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# Whole grain intake and its cross-sectional association with obesity, insulin resistance, inflammation, diabetes and subclinical CVD: The MESA Study

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We examined the relationship between whole grain intake and obesity, insulin resistance, inflammation, diabetes and subclinical CVD using baseline data from the Multi-Ethnic Study of Atherosclerosis. Whole grain intake was measured by a 127-item FFQ in 5496 men and women free of CHD and previously known diabetes. Mean whole grain intake was 0·5 (SD 0·5) servings per d; biochemical measures reflect fasting levels. After adjustment for demographic and health behaviour variables, mean differences for the highest quintile of whole grain intake minus the lowest quintile of intake were 0·6 kg/m$^2$ for BMI, 0·36 mg/l for C-reactive protein, 0·82 μmol/l for homocysteine, 0·15 mU/l*mmol/l for homeostasis model assessment (HOMA), 0·48 mU/l for serum insulin, 2·0 mg/dl for glucose and 5·7 % for prevalence of newly diagnosed impaired fasting glucose (glucose ≥ 100 mg/dl or diabetes medication). These differences represent 11–13 % of a standard deviation of BMI, HOMA, glucose and impaired fasting glucose, but 23 %, 52 % and 80 % of a standard deviation of homocysteine, C-reactive protein and insulin, respectively. An inverse association between whole grains and urine albumin excretion was suggested but retained statistical significance after adjustment only in Chinese and Hispanic participants. No associations were observed between whole grain intake and two subclinical disease measures: carotid intima-media thickness and coronary artery calcification. Concordant with previous research, whole grain intake was inversely associated with obesity, insulin resistance, inflammation and elevated fasting glucose or newly diagnosed diabetes. Counter to hypothesis, however, whole grain intake was unrelated to subclinical CVD.

**Whole grains: CVD disease risk: Microalbuminuria: subclinical CVD**

Whole grain intake has been related to reductions in total mortality (Jacobs *et al.* 1999, 2001), coronary artery disease mortality and morbidity (Morris *et al.* 1977; Fraser *et al.* 1992; Pietinen *et al.* 1996; Jacobs *et al.* 1998; Liu *et al.* 1999; Steffen *et al.* 2003*b*) and diabetes incidence (Liu *et al.* 2000; Meyer *et al.* 2000; Fung *et al.* 2002; Montonen *et al.* 2003), independent of other health behaviours. In a review of whole grain intake, Jacobs & Gallaher (2004) found that habitual consumers of whole grain consistently had a 20–40 % reduction in long-term risk of coronary artery disease and type II diabetes as compared with those who rarely ate whole grains. This evidence contributed to an emphasis on the consumption of whole grains in the 2005 US Department of Agriculture Dietary Guidelines for Americans, which state: 'Consume 3 or more ounce-equivalents of whole-grain products per day, with the rest of the recommended grains coming from enriched or whole-grain products. In general, at least half the grains should come from whole grains' (http://www.healthierus.gov/dietaryguidelines) (US Department of Health & Human Services & the US Department of Agriculture (2005).

Whole grain food intake and dietary fibre intake, especially from cereal sources, have also been associated with favourable levels of insulin sensitivity (Lovejoy & DiGirolamo, 1992; Feskens *et al.* 1994; Vitelli *et al.* 1996; Marshall *et al.* 1997; Pereira *et al.* 2002; Liese *et al.* 2003; Steffen *et al.* 2003*a*;), BMI (Pereira *et al.* 2002; Steffen *et al.* 2003*a*) and 10-year weight gain (Ludwig *et al.* 1999). Despite the strong body of evidence relating high consumption of whole grain food intake to CVD risk factors and CVD morbidity and

**Abbreviations:** A/kC, urine albumin:creatine ratio; CAC, coronary artery calcification; CRP, C-reactive protein; MESA, Multi-Ethnic Study of Atherosclerosis.

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mortality, there have been no studies of whole grain food and subclinical atherosclerosis. Additionally, little research has assessed whether racial/ethnic heterogeneity exists in the relationship between whole grain intake and various CVD risk factors.

This paper focuses on the cross-sectional relationship between whole grain intake and selected CVD risk factors and measures of subclinical atherosclerosis using baseline data from the Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that whole grain intake would be inversely associated with the following variables: BMI; serum insulin; C-reactive protein (CRP); IL-6; homocysteine; newly diagnosed diabetes and impaired fasting glucose; urine albumin:creatinine ratio (A/kC); carotid artery intima-media thickness; presence of coronary artery calcification (CAC).

## Methods

### *Subjects*

MESA is a prospective epidemiological cohort study initiated in July 2000 with the aim of exploring the prevalence, correlates and progression of subclinical and clinical CVD, with focus on assessing possible differences between non-Hispanic whites, Hispanics, African Americans and Chinese. A full description of the design and methods has been published elsewhere (Bild *et al.* 2002). The MESA protocol was approved by local institutional review committees and all subjects gave informed consent. A total of 6814 men and women between the ages of 45 and 84 years, all of whom were free of clinical CVD at baseline, were selected from six US field centres.

