

Epidemiological and clinical studies supporting health benefits of whole grain cereal products

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OUTLINE

- Potential health benefits of whole grain
- Epidemiological evidence
 - Whole grain and diabetes
 - Whole grain and CVD
- Clinical trials
 - Whole grain and diabetes
 - Whole grain and CVD
- Conclusions

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Hazard ratios (HR) for total and cause-specific mortality in the fifth vs the first quintile of total intake of whole-grain foods
(27 312 women in the Iowa Women's Health Study, 1986–2003)

	<u>Mortality</u>	<u>HR*</u>	<u>p</u>
Total		0.79	0.0001
Cardiovascular		0.73	0.0001
Cancer		0.89	0.20
Inflammatory diseases		0.66	0.008

*multivariate adjustment

D R Jacobs Jr et al, AJCN 2007

Whole grain consumption

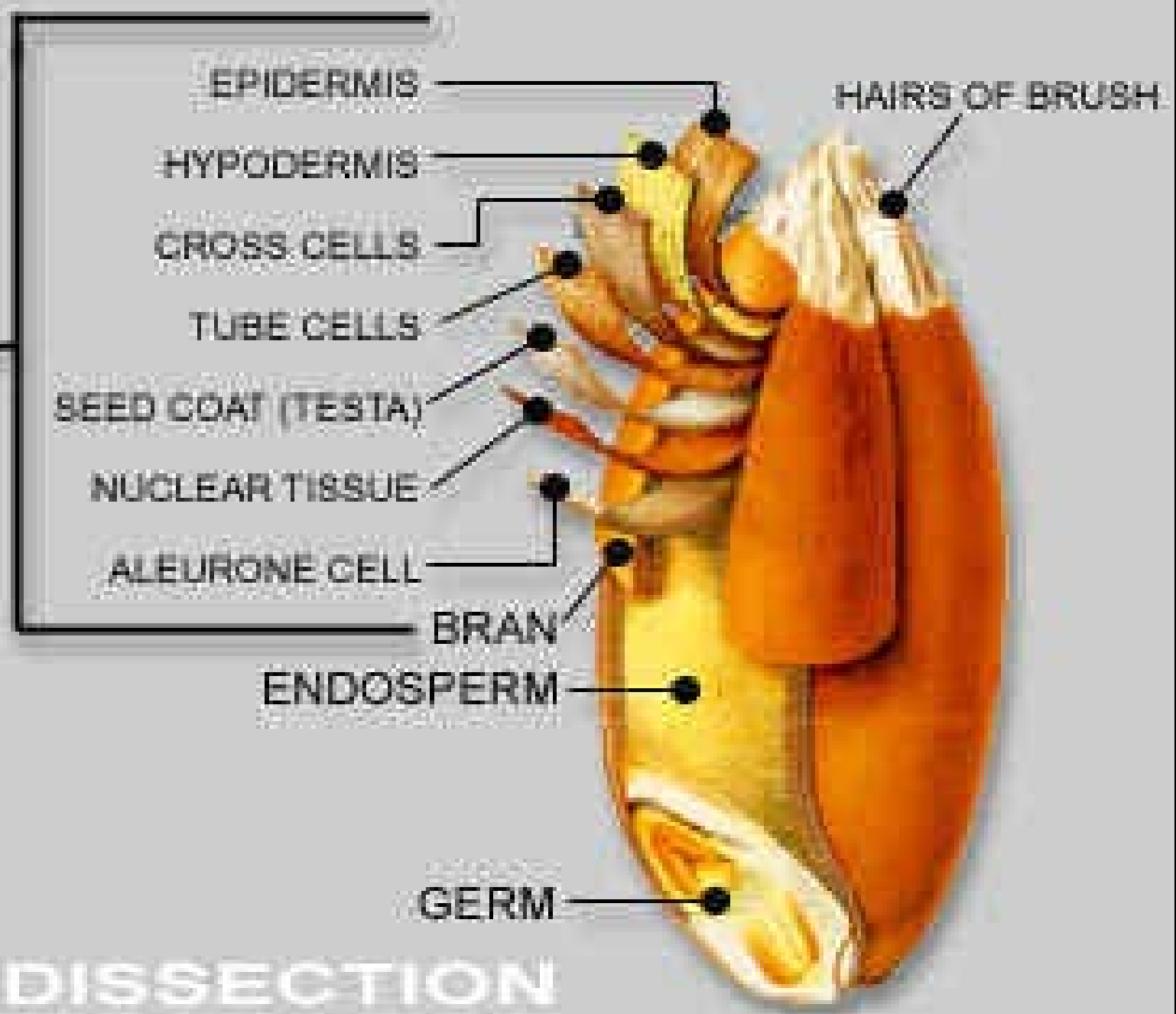
marker or cause of health
benefits?

Whole grain consumption: marker or cause of health benefits?

people who consume more whole grains are likely to have healthier lifestyle as fewer of them smoke, they exercise more frequently and they tend to have lower fat and higher fiber intake.

Harland and Garton 2007

BRAN



DISSECTION

Compositional difference between whole and refined wheat

Component	Whole wheat	Refined wheat
Bran (%)	14	<0.1
Germ (%)	2.5	<0.1
Total dietary fibre (%)	13	3
Insoluble dietary fibre (%)	11.5	1.9
Soluble dietary fibre (%)	1.1	1.0
Protein (%)	14	14
Fat (%)	2.7	1.4
Starch and sugar (%)	70	83
Total minerals (%)	1.8	0.6
<i>Selected minerals</i>		
Zinc (microg/g)	29	8
Iron (microg/g)	35	13
Selenium (microg/g)	0.06	0.02

From Slavin et al, AJCN 1999

Compositional difference between whole and refined wheat

Component	Whole wheat	Refined wheat
<i>Selected vitamins</i>		
Vitamin B6 (mg/g)	7.5	1.4
Folic acid (mg/g)	0.57	0.11
<i>Phenolic compounds</i>		
Ferulic acid (microg/g)	5	0.4
Beta-tocotrienol (microg/g)	32.8	5.7
Phytate phosphorus (mg/g)	2.9	0.1

