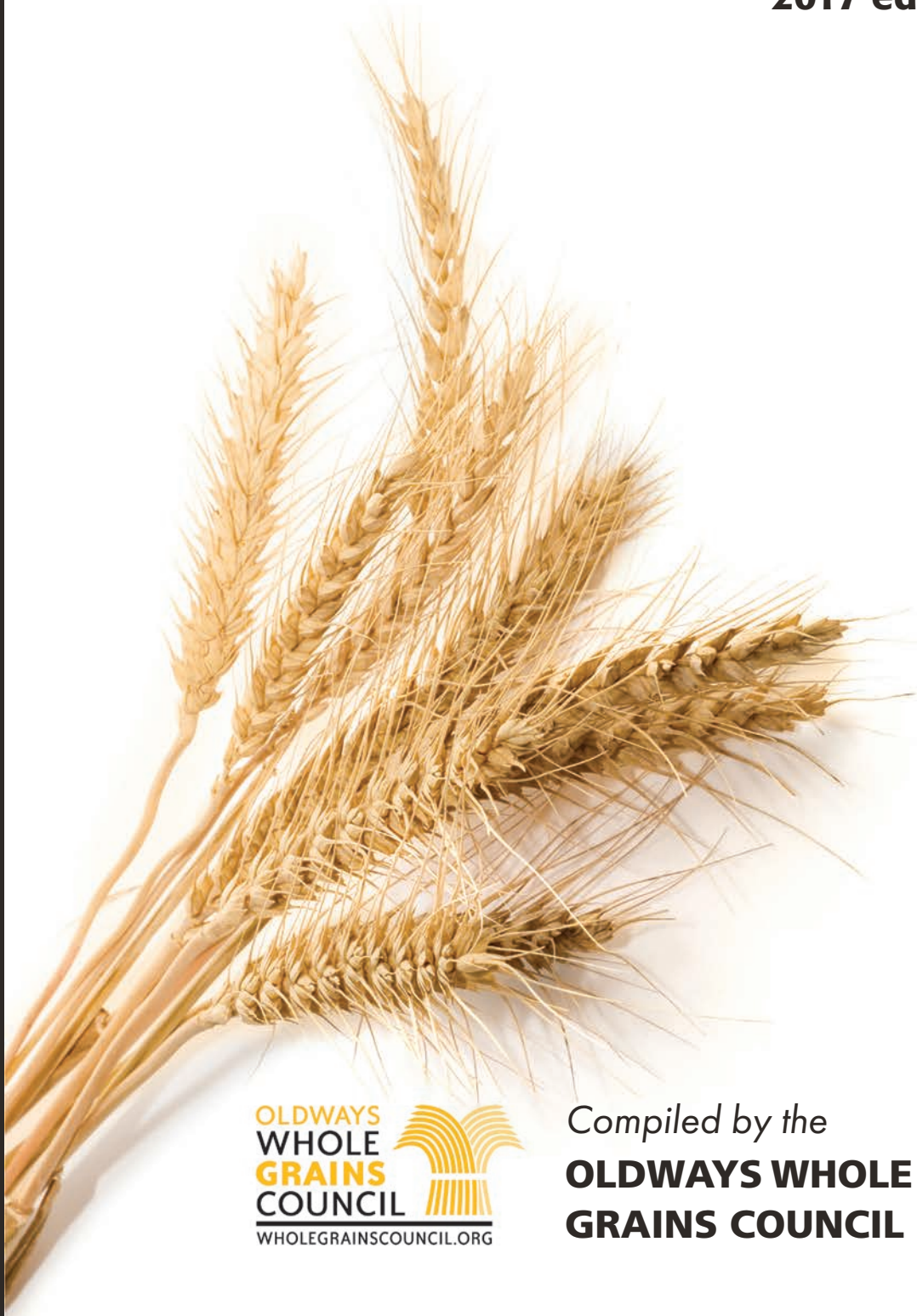


Summary of Recent Research On Whole Grains and Health

2017 edition



Compiled by the
**OLDWAYS WHOLE
GRAINS COUNCIL**

Introduction

In 2009, the Oldways Whole Grains Council released a research summary of major studies analyzing the health benefits of whole grains and published from 2004 to 2008. In the years since, more than 100 new studies on this topic have deepened our understanding of why whole grains support good health. In this new report, we've summarized 112 studies published between 2012 and 2017, to make this knowledge available to health professionals, policy makers, and anyone else who can benefit from this compilation.

This new Oldways Whole Grains Council research summary consists of:

- a. Six tables, which depict the research at a glance. The six tables are:
 1. Summary of clinical trials of whole grains
 2. Summary of studies comparing whole grain intake and survival/mortality
 3. Summary of studies comparing whole grain intake and chronic diseases or health status
 4. Summary of studies comparing dietary patterns with mortality, chronic diseases or health status
 5. Summary of studies comparing whole grain intake with surrogate markers of disease in non-clinical trial studies
 6. Summary of Systematic reviews

- b. A list of references, in order of the studies in the six tables.

- c. One-page overviews of the 39 clinical trials studies included in the first table — making it possible to review these studies in more depth. The overview pages are listed in citation order, corresponding to their order in Table 1 and in the References.

The Oldways Whole Grains Council would like to thank Zhenzhen Zhang, PhD, MMed, MPH, for compiling this summary. For more information about this summary, please contact Kelly Touns, Director of Nutrition at Oldways, 617-896-4884, or Kelly@oldwayspt.org. We also invite you to visit www.WholeGrainsCouncil.org.

About Oldway and the Whole Grains Council



Oldways is a 501(c)3 non-profit food and nutrition education organization, with a mission to inspire healthy eating through cultural food traditions and lifestyles. Oldways develops and organizes a wide variety of effective programs and materials about healthy, traditional and sustainable food choices for consumers, scientists, the food industry, health professionals, chefs, journalists and policy makers. We're widely known for creating the Mediterranean Diet pyramid in 1993, for our culinary travel adventures, and for our grassroots African Heritage cooking classes, along with many other innovative programs that advocate for the healthful pleasures of real food.



The Oldways Whole Grains Council (WGC) was founded and is managed by Oldways. The WGC's many initiatives help consumers to find whole grain foods and understand their health benefits; help manufacturers and restaurants to produce delicious whole grain products; and help the media to create accurate, compelling stories about whole grains.

In 2005, the WGC created the Whole Grain Stamp, a packaging symbol now on more than 11,000 foods that offer at least 8 grams of whole grain ingredients. As of September 2017, the Whole Grain Stamp is used in 58 countries.



Summary of Recent Research on Whole Grains and Health (2012-2017)

Summary of clinical trials of whole grains


STUDY	SAMPLE SIZE	STUDY TYPE AND DURATION	TREATMENT	RESULTS
Cooper et al., 2017 ¹	46	Randomized block design, 6 weeks	Whole grain vs. refined grain provided in weekly "market baskets"	↓ total, LDL, and non-HDL cholesterol; ↑ bowel movement; No differences in fecal microbiota
Karl et al., 2017 ²	81	Parallel-arm, 6 weeks (2-week run-in)	Diet rich in whole grain vs. refined grains	↑ Plasma alkylresorcinols, resting metabolic rate, stool weight, stool energy content
Kim et al., 2017 ³	49	Crossover, 4 weeks per diet (3-week washout)	Diet high in whole grains, nuts, legumes, dairy and devoid of red and processed meat vs. red and processed meat & refined grains	↓ insulin glucose; ↑ insulin sensitivity index
Lee et al., 2017 ⁴	21	Crossover, over 8 hour	Two rye porridges (40 g and 55 g), three 40 g rye porridges with addition of inulin: gluten (9:3; 6:6; 3:9 g); refined wheat bread control (55 g)	↓ hunger by 20 % and desire to eat by 22 %, plasma glucose after lunch ↑ fullness by 29 %; No difference in ad libitum food intake, insulin or GLP-1
Vanegas et al., 2017 ⁵	81	Parallel-arm, 6 weeks (2-week run-in)	Diet rich in whole grain vs. refined grains	↑ plasma total alkylresorcinols, stool weight, stool frequency, short-chain fatty acid (SCFA) producer Lachnospira, total SCFA, stool acetate, blood terminal effector memory T cells, LPS-stimulated ex vivo production of TNF-α; ↓ pro-inflammatory Enterobacteriaceae
Ampatzoglou et al., 2016 ⁶	33	Crossover, 6 weeks (4-week washout)	Diet high in whole grain vs. diet low in whole grain	↑ plasma alkylresorcinols, fiber intake, % of CD4(+) central memory T cells and circulating levels of adiponin; ↓ ex vivo activation of CD4(+) T cells and circulating concentrations of IL-10, C-reactive protein, C-peptide, insulin and plasminogen activator inhibitor-1
Kirwan et al., 2016 ⁷	40	Crossover, 2x 8 weeks (10-week washout)	Whole grain vs. refined grain	↓ diastolic blood pressure, ↓ of plasma adiponectin in whole grain diet was less obvious than refined-grain diet
Li et al., 2016 ⁸	298	Randomized controlled trial, prospective, 30 days, 1-year follow-up	No intervention vs. low-fat and high-fiber diet ("healthy diet") vs. "healthy diet" with the same amount of cereals replaced by 50 g oats vs. "healthy diet" with the same amount of cereals replaced by 100 g oats	50 g-oats group had larger ↓ in PPG (postprandial plasma glucose) and TC (total triglycerides); 100 g-oats group had a larger ↓ in PPG, HOMA-IR (homeostasis model assessment of insulin resistance), TC and LDL-c (low-density lipoprotein cholesterol). At 1-year follow-up, greater effects in ↓ weight, HbA1c (glycosylated hemoglobin) and TG (total triglycerides) observed in 100 g-oats group
McKeown et al., 2016 ⁹	19	Crossover, 1 week (2-week washout)	3 servings (48 g) or 6 servings (96 g) of WG wheat daily	Urinary total AR metabolites after 6 servings > after 3 servings
Nelson et al., 2016 ¹⁰	10	Double-blind, crossover, 2x 4 weeks	Malted wheat vs. white wheat	↓ diastolic blood pressure, insulin resistance; ↑ LDL
Sawicki et al., 2016 ¹¹	13	Crossover, 24 hour (2-day run-in, 1-week washout)	48 g whole oat flour, whole barley flour, or refined wheat flour plus cellulose (control)	No changes on acute bioavailability or pharmacokinetics of major phytochemicals, or bioavailability or postprandial effects
Sereni et al., 2016 ¹²	45	Crossover, 8 weeks	Bread derived from ancient wheat varieties vs. modern wheat variety	↓ total cholesterol, low-density lipoprotein (LDL)-cholesterol & blood glucose; ↑ circulating endothelial progenitor cells
Vetrani et al., 2016 ¹³	54	Parallel-arm, 12 weeks	Whole grain vs. refined cereal products	↑ fasting plasma propionate




Continued

TABLE 1	STUDY	SAMPLE SIZE	STUDY TYPE AND DURATION	TREATMENT	RESULTS
	Ampatzoglou et al., 2015 ¹⁴	33	Crossover, 6 weeks (4-week washout)	Diet high in whole grain vs. diet low in whole grain	↑ plasma alkylresorcinols No effect on energy or other macronutrients
	Hanhineva et al., 2015 ¹⁵	106	Parallel-arm, 12 weeks	1) Whole grain (WG) products, fatty fish, and bilberries [healthy diet (HD)]; 2) WG-enriched diet with the same grain products as in the HD but with no change in fish or berry consumption; 3) refined-wheat breads & restrictions on fish & berries	↑ glucuronidated alk(en)-ylresorcinols, furan fatty acids [3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF)], hippuric acid, and various lipid species incorporating polyunsaturated fatty acids
	Santaliestra-Pasias et al., 2015 ¹⁶	11	Crossover, Two different test days (7-day washout)	Whole grain bread vs. conventional bread	↑ satiety perception; ↓ energy intake remainder of testing day, and ↓ postprandial response of peptide YY
	Vitaglione et al., 2015 ¹⁷	80	Randomized parallel, 8 weeks	Whole grain vs. refined wheat	↑ excreted fecal ferulic acid (FA) and circulating dihydroferulic acid (DHFA)
	Wu et al., 2015 ¹⁸	27	Randomized parallel, 12 weeks	Whole grain vs. refined grain	↑ plasma and adipose tissue alkylresorcinols (AR) concentrations
	Durazzo et al., 2014 ¹⁹	13	Crossover, 6 weeks per diet (2-week washout)	Whole grains high in lignans vs. refined grain foods	↓ cholesterol; ↑ urinary enterodiol excretion
	Foerster et al., 2014 ²⁰	20	Crossover, 10 weeks	Diet rich in whole grain (WG) products vs. red meat (RM)	WG diet ↓ obesity parameters; RM diet ↑ serum levels of uric acid and creatinine
	Giacco et al., 2014 ²¹	61	Parallel, 12 weeks (4-week run-in)	Whole grain vs. refined cereal	↓ postprandial insulin and triglyceride responses; No change in postprandial response of glucose and other parameters evaluated
	Hajihashemi et al., 2014 ²²	44	Crossover, 6 weeks per diet (4-week washout)	Whole grain vs control (avoid whole grains)	↓ serum high-sensitive C-reactive protein, soluble intercellular adhesion molecule-1, serum amyloid A, leptin
	Hartvigsen et al., 2014 ²³	15	Crossover, 270 minutes postprandial	Wheat bread with concentrated arabinoxylan (AX) or β-glucan (BG), rye bread with kernels (RK) and wheat bread (WB) as control	BG and RK ↓ initial glycemic responses compared to WB; AX ↓ glucose peak value; RK ↓ insulin and glucose-depend insulinotropic peptide (GIP)
	Jackson et al., 2014 ²⁴	50	Randomized, controlled, open-label, parallel, 12 weeks	Weight-loss diet containing either whole grain (WG) vs. refined grains (RG)	RG had higher triglycerides and lower high-density lipoprotein (HDL) cholesterol (P = 0.06). Alkylresorcinols increased with consumption of WG diet and did not change with RG diet (time x treatment, P < 0.0001). No changes in anthropometric indices; weight, BMI, and % body AT ↓ at both 6 and 12 wks (P < 0.05); reductions in % of abdominal AT occurred by 6 wks and did not change between 6 and 12 wks (P = 0.09). ↓ glucose (P = 0.02) and HDL cholesterol (P = 0.04)
	Kang et al., 2014 ²⁵	185	Randomized, open label, controlled trial, 12 weeks	Whole grain and legume meals vs. refined rice control	↓ fasting glucose, HOMA-IR, and triglyceride; ↑ apoA-V irrespective of genotype
	Kazemzadeh et al., 2014 ²⁶	40	Crossover, 4 weeks per diet (2-week washout)	Cooked brown rice (BR) vs. white rice (WR)	↓ weight, waist and hip circumference, BMI, Diastole blood pressure and hs-CRP; No change in lipid profiles and fasting blood glucose



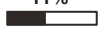





Continued

TABLE 1	STUDY	SAMPLE SIZE	STUDY TYPE AND DURATION	TREATMENT	RESULTS
	Magnusdottir et al., 2014 ²⁷	158	Randomized, multicenter, parallel group study, 18/24 weeks	Healthy Nordic diet rich in whole grain rye and wheat vs. control diet	Total plasma AR at 18/24 weeks not associated with blood lipids but AR ratio C17:0/C21:0 was inversely associated with LDL cholesterol level (B (95% CI): -0.41 (-0.80 to -0.02)), log LDL/HDL cholesterol ratio (-0.20 (-0.37 to -0.03)), log non-HDL cholesterol (-0.20 (-0.37 to -0.03)), log apolipoprotein B (-0.12 (-0.24 to 0.00)) and log triglyceride concentrations (-0.35 (-0.59 to -0.12)).
	Mohan et al., 2014 ²⁸	15	Crossover, 5 days	Brown rice (BR) vs. BR with legumes (BRL) vs. white rice (WR)	↓ 24-h glucose and fasting insulin responses
	Poquette et al., 2014 ²⁹	10	Crossover, postprandial (1-week washout)	Grain sorghum muffin vs. whole-wheat flour muffin (control)	↓ glucose, insulin
	Tovar et al., 2014 ³⁰	46	Crossover, 4 weeks per diet	Diet rich in kernel-based barley products, brown beans and chickpeas vs. control diet of similar macronutrient composition but lacking legumes and barley	↓ total cholesterol and LDL-cholesterol, apoB, γ-glutamyl transferase, diastolic blood pressure, Framingham cardiovascular risk estimate; ↑ colonic fermentative activity
	Zhang et al., 2014 ³¹	22	Crossover, 8 weeks	Oat-enriched diet vs following reinforced standard dietary advice	↓ concentrations and proportions of fibrinogen- and tissue factor-related microparticles (MP) released from platelets (PMP) and monocytes (MMP) _{11b}
	Brownlee et al., 2013 ³²	266	Randomized, 16 weeks WHOLEheart Study	Whole grain (WG) vs. control (no changes during intervention)	WG consumption 6 & 12 months after the intervention was significantly ↑ in subjects receiving WG during the intervention
	Christensen et al., 2013 ³³	72	Open-label parallel, 12 weeks (2-week run-in)	Whole grain wheat vs. refined wheat	No significant changes in microbiota composition; ↑relative abundance of Bifidobacterium
	Giacco et al., 2013 ³⁴	146	Parallel, 12 weeks (2-4 week run-in)	Whole grain vs. refined cereal	No change in peripheral insulin sensitivity
	Langkamp-Henken et al., 2012 ³⁵	83	Randomized intervention, 6 weeks	Whole grain vs. refined grain	Fecal bifidobacteria ↑from baseline with both interventions; ↑acid bacteria (LAB); No difference in stool frequency, serum antioxidant potential, or in vitro LPS-stimulated peripheral blood mononuclear cell production of inflammatory cytokines
	Lappi et al., 2013 ³⁶	51	Parallel, 12 weeks	Whole grain and fiber-rich rye breads vs. refined wheat breads	No change in intestinal microbiota composition between groups; In the refined wheat group, ↓ of Bacteroidetes (P<0.05) was in parallel with ↓ of alkylresorcinol concentration (P<0.001) before and after the intervention.
	Martinez et al., 2013 ³⁷	28	Crossover, 4 weeks per diet (4-week washout)	Whole grain barley (WGB), brown rice (BR), or an equal mixture of the two (BR+WGB)	All treatments ↑ microbial diversity, the Firmicutes/Bacteroidetes ratio, and the abundance of the genus Blautia in fecal sample. WGB enriched the genera Roseburia, Bifidobacterium and Dialister, and the species Eubacterium rectale, Roseburia faecis and Roseburia intestinalis. BR+WGB ↓ plasma IL-6 and peak postprandial glucose.
	Kristensen et al., 2012 ³⁸	79	Open-label randomized trial, 12 weeks (2-week run-in)	Energy-restricted diet (deficit of ~1250 kJ/d) with refined grains (RW) or whole grain wheat (WW)	↓ in body fat % in WW group (-3.0%) > RW group (-2.1%); serum total and LDL cholesterol ↑ by ~5% in RW group but no change in WW group

