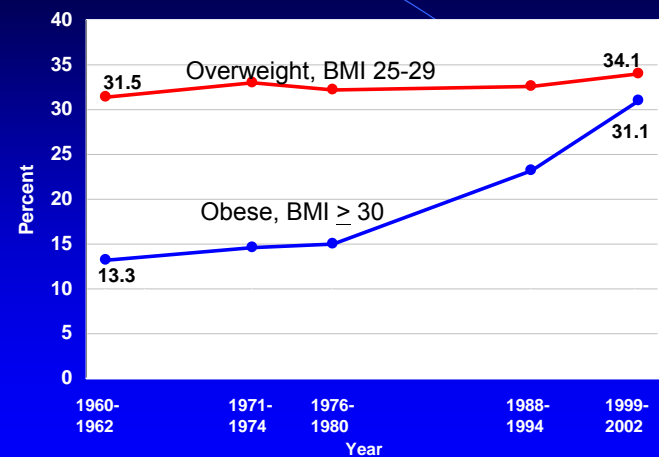


## Healthy Body Weight and Regular Exercise: The Keys to Longevity?

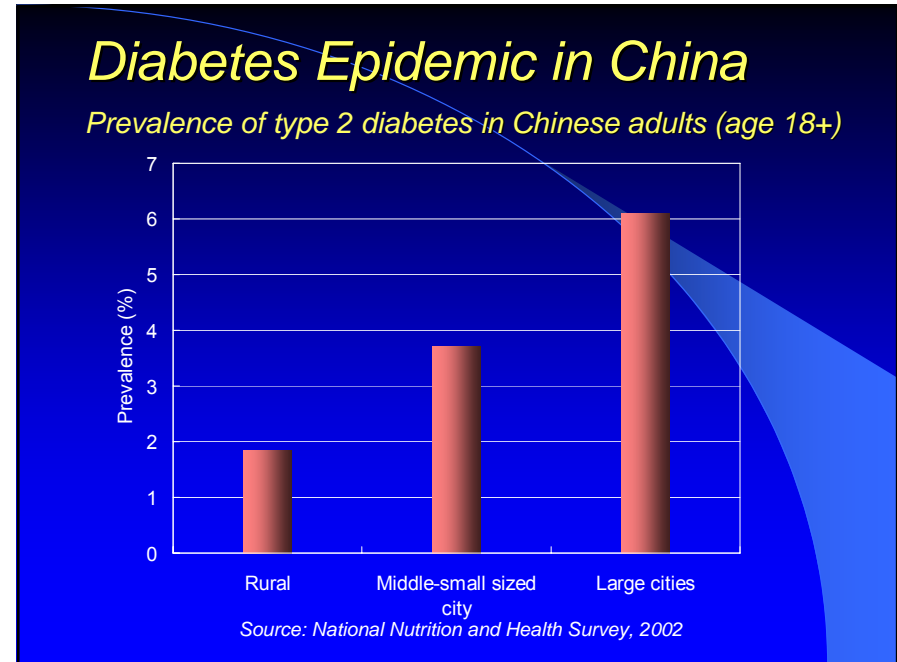
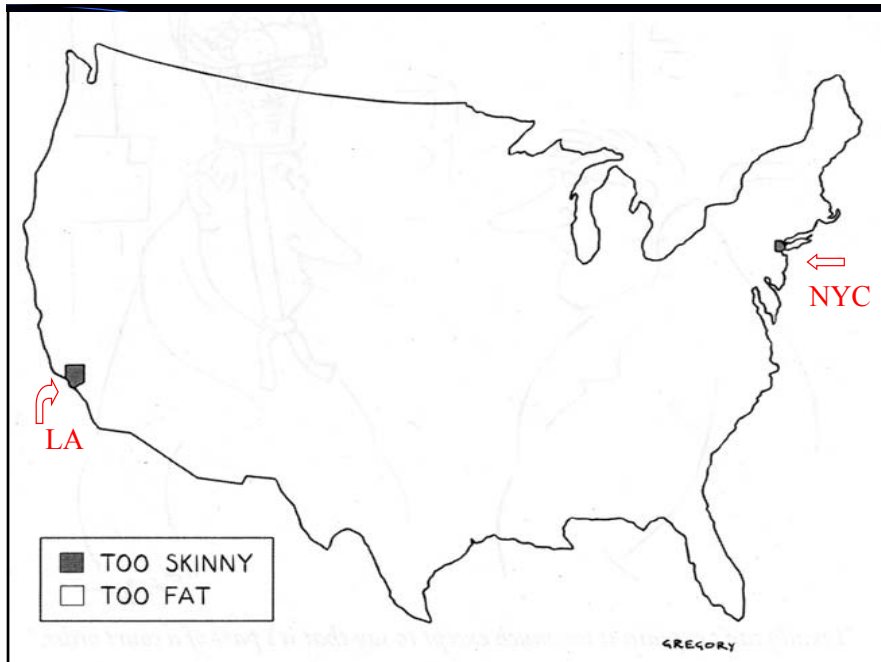
Frank B. Hu, MD, PhD  
Associate Professor  
Departments of Nutrition and Epidemiology  
Harvard School of Public Health  
Channing Laboratory, Harvard Medical School and Brigham and  
Women's Hospital

## Prevalence of overweight and obesity: United States, 1960-2002



SOURCES: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Examination Survey and National Health and Nutrition Examination Survey. Health, United States, 2004







## Obesity and Mortality

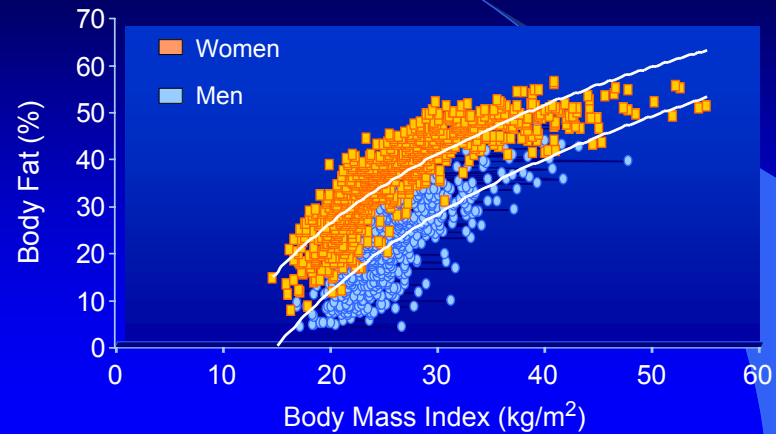
Sudden death is more common in those who are naturally fat than in the lean.

– Hippocrates (431 BC)

## How to Measure Obesity?

- Quetelet (Quetelet, 1835), a mathematician in Belgium, developed an obesity index (weight/height<sup>2</sup>), which was later termed as body mass index (BMI).
- Hydrodensitometry
- Dual-energy X-ray Absorptiometry (DXA),
- Computed tomography (CT), and Magnetic Resonance Imaging (MRI)

## Relationship Between BMI and Percent Body Fat in Men and Women



Adapted from: Gallagher et al. *Am J Clin Nutr* 2000;72:694.

