ΠΕΤΡΟΣ Γ.ΚΑΛΟΓΕΡΟΠΟΥΛΟΣ
ΚΑΡΔΙΟΛΟΓΟΣ

# ΙΑΤΡΕΙΟ ΥΠΕΡΤΑΣΗΣ 7ον ΝΟΣΟΚΟΜΕΙΟ ΙΚΑ

ΕΚΕ ΟΜΑΔΕΣ ΕΡΓΑΣΙΑΣ ΘΕΣΣΑΛΟΝΙΚΗ 2/2010

# ΓΙΑΤΙ ΧΡΗΖΕΙ ΑΞΙΟΛΟΓΗΣΗΣ Ο ΣΥΝΟΛΙΚΟΣ ΚΙΝΔΥΝΟΣ

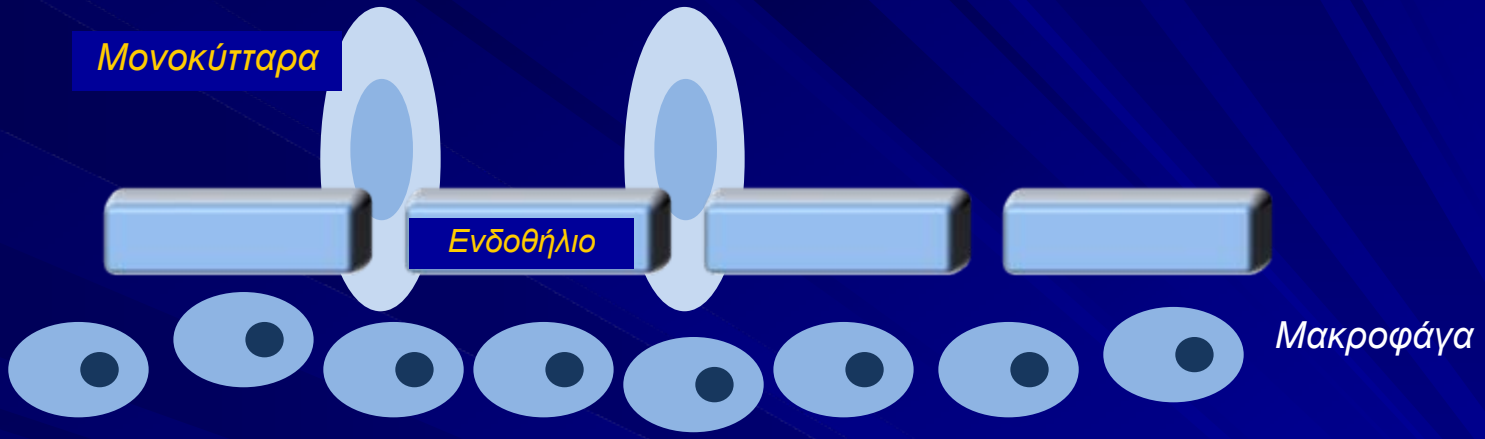
- Τα καρδιοαγγειακά νοσήματα (ΚΑΝ) είναι κύρια αιτία θνητότητας και νοσηρότητας στις δυτικές βιομηχανικές χώρες .Η φροντίδα ασθενών που έχουν υποστεί μη θανατηφόρα ΑΕΕ και καρδιακές προσβολές καταναλώνει σημαντικο μέρος των δαπανών της δημόσιας υγείας και φέρει σοβαρό πλήγμα στην ποιότητα ζωης τόσο των ασθενών όσο και των συγγενών αυτών

# ΠΑΡΑΓΟΝΤΕΣ ΚΙΝΔΥΝΟΥ ΚΛΑΣΙΚΟΙ ΚΑΙ ΝΕΩΤΕΡΟΙ

Υπέρταση Δυσλιπιδαιμία Διαβήτης RAAS
Καρ. Συχνότητα
Κάπνισμα Παχυσαρκία SNS Υπερομοκυστεϊναιμία
CRP Ουρικό οξύ

*ΔΥΣΛΕΙΤΟΥΡΓΙΑ ΕΝΔΟΘΗΛΙΟΥ*

# ΔΥΣΛΕΙΤΟΥΡΓΙΑ ΕΝΔΟΘΗΛΙΟΥ




↑ Ενδοθηλιακή Διαπερατότητα
↑ Επαφή LP με αγγειακό τοίχωμα
↑ Προσκόλληση στο ενδοθήλιο
↑ Αύξηση παραγωγής $O^{\cdot}_2$ (Ελ. Ρίζες)
↑ Κυτταροκίνες

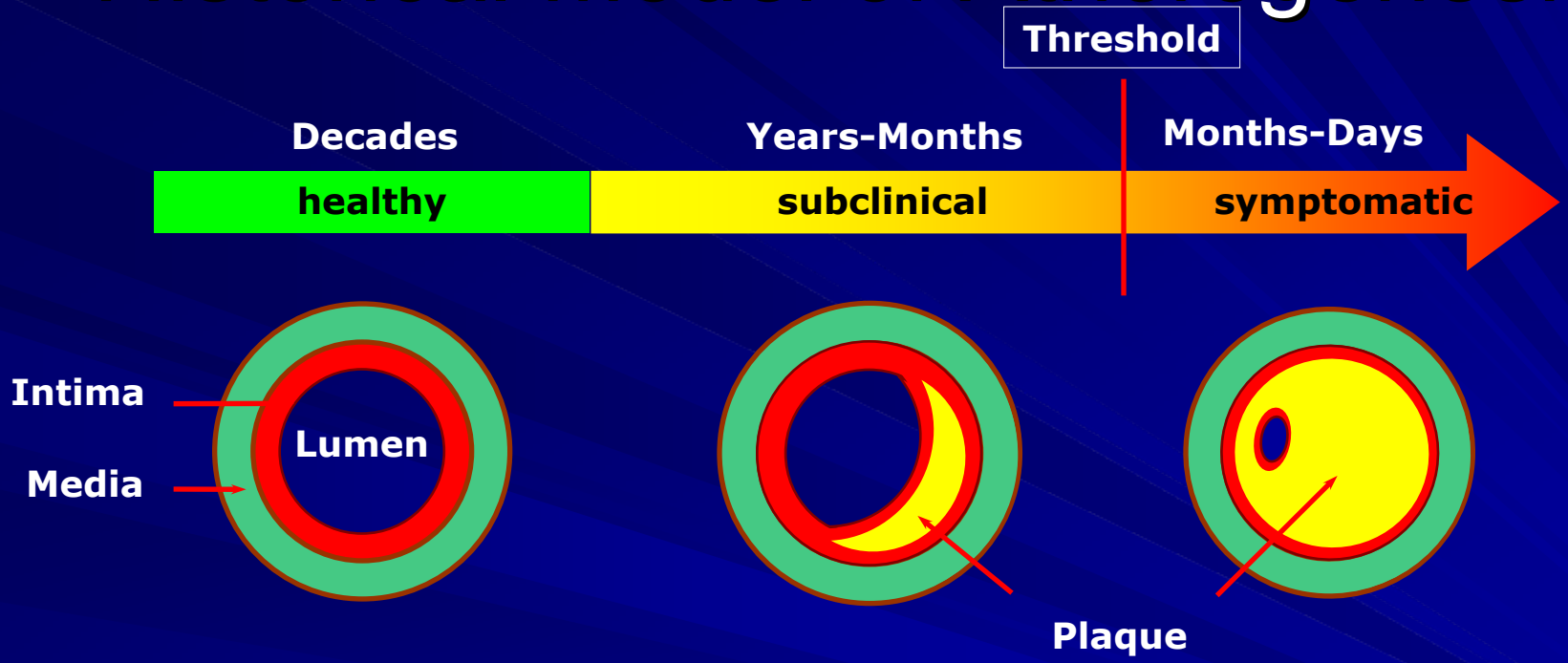
↑ Πρόσληψη οξειδωμένης LDL
↑ Ιστικός Παράγων
↑ PAI-1
↑ ICAN, VCAM
↑ MCP-1

↓ eNOS
↓ Προστακυκλίνη
↑ Κατεχολαμίνες
↑ Αγγειοτασίνη ΙΙ
↑ Πολλαπλασιασμός ΛΜΙ

*Αγγειοσύσπαση* *Κυτταρική Προσκόλληση και/ ή διήθηση* *Πολλαπλασιασμός* *Συσσώρευση Λιπιδίων*

*Ισχαιμική Καρδιοπάθεια* *Εγκεφαλική Αγγειακή Νόσος* *Περιφερειακή Αγγειοπάθεια*

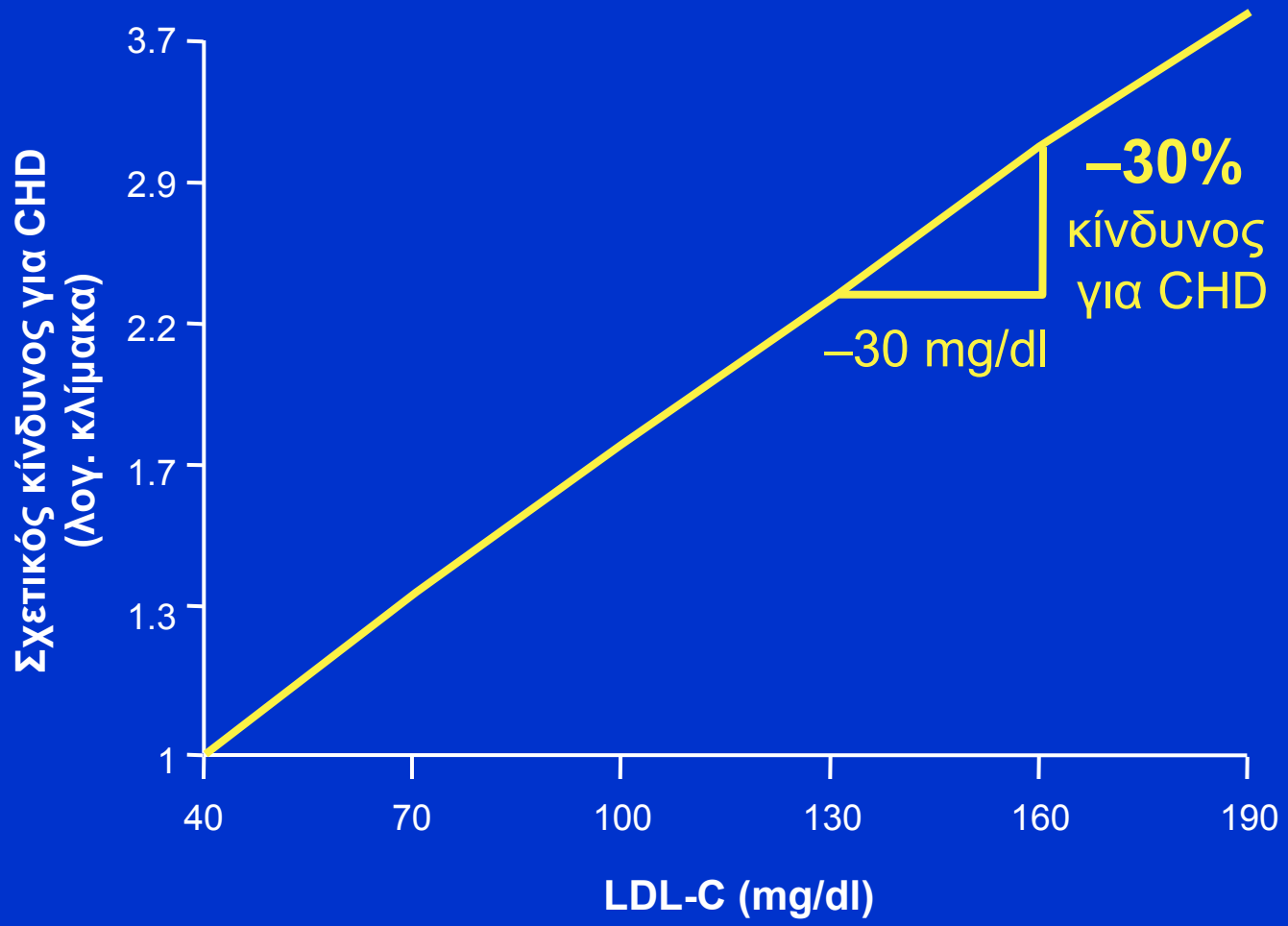
# Historical Model of Atherogenesis




- Stable angina
- Stable plaques with narrowing
- Simple diagnostic (ECG, angiography)
- Rare MI
- Easy to treat

Antischkow N. *Beitr Path Anat Allg Path* 1913;56:379-404.

# Η μείωση της LDL-C μειώνει τον κίνδυνο για Σ.Ν.




Τροποποιημένο από Grundy SM et al *Circulation* 2004;110:227–239.

