

Framingham at Fifty: What Have We Learned?

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Disclosures

Grants: Merck

Advisory Board: Merck, Janssen, XZK

Outline

- **Origins of “Risk Factors”**
- **Conventional factors**
 - Age,
 - Total Cholesterol (or LDL-C)
 - HDL Cholesterol
 - Blood Pressure
 - Smoking
 - Diabetes mellitus
- **Other Risks**
 - Lifetime risk
 - Population Attributable Risk
- **Controversies**
 - Common risk factors and CHD risk
 - Diabetes as CHD Risk Equivalent
 - Inflammatory markers
- **New Strategies**
 - Reclassification Analysis

Initial Hypotheses

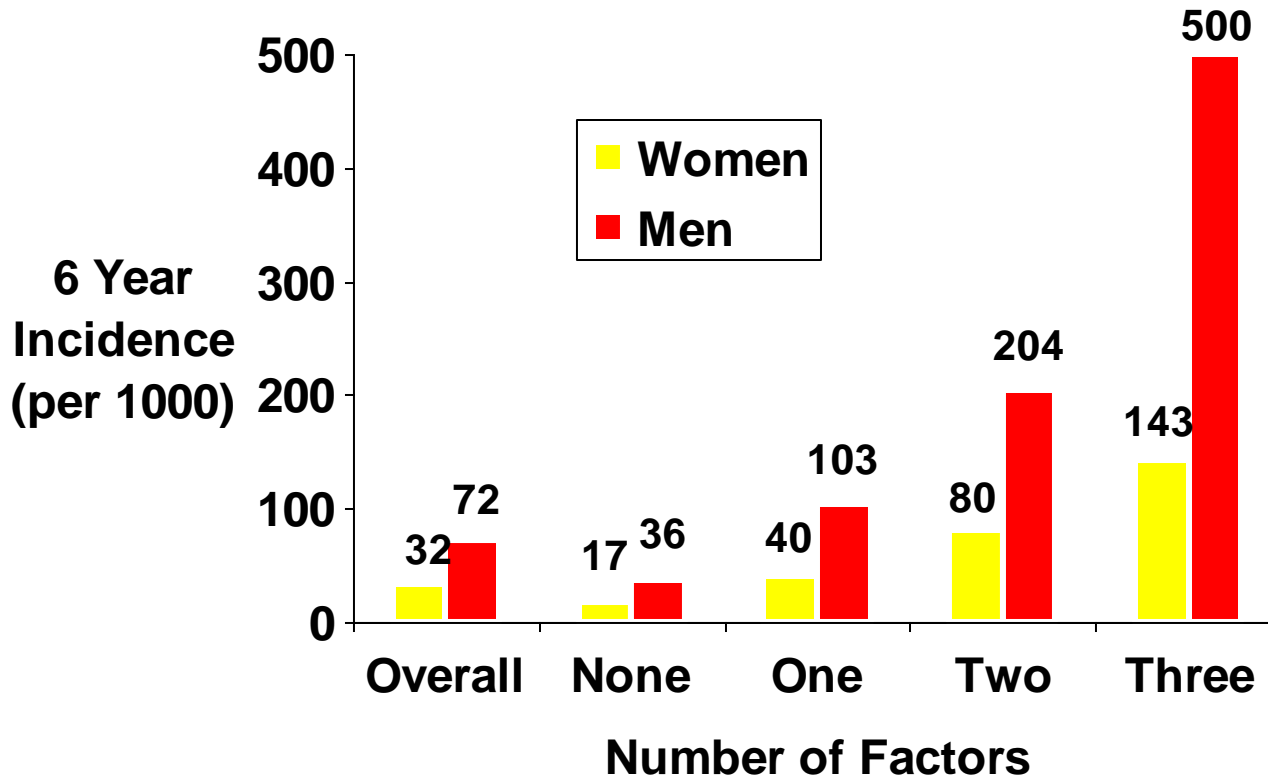
Framingham Heart Study 1948

- Major hypotheses
 - CVD increases with age.
 - Occurs earlier and more frequently in men
 - Hypertension increases CVD rates
 - Elevated blood cholesterol increases CVD rates
 - Tobacco smoking increases CVD rates
 - Alcohol (habitual use) increases CVD
 - Increased physical activity decreases CVD
 - Obesity increases CVD
 - Diabetes increases CVD
 - Population importance of rheumatic heart disease

Framingham Heart Study

- **Original Cohort**
Started 1948
N=5209
Exams every 2 years
- **Offspring (2nd generation)**
Started 1970
N=5135
Exams every 4 years
- **3rd Generation**
Started 2002
Exams every 4 years

Risk of CHD According to Elevated BP, Elevated Cholesterol* and LVH Framingham Cohort 6 Year Follow up

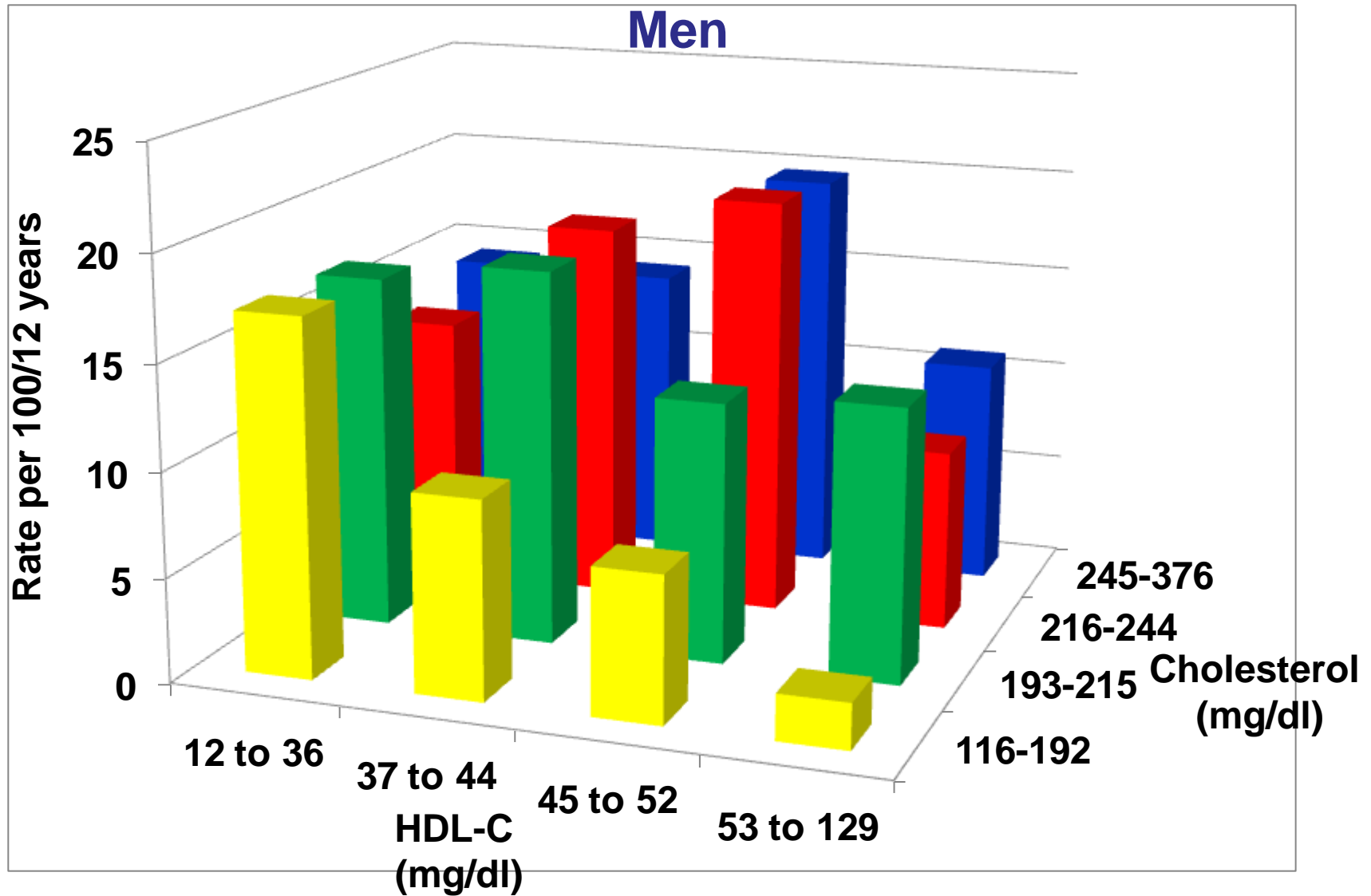


Elevated BP (>160/95 or therapy), cholesterol (>260 mg/dL)
Kannel Ann Intern Med 1961; 55: 33

Factors of Risk in the development of coronary heart disease—Six-Year follow-up experience, The Framingham Study

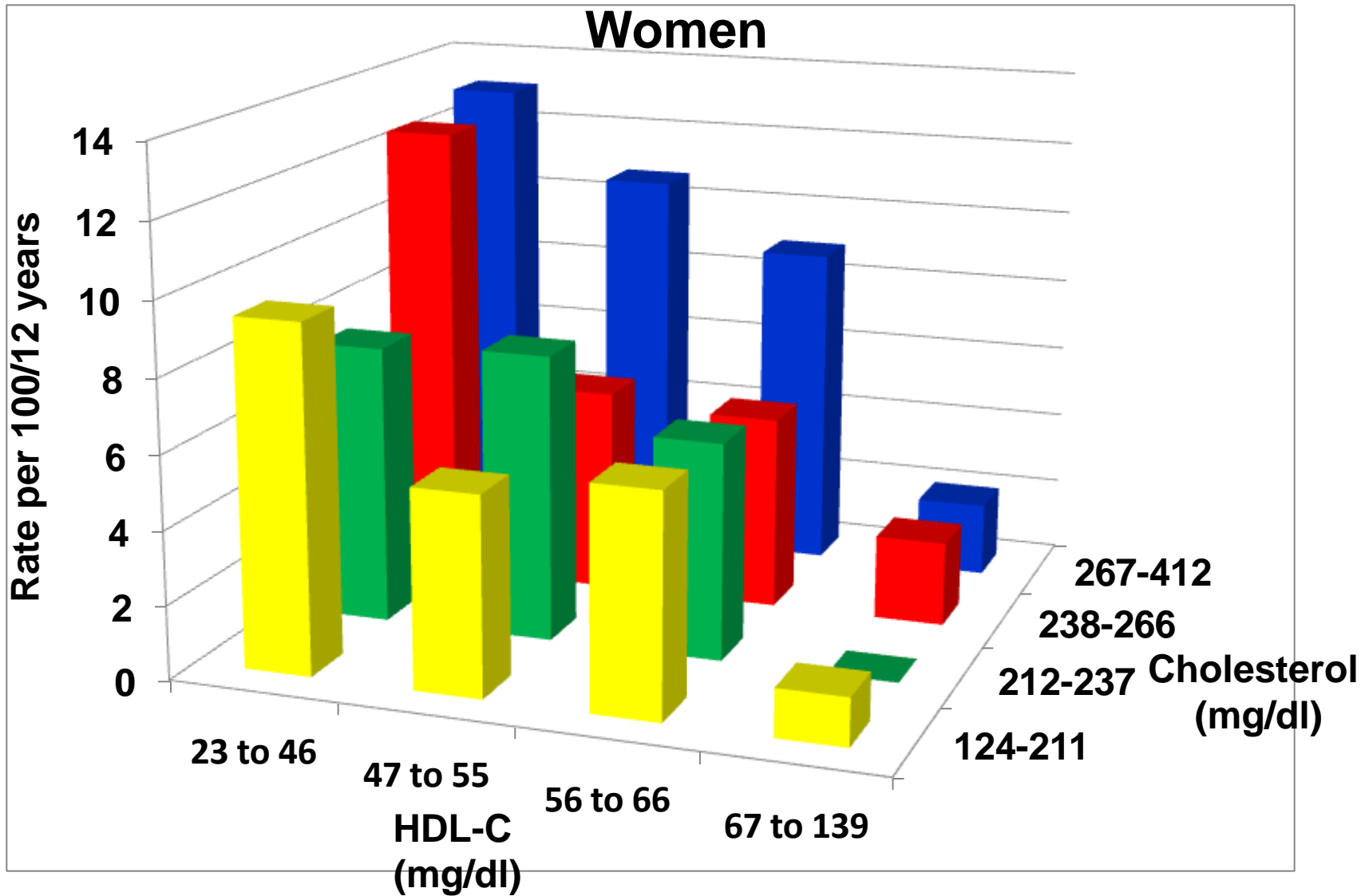
Combinations of the three risk factors under consideration appear to augment further the risk of subsequent development of coronary heart disease....As additional longitudinal observations are made, it is hoped that additional risk factors will be determined.

