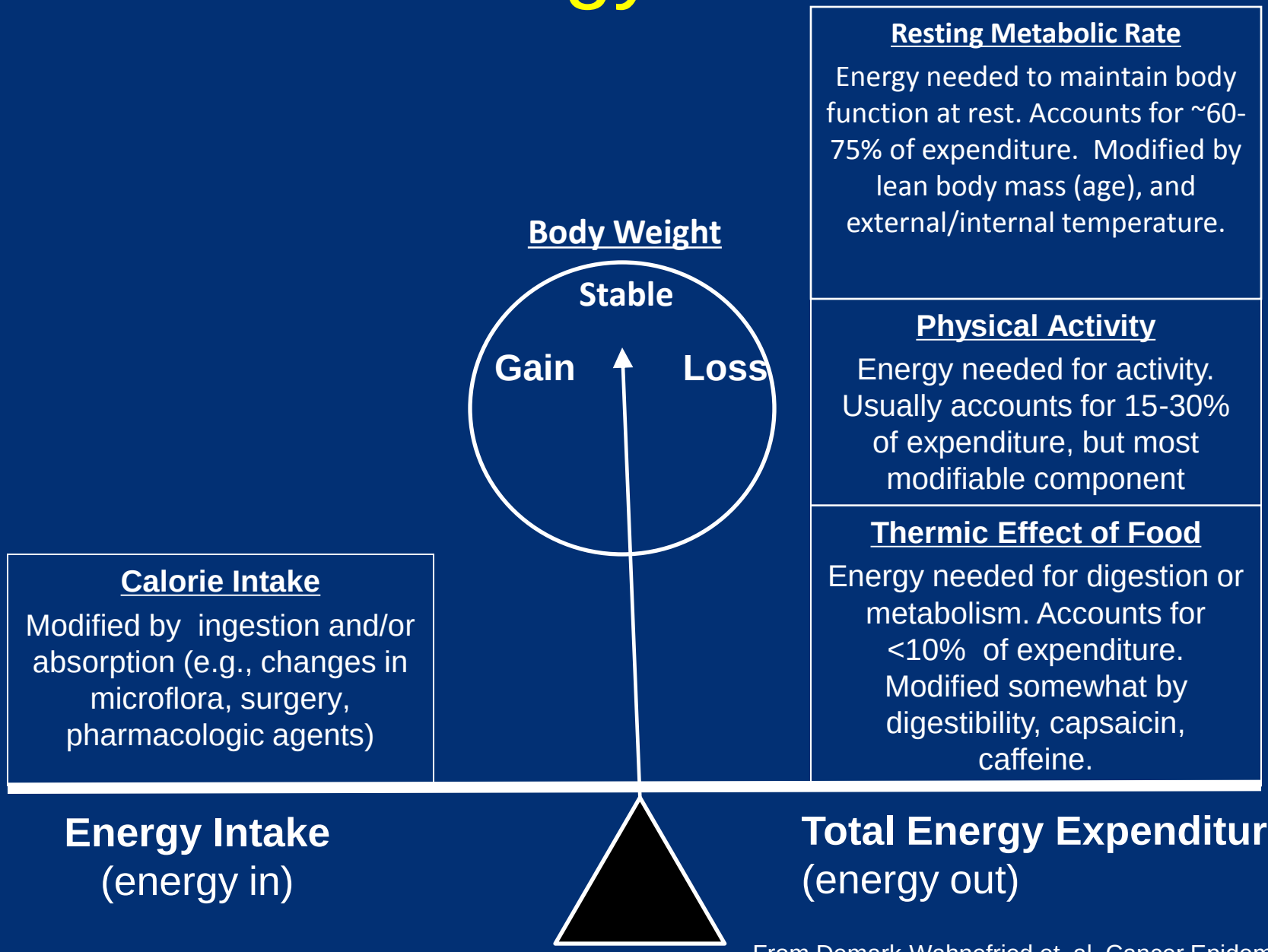
Outline

- Diet / Exercise and CRC: Primary Prevention
- Diet / Exercise and CRC in Cancer Patients
  - Should I exercise?
  - What should I eat?
- Where do we go from here

Colorectal Cancer: Risk Factors Overview

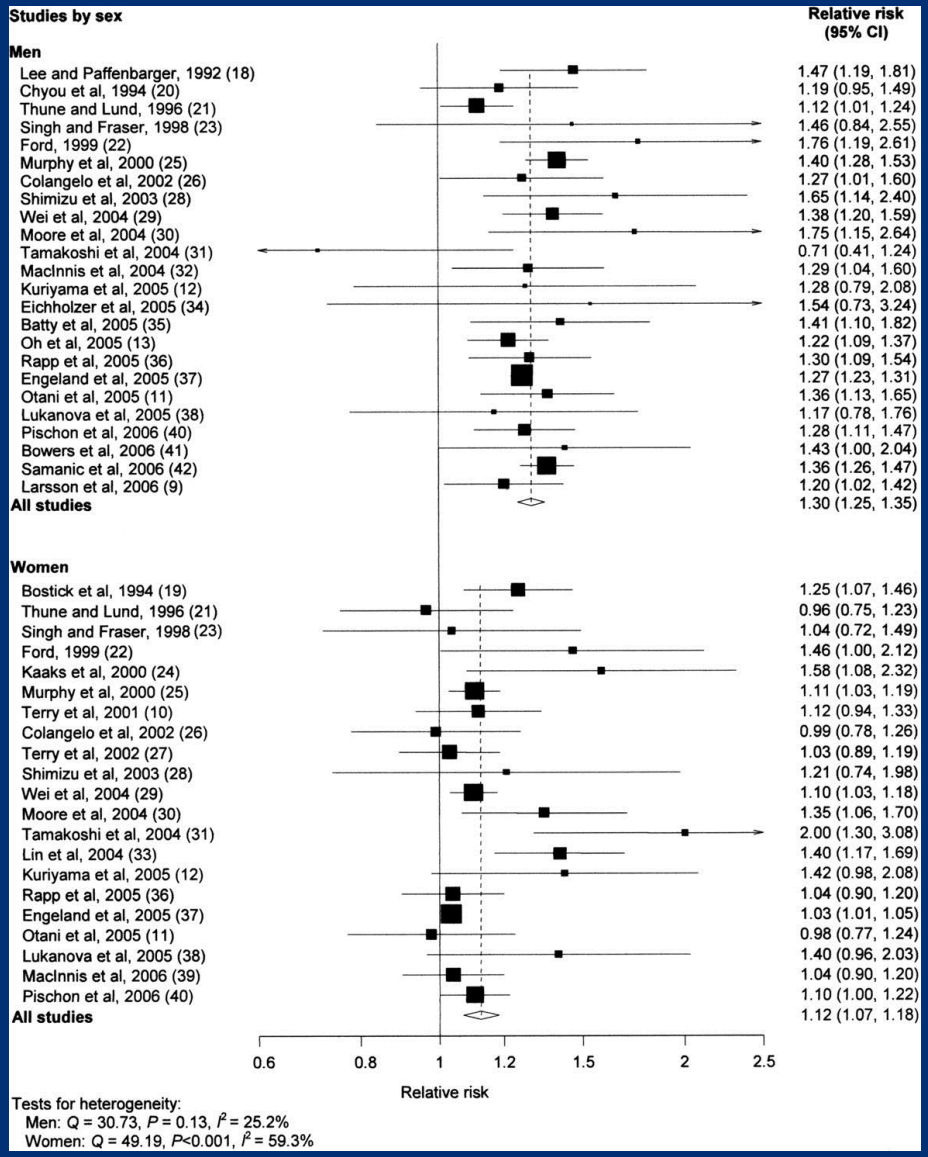
Decrease Risk	Increase Risk	Uncertain Impact
Screening	Family history	Statins
Exercise	Ulcerative colitis/ Crohn's Disease	Fiber
Aspirin / NSAIDs		Glycemic load
Vitamin D	Diabetes	Fruits/Vegetables
Post-menopausal estrogen	Obesity	Folic Acid
Calcium	Red meat	
	Western diet	
	Alcohol	
	Smoking	

Energy Balance



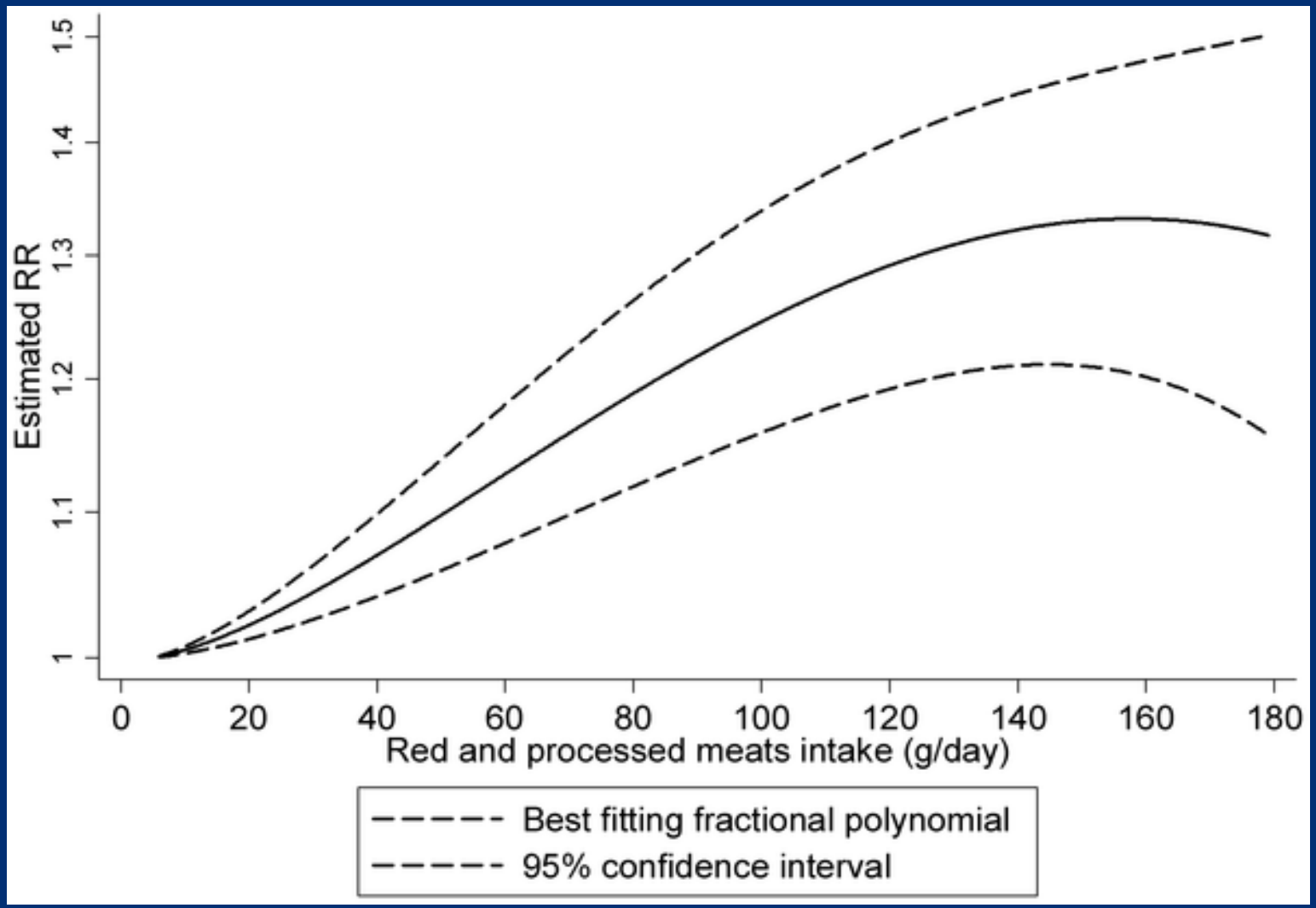
From Demark-Wahnefried et. al. Cancer Epidemiol Biomarkers Prev. 2012 Aug;21(8):1244-59.,

Relative risk of colon cancer per 5-unit increase in BMI (in kg/m2)



