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Whole- and Refined-Grain Consumption and Longitudinal Changes in Cardiometabolic Risk Factors in the Framingham Offspring Cohort

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ABSTRACT

Background: Greater whole grain (WG) consumption is associated with reduced risk of cardiovascular disease (CVD); however, few prospective studies have examined WG or refined grain (RG) intake and intermediate cardiometabolic risk factors.

Objectives: We examined the longitudinal association between WG and RG intake on changes in waist circumference (WC); fasting HDL cholesterol, triglyceride, and glucose concentrations; and blood pressure.

Methods: Subjects were participants in the Framingham Offspring cohort study [$n = 3121$; mean ± SD baseline age: 54.9 ± 0.2 y; BMI (kg/m^2) 27.2 ± 0.1]. FFQ, health, and lifestyle data were collected approximately every 4 y over a median 18-y follow-up. Repeated measure mixed models were used to estimate adjusted mean changes per 4-y interval in risk factors across increasing categories of WG or RG intake.

Results: Greater WG intake was associated with smaller increases in WC (1.4 ± 0.2 compared with 3.0 ± 0.1 cm in the highest compared with the lowest category, respectively; *P*-trend < 0.001), fasting glucose concentration (0.7 ± 0.4 compared with 2.6 ± 0.2 mg/dL; *P*-trend < 0.001), and systolic blood pressure (SBP; 0.2 ± 0.5 compared with 1.4 ± 0.3 mm Hg; *P*-trend < 0.001) per 4-y interval. When stratified by sex, a stronger association with WC was observed among females than males. Higher intake of WG was associated with greater increases in HDL cholesterol and declines in triglyceride concentrations; however, these differences did not remain significant after adjustment for change in WC. Conversely, greater RG intake was associated with greater increases in WC (2.7 ± 0.2 compared with 1.8 ± 0.1 cm, *P*-trend < 0.001) and less decline in triglyceride concentration (−0.3 ± 1.3 compared with −7.0 ± 0.7 mg/dL, *P*-trend < 0.001).

Conclusions: Among middle- to older-age adults, replacing RG with WG may be an effective dietary modification to attenuate abdominal adiposity, dyslipidemia, and hyperglycemia over time, thereby reducing the risk of cardiometabolic diseases. *J Nutr* 2021;151:2790–2799.

Keywords: whole grain, refined grain, cardiovascular disease, Framingham Heart Study, waist circumference, fasting glucose, blood lipids, blood pressure

Introduction

Cardiovascular disease (CVD) is the underlying cause in approximately 1 out of every 3 deaths in the United States (1). Though there are many factors that contribute to the development of CVD, diet is an important factor not only because it has been associated with CVD risk in multiple cohort studies, but also because it is a modifiable target for CVD prevention (2).

Evidence from observational studies have found that greater whole grain (WG) consumption is associated with lower risk of CVD (3–6), as well as obesity (7), type 2 diabetes (T2D), hypertension (8–10), and all-cause mortality (11–13). In the United States, WG intake is low, with adults consuming an average of <1 serving per d (e.g., 1 serving is equivalent to a 1 oz slice of bread, which typically contains 16 g of WG) (14). In contrast, refined grain (RG) intake remains high, averaging 5–6 servings per d (15). Some (16–18), but not all (4, 19–21), studies indicate higher intake of RG is associated with greater risk of CVD. Therefore, higher WG intake, substituted for RG, is a potential dietary strategy to lower CVD risk.

WG is defined as the intact, ground, cracked, or flaked fruit of the grain, that includes the endosperm, germ, and bran (22), whereas RG only contains the endosperm. Compared with RGs, WGs are higher in fiber, magnesium, vitamin E, potassium,

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and many other phytochemical and bioactive components, each of which has different cardiometabolic health benefits (23). For example, the soluble fibers have been reported to increase satiety and modulate postprandial glucose and insulin responses. Magnesium has been shown to improve insulin sensitivity, and polyphenols or other bioactive components have been reported to alter the composition of the gut microbiota (23, 24).

Clinical measures that have been demonstrated to predict the risk of CVD and other cardiometabolic diseases can serve as intermediate risk factors, or early warning signs, of nascent disease. These include measures of central adiposity [i.e., waist circumference (WC)], blood lipid and lipoprotein concentrations, blood pressure, and fasting glucose concentrations and/or insulin resistance. The majority of previous observational studies that have examined grain intake in relation to these intermediate risk factors were limited by cross-sectional design (25–39), with some reporting favorable associations between WG intake and blood glucose concentrations (25, 27, 31), abdominal adiposity (29, 31, 34, 36–38, 40), and blood lipid and lipoprotein concentrations (26, 28–30). Some randomized controlled trials have demonstrated beneficial effects of WG intake on total cholesterol (41) and glucose concentrations (3), blood pressure (42, 43), and abdominal adiposity (44), whereas others have not (45–48). Inconsistencies among trial results may be due to heterogeneous study designs, insufficient statistical power, or insufficient intervention period (49–52). To our knowledge, no long-term, prospective observational studies have yet examined the relation between WG or RG intake and changes in blood lipids or blood glucose concentrations.

The main objective of this study was to examine habitual grain consumption and periodic changes in cardiometabolic risk factors, including WC, systolic blood pressure (SBP) and diastolic blood pressure (DBP), and fasting plasma HDL cholesterol, plasma triglyceride, and serum glucose concentrations.