12 Year Incidence of Myocardial Infarction Framingham Cohort

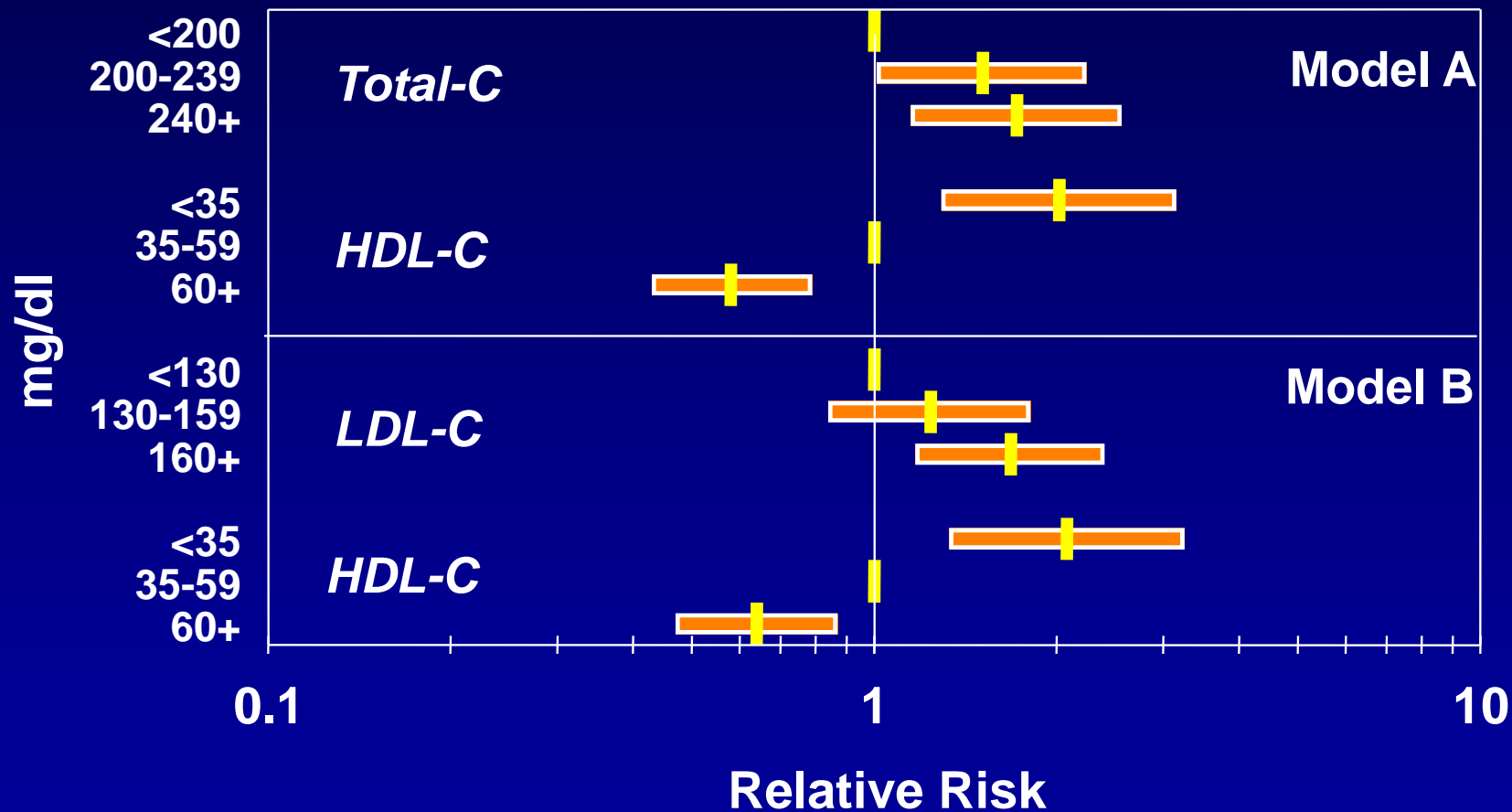


12 Year Incidence of Myocardial Infarction Framingham Cohort

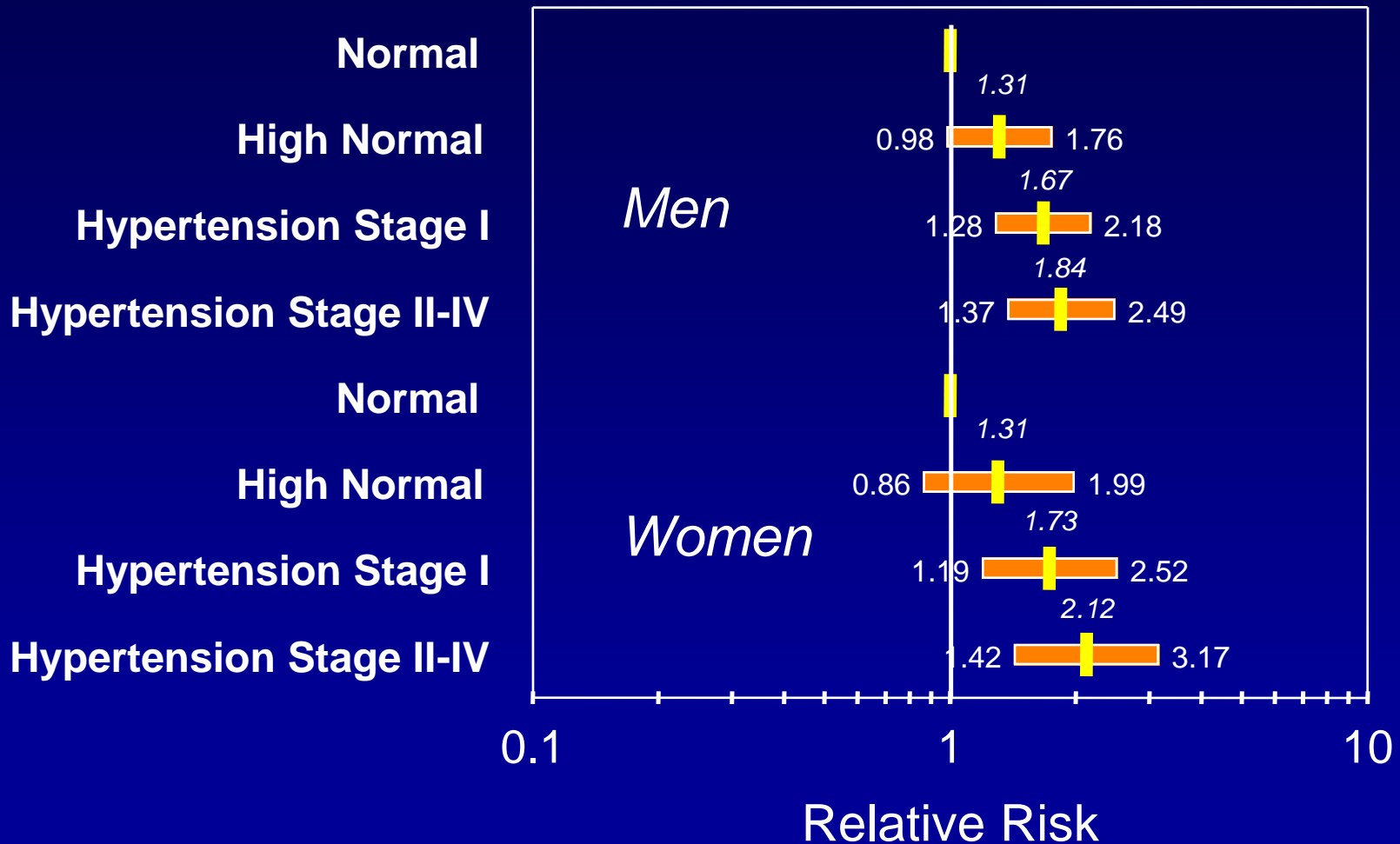
Women



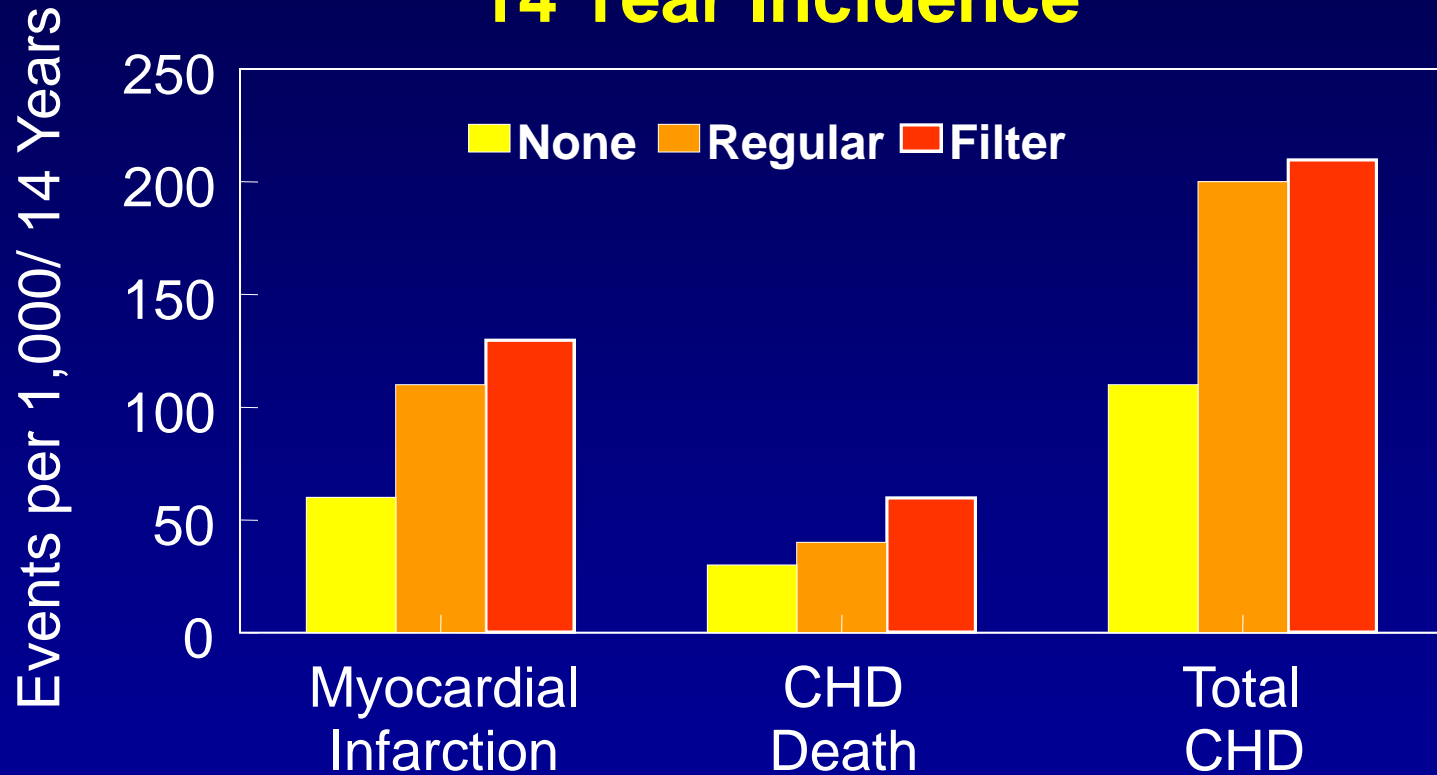
12 Year CHD Incidence According to Lipid Categories Women



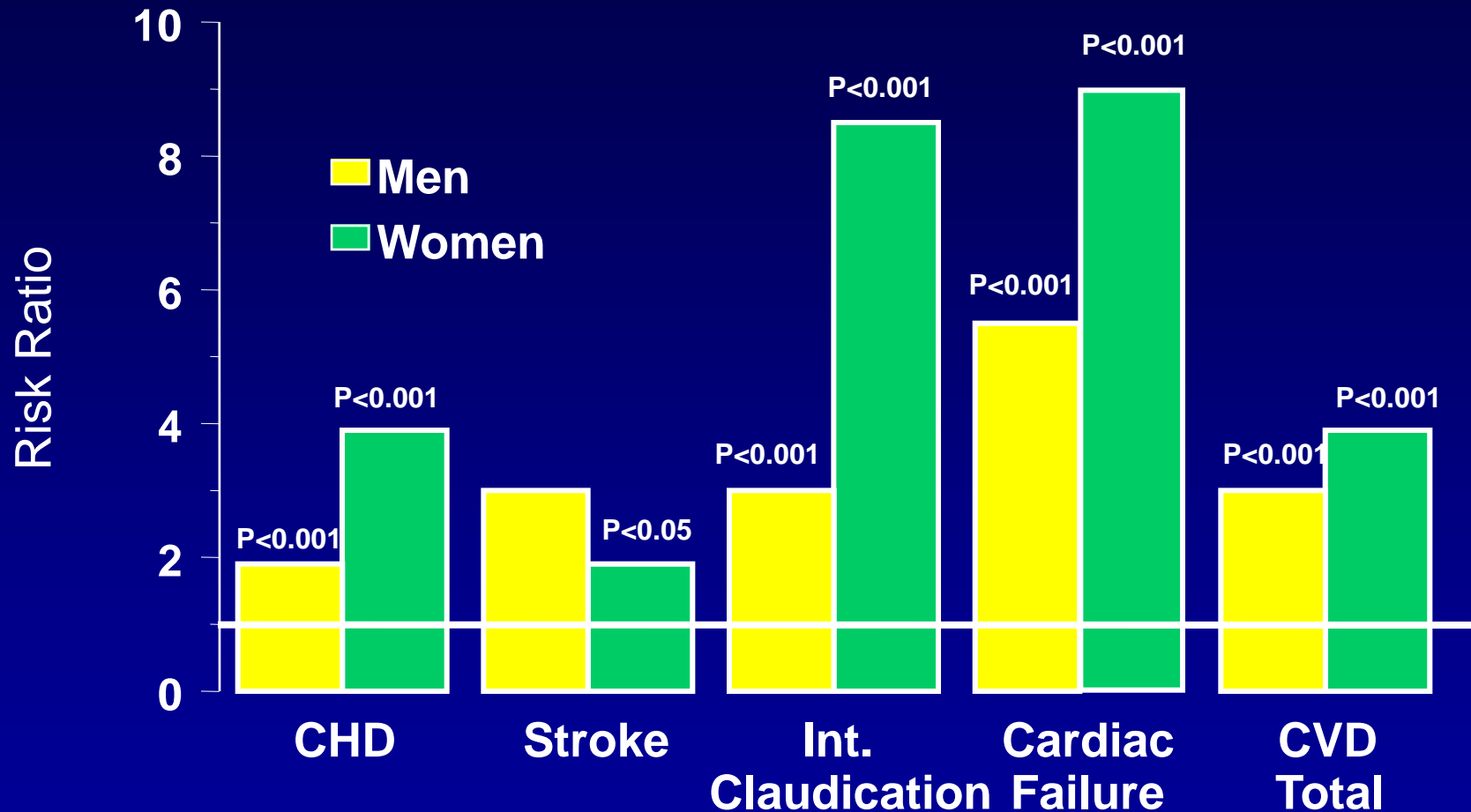
12 Year CHD Incidence According to BP Category



