

# Evidence and Recommendations for the Use of Prebiotics in Clinical Settings

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PREBIOTIC AS A HEALTH BENEFIT OF FIBER: FUTURE RESEARCH AND GOALS  
'Workshop by Life Sciences Research Organization (LSRO)'  
*February 10, 2011, Bethesda, MD*

# Prebiotics and Fiber in Clinical Settings

## Life Sciences Research Organization (LSRO) Focus Questions:

**“The focus is to identify/define the prebiotic health benefits of fiber”**

“Fiber can have many benefits, regularity (reliving constipation and preventing hemorrhoids), preventing diverticulitis, weight management, preventing chronic diseases (cardiovascular, cancer, diabetes). Which among these are related to its prebiotic effects? “

“Can we define the fiber benefits that are prebiotic-related? “

“Can we identify a path whereby the benefits are recognized and can be translated for the consumer? ?

“What are the regulatory hurdles and what research will be required to overcome those burdens?”

# Prebiotics and Fiber in Clinical Settings

- **Prebiotics**
- **Fiber**
- **Fiber as prebiotics**
  - Scientific Data
  - Physicians' perspectives
    - clinical trials
    - professional recommendations/guidelines
  - Patients/Consumers' perspectives

# Prebiotics and Fiber in Clinical Settings

- **Prebiotics**
- **Fiber**
- **Fiber as prebiotics**
  - **Scientific Data**
    - Prebiotics = 869 (Humans 606)
    - Probiotics = 6,654 (Humans 4,395)
    - Fiber = 99,494 (Humans 42,614)
    - Prebiotics and Fiber = 241 (Humans 168)
  - **Physicians' perspectives - clinical trials**
    - Prebiotics RCT humans = 79 (including children), 43 only adults
    - Probiotics RCT humans = 794 (including children), 505 only adults
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### *“Prebiotic Effects: Metabolic and Health Benefits”*

The document has been written by a group of both academic and industry experts (in the ILSI Europe Prebiotic Expert Group and Prebiotic Task Force, respectively). It aimed to validate and expand the idea of the prebiotic concept ('prebiotic effects')

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- ✓ “Thanks to methodological and fundamental research of microbiologists, immense progress has very recently been made in our understanding of the gut microbiota.”
- ✓ “A large number of human intervention studies have been performed that have demonstrated that dietary consumption of certain food products can result in significant changes in the composition of the gut microbiota in line with the prebiotic concept.”
- ✓ “... it has become clear that products that cause a selective modification in the gut microbiota’s composition and/or activity(ies) and thus strengthens normobiosis could either induce beneficial physiological effects in the colon and also in extra-intestinal compartments or contribute towards reducing the risk of dysbiosis and associated intestinal and systemic pathologies.”

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### *“Prebiotic Effects: Metabolic and Health Benefits”*

#### **Areas/conditions of interest**

“Thus the prebiotic effect is now a well-established scientific fact. The more data are accumulating, the more it will be recognized that changes in the microbiota's composition, especially increase in bifidobacteria, can be regarded as a marker of **intestinal health**”

“... metabolic processes associated with **syndrome X**, especially **obesity** and **diabetes type 2**”

“Numerous experimental studies reported reduction in incidence of **tumors and cancers**.”

“prebiotic effect has been shown, especially in adolescents, but also tentatively in postmenopausal women, to increase **Ca absorption** as well as bone Ca accretion and **bone mineral density**.”



### *“Prebiotic Effects: Metabolic and Health Benefits”*

#### **Effect on ‘Intestinal Health’**

“Changes in the gut microbiota composition are classically considered as one of the many factors involved in the pathogenesis of either inflammatory bowel disease or irritable bowel syndrome.

**<How established is the role of the intestinal microbiota in the pathogenesis of GI diseases?>**

“Thus the prebiotic effect is now a well-established scientific fact. The more data are accumulating, the more it will be recognized that changes in the microbiota's composition, especially increase in bifidobacteria, can be regarded as a marker of **intestinal health**”

**<What is ‘normobiosis’ or ‘intestinal health’. Dose increased levels of bifido always good?>**

“The use of particular food products with a prebiotic effect has thus been tested in clinical trials with the objective to improve the clinical activity and well-being of patients with such disorders.”