Subjects and Methods

This prospective study used data collected from the National Heart, Lung, and Blood Institute (NHLBI) Framingham Heart Study (FHS) Offspring Cohort. The FHS is a long-term, community-based population study, initiated in 1948, with the aim of studying determinants of CVD. In 1971, 5124 offspring of the original cohort were recruited into the Offspring cohort. Approximately every 4 y, participants undergo standardized medical history and physical examinations. Dietary assessment began in the 5th examination cycle (1991–1995), which was considered as the baseline of the current study. As of 2014, a total of 9 study examinations have been completed. We used data from the 5th (1991–1995, n = 3799), 6th (1995–1998, n = 3532), 7th (1998–2001, n = 3539), 8th (2005–2008, n = 3021), and 9th (2011–2014, n = 2430) study examinations. Subjects were included only if they attended ≥2 consecutive examinations with valid dietary data (n = 3365). Therefore, the baseline exam varied by subject and was defined as the 1st exam for which there was also consecutive exam data available. Subjects could contribute multiple observations if they had data from >2 consecutive exams. Subjects with diabetes at baseline, defined as blood glucose ≥200 mg/dL, or fasting blood glucose ≥126 mg/dL, or currently being treated for diabetes were excluded (n = 244). Therefore, 3121 subjects were included in the final analyses, contributing 9231 exam-interval observations (**Figure 1**).

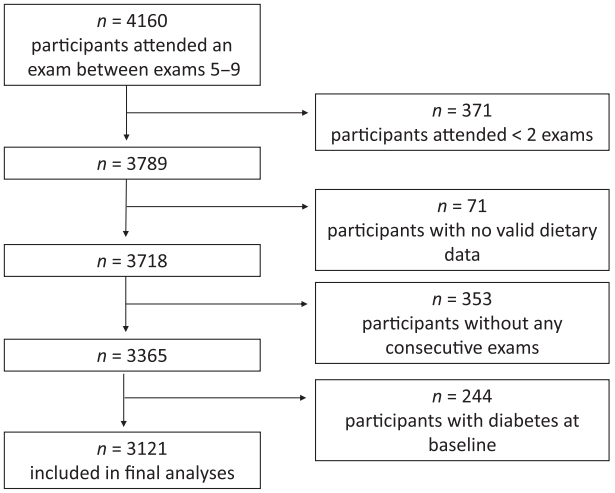

FIGURE 1 Flow chart of included participants from the Framingham Cohort Study and reasons for exclusion from analyses.

All FHS study protocols and procedures were approved by the institutional review board for human research at Boston University. The Tufts Health Sciences Institutional Review Board reviewed the current study. All subjects provided their written informed consent for participation.

Dietary assessment

Diet was assessed using the Harvard semiquantitative FFQ, which was designed to capture habitual dietary intake of the previous year (53). The FFQ included a list of foods with standard serving sizes and 9 frequency categories, ranging from never or <1 serving per mo to ≥6 servings per d, and also asked about brands or types of cold breakfast cereal usually consumed. The daily intakes of food groups (e.g., fruits and vegetables) were calculated by multiplying the portion size of each food that was consumed by the consumption frequency and summing across all food items. Nutrient intakes were calculated by multiplying the frequency of consumption of each food item by the nutrient content of the specified portion. Nutrient composition was based on the USDA food composition database and supplemented with other published sources (53). The relative validity of this FFQ to capture both foods and nutrients has been evaluated in several populations (53–55). Invalid dietary data was defined as a total energy intake of <600 kcal/d for all or ≥4000 kcal/d for females and ≥4200 kcal/d for males or >12 blank food items.

A WG database developed by the Harvard School of Public Health was used to quantify the amount of WG in each food and breakfast cereal as described previously (56). The database identified ingredients and cereal grains (barley, brown rice, brown rice flour, buckwheat groats, bulgur, cornmeal, corn flour, millet, oats, oat flour, rye, rye flour, and whole wheat flour) using the recipes obtained from manufacturers' product labels, the USDA Nutrient Database, and cookbooks sold in supermarkets. The amount of WG in each food was then designated as equivalent to the dry weight of the WG ingredients (i.e., calculated

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Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn.

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Abbreviations used: CVD, cardiovascular disease; DBP, diastolic blood pressure; DGAI, Dietary Guidelines Adherence Index; FHS, Framingham Heart Study; PUFA:SFA, ratio of polyunsaturated fatty acid to saturated fatty acid; RG, refined grain; SBP, systolic blood pressure; SSB, sugar-sweetened beverage; T2D, type 2 diabetes mellitus; WC, waist circumference; WG, whole grain

by subtracting the water component). The amount of bran and germ added during processing was also identified. Accordingly, the WG intake (in grams per day) for each participant was then estimated, including both with and without added bran and germ. For the present analyses, we only considered the grams per day without added bran and germ, according to the current consensus on how to define WG (57). Grams of WG per day were then translated into servings per day by dividing by 16 grams/serving, the amount of WG typically present in 1 ounce (or 1 serving) of a 100% WG food item, to allow comparison to RG intake (58).

RG was captured as servings per day from the FFQ for the following food items: refined cold ready-to-eat breakfast cereal (defined as containing <25% WG by weight), cooked breakfast cereal (not oatmeal), white bread, English muffins, bagels, muffins, biscuits, white rice, pasta, pancakes, waffles, crackers, and pizza. A serving of RG was a 1 oz equivalent and defined as 1 cup cold ready-to-eat breakfast cereal, 0.5 cup cooked cereal, 1 slice white bread, one-half English muffin or bagel, 1 muffin or biscuit, 0.5 cup white rice or pasta, 1 pancake or waffle, 7 crackers, or 1 slice pizza. RG from sweet/dessert food items was not included so that RG would better reflect WG counterparts. WG and RG were estimated as an average over each examination interval (i.e., an average of 2 exams) to better estimate habitual intake and minimize potential systematic error in dietary assessment.

