Metabolic Syndrome :Mechanisms and Management

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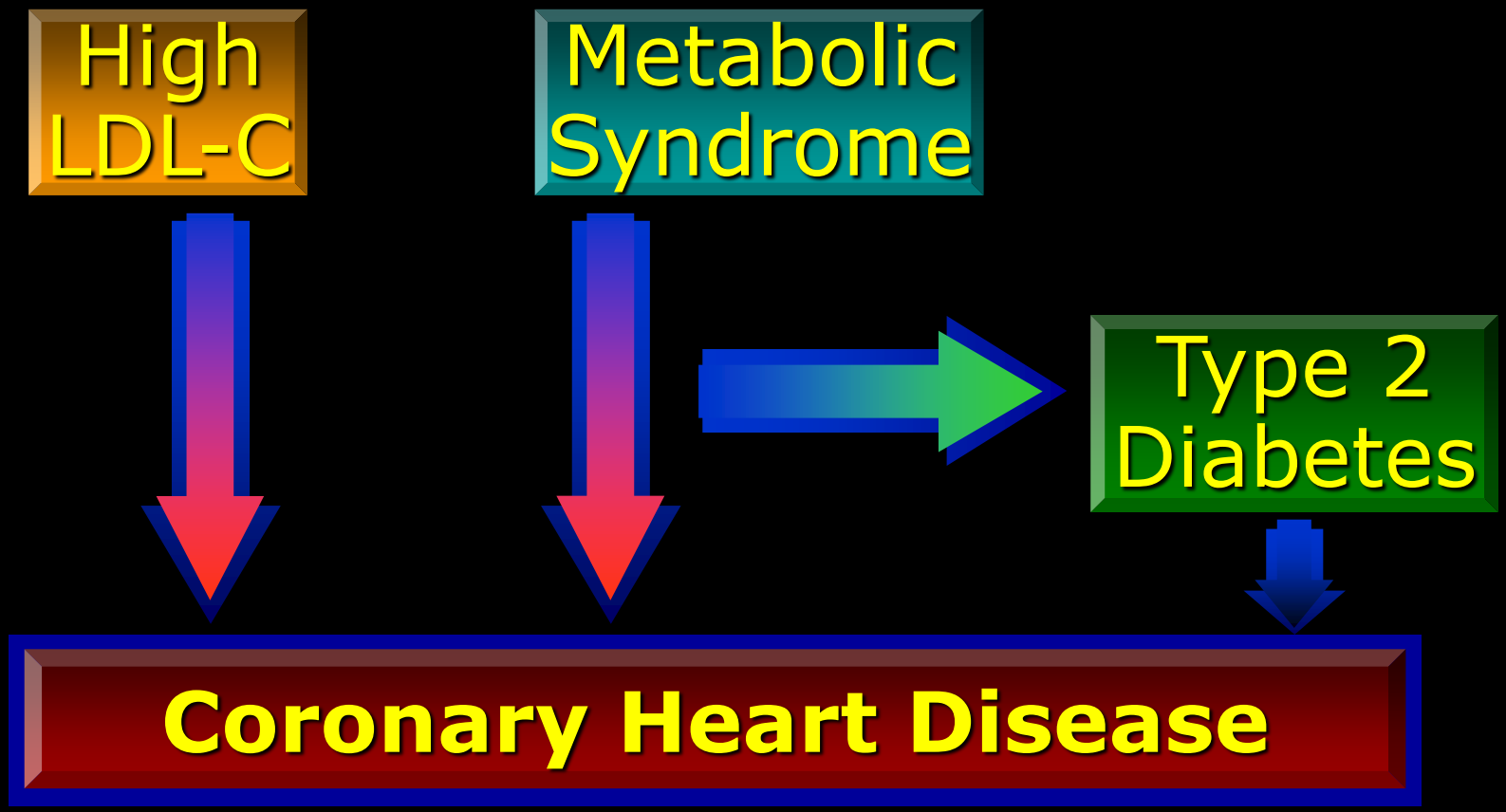
Metabolic Syndrome Increases Risk for CHD and Type 2 Diabetes



Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-2497.

National Cholesterol Education Program Clinical Identification of the Metabolic Syndrome

RISK FACTOR	DEFINING MEASURES
Abdominal obesity	Waist circumference:
Men	>40 in (>102 cm)
Women	>35 in (>88 cm)
Triglycerides	≥150 mg/dL
HDL-C Men	<40 mg/dL
HDL-C Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥100 mg/dL*

≥3 Risk factors comprise the metabolic syndrome.
ICD-9 Code 277.7

* Recent ADA change: *Diabetes Care* 2004;27:S5-S10. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

Criteria for Clinical Diagnosis of the Metabolic Syndrome

Measure	Categorical Cut Points
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator	Systolic ≥130 and/or diastolic ≥85 mm/Hg
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

Alberti et al., Circulation 2009

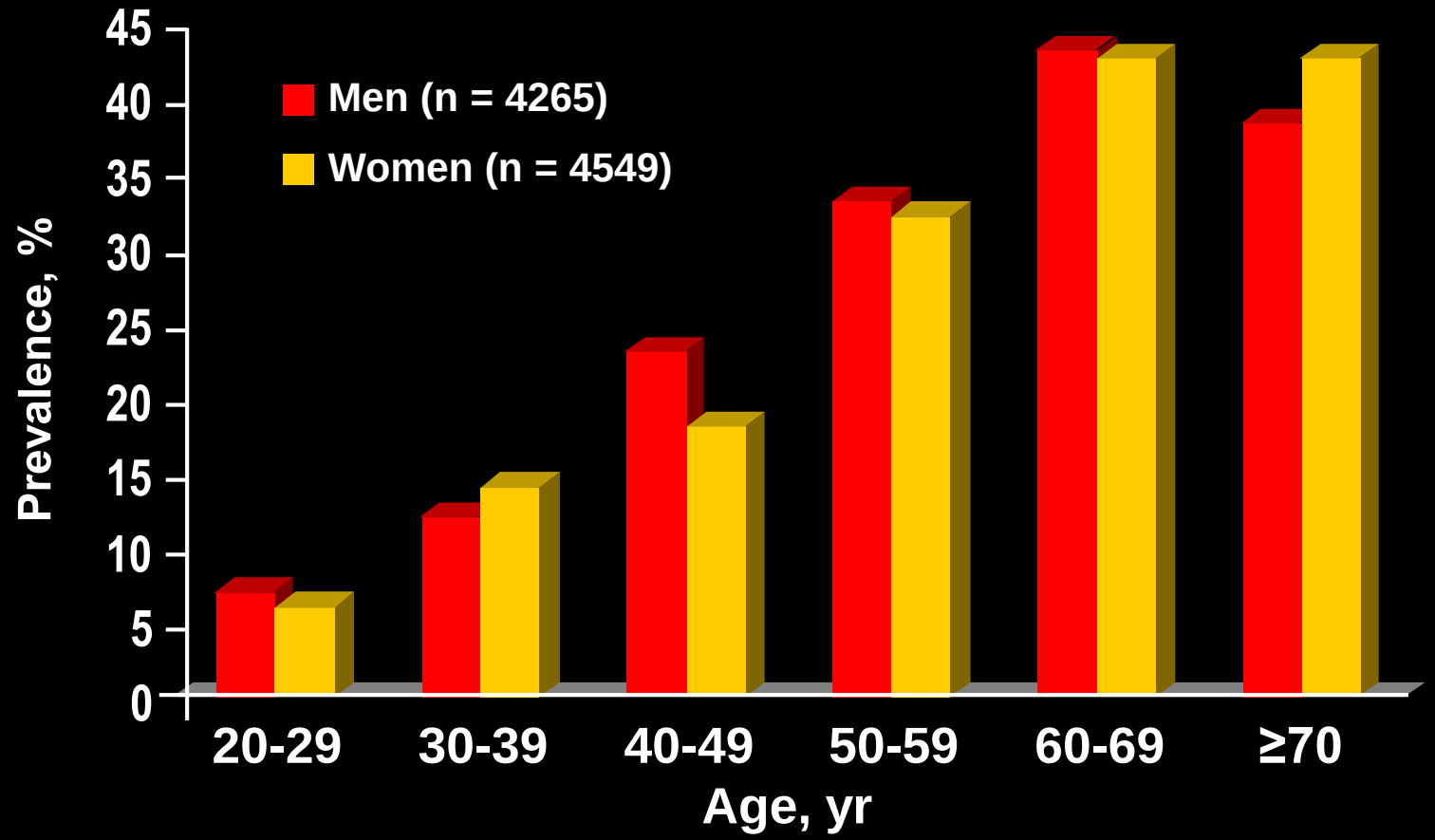
IDF ethnic- and gender-specific criteria for central obesity

	Waist circumference (inches)	
	Men	Women
European Sub-Saharan African Middle Eastern	≥37	≥32
South Asian South/Central American	≥35	≥32
Chinese	≥35	≥32
Japanese	≥34	≥35

www.idf.org. Accessed August 2005.

Metabolic Syndrome: Prevalence Increases With Age

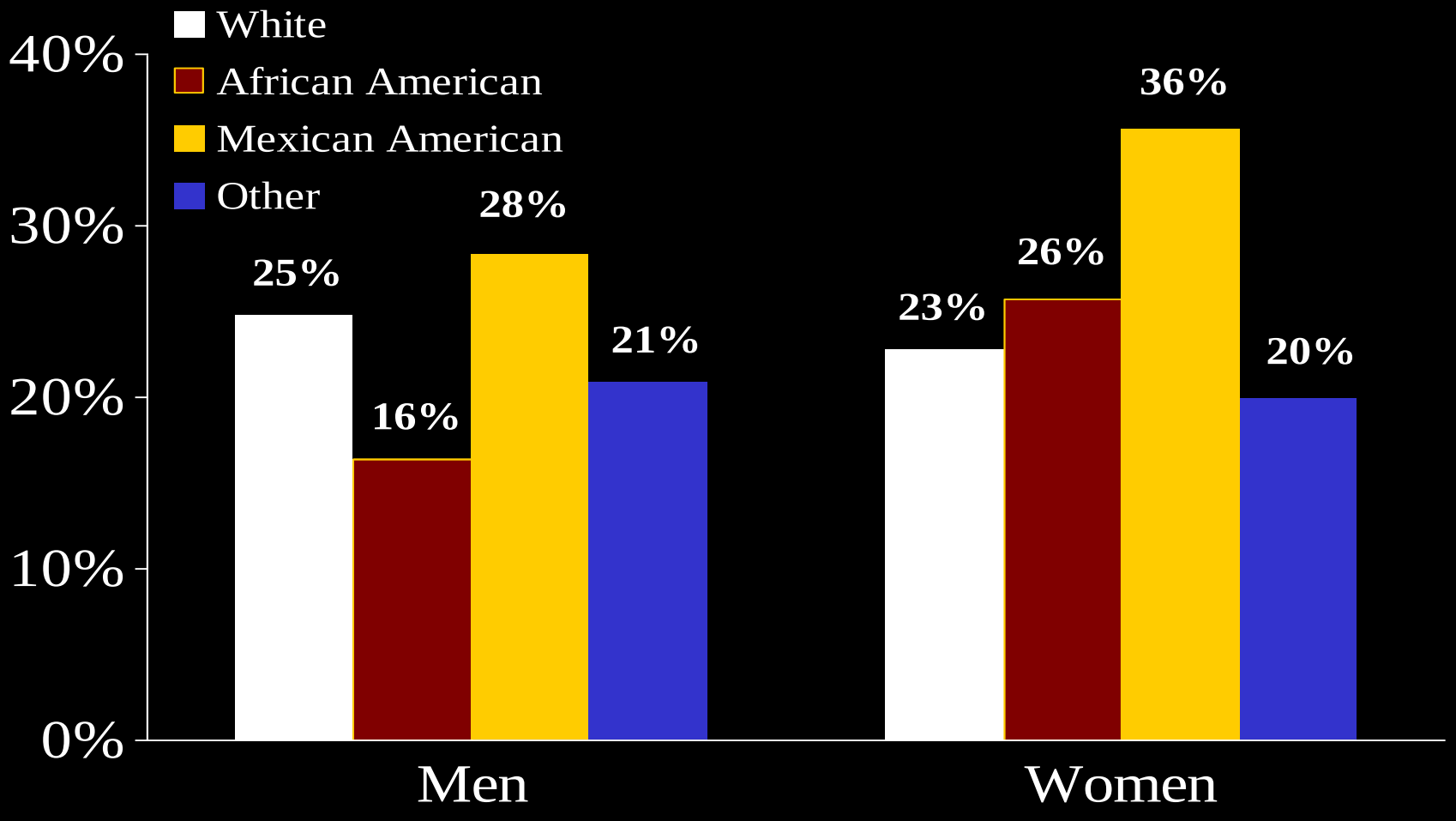
35% of US Adults have the metabolic syndrome



NCEP criteria.

Adapted from Ford ES, et al. *JAMA.* 2002;287:356-359.

Prevalence of the NCEP Metabolic Syndrome NHANES III by Sex and Race/Ethnicity



Ford et al JAMA 2002;287:356-9

Metabolic Syndrome, Related Disorders, and Other Predisposing Factors

- Non-alcoholic SteatoHepatitis (NASH)
- Polycystic Ovarian Syndrome (PCOS)
- Obstructive Sleep Apnea
- Cholesterol Gallstones
- Gout
- HIV-Protease Inhibitor Therapy
- Cancers(Breast and Colon etc)

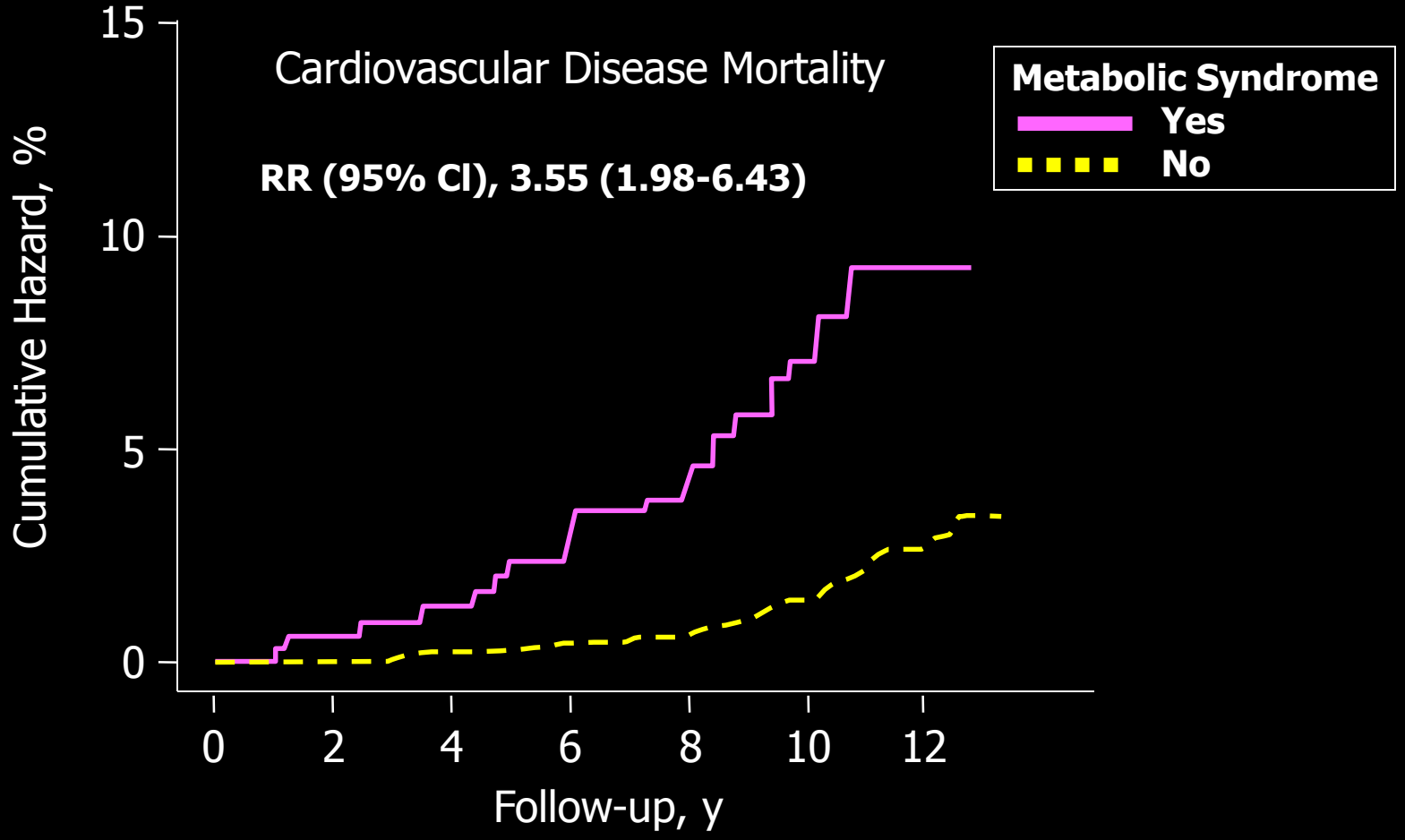
Metabolic Syndrome and Risk of Diabetes and CVD

Metabolic Syndrome confers

- 2-fold increased risk of CVD
- 5-fold increased risk of Diabetes

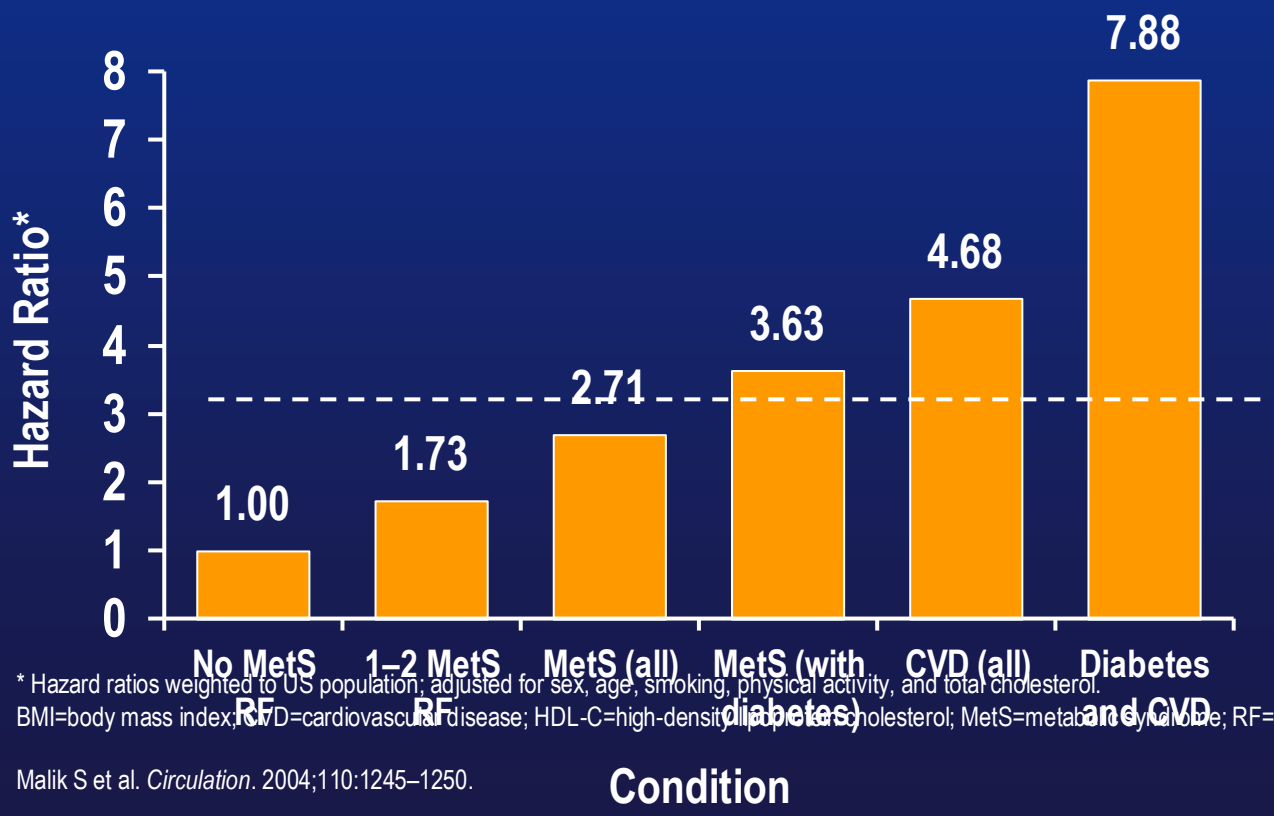
1. Grundy SM. *J Clin Endocrinol Metab*. 2004;89:2595–2600.
2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486–2497.

Cardiovascular Disease Mortality Increased in the Metabolic Syndrome



Lakka HM, et al. *JAMA*. 2002;288:2709-2716.

Risk Factors for Metabolic Syndrome and CVD Mortality



Risk factors
- Obesity (BMI ≥30 kg/m^2)
- Low HDL-C
- High triglycerides
- High blood pressure
- High blood glucose concentrations

* Hazard ratios weighted to US population; adjusted for sex, age, smoking, physical activity, and total cholesterol.
BMI=body mass index; CVD=cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; MetS=metabolic syndrome; RF=risk factor; T2DM=type 2 diabetes.

Malik S et al. *Circulation*. 2004;110:1245–1250.

Increased Risk of Diabetes in the Metabolic Syndrome

Fasting Glucose	Met Syndrome	OR (95%CI)
Normal	No	Ref
Normal	Yes	5.03 (3.39-7.48)
IFG	No	7.07 (3.32-15.1)
IFG	Yes	21.0 (13.1-33.8)

San Antonio Heart Study
7.4 yr follow-up

Lorenzo et al Diabetes Care 2007

Metabolic Syndrome

Causes

- Acquired causes
  - Overweight and obesity
  - Physical inactivity
  - High carbohydrate diets (>60% of energy intake) in some persons
- Genetic causes

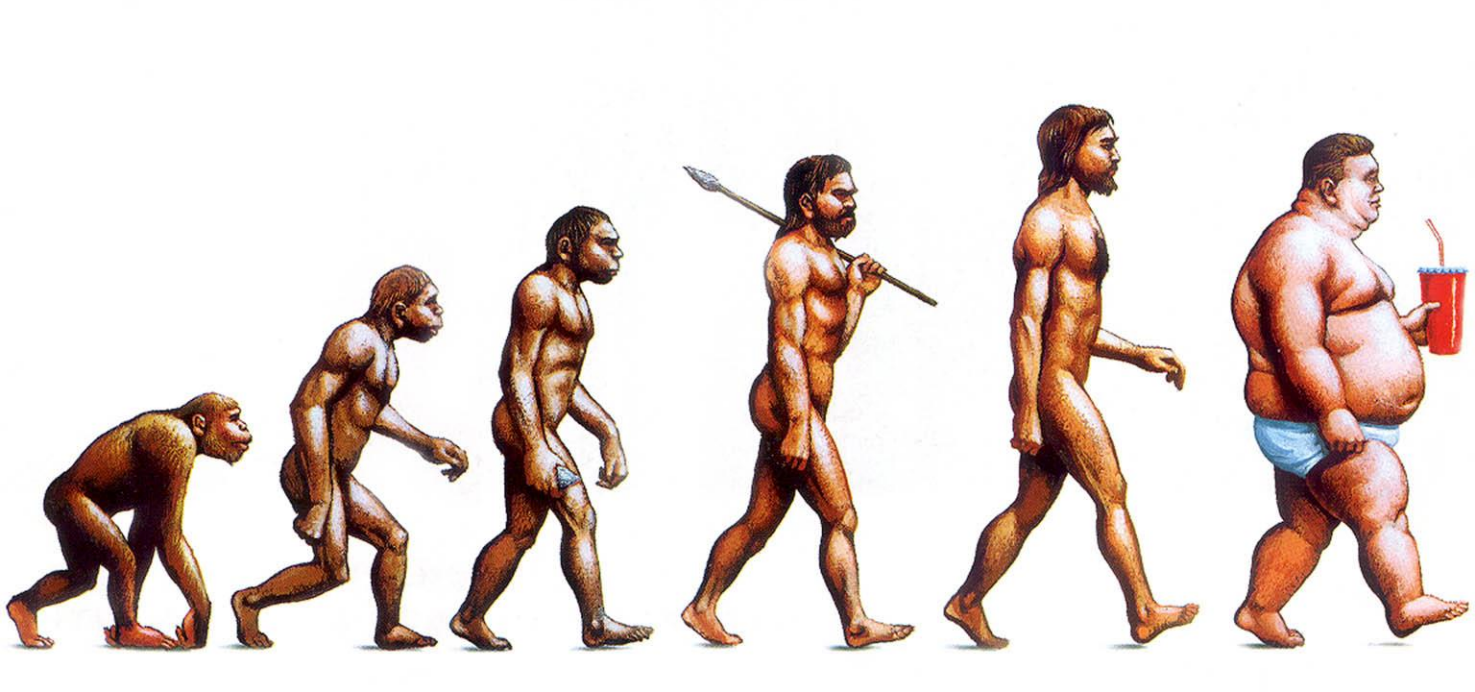
  GWAS-TCF7L2

  Epigentic programming ?

