

# Clinical & Epidemiological Studies: Health Measures of Prebiotic Success

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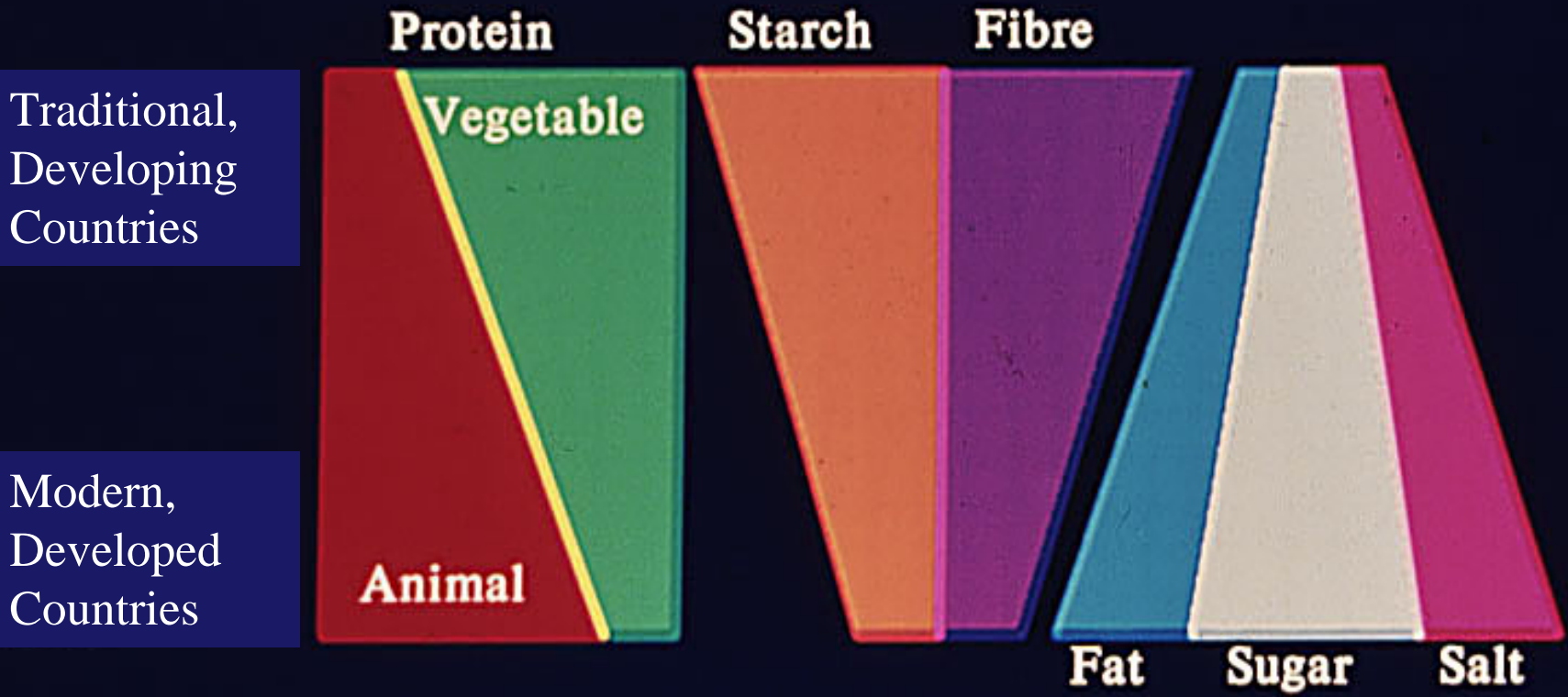
# Fiber Hypothesis

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Dr. Dennis Burkitt (observational studies in Africa)

- African diet - ↑ fiber & ↓ fat
- ↑ stool output
- ↓ chronic disease (cancer, heart disease diabetes)

# DIETARY CHANGES WITH PROSPERITY



# Current Problem → Chronic Diseases

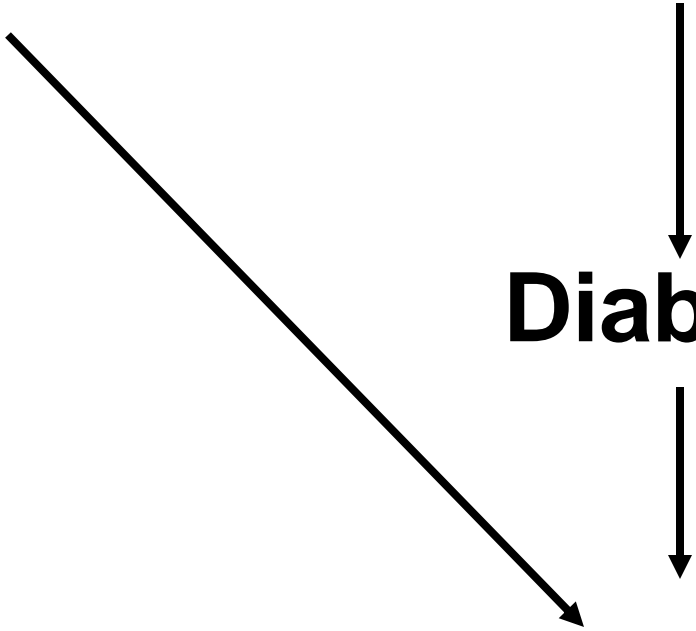
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**Metabolic Syndrome**

↑Waist Circumference  
↑BP  
↑Disglycemia  
↑Inflammation

**Diabetes**

**CHD**



# Fiber and Colon & Breast Cancers

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## Human Studies (↑ fiber & ↓ fat)

### Population Studies

- Finland, Scotland, USA - ↑ incidence
- Latin America, Africa, Japan - ↓ incidence

### Migrating Populations

- Japanese (Japanese, Hawaii, USA)

### Case-Control Studies

# Fiber and Colon Cancer

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## High Fiber Diets

- ↑ fecal bulk (dilution effect)
- ↓ transit time ( ↓ contact time)
- promote healthy bacteria
- ↓ secondary bile acid concentrations
- ↑ butyrate concentrations

# Fiber and Colon Cancer

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## Human Studies (prospective)

61,463 healthy Swedish women (~10y follow-up)

- ↑ fruit & vegetable intake - ↓ CRC development
- ↓ cereal fiber intake – no effect

*(Terry et al. J Natl Canc Inst 2001)*

88,757 American women (16 y follow-up)

- ↑ dietary fiber (cereal, fruit or vegetable) – no effect on development of CRC or adenomas

*(Fuchs et al. N Engl J Med 1999)*

# Fiber and Colon Cancer

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## Human Studies (intervention – high risk groups)

1,905 subjects followed for ~4 years

- adopting a diet low in fat & high in fiber, fruit and vegetables did not influence recurrence of CRC adenomas (*Schatzkin et al. N Engl J Med 2000*)

1,303 subjects followed for ~3 years

- wheat bran fiber (13 g/d) did not protect from recurrent CRC adenomas (*Alberts et al. N Engl J Med, 2000*)



# Breast Cancer

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## Risk Factors (population studies)

- ↑ estrogen (early menses, late 1<sup>st</sup> pregnancy, late menopause)
- ↑ body weight
- ↓ physical activity
- ↑ fiber & ↓ fat diets
- ↓ fruit & vegetable intakes

# Fiber and Breast Cancer

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## High Fiber Diets

- ↑ estrogen excretion
- ↓ circulating estrogen levels
- flavonoids (anti-estrogens)

# Fiber and Breast Cancer

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## Human Studies (prospective)

Nurses' health Study followed for ~10 years

- HRT - ↑ breast cancer risk

*(Colditz et al. N Engl J Med 1995)*

## Combined Prospective Studies

- ↑ fiber & ↓ fat – no effect

*(Willett. Cancer 1994)*

# Fiber and Breast Cancer

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## Human Studies (intervention – high risk groups)

291 women followed for ~1 year

- adopted a diet low in fat & high in fiber, fruit and vegetables.
- ↓ circulating estrogen levels

*(Rock et al. J Clin Oncol, 2004)*

# Significant Scientific Agreement on Fiber

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- Dietary guidance on increasing fiber (cereal grains, vegetables, fruits)
  - Recommend 25-38 g/d DF
  - Usual dose only 15 g
- Laxation benefits
  - High fibre cereals/bulk laxative
- Body Weight Control
  - High fibre diets associated with lower body weight
- Cholesterol lowering effects
  - Health claims for oat bran, psyllium, B-glucan

# Wheat Bran & Colonic Function

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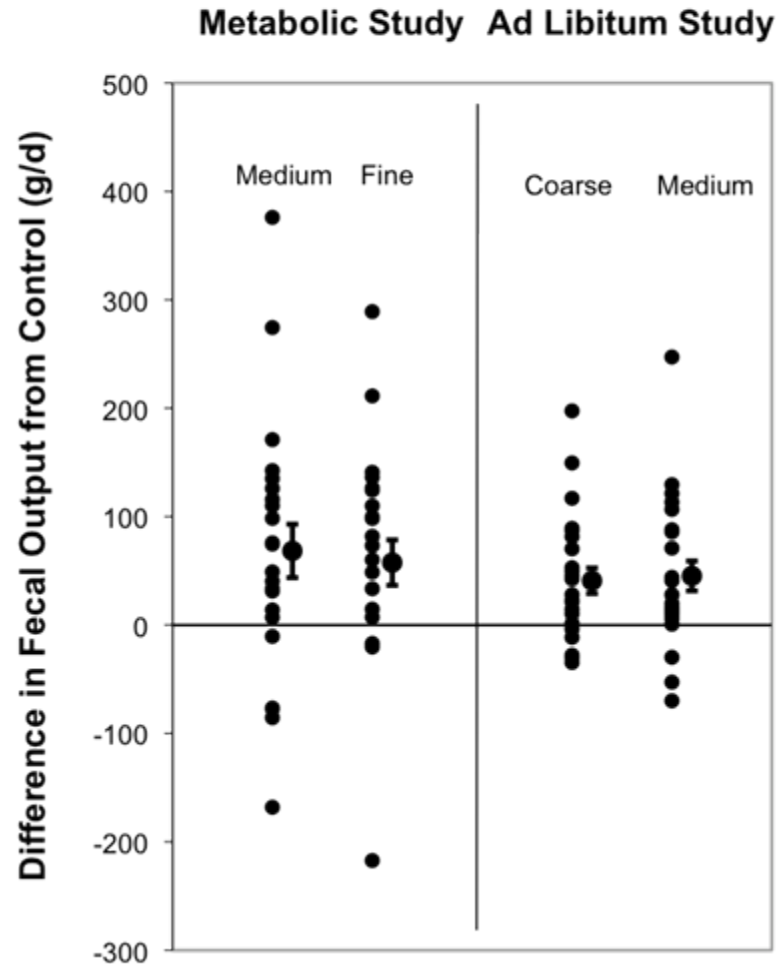
## **Metabolic Study (n=23):**

- Randomized controlled crossover study
- 4 week treatments (breads & breakfast cereals).
- Control Diet
- + 19 g/d fiber WB - Fine particle size (50 um)
- + 19 g/d fiber WB - Medium particle size (735 um)

## **Ad Libitum Study (n=24):**

- Randomized controlled crossover study
- 4 week treatments (breads & breakfast cereals).
- Control Diet
- + 17 g/d fiber WB – Medium (692 um)
- + 17 g/d fiber WB - Coarse (1158 um)

# Fiber and Colonic Health



# Wheat Bran: Fecal & SCFA Output

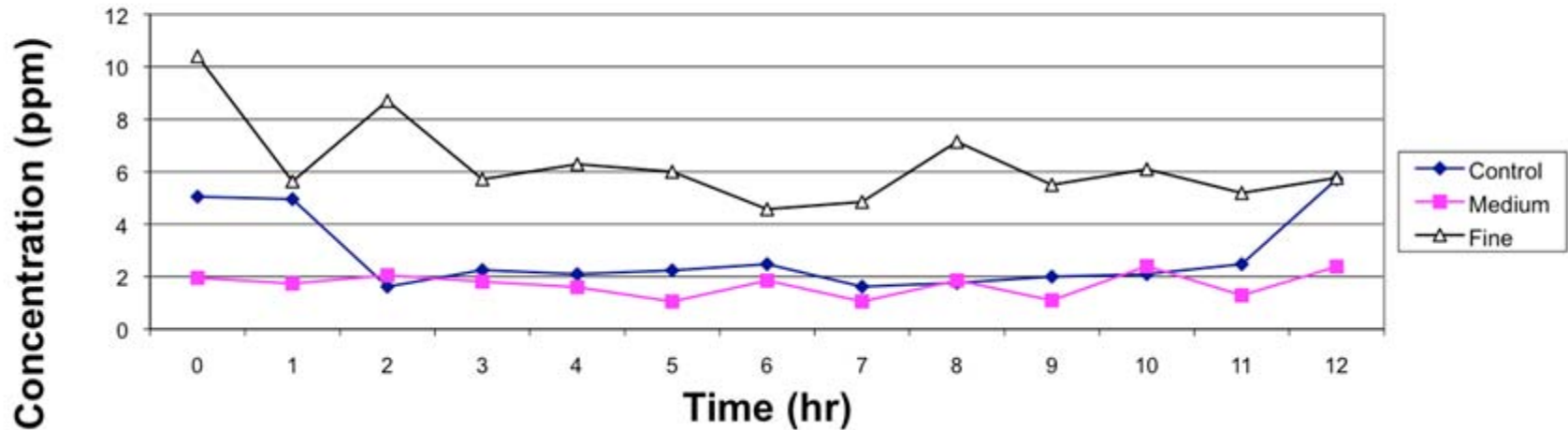
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	Control	Wheat Bran Medium	Wheat Bran Fine
<b>Fecal (g/d)</b>	211 $\pm$ 23 <sup>a</sup>	279 $\pm$ 23 <sup>b</sup>	268 $\pm$ 23 <sup>b</sup>
<b>Total SCFA (mmol/d)</b>	24.7 $\pm$ 3.1 <sup>a</sup>	32.4 $\pm$ 3.0 <sup>b</sup>	35.3 $\pm$ 3.5 <sup>b</sup>
<b>Acetate</b>	12.5 $\pm$ 1.8 <sup>a</sup>	16.1 $\pm$ 1.9 <sup>a,b</sup>	18.1 $\pm$ 2.0 <sup>b</sup>
<b>Propionate</b>	3.1 $\pm$ 0.5 <sup>a</sup>	3.8 $\pm$ 0.4 <sup>a,b</sup>	4.4 $\pm$ 0.5 <sup>b</sup>
<b>Butyrate</b>	3.4 $\pm$ 0.5 <sup>a</sup>	4.8 $\pm$ 0.6 <sup>b</sup>	5.9 $\pm$ 0.8 <sup>c</sup>



# Wheat Bran: Fermentation Breath Hydrogen

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# What is a Heart-Healthy Diet?