Cardiometabolic risk factors

For the present study, we focused on the risk factors that have been used to define metabolic syndrome: WC (cm), SBP and DBP (mm Hg), and fasting plasma HDL cholesterol (mg/dL), plasma triglyceride (mg/dL), and serum glucose (mg/dL). During physical examinations, WC was measured by a trained professional by applying anthropometric tape at the level of the umbilicus with the participant standing, at midrespiration with participant breathing normally, and rounding of the measurement to the nearest 0.25 inches. Measurements were converted to units of centimeters for analyses. Sitting blood pressure was measured twice on each participant after a 5-min rest using a random-zero sphygmomanometer, and the 2 readings were averaged. Fasting (≥8 h) blood samples were drawn for assessing the concentration of glucose and lipids. Serum glucose was measured with a hexokinase reagent kit (A-Gent glucose test; Abbot). Plasma HDL cholesterol and triglyceride concentrations were measured using automatic enzymatic/colorimetric methods (Roche Cobas Analyzer c501, Roche Diagnostics).

Changes in outcomes were calculated as the change between consecutive exams. Since the actual time interval between exams could differ by subject, changes in outcomes were standardized by dividing the raw change by the number of years between exam dates and then expressing as 4-y change (because exams are approximately 4 y apart, on average). Outcome data was excluded from final analyses if the 4-y change in the outcome was not within ± 4 SDs of the mean 4-y change for that outcome. Final sample sizes varied by outcome [$n = 3104$ (9064 observations) for WC, $n = 3072$ (8857) for HDL cholesterol, $n = 3070$ (8843) for triglyceride, $n = 3118$ (9168) for SBP, $n = 3121$ (9187) for DBP, and $n = 3073$ (8863) for glucose].

Covariates

Several potential confounders of the relation between WG or RG intake and CVD risk factors were included as covariates in analyses. These included age (years); sex (male/female); current smoker (yes/no reported smoking regularly in the last year); physical activity [measured by the physical activity index (PAI), a score based on the sum of sedentary, light, moderate, and vigorous metabolic equivalent task (MET, hrs/wk)]; alcohol consumption (g/d); pharmacological treatment of dyslipidemia (for lipid outcomes), hypertension (for blood pressure outcomes), or diabetes (all yes/no); menopausal status (yes/no periods had stopped for ≥1 y); BMI (calculated as kg/m^2); change in waist circumference (cm); fruit, vegetable, and sugar-sweetened beverage (SSB) intake (all in serving/d); and the ratio of PUFAs to SFAs. Since PAI was not available for exam 6, exam 5 values were carried forward. Baseline age and sex, BMI as measured at the beginning of each exam interval (also referred to as the periodic baseline), and the change in WC over each exam interval (for example, the change from exam 5 to 6) were used. All other covariates were estimated as an average over each exam interval.

Statistical analyses

Repeated measure mixed models with an unstructured covariance matrix were used, as previously described (59), to estimate adjusted mean 4-y changes in each risk factor per category of energy-adjusted WG (g/day) or RG intake (serving/day). Grain intakes were adjusted for total energy intake using the residual method, averaged over each exam interval, and grouped into 4 categories. The WG categories were <8, 8 to <24, 24 to <48, and ≥48 g/d (or approximately <0.5, 0.5 to <1.5, 1.5 to <3, and ≥3 serving/d), and the RG categories were <2, 2 to <3, 3 to <4, or ≥4 serving/d. A test for linear trend across categories of WG and RG intake was performed by assigning the median value of grain intake for each category and treating these as a continuous variable. We adjusted sequentially for *1*) age, sex, energy intake, smoking, physical activity, alcohol consumption, menopausal status, BMI at the baseline of each exam interval (adjusted for in the 2nd model for WC), and diabetes, lipid, and hypertension medications; 2) change in WC (except when WC was the outcome we adjusted for BMI in this model); and *3*) consumption of fruits, vegetables, SSBs, and PUFA:SFA ratio, to capture other aspects of a healthy diet. We alternatively adjusted for overall diet quality score, captured using the 2015 Dietary Guidelines Adherence Index; however, this did not alter estimates (not shown). Because there was some concern for potential collinearity between WC and BMI, models that adjusted for WC were tested again, removing baseline BMI (not shown). Since this did not alter estimates, we retained BMI in the models. We also mutually adjusted for WG and RG in a separate model, but this did not alter the estimates (not shown). We tested for effect modification in the final model by assessing the interactions between WG or RG with sex, age, BMI category (BMI >25 kg/m^2 compared with ≤25 kg/m^2), total carbohydrate intake, and between WG and RG by including the corresponding cross-product terms in the mixed models and assessing the statistical significance of the likelihood ratios. When significant interactions were detected, stratified analysis was performed.

All analyses were conducted in SAS 9.4 (SAS Institute). All statistical tests were 2-sided, and statistical significance was set at a Bonferroni-corrected $P < 0.025$ (0.05/2 exposures of interest). We did not further adjust according to the number of individual outcome measures as all of these cardiometabolic risk factors are correlated and are considered together to increase the risk of CVD. Because tests for interactions were exploratory, these were considered statistically significant at a Bonferroni-corrected $P < 0.005$ (0.025/5 interactions).

Results

A total of 9231 observations were included from 3121 subjects who had ≥1 consecutive follow-up exam (i.e., attended ≥2 consecutive exams with valid data). The average number of exams attended was 4 (of a possible 5), with a median total follow-up time of 18.1 y (IQR: 7.0 y). At baseline, study participants had a mean ± SE age of 54.9 ± 0.17 y, 54.5% were females, and the majority were overweight or obese (64.4%) (**Table 1**). Study participants reported consuming an average of 16.0 ± 0.28 g/d (or 1.0 ± 0.02 serving/d) of WG and 3.0 ± 0.03 serving/d of RG. Only 3.8% of subjects reported consuming ≥48 g/d (~3 serving/d) of WG. The greatest contributors to WG intake were dark or whole wheat breads (47%) and ready-to-eat breakfast cereal (36%). For RG, the greatest contributors were white bread (22%) and pasta (20%).

