Dietary carbohydrates and metabolic outcomes: assessing the totality, consistency and quality of epidemiologic observations and clinical interventions

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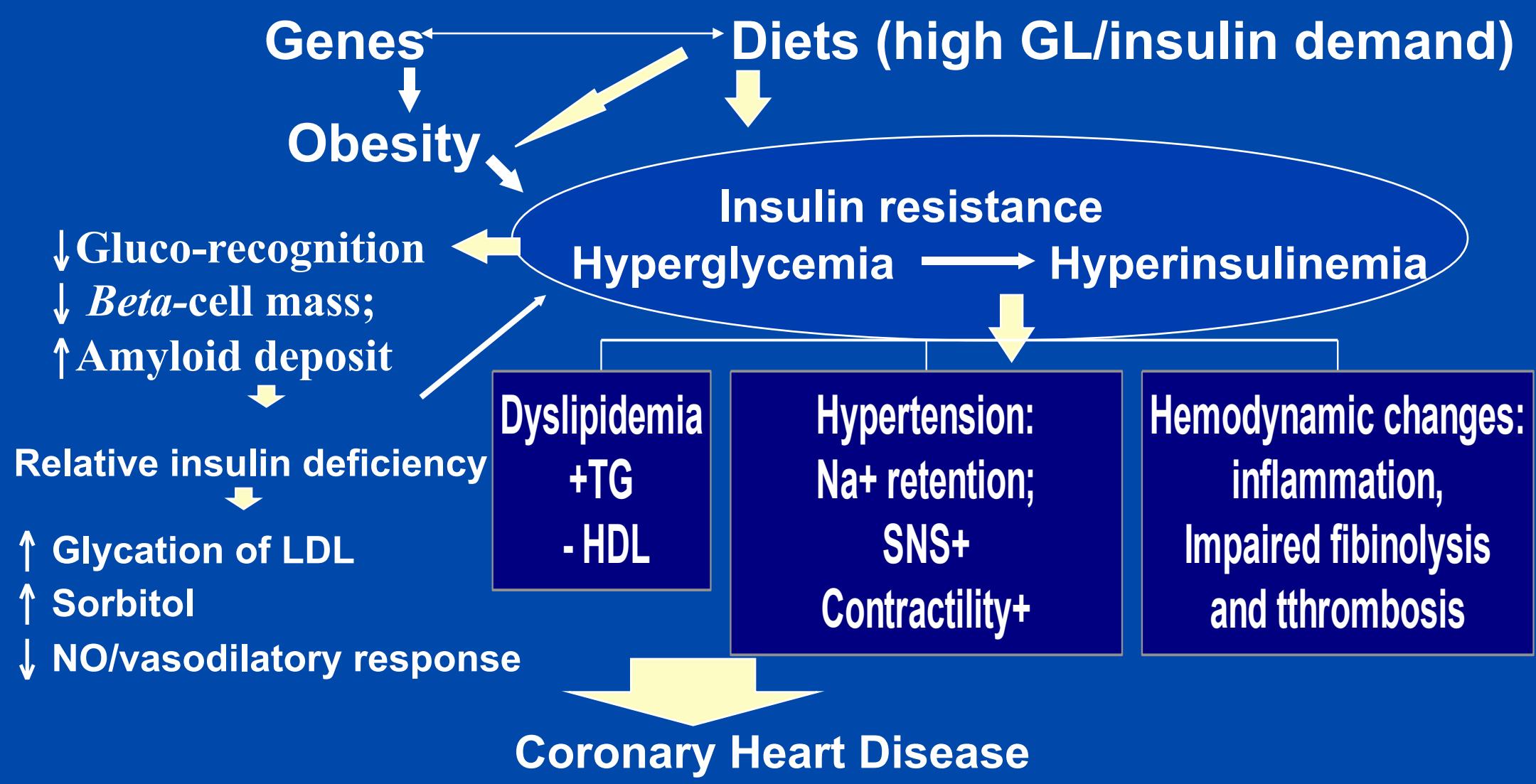
Overview

- A diet that affects glucose homeostasis may be fundamental to vascular health outcomes
  - Glycemic response, glycemic index, and glycemic load
  - Supports from evolutionary theory, epidemiologic observations, and experimental evidence
    - Functional measures to study diet and disease in human populations
    - Biological intermediaries for diabetes and cardiovascular disease
    - Sex, body weight, and age as important modifiers

- Conclusions
  - Integrative framework for research
  - Preventive recommendation

Pathogenesis of DM/CHD Related to Insulin Resistance



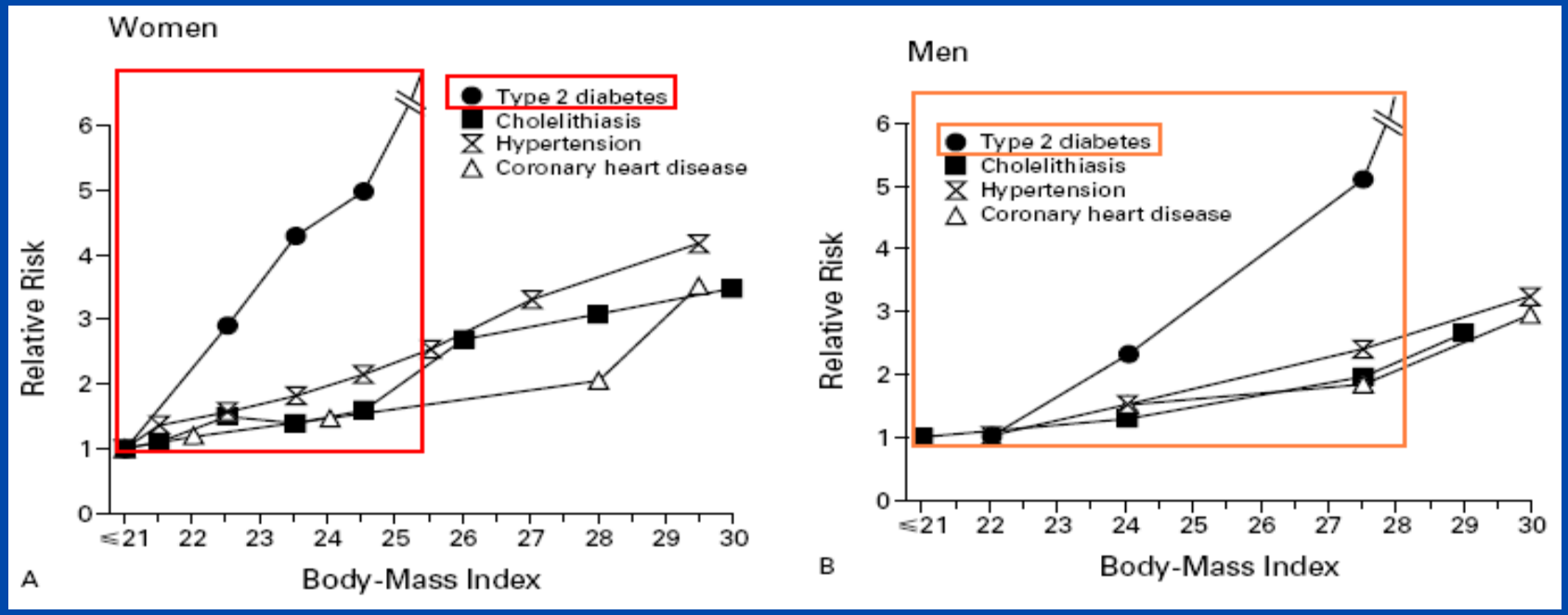
Liu, 1998; Liu and Manson, 2001

Traditional Epidemiology: Common Risk Factors for Three Major Metabolic Diseases

Risk factors	Type 2 DM	CHD	Colon Ca.
Age	↑↑↑	↑↑↑	↑↑↑
Tobacco	↑	↑↑	↑↑
Physical inactivity	↑↑	↑↑	↑↑
Obesity	↑↑↑↑↑↑↑	↑↑	↑↑
Sex??			
Excess energy intake	↑?	↑?	↑?
Saturated fat	↑ ?	↑?	↑?
Red meat	↑?	↑?	↑
Refined carbohydrates	↑↑?	↑↑?	↑↑?
Dietary fibers	↓↓?	↓↓	↓?
Fruits & vegetables	↓↓?	↓↓	↓?
Whole grains	↓↓	↓↓	↓?
Nuts/legumes	↓↓?	↓↓	↓?
Moderate Alcohol	↓↓	↓↓	↑?
……			

Modified from Giovannucci 1995 and Liu 1998

Sex differences related to vascular outcomes in prospective studies



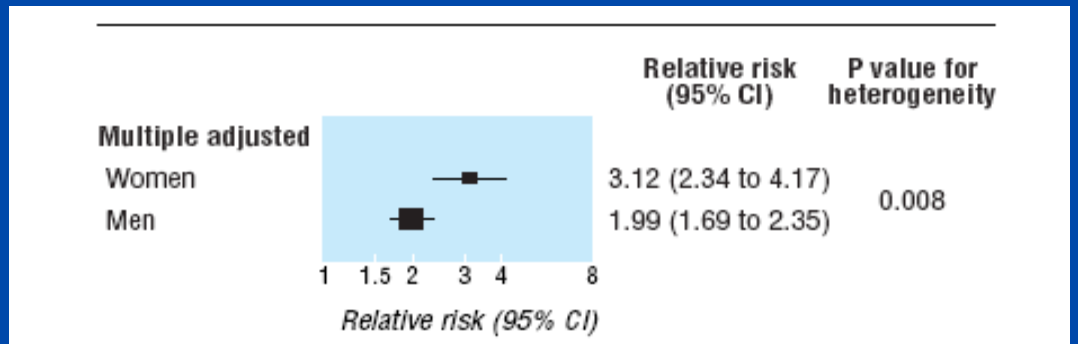


Fig 2 Overall summary estimates of relative risks and 95% confidence intervals for fatal coronary heart disease in men and women with and without diabetes in 22 studies that reported both age and multiple adjusted coefficients