Participants who had no diet data (*n* 577) or implausible energy intakes as defined by consuming $>25\ 081$ kJ/d (6000 kcal/d) or $<2508$ kJ/d (600 kcal/d) (*n* 157) were excluded. Furthermore, participants were excluded if they had been previously diagnosed with diabetes (*n* 610), as these individuals may have changed their diets in response to disease. These criteria were not mutually exclusive, thus the present report includes baseline data on 5496 participants.

### *Data collection*

*Dietary assessment.* At baseline, diet was assessed using a staff-assisted self-administered 127-item FFQ and dietary supplement form in Block format (Block *et al.* 1990). For each questionnaire item, participants were asked to report their frequency of consumption of various foods from among nine categories, ranging from rarely or never to two or more servings/d (six or more servings/d for beverages) and also their serving size as either small, medium or large. Servings per d were calculated from these categories. The FFQ was patterned after the FFQ used in the Insulin Resistance Atherosclerosis Study, which has been validated in non-Hispanic white, African-American and Hispanic persons (Mayer-Davis *et al.* 1999). Concerning validity, the mean correlation coefficients between nutrient intake estimated from the FFQ and intake from the average of eight 24-h recalls were 0·62 for non-Hispanic whites, 0·50 for African Americans and 0·41 for Hispanics. For total carbohydrates the correlation coefficient was 0·39. Among non-Hispanic whites, however, carbohydrate intake estimated from the FFQ tended to be lower than carbohydrate intake estimated from the dietary recalls. Concerning reproducibility, the mean correlation coefficient for nutrients across two administrations of the FFQ was 0·62 and did not differ by ethnic subgroup. In order to accommodate the MESA subject population, the Insulin Resistance Atherosclerosis Study FFQ was modified to include Chinese foods and culinary practices.

### *Whole grain intake*

Servings per d of the following foods were summed to calculate total whole grain intake: whole grain breakfast cereal; oatmeal; dark bread; bran muffins; brown or wild rice. Further descriptions of whole grain food items, including verbatim FFQ wordings, are provided in Table 1.

If participants reported eating cold cereal, they were asked to name the breakfast cereal that they usually ate. Breakfast cereals mentioned were then evaluated for dietary fibre and whole grain content as determined by package labels, dietary

**Table 1.** Descriptions of mean intake of whole grain food groups among Multi-Ethnic Study of Atherosclerosis participants†

| Whole grain item | No. of servings/d | | No. and proportion consuming | | No. of servings/d among consumers | | Verbatim wording for food items included |
|---|---|---|---|---|---|---|---|
| | Mean | SD | *n* | % | Mean | SD | |
| Total whole grains | 0·54 | 0·54 | 4973 | 90·5 | 0·59 | 0·53 | |
| ≥ 1 serving/d | | | 1074 | 19·5 | | | |
| ≥ 3 serving/d | | | 18 | 0·33 | | | |
| Cold cereal* (whole grain) | 0·15 | 0·29 | 2082 | 37·9 | 0·40 | 0·36 | Cold breakfast cereal; If you eat cold cereal, what is the name of the cold cereal that you most often eat? |
| Oatmeal | 0·17 | 0·28 | 3331 | 60·6 | 0·28 | 0·31 | Oatmeal |
| Dark bread | 0·13 | 0·25 | 2761 | 50·2 | 0·25 | 0·30 | Dark, whole grain breads or rolls (hamburger buns, bagels, pita, English muffins, etc.) |
| Bran muffins | 0·03 | 0·10 | 1390 | 25·3 | 0·10 | 0·19 | Bran muffins |
| Brown or wild rice | 0·06 | 0·17 | 2301 | 41·9 | 0·14 | 0·23 | Brown or wild rice |

* Cold cereals were classified as either whole grain or refined grain. The classification criteria are described in Methods.
† For details of subjects and procedures, see Methods.

databases, such as the Nutrition Data System and the US Department of Agriculture Food Composition Data, or by records shared in 1996 by General Mills, Inc (Minneapolis, MN, USA). Of the 144 breakfast cereals mentioned, 121 were classified as whole grain cereals (most mentioned by very few participants) as they contained ≥3 g dietary fibre per 100 g dry weight. Given that 12 g dietary fibre corresponds to 100 g whole wheat, all wheat cereals classified as whole grain contained at least 25 % of a serving of whole grain/100 g. Of breakfast cereal consumers, 54·5 % consumed whole grain varieties, while 45·6 % consumed refined grain varieties. No nutrient available in the MESA database was closely correlated with whole grain food intake; the correlation with dietary fibre was 0·36 ($P<0·0001$), while with total carbohydrates it was 0·29 ($P<0·0001$).

