Effects of whole grain intake on weight changes, diabetes, and cardiovascular Disease

Simin Liu, MD, ScD

Professor of Epidemiology and Medicine
Director, Center for Global Cardiometabolic Health
Brown University

"I just know"
at top of evidence pyramid

Level 1
"I just know"

Background

- A greater intake of whole grain was associated with a reduced risk of coronary mortality (Jacobs, 1998), risk of myocardial infarction (Liu, AJCN 1999), stroke (Liu JAMA 2000), diabetes (Liu AJPH 2000, weight change (Liu AJCN 2001)

- No better or higher quality prospective cohort studies since then…

Background

- The dietary fibre hypothesis was that a diet rich in unrefined plant foods was associated with lower incidence of western diseases.

- The hypothesis has largely been proven and forms the basis for dietary guidelines that promote a natural high fibre diet rich in fruit vegetables and unrefined cereal products

- From a public health perspective the definition and measurement of dietary fibre has implications for 'reference intake values' and 'health claims'

Whole grain intake and CHD Risk
(Liu et al. 1999)

	Fatal	Non-fatal MI
Whole grain (Age-adjusted relative risk comparing extreme quintiles)	0.53	0.50
95% CI	0.35 -0.82	0.38-0.65
P for trend	0.002	<0.0001

Whole grain and risk of CHD among subgroups of participants

Whole grain	RR 95% CI	P for trend
	(Highest vs. Lowest quintiles)	
No hypercholesterolemia	0.70(0.54-0.91)	0.01
Never smokers	0.49(0.30-0.79)	0.003
Non-drinkers	0.72 (0.49-1.08)	0.06
Non-HRT users	0.7(0.54-1.02)	0.02

Available literature

- Both observational and randomized-interventions

  - Observational (outcome): 1) free living humans, 2) type 2 diabetes, cardiovascular disease, or changes in weight gain/obesity, 3) quantitative methodology used in assessing whole grain and/or dietary fiber intake, 4) effect size measures, and 5) multivariable adjustments

  - Interventional (metabolic intermediates) : 1) >18 yrs old (e.g., overweight, abdominal obesity, impaired glucose tolerance or insulin resistance), 2) interventions involving either dietary fiber or whole grains, 3) mean changes in weight, glucose, HbA1c, insulin, blood pressure, and other metabolic intermediates including lipids (triglycerides, high-density lipoprotein cholesterol (HDL), LDL cholesterol)
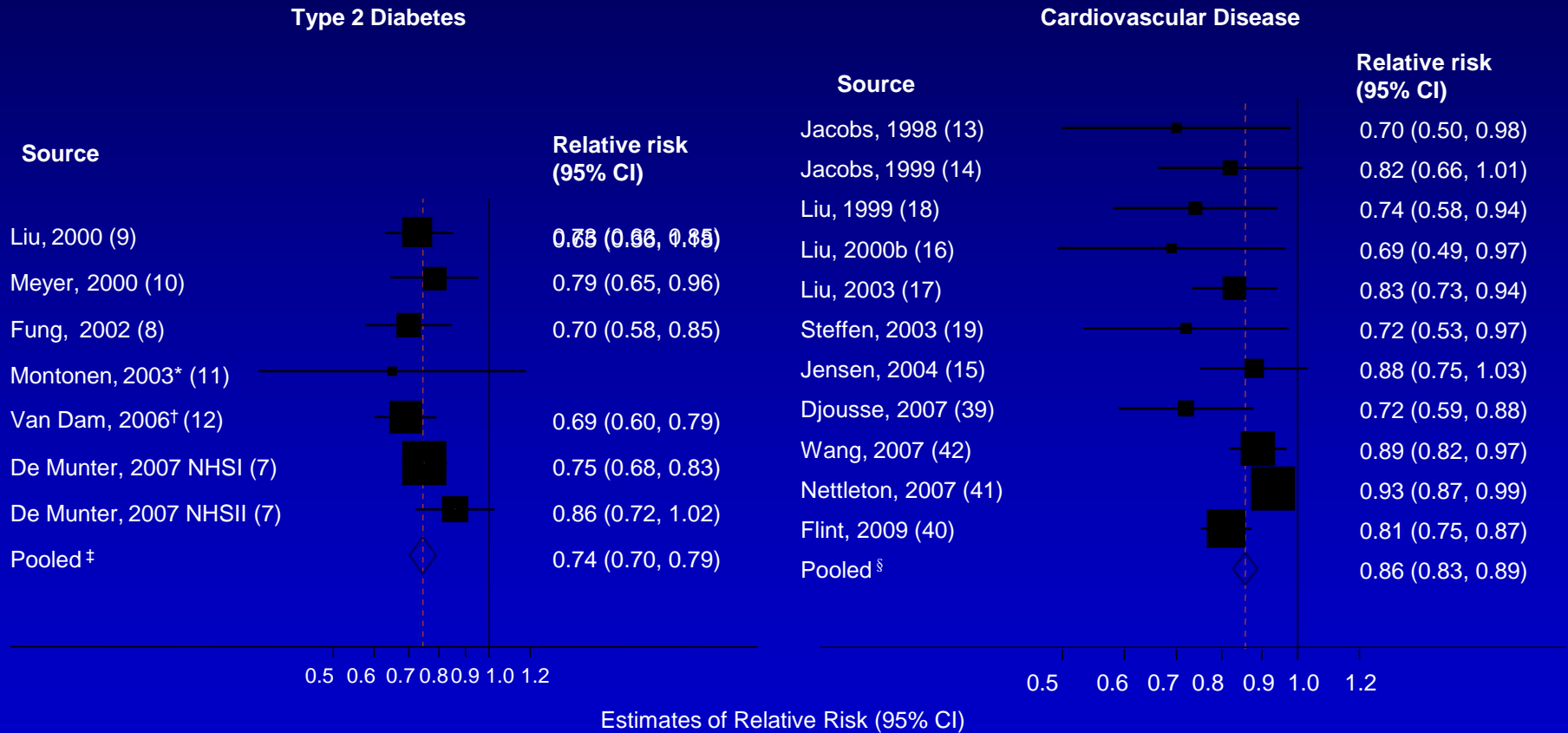
Identifying relevant studies