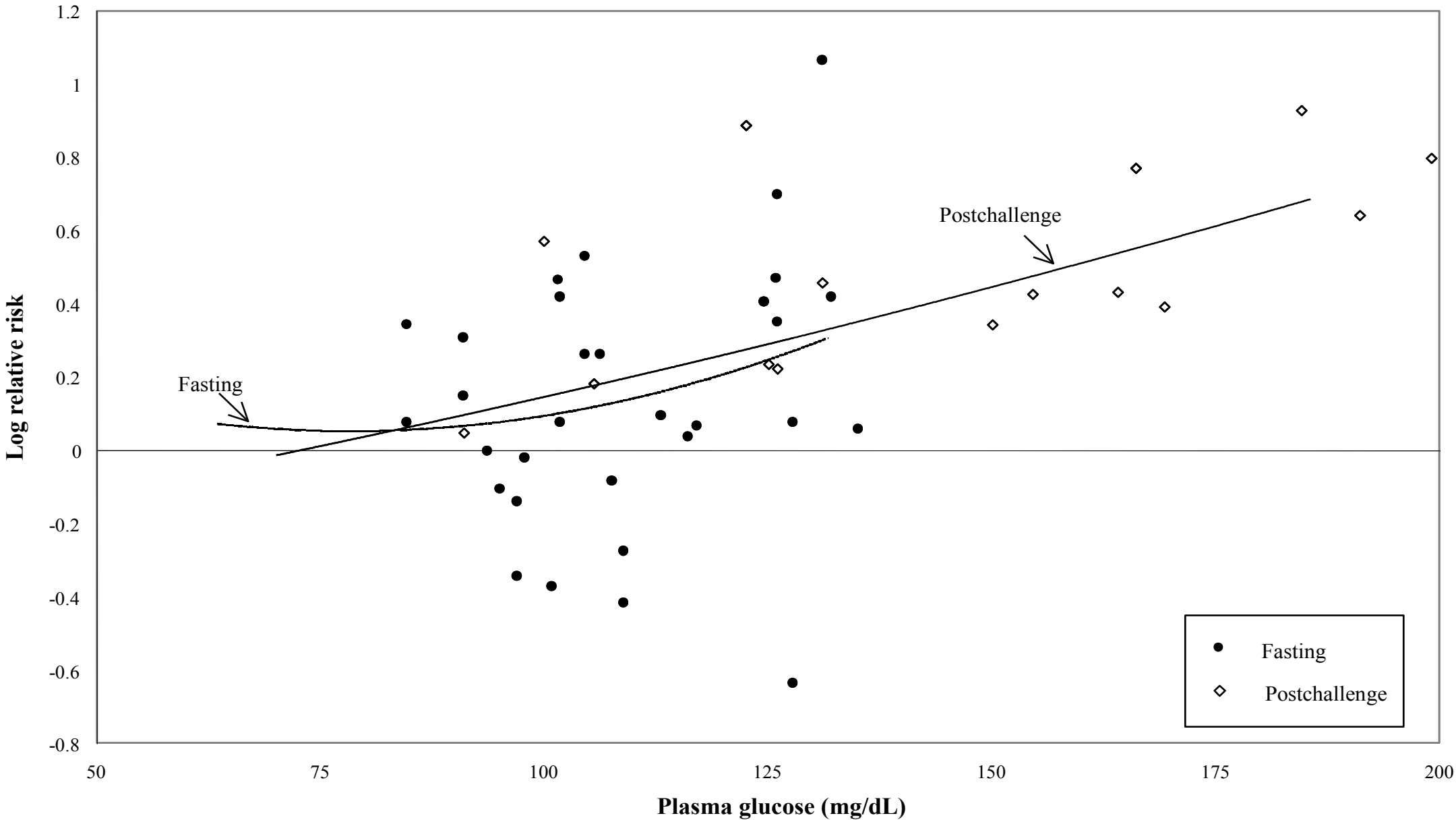
BMI and risk of type 2 diabetes → stronger in women

Diabetes and risk of CVD mortality → stronger in women

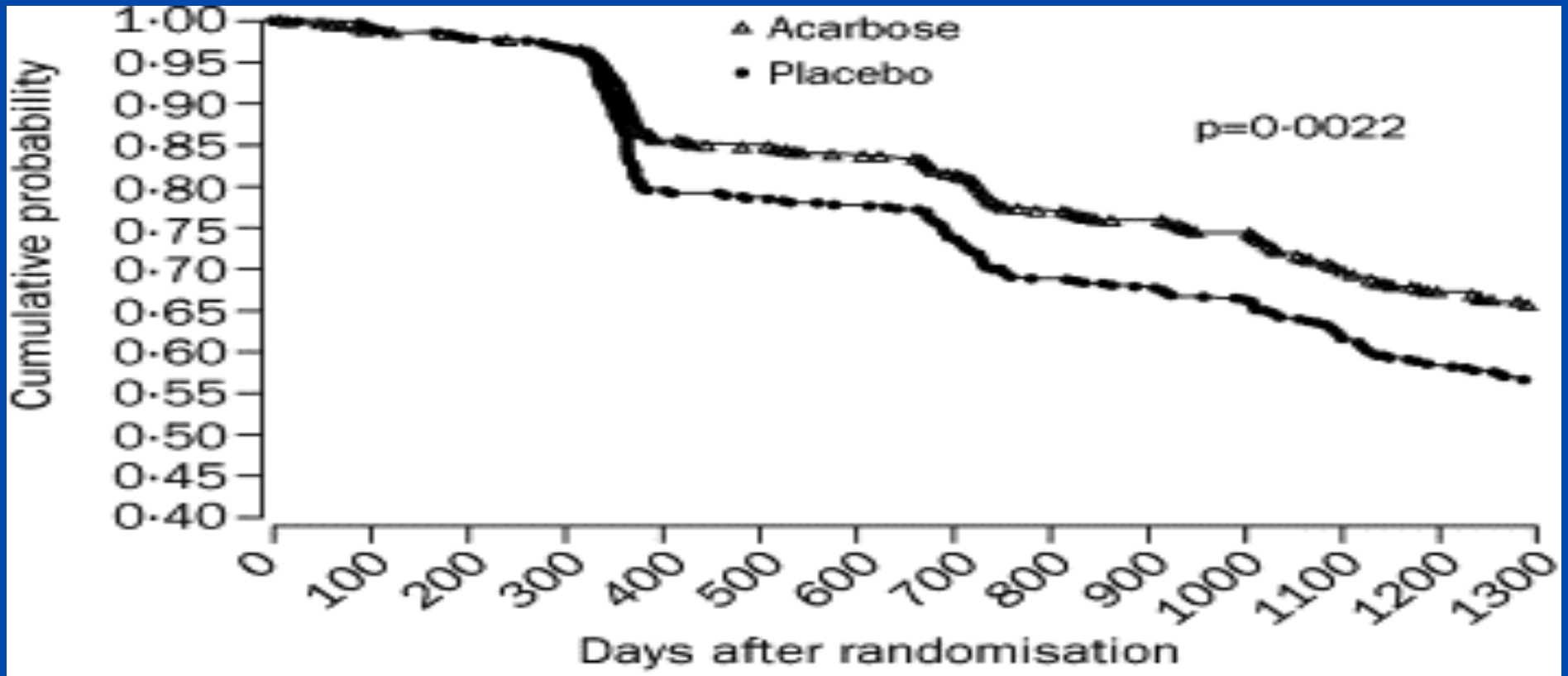
Willett NEJM 1999; Huxley BMJ 2005

Dose-response relation between blood glucose and CHD risk

(Levitan et al. Arch Int Med, 2004)



The effect of decreasing PPG with acarbose, an -glucosidase inhibitor, on DM development in a multicenter double-blind, placebo-controlled, randomized trial Chiasson et al. Lancet 2002

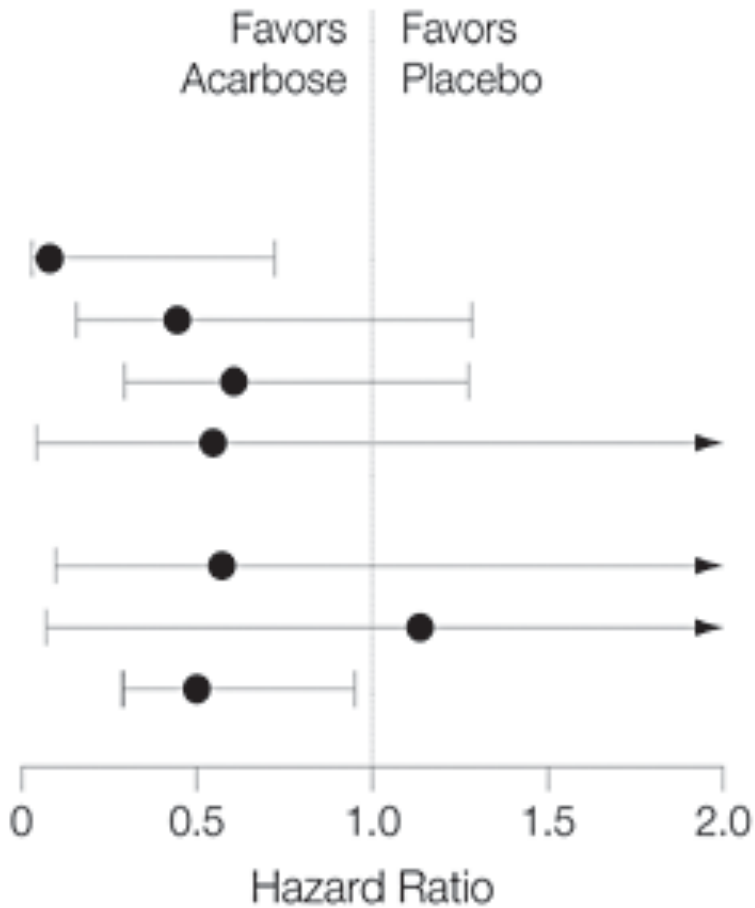


Patients at risk

Acarbose	682	655	628	612	531	523	515	497	463	447	432	349	268	212
Placebo	686	671	655	640	512	505	497	470	434	427	414	331	255	208

