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Wholegrain Intake and Long-term Weight Change in Men and Women in the REGARDS Study

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2017

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Abstract

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Background: Wholegrain products are recommended to maintain healthy body weight and lower the risk of several diseases. Prospective cohort studies that examine the association between wholegrain intake and long-term weight change among both genders are limited.

Objective: This study aimed to assess the association between wholegrain intake and weight change over 10-years follow-up among men and women in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study.

Methods: A total of 3,911 women and 2,850 men aged 45 years or older, with repeated measurements of body weight and wholegrain intake between 2006 and 2016, were included in the analysis, after excluding those with cancer, diabetes and kidney failure at baseline. Dietary information was collected via Block98 FFQ. Associations between wholegrain intake and long-term weight change and obesity were assessed using longitudinal analysis methods, controlling for multiple confounders.

Results: Participants in the highest tertile of baseline wholegrain intake tended to be heavier and had less weight gain over 10 years compared with those in the lowest tertile of intake. In multivariable models, reduced weight gain in the highest, compared to the lowest, tertiles of wholegrain intake was ≈ 0.66 kg for women (T3 vs. T1, -1.11 ± 0.29 kg vs. -0.45 ± 0.28 kg) and ≈ 1.14 for men (T3 vs. T1, -1.18 ± 0.33 kg vs. -0.04 ± 0.74 kg). People who consumed more wholegrain foods at baseline had ≈ 15% lower risk of developing obesity during the follow-up (T3 vs. T1, women: OR= 0.85, 95% CI: 0.62, 1.16; men: OR= 0.86, 95% CI: 0.61, 1.23).

Conclusion: Dietary wholegrain consumption was inversely associated with long-term weight gain and the development of obesity. The protective effect of wholegrain on 10-year weight gain was stronger among men than women (P- interaction < 0.05). Future high-quality, prospective cohort studies and clinical trials that directly measure this association are needed.

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Introduction

Obesity, defined as body mass index (BMI) of 30 kg/m^2 or more, is a serious public health concern. According to the National Center for Health Statistics (NCHS), 39.8% of US adults are obese. Further, there was an increasing trend in obesity among adults from 1999-2000 through 2015–2016 (1). Overweight (defined as BMI between 25 - 30 $kg/m^{2)}$ and obesity may increase the risk of hypertension, dyslipidemia, type 2 diabetes, heart disease and many other chronic disorders (2-6).

Previous epidemiologic evidence suggests the intake of wholegrain foods may influence body weight and have protective effects on health (7-10). Wholegrains, by definition, include cereal grains that contain intact, ground, cracked or flaked fruit of the grains which retain the same relative proportions as in the intact grain (11). The term "Wholegrain food" has been defined in a variety of ways by different countries. Even within the US the definitions are inconsistent; some definitions consider percent of the total grain that is wholegrain (USDA), others consider the percent of total food weight that is wholegrain (FDA for Wholegrain Health Claim), and still others (food industry) rely on wholegrain being the first ingredient on the food label. In the currently available scientific literature, some studies considered wholegrain-products as containing more than 25% wholegrain or bran content by weight, while others use 50% as the cutoff (12, 13) for defining wholegrain foods, making it challenging to compare results across studies. Wholegrain products generally include whole wheat and dark bread and crackers, oats, brown rice, rye, barley, and bulgur (14). Because of the physical form and high viscous fiber content, wholegrain foods are generally lower in energy density and are digested and absorbed slowly when compared with foods containing more refined grains because the refining process removes the bran and germ (13, 15, 16). In addition, wholegrains contain antioxidants, resistant starch, oligosaccharides, vitamins, minerals as well as phytate, phytoestrogens and phytosterols, which may be potentially helpful for weight control (17, 18). Consuming wholegrains may contribute to maintaining a healthy weight through promoting satiety (19), slowing starch digestion or absorption, and leading to lower glucose and insulin responses (20-22). According to recent Dietary Guidelines for Americans, at least three ounce equivalents/servings, where a serving is defined as ½ cup cooked brown rice, wholegrain pasta, or cooked hot cereal, such as oatmeal, 1 cup 100% wholegrain ready-to-eat, or 1 slice 100% wholegrain bread, should be consumed per day (23). The American Heart Association also recommends that at least half of the intake of grain products should be wholegrains in order to improve diet quality and lower cardiovascular disease risk (24). Unfortunately, according to data from the Continuing Survey of Food Intake by Individuals (CSFII), on average, American adults consumed 6.7 servings of grain products per day and less than 1 serving was from wholegrains (25-27).

The majority of previous studies have focused on the effect of wholegrain intake on risk of type 2 diabetes, cardiovascular disease and cancer; studies focusing on the relationship between wholegrain intake with body weight are scarce. Additionally, few studies looked at this association among men and women (18). Finally, only a few relatively short clinical trials of modest size focused on whole-grain diet and change in body weight. Based on these considerations, we will use the large bi-racial, geographically diverse REGARDS prospective cohort study to study the associations between wholegrain intake and weight change over time. We hypothesize that relatively high habitual intake of wholegrain is associated with weight management and with less likelihood of developing obesity over 10 years.

Furthermore, we will test whether the association of whole-grain intake with weight change is attenuated by further adjustment for dietary fiber intake, and investigate whether this association is modified by sex and baseline BMI.

Methods

Study population

The REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study is a population-based prospective cohort study focusing on racial and geographical influences on stroke mortality (28). Subjects were 30,183 non-Hispanic black and white adults, aged 45 years or older at baseline, and were recruited between January 2003 and October 2007 by mail contact first followed by phone-interview by trained interviewers, to determine eligibility. Subjects from the Stroke Belt (southeastern United States), a region of the country that has a particularly high risk of stroke, were oversampled by study design (including Alabama, Arkansas, Georgia, Louisiana, Mississippi, Tennessee, North Carolina, and South Carolina) (29). The final REGARDS cohort consists of 42% blacks and 55% women. Computer-assisted phone interviews were utilized to collect medical history, medication use, demographic and lifestyle information. Blood and urine samples and anthropometric data were collected via in-home visit, dietary intake was assessed using a self-ministered Block98 Food Frequency Questionnaire (FFQ) (28, 30). Subjects with a history of cancer, diabetes and severe kidney failure at baseline, those without a second weight or dietary intake measurement and those with implausible dietary intake (< 500 kcal/d or > 4500 kcal/d for men and < 400 kcal or > 3500 kcal for women) were excluded from the analysis. For the obesity incidence analysis, participants who were obese at baseline were excluded. Finally, 6,761 and 4,717 participants remained in the weight change and incidence of obesity analyses respectively (**Figure 1**.). All procedures related to human participants were approved by the Institutional Review Boards of all participating universities, written informed consent was obtained from all participants.