**<Is there evidence that changing the structure or function lead to clinical benefit? >**

## Prebiotics in Clinical Settings - Physicians' perspectives

**Prebiotic effects: IBD** *<Is there evidence beneficial effect/s of prebiotics in IBD? >*

### Ulcerative Colitis

*“A randomized controlled trial on the efficacy of synbiotic versus probiotic or prebiotic treatment to improve the quality of life in patients with ulcerative colitis.”*

- 120 patients; three groups probiotic, prebiotic, or synbiotic therapy (n=40 in each)
- *Bifidobacterium longum* 2 x 10<sup>9</sup> CFU or psyllium 8.0g or both

**Results:** Total IBDQ improvement by the end of the trial:

probiotics 162 to 169, NS; prebiotics 174 to 182, NS; synbiotics 168 to 176, P = 0.03

=> Patients with UC on synbiotic therapy experienced greater QOL changes than patients on probiotic or prebiotic treatment

*Fujimori et al., Nutrition 2009;25(5):520-5.*

*“Synbiotic therapy (*Bifidobacterium longum*) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial.”*

- 18 patients, one month, only endoscopic and laboratory data

*Furrie E, Gut 2005;54(2):242-9.*

### Prebiotic effects: IBD

#### Crohn's Disease

*“Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease”*

- A prospective multicenter, randomized study.
- Patients (n=30) were randomized to active treatment or placebo in a 2:1 ratio.
- Follow-up consisted of endoscopic, clinical, and laboratory parameters.
- Synbiotic 2000 is a cocktail containing 4 probiotic species and 4 prebiotics

**Results:** No difference in either endoscopic or clinical relapse rate was found between patients treated with once daily dose of Synbiotic 2000 or placebo

=> Synbiotic 2000 had no effect on postoperative recurrence of patients with CD

*Chermesh et al., Dig Dis Sci 2007;52(2):385-9.*

### Prebiotic effects: Irritable Bowel Syndrome (IBS)

*“Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome.”*

- A prospective, single centre, parallel crossover, controlled clinical trial.
- Mixed group of IBS patients (n=44; Rome II)
- Three arms 3.5 g/d prebiotic, 7 g/d prebiotic or 7 g/d placebo.
- IBS symptoms were monitored weekly on a 7-point Likert scale for 12 weeks.

#### Results:

- The prebiotic significantly enhanced faecal bifidobacteria
- Placebo was without effect on the clinical parameters monitored ?
- Prebiotic at 3.5 g/d improved stool consistency (P < 0.05), flatulence (P < 0.05) bloating (P < 0.05), composite score of symptoms (P < 0.05) and SGA (P < 0.05)
- Prebiotic at 7 g/d improved SGA (P < 0.05) and anxiety scores (P < 0.05)

=> The galactooligosaccharide acted as a prebiotic ... and is effective in alleviating symptoms

=> These findings suggest that the  prebiotic has potential as a therapeutic agent in IBS

*Silk, Gibson et al., Aliment Pharmacol Ther. 2009;29(5):508-18*

### Prebiotic effects: Gastrointestinal Disorders



- => Scientific data from *in vitro* and animal studies provide a reasonable rationale for the use of prebiotics in the management of IBD and possibly IBS
- => There is no scientific evidence from 'randomized controlled clinical trials' that prebiotic interventions improve the clinical activity and well-being of patients with IBD or IBS
- => The use of prebiotic interventions in the context of these disorders cannot be recommended and at this point should be considered experimental

**Prebiotics are not included in guidelines for prevention or treatment of GI disease conditions !**

## Prebiotics in Clinical Settings - Physicians' perspectives

### Search Results for "prebiotics":



UpToDate is a clinical decision support system that helps clinicians throughout the world provide the best patient care. We use current evidence to answer clinical questions quickly and easily at the point of care.

**=> No specific article on prebiotics**

## Prebiotics in Clinical Settings - Patients' perspectives

### Search Results for "prebiotics":



<http://www.americanheart.org>

Your search - **Prebiotics** - did not match any documents.  
No pages were found containing "**Prebiotics**".