Continued

TABLE 1	STUDY	SAMPLE SIZE	STUDY TYPE AND DURATION	TREATMENT	RESULTS
	Mofidi et al., 2012 ³⁹	Part 1 n=12; Part 2 n=11	Crossover, 4 weeks per diet (4-week washout)	11-grain, sprouted-grain, 12-grain, sourdough, or white bread	Part 1: ↓ glucose for sprouted-grain than 11-grain, sourdough, and white breads; ↓ insulin for sourdough and white than 11-grain and sprouted-grain bread; ↓ GLP-1 for sourdough than other breads Part 2: ↑ glucose and insulin for sourdough than 11-grain, sprouted-grain, and 12-grain breads; sprouted-grain ↓ glucose and ↑ GLP-1

Summary of studies comparing whole grain intake and survival/mortality

TABLE 2	STUDY	SAMPLE SIZE	TYPE OF STUDY	WHOLE GRAIN TYPE	ENDPOINT ASSESSED	RESULTS	DIFFERENCE IN RISK
							0%  25%
	Johnsen et al., 2015 ⁴⁰	120,010 with 7,839 deaths	Prospective (Scandinavian HELGA cohort)	WG products (e.g. bread, cereal) and WG types (e.g. oats, rye, wheat)	All-cause and cause-specific mortality	Higher WG intake ↓ all-cause mortality (women: 11% ↓; men: 11% ↓) for a doubling of intake. Intake of breakfast cereals and non-white bread was associated with lower mortality.	11% 
	Huang et al., 2015 ^{41,42}	367,442 participants at baseline with 46,067 deaths	Prospective cohort studies (NIH-AARP Diet and Health Study), with average 14-year follow-up	Whole grains and cereal fiber	All-cause and cause-specific mortality	Highest WG intake had a 17% ↓ risk of all-cause mortality and 11-48% ↓ risk of disease-specific mortality; highest intake of cereal fiber had a 19% ↓ risk of all-cause mortality and 15-34% ↓ risk of disease-specific mortality.	17% 
	Wu et al., 2015 ⁴³	74,341 women and 43,744 men	Prospective cohort studies (Nurses' Health Study and Health Professionals Follow-up Study)	Whole grain	Total, CVD and cancer mortality	Highest quantile intake of whole grain is associated with lower total (↓ 9%) and CVD (↓ 15%) mortality in US men and women.	9% 
	Buil-Cosiales et al., 2014 ⁴⁴	7,216 with 425 deaths	Prospective cohort studies [Prevencción con Dieta Mediterránea (PREDIMED)]	Dietary fiber and whole grains	All-cause mortality	↓ 37% risk comparing the fifth vs. first quintile of baseline dietary fiber intake; No association between baseline whole grain consumption and all-cause mortality	
	Rebello et al., 2014 ⁴⁵	53,469 participants	Prospective cohort studies (Singapore Chinese Health Study)	Various sources of carbohydrates	Ischemic heart disease (IHD) mortality	Replacing 1 serving/day of rice with one of vegetables (difference in HR=-23.81%; 95% CI: -33.12%, -13.20%), fruit (-11.94%; 95% CI: -17.49%, -6.00%), or whole-wheat bread (-19.46%; 95% CI: -34.28%, -1.29%) was associated with ↓ risk of IHD death.	19.46% 
	Skeie et al., 2014 ⁴⁶	1,119 participants	Case-only study of Scandinavian HELGA cohort	Whole grain intake	Survival with colorectal cancer	No association was found for total whole grain intake or for specific grains.	

Summary of studies comparing whole grain intake and chronic diseases or health status

STUDY	SAMPLE SIZE	TYPE OF STUDY	WHOLE GRAIN TYPE	DISEASE STUDIED	RESULTS
Bakken et al., 2016 ⁴⁷	78,254 participants with 795 CRC cases	Prospective Cohort (the Norwegian Women and Cancer Study)	Whole grain bread	Colorectal Cancer (CRC)	No association
Farvid et al., 2016 ⁴⁸	90,534 participants	Prospective (Nurses' Health Study II)	Dietary fiber Whole grain	Breast cancer	Early adulthood total dietary fiber ↓19% for BC risk; soluble fiber ↓14% and insoluble fiber ↓20%; total dietary fiber intake in adolescence ↓16% BC risk; fiber intake during adolescence and early adult life ↓25% BC risk; 1.5 servings whole grains / day ↓18% BC compared to 0.2 servings; brown rice and pasta (white or whole grain) ↓BC, white bread ↑BC
Gopinath et al., 2016 ⁴⁹	1609 with 249 (15.5%) participants had aged successfully 10 years later	Prospective	Dietary fiber	Aging	Total fiber intake linked to greater odds of aging successfully than suboptimal aging, OR=1.79 (95% CI: 1.13-2.84) comparing highest vs. lowest quartile. Those below median in fiber consumption from breads/cereal and fruit were less likely to age successfully, OR=0.53 (95% CI 0.34-0.84) and OR=0.64 (95% CI 0.44-0.95).
Gopinath et al., 2016 ⁵⁰	2334 participants aged 55+ years and 1952 participants aged 60+ years	Prospective	Dietary fiber	Depression	Total fiber, vegetable fiber and breads/cereal fiber intakes were all inversely associated with the prevalence of depressive symptoms.
Helnaes et al., 2016 ⁵¹	54,871 adults with 2,329 developing myocardial infarction	Prospective Cohort (the Danish Diet, Cancer and Health Cohort)	Whole grain and whole grain species (wheat, rye and oats)	Myocardial infarction	↓ 25% risk comparing highest vs. lowest quartile of total whole grain intake. Rye and oats, but not wheat, associated with lower myocardial infarction risk in men.
Mourouti et al., 2016 ⁵²	250 cases, 250 controls	Case-control study	Whole grain	Breast cancer	Whole grain consumption > 7 times/week was associated with ↓ risk for breast cancer (OR = 0.49; 95% CI, 0.29, 0.82).
Nielsen et al., 2016 ⁵³	6,052	Cross-sectional	Whole grain, fiber	Severe periodontal Disease	↑ 27% risk comparing lowest vs. highest quartile of dietary fiber ↑ 32% risk comparing lowest vs. highest quartile of whole grains
InterAct Consortium, 2015 ⁵⁴	15,258	Case cohort study (EPIC-InterAct Study)	Cereal fiber	Type 2 diabetes	↓ 19% risk comparing quartile 4 vs. 1
Li et al. 2015 ⁵⁵	84,628 women and 42,908 men	Prospective (Nurses' Health Study, Health Professionals Follow-up Study)	Sources of carbohydrates	Coronary heart disease (CHD)	Carbohydrates from whole grains linked with ↓ CHD risk (HR: 0.90, 95% CI: 0.83-0.98; P _{trend} = 0.003).
Drake et al., 2014 ⁵⁶	1,016 cases, 1,817 controls	Nested case-control	Plasma alkylresorcinol (AR) metabolites as biomarkers for whole grain intake	Prostate cancer (PCa)	AR metabolites correlated with whole grain (r = 0.31) and fiber (r = 0.27) intake. Metabolite concentration positively associated with PCa but association was not linear. 41% ↑ risk comparing high vs. moderate plasma AR metabolites.


Continued

STUDY	SAMPLE SIZE	TYPE OF STUDY	WHOLE GRAIN TYPE	DISEASE STUDIED	RESULTS
Knudsen et al., 2014 ⁵⁷	522 cases, 522 controls	Nested case-control study	Whole grain (WG) intake and plasma alkylrescorcinol (AR) Howe's score with Ranks: according to reported WG intake from the FFQs (q) and plasma AR (m), the ranks were summed as: q + m, giving each participant a score	Colorectal cancer	Plasma AR alone and Howe's score with ranks were inversely associated with distal colon cancer risk comparing highest vs. lowest (for AR, RR = 0.34, 95% CI: 0.13-0.92; for Howe's score with ranks, RR = 0.35, 95% CI: 0.15-0.86). No association between WG intake and any colorectal cancer when using an FFQ as the measure.
Kyro et al., 2014 ⁵⁸	1372 incident colorectal cancer cases and 1372 controls	Case-control study	Plasma AR	Colorectal cancer	Total AR ↓ distal colon cancer (52%) comparing highest vs. lowest quartile of plasma total AR. For total colon cancer, reduced association (↓ 17%) was found only among Scandinavian population. No association with overall colorectal cancer, proximal colon cancer, or rectal cancer
Mostad et al., 2014 ⁵⁹	50 339	Cross-sectional	Whole grain bread	Central obesity	Central obesity was associated with a ↓ intake of any bread, and of whole grain bread (-13%) in particular
Ananthakrishna et al., 2013 ⁶⁰	170,776 women, followed up over 26 years	Prospective (Nurses' Health Study)	Dietary fiber	Crohn's disease (CD) and ulcerative colitis (UC)	Long-term intake of dietary fiber, particularly from fruit, is associated with ↓ risk of CD (↓ 40%) but not UC. Reduction appeared greatest for fiber derived from fruits; fiber from cereals, whole grains, or legumes did not modify risk.
Daniel et al., 2013 ⁶¹	491,841 with 1816 incident cases of RCC	Prospective (NIH-AARP Diet and Health Study)	Fiber and fiber-rich plant foods	Renal cell carcinoma (RCC)	Total dietary fiber intake significantly ↓ 15-20 % risk of RCC in the 2 highest quintiles vs. lowest ($P_{trend} = 0.005$). Intakes of legumes, whole grains, and cruciferous vegetables ↓ 16-18% risk of RCC.
Kyro et al., 2013 ⁶²	108,000 with 1,123 incident cases	Prospective (Scandinavian HELGA cohort)	Whole grains	Colorectal cancer	Each 50-g ↑ of whole grain products is associated with 6% ↓ in colorectal cancer
Parker et al., 2013 ⁶³	72,215 with 3465 cases of incident T2D	Prospective (Women's Health Initiative), median follow-up of 7.9 years	whole grain	Type 2 diabetes	Increasing categories of whole grain consumption ↓ risk of incident T2D (17%, 27%, 31%, 39%, 43%)
Aarestrup et al., 2012 ⁶⁴	24,418 with 217 incident endometrial cancer cases	Prospective (Danish cohort study)	Whole grain, dietary fiber	Endometrial cancer	No associations between whole grains or dietary fiber and the incidence of endometrial cancer.
Torfadottir et al., 2012 ⁶⁵	2,268 with 347 incident PCa	Prospective (AGES-Reykjavik cohort study)	Rye bread	Prostate cancer (PCa)	Rye bread consumption in adolescence (vs. less than daily) ↓ risk of PCa (-24%), and advanced PCa (-53%).


Summary of studies comparing dietary patterns with mortality, chronic diseases or health status

STUDY	SAMPLE SIZE	STUDY DESIGN	DIETARY PATTERN STUDIED	DISEASE OR HEALTH STUDIED	DIFFERENCE IN RISK
Fayet-Moore et al., 2017 ⁶⁶	9,341	Cross-sectional	Core grain foods: cereals and cereal products (both whole and refined) leaving out discretionary foods like cakes	Anthropometric measures	Inverse relationship between core grain serves intake and BMI, waist circumference, and a positive relationship with fiber
Hansen et al., 2017 ⁶⁷	55,338 with 2,283 incident stroke cases	Prospective	Nordic diet: high intakes of fish, apples and pears, cabbages, root vegetables, whole grains from oat, barley and rye, berries, and rapeseed oil	Stroke	↓ 14% comparing the highest vs. the lowest adherence
Ozawa et al., 2017 ⁶⁸	5083	Prospective	Inflammatory dietary pattern: higher intake of red meat, processed meat, peas and legumes, and fried food, and lower intake of whole grains	Cognitive decline	↓ in reasoning comparing highest (-0.37) vs. lowest (-0.31) tertile of adherence to inflammatory dietary pattern. Inflammatory dietary pattern was associated with faster cognitive decline. Associations were stronger in younger subjects (<56 yrs).
Rai et al., 2017 ⁶⁹	44,444 with 1,731 incident gout cases	Prospective	DASH diet: based on high intake of fruits, vegetables, nuts and legumes, low fat dairy products, and whole grains, and low intake of sodium, sweetened beverages, and red and processed meats) Western diet: on high intake of red and processed meats, French fries, refined grains, sweets, and desserts	Gout	↓ 32% risk comparing highest vs. lowest quintile of DASH diet score; ↑ 42% risk comparing highest vs. lowest quintile of Western diet score
van den Brandt et al., 2017 ⁷⁰	62,573 with 2,321 incident breast cancer cases	Prospective	Mediterranean diet: Higher intake of Vegetables, legumes, fruits, nuts, whole grains, fish and the ratio of monounsaturated to saturated fatty acid intake, and lower intake of red/ processed meat	Postmenopausal estrogen responsive (ER+ BC) or non-responsive (ER- BC) breast cancer	↓ 40% for ER- BC comparing highest vs. lowest adherence; No association for ER+ BC
Mehta et al., 2016 ⁷¹	121,700 women 51,529 men	Prospective	Prudent diets (rich in whole grains and dietary fiber) and Western diets (rich in red and processed meat, refined grains, and desserts)	Incidence of colorectal carcinoma subclassified by F nucleatum status in tumor tissue	Prudent diet score associated with lower risk (↓ 57%) of F nucleatum-positive cancers but not with F nucleatum-negative cancers
Satija et al., 2016 ⁷²	69,949 women from the Nurses' Health Study 1, 90,239 women from the Nurses' Health Study 2, and 40,539 men from the Health Professionals Follow-Up Study With 16,162 incident T2D cases	Prospective	Healthful plant-based diet index (hPDI): where healthy plant foods (whole grains, fruits, vegetables, nuts, legumes, vegetable oils, tea/coffee) received positive scores, while less healthy plant foods (fruit juices, sweetened beverages, refined grains, potatoes, sweets/desserts) and animal foods received reverse scores. Unhealthful plant-based diet index (uPDI): assigning positive scores to less healthy plant foods and reverse scores to healthy plant foods and animal foods.	Type 2 Diabetes (T2D)	↓ 20% for extreme deciles of PDI; ↑ 16% for extreme deciles of hPDI


Continued

TABLE 4	STUDY	SAMPLE SIZE	STUDY DESIGN	DIETARY PATTERN STUDIED	DISEASE OR HEALTH STUDIED	DIFFERENCE IN RISK
	Shakersain et al., 2016 ⁷³	2,223	Prospective	Prudent diet: characterized by more frequent intakes of vegetables, fruit, cooking/dressing oil, cereals and legumes, whole grains, rice/pasta, fish, low-fat dairy, poultry, and water Western diet: characterized by more frequent intakes of red/processed meat, saturated/trans-fat, refined grains, and sugar	Cognitive decline	The highest adherence to prudent pattern was related to less cognitive decline; the highest adherence to Western pattern was associated with more cognitive decline ($\beta = -0.156$, $P < .001$).
	Boggs et al., 2015 ⁷⁴	19,885	Prospective	Alternate Healthy Eating Index-2010 (AHEI-2010) DASH diet	Obesity	Highest vs. lowest quintiles of the AHEI-2010 ↓ 24% risk Highest vs. lowest quintiles of the DASH ↓ 32% risk
	Merle et al., 2015 ⁷⁵	2,525	Prospective	Alternate Mediterranean diet (aMeDi): vegetables, fruit, legumes, whole grains, nuts, fish, red and processed meats, alcohol, and the ratio of monounsaturated to saturated fats	Advanced macular degeneration	High aMeDi score (score of 6-9) ↓ risk 26%
	Morris et al., 2015 ⁷⁶	923	Prospective	Hybrid Mediterranean-Dietary Approaches to Stop Hypertension diet (MIND Diet)	Alzheimer's disease (AD)	↓ 35% for the second highest vs. lowest tertile, ↓ 53% for the highest tertile vs. lowest tertile of MIND diet score.
	Tektonidis et al., 2015 ⁷⁷	32,921	Prospective	Modified Mediterranean diet (mMED): high consumption of vegetables, fruits, legumes, nuts, whole grains, fermented dairy products, fish and monounsaturated fat, moderate intakes of alcohol and low consumption of red meat	Myocardial infarction, heart failure and stroke	High adherence to mMED score (6-8), ↓ 26% risk for MI, 21% for HF and 22% for ischemic stroke; No association with hemorrhagic stroke.
	Shin et al. ⁷⁸ 2015	1,828	Prospective	1. Rice and kimchi 2. Eggs, meat and flour 3. Fruit, milk and whole grains 4. Fast food and soda	Bone mineral density (BMD)	'Fruit, milk and whole grains' pattern associated with ↓ risk of low BMD in men by 62% and in women 55%.
	Varraso et al., 2015 ⁷⁹	73,228 women 47,026 men	Prospective	Alternate Healthy Eating Index (AHEI-2010)	Chronic obstructive pulmonary disease (COPD).	↓ 33% for highest vs. lowest quintile of AHEI-2010 score
	Yang et al., 2015 ⁸⁰	926	Prospective	Prudent pattern: higher intake of vegetables, fruits, fish, legumes, and whole grains Western pattern: higher intake of processed and red meats, high-fat dairy and refined grains	Prostate cancer-specific and total mortality	↓ 36% of prostate cancer-specific mortality and no association with all-cause mortality comparing the highest vs. lowest quartile of the Prudent pattern; ↑153% of prostate cancer-specific mortality and ↑67% all-cause mortality comparing the highest vs. lowest quartile of the Western pattern.