From Slavin et al, AJCN 1999

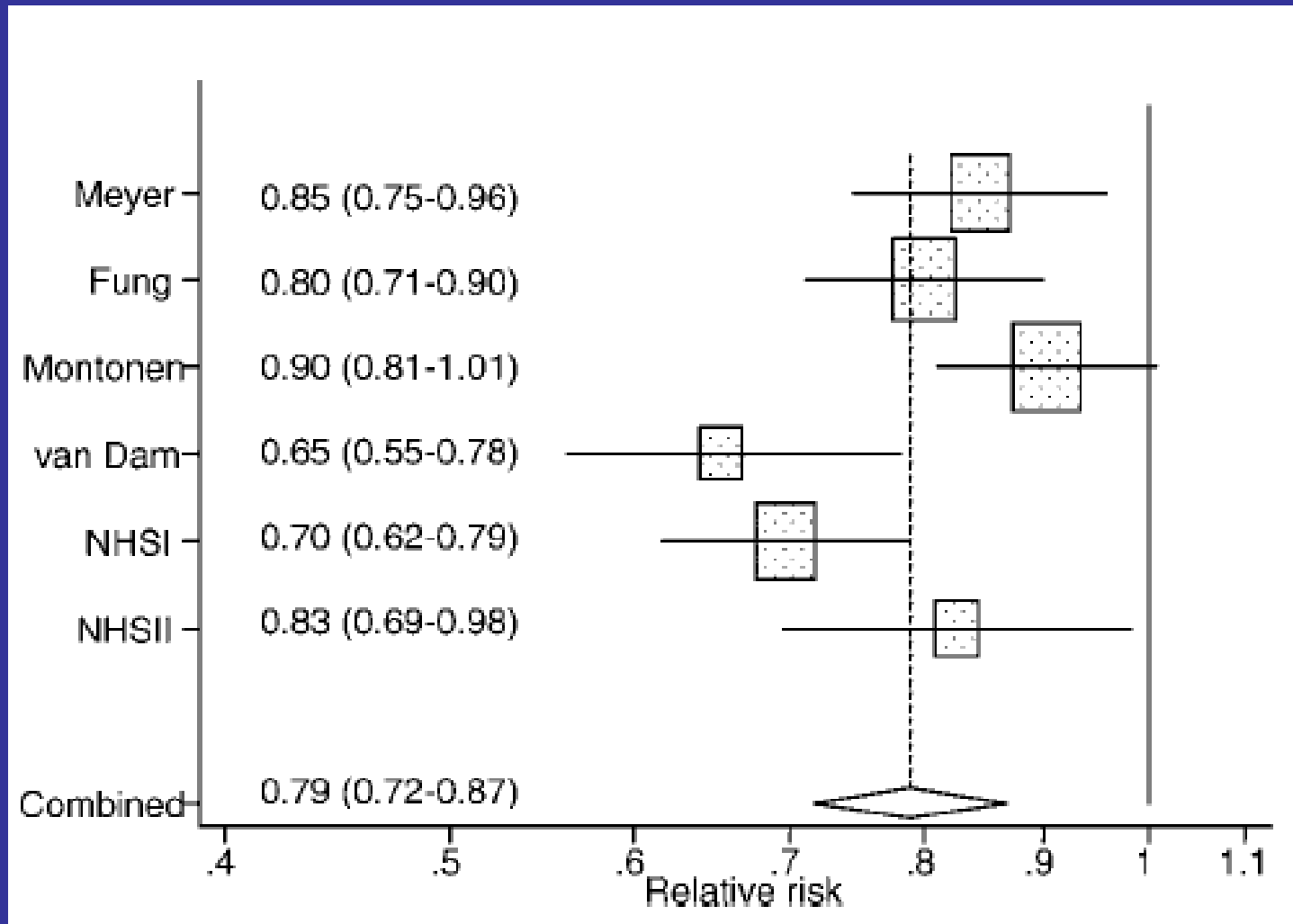
Selected cereal components that might contribute to the health benefits associated with whole grain consumption

- Dietary fibre
- Oligosaccharides
- Flavonoids
- Lignin
- Tocopherols
- Phenolics
- Phytoestrogens
- N-3 fatty acids
- Protease inhibitors
- Saponins
- Magnesium
- Selenium
- Zinc

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Multivariate-Adjusted RR of Type 2 Diabetes for a Two-Servings-per-Day Increment in Whole Grain Intake



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Effect of wholegrain intake on CHD risk – prospective epidemiologic studies

<i>Author</i>	<i>Participants</i>	<i>Outcome variable</i>	<i>Follow up (years)</i>	<i>Relative risk (95% CI)</i>
Fraser et al (1992)	US Seventh Day Adventists	CHD events	8	0.56 (0.35-0.89)
Jacobs et al (1998)	Iowa sample (driving lic.)	CHD death	9	0.70 (0.50-0.98)
Jacobs et al (1999)	Iowa sample (driving lic.)	CHD death	9	0.82 (0.66-1.01)
Liu et al (1999)	US nurses	CHD events	10	0.72 (0.54-0.91)
Liu et al (2000)	US nurses	Ischaemic stroke	12	0.69 (0.50-0.98)
Jacobs et al (2001)	Norwegians (three counties)	CVD death	14	0.77 (0.60-0.98)
Liu et al (2003)	US physicians	CVD death (MI and stroke)	6	0.80 (0.66-0.97)
Mozaffarian et al (2003)	US residents >65 years	CVD events	9	0.76 (0.64-0.90)
Steffen et al (2003)	US sample-four cities	CHD event ischaemic stroke	11	0.72 (0.53-0.97) CHD 0.75 (0.46-1.22) stroke
Bazzano et al (2003)	US population based sample	CHD event	19	0.80 (0.63-1.01)