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## National Cholesterol Education Program (ATP III):

- 25-35% total fat
- <7% saturated fat; <10% PUFA; <20% MUFA
- <200 mg dietary cholesterol
- 20-30 g/d fiber
- healthy whole foods (whole grains, fruit & vegetables)
  - viscous (soluble ) fiber (10-25 g/d)
  - plant stanol/sterols (2 g/d)
  - nuts – source of healthy fat, ↑ fiber (*AHA, 2000*)
  - soy protein – high risk individuals (*AHA, 2000*)

(*JAMA, 2001*)

# Each Additional g of Fiber in the Diet Reduces CHD Risk

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- **Men**

- 6 g/d ↑ → 24% ↓ CHD (Khaw&Barrett-Connor, 1987)
- 10 g/d ↑ → 29% ↓ CHD (Rimm et al, 1996)

- **Women**

- 6 g/d ↑ → 33% ↓ CHD (Khaw&Barrett-Connor, 1987)
- 5 g/d ↑ → 37% ↓ CHD (Wolk et al, 1999)
- 14g/d ↑ → 54% ↓ MI (Liu et al., 2002)

- **Meta-analysis**

- 10g/d ↑ → 27% ↓ CHD death (Pereira et al. 2004)

# Serum Lipid Response to a Diet Very High in Fiber From Vegetables and Fruit (Simian Diet)

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- Low-fat therapeutic diet (NCEP Step 2)  
low-fat dairy, white rice, potato, fruit & vegetables (5 servings/d)
- High-fiber starch-based (Neolithic)  
low-fat yogurt, whole grains, lentils, fruit & vegetables (5 servings/d)
- High-fiber vegetable-based (Simian)  
63 servings/d fruit & vegetables, nuts

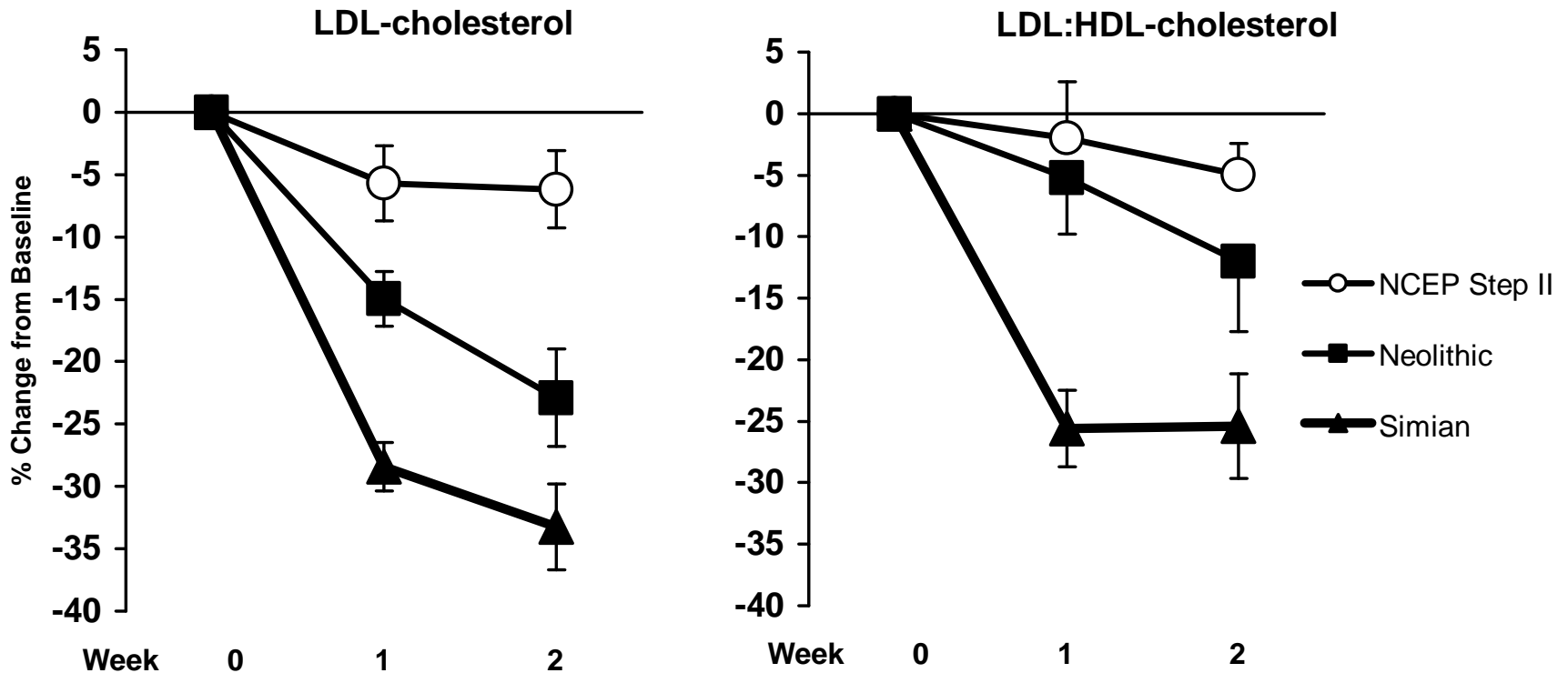
# Daily Intakes of Vegetable Protein, Fiber, Phytosterols & Nuts

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	NCEP Step 2	High-Fiber Starch-Based	High-Fiber Vegetable-Based Simian
Vegetable Protein (g/d)	28	64	93
Total Dietary Fiber (g/d)	26	46	143
Phytosterols (g/d)	0.3	0.5	1.0
Nuts (g/d)	0	0	84

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# Serum Lipid Response to a Diet Very High in Fiber From Vegetables and Fruit (Simian Diet)