Whole grain

After adjusting for demographic and lifestyle factors, participants in the highest category (≥48 g or ~3 serving/d) of WG intake compared with those in the lowest category

TABLE 1 Baseline participant characteristics by grain intake categories in 3121 participants of the Framingham Cohort Study[1]

		WG (g/d)[2]				RG (serving/d)			
	Total	<8	8 to <24	24 to <48	≥48	<2	2 to <3	3 to <4	≥4
Characteristics[3]									
n	3121	1226	1159	617	119	1009	840	580	692
Age, y	54.9 ± 0.17	55.4 ± 0.27	54.0 ± 0.28	55.8 ± 0.38	54.1 ± 0.88	56.4 ± 0.3	55.0 ± 0.33	53.9 ± 0.4	53.5 ± 0.36
Male sex, %	45.5	45.4	47.8	42.7	40.5	44.1	42.4	46.1	51.0
Weight, kg	76.9 ± 0.25	76.8 ± 0.4	77.7 ± 0.41	76.4 ± 0.56	73.4 ± 1.28	76.2 ± 0.44	77.1 ± 0.48	76.3 ± 0.58	78.4 ± 0.53
BMI	27.2 ± 0.09	27.3 ± 0.14	27.4 ± 0.14	26.8 ± 0.19	25.8 ± 0.44	27.0 ± 0.15	27.3 ± 0.16	26.9 ± 0.20	27.7 ± 0.18
WC, cm	92.6 ± 0.23	92.8 ± 0.36	93.1 ± 0.37	91.8 ± 0.51	90.3 ± 1.16	92.4 ± 0.4	92.7 ± 0.44	91.7 ± 0.53	93.7 ± 0.48
Fasting plasma HDL cholesterol, mg/dL	51.4 ± 0.25	51.4 ± 0.41	51.4 ± 0.41	51.1 ± 0.57	53.3 ± 1.3	52.2 ± 0.45	51.9 ± 0.49	51.2 ± 0.59	49.9 ± 0.54
Fasting plasma triglyceride, mg/dL	139.2 ± 1.83	142.3 ± 2.93	140.6 ± 3.00	132.9 ± 4.12	126.8 ± 9.39	136.1 ± 3.23	137.3 ± 3.53	142.4 ± 4.25	143.4 ± 3.89
SBP, mg/dL	125.4 ± 0.3	125.8 ± 0.49	125.8 ± 0.5	124.7 ± 0.69	122.0 ± 1.56	125.0 ± 0.54	124.5 ± 0.59	125.9 ± 0.71	126.8 ± 0.65
DBP, mg/dL	74.6 ± 0.17	74.4 ± 0.28	74.9 ± 0.29	74.5 ± 0.39	73.6 ± 0.89	74.3 ± 0.31	74.1 ± 0.34	74.9 ± 0.40	75.3 ± 0.37
Fasting serum glucose, mg/dL	95.4 ± 0.17	95.7 ± 0.26	95.5 ± 0.27	94.9 ± 0.37	94.6 ± 0.85	95.1 ± 0.29	94.8 ± 0.32	96.1 ± 0.38	96.1 ± 0.35
PAI score	34.9 ± 0.11	35.0 ± 0.18	35.0 ± 0.18	34.6 ± 0.25	36.2 ± 0.58	34.9 ± 0.2	35.0 ± 0.21	35.0 ± 0.26	35.0 ± 0.23
Current smoker, %	18.0	26.1	15.1	9.4	8.0	22.8	15.5	18.0	14.1
Overweight/obese, %	64.4	64.8	66.9	59.0	58.7	62.5	64.0	65.5	66.9
Hypertension, %	46.7	48.1	46.9	44.6	41.1	45.0	44.8	47.8	50.5
BP medication, %	17.9	17.2	18.4	18.3	16.2	17.8	17.5	17.4	18.7
Lipid medication, %	7.5	6.5	8.2	8.5	7.3	7.2	7.7	7.5	7.8
Menopausal, %	36.2	36.8	35.6	36.5	34.1	36.6	35.8	34.0	37.9
College graduate, %	38.9	30.0	41.1	50.2	45.7	35.0	40.8	42.5	39.2
Dietary intakes[4]									
Total energy, kcal/d	1868 ± 10.8	1683 ± 16.5	1927 ± 17.0	2033 ± 23.3	2347 ± 52.9	1510 ± 16.1	1782 ± 17.5	2002 ± 21.1	2382 ± 19.4
Whole grain, g/d	16.0 ± 0.28	4.2 ± 0.21	14.4 ± 0.21	32.7 ± 0.29	66.2 ± 0.66	18.2 ± 0.53	17.3 ± 0.54	14.9 ± 0.65	11.9 ± 0.65
WG, serving/d	1.0 ± 0.02	0.3 ± 0.01	0.9 ± 0.01	2.0 ± 0.02	4.1 ± 0.04	1.1 ± 0.03	1.1 ± 0.03	0.9 ± 0.04	0.7 ± 0.04
RG, serving/d	3.0 ± 0.03	3.1 ± 0.04	3.0 ± 0.04	2.8 ± 0.06	2.4 ± 0.13	1.5 ± 0.03	2.5 ± 0.03	3.4 ± 0.03	5.4 ± 0.03
Total carbohydrate, g/d	238.5 ± 0.76	230.8 ± 1.21	237.3 ± 1.22	250.0 ± 1.69	271.3 ± 3.86	232.7 ± 1.44	238.3 ± 1.47	238.8 ± 1.77	247.0 ± 1.79
Total fat, g/d	62.4 ± 0.25	65.2 ± 0.40	62.9 ± 0.40	58.2 ± 0.56	51.0 ± 1.27	63.4 ± 0.48	62.6 ± 0.49	62.0 ± 0.59	61.1 ± 0.59
Total protein, g/d	77.5 ± 0.28	74.1 ± 0.44	78.5 ± 0.45	81.7 ± 0.62	80.7 ± 1.41	77.3 ± 0.53	77.7 ± 0.54	77.9 ± 0.65	77.1 ± 0.65
Total alcohol, g/d	10.9 ± 0.28	13.2 ± 0.45	10.3 ± 0.45	8.1 ± 0.62	7.4 ± 1.43	13.9 ± 0.52	11.0 ± 0.53	10.6 ± 0.64	6.6 ± 0.65
Fruit, serving/d	2.1 ± 0.03	1.9 ± 0.04	2.1 ± 0.04	2.5 ± 0.06	2.8 ± 0.13	2.2 ± 0.05	2.2 ± 0.05	2.1 ± 0.06	1.9 ± 0.06
Vegetables, serving/d	2.8 ± 0.03	2.6 ± 0.05	2.9 ± 0.05	3.3 ± 0.07	4.3 ± 0.16	3.0 ± 0.06	2.9 ± 0.06	3.0 ± 0.07	2.8 ± 0.07
SSBs, serving/d	0.4 ± 0.01	0.5 ± 0.02	0.4 ± 0.02	0.3 ± 0.03	0.1 ± 0.06	0.5 ± 0.02	0.4 ± 0.02	0.4 ± 0.03	0.3 ± 0.03
PUFA:SFA	0.6 ± 0.01	0.6 ± 0.01	0.6 ± 0.01	0.7 ± 0.01	0.8 ± 0.02	0.6 ± 0.01	0.6 ± 0.01	0.6 ± 0.01	0.6 ± 0.01
2015 DGAI score	58.3 ± 0.2	54.1 ± 0.31	59.1 ± 0.31	63.9 ± 0.43	65.7 ± 1.02	57.6 ± 0.38	59.3 ± 0.39	59.1 ± 0.47	57.4 ± 0.47