From Flight and Clifton EJCN 2006

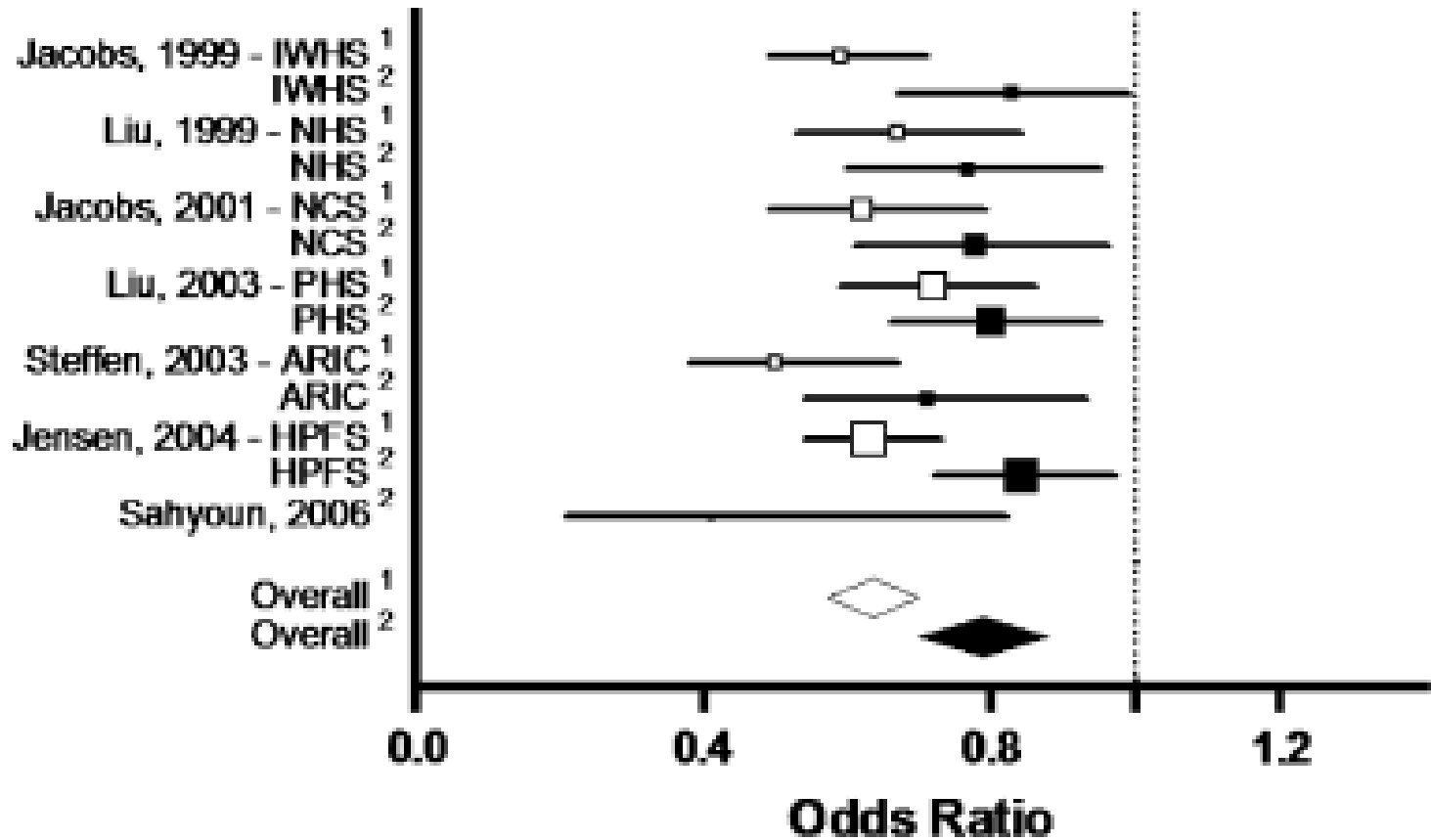


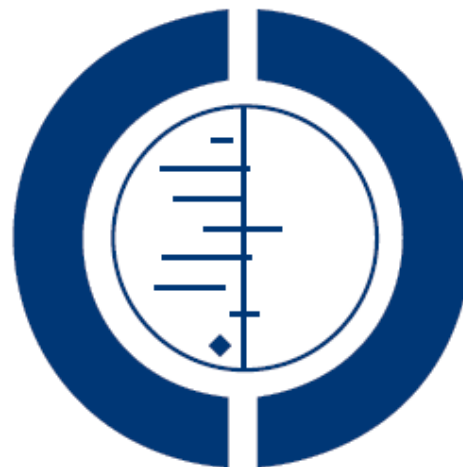
Figure 1 Odds ratios of incident cardiovascular disease, comparing high versus low whole grain intake.

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Whole grain foods for the prevention of type 2 diabetes mellitus (Review)

