

WHI Observational Study

Opening Comments

Moderator:

Teri Manolio, MD, PhD

National Heart, Lung, and Blood Institute

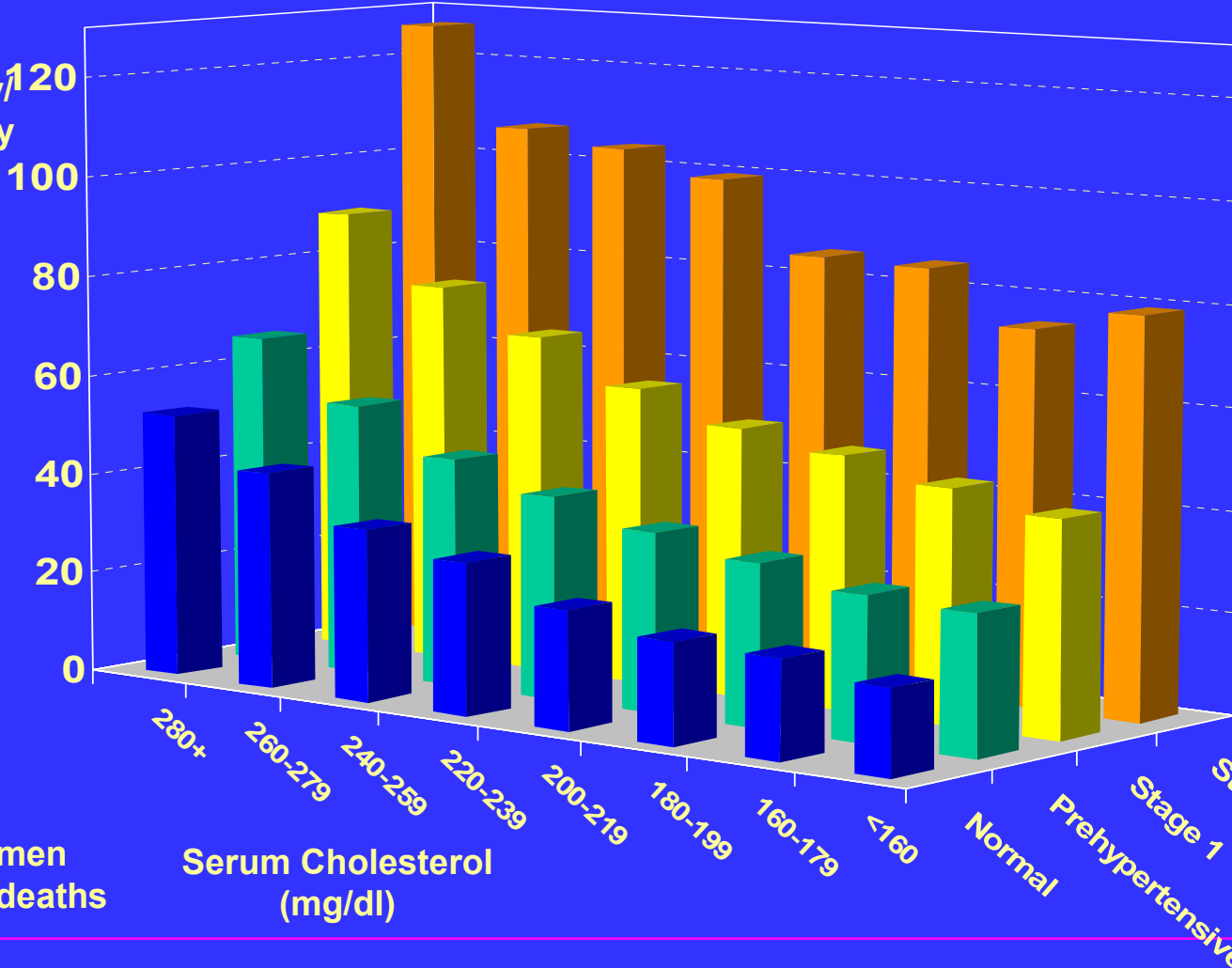
Senior Advisor to the Director for Population Genomics,

National Human Genome Research Institute



Value of Large Cohort Studies: 25 Year CVD Mortality for MRFIT Screenees

CVD Mortality/
10,000 py



353,340 men
36,616 deaths

Serum Cholesterol
(mg/dl)

JNC-VII
BP Category

Courtesy J Neaton and J Cutler



Observational

Characteristics of an Ideal Cohort Study

- **Size matters**
- **Representative sample, high response rate**
- **Diverse in geography, socioeconomic status, race/ethnicity**
- **Extensive, standardized, reproducible characterization at entry**
- **Repeated interim measures to assess change in exposures and disease status and to add new exposure measures**
- **Comprehensive, standardized assessment of outcomes**



Importance of Data Sharing

- Long-term epidemiologic studies generally collect more data than any group of investigators, no matter how large or how dedicated, can mine completely
- New investigators and new disciplines often bring new ideas, even though some may seem outlandish
- Collaboration with investigators knowledgeable about study generally leads to greater efficiency, better science
- WHI OS dataset available at <http://www.nhlbi.nih.gov/resources/deca/whios/>



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Teri Manolio, MD, PhD

The OS Resource

Robert Langer, MD, MPH

Selected Major Findings

- **Heart and Brain**
- **Blood Pressure/Depression**
- **Breast Cancer**
- **Bones**
- **Body Weight**
- **Diabetes**
- **Access to Medical Care**

JoAnn Manson, MD, DrPH
Sylvia Wassertheil-Smoller, PhD
Anne McTiernan, MD, PhD
John Robbins, MD
Lewis Kuller, MD, DrPH
Karen Margolis, MD, MPH
F. Allan Hubbell, MD

**Audience Q and A
and
Closing Comments**

Teri Manolio, MD, PhD
Moderator



WHI Observational Study

The OS Resource

Robert Langer, MD, MPH
Principal Investigator
La Jolla Clinical Center

Director, Outcomes Research Institute
Geisinger Health System
Danville, Pennsylvania



WHI OS: Objectives and Composition

- To explore the predictors and natural history of important health problems in postmenopausal women
- To serve as a secular control for the Clinical Trials
- Two paths to enroll, about half from each source:
 - CT interested but ineligible or unwilling to be randomized
 - direct enrollment into the OS
- Eligibility:
 - 50 to 79 years old, postmenopausal
 - reliable/mentally competent
 - expected survival and local residency for at least 3 years
- 93,676 women enrolled between 1994 and 1998



Details of the WHI OS

- **Average follow-up about 7 years**
 - **Brief physical exams at baseline and 3 years**
 - **height, weight, blood pressure**
 - **blood samples for biomarkers and DNA**
 - **Annual mailed questionnaires for all other years**
 - **more extensive than those in the CT**
 - **allow study of a wide range of risk factors, socioeconomic influences, and less common diseases**
 - **have a common core,* and a variable section**
- * major medical events, exercise, smoking, weight, marital status, hormone use, specific conditions e.g. arthritis**



Examples of Supplemental Items in OS Exposure Forms

- weight & weight change
- types of fats eaten
- red/white wine
- HT, phytoestrogens
- insecticides
- pets
- electromagnetic fields
- hair dyes, talc
- sun exposure
- passive smoking
- caffeine, diet drinks
- life stress
- religious practices
- alternative medicine
- dental health
- places of residence