### *BMI, serum insulin, newly diagnosed diabetes and impaired fasting glucose*

BMI was calculated as weight over height squared (kg/m$^2$). Participants were asked to fast for at least 8 h. Serum insulin was measured by the Linco Human Insulin Specific RIA Kit (Linco Research, Inc., St. Charles, MO, USA), and serum glucose by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY, USA) at the Collaborative Studies Clinical Laboratory at Fairview University Medical Center (Minneapolis, MN, USA). Non-medicated participants with fasting glucose ≥7·0 mmol/l (126 mg/dl) who did not self-report pre-existing diabetes were classified as newly diagnosed diabetics and those with fasting glucose levels between 5·6 mmol/l (100 mg/dl) and 6·9 mmol/l (125 mg/dl) were classified as having impaired fasting glucose. The homeostasis model assessment (Matthews *et al.* 1985) estimate of insulin resistance was calculated as insulin*glucose/22·5 (mU/l*mmol/l).

### *C-reactive protein, IL-6 and homocysteine*

CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL, USA) and IL-6 by an ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN, USA), both at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT, USA). Plasma total homocysteine was measured by a fluorescence polarization immunoassay (IMx Homocysteine Assay; Axis Biochemicals ASA, Oslo, Norway) using the IMx Analyzer (Abbott Diagnostics, Abbott Park, IL, USA) at the Biochemical Genetics Clinical Laboratory at Fairview University Medical Center (Minneapolis, MN, USA).

### *Urine albumin excretion*

Urine albumin and creatinine concentrations were assayed in a single untimed urine sample at the Fletcher Allen Health Care Clinical Chemistry Laboratory (Burlington, VT, USA) Urine albumin was measured by the Array 360 CE Protein Analyzer (Beckman Instruments, Inc., Drea, CA, USA). Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc.). To estimate albumin excretion rate, sex-standardized A/kC (where albumin is expressed as μg/ml and creatinine is expressed as mg/ml) were calculated after multiplying men's urine creatinine concentrations by k 17/25, based on the higher rate of creatinine excretion typical of men compared with women (Warram *et al.* 1996; Jacobs *et al.* 2002). The sex-standardized A/kC is represented both linearly and dichotomously, with participants having values ≥25 and <250 defined as having microalbuminuria (Jacobs *et al.* 2002). Participants with macroalbuminuria (A/kC ≥250 mg/g) (*n* 127) were excluded in analyses of the urine albumin data.

### *Carotid artery intima-media thickness*

Images of bilateral common carotid and internal carotid arteries were obtained via high-resolution B-mode ultrasonography using a Logiq 700 ultrasound machine (GE Medical Systems, Waukesha, WI, USA). Images of the near and far walls were obtained, on the basis of a previous study (O'Leary *et al.* 1999). Central reading of the intima-media thickness was done at Tufts-New England Medical Center (Boston, MA, USA) (Espeland *et al.* 2003); maximal intima-media thickness at any site was used in analysis. Additionally, a dichotomous variable indicated the presence of atherosclerotic plaque (any stenosis in either the right or left carotid artery).

### *Coronary artery calcification*

Computed tomography of the coronary arteries was performed, as has been previously described (Carr *et al.* 2005), with electron beam scanners (Imatron C-150; Imatron, Inc., San Francisco, CA, USA) cardiac-gated at 80 % of the R-R interval at three centres and with a prospective electrocardiogram-triggered scan acquisition at 50 % of the R-R interval with multidetector scanners at the remaining three centres. The scanners are comparable in their ability to measure Ca (Carr *et al.* 2000). Scans were read centrally at Harbor University of California Medical Center (Los Angeles, CA, USA) and Agatston coronary artery Ca scores were quantified by blinded computer tomography (CT) image analysts. Participants with CAC scores >0 were considered to have CAC in the dichotomous variable representation.

### *Additional variables*

Sex, race, age, educational level (< high school, high school, some college, bachelor's degree, graduate or professional degree), current cigarette smoking (Yes/No), current alcohol use (Yes/No) and current hormone replacement therapy use (Yes/No) were self-reported. Physical activity was assessed using a detailed, semi-quantitative questionnaire adapted from the Cross-Cultural Activity Participation Study (B. Ainsworth, personal communication, San Diego State University). Leisure physical activity was computed as the sum of metabolic equivalent min/week of walking, conditioning, sports and dance, while a sedentariness score was the sum metabolic equivalent min/week of sitting or reclining, reading, knitting, sewing, etc, driving a car or watching television; metabolic equivalent activity

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intensity codes were based on a published table (Ainsworth *et al.* 2000). Neither separating former and never smokers nor treating alcohol as a continuous variable altered findings noticeably (data not shown).