Continued

TABLE 4	STUDY	SAMPLE SIZE	STUDY DESIGN	DIETARY PATTERN STUDIED	DISEASE OR HEALTH STUDIED	DIFFERENCE IN RISK
	Yu et al., 2015 ⁸¹	84,735	Prospective	Healthy Eating Index (HEI) , 2010 and 2005 editions: both HEIs comprise 12 components with a total score of 100 points. HEI-2010 recommended increasing consumption of nine components: total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and the ratio of unsaturated to saturated fatty acids; and decreasing consumption of: refined grains, sodium, and calories from solid fats, excessive alcohol, & added sugars	Total and cause-specific mortality	↓ 20% for all-disease mortality, ↓ 19% for CVD mortality, ↓ 19% for cancer mortality and ↓ 23% for other disease mortality comparing highest quintile vs. lowest quintile
	Englund-Ögge et al., 2014 ⁸²	66,000	Prospective	1. Prudent (vegetables, fruits, oils, water as beverage, whole grain cereals, fiber rich bread) 2. Western (salty and sweet snacks, white bread, desserts, processed meat products) 3. Traditional (potatoes, fish)	Preterm delivery	↓ 12% for highest vs. lowest tertile of prudent diet
	Hillesund et al., 2014 ⁸³	66,597	Prospective (Norwegian Mother and Child Cohort Study)	New Nordic diet (NND)	Gestational weight gain and fetal growth	Higher NND adherence ↓ 7% gestational weight gain, ↓ 8% risk of infant being born small for gestational age, ↑ 7% of the baby being born large for gestational age
	Arthur et al., 2013 ⁸⁴	542	Prospective	Whole-foods pattern: high intakes of vegetables, fruit, fish, poultry, and whole grains Western pattern: high intakes of red and processed meats, refined grains, potatoes, and French fries	Head and neck cancer prognosis	High adherence to whole-foods patterns ↓ 44% risk of death
	Levitan et al., 2013 ⁸⁵	1385 of 3215 (43.1%) participants who experienced a heart failure (HF) hospitalization died	Prospective (Women's Health Initiative)	Mediterranean and DASH diet	Mortality	Higher DASH diet scores modestly lowered mortality in women with HF, and nonsignificant trend toward an inverse association with Mediterranean diet scores
	Wengreen et al., 2013 ⁸⁶	3,831	Prospective	Dietary Approaches to Stop Hypertension (DASH) and Mediterranean-style dietary patterns, whole grains	Cognitive function assessed by Modified Mini-Mental State Examination (3MS)	Higher intakes of whole grains and nuts and legumes were also associated with higher average 3MS scores

Summary of studies comparing whole grain intake with surrogate markers of disease in non-clinical trial studies

TABLE 5	STUDY	SAMPLE SIZE	TYPE OF STUDY	ENDPOINT ASSESSED	RESULTS
	Mann et al., 2015 ⁸⁷	3,073	Cross-sectional	Markers of health	Higher concentrations of C-reactive protein were seen in adults in the lowest tertile of whole grain intake.
	Goletzke et al., 2014 ⁸⁸	205	Prospective	IL-6	Higher dietary glycemic load and a lower intake of whole grains during puberty were independently associated with higher IL-6 concentrations.
	Wang et al., 2014 ⁸⁹	4,282	Cross-sectional (NHANES 2003-2006)	Serum cholesterol concentrations	Use of statins was associated with healthier lipoprotein profiles when combined with higher WG vs. lower WG intake.
	Montonen et al., 2013 ⁹⁰	2,198	Cross-sectional study (European Prospective Investigation into Cancer and Nutrition-Potsdam study)	Biomarkers of obesity, inflammation, glucose metabolism and oxidative stress	Whole grain bread was associated with ↓ GGT, ALT and hs-CRP.
	Heikkila et al., 2012 ⁹¹	1,261	Cross-sectional study (the DR's EXTRA Study)	Impaired fasting plasma glucose (IFG), glucose tolerance (IGT), maximal oxygen uptake (VO ₂ max)	Additional whole grain bread (50 g/1000 kcal) and dietary fiber intake (g/1000 kcal) ↓ IGT (39%, and 9% respectively).

Summary of Systematic reviews

TABLE 6	STUDY	SAMPLE SIZE	EXPOSURE	ENDPOINT ASSESSED	RESULTS
	Schwingshackl et al., 2017 ⁹²	23 publications for whole grains	Food groups including whole grains	Type 2 diabetes (T2D)	Each additional daily 30g of whole grains was associated with 13% ↓ risk
	Schwingshackl et al., 2017 ⁹³	19 publications for whole grains analyses	Food groups including whole grains	All-cause mortality	Each daily serving increase of whole grain is associated with 8% ↓ risk
	Aune et al., 2016 ⁹⁴	45 prospective studies	Whole grain	Cardiovascular disease (CVD), cancer, all cause and cause specific mortality	Whole grain intake is associated with a ↓ risk of coronary heart disease, CVD, and total cancer, and mortality from all causes, respiratory diseases, infectious diseases, diabetes, and all non-CVD, non-cancer causes.
	Chen et al., 2016 ⁹⁵	13 studies	Whole grain	Total, cardiovascular and cancer mortality	Significant inverse relations between whole grain intake and mortality due to any cause, CVD, or cancer
	Chen et al., 2016 ⁹⁶	7 prospective studies (n=446,451, n=5,892 stroke vents)	Whole grain	Stroke	Whole and refined grain consumption is not associated with total stroke risk; however, whole grain consumption is associated with ↓ ischemic stroke risk.
	Lei et al., 2016 ⁹⁷	8 observational studies	Whole grain	Pancreatic cancer	24% ↓ risk comparing high vs. low whole grain intake
	Li et al., 2016 ⁹⁸	10 prospective cohort studies	Whole grains	Mortality from all causes, cardiovascular disease, and diabetes	Whole grain intake is associated with ↓ risk of mortality from all-cause (7%), CVD (5%) and CHD (7%). No association with risk of death from stroke and diabetes.
	Wei et al., 2016 ⁹⁹	11 prospective studies (n=816,599 with 89,251 cases of all-cause mortality)	Whole grain	All-cause, CVD and cancer mortality	13% ↓ risk of all-cause mortality, 19% ↓ risk of CVD mortality and 11% ↓ risk of all cancer mortality comparing highest vs. lowest whole grain intake
	Zong et al., 2016 ¹⁰⁰	14 prospective cohort studies (n=786,076)	Whole grain	Mortality From All Causes, Cardiovascular Disease, and Cancer	16% ↓ risk for mortality, 18% ↓ risk for CVD mortality, ↓ risk for cancer mortality comparing high vs. low whole grain intake
	Chanson-Rolle et al., 2015 ¹⁰¹	8 observational studies with N=15,573 T2D cases among 316,051 participants	Whole grain	Type 2 diabetes	↓ 0.3% in T2D rate for each additional 10 g of whole grain ingredients consumed daily
	Fang et al., 2015 ¹⁰²	6 prospective studies with 247,487 participants	Whole grain	Stroke	16% ↓ risk comparing highest vs. lowest whole grain consumption
	Hollænder et al., 2015 ¹⁰³	24 randomized controlled comparisons between whole grain foods and a non-whole grain control in adults	Whole grain	Changes in total cholesterol (TC), LDL cholesterol, HDL cholesterol, and triglycerides	Consumption of whole grain diets ↓ LDL cholesterol (weighted difference: -0.09 mmol/L) and TC (weighted difference: -0.12 mmol/L), but not HDL cholesterol or triglycerides. Whole grain oat appears to be most effective whole grain for ↓ cholesterol (weighted difference: -0.04 mmol/L).
	InterAct Consortium, 2015 ⁵⁴	19 prospective cohorts	Dietary fiber	Type 2 diabetes	10 g/day increase in total fiber was associated with 9% ↓ risk; cereal fiber 25% ↓ risk; fruit fiber 5% ↓ risk; and vegetable fiber 7% ↓ risk.

Continued

TABLE 6	STUDY	SAMPLE SIZE	EXPOSURE	ENDPOINT ASSESSED	RESULTS
	Tang et al., 2015 ¹⁰⁴	18 studies (15 cohort & 3 case-control studies) 14,427 patients with CHD and 400,492 participants	Whole grain	Coronary heart disease (CHD)	↓ CHD (relative risk 0.787) with highest vs. lowest whole grain intake
	Tosh et al., 2015 ¹⁰⁵	20 publications including 56 individual tests, additional 17 unpublished tests	Processing of whole grain oat cereals	Glycemic index (GI)	Quick-cooking oats and instant oatmeal produced higher glycemic response. Steel-cut oats (GI=55 (se 2.5)), large-flake oats (GI=53 (se 2.0)) and muesli and granola (GI=56 (se 1.7)) elicited low to medium glycemic response.
	Kim et al., 2014 ¹⁰⁶	7 studies (62,314 death among 908,135 participants)	Dietary fiber	Total mortality	10-g/day ↑ of dietary fiber intake was associated with 11% ↓ risk.
	Thielecke et al., 2014 ¹⁰⁷	75 articles	Whole grain	Weight management	Higher intake of whole grain is associated with lower body weight, BMI, waist circumference, abdominal adiposity, and weight gain.
	Thies et al., 2014 ¹⁰⁸	64 studies	Oats	CVD risk markers	37 (58%) and 34 (49%) of studies showed a significant ↓ in total cholesterol (2-19 % ↓) and LDL-cholesterol (4-23 % ↓) respectively, mostly in hypercholesterolaemic subjects
	Thies et al., 2014 ¹⁰⁹	39 articles	Oats	Bowel disease	Oats or oat bran could benefit inflammatory bowel disorders, still remaining to be proven. A protective effect on colorectal adenoma and cancer incidence has not yet been convincingly shown. The majority of patients with coeliac disease could consume up to 100 g/d of uncontaminated oats, which would ↑ the acceptability of, and adherence to, a gluten-free diet.
	Aune et al., 2013 ¹¹⁰	16 cohort studies	Whole grain and refined grain	Type 2 diabetes	Relative risk was 0.68 (95% CI 0.58-0.81) per 3 servings/day of whole grain and 0.95 (95% CI 0.88-1.04) per 3 servings/day of refined grains.
	Pol et al., 2013 ¹¹¹	26 randomized controlled studies (n=2060)	Whole grain vs. a non-whole grain control	Body weight changes	No effect on body weight, small effect (-0.48%) on % of body fat
	Ye et al., 2012 ¹¹²	45 prospective cohort studies and 21 RCT	Whole grain	Type 2 diabetes (T2D), cardiovascular disease (CVD), weight gain, and metabolic risk factors	48-80 g whole grain/d (3-5 serving/d) had a ~26% ↓ risk of T2D [RR = 0.74 (95% CI: 0.69, 0.80)], ~21% ↓ risk of CVD [RR = 0.79 (95% CI: 0.74, 0.85)], and less weight gain during 8-13 y (1.27 vs 1.64 kg; P = 0.001). Among RCT, weighted mean differences in post-intervention circulating concentrations of glucose and total and LDL-cholesterol indicated lower concentrations after whole grain interventions [differences in fasting glucose: -0.93 mmol/L (95% CI: -1.65, -0.21), total cholesterol: -0.83 mmol/L (-1.23, -0.42); and LDL-cholesterol: -0.82 mmol/L (-1.31, -0.33)].

References

1. Cooper DN, Kable ME, Marco ML, et al. The Effects of Moderate Whole Grain Consumption on Fasting Glucose and Lipids, Gastrointestinal Symptoms, and Microbiota. *Nutrients*. 2017;9(2).
2. Karl JP, Meydani M, Barnett JB, et al. Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women. *Am J Clin Nutr*. 2017;105(3):589-599.
3. Kim Y, Keogh JB, Clifton PM. Consumption of red and processed meat and refined grains for 4weeks decreases insulin sensitivity in insulin-resistant adults: A randomized crossover study. *Metabolism*. 2017;68:173-183.
4. Lee I, Shi L, Webb DL, Hellstrom PM, Riserus U, Landberg R. Effects of whole-grain rye porridge with added inulin and wheat gluten on appetite, gut fermentation and postprandial glucose metabolism: a randomised, cross-over, breakfast study. *Br J Nutr*. 2016;116(12):2139-2149.
5. Vanegas SM, Meydani M, Barnett JB, et al. Substituting whole grains for refined grains in a 6-wk randomized trial has a modest effect on gut microbiota and immune and inflammatory markers of healthy adults. *Am J Clin Nutr*. 2017;105(3):635-650.
6. Ampatzoglou A, Williams CL, Atwal KK, et al. Effects of increased wholegrain consumption on immune and inflammatory markers in healthy low habitual wholegrain consumers. *Eur J Nutr*. 2016;55(1):183-195.
7. Kirwan JP, Malin SK, Scelsi AR, et al. A Whole-Grain Diet Reduces Cardiovascular Risk Factors in Overweight and Obese Adults: A Randomized Controlled Trial. *J Nutr*. 2016;146(11):2244-2251.
8. Li X, Cai X, Ma X, et al. Short- and Long-Term Effects of Wholegrain Oat Intake on Weight Management and Glucolipid Metabolism in Overweight Type-2 Diabetics: A Randomized Control Trial. *Nutrients*. 2016;8(9).
9. McKeown NM, Marklund M, Ma J, et al. Comparison of plasma alkylresorcinols (AR) and urinary AR metabolites as biomarkers of compliance in a short-term, whole-grain intervention study. *Eur J Nutr*. 2016;55(3):1235-1244.
10. Nelson K, Mathai ML, Ashton JF, et al. Effects of malted and non-malted whole-grain wheat on metabolic and inflammatory biomarkers in overweight/obese adults: a randomised crossover pilot study. *Food Chem*. 2016;194:495-502.
11. Sawicki CM, McKay DL, McKeown NM, Dallal G, Chen C, Blumberg JB. Phytochemical Pharmacokinetics and Bioactivity of Oat and Barley Flour: A Randomized Crossover Trial. *Nutrients*. 2016;8(12).
12. Sereni A, Cesari F, Gori AM, et al. Cardiovascular benefits from ancient grain bread consumption: findings from a double-blinded randomized crossover intervention trial. *Int J Food Sci Nutr*. 2017;68(1):97-103.
13. Vetrani C, Costabile G, Luongo D, et al. Effects of whole-grain cereal foods on plasma short chain fatty acid concentrations in individuals with the metabolic syndrome. *Nutrition*. 2016;32(2):217-221.
14. Ampatzoglou A, Atwal KK, Maidens CM, et al. Increased whole grain consumption does not affect blood biochemistry, body composition, or gut microbiology in healthy, low-habitual whole grain consumers. *J Nutr*. 2015;145(2):215-221.
15. Hanhineva K, Lankinen MA, Pedret A, et al. Nontargeted metabolite profiling discriminates diet-specific biomarkers for consumption of whole grains, fatty fish, and bilberries in a randomized controlled trial. *J Nutr*. 2015;145(1):7-17.
16. Santaliestra-Pasias AM, Garcia-Lacarte M, Rico MC, Aguilera CM, Moreno LA. Effect of two bakery products on short-term food intake and gut-hormones in young adults: a pilot study. *Int J Food Sci Nutr*. 2015;67(5):562-570.
17. Vitaglione P, Mennella I, Ferracane R, et al. Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber. *Am J Clin Nutr*. 2015;101(2):251-261.
18. Wu H, Kolehmainen M, Mykkanen H, et al. Alkylresorcinols in adipose tissue biopsies as biomarkers of whole-grain intake: an exploratory study of responsiveness to advised intake over 12 weeks. *Eur J Clin Nutr*. 2015;69(11):1244-1248.
19. Durazzo A, Carcea M, Adlercreutz H, et al. Effects of consumption of whole grain foods rich in lignans in healthy postmenopausal women with moderate serum cholesterol: a pilot study. *Int J Food Sci Nutr*. 2014;65(5):637-645.
20. Foerster J, Maskarinec G, Reichardt N, et al. The influence of whole grain products and red meat on intestinal microbiota composition in normal weight adults: a randomized crossover intervention trial. *PLoS One*. 2014;9(10):e109606.
21. Giacco R, Costabile G, Della Pepa G, et al. A whole-grain cereal-based diet lowers postprandial plasma insulin and triglyceride levels in individuals with metabolic syndrome. *Nutr Metab Cardiovasc Dis*. 2014;24(8):837-844.
22. Hajihashemi P, Azadbakht L, Hashemipour M, Kelishadi R, Esmailzadeh A. Whole-grain intake favorably affects markers of systemic inflammation in obese children: a randomized controlled crossover clinical trial. *Mol Nutr Food Res*. 2014;58(6):1301-1308.
23. Hartvigsen ML, Gregersen S, Laerke HN, Holst JJ, Bach Knudsen KE, Hermansen K. Effects of concentrated arabinoxylan and beta-glucan compared with refined wheat and whole grain rye on glucose and appetite in subjects with the metabolic syndrome: a randomized study. *Eur J Clin Nutr*. 2014;68(1):84-90.
24. Harris Jackson K, West SG, Vanden Heuvel JP, et al. Effects of whole and refined grains in a weight-loss diet on markers of metabolic syndrome in individuals with increased waist circumference: a randomized controlled-feeding trial. *Am J Clin Nutr*. 2014;100(2):577-586.
25. Kang R, Kim M, Chae JS, Lee SH, Lee JH. Consumption of whole grains and legumes modulates the genetic effect of the APOA5 -1131C variant on changes in triglyceride and apolipoprotein A-V concentrations in patients with impaired fasting glucose or newly diagnosed type 2 diabetes. *Trials*. 2014;15:100.
26. Kazemzadeh M, Safavi SM, Nematollahi S, Nourieh Z. Effect of Brown Rice Consumption on Inflammatory Marker and Cardiovascular Risk Factors among Overweight and Obese Non-menopausal Female Adults. *Int J Prev Med*. 2014;5(4):478-488.
27. Magnusdottir OK, Landberg R, Gunnarsdottir I, et al. Whole grain rye intake, reflected by a biomarker, is associated with favorable blood lipid outcomes in subjects with the metabolic syndrome--a randomized study. *PLoS One*. 2014;9(10):e110827.
28. Mohan V, Spiegelman D, Sudha V, et al. Effect of brown rice, white rice, and brown rice with legumes on blood glucose and insulin responses in overweight Asian Indians: a randomized controlled trial. *Diabetes Technol Ther*. 2014;16(5):317-325.
29. Poquette NM, Gu X, Lee SO. Grain sorghum muffin reduces glucose and insulin responses in men. *Food Funct*. 2014;5(5):894-899.
30. Tovar J, Nilsson A, Johansson M, Bjorck I. Combining functional features of whole-grain barley and legumes for dietary reduction of cardiometabolic risk: a randomised cross-over intervention in mature women. *Br J Nutr*. 2014;111(4):706-714.
31. Zhang X, McGeoch SC, Megson IL, et al. Oat-enriched diet reduces inflammatory status assessed by circulating cell-derived microparticle concentrations in type 2 diabetes. *Mol Nutr Food Res*. 2014;58(6):1322-1332.