Cigarette Smoking and CHD Framingham Heart Study Men 14 Year Incidence



Diabetes and CVD Risk in Framingham Cohort Age 35-64 Years--30 Year Follow-up



Assessing Hard CHD Risk in Men

Step 1: Age

Years	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Step 4: Systolic Blood Pressure

Systolic BP (mm Hg)	Points if Untreated	Points if Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Step 6: Adding Up the Points

Age	_____
Total cholesterol	_____
HDL-cholesterol	_____
Systolic blood pressure	_____
Smoking status	_____
Point total	_____

Step 2: Total Cholesterol

TC (mg/dL)	Points at Age 20-39	Points at Age 40-49	Points at Age 50-59	Points at Age 60-69	Points at Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Step 7: CHD Risk

Point Total	10-Year Risk	Point Total	10-Year Risk
<0	<1%	11	8%
0	1%	12	10%
1	1%	13	12%
2	1%	14	16%
3	1%	15	20%
4	1%	16	25%
5	2%	≥17	≥30%
6	2%		
7	3%		
8	4%		
9	5%		
10	6%		

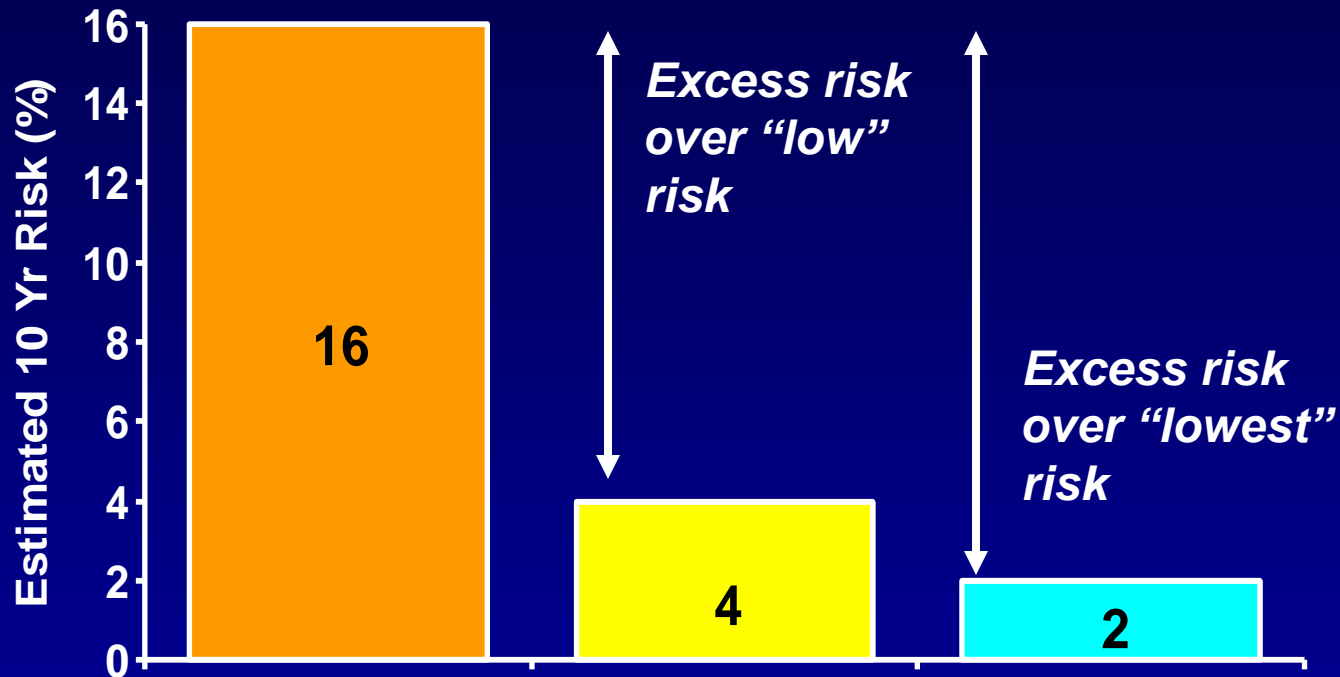
Step 3: HDL-Cholesterol

HDL-C (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Step 5: Smoking Status

	Points at Age 20-39	Points at Age 40-49	Points at Age 50-59	Points at Age 60-69	Points at Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Estimated 10 Year Hard CHD Risk in 55 year old Man According to Levels of Various Factors



	Patient	Low	Lowest
Cholesterol	250	160-199	<160
HDL-C	39	50-59	>60
BP systolic	146	<130	<120
Cigarettes	No	No	No
BP Rx	No	No	No

Performance Measures for Risk Estimation

- **Relative Risk**

Are the coefficients (Log RR) of the FHS and study's optimal models the same within random fluctuations?

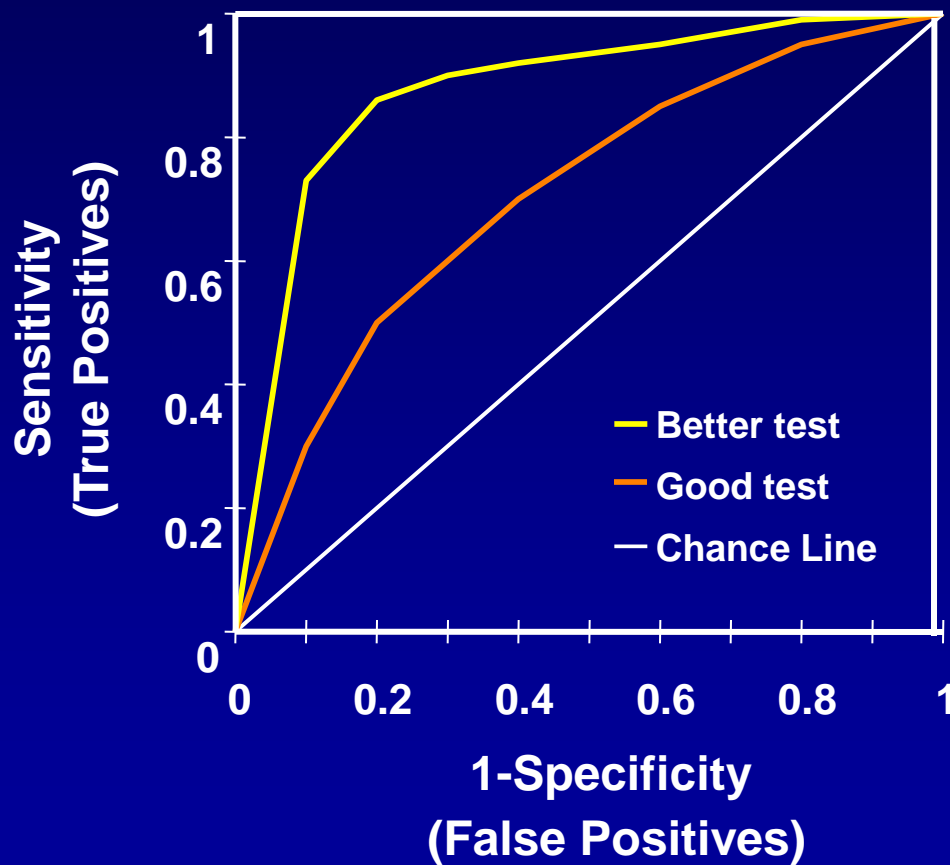
- **Discrimination**

Ability of the model to distinguish events from non-events. (C-statistic used as a measure)

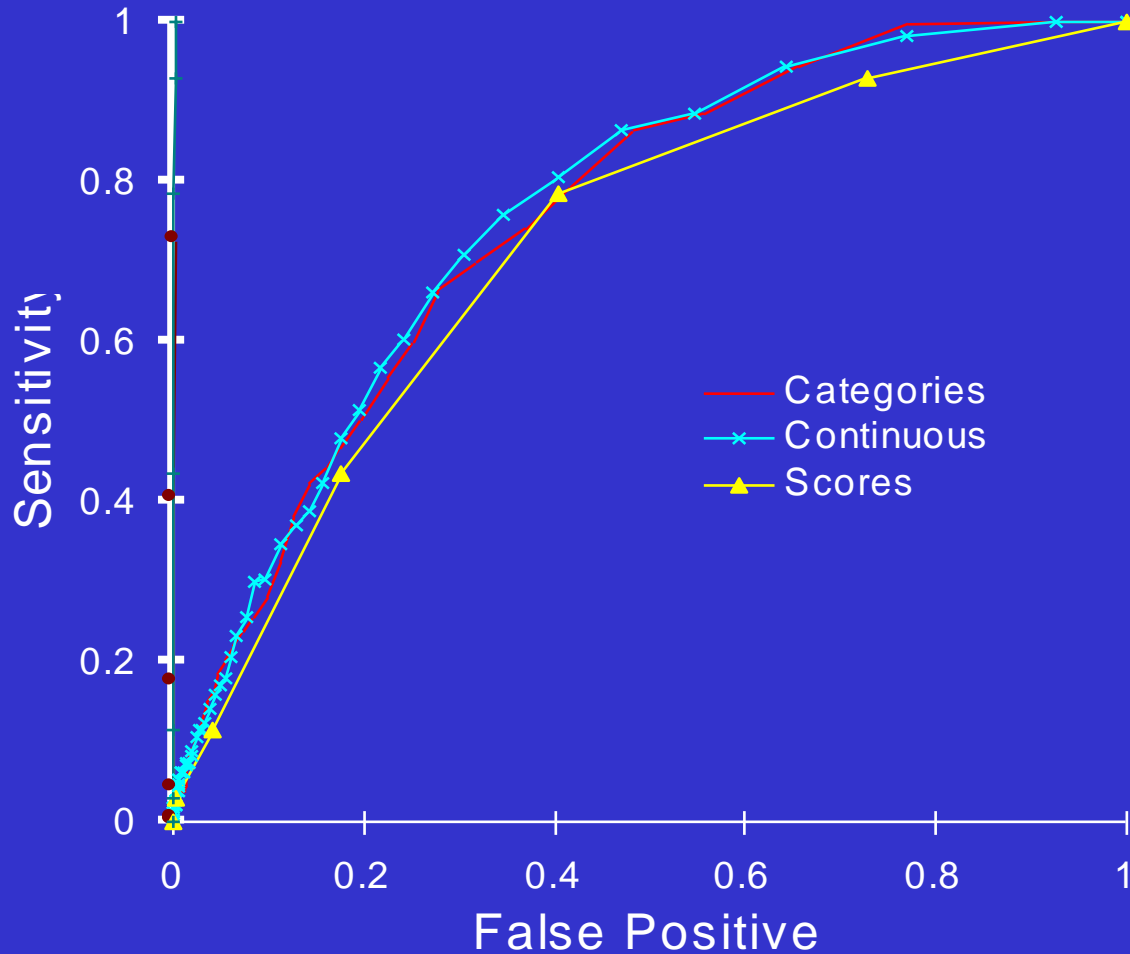
- **Calibration**

Closeness of predicted probability to observed (Adjusted Hosmer-Lemeshow Chi-Square < 20 and calibration bar plot as measures)

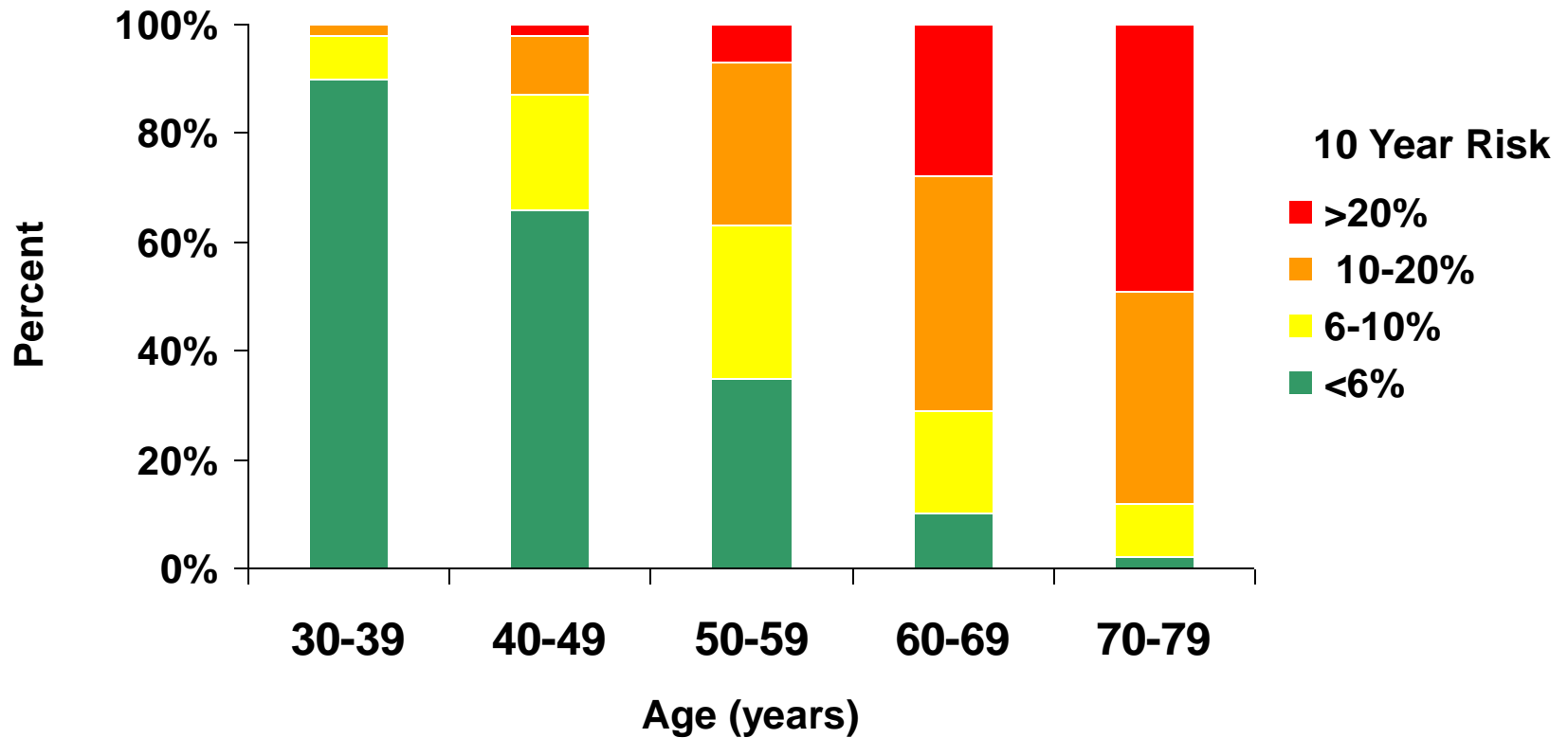
Receiver Operating Characteristic Curves and Disease Prediction