Your search - **prebiotic food** - did not match any documents.  
No pages were found containing "**prebiotic food**".



<http://www.diabetes.org>

Your search - **prebioits** - did not match any documents.

Your search - **prebiotic food** - did not match any documents.

## Report of the Dietary Guidelines Advisory Committee (DGAC) on the Dietary Guidelines for Americans, 2010

- The DGAC believes that the gut microbiota do play a role in health, although the research in this area is still developing.
- No recommendations for intake of prebiotics or probiotics for the American people can be made, although foods high in prebiotics (wheat, onions, garlic) should be consumed, as well as food concentrated in probiotic (yogurt).



U.S. Department of Agriculture,  
Center for Nutrition Policy and Promotion

<http://www.cnpp.usda.gov>



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# Evidence for Use of Fiber in Clinical Settings

## Search Results for “fiber“:



UpToDate is a clinical decision support system that helps clinicians throughout the world provide the best patient care. We use current evidence to answer clinical questions quickly and easily at the point of care.

## Prebiotics => No specific article

## Fiber:

- [Patient information: High fiber diet \(Beyond the Basics\)](#)
- [Dietary recommendations for toddlers, preschool, and school-age children](#)
- [Lipid lowering with diet or dietary supplements](#)
- [Management of chronic constipation in adults](#)
- [Treatment of chronic functional constipation and fecal incontinence in infants and children](#)
- [Colorectal cancer: Epidemiology, risk factors, and protective factors](#)
- [Mahaim fiber tachycardias](#)
- [Nutritional support in critically ill patients: Enteral nutrition](#)
- [Diet in the treatment and prevention of hypertension](#)
- [Others . . .](#)

# Evidence for Use of Fiber in Clinical Settings

## Search Results for “fiber“:

This topic last updated: August 20, 2010



BENEFITS OF A HIGH FIBER DIET — The health effects of a high fiber may depend to some extent on the type of fiber eaten. However, the difference between the health effects of two types of fiber are not very clear and may vary between individuals, so many providers encourage adding fiber in whatever way is easiest for the patient.

There are several potential benefits of eating a diet with high fiber content:

- Soluble fiber can reduce the risk of **coronary artery disease** and stroke by 40 to 50 percent (compared to a low fiber diet). ... can also reduce the risk of developing **type 2 diabetes**. ... can help to control blood glucose levels.
- Insoluble fiber has been recommended to treat digestive problems such as **constipation**, hemorrhoids, chronic diarrhea, and fecal incontinence. Fiber bulks the stool, making it softer and easier to pass. Fiber helps the stool pass regularly, although it is not a laxative.
- It is not clear if a high fiber diet is beneficial for people with **irritable bowel syndrome** or diverticulosis. Fiber may be helpful for some people with these diagnoses while it may worsen symptoms in others.

### Diet for Prevention of Cardiovascular Diseases



*“Cereal, Fruit, and Vegetable Fiber Intake and the Risk of Cardiovascular Disease in Elderly Individuals”*

- A population-based multicenter study on 3588 elderly men and women

**Results:** an inverse association between the consumption of fiber from cereal sources (insoluble fiber) and the risk of incident cardiovascular disease.

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### Does the clinical benefit relate to the ‘Prebiotic Effect’ of Fiber?

There are biologically plausible mechanisms for beneficial effects of cereal fiber intake on CVD risk in elderly individuals.

...fiber intake has been shown to affect serum lipid levels, postprandial absorption, blood pressure, and insulin sensitivity... affect fibrinolysis and coagulation... endothelial cell function ...prevents impaired vascular reactivity in response to a high-fat meal.

Cereal fiber consumption may also reduce CVD risk via a substitution effect, replacing intake of other foods having potentially detrimental effects.

In our study, cereal fiber consumption was associated with slight differences in blood pressure, serum lipid and glucose measures, as well as lower meat and saturated fat intake;

**Not a word on prebiotic effect of fiber !**

## Fiber in Clinical Settings - Physicians' perspectives

### Diet for Prevention of Cardiovascular Diseases

**ARCHIVES**  
INTERNAL MEDICINE

#### *'Dietary Fiber and Risk of Coronary Heart Disease A Pooled Analysis of Cohort Studies'*

- Analysis of original data from 10 prospective cohort studies from the United States and Europe to estimate the association between dietary fiber intake and the risk of coronary heart disease.