References

32. Brownlee IA, Kuznesof SA, Moore C, Jebb SA, Seal CJ. The impact of a 16-week dietary intervention with prescribed amounts of whole-grain foods on subsequent, elective whole grain consumption. *Br J Nutr*. 2013;110(5):943-948.
33. Christensen EG, Licht TR, Kristensen M, Bahl MI. Bifidogenic effect of whole-grain wheat during a 12-week energy-restricted dietary intervention in postmenopausal women. *Eur J Clin Nutr*. 2013;67(12):1316-1321.
34. Giacco R, Lappi J, Costabile G, et al. Effects of rye and whole wheat versus refined cereal foods on metabolic risk factors: a randomised controlled two-centre intervention study. *Clin Nutr*. 2013;32(6):941-949.
35. Langkamp-Henken B, Nieves C, Jr., Culpepper T, et al. Fecal lactic acid bacteria increased in adolescents randomized to whole-grain but not refined-grain foods, whereas inflammatory cytokine production decreased equally with both interventions. *J Nutr*. 2012;142(11):2025-2032.
36. Lappi J, Salojarvi J, Kolehmainen M, et al. Intake of whole-grain and fiber-rich rye bread versus refined wheat bread does not differentiate intestinal microbiota composition in Finnish adults with metabolic syndrome. *J Nutr*. 2013;143(5):648-655.
37. Martinez I, Lattimer JM, Hubach KL, et al. Gut microbiome composition is linked to whole grain-induced immunological improvements. *ISME J*. 2013;7(2):269-280.
38. Kristensen M, Toubro S, Jensen MG, et al. Whole grain compared with refined wheat decreases the percentage of body fat following a 12-week, energy-restricted dietary intervention in postmenopausal women. *J Nutr*. 2012;142(4):710-716.
39. Mofidi A, Ferraro ZM, Stewart KA, et al. The acute impact of ingestion of sourdough and whole-grain breads on blood glucose, insulin, and incretins in overweight and obese men. *J Nutr Metab*. 2012;2012:184710.
40. Johnsen NF, Frederiksen K, Christensen J, et al. Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort. *Br J Nutr*. 2015;114(4):608-623.
41. Huang T, Xu M, Lee A, Cho S, Qi L. Erratum: Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals. *BMC Med*. 2015;13:85.
42. Huang T, Xu M, Lee A, Cho S, Qi L. Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals. *BMC Med*. 2015;13:59.
43. Wu H, Flint AJ, Qi Q, et al. Association between dietary whole grain intake and risk of mortality: two large prospective studies in US men and women. *JAMA Intern Med*. 2015;175(3):373-384.
44. Buil-Cosiales P, Zazpe I, Toledo E, et al. Fiber intake and all-cause mortality in the Prevencion con Dieta Mediterranea (PREDIMED) study. *Am J Clin Nutr*. 2014;100(6):1498-1507.
45. Rebello SA, Koh H, Chen C, et al. Amount, type, and sources of carbohydrates in relation to ischemic heart disease mortality in a Chinese population: a prospective cohort study. *Am J Clin Nutr*. 2014;100(1):53-64.
46. Skeie G, Braaten T, Olsen A, et al. Whole grain intake and survival among Scandinavian colorectal cancer patients. *Nutr Cancer*. 2014;66(1):6-13.
47. Bakken T, Braaten T, Olsen A, Kyro C, Lund E, Skeie G. Consumption of Whole-Grain Bread and Risk of Colorectal Cancer among Norwegian Women (the NOWAC Study). *Nutrients*. 2016;8(1).
48. Farvid MS, Eliassen AH, Cho E, Liao X, Chen WY, Willett WC. Dietary Fiber Intake in Young Adults and Breast Cancer Risk. *Pediatrics*. 2016;137(3):e20151226.
49. Gopinath B, Flood VM, Kifley A, Louie JC, Mitchell P. Association Between Carbohydrate Nutrition and Successful Aging Over 10 Years. *J Gerontol A Biol Sci Med Sci*. 2016;71(10):1335-1340.
50. Gopinath B, Flood VM, Burlutsky G, Louie JC, Mitchell P. Association between carbohydrate nutrition and prevalence of depressive symptoms in older adults. *Br J Nutr*. 2016;116(12):2109-2114.
51. Helnaes A, Kyro C, Andersen I, et al. Intake of whole grains is associated with lower risk of myocardial infarction: the Danish Diet, Cancer and Health Cohort. *Am J Clin Nutr*. 2016;103(4):999-1007.
52. Mourouti N, Kontogianni MD, Papavagelis C, et al. Whole Grain Consumption and Breast Cancer: A Case-Control Study in Women. *J Am Coll Nutr*. 2016;35(2):143-149.
53. Nielsen SJ, Trak-Fellermeier MA, Joshupura K, Dye BA. Dietary Fiber Intake Is Inversely Associated with Periodontal Disease among US Adults. *J Nutr*. 2016;146(12):2530-2536.
54. InterAct C. Dietary fibre and incidence of type 2 diabetes in eight European countries: the EPIC-InterAct Study and a meta-analysis of prospective studies. *Diabetologia*. 2015;58(7):1394-1408.
55. Li Y, Hruby A, Bernstein AM, et al. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. *J Am Coll Cardiol*. 2015;66(14):1538-1548.
56. Drake I, Sonestedt E, Gullberg B, et al. Plasma alkylresorcinol metabolites as biomarkers for whole-grain intake and their association with prostate cancer: a Swedish nested case-control study. *Cancer Epidemiol Biomarkers Prev*. 2014;23(1):73-83.
57. Knudsen MD, Kyro C, Olsen A, et al. Self-reported whole-grain intake and plasma alkylresorcinol concentrations in combination in relation to the incidence of colorectal cancer. *Am J Epidemiol*. 2014;179(10):1188-1196.
58. Kyro C, Olsen A, Landberg R, et al. Plasma alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and incidence of colorectal cancer. *J Natl Cancer Inst*. 2014;106(1):djt352.
59. Mostad IL, Langaas M, Grill V. Central obesity is associated with lower intake of whole-grain bread and less frequent breakfast and lunch: results from the HUNT study, an adult all-population survey. *Appl Physiol Nutr Metab*. 2014;39(7):819-828.
60. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. *Gastroenterology*. 2013;145(5):970-977.
61. Daniel CR, Park Y, Chow WH, Graubard BI, Hollenbeck AR, Sinha R. Intake of fiber and fiber-rich plant foods is associated with a lower risk of renal cell carcinoma in a large US cohort. *Am J Clin Nutr*. 2013;97(5):1036-1043.
62. Kyro C, Skeie G, Loft S, et al. Intake of whole grains from different cereal and food sources and incidence of colorectal cancer in the Scandinavian HELGA cohort. *Cancer Causes Control*. 2013;24(7):1363-1374.
63. Parker ED, Liu S, Van Horn L, et al. The association of whole grain consumption with incident type 2 diabetes: the Women's Health Initiative Observational Study. *Ann Epidemiol*. 2013;23(6):321-327.
64. Aarestrup J, Kyro C, Christensen J, et al. Whole grain, dietary fiber, and incidence of endometrial cancer in a Danish cohort study. *Nutr Cancer*. 2012;64(8):1160-1168.

References

65. Torfadottir JE, Valdimarsdottir UA, Mucci L, et al. Rye bread consumption in early life and reduced risk of advanced prostate cancer. *Cancer Causes Control*. 2012;23(6):941-950.
66. Fayet-Moore F, Petocz P, McConnell A, Tuck K, Mansour M. The Cross-Sectional Association between Consumption of the Recommended Five Food Group "Grain (Cereal)", Dietary Fibre and Anthropometric Measures among Australian Adults. *Nutrients*. 2017;9(2).
67. Hansen CP, Overvad K, Kyro C, et al. Adherence to a Healthy Nordic Diet and Risk of Stroke: A Danish Cohort Study. *Stroke*. 2017;48(2):259-264.
68. Ozawa M, Shipley M, Kivimaki M, Singh-Manoux A, Brunner EJ. Dietary pattern, inflammation and cognitive decline: The Whitehall II prospective cohort study. *Clin Nutr*. 2017;36(2):506-512.
69. Rai SK, Fung TT, Lu N, Keller SF, Curhan GC, Choi HK. The Dietary Approaches to Stop Hypertension (DASH) diet, Western diet, and risk of gout in men: prospective cohort study. *BMJ*. 2017;357:j1794.
70. van den Brandt PA, Schulpen M. Mediterranean diet adherence and risk of postmenopausal breast cancer: results of a cohort study and meta-analysis. *Int J Cancer*. 2017;140(10):2220-2231.
71. Mehta RS, Nishihara R, Cao Y, et al. Association of Dietary Patterns With Risk of Colorectal Cancer Subtypes Classified by Fusobacterium nucleatum in Tumor Tissue. *JAMA Oncol*. 2017;3(7):921-927.
72. Satija A, Bhupathiraju SN, Rimm EB, et al. Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies. *PLoS Med*. 2016;13(6):e1002039.
73. Shakersain B, Santoni G, Larsson SC, et al. Prudent diet may attenuate the adverse effects of Western diet on cognitive decline. *Alzheimers Dement*. 2016;12(2):100-109.
74. Boggs DA, Ban Y, Palmer JR, Rosenberg L. Higher diet quality is inversely associated with mortality in African-American women. *J Nutr*. 2015;145(3):547-554.
75. Merle BM, Silver RE, Rosner B, Seddon JM. Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study. *Am J Clin Nutr*. 2015;102(5):1196-1206.
76. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement*. 2015;11(9):1007-1014.
77. Tektonidis TG, Akesson A, Gigante B, Wolk A, Larsson SC. A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: A population-based cohort study. *Atherosclerosis*. 2015;243(1):93-98.
78. Shin S, Sung J, Joung H. A fruit, milk and whole grain dietary pattern is positively associated with bone mineral density in Korean healthy adults. *Eur J Clin Nutr*. 2015;69(4):442-448.
79. Varraso R, Chiuve SE, Fung TT, et al. Alternate Healthy Eating Index 2010 and risk of chronic obstructive pulmonary disease among US women and men: prospective study. *BMJ*. 2015;350:h286.
80. Yang M, Kenfield SA, Van Blarigan EL, et al. Dietary patterns after prostate cancer diagnosis in relation to disease-specific and total mortality. *Cancer Prev Res (Phila)*. 2015;8(6):545-551.
81. Yu D, Sonderman J, Buchowski MS, et al. Healthy Eating and Risks of Total and Cause-Specific Death among Low-Income Populations of African-Americans and Other Adults in the Southeastern United States: A Prospective Cohort Study. *PLoS Med*. 2015;12(5):e1001830; discussion e1001830.
82. Englund-Ogge L, Brantsaeter AL, Sengpiel V, et al. Maternal dietary patterns and preterm delivery: results from large prospective cohort study. *BMJ*. 2014;348:g1446.
83. Hillesund ER, Overby NC, Engel SM, et al. Associations of adherence to the New Nordic Diet with risk of preeclampsia and preterm delivery in the Norwegian Mother and Child Cohort Study (MoBa). *Eur J Epidemiol*. 2014;29(10):753-765.
84. Arthur AE, Peterson KE, Rozek LS, et al. Pretreatment dietary patterns, weight status, and head and neck squamous cell carcinoma prognosis. *Am J Clin Nutr*. 2013;97(2):360-368.
85. Levitan EB, Lewis CE, Tinker LF, et al. Mediterranean and DASH diet scores and mortality in women with heart failure: The Women's Health Initiative. *Circ Heart Fail*. 2013;6(6):1116-1123.
86. Wengreen H, Munger RG, Cutler A, et al. Prospective study of Dietary Approaches to Stop Hypertension- and Mediterranean-style dietary patterns and age-related cognitive change: the Cache County Study on Memory, Health and Aging. *Am J Clin Nutr*. 2013;98(5):1263-1271.
87. Mann KD, Pearce MS, McKeivith B, Thielecke F, Seal CJ. Whole grain intake and its association with intakes of other foods, nutrients and markers of health in the National Diet and Nutrition Survey rolling programme 2008-11. *Br J Nutr*. 2015;113(10):1595-1602.
88. Goletzke J, Buyken AE, Joslowski G, et al. Increased intake of carbohydrates from sources with a higher glycemic index and lower consumption of whole grains during puberty are prospectively associated with higher IL-6 concentrations in younger adulthood among healthy individuals. *J Nutr*. 2014;144(10):1586-1593.
89. Wang H, Lichtenstein AH, Lamon-Fava S, Jacques PF. Association between statin use and serum cholesterol concentrations is modified by whole-grain consumption: NHANES 2003-2006. *Am J Clin Nutr*. 2014;100(4):1149-1157.
90. Montonen J, Boeing H, Fritsche A, et al. Consumption of red meat and whole-grain bread in relation to biomarkers of obesity, inflammation, glucose metabolism and oxidative stress. *Eur J Nutr*. 2013;52(1):337-345.
91. Heikkila HM, Schwab U, Krachler B, Mannikko R, Rauramaa R. Dietary associations with prediabetic states--the DR's EXTRA Study (ISRCTN45977199). *Eur J Clin Nutr*. 2012;66(7):819-824.
92. Schwingshackl L, Hoffmann G, Lampousi AM, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol*. 2017.
93. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2017;105(6):1462-1473.
94. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016;353:i2716.
95. Chen GC, Tong X, Xu JY, et al. Whole-grain intake and total, cardiovascular, and cancer mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr*. 2016;104(1):164-172.
96. Chen J, Huang Q, Shi W, Yang L, Chen J, Lan Q. Meta-Analysis of the Association Between Whole and Refined Grain Consumption and Stroke Risk Based on Prospective Cohort Studies. *Asia Pac J Public Health*. 2016;28(7):563-575.
97. Lei Q, Zheng H, Bi J, et al. Whole Grain Intake Reduces Pancreatic Cancer Risk: A Meta-Analysis of Observational Studies. *Medicine (Baltimore)*. 2016;95(9):e2747.

References

98. Li B, Zhang G, Tan M, et al. Consumption of whole grains in relation to mortality from all causes, cardiovascular disease, and diabetes: Dose-response meta-analysis of prospective cohort studies. *Medicine (Baltimore)*. 2016;95(33):e4229.
99. Wei H, Gao Z, Liang R, Li Z, Hao H, Liu X. Whole-grain consumption and the risk of all-cause, CVD and cancer mortality: a meta-analysis of prospective cohort studies. *Br J Nutr*. 2016;116(3):514-525.
100. Zong G, Gao A, Hu FB, Sun Q. Whole Grain Intake and Mortality From All Causes, Cardiovascular Disease, and Cancer: A Meta-Analysis of Prospective Cohort Studies. *Circulation*. 2016;133(24):2370-2380.
101. Chanson-Rolle A, Meynier A, Aubin F, et al. Systematic Review and Meta-Analysis of Human Studies to Support a Quantitative Recommendation for Whole Grain Intake in Relation to Type 2 Diabetes. *PLoS One*. 2015;10(6):e0131377.
102. Fang L, Li W, Zhang W, Wang Y, Fu S. Association between whole grain intake and stroke risk: evidence from a meta-analysis. *Int J Clin Exp Med*. 2015;8(9):16978-16983.
103. Hollaender PL, Ross AB, Kristensen M. Whole-grain and blood lipid changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies. *Am J Clin Nutr*. 2015;102(3):556-572.
104. Tang G, Wang D, Long J, Yang F, Si L. Meta-analysis of the association between whole grain intake and coronary heart disease risk. *Am J Cardiol*. 2015;115(5):625-629.
105. Tosh SM, Chu Y. Systematic review of the effect of processing of whole-grain oat cereals on glycaemic response. *Br J Nutr*. 2015;114(8):1256-1262.
106. Kim Y, Je Y. Dietary fiber intake and total mortality: a meta-analysis of prospective cohort studies. *Am J Epidemiol*. 2014;180(6):565-573.
107. Thielecke F, Jonnalagadda SS. Can whole grain help in weight management? *J Clin Gastroenterol*. 2014;48 Suppl 1:S70-77.
108. Thies F, Masson LF, Boffetta P, Kris-Etherton P. Oats and CVD risk markers: a systematic literature review. *Br J Nutr*. 2014;112 Suppl 2:S19-30.
109. Thies F, Masson LF, Boffetta P, Kris-Etherton P. Oats and bowel disease: a systematic literature review. *Br J Nutr*. 2014;112 Suppl 2:S31-43.
110. Aune D, Norat T, Romundstad P, Vatten LJ. Whole grain and refined grain consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. *Eur J Epidemiol*. 2013;28(11):845-858.
111. Pol K, Christensen R, Bartels EM, Raben A, Tetens I, Kristensen M. Whole grain and body weight changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies. *Am J Clin Nutr*. 2013;98(4):872-884.
112. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. *J Nutr*. 2012;142(7):1304-1313.