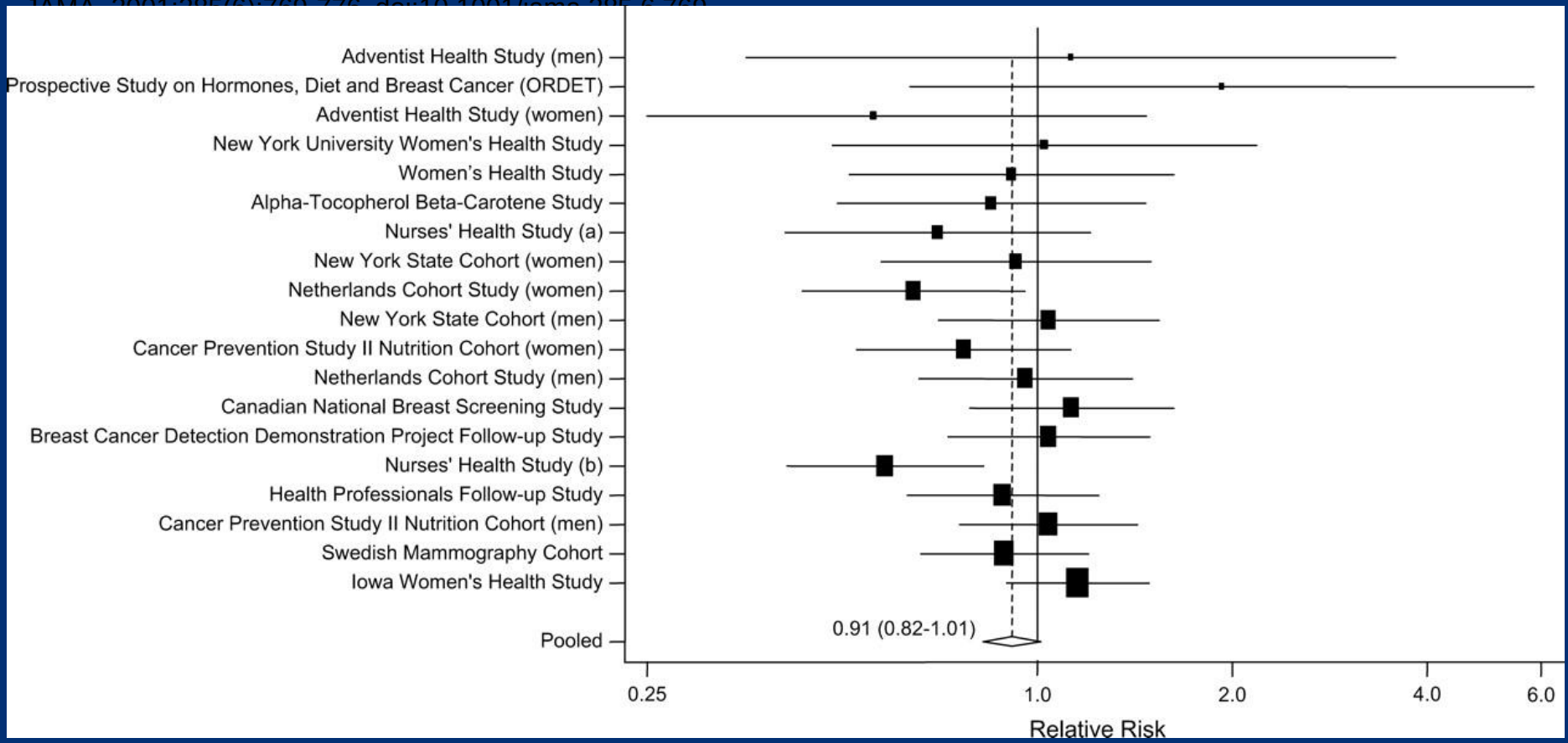
Larsson S C , and Wolk A Am J Clin Nutr 2007;86:556-565

Meta-analysis of red and processed meats consumption and the risk of colorectal cancer



Chan DSM, Lau R, Aune D, Vieira R, et al. (2011) Red and Processed Meat and Colorectal Cancer Incidence: Meta-Analysis of Prospective Studies. PLoS ONE 6(6): e20456.

Vegetables and Fruit and Risk of Colon Cancer

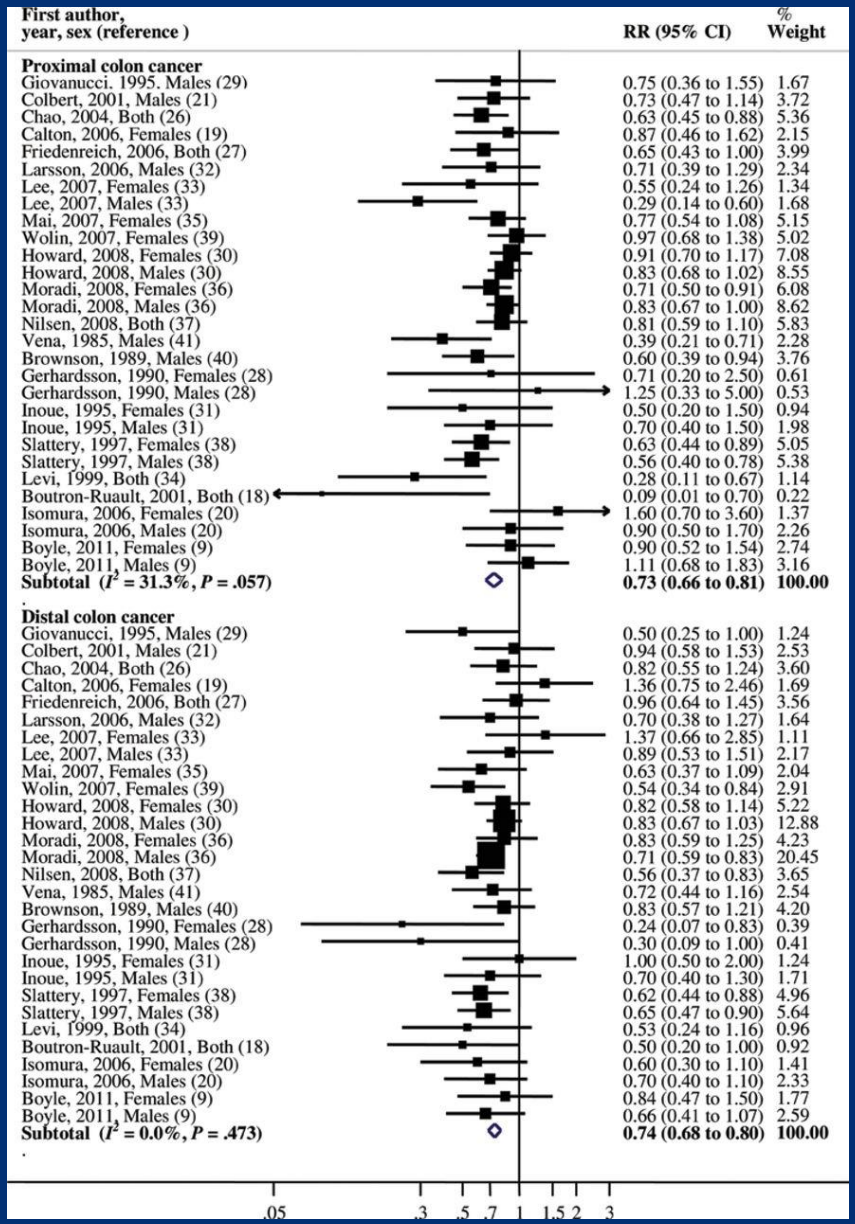


Koushik A et al. JNCI J Natl Cancer Inst 2007;99:1471-1483

Vegetables and Fruit

- Consuming vegetables and fruits may contribute to weight loss and maintenance
- Many vegetables and fruits are low in energy and high in fiber, and have a high water content, which may increase satiety and decrease overall energy intake

Physical Activity and Colon Cancer



Boyle T et al. JNCI J Natl Cancer Inst 2012;104:1548-1561

Proportion of Colon Cancer Preventable in Middle-Aged Men: HPFS

- Body mass index ≤ 25 kg/m2
- Physical activity ≥ 15 MET-hours/week
- Daily folate containing multivitamin
- Alcohol < 15 g/day
- Non-smoker
- Red meat ≤ 2 servings/week

3.1% of all men

Eliminate 71% of all colorectal cancer
(95% CI, 33-92%)

Platz Cancer Cause Contr 2000

Conclusions Regarding Diet/Lifestyle and Risk of Colorectal Cancer

- Relative consistency of the observational data suggesting diet and lifestyle associated with risk of colorectal cancer
- Many of these factors likely impact through tipping energy balance scale
- No randomized data and unclear if intervening on some or multiple factors will alter lifetime risk
  - When to alter
  - How long needed

Outline

- Diet / Exercise and CRC: Primary Prevention
  - What do we know
  - What don't we know
- Diet / Exercise and CRC in Cancer Patients
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  - Should I exercise?
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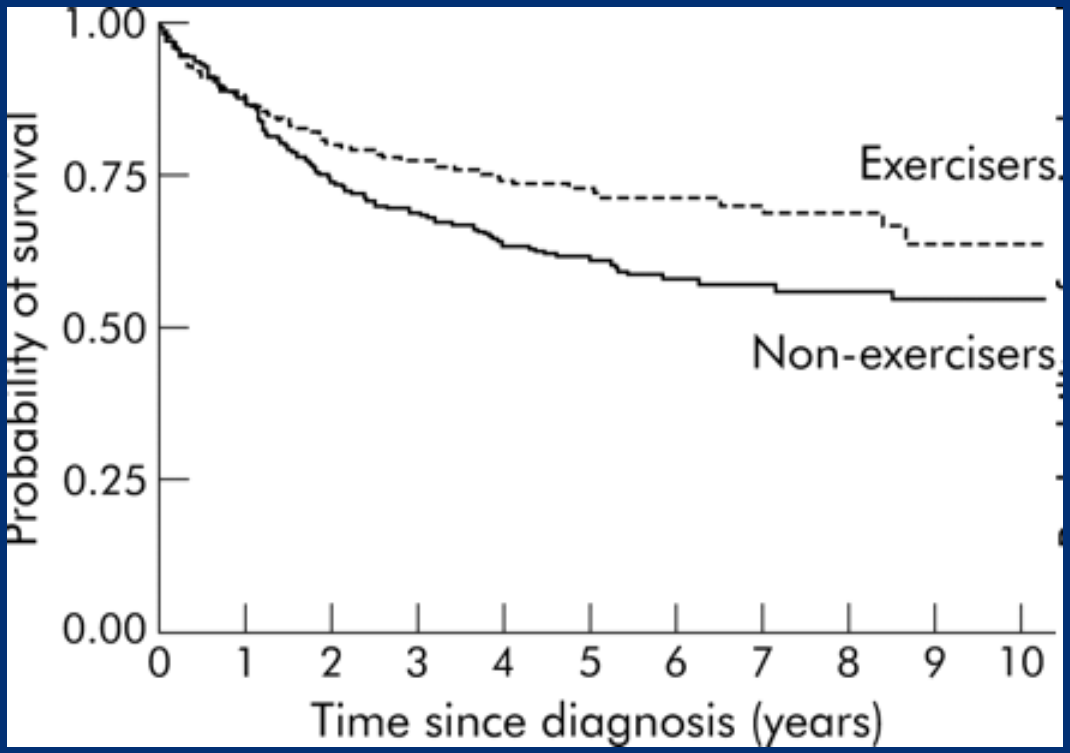
Physical Activity and Colorectal Cancer

- Many studies have looked at physical activity and quality of life during treatment or beyond treatment for colorectal cancer patients
  - Most observational
  - Few intervention (single arm or different ways of intervening)
  - Only 1 RCT of exercise intervention v control – contamination of control limits conclusions

- Focus here will be on recurrences and survival in patients

Physical Activity and Colorectal Cancer

- Cohort study from Australia of 526 colorectal cancer patients with pre-diagnosis physical activity assessment