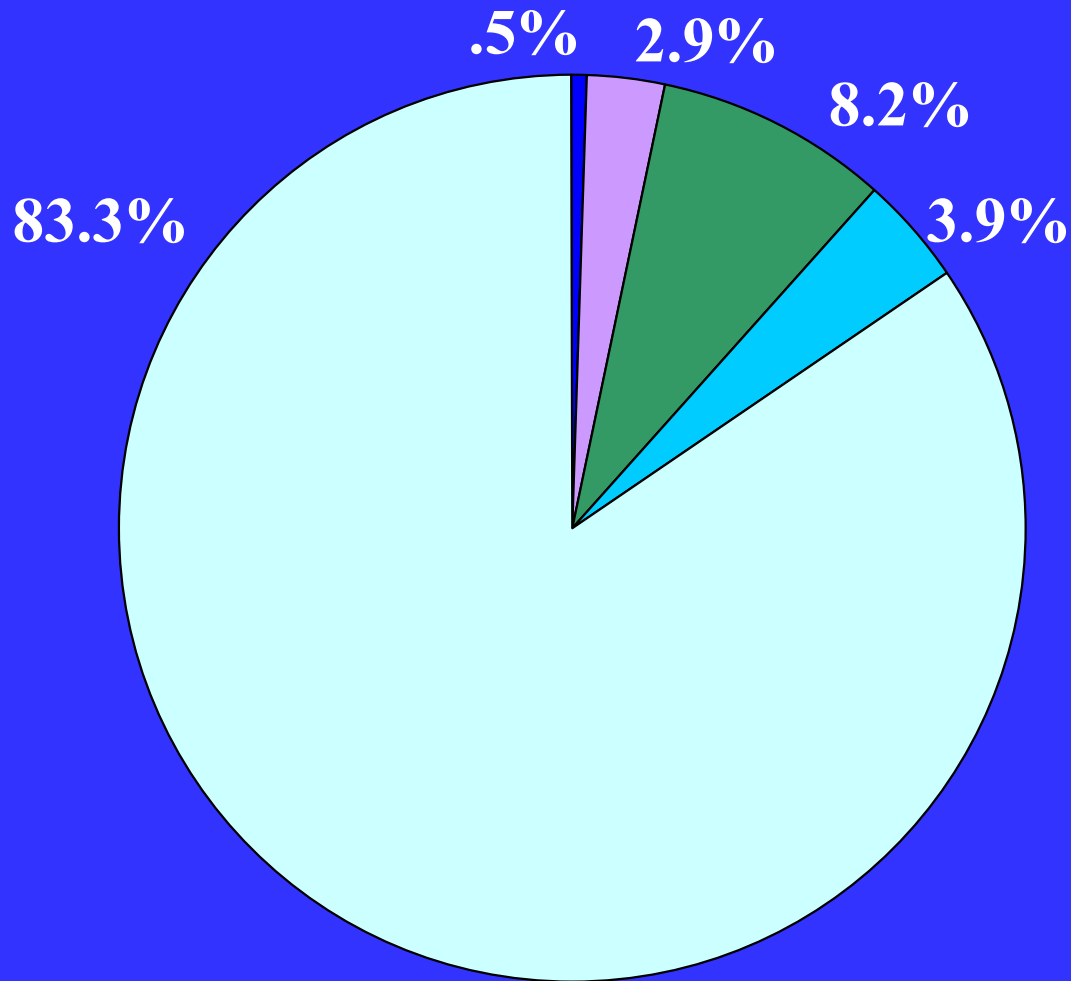


Unique Features of the WHI OS: Demographic and Cultural Diversity

- Enrolled women who came of age in four decades, from the depression-era, to the first years of the baby boom
- Wide range of socio-cultural influences on opportunities and health behaviors
- Among the first to reach out to older minority women including Native American, Asian/Pacific Islander, Hispanic and African American women



OS Racial Composition



-  **American Indian / Alaska Native**
-  **Asian / Pacific Islander**
-  **Black / African American**
-  **Hispanic / Latina**
-  **White**



Resources and Scientific Potential: WHI OS

- **Wide ranging information on risk exposures**
 - **Questionnaires & sampling schedule:**
<http://www.whiscience.org>
 - **Baseline monograph: Ann Epidemiol 2003 Oct;13(9 Suppl): S107-21.**
- **Biological samples**
 - **Blood and DNA**
 - **Size and variability of the OS allows efficient strategies to answer specific questions, while conserving samples for future studies where a small number of woman might make a difference**



Major Findings from OS: Heart and Brain (Stroke)

**JoAnn Manson, MD, DrPH
Principal Investigator
Boston Clinical Center**

**Professor of Medicine,
Harvard Medical School
Chief, Division of Preventive Medicine
Brigham and Women's Hospital
Boston, Massachusetts**



Physical Activity and Prevention of Cardiovascular Events in Women

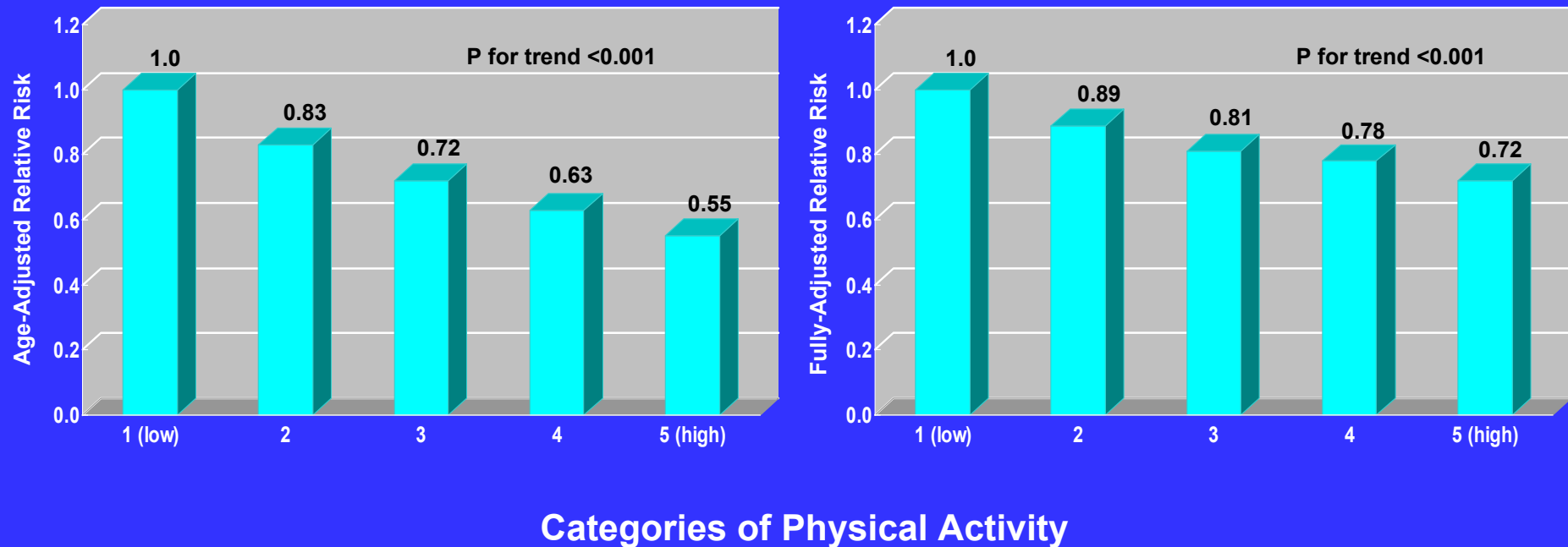
(N Engl J Med 2002; 347:716-725)

Goals:

- **To assess the relationship between physical activity and risk of cardiovascular disease (CVD), including heart disease and stroke**
- **To compare the role of moderate-intensity exercise (walking) and vigorous exercise in preventing CVD**
- **To compare the benefits of exercise in women of different ages, ethnic groups, and body weight categories**



Physical Activity and Cardiovascular Disease: The Women's Health Initiative Observational Study (N=73,743 women; 1,551 CVD events)



Physical Activity and Cardiovascular Events: Other Findings

- **Brisk walking and vigorous exercise were associated with similar (30-40%) reductions in risk of CVD.**
- **Exercise produced greater benefits for heart disease than for stroke.**
- **Physical activity appeared to have similar CVD benefits in white women and in African-American women and results did not vary appreciably by age or body weight.**



White Blood Cell (Leukocyte) Count and Risk of Cardiovascular Events in Women

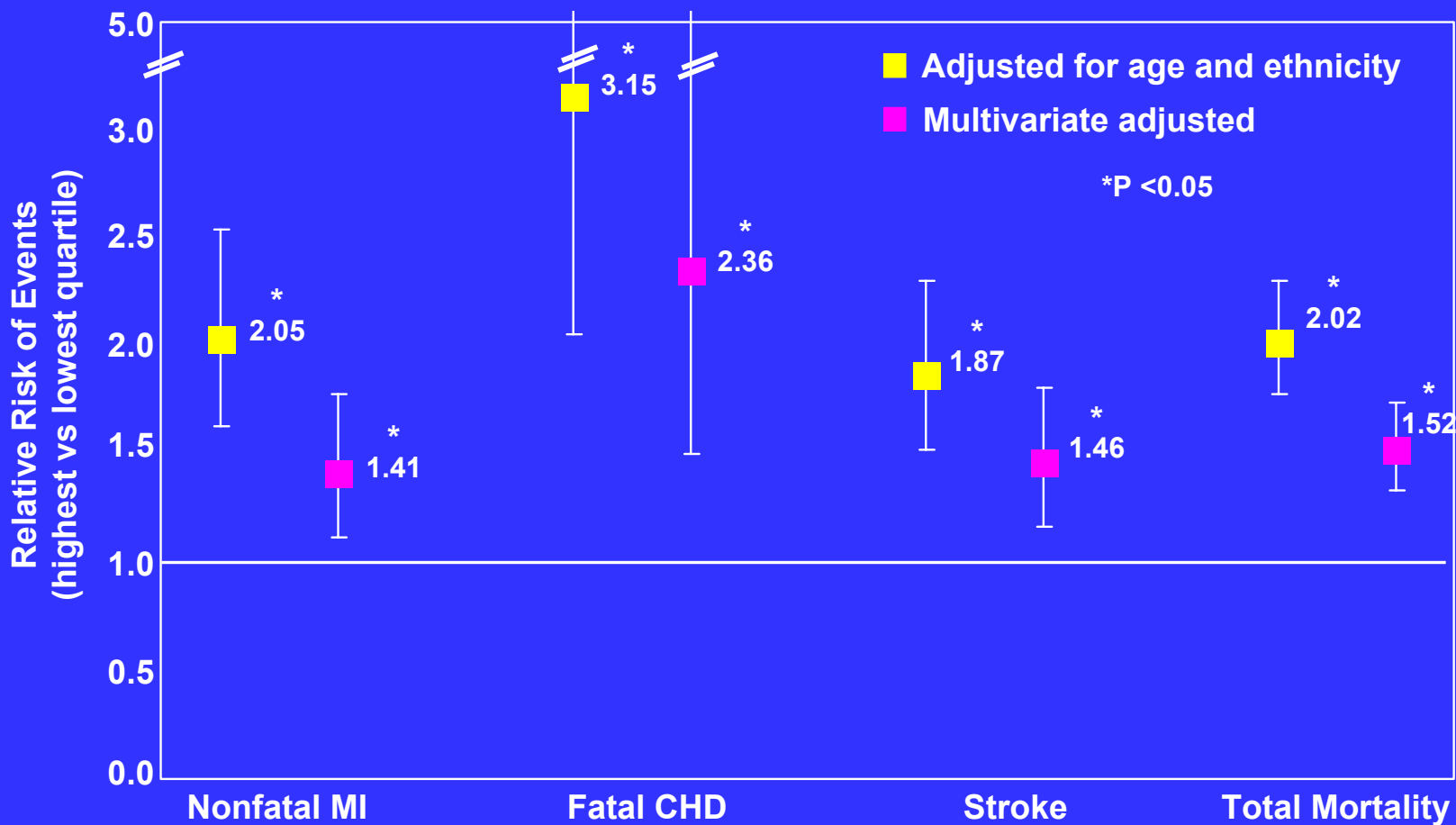
(Arch Intern Med 2005; 165:500-8)

Goals:

- **To assess the role of the white blood cell (WBC) count, a simple routine clinical test that serves as a marker for inflammation, as a predictor of future risk of heart disease, stroke, and total mortality in women.**
- **To assess the contribution of WBC count independent of traditional CVD risk factors.**



Relative Risks of Cardiovascular Events and Total Mortality According to WBC Count (Highest vs Lowest Quartile)



WBC Count and Cardiovascular Events: Summary/Conclusions

- Higher WBC counts (level $\geq 6.7 \times 10^9$ cells/L, which is within normal range) predict a significant increase in future risk of heart disease, stroke, and total mortality in women.
- Elevated risks persist even after control for other known CVD risk factors.