## BMI-Associated Disease Risk

Classification		BMI (kg/m <sup>2</sup> )	Risk
Underweight		<18.5	Increased
Normal		18.5-24.9	Normal
Overweight		25.0-29.9	Increased
Obese	I	30.0-34.9	High
	II	35.0-39.9	Very High
	III	≥40	Extremely high

### Additional risks:

- Large waist circumference (men >40 in; women >35 in)
- 5 kg or more weight gain since age 18-20 y
- Poor aerobic fitness
- Specific races and ethnic groups

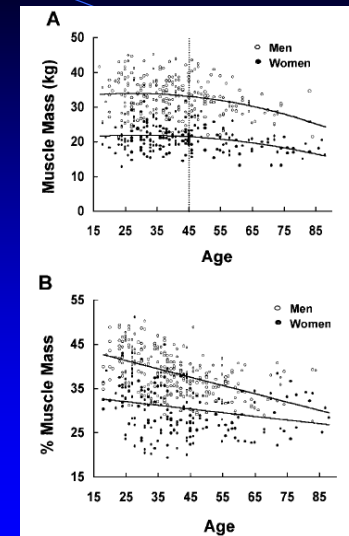
Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report. *Obes Res* 1998;6(suppl 2).

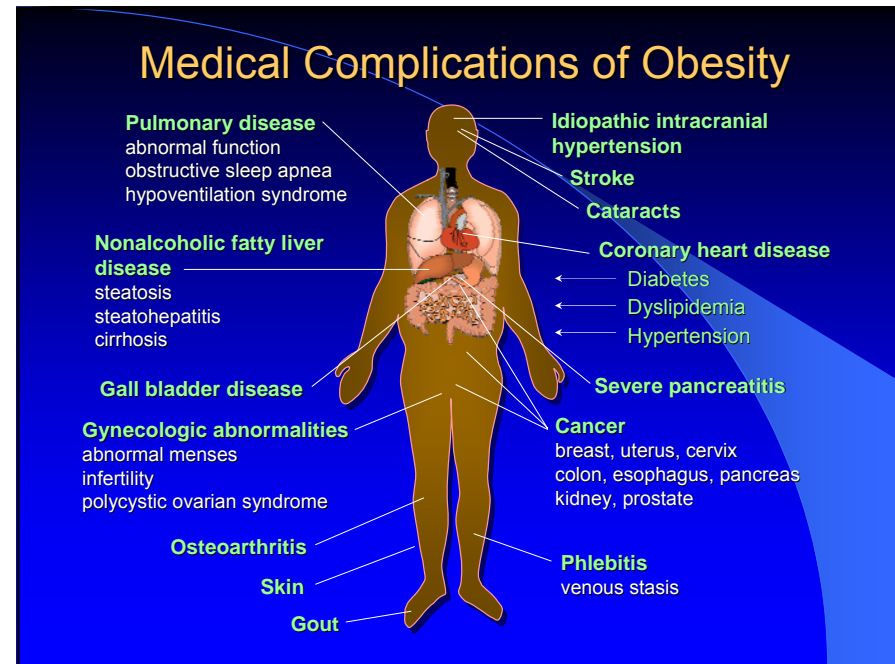
## Limitations of BMI

BMI is affected by body frame and muscularity, and is not specific for obesity.

The validity of BMI varies with age, sex, and ethnicity.

Intra-abdominal (visceral) fat is the worst, most strongly correlated with disease.



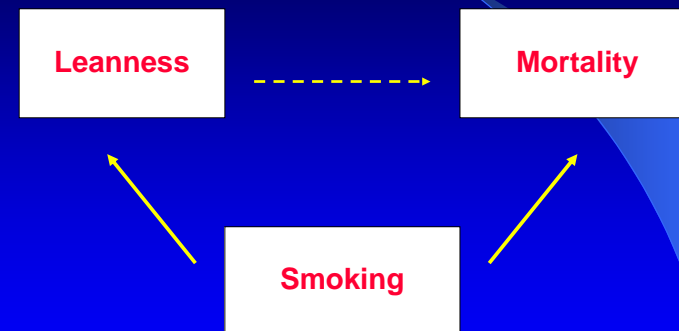


## Body Weight and Mortality: Potential Biases

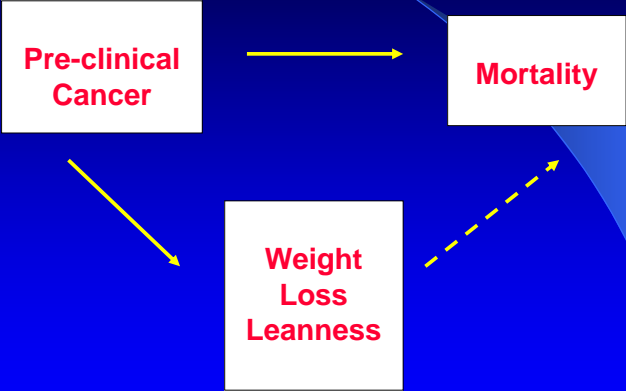
- Confounding by cigarette smoking
- Weight loss due to existing and subclinical disease (“reverse causation”)
- “Overcontrol” for intermediate variables in the causal pathway (BP, lipids, glucose)