- Examination of existing literature on July, 2010 included 42 prospective studies, and 16 randomized controlled trials (~10 million person-years)

2327 Articles Identified From Literature Database Search

2261 Excluded Based on Review of Abstracts *
Non-human Study (340)
Type 1 Diabetes (52)
Reviews, Letters, Commentaries or Editorials (934)
Case Reports (9)
Children (149)
Gestational Diabetes (10)
Not Prospective Cohort Studies or Randomized Controlled Trials (140)
Dietary Interventions Other than Whole Grain, Cereal fiber or Dietary Fiber Studied (420)
No Assessment of Whole Grain, Cereal Fiber or Dietary Fiber Intake (1461)
Interventions in Whole Grain Intake as Part of Multiple Interventions Such As Life Style Changes (78)
No Controls (31)
No Assessment of Relevant Outcomes (956)
Supplementation of Whole Grain or Dietary Fiber (ie pills, powders etc) (185)

71 Full Texts of Articles Retrieved

13 Excluded After Full Text Review
Healthy Persons with No Risk Factors(5)
Supplementation of Whole Grains (ie pills, powders etc) (5)
No Assessment of Whole Grain, Cereal Fiber or Dietary Intake (3)

58 Articles Included
42 Prospective Studies
16 Randomized Controlled Trials

Prospective studies

- Pooled relative risk estimates of T2D and CVD comparing highest vs. lowest whole grain intake using random effects models

Type 2 Diabetes

Source	Relative risk (95% CI)
Liu, 2000 (9)	0.73 (0.63, 0.85)
Meyer, 2000 (10)	0.79 (0.65, 0.96)
Fung, 2002 (8)	0.70 (0.58, 0.85)
Montonen, 2003* (11)	
Van Dam, 2006† (12)	0.69 (0.60, 0.79)
De Munter, 2007 NHSI (7)	0.75 (0.68, 0.83)
De Munter, 2007 NHSII (7)	0.86 (0.72, 1.02)
Pooled ‡	0.74 (0.70, 0.79)

0.5 0.6 0.7 0.8 0.9 1.0 1.2

Cardiovascular Disease

Source	Relative risk (95% CI)
Jacobs, 1998 (13)	0.70 (0.50, 0.98)
Jacobs, 1999 (14)	0.82 (0.66, 1.01)
Liu, 1999 (18)	0.74 (0.58, 0.94)
Liu, 2000b (16)	0.69 (0.49, 0.97)
Liu, 2003 (17)	0.83 (0.73, 0.94)
Steffen, 2003 (19)	0.72 (0.53, 0.97)
Jensen, 2004 (15)	0.88 (0.75, 1.03)
Djousse, 2007 (39)	0.72 (0.59, 0.88)
Wang, 2007 (42)	0.89 (0.82, 0.97)
Nettleton, 2007 (41)	0.93 (0.87, 0.99)
Flint, 2009 (40)	0.81 (0.75, 0.87)
Pooled §	0.86 (0.83, 0.89)

0.5 0.6 0.7 0.8 0.9 1.0 1.2

Estimates of Relative Risk (95% CI)