**Slide Source**
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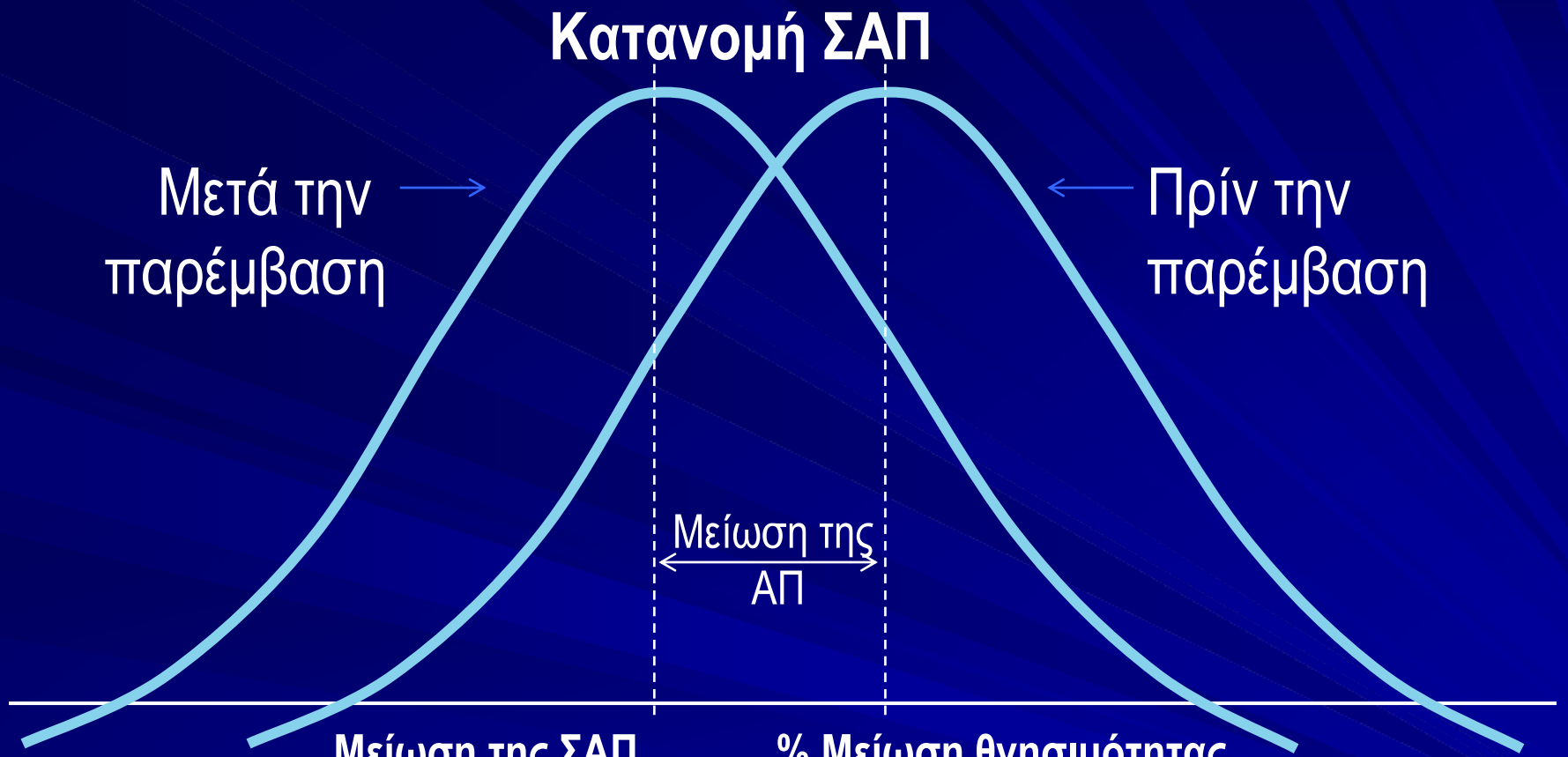
# JNC 7 Κατανομή ΣΑΠ Population based strategy




| Μείωση της ΣΑΠ mmHg | % Μείωση θνησιμότητας Εγκεφαλικά | ΣΝ | Σύνολο |
|---|---|---|---|
| 2 | –6 | –4 | –3 |
| 3 | –8 | –5 | –4 |
| 5 | –14 | – 9 | –7 |

National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program JNC 7

# ΕΡΩΤΗΜΑ ?

ΜΕΙΩΣΗ ΤΩΝ ΕΠΙΠΕΔΩΝ ΤΗΣ CRP ΑΠΟΤΡΕΠΕΙ ΤΑ ΚΑΡΔΙΟΑΓΓΕΙΑΚΑ ΣΥΜΒΑΜΑΤΑ ?

ΟΧΙ

Ann Inter Med. 2009 Oct 6;151(7):1-38

# AHA/CDC Panel: Recommendations for Use of hs-CRP in Clinical Practice

- hs-CRP independent marker of CVD risk
- Patients at intermediate risk (10–20% risk of CHD per 10 years):
  - hs-CRP may help direct further evaluation, therapy in primary prevention
- Patients with stable coronary disease, acute coronary syndromes:
  - hs-CRP measurement may be useful as independent marker of prognosis for recurrent events

Pearson TA et al. *Circulation* 2003;107:499-511.

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# AHA/CDC Panel: Recommendations for hs-CRP Laboratory Testing

- **Measurements of hs-CRP:**
  - Should be performed twice (2 weeks apart)
  - Results averaged, expressed as mg/L
  - Fasting or nonfasting, in metabolically stable patients
  - If level >10 mg/L, test should be repeated, patient examined for sources of infection or inflammation
- **Relative risk categories for hs-CRP levels:**
  - Low <1 mg/L
  - Average 1–3 mg/L
  - High >3 mg/L

Pearson TA et al. *Circulation* 2003;107:499-511.

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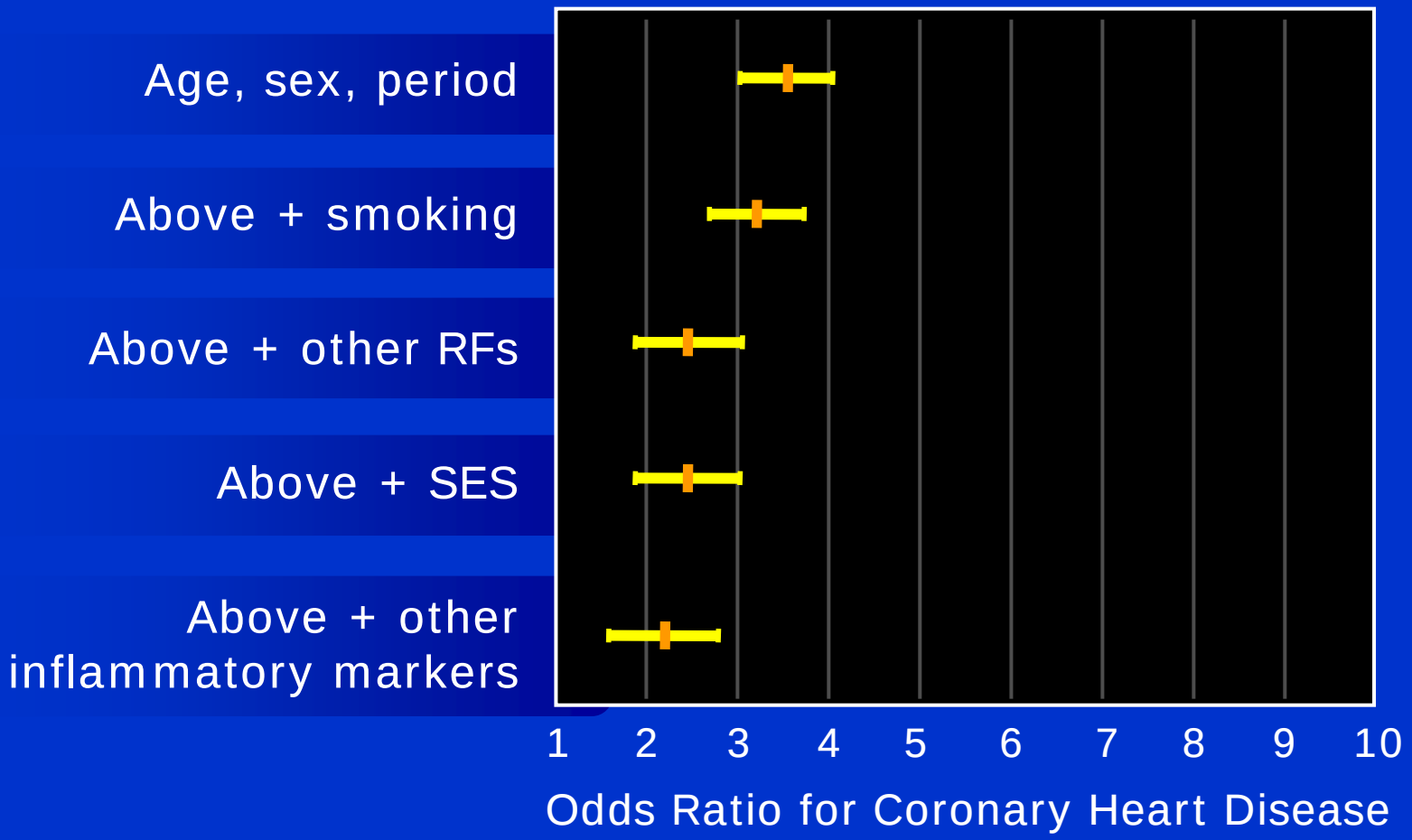
# Relative Odds of CHD for C-Reactive Protein (Top vs Bottom Tertile): Reykjavik, Iceland




Danesh J et al. *N Engl J Med* 2004;350:1387-1397. Copyright 1999 Massachusetts Medical Society. All rights reserved.

**Slide Source**
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# hs-CRP and CHD Relative Risk: Nurses' Health Study—Women

| | hs-CRP (mg/L) | | |
|---|---|---|---|
| | <1.0 | 1.0–2.9 | ≥3.0 |
| Model 1* | 1.0 | 1.22 (0.77–1.93) | 1.93 (1.25–2.99) |
| Model 2† | 1.0 | 1.21 (0.75–1.96) | 1.94 (1.21–3.10) |
| Model 3 (Model 2 + BMI) | 1.0 | 1.16 (0.71–1.90) | 1.71 (1.04–2.80) |
| Model 4 (Model 3 + TC/HDL-C) | 1.0 | 1.09 (0.66–1.82) | 1.64 (0.98–2.75) |
| Model 5 (Model 4 + DM + HTN) | 1.0 | 1.17 (0.69–2.00) | 1.53 (0.89–2.62) |

* Adjusted for age, smoking status, month of blood sampling, and fasting status

† Also adjusted for parental history of CHD before age 60, alcohol intake, physical activity, and use or nonuse of hormone therapy among postmenopausal women

Pai JK et al. *N Engl J Med* 2004;351:2599-2610. Copyright 2004 Massachusetts Medical Society. All rights reserved.

**Slide Source**
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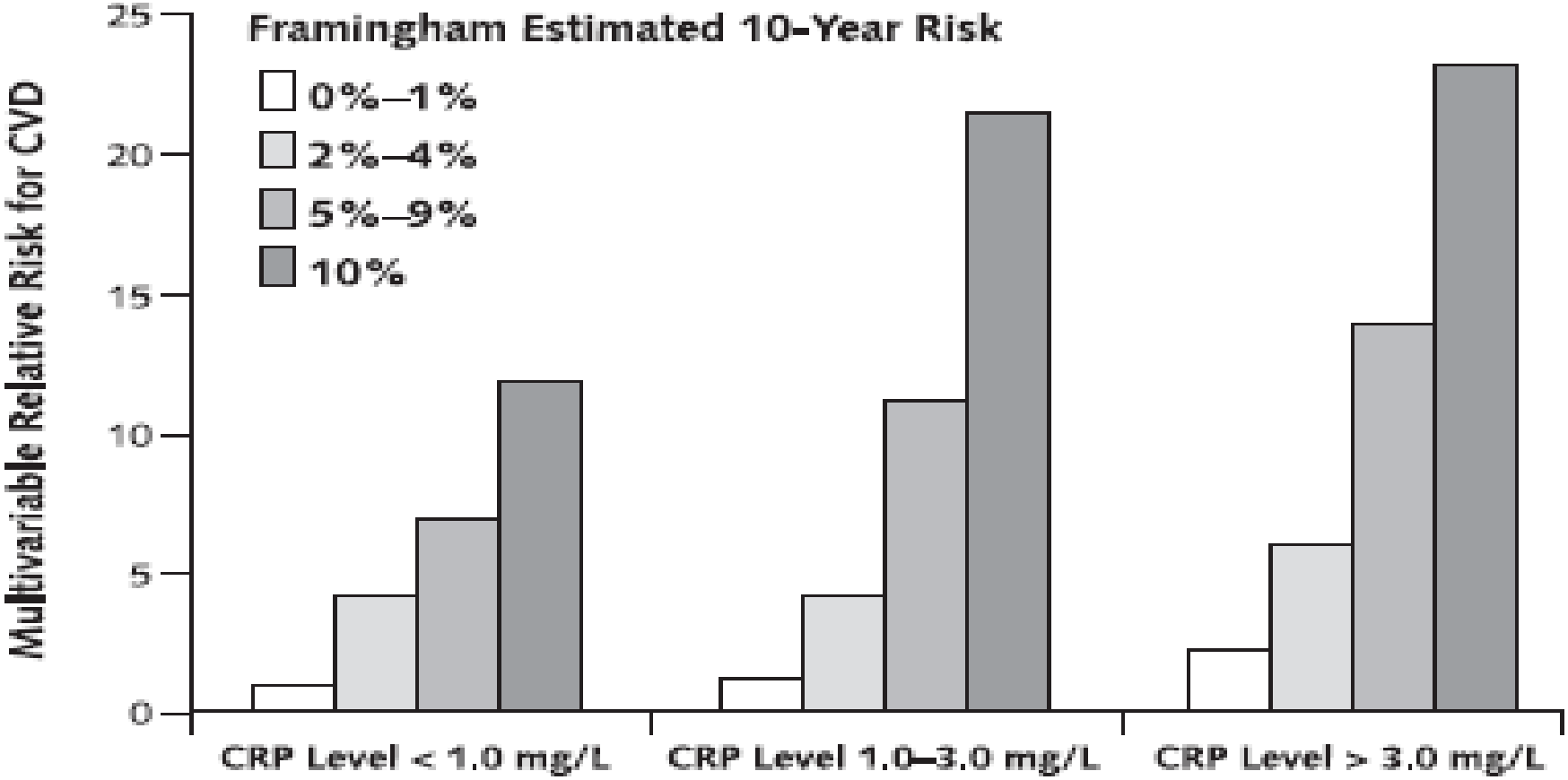
www.lipidsonline.org

*Figure.* **Multivariable relative risk for cardiovascular disease (*CVD*), based on level of C-reactive protein (*CRP*) and level of absolute predicted 10-year Framingham coronary heart disease risk in the Women's Health Study.**




Data are from reference 38.

# hs-CRP and CHD Risk: ARIC Study

| | hs-CRP Level (mg/L) | |
|---|---|---|
| | Average Risk 1.0–3.0 | High Risk >3.0 |
| Model 1* | 1.61 (1.21–2.16) | 2.53 (1.88–3.40) |
| Model 2† | 1.31 (0.96–1.80) | 1.72 (1.24–2.39) |
| Model 3† (LDL-C <130 mg/dl)‡ | 1.18 (0.71–1.96) | 1.76 (1.01–3.03) |

*Adjusted for age, sex, and race

†Adjusted for age, sex, race, smoking, systolic BP, LDL-C, HDL-C, and diabetes

‡204 cases and 369 noncases

Ballantyne CM et al. *Circulation* 2004;109:837-842.