Source: Manson, Stampfer, Hennekens, Willett, *JAMA* 1987; 257:353-8

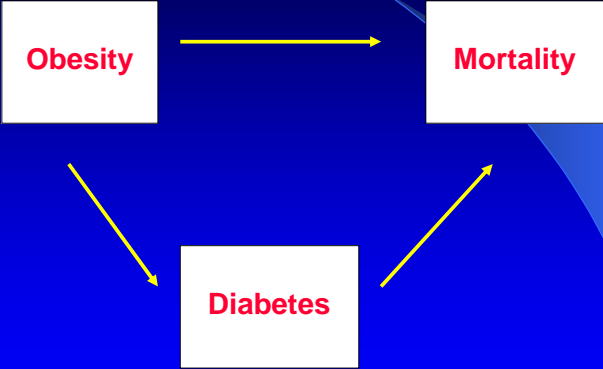
### (A) Confounding



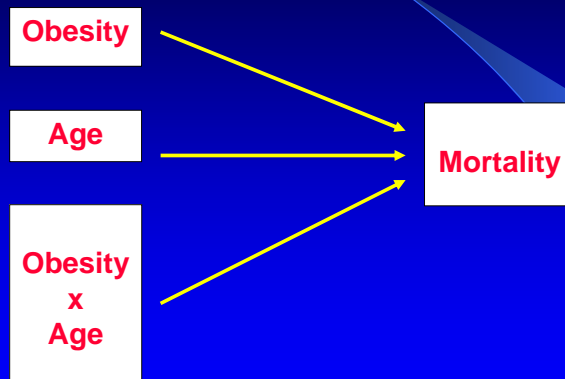
(B) Reverse Causation



(C) Mediation



(D) Effect Modification



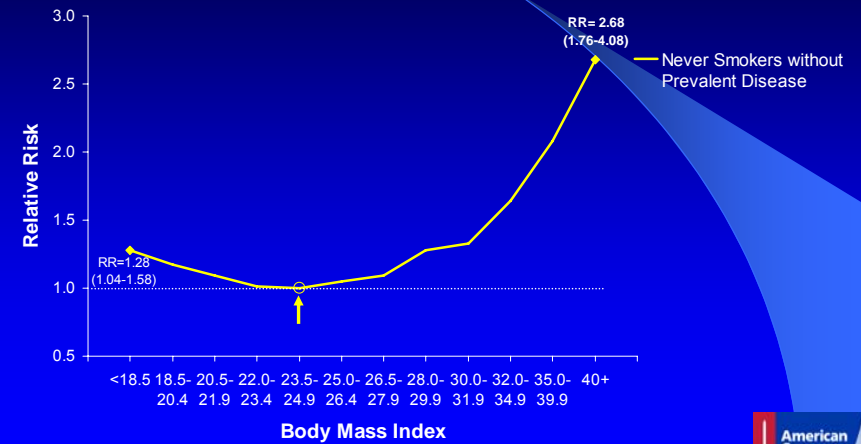
## How to Deal With Methodological Issues

- Confounding: restricting the analyses to never smokers
- Reverse causation: excluding sick people and eliminate deaths in the first few yrs of follow-up; middle-aged cohorts
- Not control for intermediate variables

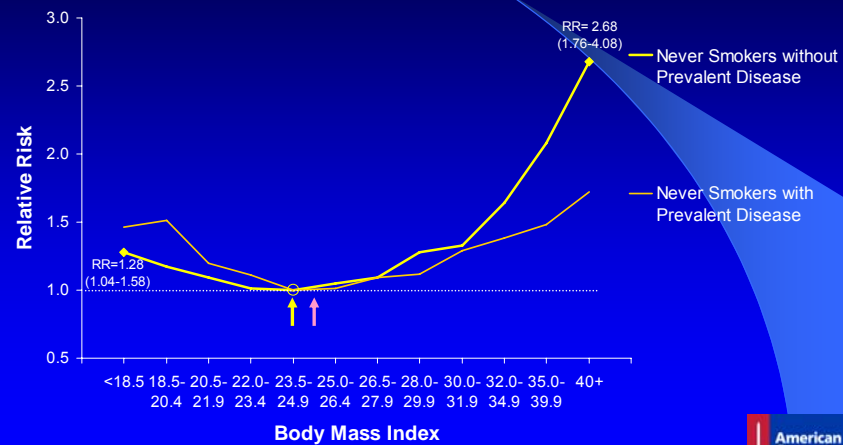
How does the inclusion of smokers and sick people obscure this relationship?



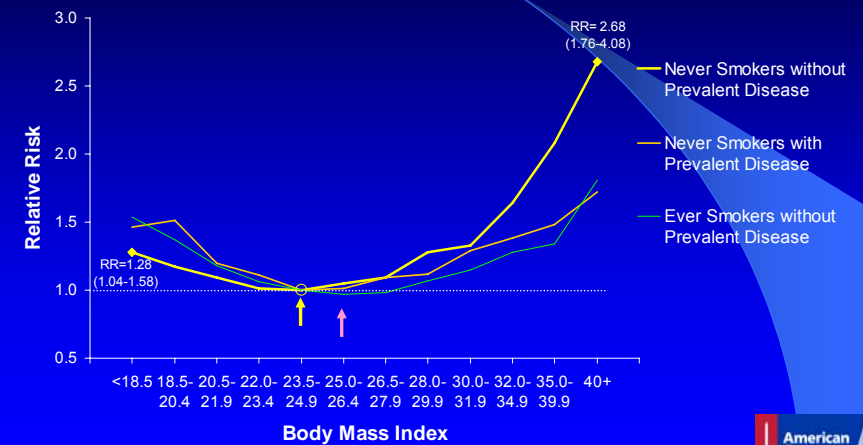
### Association between BMI and all cause mortality in CPS-II men



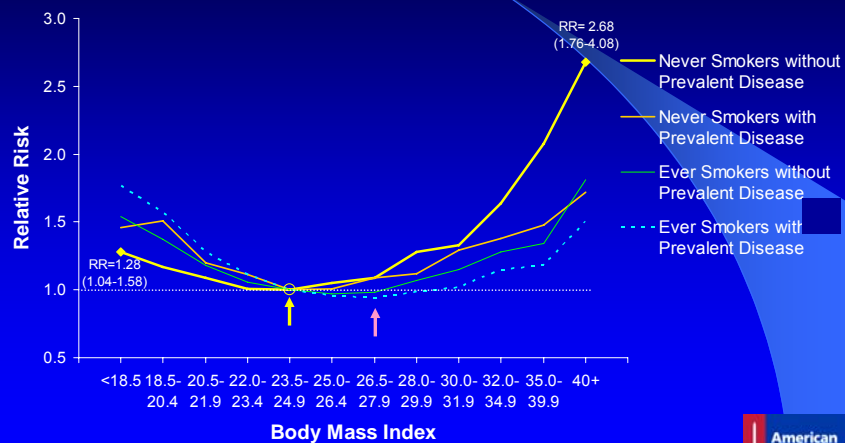
## Association between BMI and all cause mortality in CPS-II men



## Association between BMI and all cause mortality in CPS-II men



## Association between BMI and all cause mortality in CPS-II men

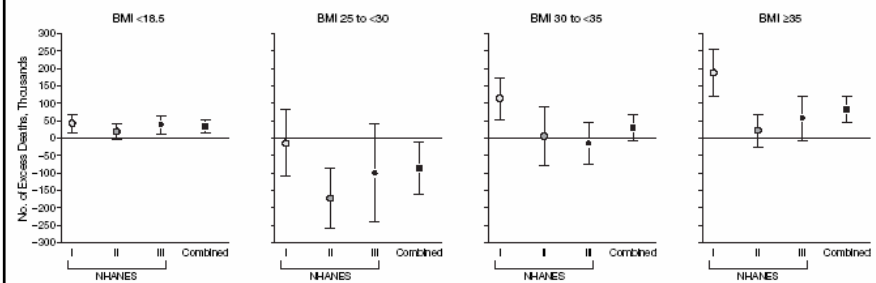


## Excess Deaths Associated With Underweight, Overweight, and Obesity

Katherine M. Flegal, PhD  
 Barry I. Graubard, PhD  
 David F. Williamson, PhD  
 Mitchell H. Gail, MD, PhD

**Context** As the prevalence of obesity increases in the United States, concern over the association of body weight with excess mortality has also increased.  
**Objective** To estimate deaths associated with underweight (body mass index [BMI] <18.5), overweight (BMI 25 to <30), and obesity (BMI ≥30) in the United States in 2000.

**Figure 2.** Estimated Numbers of Excess Deaths in 2000 in the United States Relative to the Healthy Reference BMI Category of 18.5 to <25, Shown by Survey and BMI Category



BMI indicates body mass index (measured as weight in kilograms divided by the square of height in meters). All estimates are based on the covariate distribution from NHANES 1999-2002, the number of deaths in 2000 from US vital statistics data, and the relative risks estimated from National Health and Nutrition Examination Surveys (NHANES) I, NHANES II, NHANES III, or the combined NHANES I, II, and III data set. Error bars indicate 95% confidence intervals.