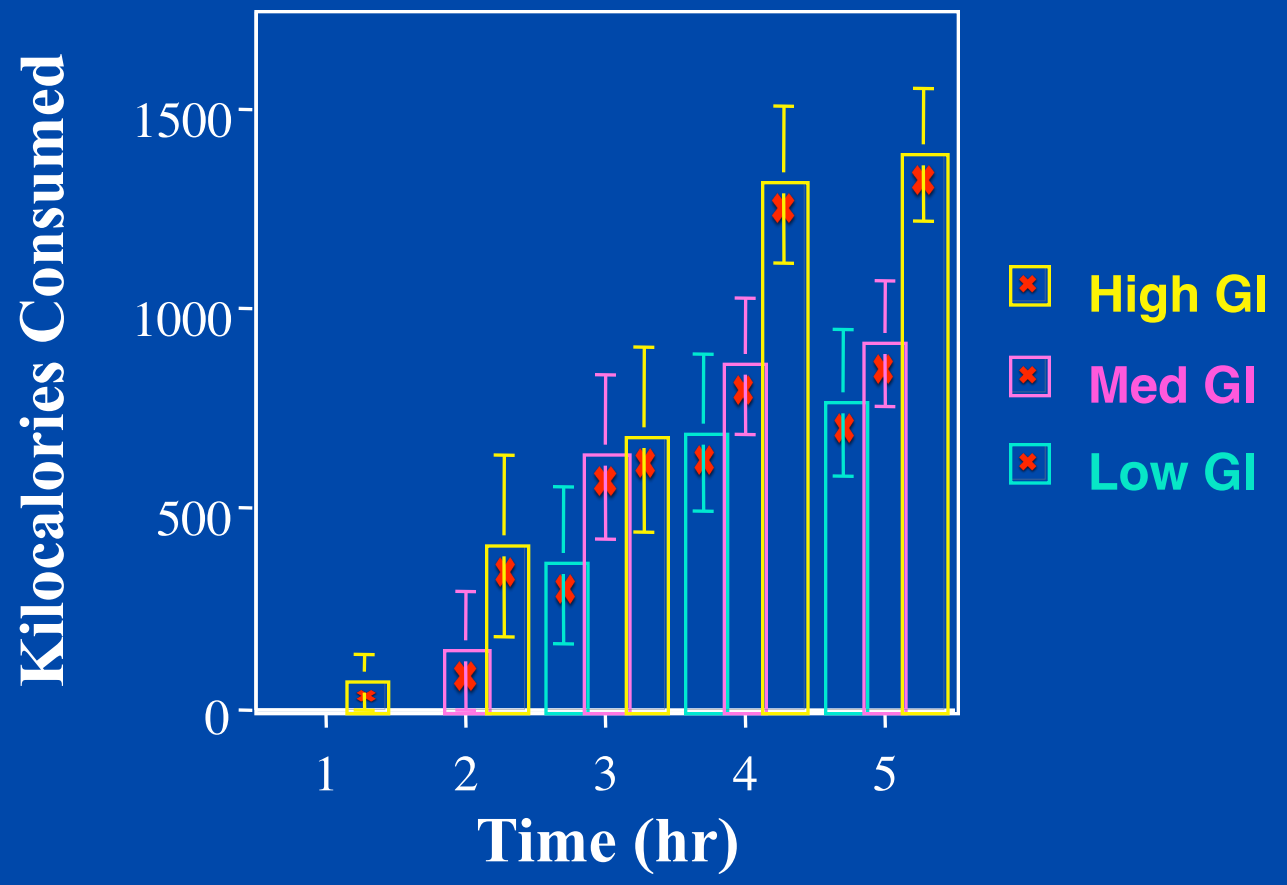
The effect of decreasing PPG with acarbose, an -glucosidase inhibitor, on CVD development in a multicenter double-blind, placebo-controlled, randomized trial Chiasson et al. JAMA 2004

	No. Experiencing Event			
	Acarbose (n=682)	Placebo (n=686)	Hazard Ratio (95% CI)	*P* Value
Coronary Heart Disease				
Myocardial Infarction	1	12	0.09 (0.01-0.72)	.02
Angina	5	12	0.45 (0.16-1.28)	.13
Revascularization Procedures	11	20	0.61 (0.29-1.26)	.18
Cardiovascular Death	1	2	0.55 (0.05-6.11)	.63
Congestive Heart Failure*	0	2	---	---
Cerebrovascular Event or Stroke	2	4	0.56 (0.10-3.07)	.51
Peripheral Vascular Disease	1	1	1.14 (0.07-18.30)	.93
Any Cardiovascular Event	15	32	0.51 (0.28-0.95)	.03



