

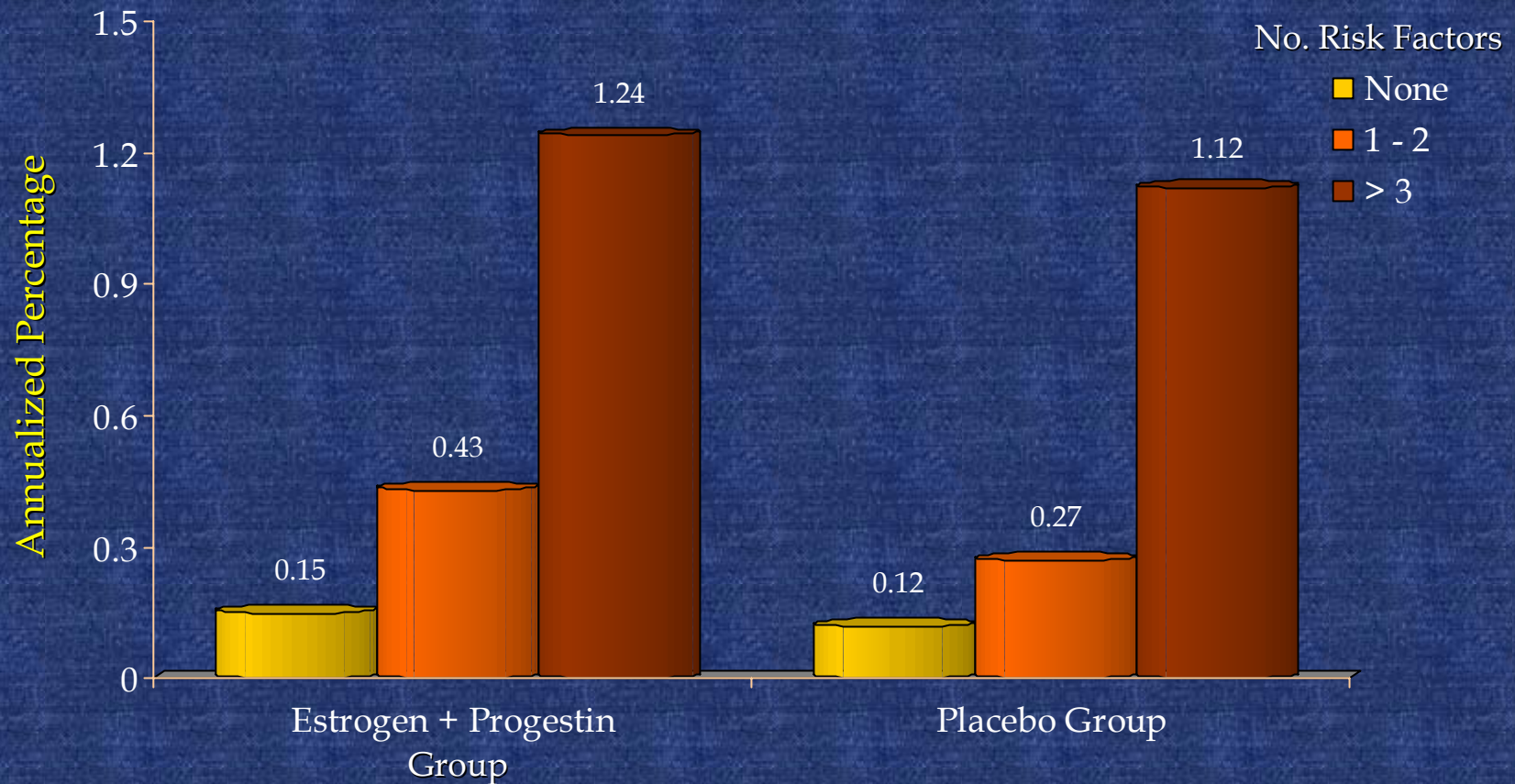
# Hormone Therapy (Estrogen or Estrogen + Progesterone) Cardiovascular Disease: Reason for Lack of Benefits

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University of Pittsburgh  
Department of Epidemiology, GSPH

# Hormone Therapy (Estrogen or Estrogen + Progesterone) Cardiovascular Disease: Reason for Lack of Benefits

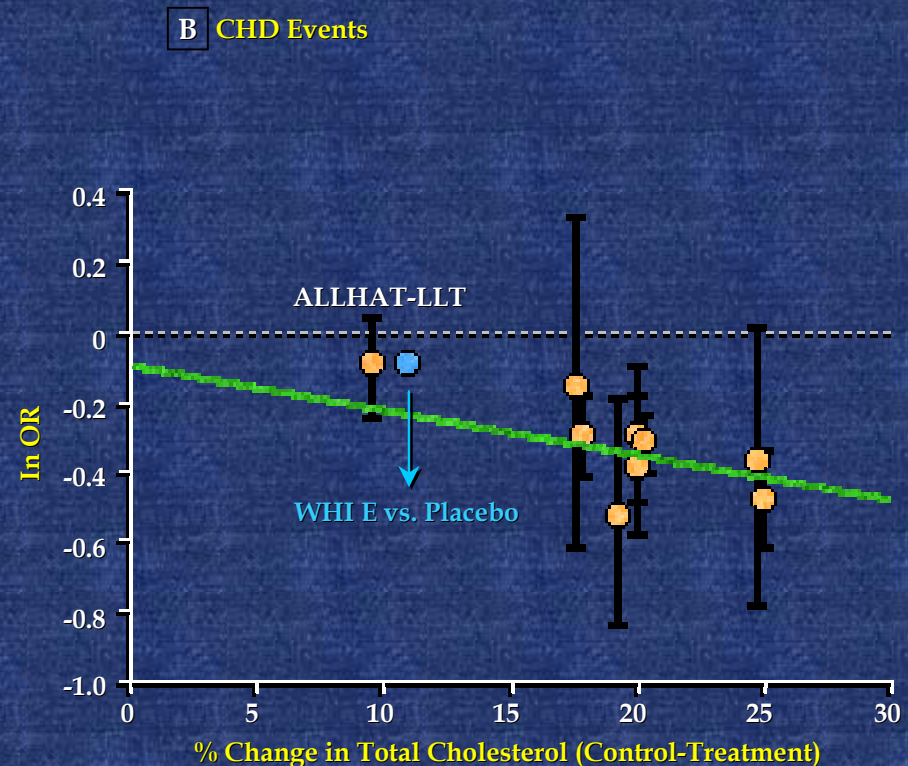
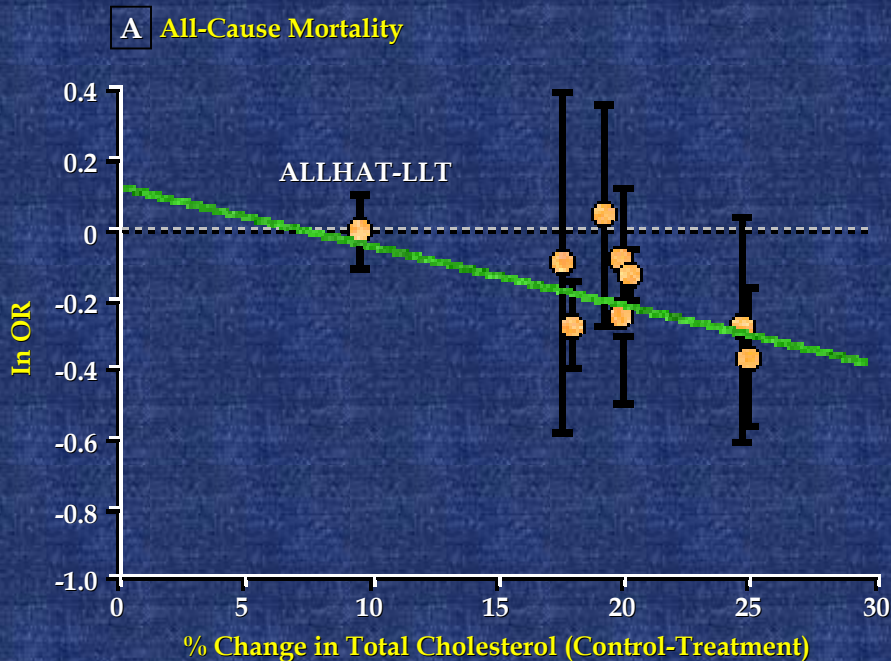
1. Poor lipid lowering
2. Changes in lipoprotein particle distribution
3. Increased risk of thrombosis
4. Different effects on pre-existing atherosclerosis (older ages) and development of atherosclerosis (perimenopausal younger ages)
5. Metabolism of oral versus transdermal or other routes (first pass through liver)
6. Genetic variations in responses:
  - a. Hormone levels
  - b. Estrogen receptors
  - c. Post translational responses
7. CoFactors, obesity, insulin resistance

# Estrogen plus Progestin and the Risk of CHD in Number of Risk Factors for CHD



Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M, for the WHI investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2002;347(6):523-534

Log odds ratio (in OR) and 95% confidence intervals for active treatment vs control for 9 large statin trials are compared with regression lines (solid) from meta-analyses of 45 long-term trials using statins and other cholesterol-lowering interventions published before December 31, 2000



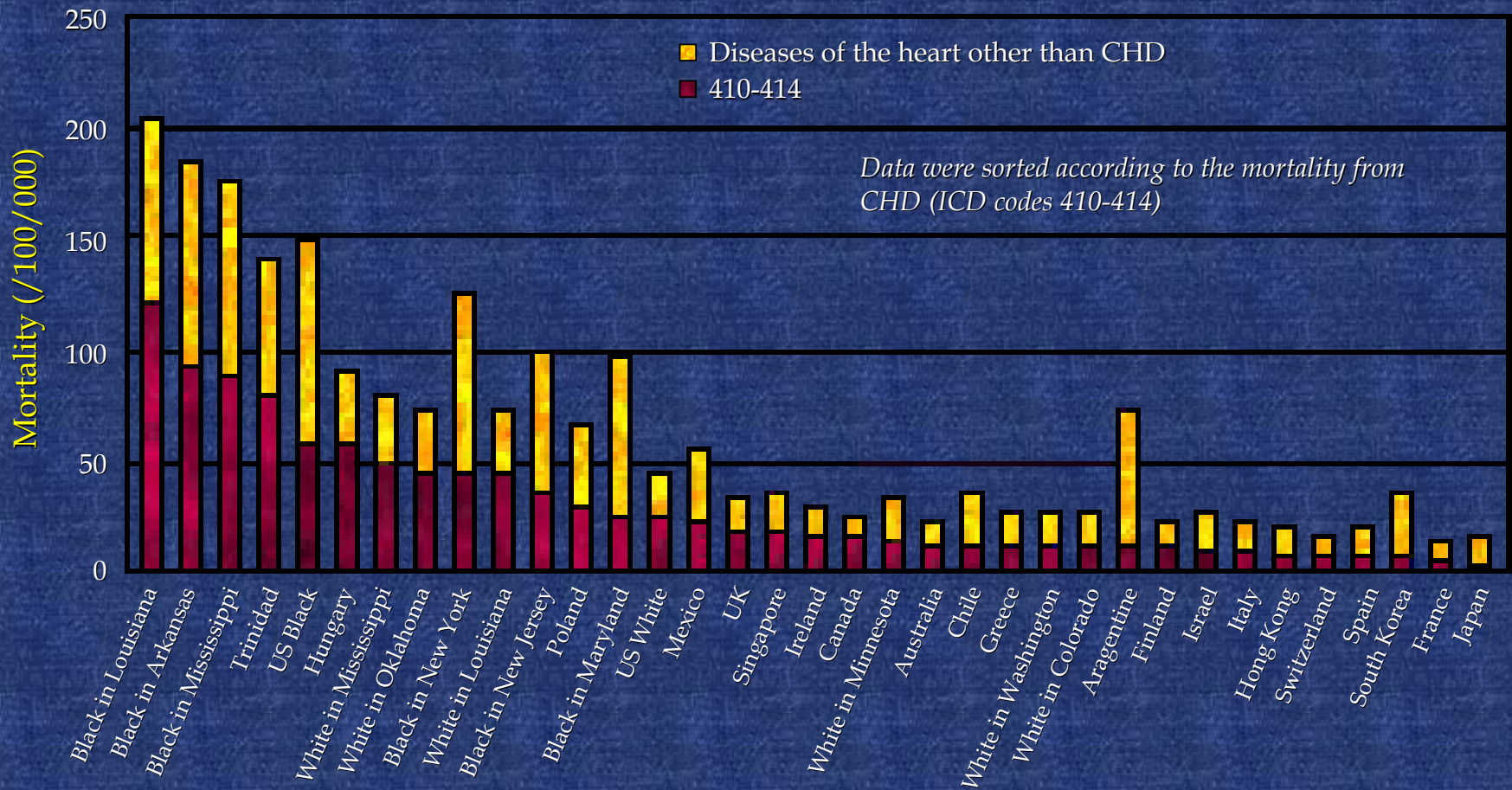
The ALLHAT officers and coordinators for the ALLHAT collaborative research team. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to Pravastatin vs usual care. The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288(23):2998-3007

# Obesity and Premenopausal Protection

- I. Increase in weight for pre- to postmenopause: 1-2 pounds/year, 45-55 on average, increase in % body fat
  
- II. Increase in central obesity or abdominal visceral fat pre- to postmenopausal may be due, in part, to estrogen deficiency; thinner women have more menopausal symptoms