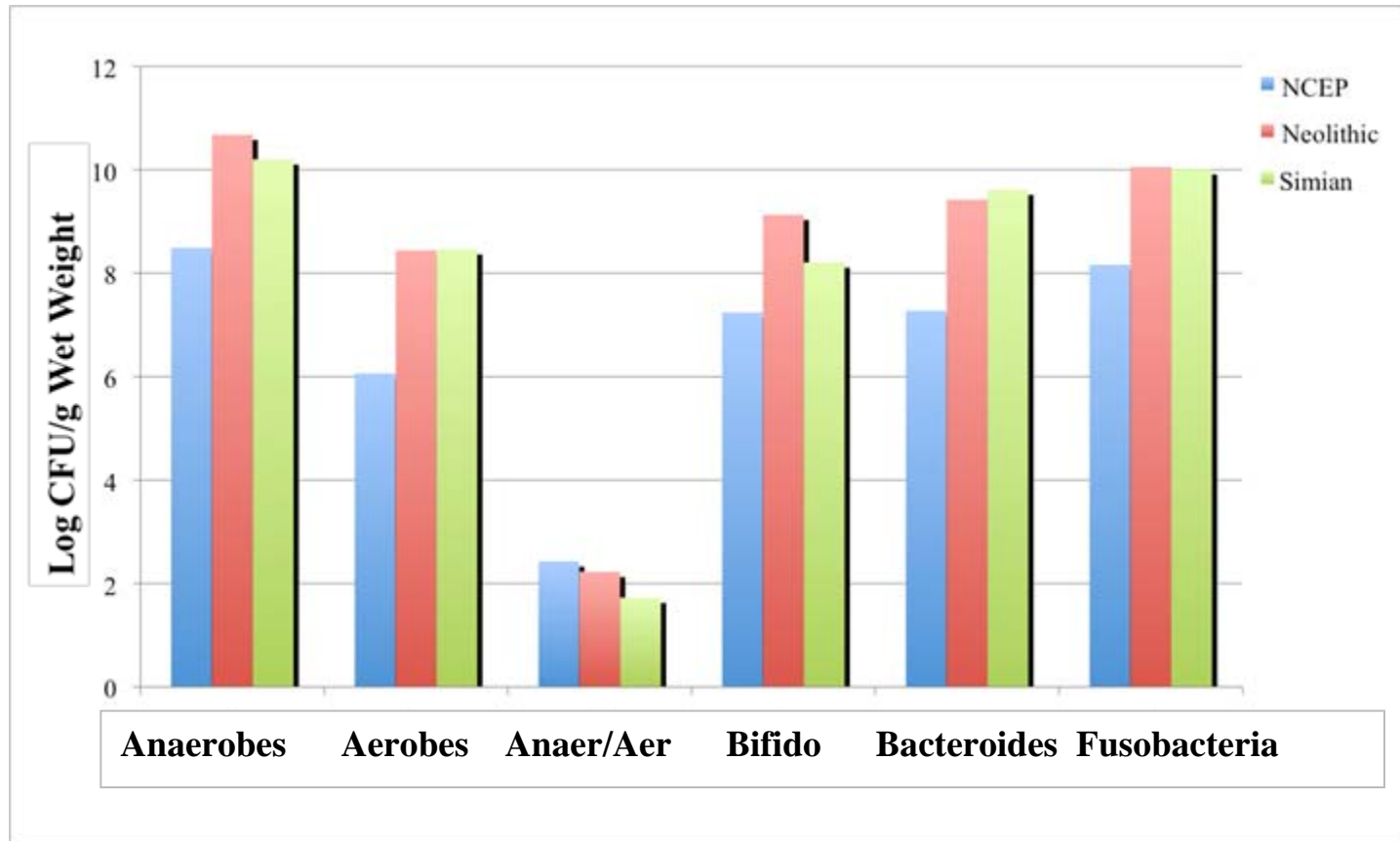
# The Simian Diet

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5.5 kg food in

1.0+ kg feces out  
& 1g bile acids

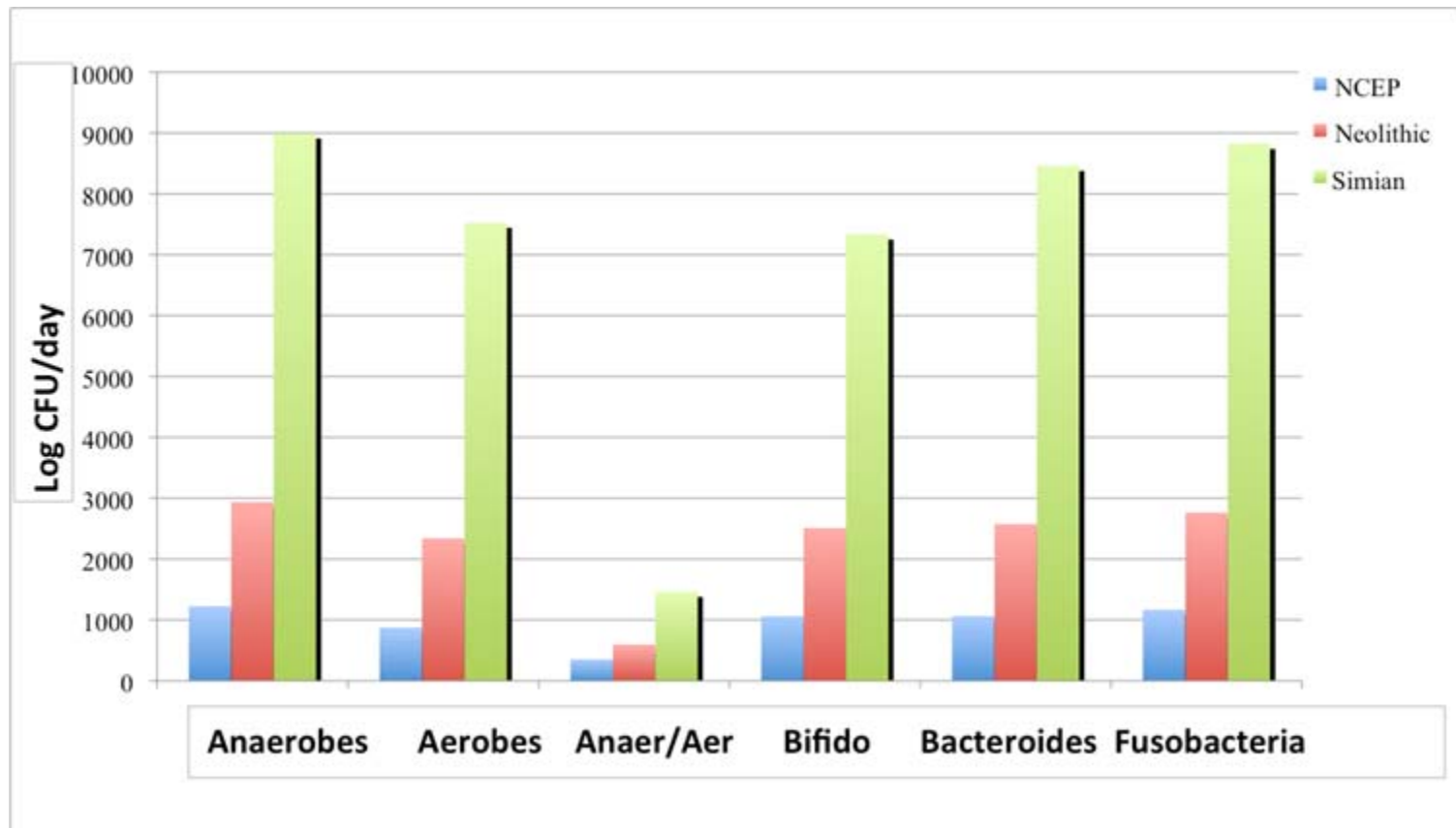
# Simian Diet & Colonic Microflora Concentration





# Simian Diet & Colonic Microflora

## Daily output



# Portfolio Diet

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## Study Foods:

Readily available in supermarkets.

**Viscous Fiber:** ~20 g/d

oats, barley, psyllium, legumes, eggplant, okra

**Vegetable Protein:** ~80 g/d

soy, beans, chick peas, lentils

**Plant Sterols:** ~2 g/d

plant sterol margarine (1g/1000 kcal)

**Nuts:** ~30 g/d

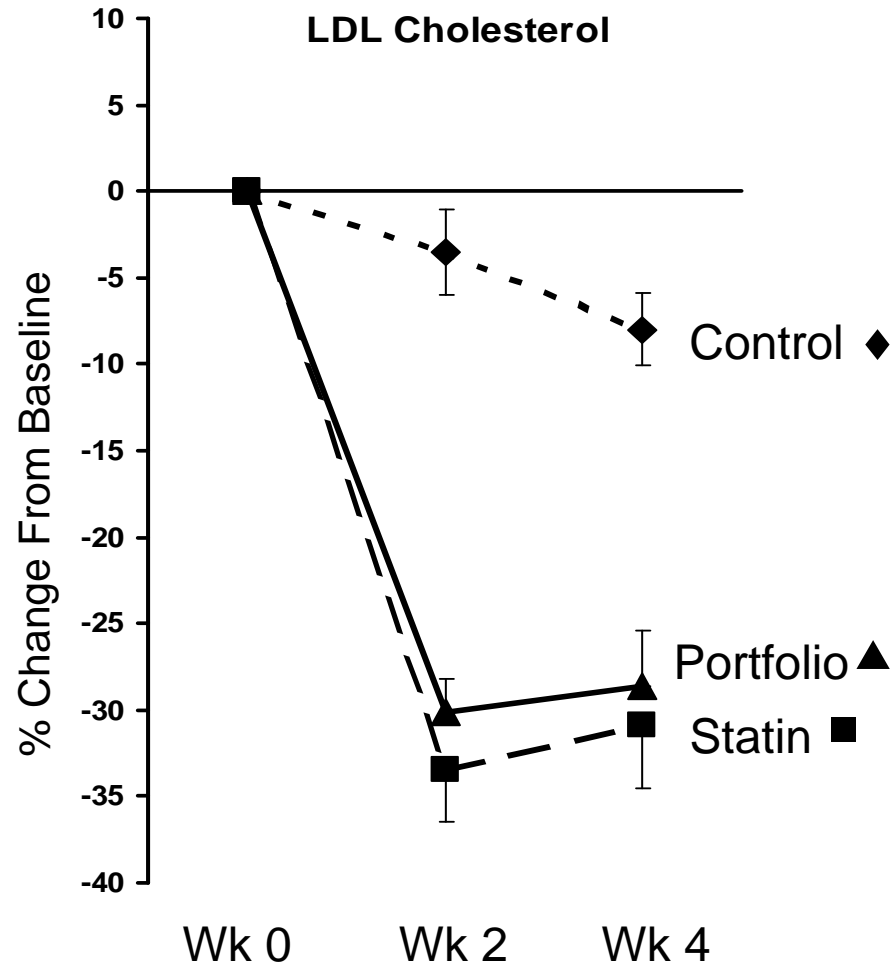
almonds

# Portfolio Diet #3: Results

Week 4 Mean $\pm$ SEM	CONTROL Diet  (n=16)	STATIN Diet  (n=14)	PORTFOLIO (Test) Diet  (n=16)
Energy (kcal/d)	2421 $\pm$ 138	2519 $\pm$ 176	2383 $\pm$ 162
Total Protein (% calories)	20.6 $\pm$ 0.5	19.9 $\pm$ 0.7	20.2 $\pm$ 0.5
Vegetable Protein (% calories)	4.0 $\pm$ 0.1	4.2 $\pm$ 0.2	19.8 $\pm$ 0.5
Available Carbohydrate (% calories)	57.9 $\pm$ 1.8	59.6 $\pm$ 2.1	57.5 $\pm$ 2.3
Total Dietary Fiber (g/1000kcal)	21.9 $\pm$ 1.0	21.6 $\pm$ 1.0	31.1 $\pm$ 1.0
Total Fat (% calories)	22.9 $\pm$ 0.7	23.5 $\pm$ 0.8	28.0 $\pm$ 1.0
SFA (% calories)	4.2 $\pm$ 0.1	4.3 $\pm$ 0.2	5.9 $\pm$ 0.2
MUFA (% calories)	9.6 $\pm$ 0.4	9.4 $\pm$ 0.3	11.9 $\pm$ 0.7
PUFA (% calories)	7.9 $\pm$ 0.3	8.7 $\pm$ 0.4	9.4 $\pm$ 0.2
Dietary Cholesterol (mg/1000kcal)	10.9 $\pm$ 0.2	11.7 $\pm$ 0.8	21.2 $\pm$ 1.5
Alcohol (% calories)	0.1 $\pm$ 0.1	0.0 $\pm$ 0.0	0.4 $\pm$ 0.1
Satiety (-4 to +4)	2.3 $\pm$ 0.4	2.4 $\pm$ 0.3	2.8 $\pm$ 0.2

# Portfolio Study #3a: Results

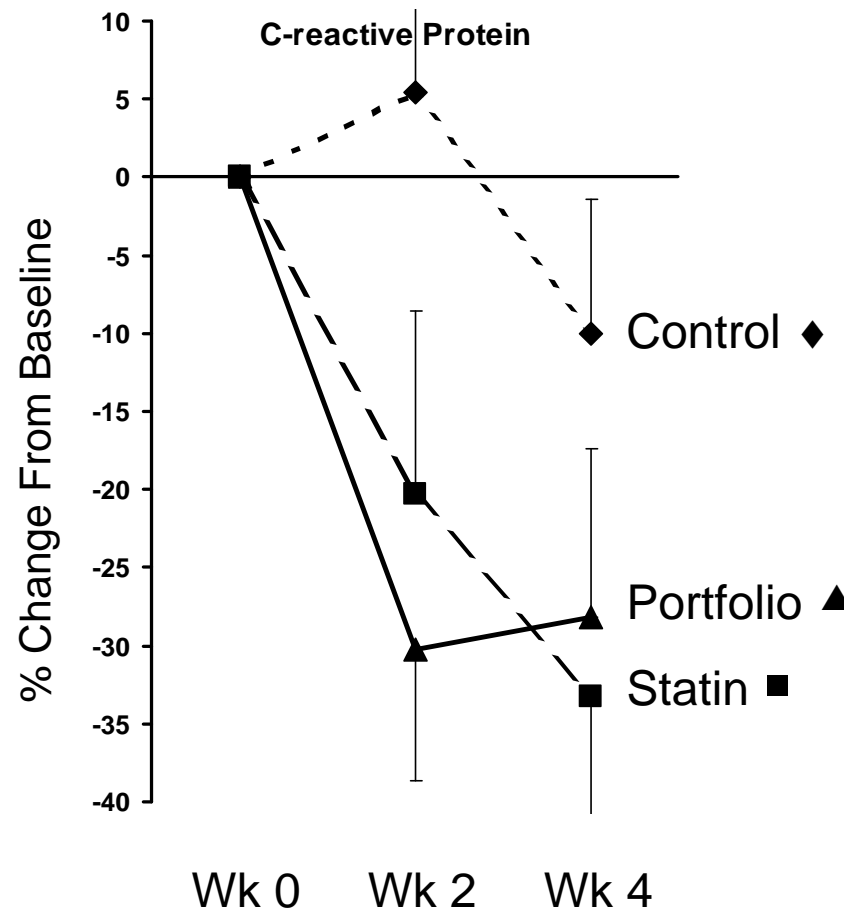
## Changes in LDL-C ( $n=46$ )



# Portfolio Diet #3: Results

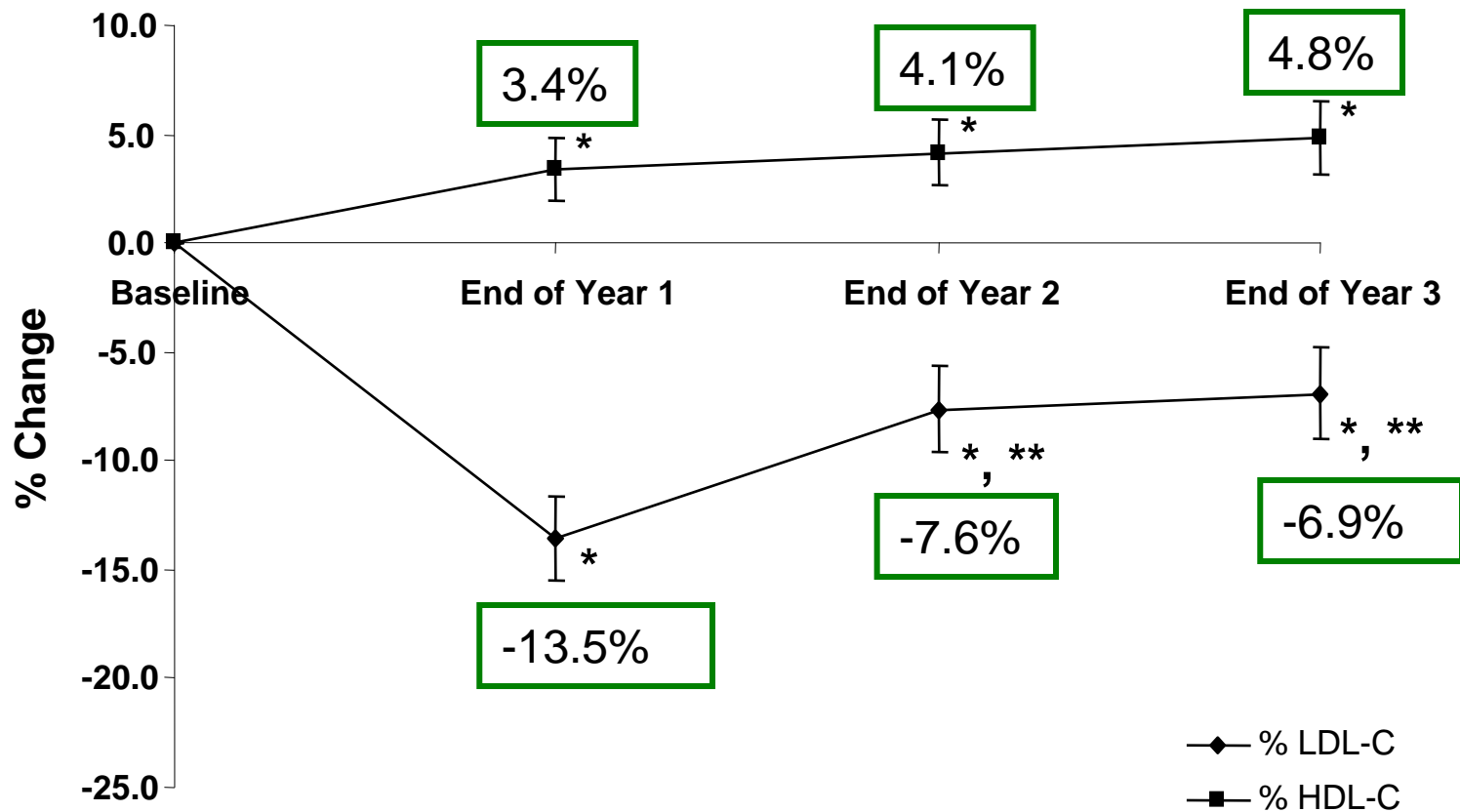
## Changes in C-Reactive Protein ( $n=46$ )