#### **Results:**

- Dietary fiber is inversely associated with risk of CHD in both men and women.
- The associations were stronger for coronary mortality (27% RR) than other events (14% RR)
- The associations were with cereal and fruit fiber but not with vegetable fiber

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Does the clinical benefit relate to the *'Prebiotic Effect'* of Fiber?

**Not a word on prebiotic effect of fiber!**

*Pereira MA, Arch Intern Med. 2004;164:370-376*

### Diet for Prevention of Cardiovascular Diseases

**JN** THE JOURNAL OF NUTRITION *'Dietary Fiber Is Associated with Reduced Risk of Mortality from Cardiovascular Disease among Japanese Men and Women'*

- A population-based a prospective study of 58,730 Japanese men and women aged 40–79y
- Dietary fiber intake was determined by a self-administered FFQ
- Participants were followed up from 1988–1990 to the end of 2003

**Results:** Inverse association between dietary fiber and CHD

=> Dietary intakes of fiber, both insoluble and soluble fibers, and especially fruit and cereal fibers, may reduce risk of mortality from CHD

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The inverse association can be explained by different mechanisms, such as improving blood lipid profile, lowering blood pressure, reduction of abdominal obesity, improvement of vascular reactivity , improving insulin sensitivity , inhibiting a postprandial rise of glucose and triglycerides , and improving fibrinolytic activity , all of which may prevent or delay the development of atherosclerosis.

**Not a word on prebiotic effect of fiber!**

### Diet for Prevention of Hypertension

**ARCHIVES**  
INTERNAL MEDICINE

*'Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials'*

- A meta-analysis of 24 randomized controlled trials

#### **Results:**

- Fiber supplementation (mean dose, 11.5 g/d) caused a nonsignificant change in systolic BP and a significant change in diastolic BP.
- The effects on BP were larger in older (>40 years) than in younger populations
- Body weight and sex did not modify the effect of fiber supplementation on BP.
- The effect of fiber on BP was estimated only from randomized placebo-controlled trials that had a high internal validity.

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**Not a word on prebiotic effect of fiber!**