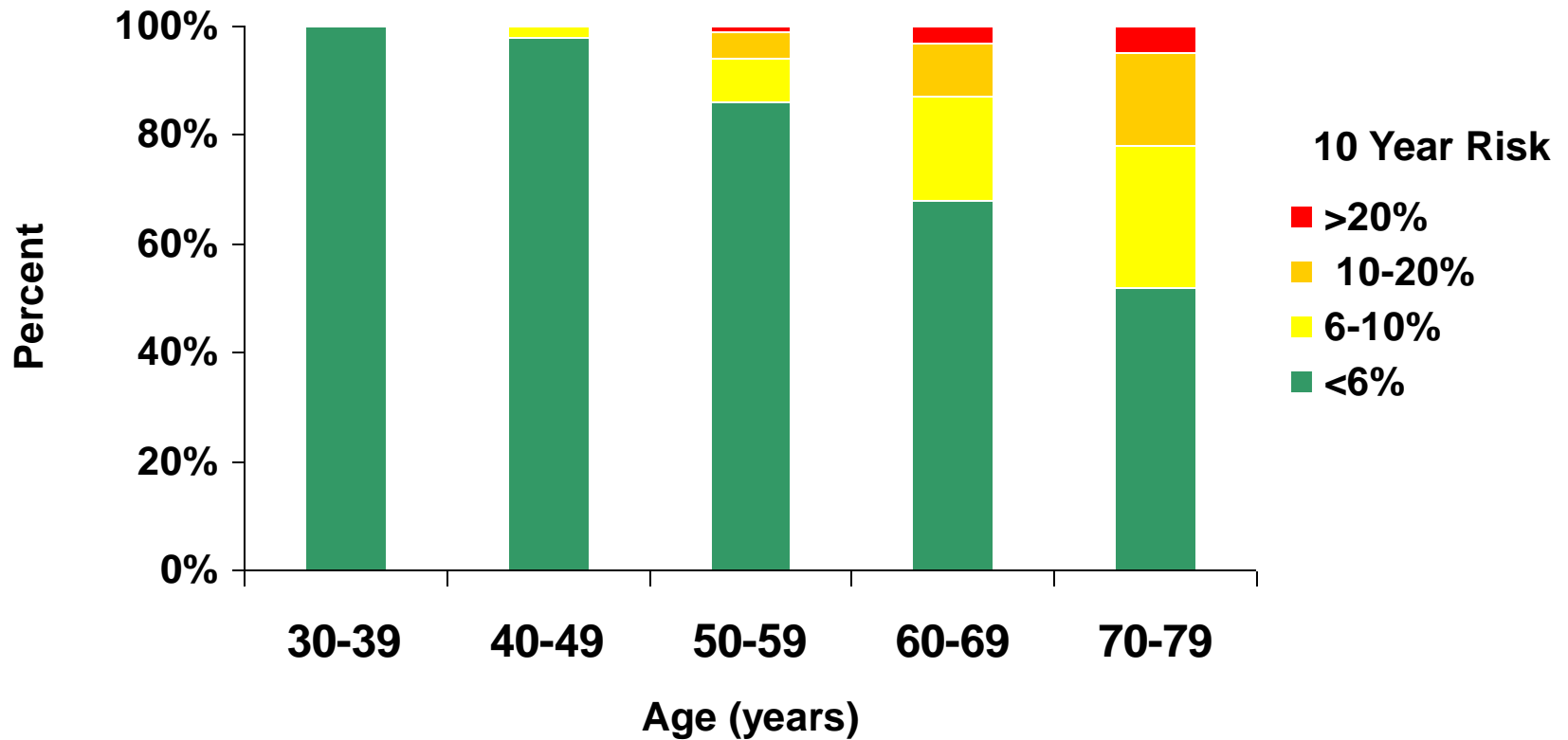
ROC Curve for CHD Prediction Framingham Men



Estimated 10 Hard CHD Risk Framingham Offspring and Cohort Men



Estimated 10 Hard CHD Risk Framingham Offspring and Cohort Women

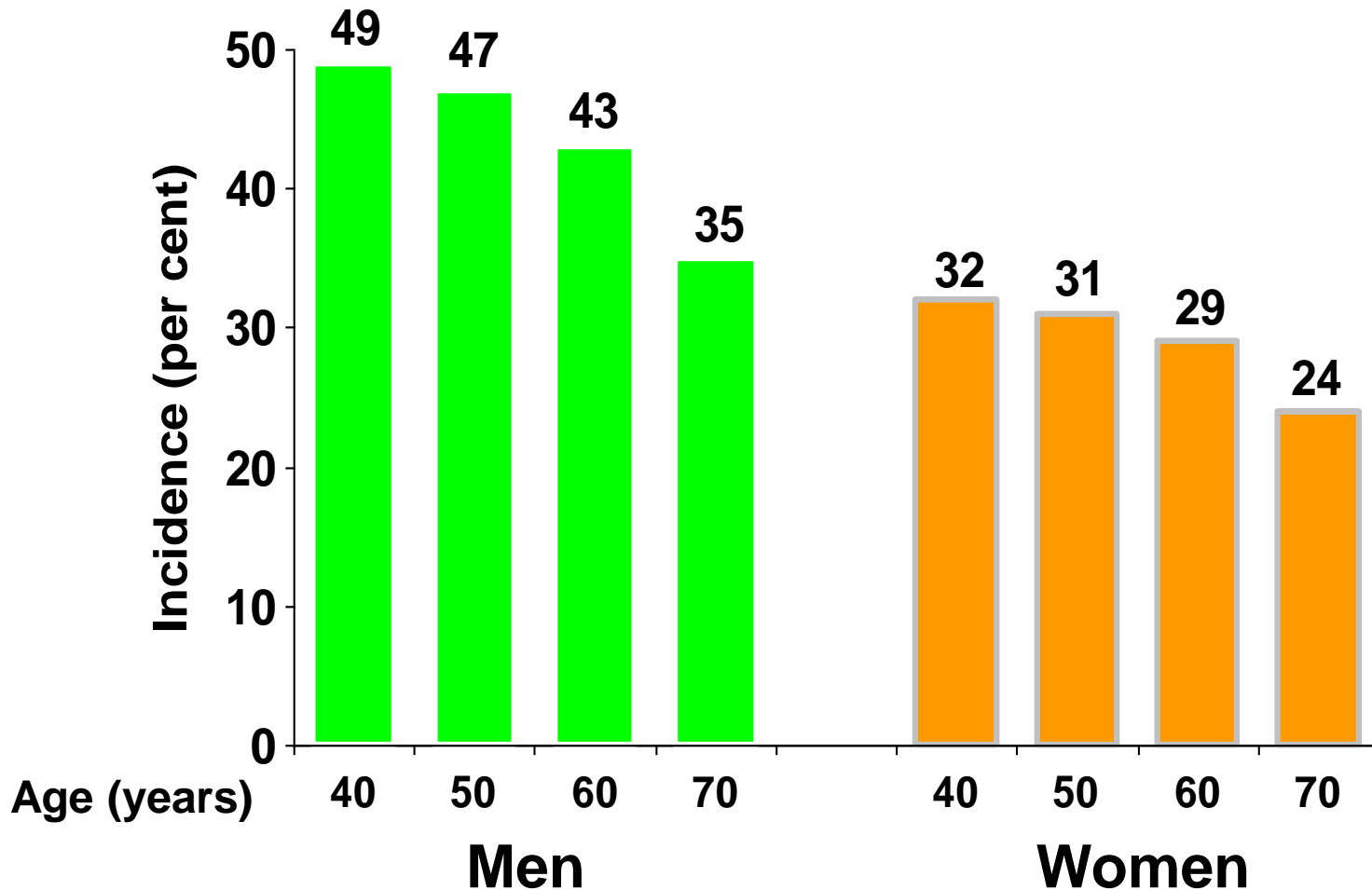


Risk Factors and Estimated CHD Risk

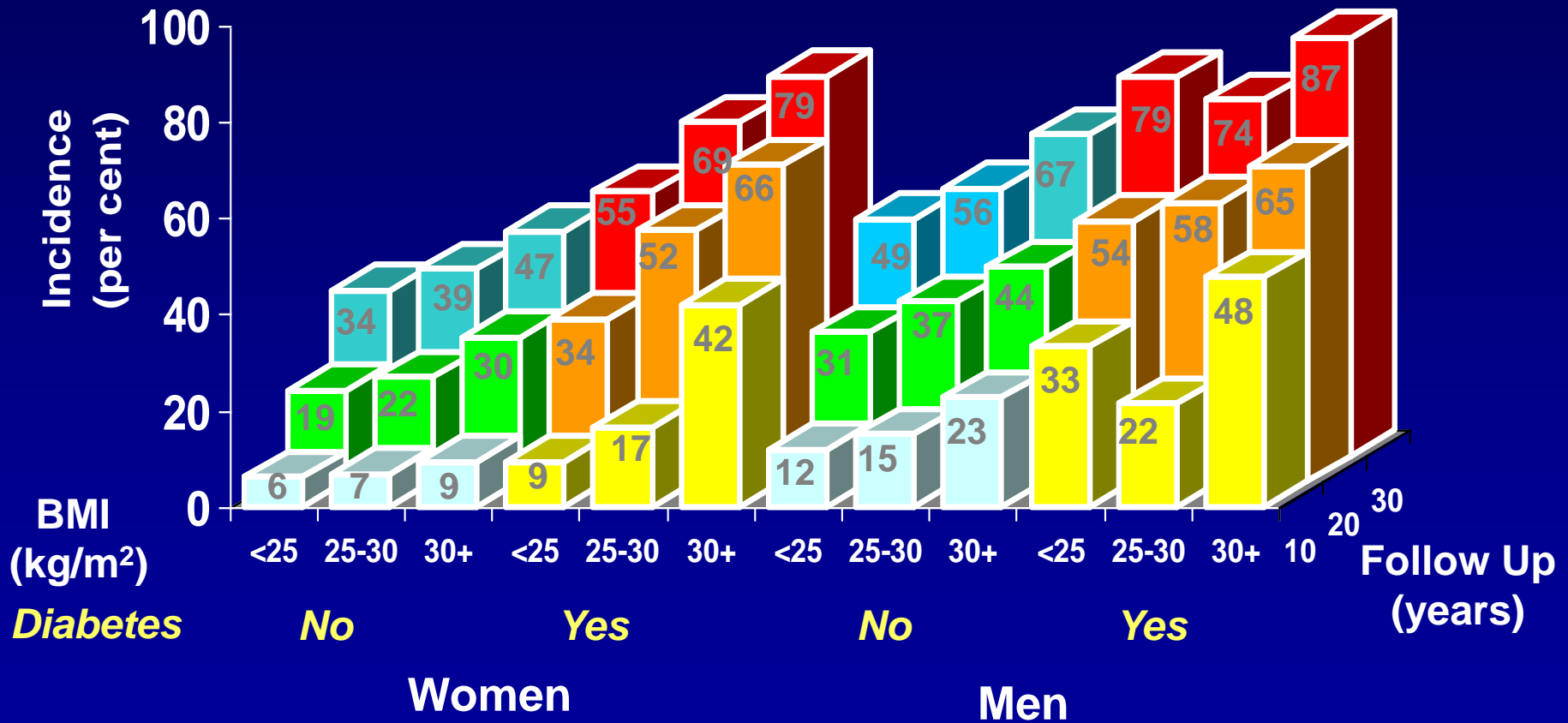
Factor	Prevalence	Relative Odds	Pop. Attrib. Risk (%)
Familial Hypercholesterolemia	0.002	35	6.4
Familial Defective Apo-B100	0.0014	40	0.4
Type III Dyslipidemia	0.0025	40	1
MTHFR gene homozygote	0.10	1.16	2
Epsilon 4 Allele	0.24	1.53	11