Dietary assessment

Dietary information was obtained at baseline and 10 years later respectively by using the Block98 FFQ. This instrument (designed by Nutrition Quest, Berkeley, California) is a self-administered, 107-item questionnaire used to assess typical food intake in the past year. The validation for most nutrients that are assessed was conducted in a population similar to REGARDS using multiple diet records. Correlation coefficients between estimates of nutrient quantities from the questionnaires and diet records were in the range of 0.5 to 0.7, indicating overall good agreement (31). REGARDS participants were asked how often (never, a few times/year, once/month, 2-3 times/month, once/week, 2 times/week, 3-4 times/week, 5-6 times/week, every day) and how much they consumed each food item (pictures were provided to help quantify the portion). Returned FFQs were analyzed and processed through Block Dietary Data Systems (Berkeley, CA) to estimate daily total energy, macro- and micro-nutrients intakes by using nutrient values according to data from the third National Health and Nutrition Examination Survey (NHANES III), the 1994 – 1996 Continuing Survey of Food Intakes by Individuals (CSFII) and using the USDA Nutrient Database for Standard Reference (31, 32).

Estimation of dietary wholegrain intake

Specific food items captured by the FFQ, such as brown rice, whole-wheat flour, bulgur (cracked wheat), oatmeal, and whole cornmeal were considered wholegrain foods. Food items were matched with similar foods in the USDA MyPyramid Equivalents Database (MPED) 2.0 for USDA Survey Foods 2003-2004 by using the unique 8-digit food code to get the ounce equivalents for each food item. The MPED 2.0 Database translates the amounts of foods eaten in USDA's What We Eat in America (WWEIA) survey as well as the dietary intake components of the National Health and the Examination Survey (NHANES) into the number of equivalents for the 32 MyPyramid major groups and subgroups. Food code and ingredient descriptions were used to identify the proportion of wholegrain and non-wholegrain components in grain-based foods. If details on grain ingredients were not available to determine the components in a grain product, guidance from food specialists of Nutrient Data Laboratory of Agricultural Research Service, U.S. Department of Agriculture was used (33). In the analysis, wholegrain intake was expressed as a nutrient density, the unit of consumption used was grams wholegrain per 1000 kilocalories of total energy per day (g/1000kcal/d).

Measurements of body weight, BMI, and weight change and potential confounders

Weights (in light clothing) and heights (without shoes) of participants were measured at baseline and follow-up by trained staff. BMI was calculated as weight in kg divided by height in square meters (kg/m^2). Weight change was calculated as the difference in weight between follow-up and baseline. Alcohol intake was categorized into none, moderate and heavy; exercise status was defined as none, 1 – 3 times/week and ≥ 4 times/week; current smoking status and current use of hormone replacement therapy (HRT) were dichotomized (yes/no). To deal with the problem of missing values of HRT at follow-up, we carried forward the baseline HRT status for women who were younger than 51 years old at baseline; for older women, we assumed they stopped using HRT at follow-up based on clinical guidelines of stopping HRT within 10 years of menopause to reduce the risk of diseases such as stroke and breast cancer (34, 35). Whether subjects developed diseases which have the potential to influence their diet and weight during follow up were considered by including a dichotomous (yes/no) variable to indicate diagnosis of any of the following: myocardial infarction (MI), coronary artery bypass grafting (CABG), angioplasty, stenting, diabetes, kidney failure and dyslipidemia.

Statistical analysis

We categorized participants into tertiles based on their baseline wholegrain intake with the lowest intakes in tertile 1. Differences in baseline characteristics across tertiles were assessed using analysis of variance (ANOVA) for continuous variables and chi-square statistics for categorical variables. We then used multivariate marginal linear models to assess the longitudinal association of tertiles of wholegrain intake with weight change (kg) (36, 37). We conducted a sex-specific analysis based on the evidence that the association could be different by sex (18, 19). In our basic model, we included age, total calorie intake and the interaction term between tertiles of baseline wholegrain intake and time, with weight (kg) treated as a continuous variable. Model 2 adjusted for other potential confounders including race, education, smoking status, physical activity, hormone replacement therapy use for women, alcohol intake, dietary total fat and protein intake, baseline BMI and disease status during follow-up. Final inclusion of potential confounders into the model was based on the following criteria: biological plausibility, relationship with the exposure and outcome of interest, and inclusion/exclusion of that variable from the model change the parameter estimates for the exposure variable by 10% or more. We further looked at whether the association was mediated by dietary fiber intake (Model 3). Tests for linear trend were conducted by ranking tertiles of baseline wholegrain intake from 1 to 3 (lowest to the highest tertile) and modeling as a continuous variable. Results were reported as adjusted means with 95% confidence intervals (95% CI). In secondary analyses, we performed generalized estimating equations (GEEs) to look at the association between baseline wholegrain intake and incidence of obesity after 10-years follow-up after excluding those who were obese at baseline. Obesity was treated as a dichotomous outcome variable (yes/no obesity), that followed similar procedures to those described above, except that results were reported as odds ratios (OR) with 95% Confidence Intervals (95% CI). Finally, we evaluated whether baseline BMI is an effect measure modifier by testing the interaction between baseline BMI and baseline wholegrain intake, evaluating the interaction with the likelihood ratio test, and stratified BMI into two groups using the median value among each gender as the cut point, and conducted stratified analysis. All statistical analyses used SAS version 9.4 and statistical significance was defined as p-value <0.05 based on two-tailed tests.

Results

The descriptive characteristics of women across tertiles of energy-adjusted baseline wholegrain intake are shown in **Table 1**. Characteristics of men according to each tertile of wholegrain intake are shown in **Supplementary Table 1**. The median intake of energy-adjusted baseline wholegrain intake ranged from 4.4 g/1000kcal/d in the lowest tertile to 27.4 g/1000kcal/d in the highest tertile for women and from 3.6 g/1000kcal/d in the lowest group to 24.5 g/1000kcal/d in the highest group for men. On average, after energy adjustment, men consumed less wholegrain than women. At baseline, the percentage of obesity was much higher in women than men (63.8% vs. 36.2%). Compared with the lowest tertile, those in the highest tertile of baseline wholegrain intake tended to have healthier lifestyles. Greater wholegrain intake was associated with lower weight and lower BMI at baseline, lower total energy, fat, alcohol, and cholesterol intake and higher fruit, vegetable and dietary vitamin E and fiber intake (all $P < 0.001$). People who had higher wholegrain consumption at baseline were more likely to be non-drinkers, non-smokers and regular exercisers. Glycemic load was slightly greater in those with higher wholegrain intakes. The average weight at baseline and follow-up for each group of wholegrain intake is shown in **Figure 2**. Weight loss was observed across each tertile of wholegrain intake in both sexes. Women in the highest tertile of wholegrain intake weighed 1.11 kg less than those in the lowest tertile at baseline, and lost ≈ 0.7 kg more weight over time (T3 vs. T1, -1.28 ± 8.44 kg vs. -0.58 ± 8.72 kg, P for trend < 0.001). For men, those in the highest group of wholegrain consumption weighed 2.34 kg less than those with the lowest intakes and lost ≈ 1.07 kg more weight during follow-up (T3 vs. T1, -1.18 ± 9.17 kg vs. -0.11 ± 8.63 kg, P for trend < 0.001).