Clinical Trials

Cooper et al.¹, *Nutrients*, 9 (2), 2017.

The effects of moderate whole grain consumption on fasting glucose and lipids, gastrointestinal symptoms, and microbiota

Introduction:

- Whole grain (WG) consumption is associated with decreased risk of type 2 diabetes and other major chronic diseases. However, inconsistent literature exists on whole grain consumption in association with alteration of glucose homeostasis, reduction of total cholesterol and low density lipoprotein (LDL).
- Alteration of the gut microbiota is proposed as a possible reason for health benefits associated with increased WG consumption.
- This study examines the effect of a 6-week intervention of WG diet vs. refined grains (RG) diet on parameters of health among healthy, habitual non-WG consumers.

Methods:

- 46 subjects were given adequate servings of either WG or RG products based on their caloric needs and asked to keep records of grain consumption, bowel movements, and GI symptoms weekly.
- Measurements of body composition, fecal microbiota, fasting blood glucose, total cholesterol, high-density lipoprotein (HDL), LDL, and triglycerides were made at baseline and 6 weeks post intervention.

Results:

- Significant decreases in total cholesterol, LDL, and non-HDL cholesterol were seen after the WG treatments but were not observed in the RG treatment.
- During week 6, bowel movement frequency increased with increased WG consumption.
- No significant differences in microbiota were seen between baseline and post intervention, although abundance of order *Erysipelotrichales* increased in RG subjects who ate more than 50% of the RG market basket products.

Discussion:

- Increasing consumption of WG can alter parameters of health especially total, LDL and non-HDL cholesterol.
- More research is needed to better elucidate the relationship between the amount consumed and the health-related outcomes.

Clinical Trials

Karl et al.², *Am J Clin Nutr*, 105 (3):589-599, 2017.

Substituting whole grains for refined grains in a 6-week randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women

Introduction:

- Inconsistent literature exists for the effect of whole grains (WG) on the regulation of energy balance.
- This study examines the effects of substituting WG for refined grains (RG) on energy-metabolism metrics and glycemic control.

Methods:

- Eighty-one men and postmenopausal women aged 40-64 years old were randomly assigned to consume 1 of 2 weight-maintenance diets for 6 weeks after 2 weeks' run-in period.
- The diet was either a whole-grain-rich diet with 207 ± 39 g whole grains plus 40 ± 5 g dietary fiber/day, or refined grain-based diet with 0 g whole grains plus 21 ± 3 g dietary fiber/day.
- Energy metabolism and body-composition metrics, appetite, markers of glycemic control, and gut microbiota were measured at the 2nd and 8th week.

Results:

- A biomarker of WG intake, plasma alkylresorcinols, increased in the WG but not in the RG group.
- Changes in the resting metabolic rate (RMR) (43 ± 25 kcal/day, $P=0.04$), stool weight (76 ± 12 g/day, $P<0.0001$) and stool energy content (57 ± 17 kcal/day; $P=0.003$), but not stool energy density, were higher in the WG.
- The favorable energetic effects in the WG group translated into a 92-kcal/day higher net daily energy loss compared with that of the RG group.
- There was a decreasing trend of the prospective consumption ($P=0.007$) and glycaemia ($P=0.10$) after an oral-glucose-tolerance test in the WG group compared to the RG group.

Discussion:

- This study is the first study examining the effects of WG compared with RG on energy metabolism during weight stability.
- This study provides new evidence of the energetic benefits and improved oral glucose tolerance associated with whole grain intake in the diet.
- Findings from this study may help explain the current epidemiologic associations between whole grain consumption and reduced body weight and adiposity.

Clinical Trials

Kim et al.³, *Metabolism*, 68:173-183, 2017.

Consumption of red and processed meat and refined grains for 4 weeks decreases insulin sensitivity in insulin-resistant adults: a randomized crossover study

Introduction:

- Dietary intake of red and processed meat and refined grains (HMD) is associated with increased risk of type 2 diabetes.
- The HMD-type diet is hypothesized to lower insulin sensitivity compared to a diet high in whole grains, nuts, dairy and legumes with no red meat (HWD).

Methods:

- Forty-nine subjects without diabetes received two 4-week weight-stable dietary interventions in a randomized crossover design.
- Participants were allocated to either a diet high in red and processed meat and refined grains (HMD) or a diet high in whole grains, nuts, legumes, dairy and devoid of red and processed meat (HWD) for 4 weeks, and were crossed over to the alternative diet for 4 weeks.
- Insulin sensitivity index (ISI) was calculated by dividing the constant glucose infusion rate (Ginf) by steady-state glucose (Gss) and normalizing this ratio to steady-state serum insulin (Iss) and expressed as glucose clearance per plasma insulin concentration: $ISI_{LDIGIT} = Ginf / (Gss * Iss)$.
- Insulin sensitivity under fasting conditions was calculated with homeostasis model assessment of insulin resistance (HOMA-IR) through the formula: $HOMA = (fasting\ insulin\ (\mu U/ml) \times fasting\ glucose\ (mmol/l)) / 22.5$.
- Serum C-peptide concentration during the first 30 minutes was measured to evaluate insulin secretion.

Results:

- Subjects fell into two distinct groups: very low insulin response in the $LDIGIT_{120-150min}$ on HMD (Group 1 < 56 pmol/L, n=24), and those with relatively normal insulin responses (Group 2 > 56 pmol/L, n=25). Group 2 had significantly decreased ISI.
- No significant difference in fasting glucose, fasting insulin and HOMA-IR was observed.
- No significant differences in fasting C-peptide were observed.
- ISI was highly correlated with BMI, fat mass and physical activity levels.

Discussion:

- This study is the first weight-stable intervention study evaluating the effect of HWD on insulin sensitivity.
- Further study is needed with prospectively enrolled insulin-resistant subjects.

Clinical Trials

Lee et al.⁴, *Br J Nutr*, 116(112):2139-2149, 2016.

Effects of whole-grain rye porridge with added inulin and wheat gluten on appetite, gut fermentation and postprandial glucose metabolism: a randomised, crossover, breakfast study

Introduction:

- Whole grain rye foods sometimes decrease appetite, insulin and glucose responses.
- This study aimed to investigate whether the appetite-suppressing effects of whole grain rye porridge could be enhanced by replacing part of the rye with fermented dietary fiber and plant protein, and to explore the role of gut fermentation on appetite and metabolic responses over 8 hours.

Methods:

- 21 healthy adults participated in a randomized, extended postprandial, single-blind, crossover study with six breakfast meals served in a random order with a washout period of ≥ 5 days.
- Six isoenergetic meals included five whole grain rye porridge meals and one refined wheat bread (WB) meal as a control. Among the five whole grain meals, two contained 40 g of rye flakes (RP40) and 55 g of rye flakes (RP55), respectively, while three contained 40 g of rye flakes with 15 g of a combination of inulin and wheat gluten.
- Standardized lunch and an ad libitum dinner were served 4 and 8 hours later.
- Appetite, breath hydrogen and methane, glucose, insulin and glucagon-like peptide-1 (GLP-1) responses were measured over 8 hours.

Results:

- Before lunch, the 55 g rye porridges lowered hunger by 20% and desire to eat by 22% and increased fullness by 29% compared with WB.
- Breath hydrogen increased proportionally to dietary fiber content.
- Plasma glucose after lunch was 6% lower after the 55 g rye porridges compared with WB and correlated to breath hydrogen.
- No differences were observed in ad libitum food intake, insulin or GLP-1.

Discussion:

- When replacing part of the rye with inulin and gluten compared with plain rye porridges, there was no further increase in satiety.
- Intake of whole grain rye porridge leads to a dose-dependent increase in gut fermentation, and an attenuated plasma glucose concentration after a second meal, but without a corresponding reduction in insulin and GLP-1 response.
- Further studies are needed to establish causality between appetite, gut fermentation and hormonal responses.

Clinical Trials

Vanegas et al.⁵, *AM J Clin Nutr*, 105(3):635-650, 2017.

Substituting whole grains for refined grains in a 6-week randomized trial has a modest effect on gut microbiota and immune and inflammatory markers of healthy adults

Introduction:

- Observational studies have suggested inverse associations between whole grain (WG) consumption and inflammation.
- Studies with interventional study design are limited.
- This study was aimed to evaluate the effects of diets rich in WG compared with refined grains (RG) on immune and inflammatory responses, gut microbiota, and microbial products in healthy adults while maintaining body weight.

Methods:

- 49 men and 32 postmenopausal women were randomly assigned to either weight-maintenance RG or WG group for 6 weeks after a 2-week run-in period, in a randomized, controlled, parallel-design human trial.
- Stool, 12-hr fasting blood and saliva samples were collected and delayed-type hypersensitivity (DTH) tests were conducted at baseline and again at the end of the dietary intervention phase.

Results:

- The WG group had increased plasma total alkylresorcinols, stool weight, stool frequency, and short-chain fatty acid (SCFA) producer *Lachnospira* but decreased pro-inflammatory *Enterobacteriaceae*.
- Changes in stool acetate and total SCFAs were more obvious in the WG group.
- *Lachnospira* was positively associated with acetate (P=0.002) or butyrate (P=0.005).
- There were a higher percentage of terminal effector memory T cells (P=0.03) and LPS-stimulated ex vivo production of tumor necrosis factor- α (P=0.04) in the WG group, which were positively associated with plasma alkylresorcinol levels.

Discussion:

- Short-term dietary intake of WG (without weight loss effect) increases stool weight and frequency and has modest positive effects on gut microbiota, SCFAs, effector memory T cells, and the acute innate immune response.
- Future studies using other WGs with higher soluble fiber and/or phenolic compounds are needed.
- Future studies using WGs with and without weight loss effects are needed.

Clinical Trials

Ampatzoglou et al.⁶, *Eur J Nutr*, 55(1):183-195, 2016.

Effects of increased wholegrain consumption on immune and inflammatory markers in healthy low habitual wholegrain consumers

Introduction:

- Whole grain (WG) consumption has been associated with decreased risk of cardiovascular disease, but clinical data on how whole grain consumption could affect inflammation and immune functions are limited and controversial.
- This study was aimed to evaluate the effect of increasing WG consumption to ≥ 80 g/day on markers of inflammation, glucose metabolism and on phenotypic and functional aspects of the immune system.

Methods:

- 12 men and 21 women (aged 40-65 years) with habitual low WG consumption were identified through use of food frequency questionnaires and subsequently completed 3-day food diaries (3DFD).
- Subjects were randomized into consuming either diets high in WG (>80 g/day) or diets low in WG (<16 g/day, refined-grain (RG)) in a crossover study with two 6-week intervention periods separated by a 4-week washout period.
- Specific dietary advice and provision of a range of cereal food products were used to promote adherence.
- Fasting blood and saliva samples were collected before and after each of the intervention periods.

Results:

- During the WG intervention, WG consumption reached as high as 168 g/day with a significant increase in plasma alkylresorcinols and total fiber intake.
- During the WG intervention, there were trends for lower ex vivo activation of CD4+ T cells and circulating concentrations of IL-10, C-reactive protein, C-peptide, insulin and plasminogen activator inhibitor-1; the % of CD4+ central memory T cells and circulating levels of adiponin tended to increase as well.

Discussion:

- Increasing WG consumption doesn't effect phenotypic or functional immune parameters, markers of inflammation or metabolic markers.
- Future study design needs to consider health status of subjects, statistical power, physical and structural properties of WG and processing conditions.

Clinical Trials

Kirwan et al.⁷, *J Nutr*, 146(11):2244-2251, 2016.

A whole-grain diet reduces cardiovascular risk factors in overweight and obese adults: a randomized controlled trial

Introduction:

- Increased dietary intake of whole grain (WG) may protect against cardiovascular disease (CVD).
- The objective of this study was to evaluate the efficacy of WG compared with refined grains (RG) on body composition, hypertension, and related mediators of CVD in overweight and obese adults.

Methods:

- 40 overweight or obese men and women (aged <50 years) with no known history of CVD were enrolled in a double-blinded, randomized, controlled crossover trial.
- WG or RG diets (50 g/1000 kcal in each diet) matched on macronutrient composition were provided for two 8-week periods, with a 10-week washout period.
- Outcome measurements included blood pressure, body composition, blood lipids and adiponectin, markers of inflammation and glycaemia.

Results:

- Thirty-three participants (% female=82%) completed the trial.
- Decreases in diastolic blood pressure (DBP) were -5.8 mmHg after the WG diet and -1.6 mmHg after the RG diet (P=0.01).
- Decreases in plasma adiponectin were -0.1 after the WG diet and -1.4 after the RG diet (P=0.05).
- No differences were observed between the two diet periods on reductions in body weight, fat loss, systolic blood pressure, total and LDL cholesterol.

Discussion:

- Improvement in DBP was >3-fold in overweight and obese adults when they consumed a WG compared with a RG diet.
- DBP predicts mortality in adults aged <50 years, therefore, increased WG intake may provide a functional approach to control hypertension and reduce vascular-related morbidity and mortality.

Clinical Trials

Li et al.⁸, *Nutrients*, 8(9), 2016.

Short- and long-term effects of wholegrain oat intake on weight management and glucolipid metabolism in overweight type-2 diabetics: a randomized control trial

Introduction:

- Effective management of overweight and obese type 2 diabetes (T2DM) needs appropriate diet to achieve glycemic control and weight reduction.
- The study aimed to evaluate the short- and long-term effects of oat intake and develop a dietary plan for overweight T2DM patients.

Methods:

- A subgroup of 298 overweight T2DM subjects received a 30-day centralized intervention and 1-year free-living follow-up (scheduled clinical checks were performed every 3 months).
- Subjects were randomly assigned to one of four groups:
 1. The usual care group (n=60) receiving no intervention;
 2. The healthy diet group (n=79) receiving a low-fat and high-fiber diet;
 - 3+4. The 50 g oats group (n=80) and 100 g oats group (n=79) receiving the “healthy diet” with the same amount of cereals replaced by 50 g and 100 g oats respectively.
- At the end of the 30-day intervention and at the end of the 1-year follow-up, outcome measurements included anthropometric measurements, body fat % and visceral fat index, changes of FPG (fasting plasma glucose), PPG (postprandial plasma glucose), HbA1c (glycosylated hemoglobin), HOMA-IR (homeostasis model assessment of insulin resistance), TC (total cholesterol), TG (total triglycerides), and LDL-c (low-density lipoprotein cholesterol).

Results:

- Compared to the healthy diet group, the 50 g oats group had a bigger reduction in PPG (mean difference (MD): -1.04 mmol/L) and TC (MD: -0.24 mmol/L).
- The 100 g oats group had a bigger reduction in PPG (MD: -1.48 mmol/L), HOMA-IR (MD: -1.77 mU·mol/L²), TC (MD: -0.33 mmol/L) and LDL-c (MD: -0.22mmol/L).
- At the 1-year follow-up, the 100 g oats group had greater effects in reducing weight (MD: -0.89 kg), HbA1c (MD: -0.64) and TG (MD: -0.70 mmol/L).

Discussion:

- Short- and long-term oat intake had beneficial effects on controlling blood glucose, lowering blood lipids and reducing weight.
- This study provided evidence recommending oats as a whole grain selection for overweight T2DM patients.

Clinical Trials

McKeown et al.⁹, *Eur J Nutr*, 55(3):1235-1244, 2016.

Comparison of plasma alkylresorcinols (AR) and urinary AR metabolites as biomarkers of compliance in a short-term, whole-grain intervention study

Introduction:

- AR are phenolic lipids present in the bran of wheat and rye.
- This study was aimed to examine plasma AR and urinary AR metabolites in response to WG wheat consumption.

Methods:

- 19 subjects (10 males and 9 females) participated in a 1-week per diet randomized crossover study with a 2-week washout period.
- Subjects were randomized into either 3 servings (48 g) or 6 servings (96 g) of WG wheat daily introduced into their regular diet for 1 week.
- Fasting blood and 24-hr urine were collected before and after each intervention.
- Plasma AR homologues (C19:0, C21:0, C23:0) were quantified by GC-MS. Urinary AR metabolites [3,5-dihydroxybenzoic acid and 3-(3,5-dihydroxyphenyl)-propanoic acid] were determined using HPLC with electrochemical detection.

Results:

- Urinary total AR metabolites were significantly higher after 6 servings of WG wheat compared with 3 servings of WG wheat (56 vs. 32 $\mu\text{mol/day}$, $P < 0.001$), independent of age, sex, energy intake and baseline urinary AR metabolite concentration.
- Plasma total AR tended to be higher after 6 compared with 3 servings of WG wheat (103.0 vs. 86.9 nmol/L), but this difference was not significant ($P = 0.42$).

Discussion:

- Urinary AR metabolites from 24-hr urine collections may be useful as biomarkers of compliance in intervention studies of WG wheat compared to plasma AR.

Clinical Trials

Nelson et al.¹⁰, *Food Chem*, 194:495-502, 2016.

Effects of malted and non-malted whole-grain wheat on metabolic and inflammatory biomarkers in overweight/obese adults: a randomised crossover pilot study

Introduction:

- Whole grains (WG) contain many bioactive compounds, which synergistically attenuate obesity-related metabolic dysfunctions.
- Malting is a process that incorporates controlled germination. Malted grain is considered a type of germinated (sprouted) grain containing increased nutritional, polyphenol and antioxidant contents but decreased anti-nutritional factors such as phytates, along with less starch and increased sugars.
- Germination/malting may increase WG bioactives including polyphenols, however, the difference of biological effects comparing non-germinated vs. germinated WG is not known.
- This study aimed to explore differences of polyphenols and biological effects between malted-wheat (MLT) and whole-grain wheat (CON) breakfast biscuit cereal.