**Slide Source**
Lipids Online Slide Library
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**Table 1. Cohort Mean and Hazard Rate Ratios for Incident Coronary Heart Disease Within 5 Years per 1-SD Increment for Single Novel Risk Factors From Case-Cohort Studies in the ARIC Study***

| | | Age Adjusted | | Adjusted for Traditional Risk Factors | |
|---|---|---|---|---|---|
| Novel Risk Factor | Mean (SD)† | Hazard Rate Ratio‡ | *P* Value | Hazard Rate Ratio§ | *P* Value |
| CRP, mg/L | 3.08 (3.34) | 1.20 | <.01 | 1.17 | .01 |
| log CRP, mg/L | 1.14 (0.70) | 1.28 | <.01 | 1.19 | <.01 |
| $LpPLA_2$, µg/L | 0.37 (0.13) | 1.49 | <.01 | 1.17 | .02 |
| log IL-6, pg/mL | 1.63 (0.60) | 1.32 | <.01 | 1.28 | .03 |
| log TIMP-1, ng/mL | 6.71 (0.25) | 1.36 | <.01 | 1.24 | .13 |
| MMP-1 ≥1.7, ng/mL | | 1.18 | .45 | 0.98 | .95 |
| ICAM-1, ng/mL | 242 (93.2) | 1.32 | <.01 | 1.40 | <.01 |
| E-selectin, ng/mL | 42.2 (26.9) | 1.12 | .05 | 1.05 | .58 |
| log D-dimer, ng/mL | 5.70 (0.66) | 1.07 | .33 | 1.36 | <.01 |
| log PAI-1, ng/mL | 2.52 (0.96) | 1.36 | <.01 | 0.97 | .80 |
| tPA, ng/mL | 8.86 (4.82) | 1.37 | <.01 | 1.02 | .89 |
| Plasminogen, % | 110 (19) | 1.09 | .25 | 1.16 | .17 |
| Soluble thrombomodulin, ng/mL | 41.8 (24.5) | 0.86 | .13 | 0.65 | .02 |
| log leptin, ng/mL | 2.09 (0.98) | 0.81 | <.01 | 0.99 | .91 |
| Homocysteine, µmol/L | 9.23 (4.29) | 1.23 | <.01 | 1.03 | .73 |
| log folate, nmol/L | 2.04 (0.85) | 0.81 | .03 | 0.91 | .51 |
| log vitamin $B_6$, nmol/L | 3.51 (1.03) | 0.73 | <.01 | 0.73 | <.01 |
| Prevalence, % | | | | | |
| Chlamydia (IgG positive) | 55 | 1.57 | .01 | 0.90 | .67 |
| CMV antibody (positive) | 70 | 1.27 | .24 | 1.38 | .26 |
| HSV-1 antibody (positive) | 75 | 0.95 | .82 | 0.76 | .36 |

**Table 2. AUCs for Incident Coronary Heart Disease Within 5 Years for a Basic Risk Factor Model Compared With the Basic Model With a Novel Risk Factor From Case-Cohort Studies in the ARIC Study**

| | AUC at 5 Years | | | No. of Case-Cohort Subjects | |
|---|---|---|---|---|---|
| Novel Risk Factor | Basic* | Basic and Factor† | Increment | CRS | CHD Cases |
| log CRP‡ | 0.767 | 0.770 | 0.003 | 845 | 666 |
| $LpPLA_2$‡ | 0.774 | 0.780 | 0.006§ | 804 | 633 |
| log IL-6‖ | 0.773 | 0.783 | 0.010 | 365 | 304 |
| log TIMP-1‖ | 0.769 | 0.769 | 0.000 | 358 | 302 |
| MMP-1‖ | 0.768 | 0.768 | 0.000 | 245 | 203 |
| ICAM-1¶ | 0.805 | 0.806 | 0.001 | 956 | 421 |
| E-selectin¶ | 0.805 | 0.804 | -0.001 | 956 | 420 |
| log D-dimer¶ | 0.805 | 0.803 | -0.002 | 728 | 306 |
| log PAI-1¶ | 0.804 | 0.801 | -0.003 | 703 | 309 |
| tPA¶ | 0.805 | 0.803 | -0.002 | 743 | 311 |
| Plasminogen¶ | 0.801 | 0.802 | 0.001 | 781 | 337 |
| Soluble thrombomodulin¶ | 0.813 | 0.818 | 0.005 | 769 | 258 |
| log leptin¶ | 0.811 | 0.812 | 0.001 | 753 | 308 |
| Homocysteine# | 0.818 | 0.819 | 0.001 | 534 | 234 |
| log folate# | 0.813 | 0.815 | 0.002 | 522 | 228 |
| log vitamin $B_6$# | 0.813 | 0.824 | 0.011 | 522 | 228 |
| Chlamydia (IgG positive)# | 0.816 | 0.816 | 0.000 | 538 | 234 |
| CMV antibody (positive)# | 0.818 | 0.820 | 0.002 | 502 | 209 |
| HSV-1 antibody (positive)# | 0.820 | 0.820 | 0.000 | 497 | 209 |

Abbreviations: ARIC, Atherosclerosis Risk in Communities; AUC, area under the receiver operating characteristic curve; CHD, coronary heart disease; CMV, cytomegalovirus; CRP, C-reactive protein; CRS, cohort random sample; HSV-1, herpes simplex virus 1; ICAM-1, intracellular adhesion molecule 1; IL-6, interleukin 6; $LpPLA_2$, lipoprotein-associated phospholipase $A_2$; MMP-1, matrix metalloproteinase 1; PAI-1, plasminogen activator inhibitor 1;

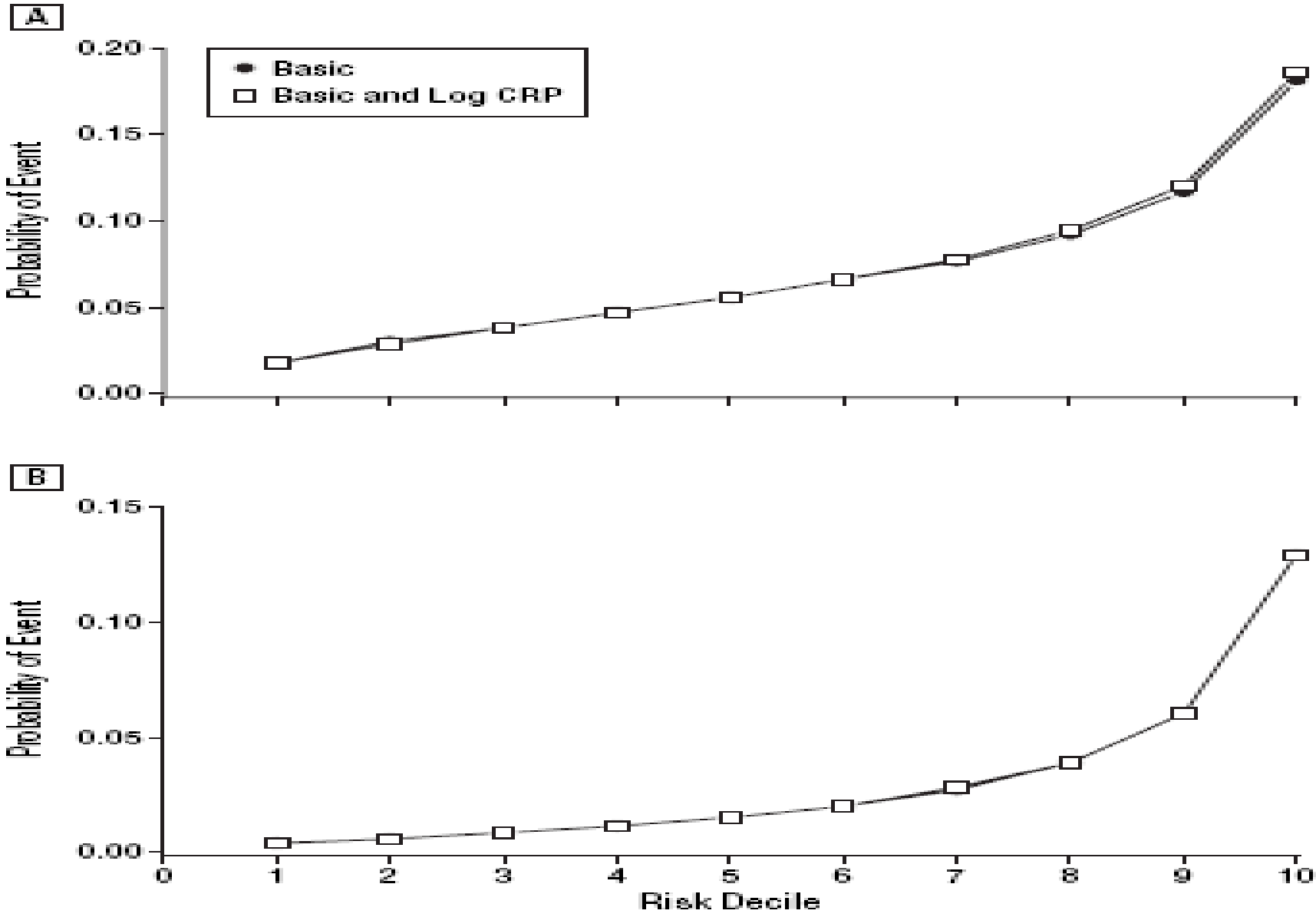



**Figure 1.** Predicted 5-year risk of an incident coronary heart disease event, comparing the basic model with the basic model plus log C-reactive protein (CRP), for men (A) and women (B) in the Atherosclerosis Risk in Communities Study.

Annals of Internal Medicine

REVIEW

# Narrative Review: Assessment of C-Reactive Protein in Risk Prediction for Cardiovascular Disease

Donald M. Lloyd-Jones, MD, ScM; Kiang Liu, PhD; Lu Tian, ScD; and Philip Greenland, MD

Some experts propose C-reactive protein (CRP) as a screening tool for prediction of cardiovascular disease (CVD). Many epidemiologic studies show positive associations between elevated CRP levels and incident CVD. Assessment of the value of new prognostic tests, however, must rely on understanding of test characteristics rather than on associations measured by relative risks. In the case of CRP, test characteristics must be judged in the context of currently available CVD risk prediction algorithms. In this review of literature published before January 2006, the authors describe what is known about the additional utility of CRP in risk prediction. They find no definitive evidence that, for most individuals, CRP adds substantial predictive value above that provided by risk estimation using traditional risk factors for CVD. Use of CRP may add to risk estimation in a limited subset of individuals who are at intermediate predicted risk according to the Framingham risk score. The authors propose that many questions still must be addressed before CRP is incorporated into risk prediction algorithms and before universal screening with CRP can be recommended.

*Ann Intern Med.* 2006;145:35-42. www.annals.org

For author affiliations, see end of text.

*Table.* Comparison of Areas under Receiver-Operating Characteristic Curve for Models with Traditional Cardiovascular Disease Risk Factors alone or with the Addition of C-Reactive Protein to the Model*

| Study, Year (Reference) | Design | Sex | Multivariate-Adjusted Relative Risk for CRP, Quartile 4 vs. Quartile 1 | AUC for Traditional Risk Factors Alone | AUC with CRP Added |
|---|---|---|---|---|---|
| Women's Health Study, 2002 (38) | Prospective | Women | 2.3 | 0.81† | 0.81 |
| Rotterdam Study, 2003 (39) | Nested case–control | Men and women | 1.2 | 0.746‡ | 0.748 |
| MONICA Augsburg Study, 2004 (40) | Prospective | Men | 2.2 | 0.735‡ | 0.750 |
| Reykjavik Cohort Study, 2004 (27) | Nested case–control | Men and women | 1.4 | 0.64§ | 0.65 |
| Framingham Offspring Study, 2004 (36) | Prospective | Men and women | 1.9 | 0.74‖ | 0.74 |
| Framingham Heart Study, 2005 (31) | Prospective | Men and women | 1.6 | 0.80¶ | 0.80 |
| Cardiovascular Health Study, 2005 (29) | Prospective | Men and women | NA | 0.73** | 0.72†† |

Ann Inter Med. 2006;145:35-42

# Assessment of c-reactive Protein inRisk Prediction for Cardiovascular Disease

- Σε αυτή την ανασκόπηση της βιβλιογραφίας που είχε δημοσιευθεί πριν από τον Ιανουάριο του 2006 οι συγγραφείς περιγράφουν αυτό που είναι γνωστό με την πρόσθετη χρησιμότητα της CRP στην πρόγνωση του κινδύνου
- Οι συντάκτες προτείνουν ότι πολλά ερωτήματα πρέπει να απαντηθούν προτού ενσωματωθεί η CRP στους αλγορίθμους πρόβλεψης κινδύνου.
- Μελλοντικές μελέτες CRP και άλλων καινοτόμων δεικτών CVD πρέπει να επικεντρώνονται στα test characteristics,και όχι μονό στο σχετικό κίνδυνο προκειμένου να ορίσει καλυτέρα την χρησιμότητα τους για την πρόβλεψη κινδύνων όταν προστίθενται στους κλασικούς παράγοντες κινδύνου

Ann Intern Med.2006;145;35-42

- Int J Epidemiol. 2009 Feb;38(1):231-4
- Ann Intern Med.2009 Oct 6;151(7)483-95
- JAMA .2009 Dec 2;302(21):2369-70

- Η προσθήκη της CRP στο FRS ελάχιστα βελτιώνει την προγνωστική αξία για πρόβλεψη καρδιαγγειακών συμβαματων σε ασυμπτωματικους.Η συμμετοχή του δείκτη είναι μικρή και ασυνεπης.Σε ασθενείς ενδιαμέσου κινδύνου κατά FRS 10-20% θα μπορούσε να αυξήση την προγνωστική αξία του δείκτη
- Δεν υπάρχουν επαρκή στοιχεία που να δείχνουν ότι μείωση των επιπέδων της CRP προλαμβάνει καρδιαγγειακά συμβαματα