Multivariate-adjusted mean weight changes (kg) over 10 years according to tertile of baseline wholegrain intake for men and women are shown in **Table 2**. On average, participants tended to lose weight during the 10-year follow-up period. In general, after the adjustment for potential confounders (Model 2), higher wholegrain intake had an inverse association with 10-year weight gain (P for trend = 0.08 for men and < 0.01 for women). Women who were in the highest tertile of baseline wholegrain intake lost ≈ 0.66 kg more weight than those in the lowest tertile of wholegrain intake (T3 vs. T1, -1.11 ± 0.29 kg vs. -0.45 ± 0.28kg). For men, multivariate-adjusted mean weight loss was ≈ 1.14 kg more for men with the greatest intakes of wholegrain compared to those with the lowest intakes (T3 vs. T1, -1.18 ± 0.33 kg vs. -0.04 ± 0.74 kg). The association was slightly attenuated with further adjustment of dietary fiber intake (Model 3). If baseline wholegrain intake was treated as a continuous variable, then for every 5g/1000kcal/d increased intake of wholegrain, weight gain was reduced by 0.25 ± 0.33 kg for men (P- value <0.01) and by 0.20 ± 0.17 kg for women (P-value < 0.01). In addition, the relationship between baseline intake of wholegrain and weight change appeared to differ by BMI status at baseline (P-interaction < 0.05). **Figure 3** shows the multivariate-adjusted average weight change (kg) overtime across tertiles of wholegrain intake stratified by baseline BMI categories of participants (Model 3). For both genders, the beneficial effects of higher dietary intake of wholegrain on weight gain were stronger among people in the normal baseline BMI category than those who were overweight or obese. Among women whose baseline BMI was normal, those in the highest tertile of wholegrain intake gained 1.00 kg less weight than did women in the lowest tertile over 10 years (T3 vs.

T1, 0.01 ± 0.38 kg vs. 1.01 ± 0.41 kg), whereas the weight difference was 0.56 kg among women who were overweight/obese (T3 vs. T1, -1.66 ± 0.37 kg vs. -1.10 ± 0.32 kg). Among men who were in the normal BMI category, the 10-year weight gain was 1.82 kg lower in the highest wholegrain intake group compared with the lowest consumption group among men (T3 vs. T1, -0.71 ± 0.35 kg vs. 1.16 ± 0.55 kg), and the weight difference was 1.03 kg among those who were overweight/obese at baseline (T3 vs. T1, -1.49 ± 0.89 kg vs. -0.25 ± 0.34 kg).

The odds ratios (OR) for development of obesity (BMI ≥ 30 kg/m^2) in 10 years according to tertiles of baseline wholegrain intake are shown in **Table 3**. During 10 years of follow-up, among those who were normal or overweight at baseline, 302 (11.6%) women and 233 (11.0%) men developed obesity. In general, the odds of developing obesity became lower with greater baseline wholegrain intake in both genders, but the effect was more pronounced among women. For women, compared with those in the lowest tertile, those in the highest group of wholegrain intake were ≈ 16% less likely to develop obesity over 10 years after controlling for potential confounders (OR=0.84, 95% CI: 0.61, 1.15). Similar results were observed among men (T3 vs. T1, OR=0.86, 95% CI: 0.61, 1.23). Further adjustment for dietary fiber intake did not appreciably change the results. We observed a significant interaction between baseline wholegrain intake and the baseline BMI status of participants (P- interaction < 0.05). Due to the small numbers of obesity among those with lower baseline BMI, we conducted stratified analyses based on the median value for baseline BMI for men and women separately, but consider these exploratory analyses. In general, the inverse association between wholegrain intake and incidence of obesity was stronger among those with lower BMI at baseline in both sexes (data not shown). The association remained unchanged after including dietary fiber intake in the model.

Discussion

In the large diverse prospective REGARDS cohort we observed an inverse association between baseline wholegrain intake and weight change over the 10-year follow-up period. This association was stronger among men and those who were in the normal BMI category at baseline. At baseline, those whose wholegrain intakes were higher had relatively lower body weight. During 10-y follow-up, those who consumed more wholegrain tended to lose more weight. For each 5/1000kcal/d increment of wholegrain intake, weight gain was reduced by 0.25 ± 0.33 kg for men (P-value <0.01) and 0.20 ± 0.17 kg for women (P-value < 0.01). In addition, compared to those with lower wholegrain intakes, participants with higher intakes of wholegrain had a ≈ 15% reduced risk of developing obesity among women (95% CI: 0.62, 1.16) and ≈ 14% reduced risk among men (95% CI: 0.61, 1.23) over the 10-year period.

A limited number of clinical trials have examined the association between wholegrain intake and weight change and their results are mixed. Some recent randomized clinical trials showed significantly reduced body weight after consumption of a wholegrain diet compared with the refined grain diet. In a recent study, 298 overweight subjects were randomly assigned to the control group (usual care group) and three intervention groups: (1) low-fat and high-fiber diet, and replacement of usual cereal intake with either (2) 50 g wholegrain oat, or (3) 100 g wholegrain oat. Subjects were followed up at 30-days and 1-year. During the 30-day period, the intervention groups had significant and similar decreases in body weight; after 1-year follow-up, the 100 g wholegrain oat group had a significantly greater decrease in body weight than other two intervention groups (weight change for each group, (1): -0.97 ±