Major Findings from OS: Blood Pressure and Depression

**Sylvia Wassertheil-Smoller, PhD
Principal Investigator
New York City Clinical Center**

**Professor of Epidemiology and Population
Health
Head, Division of Epidemiology
Albert Einstein College of Medicine
New York City, New York**



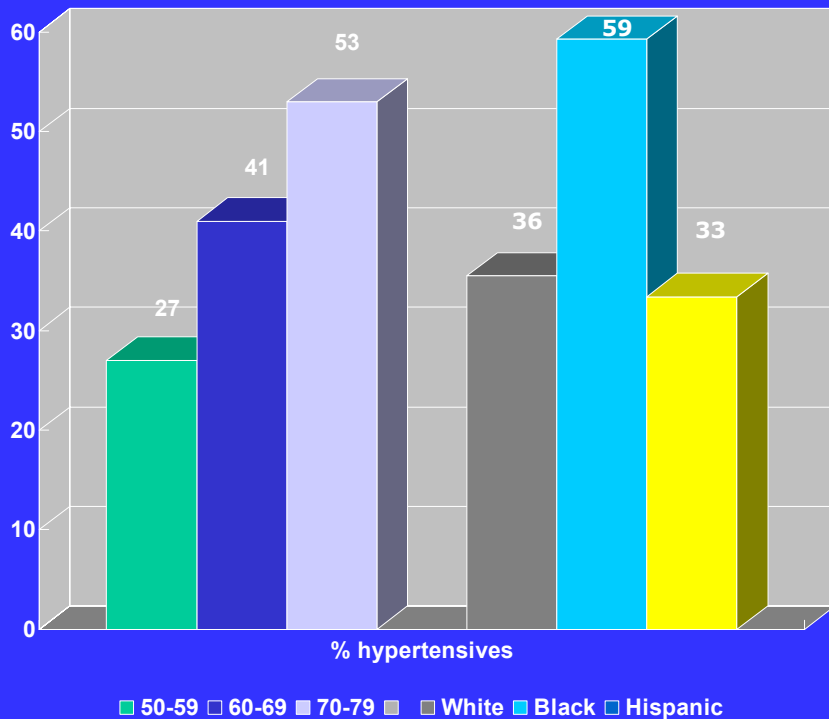
Hypertension Study: Goals

(Hypertension 2000; 36(5):780-9)

- To describe the prevalence, treatment and control of high blood pressure in postmenopausal women.
- Purpose is to:
 - evaluate how we are doing and
 - target areas for improvement in BP control.
- Hypertension = SBP \geq 140, DBP \geq 90, or on meds



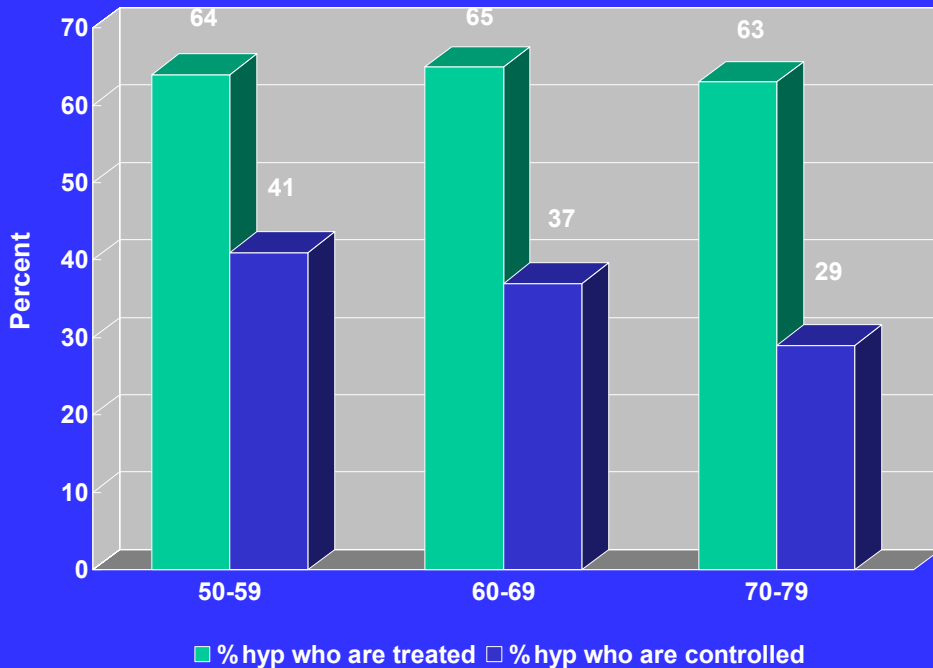
Percent Prevalence of Hypertension by Age and Race/Ethnicity (N=90,755 women)



- ★ Overall, about 4 out of 10 postmenopausal women are hypertensive. Prevalence rises with age.
- ★ 59% of Black women have hypertension compared to about a third of White or Hispanic women.



Treatment and Control of BP



- ★ About two thirds in all ages are treated, but only about one third have their BP under control.
- ★ Control of BP decreases with age, (only 29% of 70-79 year olds have BP under control).
- ★ Older women are not adequately treated.



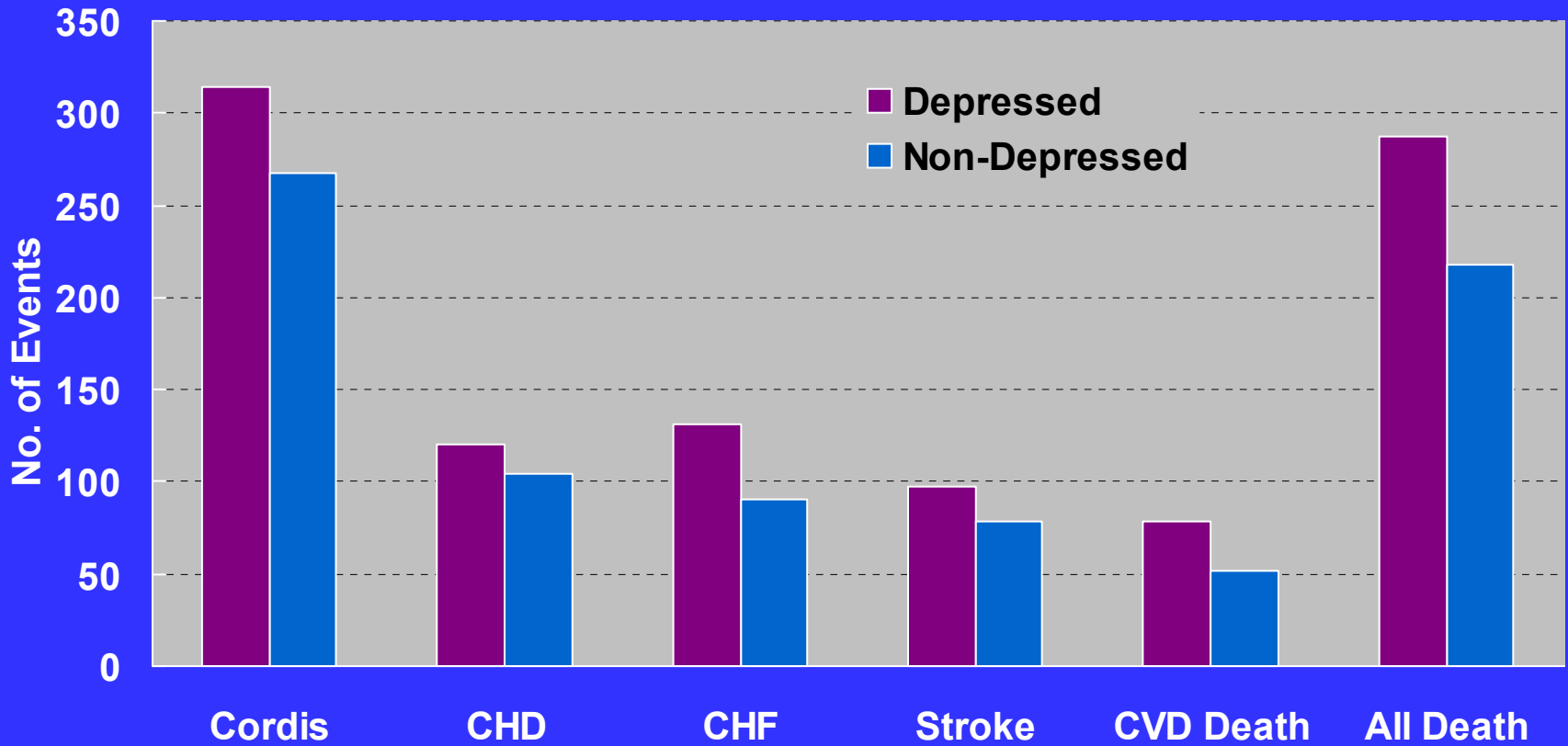
Depression and Cardiovascular Sequelae in Post-Menopausal Women: in WHI

