Early Prevention of Cardiovascular Complications in Prediabetes

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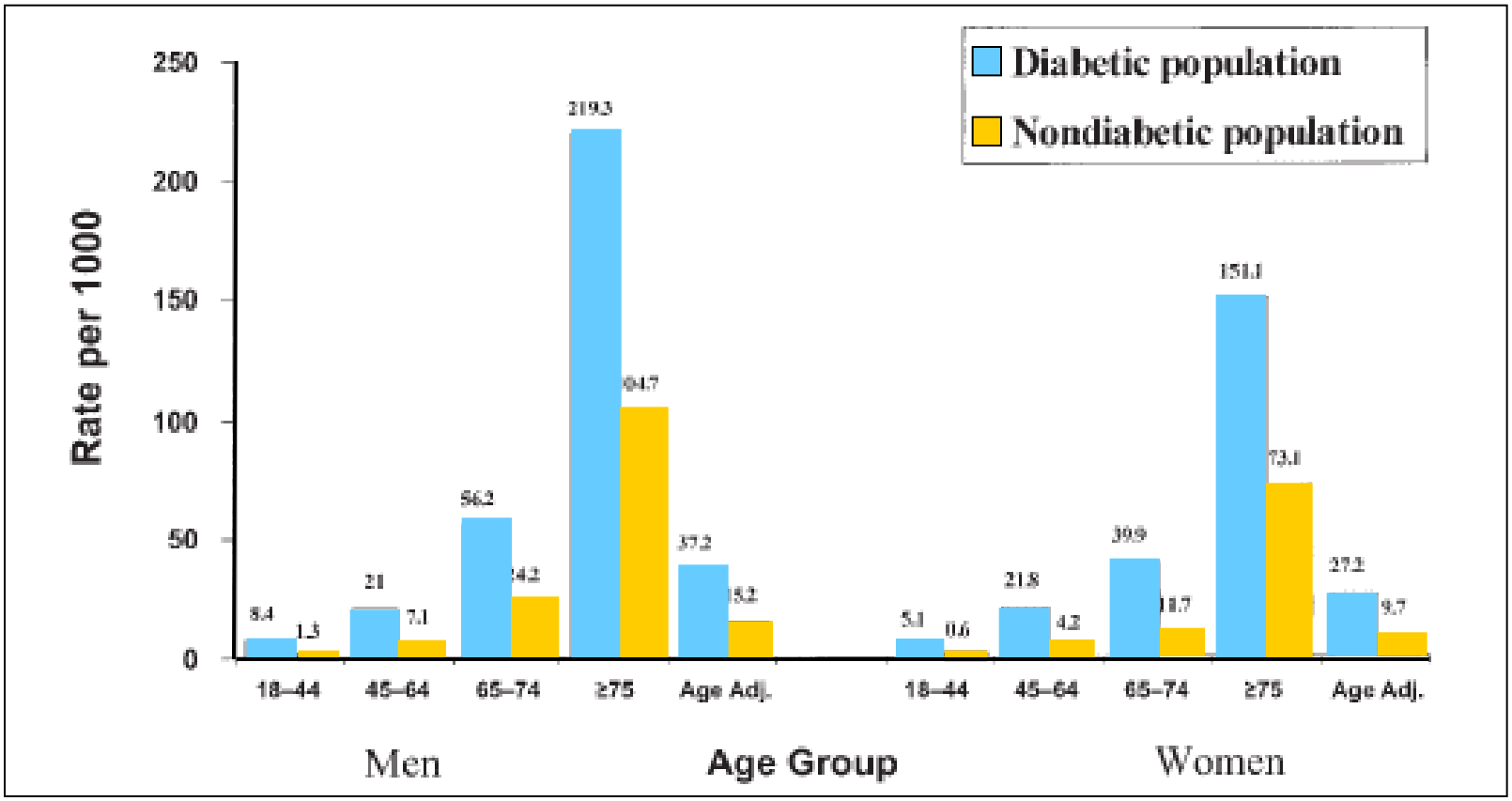
Antalya, 23 April 2015

Diseases of The Heart
Charles K Friedberg MD, WB Saunders Co. Philadelphia, 1949

"The proper control of *diabetes* is obviously desirable even though there is *uncertainty* as to whether coronary artery disease is more frequent or severe in the uncontrolled diabetic"

Overall Mortality in diabetics vs. non-diabetics

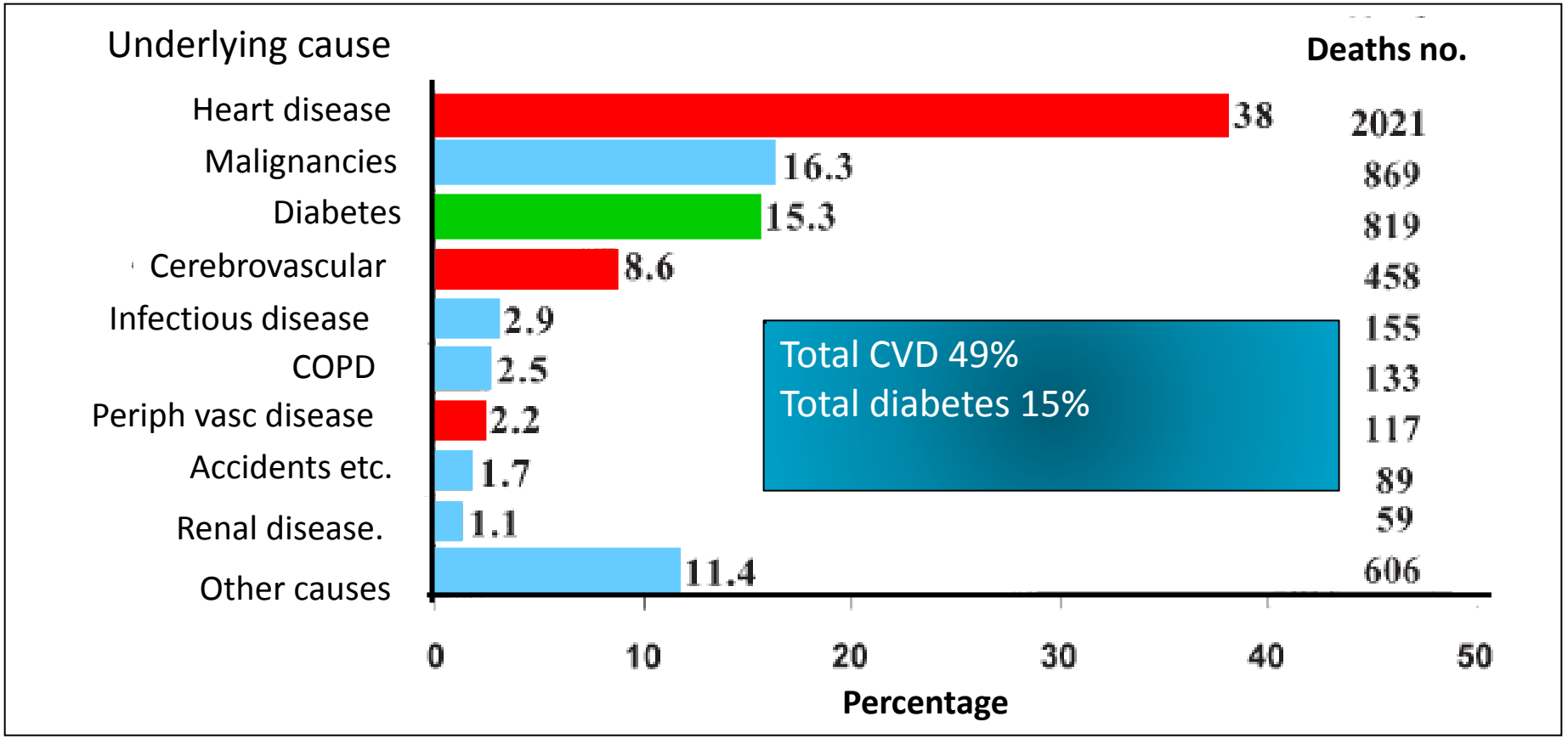
Population based age adjusted mortality 1992-1996



(Tierny et al Am J Public Health 2001; 91:84)

Mortality reasons in diabetes

Population based mortality from North Dakota



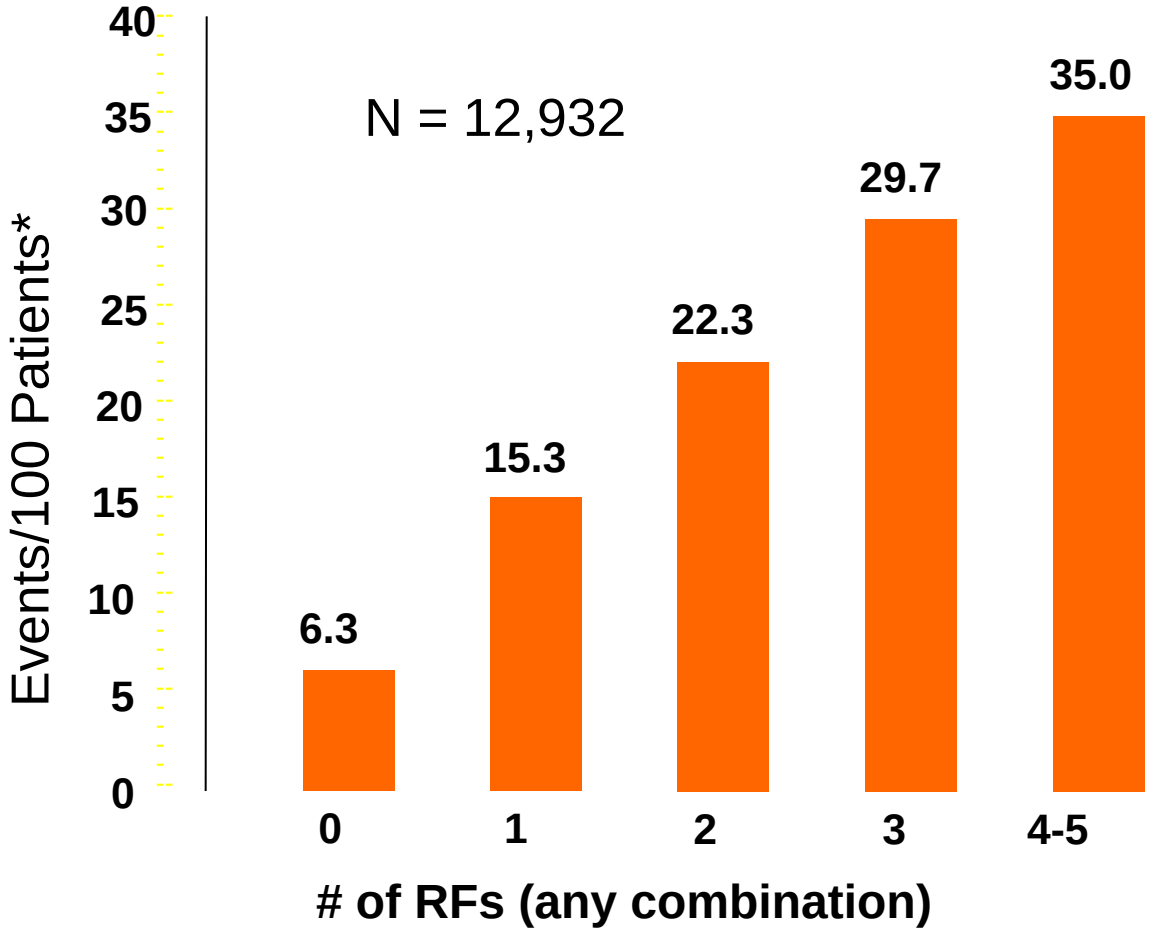
(Tierny et al Am J Public Health 2001; 91:84)

Risk of Cardiovascular Events in *Diabetics*. Framingham Study

	Age-adjusted Biennial Rate		Age-adjusted Risk Ratio	
Cardiovascular Event	Men	Women	Men	Women
Coronary Disease	39	21	1.5**	2.2***
Stroke	15	6	2.9***	2.6***
Peripheral Artery Dis.	18	18	3.4***	6.4***
Cardiac Failure	23	21	4.4***	7.8***
All CVD Events	76	65	2.2***	3.7***

Subjects 35-64; 36-year Follow-up **P<.001,***P<.0001

Risk for CHD Increases with the Number of Risk Factors: NHANES/NHEFS



Risk Factors (RFs)

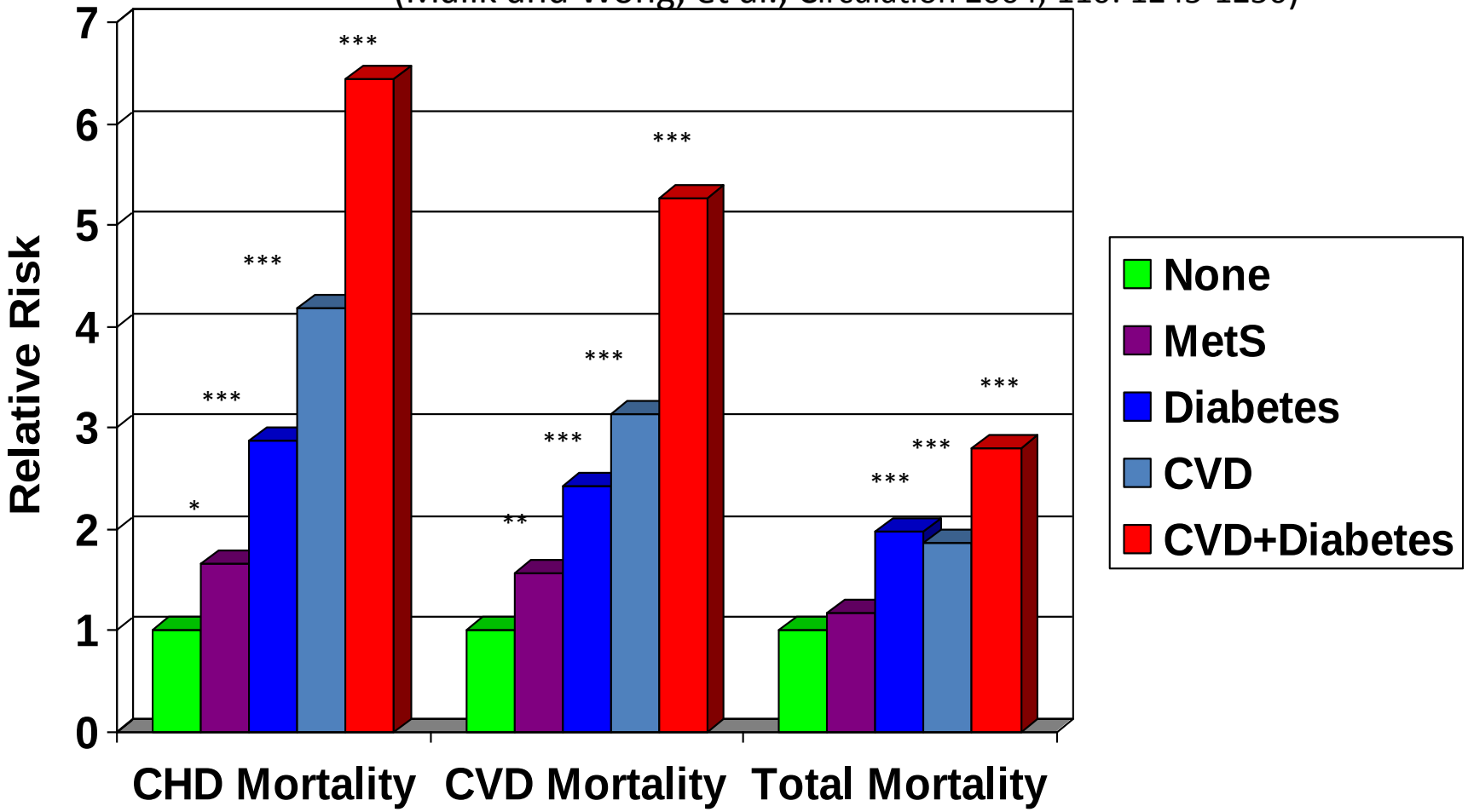
- **SBP >140 mm Hg or DBP >80 mm Hg**
- **TC >240 mg/dL**
- **BMI >27.3 kg/m^2 (women) >27.8 kg/m^2 (men)**
- **Current smoker**
- **Diabetes**

***Cumulative 21 yr. incidence *1971-1992.**

Yusuf HR, et al. *Prev Med*. 1998;27:1-9.