HDL-cholesterol was measured in EDTA plasma using the cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN, USA) after precipitation of non-HDL-cholesterol with Mg/dextran, and LDL-cholesterol was calculated in plasma specimens having a TAG value $<400$ mg/dl using the Friedewald formula, at the Collaborative Studies Clinical Laboratory at Fairview University Medical Center. Resting blood pressure was measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL, USA). The average of the last two measurements was used in analyses.

### *Statistical analysis*

SAS was used for all analyses (version 9.1; SAS Institute, Inc., Cary, NC, USA). Mean levels of demographics, behaviours and physiological variables were provided by quintile of whole grain intake. Regression analyses were used to evaluate the association of each variable with whole grain intake, providing a *P* value for trend over the continuous whole grain variable. Linear regression was used for continuous dependent variables (PROC GLM). Logistic regression (PROC GENMOD) was used for dichotomous dependent variables and provided the *P* for trend. However, as logistic regression is a nonlinear procedure and therefore gives biased estimates of probabilities, which are on the arithmetic scale, linear regression was used to compute the adjusted percentages within whole grain intake quintiles for dichotomous dependent variables. The natural logarithm transformation was utilized because of skewness in serum insulin, CRP, A/kC, the common carotid intimal-medial thickness, the internal carotid intimal-medial thickness and the Agatston score. Geometric means of these variables were reported. To account for Agatston scores of zero, one was added to all Agatston score values prior to transformation, then subtracted after exponentiation when estimating the geometric means.

Three models were developed to evaluate relationships with whole grain intake. Model 1 was adjusted for age, sex, race, education, survey centre and energy intake (base adjustment). Model 2, our primary model of interest, further adjusted for behavioural factors including current smoking (yes if one or more cigarettes/week or no), current alcohol use (Yes/No) and dietary intake of the following food groups: fruit; vegetables; refined grains; dairy; fish and poultry; meat. Model 3 (mechanistic model) was adjusted for model 2 factors as well as for BMI and serum insulin, two variables thought to be in the causal pathway between whole grain intake and CVD; these models were intended to assess whether observed relationships with whole grain intake were mediated by BMI or insulin. Furthermore, race/ethnicity interaction with whole grain food intake was assessed in each model for each dependent variable by adding the product of the continuous whole grain variable with the categorical race/ethnicity variable. Race/ethnicity interaction was insubstantial except for the dependent variable albumin excretion rate.

## Results

The mean daily intake of whole-grain foods was 0·54 servings/d (Table 1), while the median ranged from 0·02 servings/d for the lowest quintile of whole grain intake to 1·39 servings/d for the highest (Table 2). Whole grain intake varied by race, with whites having the highest mean intake (0·60 servings/d), followed by blacks (0·53 servings/d), Hispanics (0·52 servings/d) and Chinese (0·32 servings/d).

After adjustment for age, sex, race, education, survey centre and energy intake, higher whole grain intake was strongly associated with race and being older, female, more educated, a non-smoker, more leisure physical activity, a lower sedentariness score and with consuming more energy, fruits, vegetables and dairy and less refined grains, meat and alcohol. Whole grain intake was not related to hormone replacement therapy, HDL-cholesterol, LDL-cholesterol, systolic blood pressure or diastolic blood pressure.

Inverse associations were found between whole grain intake and BMI, insulin, homeostasis model assessment insulin resistance, CRP and homocysteine (Table 3). In the case of CRP, *P* for trend was not significant after possible mechanistic adjustment for BMI and insulin; however, the estimated mean CRP was lower in whole grain quintile 5 than 1 ($P=0·009$). IL-6 was inversely associated with whole grain consumption in model 1; however, this was attenuated with further adjustments. Whole grain intake was inversely related to glucose and to impaired fasting glucose or newly diagnosed diabetes (glucose $\geq 100$ mg/dl), but showed little relation to newly diagnosed diabetes when analysed separately.

Urine albumin excretion was inversely associated with whole grain intake after adjustment for age, sex, race, education, survey centre and energy intake. These relationships were attenuated with additional adjustments. The proportion of participants with microalbuminuria paralleled trends observed in urine albumin excretion levels. Associations of urine albumin excretion rate and whole grain intake (adjusted as in model 3) varied with race/ethnicity (*P* for interaction 0·03). The A/kC was 12 % and 19 % lower per whole grain food serving per d among Hispanics ($P=0·03$) and Chinese ($P=0·02$), respectively. These associations were null in whites and blacks.

Whole grain intake was inversely associated with probability of having any CAC in the base model, but this association was attenuated with further adjustment. Whole grain intake was not associated with carotid artery intima-media thickness or presence of plaque. These associations are presented in light of relatively low correlations among the different subclinical markers, which may suggest that each assesses a different aspect of subclinical CVD. The correlation between ln(Agatston score + 1) and ln(A/kC) was *r* 0·19; ln(common carotid artery intima-media thickness) and ln(A/kC) was *r* 0·19; and between ln(common carotid artery intima-media thickness) and ln(Agatston score + 1) was *r* 0·32.