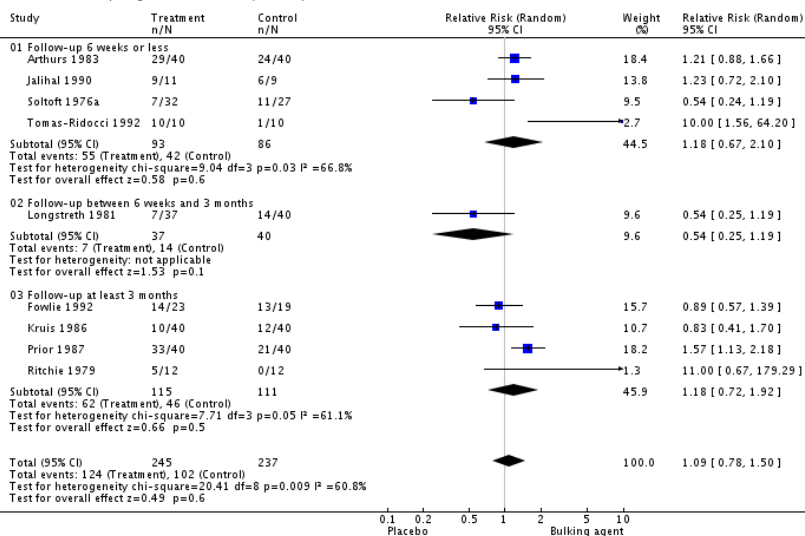


# Fiber in Clinical Settings - Physicians' perspectives

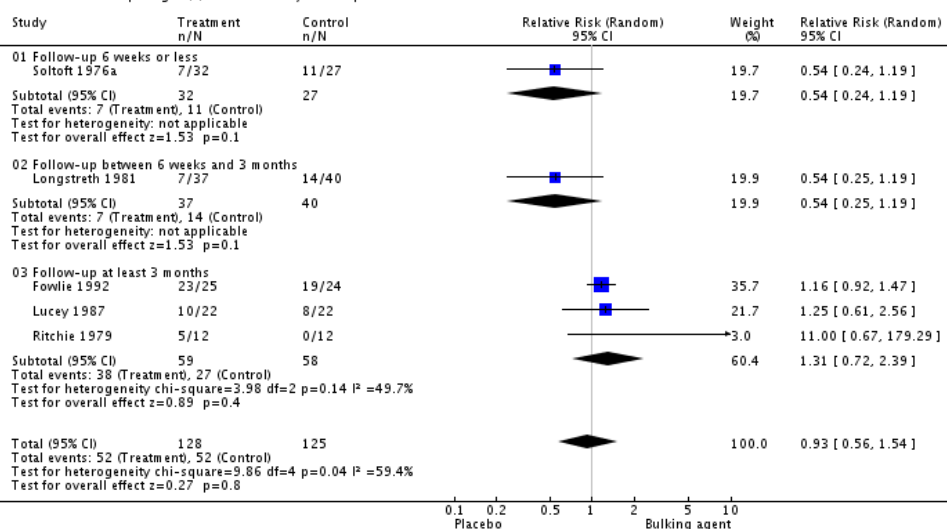
## Fiber for IBS Symptoms

- Meta-analyses and reviews that analyzed results of fiber supplementation studies in IBS often concluded lack of clinical benefit
- Studies that evaluated fiber supplementation in patients with IBS has often grouped all fibers under one term” despite differences in fibers characteristics.

Review: Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome  
 Comparison: 02 Bulking agents: Global assessment  
 Outcome: 01 Comparing n(%) of successfully treated patients



Review: Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome  
 Comparison: 03 Bulking agents: Outcome on symptom score  
 Outcome: 01 Comparing n(%) of successfully treated patients with IBS