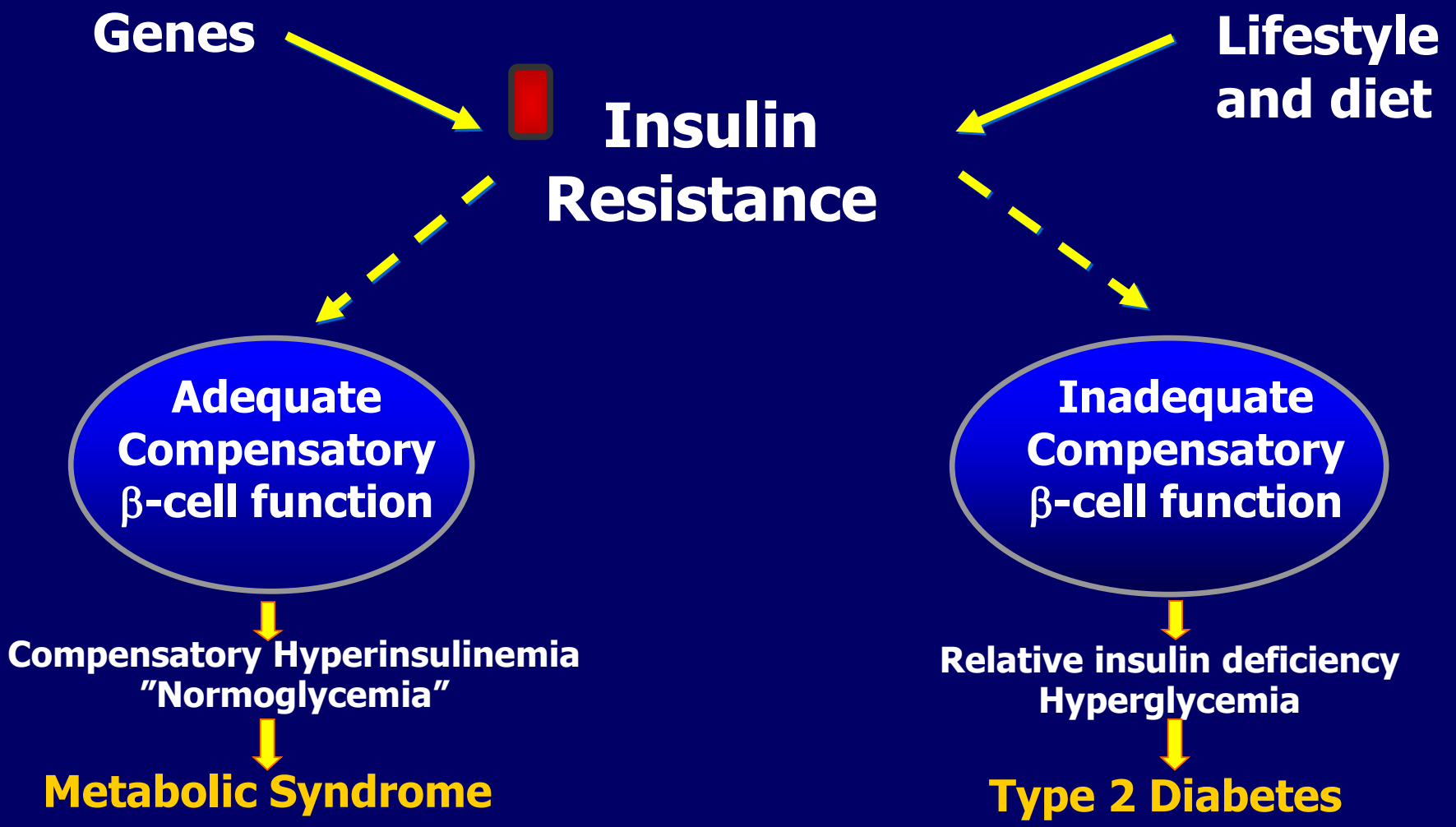
Atherogenic Dyslipidemia in Metabolic Syndrome

- Elevated Triglycerides (> 150 mg/dL)
- Elevated Non-HDL Cholesterol
- Elevated Total Apo B
- LDL size and subfractions by NMR (Small dense LDL)
- Elevated Triglyceride rich lipoproteins and Remnant Like Particle Cholesterol

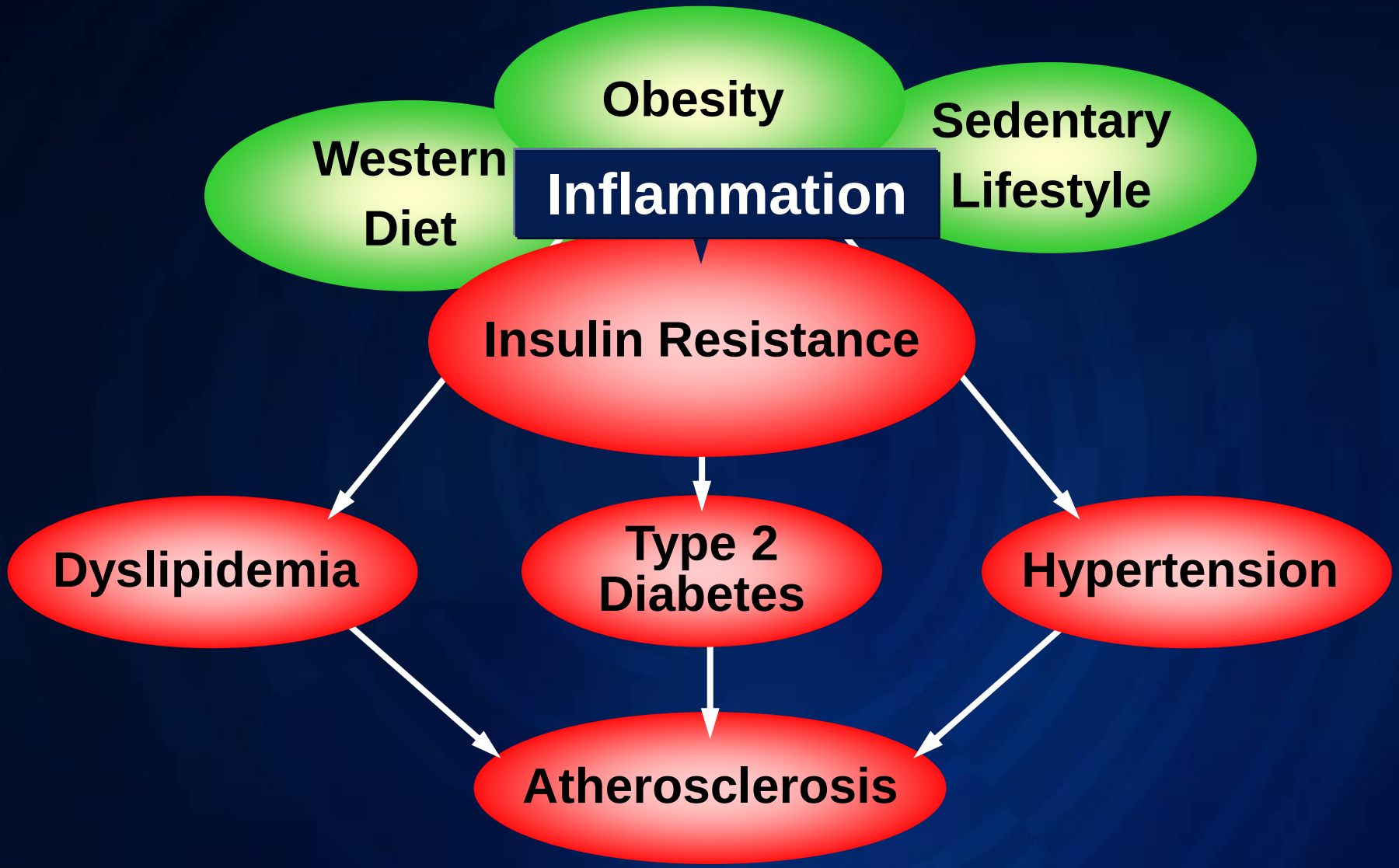
The Future is Already Here!



Etiology of Type 2 Diabetes: Insulin Resistance and Diminished Insulin Secretion



Common Soil: Metabolic Syndrome

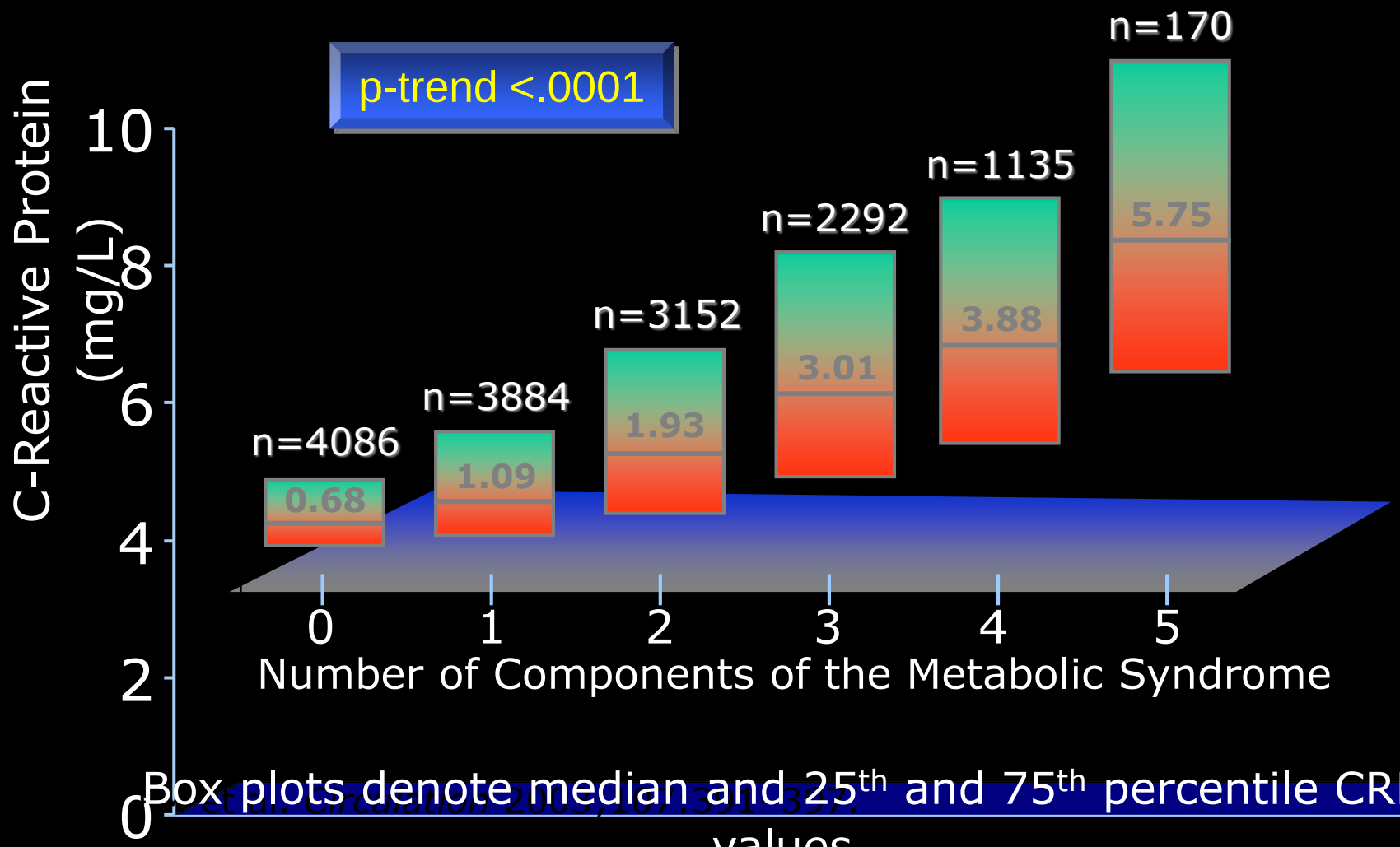


Biomarkers of Inflammation in Metabolic Syndrome

- ↑ CRP
- ↑ IL-6, 1L-8,TNF, MCP-1,Chemerin
- ↓ IL-10
- ↓ Adiponectin and Omentin-1
- ↑ Leptin
- ↑ Serum Amyloid A (SAA), Fibrinogen
- ↑ Plasminogen activator inhibitor-1 (PAI-1)
- ↑ RBP-4, Resistin,

Jialal et al JCEM, 2014

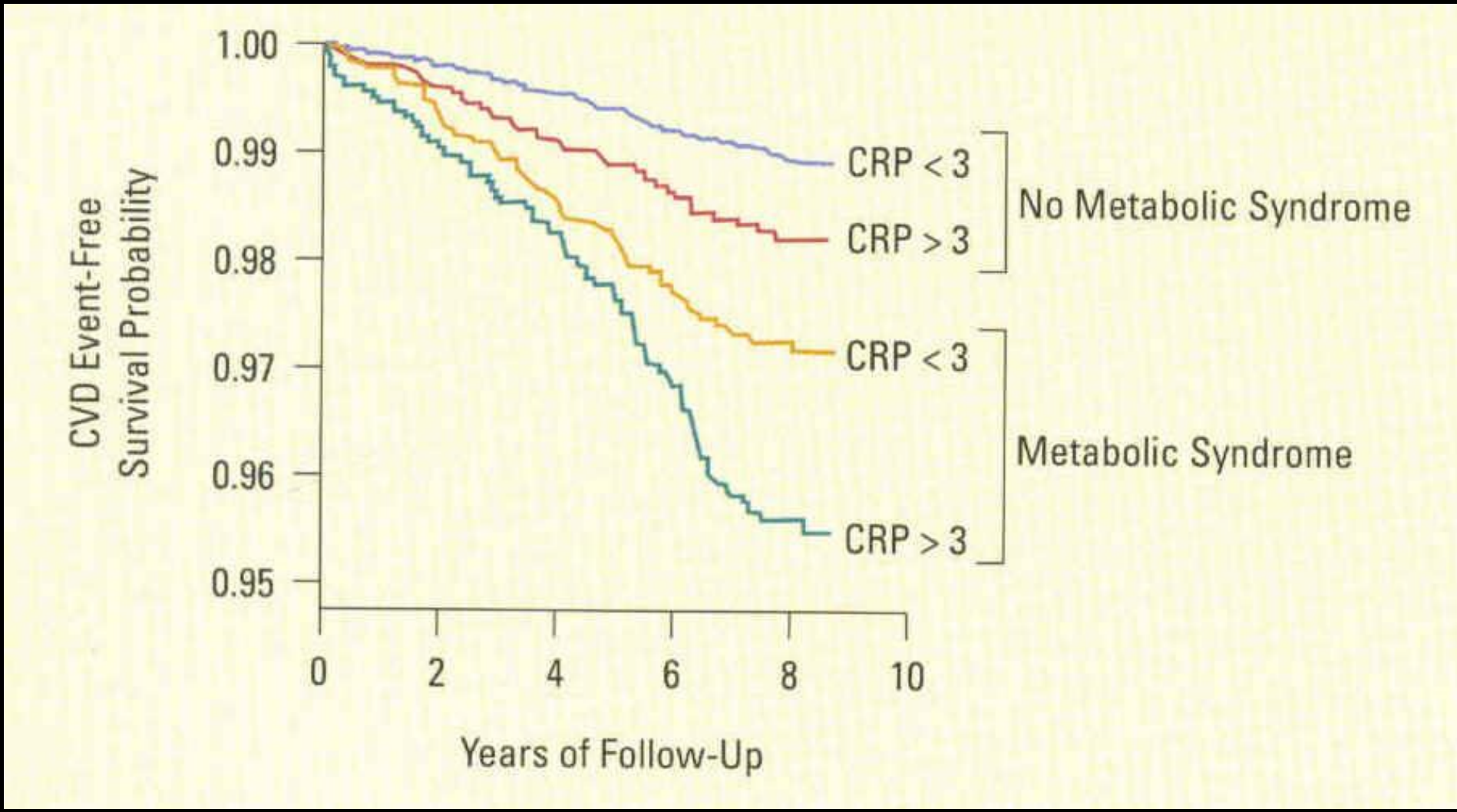
Distribution of CRP Levels by Number of Components of the Metabolic Syndrome: *WHS*



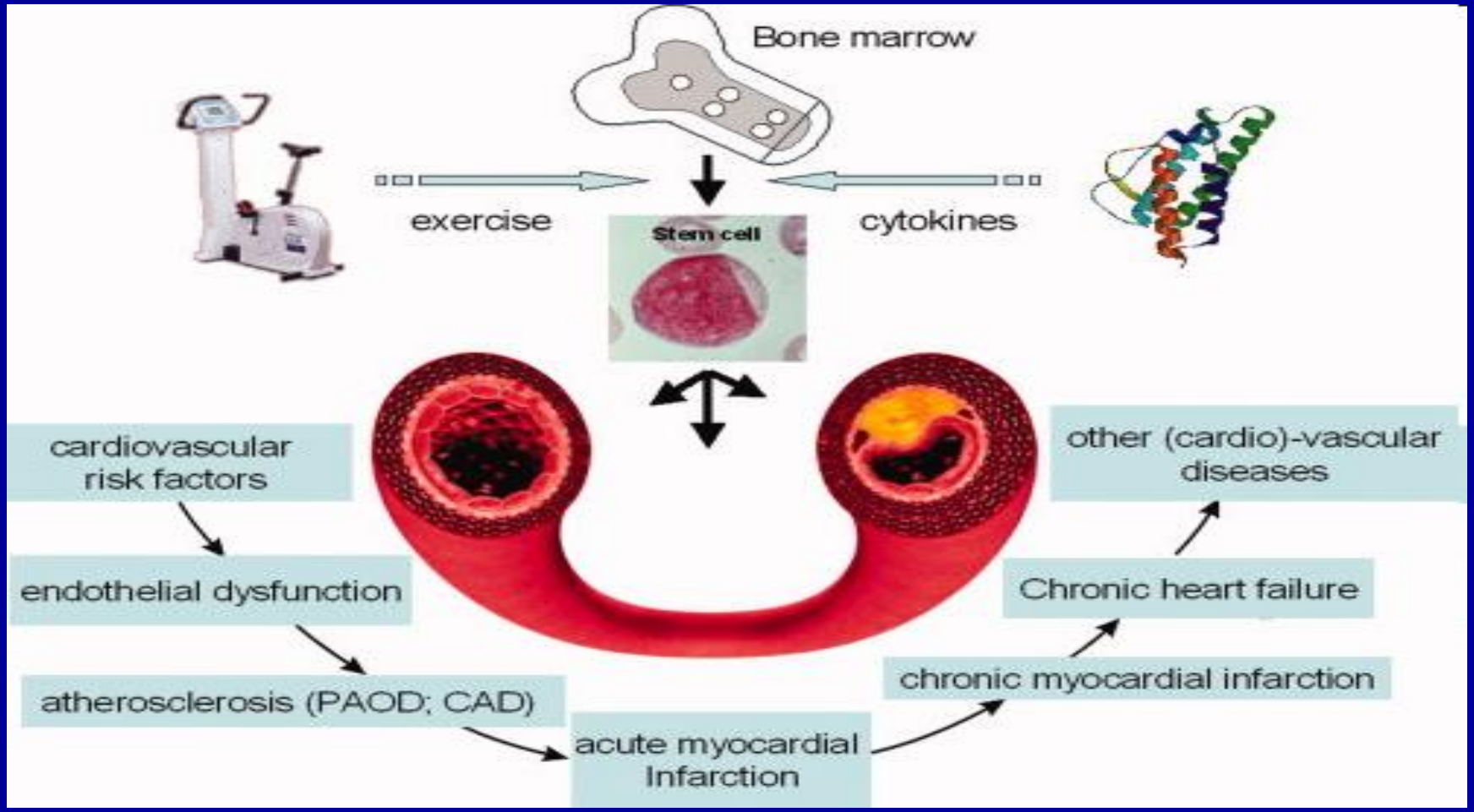
Box plots denote median and 25th and 75th percentile CRP values

et al. Circulation 2003;107:391-397.

CVE-free Survival Rates based on Metabolic Syndrome Status

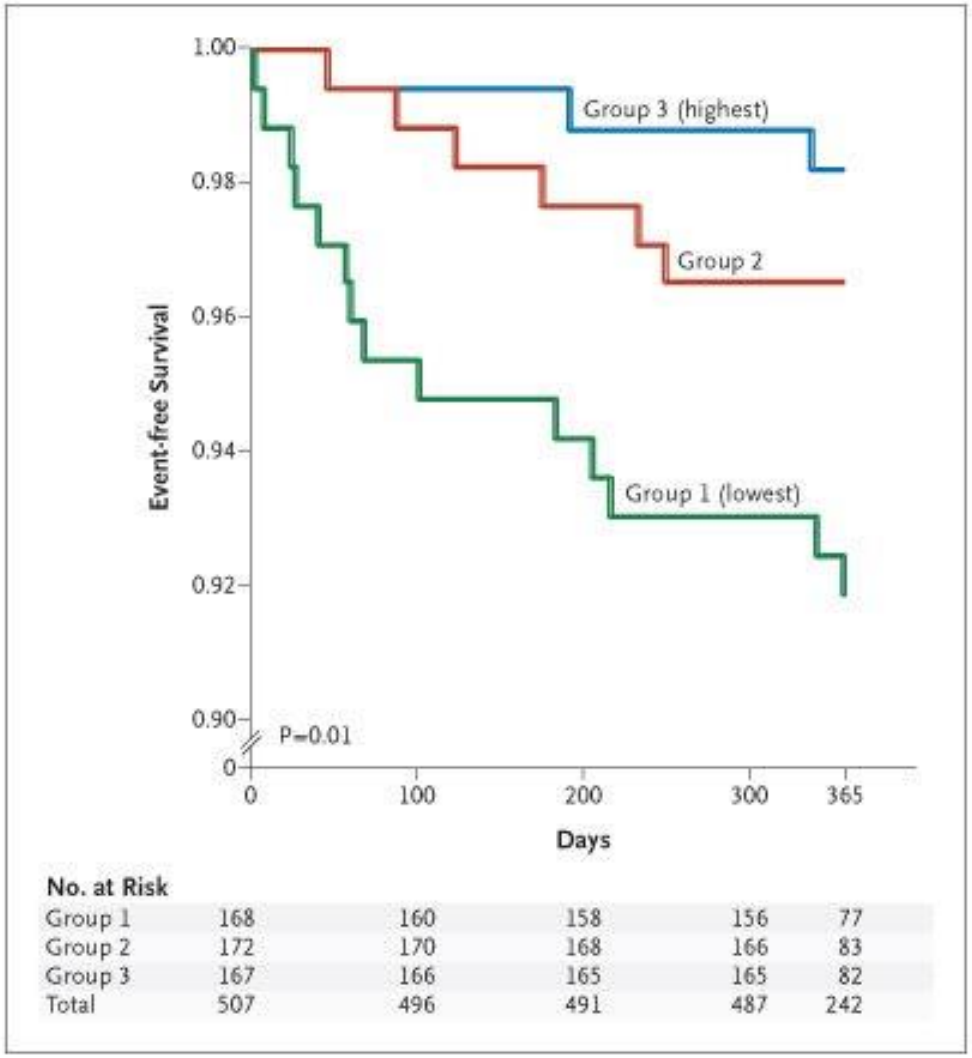


Schematic drawing of conditions influencing the liberation of EPCs from the bone marrow, and its therapeutical application in various cardiovascular diseases



Mobius-Winkler et al. Cytometry, 2009

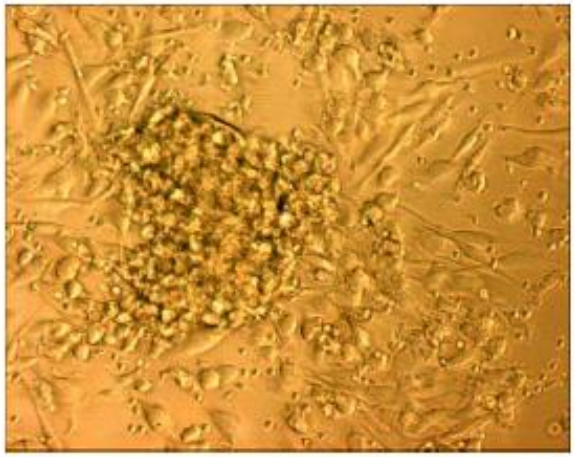
Cumulative Event-free Survival in an Analysis of Death from Cardiovascular Causes at 12 Months, According to Levels of Circulating CD34+KDR+ Endothelial Progenitor Cells at the Time of Enrollment



No. at Risk					
Group 1	168	160	158	156	77
Group 2	172	170	168	166	83
Group 3	167	166	165	165	82
Total	507	496	491	487	242