GI & Voluntary Food Intake

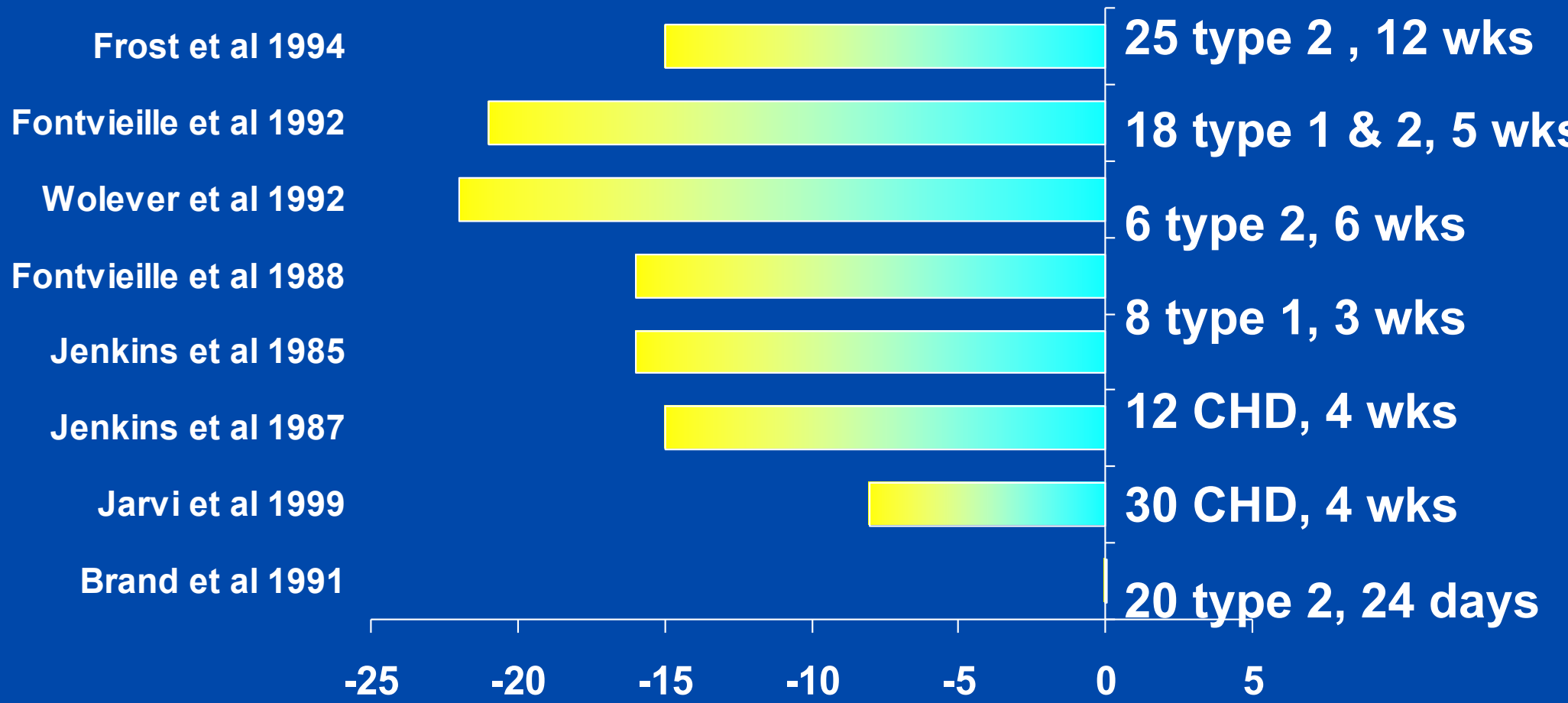
Ludwig et al. Pediatrics 1999, 103:e261



Cumulative Voluntary Food Intake

Low GI diets improve triglycerides

Low GI diet compared with high GI diet

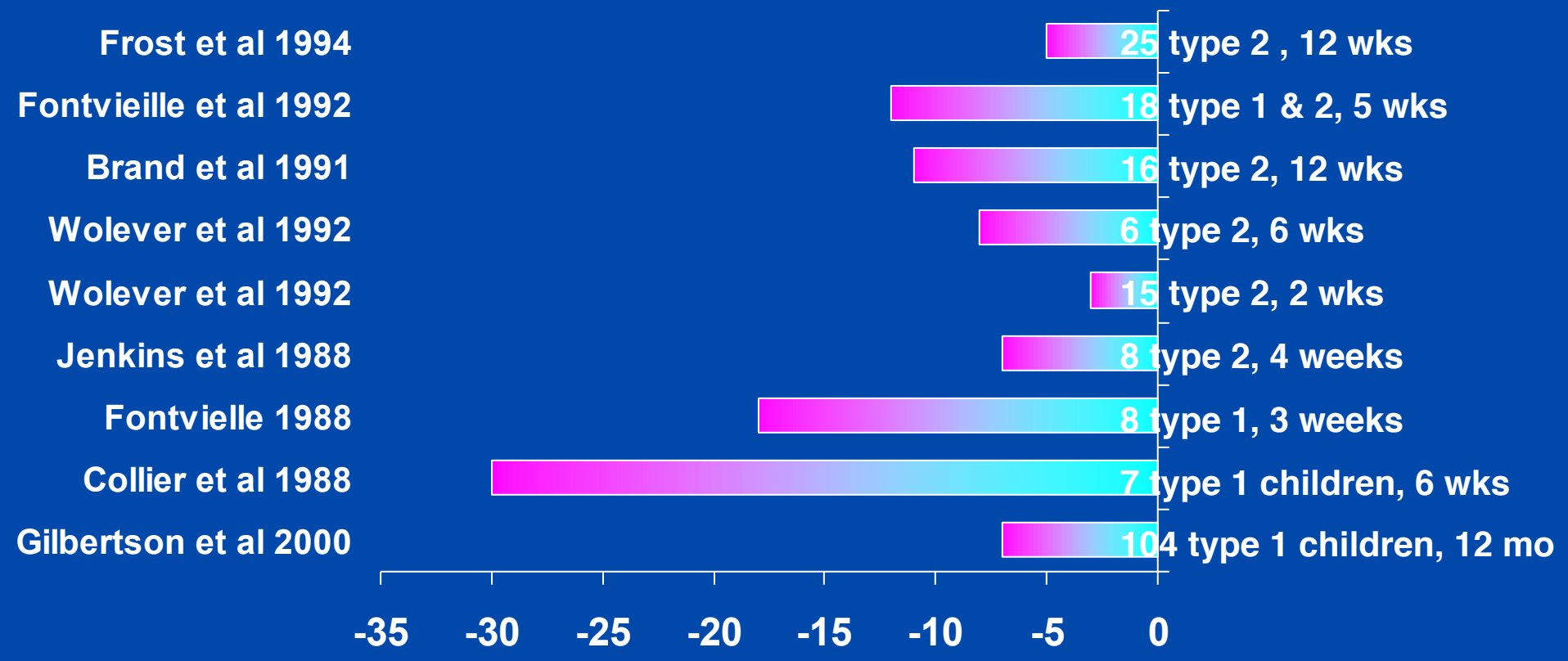


Average change in 8 studies = -12%

*Include extensive data from Prof.Y.X. Yang Chinese CDC

Changes in HbA_{1c} or fructosamine

Low GI diets compared with high GI diets



Average difference in HbA_{1c} in 9 studies = -11%

Adapted from Brand-Miller et al. 2001

Change in Glycemic Control
Low vs high GI diets

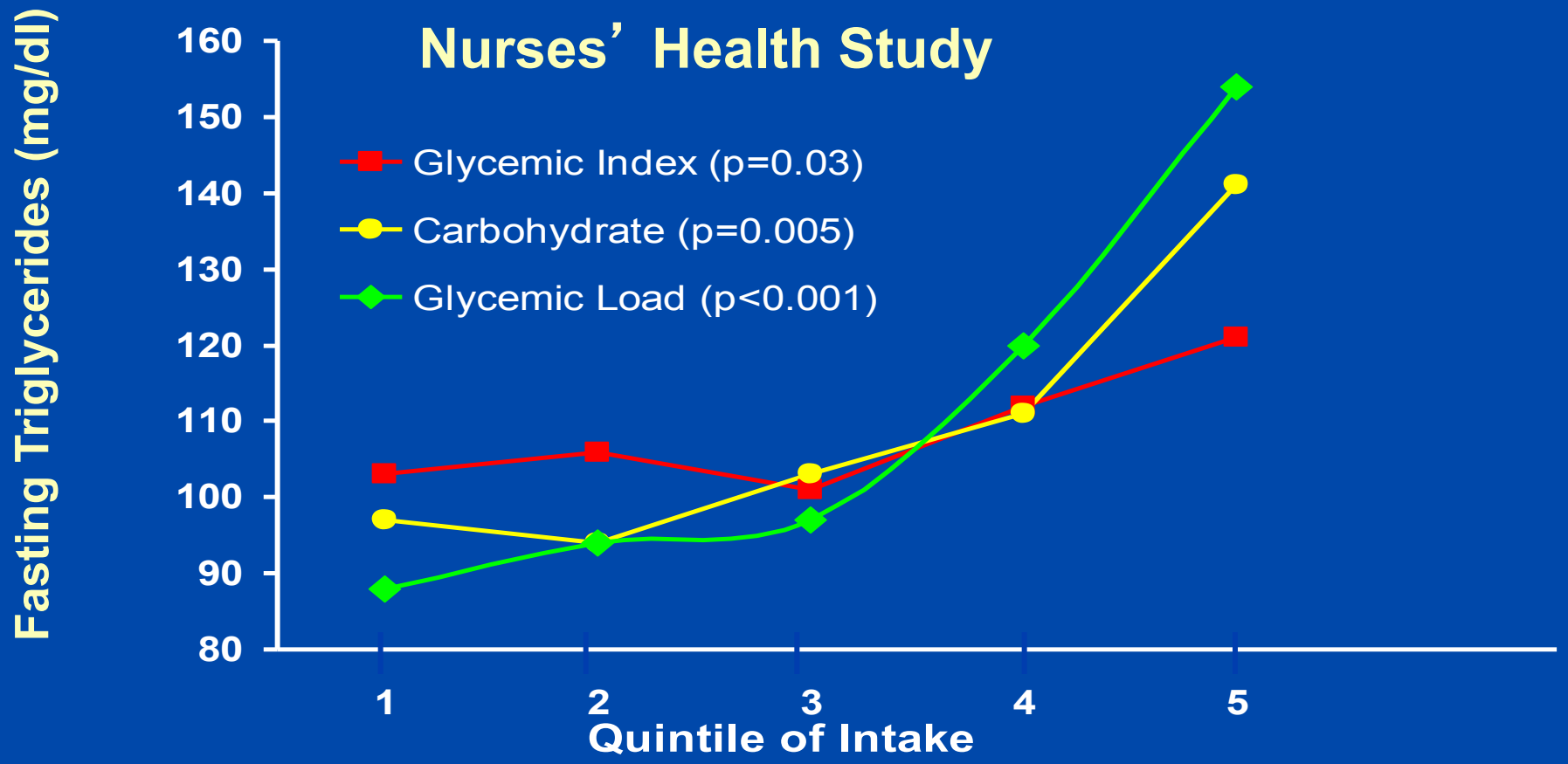
- **Glycemic control -**
  10% improvement for a 10 unit decrease in GI