## Discussion

In this multi-ethnic sample of 5496 men and women, mean whole grain consumption of about 0·5 servings per d was slightly less than that estimated for the entire US population (Cleveland *et al.* 2000), and is well below the recommended

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**Table 2.** Means and percentages* of demographics, behaviours, diet, blood lipids and blood pressure by category of whole grain intake in 5496 participants, MESA 2000–2002‖

| | Whole grain intake category | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | SEM* | *P* trend |
| Whole-grain intake (servings/d) | | | | | | | |
| Median | 0·02 | 0·15 | 0·39 | 0·72 | 1·39 | | |
| Range | 0·00–0·07 | 0·08–0·26 | 0·27–0·52 | 0·53–0·96 | 0·97–6·14 | | |
| *N* | 1069 | 1137 | 1072 | 1121 | 1097 | | |
| Demographics | | | | | | | |
| Male (%) | 55·8 | 48·3 | 44·8 | 44·3 | 43·0 | 0·015 | <0·0001 |
| Race (row %) | | | | | | | <0·0001‡ |
| White | 12·7 | 20·7 | 19·8 | 23·7 | 23·2 | | |
| Black | 16·4 | 19·7 | 19·3 | 23·3 | 21·4 | | |
| Hispanic | 23·3 | 21·8 | 20·7 | 16·8 | 17·4 | | |
| Chinese | 42·3 | 21·4 | 17·0 | 9·3 | 10·0 | | |
| Mean age (years) | 59·4 | 60·8 | 61·5 | 62·9 | 65·0 | 0·308 | <0·0001 |
| Education (row %) | | | | | | | <0·0001§ |
| < High school | 29·9 | 19·1 | 19·7 | 16·1 | 15·3 | | |
| High school | 20·3 | 20·8 | 19·8 | 19·6 | 19·5 | | |
| Some college | 18·2 | 21·0 | 19·4 | 21·2 | 20·3 | | |
| Bachelors | 16·0 | 20·8 | 19·6 | 22·9 | 20·8 | | |
| Graduate or professional degree | 14·7 | 21·9 | 19·0 | 21·2 | 23·0 | | |
| Behaviours | | | | | | | |
| Smoked within past 30 d (%) | 18·1 | 13·4 | 13·6 | 9·5 | 8·3 | 0·010 | <0·0001 |
| Alcohol (g/d) | 5·2 | 4·6 | 4·5 | 3·9 | 3·5 | 0·277 | <0·0001 |
| HRT (women only) % current use | 30·4 | 33·4 | 30·5 | 35·5 | 30·5 | 0·021 | 0·62 |
| Leisure physical activity (MET min/week) | 2285 | 2510 | 2340 | 2703 | 2610 | 94·244 | 0·0004 |
| Sedentariness score (MET min/week) | 1702 | 1755 | 1685 | 1655 | 1588 | 34·004 | 0·003 |
| Mean dietary intake | | | | | | | |
| Energy (kJ/d) | 6250 | 6672 | 7027 | 7228 | 8135 | 22·741 | <0·0001 |
| Refined grain (servings/d) | 2·03 | 1·95 | 1·92 | 1·83 | 1·64 | 0·026 | <0·0001 |
| Fruit (servings/d) | 1·89 | 2·00 | 2·09 | 2·44 | 2·69 | 0·049 | <0·0001 |
| Vegetables (servings/d) | 2·46 | 2·60 | 2·65 | 2·82 | 2·79 | 0·042 | <0·0001 |
| Dairy (servings/d) | 1·51 | 1·62 | 1·66 | 1·69 | 1·79 | 0·039 | 0·0002 |
| Fish/poultry (servings/d) | 0·98 | 0·99 | 1·00 | 1·02 | 0·94 | 0·017 | 0·02 |
| Meat (servings/d) | 0·65 | 0·61 | 0·57 | 0·52 | 0·41 | 0·012 | <0·0001 |
| Blood lipids and blood pressure (BP) | | | | | | | |
| HDL-cholesterol (mg/dl) | 51·8 | 51·8 | 51·4 | 51·5 | 51·3 | 0·429 | 0·45 |
| LDL-cholesterol (mg/dl) | 118·1 | 117·5 | 119·0 | 118·3 | 117·0 | 0·974 | 0·23 |
| Systolic BP (mmHg) | 126·3 | 125·6 | 125·4 | 125·7 | 125·0 | 0·605 | 0·17 |
| Diastolic BP (mmHg) | 72·2 | 71·7 | 72·0 | 72·1 | 71·6 | 0·302 | 0·21 |