Does T2D Carry a CVD Mortality Risk Equivalent?
US Men and Women Ages 30-74

(age, gender, and risk-factor adjusted) NHANES II Follow-Up (n=6255)
(Malik and Wong, et al., Circulation 2004; 110: 1245-1250)

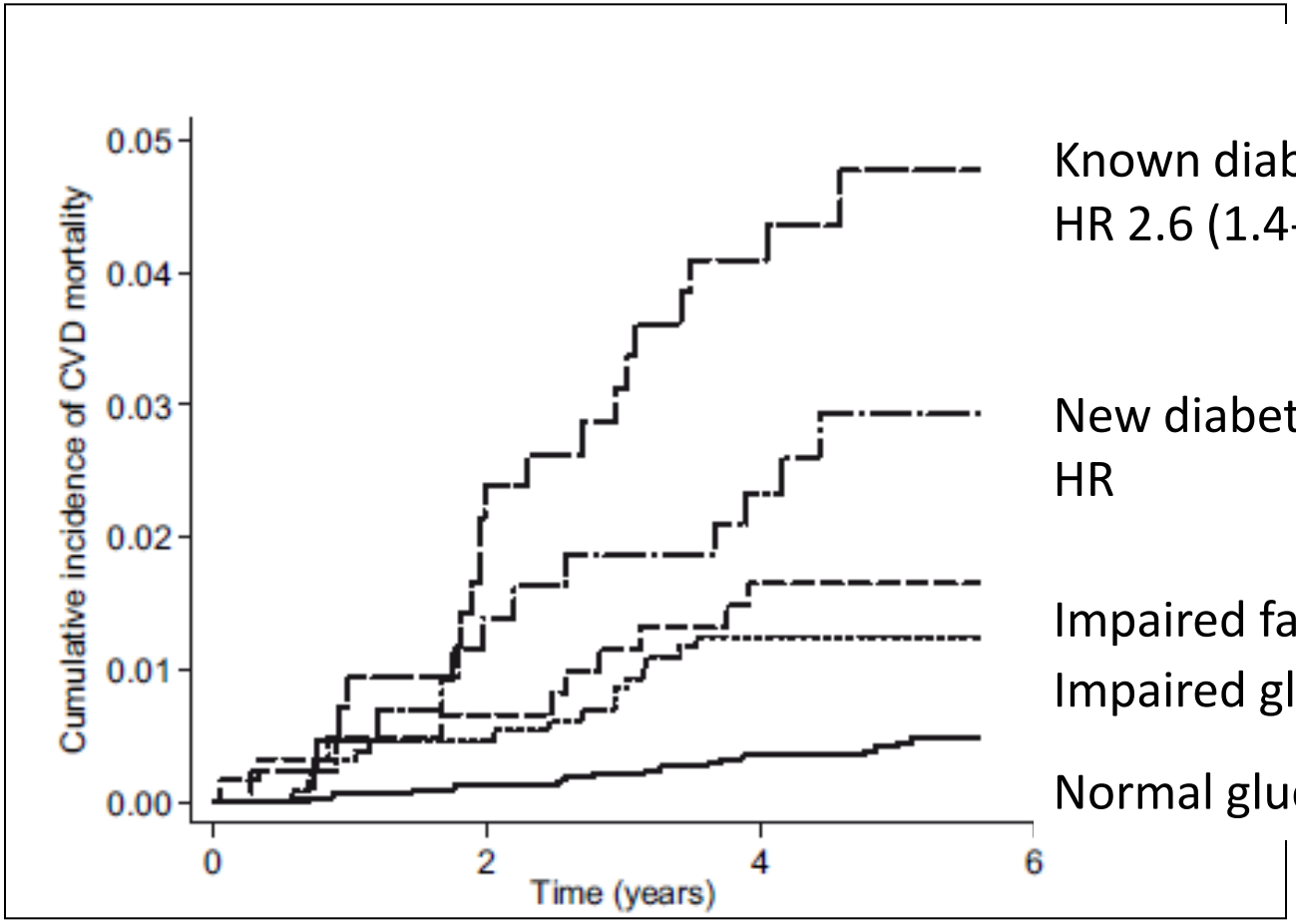


* p<.05, ** p<.01, **** p<.0001 compared to none

Glucose perturbations and cardiovascular mortality

Australian Diabetes, Obesity and Lifestyle Study

1999 – 2000 n=10 248 median follow up 5.2 years



(Barr et al Circulation 2007; 116:151)

PREDIABETES

A Synthesis

By W. P. U. JACKSON, M.A., M.D., M.R.C.P., D.C.H.

Senior Lecturer, Department of Medicine, University of Cape Town, and Physician to Groote Schuur Hospital, Cape, South Africa

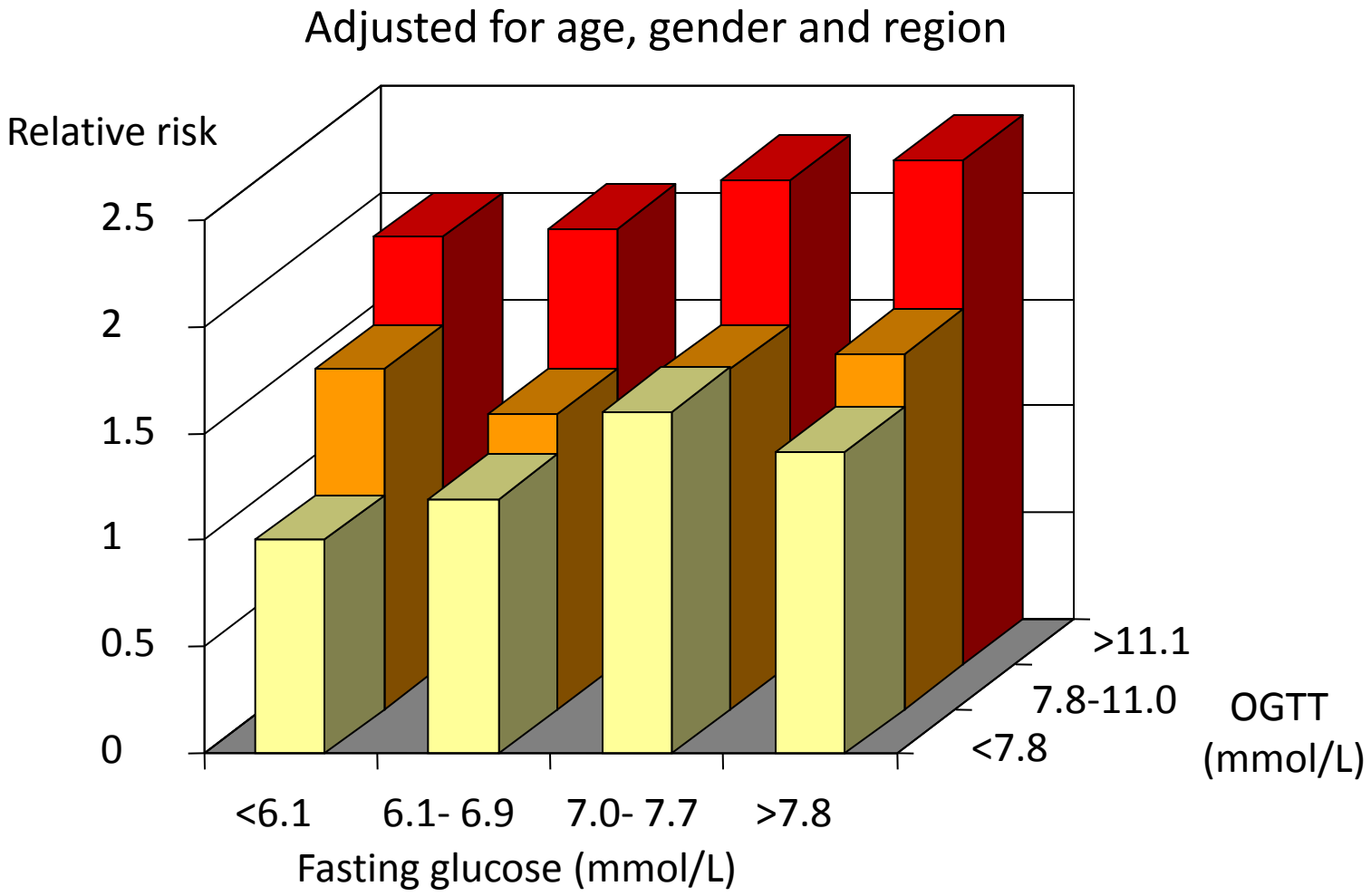
What It Is

Before you are born you are pre-natal, yet already in existence; before you are diabetic you are prediabetic—a state which is not normality nor yet a disease, but certainly there. This term 'Prediabetes' thus connotes the state of a person during the period before he or she becomes plainly and clinically diabetic, in which, however, there is a latent abnormality which may show itself under certain specific conditions.

Postgraduate Med J 1959

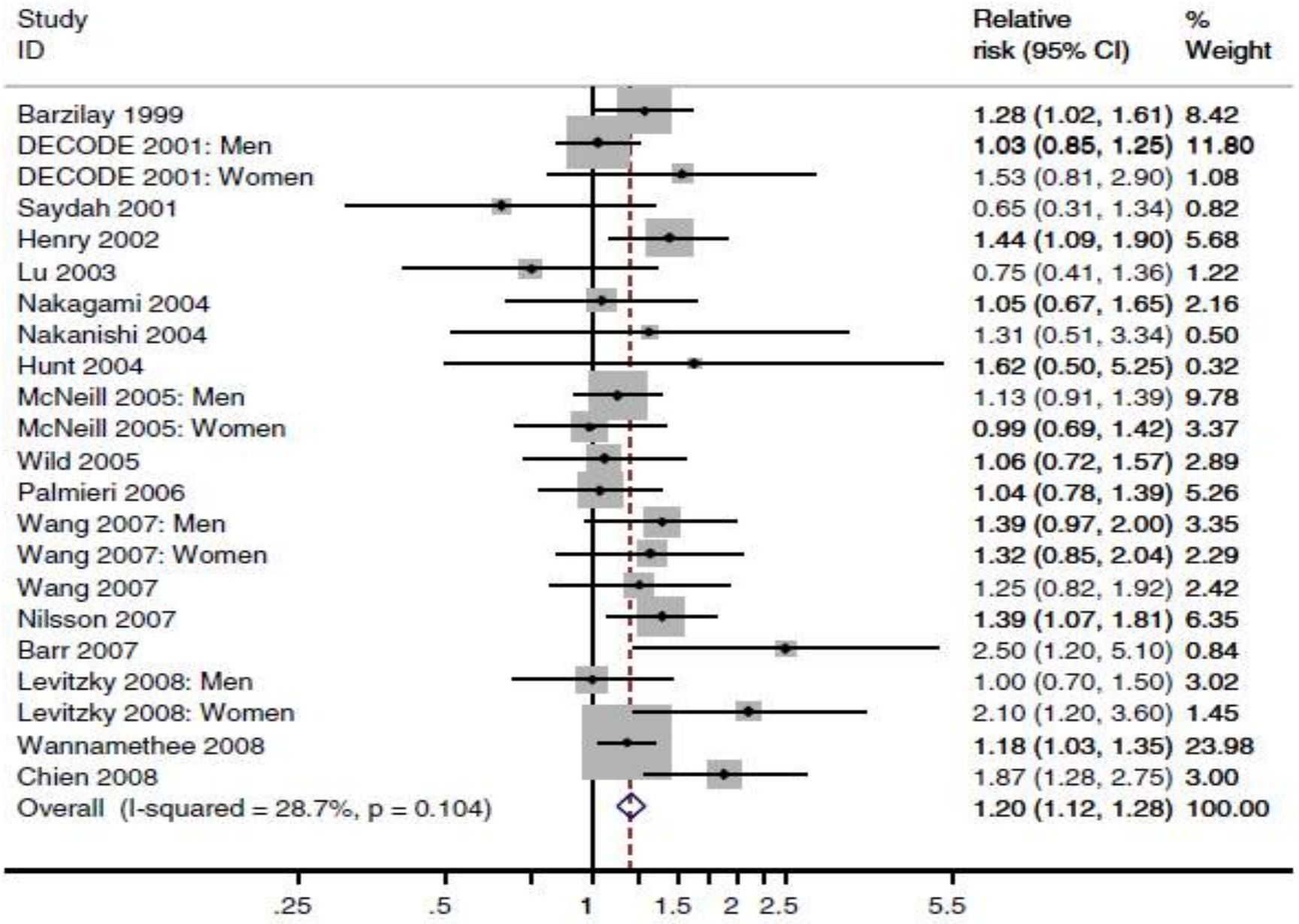
Cardiovascular Disease by Blood Glucose Status

Relation to fasting and postprandial glycemia in patients without diabetes



(The DECODE study group Lancet 1999; 354:617)

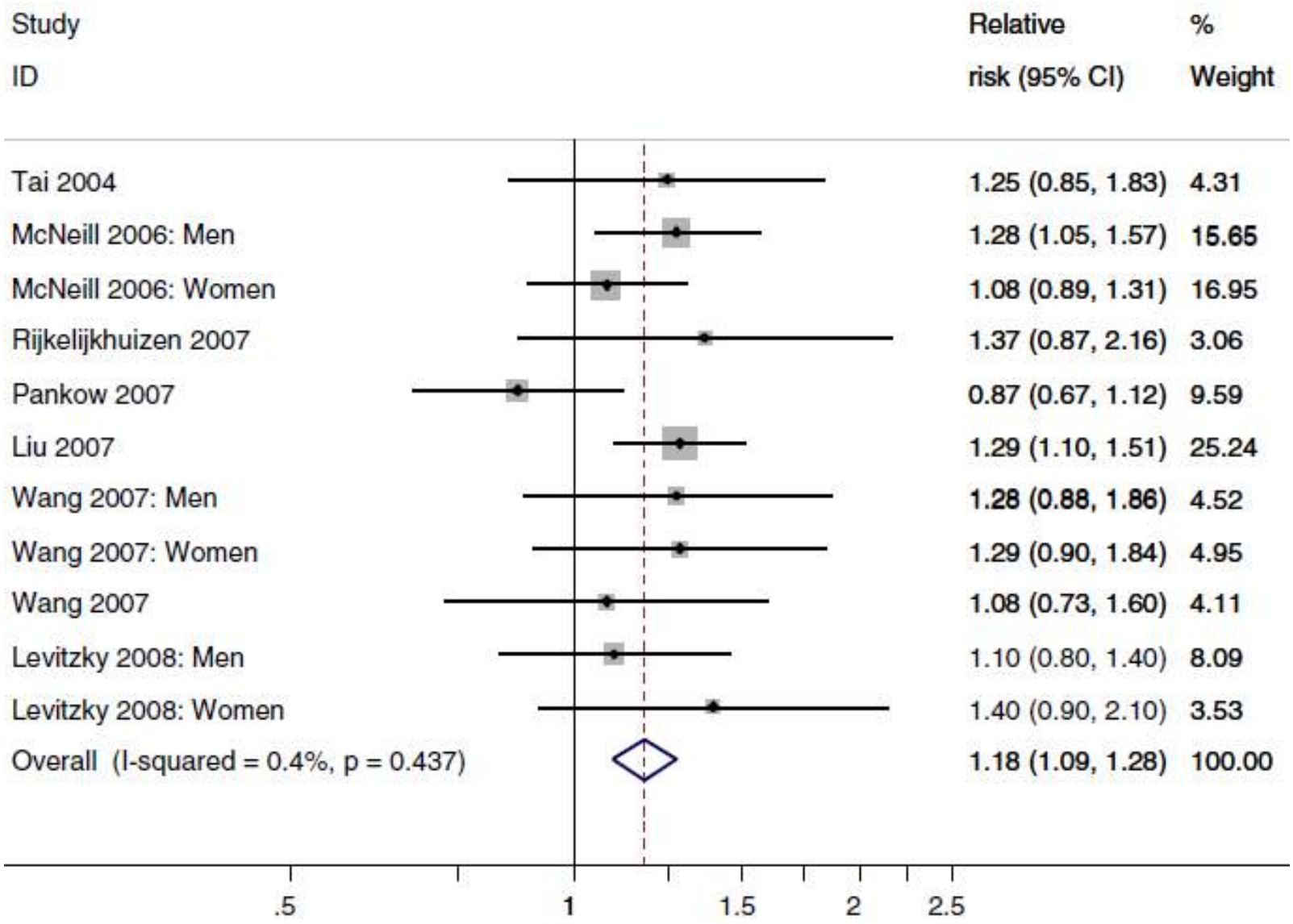
IFG as a Risk Factor for CVD– Systematic Review*