- **Comparison with other interventions**

DCCT	- 20%
UKPDS	- 11.5%
Acarbose	- 6.5%
Insulin analogues	- 2.5%

Adapted from Stephen Colagiuri Aust Nutr Soc 2001

Fasting plasma TG concentrations by GL, GI and carbohydrate intake

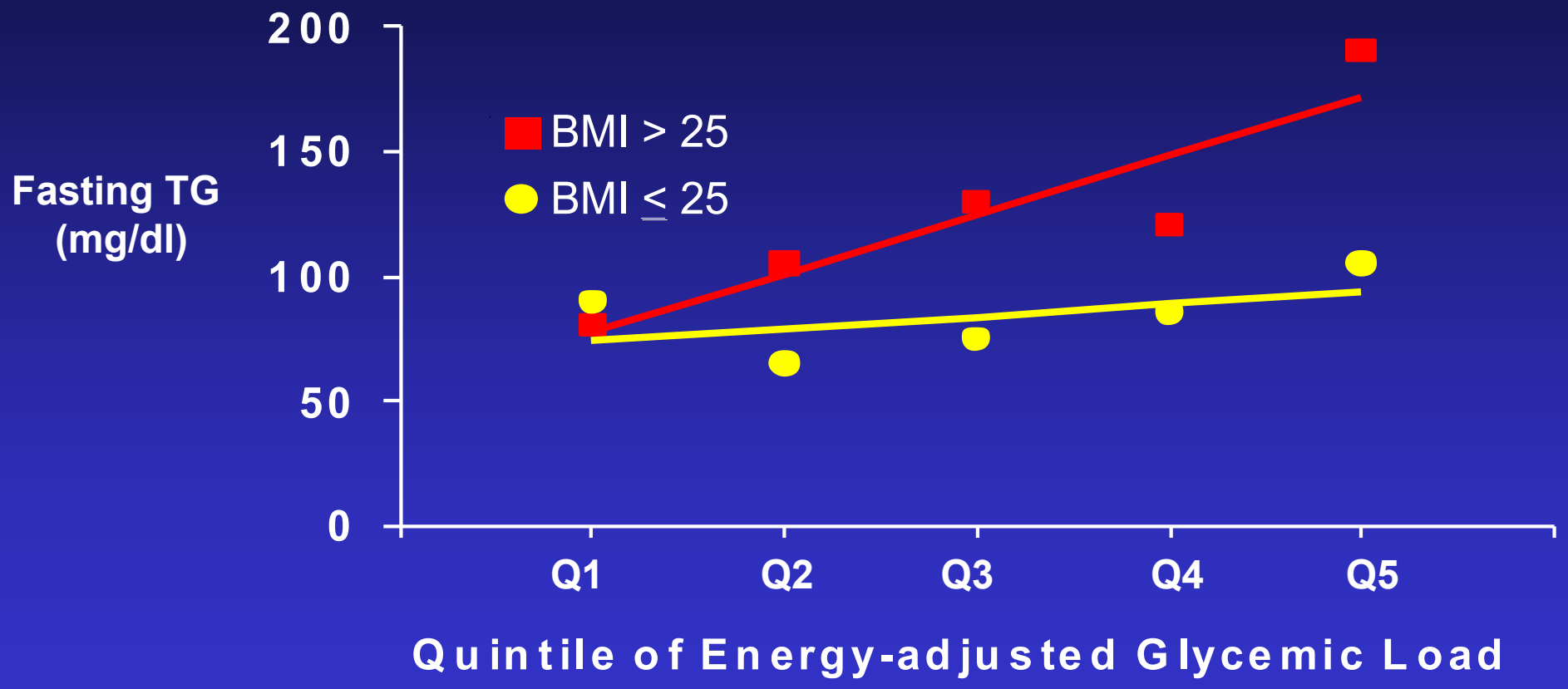


Liu et al. AJCN 2001

12.039b

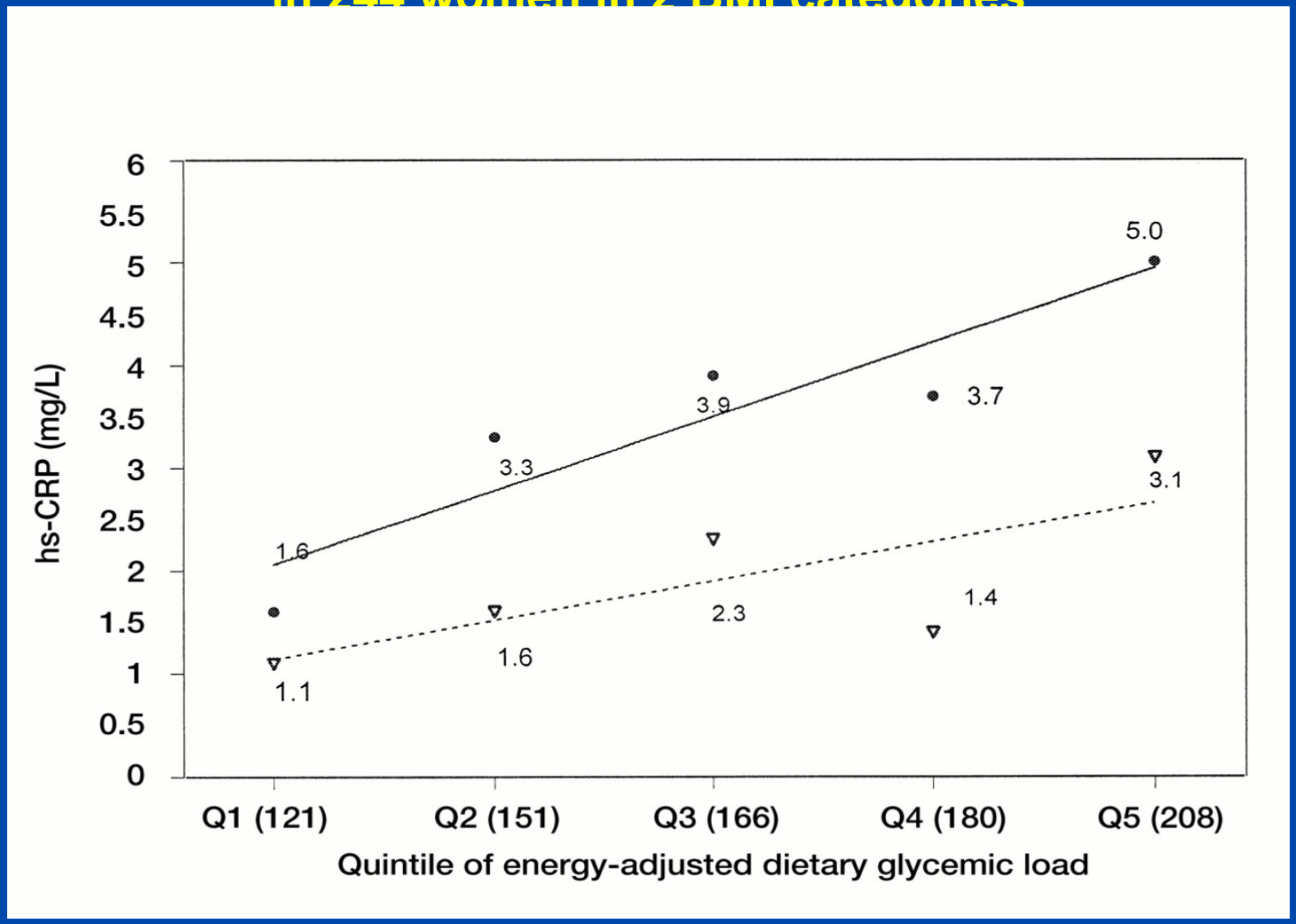
Fasting Plasma TG Levels by Dietary Glycemic Load

Postmenopausal Women with Different BMI's



Liu et al. AJCN, 2001

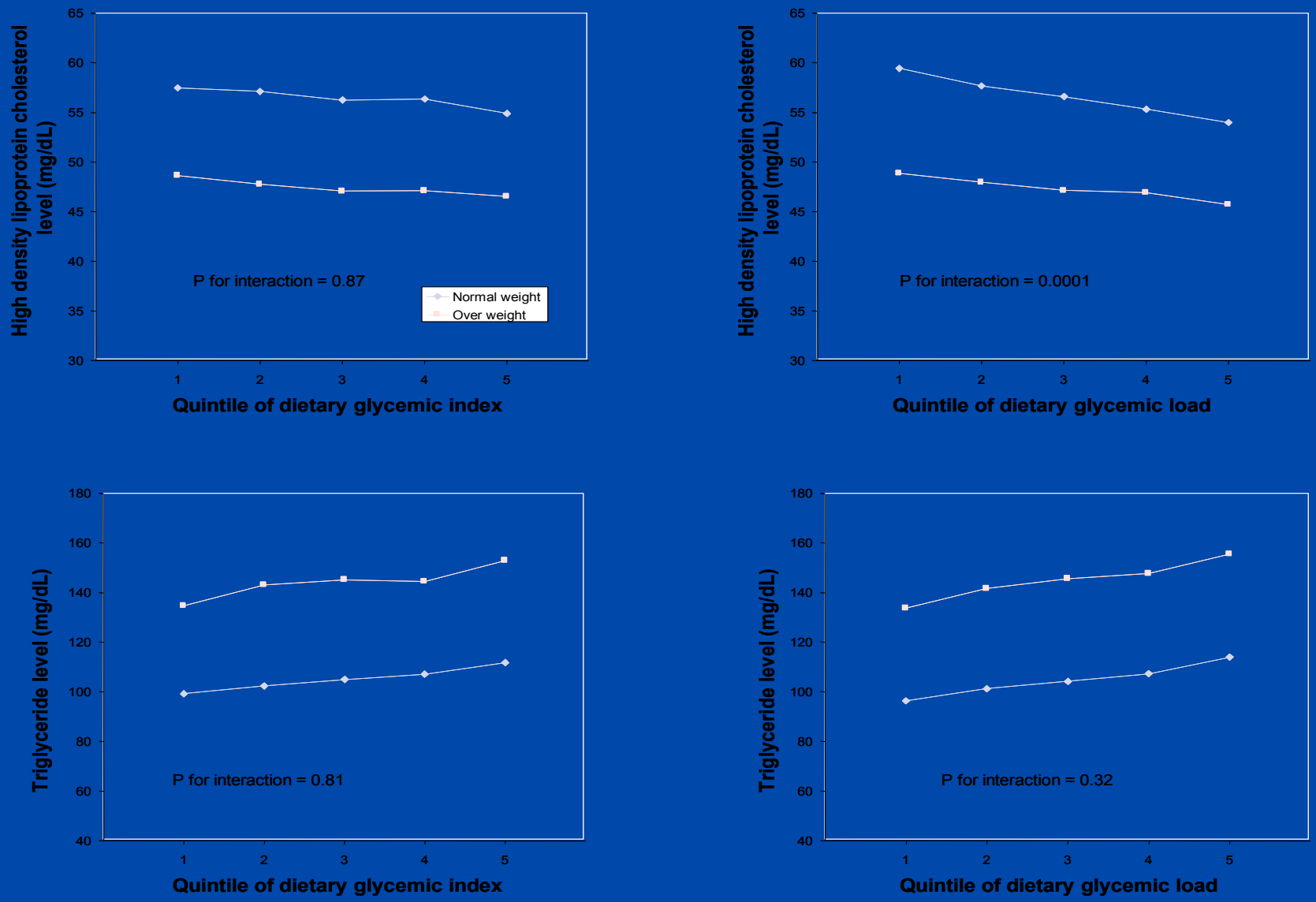
Adjusted geometric mean plasma concentrations of high-sensitivity C-reactive protein (hs-CRP) by quintiles (Q1–Q5) of energy-adjusted dietary glycemic load in 244 women in 2 BMI categories



