BMI and Mortality: Do conflicting results alter interpretation of BMI and cancer outcomes research?

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Outline/Purpose

- Overview of BMI and cancer outcomes
  - Incidence and Mortality in Cancer Patients
- Overview results in two papers on BMI and all cause mortality that were asking very different questions and used different methods
  - Flegal et al, JAMA 2013
  - Berrington et al NEJM 2010
- Discuss how question being addressed and methods influence interpretation and implications of results
- Global Burden of Disease 2010 - increased contribution of morbidity to disease burden
- If time – highlights of research on physical activity and mortality

Obesity and Cancer Risk
Bulk of Evidence is on Cancer Incidence

Type of cancer	Relative risk[a] with BMI of 25–30 kg/m²	Relative risk[a] with BMI of ≥30 kg/m²
Colorectal (men)	1.5	2.0
Colorectal (women)	1.2	1.5
Female breast (post-menopausal)	1.3	1.5
Endometrial	2.0	3.5
Kidney (renal cell)	1.5	2.5
Esophageal (adeno-carcinoma)	2.0	3.0
Pancreatic	1.3	1.7
Liver	ND	1.5–4.0
Gallbladder	1.5	2.0
Gastric cardia (adeno-carcinoma)	1.5	2.0

Fair AM, Montgomery K. Methods Mol Biol. 2009;472:57-88.

Cancer Incidence (I) and Mortality (M) Rates Between Bariatric Surgical and Nonsurgical Obese Groups

Men

Author	N	Surgical Obese Cancer Rate	Nonsurgical Obese Cancer Rate	Reduction in Cancer RR
Adams, 2009	942	I = 4.14% M = 1.06%	I = 4.14% M = 1.53%	I = No change M = 30%
McCawley, 2009	Effect on Cancer Outcomes Not Reported			
Sjostrom, 2009	590	I = 6.4%	I = 6.6%	I = 3%

Women

Author	N	Surgical Obese Cancer Rate	Nonsurgical Obese Cancer Rate	Reduction in Cancer RR
Adams, 2009	5654	I = 3.8% M = 0.55%	I = 5.23% M = 1.05%	I = 27.3% ($p<0.05$) M = 47.6% ($p<0.05$)
McCawley, 2009	1482	I = 3.6%	I = 5.8%	I = 38% ($p<0.05$)
Sjostrom, 2009	1447	I = 5.56%	I = 8.98%	I = 38% ($p<0.05$)

Ashrafian et al, Cancer 2011

Obesity and Survival in Breast Cancer Patients

Meta-Analysis

43 studies published 1963-2005 • comparison of obese vs. non-obese subjects

Subgroup	No. of estimates	Pooled HR (95% CI)		P-value
Survival measure				
All-cause	36	**1.33 (1.21-1.47)**		0.91
Breast cancer specific	19	**1.33 (1.19-1.50)**		
Obesity measure				
BMI	55	**1.33 (1.23-1.44)**		0.95
WHR	6	**1.31 (1.14-1.50)**		
Study design				
Observational cohort	48	**1.36 (1.23-1.49)**		0.53
Treatment cohort	7	**1.22 (1.14-1.31)**		
Menopausal status				
Pre-menopausal	16	**1.47 (1.19-1.83)**		0.25
Post-menopausal	12	**1.22 (0.95-1.57)**		
Both	36	**1.33 (1.23-1.43)**		
Year of diagnosis				
Pre-1995	30	**1.31 (1.16-1.46)**		0.17
Post-1995	11	**1.49 (1.31-1.68)**		

Protani M et al. BCRT 2010: 123:627-635

BMI and Quality of Dosing for Breast Cancer Adjuvant Chemotherapy

Table 4. Multivariate Analysis of Initial Chemotherapy Dose < 85% of Standard (N = 737)

Characteristic	Odds Ratio	95% CI		*P*
Age, years	1.01	0.98 to 1.05	.49	
CCI ≥ 1	1.16	0.60 to 2.25	.67	
BMI				
Normal	1.00			
Overweight	1.18	0.74 to 1.87	.65	**.0004**
Obese	**2.47**	**1.36 to 4.51**	**.003**	
Severely obese	**4.04**	**1.46 to 11.19**	**.007**	
Median household income, $ (in thousands)	1.02	0.85 to 1.22	.81	
Education less than high school	**3.07**	**1.57 to 5.99**	**.001**	
Non-white race	1.30	0.49 to 3.47	.60	
Region				
Northeast	1.00			
Central	1.67	0.43 to 6.44	.46	**< .0001**
West coast	0.90	0.26 to 3.18	.87	
South	**5.58**	**2.20 to 14.14**	**.0003**	

Griggs JJ, et al. JCO 2007; 25:3

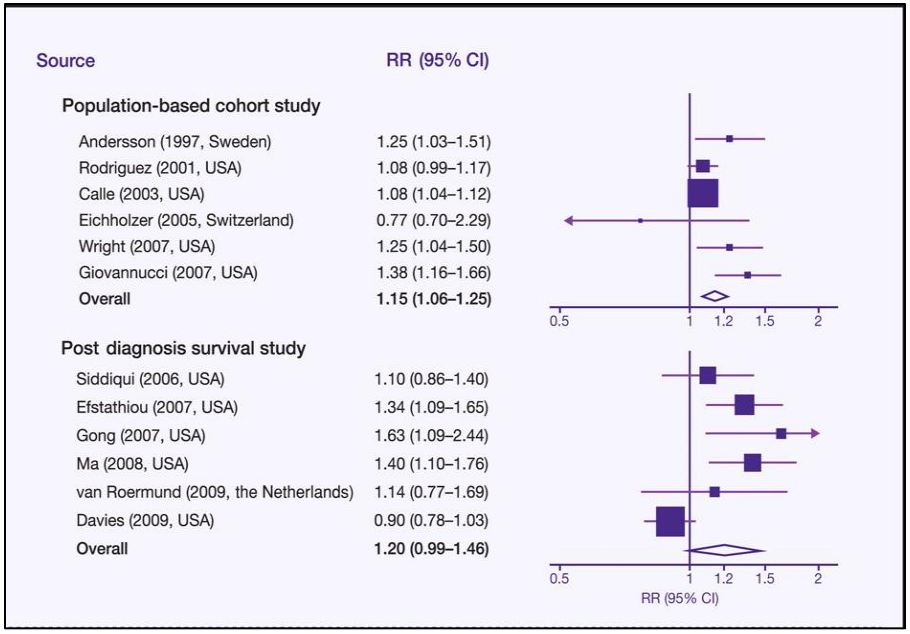
BMI and Colorectal Cancer Outcomes

Author	Stage	HR or P
Tartter 1984	Colon – B1, C1, C2 (n=279)	Recurrence: p=0.03 (weight > vs. < median)
Meyerhardt 2003	Colon – B2, B3, C (n=3759)	DFS: HR 1.11 (0.94-1.30) OS: HR 1.11 (0.96-1.29) (BMI kg/m^2 ≥ 30 vs. < 30 kg/m^2)
Meyerhardt 2004	Rectal – I, II (n=1792)	DFS: HR 1.10 (0.91-1.32) OS: HR 1.09 (0.90-1.33) Local: HR 1.31 (0.91-1.88) (BMI kg/m^2 ≥ 30 vs. < 30 kg/m^2)
Dignam 2006	Colon – B, C (n=4288)	DFS: HR 1.27 (1.05-1.53) Events: HR 1.38 (1.10-1.73) (BMI ≥ 35 kg/m^2 vs. < 30 kg/m^2)
Meyerhardt 2008	Colon – III (n=1053)	DFS: HR 1.24 (0.83-1.83) RFS: HR 1.27 (0.85-1.89) OS: HR 0.87 (0.54-1.42) (BMI ≥ 35 kg/m^2 vs. < 30 kg/m^2)

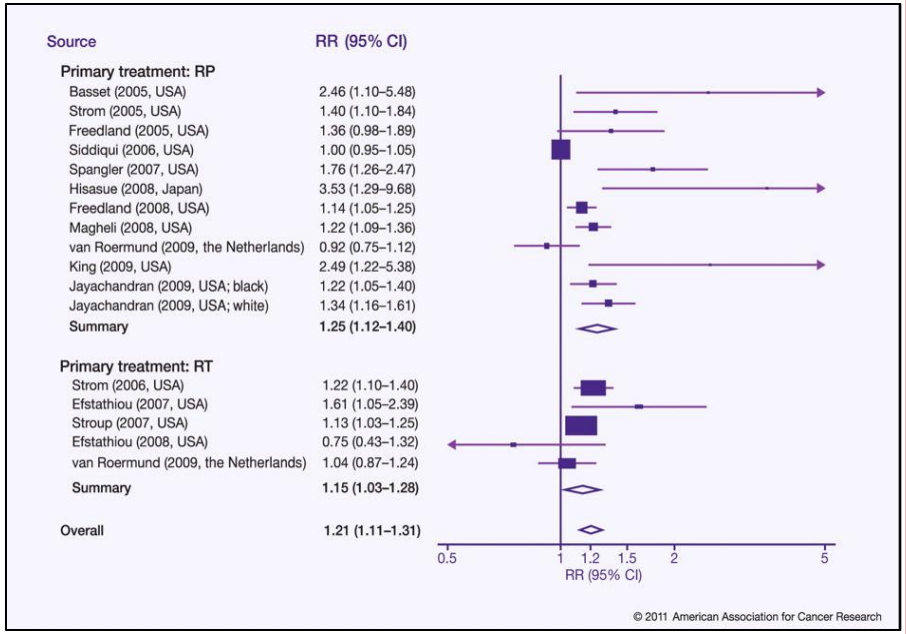
Meyerhardt JA, J Clin Oncol;2010;28:4066-4073

BMI and Prostate Cancer Specific Mortality

RRs per 5 kg/m^2 increase in BMI and prostate cancer–specific mortality



RRs per 5 kg/m^2 increase in BMI and biochemical recurrence after treatment



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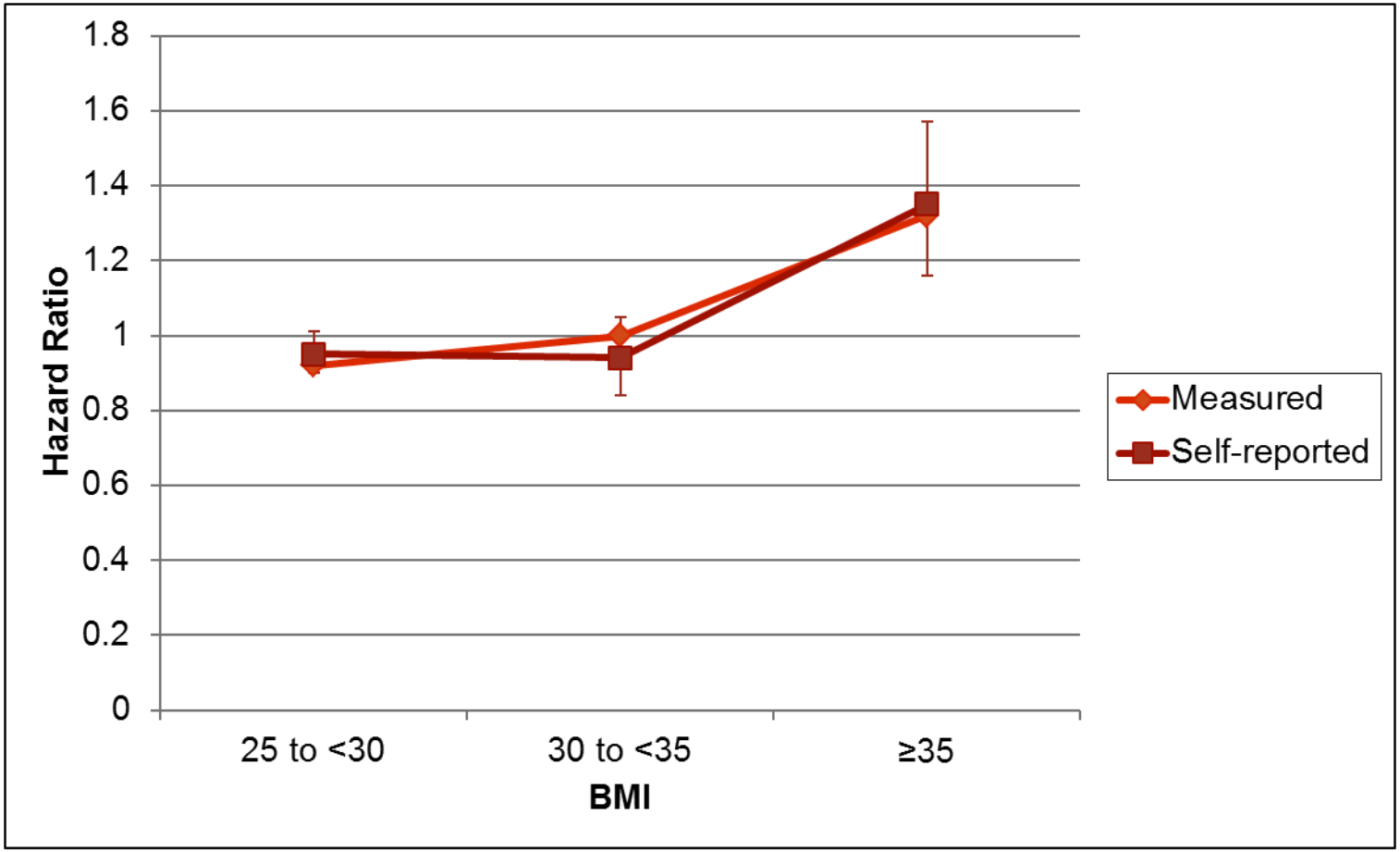
Cao Y, Ma J, Cancer Prev Res;2011;4:486-501