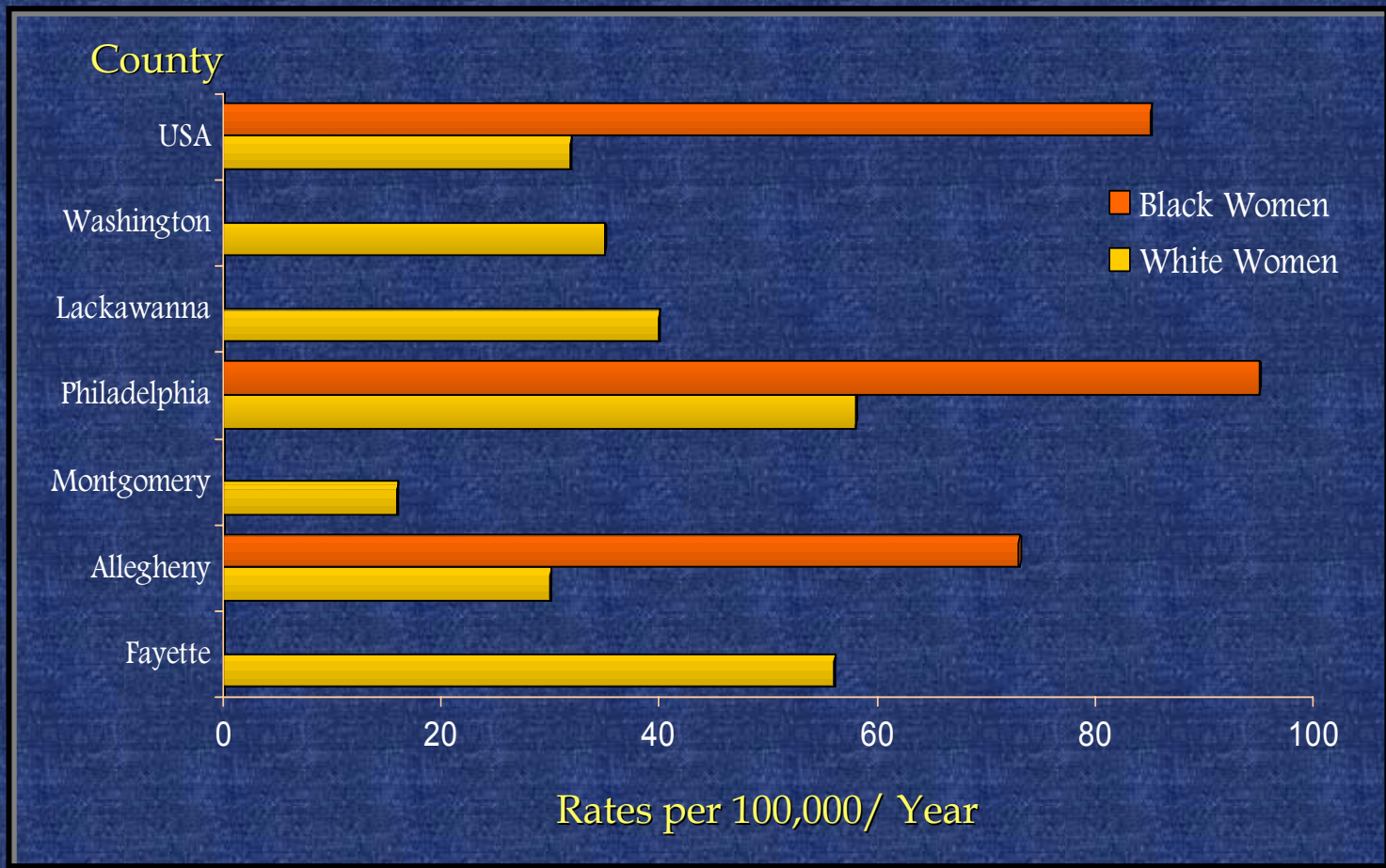
- III. Substantial international variation in both extent of atherosclerosis and coronary heart disease mortality among early postmenopausal women cannot be explained by estrogen deficiency alone
- IV. Increase in LDLc from peri- to postmenopause, in part, is related to weight gain and obesity, diet, and decreased estrogen production
- V. Weight gain and obesity, especially central obesity, associated with increased LDL particles and smaller LDL particles, both associated with increased risk of coronary atherosclerosis and heart attack

Mortality from CHD (ICD codes 410-414) and diseases of heart (ICD codes 390-398, 402, 404, 410-429) among women aged 45-54 in selected countries, U.S. white and black women as a whole, and selected states in 1994.



Sekikawa A, Kuller LH. Striking variation in coronary heart disease mortality in the United States among black and white women aged 45-54 by state. J Womens Health Gender Based Med 2000;9(5):545-556

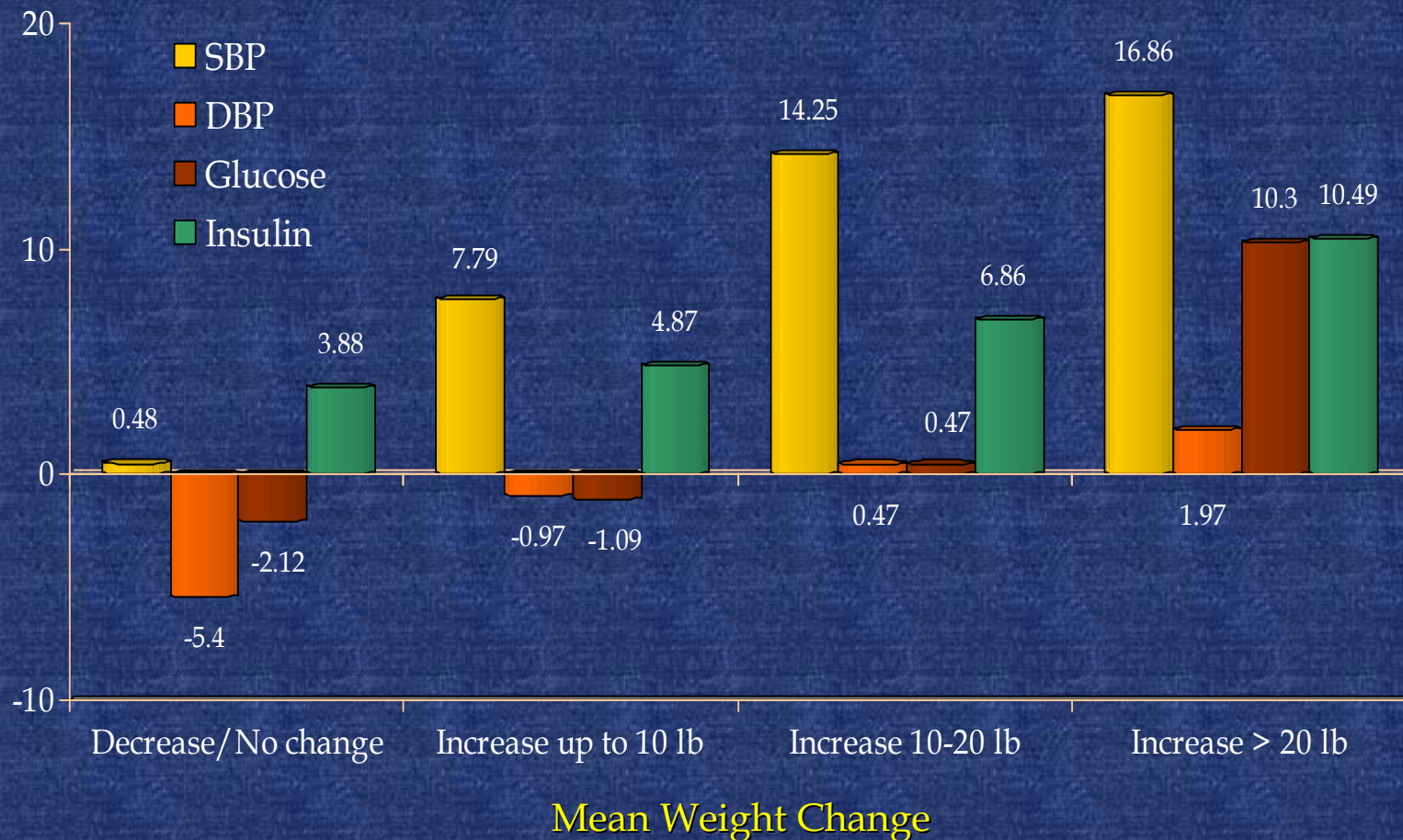
# Age-Specific CHD Death Rates: Age 45-54, 1989-98 per 100,000/year



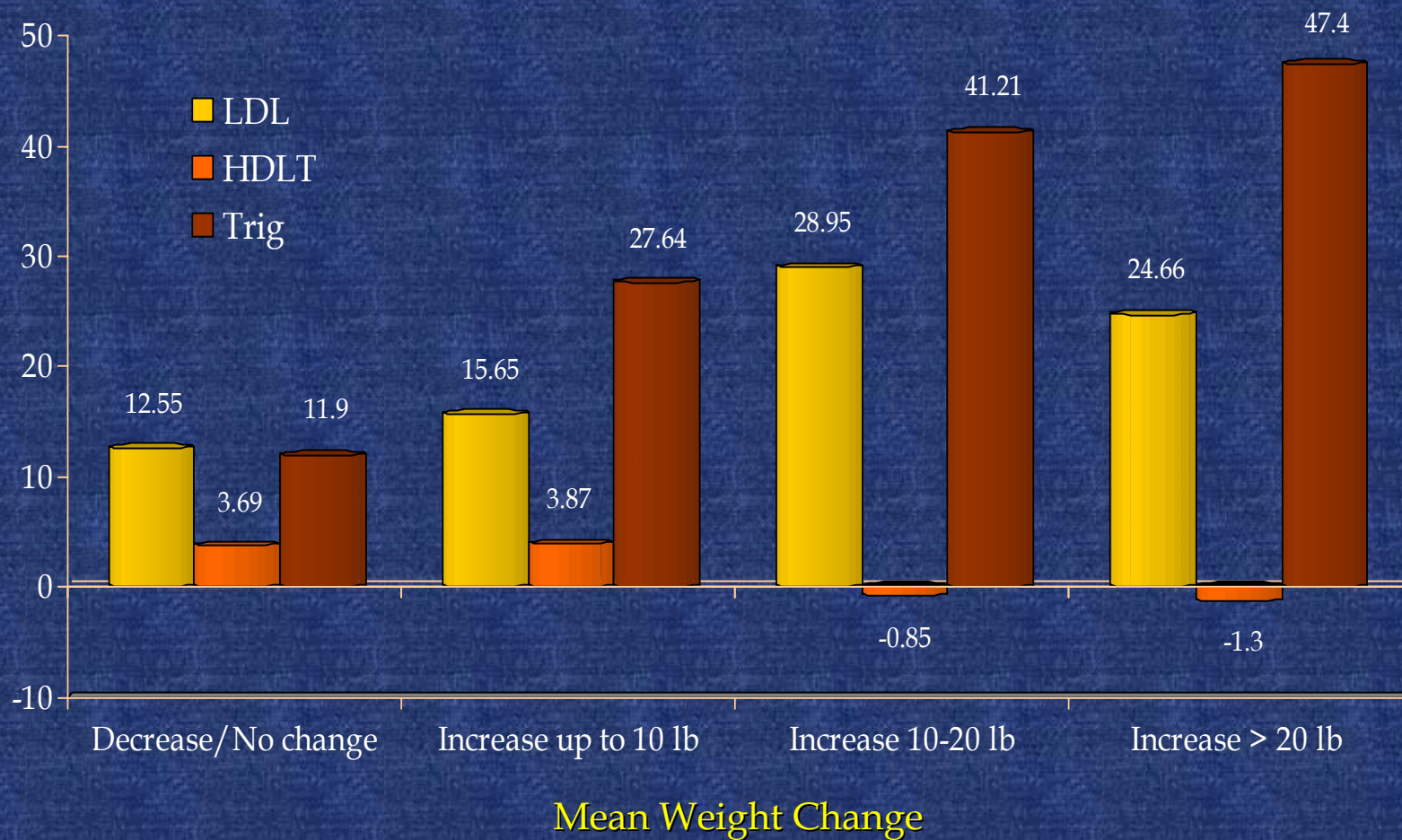


- VI. Obesity postmenopausal eliminates beneficial lipid effects of hormone therapy (LDLc, HDLc) associated with increase in triglycerides and number of LDL particles
- VII. Obesity postmenopausal and increased waist circumference associated with insulin resistance (increased insulin, decreased adiponectin, increased blood glucose); estrogen therapy decreased risk of diabetes
- VIII. Insulin resistance key risk factor for diabetes mellitus

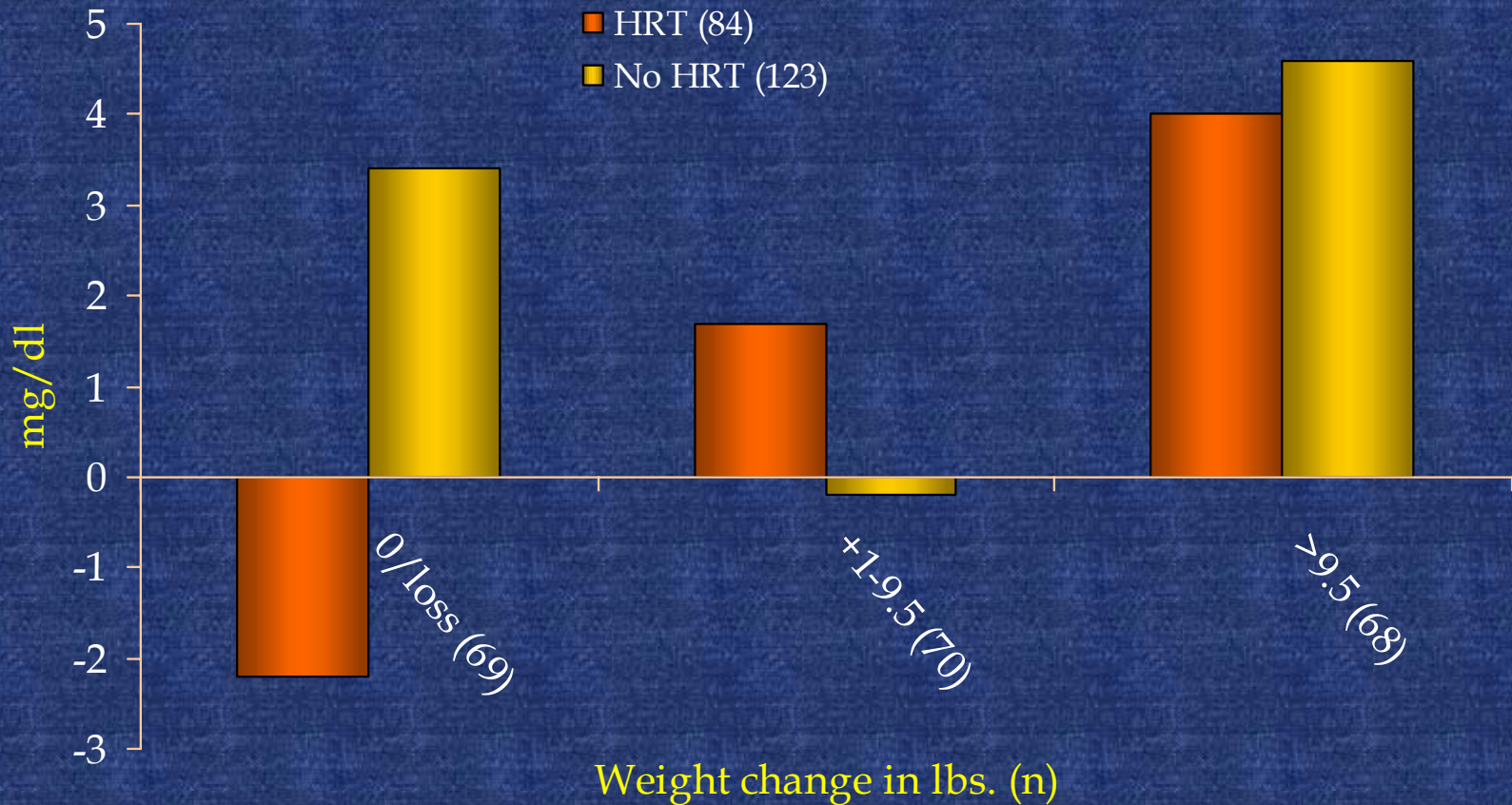
# Change in Risk Factors Between Baseline and 5<sup>th</sup> Postmenopausal Exam by Weight Change, Baseline to 5<sup>th</sup> Post: All subjects