Methods:

- 10 overweight or obese adults were enrolled in a 2x4-week (2 week washout) double-blind, randomized, crossover trial.
- Australian Standard White Wheat was used to prepare control breakfast biscuits (CON), and malted wheat was used to prepare the malted-wheat breakfast biscuits.
- Pre and post intervention biometric measurements (height, weight, waist and hip circumference, blood pressure) and blood biomarkers (blood glucose, insulin, cholesterol, triglycerides, plasma antioxidants, malondialdehyde, and high sensitivity C-reactive protein) were measured.

Results:

- MLT contained greater polyphenol diversity than CON.
- Diastolic blood pressure reduced significantly with time and low-density lipoprotein increased slightly over time ($P < 0.05$) with both interventions.
- A significant time*cereal effect was found for insulin resistance, decreasing with CON and increasing with MLT intervention.
- No other significant metabolic or inflammatory differences were found.

Discussion:

- Malting may provide a natural, practical nutritional enhancement of whole grains.
- The study is short in duration; future studies utilizing increased quantities over long periods may provide more information on the potential of malted (sprouted) grains in attenuating obesity-related metabolic dysfunctions, oxidative stress and inflammation.

Clinical Trials

Sawicki et al.¹¹, *Nutrients*, 8(12), 2016.

Phytochemical pharmacokinetics and bioactivity of oat and barley flour: a randomized crossover trial

Introduction:

- Dietary fiber is not the only component contributing to the health benefits of whole grains. Other health-beneficial ingredients are also concentrated in the outer bran layer, including alkylresorcinols, lignans, phenolic acids, phytosterols and tocopherols.
- This study examines the acute bioavailability and pharmacokinetics of the major phytochemicals found in barley and oats.

Methods:

- 13 healthy adults with a BMI of 27-35.9 kg/m² were enrolled in a randomized, three-way crossover trial with one-week washout periods between each intervention.
- Subjects were randomized to receive muffins made with either 48 g whole oat flour, whole barley flour, or refined wheat flour plus cellulose (control).
- Oral glucose tolerance, plasma phytochemical concentrations, glucose and insulin responses, biomarkers of antioxidant activity, lipid peroxidation, inflammation and vascular remodeling were measured.

Results:

- No significant effect on acute bioavailability or pharmacokinetics of major phytochemicals was found.
- No significant differences in the bioavailability or postprandial effects between whole oat and whole barley compared to the control was found.
- The source of whole grains did not attenuate the postprandial response of markers of gluco-regulation and insulin sensitivity, inflammation, nor vascular remodeling after administering a glucose bolus challenge concurrently.

Discussion:

- Reasons for the null results may include the inclusion criteria for the subjects, dose of the whole grains, and concurrent acute administration of whole grains with the glucose bolus.
- Future studies should consider about using whole grain varieties with minimal processing.

Clinical Trials

Sereni et al.¹², *Int J Food Sci Nutr*, 68(1):97-103, 2017.

Cardiovascular benefits from ancient grain bread consumption: findings from a double-blinded randomized crossover intervention trial

Introduction:

- Ancient grain varieties have been reported as potential health-promoting food sources due to their higher content of beneficial nutrients such as antioxidant molecules, vitamins and minerals.
- This study's research group had published results previously showing that the presence and quantity of beneficial components derived from the grain are dependent on the type of grain and aspects relating to the production, storage and transformation of the grain.
- This study extended previous work, aiming to test the beneficial effects of consumption of ancient grain varieties using novel risk parameters and to investigate differences between varieties derived from either organic or conventional agriculture on the cardiometabolic risk profile.

Methods:

- 45 clinically healthy subjects were recruited in this randomized, double-blinded, crossover dietary intervention trial with 3 different interventions, each lasting for 8 weeks.
- During the first intervention, participants were randomly assigned to receive bread made from the ancient wheat variety "Verna", from either organic (n=22) or conventional (n=23) cultivation.
- During the second intervention, all participants were allowed to eat the modern wheat variety "Blasco".
- During the third intervention, all participants were assigned to consume the ancient wheat varieties "Gentil Rosso" and "Autonomia B", both cultivated under conventional agriculture.
- Blood samples were taken at baseline and at the end of each intervention phase for measurements of lipid variables, blood glucose, minerals and serum electrolytes, Endothelial Progenitor Cells (EPCs), and Circulating Progenitor Cells (CPCs).

Results:

- During the first intervention phase ("Verna" ancient wheat), blood glucose, total cholesterol and LDL-cholesterol significantly decreased, and potassium and sodium significantly increased. No significant differences in the biochemical parameters were found between groups with different cultivation methods.
- No significant differences in the biochemical parameters were found during the second intervention, with consumption of a modern variety of wheat.
- During the third phase, total cholesterol, and LDL significantly decreased with "Gentil Rosso" (an ancient wheat).
- A significant increase in circulating EPCs was reported for the ancient "Verna" variety of wheat.

Discussion:

- Dietary consumption of bread obtained from ancient wheat varieties was effective in reducing cardiovascular risk factors.

Clinical Trials

Vetrani et al.¹³, *Nutrition*, 32(2):217-221, 2016.

Effects of whole-grain cereal foods on plasma short chain fatty acid concentrations in individuals with the metabolic syndrome

Introduction:

- It is hypothesized that one of the mechanisms underlying the association between habitual whole grain (WG) intake and lower risk of cardiometabolic diseases is through short-chain fatty acids (SCFAs), which are derived from dietary fiber fermentation by gut microbiota.
- This study is aimed to evaluate whether a WG wheat-based diet may increase SCFA concentrations, and to identify associations between SCFAs and metabolic changes.

Methods:

- 54 subjects were enrolled in a 12-week dietary intervention trial based on WG or refined cereal products.
- Pre- and post-intervention plasma glucose, insulin, triacylglycerol, inflammatory markers (hs-CRP, IL-1 α , IL-6, and TNF- α), and SCFAs concentrations were measured.

Results:

- In the WG group, post-intervention fasting plasma propionate concentrations were higher than baseline.
- The absolute changes (post-intervention minus baseline) of fasting plasma propionate concentrations were significantly different between the two groups (P=0.048).
- The absolute changes of fasting plasma propionate concentrations correlated with cereal fiber intake (r=0.358, P=0.023).
- Postprandial insulin was significantly decreased in the group having the absolute changes of fasting propionate concentration above the median value (0.0500 μ mol/L).

Discussion:

- A 12-week WG wheat-based diet increases fasting plasma propionate produced by colonic fermentation, suggesting WG wheat foods may promote colonic fiber fermentation.
- This increase correlates with cereal fiber intake and is associated with lower postprandial insulin concentrations.

Clinical Trials

Ampatzoglou et al.¹⁴, *J Nutr*, 145(2):215-221, 2015.

Increased whole grain consumption does not affect blood biochemistry, body composition, or gut microbiology in healthy, low-habitual whole grain consumers

Introduction:

- Whole grain (WG) consumption has been associated with decreased risk of cardiovascular disease (CVD), but how the whole grain consumption could affect CVD risk markers is unclear.
- This study was aimed to assess the impact of increasing WG consumption to at least 80 g/day on overall dietary intake, body composition, blood pressure (BP), blood lipids, blood glucose, gastrointestinal microbiology and gastrointestinal symptoms among healthy, middle-aged adults with habitual low WG intake (< 24 g/day).

Methods:

- 12 men and 21 women (aged 40-65 years) with habitual low-moderate WG consumption were identified through use of food frequency questionnaires and subsequently completed 3-day food diaries (3DFD).
- Subjects were randomized into consuming either diets high in WG (>80 g/day) or diets low in WG (<16 g/day, refined-grain (RG)) in a crossover study with 6-week intervention periods separated by a 4-week washout.
- Specific dietary advice and provision of a range of cereal food products were used to promote adherence.
- The 3DFDs, diet compliance diaries, and plasma alkylresorcinols were used to verify compliance.

Results:

- During WG intervention, WG consumption increased from 28g/day to 168 g/day with a significant increase in plasma alkylresorcinols and total fiber intake.
- No significant effects on studied variables were found.
- There were trends of increased 24-h fecal weight (P=0.08), reduced body weight (P=0.10) and BMI (P=0.08) during the WG intervention vs. RG period.

Discussion:

- A combination of dietary advice and provision of commercially available food items enabled subjects with habitual low intake of WG to increase their WG intake.
- Few effects were found on blood biochemical markers, body composition, BP, fecal measurements or gut microbiology.
- Study methodology, design, type and processing of the WGs are key determinants of study outcomes.

Clinical Trials

Hanhineva et al.¹⁵, *J Nutr*, 145(1):7-17, 2015.

Nontargeted metabolite profiling discriminates diet-specific biomarkers for consumption of whole grains, fatty fish, and bilberries in a randomized controlled trial

Introduction:

- Non-targeted metabolite profiling offers examination of a wide range of metabolites, and may be useful for identifying altered metabolic biomarkers caused by dietary intervention.
- The Nordic diet is characterized by many health-beneficial food items including whole grains, berries, root vegetables, and fatty fish.
- This study examined the effects of dietary modifications through increasing consumption of whole grains, fatty fish, and bilberries on plasma metabolite profiles.

Methods:

- 106 participants with features of metabolic syndrome were enrolled in a 12-week parallel-arm intervention.
- Participants were randomly assigned to 3 dietary interventions:
 - 1) whole grain products, fatty fish, and bilberries [healthy diet (HD)];
 - 2) a whole-grain-enriched diet with the same grain products as in the HD intervention but with no change in fish or berry consumption; and
 - 3) refined-wheat breads and restrictions on fish and berries (control diet).
- Nontargeted LC-MS-based metabolite profiling analysis was performed on 106 samples at the baseline and 106 samples at the end of the study.

Results:

- Both intervention groups had increased signals of glucuronidated alk(en)-ylresorcinols, which correlated significantly with whole grains ($P_{corr} < 0.05$).
- The HD intervention increased signals for furan fatty acids [3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF)], hippuric acid, and various lipid species incorporating polyunsaturated fatty acids ($P_{corr} < 0.05$).
- Plasma CMPF correlated significantly with fish intake, not with other food intakes ($r = 0.47$, $P < 0.001$).

Discussion:

- This study identified novel plasma metabolite biomarkers associated with health-beneficial food items included in the Nordic diet.
- CMPF was a highly specific biomarker for fatty fish intake.
- Glucuronidated alk(en)-ylresorcinols correlated with whole grain consumptions.

Clinical Trials

Santaliestra-Pasias et al.¹⁶, *Int J Food Sci Nutr*, 67(5):562-570, 2015.

Effect of two bakery products on short-term food intake and gut-hormones in young adults: a pilot study

Introduction:

- Obesity is a major health problem and one approach to control obesity is through consumption of food with a high satiety effect.
- Satiating foods have many potential health benefits including providing appetite control strategies, offering pleasure and satisfaction associated with low-energy/healthier versions of foods.
- This study aims to compare the effect of a whole grain bread vs. a conventional bread consumed as a mid-morning snack on appetite and energy intake, satiety and regulation of satiety gut-hormones.

Methods:

- 11 university students (81.2% females) were included in the analyses of a randomized, controlled crossover pilot study of a conventional or whole grain bread as a mid-morning snack, with a 7-day washout period.
- During the two testing days, satiety questionnaires, blood sample collection and consumption of standardized breakfast, mid-morning test-snacks and ad libitum lunch were completed.
- Hematology and biochemical biomarkers and several gut-hormones were analyzed, and satiety was assessed using a Visual Analogue Scale (VAS).

Results:

- The consumption of whole grain bread increased satiety perception, decreased the remaining energy intake during the testing day, and decreased the postprandial response of peptide YY ($P < 0.005$).
- No effect was observed with the other gut hormones.

Discussion:

- This study suggests that whole grain bread improved satiety and influenced the compensation effect after the test bread consumption.
- Future research should focus on the fiber type to evaluate the relationship between carbohydrates and short- and long-term appetite control.

Clinical Trials

Vitaglione et al.¹⁷, *Am J Clin Nutr*, 101(2):251-261, 2015.

Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber

Introduction:

- Epidemiologic studies show that whole-grain (WG) consumption is associated with lower risk of chronic diseases, potentially through the biological mechanisms of WG wheat polyphenols.
- No previous intervention study had been done to study the bioavailability of WG polyphenols and their biological roles in preventing chronic diseases.
- This study aimed to examine circulating concentration, excretion, and the physiologic role of WG wheat polyphenols in adults with unhealthy dietary and lifestyle behaviors.

Methods:

- 80 healthy overweight/obese adults with habitual unhealthy lifestyles (low intake of fruit and vegetables; sedentary) participated in a placebo-controlled, parallel-arm randomized trial.
- Participants replaced precise portions of refined wheat (RW) with a fixed amount of selected WG wheat or RW products for 8 weeks.
- A 100% WG wheat product was used in this study, two refined wheat products were selected as the placebo.
- Blood, urine, feces, and anthropometric and body composition measures were collected at baseline and every 4 weeks.
- Laboratory assessments of phenolic acids in biological samples, plasma markers of metabolic disease and inflammation, and fecal microbiota composition were performed.

Results:

- There was a 4-fold increase of serum dihydroferulic acid (DHFA) and a 2-fold increase in ferulic acid (FA) in the WG group while no changes were found in the RW group.
- Urinary FA concentrations at 8 weeks doubled the baseline concentrations in the WG group.
- Plasma tumor necrosis factor- α (TNF- α) levels reduced at 8 weeks and interleukin (IL)-10 levels increased only after 4 weeks with WG compared with RW (P=0.04).
- No significant changes in plasma metabolic disease biomarkers were found, but there was a trend toward lower plasma plasminogen activator inhibitor 1 with higher excretion of FA and DHFA in the WG group.
- Fecal FA was associated with baseline low *Bifidobacteriales* and *Bacteroidetes* abundances, and correlated with increased *Bacteroidetes* and *Firmicutes* but reduced *Clostridium* after WG consumption. TNF- α correlated with increased *Bacteroides* and *Lactobacillus*.
- No effect was found on anthropometric measurements and body composition.

Discussion:

- WG wheat consumption increased excreted FA and circulating DHFA in overweight/obese adults.
- WG consumption could modify gut microbiota and further influence fecal FA.
- An isocaloric dietary replacement of RW products with 70 g WG wheat can boost a positive immune response and decrease the risk of chronic disease development.

Clinical Trials

Wu et al.¹⁸, *Eur J Clin Nutr*, 69(11):1244-1248, 2015.

Alkylresorcinols in adipose tissue biopsies as biomarkers of whole-grain intake: an exploratory study of responsiveness to advised intake over 12 weeks

Introduction:

- Alkylresorcinols (ARs) have been suggested as biomarkers of whole grain wheat and rye intake.
- Plasma AR concentrations are short in half-life. Therefore, more stable long-term biomarkers are needed.
- This study aimed to evaluate the AR concentrations in adipose tissue biopsies as potential long-term biomarkers for whole-grain intake.

Methods:

- This study used biological samples and data of 27 participants from a 12-week randomized parallel-group dietary intervention study on whole grain-enriched diet (WGDG) vs. refined grain diet (RDG).
- Blood samples and adipose tissue were collected at baseline and after 12 weeks.

Results:

- Both adipose tissue AR concentrations and plasma AR concentrations did not change after 12 weeks in the WGDG group, as no significant increase in whole-grain intake was observed. (Both groups already included some level of whole grain consumption in their pre-intervention habitual diet.)
- Both adipose tissue AR concentrations and plasma AR concentrations were significantly lower than baseline in the RDG group, as this group had decreased whole-grain intake.
- Plasma and adipose tissue AR concentrations were significantly higher in the WGDG than in the RDG group, and significantly correlated with average whole-grain intake from food records.

Discussion:

- Adipose tissue AR concentrations responded to reduced intake of whole grain over 12 weeks.
- Compared to plasma AR, adipose tissue AR concentrations were highly correlated with whole grain intake and have been shown as a promising long-term biomarker of whole grain wheat and rye intake.
- More studies are needed to investigate the turnover rate, non-dietary determinants and the variation in AR adipose tissue among larger free-living populations.

Clinical Trials

Durazzo et al.¹⁹, *Int J Food Sci Nutr*, 65(5):637-645, 2014.

Effects of consumption of whole grain foods rich in lignans in healthy postmenopausal women with moderate serum cholesterol: a pilot study

Introduction:

- Lignans are among a group of cereal phytochemicals that may explain the health benefits associated with higher amounts of whole grain consumption.
- Lignans are a class of secondary plant metabolites that belong to the group of diphenolic compounds derived from the combination of two phenylpropanoid C6–C3 units at the β and β' carbon atoms.
- This study aimed to investigate the effect of whole grain foods rich in lignans on plasma and urinary excretion of enterolignans, biomarkers of lipid metabolism and immunological and antioxidant status in postmenopausal women with moderate serum cholesterol level.

Methods:

- 13 subjects completed a randomized double-blind crossover study.
- The subjects consumed whole grain foods high in lignans (30 g/d of breakfast cereals or biscuits, etc., 80 g/d of whole grain pasta) or refined grain foods for 4 weeks, separated by a 2-week washout period.

Results:

- A modest hypocholesterolemic effect ($P < 0.05$) of the whole grain diet was observed. The intake of whole grain products rich in lignans was also associated with an increase in urinary enterodiol excretion ($P < 0.05$).
- No significant differences in antioxidant parameters such as FRAP, SOD, GPX were found.
- No significant differences in inflammation and endothelial markers such as IL-6, IL-1 β , TNF- α , plasma nitric oxide concentrations between the two treatments and along each treatment were found.

Discussion:

- Whole grain cereal-based foods rich in lignans had a moderate cholesterol-lowering effect and a urinary enterodiol excretion increasing effect.
- No effect on antioxidant and inflammation markers was found.
- Small sample size and short study experimental period were study limitations.

Clinical Trials

Foerster et al.²⁰, *PLoS One*, 9(10):e109606, 2014.