0.64 kg, (2): -1.33 ± 0.69 kg, (3) -1.86 ± 0.71 kg)(38). In another clinical trial, 60 overweight Danish adults were randomly assigned to receive a wholegrain diet or a refined grain diet. After 8 weeks of follow-up, the wholegrain diet group had a significantly reduced body weight compared with the refined grain diet group (weight change, 0.9 ± 12.8 kg for the refined grain diet group, -0.2 ± 13.2 kg for the wholegrain diet group) (6). In addition, a randomized control trial with 70 overweight/obese participants reported that after 6 weeks, both body weight and fat mass decreased more in the wholegrain rye group compared with the refined grain group (39). In contrast, other clinical trials showed inconsistent results. One study, in which 25 male and 25 female with metabolic syndrome were randomly assigned to receive either a wholegrain diet or non-wholegrain diet for 12 weeks, suggested that wholegrain was not associated with weight change but was significantly inversely associated with abdominal body fat deposition (24). Another large trial which consisted of 204 overweight/obese adults, showed that weight loss was not significantly different between the intervention group (whole-grain ready-to-eat cereal group) and the control group (low-fiber food group) after 12 weeks of follow-up, but waist circumference decreased more in the intervention group (40). The lack of consistency of these studies may be partly due to the heterogeneity of types and quantity of wholegrain foods studied, variability in study duration and different characteristics of study populations (4, 41). Several prospective cohort studies have reported favorable effects of wholegrain consumption on body weight management which are consistent with our results. The Netherlands cohort study, including 2,078 men and 2,159 women, reported that people who consumed more wholegrains weighed less after 1 to 5 years of follow-up, and this association was stronger among men than women. In this study the reduced risk for becoming overweight and obese was also somewhat different by sex; 10% (95% CI: 2%-16%) among men and 4% (95% CI: 1%-7%) among women (19). We did not observe sex differences in risk of developing obesity in our study but were somewhat hampered by small numbers. Another large prospective study, the Health Professionals Follow-up Study (HPFS), found that men who consistently consumed greater amounts of wholegrain from all foods experienced less weight gain during an 8-year period (multivariate-adjusted weight gain: Q1, 1.24 ± 0.23 kg, Q5: 0.75 ± 0.22 kg, P for trend < 0.0001). A 40g/d increment in wholegrain intake was associated with a modest 0.49 kg lower weight gain (42). Similar associations were also found in the Baltimore Longitudinal Study of Aging and the Framingham Offspring Study (25). In addition, in the Nurses' Health Study (NHS), it was found that women who consumed more wholegrain consistently gained less weight during 12 years of follow-up than women who consumed less wholegrain (weight gain: Q1: 4.51 ± 0.10 kg, Q5: 4.45 ± 0.09 kg), and had a lower risk of developing obesity (OR=0.81, 95% CI: 0.73, 0.91) (2). These results correspond to our findings; however, in contrast to our results, in the NHS the beneficial effects of the increased intake of high-fiber wholegrain foods on weight change appeared to be stronger among those who were overweight or obese at baseline. The NHS participants were apparently healthy middle-aged women with a mean BMI around 25 kg/m^2 at baseline. Of the REGARDS participants, only 10.8% men and 18.6% women were normal of normal BMI at baseline (the mean BMI was 28.4 kg/m^2 for women and 27.5 kg/m^2 for men). Thus, our differential effects of wholegrain on weight change by baseline BMI status should be interpreted with caution due to the relatively small sample size in the normal BMI category.

Wholegrain might help in weight management and obesity prevention through multiple biological mechanisms, such as promoting satiety and metabolic efficiency (2). Experimental animal studies have shown that a wholegrain-rich diet reduced feed intake and body weight gain (43). The insoluble fiber content of wholegrain products may delay gastric emptying and slow the rate of starch digestion, thus enhancing the postprandial insulin functions that favor oxidation and lipolysis of fat and reduce lipogenesis and fat storage. (13, 19, 20). In a recent clinical trial (n = 131), a significant change in lipid metabolites was observed among the higher wholegrain consumption group. Diets rich in wholegrain could cause changes in high-density lipoprotein (HDL) particles changing their subclass distribution toward larger particles, which may reduce the cholesterol level and thus help to maintain a healthy body weight (44) (45). It is also possible that wholegrain consumption may help weight maintenance through controlling hormonal factors, although the active components are not clear (23).

Our study has strengths and limitations. To our knowledge, this is one of the very few investigations to look at the association between wholegrain intake and long-term weight change which performed separate analyses for men and women. The prospective design of the REGARDS study allowed for multiple measurements of body weight and potential confounders, providing us the opportunity to use longitudinal method for the analysis, which could account for the dependence between repeated measurements. Body weight and height were measured via in-home visits; thus, biases common to self-reported anthropometric data were minimized. In addition, we incorporated many potential confounders, including baseline BMI, age, education, race, several measures of dietary intake, smoking and drinking status, exercise patterns, history of chronic disease and hormone replacement therapy use among women. One of the limitations of our study was the limited sample size of normal weight individuals at baseline compared to other cohort studies. It is well known that people who are overweight or obese tend to under-report their energy intake and over-estimate healthy behaviors (19), which could have implications for misclassification of wholegrain intake in our study. Dietary wholegrain intake was derived from an FFQ not specifically designed to measure the intake of grain products. In addition, although in a validation study, the Block98 FFQ performed well, intakes of grain products were not validated. Patterns of wholegrain intake were similar to those observed in other studies; thus, it is reasonable to believe that the wholegrain estimates accurately represent true consumption. Furthermore, although we included several potential confounders, residual confounding caused by unmeasured or imperfectly measured confounders could still influence the true association between wholegrain intake and weight change. Finally, our study population had a significant proportion of older adults who might have experienced age-related loss of lean muscle mass and unintentional weight loss (46) (47) during follow-up. To address this concern we conducted exploratory analyses of the association between wholegrain intake and long-term weight change excluding those who were older than 70 years at baseline (See **Supplementary Table 2**). Participants in the highest tertile of wholegrain intake at baseline gained less weight during the follow-up compared with those in the lowest tertile of intake. These results are consistent with the protective effect of wholegrain intake on body weight observed in our main analyses.

In summary, we found that in the REGARDS population, wholegrain intake had an inverse association with 10-year weight gain independent of demographic, lifestyle and dietary factors, and the association was stronger among men. Additionally, higher intake of wholegrain foods also reduced the risk of developing obesity over 10 years.

Future Directions

Future high-quality prospective cohort studies with larger sample sizes and more accurate measurements of dietary intake and lifestyle factors are needed to elucidate the role of wholegrain on long-term weight change and disease prevention. Clinical trials that directly measure the effect of wholegrain on long-term weight change are also needed to draw conclusions about causality.

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Tables

Table 1. Characteristics of Eligible Female REGARDSs Participants by Tertiles of Wholegrain Intake