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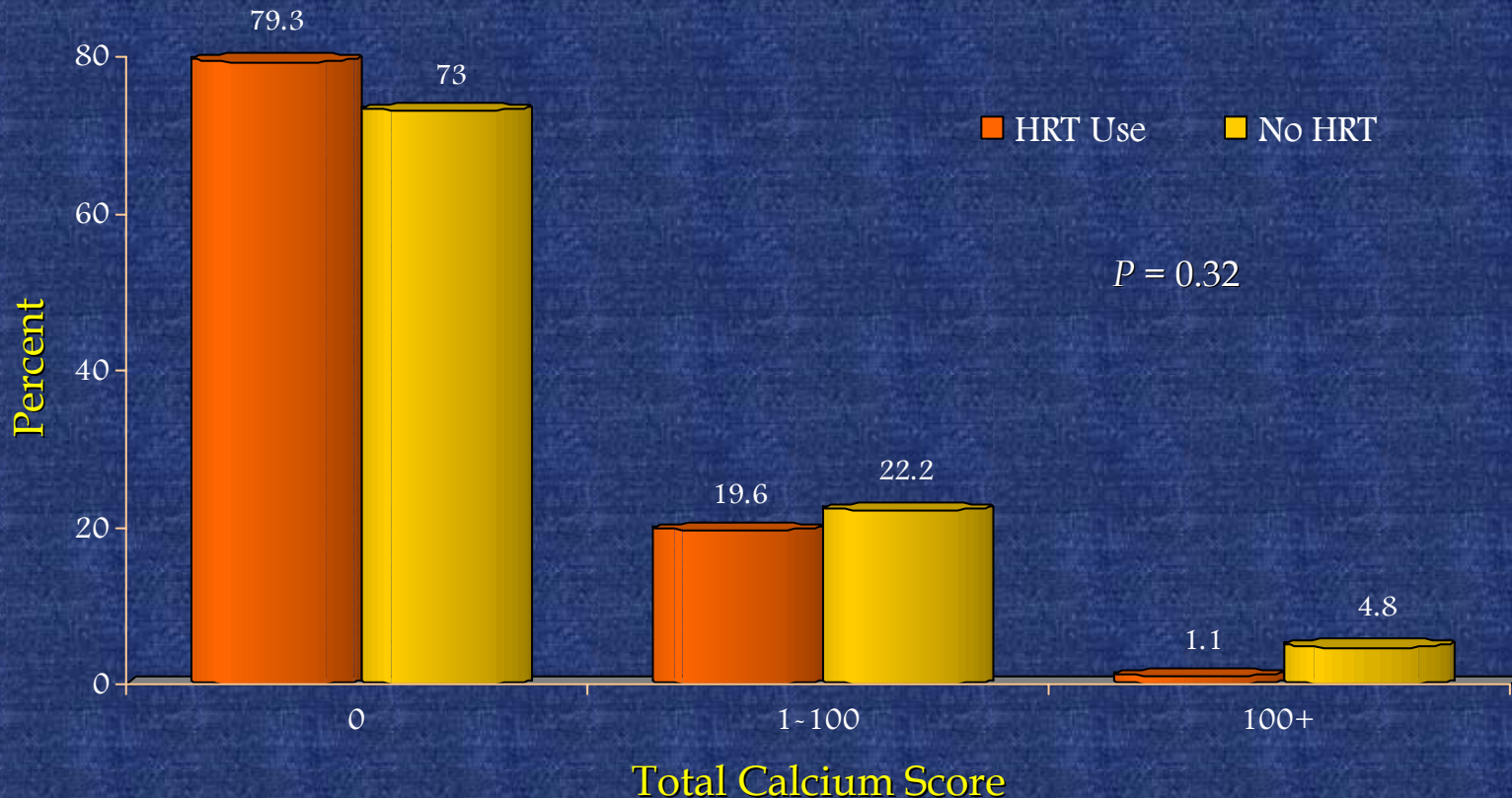


# Change in small LDL over 5 years by weight change and starting HRT

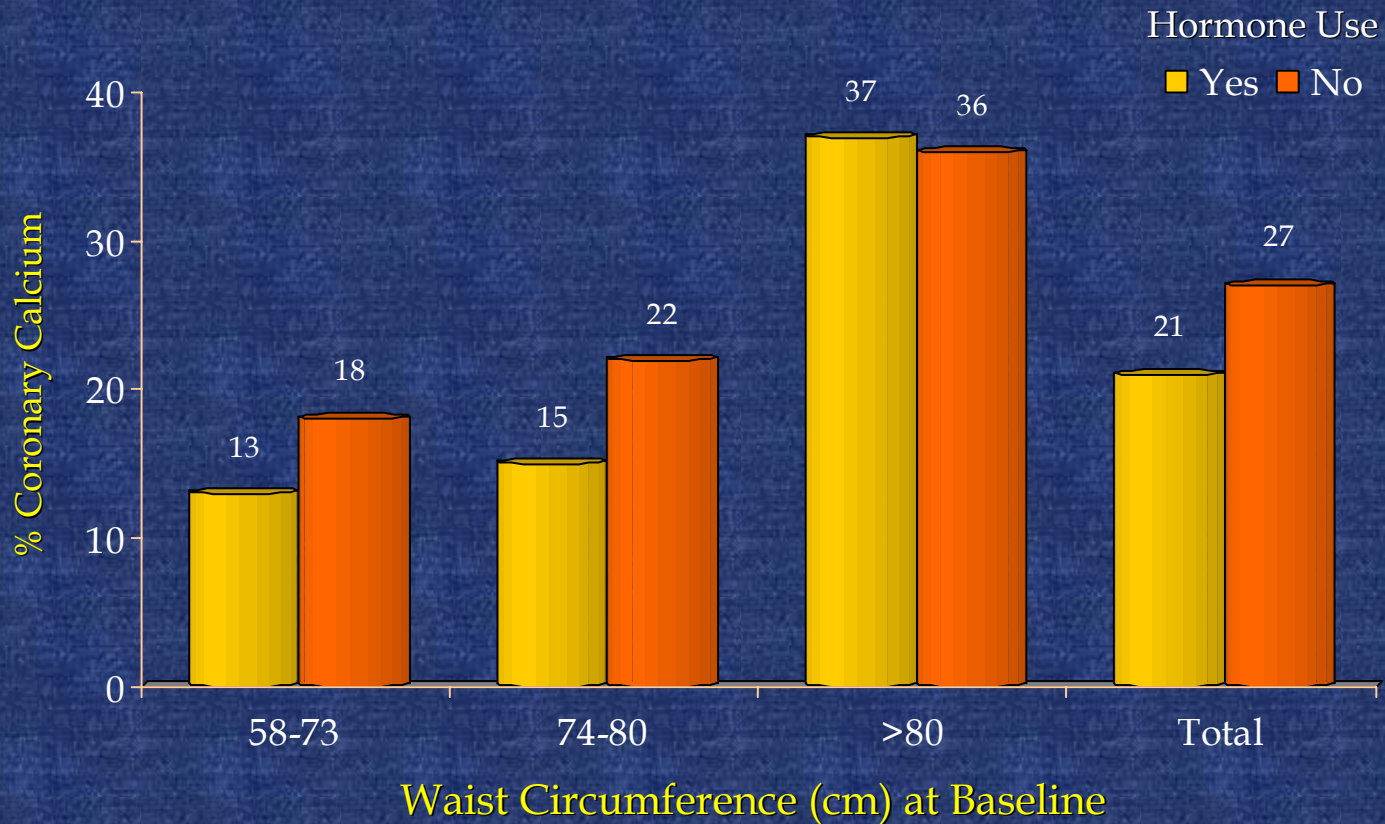


Meilahn EN, Boraz M, Kuller LH. Change in NMR spectroscopy – determined lipoprotein subfractions with weight change and HRT use among healthy middle-aged women. (WHLP) SER 2004

# Coronary Calcium Score in the Women's Healthy Lifestyle (WHLP) Project at 78 Month Follow-up; Mean Age 53 (All Postmenopausal): Almost All E+P therapy)

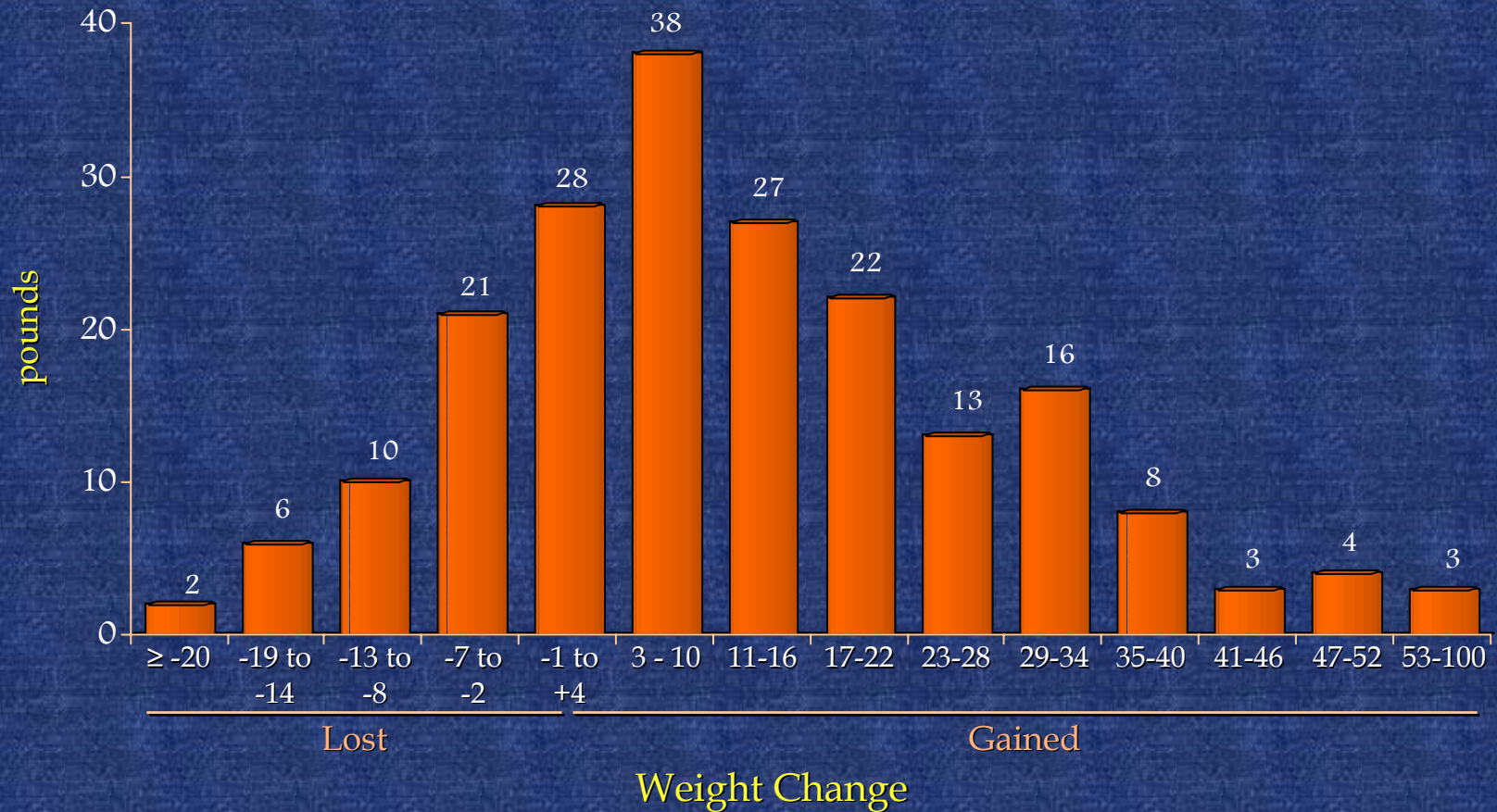


# Distribution of Coronary Calcium Postmenopausal, Mean Age 57 (Women's Healthy Lifestyle Study) by Waist Circumference and Hormone Use (n=155), 60% on Hormones



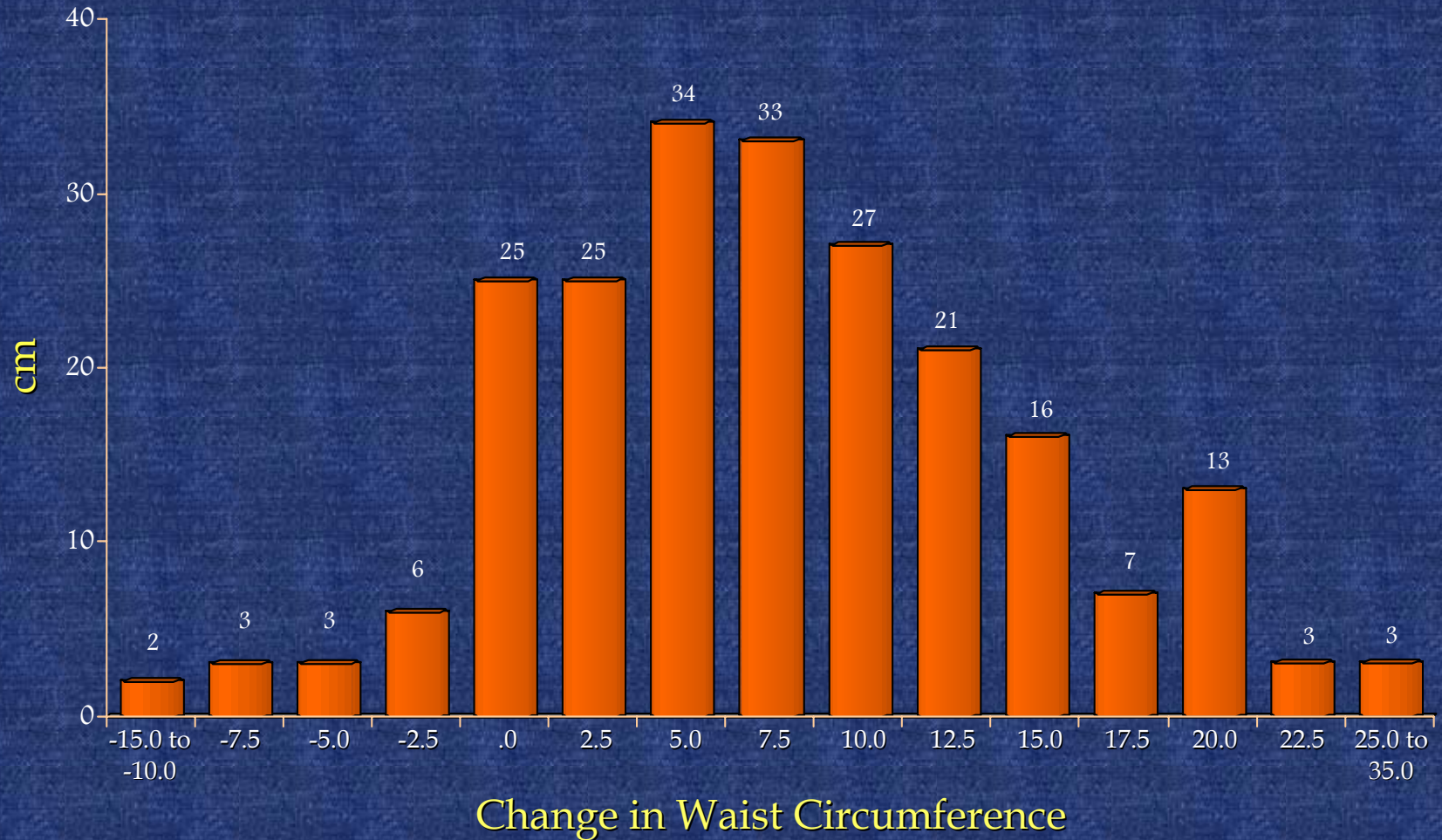
- IX. Diabetes is a major risk factor for cardiovascular disease among women. Increased blood pressure postmenopausal is associated more with aging and weight gain, salt retention, vascular stiffness, increased production of angiotensinogen by fat cells? (role of estrogen?)
- X. Weight gain, obesity postmenopause associated with increased blood estrogen levels, estrone, estradiol, decreased SHBG, decreased testosterone
- XI. Increased BMI is postmenopausal major risk factor for breast, uterine cancer