Lifetime Risk of CHD

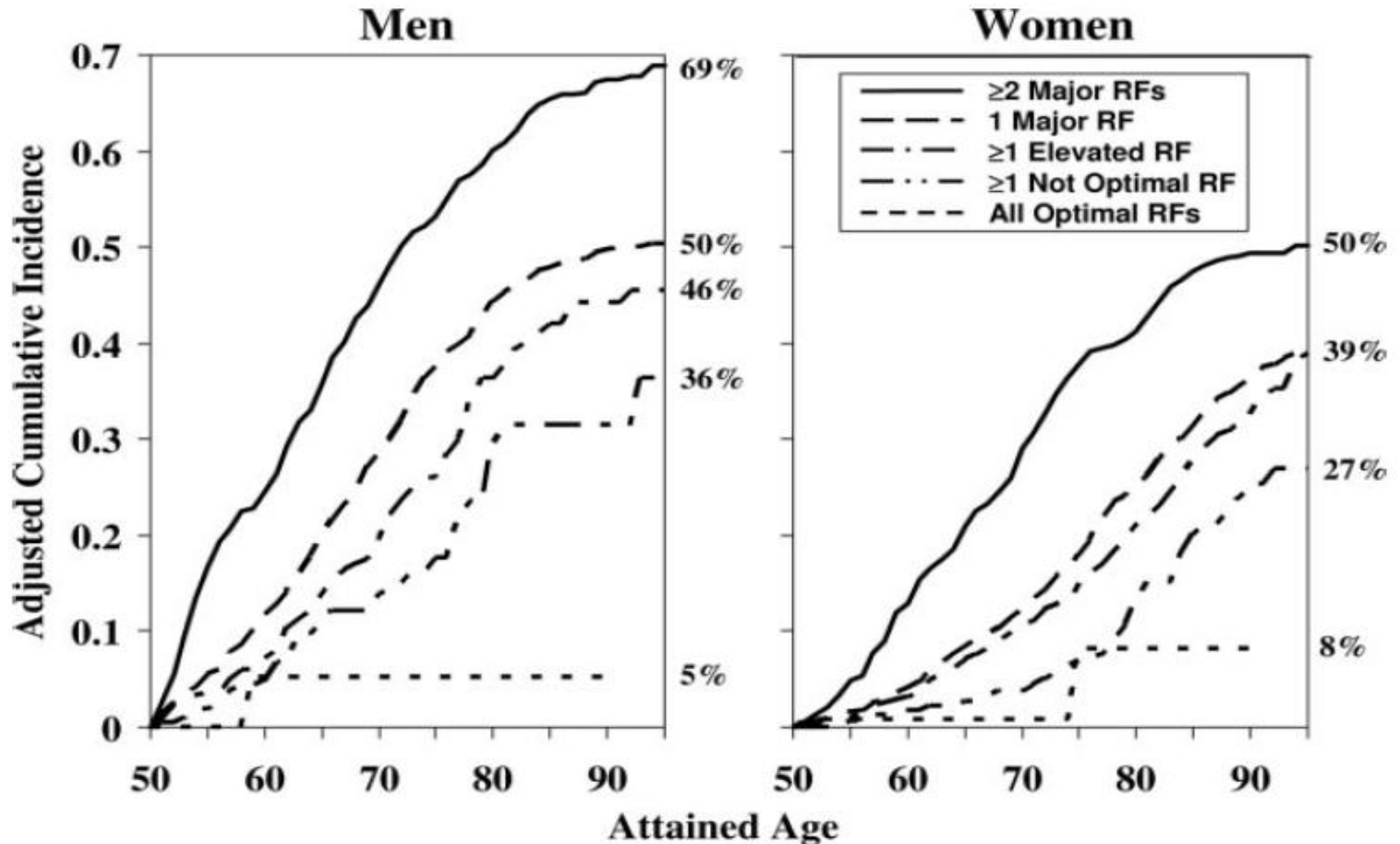
Framingham Men and Women



Long term Risk of CVD By Diabetes Status and BMI Category Framingham Men and Women

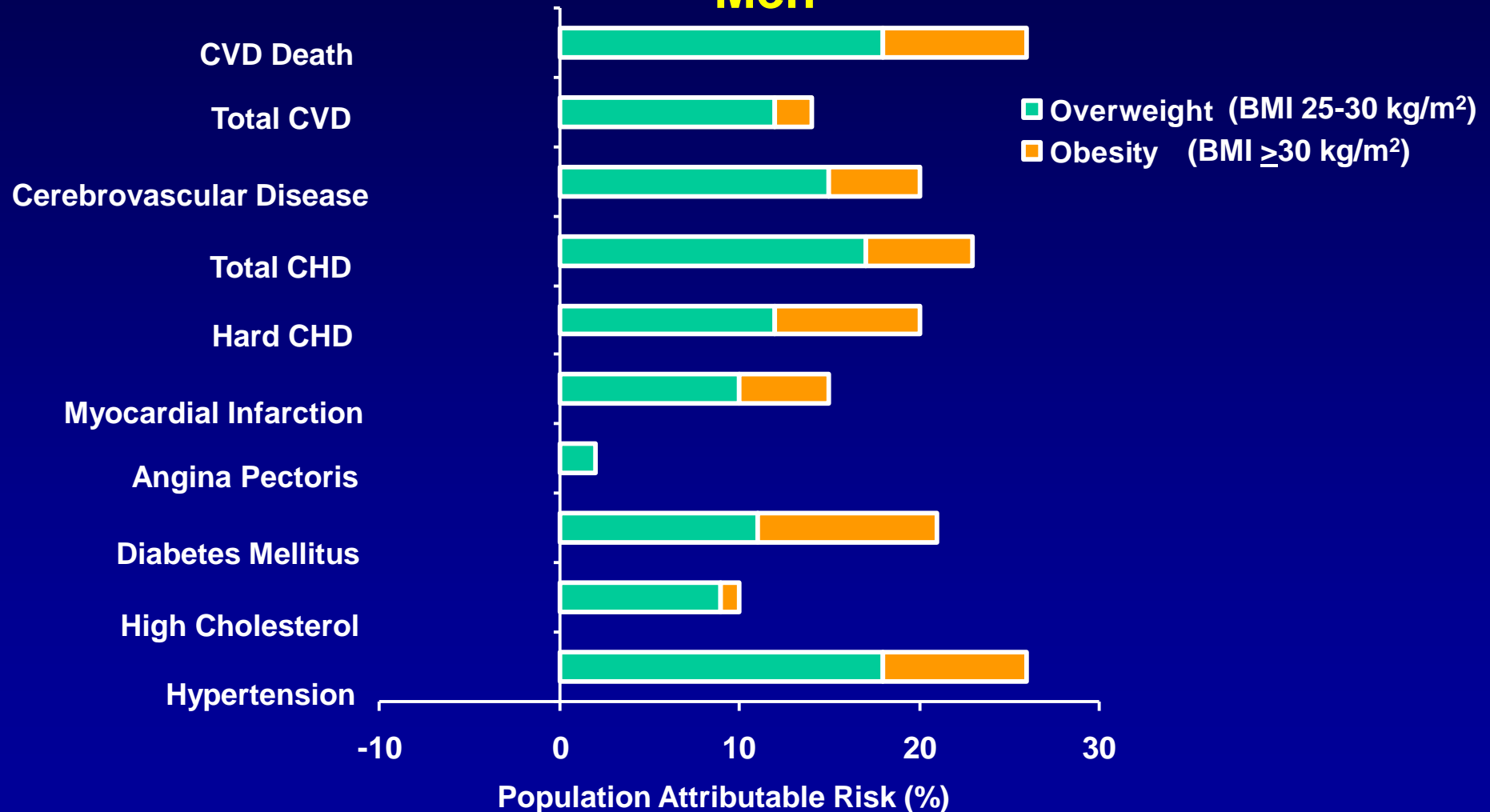


Lifetime CVD Risk and Risk Factor Burden in Framingham



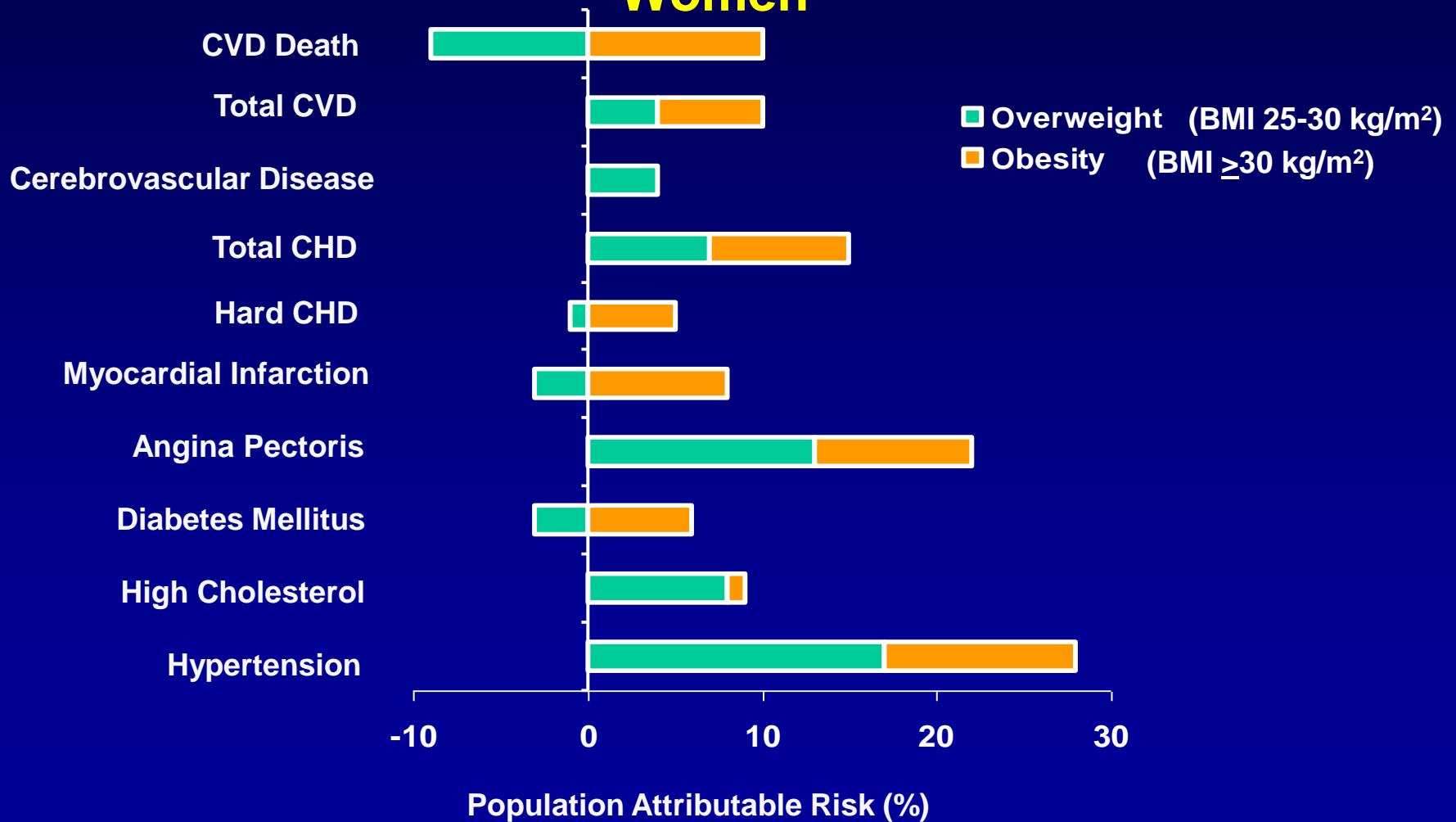
Population Attributable Risk Percent Effects for Overweight and Obesity on CVD Risk Factors and Events

Men

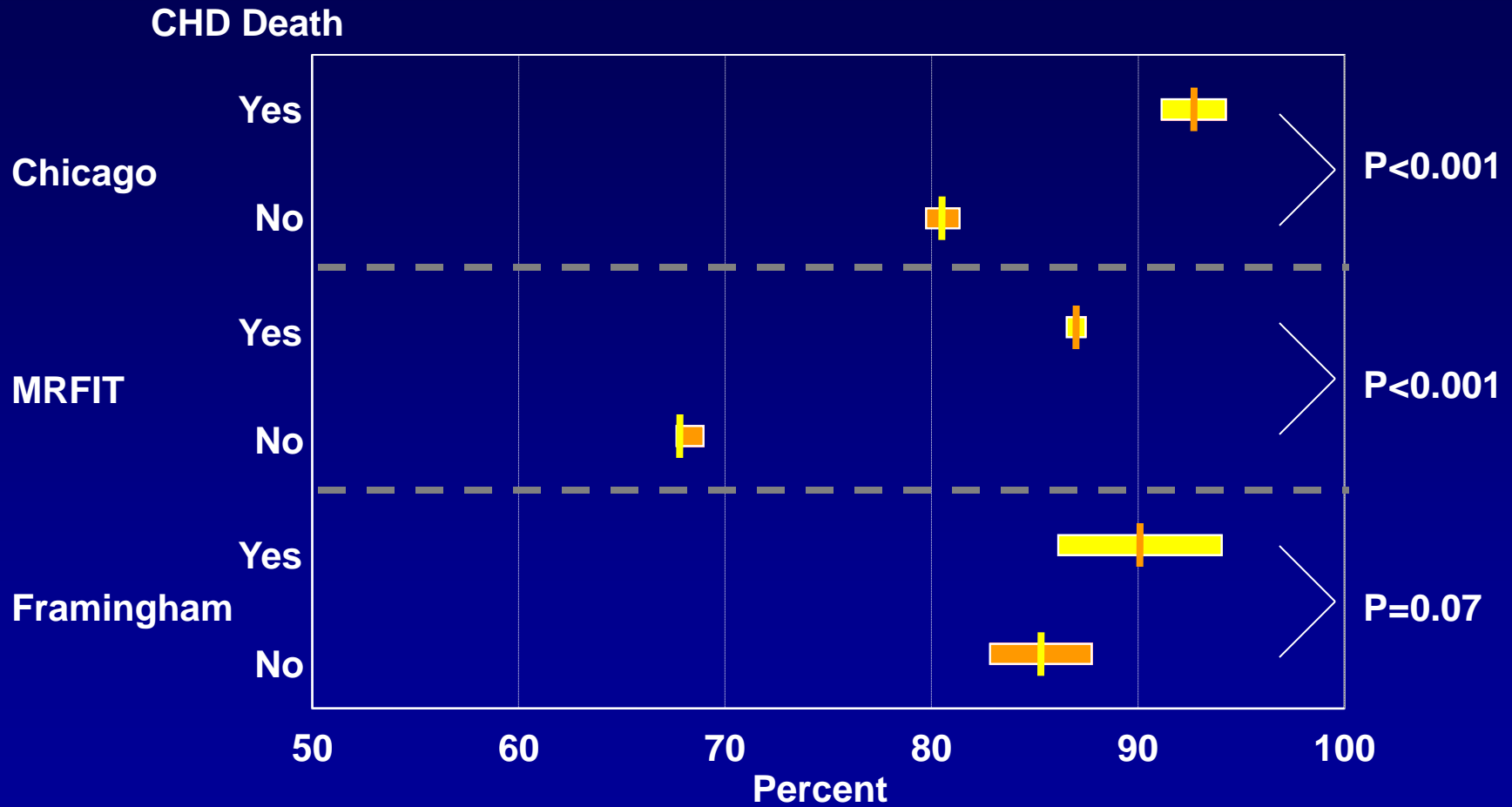


Population Attributable Risk Percent Effects for Overweight and Obesity on CVD Risk Factors and Events