# C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis

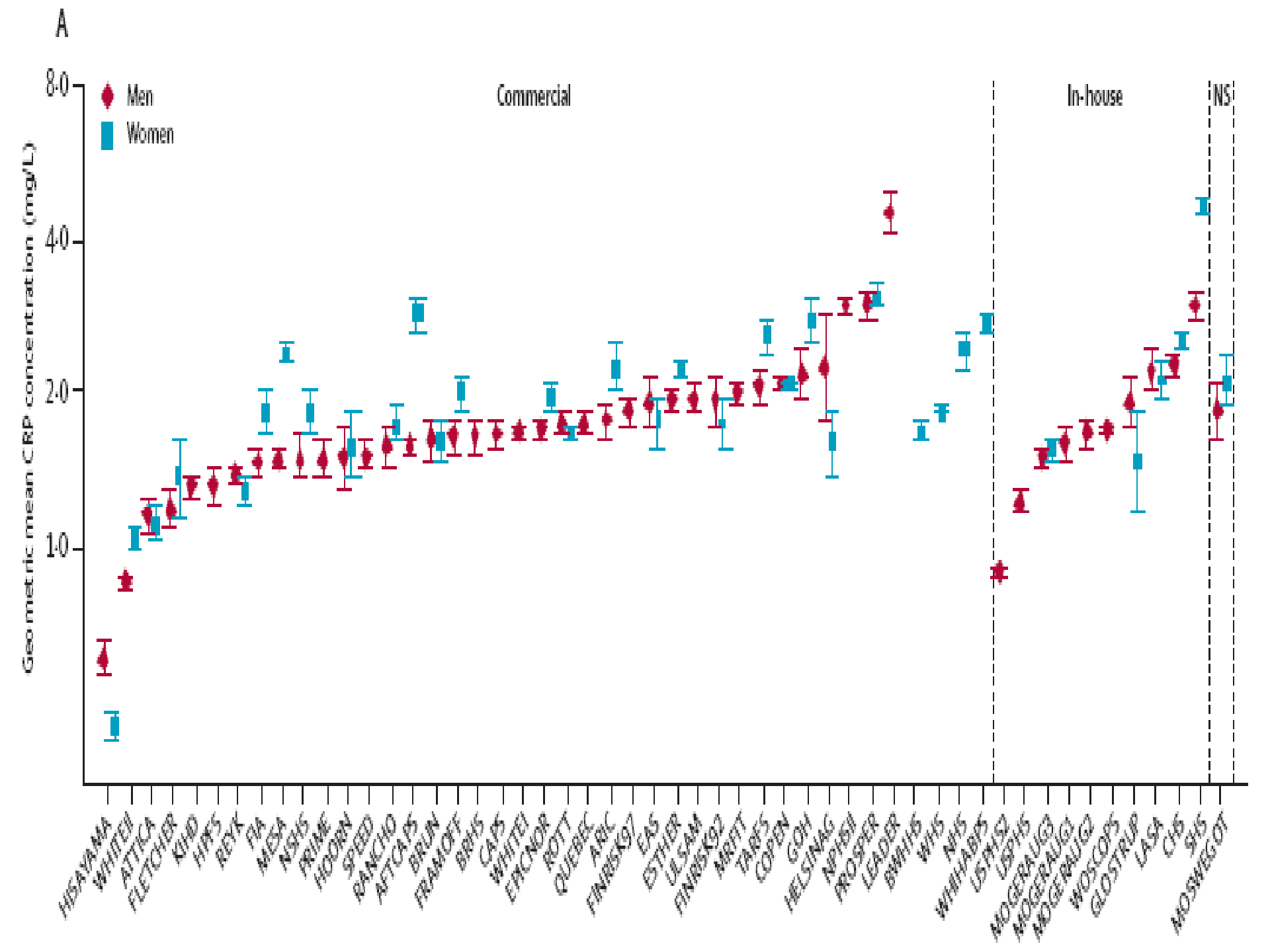
The Emerging Risk Factors Collaboration*

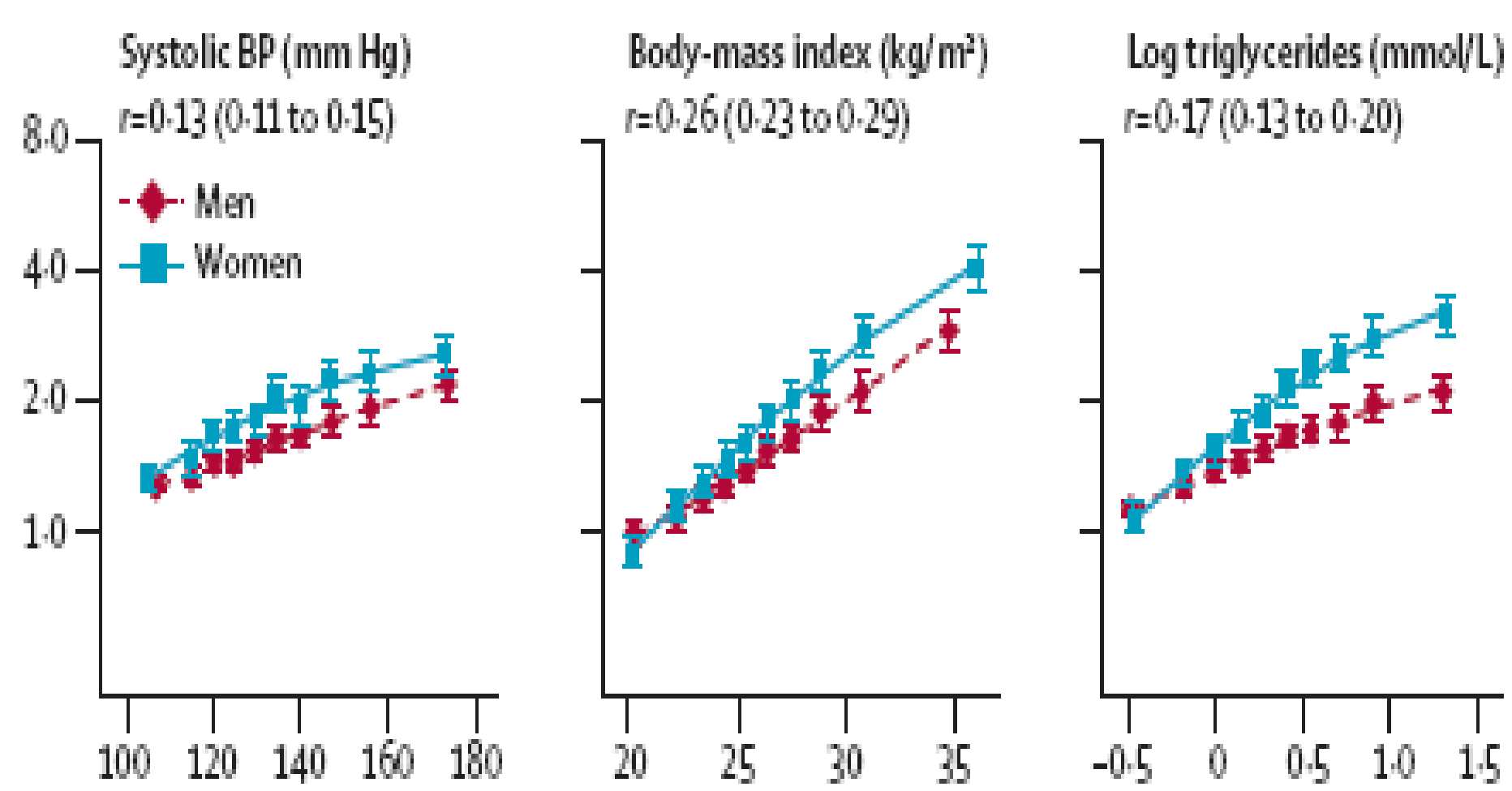
Lancet 2010 ;375:132-40

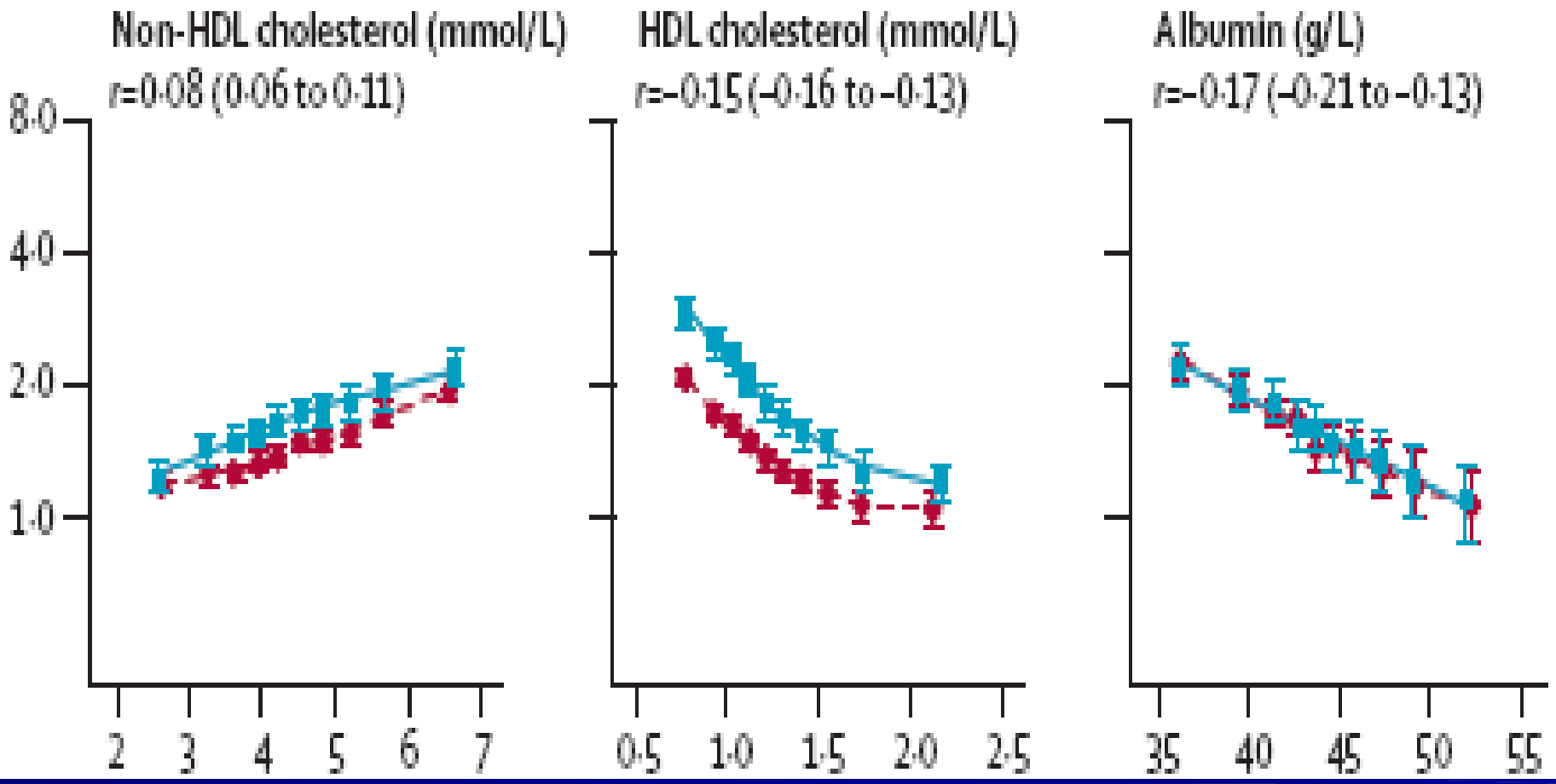
# The Emerging Risk Factors Collaboration*

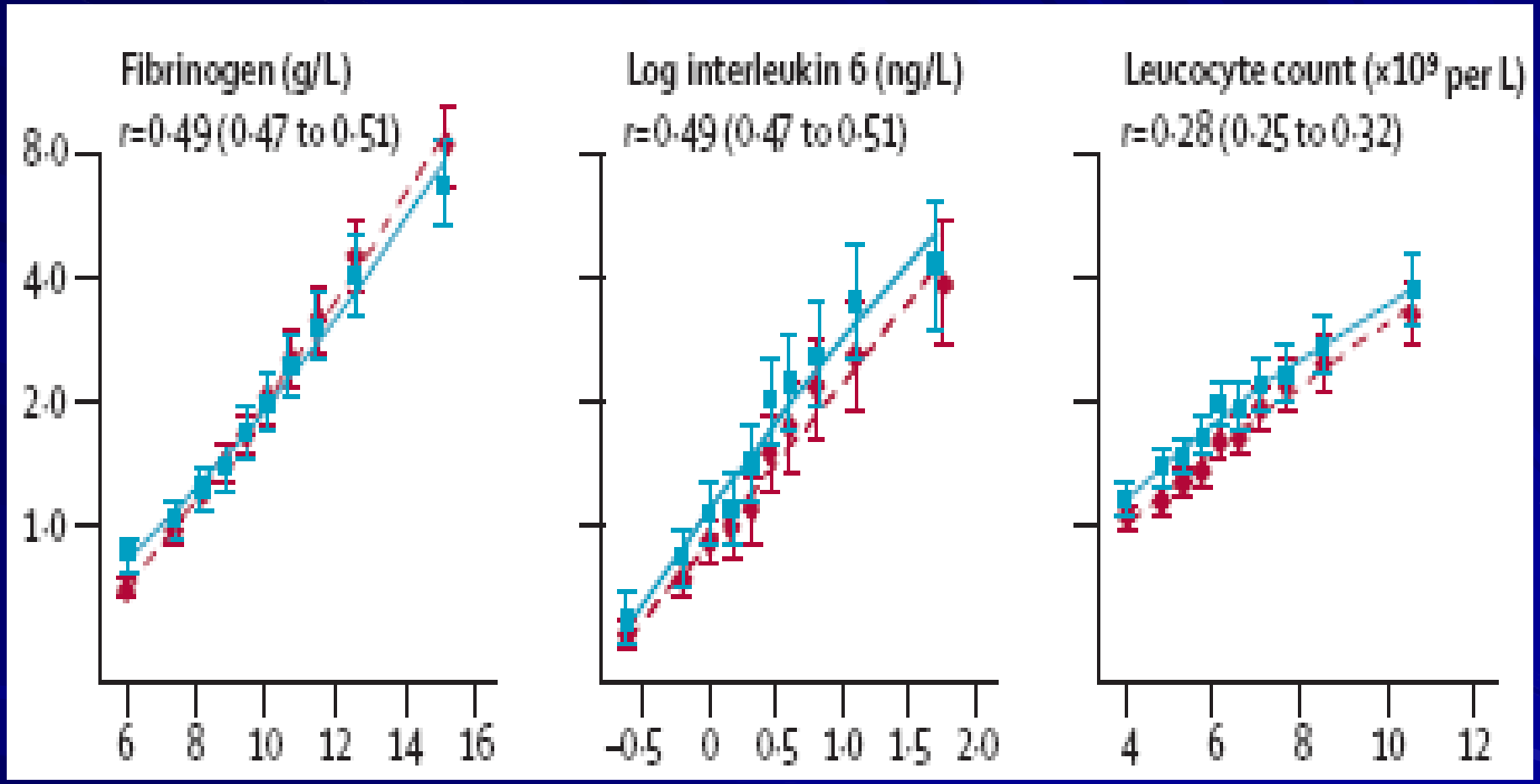
- Μετααναλυση που περιλαμβάνει 160.309 άτομα χωρίς ιστορικό καρδιαγγειακής νόσου από 54 προοπτικές μελέτες