* All means and percentages were adjusted for sex, age, race, education, site and energy intake; except for age, sex, education and energy intake, each of which is adjusted for the relevant combination of these variables only; and race, for which crude values are presented.
† $\sqrt{}$(mean squared error/mean *n* per quintile) is included to facilitate statistical comparison of pairs of whole grain quintiles.
‡ Based on $\chi^2$ statistic with 12 df.
§ Based on $\chi^2$ statistic with 16 df.
‖ For details of subjects and procedures, see Methods.
MESA, Multi-Ethnic Study of Atherosclerosis; HRT, hormone replacement therapy; MET, metabolic equivalent.

intake (US Department of Health & Human Services & the US Department of Agriculture, 2005) of three or more servings of whole grain foods per d. In fact, less than 1 % of participants met the official recommendation of three or more servings per d. About 20 % of white, black and Hispanic participants reported eating one or more servings per d, but less than 10 % of Chinese participants ate whole grain foods that often. As in previous papers (Jacobs *et al.* 1998; Steffen *et al.* 2003*b*), we found that whole grain food intake was a good indicator of other healthful behaviours, with higher consumption associated with being a non-smoker, drinking less alcohol, more leisure physical activity, less sedentary behaviour and greater consumption of fruit, vegetables and dairy and less of meat and refined grains.

These findings in the MESA database are consistent with several studies that have observed more favourable values of BMI, insulin and diabetes among whole grain eaters (Lovejoy & DiGirolamo, 1992; Feskens *et al.* 1994; Marshall *et al.* 1997; Ludwig *et al.* 1999; Liu *et al.* 2000, 2003; Meyer *et al.* 2000; Fung *et al.* 2002; Pereira *et al.* 2002; Liese *et al.* 2003; Montonen *et al.* 2003; Steffen *et al.* 2003*a*). Graded inverse relationships were observed between whole grain intake and BMI, serum insulin, homeostasis model assessment insulin resistance, glucose, and newly diagnosed impaired fasting glucose or diabetes.

As observed in other studies (Jensen *et al.* 2006; Lutsey *et al.* 2006), there was a strong inverse association between homocysteine and whole grain intake. This is as expected, since whole grains are a rich source of folate, which is inversely related to homocysteine (Wardlaw & Kessel, 2002). Several food-based feeding trials have also shown reductions in homocysteine resulting from increased consumption of whole grains

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**Table 3.** Means and percentages of body mass index, insulin resistance, inflammation, diabetes and subclinical CVD by category of whole grain intake in 5496 participants, MESA 2000–2002§