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# Intent-to-Treat Analysis (n=66)

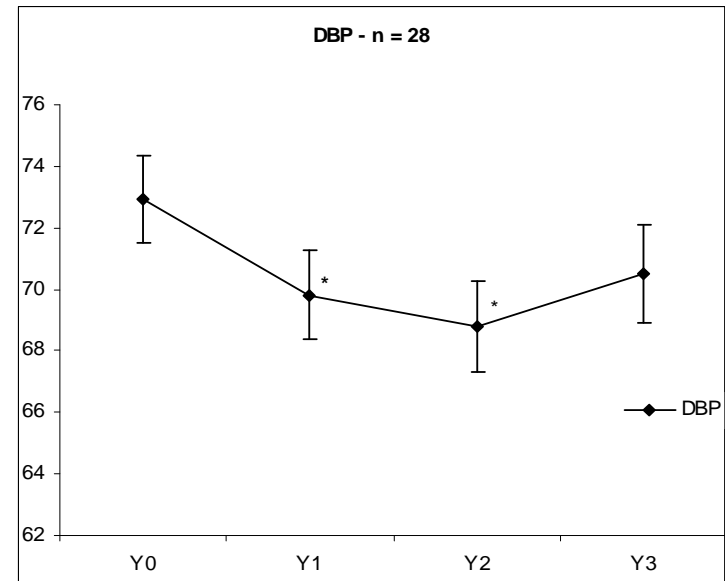
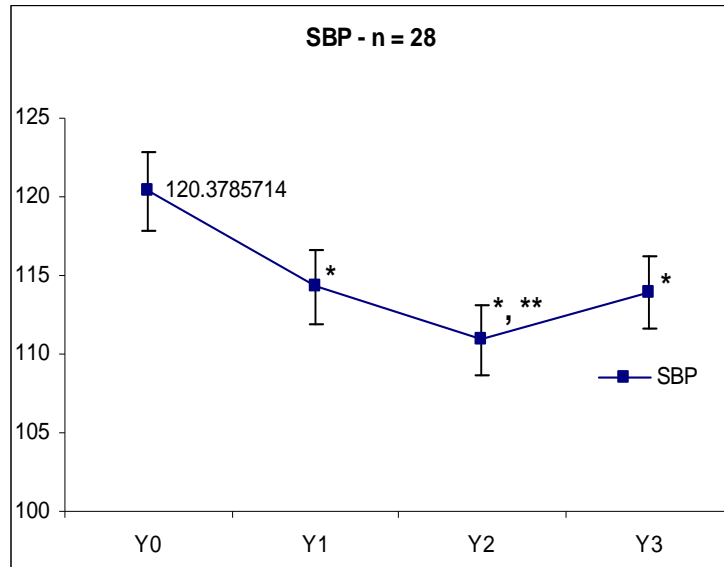
## % LDL-C and % HDL-C



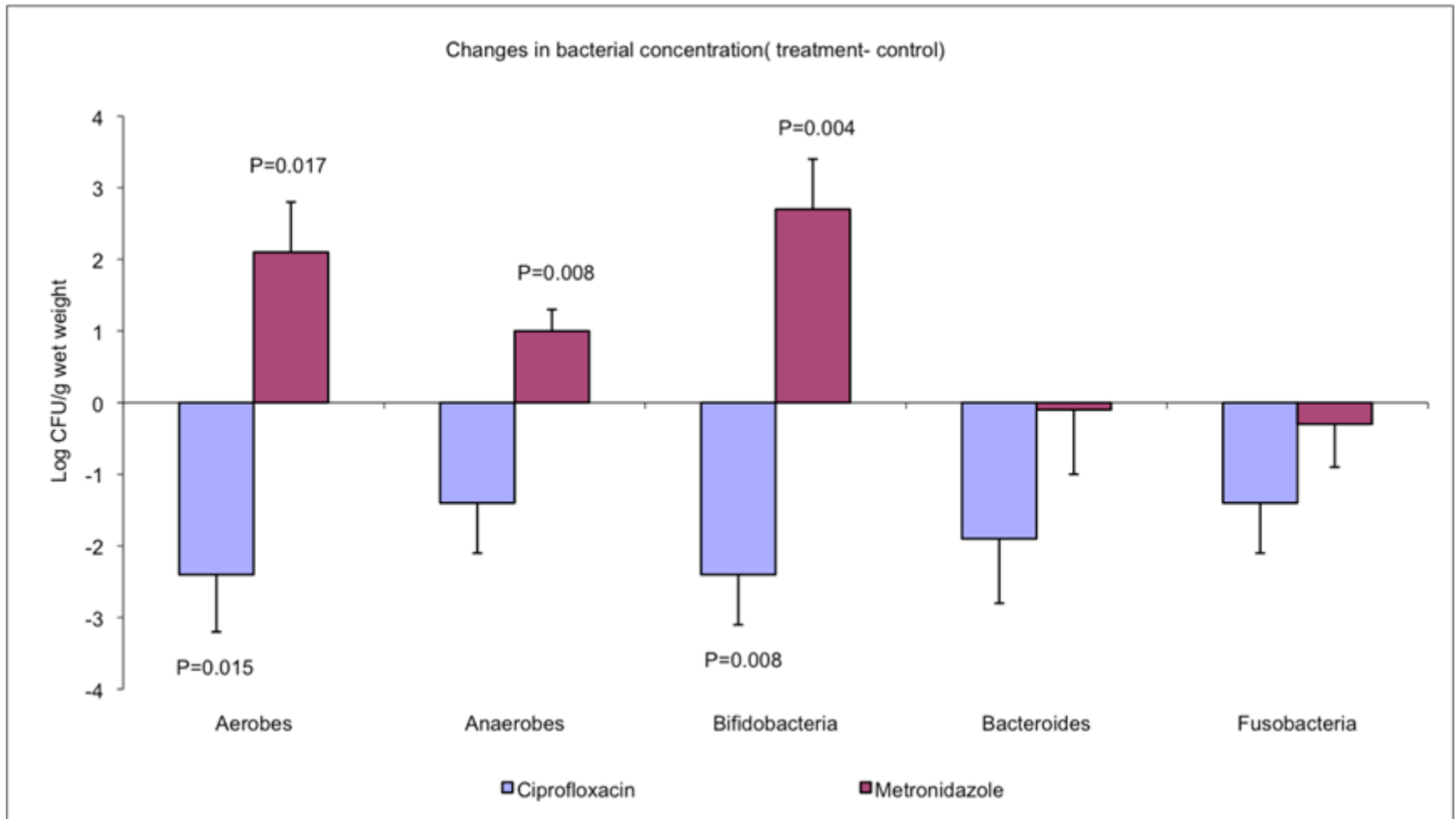
Mean  $\pm$  SE percentage change in LDL-C and HDL-C at end of each year (n = 66).  
\* and \*\* represent significant differences from baseline and year 1 respectively (P < 0.01).

# Changes from baseline in blood pressure

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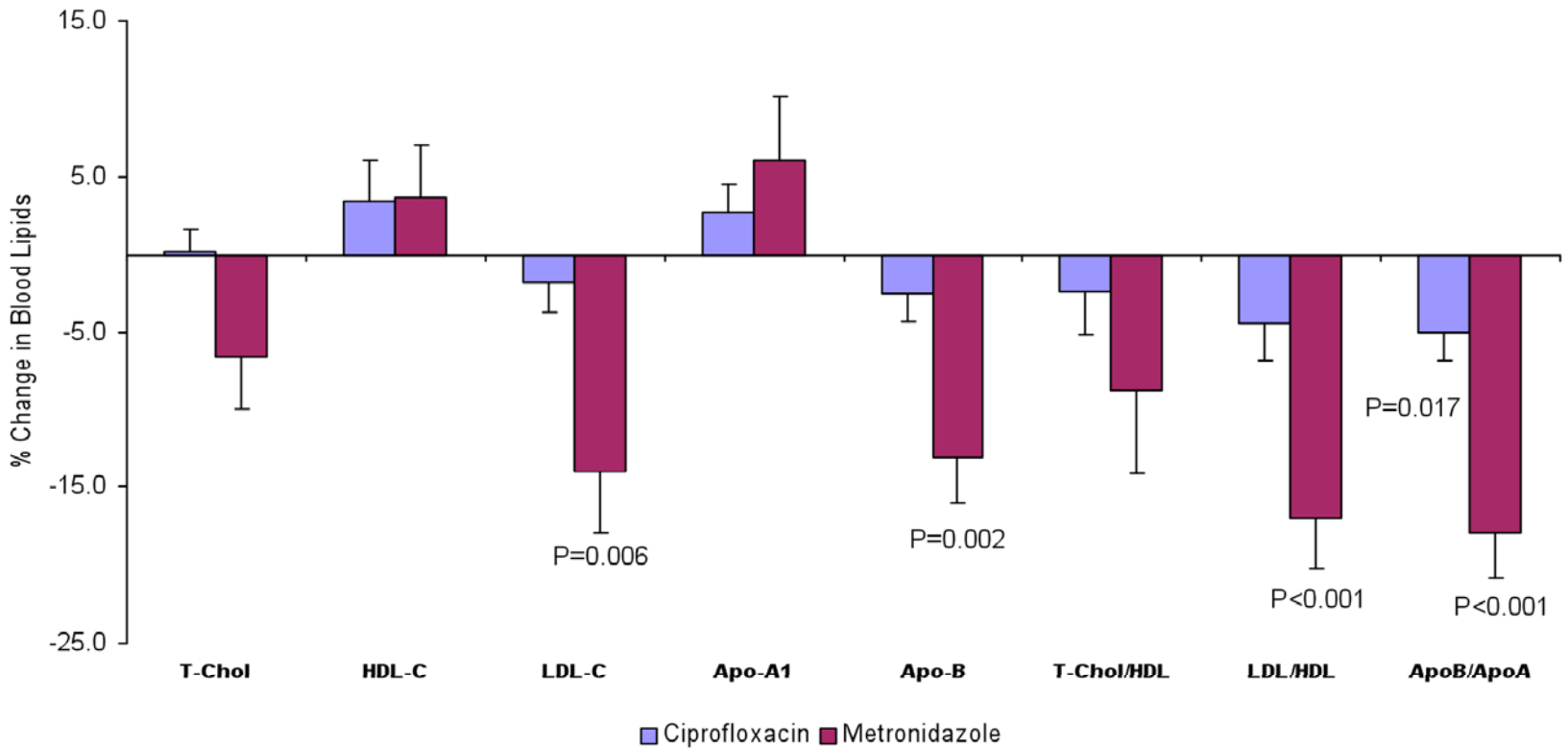


# Antibiotics & Cholesterol Reduction: Colonic Microflora and LDL-cholesterol





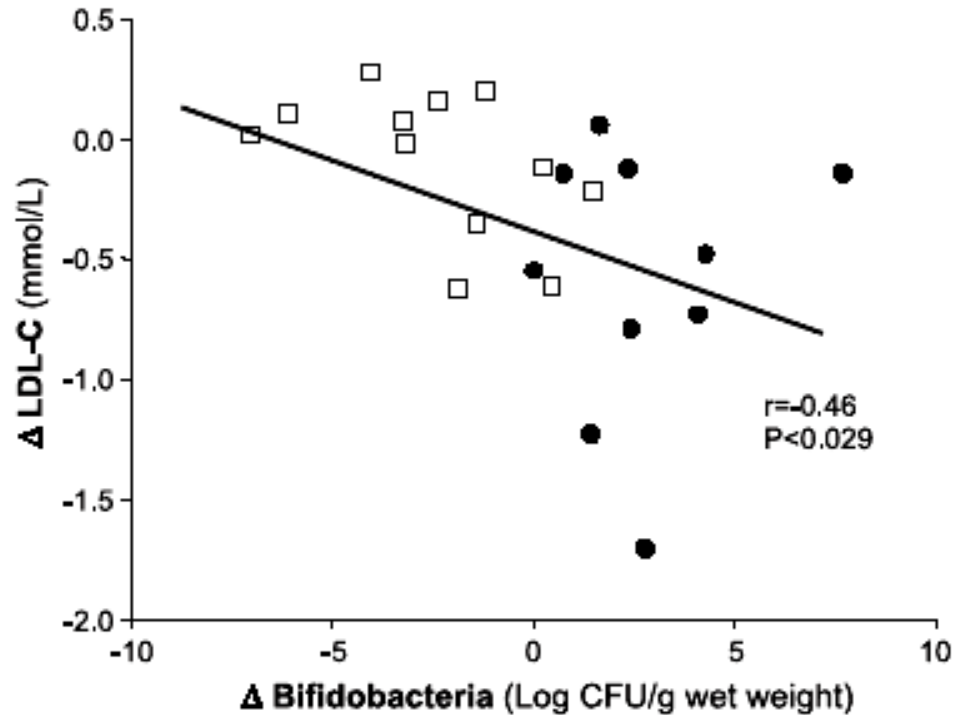
# Antibiotics & Cholesterol Reduction: Colonic Microflora and LDL-cholesterol