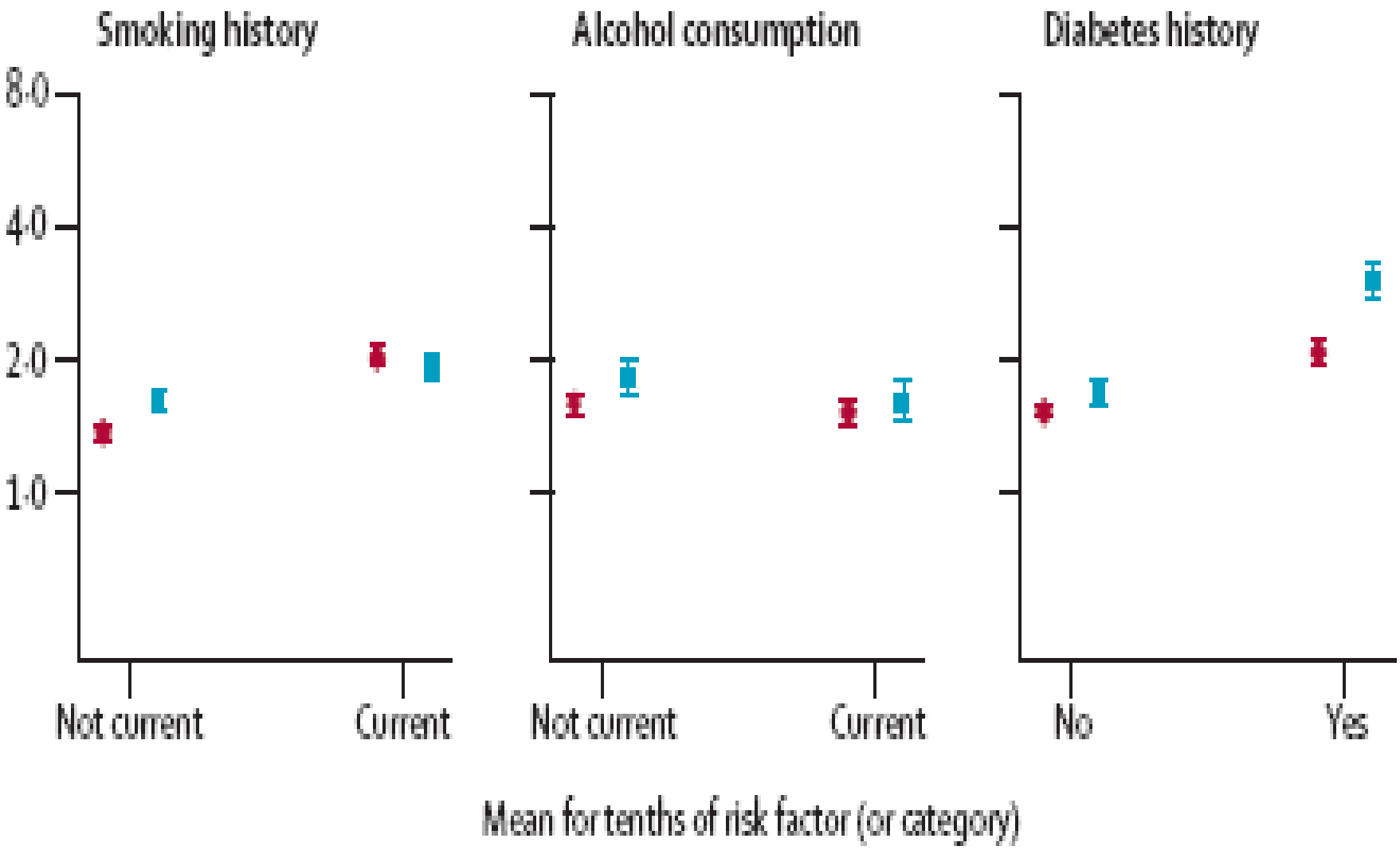
- 27.769 Θανατηφόρα και μη Θανατηφόρα συμβαματα

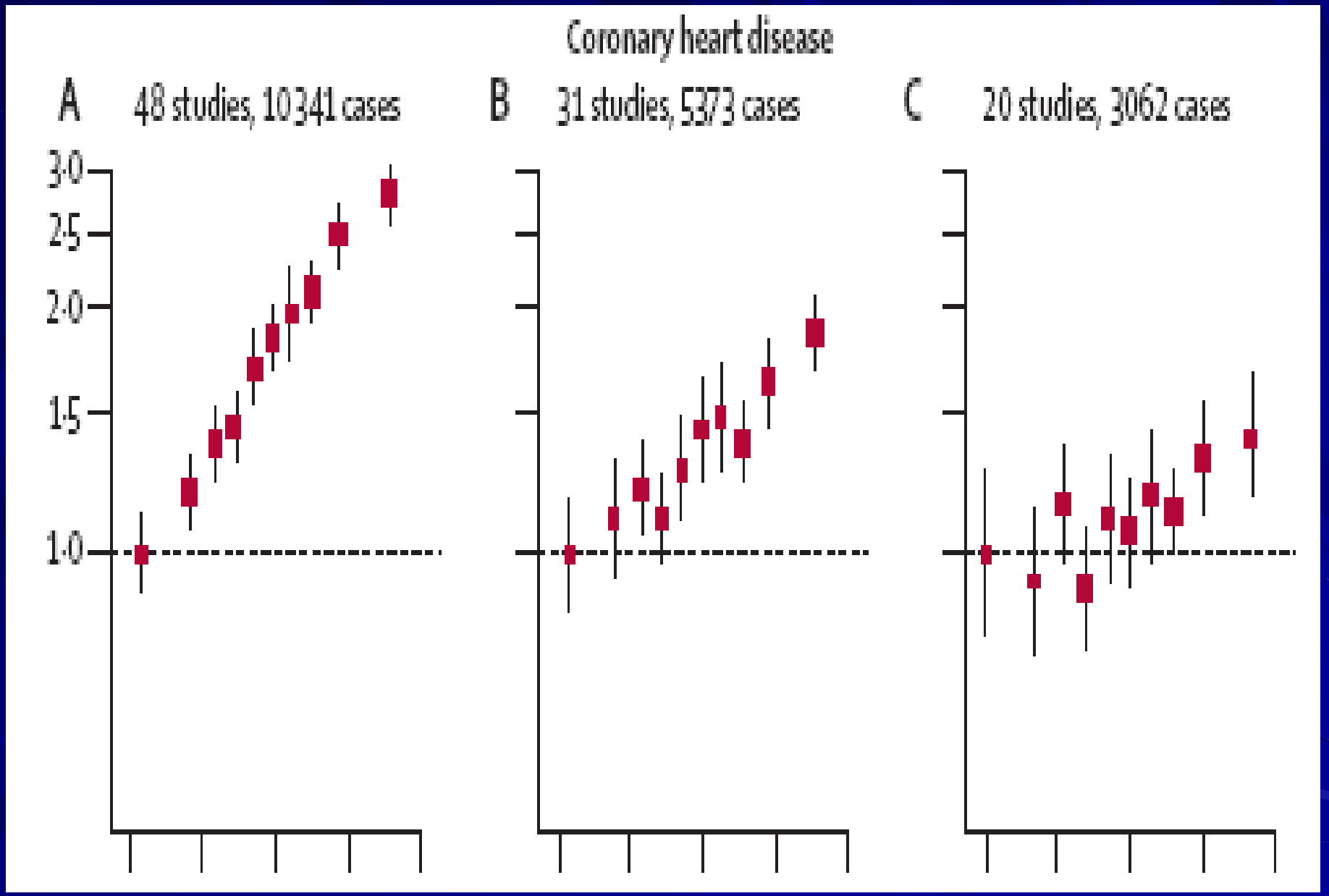

A
Men
Women
Commercial
In-house
NS
Geometric mean CRP concentration (mg/L)
8·0
4·0
2·0
1·0
MISAYAMA
WHITEII
ATTICA
FLETCHER
KIHD
HPFS
REYK
FIA
MESA
NSHS
PRIME
HOORN
SPEED
RANCHO
AFTCAPS
BRUN
FRAMOFF
BRHS
CAPS
WHITEI
ETNCNOR
ROTT
QUEBEC
ARIC
FINRISK97
EAS
ESTHER
ULSAM
FINRISK92
MRFIT
TAHS
COPEN
GOH
HELSINKI
NPHSII
PROSPER
LEADER
BWHHS
WHS
NHS
WHIHABPS
USTHI52
USPHS
MOGERAUG3
MOGERAUG1
MOGERAUG2
WOSCOPS
GLOSTRUP
LASA
CHS
SHS
MOSWEGOT


Systolic BP (mm Hg)
r=0·13 (0·11 to 0·15)
Men
Women
8·0
4·0
2·0
1·0
100
120
140
160
180
Body-mass index (kg/m²)
r=0·26 (0·23 to 0·29)
20
25
30
35
Log triglycerides (mmol/L)
r=0·17 (0·13 to 0·20)
-0·5
0
0·5
1·0
1·5

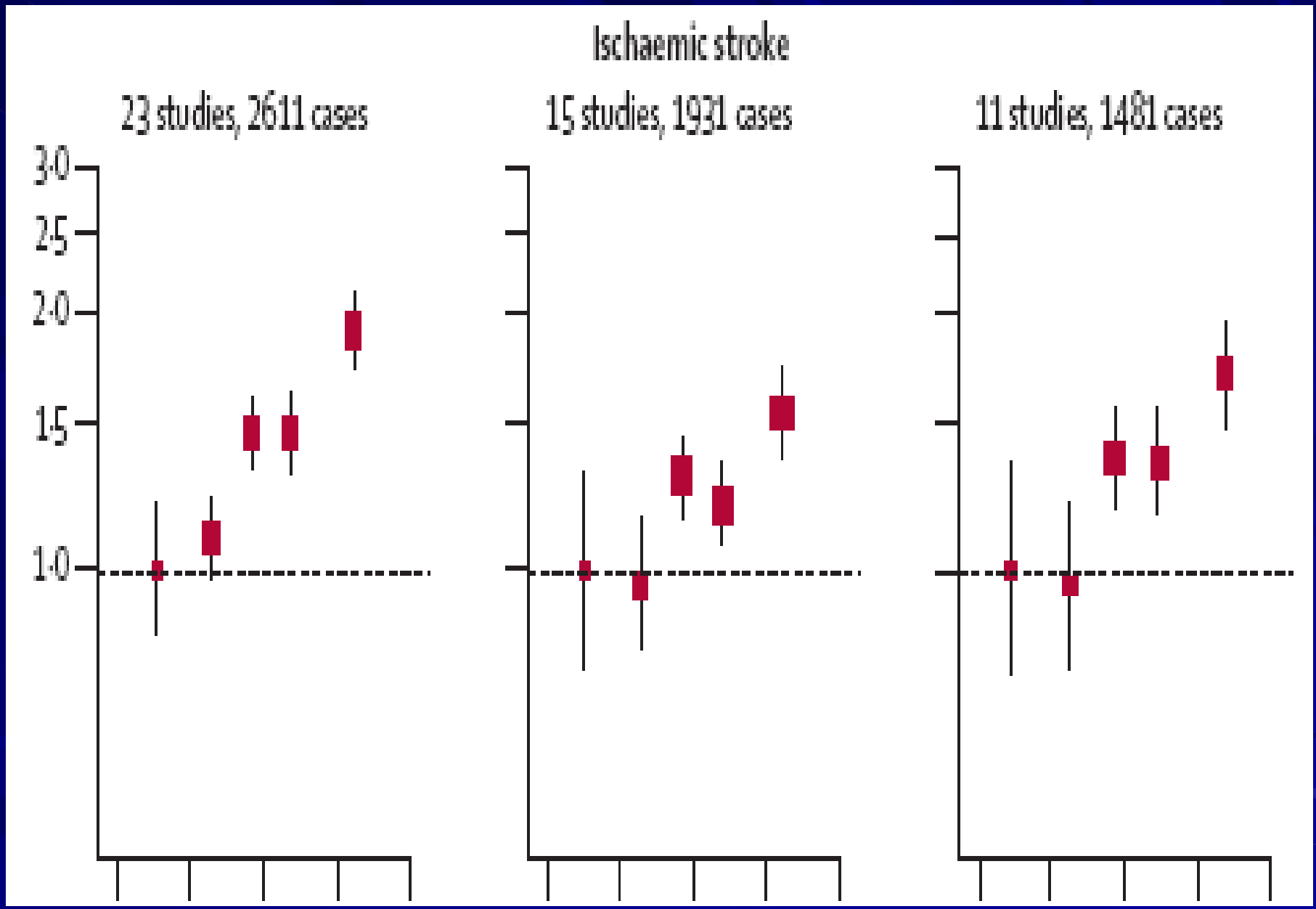

Non-HDL cholesterol (mmol/L)
r=0·08 (0·06 to 0·11)
8·0
4·0
2·0
1·0
2
3
4
5
6
7
HDL cholesterol (mmol/L)
r=–0·15 (–0·16 to –0·13)
0·5
1·0
1·5
2·0
2·5
Albumin (g/L)
r=–0·17 (–0·21 to –0·13)
35
40
45
50
55


Fibrinogen (g/L)
r=0·49 (0·47 to 0·51)
8·0
4·0
2·0
1·0
6
8
10
12
14
16
Log interleukin 6 (ng/L)
r=0·49 (0·47 to 0·51)
−0·5
0
0·5
1·0
1·5
2·0
Leucocyte count (×10⁹ per L)
r=0·28 (0·25 to 0·32)
4
6
8
10
12

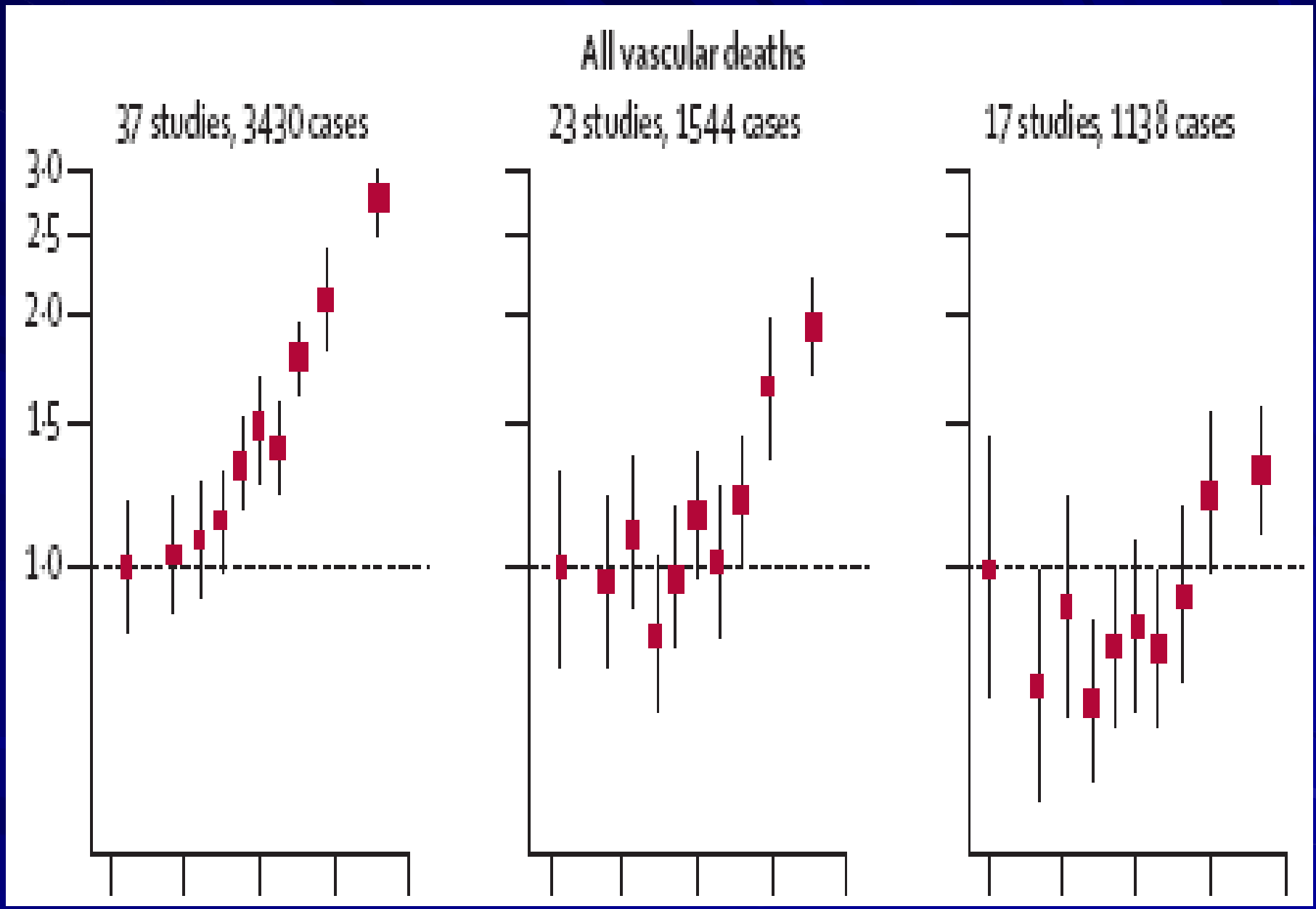

Smoking history
Alcohol consumption
Diabetes history
8·0
4·0
2·0
1·0
Not current
Current
Not current
Current
No
Yes
Mean for tenths of risk factor (or category)