| | | Whole grain intake category | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CVD risk factor | Model | 1 | 2 | 3 | 4 | 5 | SEM* | *P* trend |
| Median whole grain intake | | 0·02 | 0·15 | 0·39 | 0·72 | 1·39 | | |
| *n* | | 1069 | 1137 | 1072 | 1121 | 1097 | | |
| BMI (kg/m$^2$) | 1 | 28·2 | 28·2 | 28·0 | 27·7 | 27·4 | 0·153 | <0·0001 |
| | 2 | 28·2 | 28·2 | 27·9 | 27·8 | 27·6 | 0·151 | <0·0001 |
| Insulin† (mU/l) | 1 | 5·44 | 5·48 | 5·45 | 5·15 | 4·96 | 0·019 | <0·0001 |
| | 2 | 5·37 | 5·42 | 5·42 | 5·19 | 5·16 | 0·019 | 0·002 |
| HOMA (mU/l*mmol/l) | 1 | 1·70 | 1·72 | 1·64 | 1·54 | 1·50 | 0·043 | <0·0001 |
| | 2 | 1·68 | 1·70 | 1·63 | 1·55 | 1·53 | 0·043 | 0·002 |
| CRP† (mg/l) | 1 | 3·56 | 3·31 | 3·23 | 3·18 | 3·02 | 0·022 | <0·0001 |
| | 2 | 3·48 | 3·26 | 3·20 | 3·22 | 3·12 | 0·022 | 0·004 |
| | 3 | 3·43 | 3·22 | 3·20 | 3·24 | 3·17 | 0·021 | 0·08 |
| IL-6 (pg/ml) | 1 | 1·59 | 1·50 | 1·46 | 1·48 | 1·45 | 0·037 | 0·03 |
| | 2 | 1·56 | 1·49 | 1·45 | 1·50 | 1·48 | 0·037 | 0·39 |
| | 3 | 1·54 | 1·47 | 1·45 | 1·51 | 1·51 | 0·035 | 0·92 |
| Homocysteine (μmol/l) | 1 | 9·68 | 9·34 | 9·35 | 9·01 | 8·77 | 0·113 | <0·0001 |
| | 2 | 9·62 | 9·32 | 9·34 | 9·05 | 8·80 | 0·113 | <0·0001 |
| | 3 | 9·62 | 9·32 | 9·34 | 9·05 | 8·82 | 0·113 | <0·0001 |
| Glucose (mg/dl) | 1 | 99·3 | 99·0 | 97·3 | 98·4 | 96·9 | 0·580 | 0·001 |
| | 2 | 99·2 | 98·9 | 97·3 | 98·4 | 97·2 | 0·580 | 0·008 |
| | 3 | 99·0 | 98·7 | 97·2 | 98·5 | 97·6 | 0·580 | 0·08 |
| IFG or newly diagnosed diabetes (%) | 1 | 38·4 | 35·4 | 33·2 | 34·1 | 32·1 | 0·015 | 0·004 |
| | 2 | 38·2 | 35·1 | 33·2 | 34·2 | 32·5 | 0·015 | 0·02 |
| | 3 | 37·7 | 34·4 | 32·7 | 34·7 | 33·8 | 0·014 | 0·23 |
| Newly diagnosed diabetes (%) | 1 | 4·0 | 4·7 | 3·5 | 3·7 | 3·6 | 0·006 | 0·16 |
| | 2 | 3·9 | 4·7 | 3·5 | 3·7 | 3·8 | 0·006 | 0·33 |
| | 3 | 3·8 | 4·5 | 3·4 | 3·7 | 4·1 | 0·006 | 0·63 |
| Urine albumin excretion† (mg/g) | 1 | 7·30 | 7·59 | 6·71 | 7·00 | 6·72 | 0·006 | 0·03 |
| | 2 | 7·22 | 7·55 | 6·69 | 7·04 | 6·82 | 0·018 | 0·20 |
| | 3 | 7·19 | 7·51 | 6·66 | 7·07 | 6·88 | 0·023 | 0·38 |
| % A/kC >25 | 1 | 10·7 | 12·5 | 9·2 | 10·2 | 8·9 | 0·009 | 0·05 |
| | 2 | 10·4 | 12·3 | 9·1 | 10·4 | 9·4 | 0·009 | 0·28 |
| | 3 | 10·3 | 12·2 | 9·0 | 10·6 | 9·5 | 0·009 | 0·39 |
| Common carotid IMT† (mm) | 1 | 0·853 | 0·857 | 0·850 | 0·849 | 0·850 | 0·002 | 0·26 |
| | 2 | 0·852 | 0·856 | 0·850 | 0·850 | 0·852 | 0·003 | 0·48 |
| | 3 | 0·851 | 0·855 | 0·849 | 0·851 | 0·854 | 0·003 | 0·98 |
| Internal carotid IMT† (mm) | 1 | 0·986 | 0·994 | 0·981 | 0·966 | 0·985 | 0·007 | 0·49 |
| | 2 | 0·977 | 0·990 | 0·978 | 0·971 | 0·996 | 0·011 | 0·59 |
| | 3 | 0·975 | 0·988 | 0·977 | 0·972 | 0·999 | 0·012 | 0·42 |
| % with plaque | 1 | 42·2 | 40·9 | 39·2 | 36·9 | 39·4 | 0·014 | 0·21 |
| | 2 | 41·1 | 40·5 | 38·9 | 37·5 | 40·5 | 0·014 | 0·97 |
| | 3 | 41·1 | 40·3 | 38·8 | 37·6 | 40·6 | 0·014 | 0·84 |
| Agatston score†‡ | 1 | 7·037 | 7·130 | 7·510 | 7·993 | 6·553 | 0·025 | 0·10 |
| | 2 | 6·788 | 7·018 | 7·486 | 8·106 | 6·825 | 0·046 | 0·34 |
| | 3 | 6·711 | 6·918 | 7·445 | 8·185 | 6·975 | 0·057 | 0·58 |
| % Agatston score >0 | 1 | 48·9 | 48·6 | 48·6 | 49·8 | 46·6 | 0·014 | 0·05 |
| | 2 | 48·4 | 48·4 | 48·6 | 50·0 | 47·2 | 0·014 | 0·15 |
| | 3 | 48·2 | 48·2 | 48·5 | 50·2 | 47·6 | 0·014 | 0·33 |

Model 1 (base model), age, sex, race, education, survey centre and energy intake.
Model 2 (behavioural model), model 1 plus current smoking, current alcohol use and dietary intake of fruit, vegetables, refined grains, dairy, fish and poultry, meat, leisure physical activity, and sedentariness score.
Model 3 (mechanistic model), model 2 plus BMI and insulin.
* Calculated as root MSE/(mean *n* per quintile) is included to facilitate statistical comparison of pairs of whole grain quintiles.
† Geometric mean.
‡ Zero values were included.
§ For details of subjects and procedures, see Methods.
MESA, Multi-Ethnic Study of Atherosclerosis; HOMA, homeostasis model assessment; CRP, C-reactive protein; IFG, impaired fasting glucose; A/kC, sex-standardized albumin: creatinine ratio where k = 1 for women and 0·68 for men; IMT, intima-media thickness.

(Jang *et al.* 2001), fortified cereals (Malinow *et al.* 1998; Riddell *et al.* 2000) and cereals prior to folic acid fortification of refined grain food starting in 1998 (Tucker *et al.* 2000).