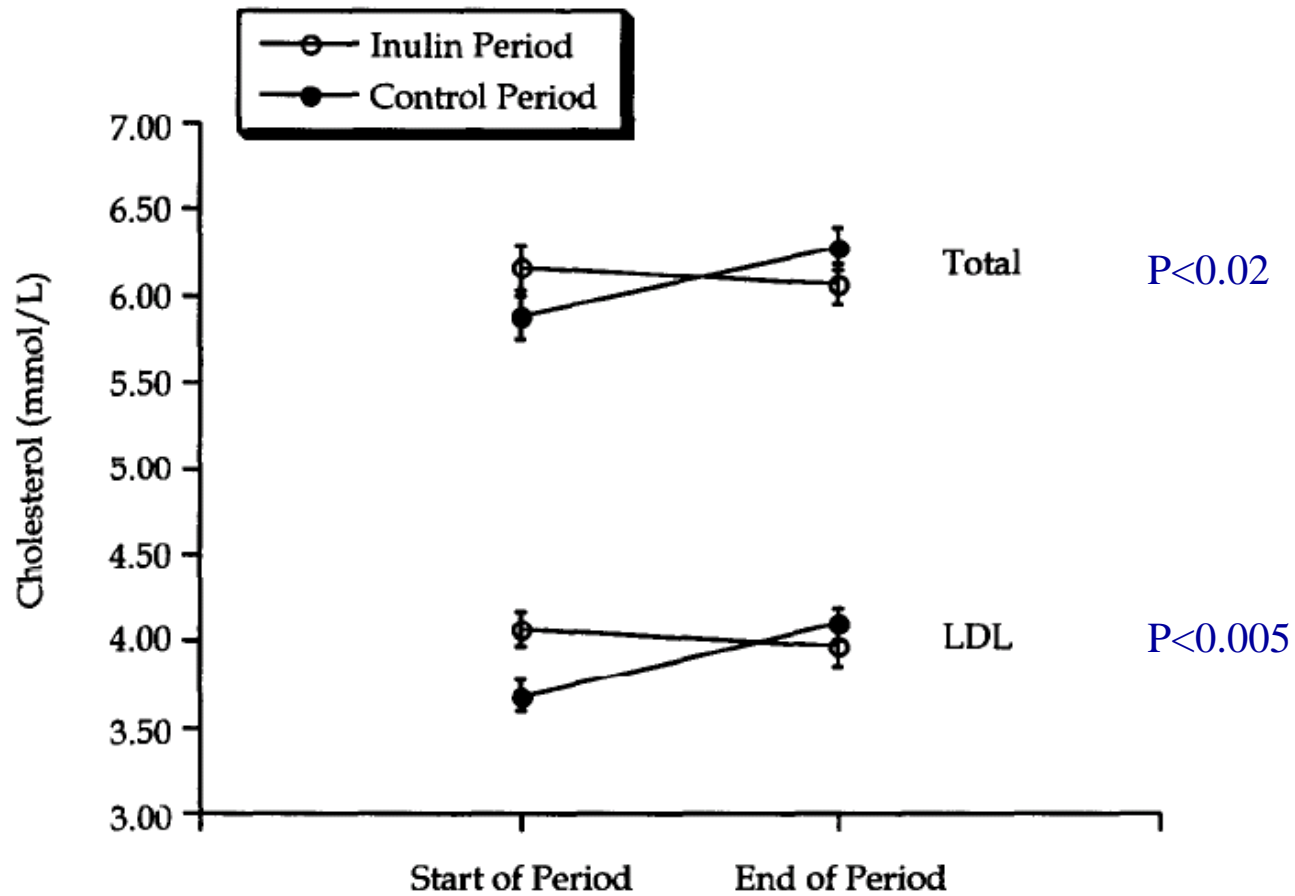
**Figure 1.** Effect of ciprofloxacin/metronidazole (1000mg/d) on blood lipids, expressed as percentage change from the respective control value.

# Antibiotics & Cholesterol Reduction: Colonic Microflora and LDL-cholesterol

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# Inulin and Lipids



# BIOTRANSFORMATION

Does ↑ FOS and Soy

= ↑ Isoflavone/Aglycone &  
Equol Synthesis?

= ↓ Cholesterol?

# Equol Production

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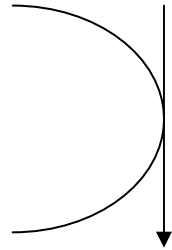
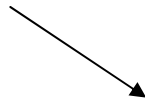
Carbohydrate  
Fermentation

Colonic  
Microflora

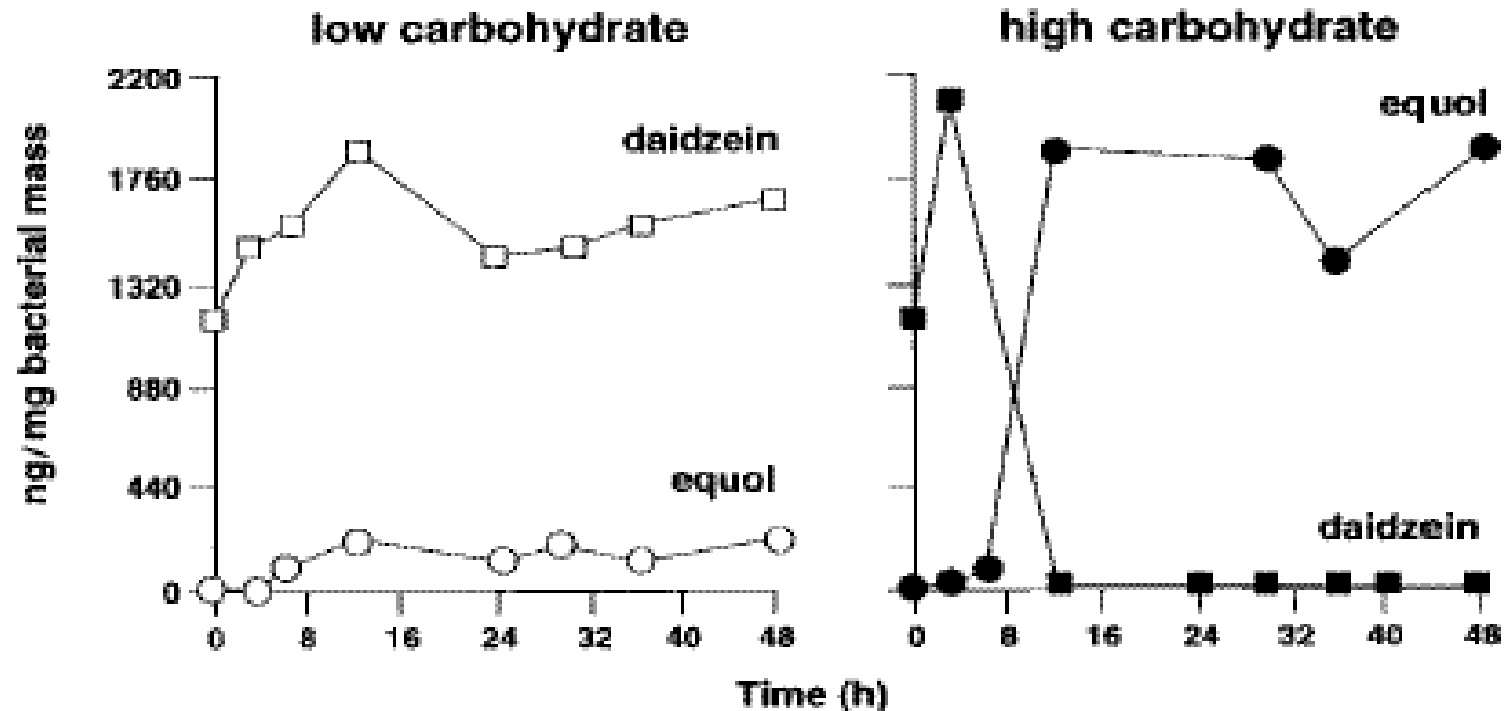
Daidzein

Equol

↓ LDL



# Equol Production: CHO Fermentation

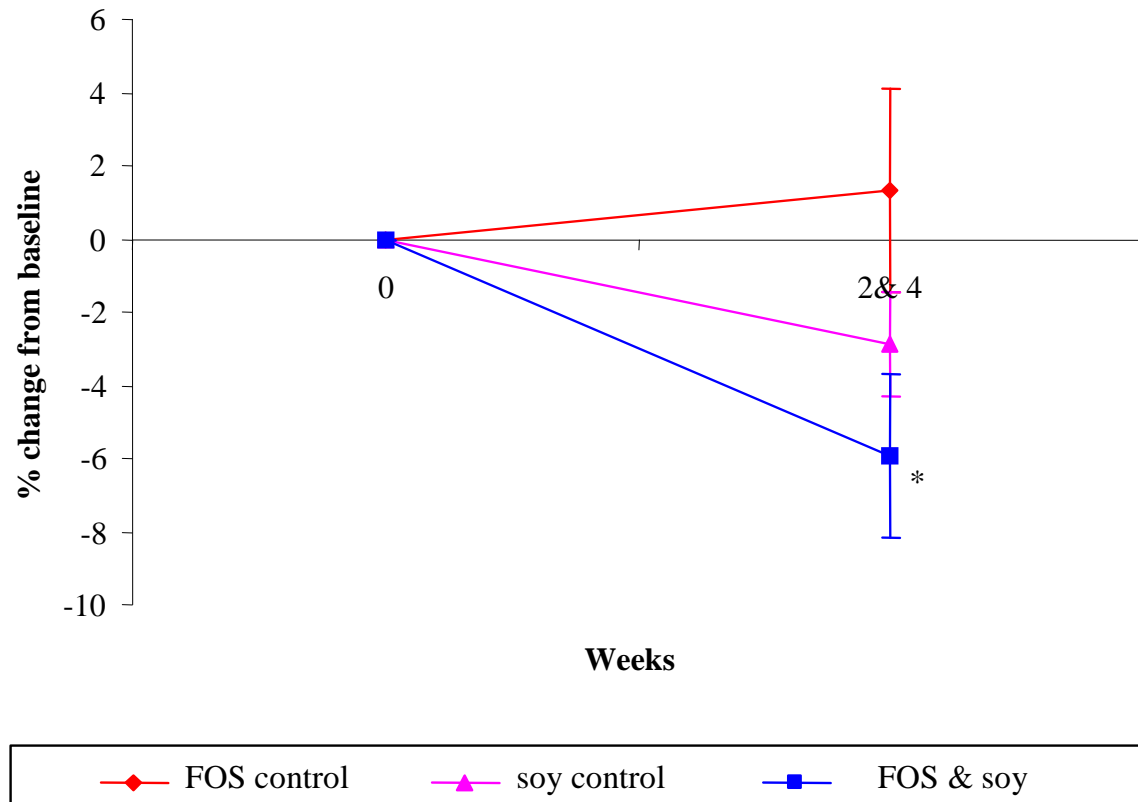


In vitro metabolism of daidzein in a colonic model of fermentation of human fecal flora showing the influence of a high CHO milieu on the rate of conversion of daidzein to the intestinal bacterially derived metabolite equol.