**The New York Times**

[NYTimes.com](#) > [Health](#)

## **Some Extra Heft May Be Helpful, New Study Says**

**By GINA KOLATA**

Published April 20, 2005

26.088

WESH.com

## **It's OK To Be Slightly Overweight, Study Says**

*Study Finds Being Overweight Associated With Reduction In Deaths*

POSTED: 6:29 pm EDT April 20, 2005

UPDATED: 6:56 pm EDT April 20, 2005

26.086

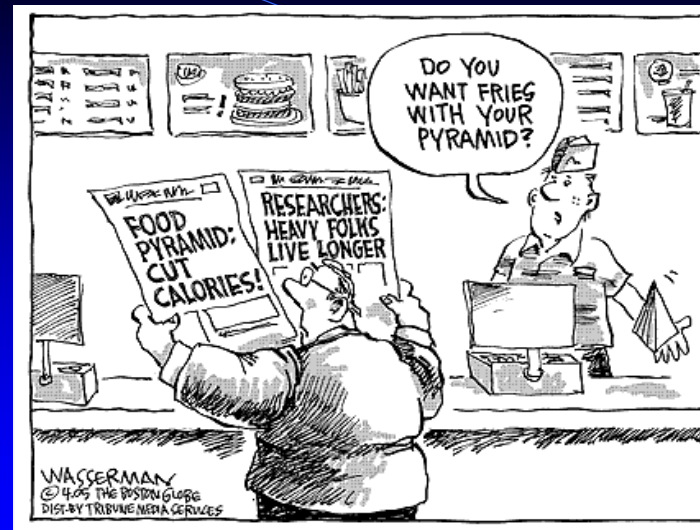
Rocky Mountain News

Campos: A weighty matter

*Latest study merely confirms  
fat haters' arguments flabby*

May 14, 2005

26.087



21.089

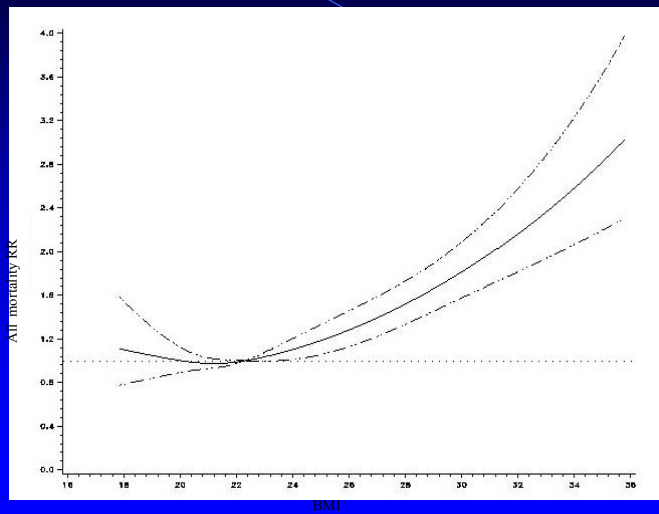
Obesity:  
~~“Epidemic”~~  
~~“Problem”~~  
~~“Threat”~~  
~~“Issue”~~  
**“Hype”**

Americans have been force-fed a steady diet of obesity myths by the “food police,” trial lawyers, and even our own government.  
Learn the truth about obesity at:  
[ConsumerFreedom.com](http://ConsumerFreedom.com)  
The Center for Consumer Freedom is a nonprofit organization dedicated to protecting consumer choice and promoting consumer issues.

## Methods

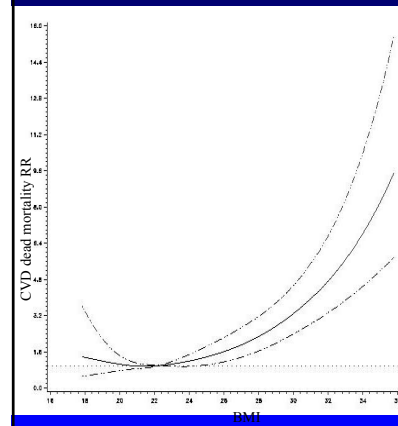
- Nurses’ Health Study 1976-2002
- N=120,360 women aged 30-55 yr in 1976.
- Total deaths: 15,266
  - CVD deaths: 3,585
  - Cancer deaths: 7,303

Spline regression of BMI and Total Mortality among never smokers: NHS 1976-2002

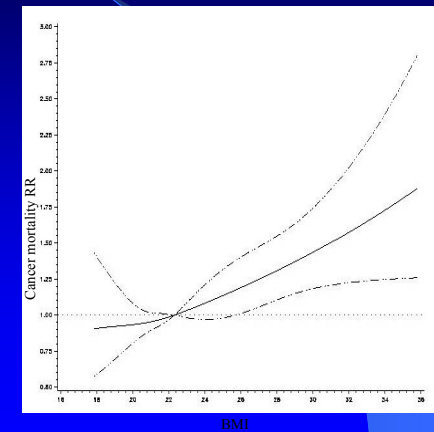


Spline regression of BMI and Mortality

CVD mortality



Cancer Mortality



## AARP Cohort: NEJM 2006 (>half million people)

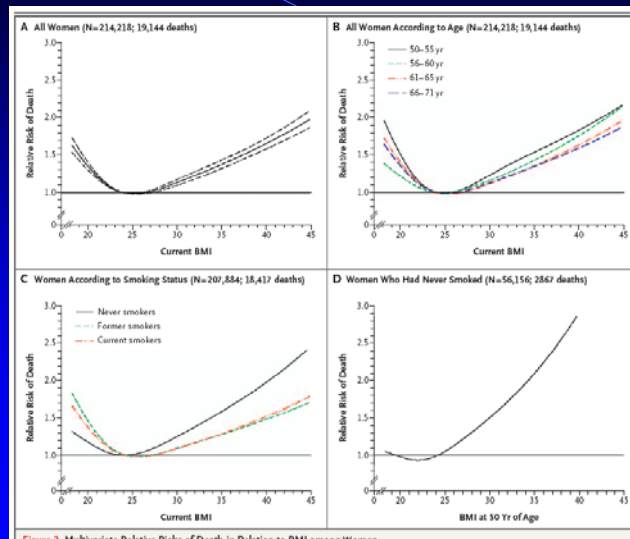
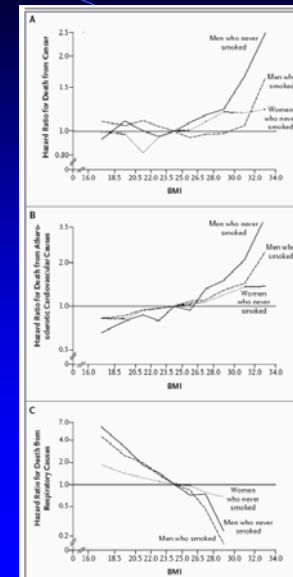


Figure 2. Multivariate Relative Risks of Death in Relation to BMI among Women.