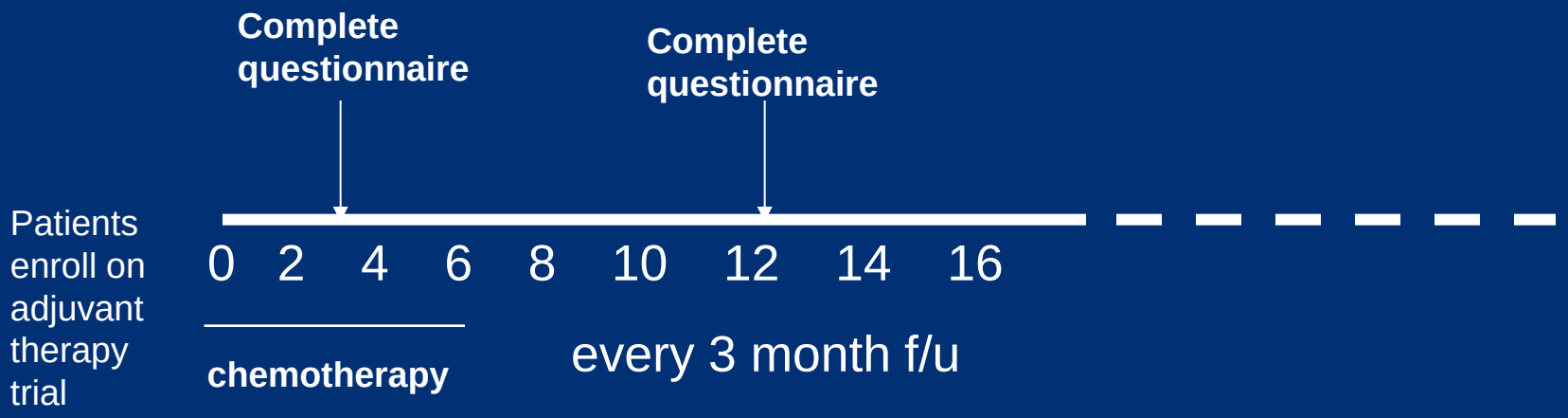


Colorectal cancer specific survival

Haydon Gut. 2006 Jan;55(1):62-7

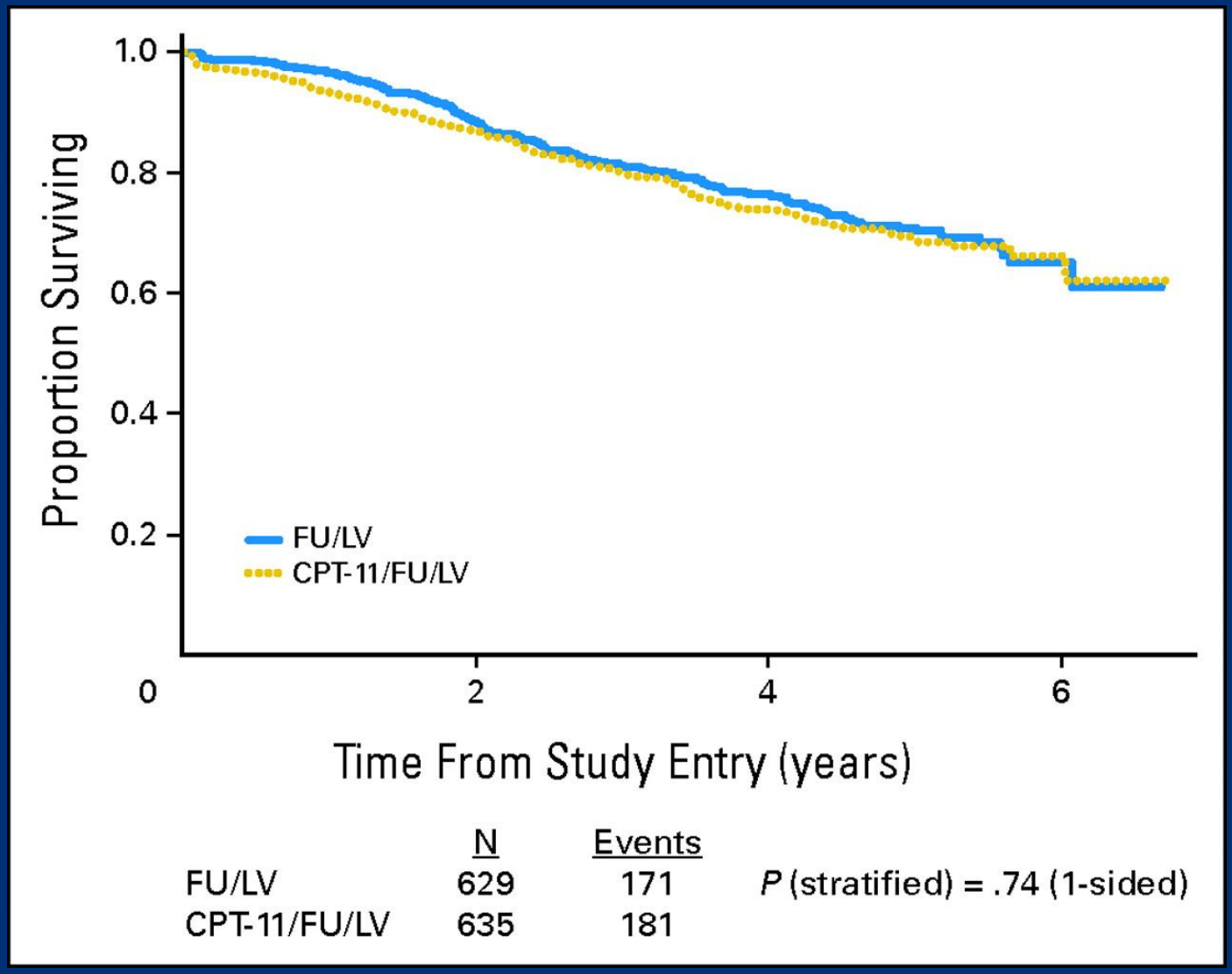
CALGB 89803

- NCI-sponsored adjuvant therapy trial for stage III colon cancer
- Patients randomized to Roswell Park 5-FU/LV or IFL (bolus 5-FU/LV/Irinotecan)
- 1264 enrolled between 1999 and 2001



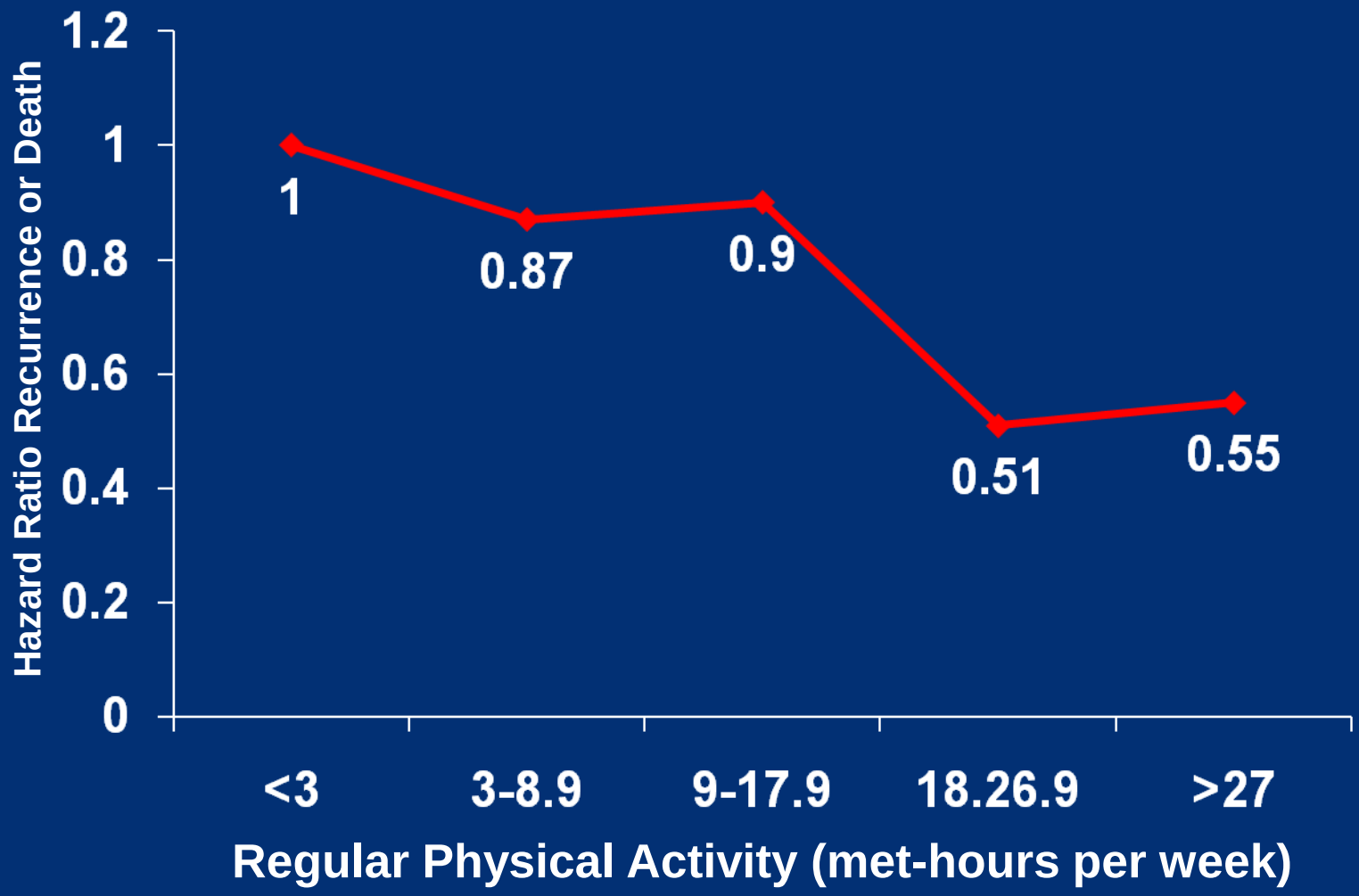
Saltz, L. B. et al. J Clin Oncol; 25:3456-3461 2007

CALGB 89803



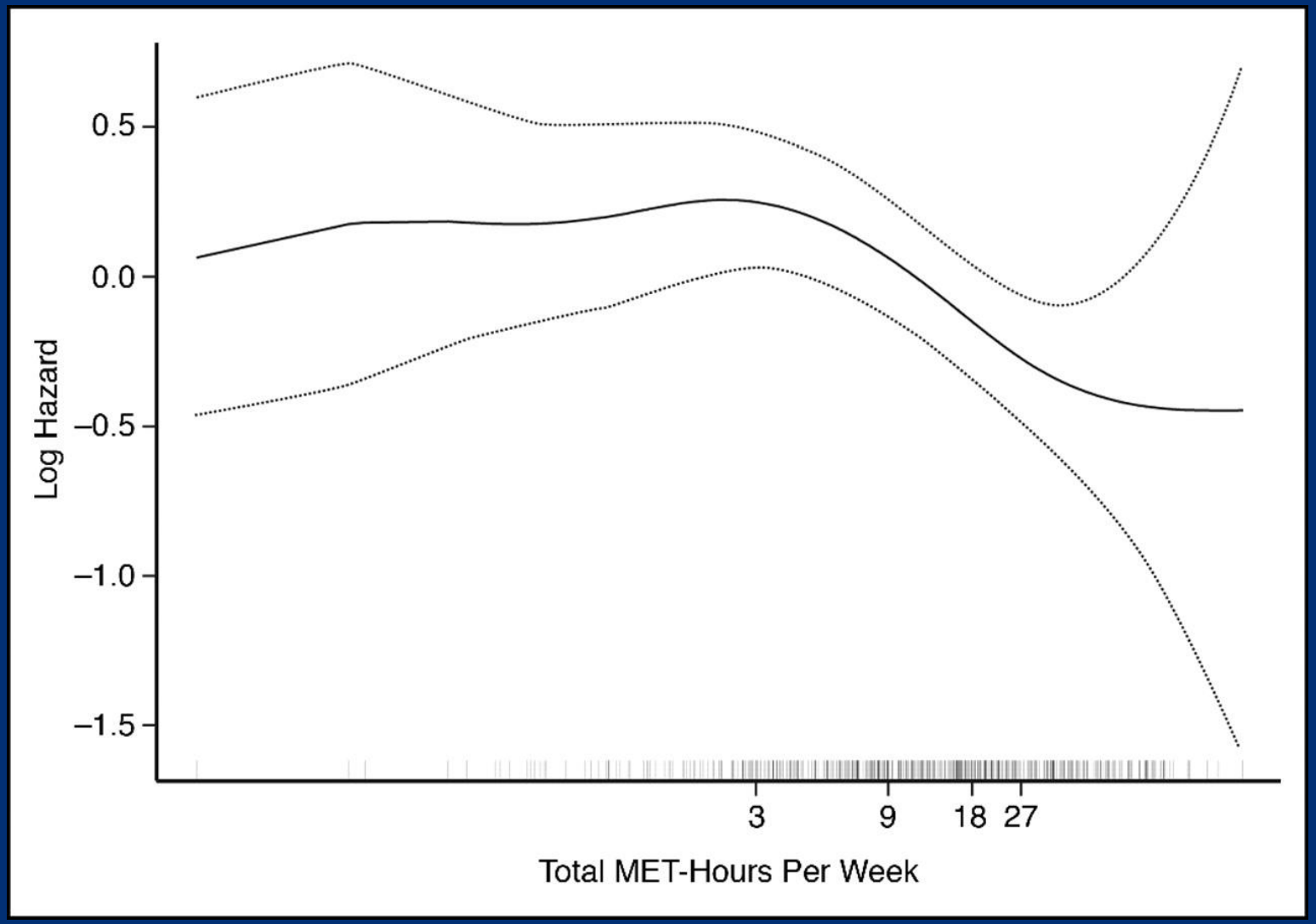
	N	Events	
FU/LV	629	171	*P* (stratified) = .74 (1-sided)
CPT-11/FU/LV	635	181	