[1] Values are means ± SEs or percentages. BP, blood pressure; DBP, diastolic blood pressure; DGAI, Dietary Guidelines Adherence Index; PAI, physical activity index; PUFA:SFA, ratio of polyunsaturated fatty acid to saturated fatty acid; RG, refined grain; SBP, systolic blood pressure; SSB, sugar-sweetened beverage; WC, waist circumference; WG, whole grain.
[2] Approximately <0.5, 0.5 to <1.5, 1.5 to <3, or ≥3 serving/d (1 serving = 16 g WG).
[3] Adjusted for age and sex.
[4] Adjusted for age, sex, and total energy intake.

(<8 g or ~0.5 serving/d) had a smaller mean increase in WC, fasting serum glucose concentration, and SBP per 4-y interval (**Table 2**). These associations remained significant after adjustment for BMI, change in WC (in glucose and SBP models), and other dietary factors. WG consumption was also associated with a greater mean increase in fasting plasma HDL cholesterol concentration and greater mean decline in fasting plasma triglyceride concentration across increasing categories of WG intake. These associations were attenuated and no longer significant after adjustment for change in WC (**Supplemental Figure 1**).

We detected a significant interaction with sex ($P < 0.001$) in the fully adjusted WC model. When stratified, both females and males had a significant trend toward a smaller mean increase in WC across increasing WG intake categories, and the effect was larger among females (**Table 3**).

Refined grain

Similar yet opposite associations were observed between higher RG intake and cardiometabolic risk factors (**Table 4**). After adjustment for demographic and lifestyle factors, participants consuming ≥4 serving/d of RG food compared with those consuming <2 serving/d had a greater mean increase in WC and smaller mean decline in fasting plasma triglyceride concentration per 4-y interval. These associations remained significant after adjustment for BMI, change in WC (in triglyceride model), and other dietary factors. No significant associations were observed between RG intake and fasting serum glucose, plasma HDL cholesterol, or blood pressure.

A significant interaction was identified between RG intake and BMI in the glucose model ($P = 0.002$). After the data were stratified by BMI, no significant associations in either strata were observed (data not shown).

Discussion

Prospective changes in several cardiometabolic risk factors linked to metabolic syndrome and CVD were examined in a community-based prospective cohort of 3121 US adults.

We observed a significant association between greater WG intake and smaller increase in WC over time, especially among females, after adjustment for several demographic and lifestyle factors, including BMI. Although the observed association was relatively small, amounting to a total difference of 8.1 cm less gain in the highest compared with lowest WG intake category over 18 y, small gains in abdominal adiposity can impact disease risk. In a meta-regression analysis of 15 prospective studies on WC and CVD events, de Koning and colleagues found that just a 1 cm increase in WC translated to a 2% increase in the risk of CVD events (60).

Evidence from many prospective observational studies has supported the inverse relation between WG intake and overall body weight or BMI (24, 61–63). However, few studies have included measures of abdominal adiposity, which may be a stronger risk factor for metabolic and CVD disorders (64–66), and consistent findings have not been reported in short-term intervention studies (47, 67). Only 1 prior prospective study (over 3 y) (68) and some cross-sectional studies (28, 31, 34, 36–38) found a significant inverse association between WG intake and WC. Two other prospective studies found that higher intake of refined (white) bread was associated with gain in WC among females but found no associations with WG bread (69, 70).

The association between WG intake and WC was significant in both males and females; however, the difference in WC change across categories of WG was greater among females than in males, and females in the lowest category of WG intake had the greatest increase in WC. This may be partially due to sex differences in body fat distribution and accumulation of adiposity over time. Rates of obesity are higher among females, and sex hormones can affect changes in central adiposity with age (71). In this cohort, males had a greater WC at baseline than females (98.4 ± 10.2 compared with 86.1 ± 13.9 cm), but the average change in WC over time was smaller among males than females (average change of 1.9 ± 4.6 compared with 3.4 ± 7.3 cm per 4-y interval). This may explain the stronger association with WG observed among women.