## Korea Study: NEJM 2006 (>1.2 million people)



ORIGINAL INVESTIGATION

### Obesity, Physical Activity, and Mortality in a Prospective Chinese Elderly Cohort

C. Mary Schooling, PhD; Tai Hing Lam, MD, MSc; Zhi Bin Li, MD; Sai Yin Ho, PhD; Wai Man Chan, MBBS; Kin Sang Ho, MBBS; May Kei Tham, MBBS; Benjamin J. Cowling, PhD; Gabriel M. Leung, MD, MPH

Table 4. Risk for All-Cause Mortality by Body Mass Index and Physical Activity of Elderly Health Center Clients in Hong Kong\*

Comorbidities, No.	Deaths, No.	BMI				P Value†	None	Physical Activity		P Value†
		<18.5	18.5 to <23	23 to <25	≥25			≤30 min/d	>30 min/d	
4-12	1481	1.78‡ (1.51-2.07)	1.00	0.72‡ (0.63-0.83)	0.55‡ (0.49-0.63)	<.001	1.00	0.81§ (0.70-0.93)	0.70‡ (0.61-0.81)	<.001
3	894	1.81‡ (1.45-2.26)	1.00	0.70‡ (0.58-0.84)	0.64‡ (0.55-0.75)	<.001	1.00	0.85 (0.70-1.03)	0.77   (0.64-0.93)	.01
2	864	2.22‡ (1.81-2.73)	1.00	0.82   (0.68-0.99)	0.72‡ (0.61-0.85)	<.001	1.00	0.74§ (0.61-0.90)	0.70‡ (0.58-0.84)	.001
1	446	1.41  (1.01-1.97)	1.00	1.04 (0.81-1.33)	0.98 (0.78-1.23)	.88	1.00	0.92 (0.70-1.21)	0.83 (0.63-1.08)	.14
0	134	1.76  (1.00-3.08)	1.00	0.96 (0.58-1.59)	1.54  (1.02-2.33)	.16	1.00	1.24 (0.71-2.19)	1.15 (0.66-1.99)	.83

Arch Int Med 2006

## Summary on Obesity and Mortality

- It is essential to exclude baseline illness and smokers (need very large sample and long follow-up).
- No evidence of a decline in the impact of obesity on mortality over time.
- A clear evidence of increased mortality in the overweight group.
- The CDC results are likely to be confounded and biased by methodological problems. More recent studies with large samples sizes and better methods showed consistent associations between BMI and mortality.

## Effect of Exercise on the Metabolic Syndrome and Diabetes

- Improves insulin sensitivity and glucose control
- Increases HDL cholesterol
- Decreases triglycerides
- Decreases blood pressure
- Decreases fibrinogen
- Decreases risk of diabetes, CAD, and stroke
- Beneficial for weight loss and maintenance

## Key Issues in the Field of Physical Activity

- ◆ Exercise intensity and type
  - Vigorous exercise vs. walking
- ◆ Fatness vs. fitness

## Intensity and Type of Physical Activity in Relation to Coronary Heart Disease in Men

Mihaela Tanasescu MD, Michael Leitzmann MD, Eric Rimm ScD, Walter Willett MD, Meir Stampfer MD, Frank Hu MD

JAMA 2002

## Study Population and Outcome Events

- HPFS: 44, 586 male health professionals (aged 40-75 years in 1986)
- Excluded
  - men with cancer and CVD at baseline
  - men with physical impairment
- 1,704 CHD endpoints 1986-1998
  - fatal CHD (definite, presumed, sudden death)
  - nonfatal MI (definite, probable)

## Assessment of Physical Activity

- average weekly time spent on
  - walking, jogging, running, bicycling, lap swimming, tennis, squash/racquetball, rowing/calisthenics (1986 questionnaire)
  - heavy outdoor work (added 1988)
  - weightlifting (added 1990)

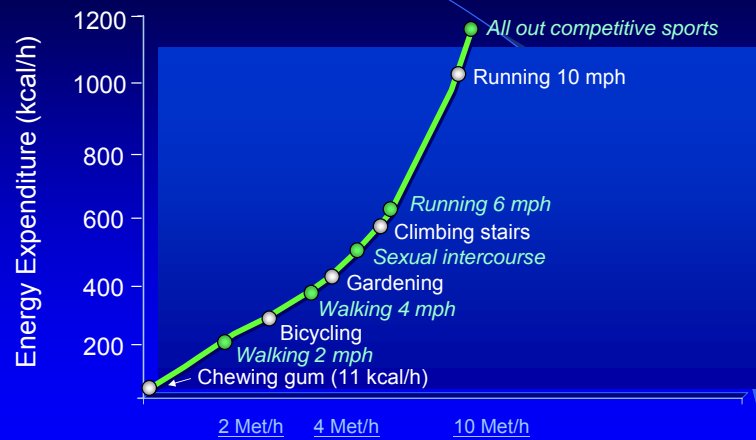
### Validity

Correl. Coef. With 1 week diaries: 0.65 total PA, 0.58 vigorous.  
Correl of vigorous activity with resting pulse -0.45, after step test -0.41.  
HDL increased by 0.06mmol/l for each 20MET-hrs/week.

## Units of Physical Activity: MET-hours

- MET-hours = number of METS \* number of hours
- METS = metabolic equivalents = typical energy expenditure for each activity
- 1MET = energy expended when resting/sitting quietly = 3.5ml oxygen/kg\*min = 1kcal/kg\*h

## Energy Expenditure of Physical Activity



Adapted from: Alpers. Undergraduate Teaching Project. Nutrition: energy and protein. American Gastroenterological Association, 1978.

## Total activity

Total amount (volume) of activity (MET-hrs) =

$$= \sum_{i=1}^n I_i * T_i$$

Average Intensity (METS) =  $\frac{\sum_{i=1}^n I_i * T_i}{\sum_{i=1}^n T_i}$

### Relative Risks for GHD Associated With Total Weekly Met-hours of Physical Activity

	Total Physical Activity (Quintiles met-hours/week)					p-trend
	0-6.32	6.33-14.49	14.50-25.08	25.09-41.98	41.99+	
#cases	433	370	339	294	268	
Person-years	94098	94245	93601	91335	103826	
Age adjusted	0.86 (0.75,0.99)	0.79 (0.69-0.92)	0.72 (0.62,0.84)	0.58 (0.50,0.68)		<0.001
Multivariate <sup>1</sup>	0.90 (0.74,0.99)	0.86 (0.74,0.99)	0.80 (0.68,0.93)	0.66 (0.56,0.77)		<0.001
Multivariate <sup>2</sup>	0.91 (0.79-1.05)	0.89 (0.7,0.97)	0.83 (0.71,0.97)	0.70 (0.60,0.83)		<0.001
Multivariate <sup>3</sup>	0.93 (0.81,1.07)	0.92 (0.79,1.07)	0.87 (0.75,1.02)	0.75 (0.64,0.88)		<0.001