	Tertiles of Wholegrain Intake (g/1000kcal/d)				
Wholegrain median	All (13.3)	T1 (4.4)	T2 (13.3)	T3 (27.4)	P - value
N	3911	1303	1304	1304	
Age (y)	62.7 (8.4) [1]	60.9 (8.4)	62.7 (8.3)	64.3 (8.5)	<0.001
Weight (kg)	75.8 (16.7)	75.7 (18)	74.8 (16.5)	73.9 (17.3)	0.22
BMI (kg/m^2)	28.4 (6.1)	28.5 (6.1)	28.4 (6.2)	28.1 (6)	0.18
Calorie Intake (kcal/d)	1561 (574)	1556 (598)	1641 (578)	1 480 (532)	<0.001
Glycemic Load (g/d)	91.2 (38.8)	86.6 (41.1)	94.8 (38.9)	91.7 (35.6)	<0.001
Fat (% kcal)	37.5 (7.7)	39.3 (8)	37.9 (7.4)	35.3 (7.1)	<0.001
Protein (% kcal)	14.7 (3.1)	14.5 (3.4)	14.7 (3)	15 (2.7)	<0.001
Alcohol (% kcal)	2.6 (5.3)	3.4 (6.4)	2.6 (5.1)	1.8 (4.1)	<0.001
Saturated Fat (g/1000 kcal /d)	11.8 (2.9)	12.7 (3.1)	11.9 (2.7)	10.8 (2.7)	<0.001
Monounsaturated Fat (g/1000 kcal /d)	15.7 (3.9)	16.6 (4.0)	16.0 (3.9)	14.7 (3.5)	<0.001
Polyunsaturated Fat (g/1000 kcal /d)	10.9 (3.2)	11.1 (3.3)	11 (3.1)	10.6 (3.2)	<0.001
Cholesterol (mg/1000 kcal /d)	115 (53.5)	124.8 (63.4)	115 (47.7)	105.5 (45.7)	<0.001
Vitamin E [3]	6.0 (2.1)	6 .0(2.4)	6.1 (2)	6.0 (1.9)	0.45
Total Fiber (g/1000 kcal /d)	10.3 (3.9)	8.5 (3.1)	10 (3.3)	12.4 (4.2)	<0.001
Fruit (servings/1000 kcal /d)	1 (0.8)	0.9 (0.7)	1.1 (0.8)	1.2 (0.8)	<0.001
Vegetable (servings/1000 kcal /d)	2.1 (1.4)	2.1 (1.5)	2.1 (1.4)	2.2 (1.4)	0.01

Alcohol Intake					<0.001
None	2331 (60.4) [2]	689 (54.5)	745 (58.4)	849 (68.2)	
Moderate	1341 (34.7)	490 (38.7)	462 (36.2)	367 (29.5)	
Heavy	187 (4.8)	86 (6.8)	69 (5.4)	28 (2.3)	
Race					<0.001
White	2749 (70.3)	960 (75.9)	913 (71.6)	786 (63.2)	
Black	1162 (29.7)	305 (24.1)	363 (28.4)	458 (36.8)	
Current smoking					<0.001
Yes	398 (10.2)	162 (12.8)	124 (9.7)	100 (8)	
No	3499 (89.8)	1103 (87.2)	1152 (90.3)	1144 (92)	
Hypertension					0.02
Yes	1876 (48.2)	582 (46)	600 (47)	642 (51.6)	
No	2020 (51.8)	683 (54)	676 (53)	602 (48.4)	
Current Hormone Replacement Therapy Use					<0.001
Yes	2527 (64.8)	865 (67.8)	802 (64.5)	779 (61.6)	
No	1374 (35.2)	411 (32.2)	442 (35.5)	486 (38.4)	
Exercise (times/week)					<0.001
None	1244 (32.1)	437 (34.5)	417 (32.7)	359 (28.9)	
1 - 3	1565 (40.4)	503 (39.8)	539 (42.2)	493 (39.6)	
>=4	1061 (27.4)	325 (25.7)	320 (25.1)	392 (31.5)	
Education					0.013
Less than high school	215 (5.5)	59 (4.7)	68 (5.3)	79 (6.4)	
High school graduate	963 (24.6)	306 (24.2)	310 (24.3)	318 (25.6)	
Some college	1101 (28.2)	384 (30.4)	325 (25.5)	357 (28.7)	
College graduate and above	1630 (41.7)	516 (40.8)	573 (44.9)	490 (39.4)	
Developed Diseases During Follow-up					0.6467
Yes	1828 (46.7)	598 (47.3)	583 (45.7)	585 (47)	
No	2083 (53.3)	667 (52.7)	693 (54.3)	659 (53)	

[1] Values are mean (std) for continuous variables
[2] No. (%) for categorical variables.
[3] Dietary vitamin E intake is defined as α-tocopherol equivalents (α-TE)

Table 2. Average Mean Weight Change (kg) Over 10 Years According to Tertiles (T) of Baseline Wholegrain Intake in the REGARDS Study

	Baseline Wholegrain Intake by Tertiles			
	T1	T2	T3	P for trend
Women (N = 3 911)	n = 1 303	n = 1 304	n = 1 304	
Wholegrain median (g/1000kcal/d)	4.36	13.28	27.36	
Un-stratified				
Model 1[2]	-0.49 (-0.97, -0.01)[1]	-0.93 (-1.40, -0.46)	-1.20 (-1.66, -0.74)	0.59
Model 2[3]	-0.45 (-1.00, 0.11)	-0.84 (-1.41, -0.28)	-1.11 (-1.67, -0.56)	< 0.01
Model 3[4]	-0.42 (-0.97, 0.14)	-0.81 (-1.38, -0.25)	-1.06 (-1.61, -0.51)	< 0.01
BMI $\leq$ 25 kg/m^2				
Model 1	0.82 (0.13, 1.51)	0.87 (0.21, 1.54)	-0.22 (-0.79, 0.35)	0.36
Model 2	0.99 (0.20, 1.79)	1.09 (0.28, 1.90)	0.03 (-0.72, 0.78)	0.38
Model 3	1.01 (0.21, 1.82)	1.10 (0.29, 1.92)	0.01 (-0.73, 0.76)	0.38
BMI > 25 kg/m^2				
Model 1	-1.11 (-1.73, -0.49)	-1.79 (-2.40, -1.18)	-1.70 (-2.32, -1.07)	0.41
Model 2	-1.07 (-1.78, -0.36)	-1.72 (-2.45, -0.99)	-1.63 (-2.36, -0.90)	0.41
Model 3	-1.10 (-1.72, -0.30)	-1.71 (-2.44, -0.98)	-1.66 (-2.39, -0.93)	0.38
Men (N = 2 850)	n = 950	n = 950	n = 950	
Wholegrain median(g/1000kcal/d)	3.57	11.39	24.48	
Un-stratified				
Model 1	0.00 (-0.56, 0.55)	-0.97 (-1.46, -0.48)	-1.10 (-1.70, -0.50)	0.24
Model 2	-0.04 (-0.59, 0.52)	-1.18 (-1.68, -0.68)	-1.18 (-1.83, -0.54)	0.08
Model 3	0.06 (-0.51, 0.63)	-1.14 (-1.65, -0.63)	-1.25 (-1.89, -0.61)	0.01
BMI $\leq$ 25 kg/m^2				
Model 1	1.30 (0.26, 2.33)	-0.32 (-1.06, 0.42)	-0.41 (-1.08, 0.25)	0.30
Model 2	1.14 (0.10, 2.18)	-0.51 (-1.23, 0.21)	-0.68 (-1.36, -0.01)	0.27
Model 3	1.16 (0.09, 2.23)	-0.51 (-1.22, 0.21)	-0.71 (-1.39, -0.02)	0.27
BMI > 25 kg/m^2				
Model 1	-0.35 (-0.99, 0.30)	-1.18 (-1.79, -0.57)	-1.37 (-2.18, -0.57)	0.22
Model 2	-0.38 (-1.03, 0.28)	-1.40 (-2.03, -0.78)	-1.41 (-2.27, -0.56)	0.33
Model 3	-0.25 (-0.91, 0.42)	-1.35 (-1.97, -0.72)	-1.49 (-2.34, -0.63)	0.26