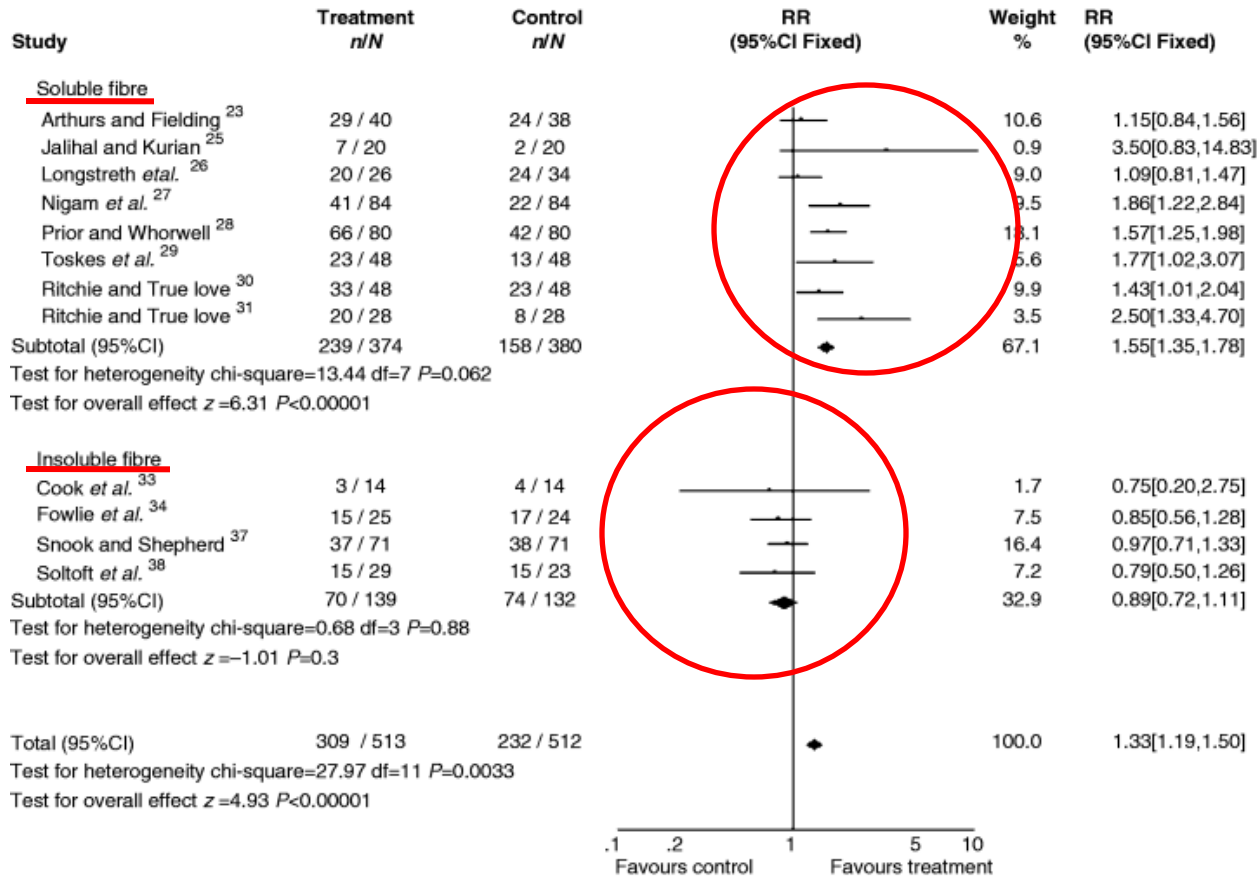
### Authors' conclusions

There is no clear evidence of benefit for antidepressants or bulking agents.

# Fiber in Clinical Settings - Physicians' perspectives

## Fiber for IBS Symptoms

Comparison of different types of fiber and control on global IBS symptom improvement:



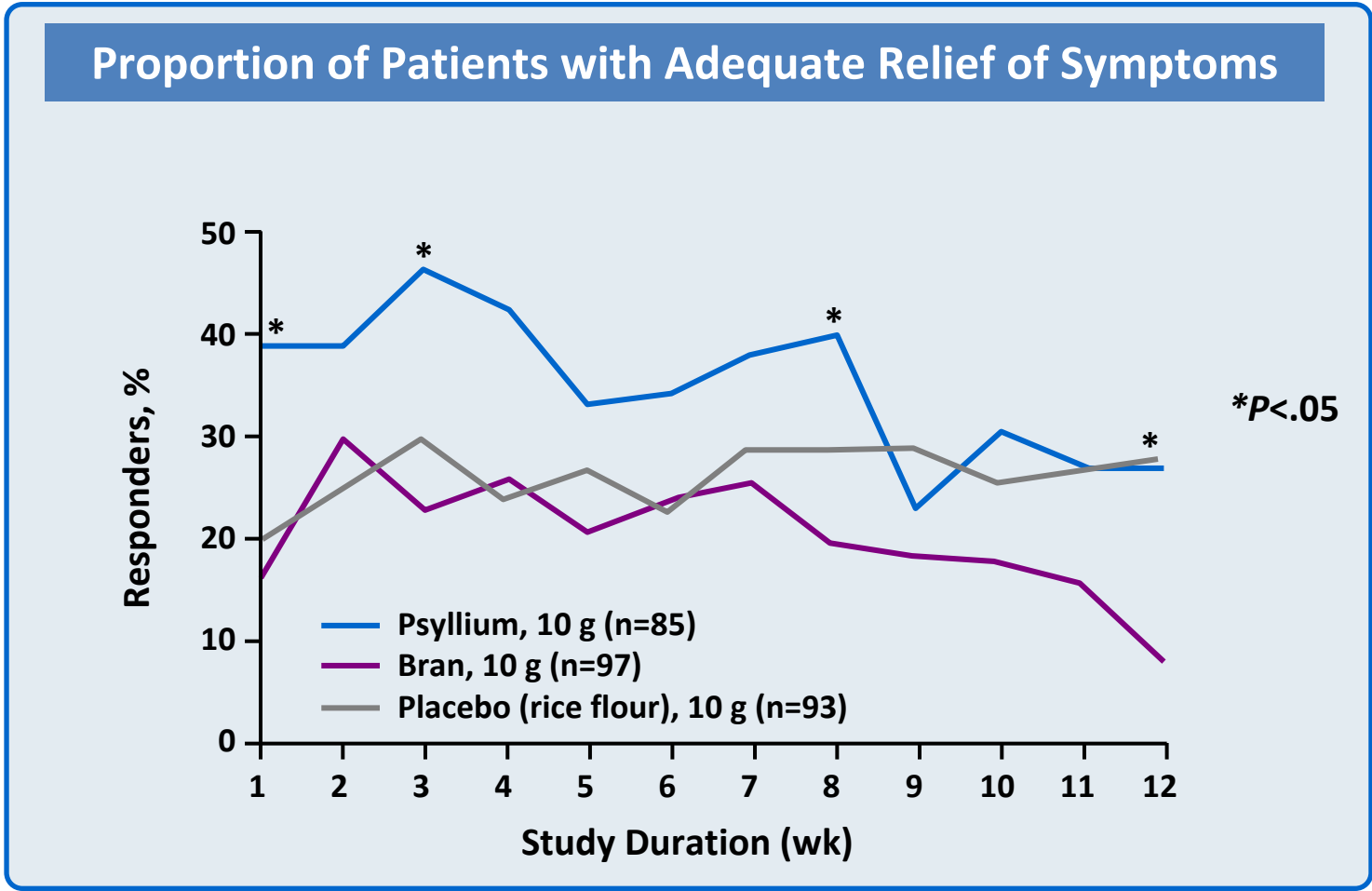
Soluble and insoluble fiber have different effects in IBS :