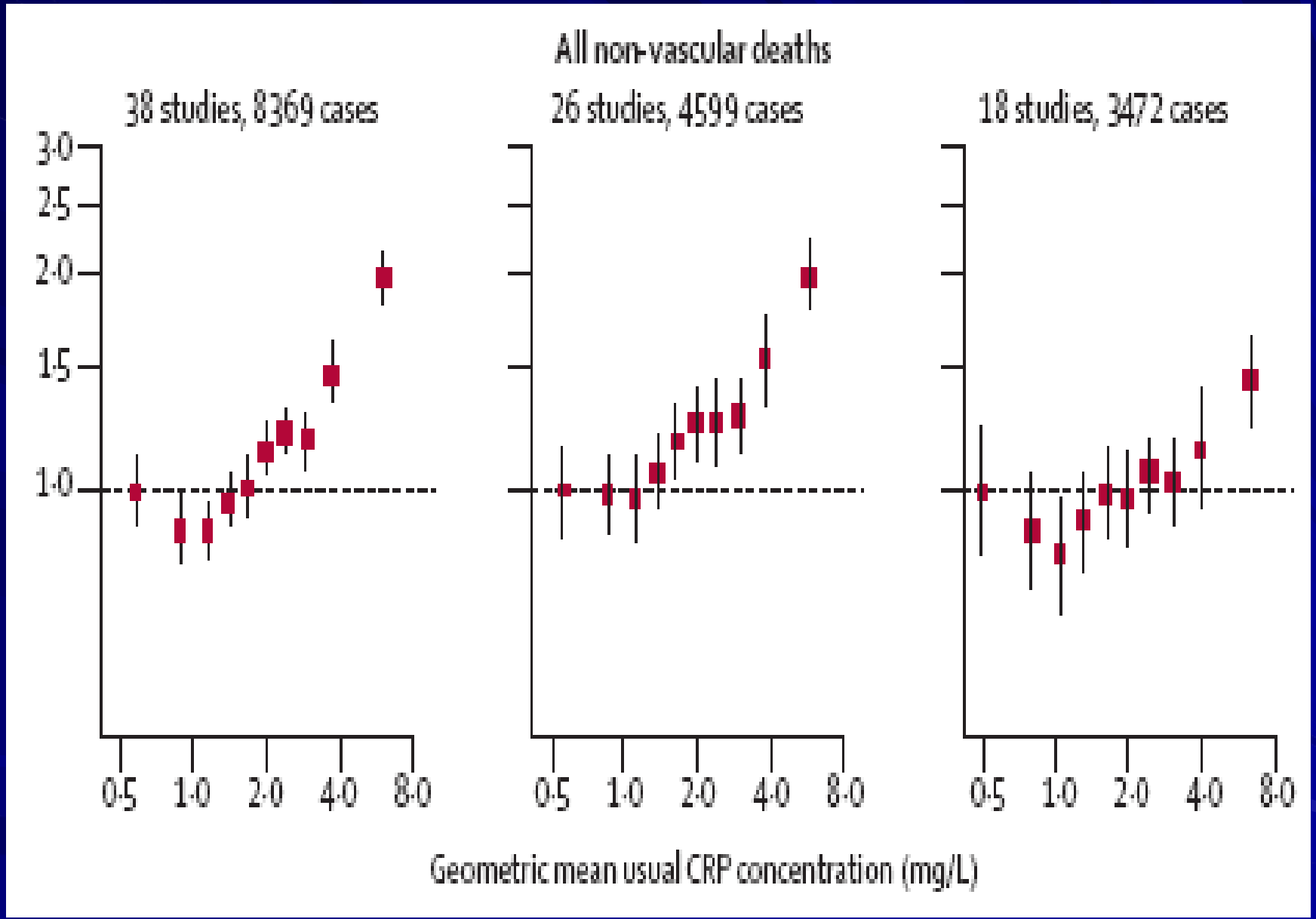

RRs 1,63 1,37 1,23




RRs 1,44 1,27 1,32



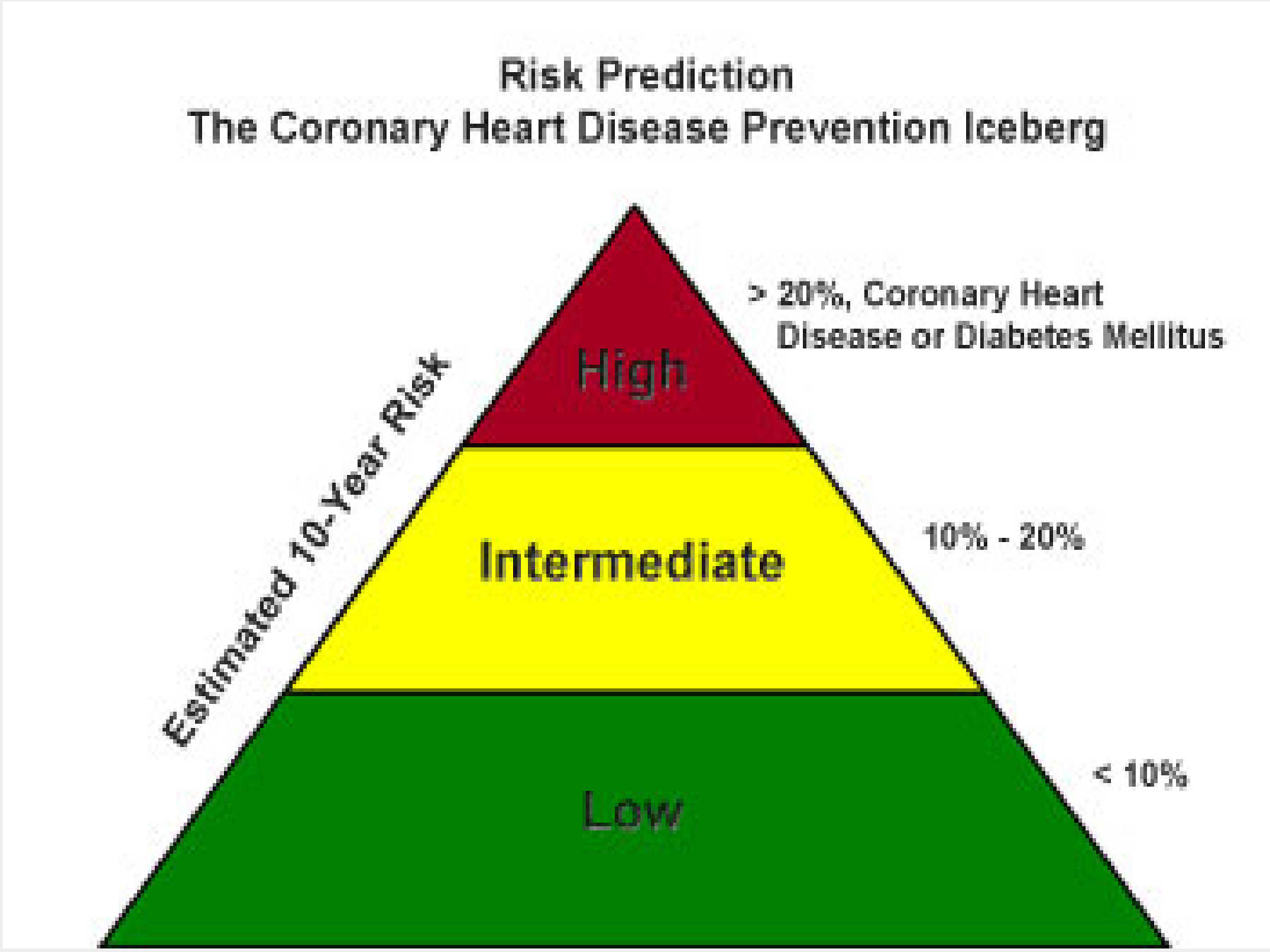

RRs 1,71 -1,55- 1,34



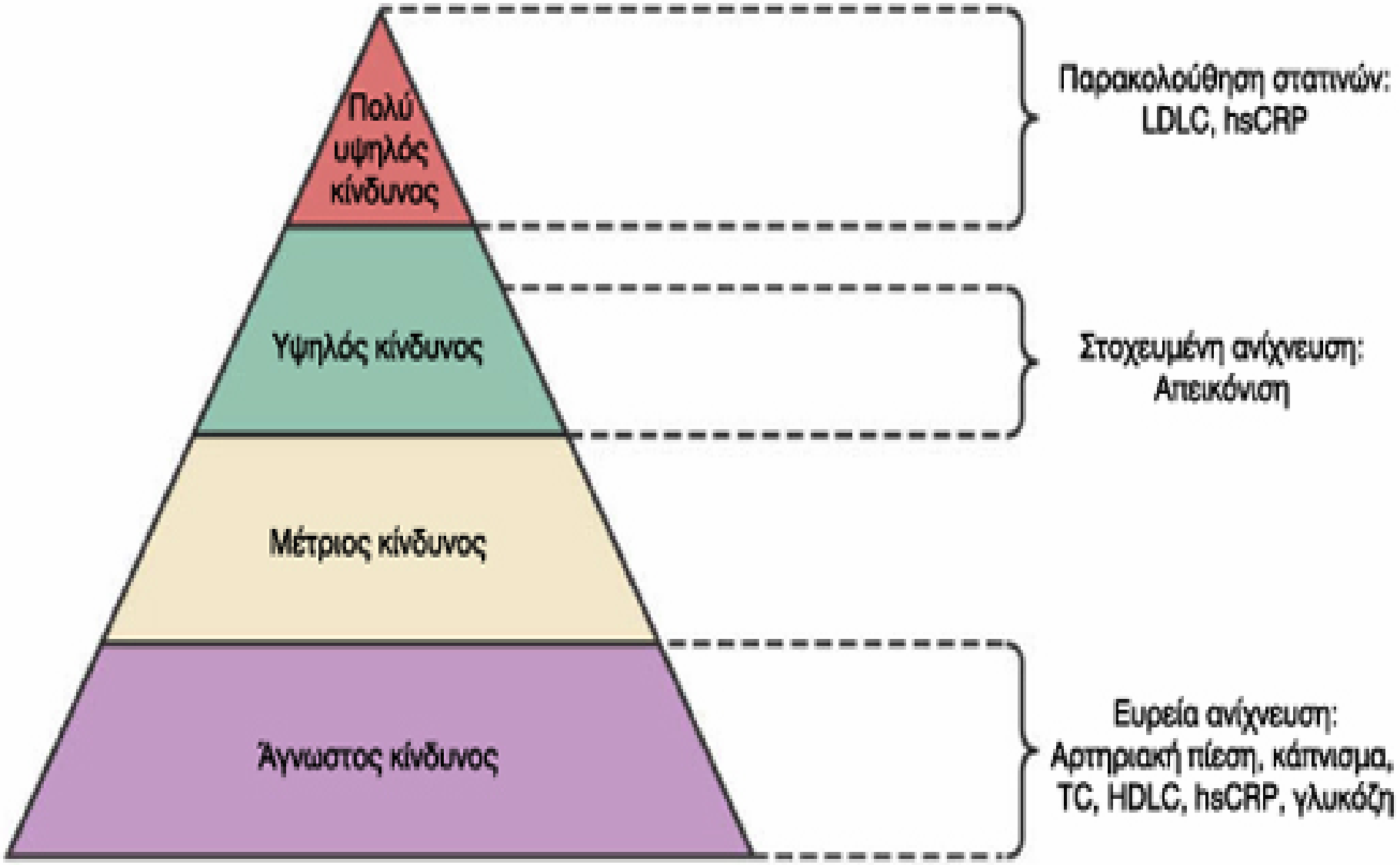

RRs 1,55- 1,54 -1,34

# The Emerging Risk Factors Collaboration

- Δεν προκύπτει αιτιολογική σχέση μεταξύ των επιπέδων CRP και καρδιοαγγειακής νόσου
- Παρά την συνεχή γραμμική συσχέτιση των επιπέδων της CRP με τον κίνδυνο για καρδιακά ισχαιμικά επεισοδια,ισχαιμικα εγκεφαλικα,αγγειακη θνητότητα και θάνατο από καρκίνο ,και παθήσεις του πνεύμονα η συσχέτιση της CRP με τις διαταραχές είναι ασαφής
- Η ισχαιμική αγγειακή νόσος εξαρτάται από τους κλασικούς παράγοντες κινδύνου και άλλους δείκτες φλεγμονής


Risk Prediction
The Coronary Heart Disease Prevention Iceberg
Estimated 10-Year Risk
High
> 20%, Coronary Heart Disease or Diabetes Mellitus
Intermediate
10% - 20%
Low
< 10%