89803 and Exercise: Disease-Free Survival in Stage III Colon Cancer Survivors



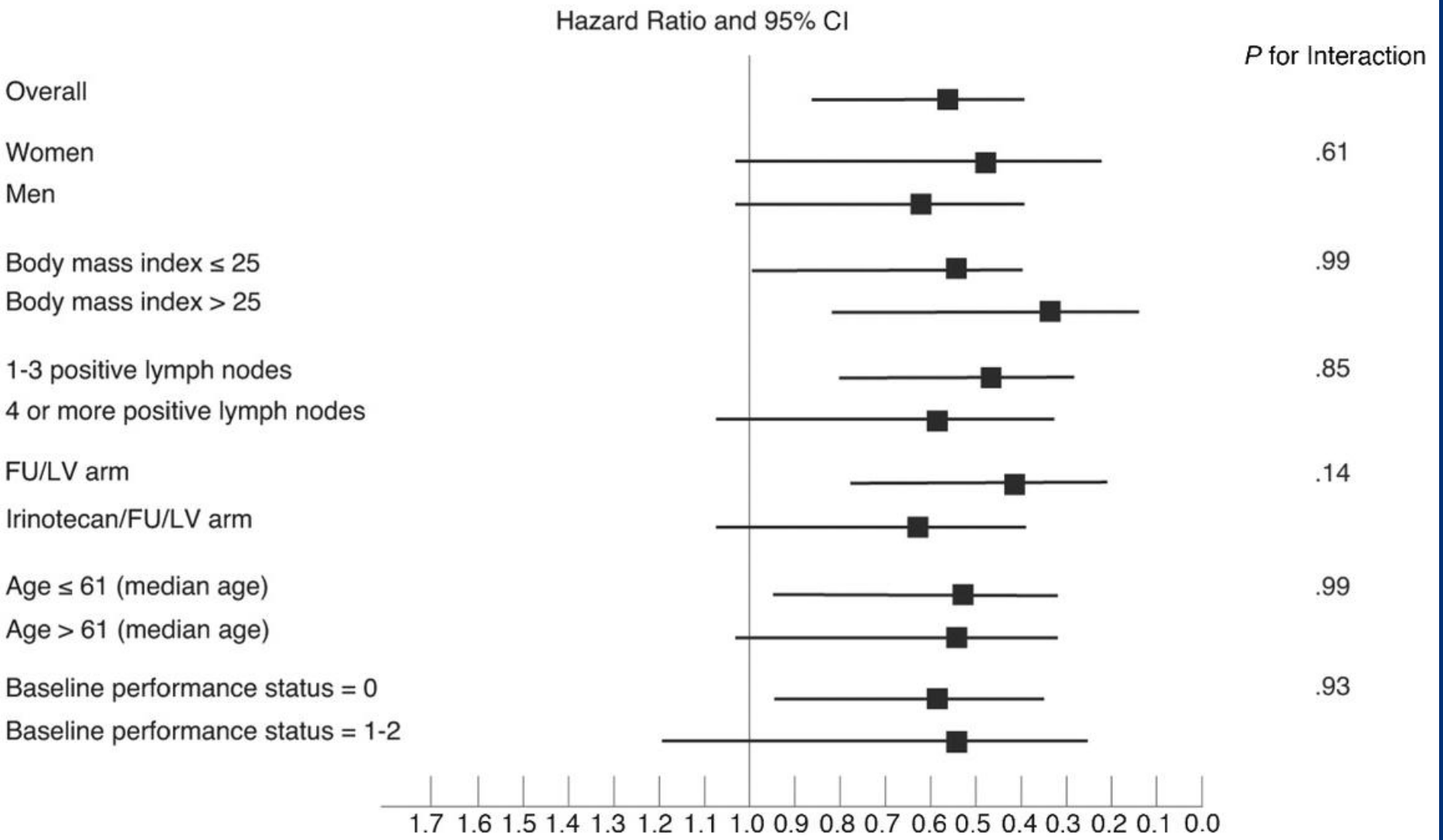
Meyerhardt, J. A. et al. J Clin Oncol; 24:3535-3541 2006

89803 and Exercise: Disease Free Survival



Meyerhardt, J. A. et al. J Clin Oncol; 24:3535-3541 2006

89803 and Exercise: Stratification



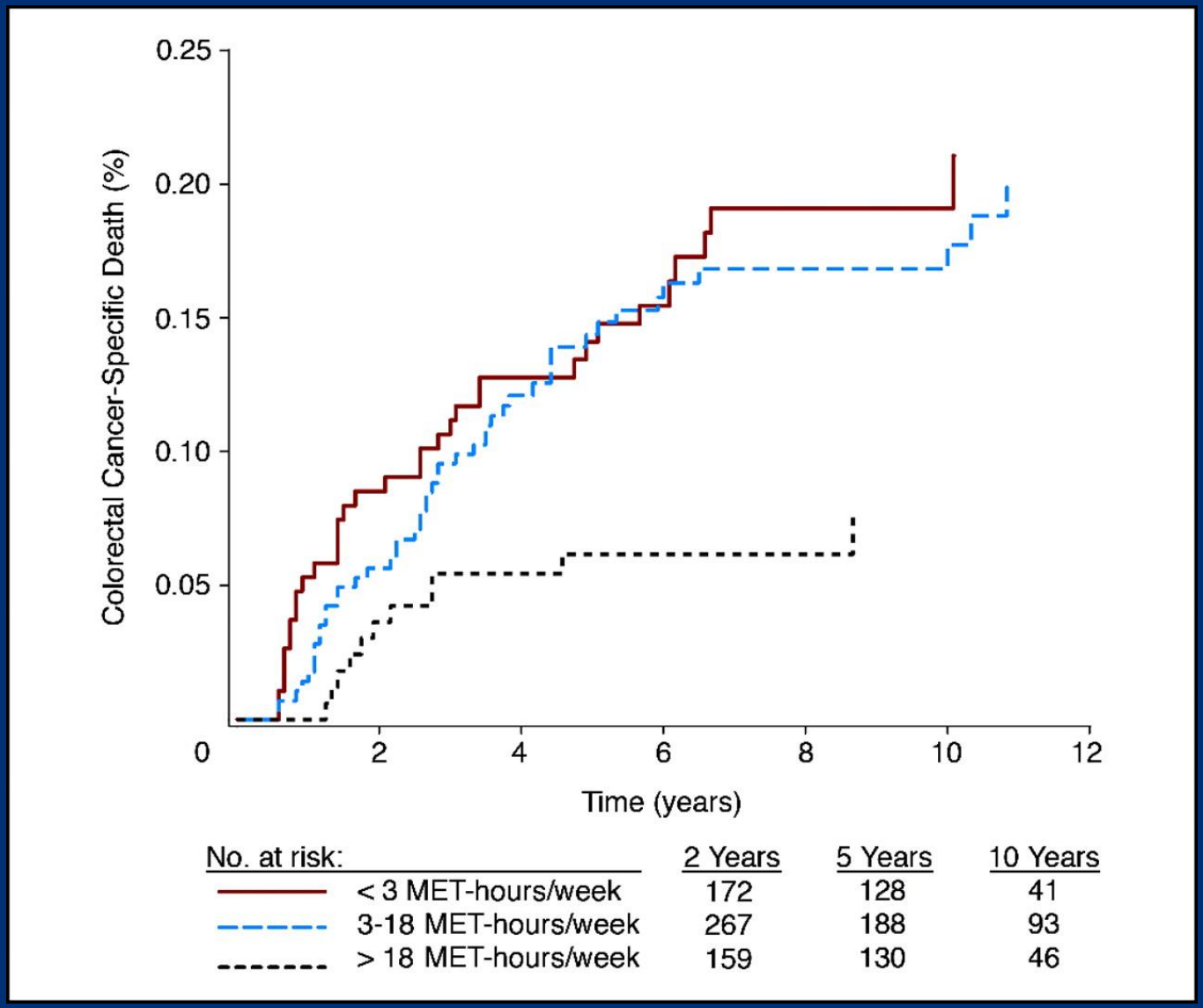
Meyerhardt, J. A. et al. J Clin Oncol; 24:3535-3541 2006

Statistical Considerations

- Reverse causality
  - Is the exposure changing outcomes or the outcome changing exposure
  - Restrict to events at least 90 days from exposure
  - Sensitivity analyses to extend restriction to 6 months and 12 months

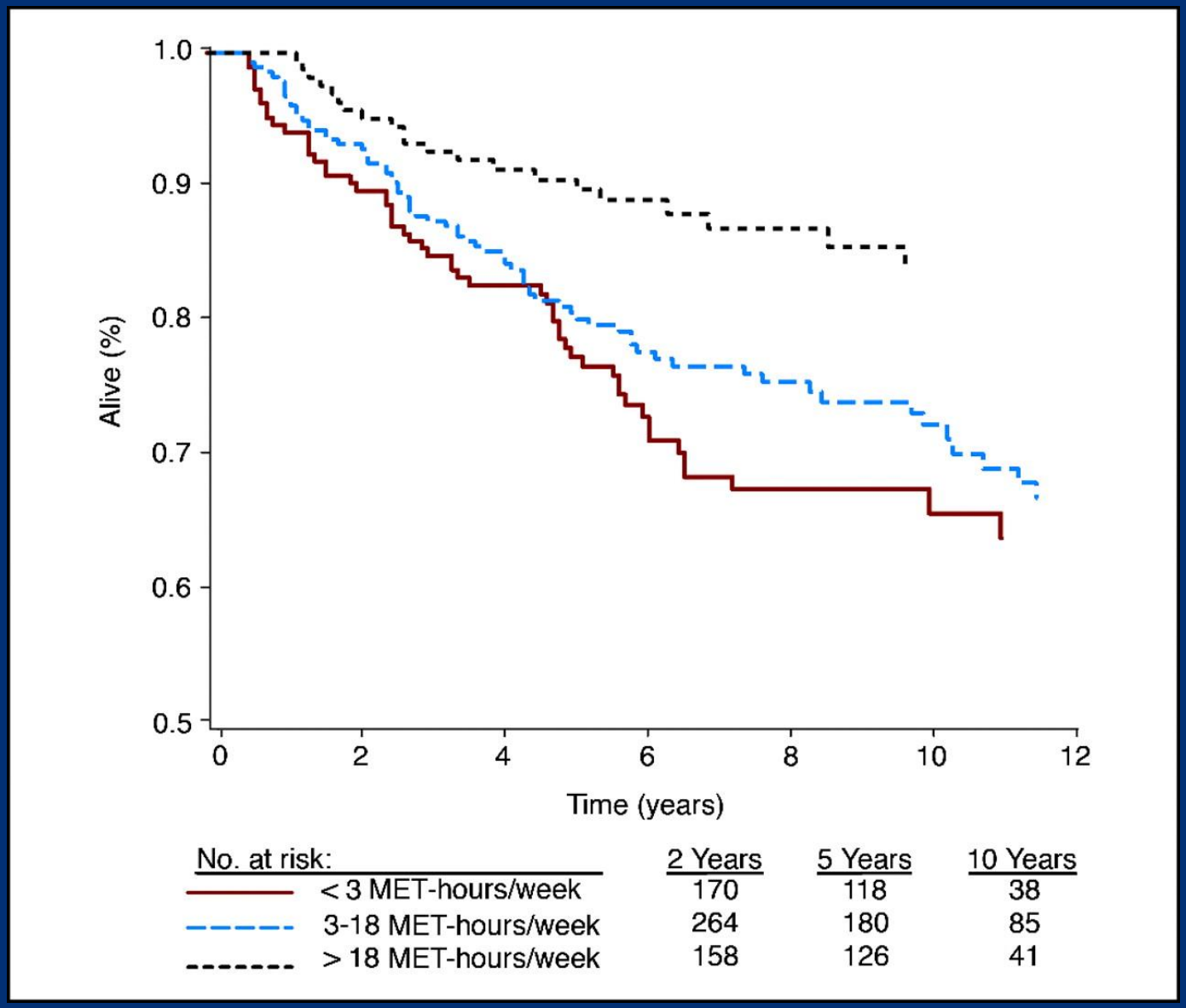
- Recall bias
  - The clock starts at time of questionnaire completion – all events are prospective beyond the exposure data
  - Limits generalizability – data speak to those that get to point of questionnaire