# Mean LDL Cholesterol

Mean LDL Cholesterol

N = 23

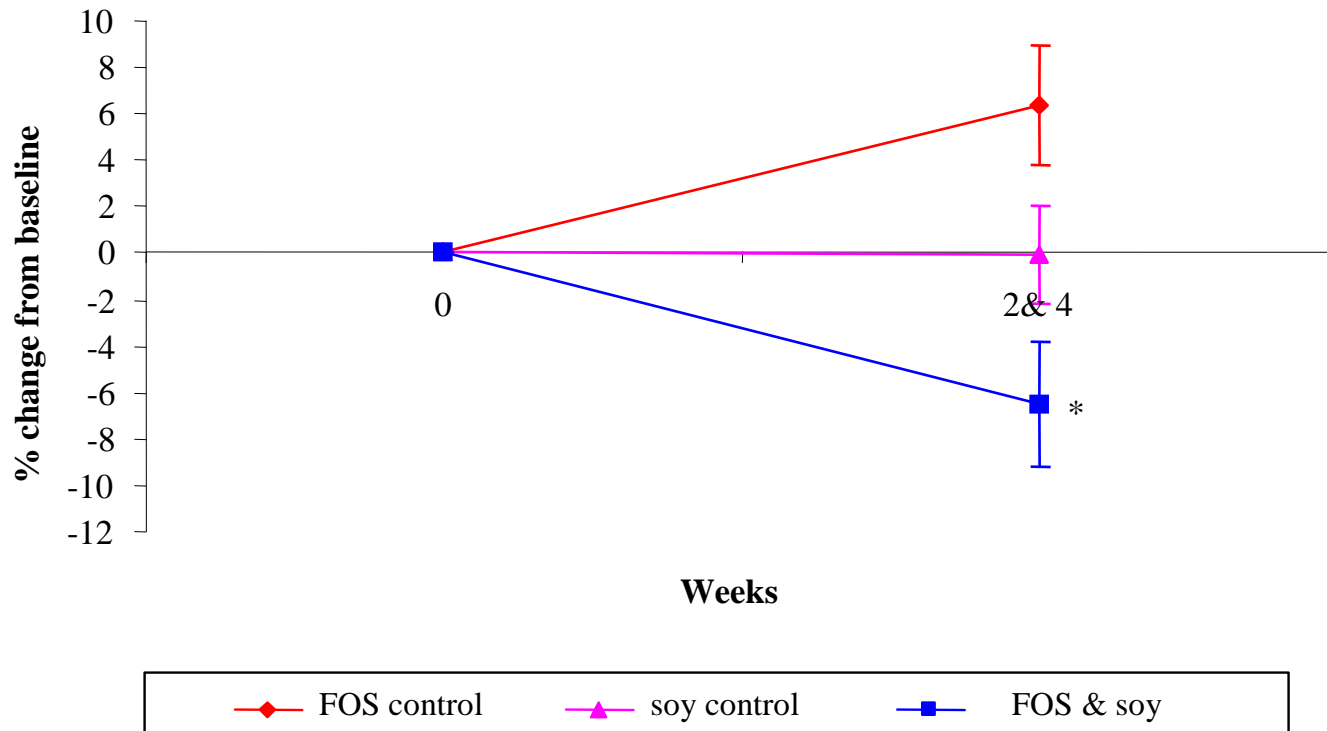


\* Significantly different from FOS control,  $P < 0.05$ .

# Mean LDL:HDL cholesterol

Mean LDL:HDL cholesterol

N = 23



\* Significantly difference from FOS control,  $P < 0.05$ .



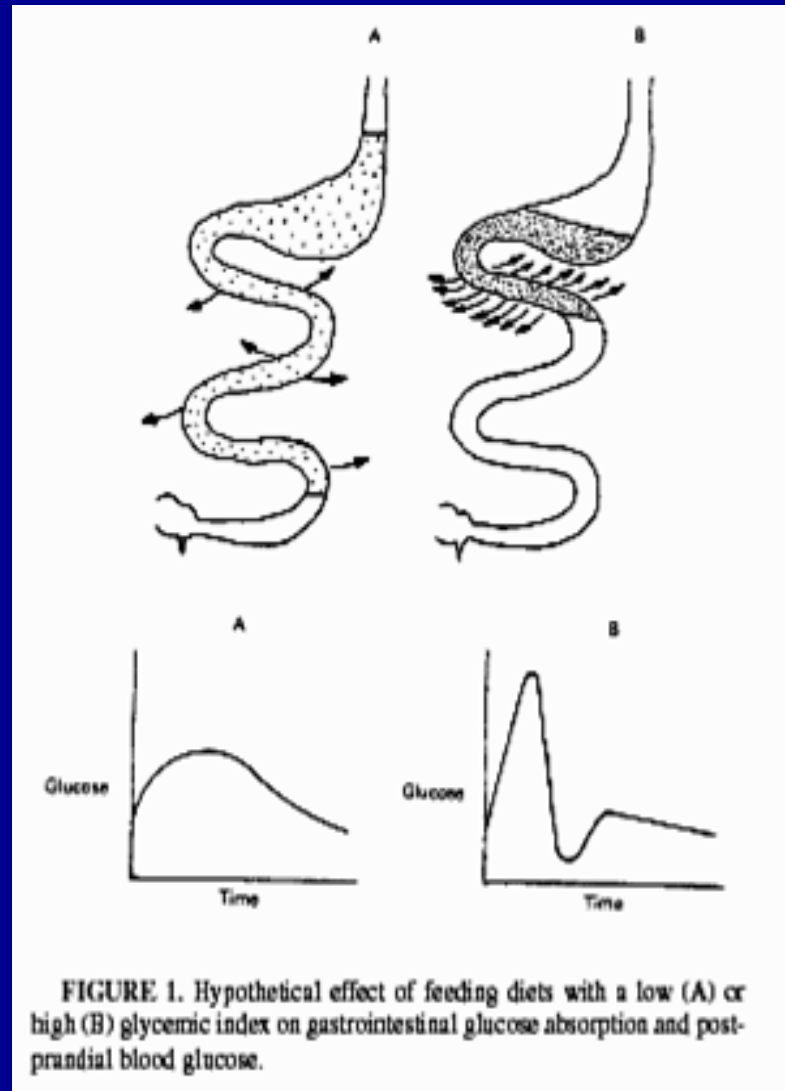
# Hyperglycemia (high 2-h blood glucose or HbA1c) is associated with all-cause and CVD mortality in non-diabetic populations

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- Helsinki Policeman Study (Pyorala et al. 1979)
- The Framingham Study (Singer et al. 1980)
- The Whitehall Study (Fuller et al. 1983)
- The Chicago Heart Study (Pan et al. 1986)
- The Rancho Bernardo Study (Park et al. 1996; Barrett-Connor et al., 1998)
- Hoorn study (De Vegt et al. Diabetologia, 1999)
- ARIC study (Vitelli et al. 1997)
- Meta-analysis DECODE study (Lancet 1999)
- EPIC-Norfolk (Khaw et al. 2001)
- The Cardiovascular Health Study (Smith et al. 2002)
- ....many more now

# Metabolic Effects

Low vs. High GI  
Foods:



# Delayed Absorption

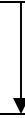
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Delayed Absorption