Priebe MG, van Binsbergen JJ, de Vos R, Vonk RJ

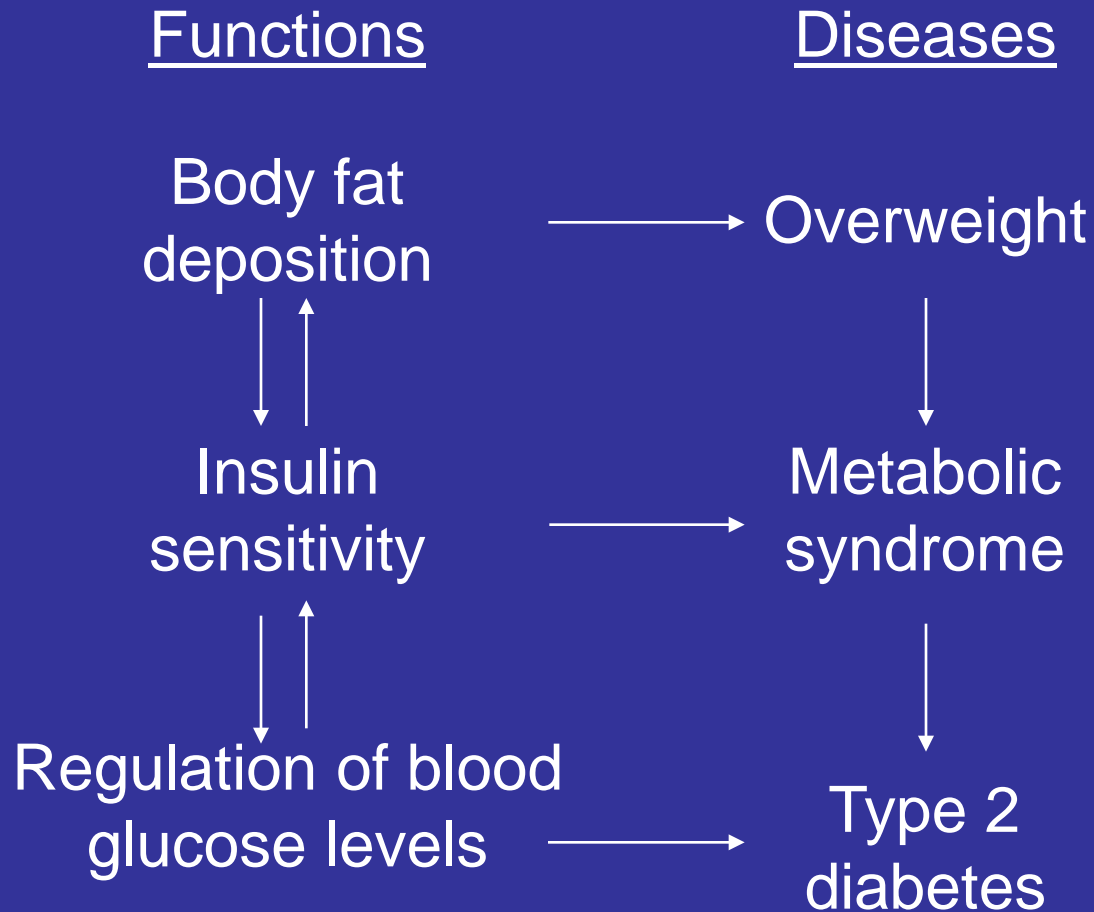


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Whole grain foods for the prevention of type 2 diabetes mellitus (Review)

- The evidence from only prospective cohort trials is considered to be too weak to be able to draw a definite conclusion about the preventive effect of whole grain foods on the development of T2DM.
- Properly designed long-term randomised controlled trials are needed.

Relationships between biological functions and their impact on health



Relation between changes in intakes of dietary fiber and grain products and development of obesity among middle-aged women (NHS)

	Odds ratio for BMI \geq 30 ($n = 6400$)					<i>P</i> for trend
	Q1	Q2	Q3	Q4	Q5	
Whole grain						
Cases (<i>n</i>)	1351	1283	1307	1252	1207	
Model 1 ¹	1.00	0.90 (0.82, 0.97) ²	0.90 (0.83, 0.98)	0.86 (0.79, 0.93)	0.85 (0.79, 0.93)	0.0002
Model 2 ³	1.00	0.85 (0.77, 0.95)	0.87 (0.78, 0.97)	0.82 (0.74, 0.92)	0.81 (0.73, 0.91)	0.0002
Refined grain						
Cases (<i>n</i>)	1264	1236	1193	1279	1427	
Model 1 ¹	1.00	0.97 (0.90, 1.06)	0.96 (0.87, 1.03)	1.03 (0.95, 1.12)	1.21 (1.11, 1.31)	< 0.0001
Model 2 ³	1.00	0.96 (0.88, 1.05)	0.94 (0.86, 1.03)	1.03 (0.95, 1.13)	1.18 (1.08, 1.28)	< 0.0001
Dietary fiber						
Cases (<i>n</i>)	1581	1350	1207	1236	1026	
Model 1 ¹	1.00	0.81 (0.74, 0.87)	0.72 (0.66, 0.78)	0.73 (0.68, 0.79)	0.61 (0.56, 0.66)	< 0.0001
Model 2 ³	1.00	0.77 (0.69, 0.86)	0.67 (0.60, 0.74)	0.69 (0.60, 0.77)	0.66 (0.58, 0.74)	< 0.0001

Liu S et al, *Am J Clin Nutr* 2003;

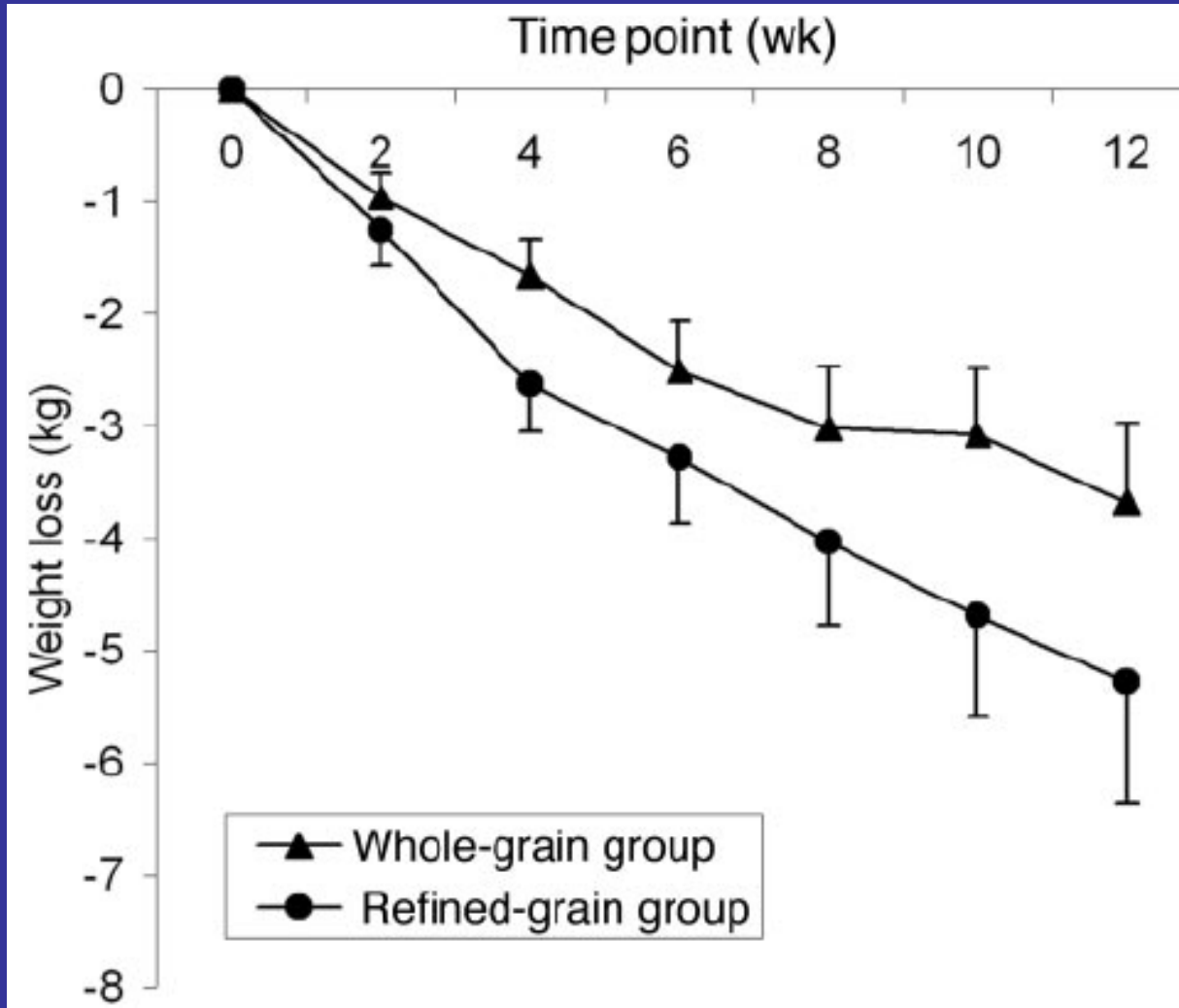
Whole-grain intake and insulin sensitivity: the Insulin Resistance Atherosclerosis Study