*IFG=110-125mg/dl

Ford ES et al: J Am Coll Cardiol 2010; 55: 1310

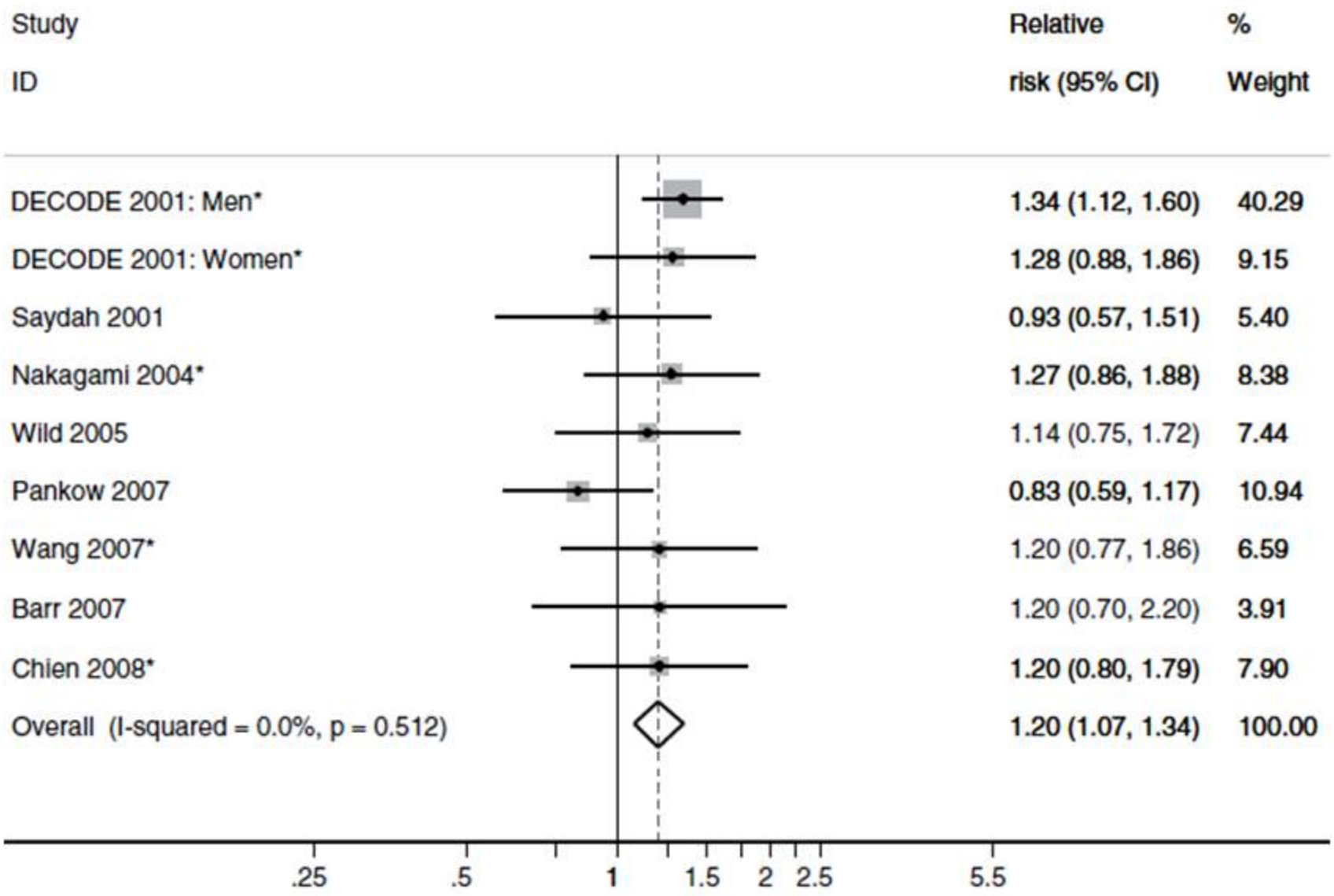
IFG as a Risk Factor for CVD– Systematic Review*



*IFG=100-125mg/dl

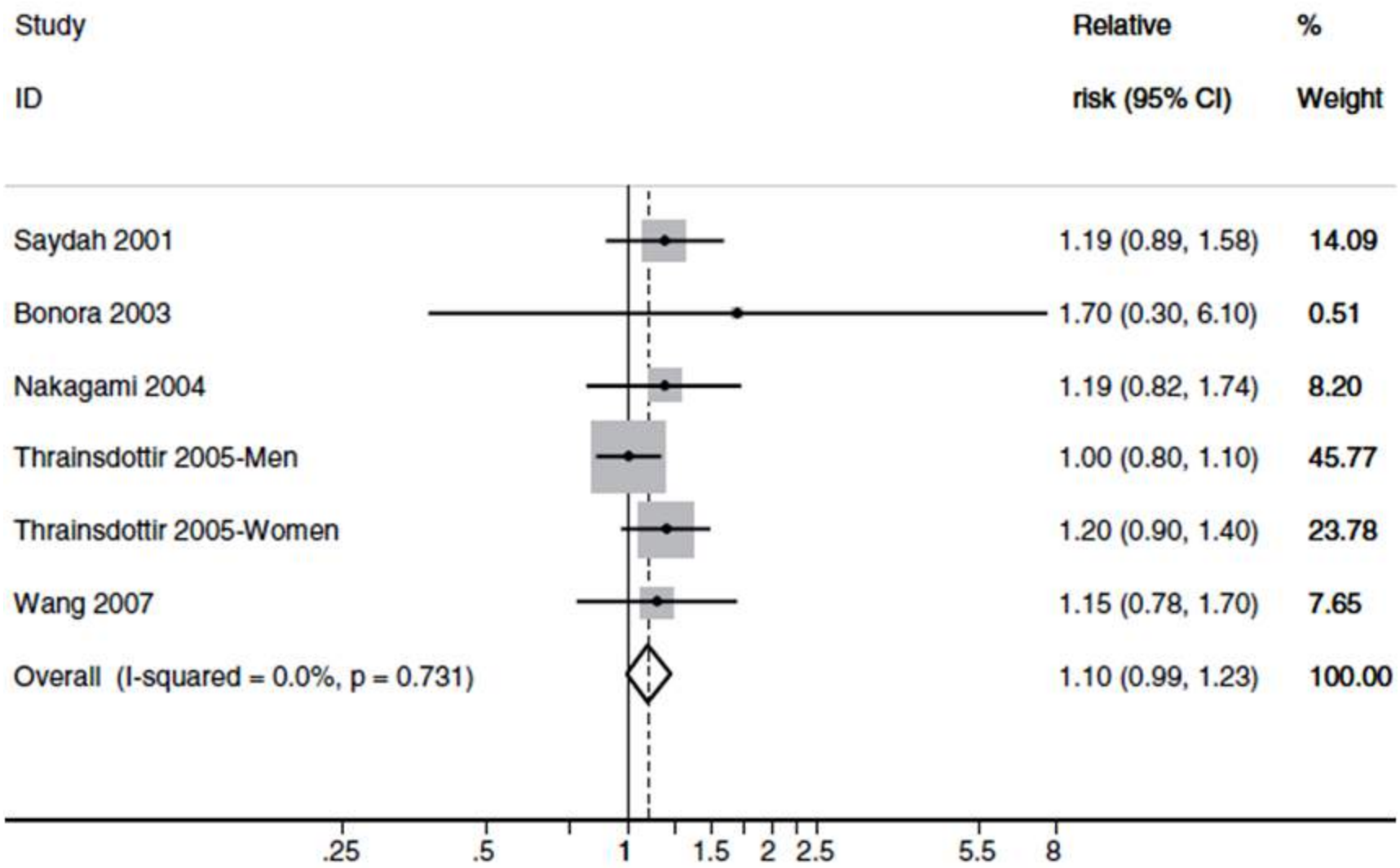
Ford ES et al: J Am Coll Cardiol 2010; 55: 1310

IGT as Risk Factor for CVD– Systematic Review



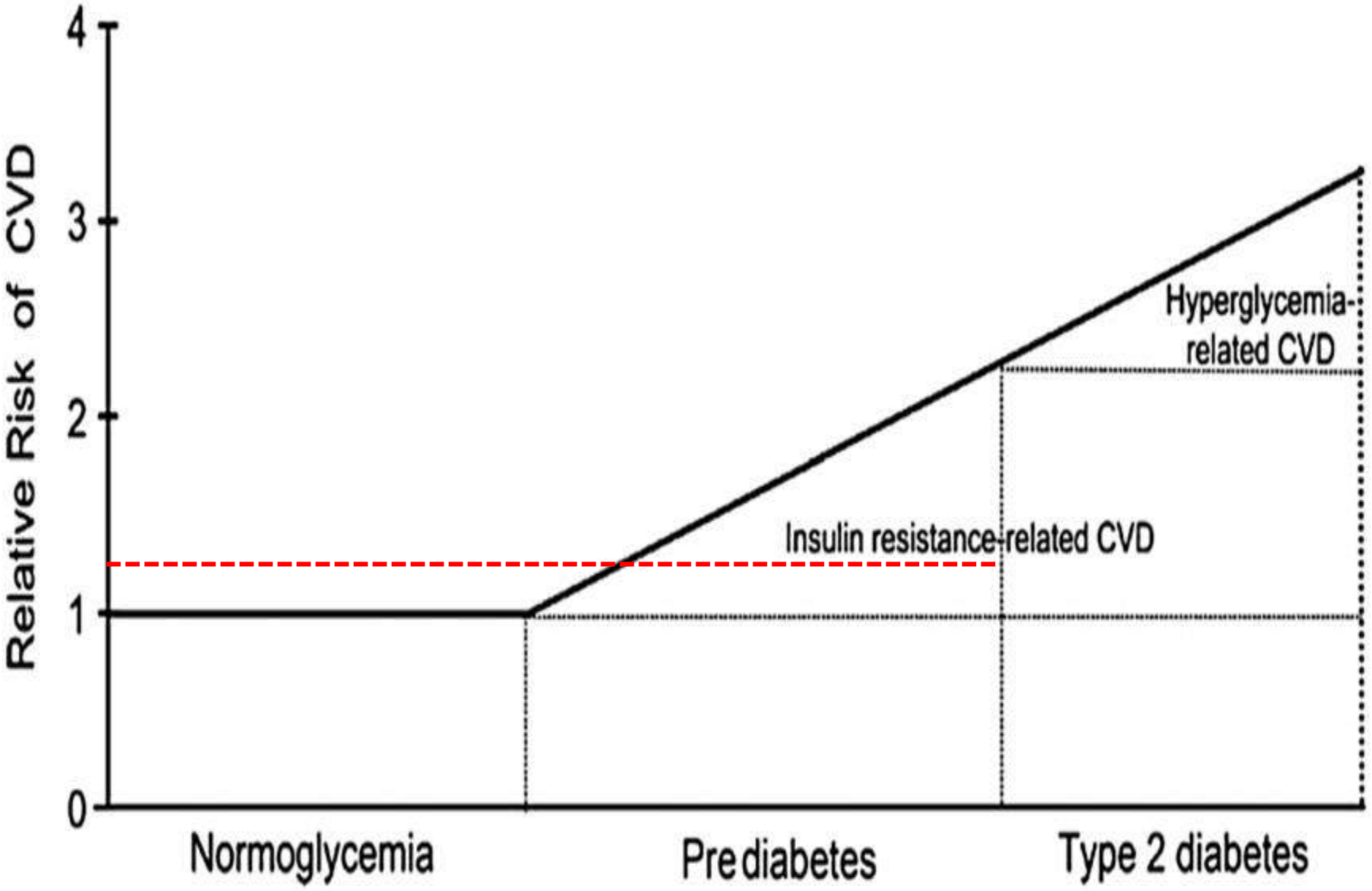
Ford ES et al: J Am Coll Cardiol 2010; 55: 1310

IFG+ITG as Risk Factor for CVD. Systematic Review



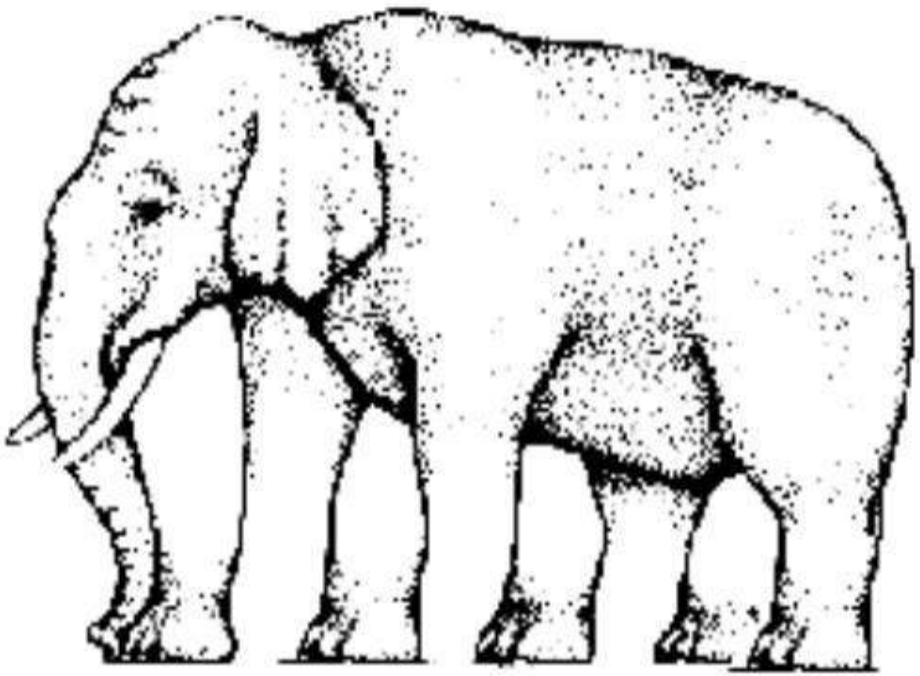
Ford ES et al: J Am Coll Cardiol 2010; 55: 1310

Dysglycaemia as Risk Factor for CVD



Laakso M: Diabetes Care 2010;33:444

Do we see all of us the same when looking at the Metabolic Syndrome?



How many legs does this elephant have?

Metabolic Syndrome as Risk Factor of CVD

CVD in 2.559 subjects 25-64 years free of CVD at baseline
Follow-up 7.4 years

	OR (95%CI) of CVD	
	Males	Females
2+RF & 10-20% risk*	11.9 (6.0-23.6)	4.4 (0.5-35.4)
MSxIDF	3.9 (2.1-7.2)	2.0 (1.0-4.1)
MSxATPIII	3.6 (2.0-6.7)	2.4 (1.1-5.1)
MSxWHO	2.5 (1.3-4.8)	2.2 (0,9-4.9)

*x Framingham

Lorenzo C et al: Diab Care 2007; 30: 8-13

Metabolic Syndrome as Risk Factor of CVD

CVD in 2.559 subjects 25-64 years free of CVD at baseline
Follow-up 7.4 years

	OR (95%CI) of CVD	
	Males ≥45year	Females ≥55year
2+FR & 10-20% risk*	11.9 (6.0-23.6)	4.4 (0.5-35.4)
MSxIDF	9.6 (5.1-17.9)	4.4 (1.9-10.1)
MSxATPIII	9.3 (4.9-17.7)	5.0 (2.1-12.0)
MSxWHO	6.5 (3.3-12.7)	5.9 (2.3-15)