NHS and Post-diagnosis Physical Activity



Meyerhardt, J. A. et al. J Clin Oncol; 24:3527-3534 2006

NHS and Post-diagnosis Physical Activity



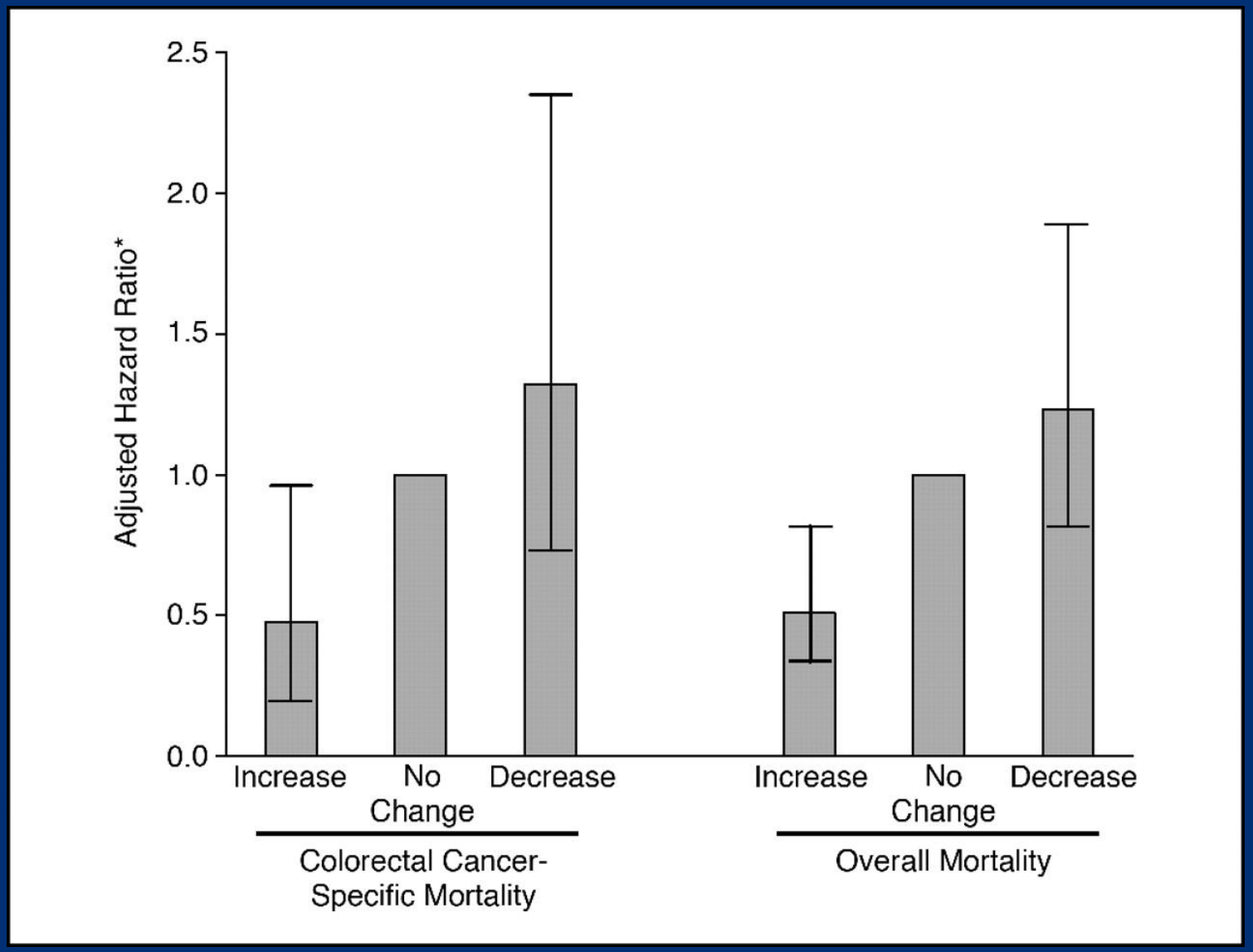
Meyerhardt, J. A. et al. J Clin Oncol; 24:3527-3534 2006

NHS and Pre-diagnosis Physical Activity

Prediagnosis Activity (MET-hours per week; n = 573)	Colorectal Cancer–Specific Mortality					
			Unadjusted		Adjusted*	
	No. of Events	No. of Patients at Risk	Hazard Ratio	95% CI	Hazard Ratio	95% CI
< 3	22	142	Referent		Referent	
3-8.9	22	152	0.92	0.51 to 1.65	0.83	0.45 to 1.53
9-17.9	19	118	1.02	0.55 to 1.88	1.05	0.56 to 1.99
≥ 18	17	161	0.70	0.37 to 1.31	0.86	0.44 to 1.67
P for trend			.26		.81	

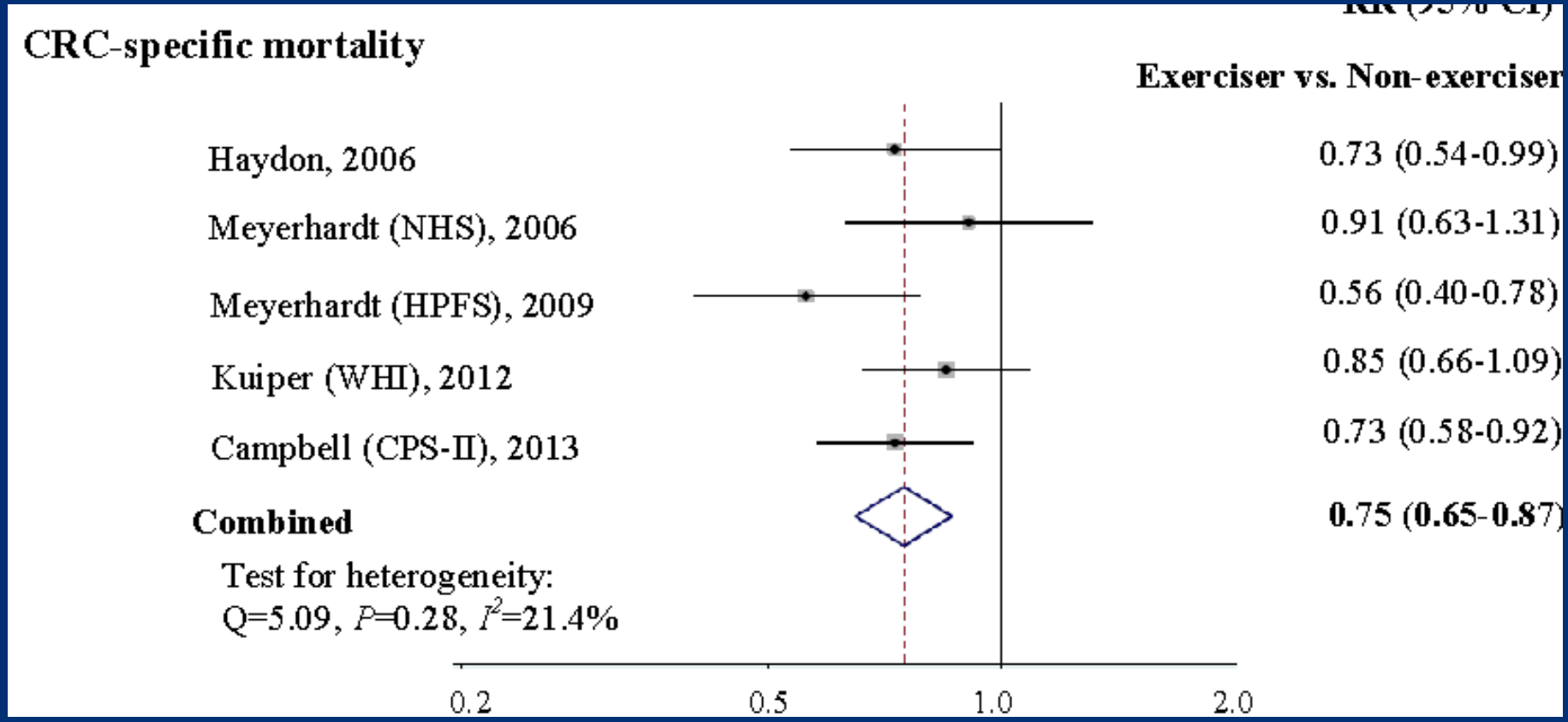
Meyerhardt, J. A. et al. J Clin Oncol; 24:3527-3534 2006

NHS and Change in Physical Activity



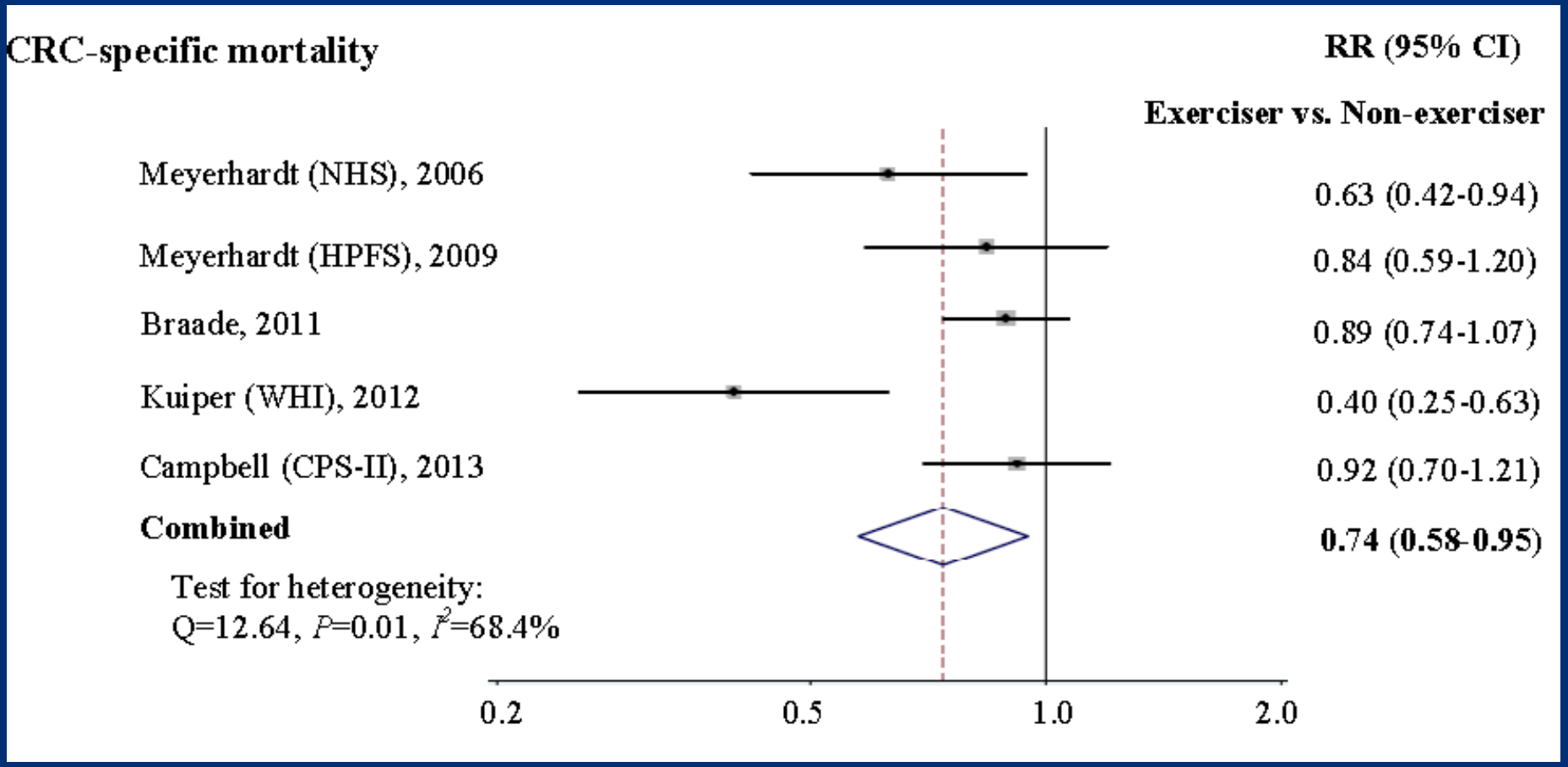
Meyerhardt, J. A. et al. J Clin Oncol; 24:3527-3534 2006