# Change in Weight by Baseline to 12<sup>th</sup> Postmenopausal Exam: *Healthy Women Study*





# Change in Waist Circumference From 1<sup>st</sup> to 8<sup>th</sup> Post in the Healthy Women Study, N=221

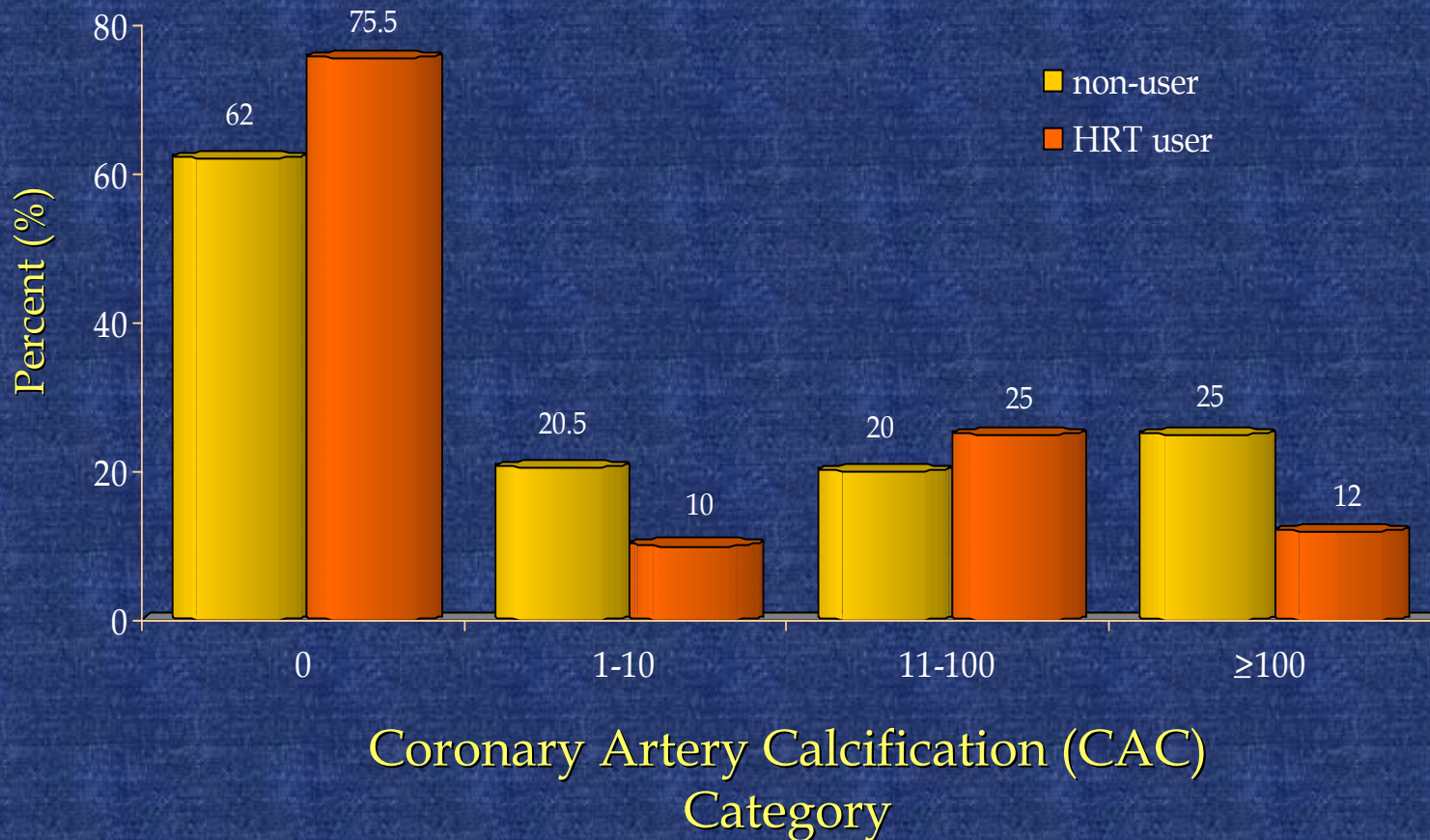


# Risk Factors for Coronary Calcium (Baseline Healthy Women Study, n=359) – Coronary Calcium = 169, No Calcium = 190

	Coronary Calcium		<i>P</i>
	No	Yes	
Age at baseline	48	48	--
Systolic blood pressure	106	110	0.001
LDLc	101	116	< .0001
HDLc	61	58	< .01
Triglycerides	73	89	< 0.001
Cigarette smoking %	19	35	< 0.001
BMI	23.7	25.8	< 0.001
Education % College graduate	56.3	42.6	< 0.009

No association, alcohol intake, physical activity, fasting or 2 hr glucose, diastolic blood pressure (weak)

# Healthy Women Study – Coronary Calcium by HRT Use at 8<sup>th</sup> Postmenopausal Visit



Mackey RH, Kuller LH, Sutton-Tyrrell K, Evans RW, Holubkov R, Matthews KA. Differences in lipoprotein subclasses and coronary artery calcification by hormone replacement therapy use, the Healthy Women Study. (Accepted: Arch Intern Med, 2004)

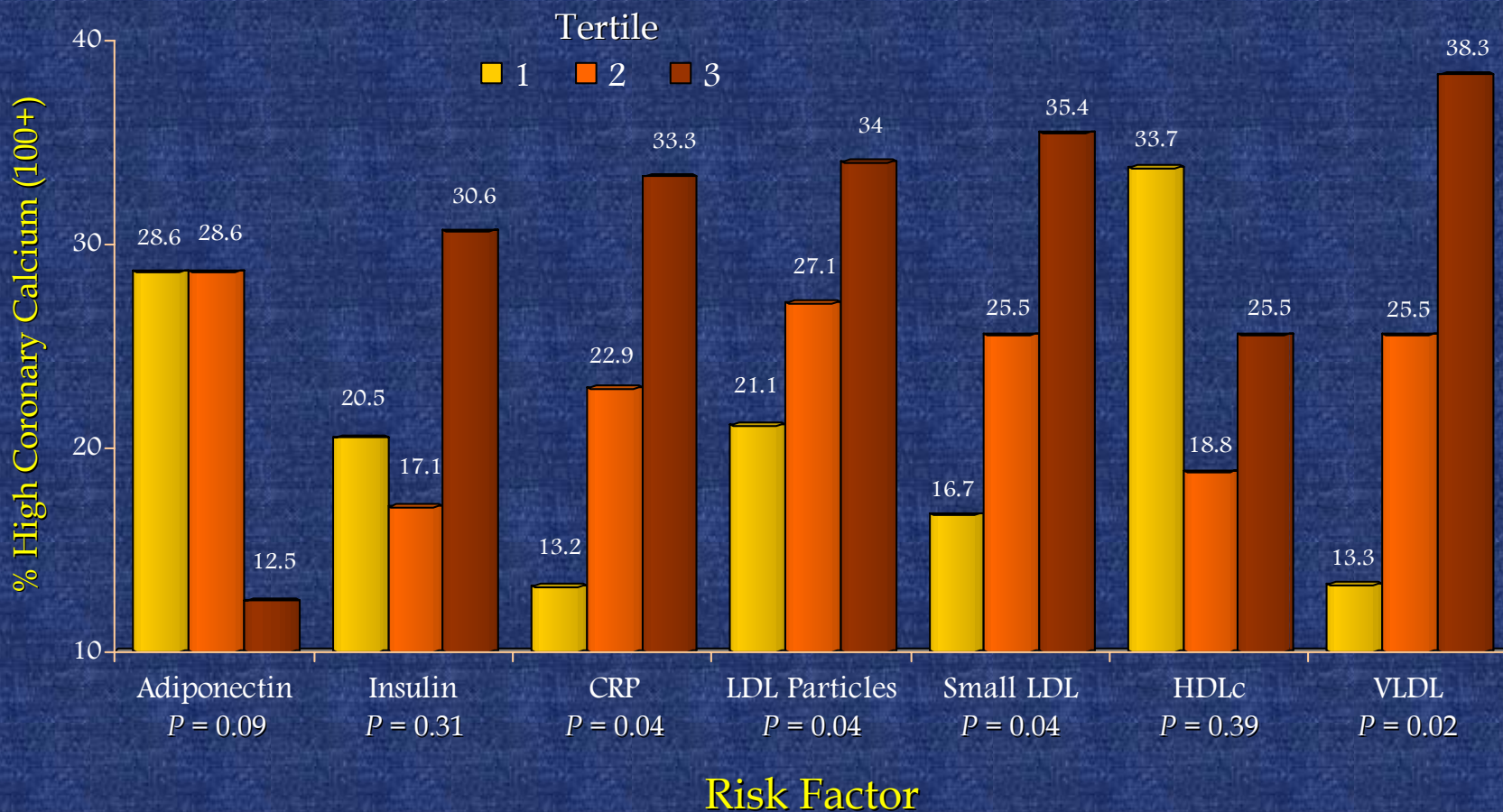
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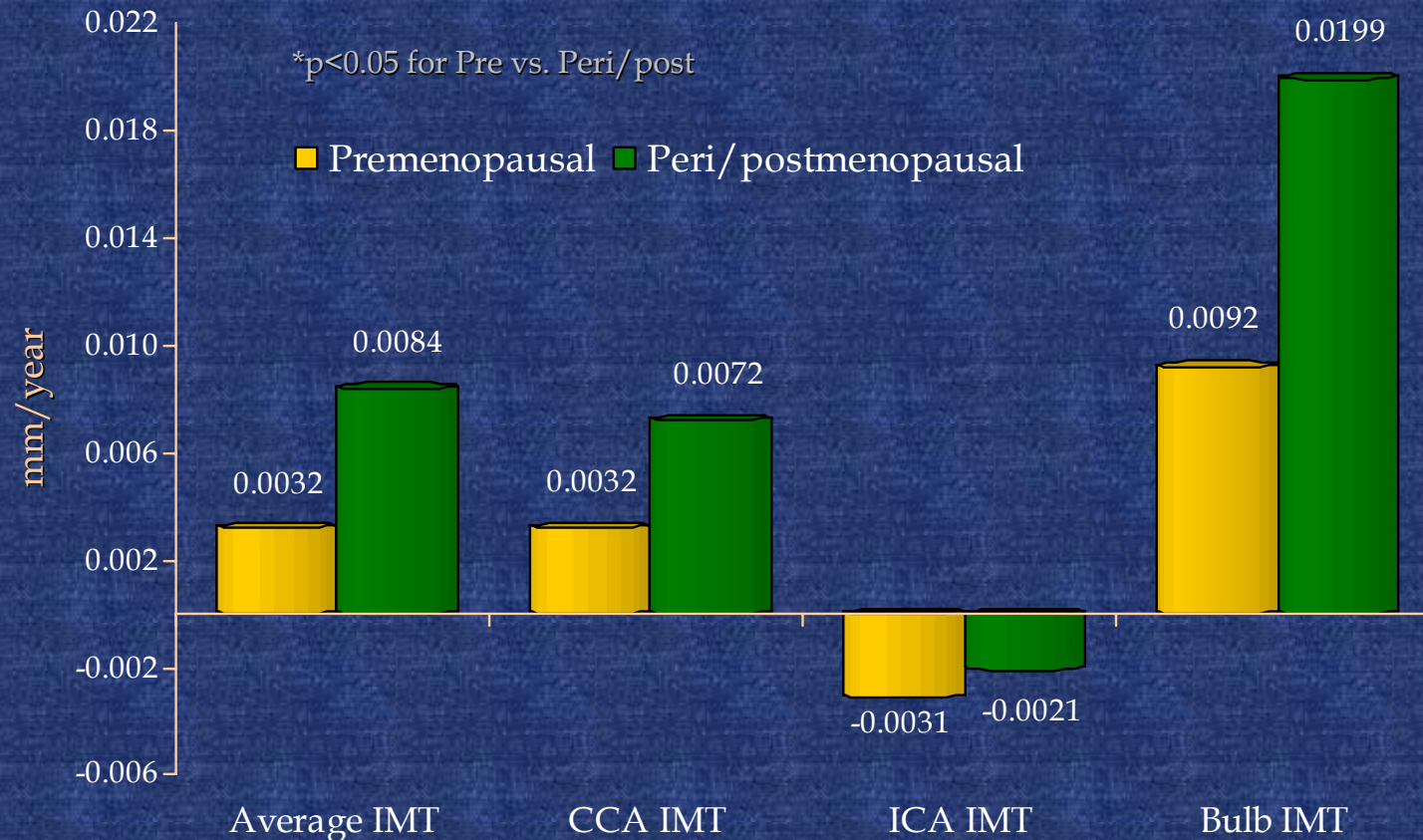
No association, alcohol intake, physical activity, fasting or 2 hr glucose, diastolic blood pressure (weak)

# Relationship of Risk Factors to High Coronary Calcium (100+) as Compared to 0 Coronary Calcium, n=147 (38 coronary calcium $\geq 100$ )