<sup>1</sup>adjusted for alcohol, smoking, family history of MI and nutrients (poly, trans, folic acid, fiber, vitamin E supplement)

<sup>2</sup>additionally adjusted for presence of diabetes, high cholesterol and hypertension at baseline

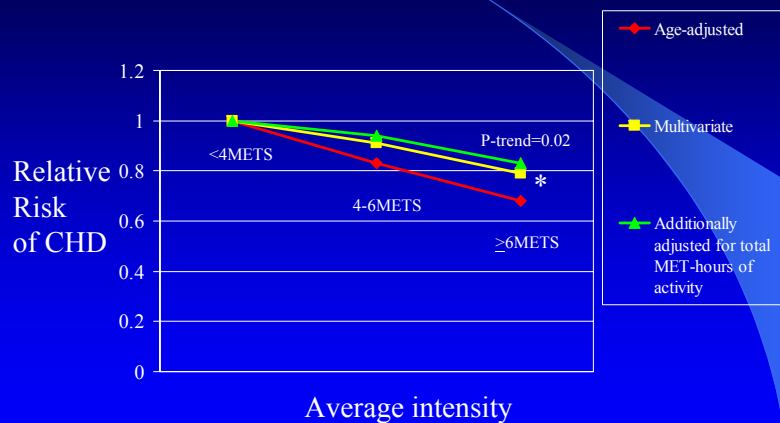
<sup>3</sup>additionally adjusted for BMI

### Correction for Measurement Error for Total Activity

Increment of 50 MET-hrs/week  
 – RR=0.75 (0.66-0.85) cumulative update

	Uncorrected	Corrected
Simple Update	0.79(0.72-0.88)	0.45(0.28-0.72)
Baseline	0.78(0.68-0.90)	0.49(0.30-0.81)

### Average Exercise Intensity and CHD Risk



### Relative Risk of CHD associated with different types of activity

Activity	RR(95%CI for ≥ 1h/wk vs. 0)	p-trend
Running	0.58 (0.44-0.77)	<0.001
Rowing	0.82 (0.68-0.99)	0.04
Jogging	0.93 (0.72-1.21)	0.51
Racquet sports	0.99 (0.84-1.17)	0.83
Cycling	1.07 (0.91-1.25)	0.50
Swimming	1.21 (0.95-1.54)	0.29

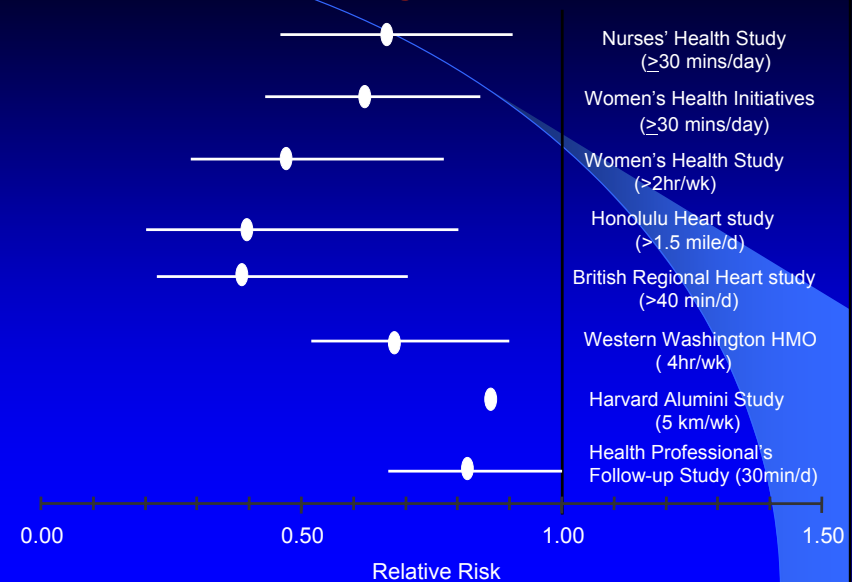
Multivariate, adjusted for each other

## Relative Risks for CHD Associated with Weight Lifting (1990-1998)

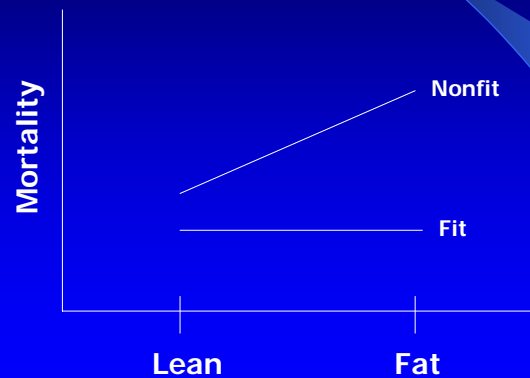
	0	<0.5 hr/wk	≥0.5hr/wk	p-trend
#cases	1011	97	89	
Person years	210176	30323	41238	
Age adjusted	1	0.82 (0.66, 1.01)	0.62 (0.50, 0.77)	<0.001
Multivariate	1	0.89 (0.72, 1.11)	0.71 (0.56, 0.89)	0.002
Multivariate*	1	0.95 (0.76, 1.19)	0.77 (0.61, 0.97)	0.002

Multivariate: adjusted for alcohol, smoking, family history of MI and nutrients (poly, trans, folic acid, fiber, vitamin E supplements), baseline diabetes, high cholesterol and hypertension  
 \* Additionally adjusted for the other activities

## Walking and CHD



## The “Fat and Fit” Hypothesis: Being fit removes the excess risk of being fat



## Methods

- Nurses' Health Study 1976-2000
- N=116,564 women aged 30-55 yrs without CVD or cancer at baseline.
- Total deaths: 10,282 CVD deaths: 2,370  
Cancer deaths: 5,223 Other causes: 2,689
- Joint analyses of BMI and physical activity
- Joint analyses of waist circumference and physical activity

**Multivariate RR of overall mortality according to joint categories of BMI & physical activity levels, NHS 1980-2000**

	Physical Activity (hr/wk)		
	≥3.5	1-3.4	<1
<b>Overall Mortality</b>			
BMI<25			
Number of cases/	807/	1540/	1091/
Person-years	352531	457290	215188
RR	1.00	1.18(1.09,1.29)	1.55(1.42,1.70)
BMI 25-29.9			
Number of cases/	298/	699/	518/
Person-years	92827	167442	89787
RR	1.28(1.12,1.46)	1.33(1.20,1.47)	1.64(1.46,1.83)
BMI≥30			
Number of cases/	136/	450/	410/
Person-years	31726	78675	53032
RR	1.91(1.60,2.30)	2.05(1.82,2.30)	2.42(2.14,2.73)