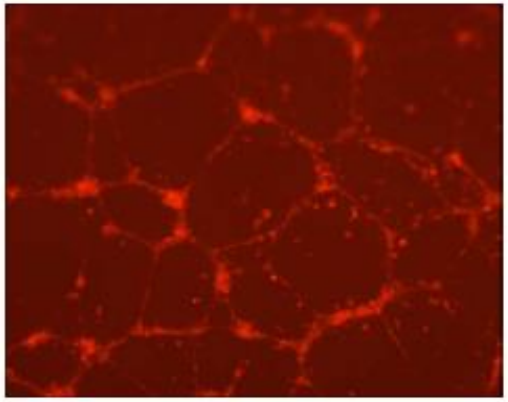
Werner N et al. N Engl J Med 2005

Assays of EPC Functionality

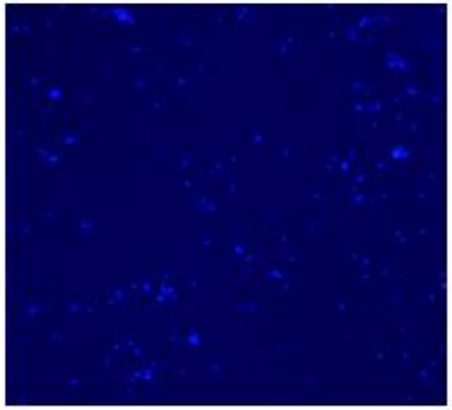


Colony Forming Unit

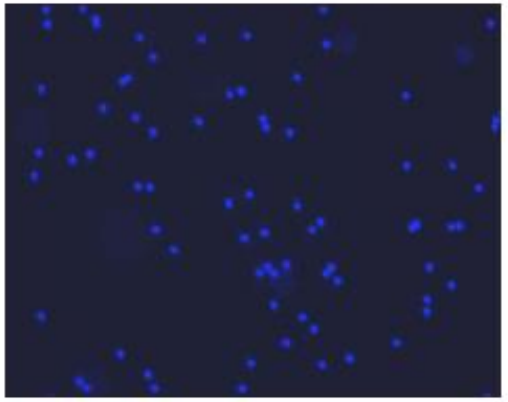
Tubule Formation



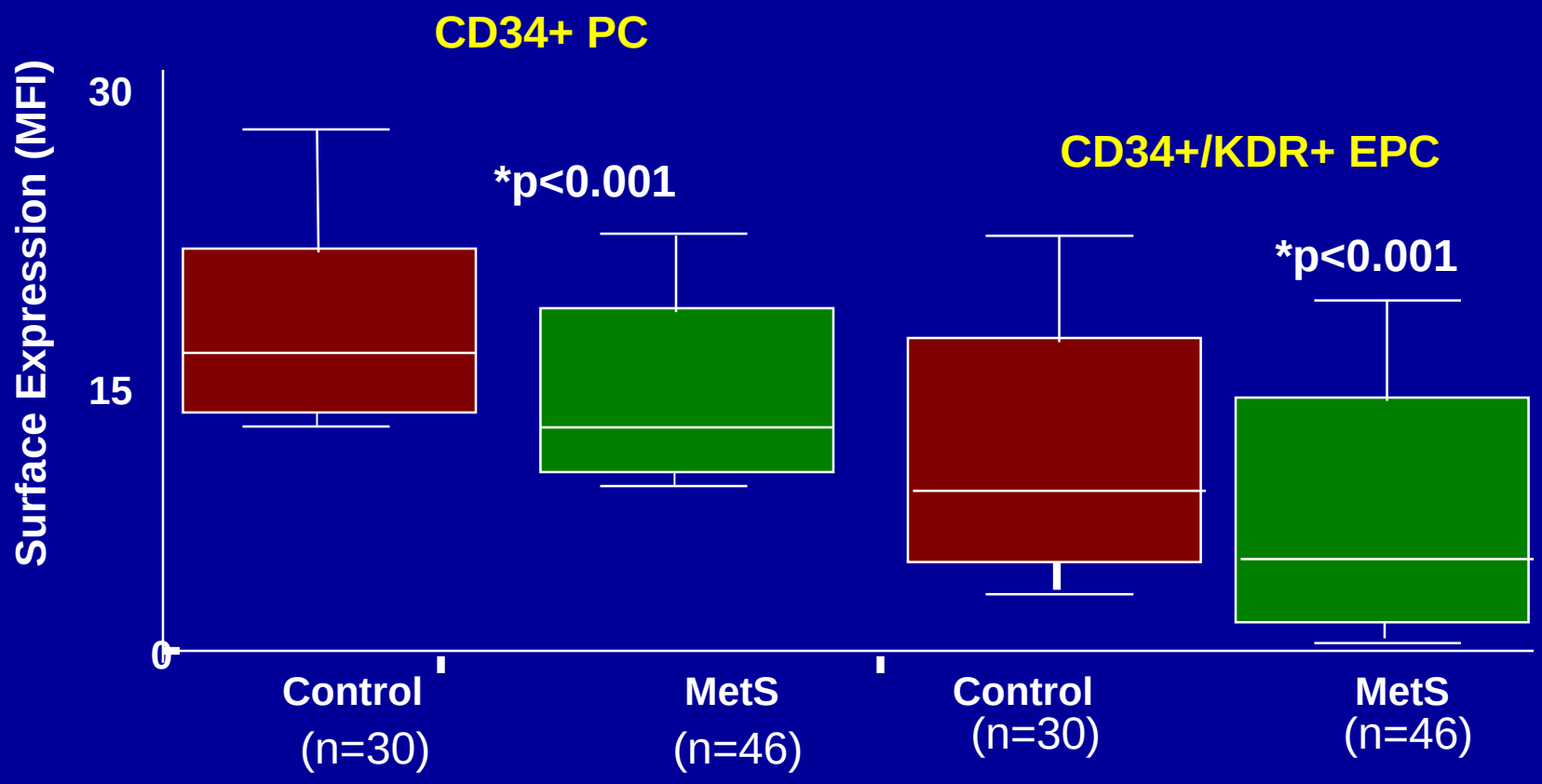
Migration Assay



Adhesion to Fibronectin

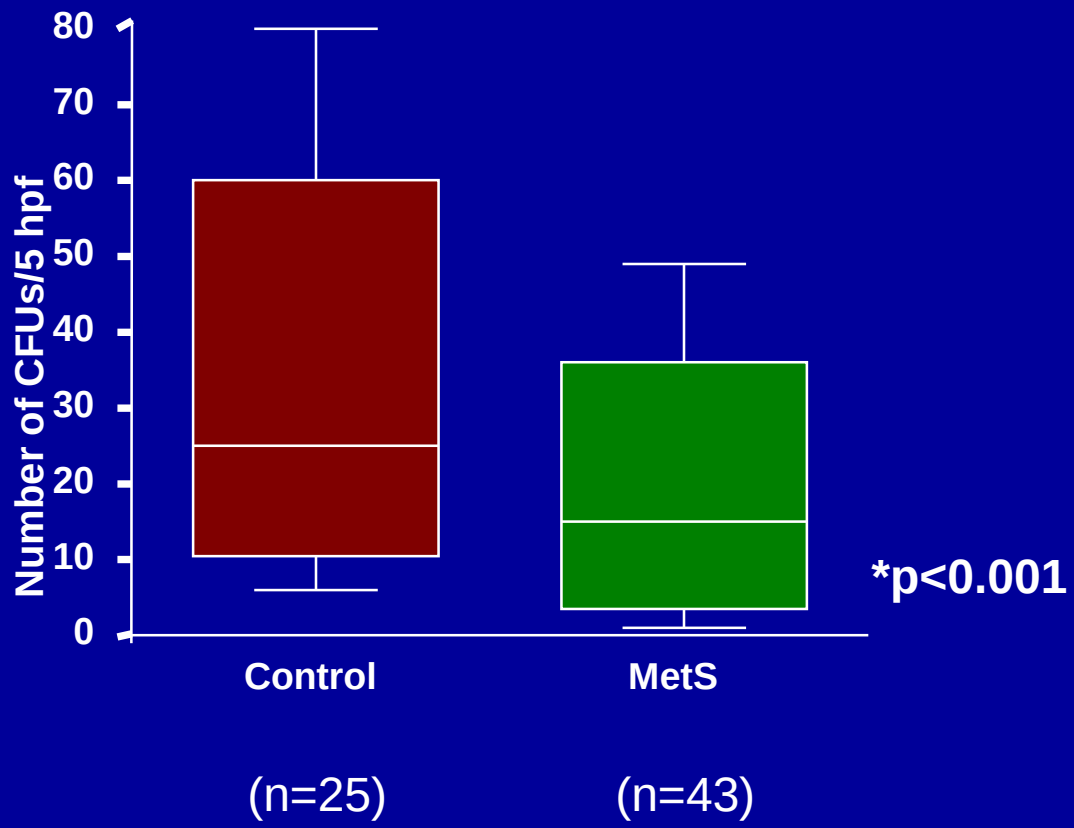


Enumeration of EPCs by FACS



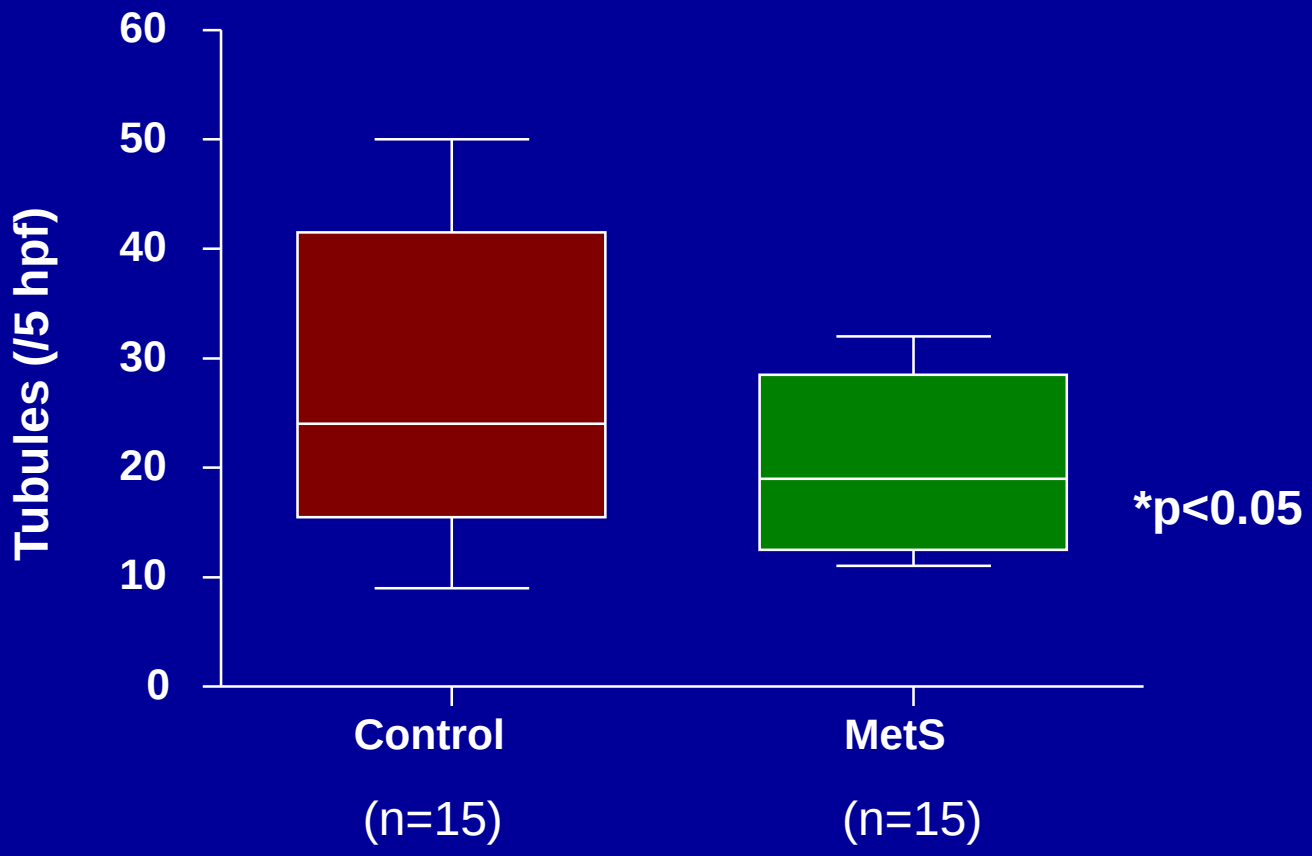
Jialal et al. Atherosclerosis, 2010

CFU in Control and Metabolic Syndrome Subjects



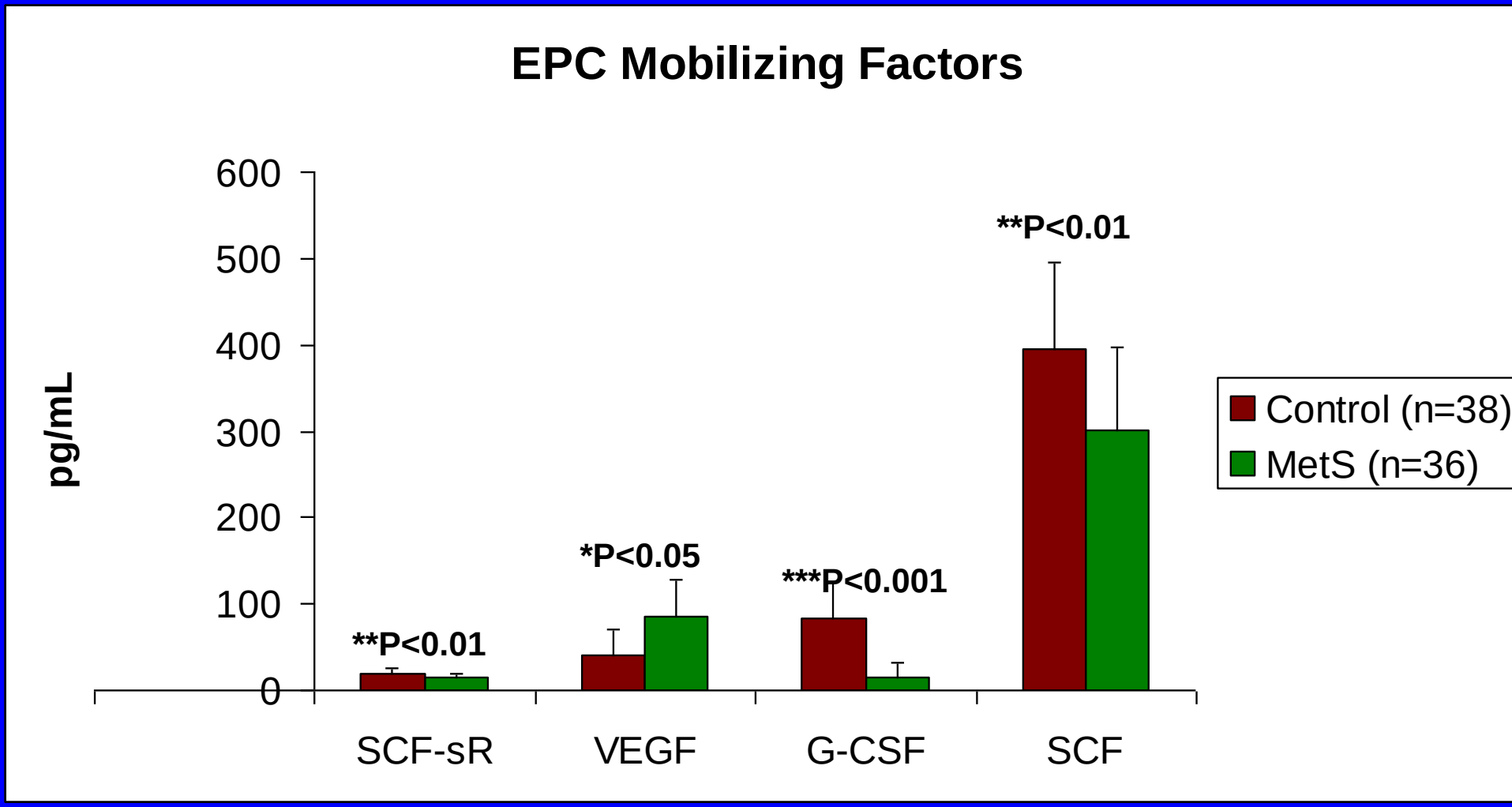
Jialal et al. Atherosclerosis, 2010

Vasculogenic capacity of EPCs in Control and MetS



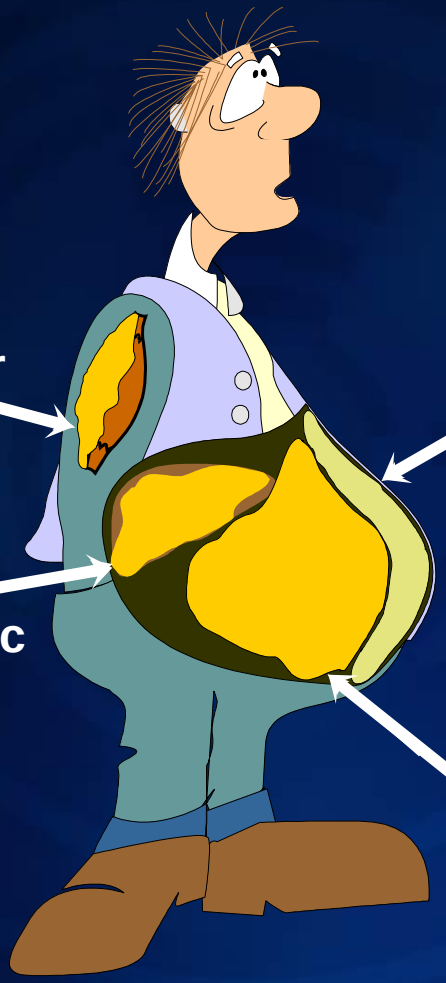
Jialal et al. Atherosclerosis, 2010

EPC Mobilizing Factors



Jialal et al. A.J.Cardiol. 2010

Fat Topography: Where Is the Fat?



High TG

Increased FFA in adipocytes and in extra-adipose organs

Intramuscular Fat

Extra-Adipocytic

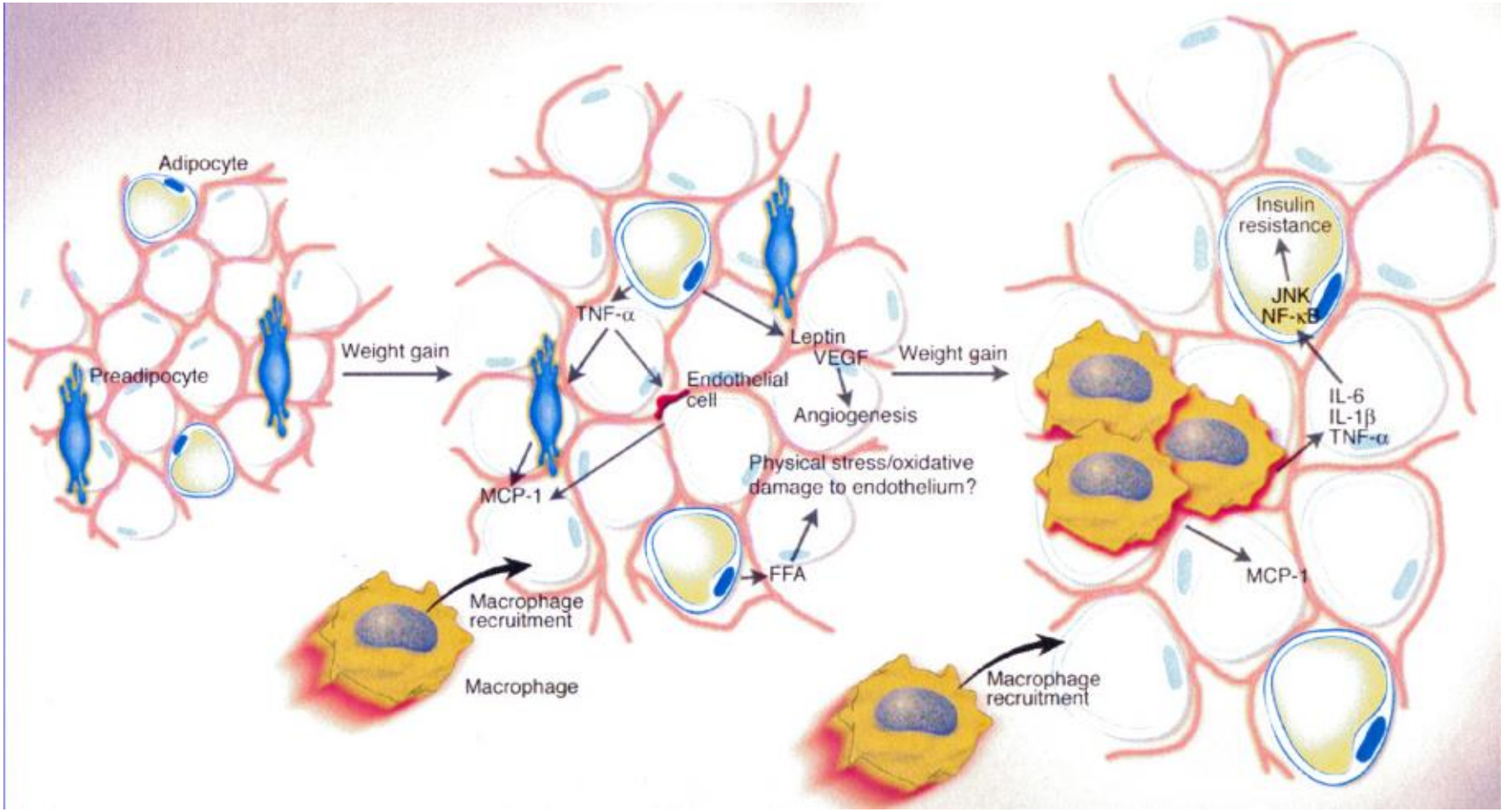
Subcutaneous Fat (Adipocytes)

Intrahepatic Fat

Intra-Abdominal Fat (Adipocytes)

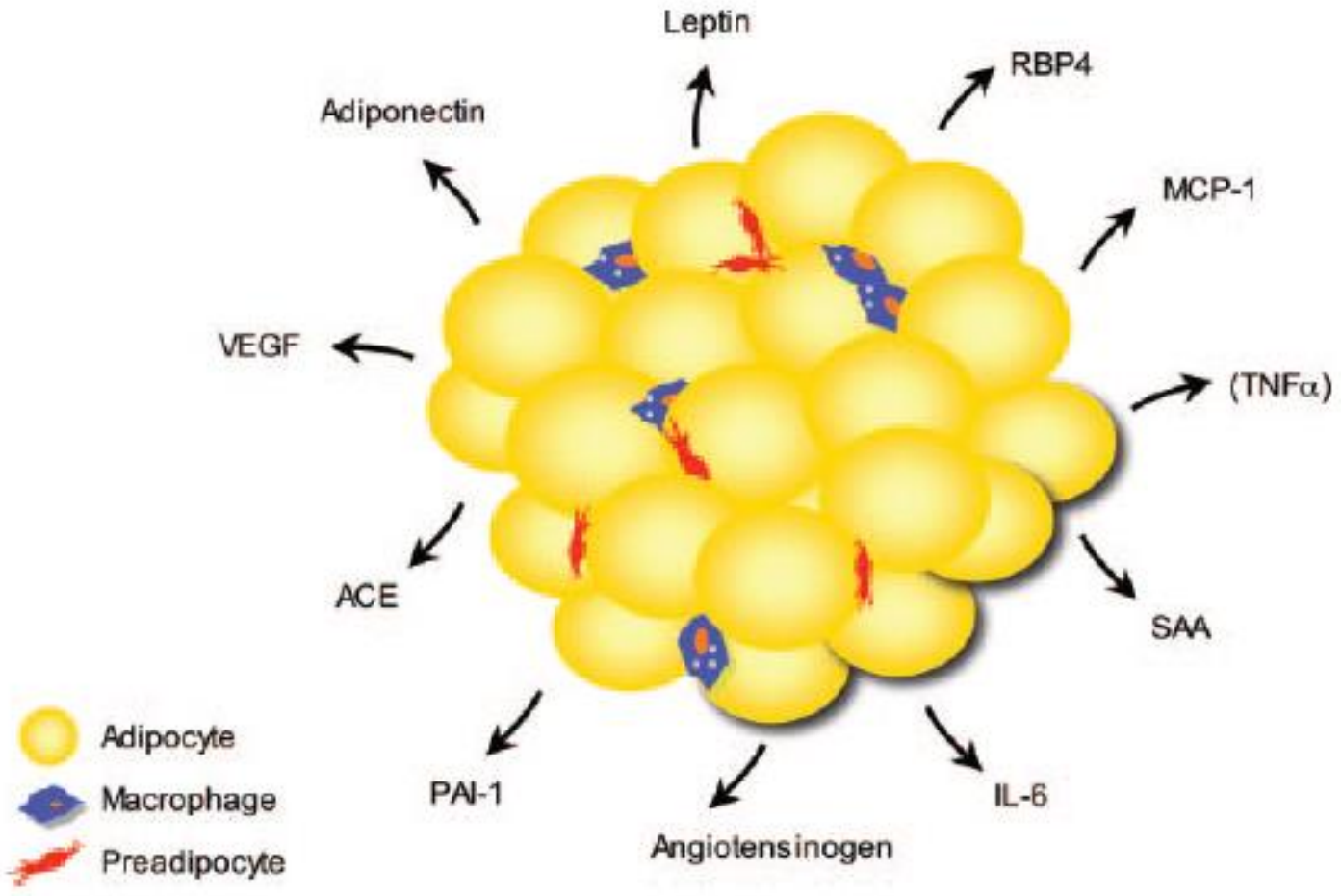
Joslin Diabetes Center

Obesity induces inflammatory changes in adipose tissue



Wellen KE, Hotamisligil GS. *J Clin Invest.* 2003;112:1785-8.