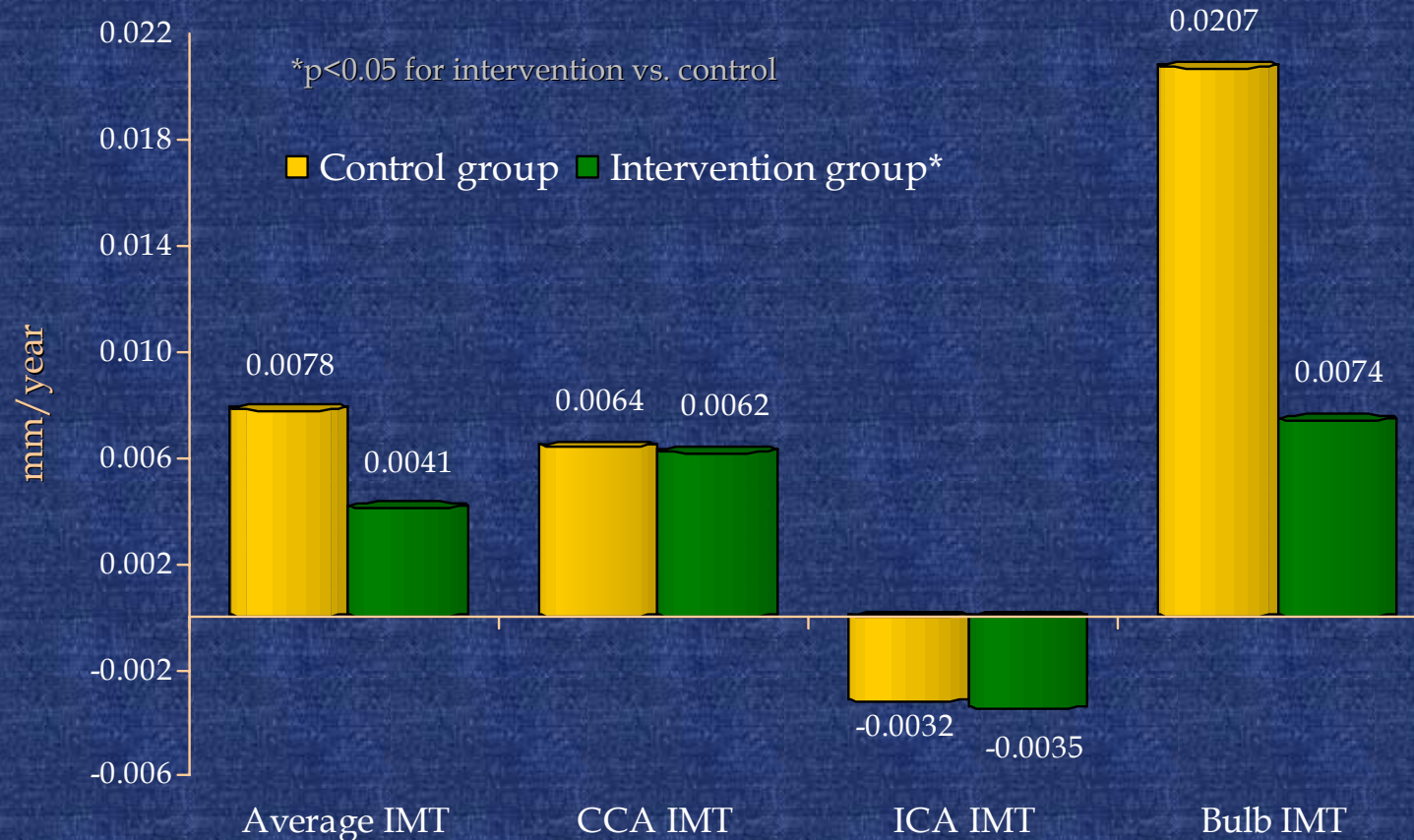
*Healthy Women Study*



# Mean Annual Intima-Media Thickness (IMT) Changes (in mm/year) Among the Control Group by Menopausal Status, Adjusted for Age and Corresponding Baseline Intima-Media Thickness

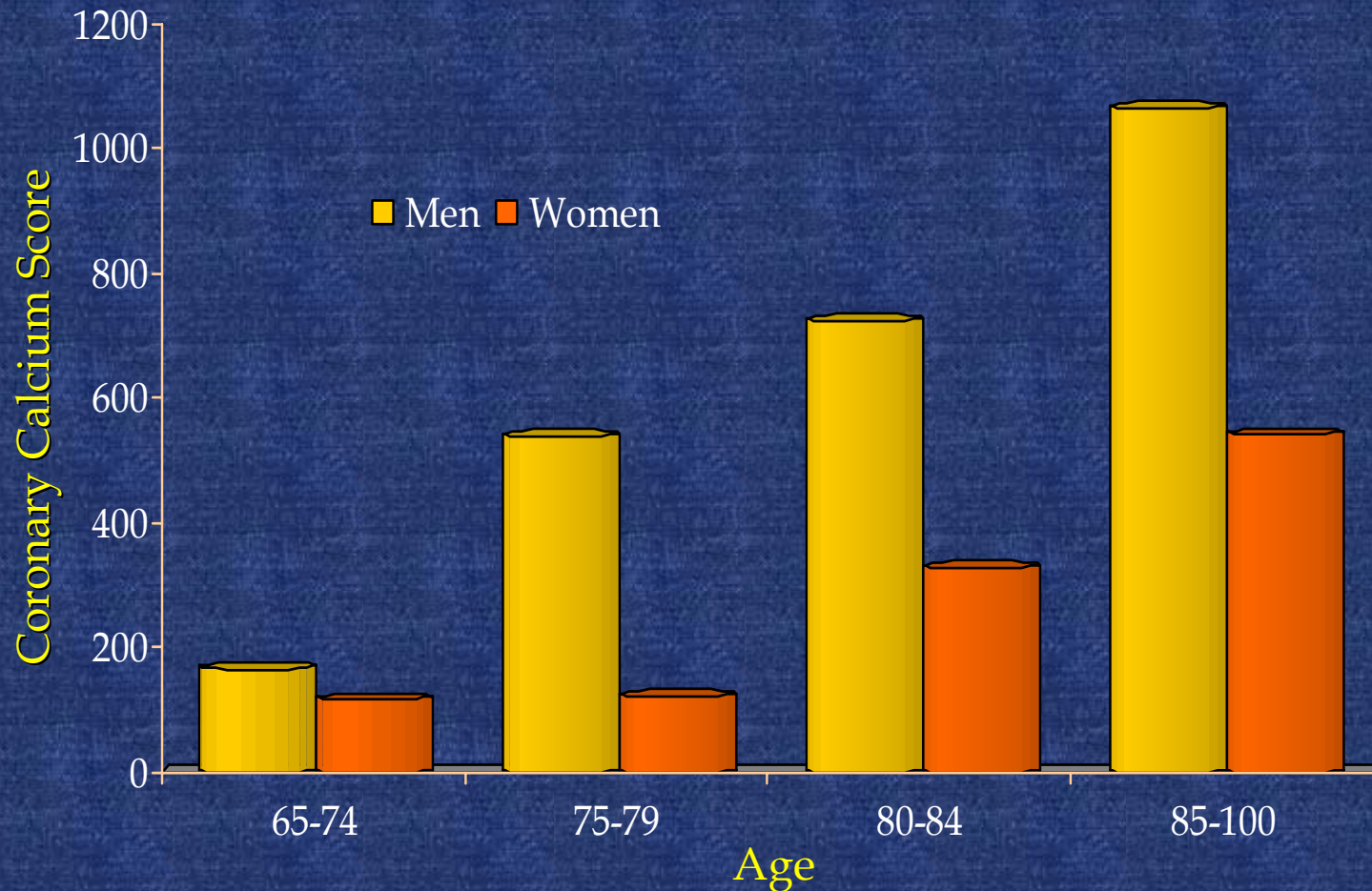


# Mean Annual Intima-Media Thickness (IMT) Changes (in mm/year) Among Perimenopausal/Postmenopausal Women by Intervention Group



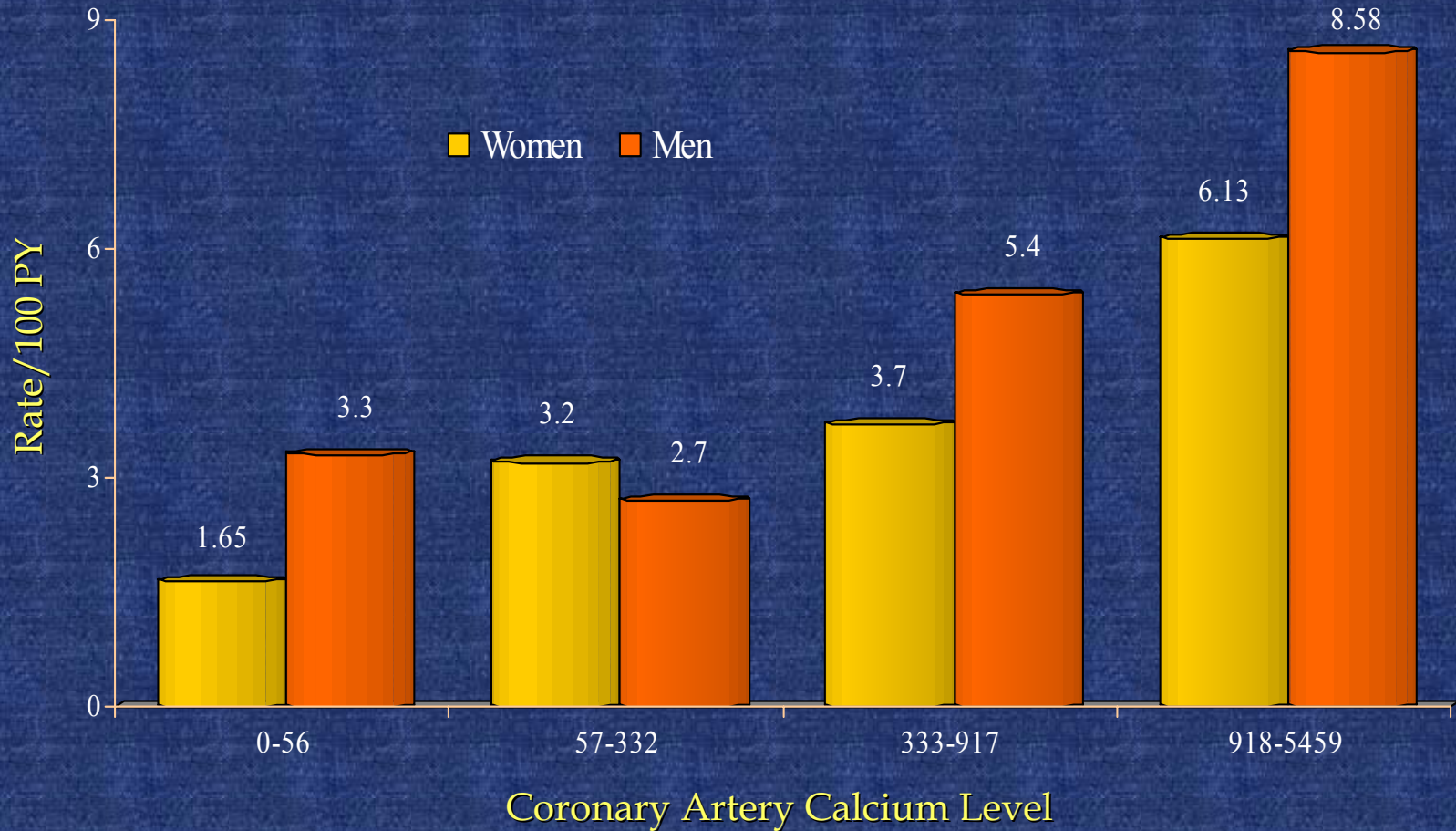
\*Adjusted for age and corresponding baseline intima-media thickness

# Median Coronary Calcium Score (Agatston units) in the CHS by Age and Sex





# Coronary Artery Calcium Predicts Total Mortality in the Elderly

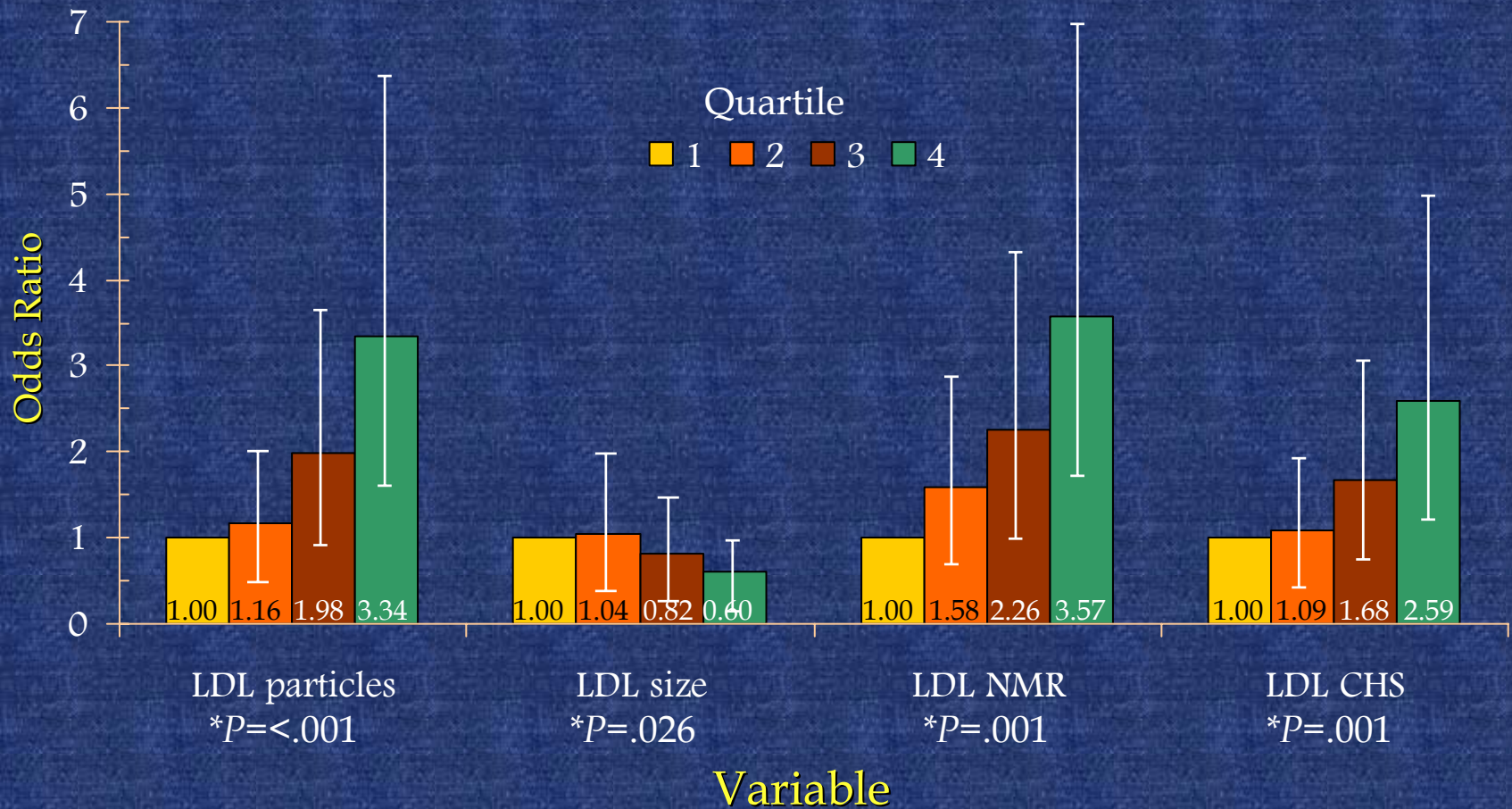


Newman AB, Naydeck BL, Ives D, Sutton-Tyrrell K, Edmundowicz D, Kuller LH. Coronary artery calcium predicts CVD and total mortality in the elderly. (Abstract) CHS