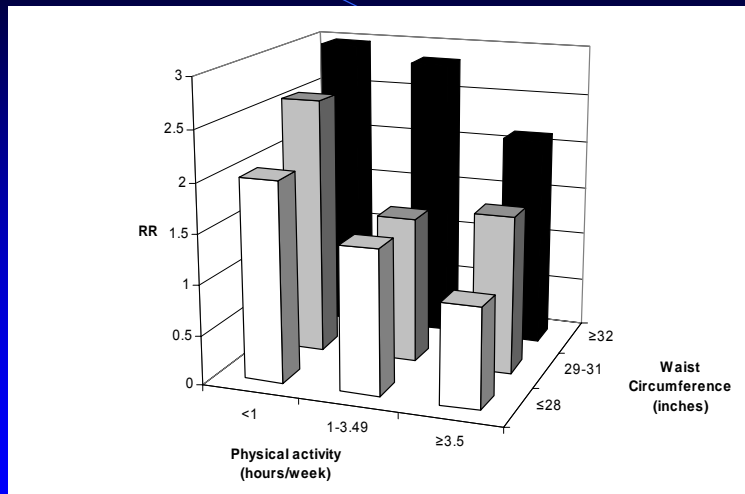
Hu et al. NEJM 2004

**Multivariate RR of CHD according to joint categories of BMI & physical activity levels, NHS 1980-2000**

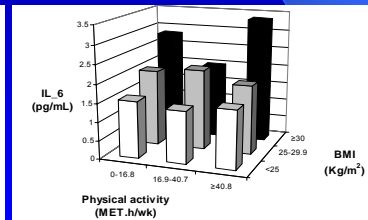
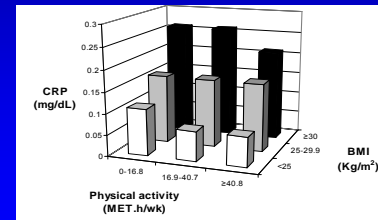
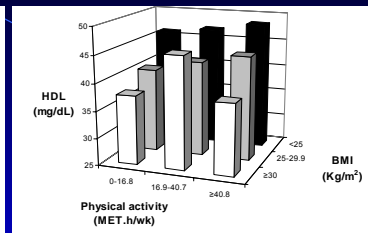
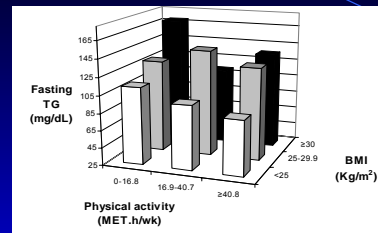
	Physical Activity (hr/wk)		
	≥3.5	1-3.4	<1
BMI<25			
RR	1.00	1.33(1.13,1.56)	1.47(1.23,1.75)
BMI 25-29.9			
RR	1.44(1.13,1.82)	1.92(1.61,2.29)	2.04(1.67,2.48)
BMI≥30			
RR	2.49(1.85,3.35)	3.32(2.75,4.01)	3.44(2.81,4.21)

P for interaction>0.30

Li et al. Circulation 2006



### BMI, physical activity, and cardiovascular biomarkers



## Summary

- Both adiposity and physical inactivity are strong and independent predictors of CHD incidence and mortality.
- Being physical active somewhat attenuates but does not eliminate the excess risk associated with overweight and obesity.
- Public health campaigns should emphasize both maintaining a healthy weight and regular physical activity.

## Other Benefits of Exercise

- Cognitive and Physical functions
- Gallstones
- Fractures
- Colon cancer
- Breast cancer incidence and survival
- Prostate cancer
- Pancreatic cancer

## Physical Activity, Including Walking, and Cognitive Function in Older Women

**Healthier Women, Inc.**  
**Dr. Eric Tang, MD**  
**Julius S. Winters, MD**  
**Michael W. S. Broderick, MD**  
**James M. Ware, PhD**  
**Frederic C. White, PhD**

**Context:** Physical activity may help maintain cognitive function in older adults.  
**Objective:** To evaluate the relation of long-term regular physical activity, including walking, to cognitive function.  
**Design:** Retrospective report of self-reported leisure-time physical activity in women 65 and older who responded to questionnaires in 1986, 1996, and 2001. Long-term regular physical activity was defined as weekly expenditures from questionnaires in 1986 through 2001 of at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity activity. We used linear regression to estimate adjusted mean differences in baseline cognitive performance and cognitive decline over 20 years.

**Table 4.** Mean Differences in Baseline Cognitive-Function Scores by Quartile of Walking\*

Test	Quartile of Walking (MET-hours/wk)				P Value for Trend
	1 (<1.9)	2 (1.9-4.2)	3 (4.3-8.5)	4 (>8.5)	
TICS (n = 7982) Adjusted mean difference (95% CI)	Reference	0.19 (0.02 to 0.36)	0.30 (0.13 to 0.47)	0.31 (0.13 to 0.48)	.003
Category fluency (n = 7674) Adjusted mean difference (95% CI)	Reference	0.28 (-0.01 to 0.57)	0.33 (0.03 to 0.63)	0.40 (0.10 to 0.70)	.03
Working memory and attention (n = 6968) Adjusted mean difference (95% CI)	Reference	0.14 (-0.02 to 0.30)	0.21 (0.04 to 0.37)	0.35 (0.18 to 0.51)	<.001
Verbal memory score (n = 6969)† Adjusted mean difference (95% CI)	Reference	0.02 (-0.02 to 0.08)	0.06 (0.01 to 0.10)	0.05 (0 to 0.10)	.07
Global score (n = 6957)† Adjusted mean difference (95% CI)	Reference	0.04 (0 to 0.08)	0.06 (0.02 to 0.10)	0.07 (0.02 to 0.11)	.007

Abbreviations: CI, confidence interval; MET, metabolic equivalent.  
 \*Includes only the 7982 women who did not report any vigorous activity. Adjusted for the variables listed in the footnote to Table 2 as well as for MET-hours expended on stair-climbing and low-intensity exercise (eg, yoga, stretching, toning).  
 †Verbal memory score averages performance in immediate and delayed 10-word recalls and immediate and delayed East Boston Memory Tests. Global score averages performance on all cognitive tests. Composite scores were computed only for women who completed all component tests.

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## The New England Journal of Medicine

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### RECREATIONAL PHYSICAL ACTIVITY AND THE RISK OF CHOLECYSTECTOMY IN WOMEN

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**TABLE 4.** RELATIVE RISK OF CHOLECYSTECTOMY IN RELATION TO VIGOROUS AND NONVIGOROUS ACTIVITY.\*