Adipokines released by the adipose tissue



Cellular Inflammation in Metabolic Syndrome

Subject Characteristics

	Control (n=26)	MetS (n=39)	P Value
Age (yrs)	44 ± 10	49 ± 11	0.12
Waist (cm)	94 ± 17	108 ± 17	< 0.001
Male to Female Ratio	10:16	14:25	
BMI (kg/m^2)	29 ± 7	34 ± 6	< 0.01
Systolic BP (mm Hg)	118 ± 18	135 ± 18	< 0.001
Diastolic BP (mm Hg)	77 ± 12	86 ± 17	< 0.001
Fasting glucose (mg/dl)	88 ± 10	102 ± 12	< 0.001
Total cholesterol (mg/dl)	187 ± 34	194 ± 38	< 0.05
HDL-C (mg/dl)	68 ± 12	44 ± 19	< 0.001
Non-HDL-C (mg/dl)	126 ± 22	148 ± 27	< 0.01
TG (mg/dl)	78 (66-94)	129 (106-149)	< 0.001

Bremer AA, et al. JCEM 2011

PLASMA LEVELS OF ADIPOKINES/BIOMEDIATORS

	Control (n=26)	MetS (n=39)	P Value
HOMA	1.1 (0.9 – 2.6)	2.1 (1.7 – 4.9)	< 0.0001
hsCRP (mg/liter)	1.2 (0.5 – 2.8)	3.4 (1.6 – 5.2)	< 0.01
Leptin (ng/ml)	34 (24 – 55)	79 (51 - 104)	< 0.001
RBP-4 (µg/ml)	41 ± 13	51 ± 19	< 0.02
Adiponectin (µg/ml)	7.8 (5.4 – 12.9)	5.4 (3.8 – 8.2)	< 0.02
SAA (µg/ml)	6.5 ± 2.7	9.5 ± 3.2	< 0.001
IL-1β (pg/ml)	9.7 (3.1 – 11.8)	20.6 (5.8 – 34.2)	< 0.05
IL-6 (pg/ml)	1.2 (0.4 – 2.7)	2.9 (1.1 – 4.5)	< 0.01
TNF (pg/ml)	1.7 (0.9 – 2.9)	2.3 (1.1 – 3.5)	> 0.05

Bremer AA, et al. JCEM 2011

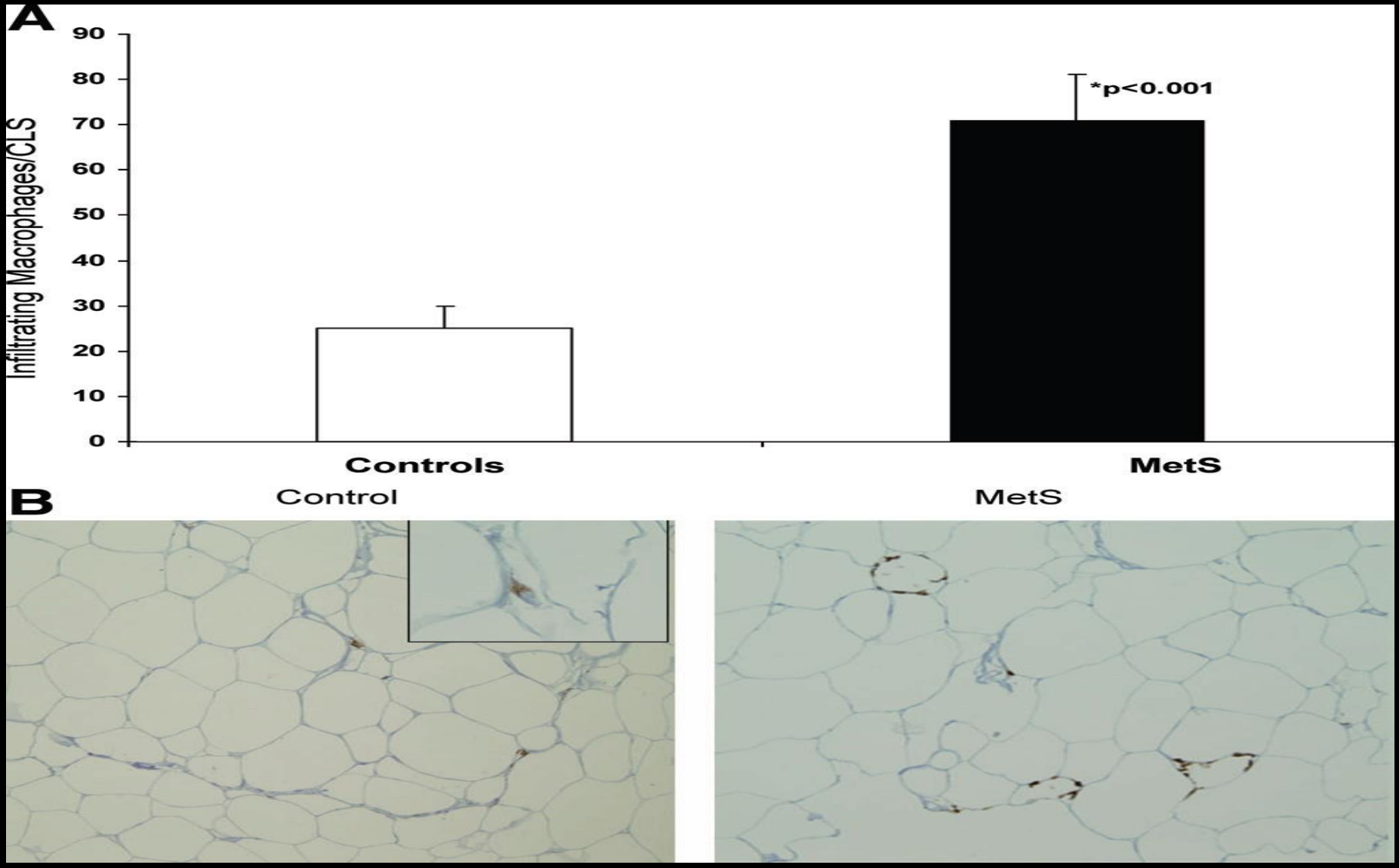
ADIPOKINE SECRETION FROM ADIPOSE TISSUE(SAT)

	Controls	MetS	Adjusted P Value
Adiponectin (ng/g)	4.2 (1.3 - 5.6)	3.7 (1.2 - 4.6)	0.077
Leptin (ng/g)	3.0 (2.1 - 6.2)	7.3 (3.8 - 18.6)*	< 0.05
RBP-4 (ng/g)	11.1 (6.4 - 18.4)	29.1 (16.2 - 33.7)**	0.069
CRP (ng/g)	2.5 (2.3 - 7.9)	5.4 (3.4 - 19.1)*	< 0.05
SAA (ng/g)	14.8 (5.1 - 34.2)	25.3 (14.5 - 55.7)*	< 0.05
PAI-1 (ng/g)	3.2 (2.2 – 6.5)	5.6 (3.1 – 9.9)**	< 0.001
MCP-1 (ng/g)	6.7 (4.3 – 9.1)	22.1 (11.8 - 33.5)**	< 0.01
IL-1β (ng/mg protein)	31.1 (21.2 – 45.1)	39.7 (24.8 – 61.5)*	< 0.05
TNF (ng/mg protein)	3.7 (1.9 – 4.6)	3.8 (2.9 – 5.3)	> 0.05
IL-6 (ng/mg protein)	16.5 (10.6 – 24.5)	18.7 (12.7 – 33.2)*	< 0.05
IL-8 (ng/mg protein)	10.9 (5.1 – 14.2)	17.4 (14.5 – 27.3)**	< 0.02

Bremer AA, et al. JCEM 2011

Cellular Inflammation & Metabolic Syndrome

Infiltrating Macrophages



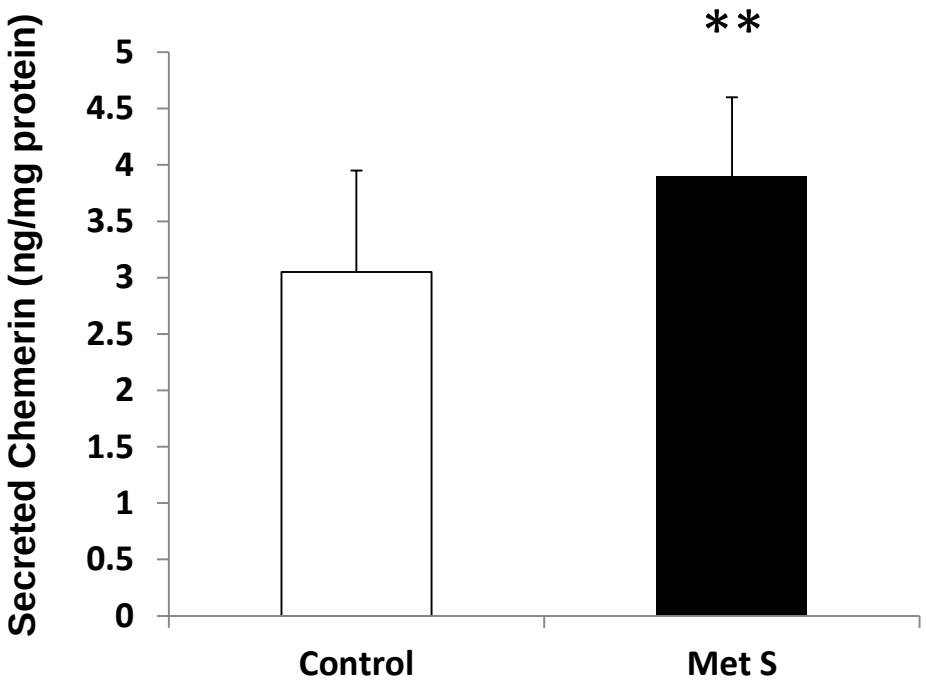
Bremer AA et al., JCEM 2011

Novel Adipokine Concentrations

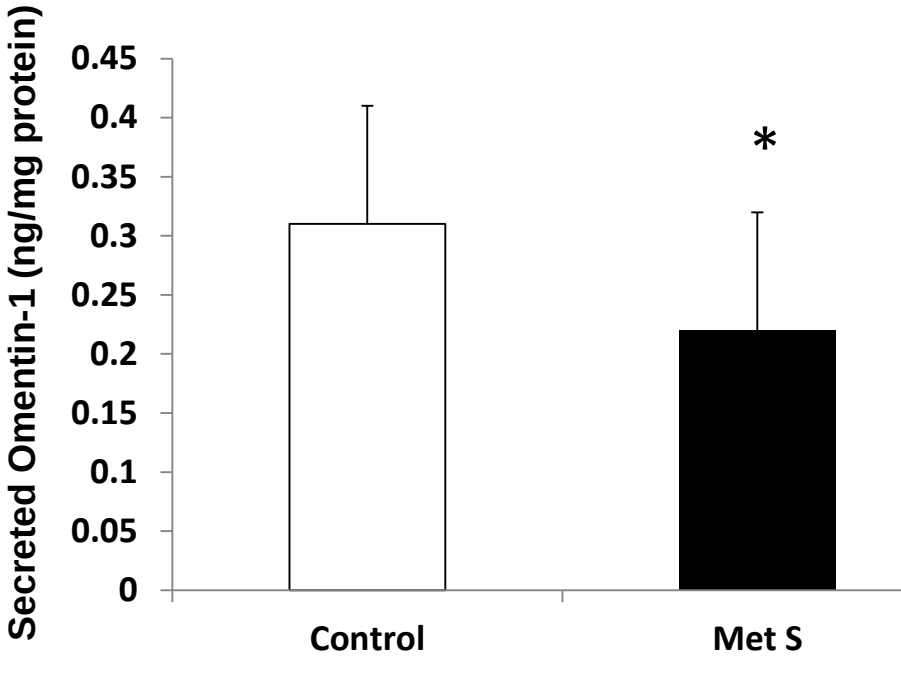
Variable	Controls (n=30)	MetS (n=45)	p-value MetS vs. Control
hsCRP (mg/L)	1.3 (0.5, 4.0)	3.1 (1.6, 5.4)	0.006
HOMA-IR	1.1 (1.0, 2.8)	2.8 (1.9, 5.1)	0.0001
Plasma Chemerin (ng/mL)	271 ± 53 n=20	366 ± 64 n=37	<0.0001 *(0.0005)
SAT Chemerin (ng/mg protein)	3.05 ± 0.94 n=30	3.94 ± 0.74 n=45	0.001
Plasma Omentin (ng/mL)	27 ± 14 n=16	16 ± 5 n=16	0.004 *(0.03)
SAT Omentin (ng/mg protein)	0.31 ± 0.09 n=30	0.22 ± 0.10 n=45	0.01
Plasma Resistin (ng/mL)	1.8 (1.5, 2.5) n=21	2.4 (1.7, 3.1) n=31	0.04 *(0.07)
SAT Resistin (ng/mg protein)	0.16 ± 0.06 n=30	0.17 ± 0.05 n=45	NS
Plasma Visfatin (ng/mL)	0.57 (0.38, 0.71) n=22	0.59 (0.31, 0.96) n=36	0.14 *(0.13)
SAT Visfatin (ng/mg protein)	0.17 ± 0.09 n=30	0.21 ± 0.1 n=45	NS

*(p-value adjusted for age and BMI)

Results are presented as Mean ± standard deviation or Median (25^{th} percentile, 75^{th} percentile).



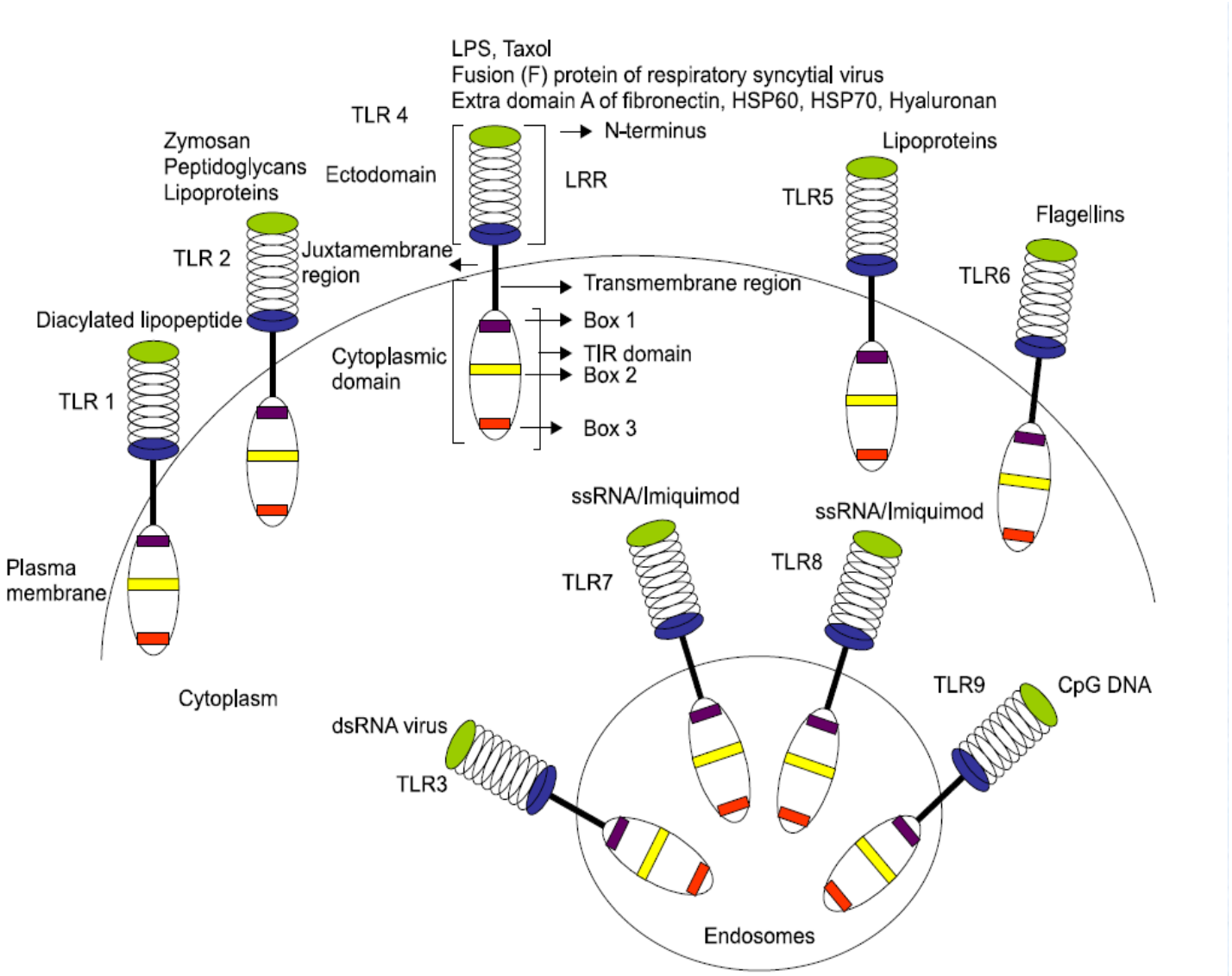
** P<0.001



*P=0.01

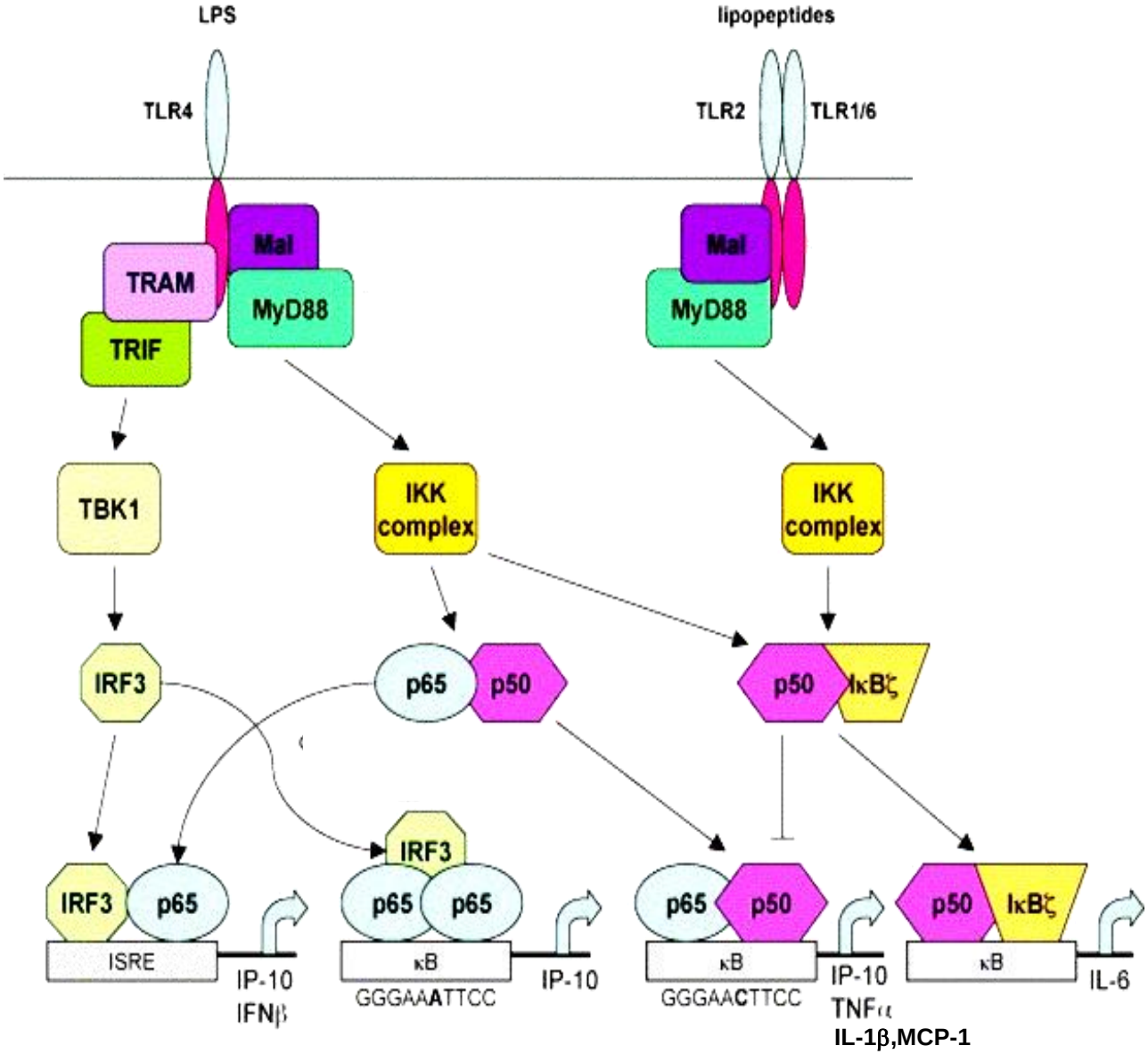
Jialal et al., J Clinical Endocrinol Metab 2013

Cellular Localization of TLR



Krishnan J et al, Exp Mol Med, 2007

Overview of the TLR2 and TLR4 Signaling



Modified from ***Doyle & O'Neill 2006***

Cellular Inflammation & Metabolic Syndrome

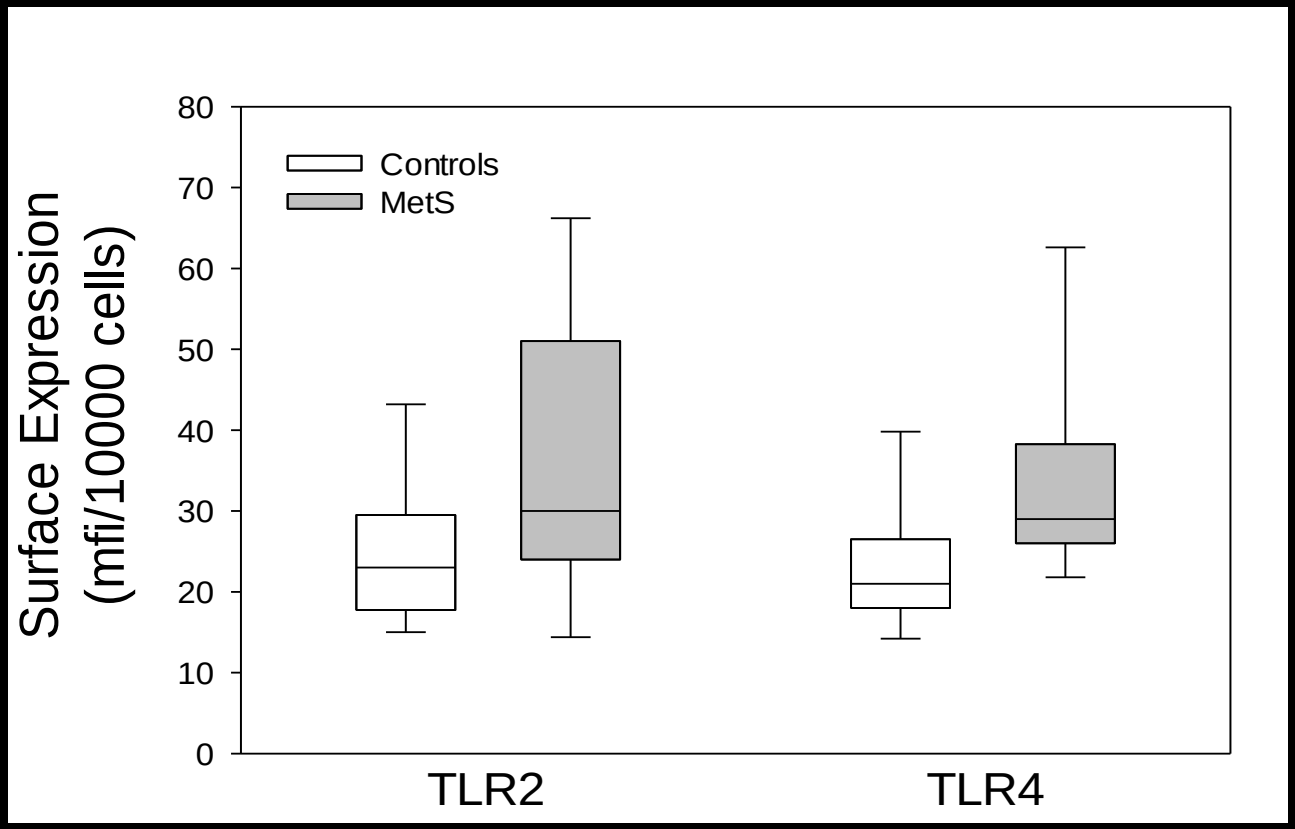
	Controls (n=41)	MetS (n=49)
hsCRP (mg/L)	1.3 (0.5, 2.8)	3.7 (1.7, 5.6)*
HOMA-IR	1.1 (0.9, 2.8)	2.4 (1.8, 5.8)*
Plasma Free Fatty Acids (mM/L)	0.34 ± 0.18	0.81 ± 0.18**
Plasma Endotoxin (EU/ml)	3.86 ± 0.59	12.95 ± 2.97**