Two Studies
Different Questions, Methods and Results

- Flegal et al JAMA 2013: All-Cause Mortality, Overweight and Obesity
  - Research Question: How are the standard BMI categories associated with mortality in published literature?
  - Methods: Meta-analysis of 97 studies with standardized measures of overweight (25 - <30), obesity (>30), grade 1 (30-<35), grade 2,3 (>35); sample of 2.88M people with 270,000 deaths
  - Included adults of all ages, and populations covered in existing studies, with FU of 5 to 42 years
  - Conclusion: Relative to normal weight (BMI <25),
    - Overall obesity (>30), and higher grade (2,3) obesity (>35) are associated with higher all-cause mortality (21% and 34% respectively)
    - Grade 1 obesity (30-<35) is not associated
    - Overweight (25-<30) is associated with modest decreased mortality (6%)

Risk of All Cause Mortality for Overweight and Obesity Relative to Normal Weight for All Ages

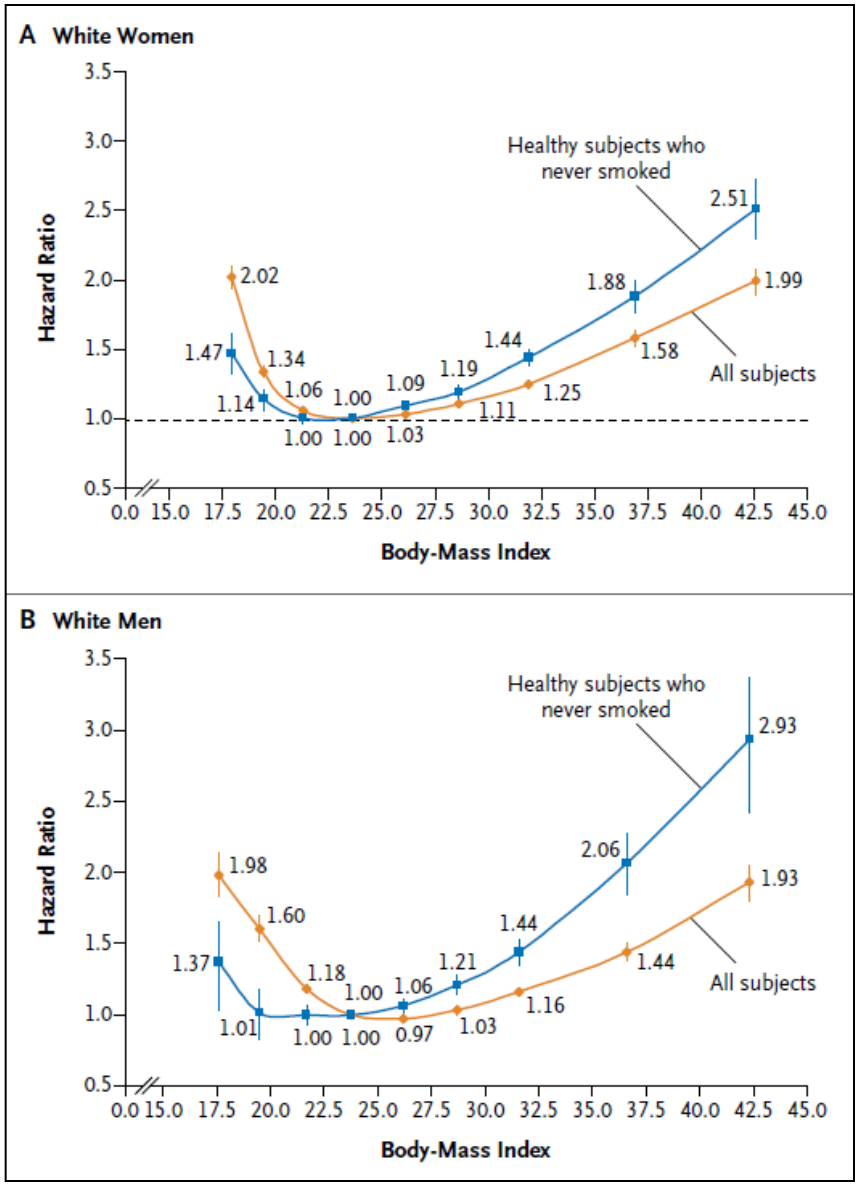


Flegal KM, et al. JAMA 2013;309:71-82

Two Studies with Different Questions, Methods and Results

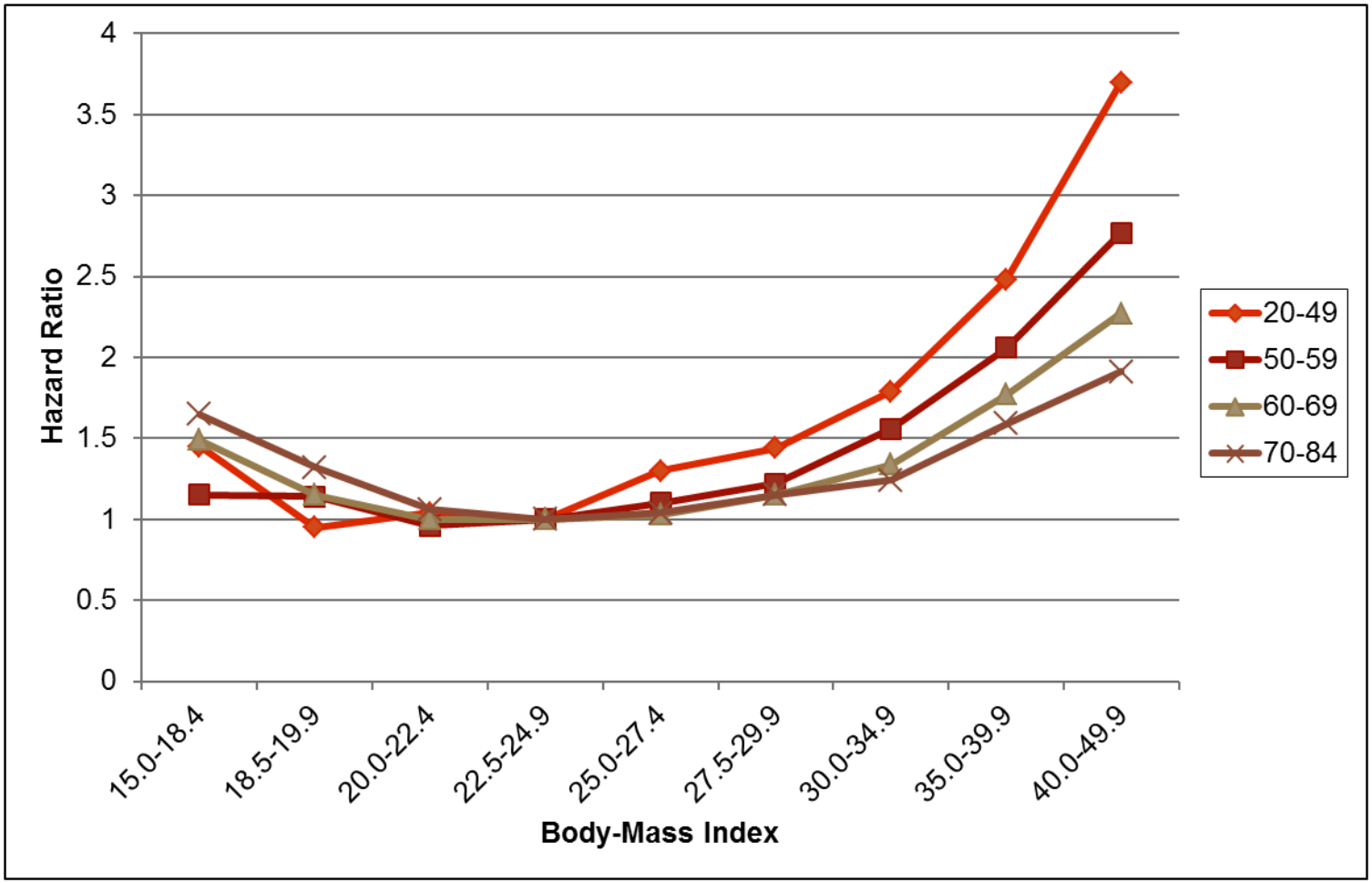
- Berrington et al, NEJM 2010: BMI and Mortality
  - Research Question: What is the independent effect of BMI on mortality in healthy non-smoking, white adults?
  - Methods: Pooled analysis of 19 studies with 1.49 M people; in examining the effect of BMI on mortality in healthy non-smokers used 560,000 health people among the 670,000 never smokers
  - Included healthy, non-smoking non-Hispanic white adults 19 to 84 years of age with BMI range of 15-49.9; studies with at least 5 yrs of FU and >1000 deaths in NHW adults, baseline year 1970
  - Conclusions:
    - In non-Hispanic white adults, overweight and obesity and underweight are associated with increased all-cause mortality.
    - All-cause mortality in healthy, non-smoking non-Hispanic white adults is lowest among the group with a BMI of 20.0-24.9

All Cause Mortality Increases with Progressively Higher and Lower BMIs



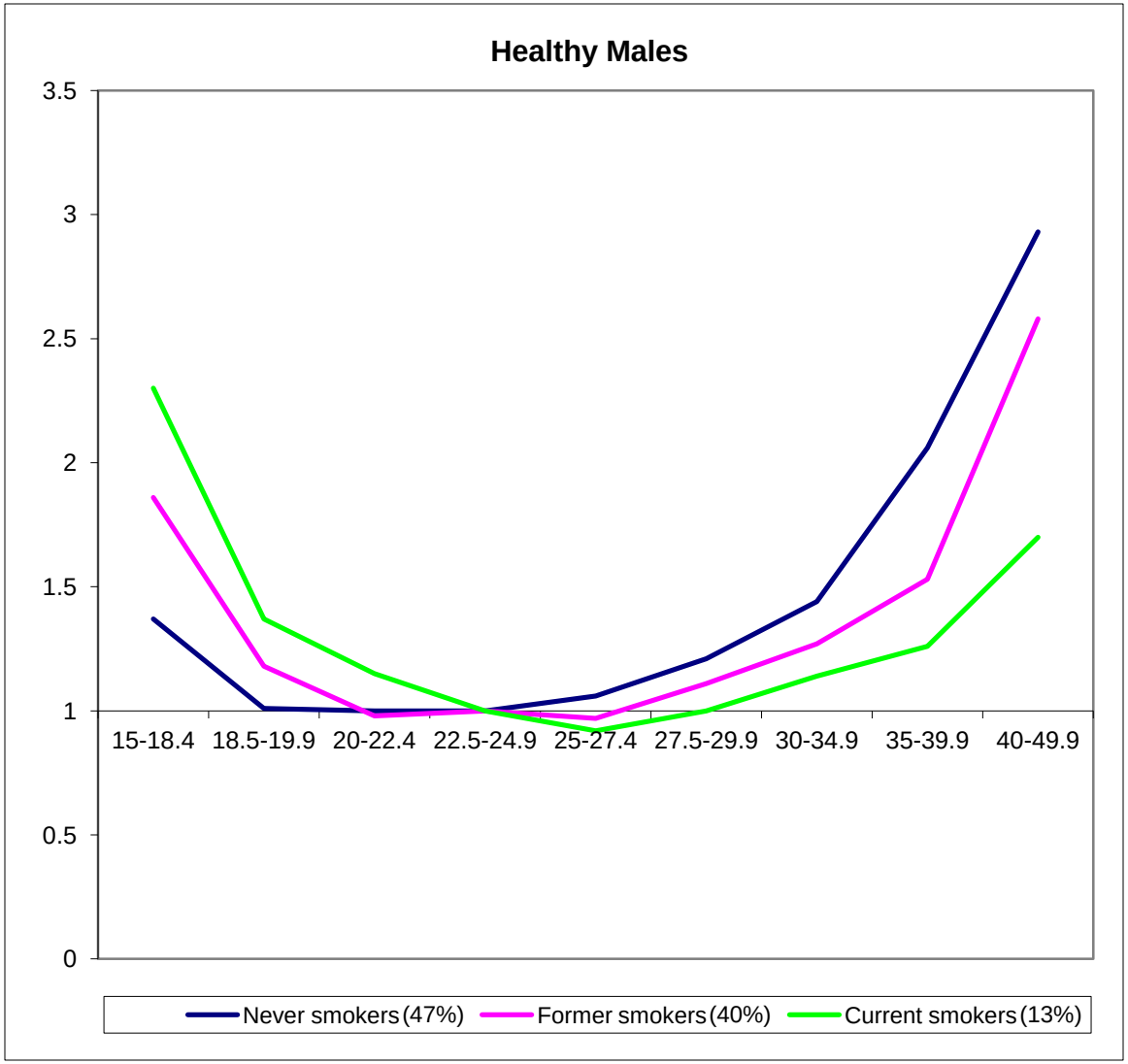
Berrington A, NEJM 2010; 363; 23: 2211-2219