Higher WG and less RG intake has also been associated with abdominal fat as measured by DXA (36, 72). In a cross-sectional study of 2834 adults in the Framingham Heart Study (the same cohort used in the present analysis), McKeown and colleagues found that WG intake was inversely associated with WC and visceral adipose tissue (VAT) volume (P-trend < 0.001 for both) (36). The beneficial association of WG on VAT was attenuated in the presence of high RG intake. This observation highlights the benefit of substituting RG with WG, rather than just addition of WG to an existing diet high in RG. Replacing RG foods with WG equivalents would increase WG intake without adding to overall total energy intake and simultaneously would lead to a reduction in RG intake. In an 8-week randomized, controlled, weight-maintenance trial, substituting WG for refined grain in an otherwise similar diet resulted in higher resting metabolic rate and higher stool energy excretion (73), which may help explain the association between WG intake and reduced adiposity. The 2020–2025 Dietary Guidelines for Americans recommends 3–5 serving/d of WGs, or to make at least half of the recommended 6 servings of grains per day WG.

We also observed a significant association between greater WG intake and better maintenance of fasting serum glucose over time. These findings support evidence from prospective studies that higher WG intake (74–78), but not RG intake (74, 75, 77–79), is linked to lower risk of T2D. Hyperglycemia is a major contributing factor in the development of T2D and 1 of the 5 components of metabolic syndrome. Prior cross-sectional studies that assessed the effect of WG and RG on fasting glucose concentrations have been mixed, with 3 finding no association between WG and blood glucose (29, 30, 32), and 3 finding significant inverse associations (25, 27, 31).

A significant inverse association was found between WG intake and SBP independent of changes in WC, although no significant association was observed between WG intake and DBP (after Bonferroni adjustment) or between RG and either SBP or DBP. This is consistent with a meta-analysis (80) of prospective studies, 4 on WG and 3 on RG, and the risk of hypertension (8–10, 81), which concluded that there was an inverse association with WG intake (RR: 0.86; 95% CI: 0.79, 0.93) but not RG intake. Body weight and central adiposity are reported to be associated with blood pressure and risk of hypertension (82–85); however, none of the prospective studies included in the meta-analysis evaluated whether the observed associations were independent of adiposity. Although slightly attenuated, we found that the association between WG intake and SBP remained significant after adjusting for changes in WC. Similarly, daily intake of 3 servings of WG wheat and oat foods has been reported to result in a 6 mm Hg reduction of SBP after 12 wk, independent of weight loss (42).

TABLE 2 Four-year change in cardiometabolic risk factors across categories of energy-adjusted WG intake in 3121 participants of the Framingham Cohort Study[1]

WG intake category[2]	0 to <8 g/d	8 to <24 g/d	24 to <48 g/d	≥48 g/d	*P*-trend[3]
WG intake,[4] g/d	4.8 (3.5)	15.0 (7.8)	31.9 (9.7)	55.3 (11.6)	
4yr Δ WC cm, *n* (observations)	2095	4049	2498	422	
Model 1[5]	2.97 ± 0.13	2.24 ± 0.08	1.74 ± 0.09	1.43 ± 0.21	<0.001
Model 2[6]	3.07 ± 0.13	2.43 ± 0.08	1.90 ± 0.10	1.74 ± 0.22	<0.001
Model 3[7]	3.01 ± 0.13	2.42 ± 0.08	1.94 ± 0.10	1.84 ± 0.23	<0.001
4yr Δ fasting plasma HDL cholesterol mg/dL, *n* (observations)	2029	3967	2439	422	
Model 1	1.96 ± 0.17	2.12 ± 0.11	2.56 ± 0.13	2.41 ± 0.33	0.007
Model 2	2.09 ± 0.16	2.09 ± 0.11	2.38 ± 0.13	2.13 ± 0.32	0.244
Model 3	2.23 ± 0.17	2.10 ± 0.11	2.29 ± 0.14	1.95 ± 0.33	0.988
4-yr Δ fasting plasma triglyceride mg/dL, *n* (observations)	2022	3963	2446	421	
Model 1	−3.84 ± 0.98	−4.95 ± 0.58	−6.76 ± 0.69	−6.95 ± 1.54	0.010
Model 2	−4.19 ± 0.97	−4.12 ± 0.58	−5.42 ± 0.68	−5.11 ± 1.53	0.211
Model 3	−4.87 ± 1.00	−4.19 ± 0.58	−5.03 ± 0.70	−4.48 ± 1.57	0.749
4yr Δ SBP, *n* (observations)	2104	4100	2535	429	
Model 1	1.37 ± 0.27	1.06 ± 0.17	0.24 ± 0.21	0.16 ± 0.48	<0.001
Model 2	1.32 ± 0.27	1.16 ± 0.17	0.41 ± 0.21	0.41 ± 0.48	0.003
Model 3	1.32 ± 0.28	1.17 ± 0.17	0.43 ± 0.21	0.55 ± 0.49	0.009
4yr Δ DBP mm Hg, *n* (observations)	2110	4107	2540	430	
Model 1	−0.36 ± 0.16	−0.44 ± 0.10	−0.75 ± 0.12	−0.69 ± 0.27	0.040
Model 2	−0.43 ± 0.16	−0.36 ± 0.10	−0.60 ± 0.12	−0.47 ± 0.27	0.320
Model 3	−0.45 ± 0.16	−0.37 ± 0.10	−0.58 ± 0.12	−0.39 ± 0.28	0.553
4yr Δ fasting serum glucose mg/dL, *n* (observations)	2030	3976	2440	417	
Model 1	2.56 ± 0.20	1.99 ± 0.13	1.62 ± 0.16	0.69 ± 0.38	<0.001
Model 2	2.51 ± 0.19	2.05 ± 0.13	1.82 ± 0.16	0.99 ± 0.37	<0.001
Model 3	2.51 ± 0.20	2.04 ± 0.13	1.82 ± 0.16	1.04 ± 0.38	0.001