*x Framingham

Lorenzo C et al: Diab Care 2007; 30: 8-13

MetS as Risk Factor of CVD

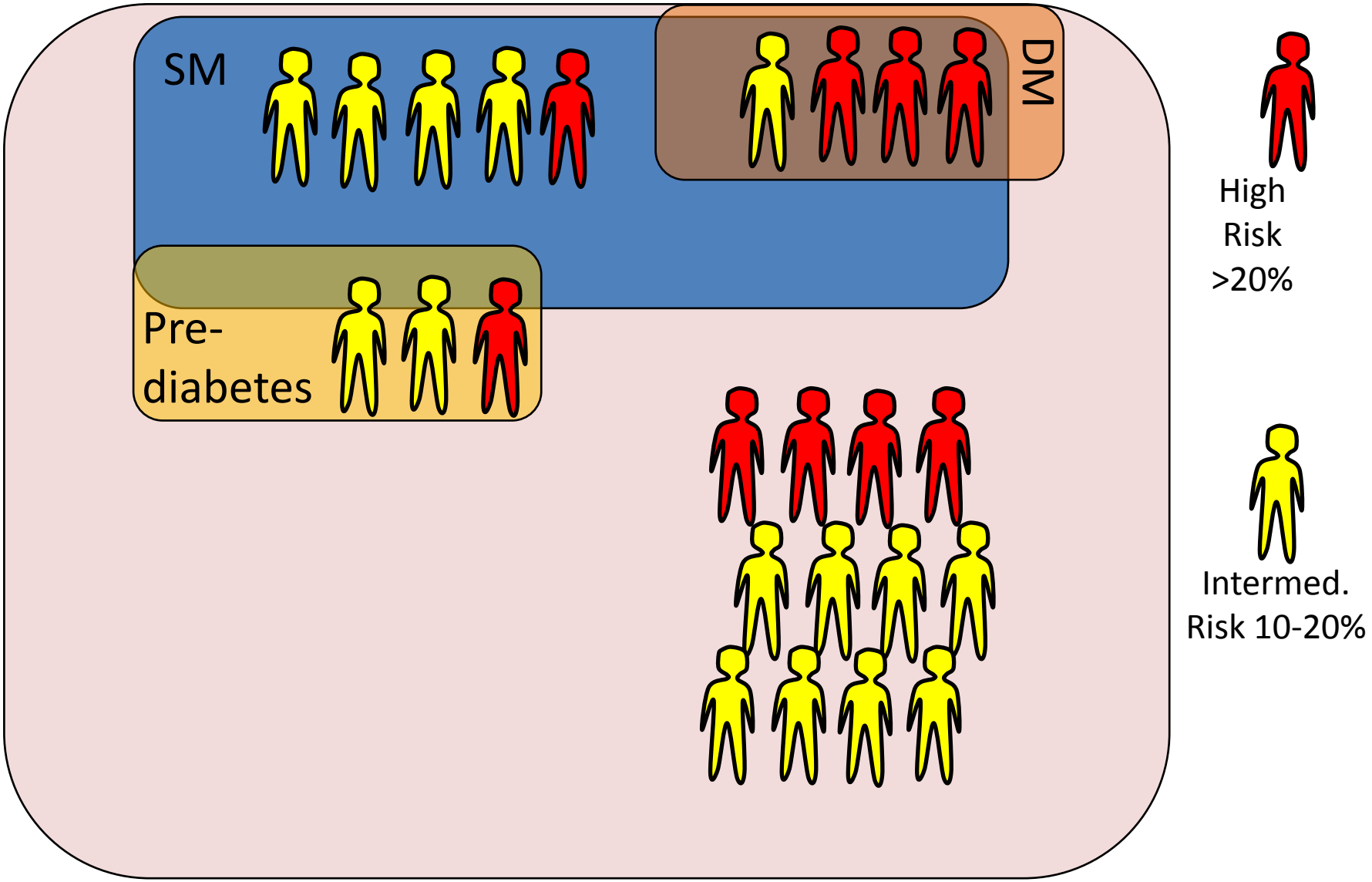
Study	F-UP.	Dx	Outcome	RR/HR (M/F)		10-y Risk %M/%F	
Framing-ham 2005	8	ATP III	CHD	2.54* (1.62-3.98)	ns	12	3.4
ARIC 2005	11	ATP III	CHD	2.05* (1.59-2.64)	1.46* (1.23-1.74)	13.8	5.8
MRFIT 2006	18	ATP III	Mortal.	1.21* (1.13-1.29)		12.4	
			CV Mort.	1.49* (1.35-1.64)		6.7	
Uppsala 2006	30	ATP III	Mortal.	1.36* (1.17-1.58)		15.5	
			CV Mort.	1.59* (1.29-1.95)		7.2	

intermediate (10-20%)

*Adjusted

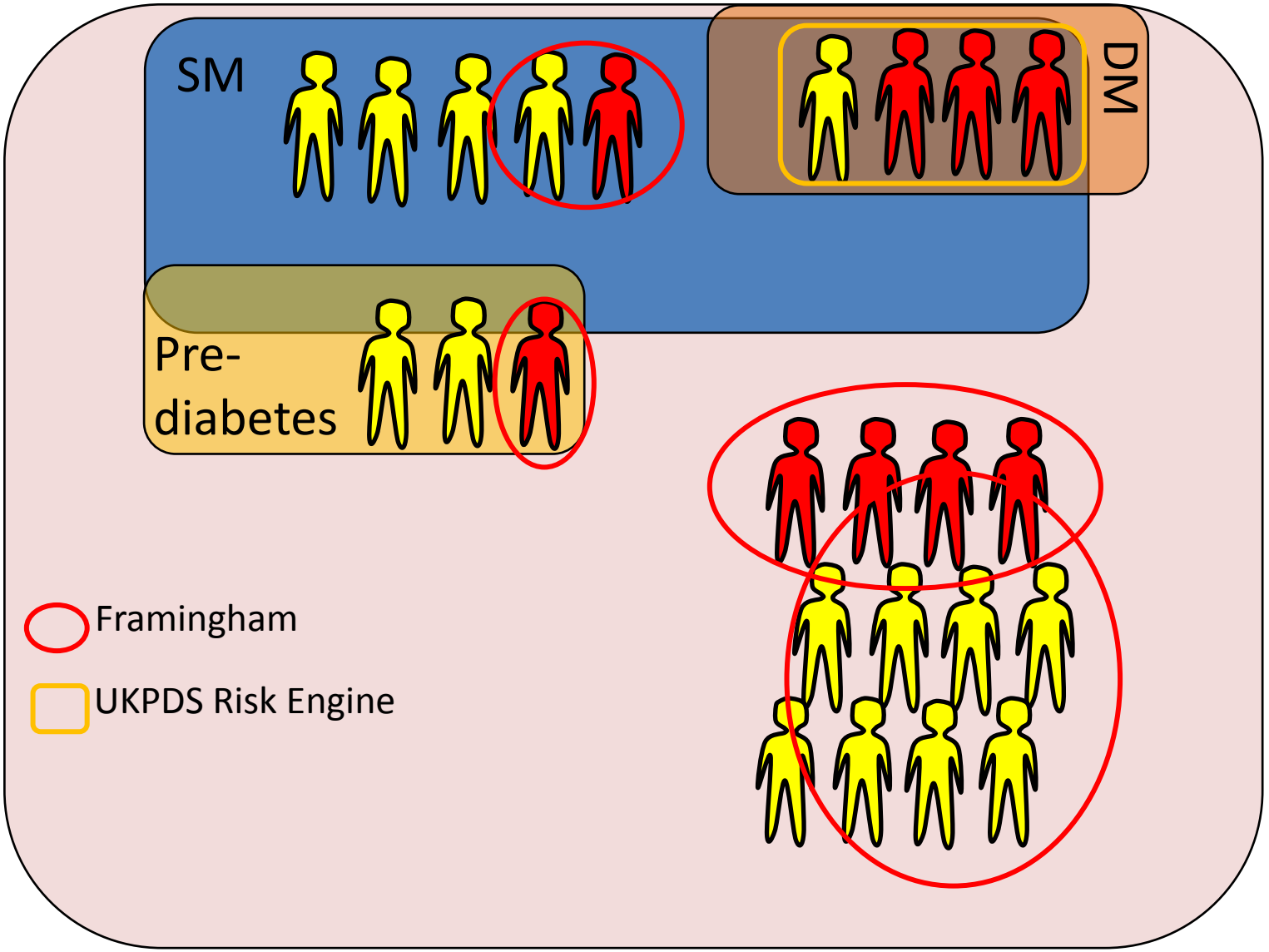
P.Aschner, 2011

CVD Risk in adults 25-34 years



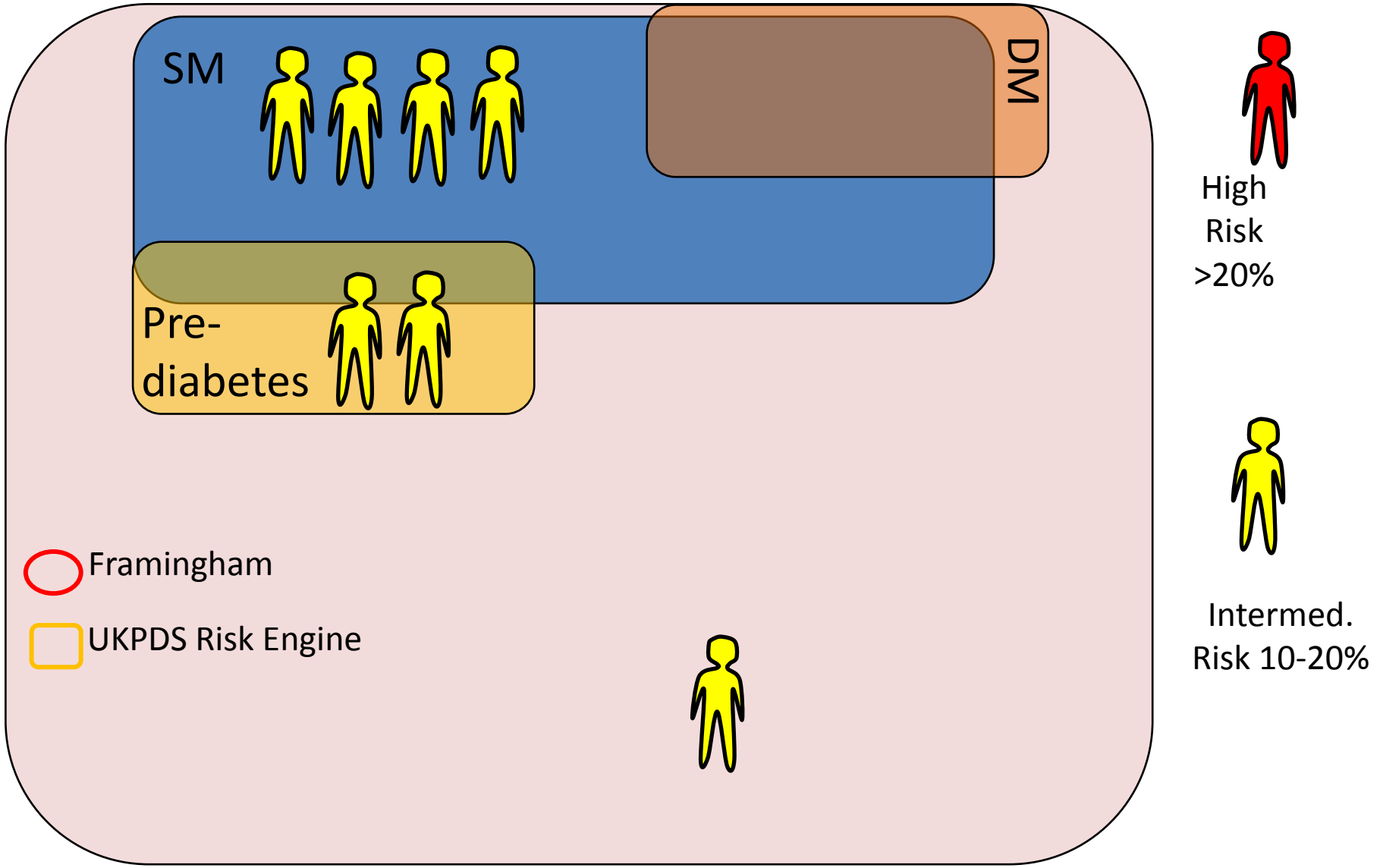
P.Aschner 2012

CVD Risk in adults >25-30 years



P.Aschner 2012

CVD Risk in adults >25-30 years



P.Aschner 2012

When does the clock start ticking for cardiovascular disease?

There is now convincing evidence that cardiovascular disease begins **before** the onset of clinical diabetes.

However, it is not known **which specific element** of the diabetic state is responsible for the increase in cardiovascular risk.

- **Hyperglycemia?**
- **Hypertension?**
- **Hemostatic factors?**
- **Proinflammatory cytokines?**
- **Changes in circulating lipids?**

None of these factors alone can account for the excess risk of cardiovascular disease.

Insulin resistance

- Insulin resistance is an underlying feature of both **the metabolic syndrome** and **type 2 diabetes.**
- It is associated with **abnormalities** in both **glucose** and **lipid metabolism.**
- These abnormalities are associated with an **increased risk** of cardiovascular disease and are often present **before** the onset of type 2 diabetes.

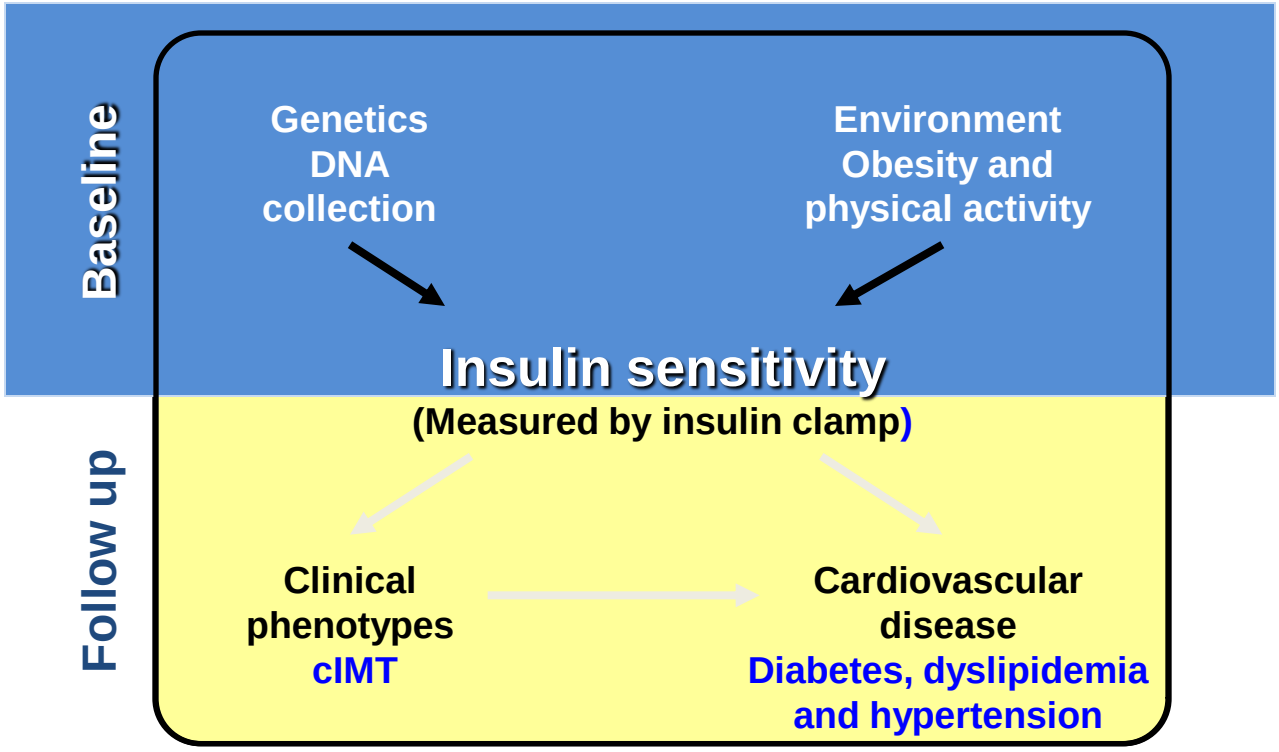
Hyperinsulinemia

The San Antonio Heart Study first and many others later have linked hyperinsulinemia with incident diabetes, hypertension and dyslipidemia.

However, hyperinsulinemia is the physiologic result of insulin resistance and insulin secretion.

Furthermore, hyperinsulinemia may have pathophysiologic effects distinct from insulin resistance itself.

The main hypothesis in the European RISC Study

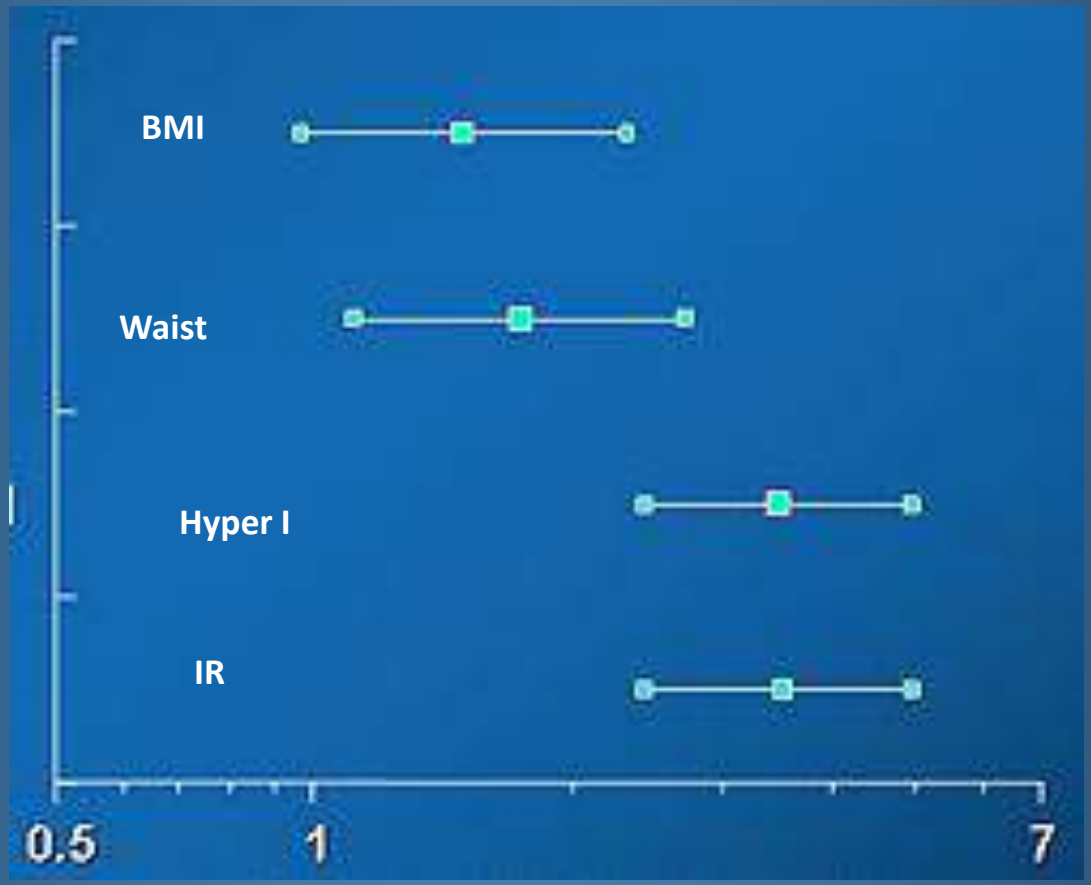


At baseline, information is obtained on genetic factors and relevant environmental factors and insulin resistance is measured.