(Arch Intern Med 2004; 164(3)289-98)

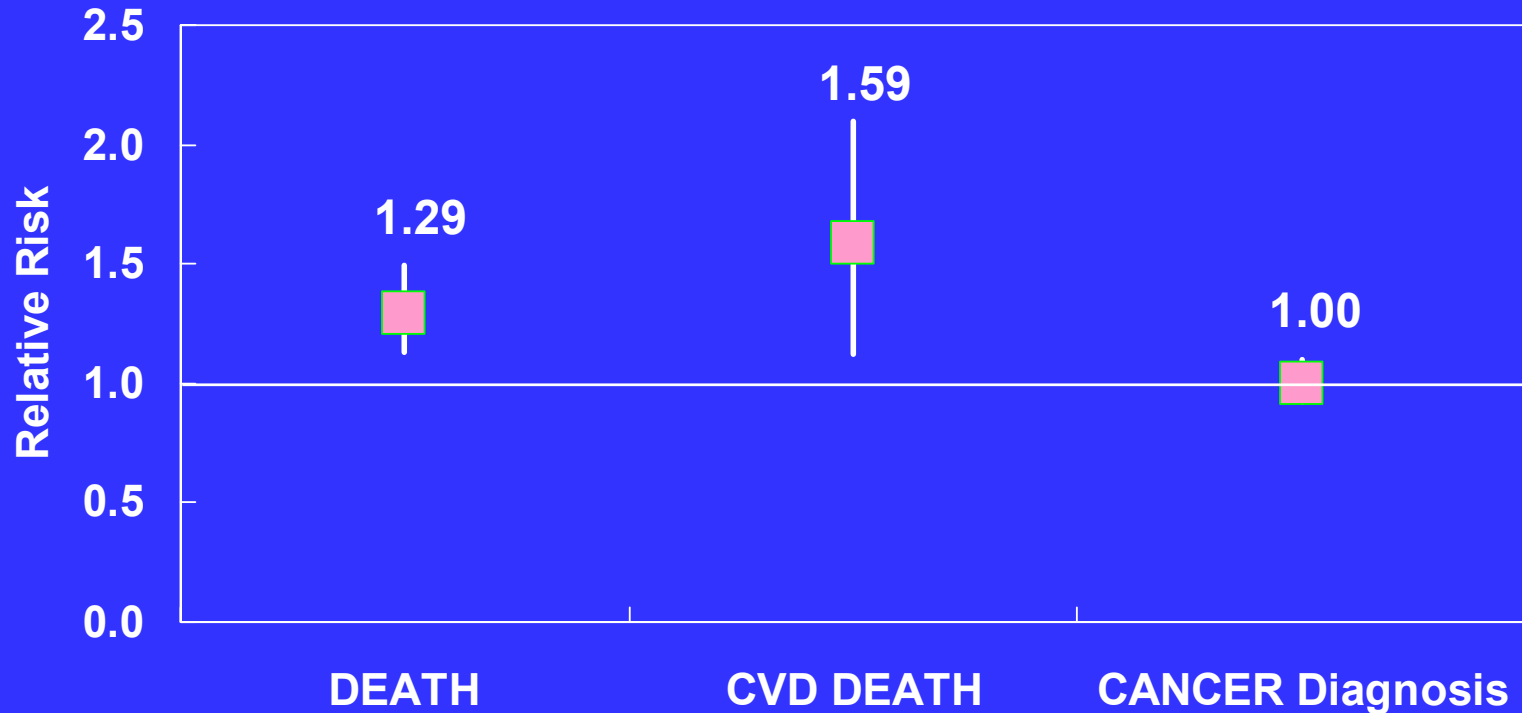
- In WHI 16% of women had symptoms of depression.
- 7.8% were taking anti-depressant medication.
- Older women (70-79) report less depression than younger ones.
- Hispanic and Black women have highest rates of depression, Asians/Pacific Islanders have lowest rates.



Crude Event Rates per 10,000 Women for Those with Current or History of Depression and Those Non-Depressed (4.1 years Follow-up)



Risks Associated With Baseline Depression Among Those With No History of CVD (N= 73,098)



Depression is an independent risk factor for CVD death.

Depression is not related to future cancer diagnosis.



Major Findings from OS: Breast Cancer

**Anne McTiernan, MD, PhD
Co-Investigator
WHI Clinical Coordinating Center**

**Member, Public Health Sciences Division
Fred Hutchinson Cancer Research Center
Seattle, Washington**



Physical Activity and Incidence of Breast Cancer

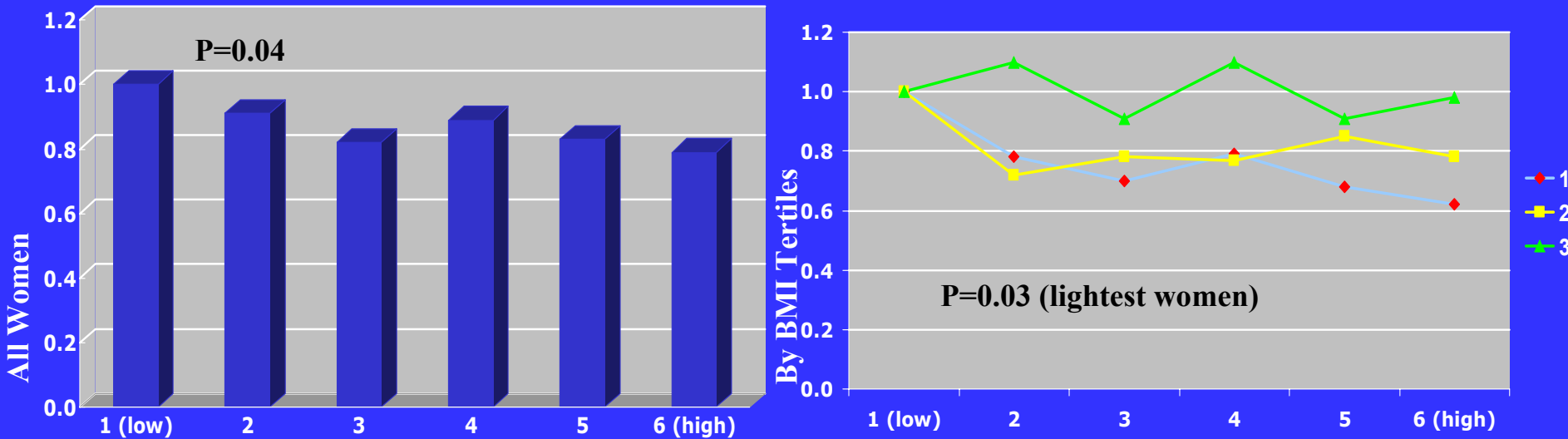
(*JAMA* 2003; 290:1331-6)

Goals:

- To assess the relationship between current total, strenuous, and moderate intensity physical activity and risk of breast cancer.
- To assess the association between past strenuous exercise and breast cancer risk.
- To compare the benefits of exercise in women of different body weight categories.



Total Physical Activity and Breast Cancer



Relative Risk According to Categories of Physical Activity

(N=74,171 women; 1780 breast cancer cases)



Other Findings: Physical Activity and Breast Cancer

- **Women who engaged in regular strenuous exercise at age 35 yrs. had a 14% lower risk of breast cancer vs. less active women.**
- **Total activity was more strongly related to breast cancer risk reduction compared with strenuous or moderate/strenuous activity.**
- **Age, parity, family history of breast cancer, and use of hormone therapy did not affect the results.**