[1] Values are means ± SE unless otherwise specified. DBP, diastolic blood pressure; PUFA:SFA, ratio of polyunsaturated fatty acid to saturated fatty acid; SBP, systolic blood pressure; SSB, sugar-sweetened beverage; WC, waist circumference; WG, whole grain.
[2] Approximately <0.5, 0.5 to <1.5, 1.5 to <3, or ≥3 serving/d (1 serving = 16g WG).
[3] $P < 0.025$ considered significant.
[4] Values are medians (IQRs).
[5] Model 1: periodic baseline age, sex, energy, periodic baseline value, current smoker (yes/no), physical activity score, alcohol (g/d), menopausal status, medication use for diabetes, dyslipidemia (for triglyceride and HDL cholesterol), and hypertension (for SBP and DBP only), and periodic baseline BMI (except for WC, which adjusted for this in model 2).
[6] Model 2: model 1 + periodic baseline BMI (for WC) or 4-y change in waist circumference (for all other outcomes).
[7] Model 3: model 2 + fruit (serving/d), vegetables (serving/d), SSB (serving/d), PUFA:SFA.

Cross-sectional studies have mostly found no associations between grain intake and triglyceride or HDL cholesterol concentrations (26, 27, 30–33, 39, 40). Other evidence has linked higher intake of carbohydrate foods, in particular carbohydrate sources with a high glycemic index, to elevated triglyceride concentration (86). We observed an association between RG intake and higher fasting plasma triglyceride, which was also independent of change in WC. However, significant associations between WG intake and triglyceride concentration, as well as fasting plasma HDL cholesterol, were attenuated and no longer significant after adjusting for change in WC.

There are several potential mechanisms by which higher WG and/or lower RG intake may have cardiometabolic benefits. First, WG is high in dietary fiber, which can have a satiating

TABLE 3 Four-year change in WC across categories of energy adjusted WG intake in 3121 participants of the Framingham Cohort Study stratified by sex[1]

WG intake category[2]	0 to <8 g/d	8 to <24 g/d	24 to <48 g/d	≥48 g/d	*P*-trend[3]
Observations, *n*					
All	2095	4049	2498	422	
Females	1042	2210	1495	266	
Males	1053	1839	1003	156	
4yr Δ WC, cm					
All	3.01 ± 0.13	2.41 ± 0.08	1.93 ± 0.10	1.83 ± 0.23	<0.001
Females	3.94 ± 0.22	3.06 ± 0.13	2.47 ± 0.15	2.14 ± 0.33	<0.001
Males	1.99 ± 0.14	1.72 ± 0.09	1.30 ± 0.12	1.48 ± 0.29	0.002

[1] Values are means ± SE adjusted for: periodic baseline age, energy, periodic baseline value, current smoker (yes/no), physical activity score, alcohol (g/d), menopausal status, medication use for diabetes, periodic baseline BMI, fruit (serving/d), vegetables (serving/d), SSB (serving/d), PUFA: SFA. PUFA:SFA, ratio of polyunsaturated fatty acid to saturated fatty acid; SSB, sugar-sweetened beverage; WC, waist circumference; WG, whole grain.
[2] Approximately <0.5, 0.5 to <1.5, 1.5 to <3, or ≥ 3 serving/d (1 serving = 16g WG).
[3] $P < 0.025$ considered significant.

TABLE 4 Four-year change in cardiometabolic risk factors across categories of energy adjusted refined grain intake in 3121 participants of the Framingham Cohort Study[1]

RG intake category	0 to <2 serving/d	2 to <3 serving/d	3 to <4 serving/d	≥4 serving/d	*P*-trend[2]
RG intake,[3] serving/d	1.6 (0.5)	2.5 (0.5)	3.4 (0.4)	4.6 (0.9)	
4yr Δ WC cm, *n* (observations)	2571	3457	1993	1043	
Model 1[4]	1.81 ± 0.09	2.18 ± 0.08	2.37 ± 0.12	2.71 ± 0.17	<0.001
Model 2[5]	2.00 ± 0.10	2.39 ± 0.09	2.49 ± 0.12	2.85 ± 0.18	<0.001
Model 3[6]	2.03 ± 0.10	2.38 ± 0.09	2.50 ± 0.12	2.87 ± 0.18	<0.001
4yr Δ fasting plasma HDL cholesterol mg/dL, *n* (observations)	2514	3369	1958	1016	
Model 1	2.42 ± 0.13	2.04 ± 0.12	2.23 ± 0.17	2.40 ± 0.23	0.811
Model 2	2.28 ± 0.13	1.98 ± 0.12	2.22 ± 0.16	2.51 ± 0.23	0.456
Model 3	2.25 ± 0.13	2.00 ± 0.12	2.22 ± 0.17	2.49 ± 0.23	0.427
4yr Δ fasting plasma triglyceride mg/dL, *n* (observations)	2518	3369	1952	1013	
Model 1	−7.02 ± 0.68	−5.73 ± 0.63	−4.87 ± 0.90	−0.31 ± 1.30	<0.001
Model 2	−5.63 ± 0.68	−5.10 ± 0.62	−4.07 ± 0.90	−0.32 ± 1.28	0.001
Model 3	−5.47 ± 0.68	−5.16 ± 0.63	−4.11 ± 0.90	−0.33 ± 1.29	0.001
4yr Δ SBP, *n* (observations)	2594	3507	2015	1052	
Model 1	0.53 ± 0.20	0.89 ± 0.18	1.04 ± 0.26	0.99 ± 0.37	0.134
Model 2	0.69 ± 0.21	1.01 ± 0.19	1.08 ± 0.26	1.01 ± 0.37	0.278
Model 3	0.67 ± 0.21	1.01 ± 0.19	1.14 ± 0.26	1.12 ± 0.38	0.163
4yr Δ DBP mm Hg, *n* (observations)	2607	3513	2018	1049	
Model 1	−0.57 ± 0.12	−0.52 ± 0.11	−0.64 ± 0.15	−0.27 ± 0.21	0.454
Model 2	−0.43 ± 0.12	−0.45 ± 0.11	−0.57 ± 0.15	−0.29 ± 0.21	0.927
Model 3	−0.42 ± 0.12	−0.46 ± 0.11	−0.58 ± 0.15	−0.27 ± 0.21	0.941
4yr Δ fasting serum glucose, mg/dL, *n* (observations)	2507	3379	1959	1018	
Model 1	1.97 ± 0.15	1.92 ± 0.14	1.87 ± 0.19	1.94 ± 0.27	0.782
Model 2	2.15 ± 0.15	2.02 ± 0.14	1.90 ± 0.19	1.90 ± 0.27	0.288
Model 3	2.16 ± 0.15	2.01 ± 0.14	1.89 ± 0.19	1.92 ± 0.27	0.306