At follow up, changes in carotid atherosclerosis are related to insulin resistance and/or clinical phenotype.

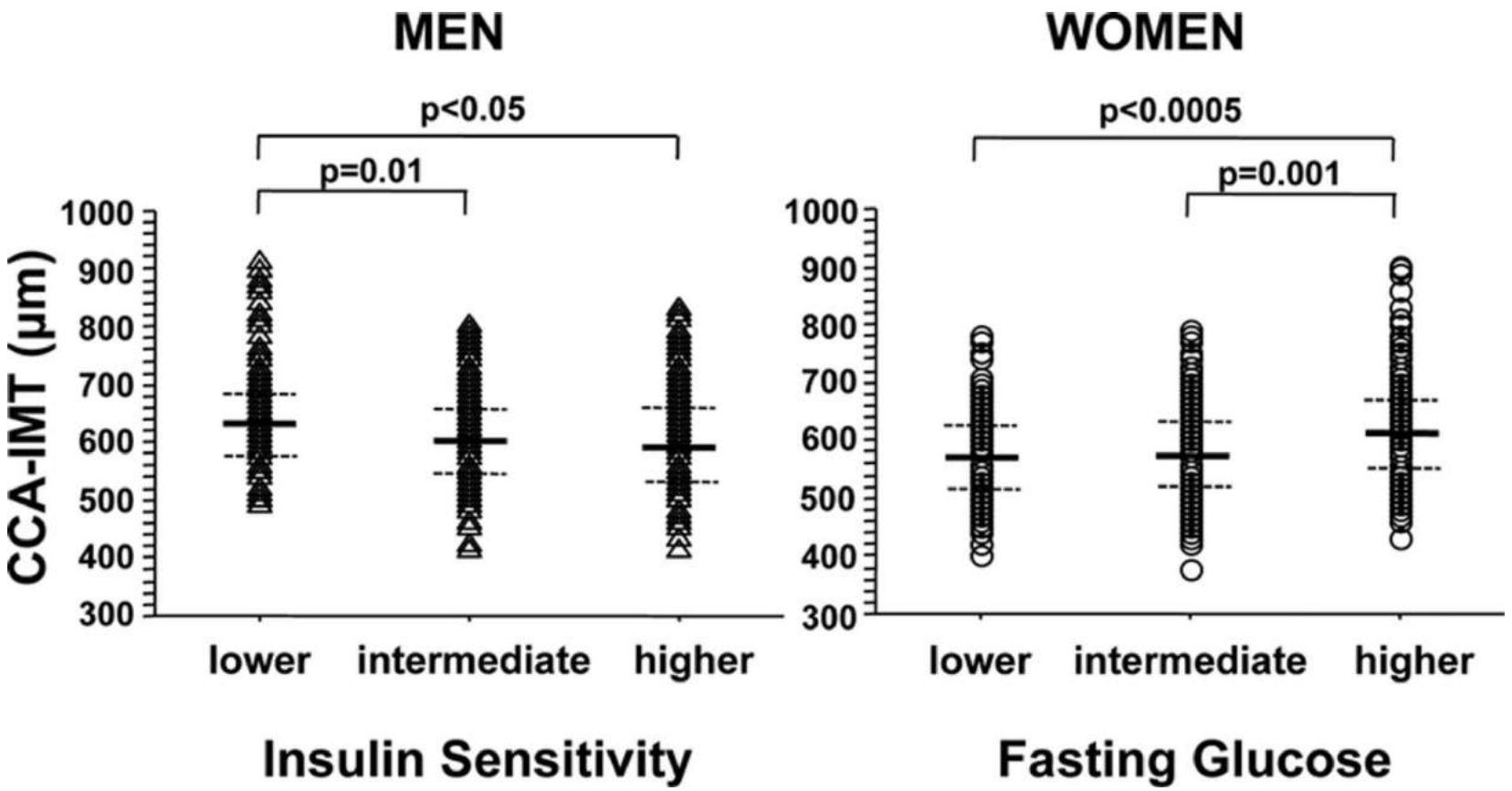
Insulin Resistance, Hyperinsulinemia, BMI, Waist Circumference and Cardiovascular Risk Score

"Risk Score" (upper quartile)*



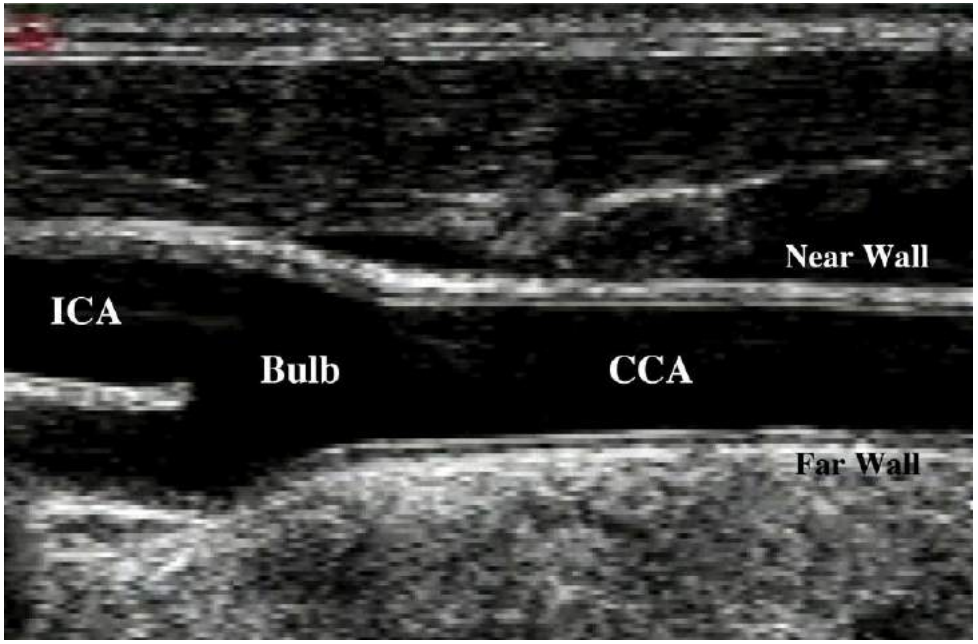
* Adjusted by centre

Baseline common carotid artery–intima-media thickness (CCA-IMT) by tertiles of insulin sensitivity and fasting plasma glucose



Michaela Kozakova et al. Arterioscler Thromb Vasc Biol. 2013;33:1409-1417

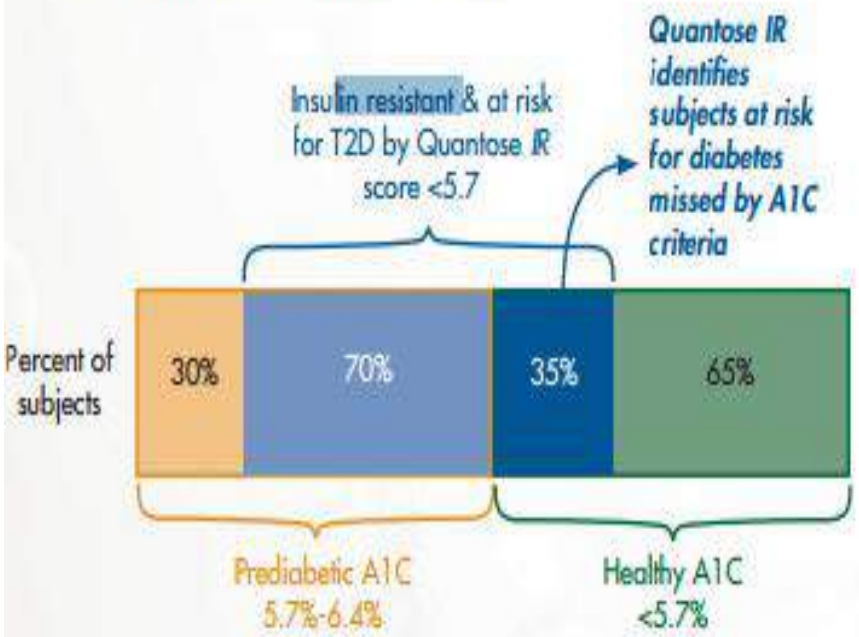
Three-year CCA-IMT changes were not associated with any cardio-metabolic risk factor in the RISC Study



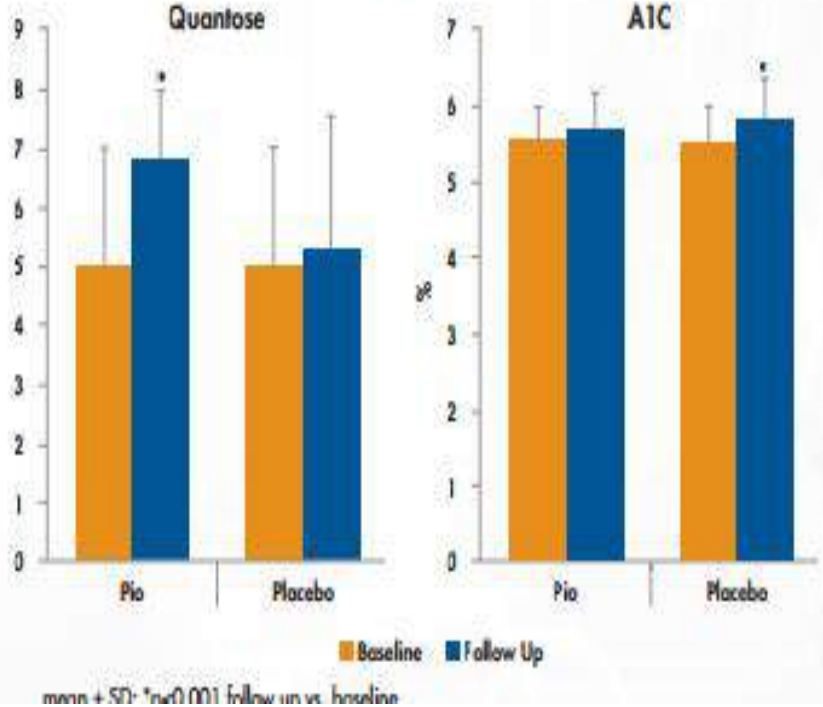
Quantose as early marker of Insulin Resistance

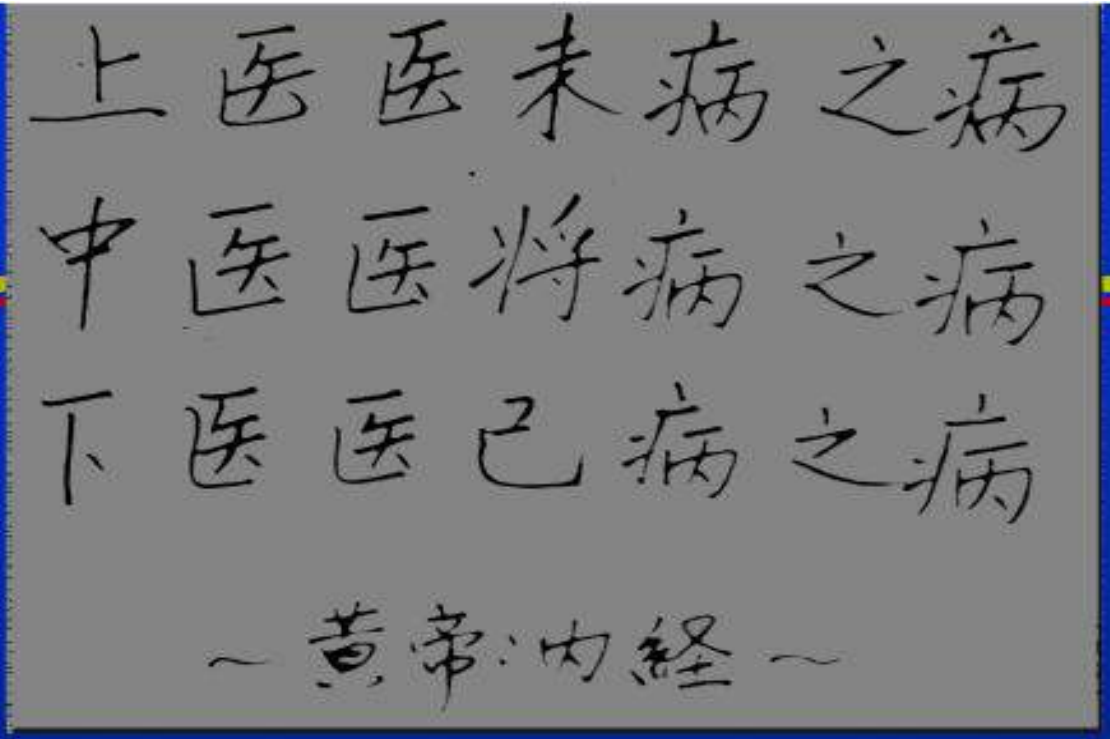
Clinical Outcome Data

1. Quantose *IR* identifies insulin resistant individuals within a healthy A1C range.[5]



2. Quantose *IR* tracked improvement in insulin sensitivity where A1C did not in the ACT NOW study.[5]





Superior doctors prevent the disease.
Mediocre doctors treat the disease
before evident.
Inferior doctors treat the full-blown disease.
--Huang Dee: Nai-Ching
(2600 BC First Chinese Medical Text)

Approaches to Primary and Secondary Prevention of CVD

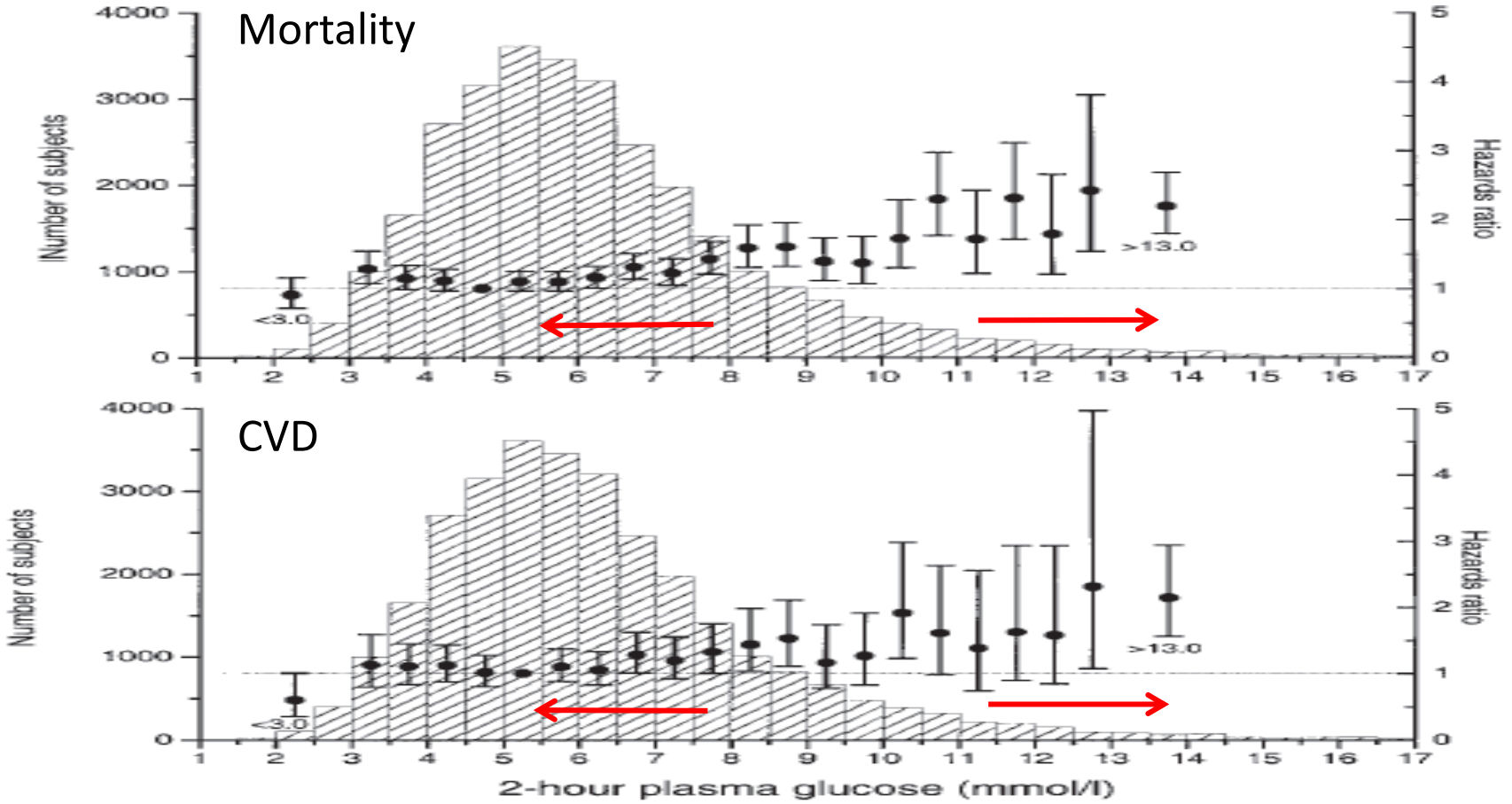
- Primary prevention involves prevention of onset of disease in persons without symptoms.
- Primordial prevention involves the prevention of risk factors causative o the disease, thereby reducing the likelihood of development of the disease.
- Secondary prevention refers to the prevention of death or recurrence of disease in those who are already symptomatic

Population vs. High-Risk Approach

- Risk factors, such as fasting and postprandial blood glucose , have a wide bell-shaped distribution, often with a “tail” of high values.
- The “high-risk approach” involves identification and intensive treatment of those at the high end of the “tail”, often at greatest risk of CVD, reducing levels to “normal”.
- But most cases of CVD do not occur among the highest levels of a given risk factor, and in fact, occur among those in the “average” risk group.
- Significant reduction in the population burden of CVD can occur only from a “population approach” shifting the entire population distribution to lower levels.