# Background

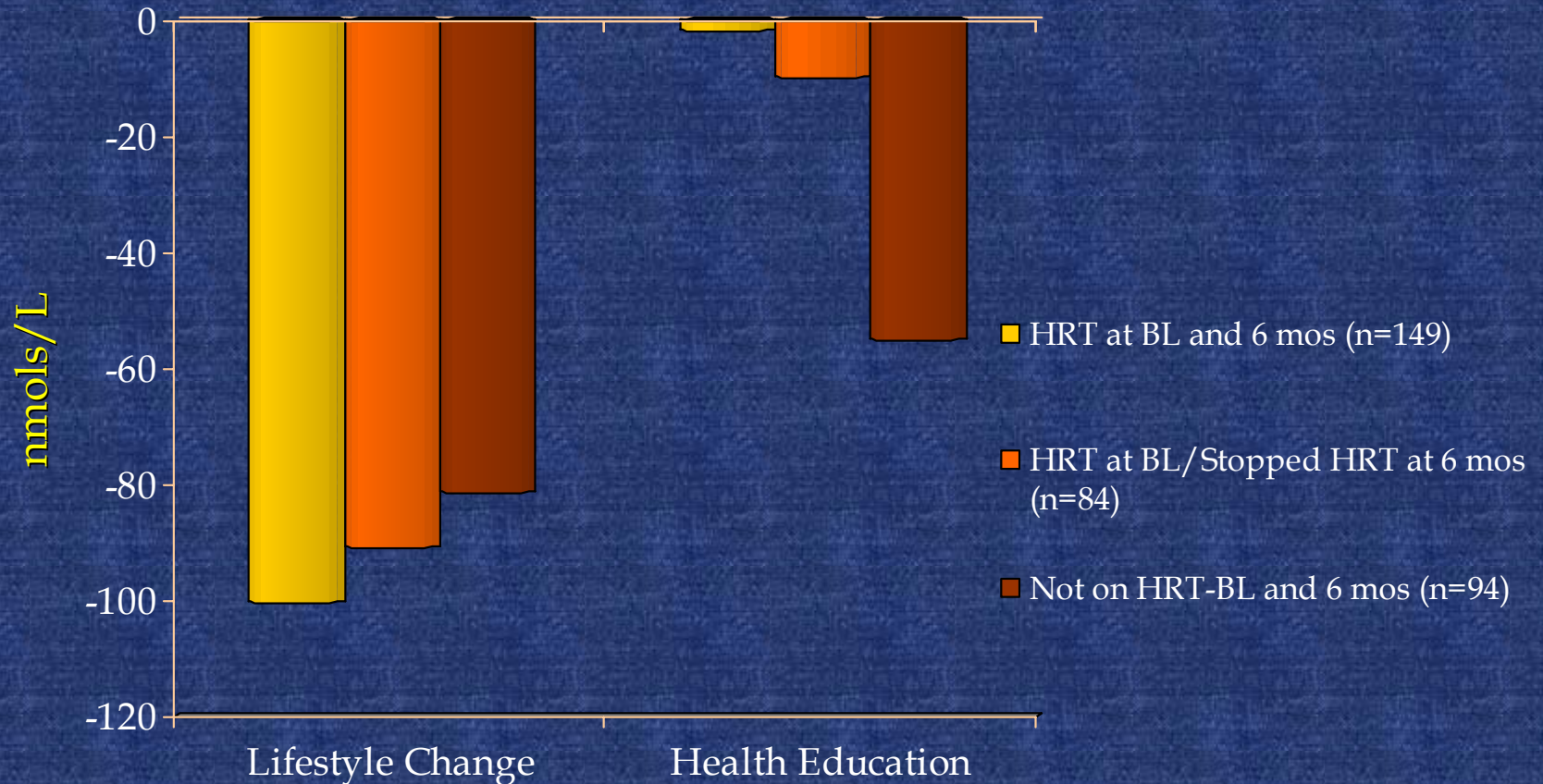
- Postmenopausal women on HRT have increased triglycerides
- High triglycerides among women have been associated with an increased risk of CHD
- High triglycerides are associated with increased waist circumference, intra-abdominal fat, and insulin resistance

# OR for MI and Angina by Quartiles of LDL, Particles and Size, Compared with Healthy CHS Women Only, Adjusted for Age & Race (\*P-values for linear trend)

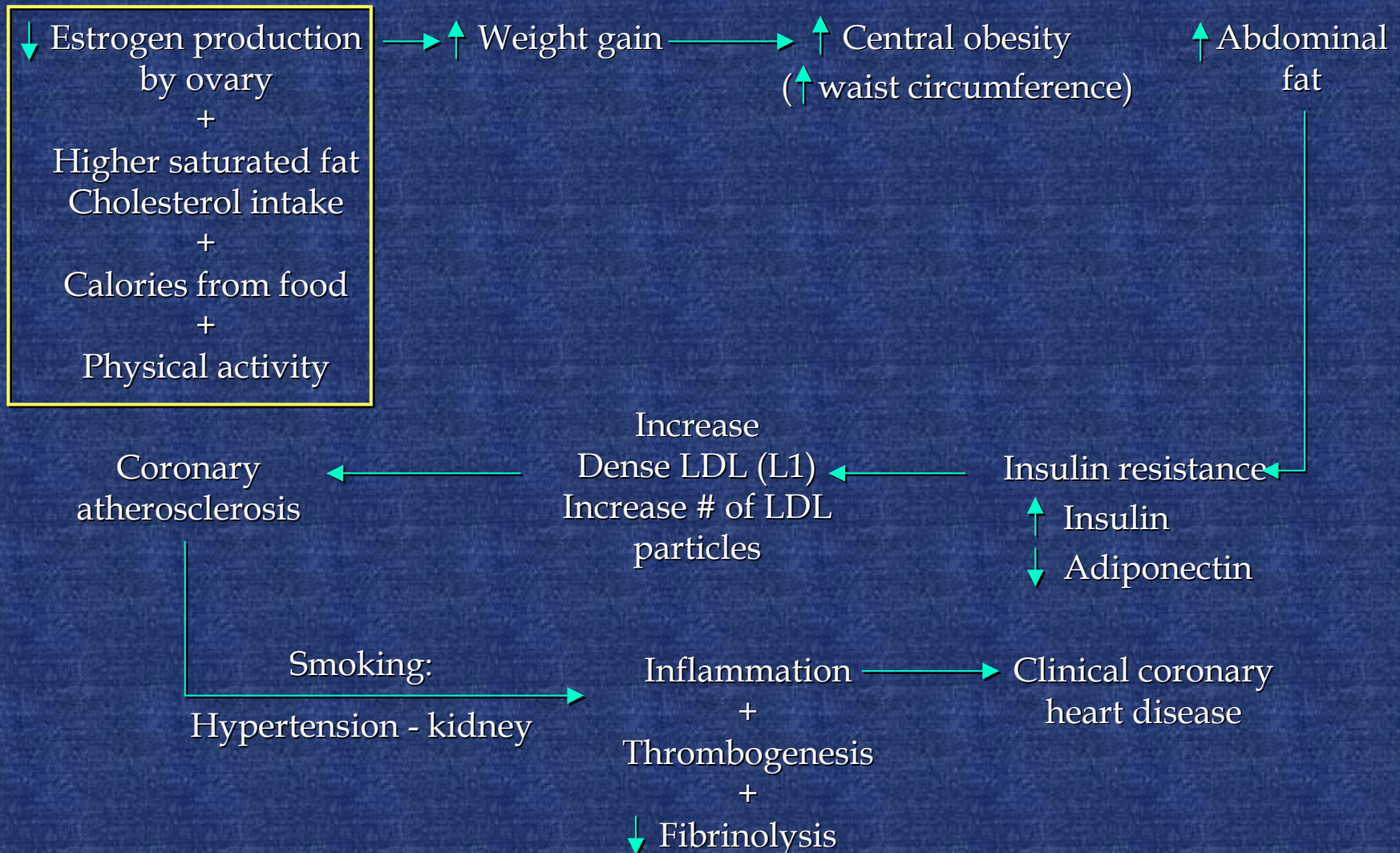


Kuller L, Arnold A, Tracy R, Otvos J, Burke G, Psaty B, Siscovick D, Freedman DS, Kronmal R. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol* 2002;22:1175-1180

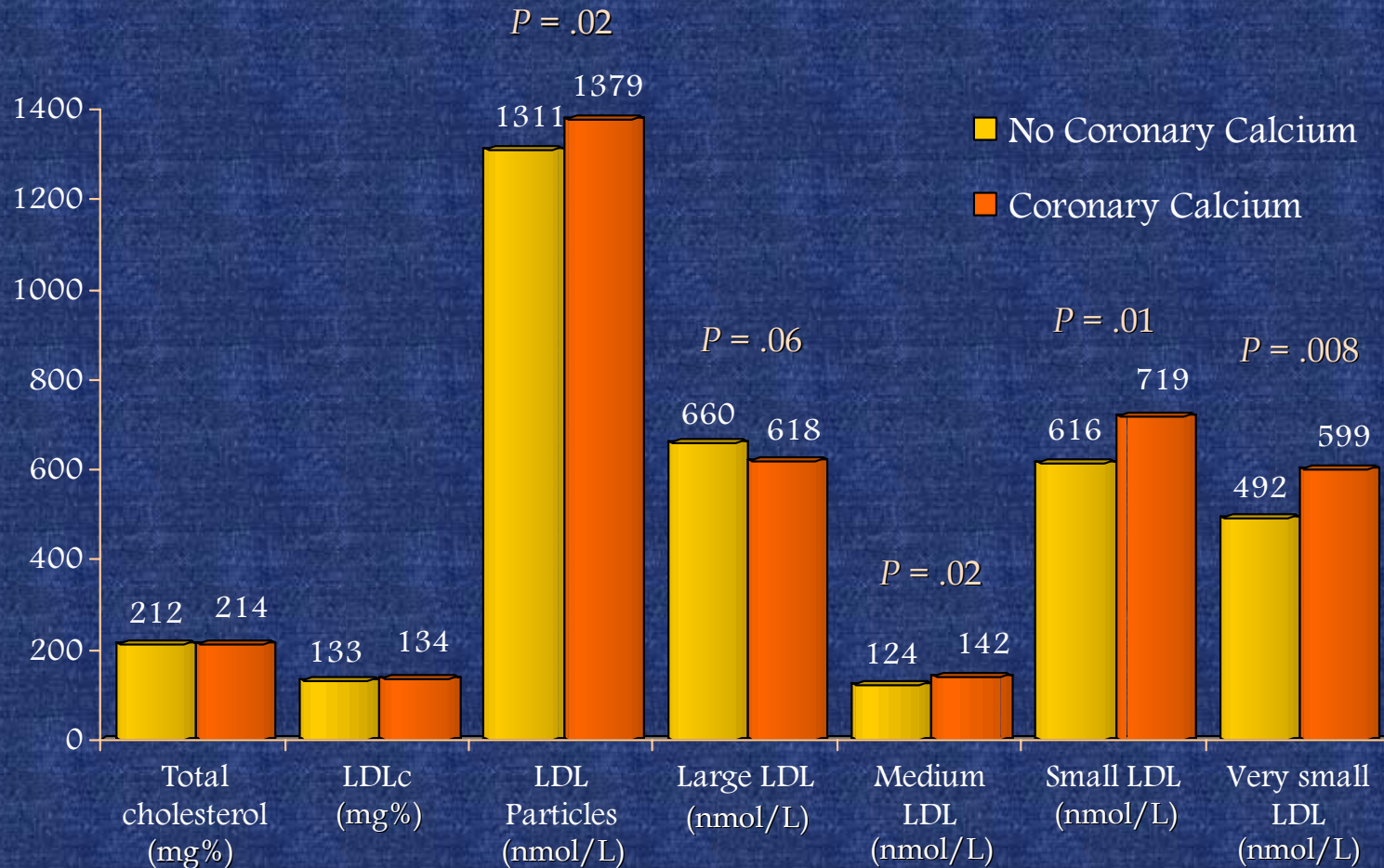
# Change in LDL Particles By Hormone Use Status



# Development of Atherosclerosis of Coronary Arteries Among Postmenopausal Women



# Baseline Lipoprotein and Coronary Calcium Levels in the WOMAN Study

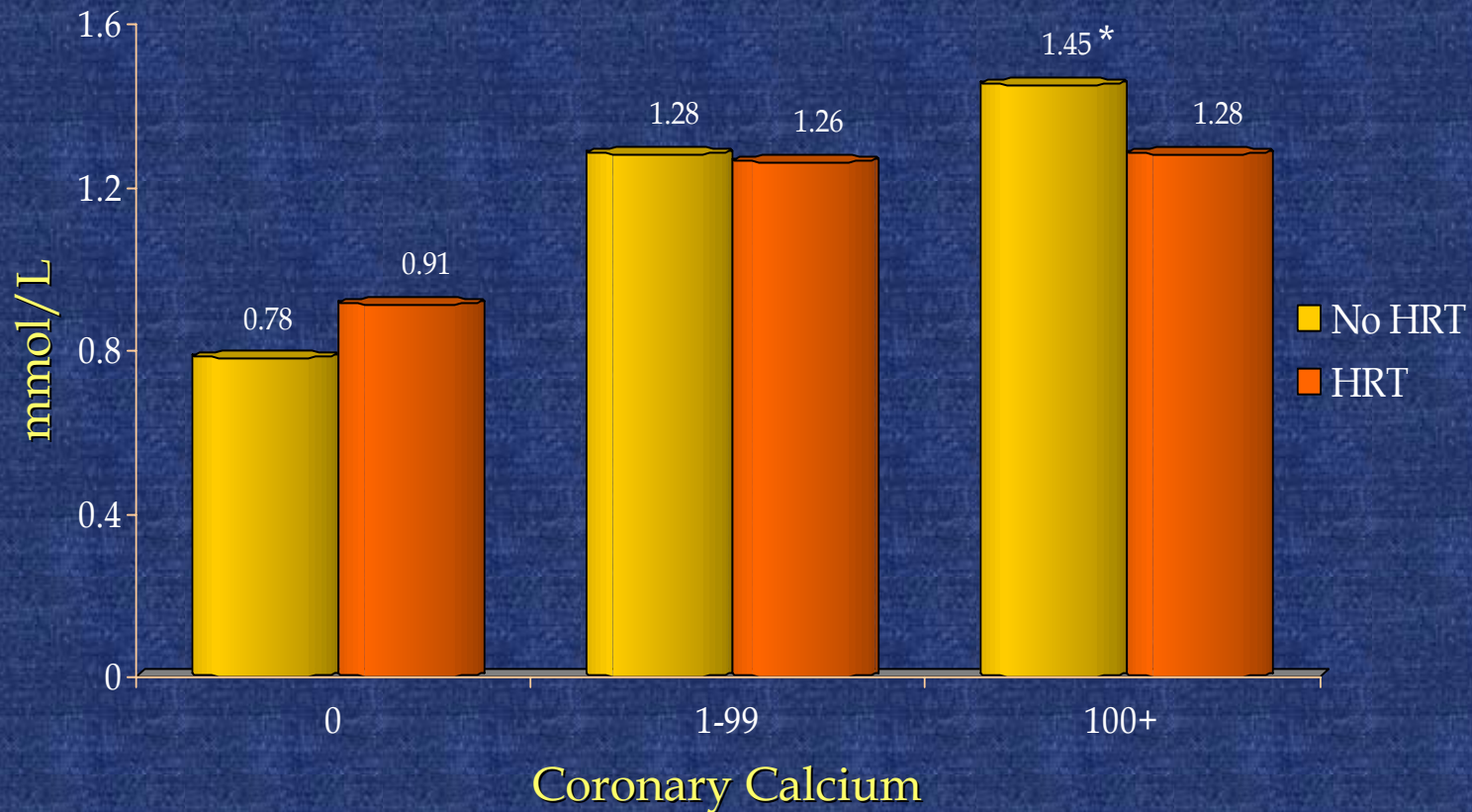


# WHI E-Along Trial: Coronary Heart Disease by Age N (Annualized Percentage)

Age (Years)	CEE N=5310	Placebo N=5429	HR (95% CI)	P value <sup>1</sup>
Total CHD	177 (0.49)	199 (0.54)	0.91 (0.75-1.12)	
50-59 (n=3310)	16 (0.14)	29 (0.24)	0.56 (0.30-1.03)	
60-69 (n=4852)	87 (0.54)	98 (0.59)	0.92 (0.69-1.23)	0.14
70-79 (n=2577)	74 (0.88)	72 (0.84)	1.04 (0.75-1.44)	