[1]Values are means ± SE unless otherwise specified. DBP, diastolic blood pressure; PUFA:SFA, ratio of polyunsaturated fatty acid to saturated fatty acid; RG, refined grain; SBP, systolic blood pressure; SSB, sugar-sweetened beverage; WC, waist circumference.
[2]$P < 0.025$ considered significant.
[3]Values are medians (IQRs).
[4]Model 1: periodic baseline age, sex, energy, periodic baseline value, current smoker (yes/no), physical activity score, alcohol (g/d), menopausal status, medication use for diabetes, dyslipidemia (for triglyceride and HDL cholesterol), and hypertension (for SBP and DBP only), and periodic baseline BMI (except for WC, which adjusted for this in model 2).
[5]Model 2: model 1 + periodic baseline BMI (for WC) or 4-y change in WC (for all other outcomes).
[6]Model 3: model 2 + fruit (serving/d), vegetables (serving/d), SSB (serving/d), PUFA:SFA.

effect, and soluble fiber, in particular, may have a beneficial effect on blood lipids. For example, evidence from randomized controlled trials has demonstrated the cholesterol-lowering effect of beta-glucan found in WG oats (87). However, not all grain varieties contain the same types of fiber, and thus some varieties may not be as effective in lowering cholesterol and triglycerides (41). Additionally, the slower digestion and absorption of WG may result in a reduction in postprandial glucose and insulin response, which may, in turn, favor the oxidation and lipolysis of fat rather than its storage. In contrast, evidence from clinical studies supports that diets rich in highly digestible carbohydrates, indicative of greater refined grain or low fiber intake, can alter lipoprotein secretion and clearance, leading to higher fasting triglyceride concentrations (86, 88). Additionally, fermentation of dietary fiber by the microbiota present in the colon produces short-chain fatty acids (SCFAs), which are involved in lipid metabolism (89) and satiety and glucose metabolism via production of peripheral peptide tyrosine–tyrosine (PYY) and glucagon-like peptide-1 (GLP)-1 (89). Other nutritional attributes of WG, such as magnesium, potassium, selenium, and zinc, as well as antioxidants and polyphenols, may contribute to lowering blood pressure and improving glucose and insulin metabolism.

A major strength of the present analyses is the large, prospective nature of the FHS cohort, with repeated measures of exposures and clinical intermediate risk factors over a median of 18 y. Although FFQs are limited by recall and self-report biases, they are widely used and are good at estimating relative dietary intake (i.e., distinguishing high and lower consumers of specific foods or nutrients). We further benefited from access to a WG database that captured WG intake in grams. This allows for the removal of the contribution of added bran or germ from estimates and provides a more accurate "absolute" estimate of WG intake from all foods rather than a qualitative estimate of servings of WG foods. The current database does not include grams of RG, and, thus, RG foods were only captured in servings. Because some RG foods may contain a mixture of WG and RG, such as breakfast cereal with <25% WG, the observed effects of RG may have been attenuated. We did not exclude individuals with cardiometabolic risk factors that exceed cut points for disease definitions as we were interested in examining these changes across the life course. If we had excluded these individuals, our sample would contain only the healthiest individuals, and we would not be able to draw conclusions generalizable to a high-risk population. The proportion of overweight and obese individuals in our sample was comparable to that in the general US population (90). Additionally, we cannot rule out the possibility of residual confounding by other lifestyle factors influencing our results. We acknowledge that WG consumption is a marker of an overall healthier lifestyle; however, our models were adjusted for other aspects of a healthy diet. Finally, the generalizability

of our conclusions may be limited, as the Framingham Offspring cohort is a relatively homogenous cohort of Caucasian Americans.

Over the past couple of decades, the prevalence of abdominal obesity and T2D has increased substantially, contributing to CVD and related health consequences. Our findings suggest that greater WG intake is prospectively associated with better maintenance of WC, especially among females, SBP, and fasting blood glucose concentrations. In contrast, higher RG intake is prospectively associated with higher gains in abdominal adiposity and triglyceride concentrations. Overall, these findings support recommendations to replace RG foods with WG equivalents, particularly as a dietary modification to attenuate abdominal adiposity, hypertension, and hyperglycemia, and thereby reduce the risk for cardiometabolic disease.

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Data Availability

Data described in the manuscript, code book, and analytic code will not be made available by the authors because the authors are prohibited from distributing or transferring the data and codebooks on which their research was based to any other individual or entity under the terms of an approved NHLBI Framingham Heart Study Research Proposal and Data and Materials Distribution Agreement through which the authors obtained these data. The data used for this project are available upon request pending application to and approval by the Framingham Heart Study.

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