2h-Blood Glucose and Mortality. DECODE STUDY

To Whom Intervene?



Too many?

High risk identification
(prediabetes)

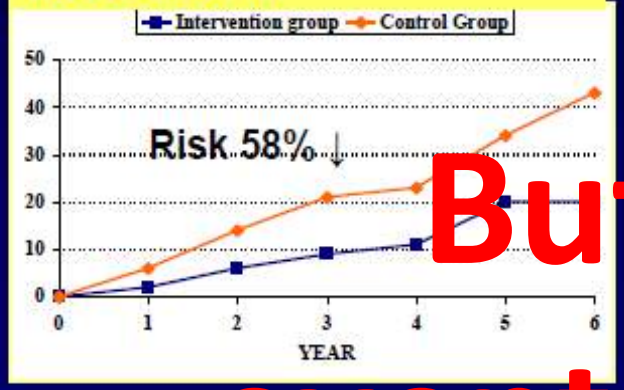
Too late!

7.8 mmol/l=140mg/dl
11.1 mmol/l=200mg/dl

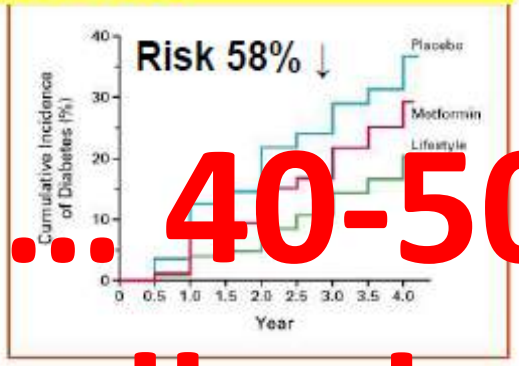
Decode Group. Diab Care 2003; 26:688

Prevention of Type 2 Diabetes by Lifestyle Management: The Evidence

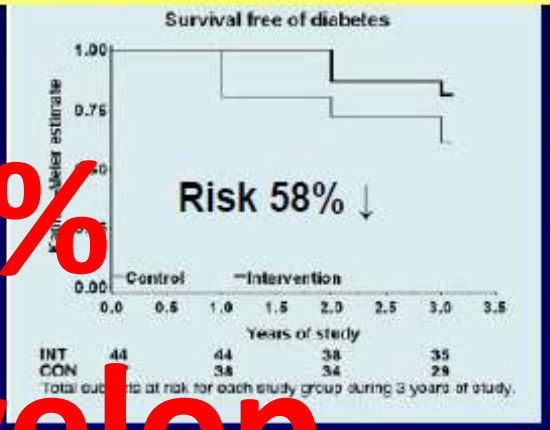
DPS - Finland



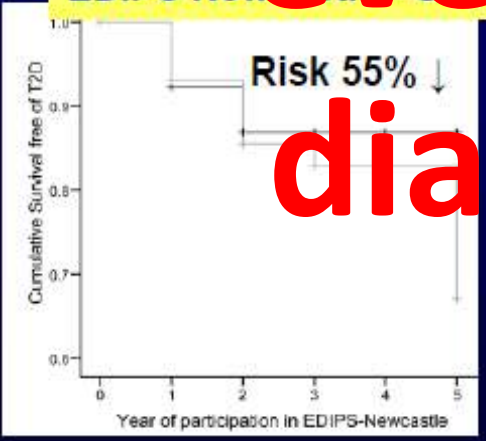
DPP - USA



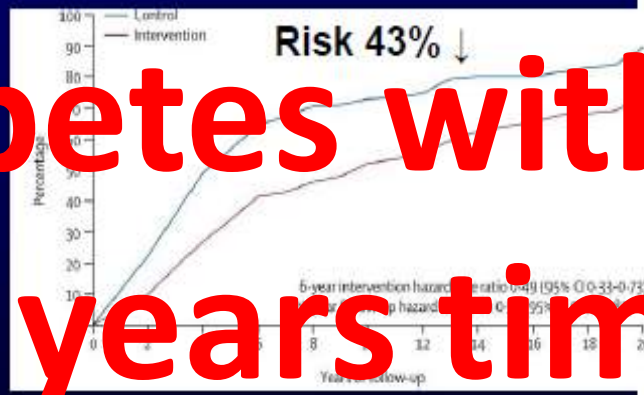
SLIM - Netherlands



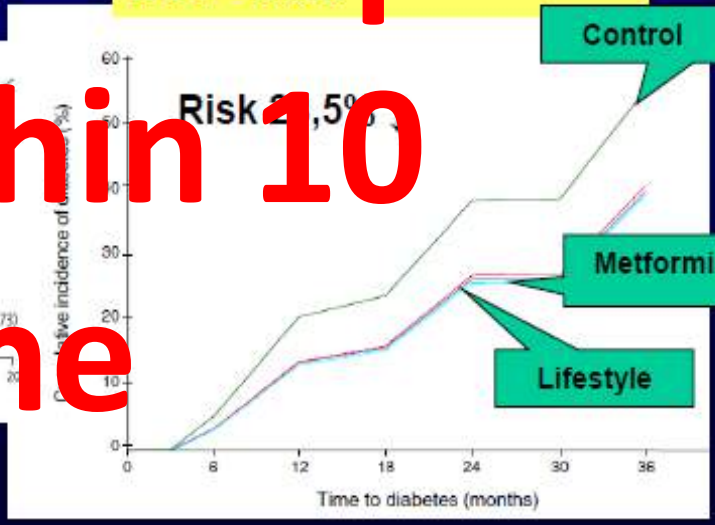
EDIPS Newcastle - UK



Da Qing - China

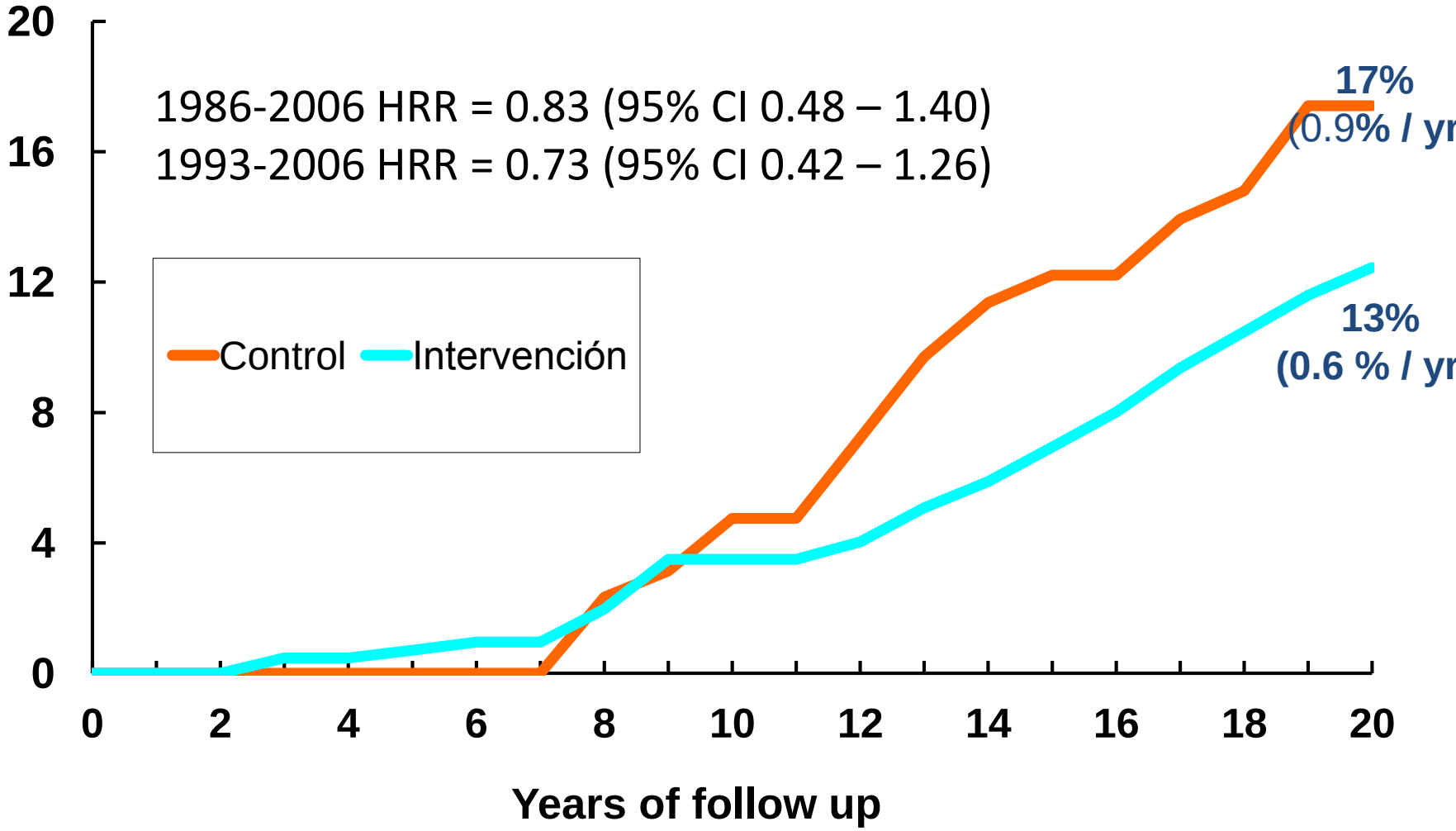


IDRP - India



But… 40-50% eventually develop diabetes within 10 years time

Cummulative CVD Mortality in DPP Study



PREDIABETES:

To treat or not to treat…

with drugs

That is the question

Dr. Shakespeare; Hamlet, Chapt. 3

ADA Consensus Panel on IFG and IGT;

CONSENSUS STATEMENT

Impaired Fasting Glucose and Impaired Glucose Tolerance

Implications for care

David M. Nathan, MD[1]
Mayer B. Davidson, MD[2]
Ralph A. DeFronzo, MD[3]
Robert J. Heine, MD, PHD, FRCP[4]
Robert R. Henry, MD[5]
Richard Pratley, MD[6]
Bernard Zinman, MD[7]

Type 2 diabetes is now epidemic. In the U.S., there has been a 61% increase in incidence between 1990 and 2001 (1). There are currently 1.5 million new cases per year, and the prevalence in 2005 was almost 21 million (2). The epidemic has affected developed and developing countries alike, and the worldwide prevalence of diabetes is projected to increase dramatically by 2025 (3). The increase in type 2 diabetes is related to lifestyle changes that have resulted in overweight, obesity, and decreased physical activity levels. These environmental changes, superimposed on genetic predisposition, increase insulin resistance, which, in concert with progressive β-cell failure, results in rising glycemia in the nondiabetic range. In addition to the risk for diabetes, insulin resistance and impaired insulin secretion are accompanied by a host of major cardiovascular disease (CVD) risk factors including hypertension and dyslipidemia. Further reduction in insulin secretion over time results in increasing glycemia and the development of diabetes, which in turn is associated with the development of microvascular and cardiovascular complications.

The transition from the early metabolic abnormalities that precede diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes may take many years, however, current estimates indicate that most individuals (perhaps up to 70%) with these pre-diabetic states eventually develop diabetes (4–10). During the pre-diabetic state, the risk of a CVD event is modestly increased (11–22). With the development of diabetes, however, there is a large increase in risk for CVD, as well as for long-term complications affecting the eyes, kidneys, and nervous system. The complications of diabetes, which are the cause of major morbidity and mortality, are related to its duration, chronic level of glycemia, and other risk factors.

Although clinical trials have demonstrated the effectiveness of intensive glycemic and blood pressure control to reduce the long-term complications of diabetes, the public health burden of the disease remains enormous. The magnitude of the epidemic, coupled with complex treatment requirements that are difficult and costly to implement, make the prevention of diabetes a critical public health goal. Between 1997 and 2006, eight major clinical trials examined whether lifestyle or pharmacologic interventions would prevent or delay the development of diabetes in populations at high risk by virtue of having IFG and/or IGT (4,5,23–28). The study populations often had other recognized risk factors for diabetes including obesity, a prior history of gestational diabetes, or a positive family history of diabetes. All of these trials demonstrated reductions in the development of diabetes of 25–60% over the period of follow-up. The largest reductions (~60%) were accomplished with lifestyle interventions aimed at weight loss and increasing physical activity and with thiazolidinediones (4,5,24,25,27). Lesser degrees of reduction (25–30%) have been achieved with other drugs (5,23,24,28).

The availability of interventions that have been shown to decrease the development of diabetes has stimulated consideration whether such interventions should be recommended and implemented, in whom, and under what circumstances. To address these issues, the American Diabetes Association convened a consensus development conference on 16–18 October 2006 focusing on the pre-diabetic states of IFG and IGT. Following the presentations of invited speakers and in-depth discussions, a seven-member panel of experts in diabetes, endocrinology, and metabolism developed this consensus position based on the questions below. The expert members were also asked to note where additional information or studies would be necessary to answer these questions.

QUESTION 1: What are IFG and IGT, and what is their natural history? — How much does IFG, IGT, or the combination of both conditions increase the risk for subsequent development of diabetes? Does IFG and/or IGT increase the development of cardiovascular disease? If so, are the effects of IFG and/or IGT independent of associated known cardiovascular risk factors including the subsequent development of diabetes?

IFG and IGT represent intermediate states of abnormal glucose regulation that exist between normal glucose homeostasis and diabetes. IFG is now defined by an elevated fasting plasma glucose (FPG) concentration (≥100 and <126 mg/dl) (29). IGT is defined by an elevated 2-h plasma glucose concentration (≥140 and

From [1]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; the [2]Clinical Center for Research Excellence, Charles R. Drew University of Medicine and Science, Los Angeles, California; the [3]University of Texas Health Science Center, San Antonio, Texas; the [4]Diabetes Center, VU University Medical Center, Amsterdam, the Netherlands; the [5]Department of Medicine, University of California, San Diego, California; the [6]Department of Medicine, University of Vermont, Burlington, Vermont; and the [7]Departments of Endocrinology and Metabolism, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada.

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Panel disclosures can be found on p. 757.

Abbreviations: CVD, cardiovascular disease; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc07-9920

Table 2—*Treatment recommendation for individuals with IFG, IGT, or both*

Population	Treatment
IFG or IGT	Lifestyle modification (i.e., 5–10% weight loss and moderate intensity physical activity ~30 min/day)
Individuals with IFG *and* IGT *and* any of the following: • <60 years of age • BMI ≥35 kg/m^2 • Family history of diabetes in first-degree relatives • Elevated triglycerides • Reduced HDL cholesterol • Hypertension • A1C >6.0%	Lifestyle modification (as above) and/or metformin*

*Metformin 850 mg twice per day.