Women

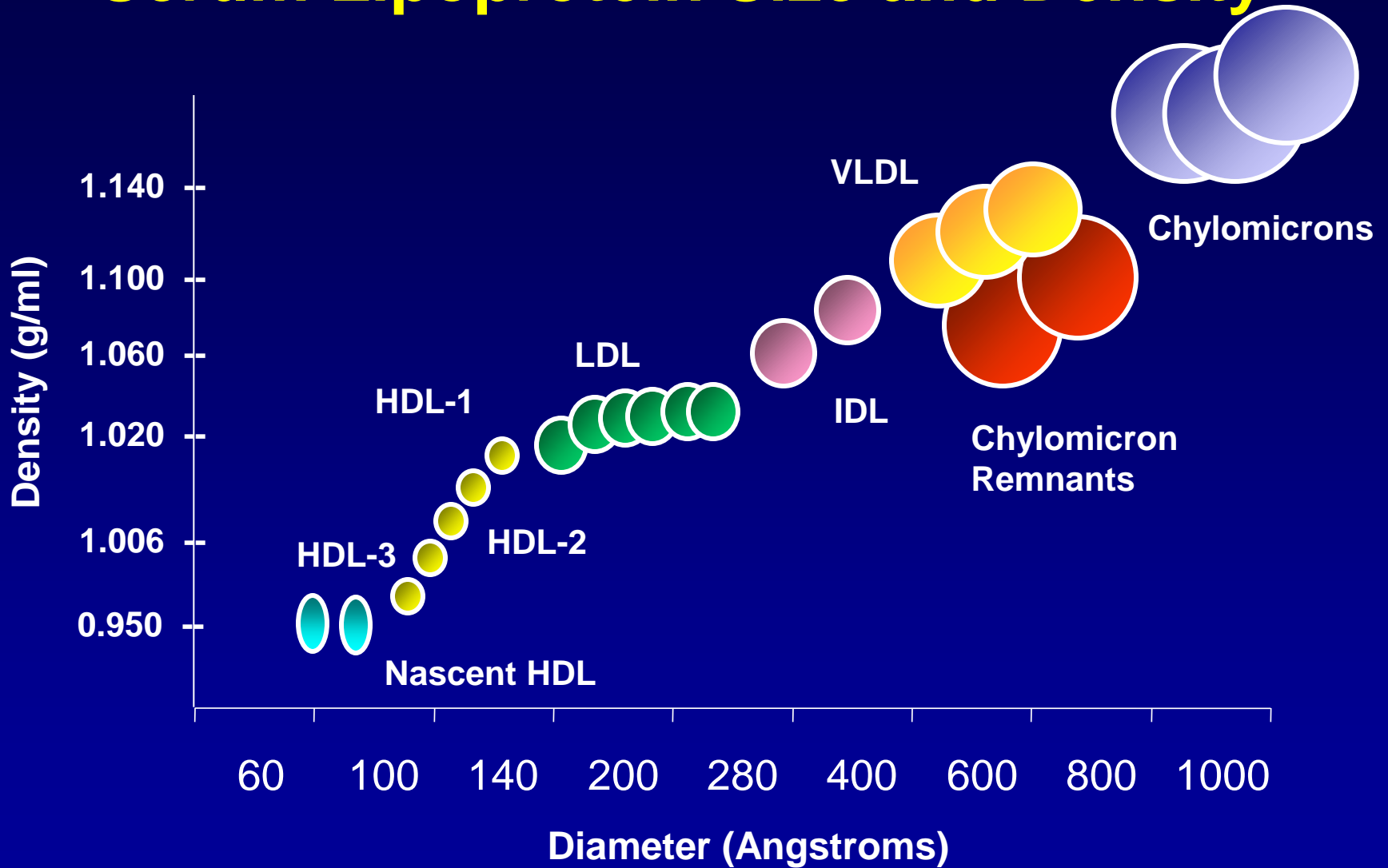


Presence of ≥ 1 Major* CHD Risk Factor and Development of CHD Death Men 40-59 Years

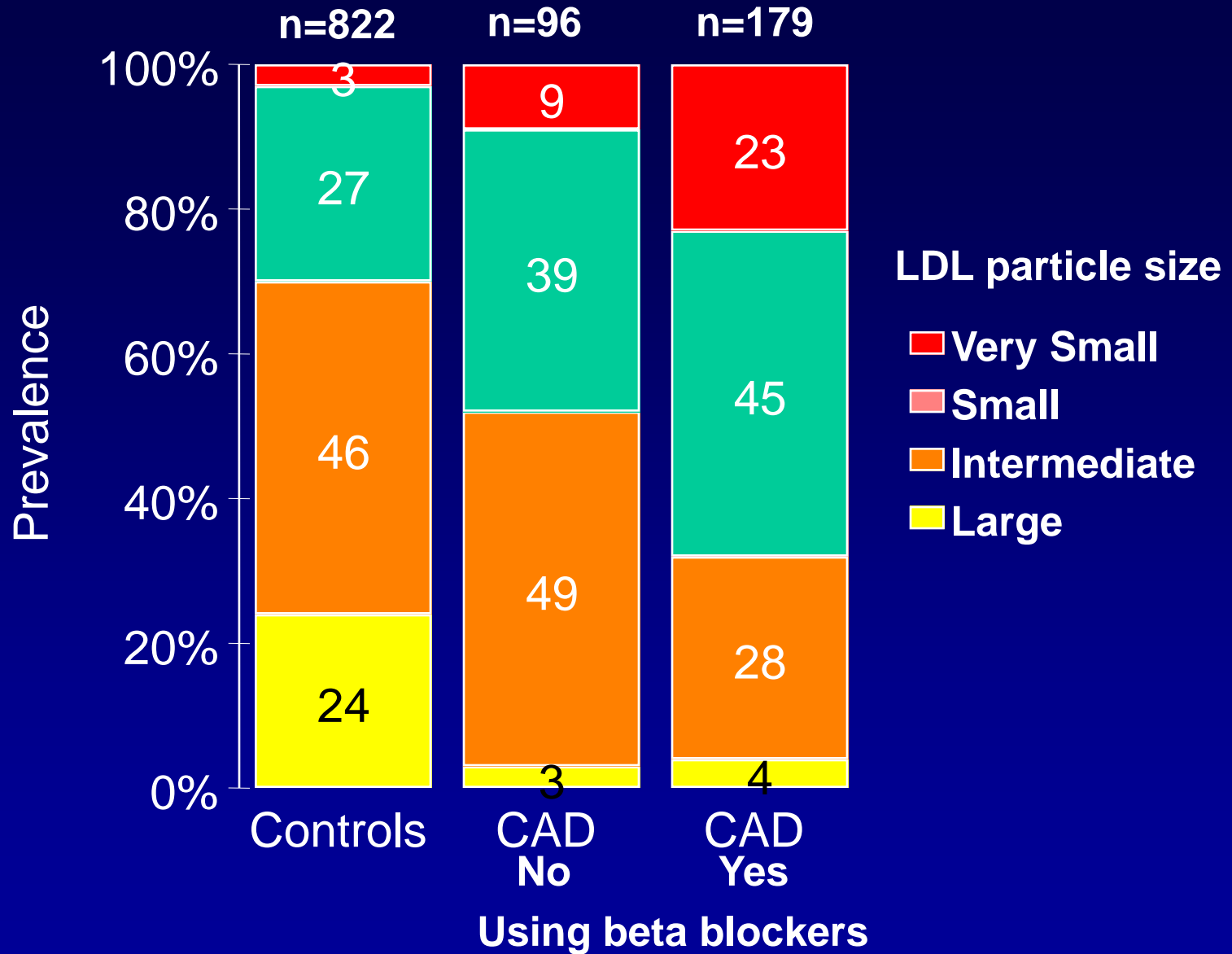


*Cholesterol > 240 mg/dl, BP systolic > 140 mm Hg,
BP diastolic > 90 mm Hg, smoking, or diabetes mellitus
Greenland JAMA 2003; 290:891