Liu S et al. Am J Clin Nutr 2002;75:492-498

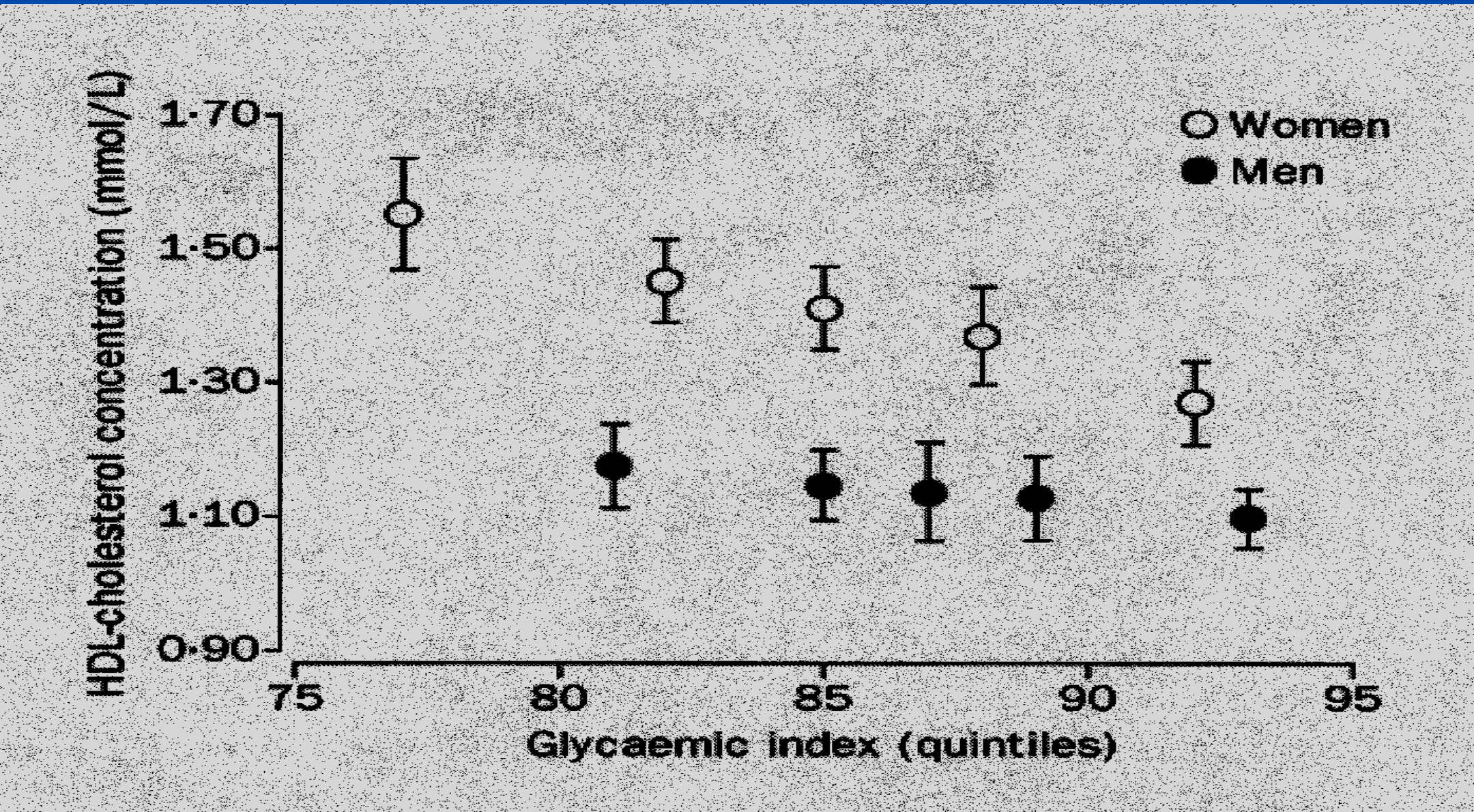
Subsequently confirmed by Rhodes et al in a randomized trial of overweight pregnant women AJCN 2010

Geometric mean high density lipoprotein cholesterol and triglyceride levels*

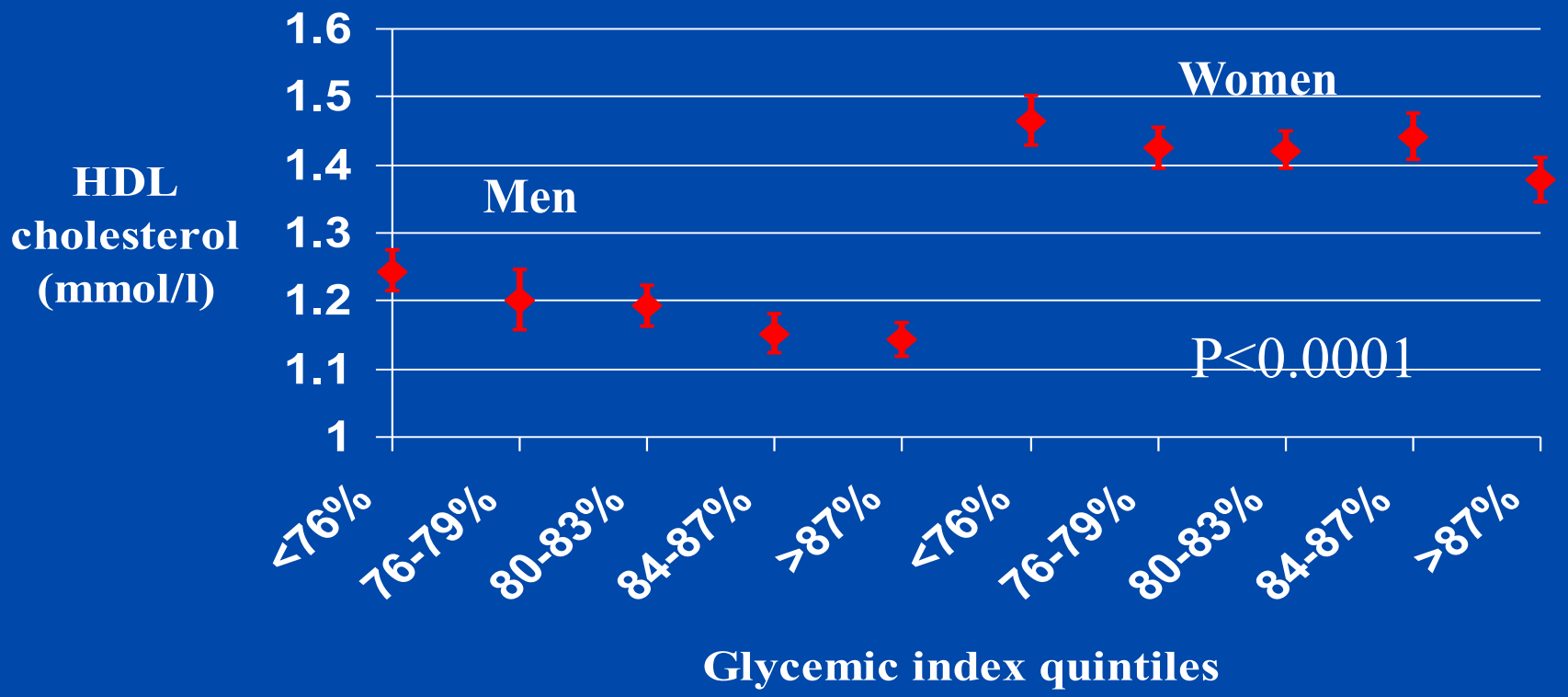


*Adjusted for age, smoking (current, past, never), exercise (4 category), hormone replacement therapy use (current, past, never), family history of MI, history of diabetes, body mass index (4 category), and intakes of total energy, alcohol intake (4 category), and quintile of total fat, protein, cholesterol, folate, and magnesium intake. Dietary glycemic load additionally adjusted for quintile of fiber intake

Relation between HDL-cholesterol concentration and glycemic index in men and women (Frost et al, 1999)

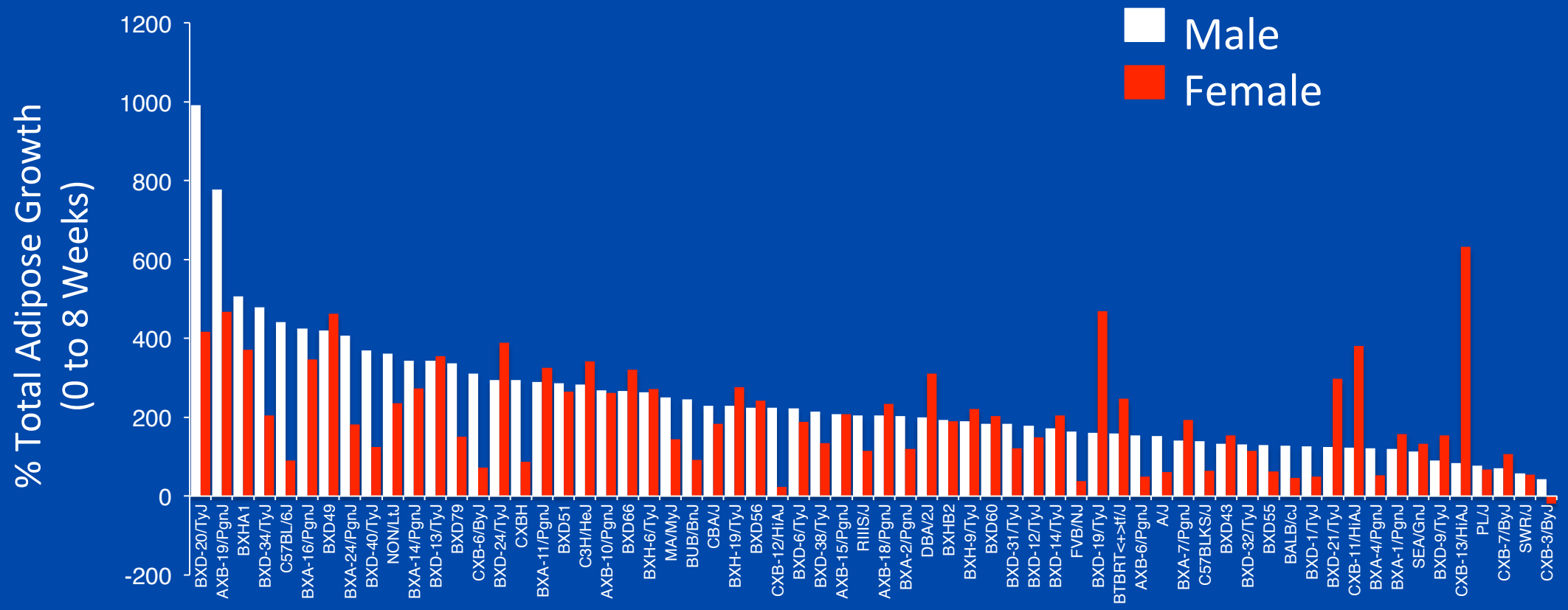


Mean concentrations of HDL by glycemic index among men and women aged 20+ years, NHANES III, 1988-1994 (Ford and Liu, Arch Int Med 2000)