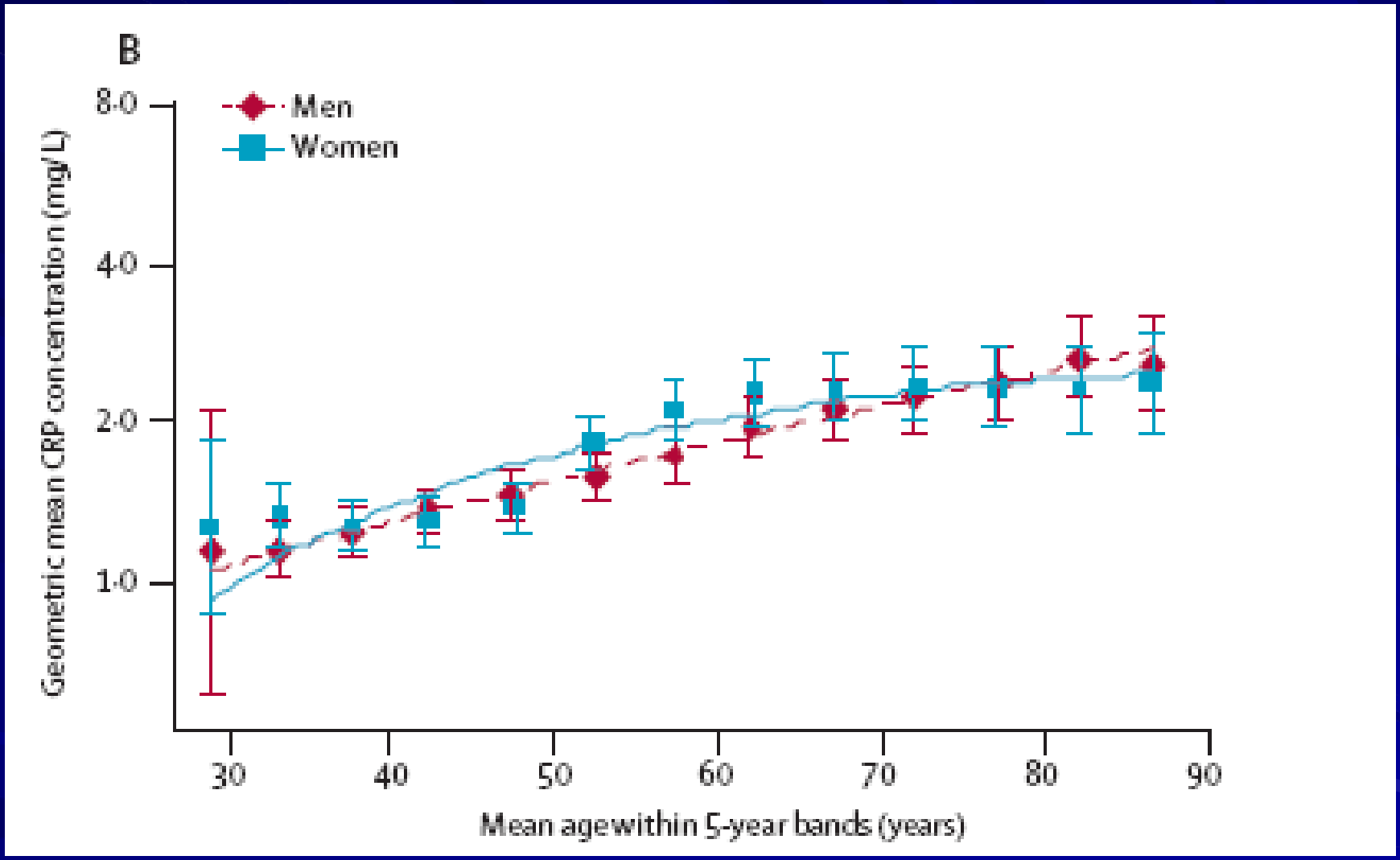
ΜΙΑ ΟΙΚΟΝΟΜΙΚΑ ΑΠΟΔΟΤΙΚΗ ΠΡΟΣΕΓΓΙΣΗ ΤΗΣ ΑΝΙΧΝΕΥΣΗΣ ΤΟΥ ΚΑΡΔΙΑΓΓΕΙΑΚΟΥ ΚΙΝΔΥΝΟΥ




**ΕΙΚΟΝΑ 39-15** Μια οικονομικά αποδοτική προσέγγιση στην ανίχνευση του καρδιαγγειακού κινδύνου.

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ


B
Men
Women
8·0
4·0
2·0
1·0
Geometric mean CRP concentration (mg/L)
30
40
50
60
70
80
90
Mean age within 5-year bands (years)

# An Assessment of Incremental Coronary Risk Prediction Using C-Reactive Protein and Other Novel Risk Markers

## *The Atherosclerosis Risk in Communities Study*

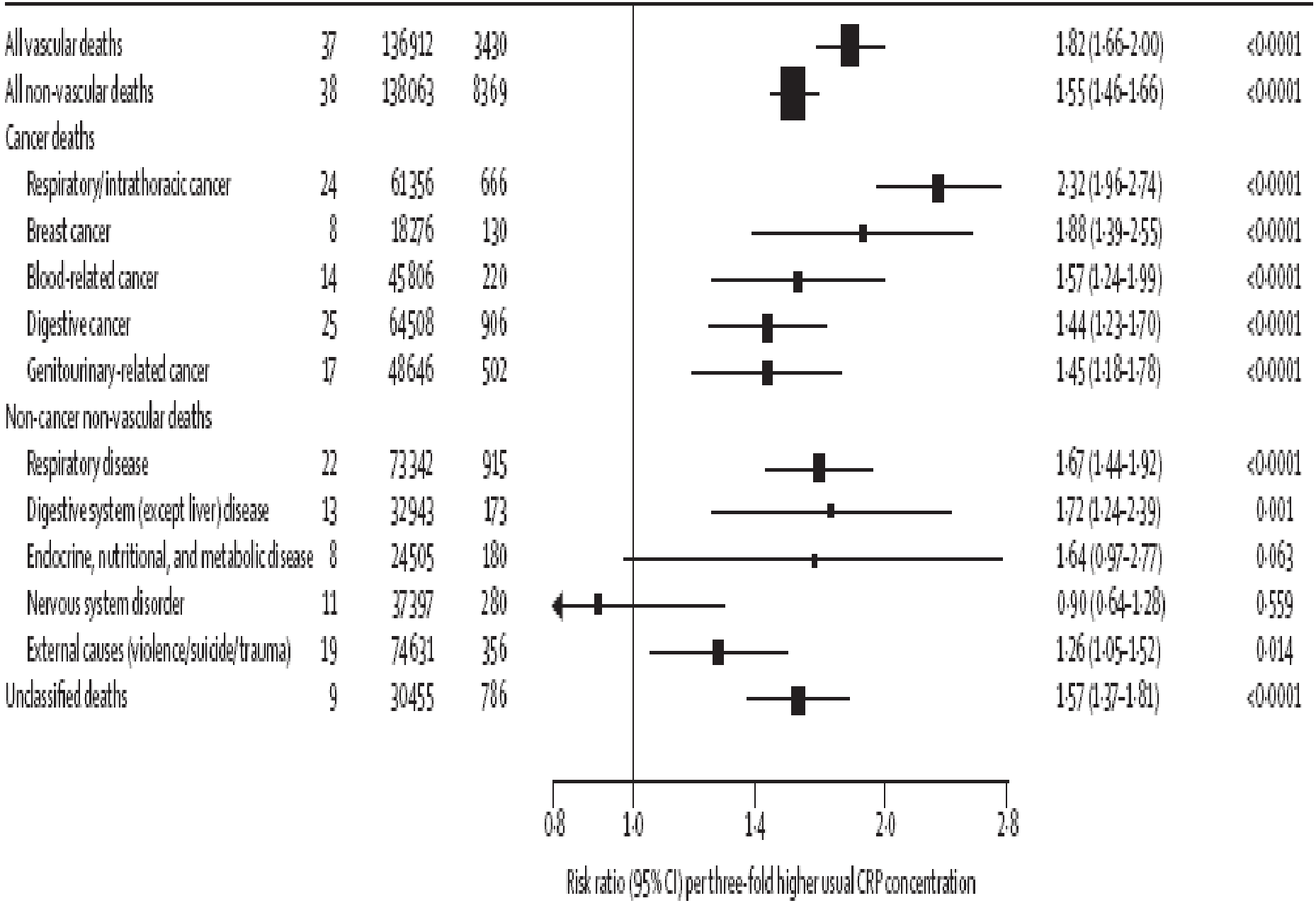
*Aaron R. Folsom, MD, MPH; Lloyd E. Chambless, PhD; Christie M. Ballantyne, MD; Josef Coresh, MD, PhD; Gerardo Heiss, MD; Kenneth K. Wu, MD, PhD; Eric Boerwinkle, PhD; Thomas H. Mosley, Jr, PhD; Paul Sorlie, PhD; Guoqing Diao, PhD; A. Richey Sharrett, MD, DrPH*

**Background:** There has been interest in recent years in whether additional, and in particular novel, risk factors or blood markers, such as C-reactive protein, can enhance existing coronary heart disease (CHD) prediction models.

**Methods:** Using a series of case-cohort studies, the prospective Atherosclerosis Risk in Communities (ARIC) Study assessed the association of 19 novel risk markers with incident CHD in 15 792 adults followed up since 1987-1989. Novel markers included measures of inflammation, endothelial function, fibrin formation, fibrinolysis, B vitamins, and antibodies to infectious agents. Change in the area under the receiver operating characteristic curve (AUC) was used to assess the additional con-

density lipoprotein cholesterol levels, systolic blood pressure, antihypertensive medication use, smoking status, and diabetes), predicted CHD well, as evidenced by an AUC of approximately 0.8. The C-reactive protein level did not add significantly to the AUC (increase in AUC of 0.003), and neither did most other novel risk factors. Of the 19 markers studied, lipoprotein-associated phospholipase $A_2$, vitamin $B_6$, interleukin 6, and soluble thrombomodulin added the most to the AUC (range, 0.006-0.011).

**Conclusions:** Our findings suggest that routine measurement of these novel markers is not warranted for risk assessment. On the other hand, our findings rein-


Studies
Participants
Outcomes
Risk ratio (95% CI)
p value
All vascular deaths 37 136912 3430 1·82 (1·66–2·00) <0·0001
All non-vascular deaths 38 138063 8369 1·55 (1·46–1·66) <0·0001
Cancer deaths
Respiratory/intrathoracic cancer 24 61356 666 2·32 (1·96–2·74) <0·0001
Breast cancer 8 18276 130 1·88 (1·39–2·55) <0·0001
Blood-related cancer 14 45806 220 1·57 (1·24–1·99) <0·0001
Digestive cancer 25 64508 906 1·44 (1·23–1·70) <0·0001
Genitourinary-related cancer 17 48646 502 1·45 (1·18–1·78) <0·0001
Non-cancer non-vascular deaths
Respiratory disease 22 73342 915 1·67 (1·44–1·92) <0·0001
Digestive system (except liver) disease 13 32943 173 1·72 (1·24–2·39) 0·001
Endocrine, nutritional, and metabolic disease 8 24505 180 1·64 (0·97–2·77) 0·063
Nervous system disorder 11 37397 280 0·90 (0·64–1·28) 0·559
External causes (violence/suicide/trauma) 19 74631 356 1·26 (1·05–1·52) 0·014
Unclassified deaths 9 30455 786 1·57 (1·37–1·81) <0·0001
0·8
1·0
1·4
2·0
2·8
Risk ratio (95% CI) per three-fold higher usual CRP concentration

| | Studies | Outcomes | RR* (95% CI) usual log, CRP concentration | Wald $\chi^2_1$ | $I^2$ (95% CI) |
|---|---|---|---|---|---|
| **Coronary heart disease** | | | | | |
| Adjusted for age, sex, and study (n=66 117) | 20 | 3062 | 1·65 (1·48–1·84) | 80 | 57% (30–74) |
| Plus conventional risk factors† | 20 | 3062 | 1·36 (1·22–1·52) | 29 | 36% (0–63) |
| Plus fibrinogen | 20 | 3062 | 1·23 (1·07–1·42) | 8 | 57% (30–74) |
| Adjusted for age, sex, and study (n=32 958) | 12 | 2689 | 1·66 (1·48–1·86) | 78 | 52% (7–75) |
| Plus conventional risk factors† | 12 | 2689 | 1·44 (1·29–1·62) | 40 | 35% (0–67) |
| Plus albumin | 12 | 2689 | 1·38 (1·26–1·51) | 47 | 15% (0–54) |
| Adjusted for age, sex, and study (n=21 917) | 11 | 2688 | 1·68 (1·48–1·91) | 65 | 60% (22–79) |
| Plus conventional risk factors† | 11 | 2688 | 1·42 (1·26–1·60) | 32 | 37% (0–69) |
| Plus log, leucocyte count | 11 | 2688 | 1·30 (1·16–1·45) | 20 | 36% (0–68) |
| Adjusted for age, sex, and study (n=19 016) | 7 | 1547 | 1·77 (1·37–2·28) | 19 | 83% (67–91) |
| Plus conventional risk factors† | 7 | 1547 | 1·42 (1·15–1·74) | 11 | 59% (5–82) |
| Plus log, interleukin 6 | 7 | 1547 | 1·19 (1·01–1·41) | 4 | 31% (0–70) |

# Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts.

- CONCLUSIONS: CRP does not perform better than the Framingham risk equation for discrimination. The improvement in risk stratification or reclassification from addition of CRP to models based on established risk factors is small and inconsistent. Guidance on the clinical use of CRP measurement in the prediction of coronary events may require updating in light of this large comparative analysis

•Int J Epidemiol. 2009 Feb;38(1):231-4.

JAMA®

Online article and related content current as of February 2, 2010.

# Novel and Conventional Biomarkers for Prediction of Incident Cardiovascular Events in the Community

Olle Melander; Christopher Newton-Cheh; Peter Almgren; et al.

*JAMA*. 2009;302(1):49-57 (doi:10.1001/jama.2009.943)

**Conclusions** Selected biomarkers may be used to predict future cardiovascular events, but the gains over conventional risk factors are minimal. Risk classification improved in intermediate-risk individuals, mainly through the identification of those unlikely to develop events.

Ann Intern Med. 2009 Oct.

**C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force.**

- CONCLUSION: Strong evidence indicates that CRP is associated with CHD events. Moderate, consistent evidence suggests that adding CRP to risk prediction models among initially intermediate-risk persons improves risk stratification. However, sufficient evidence that reducing CRP levels prevents CHD events is lacking.

JAMA. 2009 Dec 2;302(21):2345-52.

# Assessment of claims of improved prediction beyond the Framingham risk score.

Tzoulaki I, Liberopoulos G, Ioannidis JP.

Department of Epidemiology and Public Health, Imperial College of Medicine, London, England.

Comment in:

JAMA. 2009 Dec 2;302(21):2369-70.