	Insulin sensitivity		
	β	SE	<i>P</i>
Model 1, whole grain (servings/d) ²	0.075	0.024	0.001
Model 2, whole grain (servings/d) ³	0.082	0.023	0.001
Model 3, whole grain (servings/d) ⁴	0.043	0.020	0.030
Model 4, whole grain (servings/d) ⁵	0.041	0.026	0.117

Model 3: adjusted for BMI and waist

Model 4: adjusted for dietary fibre and magnesium

Average cumulative weight loss in men and women with the metabolic syndrome treated with hypocaloric diets enriched with either whole-grain or refined-grain cereals



(n 25 for each group)
not significant

Whole-Grain Foods Do Not Affect Insulin Sensitivity or Markers of Lipid Peroxidation and Inflammation in Healthy, Moderately Overweight Subjects

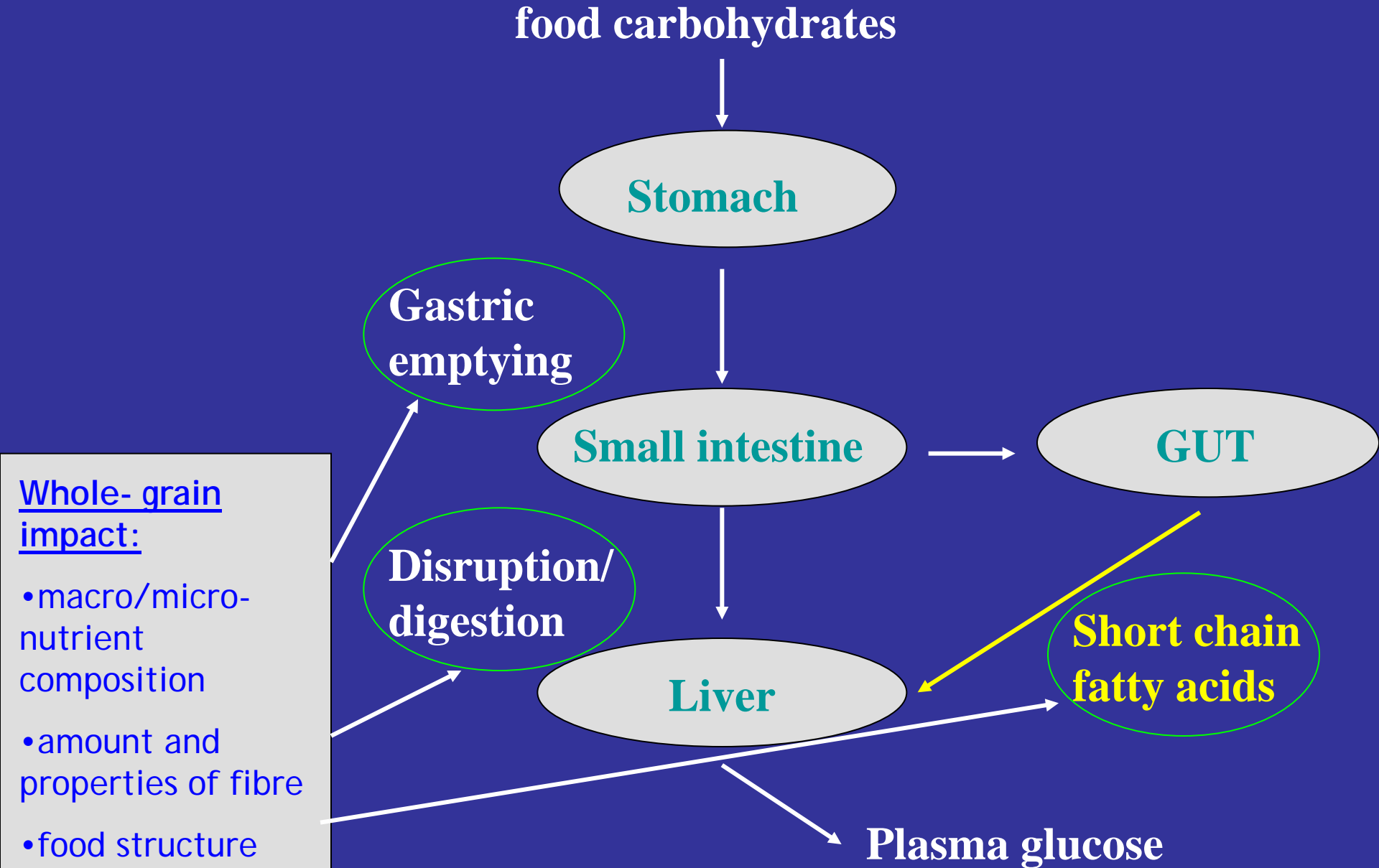
	Whole-grain period		Refined-grain period	
	Before	After	Before	After
<i>n</i>	30	30	30	30
BMI, kg/m^2	28.5 ± 2.4	28.8 ± 2.5 ^a	28.4 ± 2.1	28.6 ± 2.1
Fasting blood glucose, <i>mmol/L</i>	5.2 ± 0.8	5.3 ± 0.8	5.2 ± 0.9	5.2 ± 0.8
Fasting insulin, <i>pmol/L</i>	56.2 ± 22.9	57.6 ± 24.3	60.4 ± 30.6	57.6 ± 25.7
Insulin sensitivity, ³ <i>M</i>	5.9 ± 2.1	5.5 ± 1.7	5.7 ± 1.9	6.0 ± 2.0
<i>M/I</i>	6.8 ± 3.0	6.5 ± 2.7	6.4 ± 2.9	6.9 ± 3.2

Andersson A et al, J. Nutr. 2007.