Body Size and Incidence of Breast Cancer

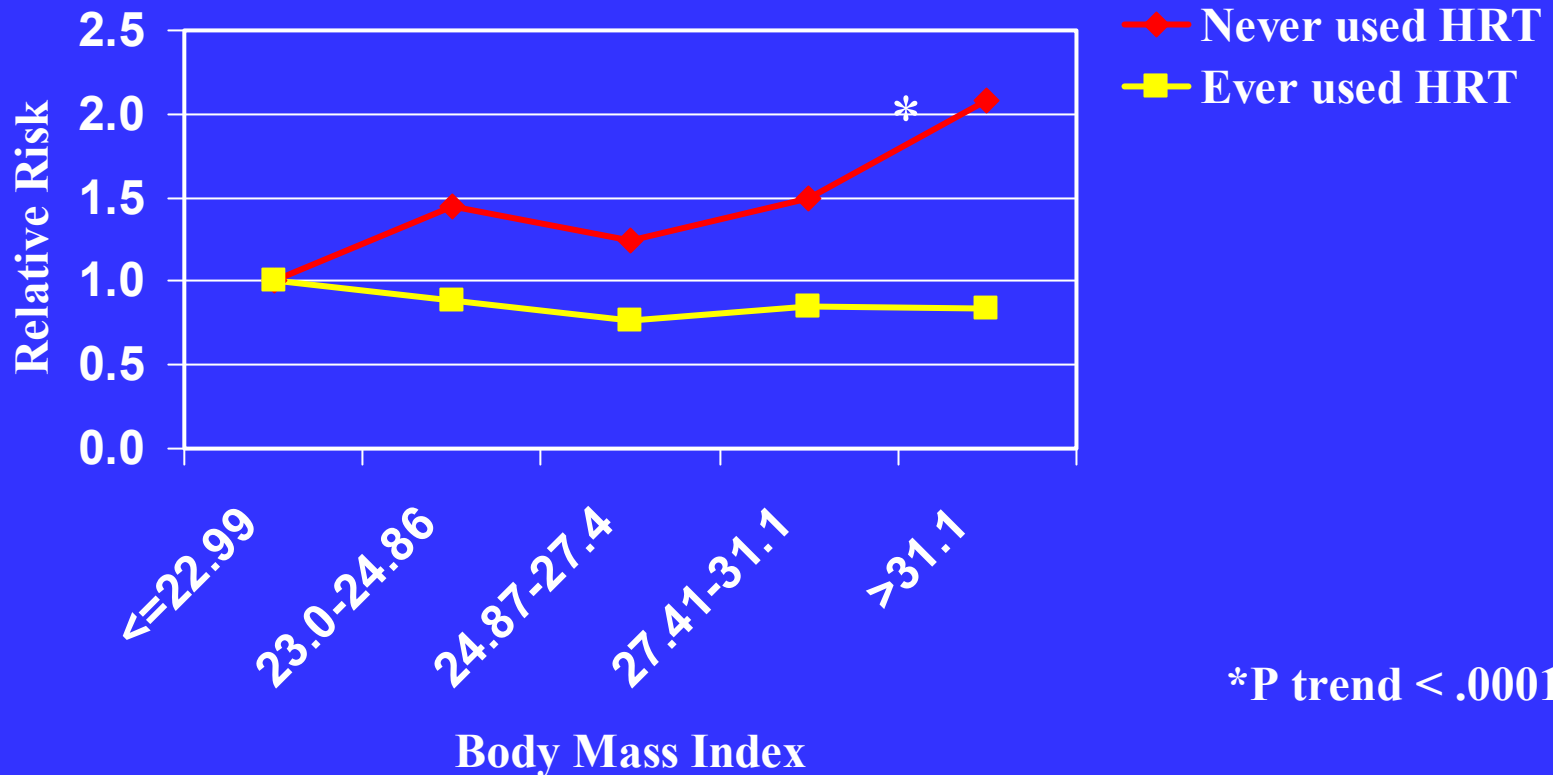
(Cancer Causes and Control 2002; 13:741-51)

Goals:

- **To assess the relationship between weight, body mass index (BMI), waist and hip circumferences, and risk of breast cancer.**
- **To assess the association between obesity at ages 18 and 50, and breast cancer risk.**
- **To estimate the relative risk of breast cancer occurrence according to change in weight and BMI from age 18 to 50.**



Risk of Breast Cancer by BMI



(N=85,917 women; 1030 invasive breast cancer cases)



Other Findings: Body Size and Breast Cancer

- BMI at age 18 was inversely associated with breast cancer risk.
- Current body size and weight were not associated with breast cancer risk in women who had ever used hormone therapy.
- In women who never used hormone therapy:
 - Increasing waist and hip circumferences were associated with increased risk (p trend < 0.001).
 - BMI increase ≥ 9.7 kg/m² from age 18 was associated with ~ 2 times increased risk vs. weight-stable (p trend 0.02).



Major Findings from OS: Bones

**John Robbins, MD
Principal Investigator
Davis Clinical Center**

**Professor of Medicine
University of California, Davis
Sacramento, California**



Fracture Papers from The WHI Observational Cohort

- Generally the fracture papers from the WHI observational cohort were not able to show significant associations.
- Showing lack of association can be important.
- This can be illustrated by the papers on:
 - Statins (Lipid lowering medications)
 - Oral Contraceptives
- More papers will be coming out



Statins and the Risk of Fracture

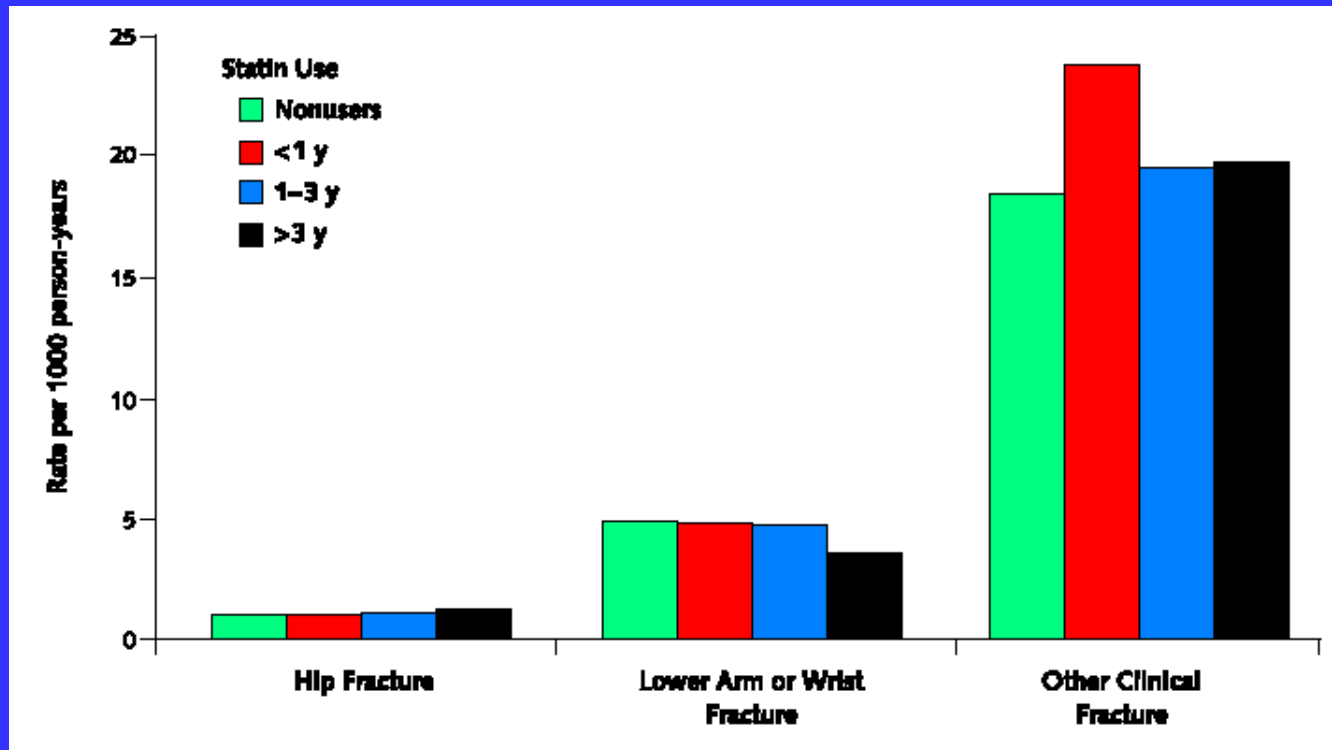
Background

- **Mouse study in Science in 1999 suggested that statins increased bone formation**
- **Case control study in *JAMA* in 2000 compared 1,222 patients with hip fractures and controls**
- **Nested case control study in *JAMA* 2000, UK general practice**
- **Case control study in *JAMA* in 2001, UK General practice data base, 81,880 cases and matched controls**



Women's Health Initiative Observational Study (*Annals Intern Med* 2003)

- Prospective observational study
- 7846 statin users and 85 870 nonusers



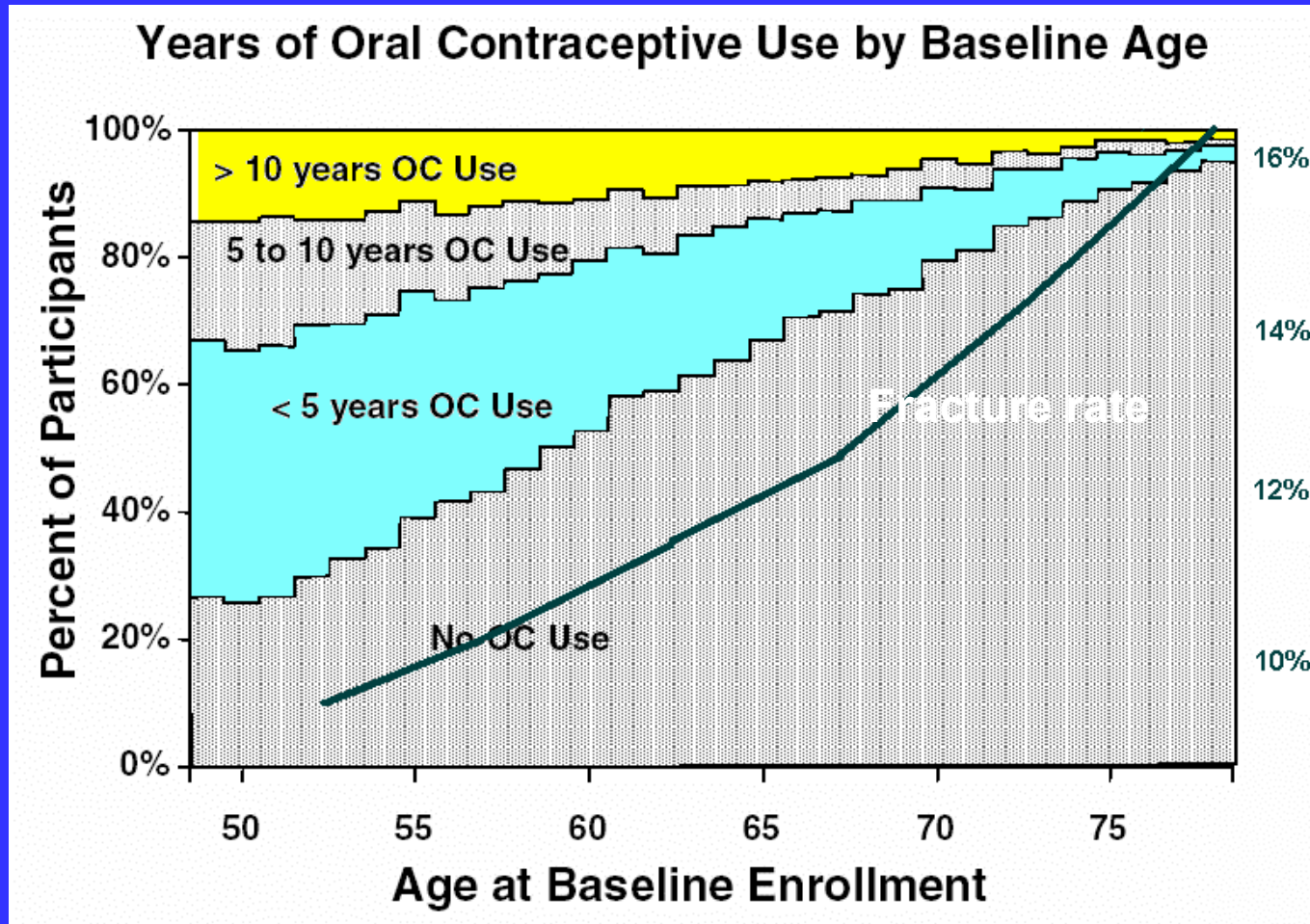
Birth Control Pills (BCPs) and Fractures