Meta-Analysis of Pre-Diagnosis Physical Activity and Colorectal Cancer Outcomes



Je, Jeon, et al Int J Cancer 2014

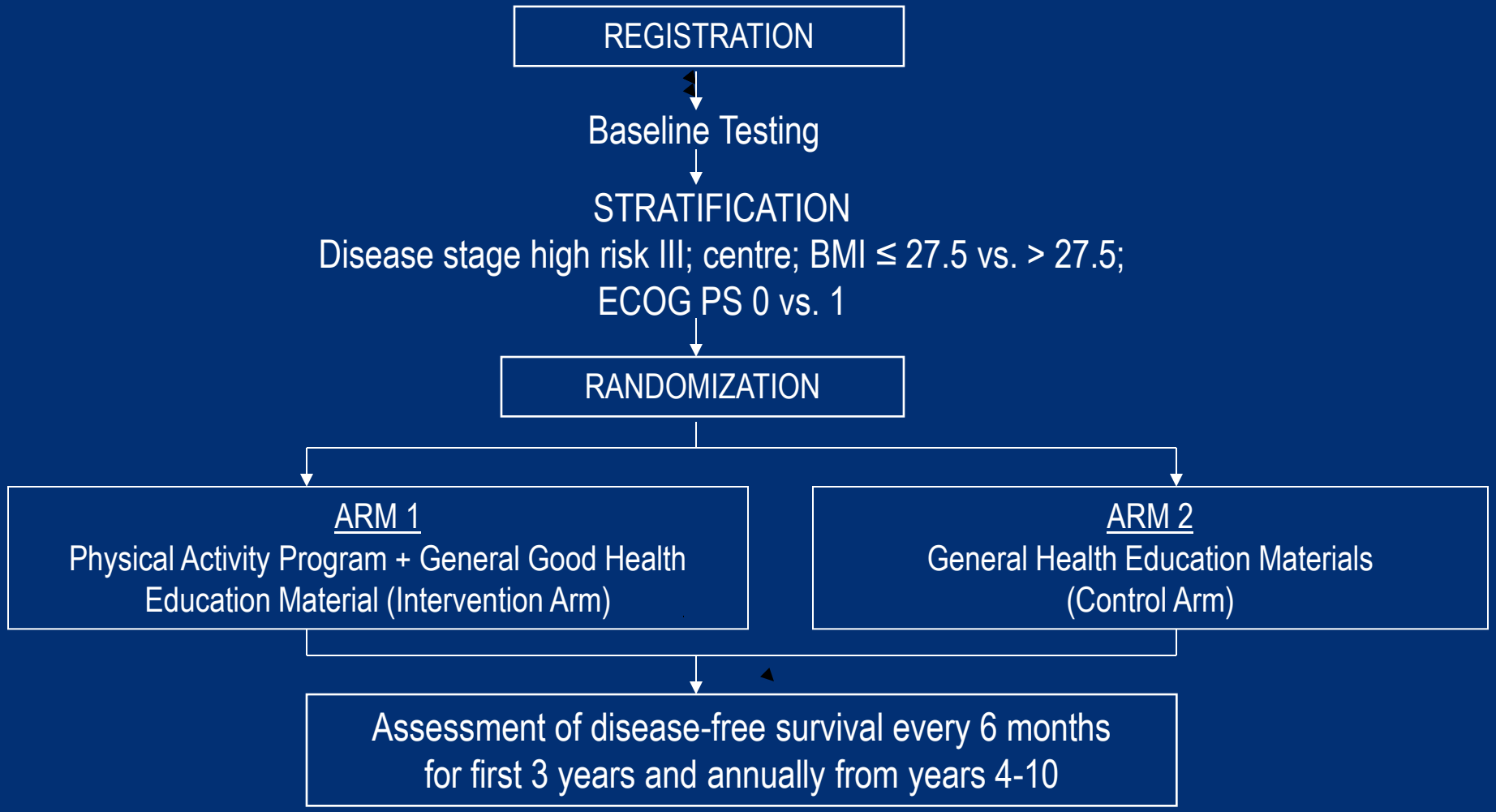
Meta-Analysis of Post-Diagnosis Physical Activity and Colorectal Cancer Outcomes



Je, Jeon, et al Int J Cancer 2014

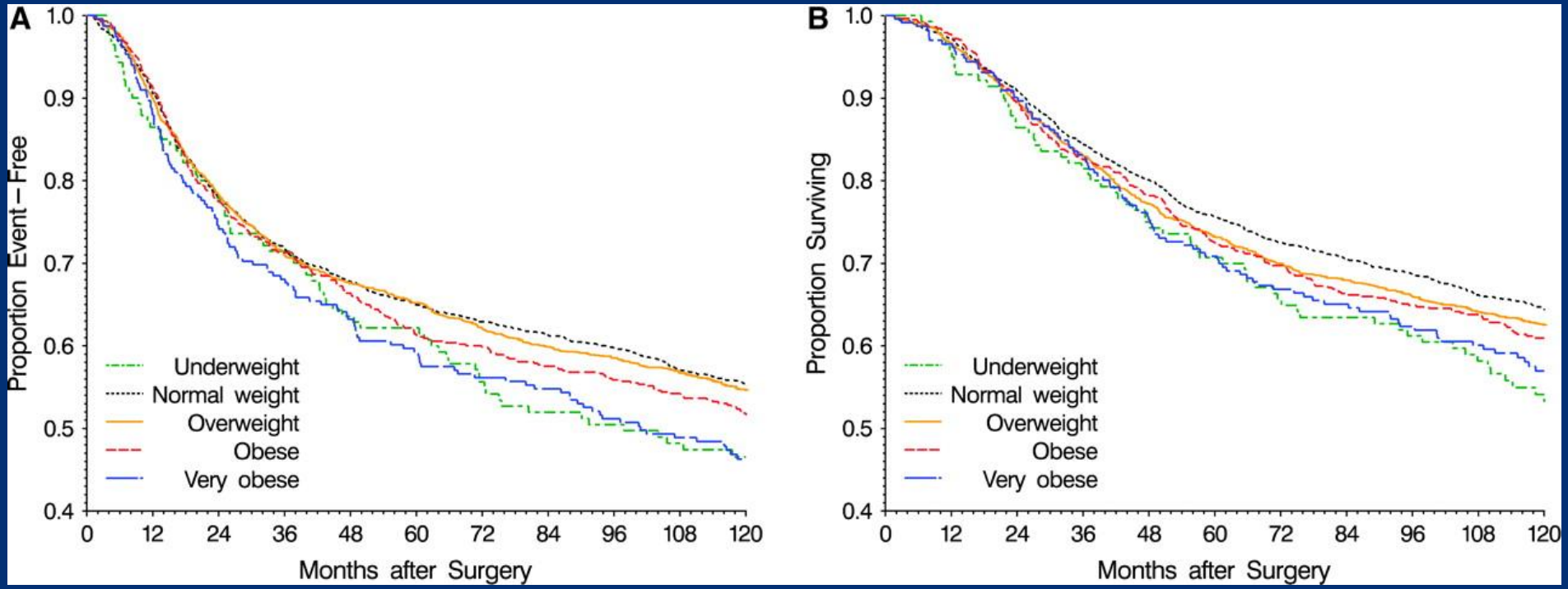
CHALLENGE: Colon Health and Life-Long Exercise Change trial

High risk Stage II or stage III colon cancer - completed adjuvant chemotherapy within 2-6 months



Courneya Curr Oncol.2008 Dec;15(6):271-8.

NSABP and Body Mass Index



Disease-free and overall survival by body mass index (BMI) category in 4288 patients from National Surgical Adjuvant Breast and Bowel Project randomized clinical trials for Dukes B and C colon cancer

Dignam, J. J. et al. J. Natl. Cancer Inst. 2006 98:1647-1654

Body Mass Index in Colon Cancer Patients over Past Decade

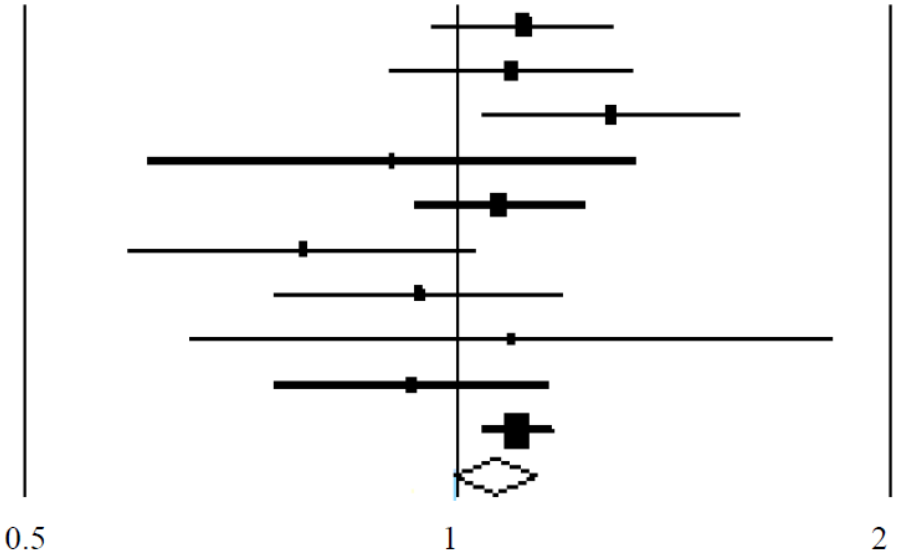
	< 21	21-24.9	25-29.9	30-34.9	≥ 35
INT-0089 (1988-92)	14 %	34 %	34 %	13 %	5 %
89803 (1999-2001)	8 %	26 %	36 %	20 %	10 %
% change in a decade	- 43%	- 24%	+ 6%	+ 54%	+ 100%

Body Mass Index and Stage I-III Colorectal Cancer

All-cause mortality: Obesity vs. Normal weight

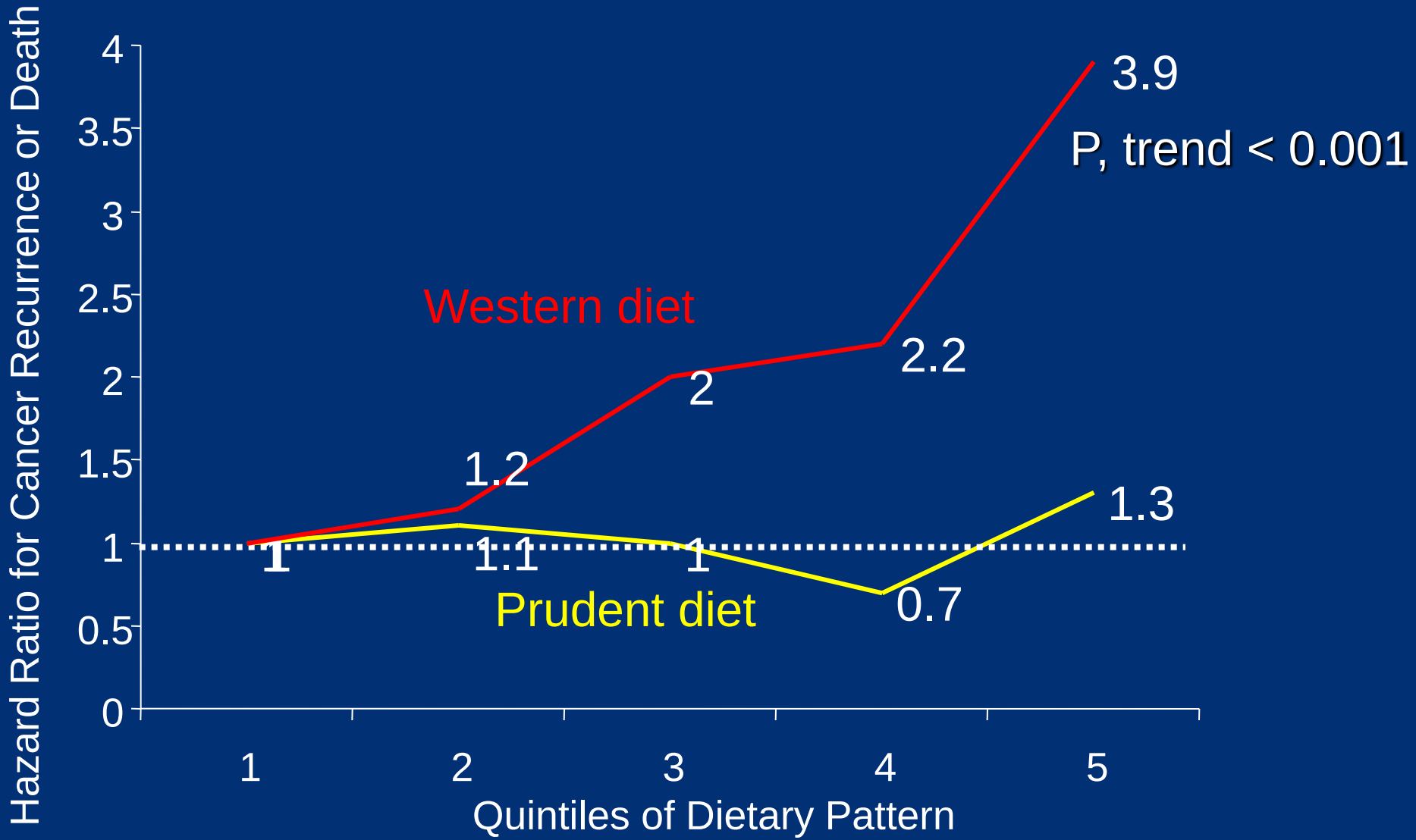
Study name	Risk ratio	Lower limit	Upper limit
Meyerhardt, 2003	1.11	0.96	1.29
Meyerhardt, 2004	1.09	0.90	1.33
Dignam, 2006	1.28	1.04	1.57
Meyerhardt,2008	0.90	0.61	1.33
Sinicrope, 2010	1.07	0.93	1.23
Baade, 2011	0.78	0.59	1.03
Chin, 2012	0.94	0.74	1.19
Kuiper, 2012	1.09	0.65	1.83
Campbell, 2013	0.93	0.74	1.16
Sinicrope, 2013	1.10	1.04	1.17
	1.08	**1.03**	**1.13**

Test for heterogeneity:
($Q=12.29$, $P=0.20$, $I^2=26.77\%$)



Lee, Meyerhardt, Giovannucci, Jeon, under review

CALGB 89803: DFS By Dietary Pattern



Meyerhardt, J. et al. JAMA 2007298(7):754-764.