BMI and Mortality Stratified by Age



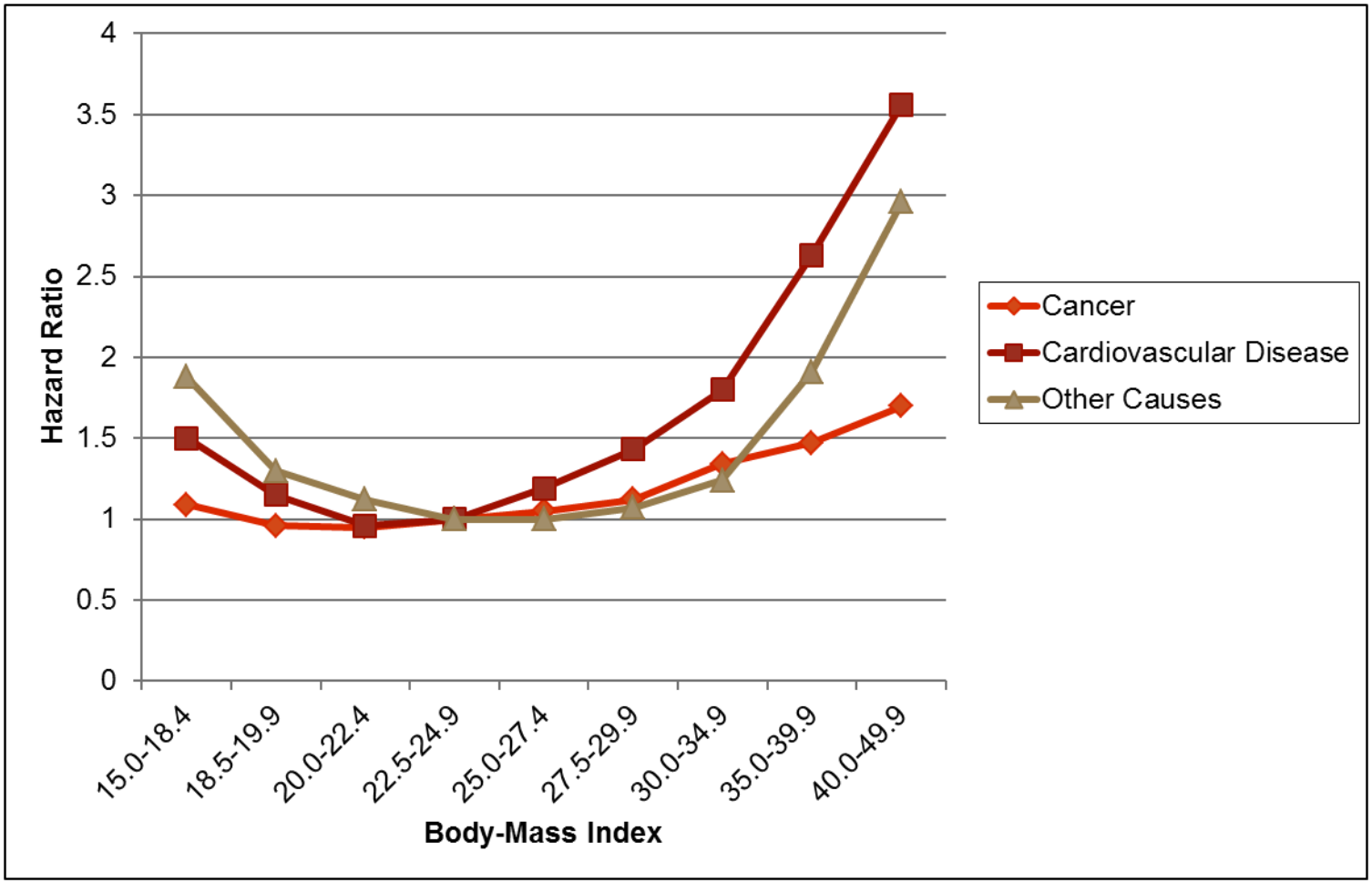
Berrington A, NEJM 2010; 363; 23: 2211-2219

BMI and Mortality by Smoking Status – Men without Cancer or CVD at Baseline



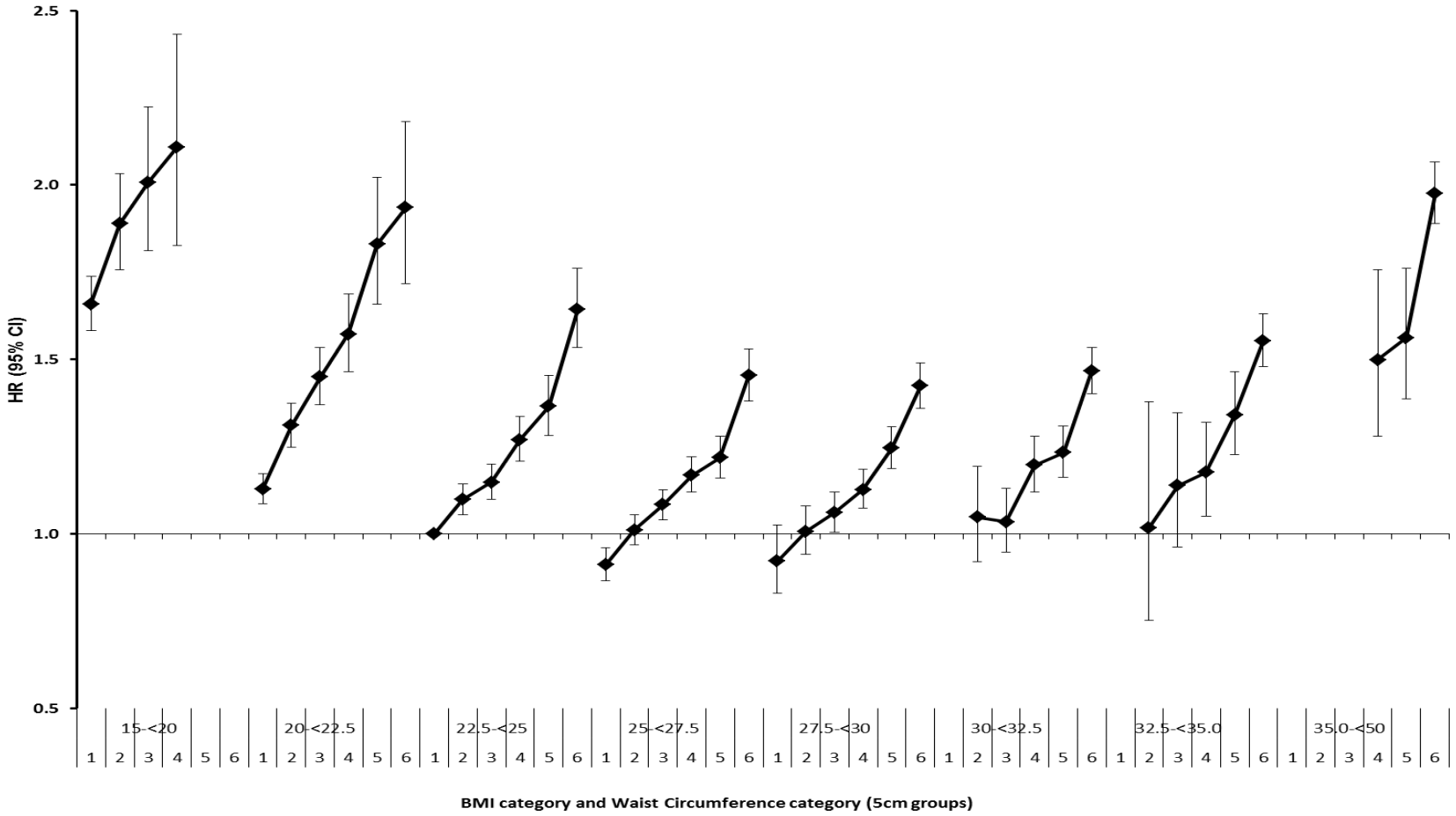
Berrington A, NEJM 2010; 363; 23: 2211-2219

BMI and Cause Specific Mortality among Healthy Never Smokers



Berrington A, NEJM 2010; 363; 23: 2211-2219

Waist Circumference and Mortality by BMI

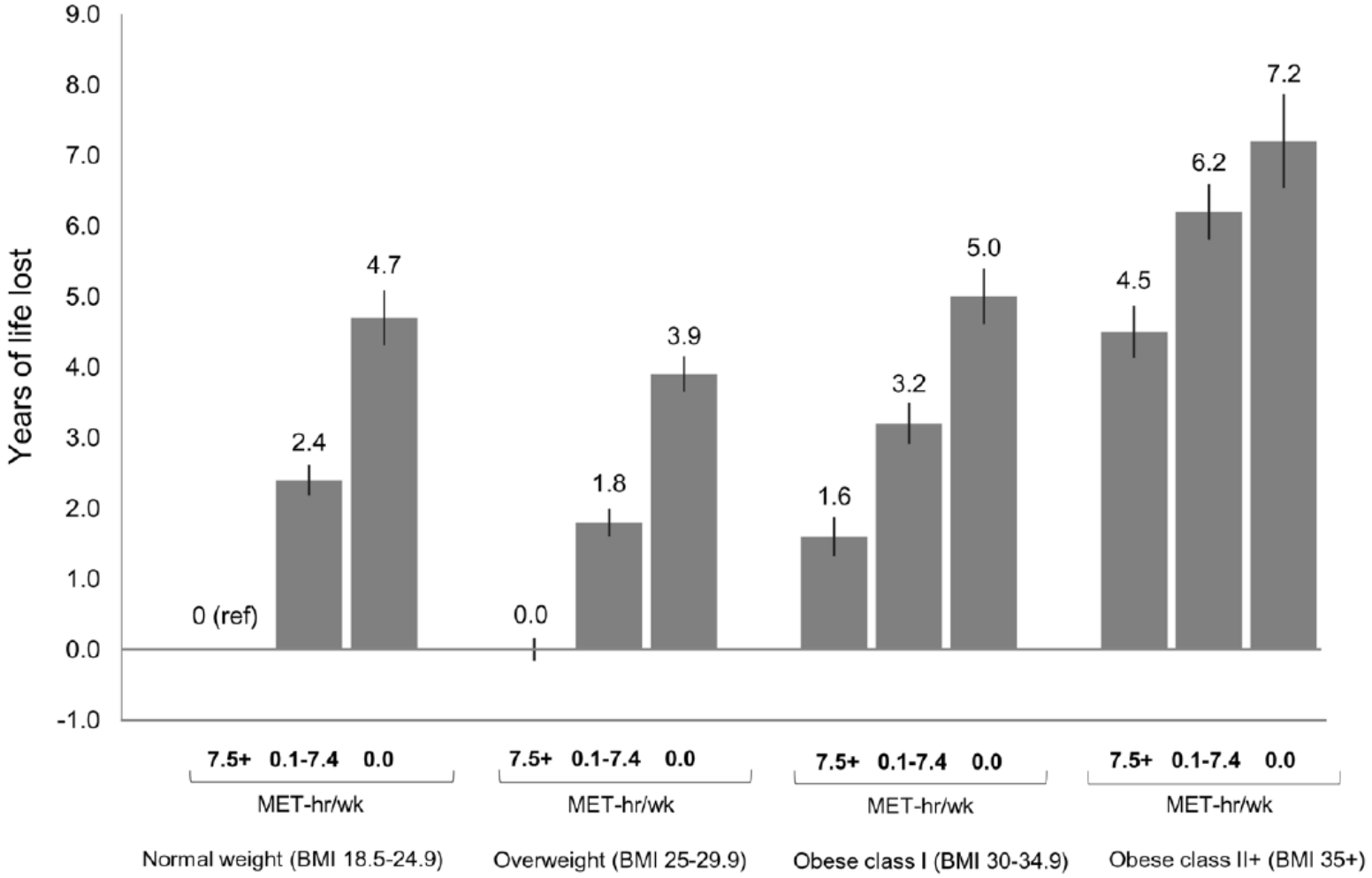


WC cutpoints (cm) for men: <90.0, 90.0-94.9, 95.0-99.9, 100.0-104.9, 105.0-109.9, 110.0+

WC cutpoints (cm) for women: <70.0, 70.0-74.9, 75.0-79.9, 80.0-84.9, 85.0-89.9, 90.0+.