***p<0.05 compared Controls; **p<0.001 compared to Controls; ***p<0.0001 compared to Controls**

Jialal I, et al. Diabetes Care 2012

Cellular Inflammation & Metabolic Syndrome

Monocyte TLR Expression

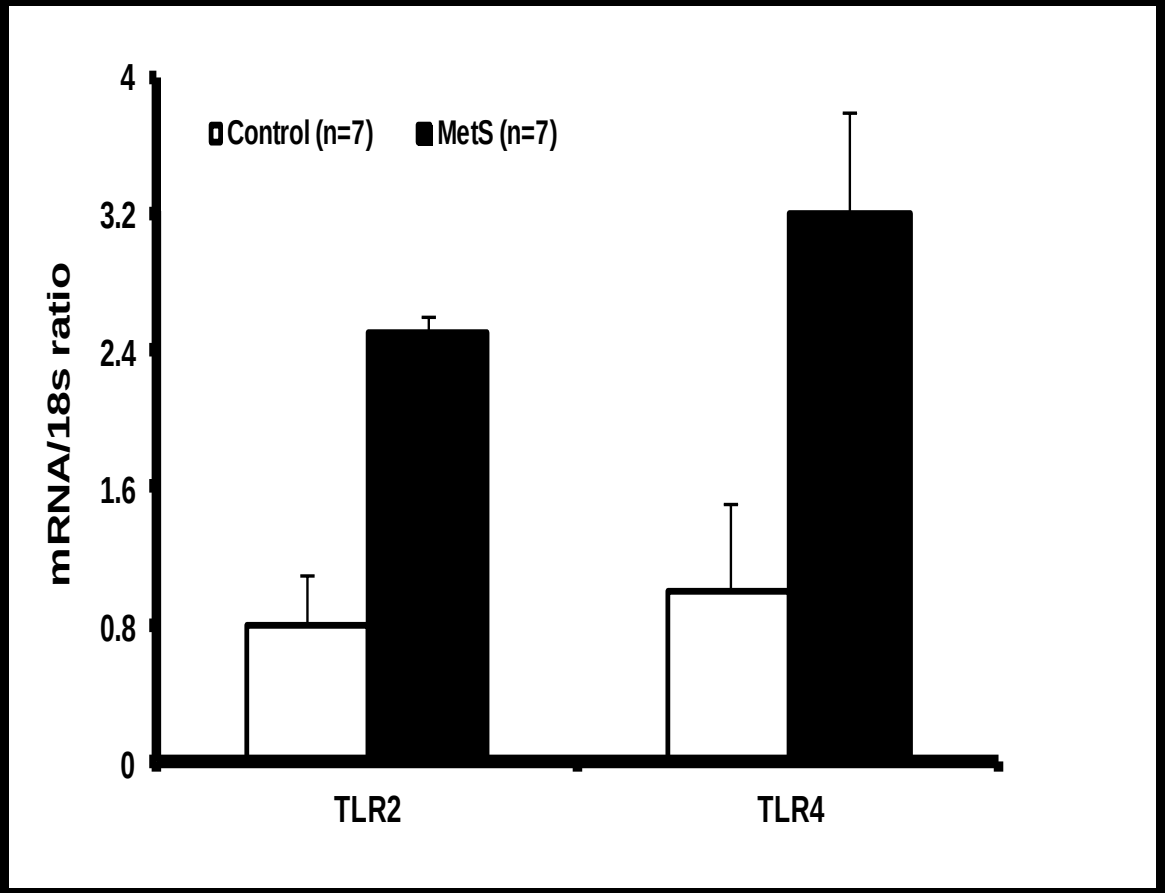


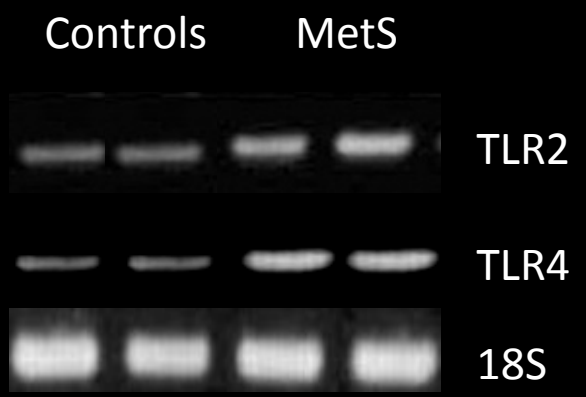
***p<0.01 compared to Controls**

Jialal I, et al. Diabetes Care 2012

Cellular Inflammation & Metabolic Syndrome

TLR2 & TLR4 mRNA expression



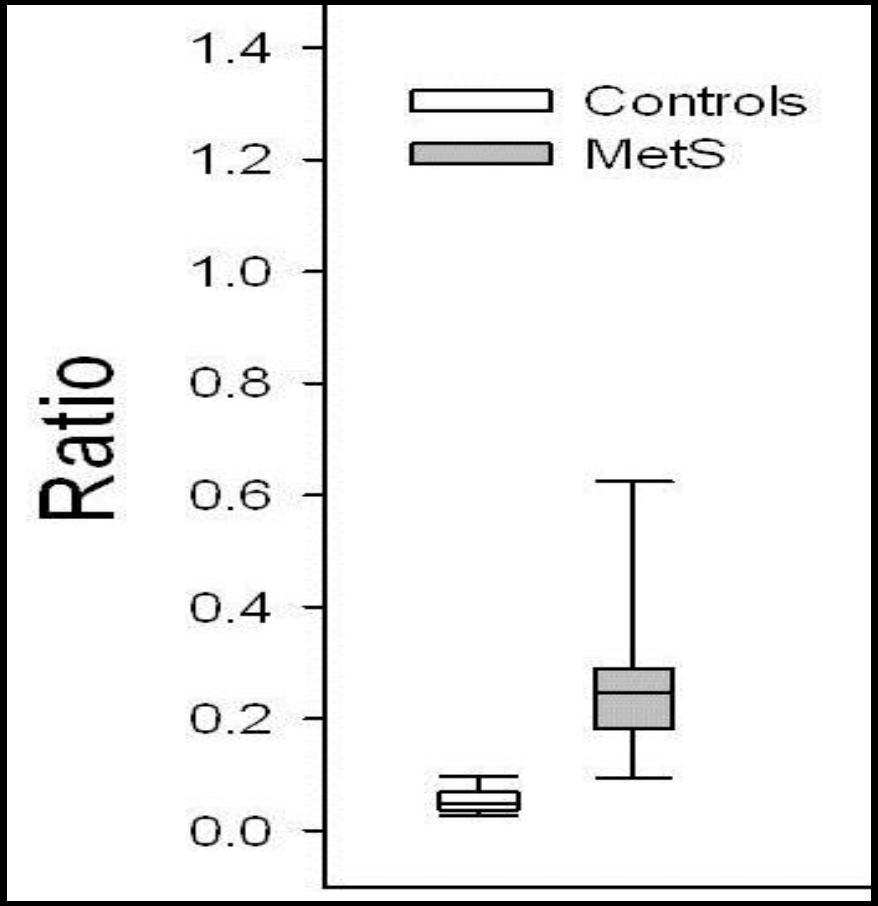


*p<0.05 compared to Controls

Jialal I, et al. Diabetes Care 2012

Cellular Inflammation & Metabolic Syndrome

Monocyte Signaling



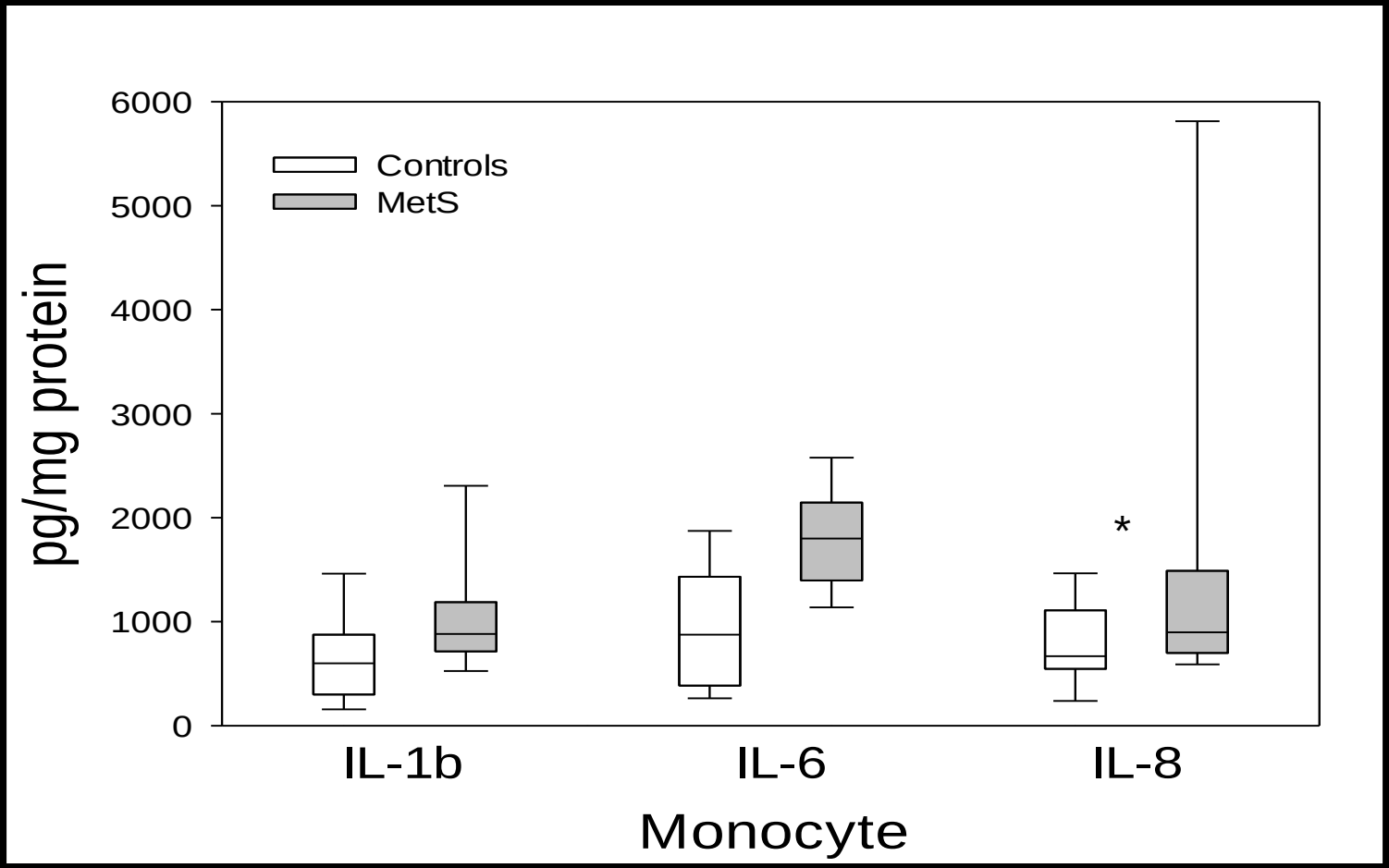
Nuclear
pp65/p65

*p<0.001 compared to Controls

Jialal I, et al. Diabetes Care 2012

Cellular Inflammation & Metabolic Syndrome

Monocyte Cytokines in MetS



*p<0.05 compared to Controls

Jialal I, et al. Diabetes Care 2012

Plasma Biomarkers of Inflammation & Metabolic Syndrome

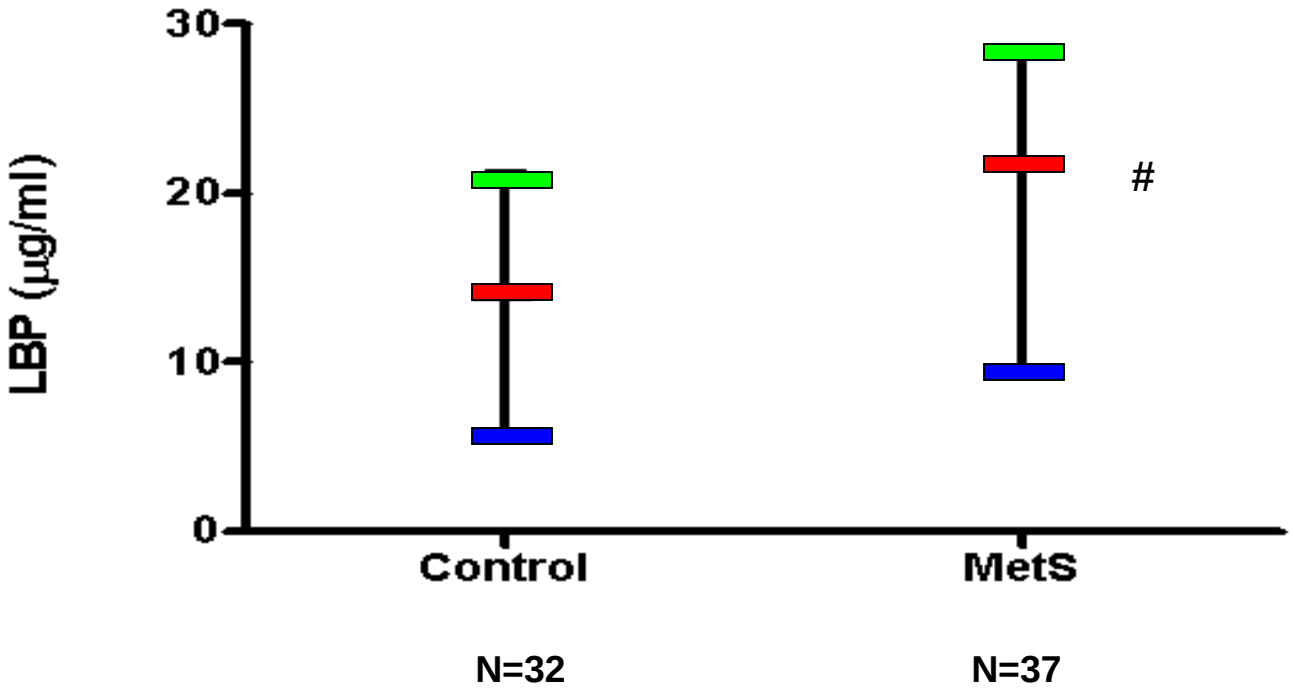
	Controls (n=41)	MetS (n=49)
Plasma sTNFR-1 (pg/ml)	933 ± 248	1220 ± 303*
Plasma sTNFR-2 (pg/ml)	2037 ± 546	2496 ± 719
Plasma IL-8 (pg/ml)	2.3 (0.4, 6.6)	4.9 (0.9, 8.9)*
Plasma MCP-1 (pg/ml)	4.2 (0.4, 7.5)	5.7 (1.0, 9.1)
Plasma IL-1β (pg/ml)	7.3 (2.4, 10.5)	15.7 (3.3, 29.1)*
Plasma TNF (pg/ml)	345 (248, 468)	287 (249, 575)
Plasma IL-6 (pg/ml)	875 (289, 1425)	1799 (1396, 2145)***

***p<0.05 compared Controls; **p<0.001 compared to Controls; ***p<0.0001 compared to Controls**

Jialal I, et al. Diabetes Care 2012

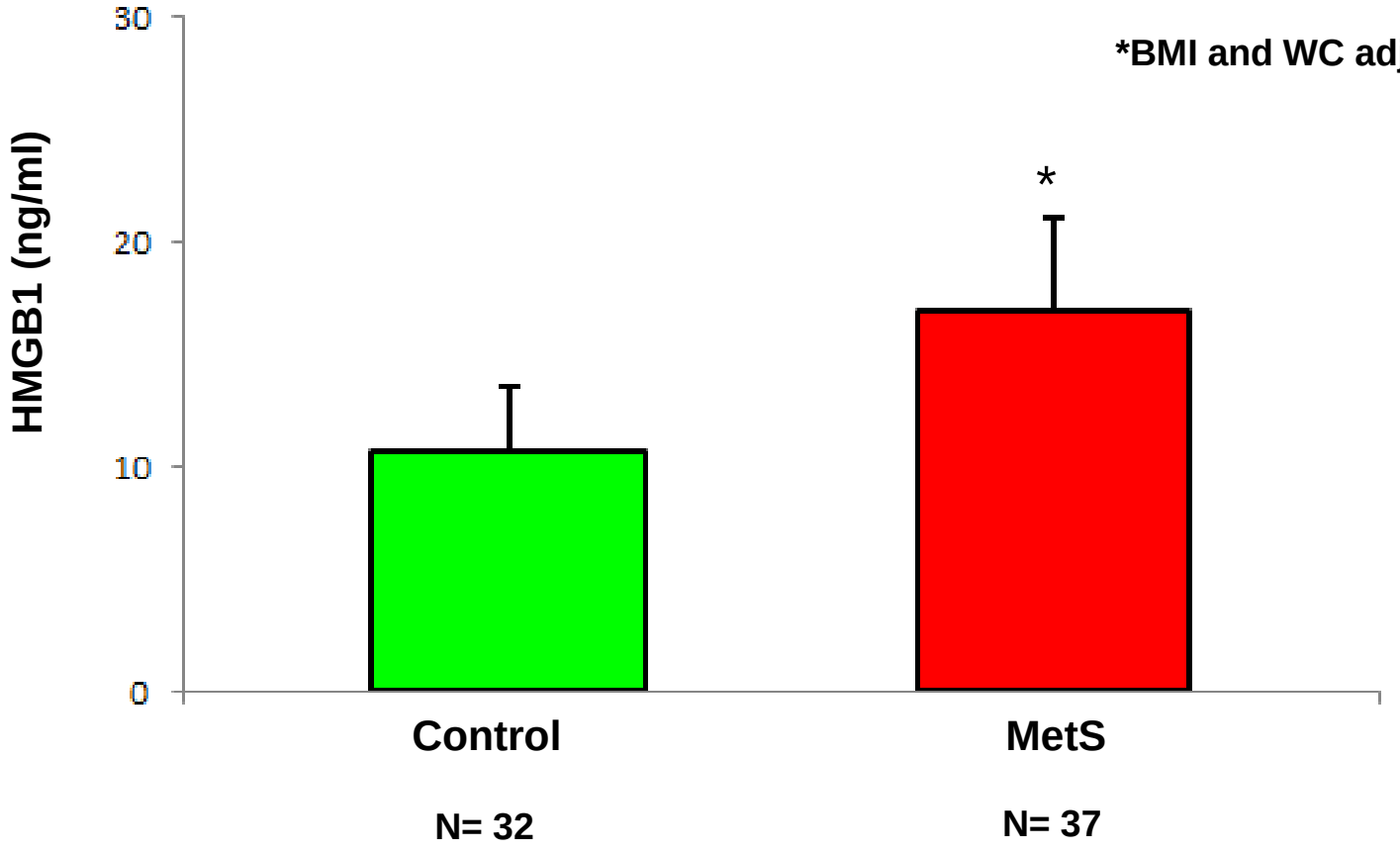
LBP levels in Metabolic Syndrome and Controls

BMI and WC adjusted, P=0.048



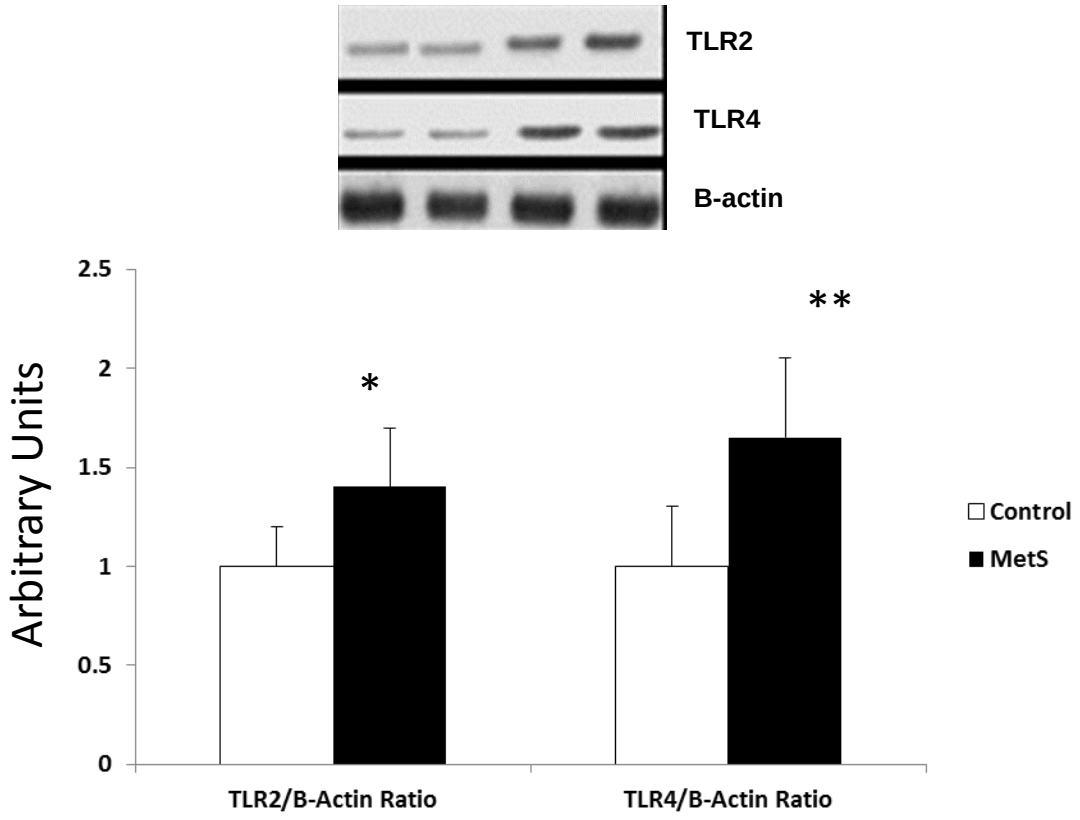
P for Trend for Number of Features of Met Syn, P=0.03

Circulating levels of HMGB1 in Metabolic Syndrome versus Controls



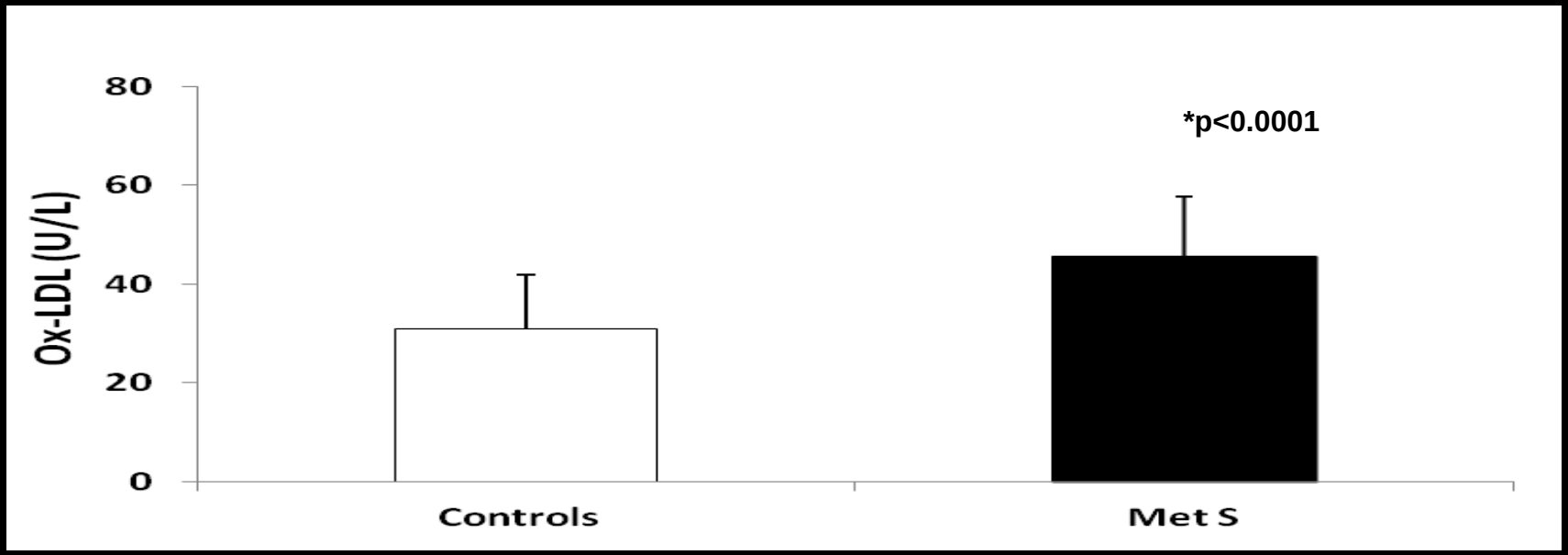
P for Trend for Number of Features of Met Syn, P=0.01

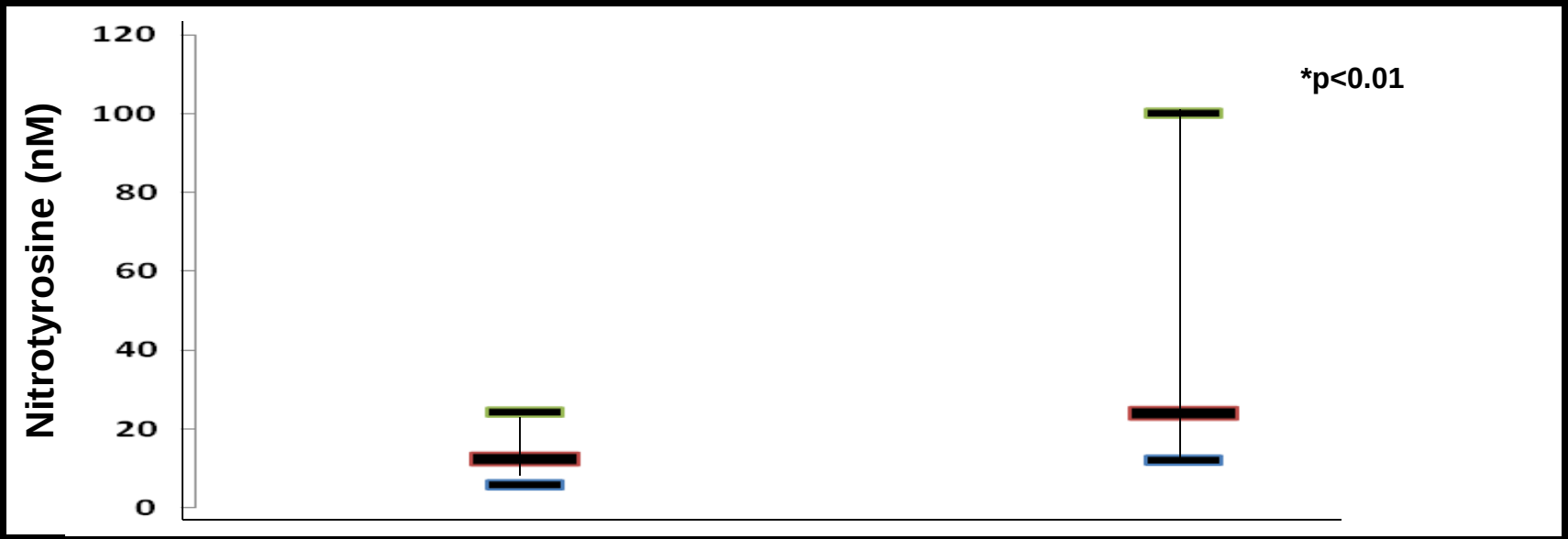
TLR2 and TLR4 protein Abundance in Subcutaneous Adipose Tissue of Metabolic Syndrome Subjects