<sup>1</sup>P-value tests interactions of CEE and age

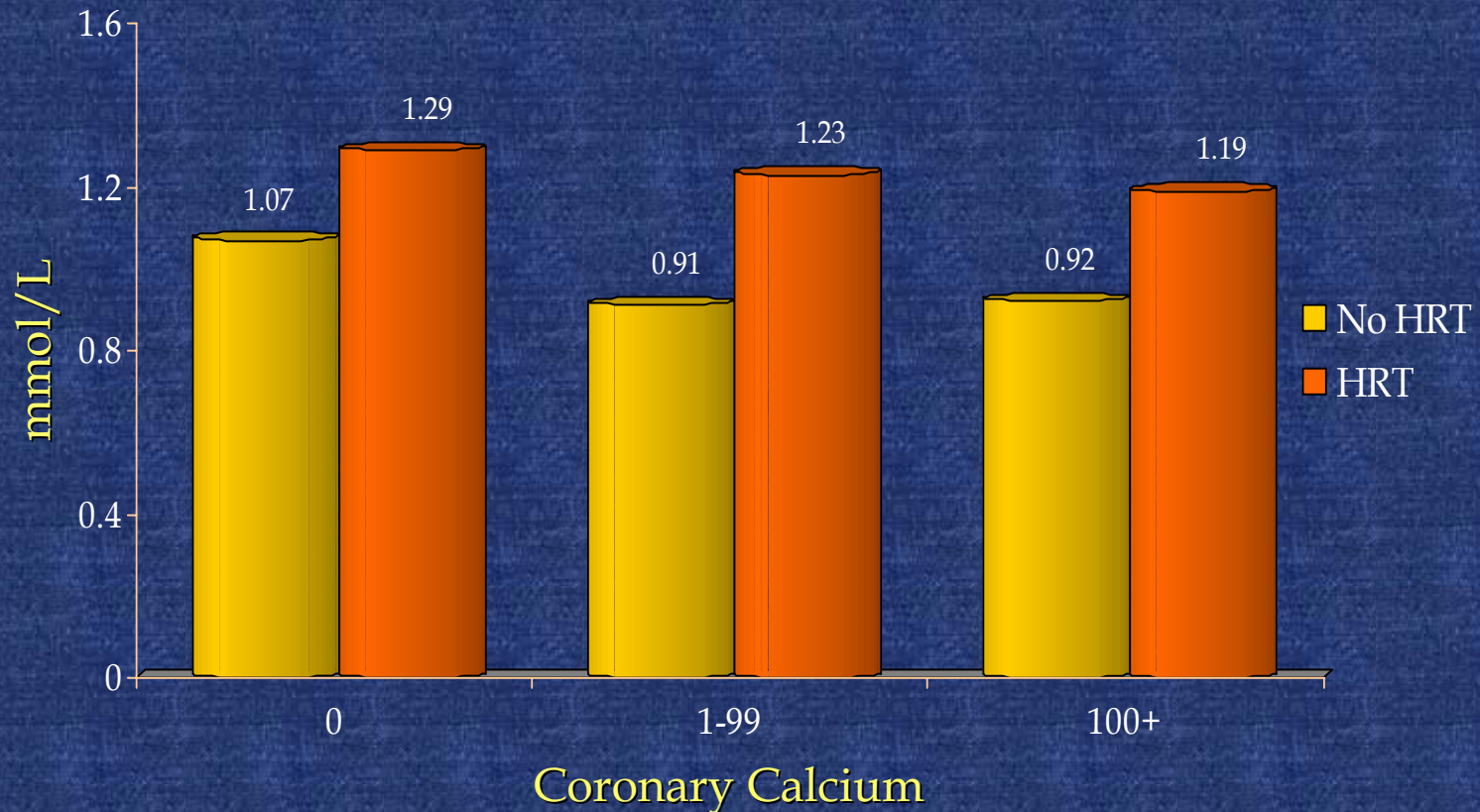
# Determinants of Coronary Calcium for HRT Users and NonUsers (NMR Spectroscopy): Small LDL