Multivariate-adjusted relative risks for highest (3 servings/day) versus lowest whole grains intake (rare or no servings/day). Box size represents the statistical weight of each study in the overall random-effects estimate. CI indicates confidence interval. The vertical dashed line represents the combined relative risk. * Finnish population † Black population ‡ p=0.56 § p=0.05 ‖ RR = 0.87 (0.83, 0.91) p =0.06 when excluding of studies using hypertension as a CVD outcome (Wang et al and Flint et al)

Randomized controlled Trials

- Pooled mean difference of T2D and CVD metabolic intermediates between whole grain intervention and control groups using random effects models

Metabolic Intermediate	Mean Difference	Confidence Interval
Fasting Blood Glucose (mmol/L)	-0.93	-1.85, -0.21
Fasting Plasma Insulin (µU/ml)	-0.29	-0.59, 0.01
Total Cholesterol (mmol/L)	-0.83	-1.24, -0.42
LDL Cholesterol (mmol/L)	-0.72	-1.34, -0.11
Systolic Blood Pressure (mmHg)	-0.06	-0.21, 0.10
Diastolic Blood Pressure (mmHg)	-0.05	-0.21, 0.11

Negative values represent lower levels among whole grain intervention groups

Summary (Editorial AJCN 2005)

- Whole grain intake is inversely associated with risk of T2D and CVD
  - Compared to rare or never consumers of whole grains, those reporting an average of 3 daily servings had a 21-30% reduction in T2D risk and 11-17% reduction in CVD risk

- Benefits of whole grains are more consistently demonstrated in prospective studies than randomized trials
  - Majority of trials had short durations (longest = 16 wks) and small sample size (largest = 185)
  - Despite limitations, RCTs show a significant inverse association between whole grain intake and total- and LDL cholesterol levels.

Possible mechanisms

- Whole grains vs. Refined
  - Whole grains may have lower glycemic load, more dietary magnesium, fiber, micronutrients, antioxidants, phytochemicals and antioxidants
    - maintain glucose and insulin homeostasis
    - lower serum cholesterol and LDL-cholesterol
    - reduce inflammation and oxidative stress

Liu et al. Whole grain and CHD AJCN 1999; Liu et al. Whole grain and diabetes AJPH 2000; Liu et al. Whole grain and ischemic stroke JAMA 2000; Liu Whole-grain foods, dietary fiber, and type 2 diabetes: searching for a kernel of truth AJCN 2003; Liu S. Intake of refined carbohydrates and whole grain foods in relation to risk of type 2 diabetes mellitus and coronary heart disease. JACN 2002; Liu S and Willett W. Dietary Carbohydrates. UptoDate Inc. 2006-2015.

Key questions:

1. Why might the evidence be inconsistent between epidemiological vs. intervention studies?

2. Why cannot regulatory bodies rely solely on epidemiology evidence?

3. What are the research gaps in intervention and epidemiological studies?

4. How can we demonstrate cause & effect for whole grain health benefits?

1. Interventions vs. Observations

- First, randomized intervention trials are one type of epidemiological studies
- So the question becomes: "interventional" vs. "observational", and what are the pros and cons of each type
  - Different outcomes in different populations
  - Measurements of outcome and intake
  - Confounding
  - Duration of followup
  - Compliance and loss to followup

Key questions:

1. Okay?

2. Why cannot regulatory bodies rely solely on epidemiology evidence?

3. ?

4. ?

Regulatory bodies cannot:

2. Rely solely on epidemiologic evidence, because:

They also cannot rely solely on any one single type of evidence

Key questions:

1. Okay?

2. Okay?

3. What are the research gaps in intervention and epidemiological studies?

4. ?

Key questions:

1. Okay?

2. Okay?

3. Okay?

4. How can we demonstrate cause & effect for whole grain health benefits?

The end game: A large randomized intervention trial to evaluate the effects of whole grains on clinical outcomes of significance

Multiple centers (in North America, Europe, Asia and Africa), large sample size (5,000~10,000 men and women) in 4 years of followup

Follow a standard protocol to give participants whole grains and measure compliance with biomarkers and document clinical outcomes

Cost: $350 million to $400 millions

- Far reaching implications for public health
- Let's have a public-private partnership to get this done!