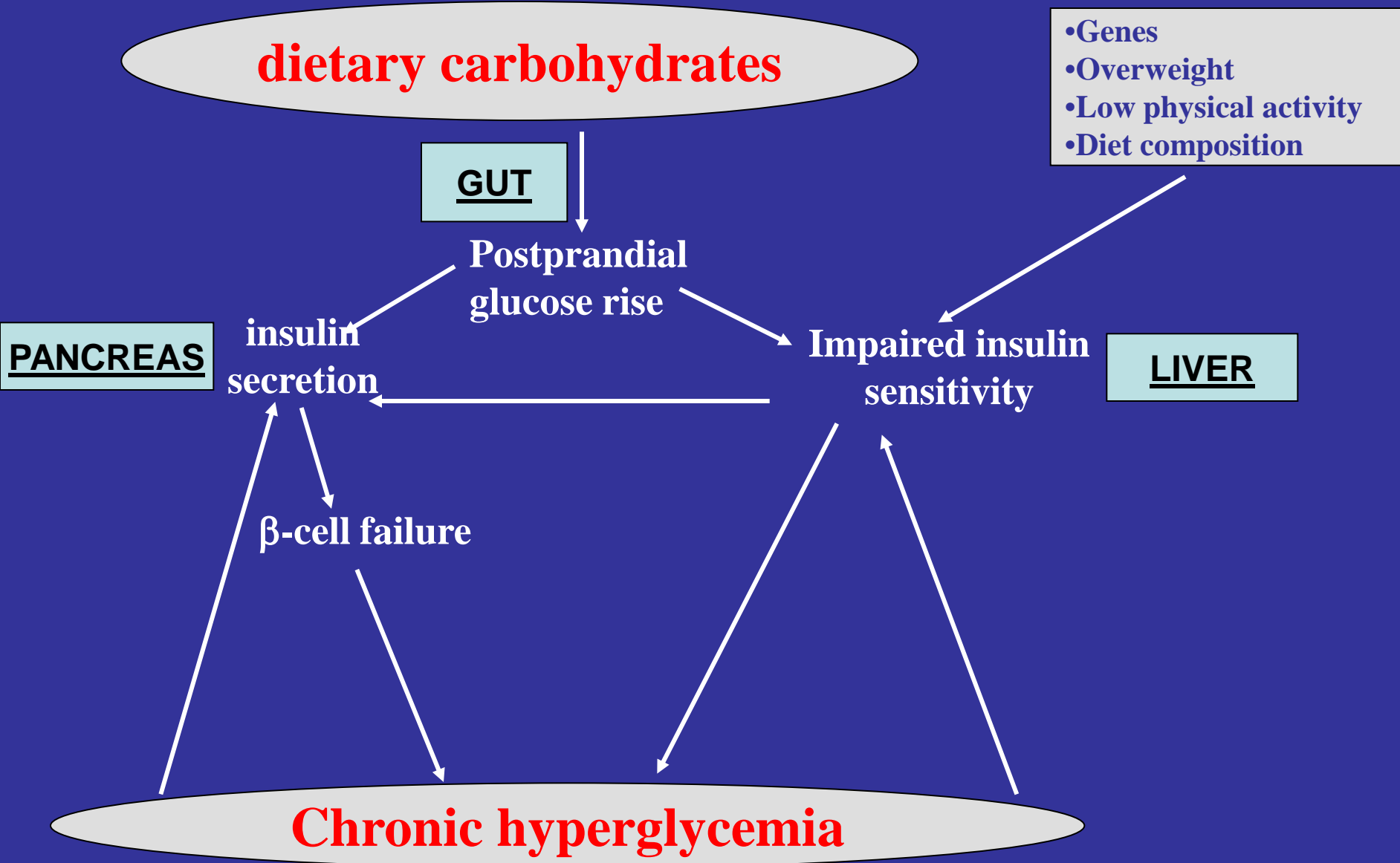
Clinical trials on whole grain and risk of type 2 diabetes

*Are all the available markers
equally appropriate?*

Factors influencing post-prandial blood glucose rise



Plasma glucose regulation in the postprandial period



Clinical trials on whole grain and risk of type 2 diabetes

Evaluation of insulin sensitivity

- *Muscles/adipose tissue:*

euglycemic clamp, FSIVGTT, HOMA

- *Gut/liver:*

OGTT, Meal test, hepatic glucose clearance/production

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Wholegrain cereals for coronary heart disease (Review)