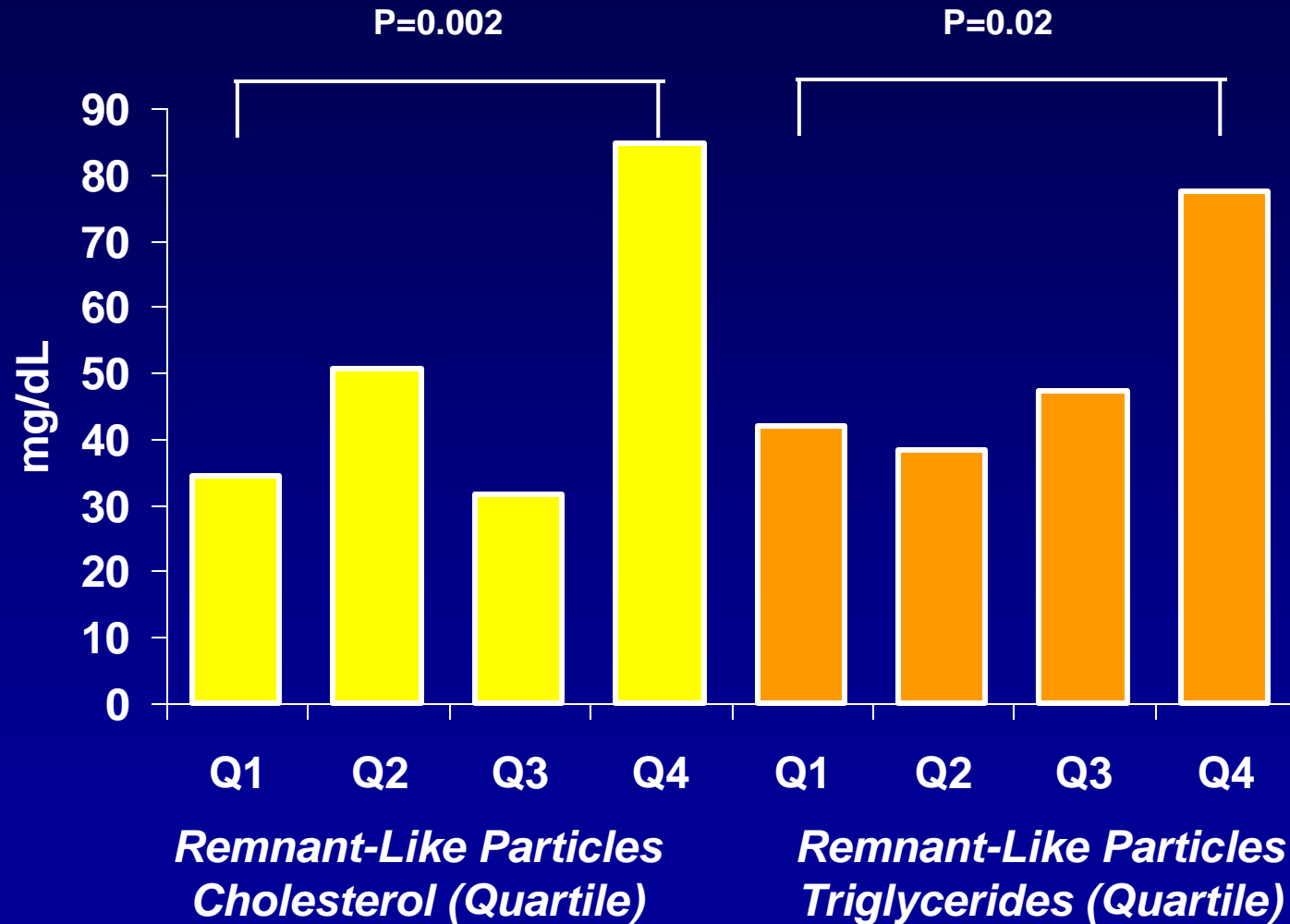
Serum Lipoprotein Size and Density



Prevalence of CAD and LDL Particle Size in Men



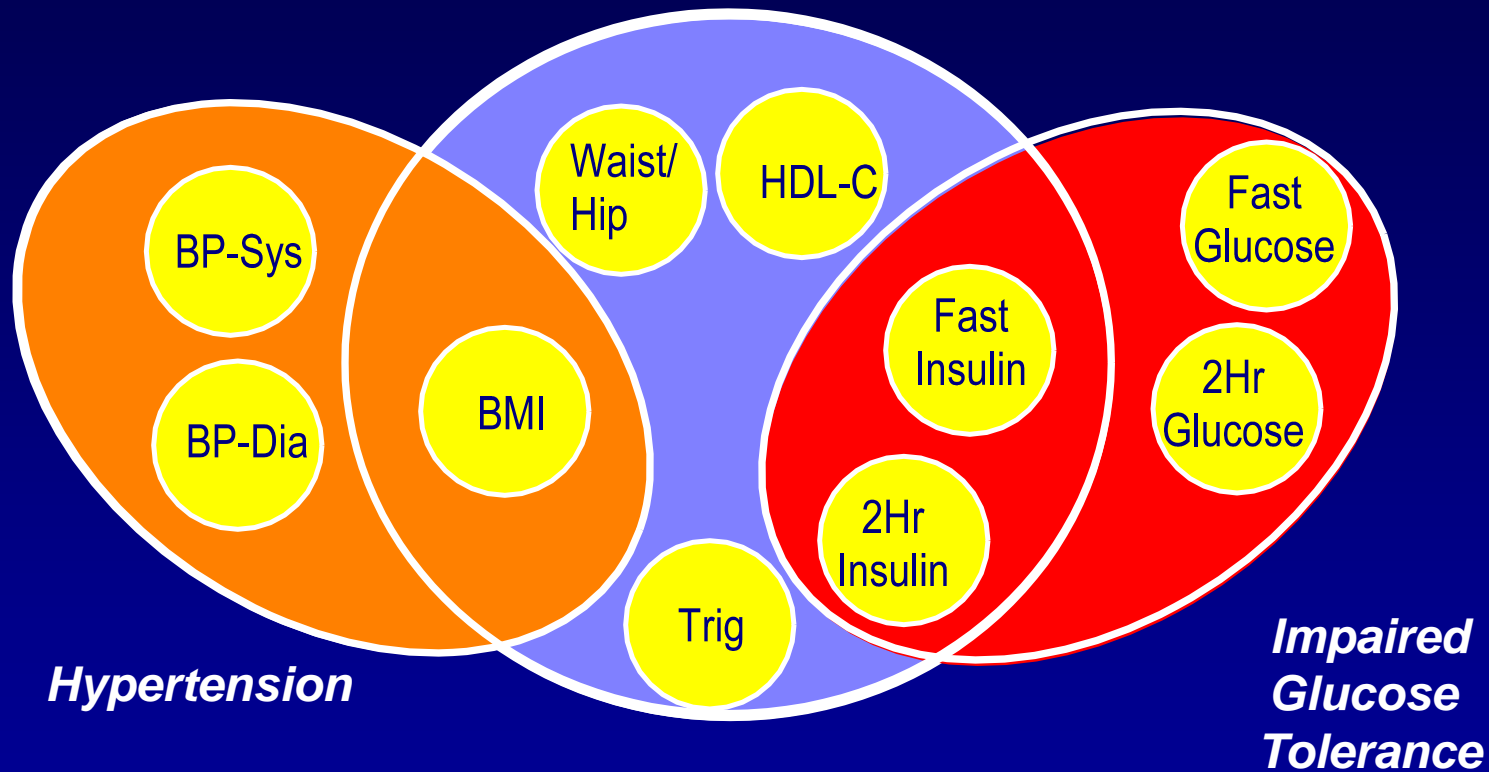
Remnant Lipoprotein Particles and CVD Prevalence Framingham Offspring Women Exam 4



Risk Variables for a Metabolic Syndrome



Risk Variables for a Metabolic Syndrome



62% Variance Explained

Central Metabolic Syndrome

ATP III: The Metabolic Syndrome*

Risk Factor	Definition
1. Waist circumference	>102 cm (>40 in) men >88 cm (>35 in) women
2. Triglycerides	≥150 mg/dL
3. HDL-Cholesterol	<40 mg/dL men <50 mg/dL women
4. Blood Pressure	≥130/≥85 mm Hg
5. Fasting Glucose	110-126 mg/dL*

Cardiometabolic Factors Age-Adjusted Risk for Outcomes Framingham Offspring—8 Year Follow up

Event	Number of MetS Factors	Men Relative Risk and 95% Confidence Interval	Women Relative Risk and 95% Confidence Interval
CVD	0	Referent	Referent
	1 or 2	1.48 (0.69-3.16)	3.39 (1.31-8.81)
	≥3	3.99(1.89-8.41)	5.95 (2.20-16.11)
Hard CHD	0	Referent	Referent
	1 or 2	0.98 (0.36-2.67)	3.77 (0.45-31.28)
	≥3	2.55 (0.96-6.79)	7.21 (0.81-64.37)
Total CHD	0	Referent	Referent
	1 or 2	1.24 (0.54-2.83)	3.29 (0.95-11.34)
	≥3	3.01 (1.33-6.83)	3.96 (1.02-15.38)
Type 2 DM	0	Referent	Referent
	1 or 2	4.16 (0.98-17.64)	6.10 (1.85-20.10)
	≥3	23.83 (5.80-98.01)	29.69 (9.10-96.85)

CVD Risk over 24 Years According to Obesity Level Framingham Offspring Study

Characteristic	BMI <30 kg/m ² (n=4143)	BMI ≥30 kg/m ² (n=637)	Total (n=4780)
Coronary Heart Disease			
Events	n=381 (9.2%)	n=111 (17.4%)	n=492 (10.3%)
Median time to first event	12.4 yr	14.2 yr	12.6 yr
Cardiovascular Disease			
Events	n=534 (12.9%)	n=150 (23.6%)	n=684 (14.3%)
Median time to first event	17.6 yr	17.1 yr	17.6 yr

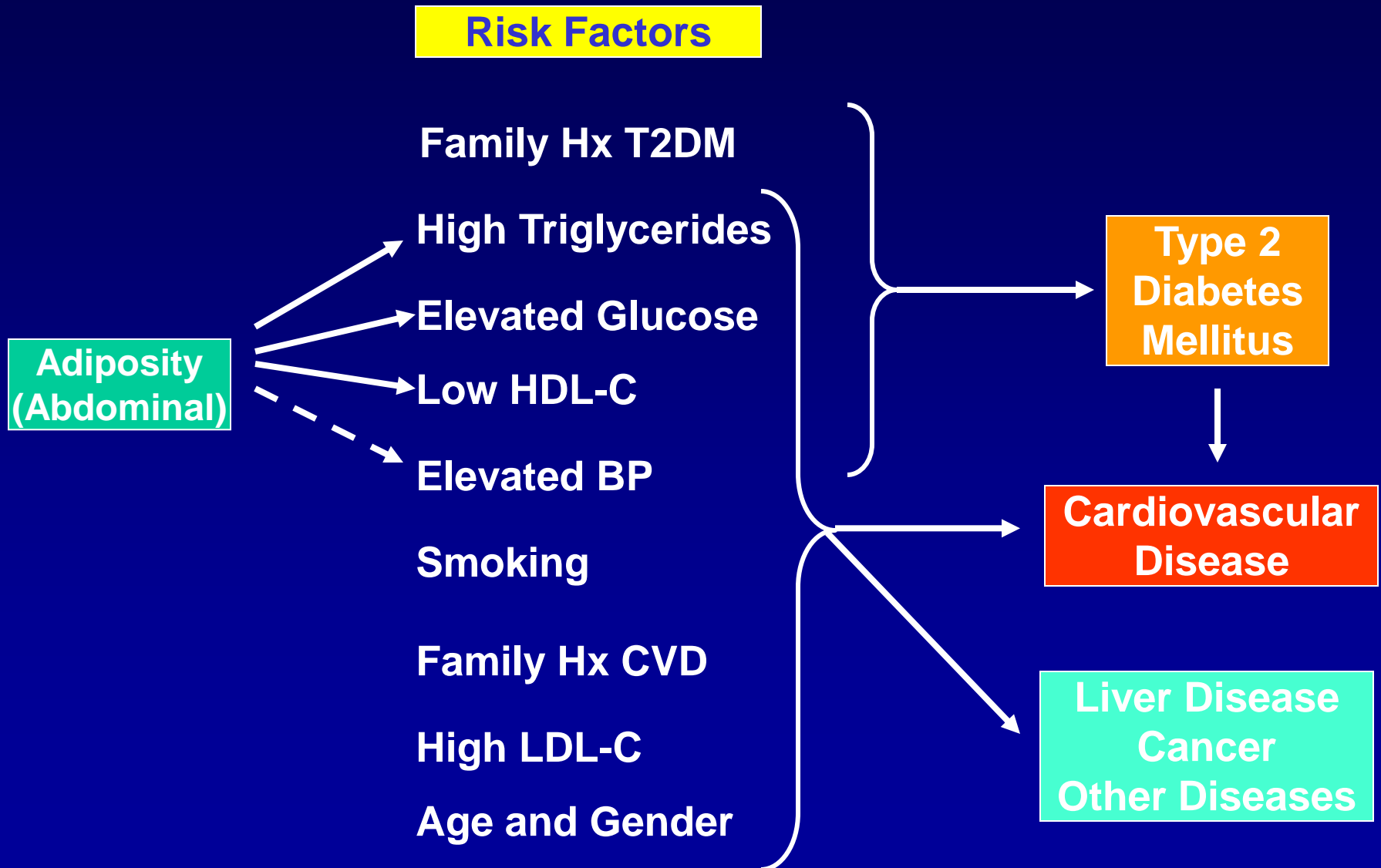
Risk Models for CVD in Framingham Offspring According to BMI and other Factors

Predictor	Units	Different CVD Prediction Models						
		A No BMI	A	B	C	D	E	E No BMI
BMI	4.33 kg/m ²	---	1.28 (1.17-1.39)	1.17 (1.07-1.28)	1.21 (1.11-1.33)	1.11 (1.01-1.23)	1.10 (1.00-1.21)	---
Chol/HDL	1.61	---	---	1.38 (1.30-1.47)	---	1.38 (1.30-1.46)	1.37 (1.29-1.46)	1.39 (1.31-1.47)
BP systolic	16.67 mm Hg	---	---	---	1.18 (1.08-1.27)	1.18 (1.09-1.28)	1.17 (1.08-1.28)	1.20 (1.11-1.30)
Diabetes Mellitus	Yes/No	---	---	---	---	---	1.60 (1.16-2.21)	1.66 (1.20-2.28)
Age	5 yr	1.57 (1.49-1.64)	1.55 (1.47-1.62)	1.53 (1.46-1.61)	1.50 (1.43-1.58)	1.49 (1.42-1.57)	1.48 (1.40-1.56)	1.48 (1.40-1.56)
Female	Yes/No	0.35 (0.25-0.43)	0.38 (0.31-0.47)	0.48 (0.39-0.59)	0.40 (0.33-0.49)	0.49 (0.40-0.60)	0.49 (0.40-0.61)	0.49 (0.40-0.60)
Current Smoker	Yes/No	2.01 (1.68-2.41)	2.09 (1.74-2.50)	1.91 (1.60-2.29)	2.13 (1.78-2.55)	1.97 (1.64-2.36)	1.97 (1.64-2.36)	1.94 (1.63-2.33)
C Statistic		0.784	0.791	0.808	0.796	0.812	0.813	0.814

CHD Risk Attributable to BMI

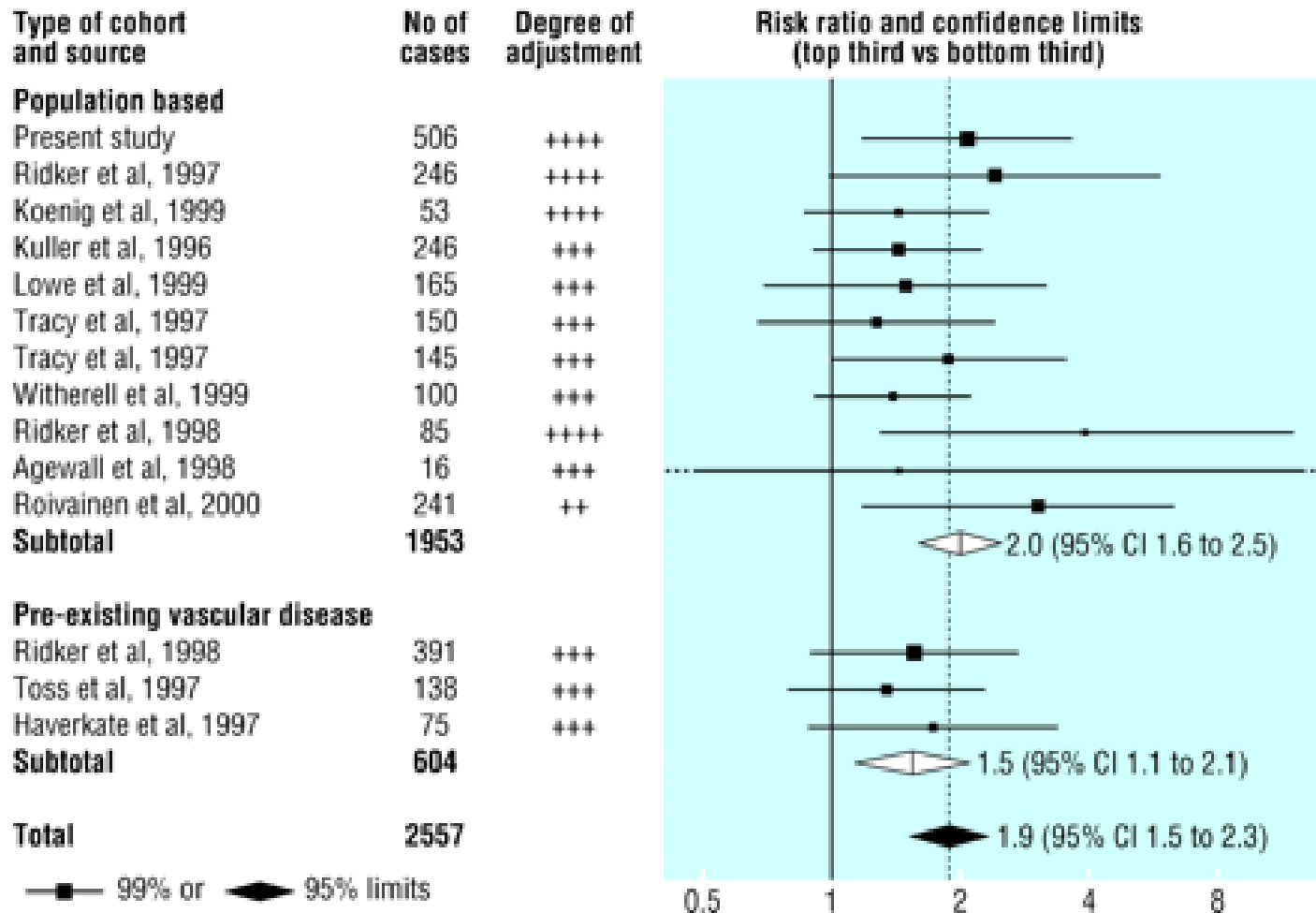
$$\begin{aligned}\text{Proportion of Risk} &= \frac{\text{HR}_{\text{unadjusted}} - \text{HR}_{\text{adjusted}}}{\text{HR}_{\text{unadjusted}} - 1.00} \\ &= \frac{1.28 - 1.10}{1.28 - 1.00} \\ &= 64\%\end{aligned}$$