**p<0.005 compared to control; *p<0.05 compared to control

PLASMA BIOMARKERS OF OXIDATIVE STRESS



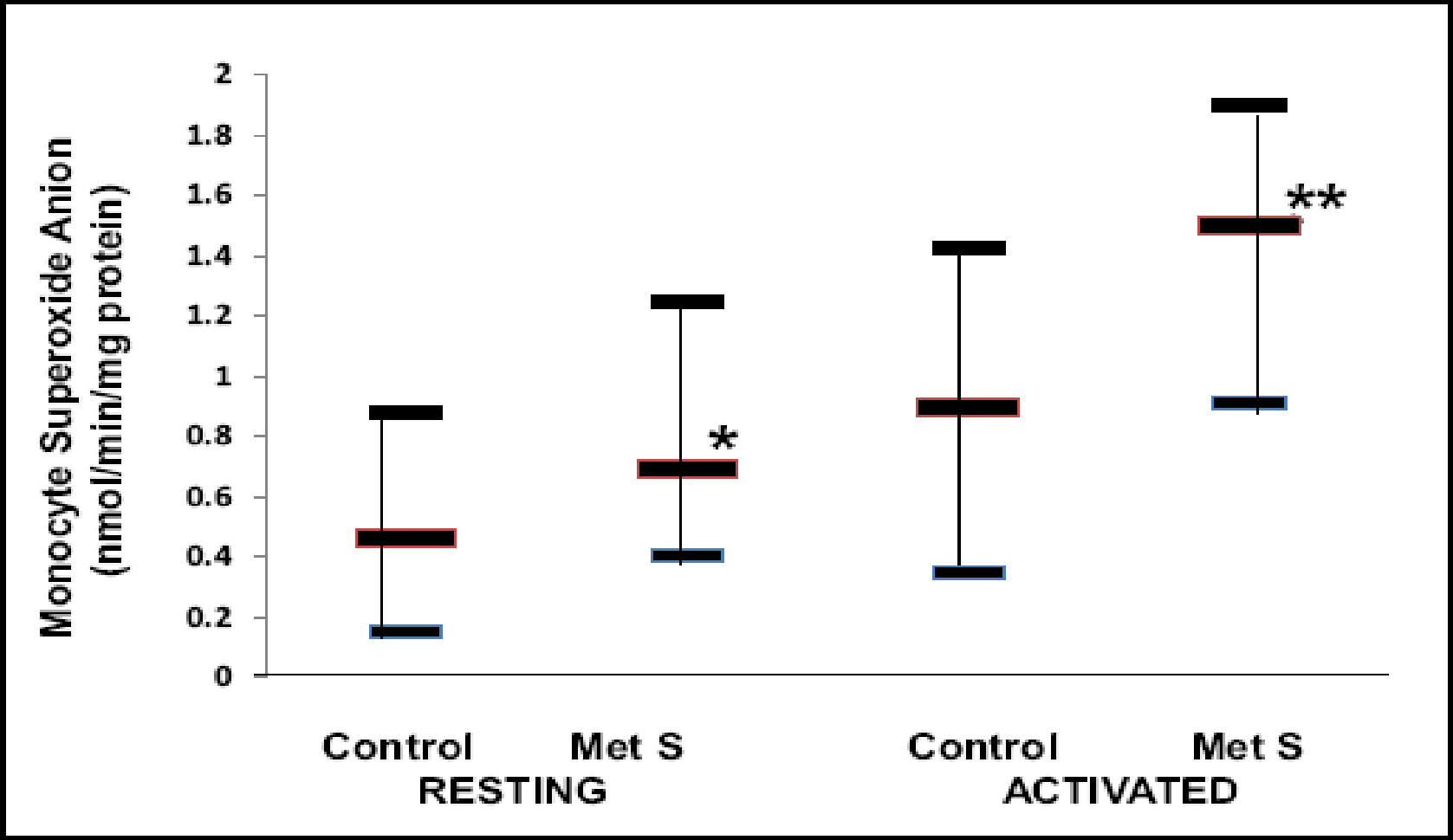


Jialal I, et al. JCEM:2012

Control

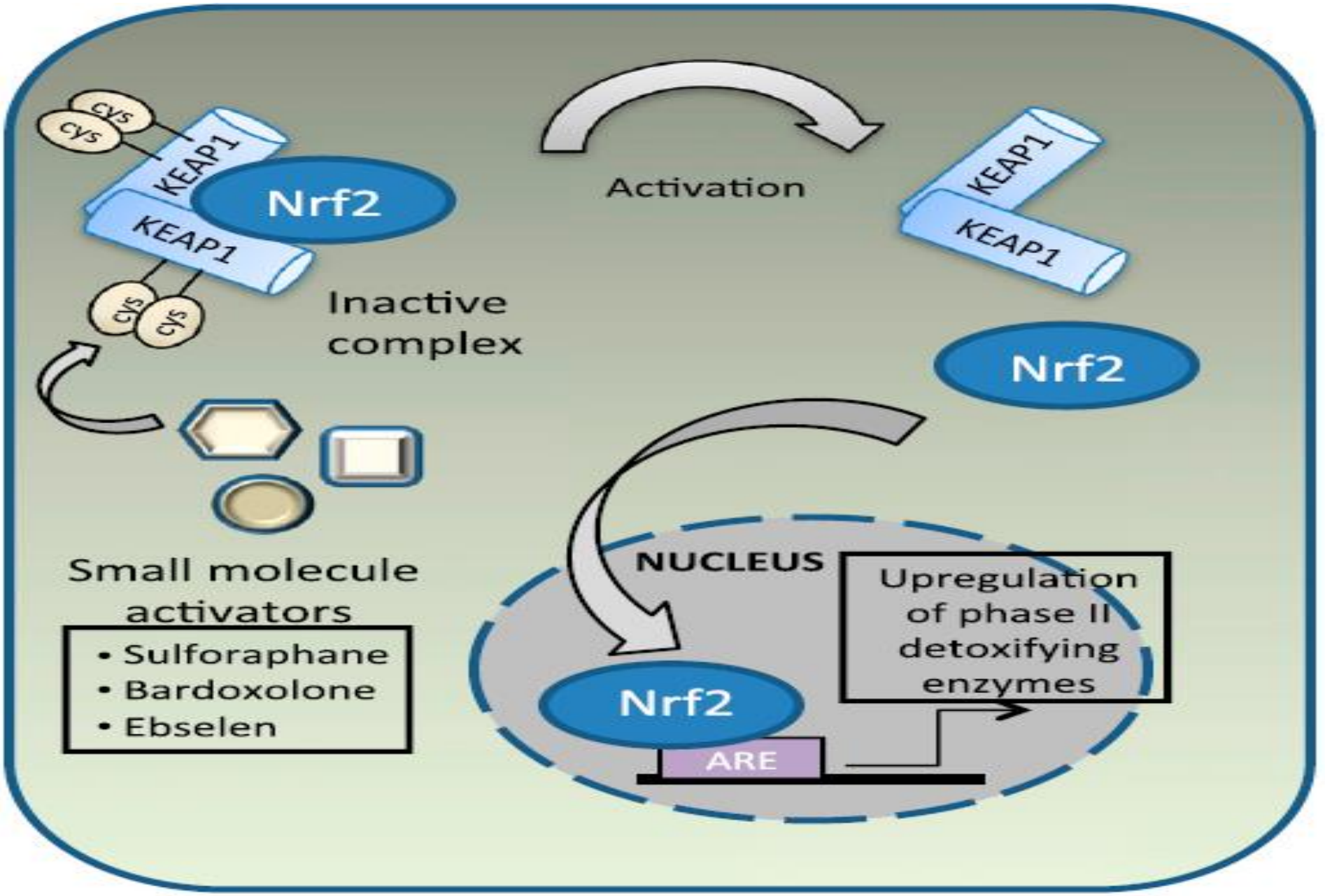
MetS

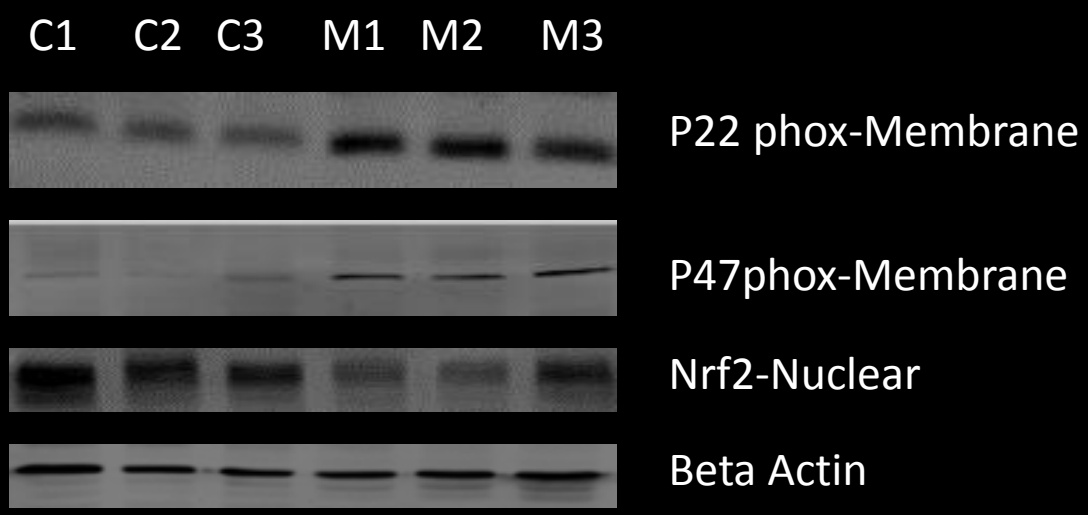
SUPEROXIDE ANION

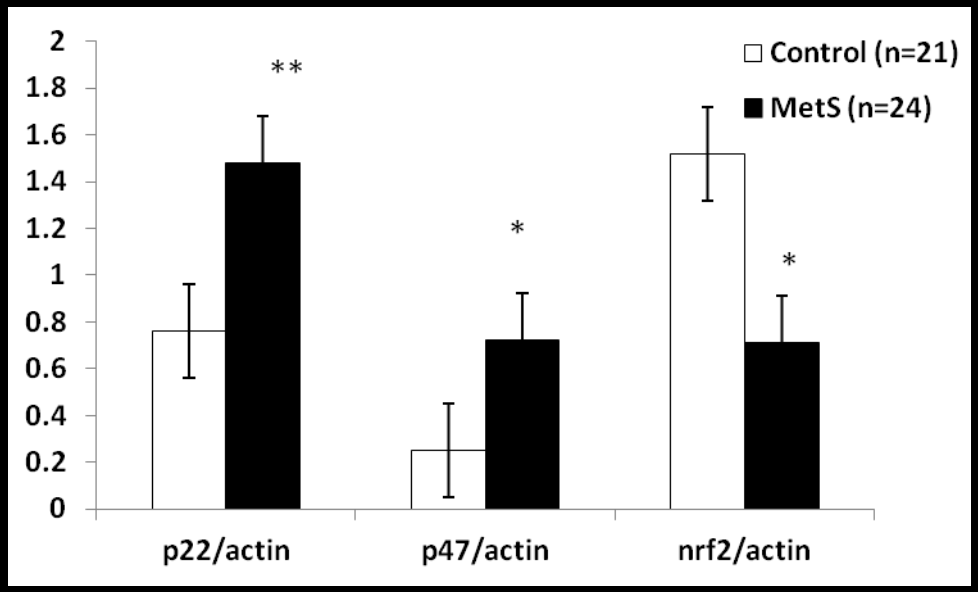


Release of superoxide anion by monocytes under resting and activated conditions in controls and nascent MetS subjects. Levels of superoxide anion were assessed in MetS subjects and matched controls subjects as described in *Materials and Methods*.
***P* < 0.05 compared with controls; ****P* < 0.001 compared with controls.**

Jialal et al., JCEM 2012


Cys
Cys
KEAP1
Nrf2
KEAP1
Cys
Cys
Inactive complex
Activation
KEAP1
KEAP1
Nrf2
Small molecule activators
• Sulforaphane
• Bardoxolone
• Ebselen
NUCLEUS
Upregulation of phase II detoxifying enzymes
Nrf2
ARE



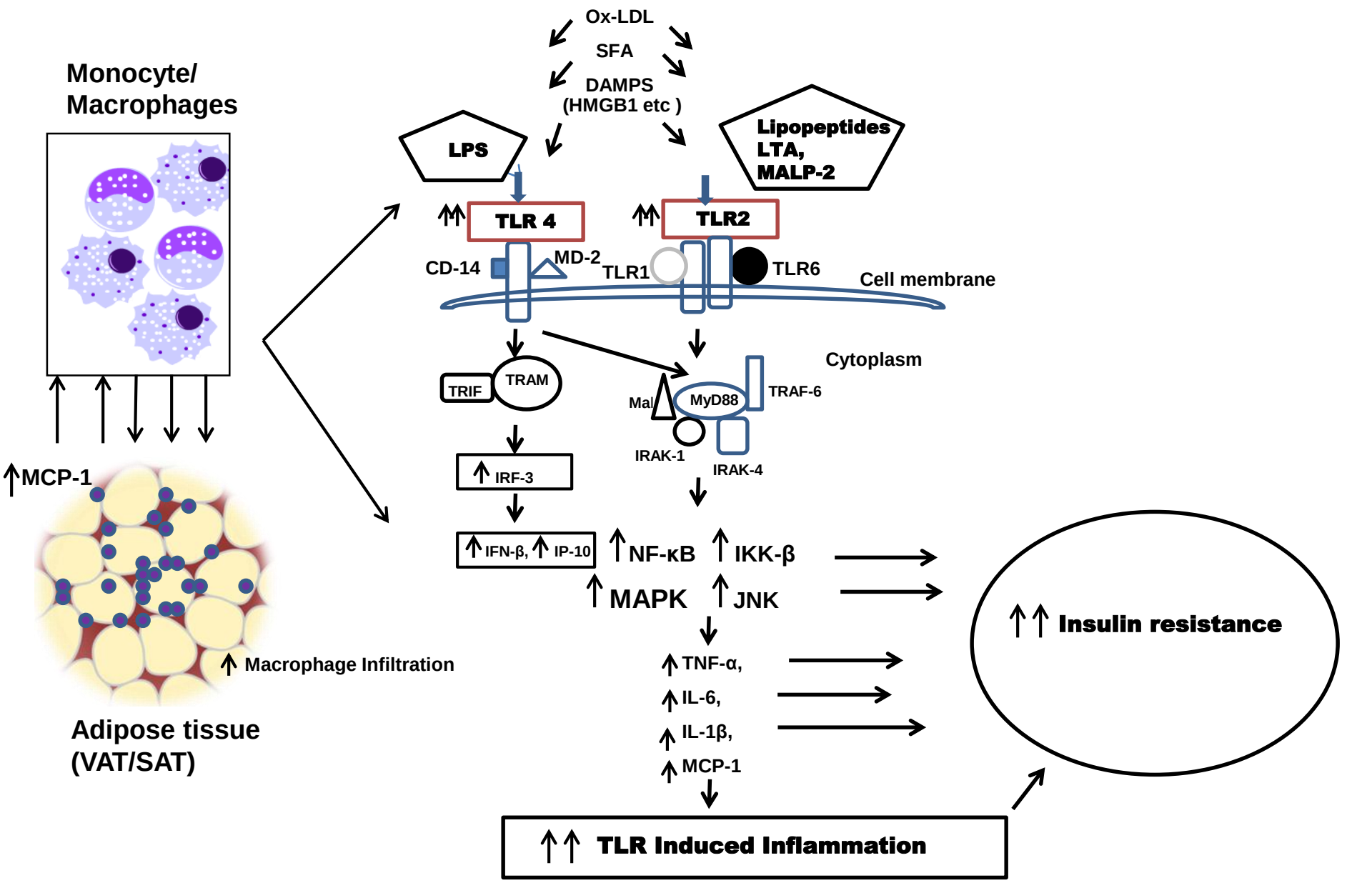


NADPH subunit expression and Nrf2 activity in controls and Nascent MetS subjects. Western blotting was performed for different proteins as described in Methods. Densitometric ratios represent adaptor protein to beta actin ratios.

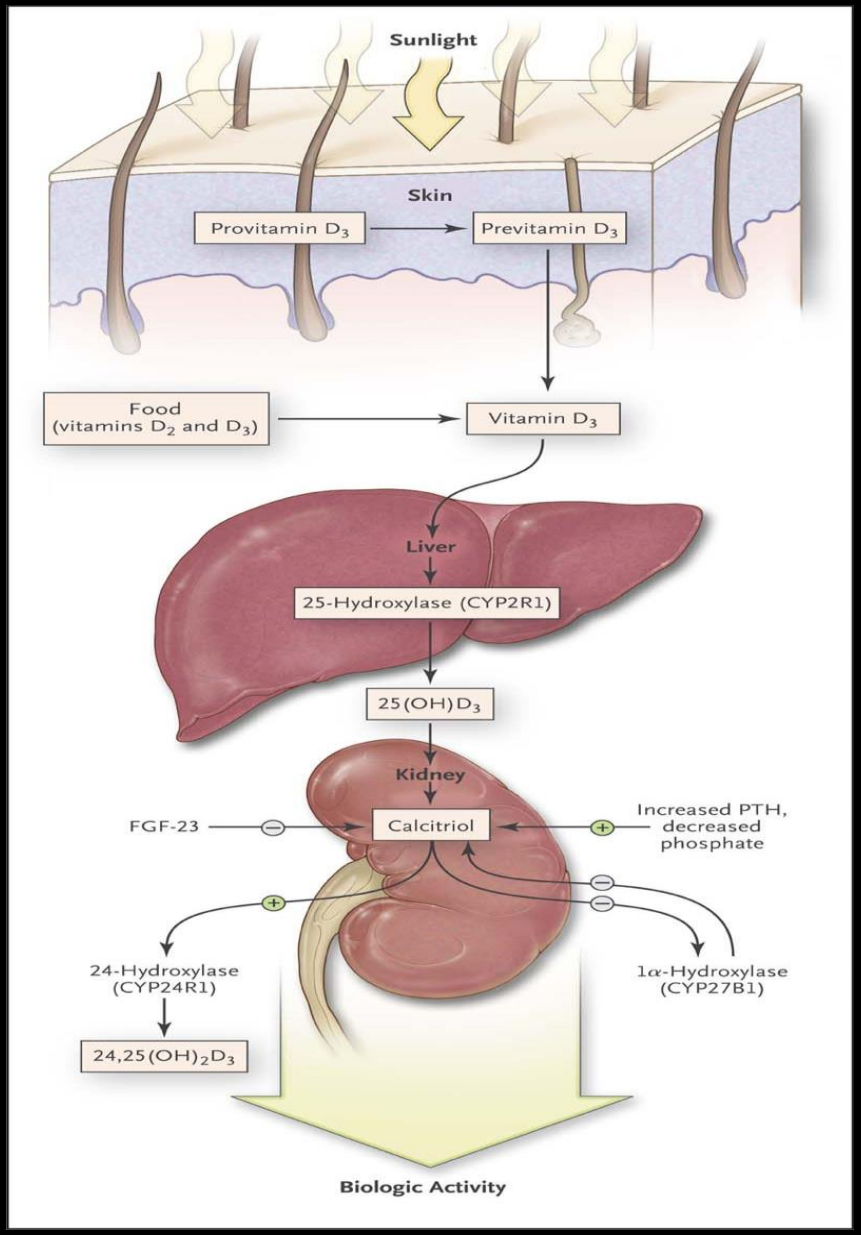
** indicates P<0.01 compared to control
* indicates P<0.05 compared to controls

Jialal I, et al. JCEM:2012

OBESITY AND METABOLIC SYNDROME



Synthesis and Metabolism of Vitamin D.



Rosen CJ. N Engl J Med 2011;364:248-254

The NEW ENGLAND JOURNAL of MEDICINE

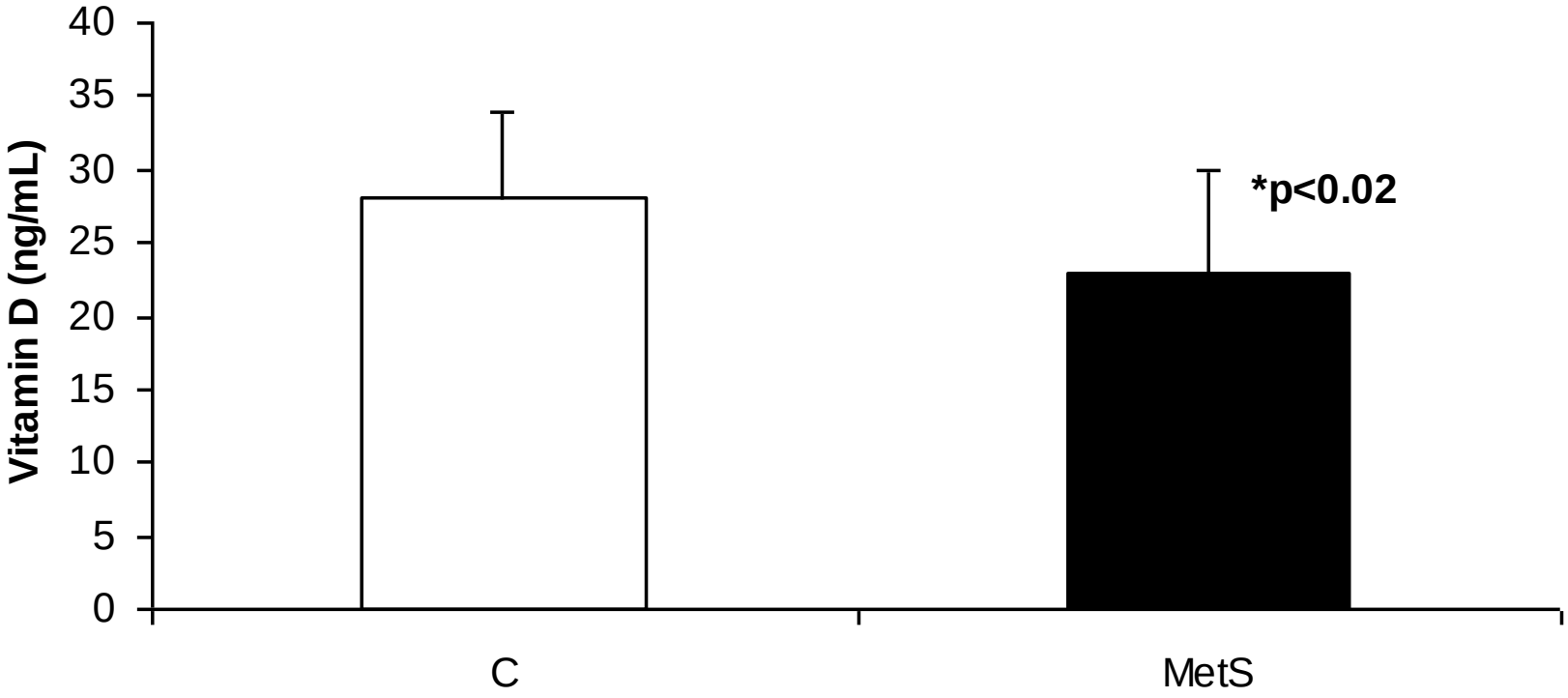
Table 1: Baseline Subject Characteristics

	Controls (n=37)	Met S (n=44)
Age	49 ± 12	50 ± 11
Male/Female Ratio	7M/30F	10M/34F
Waist (in)	36.1 ± 5.6	43.4 ± 5.4*
BMI (kg/sq.m)	30.1 ± 8.3	35.1 ± 6.6*
BP-Systolic (mm Hg)	117.7 ± 12.8	131.147 ± 12.7*
BP-Diastolic (mm Hg)	72.9 ± 8.3	82.5 ± 9.5
Glucose (mg/dL)	88.3 ± 6.5	100.9 ± 11.7*
HDL-Cholesterol (mg/dL)	54.4 ±14.5	40.6 ± 10.4*
Triglycerides (mg/dL)	83.6 ± 46.9	148.8 ± 57.1*
CRP (mg/L)	1.4	3.3*
HOMA	1.3	3.8*
Creatinine (mg/dL)	0.78 ± 0.24	0.82 ± 0.22
Calcium (mg/dL)	8.9 ± 0.3	8.9 ± 0.8
Phosphate (mg/dL)	3.6 ± 0.5	3.5 ± 0.5
Leptin (ng/mL)	47.9 ± 40.1	84.4 ± 47.9**
Adiponectin (ug/mL)	8.7 ± 6.6	6.6 ± 4.1*

Devaraj et al Horm Metab Res 2011

Data are provided as mean ± SD or median for HOMA and CRP.
CRP-C-reactive protein; HOMA-Homeostasis Model Assessment
*p<0.05 compared to Controls and **p<0.01 compared to Controls

25-OHD Levels are Significantly Decreased in MetS compared to Controls



S. Devaraj l et al Horm Metab Res 2011

Summary of Results

- 8% of controls and 30% of MetS adult subjects were deficient in 25 OHD (<20 ng/mL; p=0.0236,

- Also, there were no significant differences between the groups with respect to blood sampling in winter and summer months (Chi-square p=0.47).
- Total calcium and phosphate were similar between groups.
- There were significant correlations of 25 OHD levels with fasting glucose (r=-0.29, p=0.04) and HOMA-insulin resistance (r=-0.34, p=0.04).