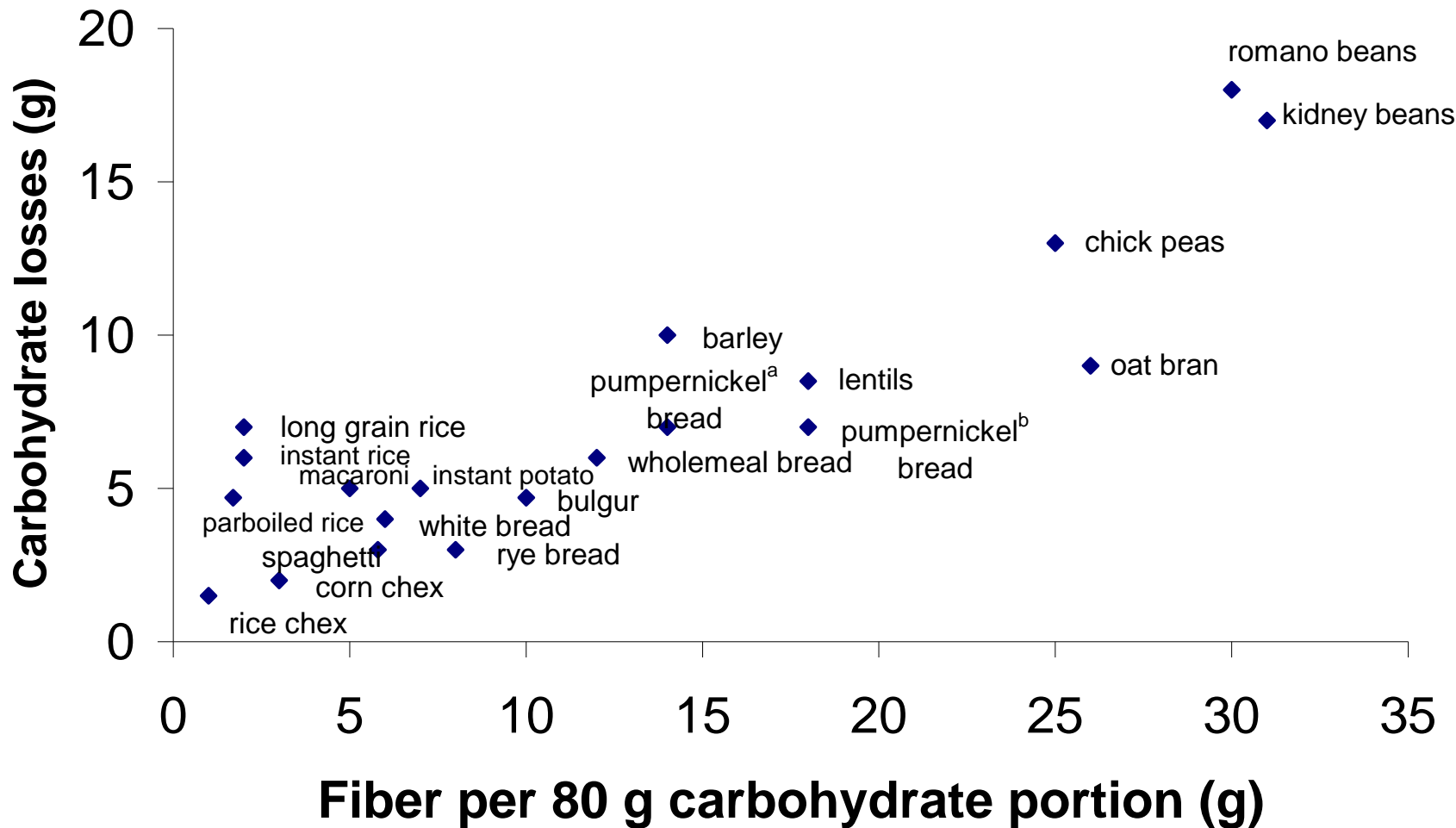


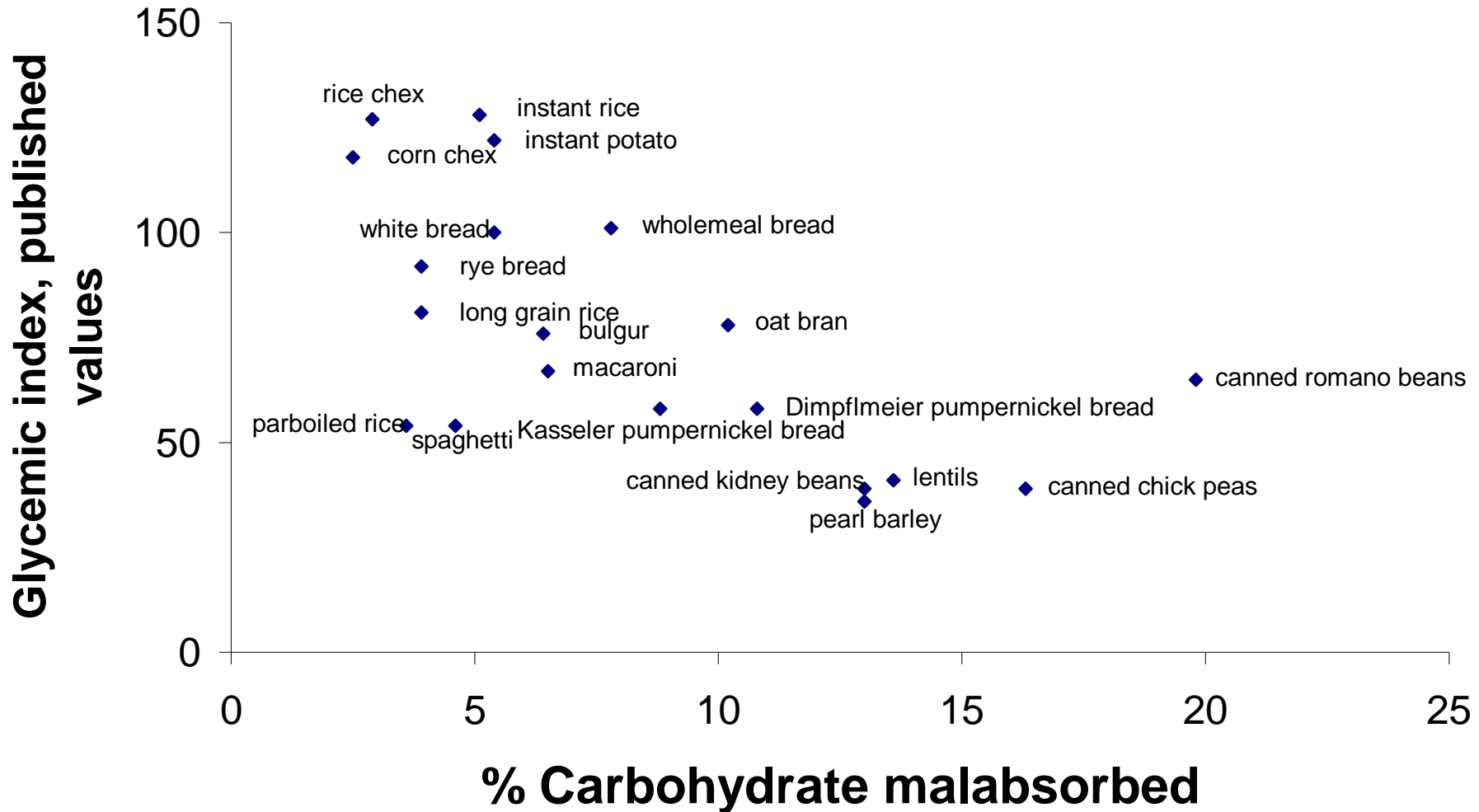
↑ Colonic Fermentation

Small  
Intestine

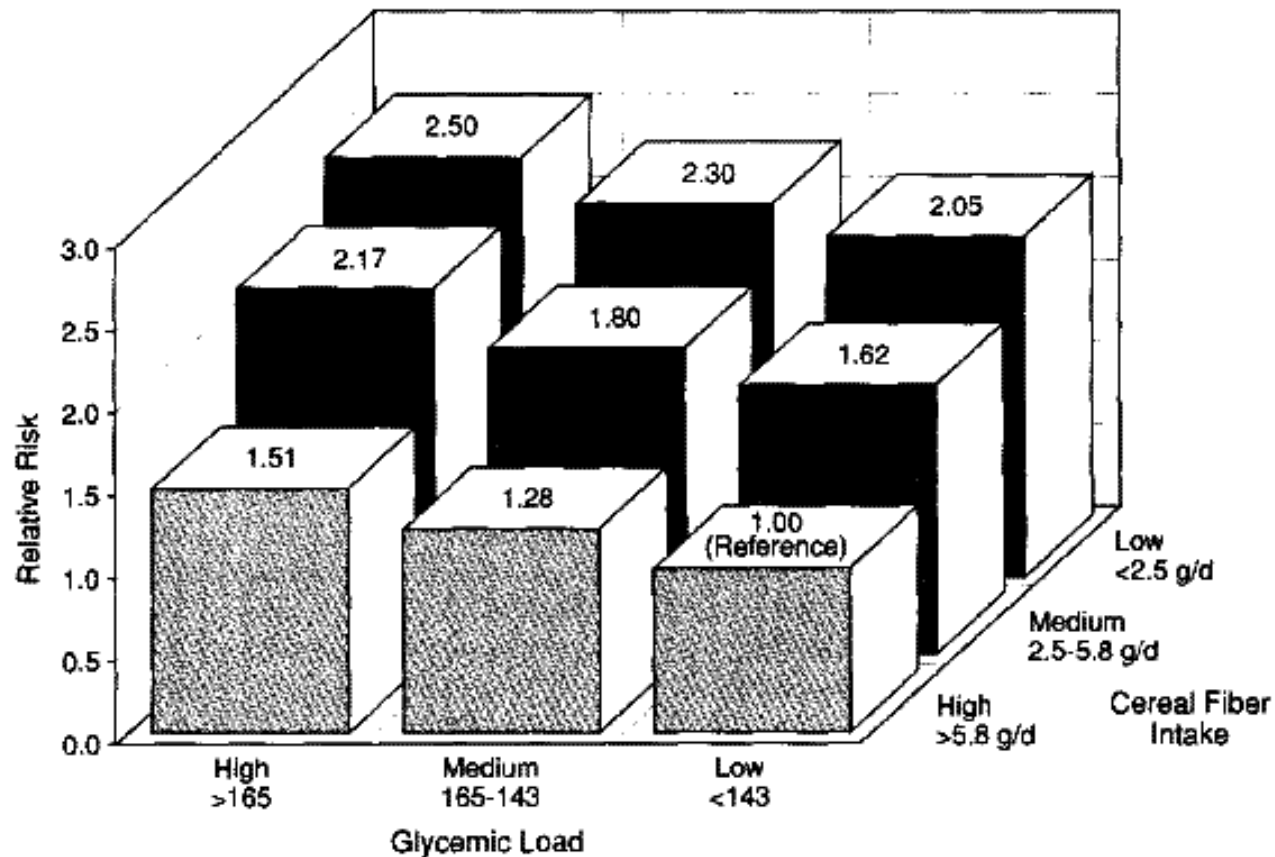


Colon





# Glycemic Load and Cereal Fiber Intake in Women at Risk of Type 2 Diabetes



# Dietary CHO Quantity and Quality and Risk of Type 2 Diabetes

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EPIC NL Study ~ 40,000 subjects

Diabetes Cases (915)

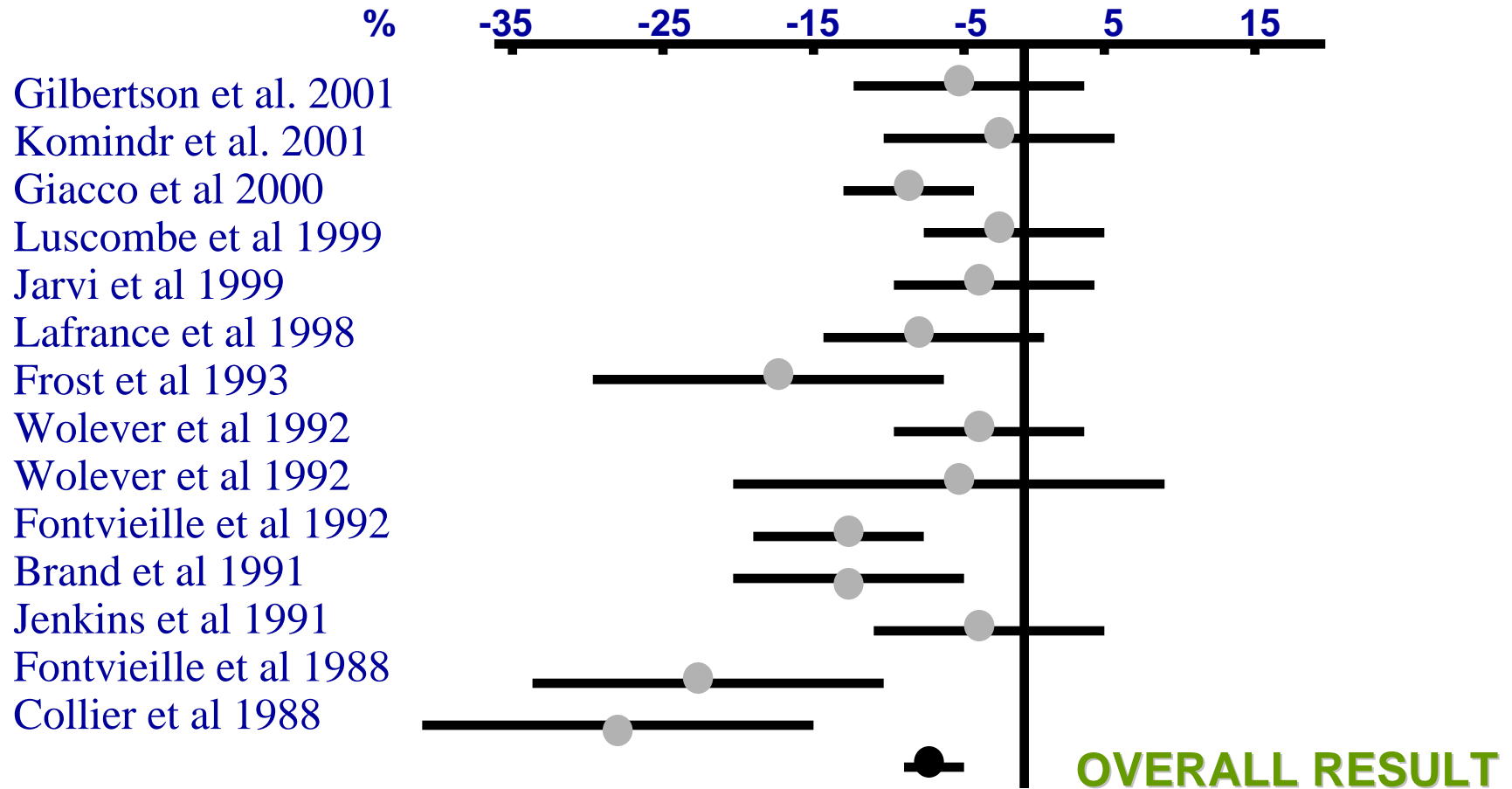
Increased risk – diets high in glycemic load,  
glycemic index, total  
CHO,

starch

Decreased risk – diets high in fiber

# Low vs High GI Diet: a Meta-Analysis

## % Difference in Glycated Proteins



**Mean %difference in 14 studies = -7.4% (CI -8.8 to -6.0%)**



# Recommended Study Foods

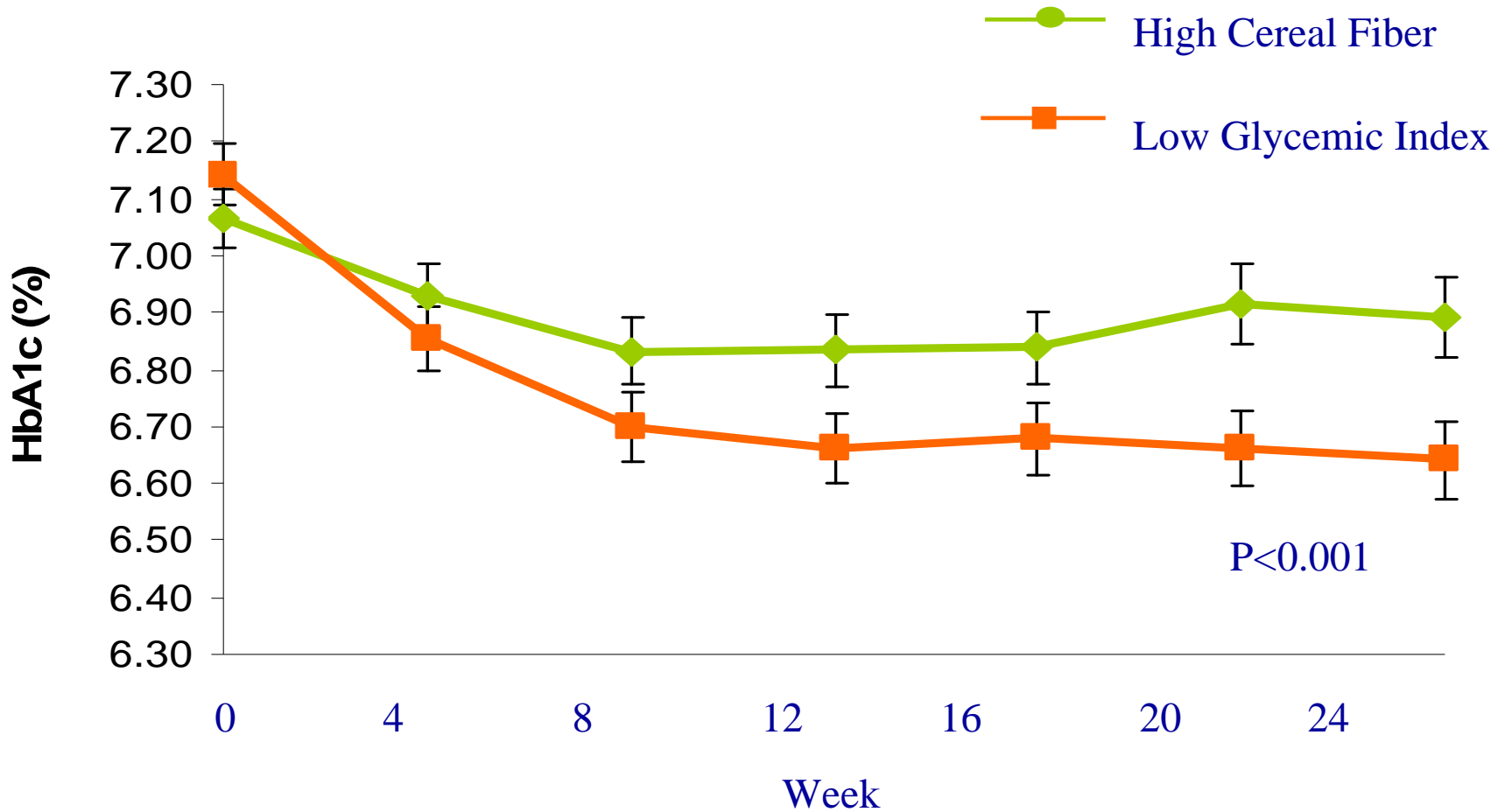
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<b>Low GI Diet (Test)</b>	<b>High Cereal Fiber Diet (Control)</b>
Pasta (al dente)	Potato (baked, mashed)
Parboiled rice	White / Brown rice
Beans, Chickpeas, Lentils	Vegetable soup
Pumpernickel bread (Dimpflmeier)	Whole wheat bread
Barley	Rye crackers
Bulgur	Whole wheat crackers
Oatmeal	Bran flakes
Red River cereal	Shredded Wheat