Kelly SAM, Summerbell CD, Brynes A, Whittaker V, Frost G

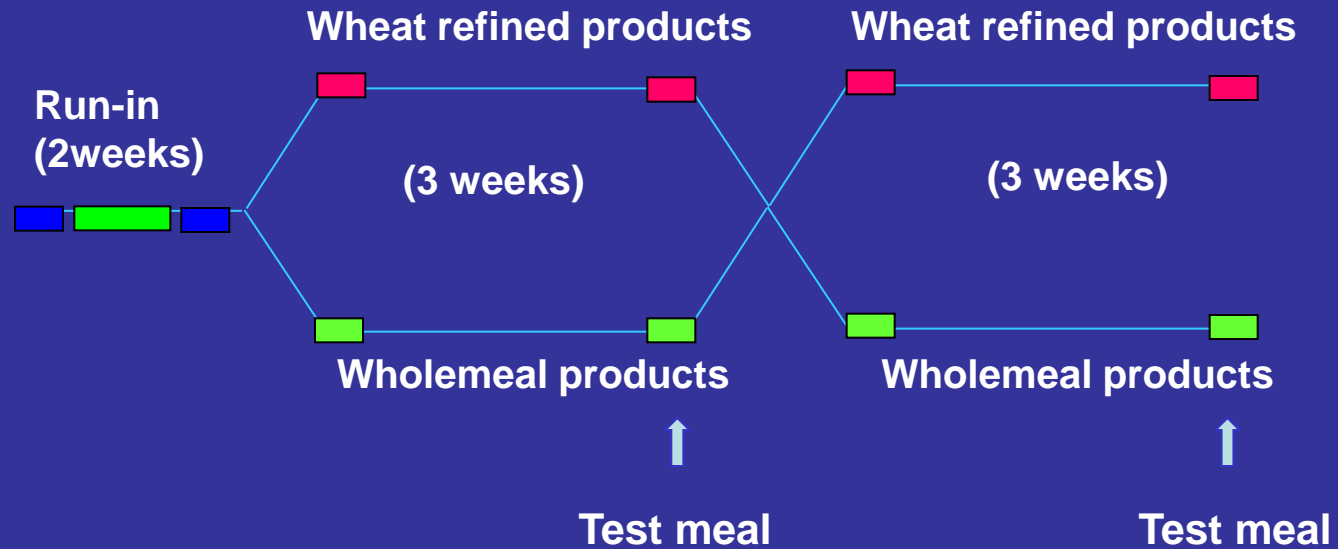


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Whole grain cereals for coronary heart disease (review)

- None of the studies found reported the effect of wholegrain diets on CHD mortality or CHD events or morbidity.
- There is a need for well-designed, adequately powered, longer term randomised controlled studies in this area.

Study Design



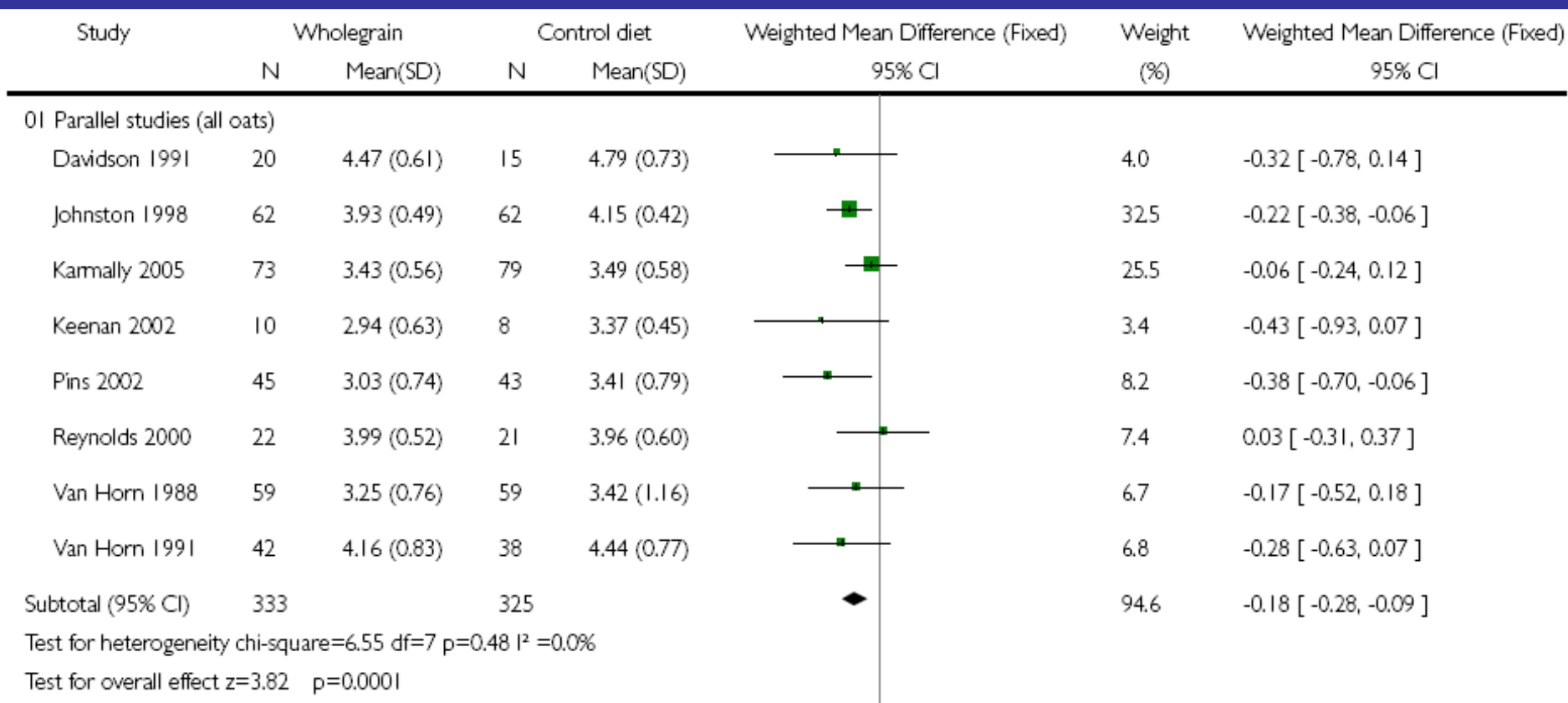
Fasting plasma lipids after run-in and at the end of two experimental diets

	<i>Run-in (A)</i>	<i>Wholemeal (B)</i>	<i>Refined Wheat (C)</i>		$\Delta B-A$ (%)	$\Delta C-A$ (%)	$\Delta B-C$ (%)
Cholesterol (mg/dl)	205 40	175 27 **	183 271 **		-14	-10	-4.3
HDL-chol (mgdl)	51 173	42 12	44 14				
Triglycerides (mg/dl)	105 34	94 33	98 31				