Adiposity and Outcomes

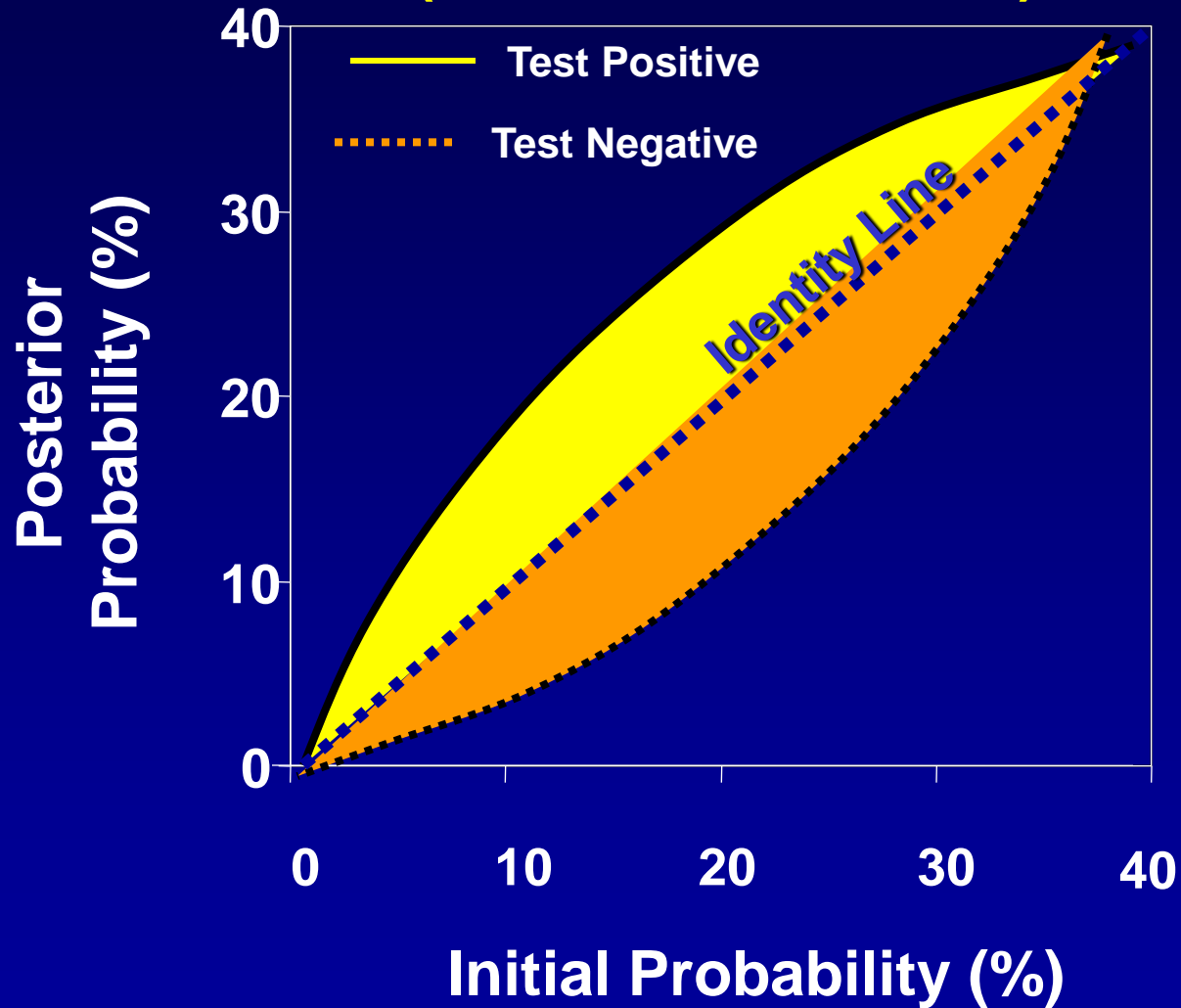


Prospective studies of C reactive protein and coronary heart disease

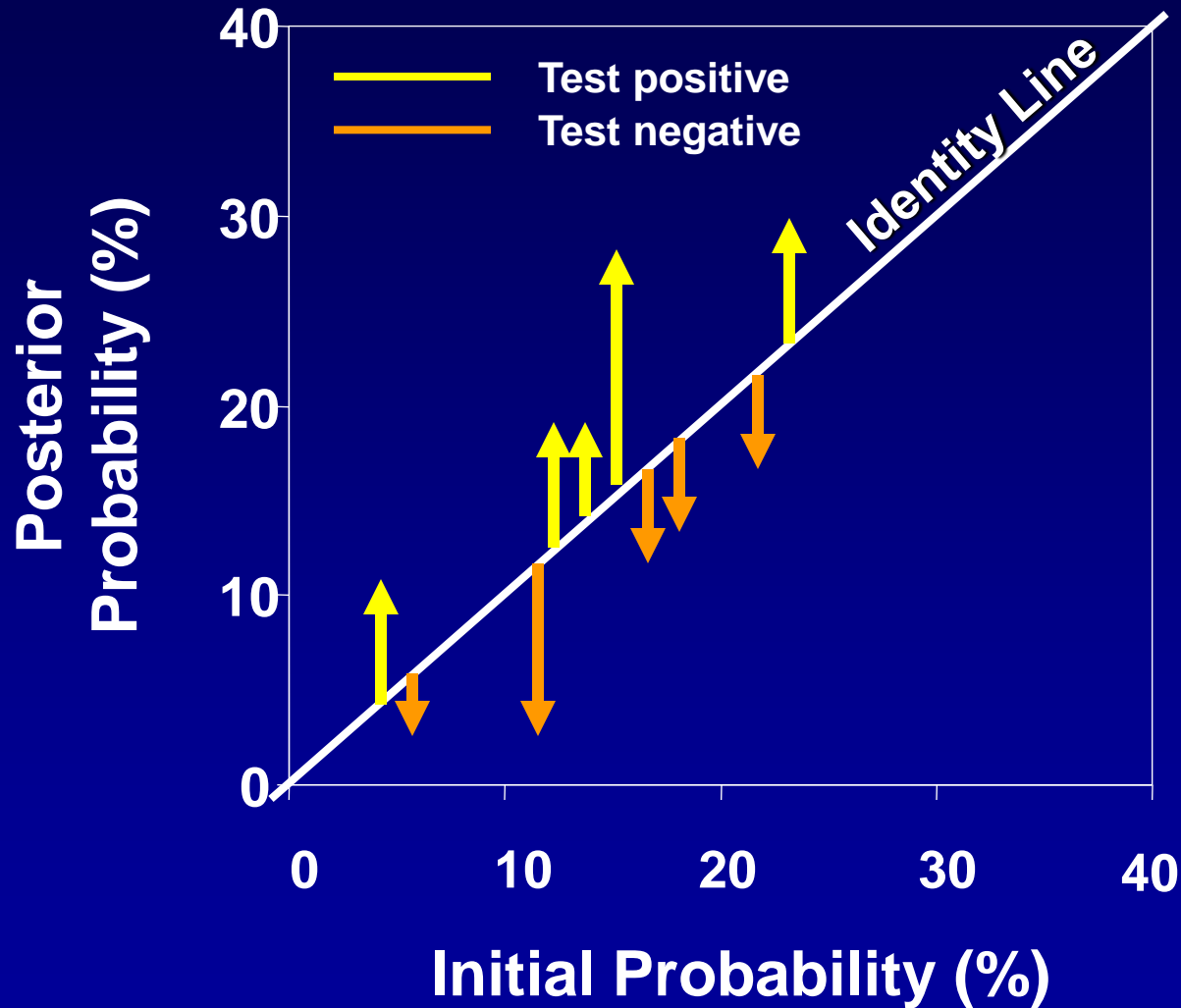
Relative risk top vs bottom tertile at baseline



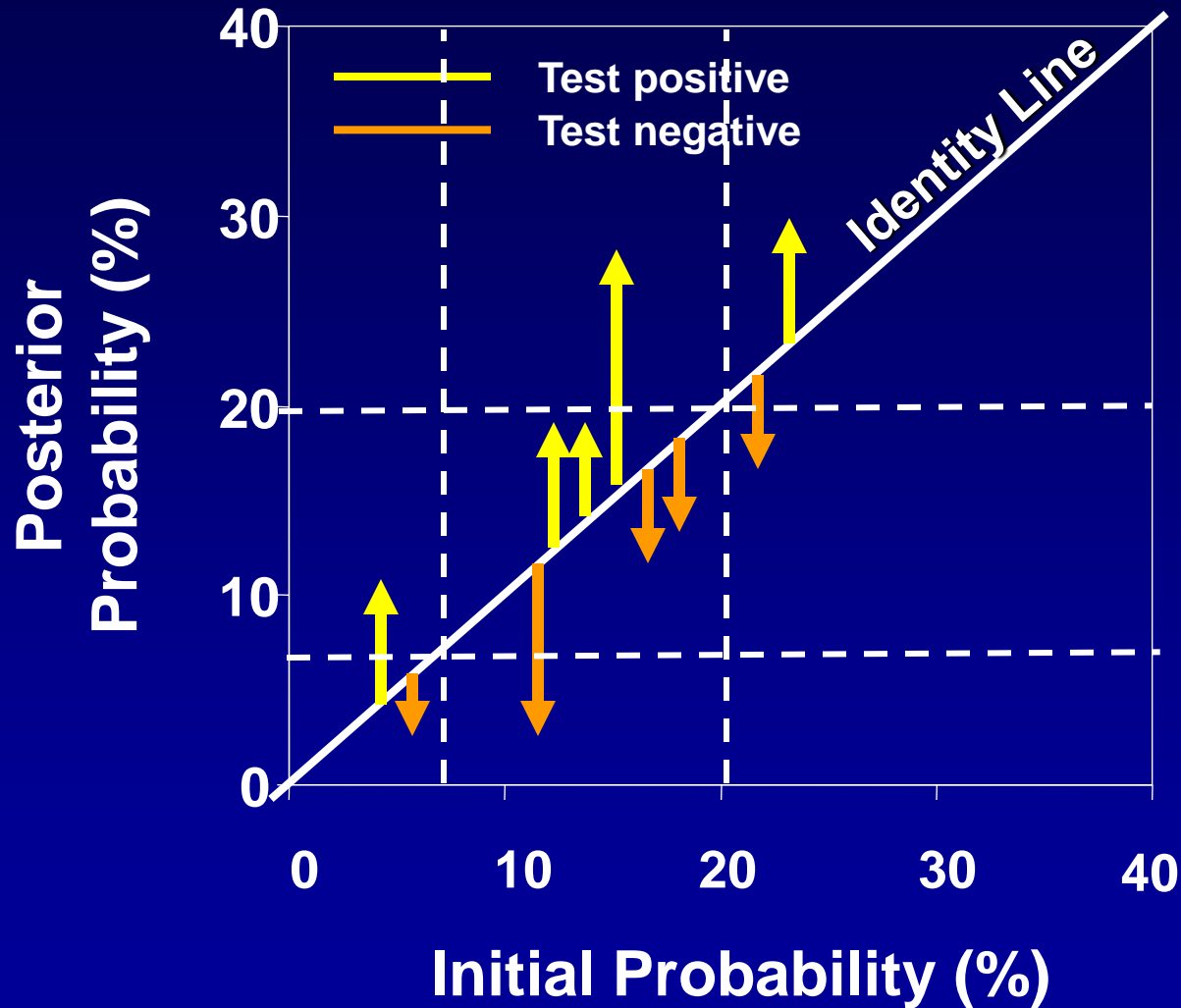
Serial Testing and Risk of CHD (Diamond et al, 1981)



Serial Testing and Risk of Disease





Serial Testing and Risk of Disease



Risk Reclassification with CRP

Framingham Offspring Experience

Reclassification Characteristic	Color Code	Cases	Non Cases
Up		14%	2%
Down		6%	1%
Difference		8%	1%
Net Reclassification		9%	

Risk Reclassification and Prediction of CVD in US Adults

Assessment	Net Reclassification*
C-Reactive Protein	5% to 15%
Carotid IMT	10% to 15%
Coronary Artery Calcification	25%

* Basic models with age, sex, cholesterol, HDL-C, blood pressure, diabetes, smoking

Summary

- **Origins of CHD Risk Estimation**
- **Conventional factors**
- **Other Risks**
- **New Strategies**