Cerhan JR, et al. Submitted 2013

Years of Life Lost with Physical Inactivity across BMI Categories

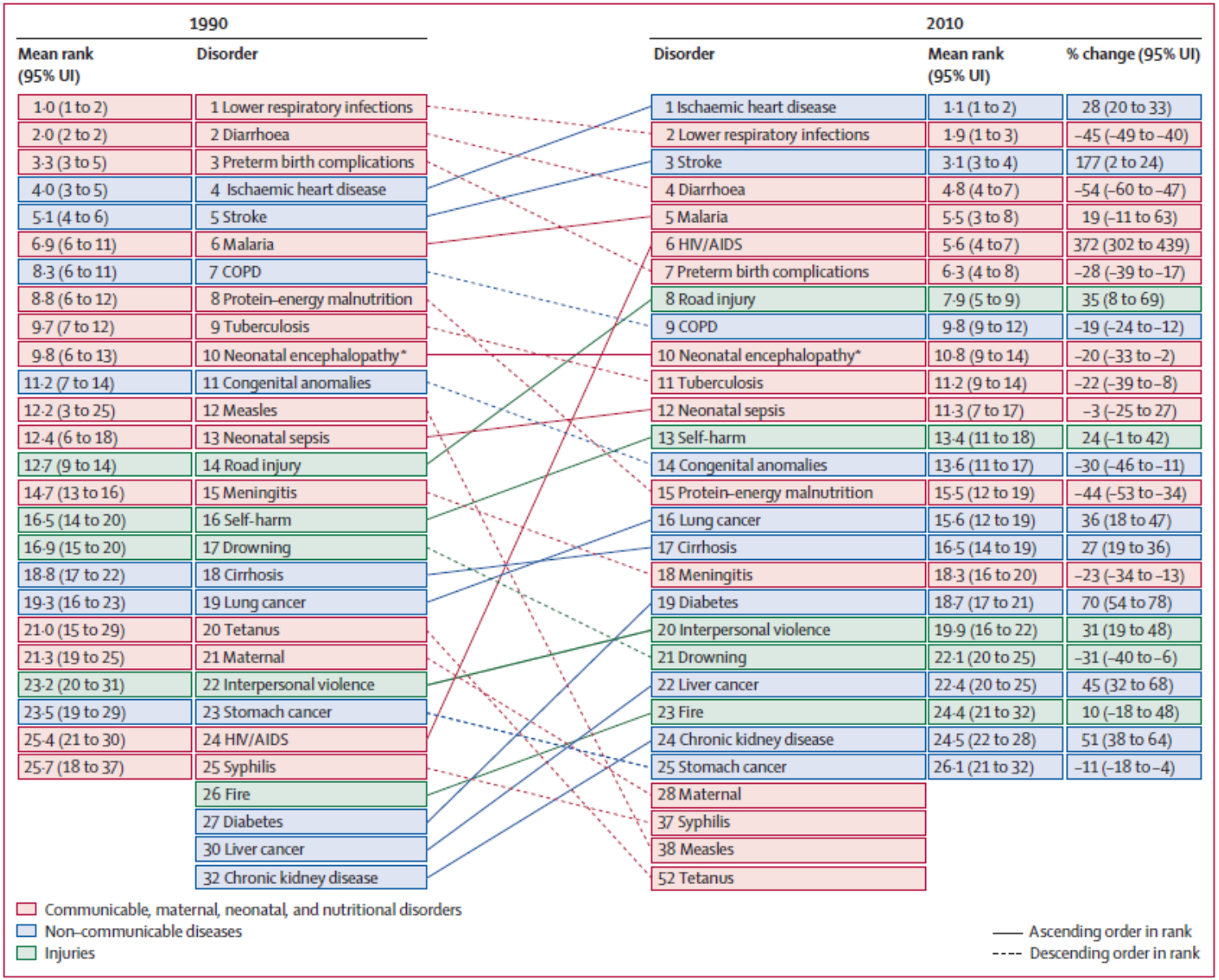


Moore SC, et al. PLoS Med 2012;9(11)

Issues in Interpretation

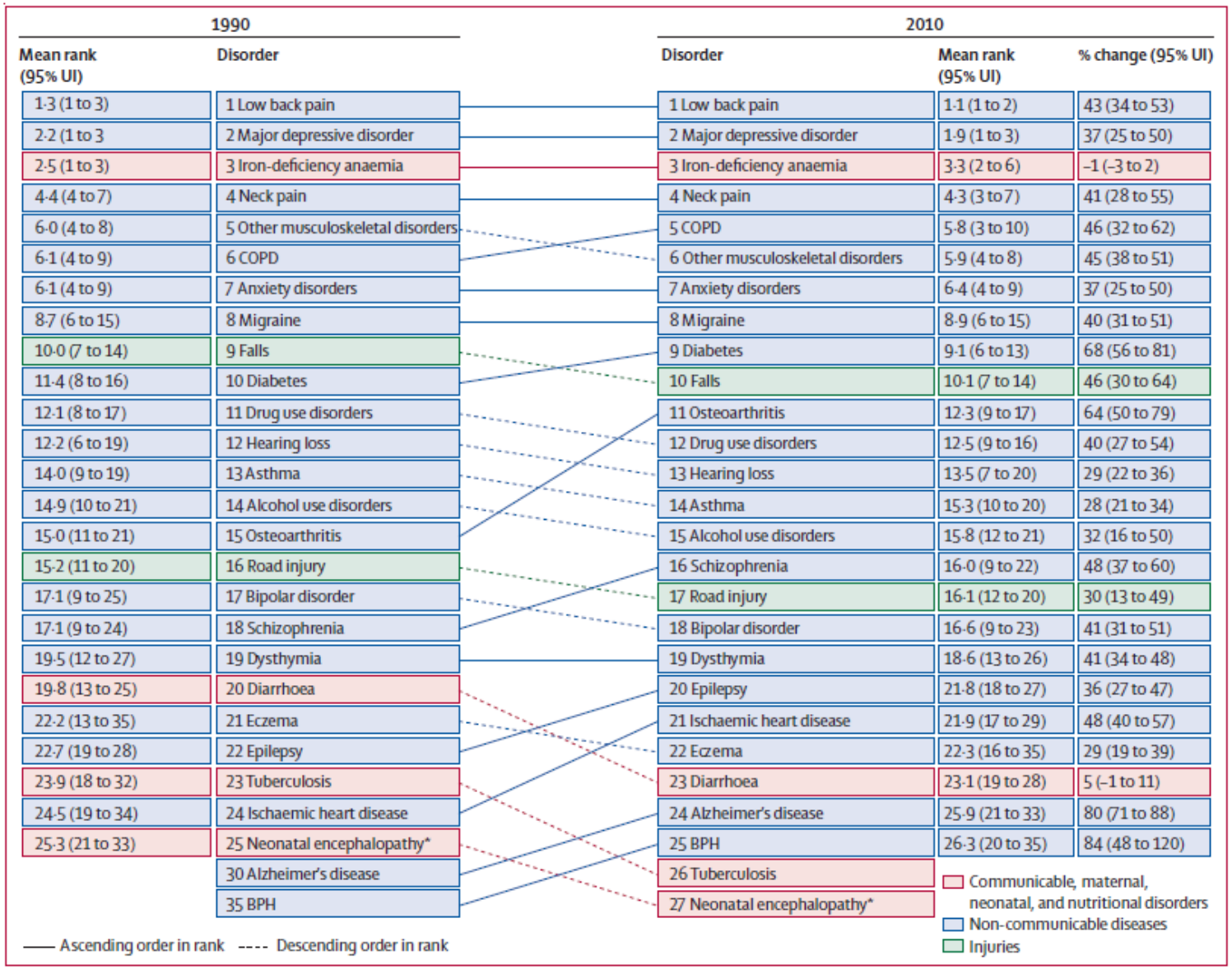
- Critical to consider the question being addressed
- BMI correlates with obesity but is not a precise measure of metabolically active fat mass
- Epidemiologic analysis of independent effect of BMI is addressed by analyses of healthy, non-smokers
  - Removes bias from two strong predictors of mortality
  - But difficult to extrapolate to other patient groups
- BMI/mortality and cause-specific mortality may differ by
  - Age at time BMI is assessed
  - Smoking status
  - Gender and racial/ethnic population mix
  - Elimination of people with comorbid disease at baseline
  - Body fat distribution
  - Other risk factors for overweight/obesity – PA, Diet, Alcohol

Global Years of Life Lost Ranks for the Top 25 Causes, 1990 and 2010



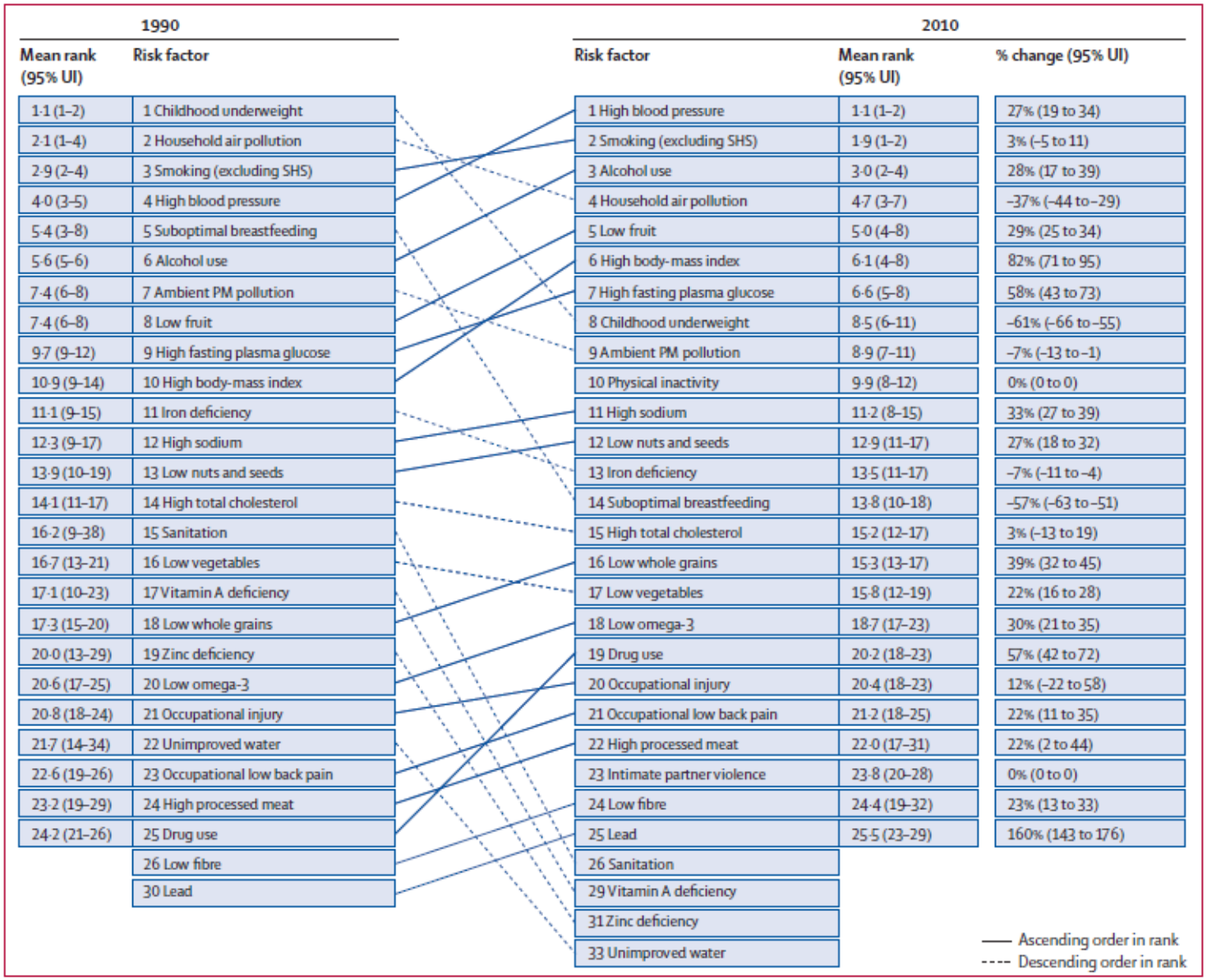
Lozano R, et al. Lancet 2012; 380: 2095-128