[1] $\bar{x}$ (95% CI) Weight change during the 10-year follow-up, values derived from generalized estimating equation including an interaction term with time

[2] Model 1 adjusted for age and total calorie intake at baseline

[3] Model 2 (For women) adjusted for age, education, race, total calorie, fat, protein intake, smoking status, drinking status, hormone replacement therapy use, baseline BMI, disease status during follow-up

(For men) adjusted for age, education, race, total calorie, fat, protein intake, smoking status, drinking status, baseline BMI, disease status during follow-up

[4] Model 3 additionally adjusted for dietary fiber intake to model 2

Table 3. ORs (95% CIs) of Incidence of Obesity (BMI ≥ 30) by Tertiles of Baseline Wholegrain Intake for Participants in REGARDs Study

Wholegrain Intake in Tertiles	Median Intake (g/1000kcal/d)	Cases (n)	Odds of Developing Obesity		
			Model1 [1]	Model2 [2]	Model 3 [3]
Women					
T1	4.43	108	1.00	1.00	1.00
T2	13.70	108	1.07 (0.85, 1.43)	1.07 (0.80, 1.43)	1.07 (0.80, 1.43)
T3	27.90	86	0.90 (0.66, 1.23)	0.84 (0.61, 1.15)	0.85 (0.62, 1.16)
P for trend			0.60	0.52	0.53
Men					
T1	3.57	85	1.00	1.00	1.00
T2	11.56	82	1.01 (0.73, 1.41)	1.05 (0.76, 1.47)	1.05 (0.76, 1.47)
T3	24.82	66	0.85 (0.60, 1.20)	0.86 (0.61, 1.23)	0.86 (0.61, 1.23)
P for trend			0.36	0.49	0.49

[1] Model 1 adjusted for age and total calorie intake at baseline

[2] Model 2 (For women) adjusted for age, education, race, total calorie, fat, protein intake, smoking status, drinking status, hormone replacement therapy use, baseline BMI, disease status during follow-up

(For men) adjusted for age, education, race, total calorie, fat, protein intake, smoking status, drinking status, baseline BMI, disease status during follow-up

[3] Model 3 additionally adjusted for dietary fiber intake to model 2

Figures

Figure 1. Flow chart to determine the analytic cohort of 6,717 REGARDS participants without self-reported cancer, diabetes, kidney failure at baseline, with data at both time points and plausible dietary energy intake. REGARDS, Reasons for Geographic and Racial Differences in Stroke

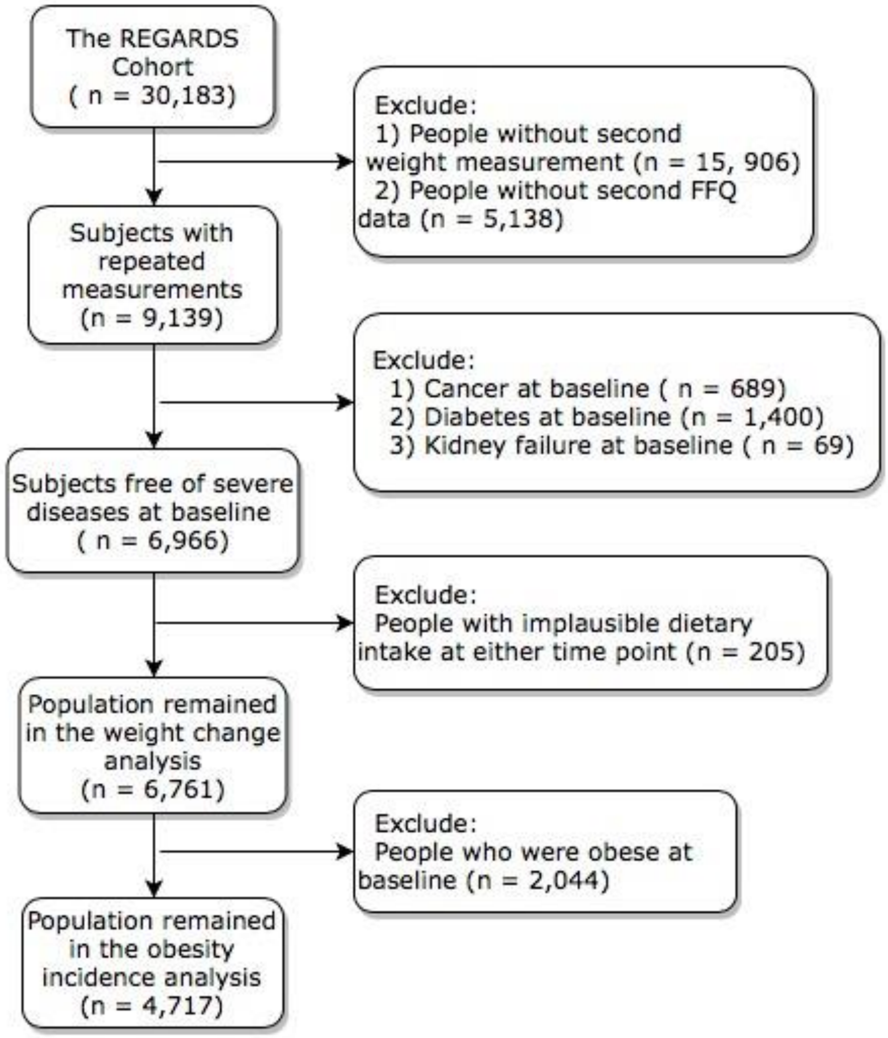


Figure 2. A: Mean weight in 2006 and 2016 according to tertiles of wholegrain intake for women. B: Mean weight in 2006 and 2016 according to tertiles of wholegrain intake for men