CONCLUSION: The majority of examined studies claimed that they found factors that could offer additional predictive value beyond what the FRS could achieve; however, most had flaws in their design, analyses, and reporting that cast some doubt on the reliability of the claims for improved prediction.

| Ischaemic stroke | | | | | |
|---|---|---|---|---|---|
| Adjusted for age, sex, and study (n=47 353) | 11 | 1481 | 1·49 (1·34–1·67) | 49 | 16% (0–57) |
| Plus conventional risk factors† | 11 | 1481 | 1·32 (1·18–1·47) | 24 | 0 (0–60) |
| Plus fibrinogen | 11 | 1481 | 1·32 (1·18–1·49) | 22 | 0 (0–60) |
| Adjusted for age, sex, and study (n=19 382) | 6 | 890 | 1·37 (1·23–1·52) | 35 | 0 (0–75) |
| Plus conventional risk factors† | 6 | 890 | 1·28 (1·14–1·44) | 16 | 0 (0–75) |
| Plus albumin | 6 | 890 | 1·21 (1·07–1·35) | 10 | 0 (0–75) |
| Adjusted for age, sex, and study (n=14 076) | 7 | 1252 | 1·40 (1·26–1·55) | 42 | 0 (0–71) |
| Plus conventional risk factors† | 7 | 1252 | 1·25 (1·11–1·41) | 13 | 0 (0–71) |
| Plus log, leucocyte count | 7 | 1252 | 1·15 (1·02–1·29) | 5 | 0 (0–71) |
| Adjusted for age, sex, and study (n=9918) | 3 | 480 | 1·63 (1·15–2·29) | 8 | 63% (0–89) |
| Plus conventional risk factors† | 3 | 480 | 1·47 (1·09–1·98) | 6 | 42% (0–83) |
| Plus log, interleukin 6 | 3 | 480 | 1·18 (0·98–1·41) | 3 | 0 (0–90) |

# High-sensitivity C-reactive protein is only weakly related to cardiovascular damage after adjustment for traditional cardiovascular risk factors

Michael H. Olsen[a,b], Marina K. Christensen[c], Tine W. Hansen[a], Finn Gustafsson[d], Susanne Rasmussen[a], Kristian Wachtell[b], Knut Borch-Johnsen[e], Hans Ibsen[f], Torben Jørgensen[a] and Per Hildebrandt[d]

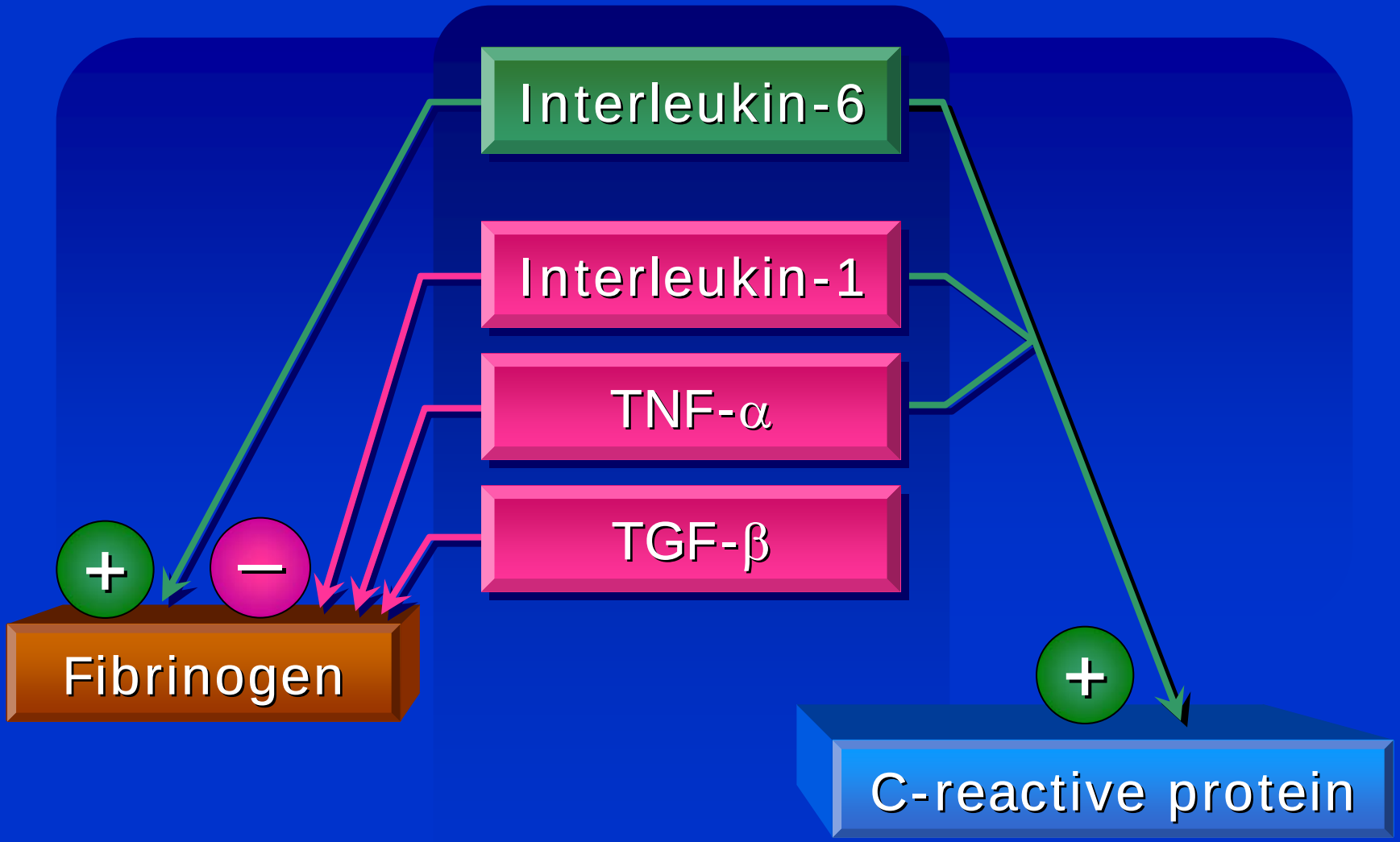
***Background*** The independent prognostic value of high-sensitivity C-reactive protein (hsCRP) has been questioned, and consequently we decided to investigate whether hsCRP was associated with subclinical cardiovascular (CV) damage independently of traditional CV risk factors.

***Methods*** In a population-based sample of 2028 apparently healthy individuals without prior stroke or myocardial infarction not receiving any CV, anti-diabetic or lipid-lowering treatment, aged 41, 51, 61 or 71 years, we measured in 1993 serum hsCRP, traditional CV risk factors (lifestyle, metabolic and hemodynamic) and assessed subclinical CV damage [atherosclerotic plaques in the carotid arteries, pulse wave velocity (PWV), urine albumin/creatinine ratio (UACR), left ventricular (LV) mass and index ($\beta = 0.14$), higher heart rate ($\beta = 0.06$, all $P < 0.01$); and higher log(plasma glucose) ($\beta = 0.05$, $P < 0.05$) (adj. $R^2 = 0.19$, $P < 0.001$).

***Conclusion*** After adjustment for traditional CV risk factors hsCRP was only associated with PWV and atherosclerotic plaques, indicating a possible effect of low-grade inflammation on macrovascular damage. The close relationship between traditional CV risk factors and hsCRP suggested that hsCRP was an integrated CV risk marker early in the development of atherosclerosis. *J Hypertens* 24:655–661 © 2006 Lippincott Williams & Wilkins.

Journal of Hypertension 2006, 24:655–661

# Interleukin and Vascular Inflammation




Gabay C et al. *N Engl J Med* 1999;340:448-454.

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# C-Reactive Protein Determinants

| Increase | Decrease |
| --- | --- |
| Smoking | Aspirin |
| Chronic inflammation | Statins |
| Obesity | Thiazolidinediones |
| Estrogen | |

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# hs-CRP and CHD Relative Risk: Health Professionals Follow-up Study—Men

| | hs-CRP (mg/L) | | |
|---|---|---|---|
| | <1.0 | 1.0–2.9 | ≥3.0 |
| Model 1* | 1.0 | 1.90 (1.34–2.71) | 2.20 (1.46–3.32) |
| Model 2† | 1.0 | 1.88 (1.31–2.69) | 2.17 (1.43–3.31) |
| Model 3 (Model 2 + BMI) | 1.0 | 1.85 (1.28–2.68) | 2.08 (1.34–3.23) |
| Model 4 (Model 3 + TC/HDL-C) | 1.0 | 1.71 (1.17–2.49) | 1.91 (1.22–3.00) |
| Model 5 (Model 4 + DM + HTN) | 1.0 | 1.60 (1.09–2.34) | 1.79 (1.14–2.83) |

* Adjusted for age, smoking status, and month of blood sampling

† Also adjusted for parental history of CHD before age 60, alcohol intake, and physical activity

Pai JK et al. *N Engl J Med* 2004;351:2599-2610. Copyright 2004 Massachusetts Medical Society. All rights reserved.

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# An Assessment of Incremental Coronary Risk Prediction Using C-Reactive Protein and Other Novel Risk Markers

*The Atherosclerosis Risk in Communities Study*

*Aaron R. Folsom, MD, MPH; Lloyd E. Chambless, PhD; Christie M. Ballantyne, MD; Josef Coresh, MD, PhD; Gerardo Heiss, MD; Kenneth K. Wu, MD, PhD; Eric Boerwinkle, PhD; Thomas H. Mosley, Jr, PhD; Paul Sorlie, PhD; Guoqing Diao, PhD; A. Richey Sharrett, MD, DrPH*

therapy.[25,26] Based on the totality of evidence, however, CRP level does not emerge as a clinically useful addition to basic risk factor assessment for identifying patients at risk of a first CHD event.

*Arch Intern Med. 2006;166:1368-1373*

***Conclusion*** After adjustment for traditional CV risk factors hsCRP was only associated with PWV and atherosclerotic plaques, indicating a possible effect of low-grade inflammation on macrovascular damage. The close relationship between traditional CV risk factors and hsCRP suggested that hsCRP was an integrated CV risk marker early in the development of atherosclerosis. *J Hypertens* 24:655–661 © 2006 Lippincott Williams & Wilkins.

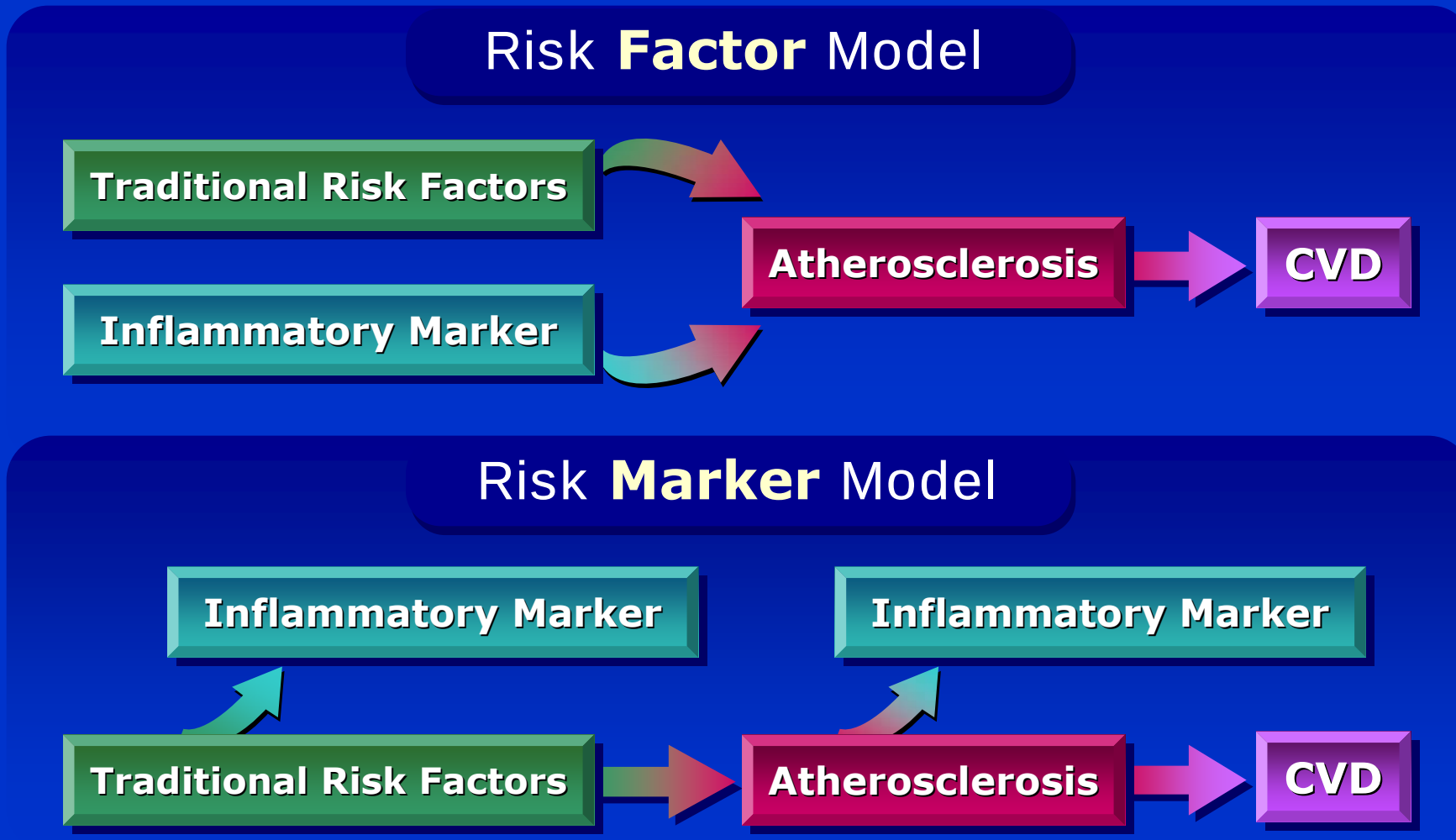
Journal of Hypertension 2006, 24:655–661

**Table 3 Levels of high-sensitivity C-reactive protein in subjects with increasing amounts of atherosclerotic plaques in the carotid arteries**

| Number of plaques | Number of subjects | Level of hsCRP |
|---|---|---|
| 0 | 1559 | 1.47 (0.72–3.15) |
| 1 | 192 | 1.79 (0.85–4.47)* |
| 2 | 120 | 2.05 (0.94–5.10)** |
| > 2 | 153 | 2.26 (1.19–4.06)*** |

hsCRP, high-sensitivity C-reactive protein. Median values and inter-quartile ranges. One-way ANOVA: $P < 0.001$. Post-hoc compared to 0 plaque: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

# Alternative Models for Role of Inflammatory Markers in CVD




Pearson TA et al. *Circulation* 2003;107:499-511.

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# Summary

- Growing body of evidence that inflammatory markers are important determinants of vascular disease risk
- Evidence includes leukocyte count, fibrinogen, CRP, and other biomarkers
- hs-CRP now considered an independent marker of CVD risk
- Debate continues for utility of CRP to assess CHD risk over and above traditional risk factors

Pearson TA et al. *Circulation* 2003;107:499-511.

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