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The association of whole grain ontakes with the metabolic syndrome: The Baltimore Longitudinal Study of Aging (BLSA)

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The Association of Whole Grain Intakes with the Metabolic Syndrome: The Baltimore Longitudinal Study of Aging (BLSA)

by

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ABSTRACT

Background: Whole grains and their nutrient components have an important protective effect on the metabolic syndrome. Studies are needed to examine their bioactive components in relation to diet and the metabolic syndrome.

Objective: Our objective was to examine the associations between dietary intakes of whole grains and the metabolic syndrome.

Design: The study subjects were 1516 healthy men and women participating in the Baltimore Longitudinal Study of Aging. Dietary information was collected with 7-day food records, and estimates of whole grain intake were obtained from a newly developed database.

Results: A total of 17% (n = 251) of subjects met the definition for the metabolic syndrome. After adjustments for age, sex, and total energy, a modest inverse association was observed between whole-grain intake and the metabolic syndrome [odds ratio (OR): 0.90; 95% CI: 0.83, 0.97]; however, this was no longer statistically significant after adjustment for physical activity.

Conclusions: Although our study shows a modest inverse association between whole grains and the metabolic syndrome, this relationship was no longer statistically significant after controlling for other lifestyle factors.

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CHAPTER 1: INTRODUCTION

The term *metabolic syndrome* is defined as a cluster of multiple-risk factors that are associated with insulin resistance and that predisposes individuals to a greater risk of diabetes [1, 2] and cardiovascular disease.[3, 4] The National Cholesterol Education Program (NCEP) issued a statement called The Adult Treatment Panel III (ATP III) to provide guidelines for identifying people with the metabolic syndrome.[5] If a person has three or more of the following risk factors, the individual has metabolic syndrome: glucose intolerance, hypertension, elevated triglycerides, low HDL cholesterol, and central adiposity, measured as high waist circumference.[6] The current epidemic of Americans' developing different types of metabolic and vascular disease has led to focusing on identifying and treating people with metabolic syndrome. In the National Health and Nutrition Examination Surveys (NHANES 1999-2000), approximately 27% of the population between the ages of 40-49 years reported having this condition, and the prevalence increased with age.[7] Similar to with type 2 Diabetes Mellitus, ethnic differences have also been observed with the prevalence of MS, with the highest rates observed in Mexican Americans.[7]

The development of the metabolic syndrome is linked to diet. The source and quality of dietary carbohydrates is one aspect of diet that may affect metabolic risk factors associated with this syndrome.[2] Current evidence suggests that refined-carbohydrate diets are associated with an increased risk of the metabolic syndrome.[8] Conversely, diets containing higher amounts of whole-grain foods are associated with a decreased risk of disease.[9] However, the long-term effect of diets high in refined carbohydrates on the risk of developing the metabolic syndrome has been examined in only a few large prospective studies.[10, 11]

In 2005, the U.S. Departments of Agriculture and Health and Human Services released the sixth edition of "The Dietary Guidelines for Americans," which set guidelines for the public on the basis of scientific evidence in order to help prevent disease.[12] The guidelines emphasized consumption of whole-grain foods, recommending three or more one-ounce servings of whole-grain products per day in order to reduce the risk of several chronic diseases and help with weight maintenance.[13] The FDA has since drafted guidelines for what the agency considers to be whole grains, that is, "cereal grains that consist of the intact, ground, cracked or flaked fruit of the grains whose starchy endosperm, germ and bran are in the same proportions to the intact grain".[14]

The mechanism by which whole grains establish their protective effect has yet to be determined, but they appear to lower cholesterol through the action of fiber,[15] provide protective antioxidants,[16] and have a positive effect on glucose/insulin serum concentration.[17] Some studies have linked various aspects of diet to individual components of the metabolic syndrome.[18-24] It has been suggested that a high intake of lipids obstructs the body's ability to efficiently move blood glucose into the muscle cells, thus contributing to insulin resistance. Therefore, decreasing plasma lipids by increasing intake of soluble fiber may lower insulin resistance and reduce the risk of the metabolic syndrome.

The primary objective of this study was to examine the relationship between whole-grain intake and the prevalence of the metabolic syndrome among women and men participating in the Baltimore Longitudinal Study on Aging (BLSA). The researchers hypothesize that intakes of whole grains are protective against the metabolic syndrome.

CHAPTER 2: REVIEW OF LITERATURE

Whole grain intake appears to have a positive association with the decreased prevalence of the metabolic syndrome. Recent studies quantifying whole grain intake suggest that one to three servings of whole grains per day may reduce the risk of developing the metabolic syndrome.