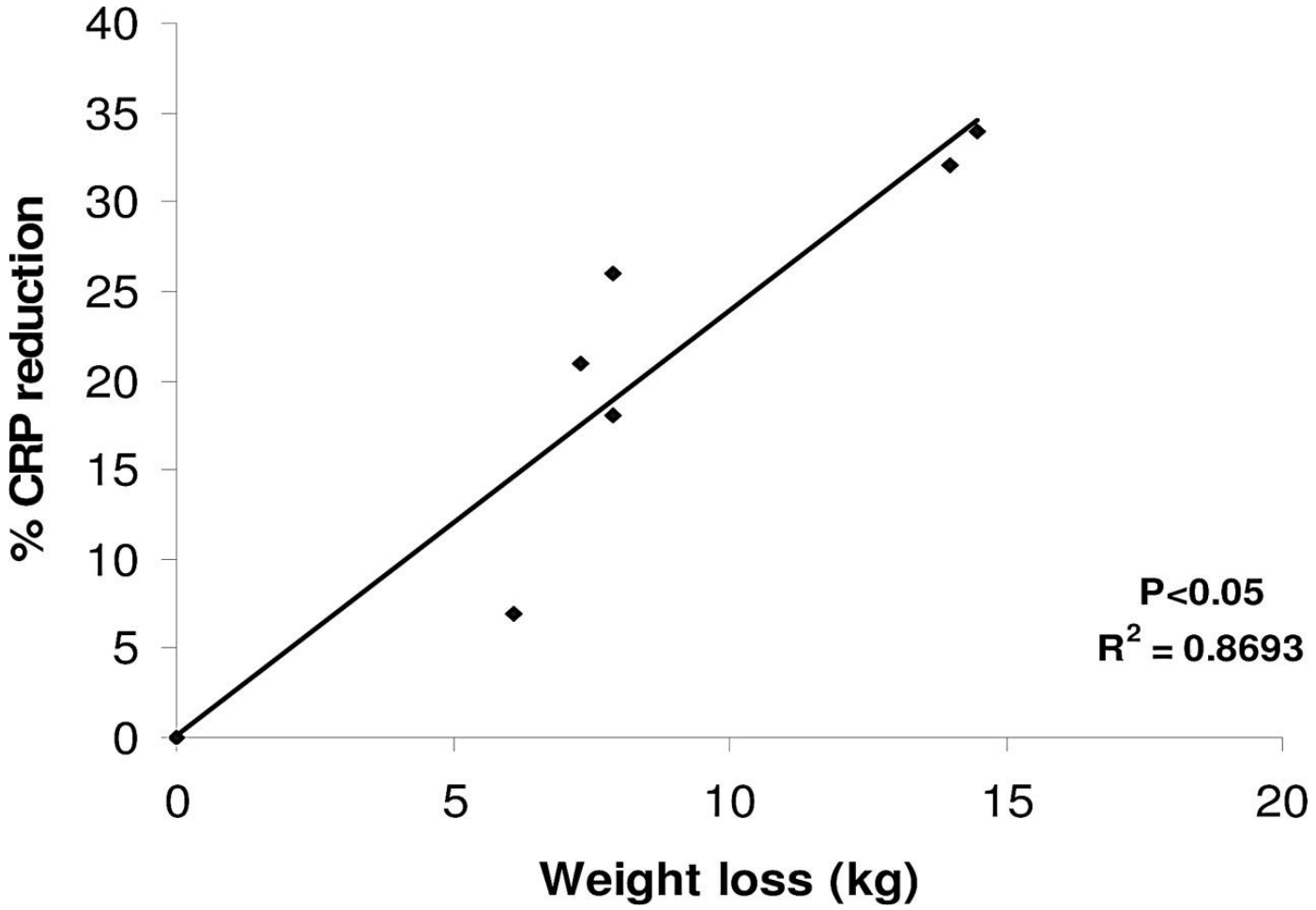
ANTI-INFLAMMATORY STRATEGIES FOR DIABETES

- WEIGHT LOSS (DIET + EXERCISE)
- METFORMIN
- STATINS
- ARBS
- GLITAZONES
- VITAMIN D

Changing Portion Sizes

National Geographic, August 2004

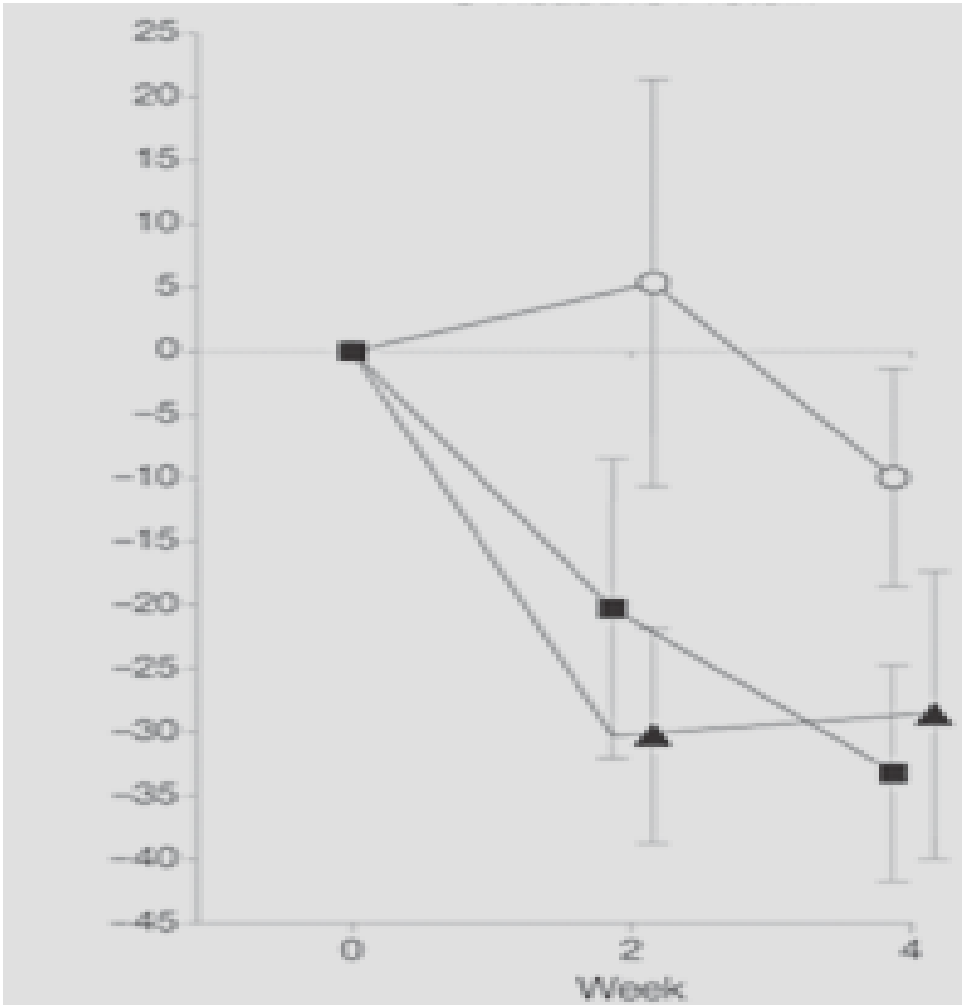
Correlation between weight loss and CRP reduction from intervention trials



Basu, A. et al. Arterioscler Thromb Vasc Biol 2006;26:995-1001

Portfolio Diet and C-Reactive Protein

- n=16 subjects on control diet
- n=14 subjects on statin +control diet
- n=16 subjects on portfolio diet (Low in sat fat, included viscous fiber, almonds, soy protein, plant sterols)
- Duration 4 weeks



Control

Statin

Diet

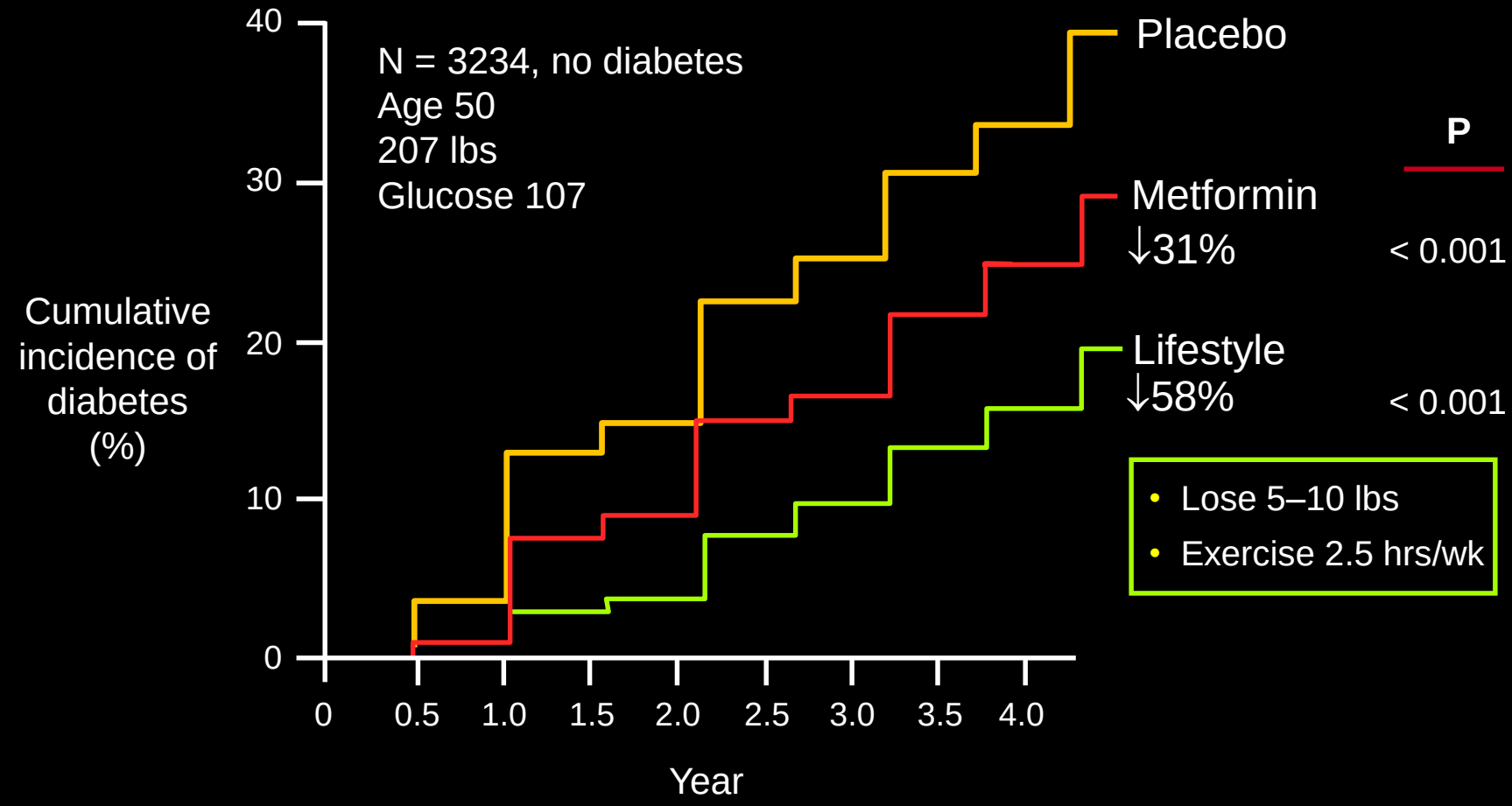
Jenkins, D. J. A. et al. JAMA 2003;290:502-510.

Metabolic Syndrome in the Diabetes Prevention Program

- Randomized controlled trial in participants that had impaired glucose tolerance (WHO criteria plus fasting glucose > 95 mg/dL)
  - Intensive lifestyle intervention (n=1079), to achieve 7% weight loss and 150 minutes exercise per week
  - Metformin (850 mg bid, n=1073)
  - Placebo (n=1082)
- NCEP metabolic syndrome
- 3.2 year follow-up

Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

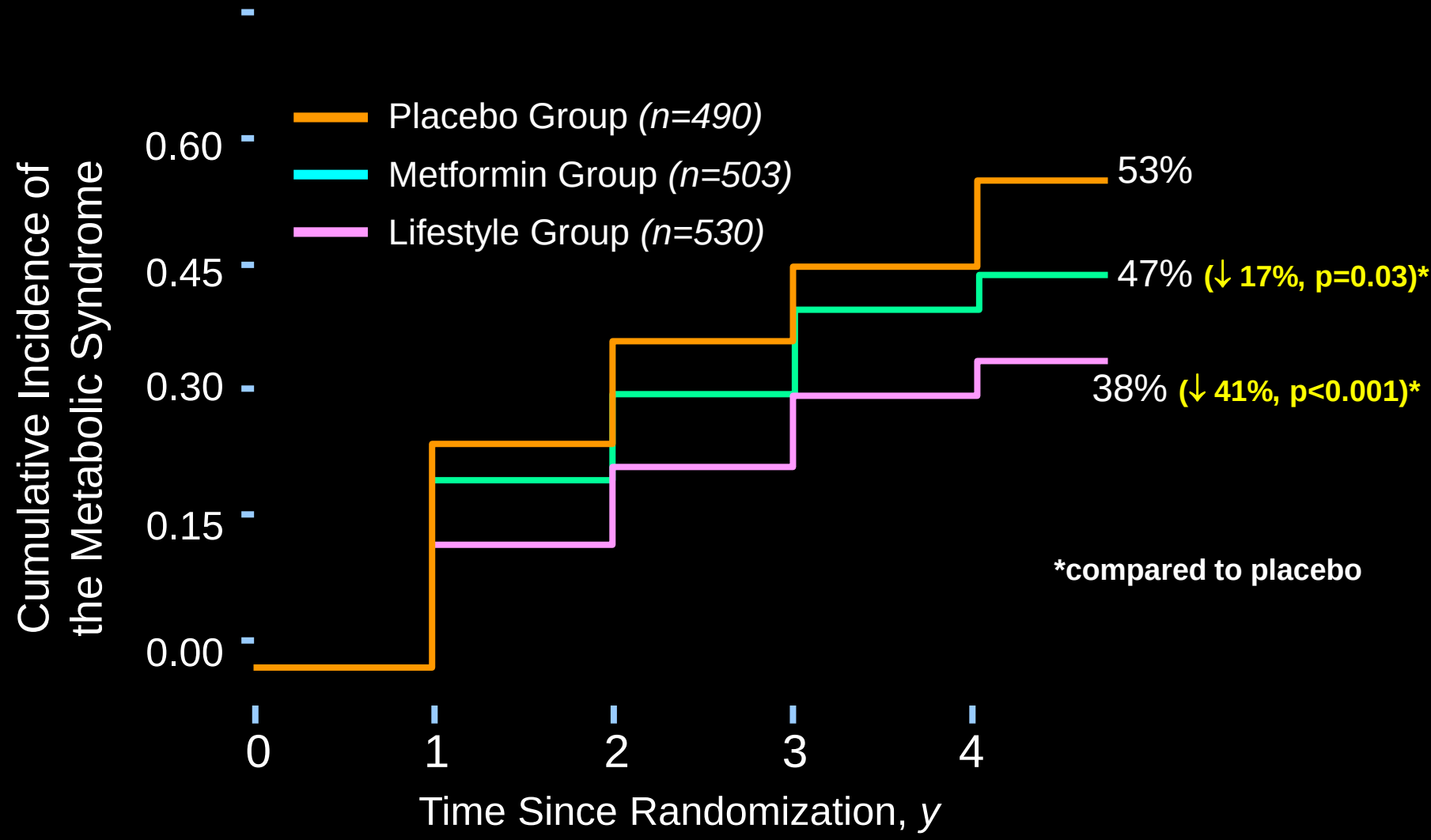
DPP: Impact of lifestyle intervention or metformin on diabetes



DPP = Diabetes Prevention Program

DPP Research Group. *N Engl J Med*. 2002;346:393-403.

Incidence of Metabolic Syndrome among Participants without the Syndrome at Baseline



Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

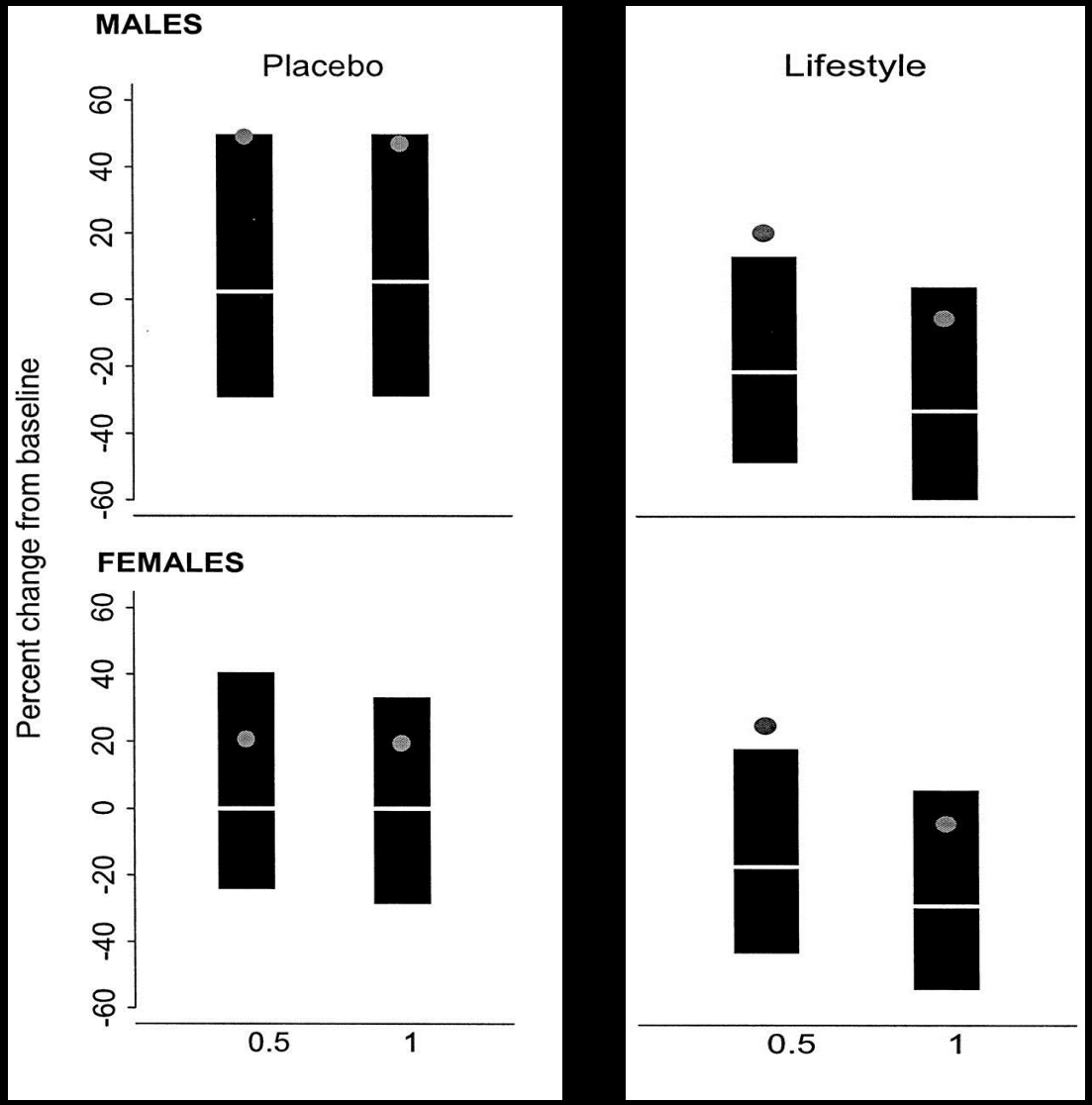
Prevalence of the Metabolic Syndrome in All Participants at 3 Years

	Baseline	Follow-up	P-Value
Placebo	55%	61%	p = 0.003
Metformin	54%	55%	p > 0.2
Lifestyle	51%	43%	p < 0.001

Orchard TJ, et al. Ann Intern Med, 2005; 142:611-619.

Intensive Lifestyle Intervention and Inflammation-DPP

HsCRP



*p<0.001 for intensive lifestyle vs placebo for men and women at 6 months and 1 yr

Years

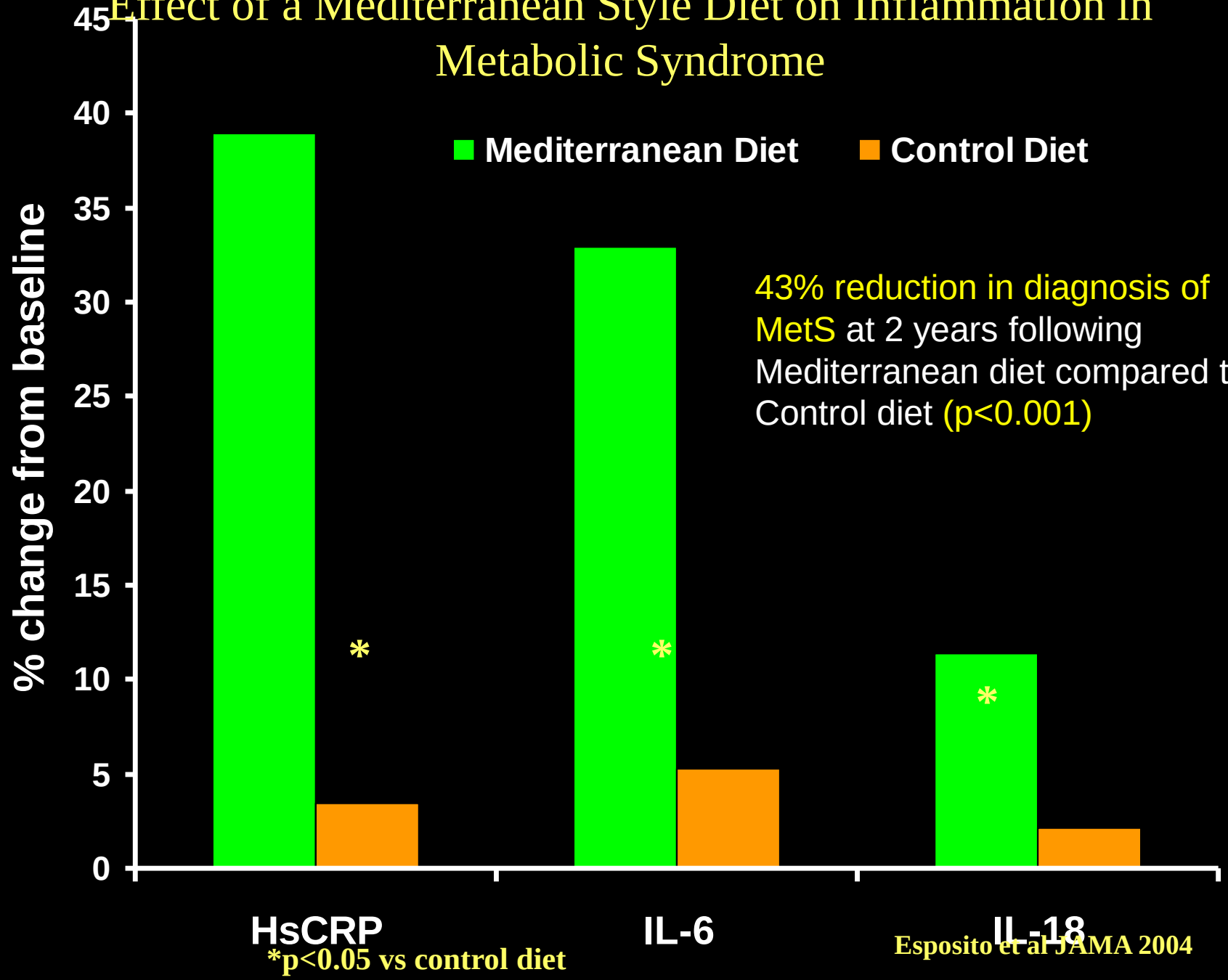
Haffner et al Diabetes 2005

Effect of a Mediterranean Style Diet on Inflammation in Metabolic Syndrome

- Randomized single blind trial in 180 patients with ATP-III defined MetS
- n=90/group on conventional or Mediterranean style diet for 2 years
- Mediterranean Diet:
  - **Carbohydrate 50-60%**
  - **Proteins 15-20%**
  - **Total Fat <30%**
  - **Saturated Fat <10%**
  - **Cholesterol <300 mg/day**
  - **Fruits 250-300 g**
  - **Vegetables 125-150 g vegetables**
  - **Walnuts 25-50 g**
  - **Whole grains 400g**
  - **Increase olive oil consumption**