Global Years Lived with Disability Ranks for the 25 Most Common Causes, 1990 and 2010



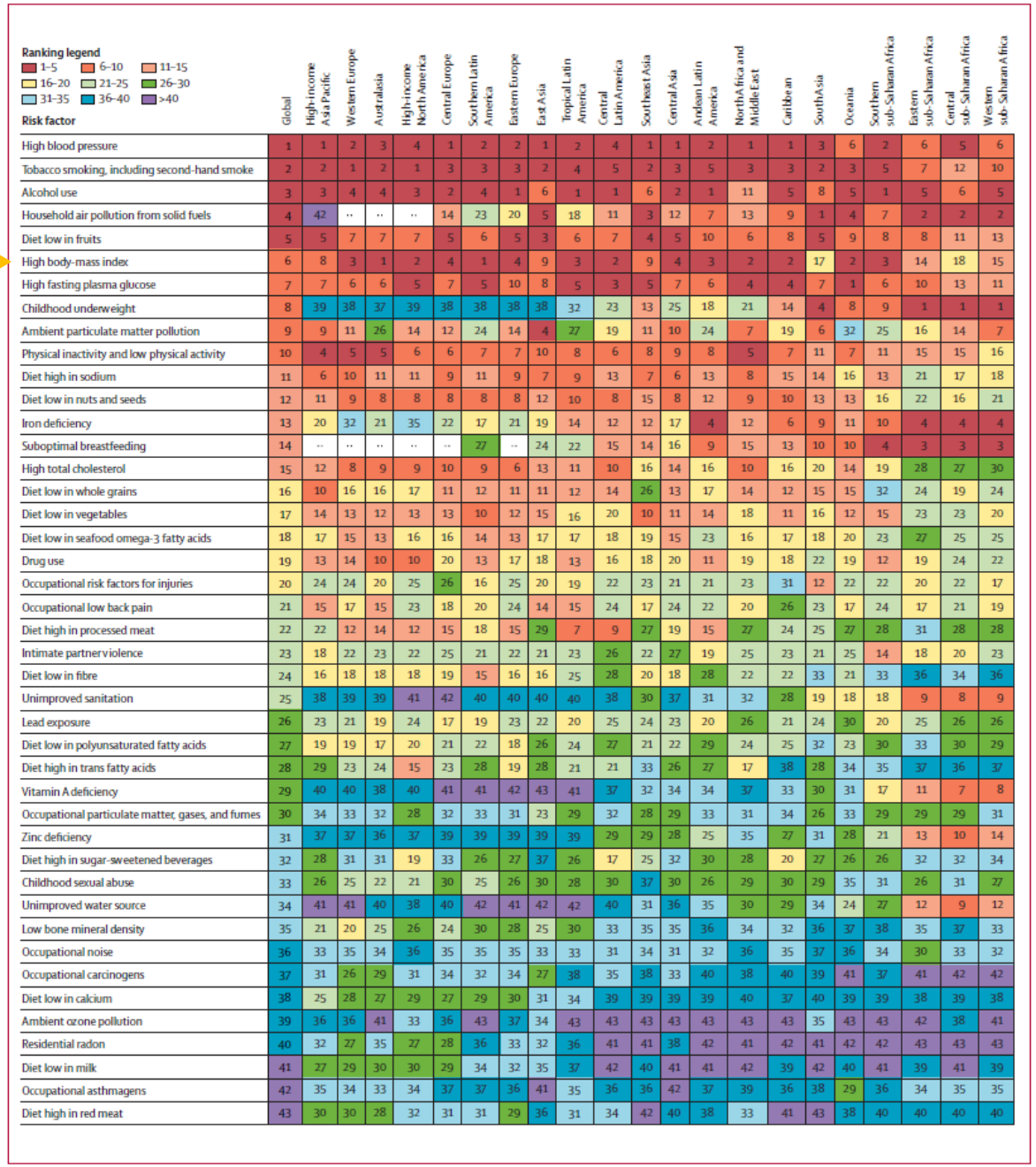
Vos T, et al. Lancet 2012; 380: 2163-96

Global Risk Factor Ranks for All Ages and Sexes Combined, 1990 and 2010



Lim SS, et al. Lancet 2012; 380: 2224-60

Risk Factors Ranked by Attributable Burden of Disease, 2010

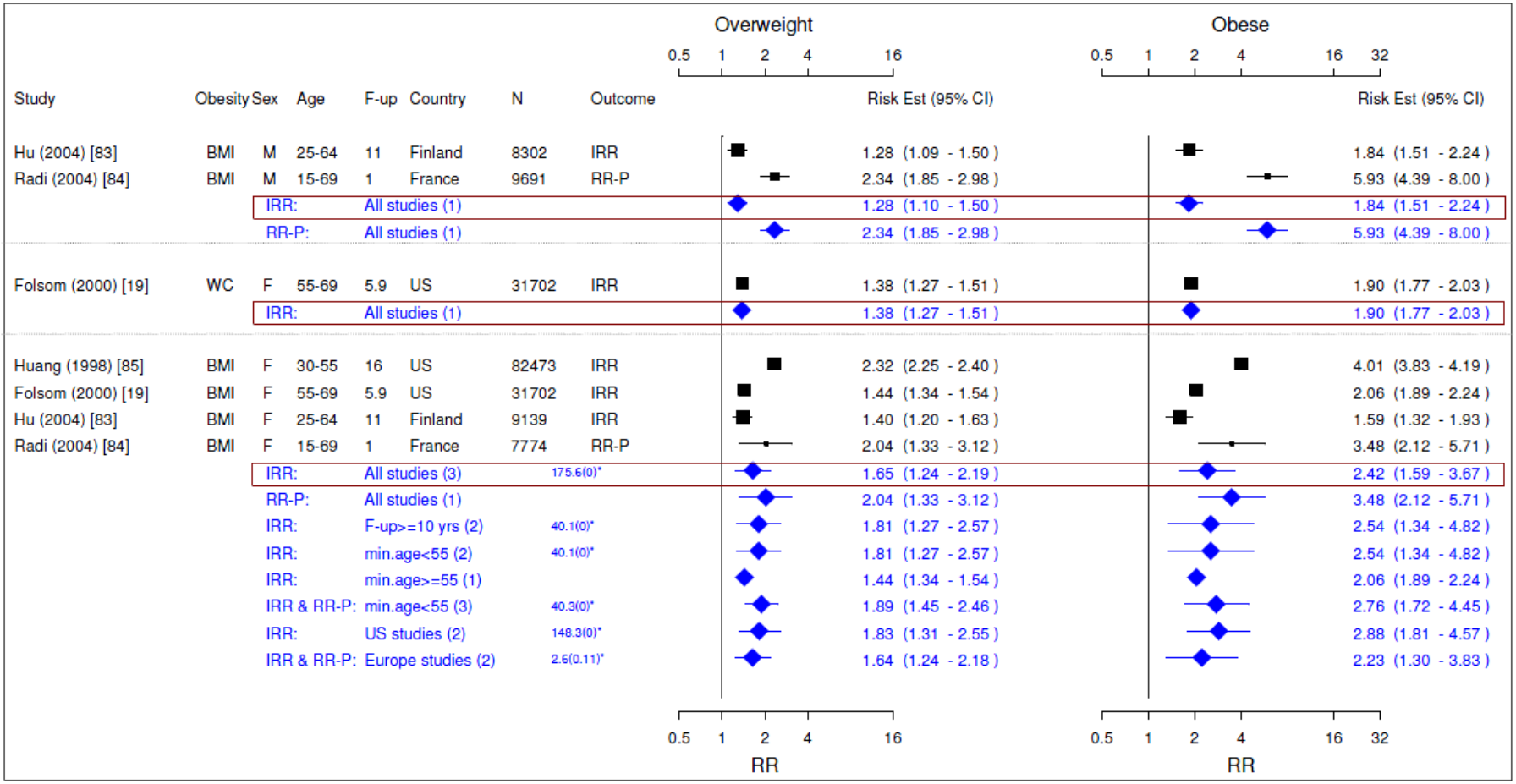


Ranking legend
1–5 6–10 11–15
16–20 21–25 26–30
31–35 36–40 >40

Risk factor	Global	High-income Asia Pacific	Western Europe	Australasia	High-income North America	Central Europe	Southern Latin America	Eastern Europe	East Asia	Tropical Latin America	Central Latin America	Southeast Asia	Central Asia	Andean Latin America	North Africa and Middle East	Caribbean	South Asia	Oceania	Southern sub-Saharan Africa	Eastern sub-Saharan Africa	Central sub-Saharan Africa	Western sub-Saharan Africa
High blood pressure	1	1	2	3	4	1	2	2	1	2	4	1	1	2	1	1	3	6	2	6	5	6
Tobacco smoking, including second-hand smoke	2	2	1	2	1	3	3	3	2	4	5	2	3	5	3	3	2	3	5	7	12	10
Alcohol use	3	3	4	4	3	2	4	1	6	1	1	6	2	1	11	5	8	5	1	5	6	5
Household air pollution from solid fuels	4	42	..	..	..	14	23	20	5	18	11	3	12	7	13	9	1	4	7	2	2	2
Diet low in fruits	5	5	7	7	7	5	6	5	3	6	7	4	5	10	6	8	5	9	8	8	11	13
High body-mass index	6	8	3	1	2	4	1	4	9	3	2	9	4	3	2	2	17	2	3	14	18	15
High fasting plasma glucose	7	7	6	6	5	7	5	10	8	5	3	5	7	6	4	4	7	1	6	10	13	11
Childhood underweight	8	39	38	37	39	38	38	38	38	32	23	13	25	18	21	14	4	8	9	1	1	1
Ambient particulate matter pollution	9	9	11	26	14	12	24	14	4	27	19	11	10	24	7	19	6	32	25	16	14	7
Physical inactivity and low physical activity	10	4	5	5	6	6	7	7	10	8	6	8	9	8	5	7	11	7	11	15	15	16
Diet high in sodium	11	6	10	11	11	9	11	9	7	9	13	7	6	13	8	15	14	16	13	21	17	18
Diet low in nuts and seeds	12	11	9	8	8	8	8	8	12	10	8	15	8	12	9	10	13	13	16	22	16	21
Iron deficiency	13	20	32	21	35	22	17	21	19	14	12	12	17	4	12	6	9	11	10	4	4	4
Suboptimal breastfeeding	14	..	..	..	..	..	27	..	24	22	15	14	16	9	15	13	10	10	4	3	3	3
High total cholesterol	15	12	8	9	9	10	9	6	13	11	10	16	14	16	10	16	20	14	19	28	27	30
Diet low in whole grains	16	10	16	16	17	11	12	11	11	12	14	26	13	17	14	12	15	15	32	24	19	24
Diet low in vegetables	17	14	13	12	13	13	10	12	15	16	20	10	11	14	18	11	16	12	15	23	23	20
Diet low in seafood omega-3 fatty acids	18	17	15	13	16	16	14	13	17	17	18	19	15	23	16	17	18	20	23	27	25	25
Drug use	19	13	14	10	10	20	13	17	18	13	16	18	20	11	19	18	22	19	12	19	24	22
Occupational risk factors for injuries	20	24	24	20	25	26	16	25	20	19	22	23	21	21	23	31	12	22	22	20	22	17
Occupational low back pain	21	15	17	15	23	18	20	24	14	15	24	17	24	22	20	26	23	17	24	17	21	19
Diet high in processed meat	22	22	12	14	12	15	18	15	29	7	9	27	19	15	27	24	25	27	28	31	28	28
Intimate partner violence	23	18	22	23	22	25	21	22	21	23	26	22	27	19	25	23	21	25	14	18	20	23
Diet low in fibre	24	16	18	18	18	19	15	16	16	25	28	20	18	28	22	22	33	21	33	36	34	36
Unimproved sanitation	25	38	39	39	41	42	40	40	40	40	38	30	37	31	32	28	19	18	18	9	8	9
Lead exposure	26	23	21	19	24	17	19	23	22	20	25	24	23	20	26	21	24	30	20	25	26	26
Diet low in polyunsaturated fatty acids	27	19	19	17	20	21	22	18	26	24	27	21	22	29	24	25	32	23	30	33	30	29
Diet high in trans fatty acids	28	29	23	24	15	23	28	19	28	21	21	33	26	27	17	38	28	34	35	37	36	37
Vitamin A deficiency	29	40	40	38	40	41	41	42	43	41	37	32	34	34	37	33	30	31	17	11	7	8
Occupational particulate matter, gases, and fumes	30	34	33	32	28	32	33	31	23	29	32	28	29	33	31	34	26	33	29	29	29	31
Zinc deficiency	31	37	37	36	37	39	39	39	39	39	29	29	28	25	35	27	31	28	21	13	10	14
Diet high in sugar-sweetened beverages	32	28	31	31	19	33	26	27	37	26	17	25	32	30	28	20	27	26	26	32	32	34
Childhood sexual abuse	33	26	25	22	21	30	25	26	30	28	30	37	30	26	29	30	29	35	31	26	31	27
Unimproved water source	34	41	41	40	38	40	42	41	42	42	40	31	36	35	30	29	34	24	27	12	9	12
Low bone mineral density	35	21	20	25	26	24	30	28	25	30	33	35	35	36	34	32	36	37	38	35	37	33
Occupational noise	36	33	35	34	36	35	35	35	33	33	31	34	31	32	36	35	37	36	34	30	33	32
Occupational carcinogens	37	31	26	29	31	34	32	34	27	38	35	38	33	40	38	40	39	41	37	41	42	42
Diet low in calcium	38	25	28	27	29	27	29	30	31	34	39	39	39	39	40	37	40	39	39	38	39	38
Ambient ozone pollution	39	36	36	41	33	36	43	37	34	43	43	43	43	43	43	43	35	43	43	42	38	41
Residential radon	40	32	27	35	27	28	36	33	32	36	41	41	38	42	41	42	41	42	42	43	43	43
Diet low in milk	41	27	29	30	30	29	34	32	35	37	42	40	41	41	42	39	42	40	41	39	41	39
Occupational asthmagens	42	35	34	33	34	37	37	36	41	35	36	36	42	37	39	36	38	29	36	34	35	35
Diet high in red meat	43	30	30	28	32	31	31	29	36	31	34	42	40	38	33	41	43	38	40	40	40	40