The Harvard Nurse's Health Study (n = 75,521) showed that approximately three servings of whole grain per day decrease risk of ischemic stroke by 30-36%.[11] Additionally, consumption of a diet high in refined grains, such as white bread, rice, pasta, and bakery products, was shown to increase the risk for CVD in women.[25]

In the Iowa Women's Health Study (n = 35,988), eating an average of three servings of whole grains per day decreased the risk of type 2 diabetes by 21%.[26] Similarly, in the Health Professionals Follow-Up Study (n = 42,898), eating 3.2 servings of whole grains per day decreased diabetes by 30% in men. The relative risk of type 2 diabetes was 0.58 when comparing the highest quintile (3.2 servings a day) to the lowest quintile of whole grain intake (0.4 servings a day).[27] Also, Pereira and colleagues [28] examined whole grain intake and its effect on insulin sensitivity in obese adults and found that whole grain consumption reduced the risk of type 2 diabetes and heart disease. Improvement of insulin sensitivity may be an important mechanism by which whole grain consumption decreases the risk of type 2 diabetes and heart disease.

In the Framingham Offspring Study, whole grain intake was associated with decreased risk of type 2 diabetes and cardiovascular disease.[29] Whole grain intake and metabolic risk markers were assessed in a cross-sectional study of 2,941 subjects. The study found that people who ate three or more servings of whole grains a day were less likely to

develop insulin resistance and metabolic syndrome. Lichtenstein and colleagues [30] reported an association between whole grain intake and decreased risk of coronary artery disease (CAD). This prospective-cohort study used a food frequency questionnaire to examine the whole grain intake of 229 postmenopausal women who were diagnosed with CAD. The study showed a positive inverse association for women who ate 6 or more servings of whole grains per week.

More recent studies on whole grain benefits have tried to quantify the gram amount rather than the number of servings. Koh-Banerjee and colleagues [31] examined whole grain intake in association with weight gain by studying 72,000 men in the Health Professionals Follow-up Study (HPFS). Subjects who consumed 40 g of whole grains per day reduced their weight gain by up to 3.5 pounds. Similarly, consumption of 20 grams of whole grains per day decreased risk of heart disease by 6%, according to a study by Jenson and colleagues.[10] In a previous study,[17] the same authors found improved glycemic control and plasma homocysteine concentrations in subjects who were in the highest quintiles of whole grain intake.

Mckeown and colleagues [18] found that elderly adults (aged 60-98 y) who ate more whole grain had a lower prevalence of the metabolic syndrome. This cross-sectional study used three-day food records to estimate whole grain intake and measure each participant's blood for metabolic risk factors. The authors found that whole grain intake was inversely associated with BMI and fasting glucose and that the consumers with the highest intake of whole grain intake (2.9 servings/d) had a 40% lower risk for having the metabolic syndrome.[18]

CHAPTER 3: RESEARCH DESIGN AND METHODOLOGY

Study Sample

The study population consisted of The Baltimore Longitudinal Study on Aging (BLSA), a longitudinal study of volunteers largely from the Baltimore, MD, and Washington, DC, areas.[32] The BLSA study was initiated by the National Institutes of Health in 1958 and has been previously described as a study that is designed to look at the normal functions of the body and cognitive aspects of aging and diseases.[33] Initially, the subjects were Caucasian, healthy men aged 30-90 years in the Baltimore area. In 1978, women and minorities started enrolling in the BLSA. Once enrolled, subjects return to the Gerontology Research Center in Baltimore every 2 years for routine examinations, including height, weight, body composition, diet, and a variety of other physiologic, psychological, and behavioral measures.

Our study sample was a subset of approximately 1516 subjects, ages 30-90 years of age (mean age: 60 y). These 999 men and 517 women were primarily healthy Caucasians and were middle to upper class. The design of this analysis is cross-sectional. We utilized data from the baseline visit, recorded for men and women who participated between 1980 through 2004. The measures used for this study are described below.

Dietary Intake

Dietary data were collected with 7-day diet records. BLSA participants were trained to record their food intake by dietitians during their examination visits. Ambiguous or incomplete records were clarified by telephone interview. Dietary data were entered into the Minnesota Nutrient Data System (NDS) at Tufts University [34] for nutrient analysis. The dietary exposure of interest in this study was intake of whole grains.