A Conceptual Framework:
Evaluating the totality, consistency and quality of evidence
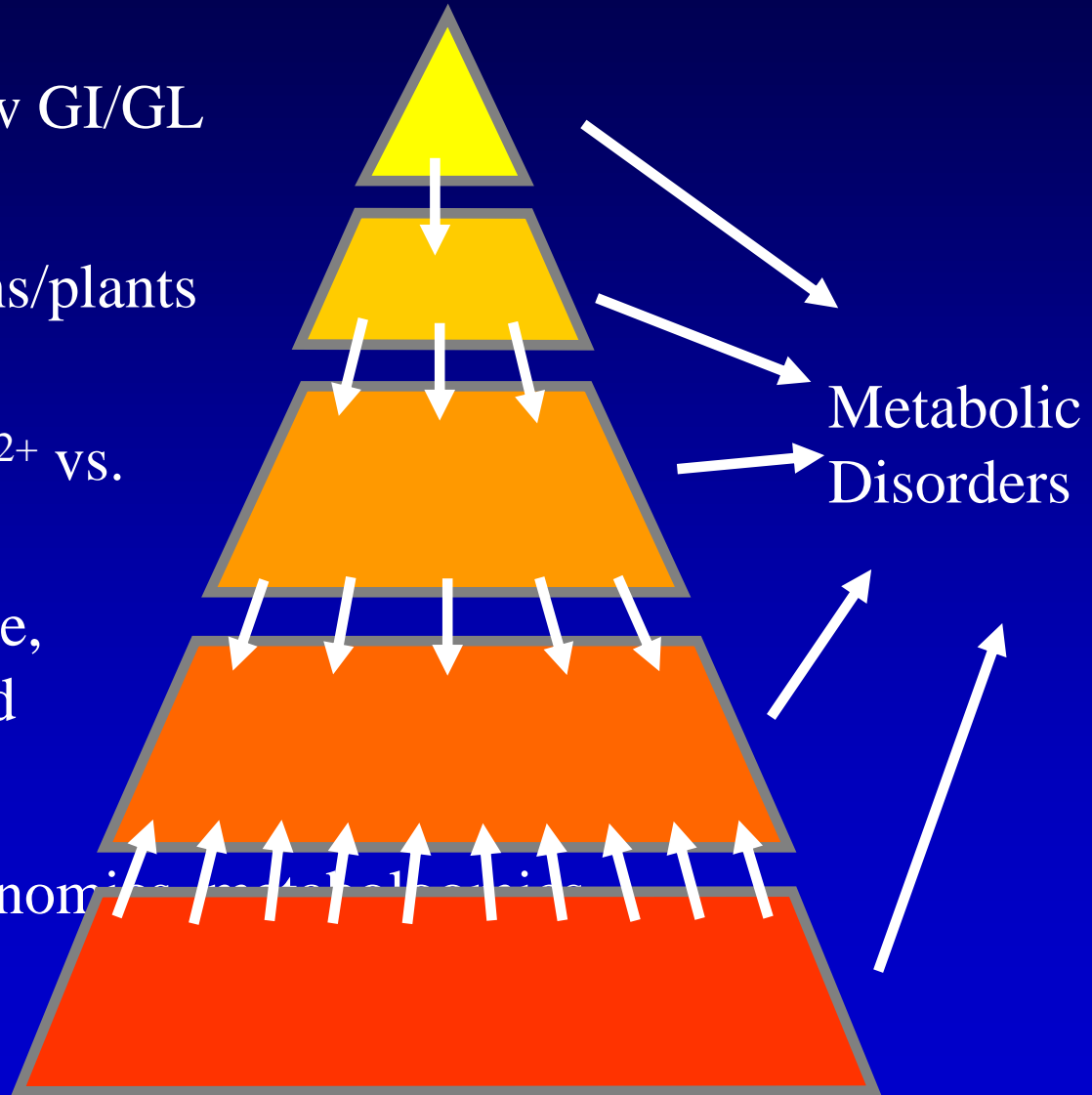
Dietary Pattern: low GI/GL

Foods: Whole grains/plants

Nutrients: fiber/Mg^{2+} vs. Sugar

Bio-markers: glucose, lipids, cytokines and hormones etc.

Genetic variants (genomics, metabolomics, microbiota:

AR, ER, SHBG etc.

Metabolic Disorders

RCT

Unknown Confounders

Received SHBG treatment ┄┄┄┄➤ T2D

↑ *Compliance*

Randomization (of recombinant SHBG treatment versus placebo)

Randomized controlled trial (RCT)

MR

Unknown Confounders

Intermediate phenotype (Plasma SHBG levels) ┄┄┄┄➤ T2D

↑ *Penetrance, functionality*

Randomization (of alleles)

Mendelian Randomization (MR)

……All foods are nutritious and all nutritional concepts good;…it depends on the populations and circumstances;…therefore, we should learn how to embrace them with gratitude, let go of them with grace, and enjoy them freely in our pursuit of happiness with family and friends……

Simin Liu, MD, ScD@
Whole grain summit 2015,
Portland, Oregon

…All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. — Hill, Austin Bradford (1965). The Environment and Disease: Association or Causation?