The influence of whole grain products and red meat on intestinal microbiota composition in normal weight adults: a randomized crossover intervention trial

Introduction:

- The composition of intestinal microbiota is influenced by many lifestyle factors such as diet and is associated with chronic diseases.
- This study aimed to investigate how a diet rich in whole grain (WG) and red meat (RM) influenced microbiota.

Methods:

- 20 healthy free-living adults participated in a 10-week crossover dietary intervention study with two isocaloric diets consumed, one rich in WG and one rich in RM.
- Blood samples were analyzed for clinical blood parameters including C-reactive protein (CRP), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), uric acid and creatinine.
- Fecal microbiota composition was assessed by 16S rRNA based denaturing gradient gel electrophoresis (DGGE).

Results:

- *Collinsella aerofaciens* was associated with increased WG intake and *Clostridium sp* was associated with RM intake.
- The WG intervention lowered obesity parameters while the RM diet increased serum uric acid and creatinine levels.

Discussion:

- This study demonstrated that diet was influential on intestinal microbiota and WG had an important role for health.
- This study's results could be used as a guidance for future observational prospective cohort studies on diet and microbiota.

Clinical Trials

Giacco et al.²¹, *Nutr Metab Cardiovasc Dis*, 24(8):837-844, 2014.

A whole-grain cereal-based diet lowers postprandial plasma insulin and triglyceride levels in individuals with metabolic syndrome

Introduction:

- Existing literature on the effects of whole grain intake on postprandial glucose, insulin and lipid metabolisms have been controversial.
- This study aimed to evaluate how a short-term dietary intervention with either a whole grain-based or a refined cereal-based diet could affect postprandial glucose, insulin and lipid metabolisms in individuals with metabolic syndrome.

Methods:

- 61 adults (aged 40-65 years) with metabolic syndrome were recruited to this randomized, controlled, parallel-arm study with a 12-week intervention period after a 4 week run-in period.
- Participants were randomly assigned to either a group consuming whole grain cereal or a group consuming refined cereal products (control).
- Blood samples were collected at the beginning and end of the intervention, both fasting and 3 hours after lunch, for biomarker measurements.

Results:

- 26 subjects in the control group and 28 in the whole grain group completed the dietary intervention.
- Postprandial insulin and triglyceride responses decreased by 29% and 43% respectively in the whole grain group compared to the run-in period.
- Postprandial insulin and triglyceride responses were significantly lower at the end of the intervention in the whole grain group vs. control (refined grain) group (P=0.004 vs. P=0.005 respectively).
- There was no change in postprandial response of glucose and other parameters measured.

Discussion:

- Consumption of whole grain cereal foods for 12 weeks reduced postprandial insulin and triglycerides in adults with metabolic syndrome.
- The findings may partially explain the biological mechanisms of the decreased risk of type 2 diabetes and cardiovascular diseases associated with whole grain consumption.
- Future trials with longer duration and hard endpoints are warranted.

Clinical Trials

Hajhashemi et al. ²², *Mol Nutr Food Res*, 58(6):1301-1308, 2014.

Whole-grain intake favorably affects markers of systemic inflammation in obese children: a randomized controlled crossover clinical trial

Introduction:

- Whole grain foods have been suggested to affect serum inflammatory cytokines levels in adults, however, studies in children are lacking.
- This study aimed to examine the effect of whole grain intake on serum inflammatory biomarkers in overweight/obese children and adolescents.

Methods:

- 44 overweight/obese girls aged 8-15 years participated in a randomized crossover clinical trial (6 weeks each intervention) after a 2-week run-in period and a 4-week washout period.
- Participants were randomized into either whole grain or control groups.
- Fasting blood samples were taken before and after each phase of the study for assessment of inflammatory biomarkers.

Results:

- No significant effect of whole grain intake on weight and BMI as compared with the control group was found.
- There was a significant effect of whole grain intake on serum high-sensitive C-reactive protein (P=0.03), soluble intercellular adhesion molecule-1 (P=0.02), serum amyloid A (P=0.02), and leptin (P=0.02) after 6 weeks.
- A trend toward a significant effect of whole grain intake on serum soluble vascular cell adhesion molecule-1 was observed (P=0.07)

Discussion:

- This study showed whole grain consumption could benefit systemic inflammation biomarkers and adipocytokines levels in overweight/obese children and adolescents.

Clinical Trials

Hartvigsen et al.²³, *Eur J Clin Nutr*, 68(1):84-90, 2014.

Effects of concentrated arabinoxylan and beta-glucan compared with refined wheat and whole grain rye on glucose and appetite in subjects with the metabolic syndrome: a randomized study

Introduction:

- Whole grain foods have a higher content of dietary fiber (DF) than refined grain products. The predominant DF in wheat and rye is arabinoxylan. Mixed linked (1-3)(1-4)- β -glucan (β -glucan) is found primarily in the endosperm and subaleurone cell walls of oat and barley. Arabinoxylan and β -glucan have both soluble and insoluble forms, but the soluble form of both types of DF can be concentrated by various means.
- Previous studies had suggested that both arabinoxylan and β -glucan had more beneficial effects on glucose metabolism than meals low in dietary fiber.
- Fewer studies have been made on the effects of concentrated DF compared with whole grain. This study aimed to examine the effects of DF and whole grain on glucose, hormone responses and appetite in subjects with metabolic syndrome (MetS).

Methods:

- 15 subjects participated in this acute, randomized, crossover intervention study, with 4 test breads provided in a random order and with a 1-week washout period between tests.
- The test breads each provided 50 g of digestible carbohydrate: wheat bread with concentrated arabinoxylan (AX) or β -glucan (BG), rye bread with kernels (RK) and wheat bread (WB) as control.
- Blood samples were collected for 270 min (at 0, 15, 30, 45, 60, 90, 120, 180, 240 and 270 mins) to determine glucose, insulin, glucagon-like peptide-1, glucose-dependent insulinotropic peptide (GIP) and ghrelin levels.
- Appetite score was assessed every 30 minutes during test periods.
- *Ad Libitum* energy intake (EI) was measured 270 min after test meals.

Results:

- BG and RK induced lower initial glycemc responses ($P < 0.001$).
- AX only reduced the glucose peak value ($P < 0.001$).
- RK reduced insulin ($P < 0.001$) and GIP responses ($P < 0.001$).
- BG lowered insulin responses more than AX ($P < 0.001$).
- AX, BG and RK increased satiety feeling ($P < 0.001$) more than WB, but didn't differ significantly in terms of subsequent EI ($P = 0.089$).

Discussion:

- BG and RK had beneficial impact on the glucose response, while AX had only minor effects on the postprandial glucose peak.
- Rye whole grain with kernels is particularly beneficial in balancing circulating glucose and insulin levels.
- The effect of AX bread was influenced by higher protein content.

Clinical Trials

Harris et al.²⁴, *Am J Clin Nutr*, 100(2):577-586, 2014.

Effects of whole and refined grains in a weight-loss diet on markers of metabolic syndrome in individuals with increased waist circumference: a randomized controlled-feeding trial

Introduction:

- Metabolic syndrome (MetS) is very common among US adults and epidemiological studies have shown higher whole grain (WG) intake is associated with lower prevalence of MetS, although the magnitude of the effect is small.
- Clinical studies evaluating the effects of WG on MetS have mixed findings with beneficial effects being reported for different MetS components.
- To better control the variability existing in the previous studies, this study used a controlled-feeding study design to better assess the effects of WG diet on MetS criteria.

Methods:

- 50 overweight and obese adults with increased waist circumference and one or more other MetS criteria participated in this randomized, controlled, open-label parallel study.
- Participants were randomly assigned to a controlled weight-loss diet containing either WG or refined grains (RG) for 12 weeks.
- Body composition, MetS criteria and related markers, and plasma alkylresorcinols were measured at baseline and at 6 and 12 weeks.
- A subgroup (n=28) had magnetic resonance imaging to get measurement of subcutaneous and visceral adipose tissue (AT).

Results:

- Subjects' dietary compliance was good, as confirmed by alkylresorcinols (time * treatment, P<0.0001).
- Similar anthropometric changes were observed in both groups. Weight, body mass index, and body AT% decreased at both 6 and 12 weeks, reductions in abdominal AT% occurred dramatically by 6 weeks and didn't change between 6 and 12 weeks.
- Glucose and HDL cholesterol levels were significantly lower in the WG group. However, the effect of glucose was stronger while HDL-cholesterol was no longer significant, after removing 3 noncompliant subjects.

Discussion:

- Replacing RGs with WGs in a weight-loss diet didn't beneficially affect abdominal AT loss, but it might be effective in maintaining normal glucose level.
- WGs may improve glucose status in adults with prediabetes and prevent the occurrence of diabetes.

Clinical Trials

Kang et al.²⁵, *Trials*, 15:100, 2014.

Consumption of whole grains and legumes modulates the genetic effect of the APOA5 -1131C variant on changes in triglyceride and apolipoprotein A-V concentrations in patients with impaired fasting glucose or newly diagnosed type 2 diabetes

Introduction:

- The apolipoprotein A5 gene (*APOA5*)-1131 T>C polymorphism is associated with mild hypertriglyceridemia in type 2 diabetes. It also interacts with dietary fat in affecting triglyceride concentrations.
- This study aimed to examine whether replacing refined rice with whole grains and legumes in a high carbohydrate diet (about 65% of energy from CHO) could modify the effect of this variant on changes in apolipoprotein A-V (apoA-V) and triglyceride concentrations.

Methods:

- 185 adults (%female=79%) with impaired fasting glucose (IFG) or newly diagnosed type 2 diabetes completed a randomized, open label, controlled, intervention trial.
- Dietary intervention involved consuming whole grain & legume meals daily (n=92) or a refined rice (control) diet (n=93) for 12 weeks.
- All the participants had been genotyped the *APOA5*-1131 T>C polymorphism.

Results:

- There were significant interactions between the *APOA5*-1131 T>C polymorphism and carbohydrate sources (whole grains and legumes vs. refined rice) in the mean % changes in triglyceride and apoA-V ($P_{\text{interactions}} < 0.001$ and $= 0.038$ respectively).
- In the control group, carriers of the risk C allele had a greater increase in the mean % changes of triglyceride and apoA-V than non-carriers.
- In the intervention group, there was a decrease in fasting glucose, HOMA-IR, and triglyceride, and an increase in apoA-V, irrespective of genotype.

Discussion:

- The genetic effect of the *APOA5*-1131C variant on triglyceride and apoA-V levels could be modulated by more consumption of whole grains and legumes as a carbohydrate source in IFG or diabetic subjects.
- This study is consistent with previous studies on the role of dietary modification in affecting the biological effect of genetic predisposition on metabolic profiles and diabetic risk.

Clinical Trials

Kazemzadeh et al.²⁶, *Int J Prev Med*, 5(4):478-488, 2014.

Effect of brown rice consumption on inflammatory marker and cardiovascular risk factors among overweight and obese non-menopausal female adults

Introduction:

- Brown rice (BR) is unpolished rice rich in various beneficial nutritional compounds.
- This study examined the effects of BR in comparison with white rice (WR) on the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) and cardiovascular (CVD) risk factors among non-menopausal overweight or obese women.

Methods:

- 40 overweight/obese women (body mass index >25) participated in a randomized crossover study and were randomly assigned to either BR diet group or WR diet group (150 g cooked BR or WR) for 6 weeks during each intervention.
- CVD risk factors including BMI, waist circumference, hip circumference, blood pressure, serum lipid profiles, fasting blood glucose (FBG) and hs-CRP were measured in weeks 0, 6, 8 and 14 of the study.

Results:

- BR diet in comparison with WR diet significantly reduced weight, waist and hip circumference, BMI, diastole blood pressure and hs-CRP.
- No significant differences were found in lipid profiles and FBG between the two groups.

Discussion:

- BR replacement diet may be useful to decrease inflammatory markers and several CVD risk factors in non-menopausal overweight/obese women.
- This study considered the effect of menstruation date on biochemical measurements, thus having a good external validity.

Clinical Trials

Magnusdottir et al.²⁷, *PLoS One*, 9(10):e110827, 2014.

Whole grain rye intake, reflected by a biomarker, is associated with favorable blood lipid outcomes in subjects with the metabolic syndrome -- a randomized study

Introduction:

- Many intervention studies have shown that whole grains (WG) could lower serum total and LDL cholesterol concentrations, blood pressure and improve insulin sensitivity.
- No previous intervention studies have studied the effects of rye on blood lipids in humans, although rye products have compounds such as extractable arabinoxylans and β -glucans that contribute to lowering cholesterol level.
- This study is a secondary analysis using data from an intervention trial to investigate the association between plasma alkylresorcinols (AR) and blood lipid concentrations in adults with MetS.

Methods:

- 158 participants (30-65 yrs.) were recruited through six centers in the Nordic countries into the SYSDIET (Systems biology in controlled dietary interventions and cohort studies) study, a randomized controlled multicenter parallel group study with balanced randomization.
- Intervention diets included either a healthy Nordic diet (ND, n=93) rich in WG rye and wheat, as well as berries, fruits and vegetables, rapeseed oil, three fish meals per week and low-fat dairy products, or a control diet (n=65) for 18 or 24 weeks.
- Data analyses pooled ND and control groups to examine the total plasma AR concentration and C17:0/C21:0 homologue ratio and blood lipids through regression analyses adjusting for confounding factors.

Results:

- Total plasma AR at 18/24 weeks was not significantly associated with blood lipid levels.
- AR ratio C17:0/C21:0 was inversely associated with LDL cholesterol concentrations, log LDL/HDL cholesterol ratio, log non-HDL cholesterol, log apolipoprotein B and log triglyceride concentrations.

Discussion:

- Increased WG rye consumption in a Nordic diet was associated with favorable blood lipid outcomes.
- By using AR as a dietary biomarker for WG rye intake instead of self-reported dietary estimates, findings of this secondary analysis study were strengthened.

Clinical Trials

Mohan et al.²⁸, *Diabetes Technol Ther.*, 16(5):317-325, 2014.

Effect of brown rice, white rice, and brown rice with legumes on blood glucose and insulin responses in overweight Asian Indians: a randomized controlled trial

Introduction:

- Compared to brown rice (BR), white rice (WR) lacks phytochemicals, vitamins and minerals that are beneficial to human health. Replacing WR with BR could reduce the risk of diabetes and related complications.
- This study aimed to evaluate the effect of replacing WR with BR or with BR and legumes (BRL) on the 24-hour glycemic response among overweight/obese Asian Indian adults.

Methods:

- 15 overweight or obese Asian Indians (body mass index $\geq 23\text{kg/m}^2$) without diabetes participated in a randomized crossover study.
- Test meals (nonisocaloric, ad libitum) were identical except for the type of rice and the addition of legumes (50 g/day) and were provided for 5 consecutive days.
- Glucose profiles were assessed using a continuous glucose monitoring device.
- The mean positive change from baseline glucose concentration was calculated as the daily incremental area under the curve (IAUC) on each test day for 5 days and averaged.
- Fasting serum insulin was measured before and at the end of each test diet.

Results:

- The % difference in 5-day average IAUC was 19.8% lower in the BR than in the WR group (P=0.004).
- BRL decreased the glycemic response (22.9% lower compared with WR; P=0.02).
- The 5-day % change in fasting insulin was 57% lower (P=0.0001) for the BR group and 54% lower for the BRL group compared with the WR group.
- No significant difference in the glycemic and insulinemic response between the BR and BRL diets was found.

Discussion:

- Replacing WR with BR can help reduce 24-hour glucose and fasting insulin responses among overweight/obese Asian Indians.
- In populations with WR as the major cereal staple food, substituting BR for WR may offer substantial health benefits and decrease the risk of early development of type 2 diabetes and heart disease.

Clinical Trials

Poquette et al.²⁹, *Food Funct.*, 5(5):894-899, 2014.

Grain sorghum muffin reduces glucose and insulin responses in men

Introduction:

- Whole grain sorghum has been known to be a slowly digestible cereal. However, research on its health benefits in humans is limited.
- This study aimed to measure the contents of functional starch fractions, slowly-digestible starch (SDS) and resistant starch (RS) in foods made with sorghum.

Methods:

- 10 healthy men were enrolled in the randomized-crossover study.
- The intervention included a grain sorghum muffin and a whole wheat flour muffin (control), both containing 50 g total starch.
- Participants consumed intervention muffins with a 1-week washout period between interventions. Glucose and insulin levels were observed at 15 minutes before and 0, 15, 30, 45, 60, 75, 90, 120, 180 minutes after consumption.

Results:

- Mean glucose responses reduced after consuming sorghum, particularly at 45-120 minute intervals.
- Mean insulin responses reduced at 15-90 minute intervals after consuming sorghum ($P < 0.05$), compared to control.
- The mean incremental area under the curve (iAUC) was significantly lowered (about an average of 35%) for plasma glucose responses.
- Insulin responses also significantly reduced with sorghum ($P < 0.05$).

Discussion:

- Grain sorghum is a good functional food for managing glucose and insulin levels in healthy men.
- Functional starch fractions of sorghum showed increased SDS and RS contents and lower RDS content and decreased glucose and insulin responses in healthy men.
- Further research is needed among pre-diabetic or diabetic subjects.

Clinical Trials

Tovar et al.³⁰, *Br J Nutr.*, 111(4):706-714, 2014.

Combining functional features of whole-grain barley and legumes for dietary reduction of cardiometabolic risk: a randomized cross-over intervention in mature women

Introduction:

- Legumes and whole grains can modulate risk markers associated with cardiometabolic diseases, but their possible additive/synergistic actions are unknown.
- This study aimed to assess the effect of a diet including whole grain barley and legume products with prior favorable outcomes on cardiometabolic risk parameters among healthy adults.