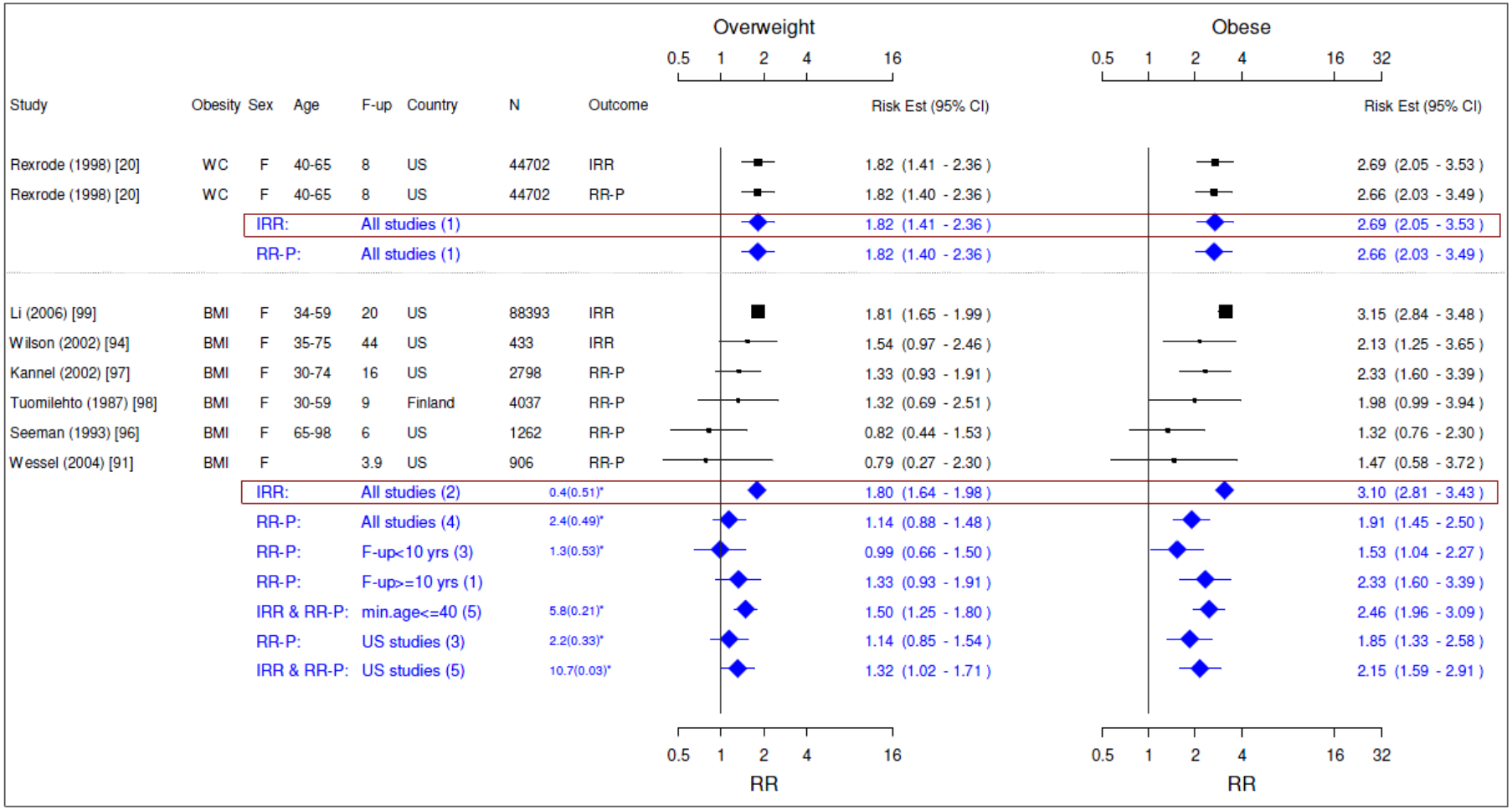
Lim SS, et al. Lancet 2012; 380: 2224-60

BMI and Hypertension Incidence



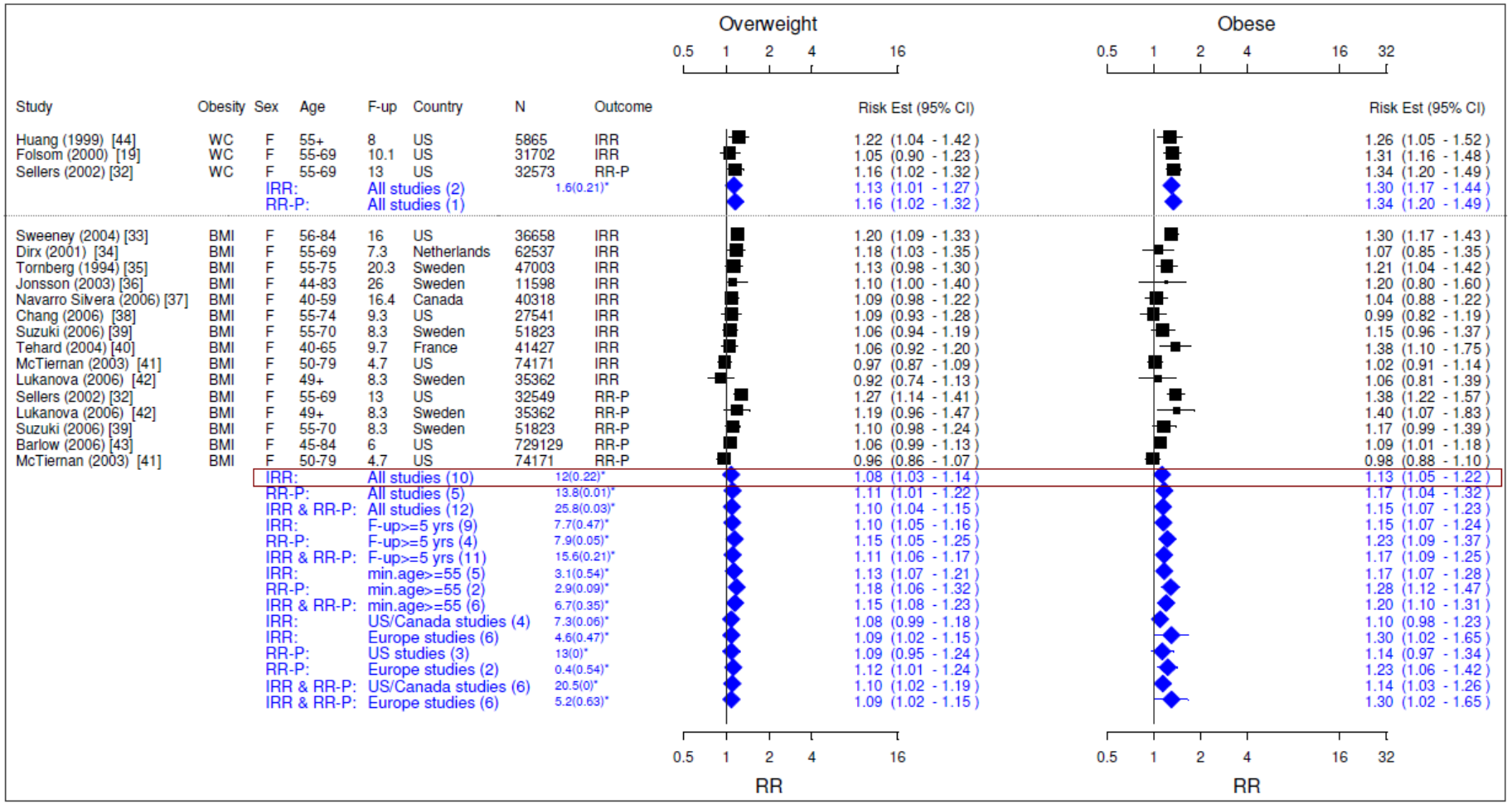
Guh DP, et al. BMC Public Health 2009; 9:88