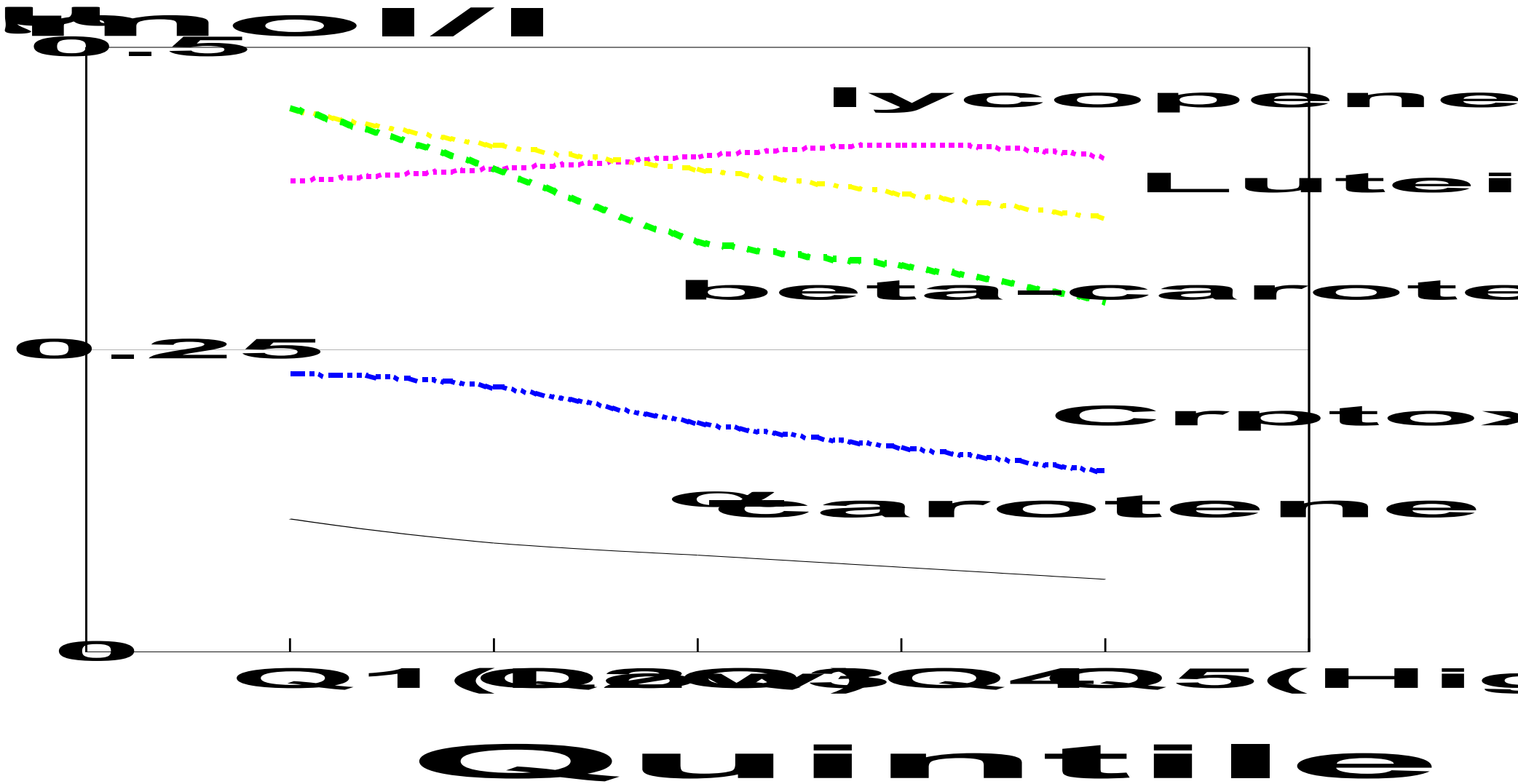
Adjusted for age, race or ethnicity, education, smoking status, body mass index, alcohol intake, physical activity, percent kilocalories from protein (quintiles), percent kilocalories from fat (quintiles), total energy intake (quintiles).

Results: Diet-by-sex interaction



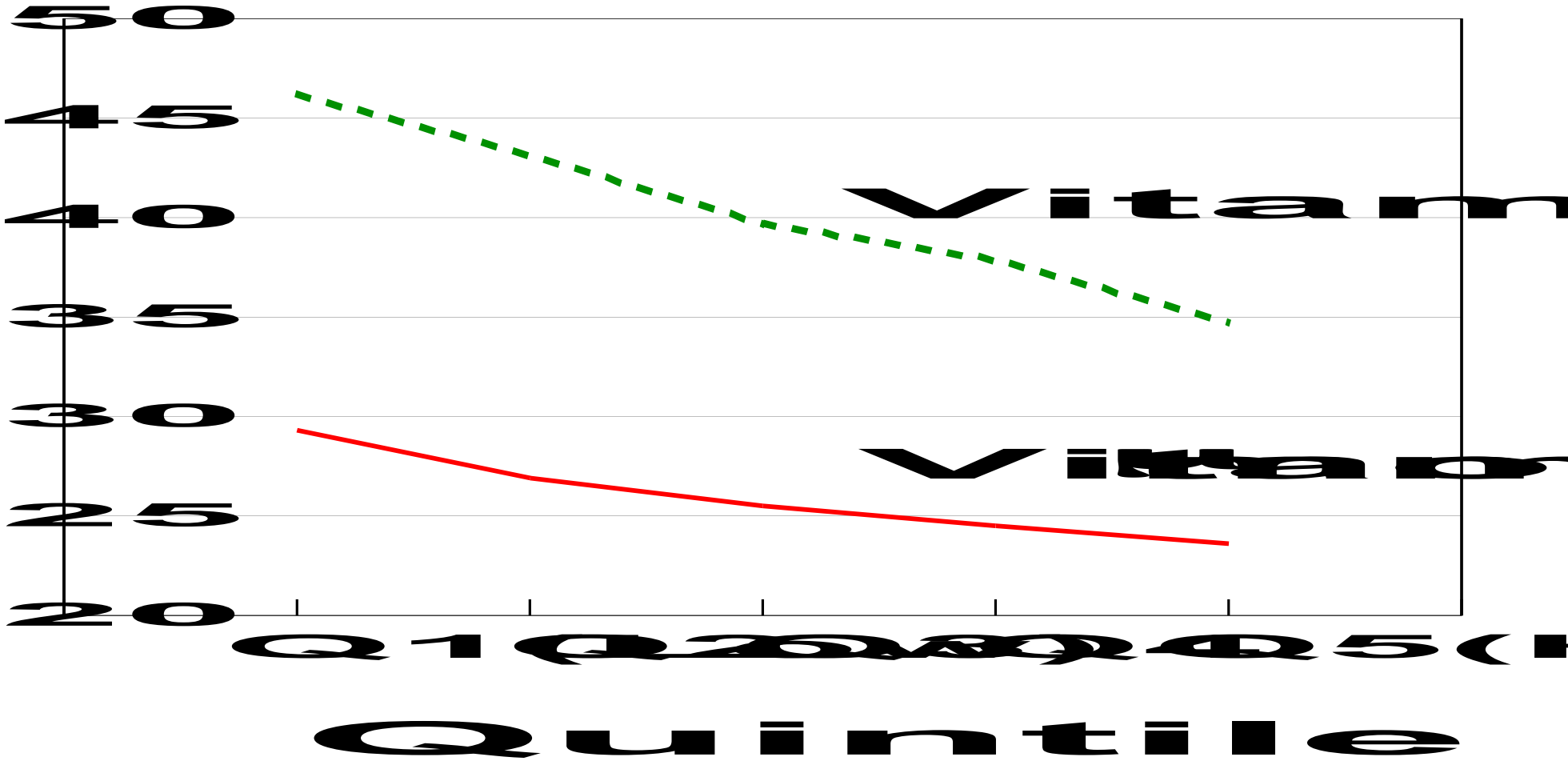
Slide courtesy of Drs Tom Drake & Jake Lusis