Development of the Whole-Grains Database

As the BLSA dietary data were collected during four separate time periods, the researchers developed the whole-grains database separately for each time period. This allowed for adjustment for changes in the whole-grain content of foods over time. For this study, all foods containing grains and mixed dishes with grains, either whole or refined, were identified. Each of these foods was then assigned the best-matched pyramid code from the Pyramid Servings Database,[35] a reference database of serving sizes for 30 food groups, including three grain groups (total grain, whole grain, and non-whole grain).

In most cases, an exact match was available in the pyramid servings database for all of the foods consumed by the study participants. However, there were some instances in which seldom-consumed foods listed in the participants' dietary records were not found in the pyramid servings database (e.g., rice flour, rye flour, potato flour, quinoa, and triticale). In these cases, the researchers matched these foods to the best possible match in the whole-grains database on the basis of whole-grain content. For example, rye flour was matched to the pyramid servings database food code for whole-wheat flour. When questions remained about whether a product was made with whole or refined grains (such as the whole-grain content of corn-based salty snacks, for example), food manufacturers were contacted to obtain information about ingredients and whole-grain content.

An important goal of building the whole grains database was to use the dietary data from the 7-day dietary records to estimate grain intake in gram weight per day rather than servings per day. This process involved several steps because of changes in the nutrient database over time (e.g., foods vs. ingredients) and challenges in quantifying how many grams of whole grains are contained in a given serving of grain food.

Many of the foods in the whole grains database are recipes or mixed dishes, which are foods composed of more than one ingredient, such as sandwiches, soups, and casseroles. To quantify the whole grain content and the percent contribution of grains (whole-grain and non-whole grain) from these mixed dishes and recipes, we merged the whole-grains database to the CSFII 1994-96 recipe database to disaggregate whole foods into ingredients and to obtain gram weights of individual ingredients. The grain components of the ingredients were first calculated on the basis of 100 g of the total recipe and then remerged with the pyramid servings database to obtain grain servings. For example, in a cookie with 11 ingredients and 10 g of white flour per 100 g of the total cookie, the flour gram weight was merged to the pyramid servings database to obtain .63 servings of a non-whole grain.

In the whole grains database, some foods are unable to be disaggregated to the ingredient level. In these cases, the reference gram amount of grains was determined by multiplying by the number representing the pyramid serving. Specifically, a grain serving of one slice of bread contains 16 g of flour, and a grain serving of 1 cup of cereal contains 28 g of flour. Once the whole grains database was completed, the researchers calculated the absolute amount of grain consumed by multiplying the gram amount eaten by the reference values/100 for both servings and grams.

As the researchers were able to estimate precise quantities of grains at both the ingredient and food levels, it was surprising when the whole grains database indicated that some foods contained grain servings. For example, imitation mayonnaise contributes non-whole grains. This is mostly because many foods contain ingredients such as corn starch or other stabilizers and fillers, which are made from grains. Because the dietary data came from

diet records, the researchers were able to count these foods as contributing to grain consumption despite their limited contribution.

Plasma Lipid Measurements

At each examination, every two years, an antecubital venous blood sample was drawn after an overnight fasting. The plasma triacylglycerols and total cholesterol were measured by the use of an enzymatic method (ABA-200 ATC Biochromatic Analyzer; Abbott Laboratories, Irving, TX). HDL cholesterol was measured by a dextran sulfate-magnesium precipitation procedure,[36] and LDL cholesterol concentrations were calculated by using the Friedewald formula.[37] Fasting plasma glucose concentrations were measured by glucose oxidase method (Abbott Laboratories ADB 200 ATC Series II Biochromatic Analyzer 1983-1992, Irving, Tex: Abbott Spectrum CCX 1992-1999).

Anthropometric and Covariate Assessment

Anthropometric measurements were made by following standardized procedures [38] as fully described elsewhere.[39] Waist circumference was measured at each visit with an inelastic tape at the narrowest part of the torso at the end of expiration.[39] Demographic data were collected from each subject at the first visit and were used to adjust for regression analysis to remove confounding effects. Physical activity, smoking, and vitamin supplement intake were collected. Physical activity was measured by an adapted version of the Harvard Alumni questionnaire, which asked participants about all daily activities (e.g., activities at home, work, and during recreation or sports).[40] The amount of time spent for each activity was summed across all activities to determine the daily energy output based on body weight (kilojoules/kg), as described elsewhere.[40, 41]