BMI and CHD Incidence in Women



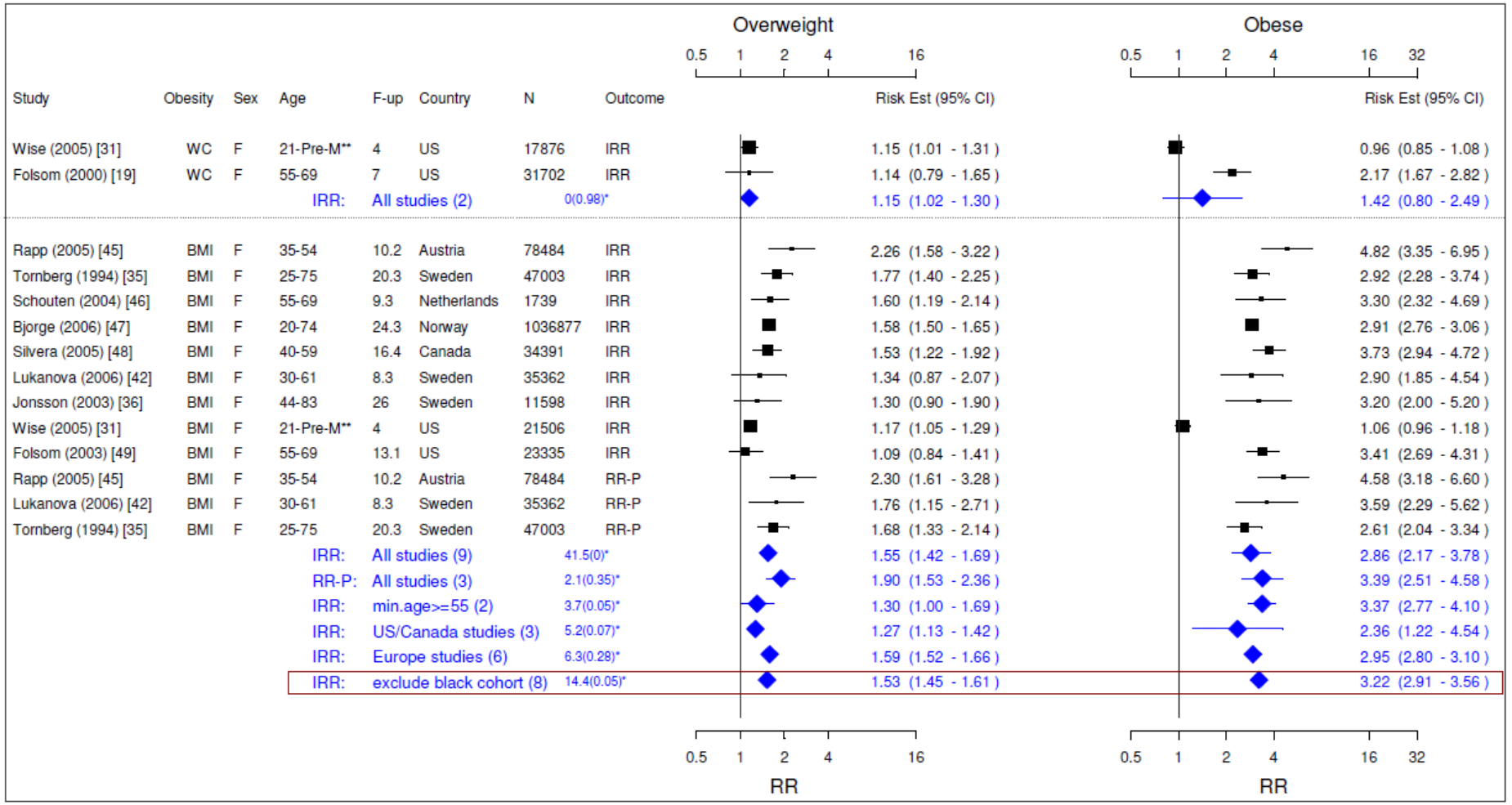
Guh DP, et al. BMC Public Health 2009; 9:88

BMI and Post Menopausal Breast Cancer Risk



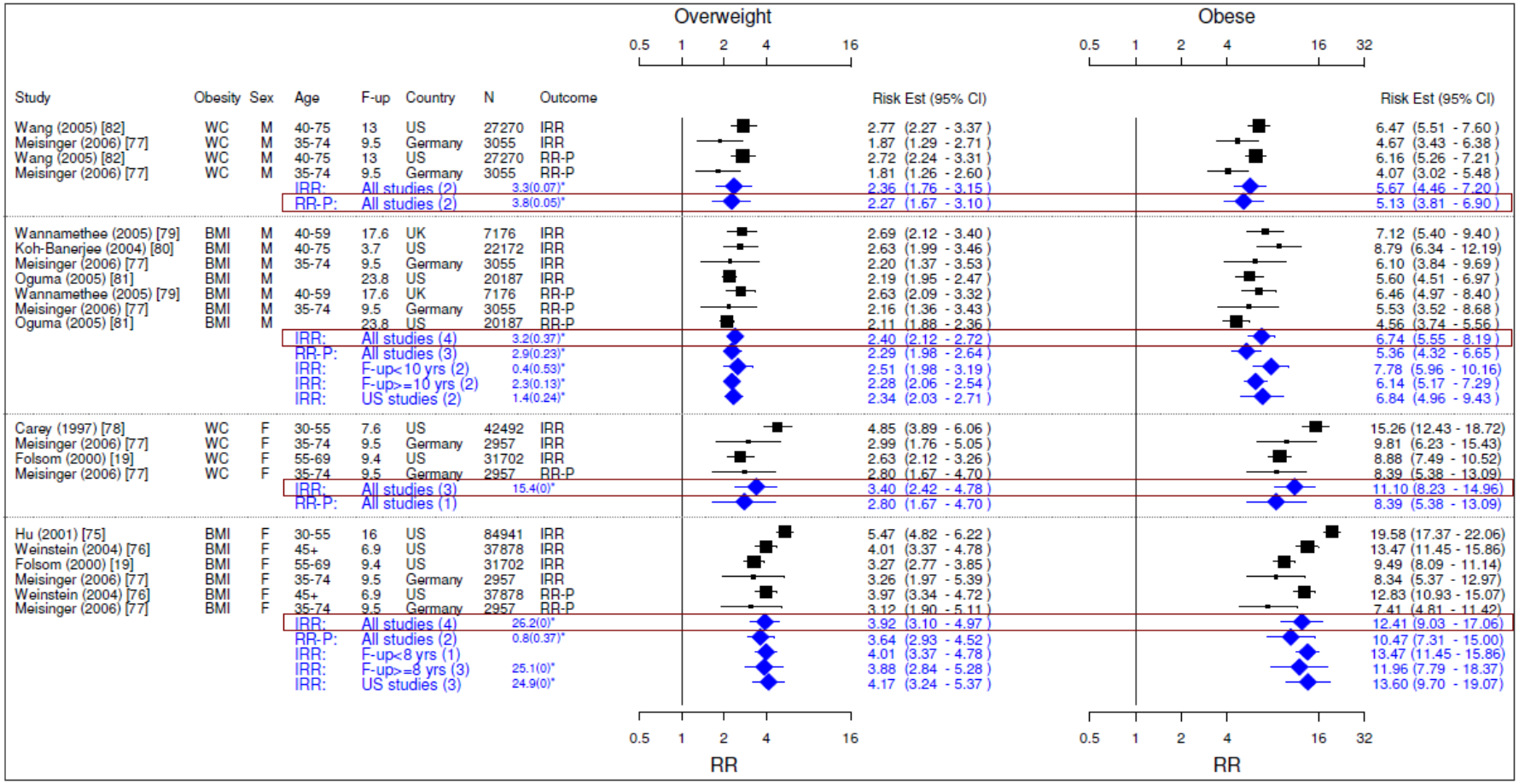
Guh DP, et al. BMC Public Health 2009; 9:88

BMI and Endometrial Cancer Risk



Guh DP, et al. BMC Public Health 2009; 9:88

BMI and Type 2 Diabetes Risk



Guh DP, et al. BMC Public Health 2009; 9:88

Prevalence of Common Comorbidities among Patients with the Three Most Common Cancers

Condition	All claims (%)			
	Breast	Prostate	Colorectal-female	Colorectal-male
Chronic pulmonary disease	7.2	16.2	4.7	4.8
Diabetes	10.2	17.4	6.4	5.4
Congestive heart failure	5.7	9.8	5.1	3.6
Cerebrovascular disease	3.6	7.4	2.4	2.2
Peripheral vascular disease	2.1	4.6	1.5	1.5
Old myocardial infarction	0.8	2.9	0.5	1.0

Klabunde CN, et al. Ann Epidemiol 2007;17:584–590. Medicare data from 1992-1996.

Risk of Death Varies by Comorbidity for Patients with the Three Most Common Cancers

Condition	Hazard Ratios (HRs)		
	Breast n=13,247 (841 non-CA deaths)	**Prostate** n=26,766 (2,122 non-CA deaths)	**Colorectal** n=16,829 (1,756 non-CA deaths)
Mod./severe renal disease	3.28	1.97	2.63
Congestive heart failure	2.33	2.40	2.16
Dementia	3.29	2.17	1.92
Chronic pulmonary disease	1.60	2.06	1.40
Cerebrovascular disease	2.04	1.30	1.41
Paralysis	1.23	1.48	1.65
Diabetes	1.57	1.27	0.99

Klabunde CN, et al. Ann Epidemiol 2007;17:584–590. Medicare data from 1992-1996.

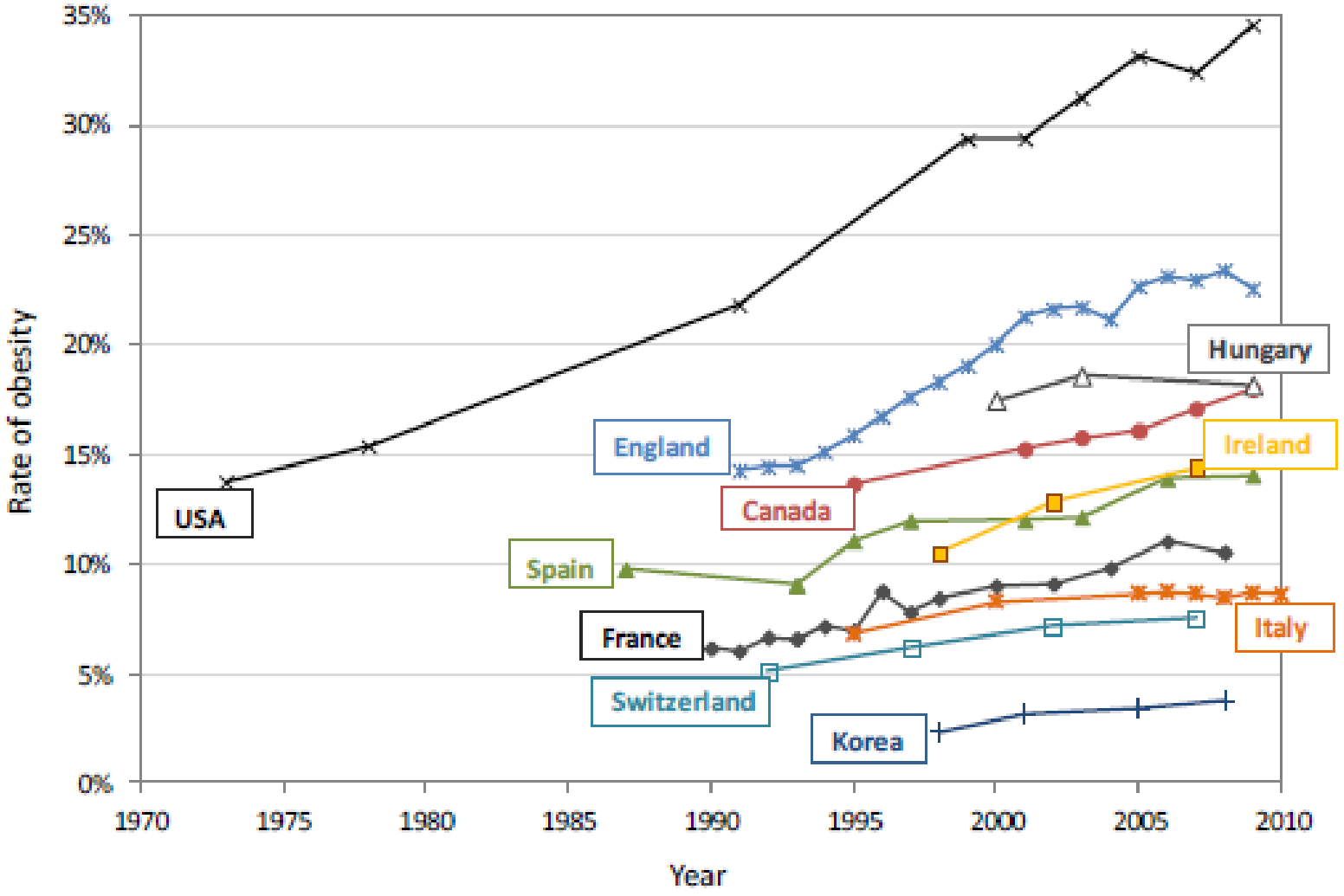
Conclusion

- A number of health behaviors, different obesity phenotypes, and health conditions may alter BMI and mortality association
- Associations may vary across racial/ethnic or immigrant populations but this may vary in US vs country of origin
- Disease burden is shifting from mortality to morbidity, particularly in developed countries – estimated to be 50% for the US in 2010
- This change in disease burden suggests a need for a shift from a focus on mortality as a predominant measure of disease burden
- Obesity is a complex multi-factorial health problem that is being explored with complex systems science approaches

Complex Adaptive Systems: Challenges for Science and Policy

- Features (nonlinearity, interdependence, spatial and dynamic complexity, heterogeneity) make system behavior difficult to capture fully using traditional scientific tools or analyses
- "Mental models" and intuition can be very limiting, misleading
- Policy Resistance
  - Policies that do not take complexity into account may have unanticipated consequences… or even backfire
  - Interventions that are successful in one area alone may be offset by response elsewhere in system
  - Heterogeneity means policy solutions may not be "one size fits all"
- Multiple levels of scale (neurons to nations) necessitate interdisciplinary communication, make policy focus challenging
- The best policies may be subtle, novel, unconventional; may leverage hidden synergies; and may need to use "systems" approach