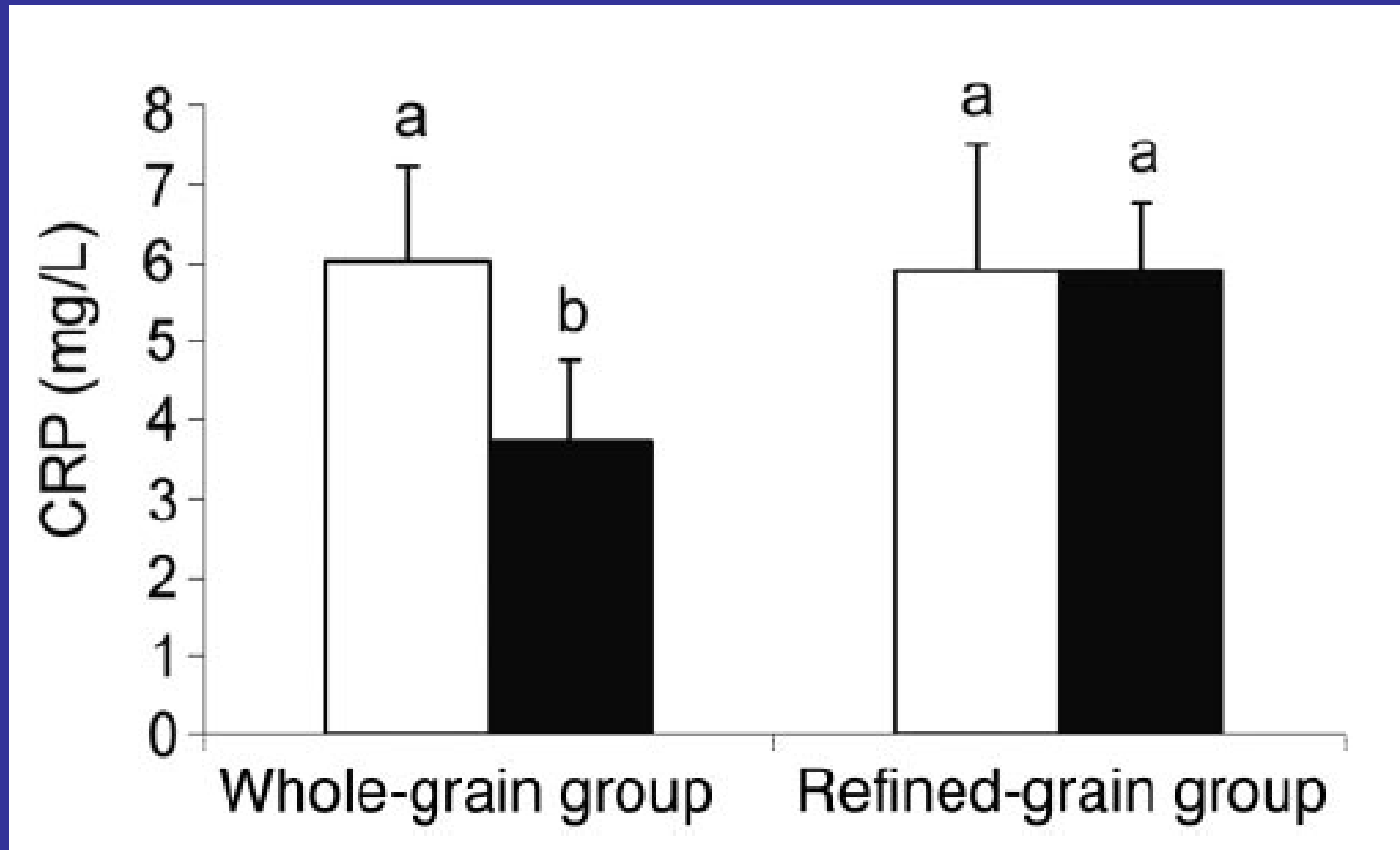
**p<0.01 vs run-in
p<0.05 vs refined

(M±SD)

Metanalysis of intervention studies evaluating the effects of wholegrain cereals (oats) intake on LDL cholesterol levels



Average concentrations of C-reactive protein (CRP) in participants in the whole-grain and refined-grain groups ($n=25$ for each) at baseline (white) and week 12 (black)



Markers of lipid peroxidation, inflammation & antioxidants

n=30	Whole grain period		Refined period		diff vs diff
	Before	During	Before	During	
α -tocopherol	13.8 \pm 2.5	14.3 \pm 2.9	12.8 \pm 3.6	14.0 \pm 3.0	0.40
γ -tocopherol	0.74 \pm 0.36	0.67 \pm 0.23	0.73 \pm 0.32	0.74 \pm 0.28	0.07
8-iso-PGF ₂ α (nmol/L*)	0.43 \pm 0.14	0.43 \pm 0.14	0.42 \pm 0.15	0.44 \pm 0.21	0.48
CRP (mg/l)	2.03 \pm 1.62	2.38 \pm 2.29	2.86 \pm 2.96	2.34 \pm 1.57	0.55
IL-6 (pg/ml)	14.8 \pm 32.2	15.2 \pm 33.2	15.9 \pm 32.4	15.8 \pm 30.9	0.79
PAI-1 (IU/ml)	24.7 \pm 15.8	26.9 \pm 20.3	24.8 \pm 19.9	22.1 \pm 19.5	0.26

Andersson A et al, J. Nutr. 2007.

Wholegrain and CVD

- **Beneficial effects demonstrated on:**
 - plasma lipid profile
 - blood pressure levels
 - antioxidant capacity
 - systemic subclinical inflammation (?)

They may account for most of the reduction in CVD events associated with whole grain consumption (-20%)

SUMMARY

The associations between a high intake of whole grain and a low risk of cardiovascular disease and diabetes are strong.

Different biological mechanisms that might explain the associations have been suggested and some of them have been shown to be operative

The results of controlled intervention studies investigating the effects of an increased intake of whole grain cereals are unsatisfactory

Conclusions

In search of the optimal strategy to perform intervention studies for the evaluation of the health benefits of whole grain cereal products :

- Study duration and sample size
- Markers of functions/end-points
- Selection of appropriate cereal species and food technologies
- Real life approach vs excessive constraints

Background for the search of the optimal strategy to evaluate either a drug or a dietary modification in intervention trials

<u>Intervention</u>	<u>Drug</u>	<u>Dietary change</u>
example	ACE-inhibitor	wholegrain
active compounds	One (enalapril)	Many (fibre, ferulic acid, folate, etc)
body functions that are modified	One, markedly (blood pressure regulation)	Many, moderately (plasma cholesterol, blood pressure, blood glucose, plasma triglycerides, etc
Impact on disease prevention	strong	strong

Clinical trials on whole grain and risk of cardiovascular disease

Are studies with hard end-points more promising than those on a single risk factor?

Cumulative effects of small changes in multiple risk factors might have a relevant impact on the global risk!



Thank you for your attention