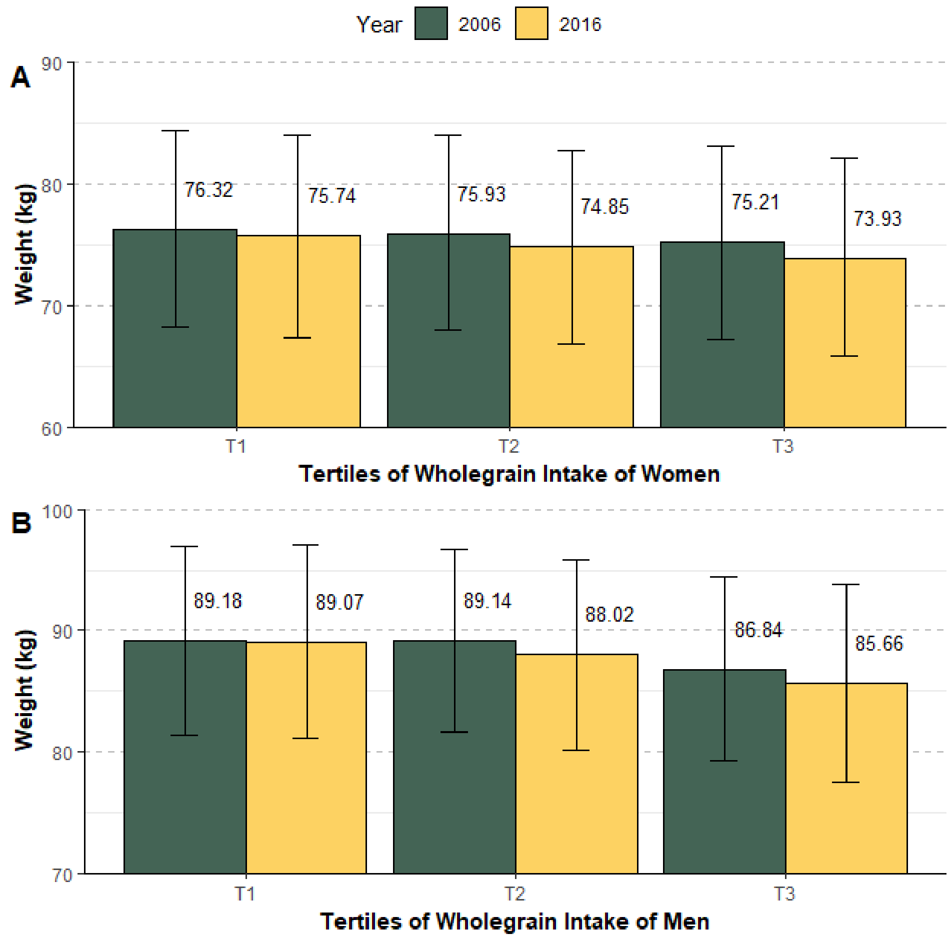
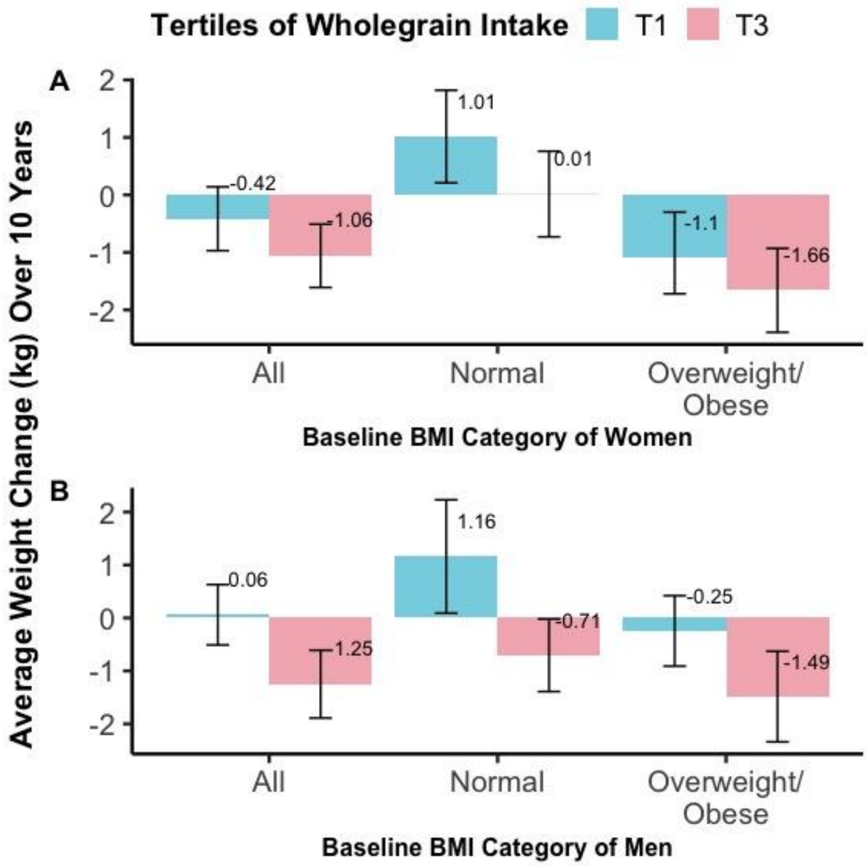


Figure 3. Multivariate-adjusted average weight change (kg) over time across tertiles (T) of baseline wholegrain intake for women and men (P for trend < 0.01 for both genders); Covariates adjusted for were (Model 3): age, race, education, total calorie, fat, protein intake, smoking, alcohol intake, baseline BMI, disease development during follow-up and dietary fiber for men, and additional adjustment of hormone replacement therapy use for women



Appendices

Supplementary Table 1. Characteristics of Eligible Male REGARDSs Participants by Tertiles of Wholegrain Intake

	Tertiles of Wholegrain Intake (g/1000kcal/d)				
Wholegrain median	All (11.4)	T1 (3.6)	T2 (11.4)	T3 (24.5)	P-value
N	2850	950	950	950	
Age (y)	63.7 (8.2) [1]	62 (7.9)	63.7 (8.3)	65.3 (8.1)	< 0.01
Weight (kg)	88.4 (15.1)	89.1 (15.4)	89.1 (14.7)	86.9 (14.9)	< 0.01
BMI (Kg/m²)	27.9 (4.3)	28.1 (4.4)	28.1 (4.3)	27.5 (4.2)	< 0.01
Calorie Intake (kcal/d)	1890 (666)	1907 (705)	1962 (649)	1802 (638)	< 0.01
Glycemic Load (g/d)	108.6 (43.7)	103 (44.6)	111.1 (42.4)	111.3 (43.6)	< 0.01
Fat (% kcal)	37.3 (7.5)	39 (8)	37.8 (6.9)	35.1 (6.9)	< 0.01
Protein (% kcal)	14.6 (2.9)	14.5 (3.2)	14.6 (2.8)	14.9 (2.7)	< 0.01
Alcohol (% kcal)	4.6 (6.8)	5.8 (7.9)	4.9 (6.6)	3.1 (5.1)	< 0.01
Saturated Fat (g/1000kcal/d)	11.9 (2.9)	12.8 (3)	12 (2.7)	10.8 (2.6)	< 0.01
Monounsaturated Fat (g/1000kcal/d)	15.9 (3.7)	16.7 (3.9)	16.2 (3.4)	14.9 (3.5)	< 0.01
Polyunsaturated Fat (g/1000kcal/d)	10.4 (3.2)	10.5 (3.6)	10.6 (2.9)	10.2 (3)	0.03
Cholesterol (mg/1000kcal/d)	123.2 (55)	133 (61.6)	124.8 (50.9)	112.3 (50.3)	< 0.01
Vitamin E [3]	5.4 (1.9)	5.3 (1.8)	5.5 (1.9)	5.6 (1.8)	< 0.01
Total Fiber (g/1000kcal/d)	9.2 (3.6)	7.4 (2.6)	8.8 (2.5)	11.5 (4)	< 0.01
Fruit (servings/1000kcal/d)	0.8 (0.6)	0.7 (0.6)	0.8 (0.6)	0.9 (0.6)	< 0.01
Vegetable (servings/1000kcal/d)	1.7 (1.1)	1.6 (1.1)	1.6 (1)	1.8 (1.3)	< 0.01
Alcohol Intake					< 0.01
None	1168 (41.6) [2]	341 (36.9)	343 (37.4)	460 (50.1)	
Moderate	1464 (52.1)	494 (53.5)	520 (56.7)	427 (46.5)	
Heavy	178 (6.3)	88 (9.5)	54 (5.9)	31 (3.4)	
Race					
White	2330 (81.8)	805 (87.2)	780 (85.1)	681 (74.2)	< 0.01
Black	520(18.2)	118 (12.8)	137 (14.9)	237 (25.8)	
Current smoking					< 0.01
Yes	277 (9.8)	113 (12.2)	89 (9.7)	67 (7.3)	
No	2565 (90.2)	810 (87.8)	828 (90.3)	851 (92.7)	
Hypertension					< 0.01
Yes	1227 (43.3)	367 (39.8)	380 (41.4)	440 (47.9)	
No	1604 (56.7)	556 (60.2)	537 (58.6)	478 (52.1)	
Exercise (times/week)					< 0.01