Esposito et al JAMA 2004

Effect of a Mediterranean Style Diet on Inflammation in Metabolic Syndrome



*p<0.05 vs control diet

Esposito et al JAMA 2004

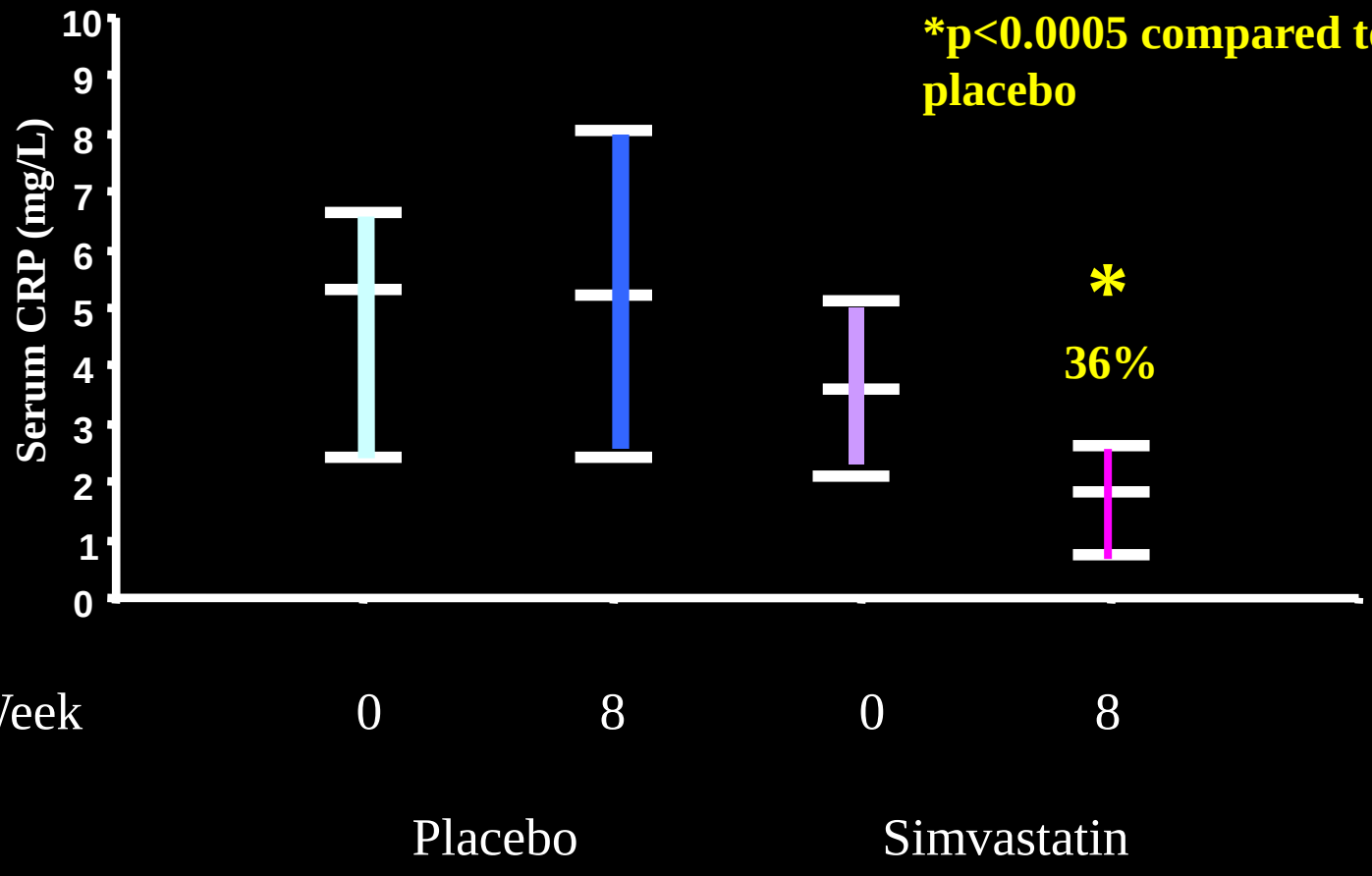
Simvastatin therapy in Metabolic Syndrome

Compared to placebo, Simvastatin therapy (40mg/d) resulted in :

- **32% reduction in LDL-Cholesterol (117 to 99 mg/dL, p<0.005)**
- **42% reduction in non-HDL cholesterol (135 to 121 mg/dL, p<0.005)**
- **36% reduction in hsCRP (1.3 to 0.9 mg/L, p<0.005)**

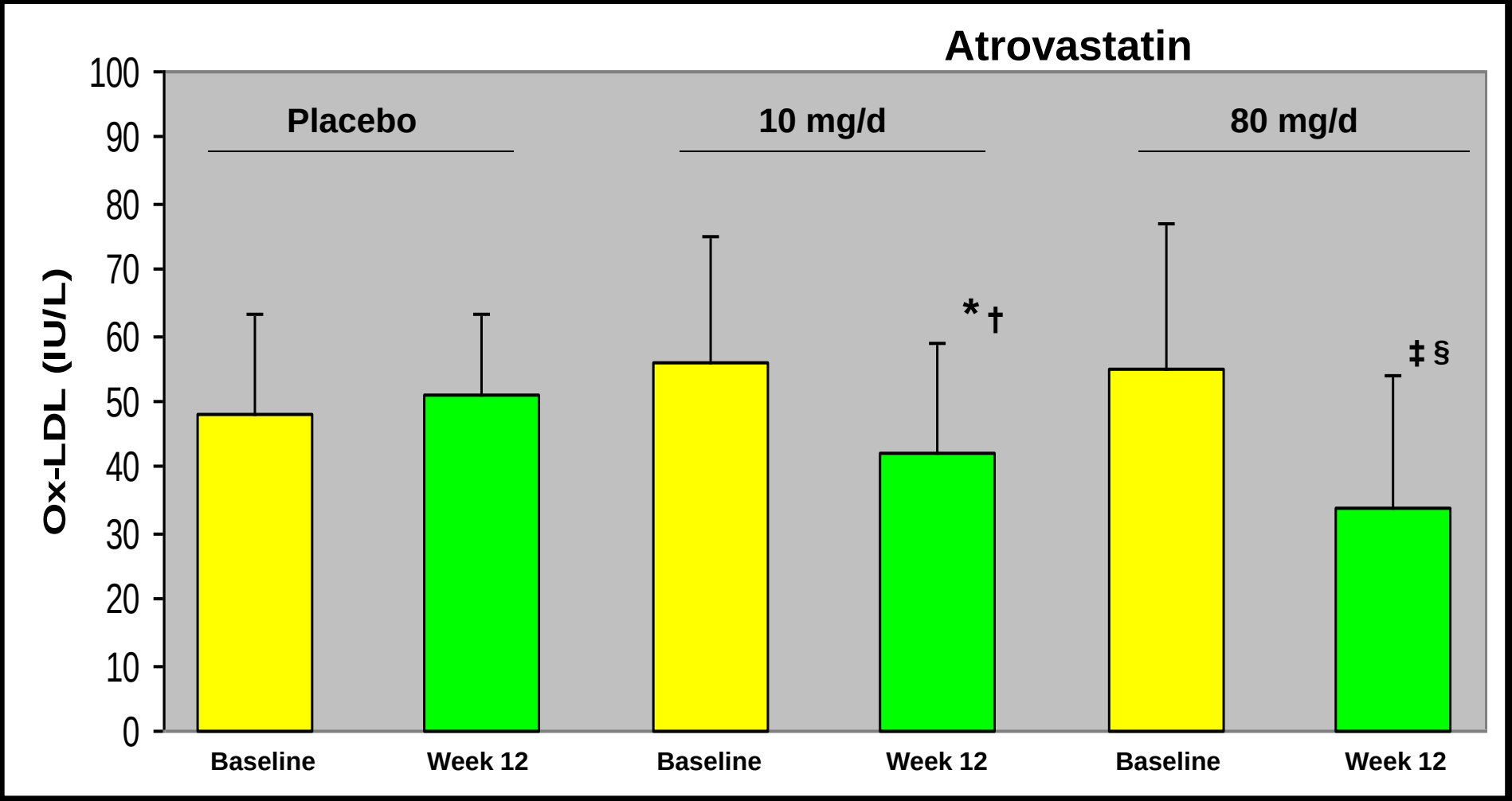
Devaraj et al JCEM 2006

Effect of Simvastatin on CRP in Patients with the Metabolic Syndrome



Devaraj , Chan, Jialal, JCEM 2006

Atorvastatin Therapy: Effect on Ox-LDL



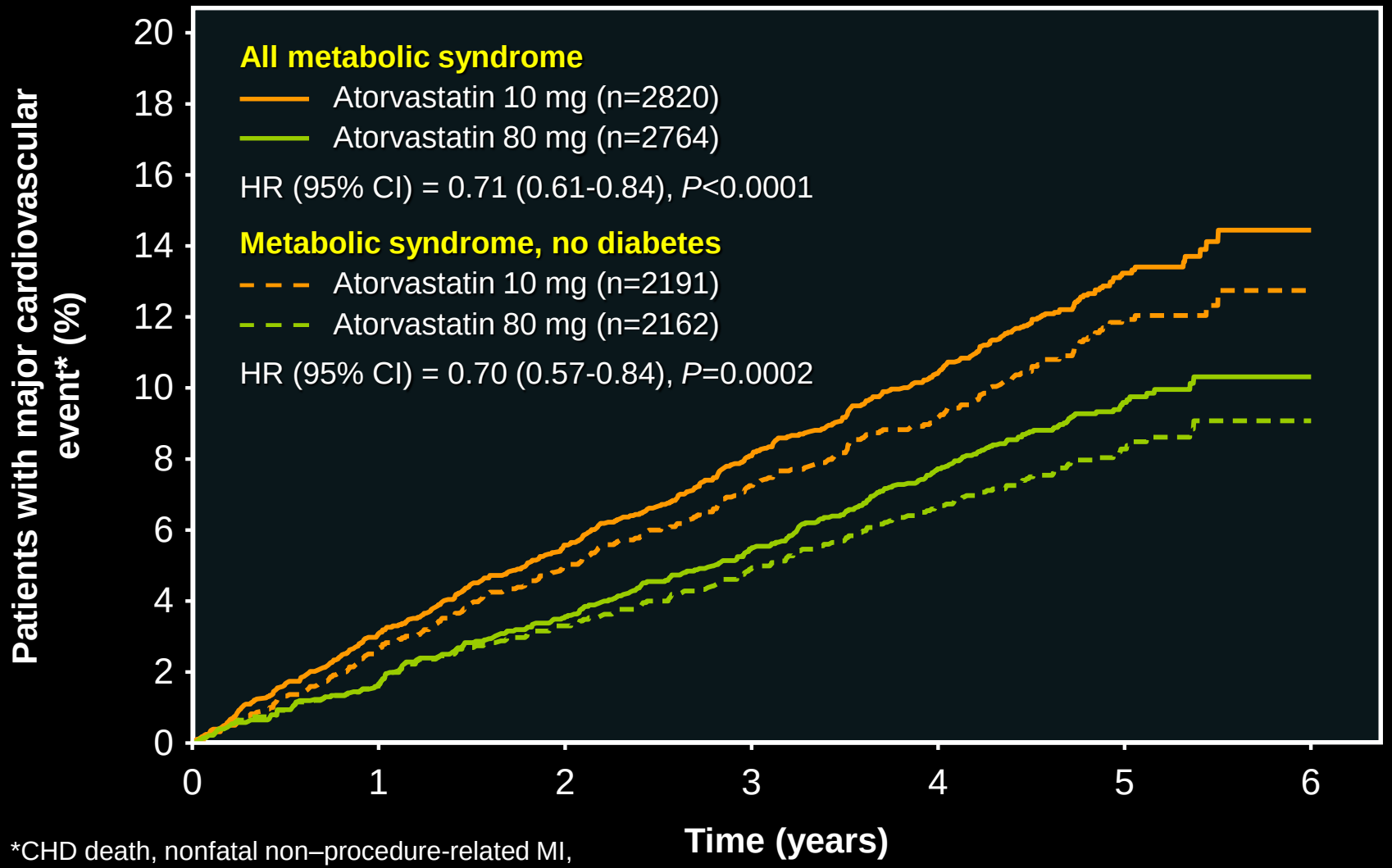
* p < 0.02 compared with baseline
† p = 0.044 compared with placebo
‡ p < 0.001 compared with baseline and placebo
Singh et al 2010,AJC

Time to First Major Cardiovascular Event in Patients With Metabolic Syndrome

- Prospective double-blind, parallel group trial
- 10,001 patients , aged 35-75 yrs with clinically evident CAD
- 5584 patients with MetS based on NCEP ATPIII
- Randomized to
  - -Atorvastatin 10 mg/d (n=2820)
  - -Atorvastatin 80 mg/d (n=2764)
- Median follow-up of 4.9 yrs
- Primary outcome-Time to first major cardiovascular event

Deedwania P, et al. *Lancet.* 2006;368:919-28

Time to First Major Cardiovascular Event in Metabolic Syndrome Patients Without Diabetes



*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke

Deedwania P, et al. *Lancet.* 2006;368:919-28

JUPITER STUDY

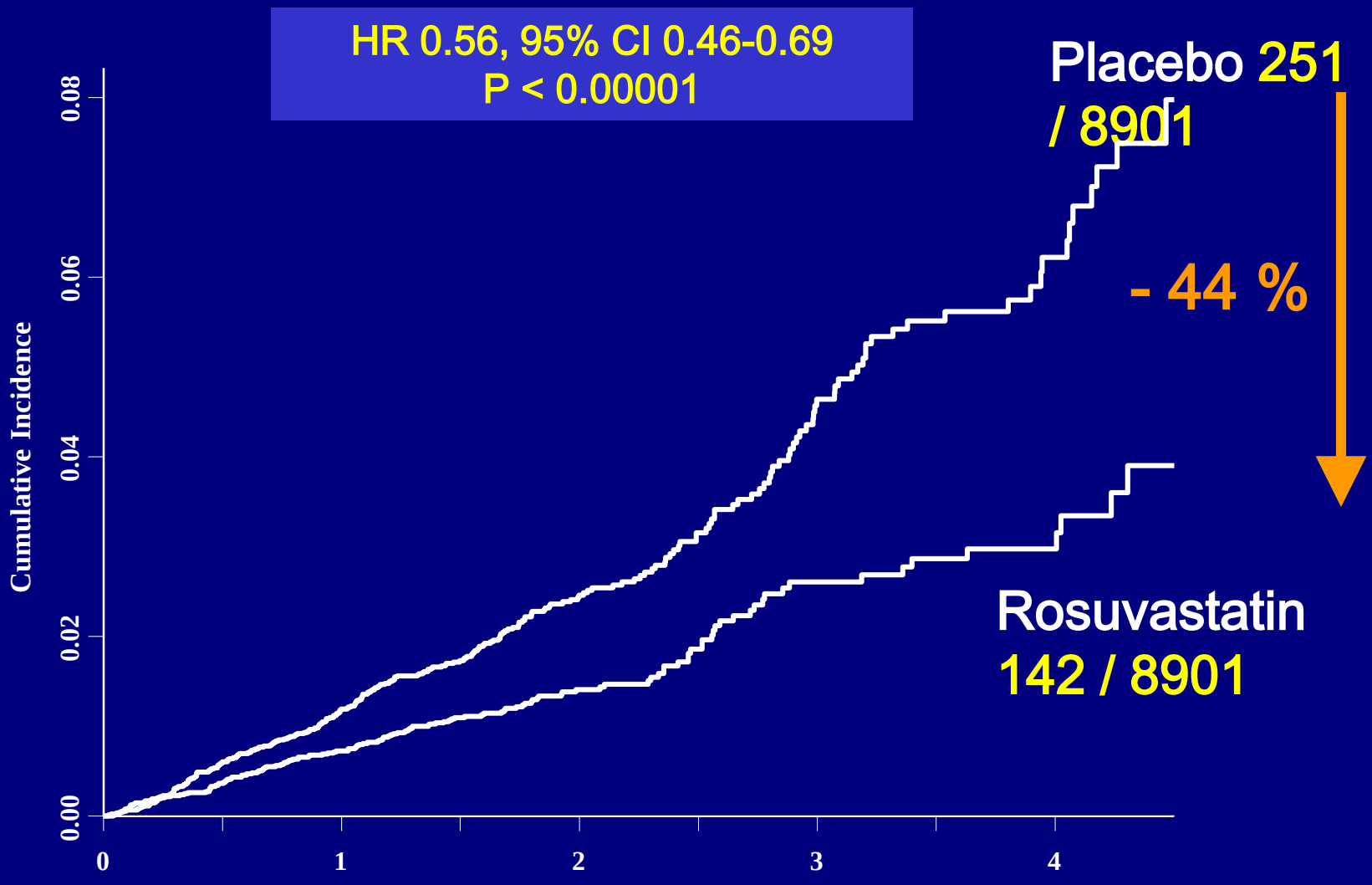
- Primary Prevention study conducted in 26 countries
- Rosuvastatin (20 mg/d) vs Placebo
- Inclusion Criteria; LDL < 130 mg/dL
  & CRP ≥ 2.0 mg/L
- Primary Endpoint: CV Death, MI, stroke, unstable angina, arterial revascularization
- 17,802 recruited (median LDL 108 mg/dL)

Ridker et al AJC

JUPITER

Ridker et al NEJM 2008

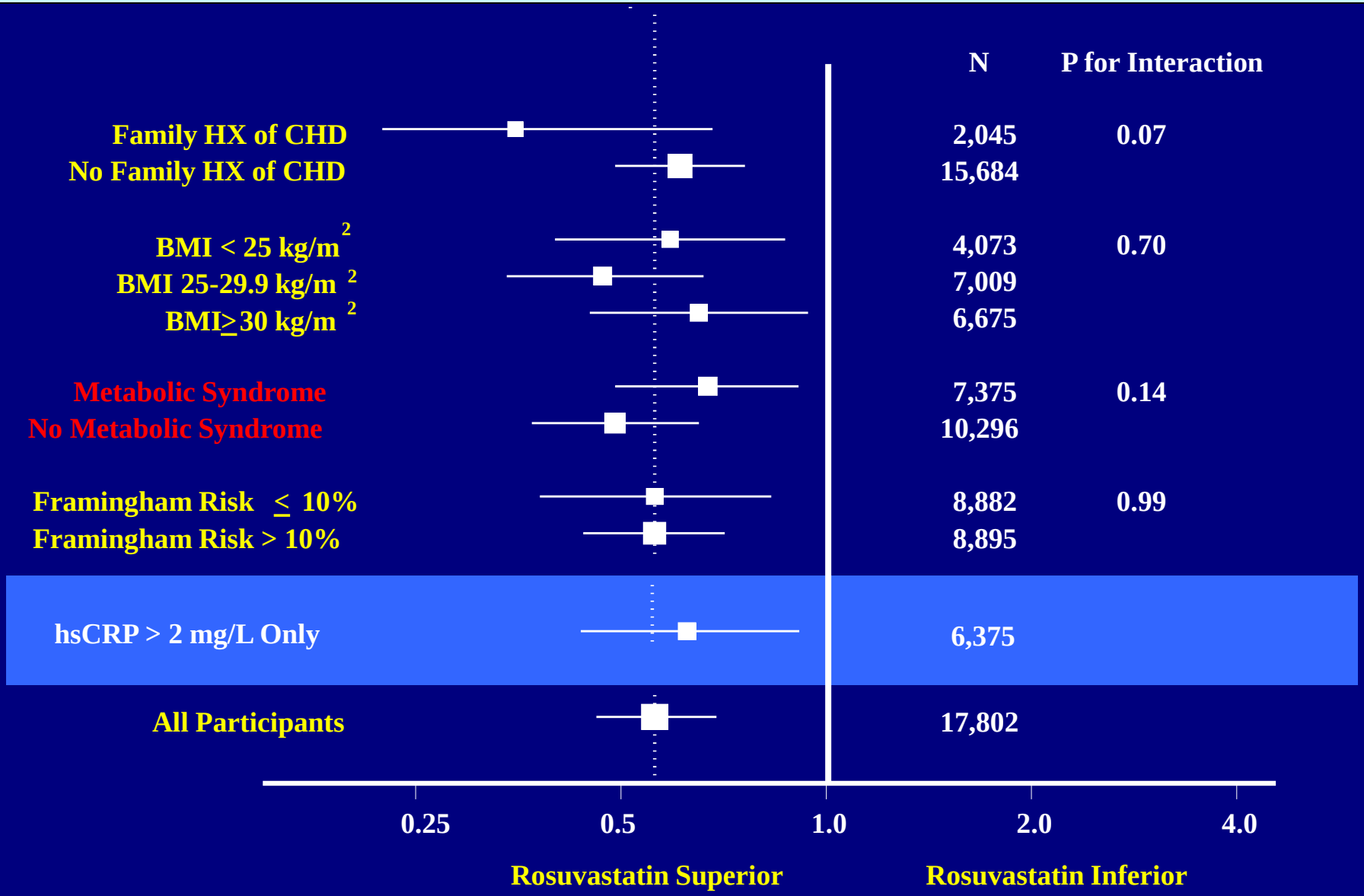
Primary Trial Endpoint：MI, Stroke, UA/Revascularization, CV Death



Number at Risk										
Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	544	157
Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	534	174

JUPITER
Primary Endpoint – Subgroup Analysis II

Ridker et al NEJM 2008



Summary

- **LDL-C: primary target of lipid lowering therapy**
- **VLDL-C: secondary target**
  - **In practice, use non-HDL-C as secondary target**

    LDL-C GOAL PLUS 30 mg/dl
- **HDL-C: tertiary target**
  - **Benefit of HDL-raising therapies not proven**

Effect of Pioglitazone on Biomarkers of Inflammation in Metabolic Syndrome

- n = 60
- Duration 12 weeks
- Pioglitazone (PIO) 45 mg/d or Placebo
- Results:
  - PIO ↓median hsCRP by 31% (P < 0.001)
    ↓resistin by 10% (P = 0.02)
    ↑adiponectin by 111% (P < 0.001)

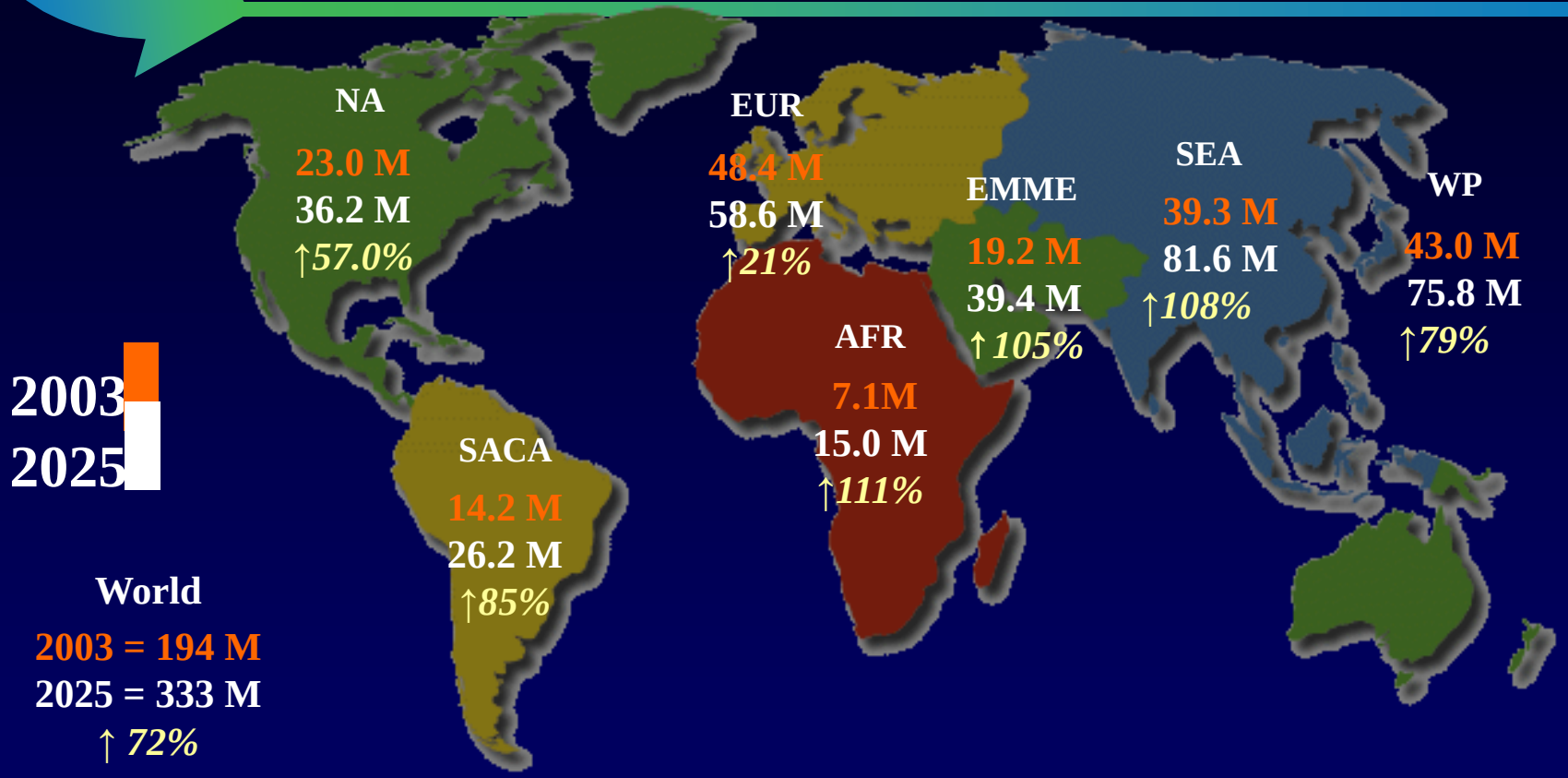
Szapary et al. Arterioscler Thromb Vasc Biol. 2006

Candidate Pharmacotherapies for Metabolic Syndrome

- 11 beta-hydroxy steroid dehydrogenase 1 Inhibition
- AMP kinase activation
- Anti-Inflammatory Therapies -anti-IL1therapy etc

SAFETY AND EFFICACY

Global Projections for the Diabetes Epidemic: 2003-2025



M = million, AFR = Africa, NA = North America, EUR = Europe, SACA = South and Central America, EMME = Eastern Mediterranean and Middle East, SEA = South-East Asia, WP = Western Pacific

Diabetes Atlas Committee. *Diabetes Atlas.* 2nd Edition: IDF 2003.