(Fertil Steril 2005)

- **It had been suggested that there was a decreased fracture rate with BCP use**
- **However the analysis is difficult**
 - **The use of BCPs changed greatly over time**
 - **Older women had more fractures and less BCP use**
 - **The formulation of the pills changed**
 - **Factors such as smoking, weight, differed in BCP users**



Birth Control Pills and Fractures



BCP use ≥ 5 years: HR of 1.09 (95% CI, 0.97–1.23) compared with never users.



Major Findings from OS: Body Weight

**Lewis Kuller, MD, DrPH
Principal Investigator
Pittsburgh Clinical Center**

**Professor of Epidemiology,
Department of Epidemiology
University Professor of Public Health,
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania**



Health Outcomes in Extremely Obese Women

(*Circ* 2005; 111(14):212; Abstract)

Goals:

- To compare the prevalence of overweight and three categories of obesity (mild, moderate, severe) in women according to ethnicity
- To assess the risk of all-cause mortality, diabetes, and cardiac outcomes by weight category and by waist circumference
- To compare the weight-mortality association according to ethnicity

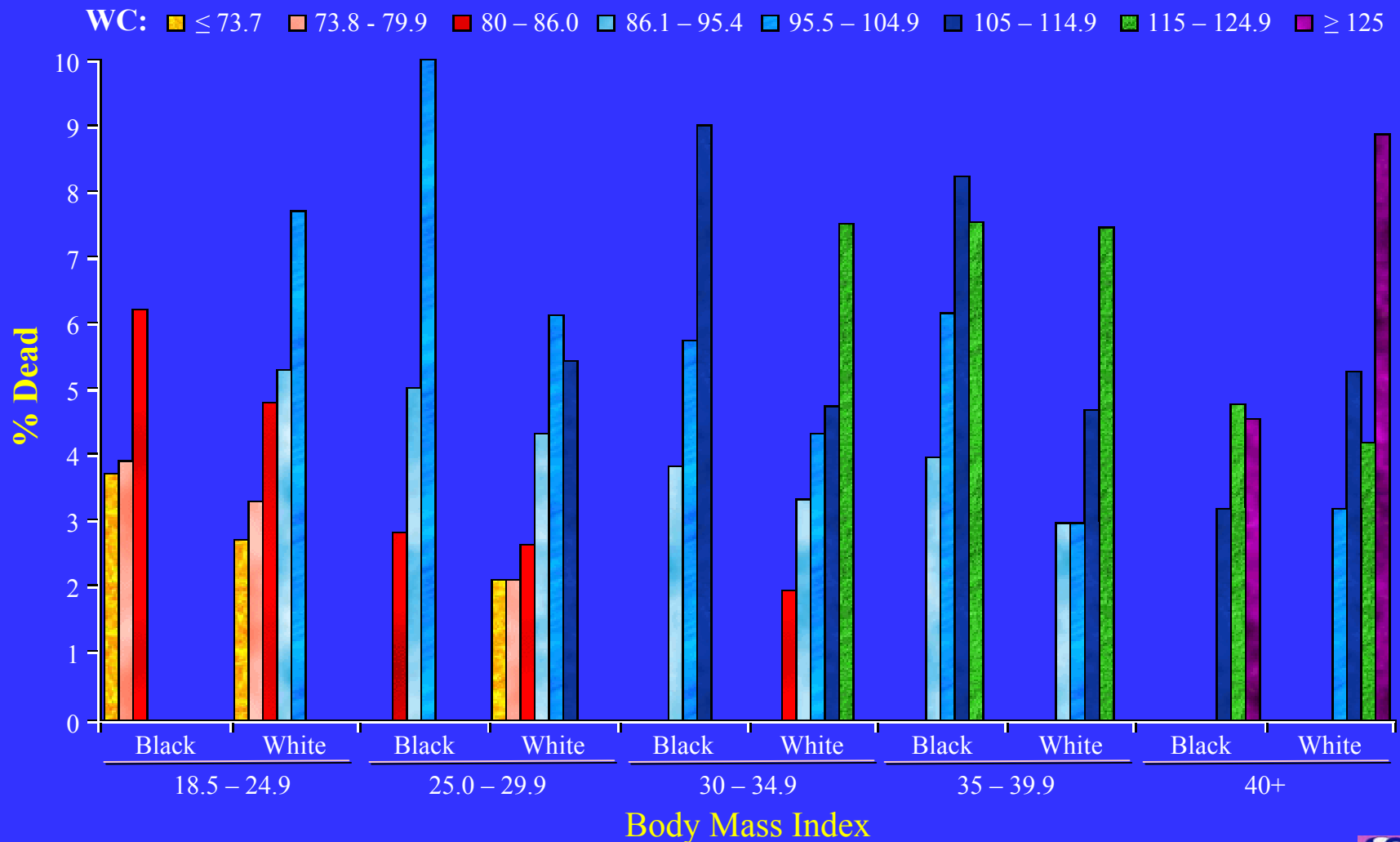


Distribution of Baseline Characteristics, in the Total Sample (n=90185) and by Body Mass Index Class: Healthy (n=36217); Overweight (n=30993); Obese I (n=14730); Obese II (n=5371); Obese III (n=3234)

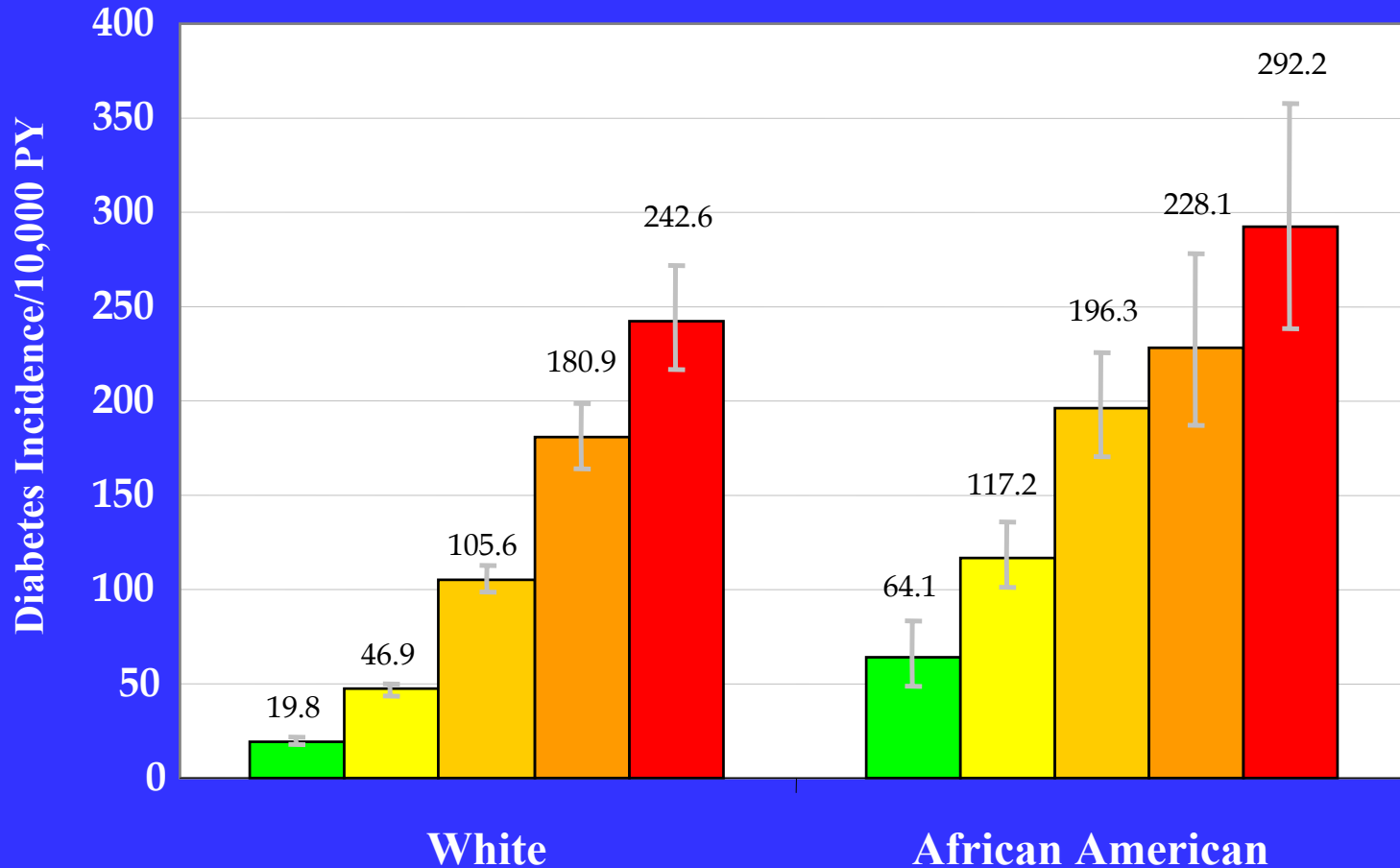
<i>Race/Ethnicity</i>	<u>Total</u>		Healthy	Overwt	Obese I	Obese II	Obese III
	<i>N</i>	(%)	%	%	%	%	%
African American	7487	(8)	19	34	25	12	10
Asian/Pac. Island	2535	(3)	62	30	6	1	1
Hispanic	3555	(4)	29	38	21	8	4
Native American	404	(1)	28	29	25	11	8
White	76204	(85)	42	34	15	5	3