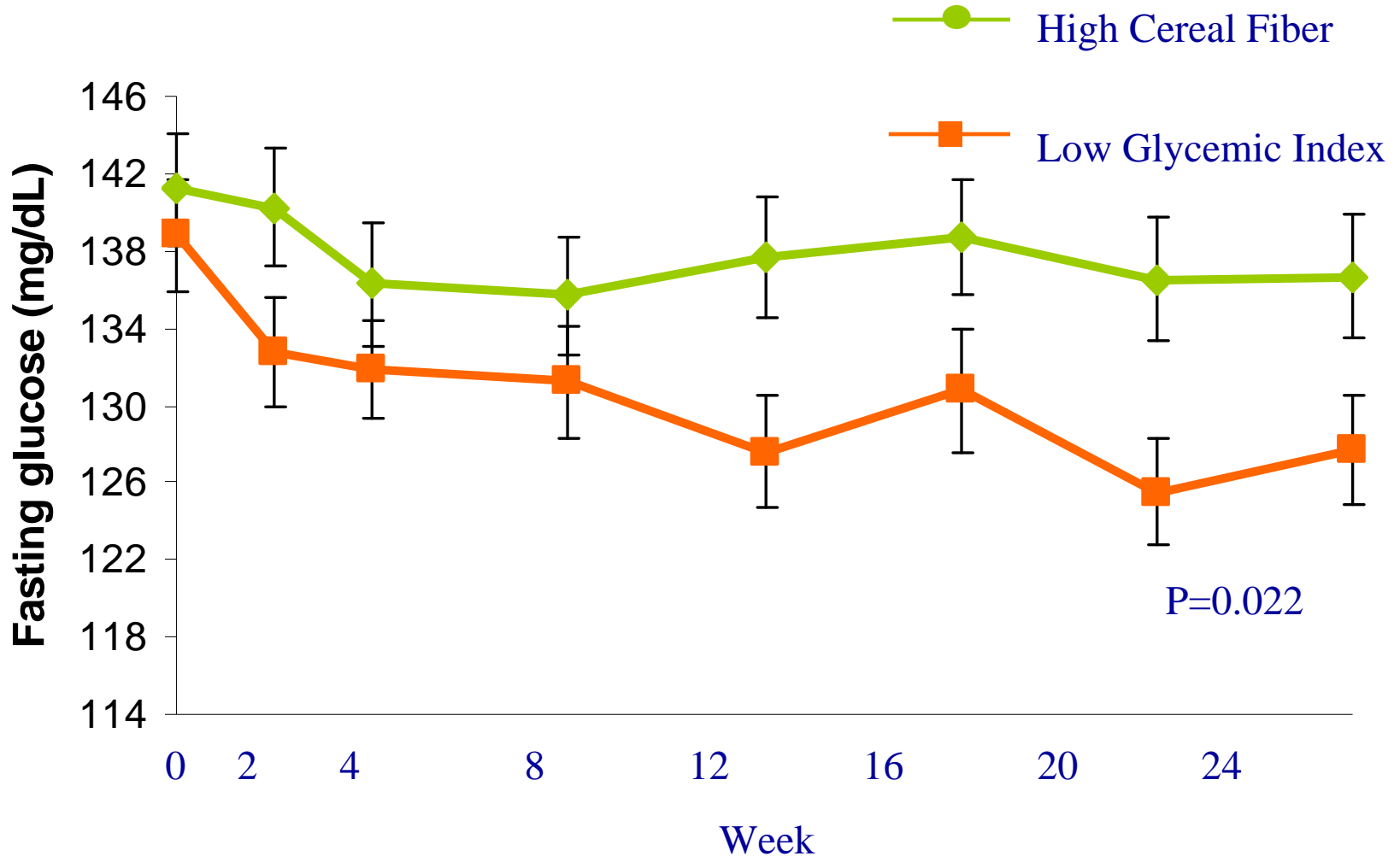
**GI < 70**

**GI = 80**

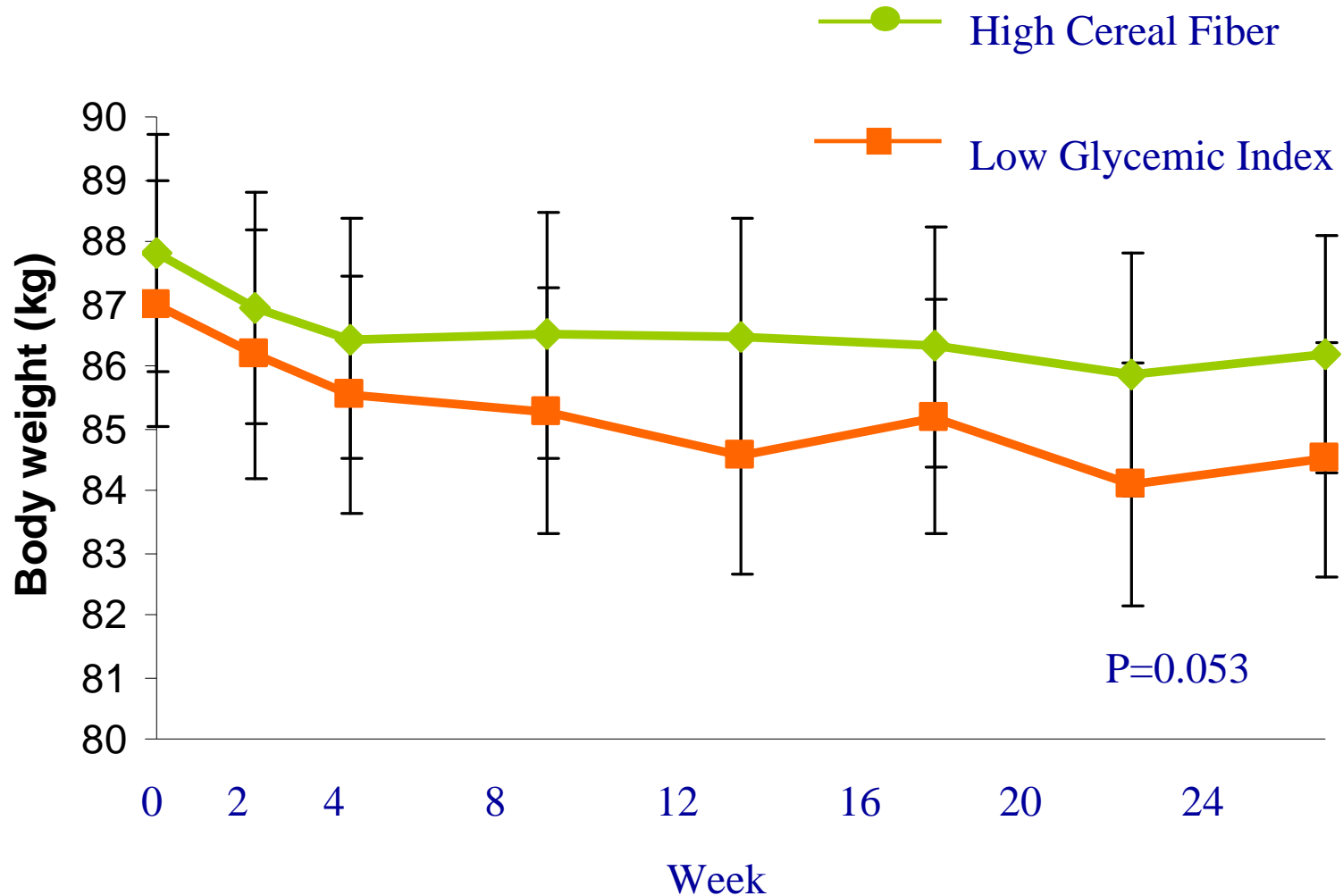
# Low Glycemic Index Diets and Diabetes Control



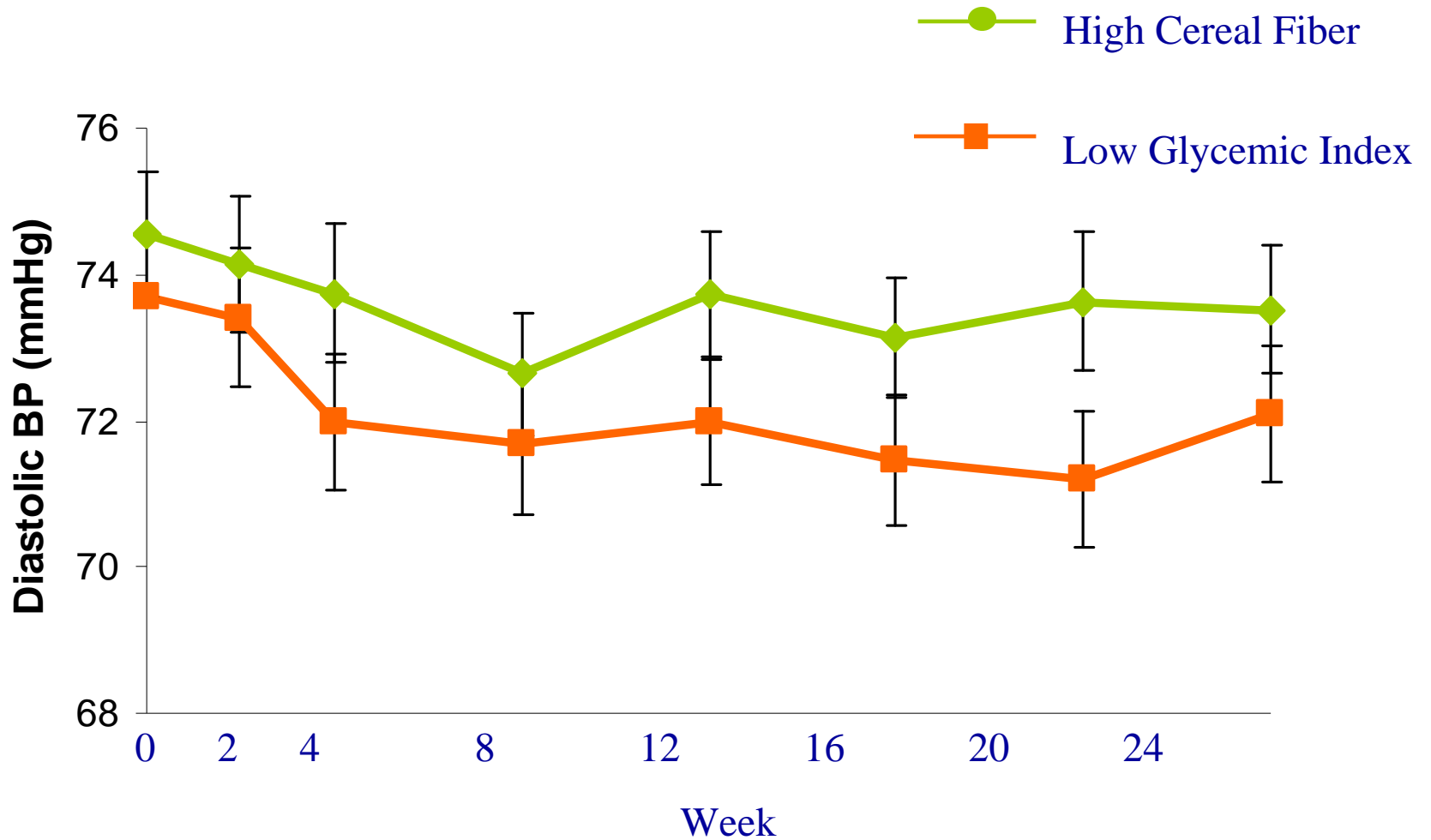
# Low Glycemic Index Diets and Diabetes Control



# Low Glycemic Index Diets and Diabetes Control



# Diastolic BP



# Plasma SCFA's vs. B-glucose AUC, insulin AUC and fasting serum FFA with a standardised breakfast

		Glucose AUC 0-120 min		Insulin AUC 0-120 min		Fasting p-FFA	
		r	p	r	p	r	p
Fasting	Butyrate	<b>-0.30</b>	<b>0.006</b>	<b>-0.19</b>	<b>0.046</b>	-0.09	0.36
	Propionate	-0.08	0.46	-0.12	0.24	-0.07	0.49
	Acetate	-0.15	0.16	-0.01	0.89	0.14	0.14
30 min	Butyrate	<b>-0.23</b>	<b>0.009</b>	-0.08	0.44	<b>-0.22</b>	<b>0.056</b>
	Propionate	-0.16	0.13	0.08	0.37	-0.05	0.62
	Acetate	-0.12	0.28	-0.06	0.61	-0.07	0.46

# Overview

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- High fiber diets improve laxation and gastrointestinal health.
- Wheat bran and other particulate fibers are to some extent fermented.
- In large cohort studies high fiber intakes, which is predominantly wheat bran in North America, are associated with reduced risk of cardiovascular disease and diabetes.
- Both insoluble and soluble fibers may produce metabolic advantages other than the traditional markers of cholesterol lowering and blunting postprandial glucose.

Thank you for your attention

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