Soluble fiber (ispaghula, methyl-cellulose) may be effective in IBS  
- global symptom improvement  
- constipation

Insoluble fiber are probably no better than placebo and may, in some patients, worsen symptoms

n: number of events in treatment or control group; N: number of participants in treatment or control group; RR: relative risk

Fiber for IBS Symptoms - Psyllium



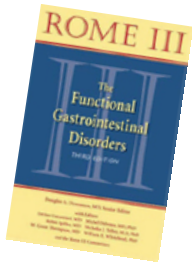
### Fiber for IBS Symptoms



#### AGA Technical Review on Irritable Bowel Syndrome

GASTROENTEROLOGY 2002;123:2108–2131

“Although fiber has an established role in treating constipation, its value for IBS, for the relief of diarrhea is controversial and not helpful for pain. In 2 randomized crossover studies of IBS the groups receiving fiber (15g barn, and 20g corn fiber) and control groups had similar degree of symptomatic improvement”



#### Functional Bowel Disorders

GASTROENTEROLOGY 2006;130:1480–1491

“Dietary fiber is a time-honored therapy that is inexpensive and safe”

“Global placebo response is marginal “

“insoluble fiber may increase symptoms, including flatulence”



#### Evidence-Based Position Statement on the Management of Irritable Bowel Syndrome in North America

American College of Gastroenterology Functional Gastrointestinal Disorders Task Force

“Bulking agents commonly available in the US are not more effective than placebo at relieving global IBS symptoms”

“Fiber is appropriate for treatment of constipation but may not be recommended for IBS”

### Evidence-based Summary of Medical Therapies for D-IBS

	Improvements in Symptoms					Grade/ Recommendation	
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency	Recommendation	Grade
Fiber (Psyllium)						Insufficient evidence	
Loperamide				+	+	2	C
Antispasmodics	±	+				2	C
Antidepressants*	+	+				1	B
Alosetron	+	+	+	+		1	B

**Recommendations**—based on the balance of benefits, risks, burdens, and sometimes cost: Grade 1=strong, Grade 2=weak.

**Assessment of Quality of evidence**—according to the quality of study design, consistency of results among studies, directness and applicability of study endpoints: Grade A=high, Grade B=moderate, Grade C=low.