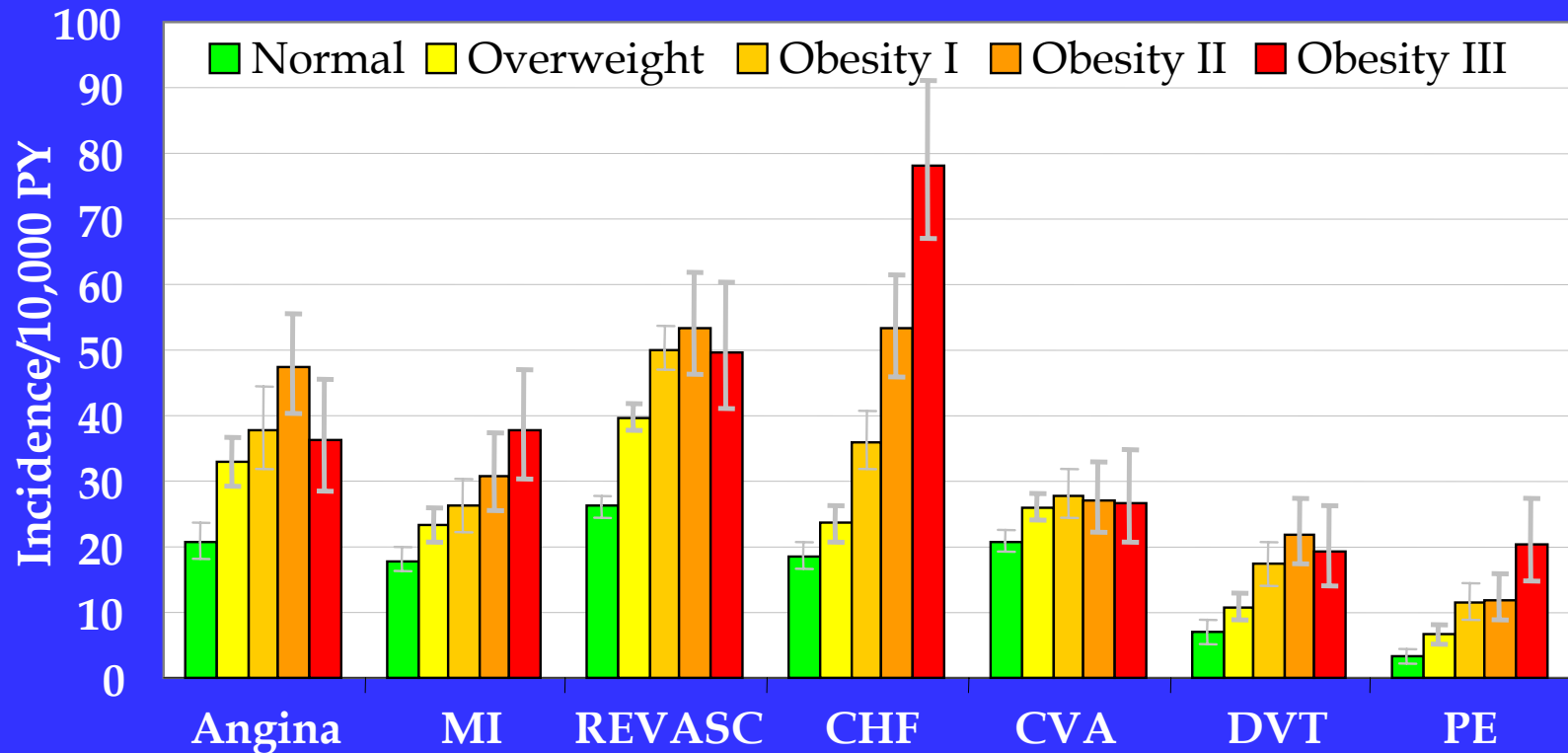
All-Cause Mortality by Body Mass Index, Waist Circumference (WC) and Race



Diabetes Incidence by Body Mass Index Category



Incidence of Cardiac and Vascular Outcomes by Body Mass Index Category



MI = myocardial infarction REVASC= revascularization
CHF = coronary heart failure CVA= stroke
DVT= deep vein thrombosis PE= pulmonary embolism



Summary/Conclusions

- 1. In women, waist circumference over 32-34” is associated with increased risk of disease such as diabetes and cardiovascular disease. Measuring waist circumference will help to identify women at increased risk.**
- 2. Risk of disease increases across spectrum of increasing weight to severe obesity BMI ≥ 40 .**
- 3. Having diabetes, hypertension, and smoking substantially increases risk by BMI classification. Treatment of these risk factors should be a high priority.**



Major Findings from OS: Diabetes

**Karen Margolis, MD, MPH
Principal Investigator
Minneapolis Clinical Center**

**Associate Professor of Medicine
University of Minnesota
Minneapolis, Minnesota**



Physical Activity and Diabetes Risk in Postmenopausal Women

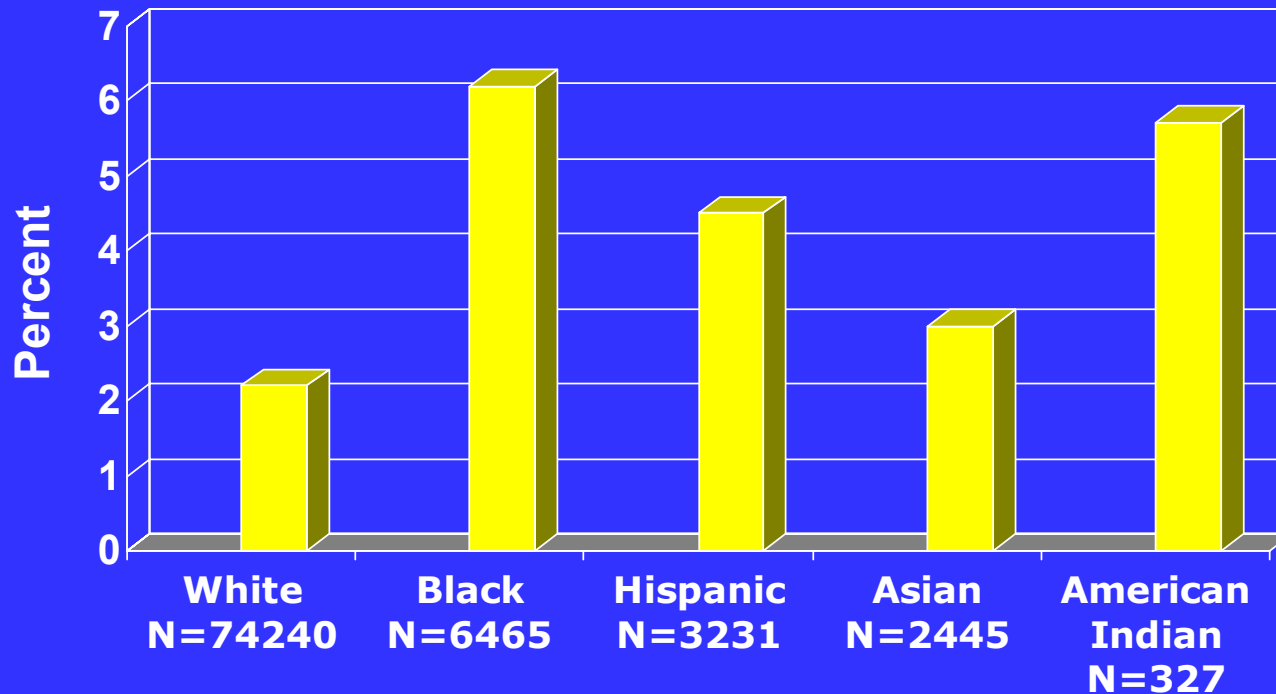
(Am J Prev Med 2005; 28:19-25)

Goals:

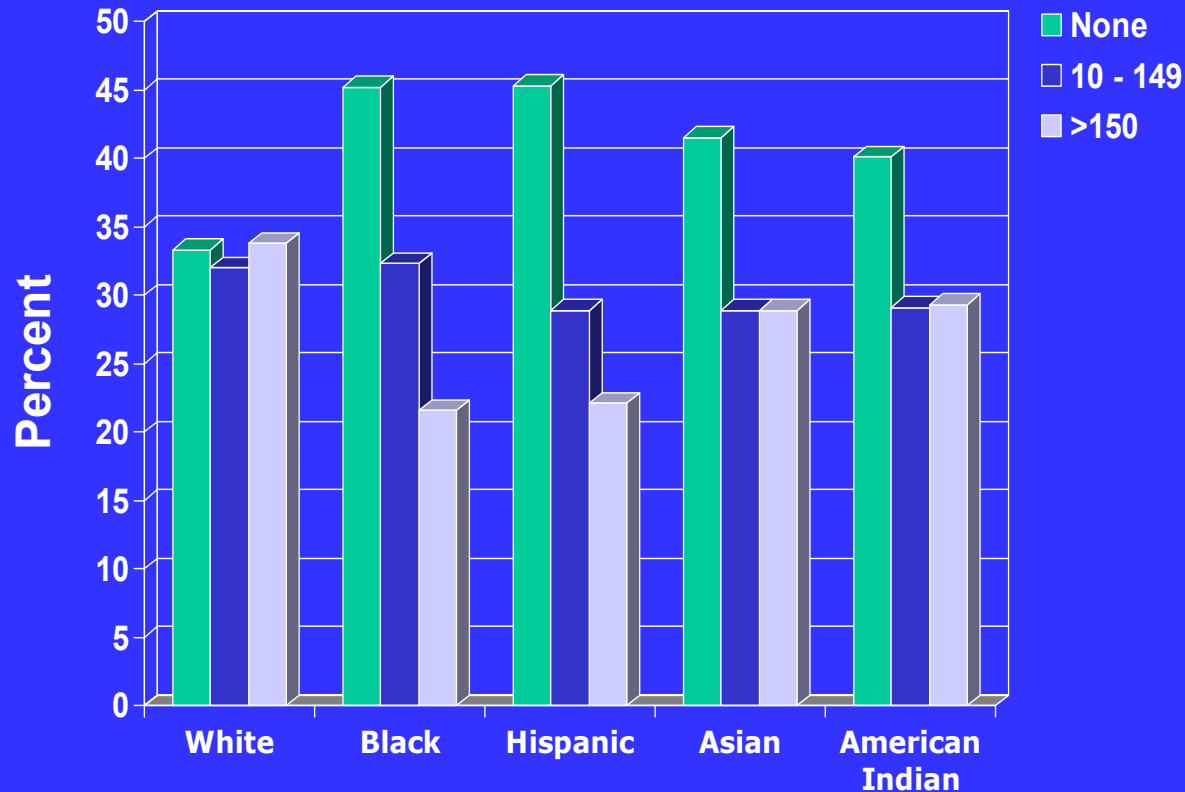
- To compare the incidence of new onset diabetes in different ethnic groups
- To assess the relationship between physical activity and risk of diabetes
- To compare the benefits of exercise in women of different ethnic groups.



Incidence of Treated Diabetes During 5 Years of Follow-up

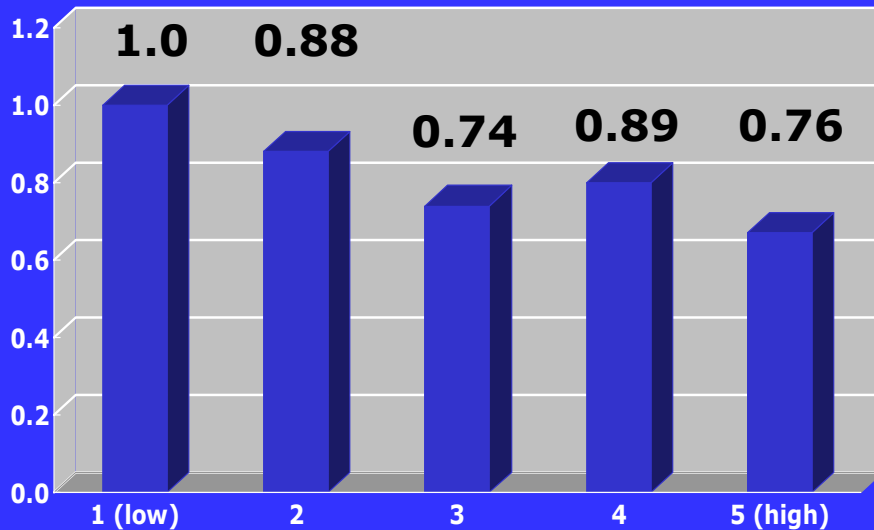


Minutes of Physical Activity/Week According to Ethnicity

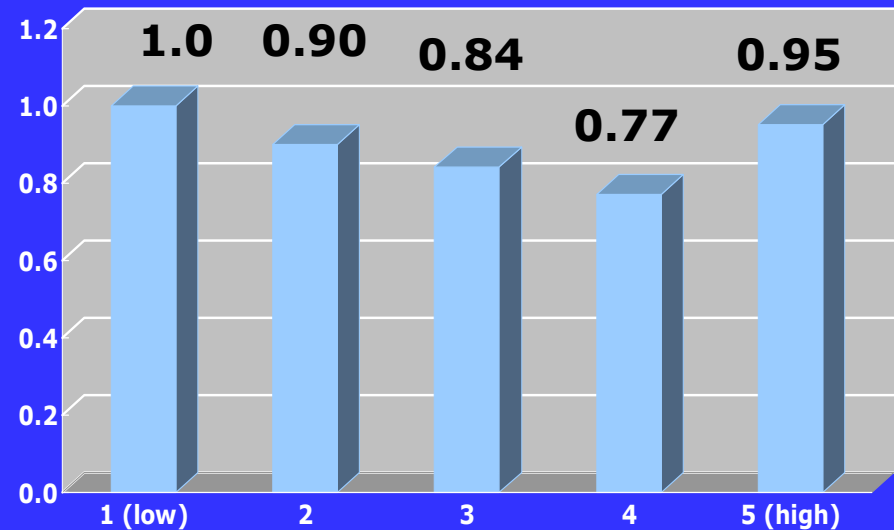


Physical Activity and Risk of New-Onset Diabetes

White Women



Black Women



Relative Risk According to Categories of Physical Activity

(N=74,240 White Women; 6465 Black Women)



Summary and Conclusions

- **Confirms higher incidence of diabetes in postmenopausal minority women**
- **Non-white women were more likely to report physical inactivity**
- **Physical activity is associated with a lower risk for diabetes in white women; this association was less clear in non-white women (but statistical power may have been limited).**



Major Findings from OS: Access to Medical Care

**F. Allan Hubbell, MD
Principal Investigator
Irvine Clinical Center**

**Professor and Chair, Department of Medicine
University of California, Irvine
Irvine, California**



Importance of Health Insurance as a Determinant of Cancer Screening: Evidence from the Women's Health Initiative (*Prev Med* 2000;31:261-70)

Goal:

To determine whether health insurance coverage independently predicts the use of screening tests for breast, cervical, and colorectal cancer in the observational cohort



Participant Characteristics (n=55,278)

<u>Characteristic</u>	<u>%</u>
• Race/Ethnicity (White)	85
• Income (>\$50,000)	41
• Currently Married	63
• Education (\geq College)	43
• Have Medical Care Provider	95
• Have Health Insurance	97



Predictors of Mammogram Screening in Past 2 Years

Characteristic	Odds Ratio <65 yr (n=31,684)	Odds Ratio ≥65 yr (n=23,594)
Race/Ethnicity		
Native American	0.60	1.18
Asian American/ Pacific Islander	0.57*	0.85
Black	0.95	0.94
Latina	0.82*	0.93
White	1.00	1.00
Other	0.80	1.04
Income		
<\$20,000	0.71*	0.73*
\$20-50,000	1.00	1.00
>\$50,000	1.49*	1.24*
Not Married	0.92*	0.89*

* P < 0.05



Predictors of Mammogram Screening in Past 2 Years

Characteristic	Odds Ratio <65 yr (n=31,684)	Odds Ratio ≥65 yr (n=23,594)
Education		
<High School	0.75*	0.84*
≥High School	0.84*	0.90*
College or more	1.00	1.00
Chronic Disease		
Diabetes	0.92*	0.85*
High Cholesterol	1.35*	1.25*
Medical Provider		
Visit > One Year Ago	0.33*	0.34*
Visit Within Past Year	1.00	1.00
No Provider	0.17*	0.16*

* P < 0.05



Predictors of Mammogram Screening in Past 2 Years

Characteristic	Odds Ratio <65 yr (n=31,684)	Odds Ratio ≥65 yr (n=23,594)
Insurance		
None	0.30*	
Prepaid	1.00	
Fee for Service	0.84*	
Prepaid + Medicare		1.17*
Medicare only		0.81*
Fee for Service + Medicare		1.00
Other	0.67*	1.06

* P < 0.05



Summary

- **Predictors of Mammogram Screening**
 - **Health insurance status**
 - **Type of health insurance**
 - **Usual medical care provider**
 - **Years of formal education, household income, and certain chronic diseases**
 - **Race/Ethnicity in the < 65 year old group**



WHI Observational Study Questions and Answers

Moderator:

Teri Manolio, MD, PhD

National Heart, Lung, and Blood Institute

**Senior Advisor to the Director for
Population Genomics,**

National Human Genome Research Institute



WHI Observational Study Closing Comments

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