CALGB 89803: Dietary Pattern

	Mean (SD) Intake by Quintile				
	1 (n = 201)	2 (n = 202)	3 (n = 202)	4 (n = 202)	5 (n = 202)
Red meat, servings/wk	2.3 (1.5)	3.1 (1.8)	3.7 (2.1)	4.7 (2.5)	6.1 (3.0)
Processed meats, servings/wk	1.8 (1.7)	2.3 (1.8)	3.0 (2.6)	4.2 (2.9)	5.6 (4.1)
Refined grains, servings/d	2.0 (1.3)	2.8 (1.6)	3.5 (1.8)	4.2 (2.2)	5.8 (2.7)
Dessert, servings/d	0.7 (0.6)	1.1 (0.8)	1.3 (0.9)	1.6 (1.0)	2.5 (1.6)
Total fat, g/d	69 (15)	72 (18)	73 (13)	77 (15)	80 (13)

[a] Values are rounded to nearest 0.5. The median total servings of poultry and fish were similar across each quintile (approximately 2 servings per week of poultry and 1.5 servings per week of fish).

Meyerhardt, J. et al. JAMA 2007;298:2263-a.

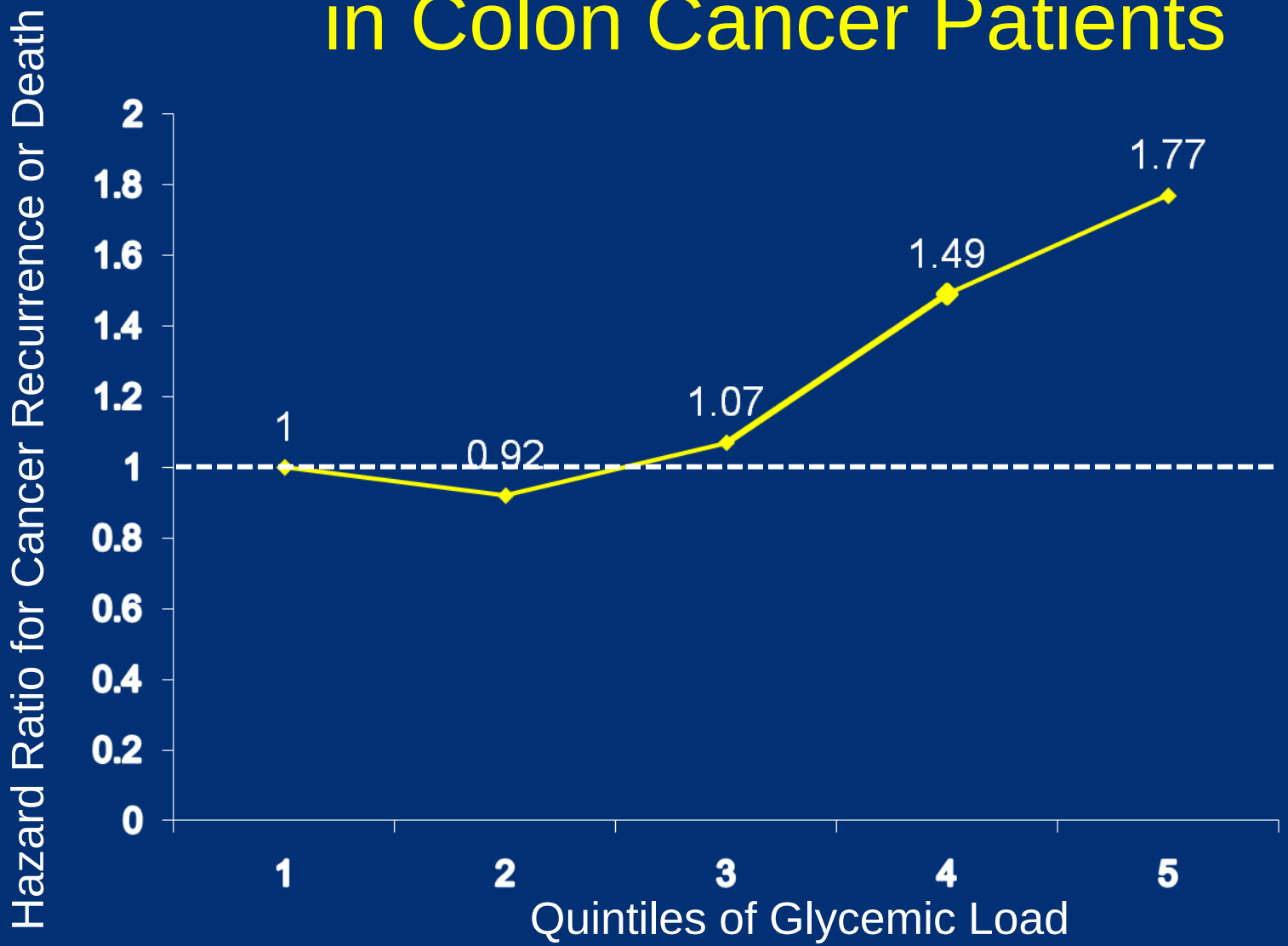
Dietary Patterns

- Study of 529 colorectal cancer patients in Newfoundland
- Pre-diagnosis diet

Processed meat pattern	DFS – CRC	Colon	Rectal
Q1 38/132	1.00	1.00	1.00
Q2 45/132	1.51 (0.95 to 2.41)	1.69 (0.97 to 2.96)	0.91 (0.39 to 2.14)
Q3 58/132	1.56 (0.97 to 2.49)	1.37 (0.76 to 2.48)	1.72 (0.85 to 3.95)
Q4 57/132	1.82 (1.07 to 3.09)	2.29 (1.19 to 4.40)	0.97 (0.38 to 2.45)
p Value for trend ‡	0.09	0.12	0.91
Prudent vegetable pattern			
Q1 46/132	1.00	1.00	1.00
Q2 54/132	1.21 (0.79 to 1.85)	1.35 (0.78 to 2.34)	0.97 (0.47 to 2.01)
Q3 50/133	1.18 (0.75 to 1.86)	1.16 (0.63 to 2.13)	1.30 (0.65 to 2.60)
Q4 48/131	1.12 (0.69 to 1.84)	1.02 (0.52 to 1.99)	1.28 (0.58 to 2.83)
p Value for trend‡	0.62	0.83	0.19

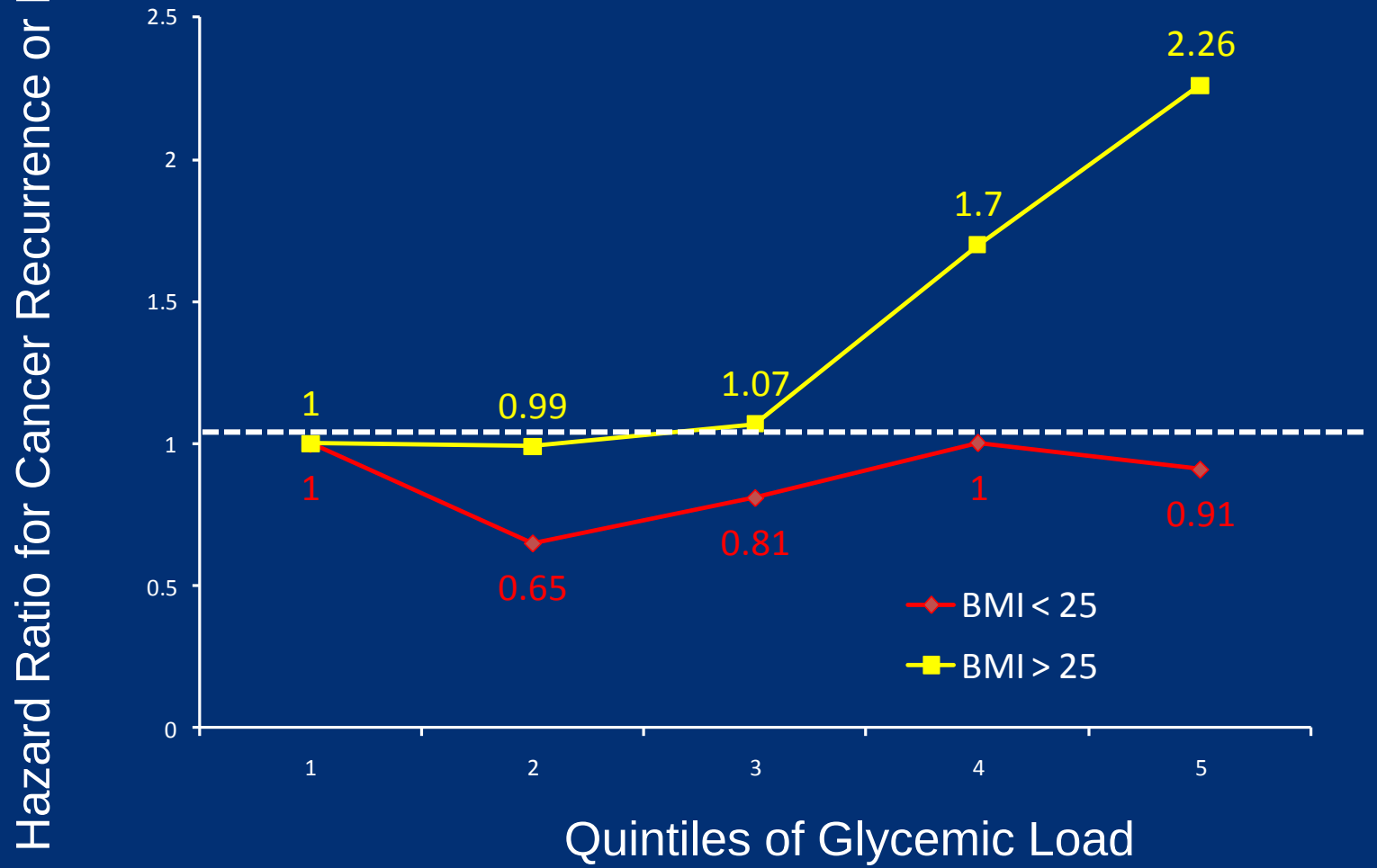
Zhu et al BMJ Open 2013 Feb 7;3(2).