US Continues to Lead the World in Obesity Rates

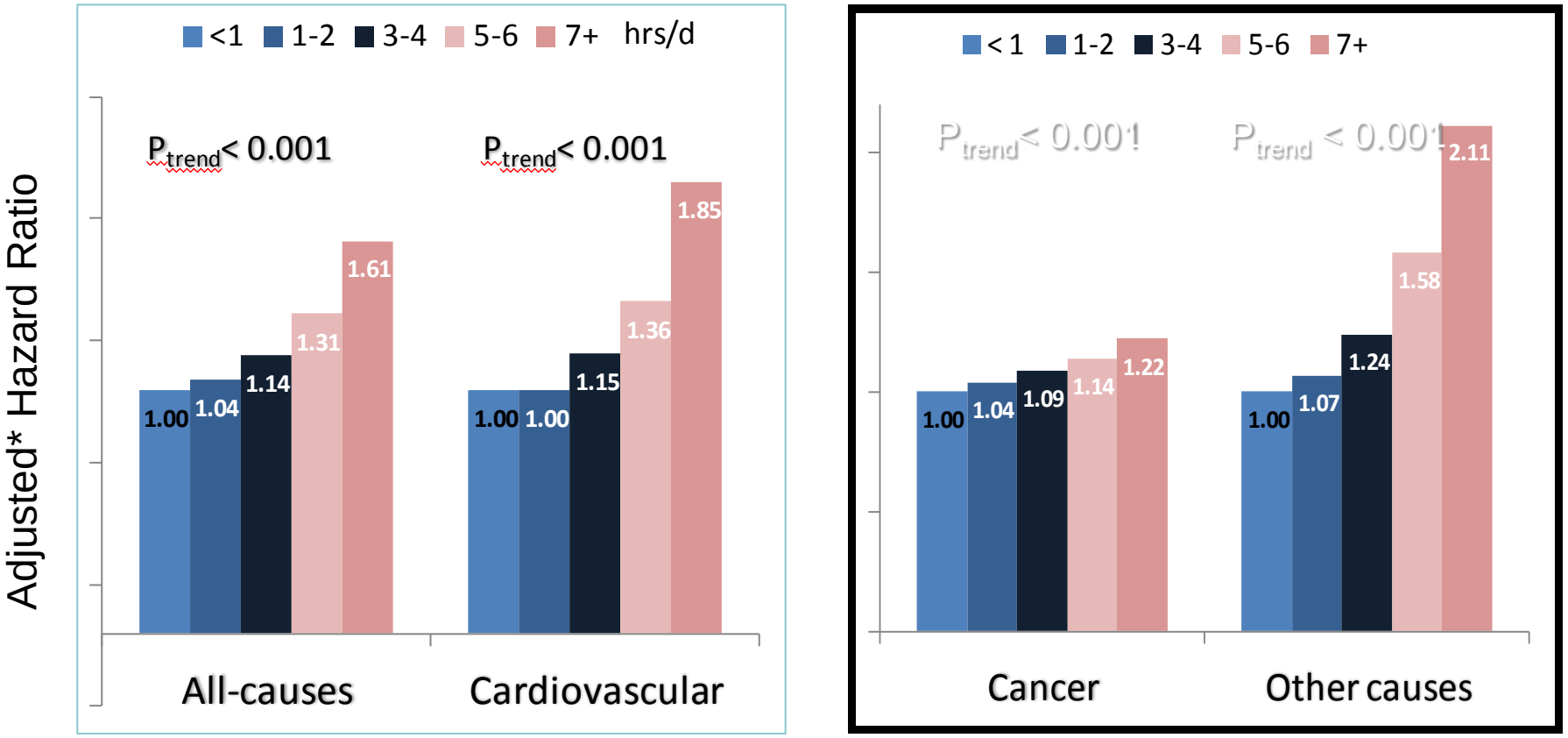


OECD Obesity Update 2012

Questions?

Highlights on Physical Activity and Cancer

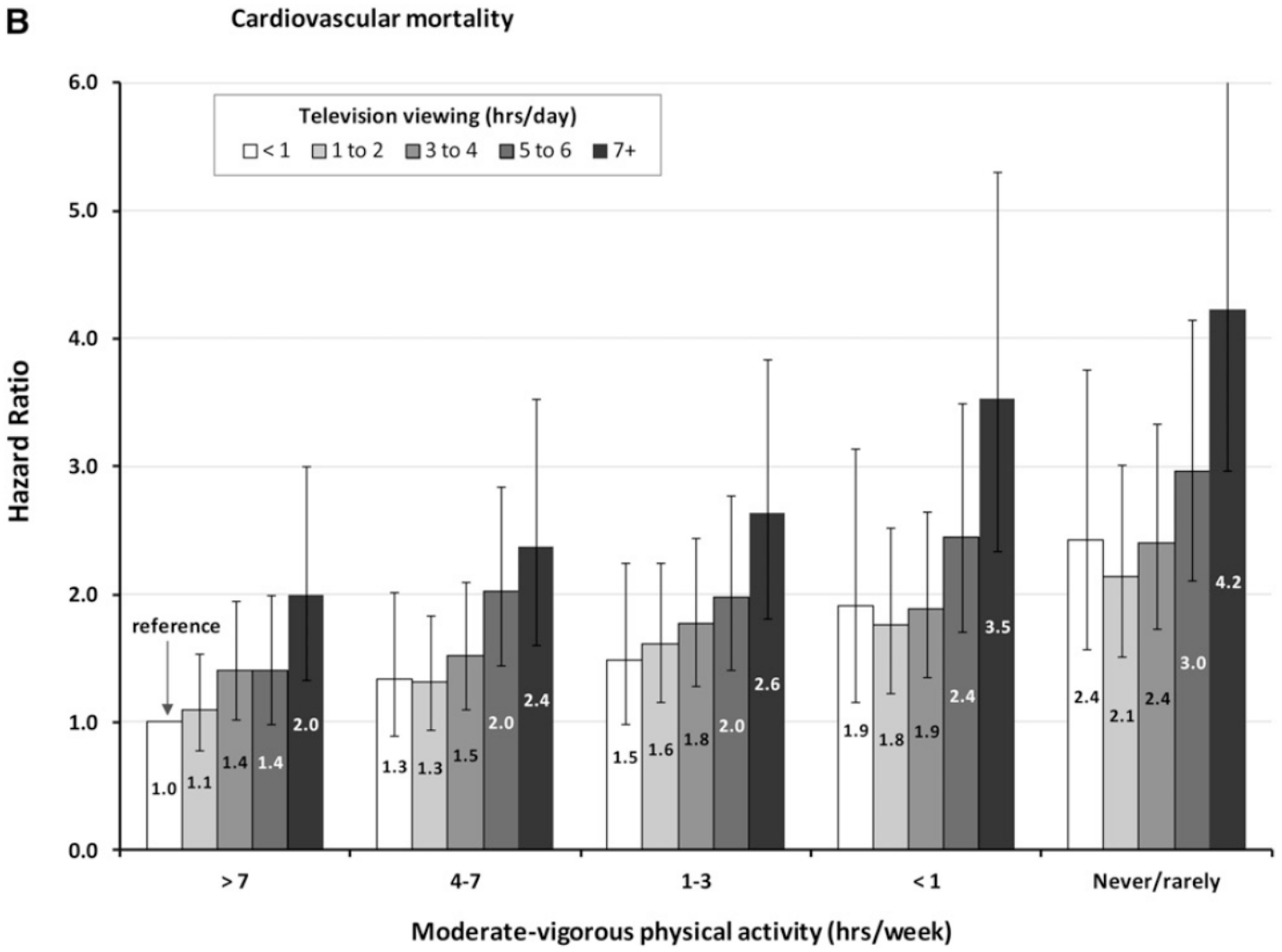
Television viewing and mortality



*Age, sex, education, race, smoking, diet quality, and moderate-vigorous physical activity

Matthews CE, George SM, et al. AJCN 2012;95:437–45.

Joint-effects of television viewing and physical activity on cardiovascular mortality



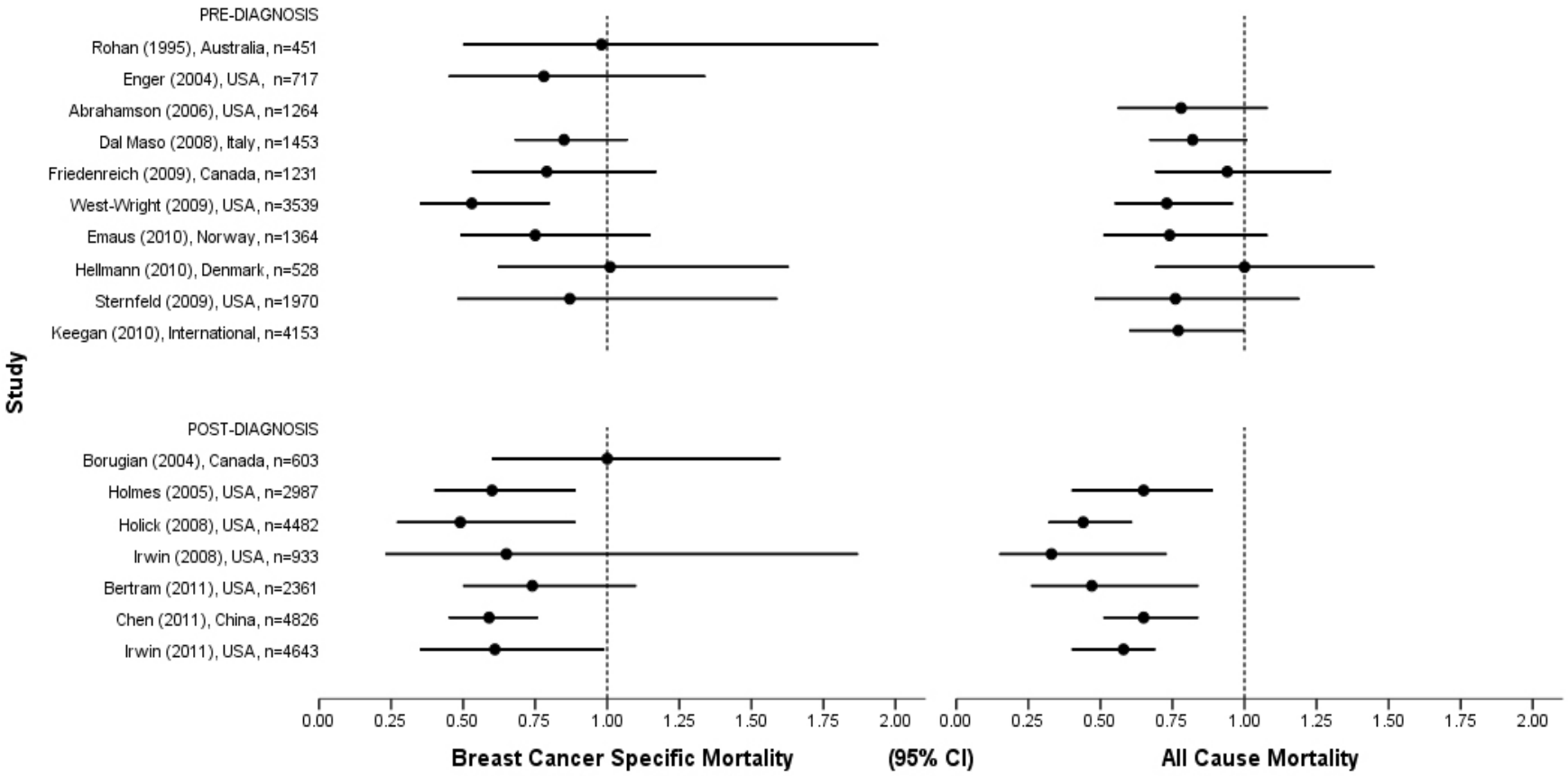
Matthews, C.E. George, S.M, et al. AJCN 2012;95:437–45.

Physical Activity & Cancer Prognosis

Cancer	Number of Studies	Decrease Risk of Cancer Death	Decrease Risk of All Cause Death
Breast	17	Yes	Yes
Colorectal	6	Yes	Yes
Prostate	1	Too few studies to reach conclusion on the effect	
Ovarian	2		
Brain	1		

Ballard-Barbash R et al, JNCI 2011

HRs for Physical Activity and Mortality Outcomes in Women with Breast Cancer



Ballard-Barbash R et al. JNCI 2012