None	566 (20.0)	215 (23.3)	176 (19.2)	159 (17.3)	
1 - 3	1161 (41.1)	379 (41.1)	389 (42.4)	372 (40.5)	
>=4	1096 (38.8)	329 (35.6)	352 (38.4)	387 (42.2)	
Education					0.51
Less than high school	120 (4.2)	38 (4.1)	31 (3.4)	42 (4.6)	
High school graduate	556 (19.5)	173 (18.7)	165 (18)	194 (21.1)	
Some college	638 (22.4)	216 (23.4)	197 (21.5)	201 (21.9)	
College graduate and above	1536 (53.9)	496 (53.7)	524 (57.1)	481 (52.4)	
Developed Diseases During Follow-up					0.92
Yes	1895 (66.5)	615 (66.6)	611 (66.6)	611 (66.6)	
No	955 (33.5)	308 (33.4)	306 (33.4)	307 (33.4)	

[1] Values are mean (std) for continuous variables
[2] No. (%) for categorical variables.
[3] Dietary vitamin E intake is defined as α-tocopherol equivalents (α-TE)

Supplementary Table 2. Average Mean Weight Change (kg) Over 10 Years According to Tertiles (T) of Baseline Wholegrain Intake of middle-aged participants in the REGARDS Study [1]

	Baseline Wholegrain Intake by Tertiles			
	T1	T2	T3	P for trend
Women (N = 3178)	n = 1059	n = 1060	n = 1059	
Median (g/1000kcal/d)	4.20	12.78	26.51	
Un-stratified				
Model 1 [2]	0.31 (-0.24, 0.85) [5]	-0.27 (-0.78, 0.25)	-0.11 (-0.62, 0.40)	0.50
Model 2 [3]	0.49 (-0.13, 1.11)	0.04 (-0.57, 0.65)	-0.19 (-0.42, 0.81)	0.11
Model 3 [4]	0.56 (-0.06, 1.19)	0.08 (-0.53, 0.69)	0.17 (-0.45, 0.78)	0.44
BMI ≤ 25 kg/m^2				
Model 1	0.91 (0.27, 1.55)	1.30 (0.73, 1.88)	0.69 (0.16, 1.23)	0.77
Model 2	1.15 (0.41, 1.88)	1.65 (0.93, 2.36)	0.97 (0.30, 1.65)	0.83
Model 3	1.17 (0.43, 1.92)	1.66 (0.95, 2.37)	0.96 (0.29, 1.64)	0.81
BMI > 25 kg/m^2				
Model 1	-0.33 (-1.20, 0.53)	-1.85 (-2.68, -1.02)	-1.00 (-1.87, -0.11)	0.71
Model 2	-0.09 (-1.07, 0.89)	-1.46 (-2.44, -0.49)	-0.57 (-1.57, 0.44)	0.77
Model 3	0.02 (-0.96, 0.99)	-1.40 (-2.37, -0.43)	-0.60 (-1.61, 0.40)	0.71
Men (N = 2243)	n = 747	n = 748	n = 748	
Median (g/1000kcal/d)	3.11	10.57	23.36	
Un-stratified				
Model 1	0.73 (0.12, 1.37)	-0.43 (-1.00, 0.14)	-0.46 (-1.17, 0.25)	0.32
Model 2	0.72 (0.08, 1.36)	-0.68 (-1.27, -0.09)	-0.65 (-1.27, -0.09)	0.34
Model 3	0.87 (0.22, 1.52)	-0.57 (-1.17, 0.02)	-0.72 (-1.48, 0.04)	0.27
BMI ≤ 25 kg/m^2				
Model 1	1.36 (0.59, 2.12)	0.35 (-0.29, 1.00)	-0.14 (-0.78, 0.50)	0.12
Model 2	1.17 (0.37, 1.96)	0.19 (-0.43, 0.82)	-0.25 (-0.91, 0.41)	0.13
Model 3	1.23 (0.41, 2.05)	0.24 (-0.39, 0.87)	-0.30 (-0.96, 0.35)	0.10
BMI > 25 kg/m^2				
Model 1	0.20 (-0.80, 1.20)	-1.08 (-1.98, -0.17)	-0.76 (-2.09, 0.58)	0.48
Model 2	0.27 (-0.73, 1.26)	-1.48 (-2.43, -0.53)	-1.00 (-2.42, 0.45)	0.50
Model 3	0.51 (-0.50, 1.52)	-1.31 (-2.28, -0.35)	-1.03 (-2.45, 0.39)	0.42

[1] Only participants who were younger than 70 years old at baseline were included in the analysis
[2] Model 1 adjusted for age and total calorie intake at baseline
[3] Model 2 (For women) adjusted for age, education, race, total calorie, fat, protein intake, smoking status, drinking status, hormone replacement therapy use, baseline BMI, disease status during follow-up
(For men) adjusted for age, education, race, total calorie, fat, protein intake, smoking status, drinking status, baseline BMI, disease status during follow-up
[4] Model 3 additionally adjusted for dietary fiber intake to model 2
[5] $\overline{x}$ (95% CI) Weight change during the 10-year follow-up, values derived from generalized estimating equation including an interaction term with time