VARIABLE	CATEGORY OF PHYSICAL ACTIVITY					P VALUE FOR TREND
	1	2	3	4	5	
<b>Vigorous activity</b>						
MET-hr/wk	0	0.1-1.6	1.7-6.9	7.0-15.9	≥16.0	
No. of women who had cholecystectomy	1,625	440	411	447	334	
Person-yr	250,459	74,271	68,730	86,238	73,683	
Relative risk (95% CI)						
Age-adjusted	1.0	0.93 (0.84-1.04)	0.94 (0.84-1.05)	0.81 (0.73-0.90)	0.71 (0.63-0.80)	<.001
Multivariate plus nonvigorous activity††	1.0	0.89 (0.80-0.99)	0.94 (0.84-1.05)	0.83 (0.74-0.92)	0.75 (0.66-0.85)	<.001
Multivariate plus nonvigorous activity, BMI, and weight change††§	1.0	0.91 (0.81-1.01)	0.97 (0.87-1.09)	0.88 (0.79-0.98)	0.82 (0.73-0.93)	0.001
<b>Nonvigorous activity</b>						
MET-hr/wk	0-0.8	0.9-2.6	2.7-4.4	4.5-10.7	≥10.8	
No. of women who had cholecystectomy	703	731	668	574	581	
Person-yr	108,368	109,170	112,549	113,257	110,037	
Relative risk (95% CI)						
Age-adjusted	1.0	1.04 (0.94-1.16)	0.92 (0.83-1.02)	0.78 (0.70-0.87)	0.80 (0.72-0.89)	<.001
Multivariate plus vigorous activity††	1.0	1.06 (0.95-1.17)	0.95 (0.85-1.06)	0.83 (0.74-0.93)	0.86 (0.77-0.98)	<.001
Multivariate plus vigorous activity, BMI, and weight change††§	1.0	1.09 (0.99-1.22)	0.99 (0.89-1.10)	0.89 (0.79-0.99)	0.95 (0.84-1.06)	0.05

## Physical Activity and Survival After Breast Cancer Diagnosis

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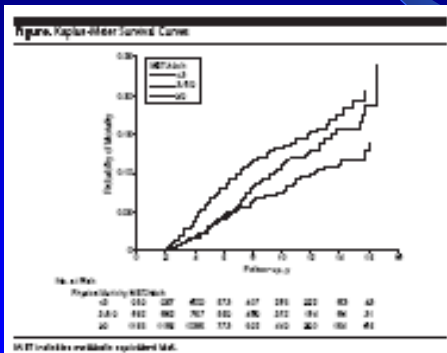
Caroline H. Kroenke, ScD

Graziela A. Colditz, MD, DrPH

**Context:** Physical activity has been shown to decrease the incidence of breast cancer, but the effect on recurrence or survival after a breast cancer diagnosis is not known.

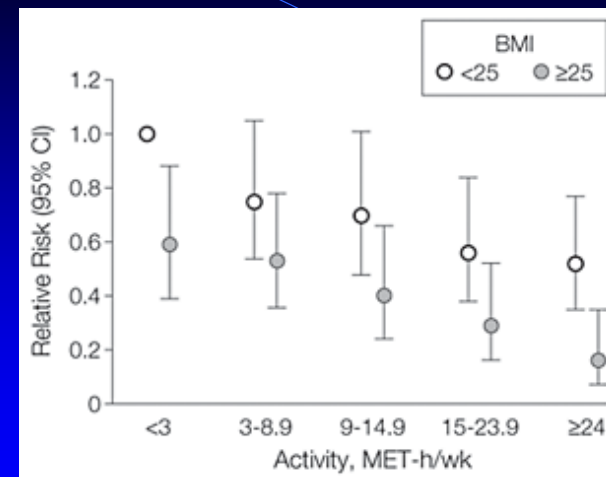
**Objective:** To determine whether physical activity among women with breast cancer decreases their risk of death from breast cancer compared with more sedentary women.

**Design, Setting, and Participants:** Prospective observational study based on re-



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## Hip Fracture Among Postmenopausal Women in the Nurses' Health Study, 1986-1998, by Body Mass Index (BMI)

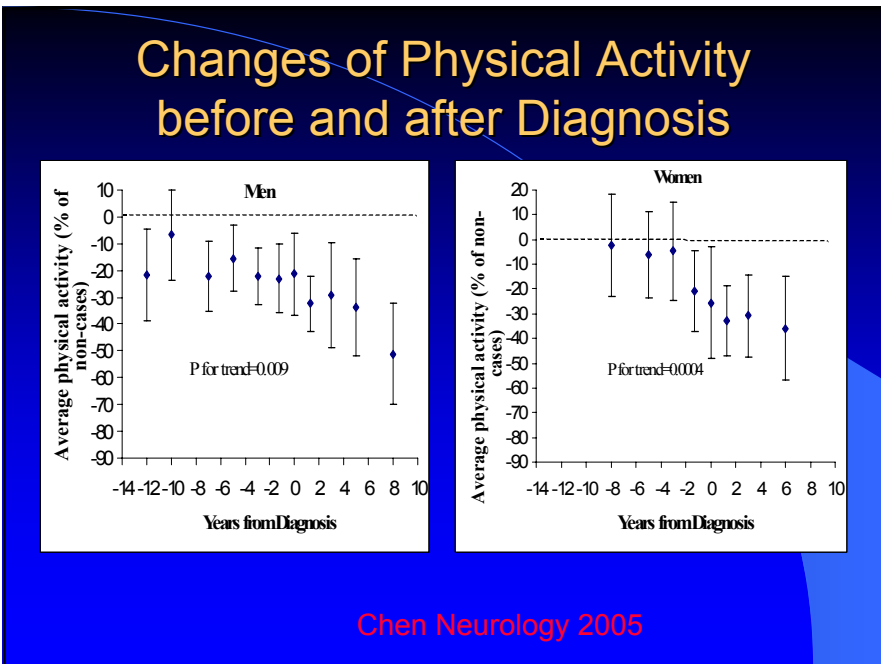


Feskanich, D. et al. JAMA 2002;288:2300-2306.

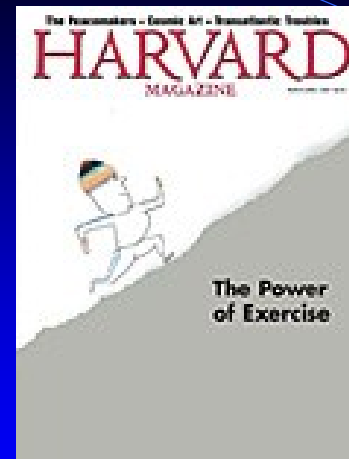
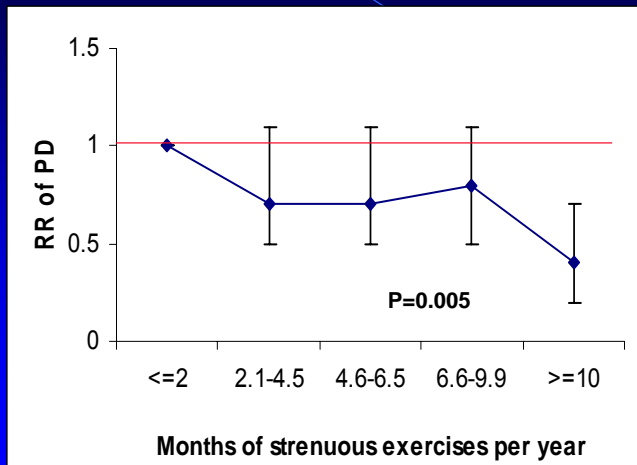
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## Early Life Strenuous Exercise (Men)



**In the bottle before you is a pill**, a marvel of modern medicine that will regulate gene transcription throughout your body, helping prevent heart disease, stroke, diabetes, obesity, and 12 kinds of cancer — plus gallstones and fractures ... Even your immune system will be stimulated. There is just one catch...

There's no such pill. The prescription is exercise.



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