Mean conce
among 1527



Liu and Ford, 2002

Mean con
by glycem



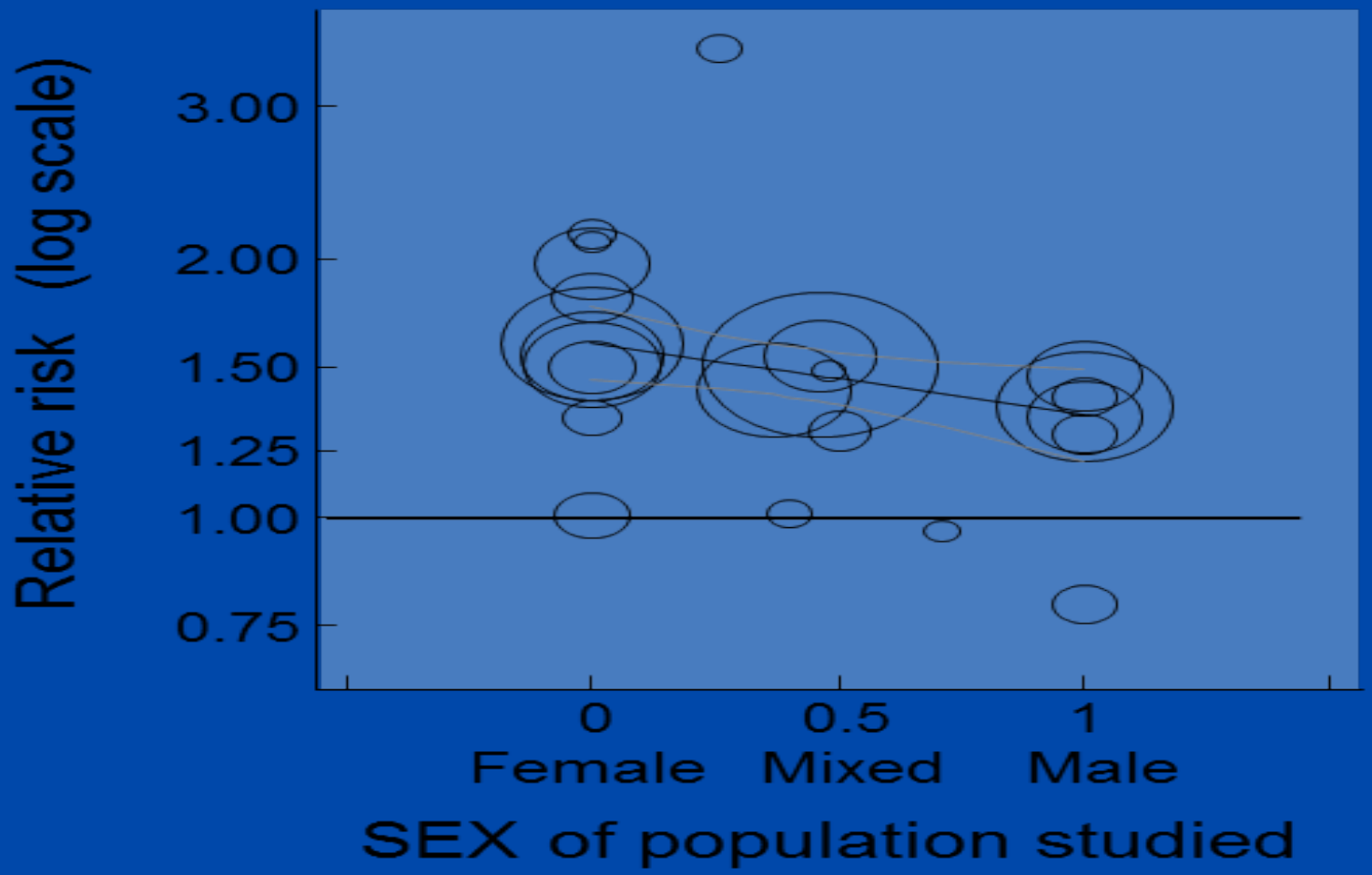
Liu and Ford, 2002

Potential biochemical mechanisms

High GI/GL feeding causes:

- **Postprandial hyperglycemia & hyperinsulinemia - (immediate responses)**
- **Counterregulatory hormonal responses which stimulate appetite, FFA production, and possibly protein breakdown – (late responses)**
- **Shifts in substrate utilization away from fat towards carbohydrates**
- **Increased enzymatic capacities for carbohydrate oxidation and lipogenesis, and decreased enzymatic capacity of fat oxidation**

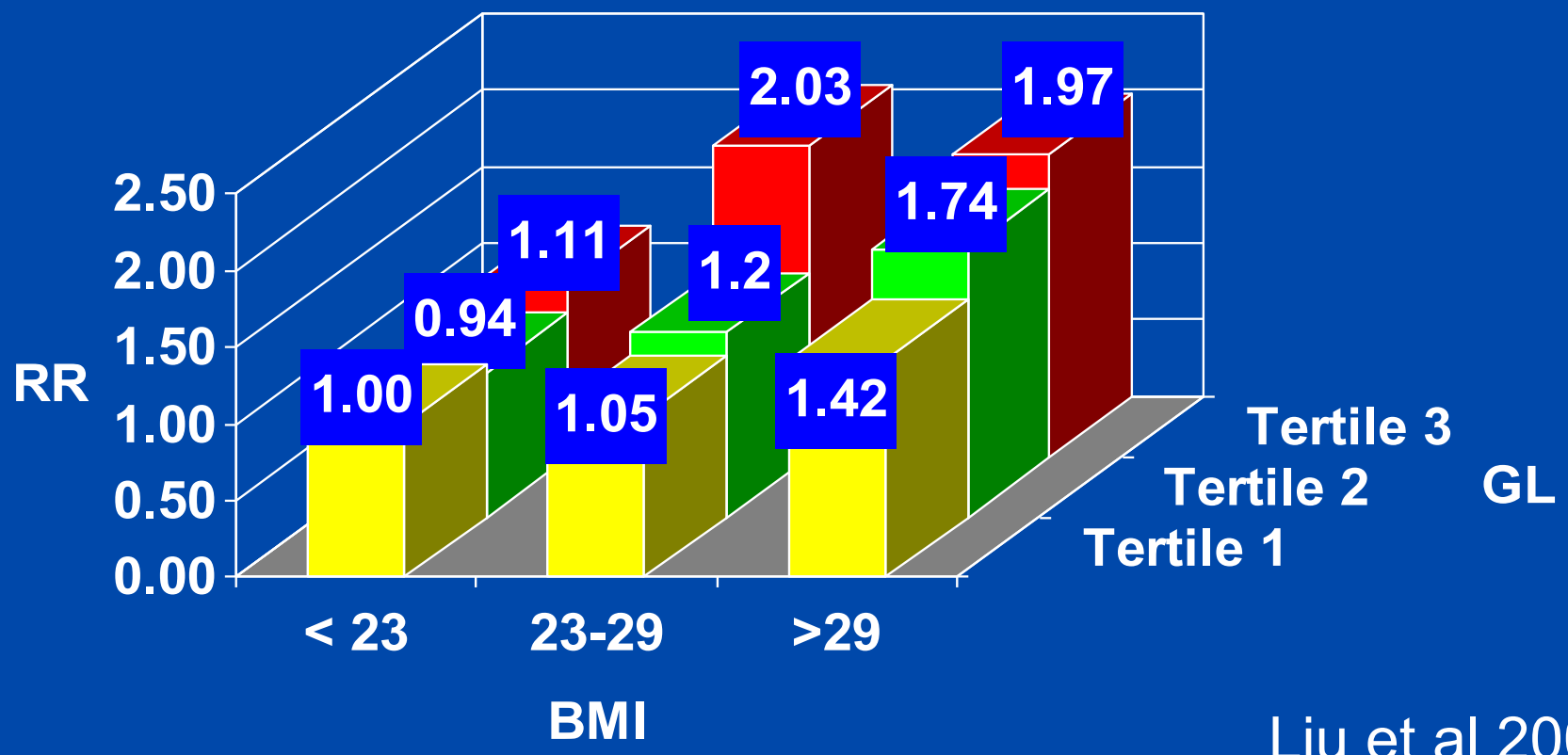
Adjusted estimates of relative risk of type 2 diabetes according to GL by sex from a meta-analysis of all prospective cohorts with 7.5 million years of followup (up to August 2012)



Livesay et al. Am J Clin Nutr 2013

Multivariate relative risk of CHD by body mass index and glycemic load

Test for interaction, P < 0.01



Liu et al 2000

Different constituents of a low GI/ GL diet

- Fruits and vegetables
- Whole grains
- Nuts
- Legumes (peas, beans, soybeans)
- Fish
- Dairy foods

Conclusion

- Due to our genetic mal-adaptation to westernized lifestyle/ environment, we are increasingly becoming a metabolically efficient population

- Substantial evidence indicates significant biological importance and clinical utilities of the GI/GL concepts, in that
  - 1) carbohydrate-containing foods differ in their abilities to raise plasma glucose and insulin (Level A),
  - 2) diets characterized by high GL adversely affect metabolic intermediates (Level B),
  - 3) may increase risk of vascular outcomes (diabetes and cardiovascular diseases) especially among those who are prone to insulin resistance (Level B and C)

- Can we conclusively demonstrate the efficacy of glucose homeostasis diet on vascular health in randomized trials:
  - Not feasible
  - Not ethical
  - Not necessary

Conclusion

- When thinking about diet, which is only one aspect of our westernized environment, we need to keep in mind what kind of people we have become metabolically.
  - Consider sex, body weight, and age as important modifiers when assessing diet-disease relation and making dietary recommendation
    - Reduce heterogeneity and improve biological understanding of the "glucose homeostasis" diet
  - Regarding the clinical utility of the GI concept,
    - It is better than the "simple/complex" in classifying carbohydrates
    - Does go beyond individual food-based guidelines, even in the context of caloric density and nutrient composition
    - GI is most useful for ranking high/dense-carbohydrate foods