In recent literature, inverse associations were observed between whole grain intake and inflammatory markers in a subset of men from the Health Professionals Follow-Up Study and women from the Nurses' Health Study II (Jensen *et al.* 2006); however, all became non-significant after accounting for lifestyle factors. In our analysis, CRP remained inversely associated with whole grain intake after adjustment for other behavioural characteristics, although the relationship was partially explained by adjustment for BMI and insulin, two factors that are believed to be in the causal pathway. IL-6 was inversely associated with whole grain intake after

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minimal adjustment; however, significance was not retained with further adjustment. No association between whole grain intake and IL-6 was observed in a previous study (Jensen *et al.* 2006). Another recent study among female nurses with type 2 diabetes observed inverse associations (Qi *et al.* 2006) of whole grain intake and both CRP and TNF receptor 2. Dietary fibre has also been inversely associated with serum CRP concentrations (King *et al.* 2003; Ajani *et al.* 2004).

As hypothesized, urine albumin excretion and microalbuminuria prevalence had inverse associations with whole grain intake in the base model. However, these associations became non-significant after additional adjustments. Urine albumin excretion was the only variable studied in which the present data suggested a race/ethnicity interaction; even in the fully adjusted models, Chinese and Hispanic participants showed an inverse association between whole grain intake and urine albumin excretion rate, whereas whites and blacks showed no relationship even in the base model. However, given the large number of variables assessed, this heterogeneity by ethnic group may have been a chance finding. To our knowledge no previous studies have examined the relationship between whole grain intake and urine albumin excretion or microalbuminuria. Total dietary fibre has, however, been evaluated, with one study showing reduced albuminuria among those consuming $>26$ g/d (Metcalf *et al.* 1993) and the other showing no effect (Watts *et al.* 1988).

In contrast and contrary to our initial hypotheses, however, whole grain intake showed little cross-sectional relationship with subclinical markers of vascular disease. There was limited evidence that whole grain intake was inversely associated with CAC, but no evidence that whole grain intake was predictive of carotid artery intima-media thickness. Associations of whole grain intake with these markers have not previously been reported. Numerous prospective studies have found graded and continuous relationships between subclinical disease and CVD outcomes (Levy *et al.* 1989; Chambless *et al.* 1997; O'Leary *et al.* 1999; Raggi *et al.* 2000), yet they occur early in the atherosclerotic process and do not reflect impending clinical disease. The subclinical disease markers used here are relatively weakly correlated and therefore heterogeneous. Thus, another possible explanation is that although whole grain may have an influence on atherosclerosis, measurement of CAC and intima-media thickness may be too loosely connected to the whole body burden of atherosclerosis to detect this influence. Furthermore, it is possible that whole grain intake reduces risk of CHD in ways other than through direct reduction of atherosclerosis. The failure to find associations between whole grain intake and these subclinical markers may reflect the cross-sectional design. A cause–effect relationship cannot be inferred from these data and reverse causality may be an issue. For example, despite participants being free of clinical CVD at baseline, it is possible that participants at greater risk for CVD may have begun taking behavioural precautions to reduce their risk of having a CVD event, such as increasing their whole grain intake. Given the lack of follow-up, whether whole grain intake is associated with progression of subclinical disease or incidence of clinical events was not studied. Ongoing MESA follow-up will help to overcome this limitation.

Another limitation of the study is that the dietary measure may have limited accuracy as it was based on a single FFQ. Further, whole grain consumption was low and there was little variation. It is possible that there could be a threshold effect in which the impact of whole grains on subclinical markers is only evident at higher levels of consumption than reported in this study. Error in the measurement of potential confounders or failure to measure and adjust for potential confounders could have resulted in residual confounding. Ruling out the possibility of residual confounding is particularly difficult in this analysis, as whole grain consumers tend to report healthier lifestyle habits than non-consumers (Jacobs *et al.* 1998; Steffen *et al.* 2003*b*).

Strengths of this study are that MESA collected an extensive set of subclinical CVD measures in a large sample of participants using standardized procedures to increase measurement validity and that whole grain intake (including specific cereal brand) was reported by participants using a FFQ, which accounted for both frequency of consumption and serving size. Additionally, in light of recent discussions concerning both the benefits of whole food approaches (Jacobs & Steffen, 2003) and possible limitations of single nutrient approaches in assessing relationships between diet and complex disease (Lichtenstein & Russell, 2005), the fact that we assessed diet in terms of whole grain intake may be considered a strength of the present study.

In summary, in this multi-ethnic sample of 5496 men and women, we found ethnic differences in whole grain intake, but few ethnic differences in the associations of whole grain foods with several dependent variables. There were strong cross-sectional associations between whole grain consumption and healthful behaviour, BMI, insulin, homocysteine, CRP and fasting glucose and possible associations with measures of urine albumin excretion rate, but no associations with measures of carotid artery intima-medial thickness or CAC.

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