IFG, impaired fasting glucose; IGT, impaired glucose tolerance

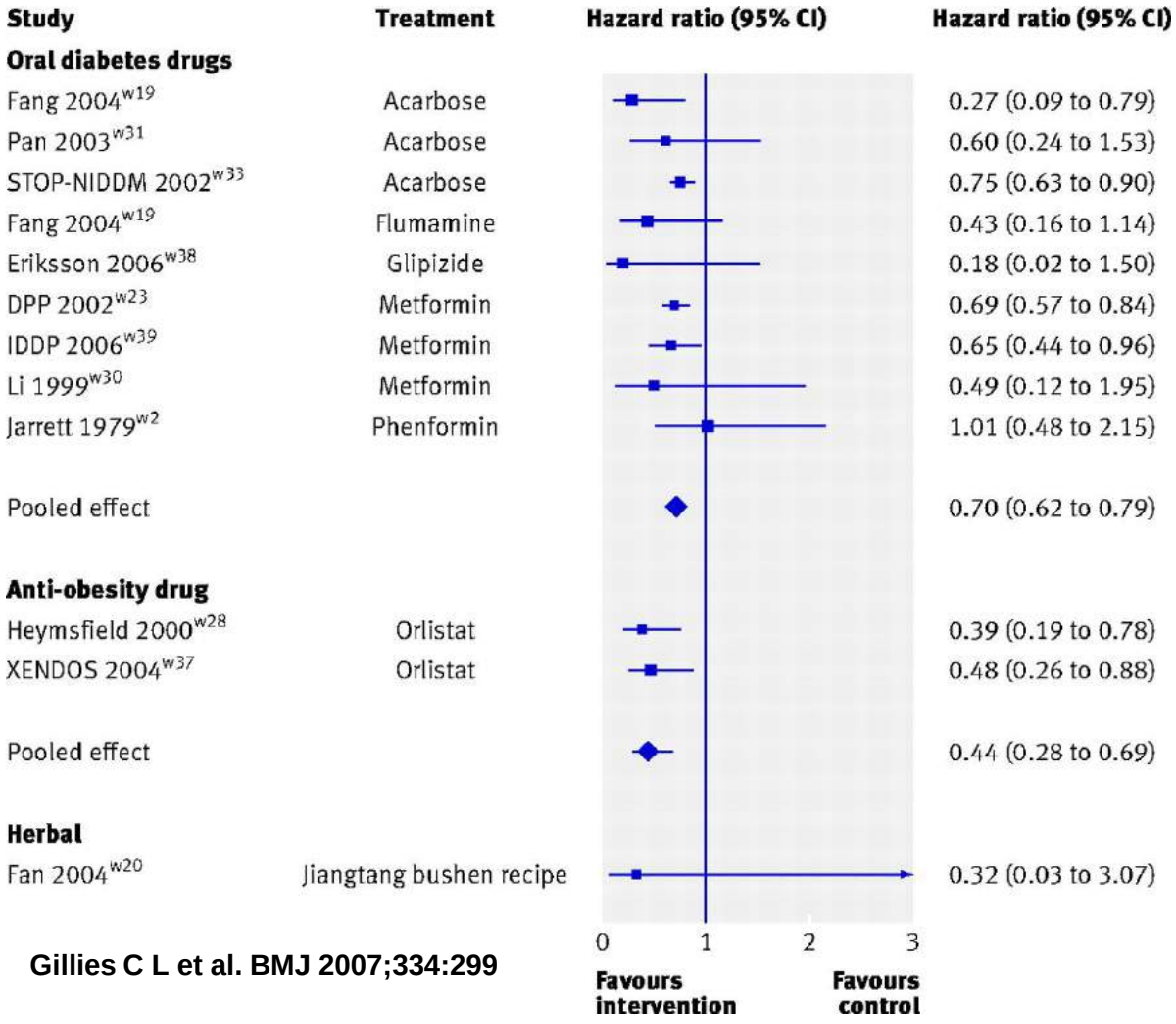
Nathan et al. *Diabetes Care* 2007; 30:753–9

Figure 2. Meta-analysis of studies of effects of metformin on prediabetes using intention-to-treat and worst-case-scenario sensitivity analysis

STUDY OR SUBCATEGORY	TREATMENT n/N	CONTROL n/N	OR (FIXED) 95% CI	WEIGHT %	OR (FIXED) (95% CI)
Li et al[22]: ITT, WCS	6/45	6/45		1.79	1.00 (0.30-3.37)
Knowler et al (ITT)[24]: WCS	237/1073	313/1082		83.76	0.70 (0.57-0.85)
Ramachandran et al[23]: ITT, WCS	53/129	73/136		14.44	0.60 (0.37-0.98)
Total (95% CI)	1247	1263		100	0.69 (0.58-0.82)
Total events: 296 (treatment), 392 (control)					
Test for heterogeneity: $\chi^2_2 = 0.67$, $P = .72$, $I^2 = 0\%$					
Test for overall effect: $Z = 4.09$, $P < .0001$					

CI–confidence interval, ITT–intention to treat, OR–odds ratio, WCS–worst-case scenario.

Meta-analyses of effect of pharmacological and herbal interventions on risk of developing type 2 diabetes.



Gillies C L et al. BMJ 2007;334:299

KEY MESSAGES REGARDING METFORMIN AND CVD PREVENTION

•The retrospective database analyses can suggest that metformin may have beneficial CV effects but cannot prove it

•The lack of of additional studies to support the findings of the UKPDS after 16 years suggests the thesis that the data are unclear
(we need at least 2 RCCT to be certain)

•The Glucose Lowering in Non-diabetic Hyperglycaemia Trial (GLINT) is being initiated to determine the effect of metformin vs placebo in reducing CV events in non-diabetic patients with Hyperglycaemia and high CV risk. This study will conclude in 2022

THE EVIDENCE OF METFORMIN IS UNCLEAR

Prevention of macrovascular complications in prediabetes

Meta-analysis de 10 RCTs (23,152 patients; 3.75 year of treatment)

NO DIFFERENCE between drug therapy and control for :

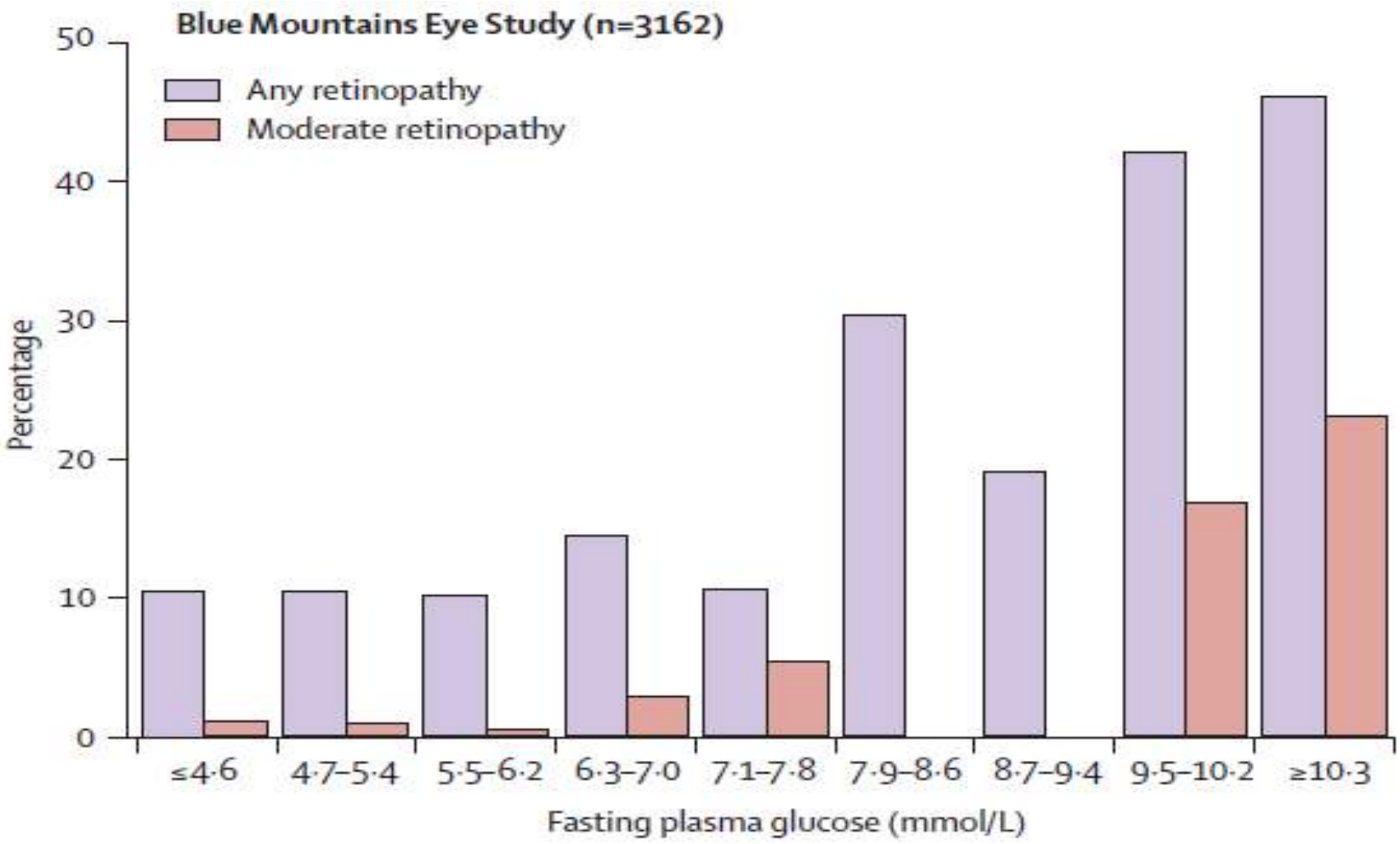
-All cause mortality (0.96; 95%CI 0.84-1.10)
-Cardiovascular death (1.04; 95%CI 0.61-1.78).
-Fatal or non-fatal MI (0.59; 95%CI 0.23-1.50).

--Reduction of Stroke in the limit of significance (0.76, 0.58-0.99)

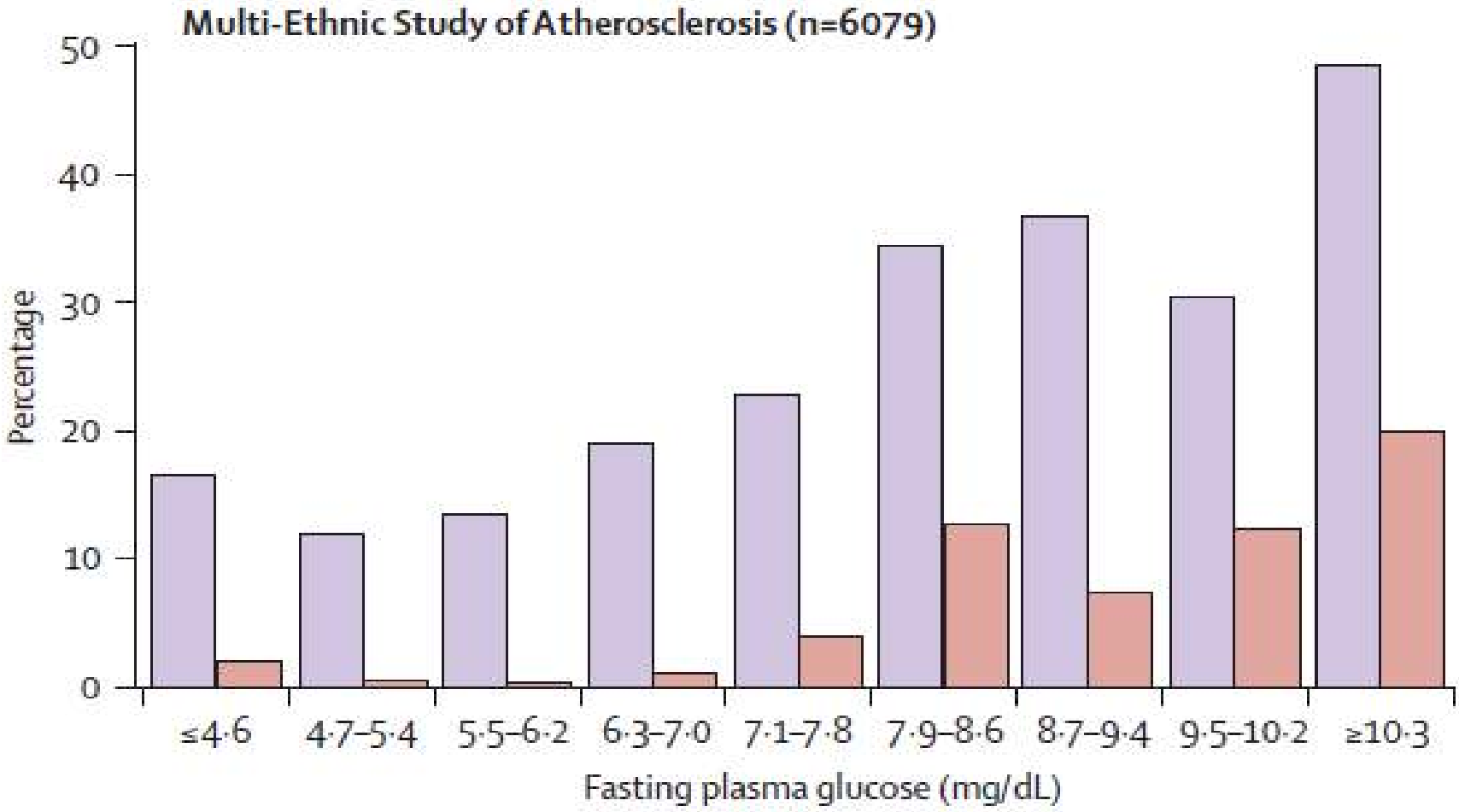
CONCLUSSION:
To date, no intervention (lifestyle or drug) has shown significant reduction of CV events, except for stroke as the only "possible exception".

Hopper I et al. Eur J Cardiovasc Prev Rehabil. 2011;18:813-23

MICROVASCULAR COMPLICATIONS



PREVALENCE OF RETINOPATHY IN PREDIABETES



Glycemic Thresholds for Diabetes-Specific Retinopathy

Implications for diagnostic criteria for diabetes

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THE DETECT-2 COLLABORATION WRITING GROUP*

RESEARCH DESIGN AND METHODS — We conducted a data-pooling analysis of nine studies from five countries with 44,623 participants aged 20–79 years with gradable retinal photographs. The relationship between diabetes-specific retinopathy (defined as moderate or more severe retinopathy) and three glycemic measures (fasting plasma glucose [FPG; n = 41,411], 2-h post oral glucose load plasma glucose [2-h PG; n = 21,334], and A1C [n = 28,010]) was examined.

Diabetes Care 34:145–150, 2011

Neuropathy

- The concept that neuropathy is an early sign of diabetes was proposed decades ago
- Disturbance of peripheral nerves appears in early phases with mild dysglycaemia.
- 50% of prediabetic people shown light-moderate neuropathy (higher Vibration Perception Thresholds)
- Most of studies have reported an association between IGT & neuropathy.