Glycemic Load in Colon Cancer Patients



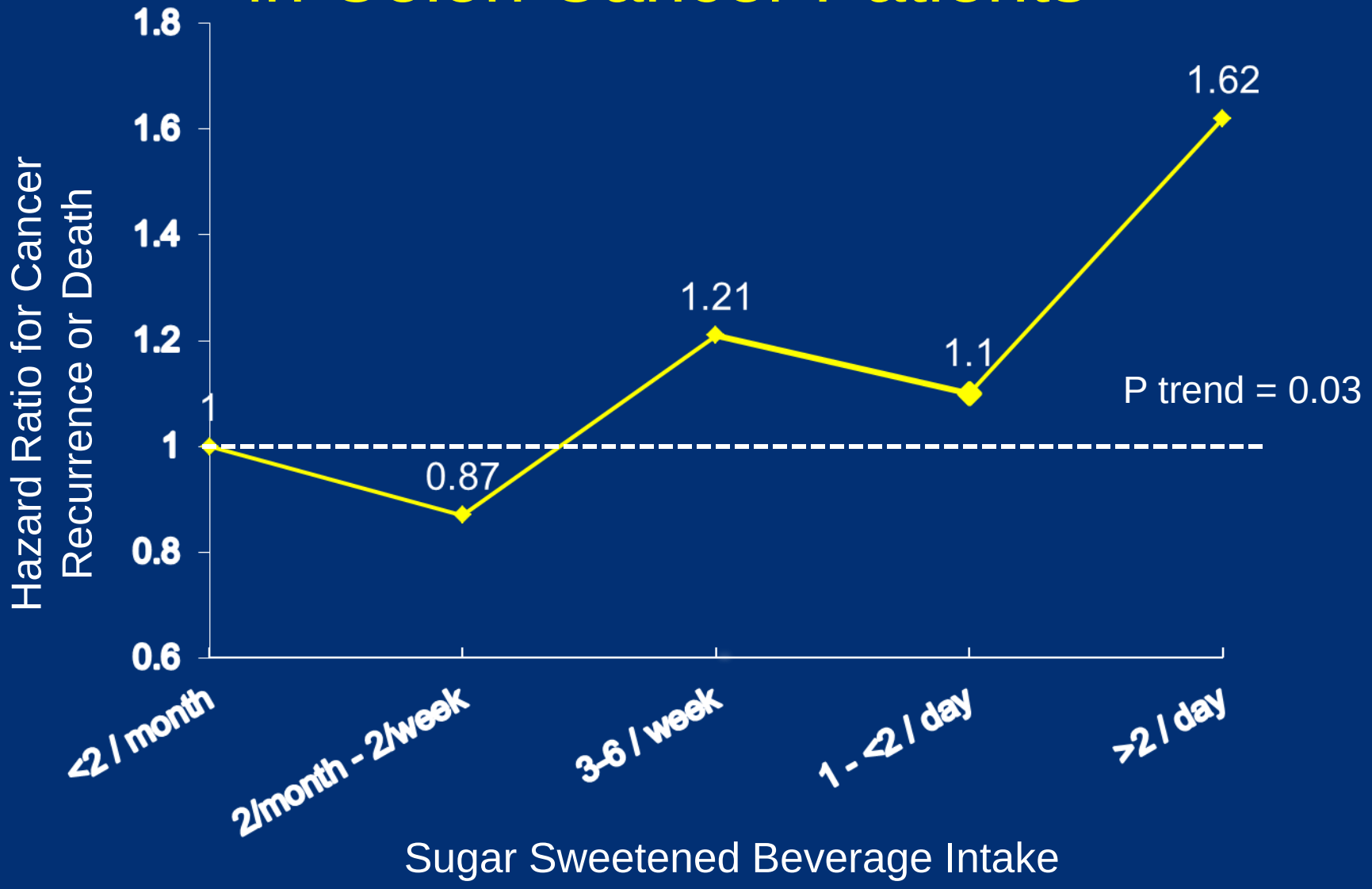
Meyerhardt, J. et al JNCI 2012

Glycemic Load in Colon Cancer Patients



Meyerhardt, J. et al JNCI 2012

Sugar Sweetened Beverage in Colon Cancer Patients



Fuchs MA et al, PLOS One 2014

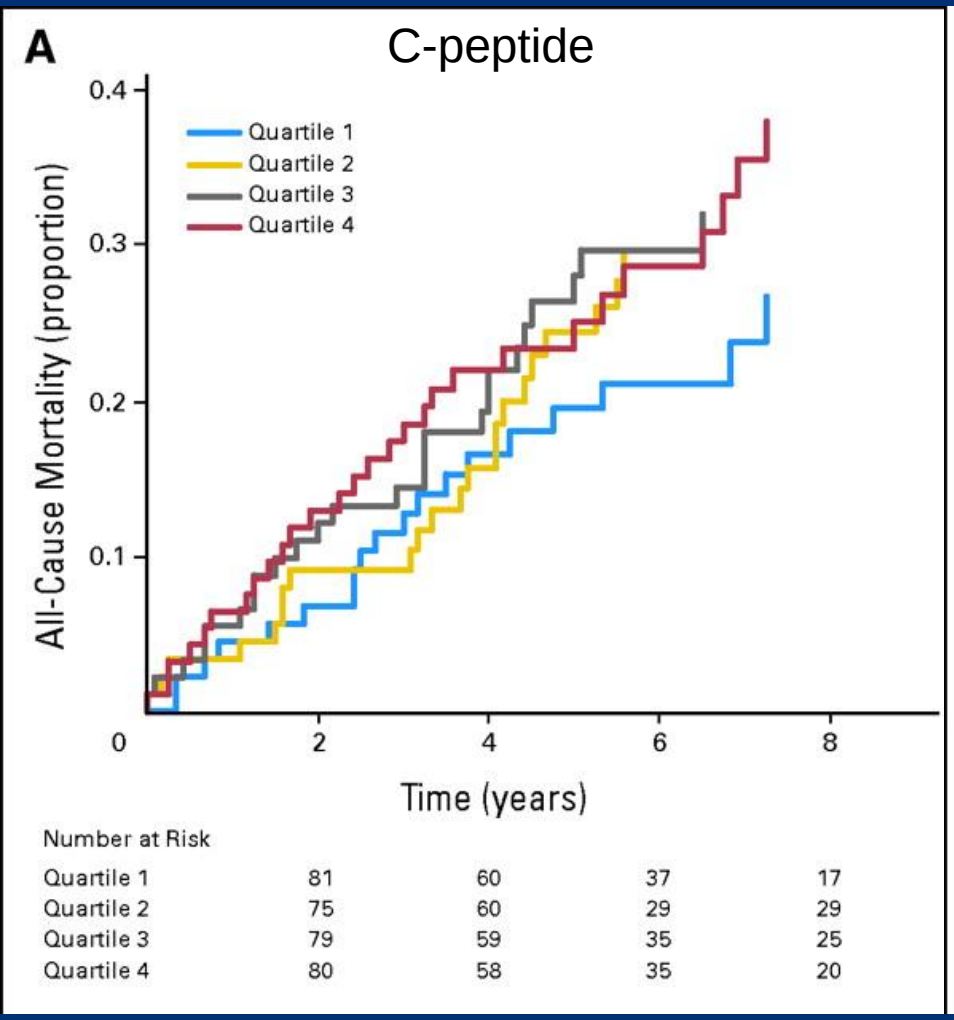
Molecular Markers of Hyperinsulinemia and Colorectal Cancer Outcomes

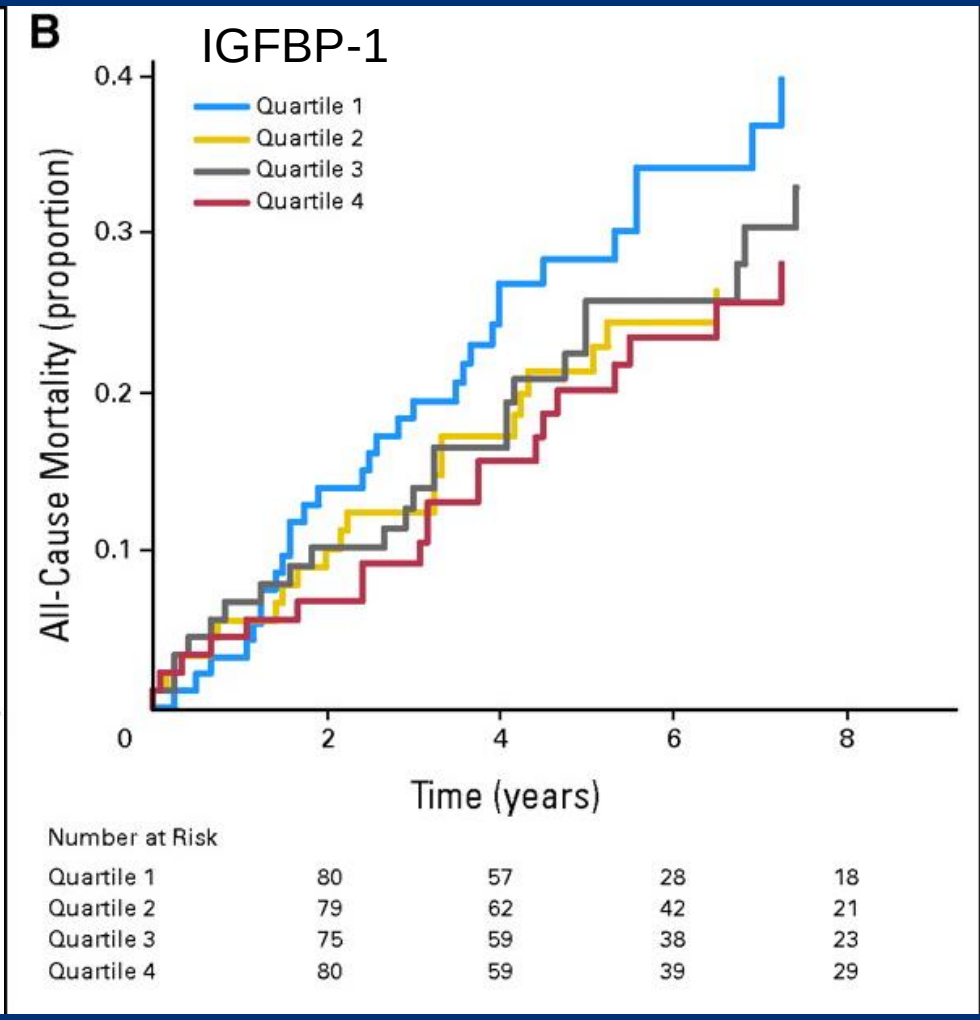
Insulin-related Growth Factors and Outcomes

- Nested case-control of 373 patients nonmetastatic colorectal cancer 1991-2004
- Prediagnosis circulating C-peptide, insulin-like growth factor-I (IGF-I), IGFBP-1, and IGFBP-3
- Colorectal cancer-specific mortality and overall mortality

Wolpin B M et al. JCO 2009;27:176-185

Insulin-related Growth Factors and Outcomes





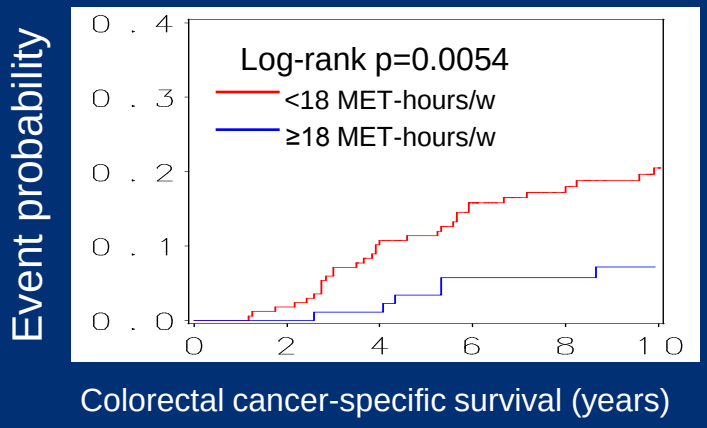
Wolpin B M et al. JCO 2009;27:176-185

Association between Physical Activity and Outcomes by CTNNB1 (β catenin) Status

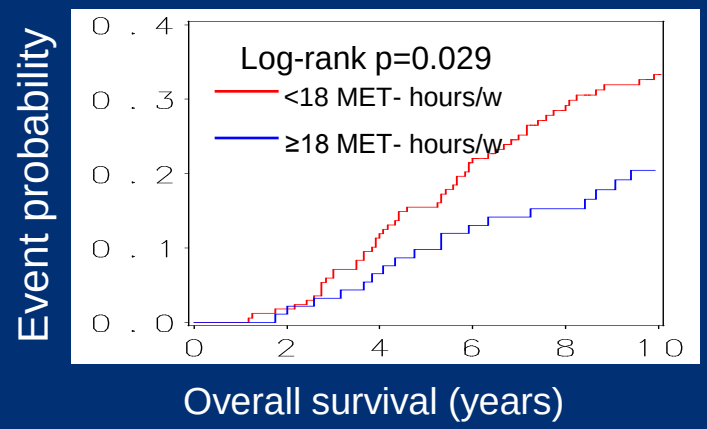
WNT-CTNNB1 signaling → adipogenesis, obesity, and metabolic diseases.

A

All stage I-III cases
with nuclear CTNNB1(-)

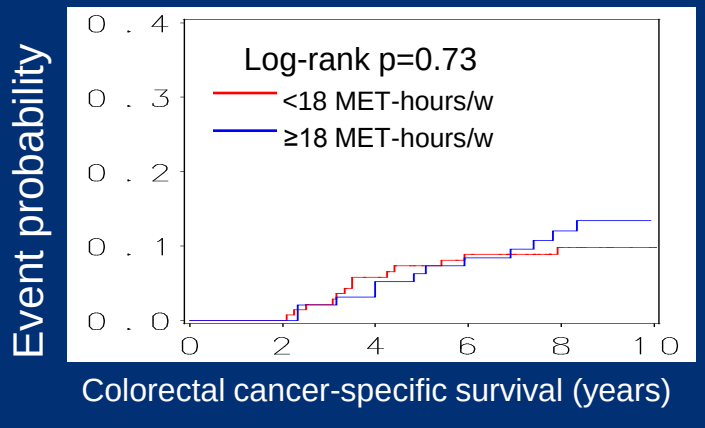


B

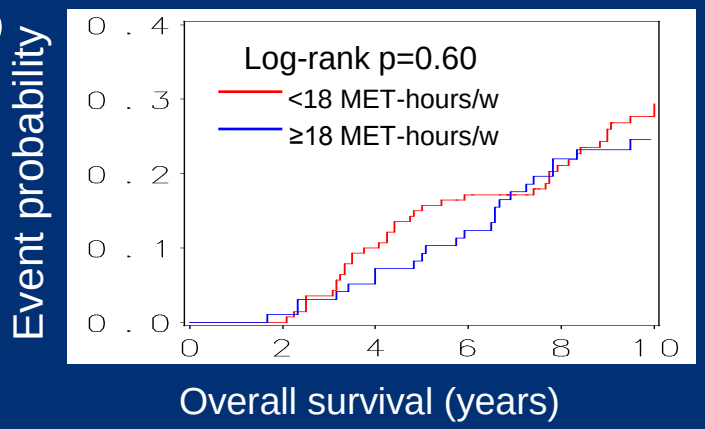


C

All stage I-III cases
with nuclear CTNNB1(+)



D



Inactive WNT-CTNNB1 signaling pathway associated with energy balance

Active WNT-CTNNB1 signaling pathway independent of energy balance

Morikawa et al JAMA 2011

Outline

- Diet / Exercise and CRC: Primary Prevention
  - What do we know
  - What don't we know
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Challenges and Next Steps

- Will change in behaviors after diagnosis impact outcomes?
- Are observational data enough? What if we do a randomized trial of better diet or increased physical activity and result is negative – what's the message?
- Survivorship raises issues of addressing other diseases down the road
- Better biomarkers to study effects – decrease sample size?
- Single exposure v multiple exposure intervention