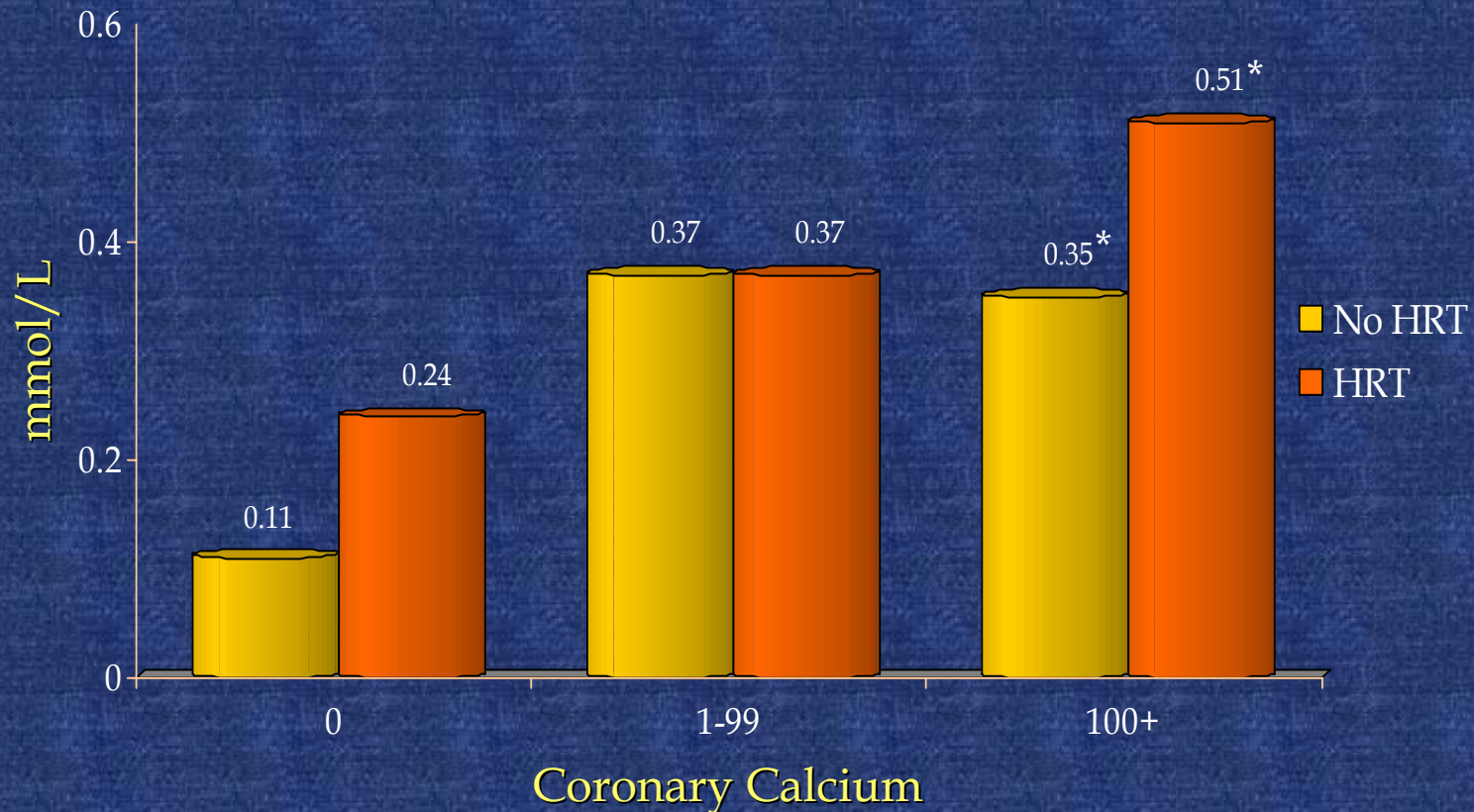
\*  $P < .05$



# Determinants of Coronary Calcium for HRT Users and NonUsers (NMR Spectroscopy): Large HDL

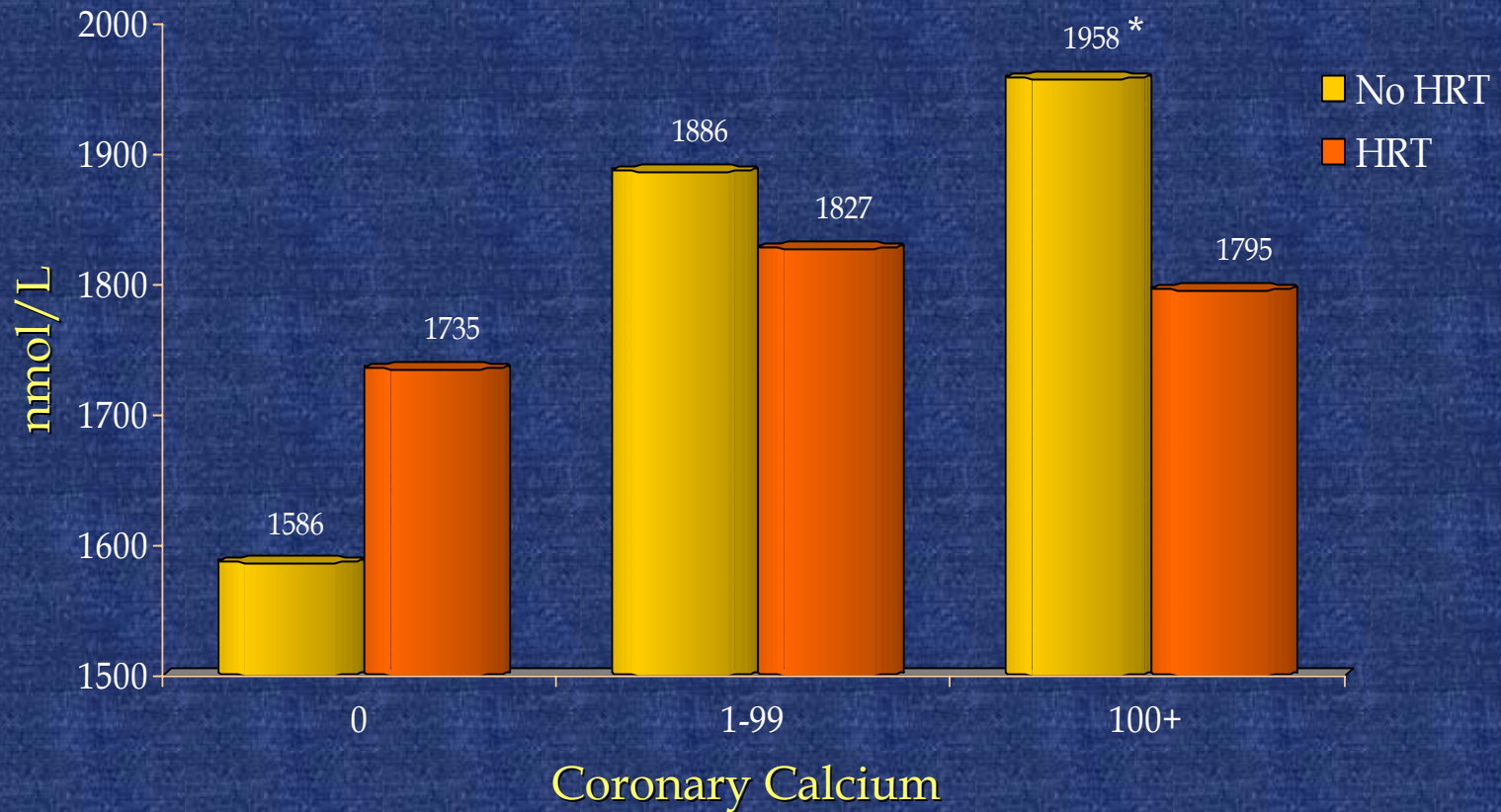


# Determinants of Coronary Calcium for HRT Users and NonUsers (NMR Spectroscopy): Large VLDL (Triglycerides)



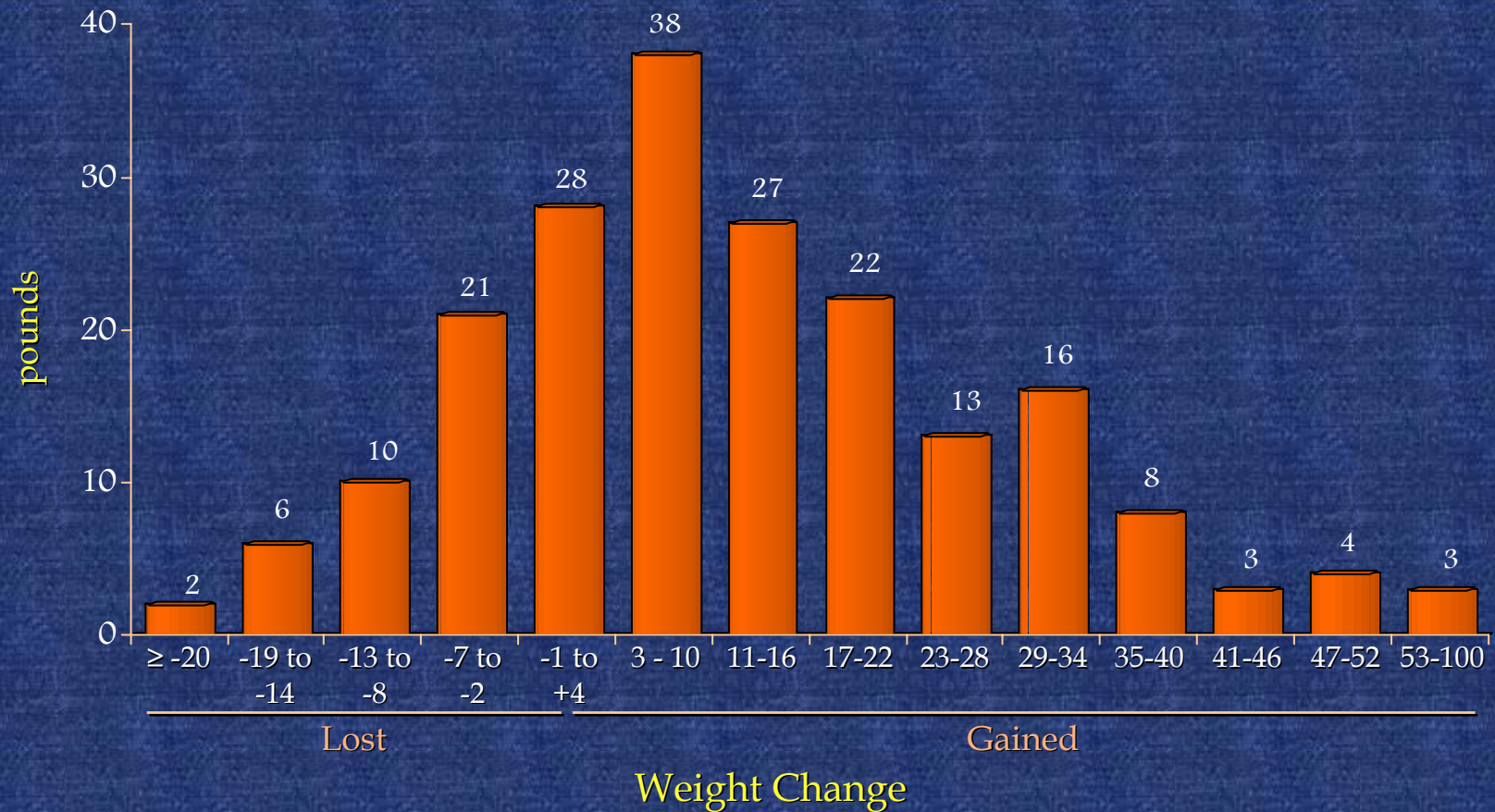
\*  $P < .05$

# Determinants of Coronary Calcium for HRT Users and NonUsers (NMR Spectroscopy): LDL Particles

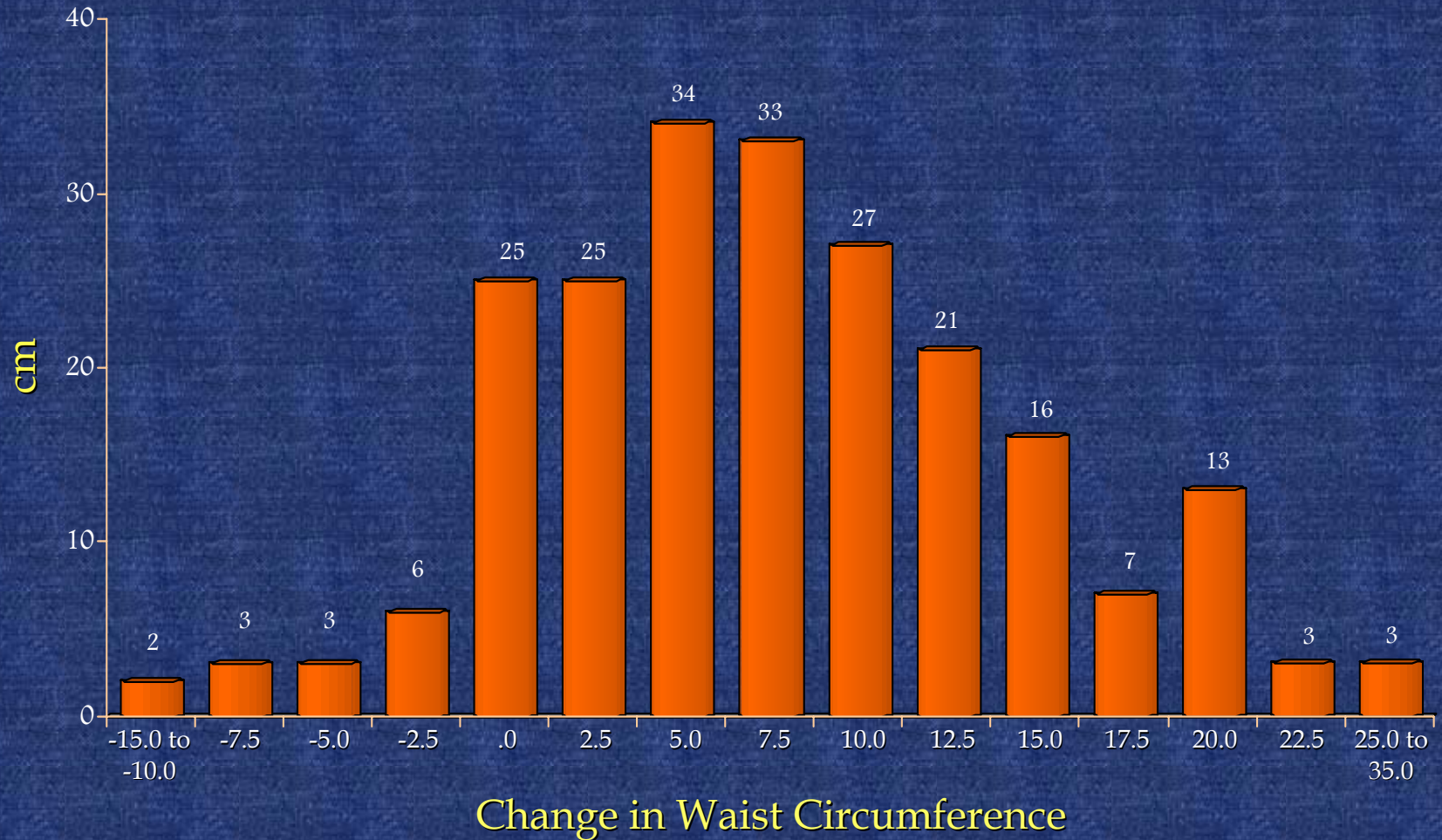


\*  $P < .05$

# Change in Weight by Baseline to 12<sup>th</sup> Postmenopausal Exam: *Healthy Women Study*



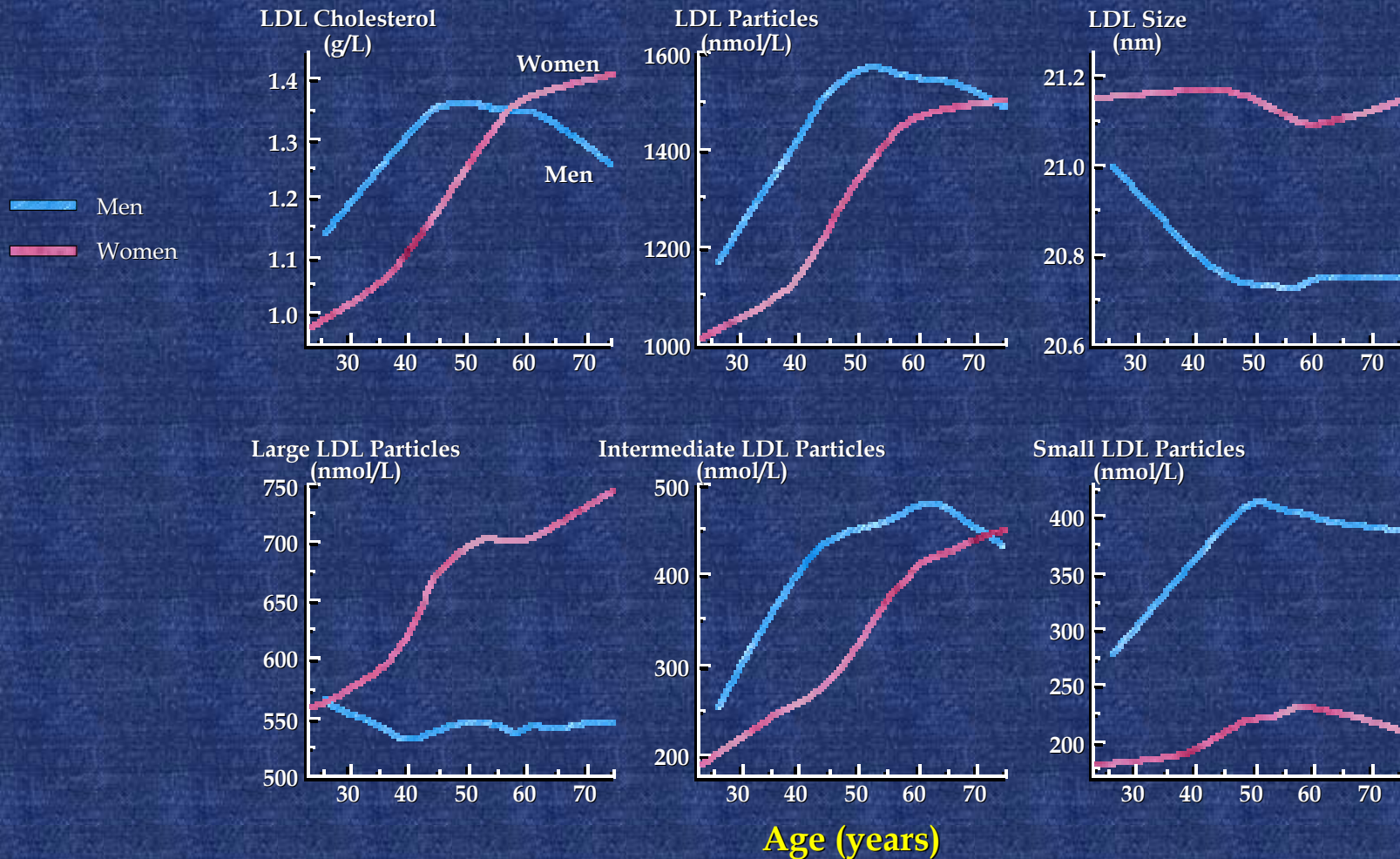
# Change in Waist Circumference From 1<sup>st</sup> to 8<sup>th</sup> Post in the Healthy Women Study, N=221



## Lipid and Lipoprotein Subclasses by Presence or Absence of Coronary Calcium by HRT Use: NMR Determined Lipoproteins & Chemicals (cont'd)

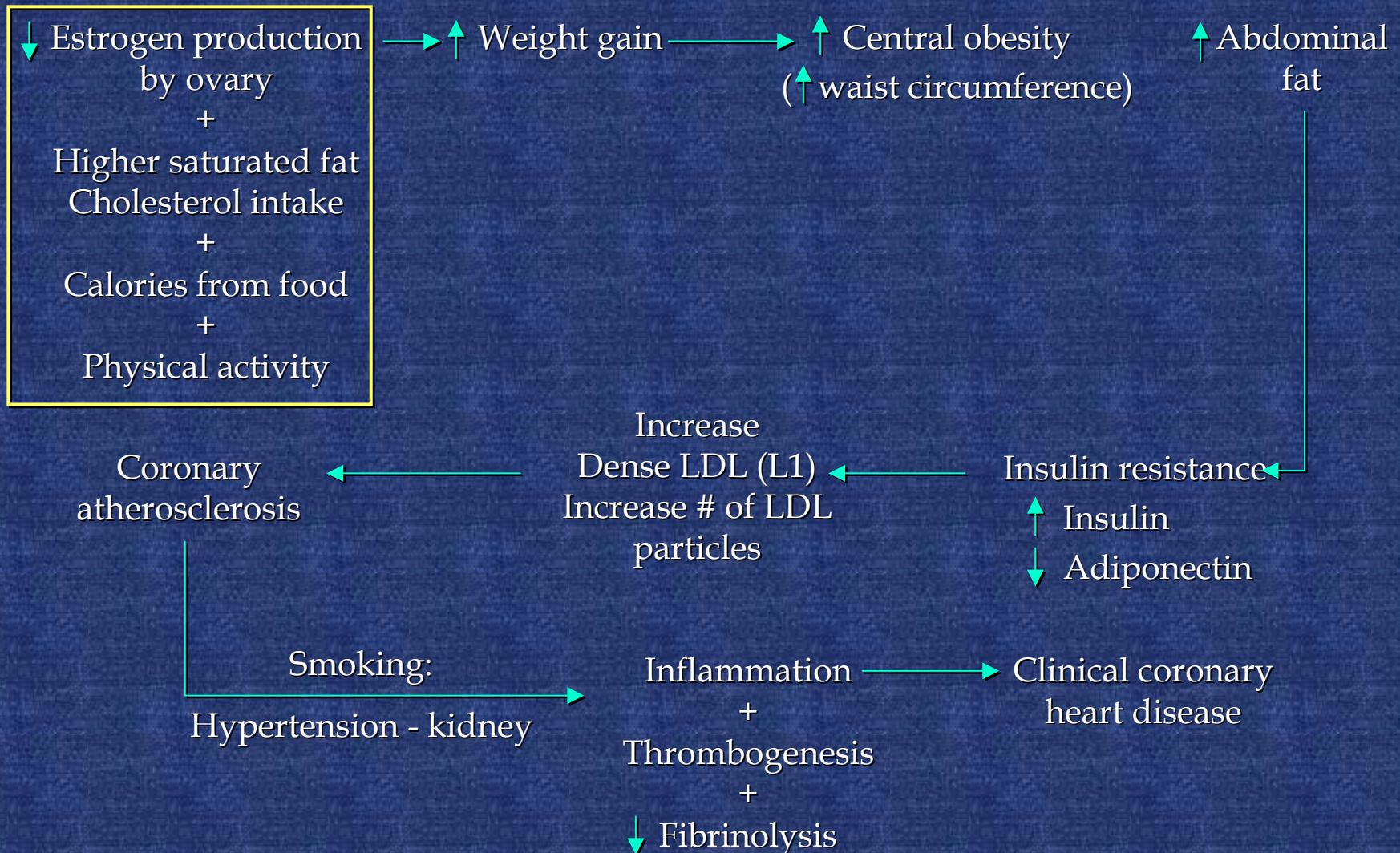
HRT Use	Coronary Calcium		P
	Present	Absent	
Small LDLc (mmol/L)			
HRT Use	0.94	0.70	0.05
No HRT Use	0.97	0.51	0.007
Large LDLc (mmol/L)			
HRT Use	2.11	2.11	0.12
No HRT Use	2.41	2.30	0.61
Large HDLc (mmol/L)			
HRT	1.16	1.25	0.36
No HRT	0.96	1.06	0.27
Small HDLc (mmol/L)			
HRT	0.47	0.46	0.84
No HRT	0.47	0.50	0.32
Large VLDL/Trig.			
HRT	0.32	0.10	0.0002
No HRT	0.12	0.02	0.005

# Relationship of LDLc, LDL Size, LDL Particle Concentration, and LDL Subclasses with Age



Freedman DS, Otvos JD, Jeyarajah EJ, Shalaurova I, Cupples LA, Parise H, D'Agostino RB, Wilson PWF, Schaerer EJ. Sex and age differences in lipoprotein subclasses measured by nuclear magnetic resonance spectroscopy: the Framingham Study. *Clin Chem* 2004;50(7):1189-1200

# Development of Atherosclerosis of Coronary Arteries Among Postmenopausal Women





Serum cholesterol levels in women with natural menopause (●) and in male subjects (●). Serum cholesterol in women with natural menopause increased significantly ( $P < .001$ ) from SEC -2 to SEC -1 and from SEC -1 to SEC +1. Serum cholesterol in men did not exhibit a sharp increase from SEC -2 to SEC +1 or from SEC -1 to SEC +1.