Outcome Measures

We defined the metabolic syndrome, using the guidelines developed by the National Cholesterol Education Program (NCEP).[42] NCEP classified individuals with metabolic syndrome if they had 3 or more of the following risk factors: (1) waist circumference >102 cm in men and >88 cm in women, (2) triacylglycerol concentrations ≥150mg/dl, (3) HDL cholesterol <40 mg/dl in men or <50 mg/dl in women, (4) blood pressure ≥130/85 mm Hg, and (5) exceeded the new, revised cut-point for fasting glucose (≥100 mg/dl).[43]

Statistical Analysis

All analyses were performed with the Statistical Analysis System (SAS) for Windows, Version 9.1 (SAS Institute, Cary, NC). We summarized the means or frequencies of sample characteristics at baseline, as well as nutrient intakes. On the basis of total energy intake, we excluded persons with unreliable estimates of intake as follows: total energy <800 kcals and >4000 kcals for women and >4200 for men. Our main analyses used logistic regression and odds ratios to estimate the relation between whole grains and each of the metabolic risk factors, including fasting glucose concentrations of ≥100 mg/dl, triacylgycerol concentrations of ≥150mg/dl, waist circumference of >102 cm in men and >88 cm in women, diastolic and systolic blood pressure of ≥130 and 85 mm Hg, respectively, and HDL cholesterol of <40 mg/dl in men and <50 mg/dl in women. In all regression models, we adjusted for age (y), sex, energy intake, physical activity, smoking, and alcohol use. For those subjects with missing waist circumference (45%), we used a BMI cut point of >28 kg/m2. For those with missing fasting glucose (24%), we included those who had a diagnosis of diabetes or took insulin. For those with missing blood pressure values (15%), we included those who reported taking blood pressure medication. Finally, if there were missing data from the first

visit, we took the values from the following visit. We only included dietary data from the first visit for each subject.

CHAPTER 4: PRESENTATION AND ANALYSIS OF DATA

Characteristics of the Population

Table 1 presents the subject characteristics of the BLSA sample, stratified by sex. The study population was composed of 999 (66%) men and 517 (35%) women with mean ages of 57.4 y for men and 57.6 y for women. Men had a mean BMI of 25.3 kg/m^2 and women had a mean BMI of 24.6 kg/m^2. The study subjects were primarily healthy Caucasians, middle to upper class. Twenty-three percent of men and 37% of women were vitamin-supplement users. Seventeen percent of men and 10% women were smokers. On average, men consumed 20 g of whole grains and 81 g of refined grains per day, whereas women reported 25 g of whole grains and 65 g of refined grains per day.

Table 1. Sample Characteristics of 1516 Men and Women Participating in the BLSA At Time of First Visit

Sample characteristics[1]	**Women (n=517)**	**Men (n=999)**
Whole grain (g/day)	25.1 ± 25.0	19.9 ± 23.0
Refined grain (g/day)	65.4 ± 31.7	80.6 ± 31.7
Age (y)	57.6 ± 16.9	57.4 ± 17.0
BMI (kg/m^2)	24.6 ± 4.2	25.3 ± 2.9
Waist circumference (cm)	78.0 ± 10.7	90.3 ± 9.54
Triacylglycerol (mg/dl)	96.4 ± 62.6	112.2 ± 67.3
Systolic Blood pressure (mmHg)	125.0 ± 21.4	131.1 ± 20.6
Diastolic Blood pressure (mmHg)	76.4 ± 10.7	81.3 ± 11.4
Fasting Glucose (mg/dl)	93.8 ± 10.4	99.5 ± 11.3
HDL (mg/dl)	55.6 ± 13.1	43.5 ± 11.6
Average Total Energy (kcal)	1751 ± 425	2225 ± 539
Physical activity (kcal/kg)	15.2 ± 5.1	13.8 ± 3.9
Vitamin users (%)	37	23
Current smokers (%)	10	17

[1]mean ± SD unless otherwise indicated

Metabolic Syndrome and Intake of Whole Grains and Nutrient Components of Whole Grains

A total of 17% (n = 251) of the analyzed population met the definition for the metabolic syndrome. Table 2 shows the results from the logistic regression models. After adjustment for age, sex, and total energy (Model 1), whole-grain intake had a positive effect on the metabolic syndrome [odds ratio (OR): 0.90; 95% CI:0.83, 0.97]. Even after further adjustment for smoking and alcohol (Model 2), the association was modestly associated with whole grain [odds ratio (OR): 0.91; 95% CI: 0.84, 0.99]. However, after further adjustment for physical activity (Model 3), the association was no longer statistically significant.