ACG Task Force on IBS. *Am J Gastroenterol.* 2009;104(suppl 1):S1-S35

### Evidence-based Summary of Medical Therapies for C-IBS

	Improvements in Symptoms					Grade/ Recommendation	
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency	Recommendation	Grade
<b>Fiber (Psyllium)</b>				+	+	2	C
<b>Laxatives (PEG)</b>				+		2	C
<b>Antidepressants</b>	+	+				1	B

**Recommendations**—based on the balance of benefits, risks, burdens, and sometimes cost: Grade 1=strong, Grade 2=weak.

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### Fiber for IBS Symptoms



#### Systematic review: the efficacy of treatments for irritable bowel syndrome – a European perspective

Include review of the clinical data but does not provide conclusions or suggests recommendations



#### Guidelines on the irritable bowel syndrome: mechanisms and practical management

Include review of the clinical data . Distinguish between insoluble and soluble fiber.

“It is worthwhile trying a period of cereal fiber exclusion...if fiber supplementation is needed then soluble fiber are probably best choice”.

## Fiber in Clinical Settings - Patients' perspectives

### Search Results for “fiber” :



[Patient information: High fiber diet \(Beyond the Basics\)](#)

“Most dietary fiber is not digested or absorbed, so it stays within the intestine where it modulates digestion of other foods and affects the consistency of stool.

There are two types of fiber, each of which is thought to have its own benefits:

- **Soluble fiber** consists of a group of substances that is made of carbohydrates and dissolves in water. Examples of foods that contain soluble fiber include fruits, oats, barley, and legumes (peas and beans).
- **Insoluble fiber** comes from plant cells walls and does not dissolve in water. Examples of foods that contain insoluble fiber include wheat, rye, and other grains. The traditional fiber - wheat bran - is a type of insoluble fiber.
- **Dietary fiber** is the sum of all soluble and insoluble fiber.



## Fiber in Clinical Settings - Patients' perspectives

### Search Results for “fiber“:



Two results of about **372**

#### [Reading Food Nutrition Labels](#)

... Get enough of these nutrients. Make sure you get 100 percent of the **fiber**, vitamins and other nutrients you need every day.

[Grocery Shopping](#)... Buy more fruits and vegetables that are good sources of **fiber**, including beans, peas, oranges, bananas, strawberries and apples.

<http://www.heart.org/HEARTORG/search>



Two results of about **1660**

#### [Do You Know What You Are Eating? - American Diabetes Association](#)

... **Eat less fat — but eat more fiber.** ... Fats, calories, sodium, and fiber are also important to control blood pressure, cholesterol, and weight. ...

#### [Meal Planning for Vegetarian Diets - American Diabetes Association](#)

... **Vegetarian diets are naturally higher in fiber**, much lower in saturated fat, and cholesterol-free when compared to a traditional American diet. ...

<http://www.diabetes.org/food-and-fitness/food/planning-meals>

# Report of the Dietary Guidelines Advisory Committee (DGAC) on the Dietary Guidelines for Americans, 2010

- Americans should choose fiber-rich foods such as whole grains, vegetables, fruits, and cooked dry beans and peas as staples in the diet. Dairy products are also a nutrient-dense source of carbohydrates in the diet and provide high quality protein, vitamins, and minerals.



U.S. Department of Agriculture,  
Center for Nutrition Policy and Promotion

<http://www.cnpp.usda.gov>

### Conclusions

1. The role of the intestinal microbiota in health, disease and illness conditions (still) needs to be proven
2. *In vitro* studies suggest beneficial effects and possibly provide 'proof of concept'
3. Most of the beneficial findings in *in vitro* and animal studies have not been (so far) demonstrated in human clinical trials
  - The few studies in this area have been small & with methodological limitations
  - The mechanisms by which foods/supplements alter human function are unclear
  - There are no standardized protocols or guidelines for recommendations/treatment

**Is there a rationale for targeting the intestinal microbiota in maintaining health, and prevention and treatment of disease conditions?**

**Does the enthusiasm for the use of diet for health/medical purposes outpace the scientific evidence?**

Fiber ✓

Prebiotics ?

### We need

Large, well-designed, controlled, clinical trials to help develop:

- Better understanding of the complex interactions between the host, the diet and the intestinal microbiota
- Better tests to identify which patient, or condition, may best gain from dietary/functional food interventions
- Better protocols and guidelines for use

**Thank you**