The best way to prevent the progression of microvascular complicacions in prediabetes?…

To prevent the progression of hyperglycaemia

Diabetologia (2011) 54:300–307
DOI 10.1007/s00125-010-1948-9

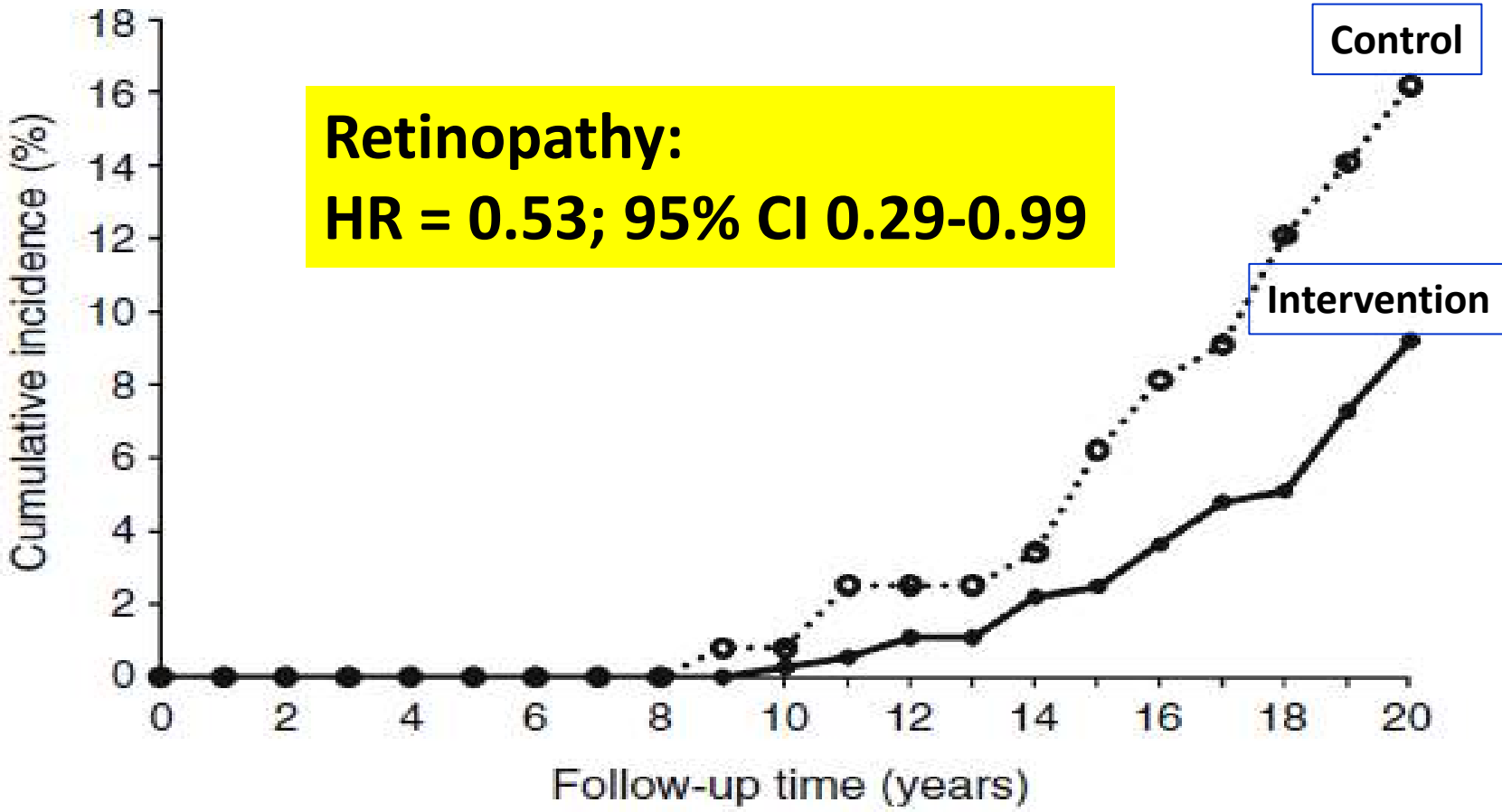
ARTICLE

Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study

Q. Gong · E. W. Gregg · J. Wang · Y. An · P. Zhang · W. Yang · H. Li · H. Li · Y. Jiang · Y. Shuai · B. Zhang · J. Zhang · R. B. Gerzoff · G. Roglic · Y. Hu · G. Li · P. H. Bennett

N= 576 with IGT

Mean age aat baseline 44 years



Number at risk:

Control	133	132	131	128	128	121	113	107	98	91	82
Intervention	407	407	402	393	387	376	364	355	339	316	290

Fig. 2 Cumulative incidence of severe retinopathy during the 20 year follow-up of the China Da Qing Diabetes Prevention Outcome Study in the control group (dotted line, white circles) and intervention group (solid line, black circles). The number at risk represents the number of

The ePREDICE Study

Early Prevention of Diabetes Complications in Individuals with hyperglycemia in Europe

Rafael Gabriel
Jaakko Tuomilehto

PRIMARY OBJECTIVE

To evaluate the 5-year impact (ITT analysis) of:

-metformin, linagliptin, or a fixed-dose combination of metformin + linagliptin, along with ifestyle (diet and physical activity) intervention

compared with (vs)

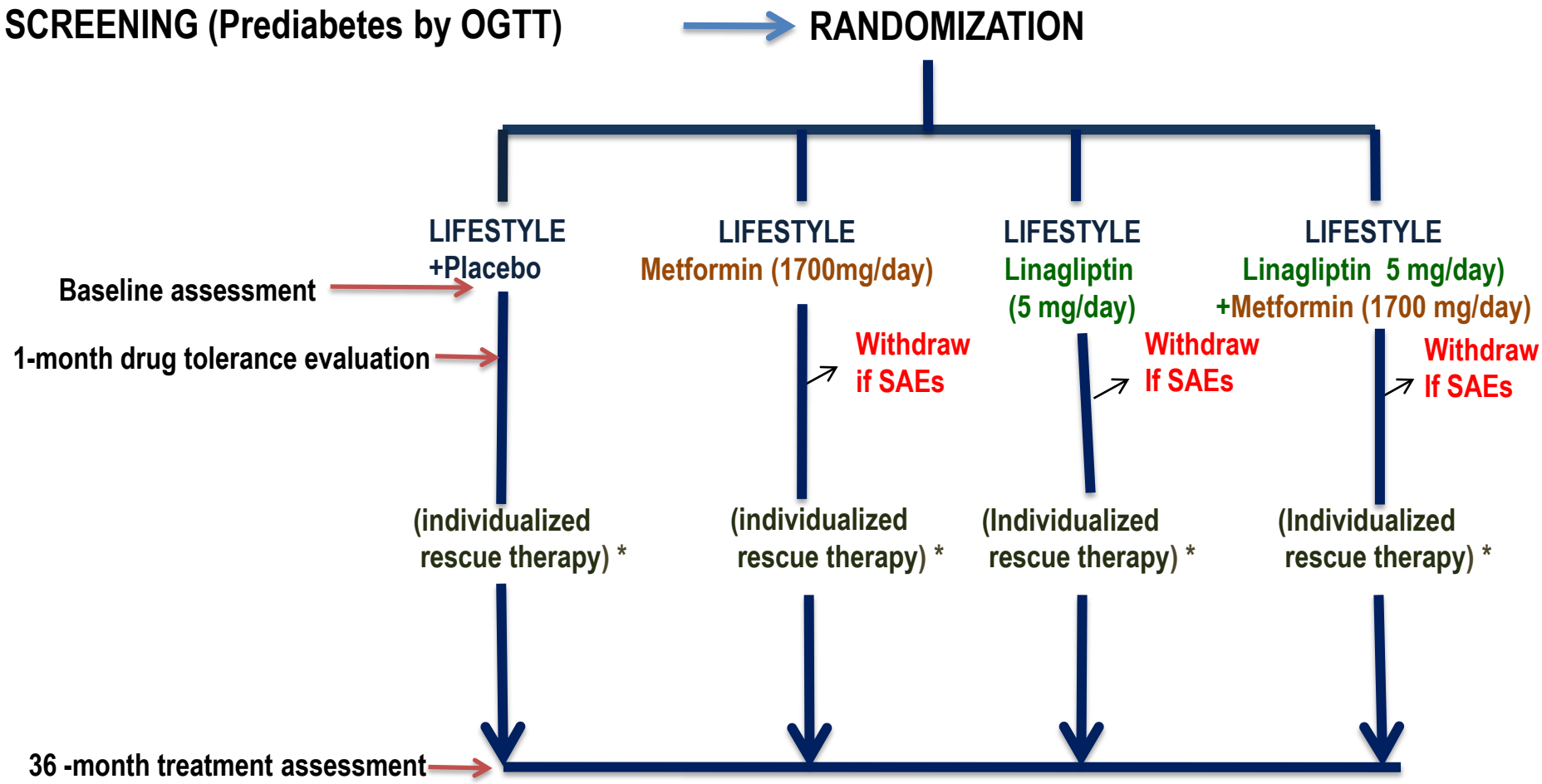
-only ifestyle (diet and physical activity) intervention

on several microvascular (retinal, renal and peripheral nerves) parameters

in people with prediabetes (IGT, IFG or IGT+IFG)

after 3-year of blinded intervention combined intervention (Lifestyle and drugs) .

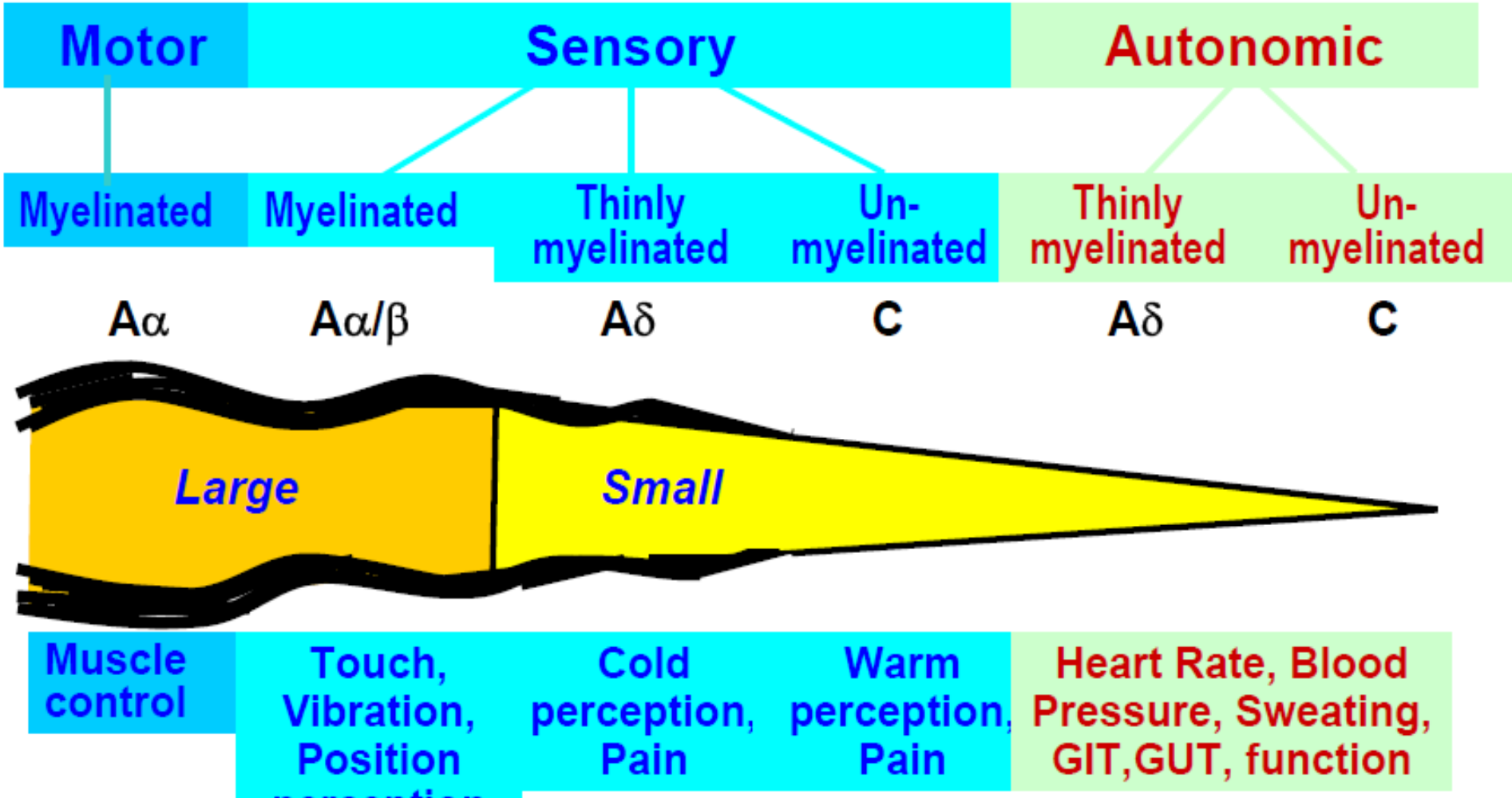
ePREDICE STUDY DESIGN



* If HbA1c >6.5% in two consecutive blood samples at any time

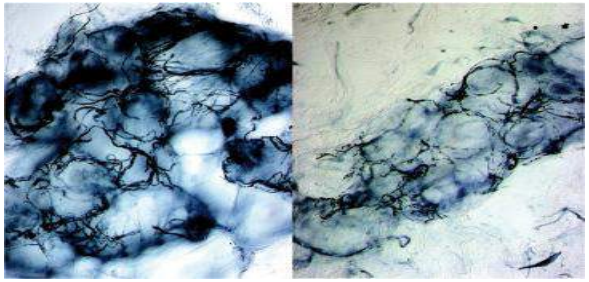
Non-midriatic retinography

A Simplified View of The PNS



Vinik, Ullal, Parson, Casellini Nature Clinical Practice 2; 1-13, 2006

Microscopic nerve fibers, early victims of diabetes



Normal innervation of a sweat gland at the distal leg in a healthy subject (left). Reduced innervation of a sweat gland in a diabetic patient (right).

Endo-PAT2000

Endothelial Function Assessment

Endo-PAT2000 Clinical Features:

- **Endothelial Function Index**
- **Augmentation Index - a Measure of Arterial Stiffness**

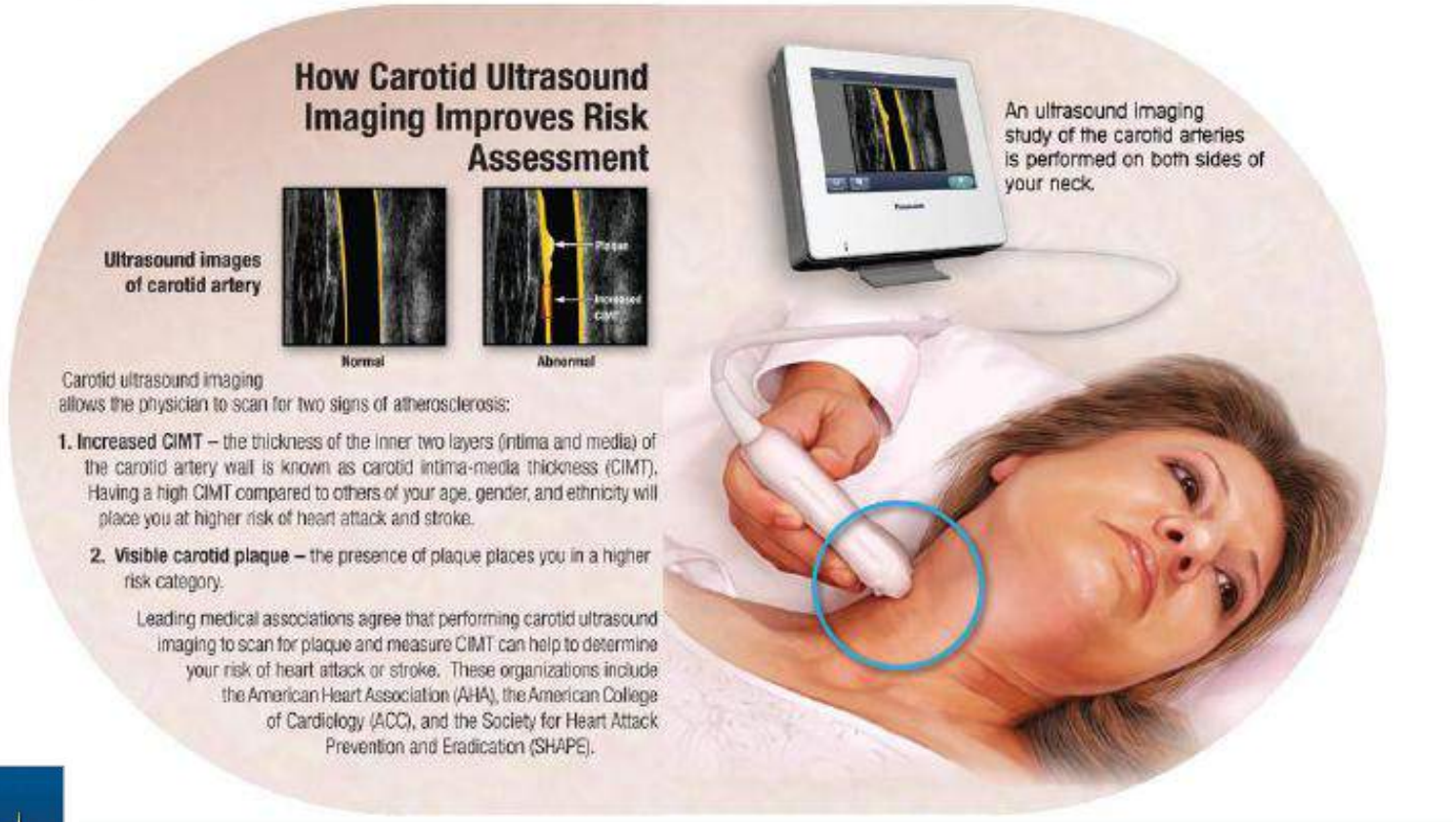
Endo-PAT2000

- Reliable & Reproducible
- Noninvasive
- User Independent
- Easy to Use
- Office-based
- Immediate and Automatic Test Analysis
- Control Arm for Systemic Changes
- FDA cleared & CE marked

Carotid-IMT assessment. Grade A Recommendation ACCF/AHA Guidelines 2010

Portable CardioHealth Station, Panasonic®

Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JMcB, Kushner FG, Lauer MS, Shaw LJ, Smith SC, Jr., Taylor AJ, Weintraub WS, Wenger NK. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:e50–103.



JACC
Journal of the American College of Cardiology

GRACIAS!