Methods:

- 46 overweight women (50-72 years, BMI 25-33 kg/m² and normal fasting glycaemia) participated in a randomized cross-over intervention study with each diet consumed for 4 weeks.
- The intervention included a diet rich in kernel-based barley products, brown beans and chickpeas (D1, diet 1, functional diet) with a control diet (D2, diet 2, control diet) of similar macronutrient composition but lacking legumes and barley.
- Both diets followed the Nordic nutrition recommendations, providing similar amounts of dietary fiber with wheat-based products as the main fiber supplier in D2.

Results:

- Both diets decreased serum total cholesterol, LDL-cholesterol and HDL-cholesterol levels, but D1 had a greater effect on total cholesterol and LDL-cholesterol levels.
- D1 also reduced apoB and γ -glutamyl transferase levels, diastolic blood pressure and the Framingham cardiovascular risk estimate.
- D1 increased colonic fermentative activity, shown from higher breath hydrogen levels.

Discussion:

- A specific barley/legume diet improves cardiometabolic risk-associated biomarkers among healthy overweight women.
- These results are consistent with previous evidence for the potential prebiotic beneficial action of barley/legume foods, which have the potential for dietary prevention of cardiometabolic diseases.

Clinical Trials

Zhang et al.³¹, *Mol Nutr Food Res.*, 58(6):1322-1332, 2014.

Oat-enriched diet reduces inflammatory status assessed by circulating cell-derived microparticle concentrations in type 2 diabetes

Introduction:

- Microparticles (MP) can be released from many cell types with the majority derived from platelets.
- The activation of MP contributes to inflammation, coagulation and vascular dysfunction events, and ultimately to the development of cardiovascular disease.
- Oats are low in glycemic index and exert direct anti-inflammatory and antioxidant properties.
- This study examined the impact on indices of MP, of consumption of either an oat-enriched diet (OAT) or one based on the standard dietary advice (SDA) provided in the UK to subjects with type 2 diabetes.

Methods:

- 22 subjects with type 2 diabetes participated in a randomized 8-week cross-over intervention trial following either OAT or reinforced SDA.
- For the OAT arm, subjects were provided with written guidelines on how to include a minimum of 70–100 g oat products into their daily diet (mean intake was 131 g/d); for the SDA arm, the subjects were asked to minimize their intake of oats (this decreased from 32 g/d habitual to 5 g/d SDA).
- Responses were compared with pre-intervention habitual intake.

Results:

- OAT reduced the concentrations and proportions of fibrinogen and tissue factor-related platelet-derived MP (PMP) and CD11b-positive monocyte-derived microparticles (MMP_{11b}).
- SDA decreased fibrinogen-activated PMP.
- A healthy (OAT) test meal led to postprandial declines in total PMP as well as tissue factor-, fibrinogen-, and P-selectin-positive PMP, all of which are linked to inflammatory or antioxidant processes.

Discussion:

- OAT improved MP status, markers of metabolic health.
- This study confirms and extends other observations that demonstrate the sensitivity of platelet number, activity, and associated circulating MP activation to various dietary interventions.

Clinical Trials

Brownlee et al.³², *Br J Nutr.*, 110(5):943-948, 2013.

The impact of a 16-week dietary intervention with prescribed amounts of whole-grain foods on subsequent, elective whole grain consumption

Introduction:

- Population-based observational studies have suggested the health benefits of dietary intake of whole-grain (WG) foods and have formed the basis for public health recommendation.
- Limited evidence exists on assessing the impact of public health recommendations on long-term dietary intake improvement.
- This study aimed to assess the impact of a previous 16-week WG intervention on subsequent, elective WG consumption in free-living individuals.

Methods:

- The present study was based on a previous dietary intervention (the WHOLEheart study) study, which recruited 266 overweight, but otherwise healthy, individuals who habitually ate <1 serving of WG/day.
- In the original dietary intervention, participants had been randomly allocated into three groups:
 - 1. a control group making no dietary changes;
 - 2. intervention group 1 (provided with WG foods, and asked to consume 3 servings/day over the 16-week period);
 - 3. intervention group 2 (provided with WG foods, and asked to consume 3 * 20g servings/day for 8 weeks, followed by 6 servings of WG/day for the subsequent 8 weeks).
- Participants completed a postal food frequency questionnaire (FFQ) 1, 6 and 12 months after the end of the WG intervention period.
- The FFQ included inputs for WG foods commonly consumed in the UK.

Results:

- In this follow-up study, WG consumption was significantly higher in participants who had received WG foods during the original intervention.
- This increased WG consumption was lower than WG intake levels required (between 60 and 120 g WG/day) by participants during the intervention period.
- Except for a significant (2-3g/d) increase in non-starch polysaccharide intake (P<0.001), there were no other obvious improvements to the pattern of foods of the intervention group.

Discussion:

- This study suggests that a period of direct exposure to WG foods in previously non-habitual WG food consumers may benefit subsequent, elective dietary patterns of WG consumption.
- The findings may aid the development of future strategies to increase WG consumption for public health and/or food industry professionals.

Clinical Trials

Christensen et al.³³, *Eur J Clin Nutr.*, 67(12):1316-1321, 2013.

Bifidogenic effect of whole-grain wheat during a 12-week energy-restricted dietary intervention in postmenopausal women

Introduction:

- The beneficial effect of whole grain (WG) consumption on health is considered to be in part through modulation of gut bacterial composition.
- This study investigated changes in human gut microbiota composition after WG or refined wheat (RW) consumption.

Methods:

- 72 postmenopausal women were randomized into either a WG (n=38) or RW (n=34) group in a 12-week energy-restricted open-label parallel dietary intervention trial.
- The intervention provided 105 g whole grain daily (WG) or no whole grain (RW).
- Quantitative PCR was used to determine changes in gut bacterial composition.
- Intestinal integrity was determined by measuring trans-epithelial resistance (TER) across a Caco-2 cell monolayer, following exposure to fecal water.

Results:

- There were no significant differences in microbiota composition between the two groups.
- WG intervention increased the relative abundance of *Bifidobacterium* compared to baseline.
- Fecal water increased TER independent of dietary intervention, showing that commensal bacteria produced metabolites that provided a positive effect on intestinal integrity.
- The study observed a tendency for a negative correlation between the relative abundance of *Bifidobacterium* and TER (P=0.09).
- Abundance of *Bifidobacterium* was positively correlated with adiposity indices.
- Abundance of *Bacteroidetes* was negatively correlated with body fat mass % and trunk fat %.

Discussion:

- This study showed that WG consumption increased the abundance of *bifidobacteria* compared to baseline and might have indirect effects on the integrity of the intestinal wall.
- More studies are needed to assess the causality of the observed associations between gut microbiota and host anthropometric/biochemical measures.

Clinical Trials

Giacco et al.³⁴, *Clin Nutr.*, 32(6):941-949, 2013.

Effects of rye and whole wheat versus refined cereal foods on metabolic risk factors: a randomised controlled two-centre intervention study

Introduction:

- Existing literature on the effects of whole grain intake and glucose/insulin metabolisms is conflicting.
- This study aimed to evaluate glucose/insulin metabolism in response to long-term consumption of rye and whole wheat compared with a diet containing the same amount of refined cereal foods, among adults with metabolic syndrome.

Methods:

- From two European locations (Kuopio, Finland and Naples, Italy), 146 adults with metabolic syndrome were recruited into this randomized, controlled, parallel intervention study with a 2-4 week run-in period.
- Subjects were randomly assigned to consume a diet based on whole grain or on refined grain cereal foods, for a duration of 12 weeks.
- Peripheral insulin sensitivity, assessed by frequently sampled intravenous glucose tolerance test (FSIGT), lipids and inflammatory (hs-CRP, TNF- α , IL-6, IL-1ra) markers were measured before and at the end of intervention.

Results:

- 61 subjects in the control group and 62 in the whole grain group completed the intervention.
- No significant difference was found on insulin sensitivity indices and secretion as well as inflammatory markers between the two groups; no difference was found compared to baseline.

Discussion:

- Whole grain wheat and rye consumption for 12 weeks changed neither glucose and insulin metabolism nor lipid and inflammatory marker levels.
- Differences in the methodologies used for analyzing glucose and insulin metabolism or differences in the amount and type of whole grain products of interventional diets contributed to the conflicting results with other studies.

Clinical Trials

Langkamp-Henken et al.³⁵, *J Nutr.*, 142(11):2025-2032, 2012.

Fecal lactic acid bacteria increased in adolescents randomized to whole-grain but not refined-grain foods, whereas inflammatory cytokine production decreased equally with both interventions

Introduction:

- Average whole grain (WG) food intake among U.S. adolescents is estimated to be 1/3 of the recommended intake of 48 g/day.
- No previous studies have examined the role of WG on gastrointestinal and immune health in adolescents.
- This study aimed to examine the effect on gastrointestinal and immune health, of incorporating refined grain (RG) or WG foods into the usual diets of healthy adolescents.

Methods:

- 83 adolescents aged 11-15 years were randomized to either the RG group (n=42) or the WG group (n=41) in a 6-week, randomized, controlled, parallel-arm study.
- Participants were encouraged to eat 3 different kinds of study foods (e.g., bread, cereals, and snacks) each day, with goals of 0 g/d of whole grain (RG group) and 80 g/d of whole grains (WG group).
- Multipass, targeted 24-hr recalls were collected and nutrient intake analyses were completed by using Food Processor software.
- Stool samples were collected in the week prior to randomization and the final week of the study to measure bifidobacteria and lactic acid bacteria (LAB) using qPCR.
- Blood was drawn at baseline and at final visits, for immune markers.

Results:

- The intake of WG was similar at baseline (18±3 g) between groups but increased to 60±5 g in the WG group and decreased to 4±1 g in the RG group.
- Fecal bifidobacteria increased from baseline with both interventions, but LAB increased (P < 0.05) from baseline in the WG group but not in the RG group.
- No significant difference was found in stool frequency, serum antioxidant potential, or in vitro LPS-stimulated mononuclear cell production of inflammatory cytokines between groups.
- The number of daily stools had a tendency to increase in both groups (P=0.08).
- Mean antioxidant potential increased by 58%, and mean production of TNF- α , IL-1 β , and IL-6 decreased by 24, 22, and 42% respectively between baseline and week 6 across both groups.

Discussion:

- Either WG or RG could increase serum antioxidant concentrations and decrease inflammatory cytokine levels.
- WG had a more beneficial effect on gastrointestinal health.

Clinical Trials

Lappi et al.³⁶, *J Nutr.*, 143(5):648-655, 2013.

Intake of whole-grain and fiber-rich rye bread versus refined wheat bread does not differentiate intestinal microbiota composition in Finnish adults with metabolic syndrome

Introduction:

- Whole grains (WG) are rich in various indigestible carbohydrates which may affect intestinal microbiota more than total carbohydrate content. It is unknown whether or how different types of WG affect intestinal microbiota differently.
- This study investigated the effects of refined low-fiber wheat bread and WG / high-fiber rye bread on the intestinal microbiota composition among adults with metabolic syndrome.

Methods:

- 51 adults (age 60 ± 6 yrs) with metabolic syndrome participated in a 12-week, parallel, controlled dietary intervention study in Finland.
- Participants were randomized to a whole grain rye bread (RB) or a refined white wheat bread (WWB) diet.
- Fecal samples were collected before and after the intervention, and were processed for microbiota analysis using a phylogenetic microarray and quantitative polymerase chain reactions targeting the 16S rRNA gene.
- Fasting plasma alkylresorcinol concentration was analyzed as a biomarker of WG intake.

Results:

- The intestinal microbiota composition did not show significant difference between the two intervention groups after intervention.
- In the WWB group, there was a 37% decrease of *Bacteroidetes* (P<0.05) in parallel to a 53% decrease in the alkylresorcinol concentration (P<0.001).
- In the WWB group, the abundance of bacteria related to *Bacteroides vulgatus*, *B. plebeius*, and *Prevotella tanneriae* decreased, whereas the bacteria related to *Collinsella* and members of the *Clostridium* clusters IV and XI increased.
- The abundance of *Bacteroides* spp. was best explained by different fat compounds among dietary variables.

Discussion:

- This study examined the impact of staple foods on the intestinal microbiota composition and didn't show significantly different impacts of high vs. low intake of WG on intestinal microbiota composition.
- This study showed that changes in microbiota composition were mostly associated with intake of fat-derived compounds.
- Future intervention studies should control different types and sources of dietary fiber as well as the amount and quality of fat to more clearly clarify the effect of diet on microbiota composition.

Clinical Trials

Martinez et al.³⁷, *ISME J.*, 7(2):269-280, 2013.

Gut microbiome composition is linked to whole grain-induced immunological improvements

Introduction:

- A diet high in whole grains/dietary fibers is associated with improved metabolic parameters, thus preventing various metabolic disorders. However, the mechanisms are not well understood.
- It has been hypothesized that one of the biological mechanisms could be through the effect of whole grains on gut microbiome.
- This study aimed to characterize the impact of whole grains on gut microbial ecology in healthy human subjects and to examine whether a connection exists with metabolic and immunological improvements.

Methods:

- 28 healthy adults participated in a randomized cross-over trial with three 4-week treatments.
- Interventions included
 1. a daily dose of 60 g whole grain barley (WGB) with 18.7 g total dietary fiber
 2. 60 g brown rice (BR) with 4.4 g total dietary fiber, or
 3. an equal mixture of the two (BR + WGB) with 11.5 g total dietary fiber
- Fecal and blood samples were collected at baseline and at the end of each treatment.
- Fecal microbiota composition was characterized by pyrosequencing of 16S rRNA gene tags, and inflammatory and metabolic markers were measured in blood samples.

Results:

- All treatments increased microbial diversity, the Firmicutes/Bacteroidetes ratio, and the abundance of the genus *Blautia* in fecal samples.
- WGB enriched the genera *Roseburia*, *Bifidobacterium* and *Dialister*, and the species *Eubacterium rectale*, *Roseburia faecis* and *Roseburia intestinalis*.
- The BR+WGB intervention reduced plasma interleukin-6 (IL-6) and peak postprandial glucose.
- Shifts in the abundance of *Eubacterium rectale* were associated with changes in the glucose and insulin postprandial response.
- The participants with greater improvements in IL-6 levels also had significantly higher proportions of *Dialister* and lower abundance of *Coriobacteriaceae*.

Discussion:

- Short-term whole grain intake induced compositional alterations of the gut microbiota that coincided with improvements in host physiological measures related to metabolic dysfunctions in humans.
- The results from this study on the relationship between whole grains, the gut microbiota and host metabolism are novel.

Clinical Trials

Kristensen et al.³⁸, *J Nutr.*, 142(4):710-716, 2012.

Whole grain compared with refined wheat decreases the percentage of body fat following a 12-week, energy-restricted dietary intervention in postmenopausal women

Introduction:

- Observational studies have shown strong evidence that higher intake of whole grain products is inversely associated with adiposity, risk of body weight gain and cardiovascular (CVD) risk.
- Whole grain foods are rich in various nutritional components such as vitamins, minerals, dietary fibers and phytochemicals, which are beneficial to health. However, intervention trials on whole grain consumption and health outcomes are still scarce.
- This study examined the effect of replacing refined wheat (RW) with whole grain wheat (WW) on body weight and composition as well as CVD risk markers, insulin sensitivity, dietary intake, and fecal energy excretion.

Methods:

- A total of 79 postmenopausal women were randomized into this open-label parallel intervention study with intake of RW or WW foods for 12 weeks after a 2-week run-in period.
- The intervention diets were energy-restricted diets with RW or WW foods providing 2 MJ/day.
- Body weight and composition, blood pressure, circulating markers were measured at weeks 0, 6 and 12.
- Fecal output and energy excretion were measured during the run-in period and at week 12.

Results:

- Plasma alkylresorcinol analysis showed good compliance with the intervention diets.
- Although body weight decreased significantly from baseline in both groups, the weight decreases didn't differ significantly between the two groups.
- The reduction in body fat % was greater in the WW group (-3.0%) than in the RW group (-2.1%) (P=0.04).
- Serum total and LDL cholesterol increased by 5% in the RW group but didn't change in the WW group.
- Daily fecal volume, fecal energy excretion and pH didn't change from baseline or differ between groups at any time point.

Discussion:

- Whole grain consumption decreased body fat mass %.
- Whole grain consumption had a cardioprotective role by maintaining optimal serum total and LDL cholesterol level.

Clinical Trials

Mofidi et al.³⁹, *J Nutr Metab.*, 2012:184710, 2012.

The acute impact of ingestion of sourdough and whole-grain breads on blood glucose, insulin, and incretins in overweight and obese men

Introduction:

- In North America, bread is the predominant carbohydrate (CHO)-containing food. Replacing white bread with whole-grain breads is suggested to improve glucose homeostasis.
- This study examined the impact of commercial breads on biomarkers of glucose homeostasis in subjects at higher risk for glucose intolerance.
- Incretin hormones, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide-1 (GLP-1) all regulated postprandial glucose homeostasis and are vital to both the acute insulinemic and glycemic responses to CHO ingestion.

Methods:

- Overweight/obese men participated in a single-blind, randomized crossover study with at least a 1-week washout period.
- Subjects consumed 5 types of bread: 11-grain, sprouted grain, 12-grain, sourdough, or white bread on different occasions. All bread types were matched for available carbohydrate (50 g) in part 1 (n = 12) and bread mass (107 g) in part 2 (n = 11).
- Blood glucose, insulin, GIP and GLP-1 were determined for 3 h.

Results:

- In part 1, glucose response for sprouted grain was lower than 11-grain, sourdough, and white breads.
- Insulin area under the curve (AUC) for sourdough and white bread was lower than 11-grain and sprouted grain breads.
- GLP-1 response to sourdough was lower than all the other breads.
- In part 2, glucose and insulin AUC for sourdough was greater than 11-grain, sprouted grain, and 12-grain breads.

Discussion:

- Sprouted-grain bread improved glycaemia by lowering glucose response and increasing GLP-1 response.
- The glycemic response to sprouted grain bread was reduced in both parts 1 and 2 while the other whole grain test breads did not improve metabolic responses in the acute postprandial state.
- The nature of the ingredients of the bread rather than the bread volume and fiber content is the influencing factor for metabolic responses to the breads.