Table 2. Adjusted Odds Ratios for the Metabolic Syndrome, Associated with Whole Grains, and with Selected Nutrient Components, among Men and Women Participating in BLSA

	Odds Ratio (95% Confidence Interval)		
	Model 1[1]	Model 2[2]	Model 3[3]
Whole Grain (g)	0.90 (0.83, 0.97) *	0.91 (0.84, 0.99) *	0.91 (0.83, 1.01)
Soluble Fiber (g)	1.04 (0.82, 1.32)	1.08 (.866, 1.37)	0.89 (0.60, 1.32)
Insoluble Fiber (g)	0.76 (0.57, 1.03)	0.86 (0.63, 1.19)	0.70 (0.46, 1.06)
Magnesium (mg)	0.99 (0.98, 1.05)	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)

[1] Model 1 is adjusted for age, sex, and total energy
[2] Model 2 is also adjusted for smoking, and alcohol
[3] Model 3 is adjusted for all variables in model 2 also for physical activity
*P-value significant (< 0.05)
BLSA = Baltimore Longitudinal Study of Aging

We also examined the interaction between whole grains and nutrient components of whole grains and the metabolic syndrome. We first separated dietary fiber into soluble fiber and insoluble fiber. We found no significant association with soluble fiber but found insoluble fiber to have a modest association with the MS after adjusting for sex and total energy intake [odds ratio (OR): 0.76; 95% CI: 0.57, 1.03]. We also examined the association with magnesium but found no significant relationship between total Mg intake and the MS in this cohort.

CHAPTER 5: DISCUSSION

In this study, which used 7-day dietary records to measure dietary intakes, we found that whole-grain intake was associated with a modest risk reduction in the metabolic syndrome (Model 2) [odds ratio (OR): 0.90; 95% CI: 0.83, 0.97] even after controlling for several risk factors. The mechanisms for this association lie in the nutrient components of whole grains, such as fiber, vitamins and antioxidants, lignans, phenolic, phytoestrogens, and other phytochemicals, which may all help reduce the risk for the metabolic syndrome.[44] The findings of this study are supported by a recent cross-sectional study that also used food records to estimate whole-grain intake but found a stronger protective relationship between whole-grain intake and metabolic syndrome.[18] Furthermore, McKeown et al.[2] showed that individuals with the greatest whole-grain intake, as estimated from food frequency questionnaires (FFQs), had the lowest prevalence of insulin resistance. Other studies have found that higher consumption of whole grains is protective against chronic diseases such as cancer and cardiovascular disease.[45] A crossover interventional trial also supports the hypothesis that high intakes of whole grains are associated with lower insulin levels, a surrogate marker of insulin resistance.[17] That study showed that whole-grain intake and bran consumption, as estimated from FFQs, were associated with decreased concentrations of C-reactive protein (CRP) and tumor necrosis factor-a receptor 2 (TNF-R2).

We also found insoluble fiber to be associated with a modest risk reduction for the metabolic syndrome after adjusting for confounding variables [odds ratio (OR): 0.76; 95% CI: 0.57, 1.03]. Eating more insoluble fiber may also reduce the risk of some cancers, especially colon cancer, by removing the waste and toxic materials in the body.[46]

A strength of this study was the use of 7-day food records to obtain whole-grain intake in grams per day. To date, most studies on whole grain and disease outcomes have been based on frequency of whole-grain intakes.[30] However, by creating a whole-grains database, we were able to quantify intakes and not just record reported frequency. This is important when totaling the amount of whole grain consumed in one day.

However, there are also several limitations to our study. First, the cross-sectional design does not allow us to make inferences about the direction of our associations. Another limitation is that the selection of participants was not randomized. We also cannot rule out other unmeasured confounding factors that could influence the intake of whole grain and its relationship with the metabolic syndrome. Finally, our study did not include markers for inflammation such as C-reactive protein or tumor necrosis factor-alpha receptor 2 (TNF-R2), which are other important metabolic disturbances of the metabolic syndrome.[47] To our knowledge, our study is the first to quantify whole-grain intakes in detail using 7-day dietary records and to relate these estimates to the metabolic syndrome. The findings are consistent with those of other studies that estimated whole-grain intake, using 3-day dietary records [18] and food-frequency questionnaires [30] and suggest that diets high in whole grains may lead to a lower risk of the metabolic syndrome.

CHAPTER 6: CONCLUSION

In conclusion, we saw a modest association between whole-grain intake and reduced risk of the metabolic syndrome. Whole-grain intake should therefore be considered a modifiable risk factor for the metabolic syndrome. Further studies using biomarkers to examine the protective mechanisms of whole grains are needed.

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