Association between statin use and serum cholesterol concentrations is modified by whole-grain consumption: NHANES 2003–2006[1–3]

Huifen Wang, Alice H Lichtenstein, Stefania Lamon-Fava, and Paul F Jacques

ABSTRACT

Background: Statins are used to lower cardiovascular disease risk in part because of their effects on plasma lipid profiles. Dietary whole grains have been reported to improve plasma lipid profiles. Little is known about potential interactions between statins and whole grains.

Objective: We aimed to assess the interaction between statin use and whole-grain intake in relation to serum lipid concentrations in adults.

Design: In this cross-sectional study, we used data from 4284 adults aged ≥45 y with reliable and complete dietary data who were participating in the NHANES 2003–2006. Usual whole-grain intake was estimated from two 24-h diet recalls by using the MyPyramid Equivalents Database. Participants self-reported statin use. Total cholesterol and HDL-cholesterol concentrations were measured in all adult participants. The non-HDL-cholesterol concentration and total cholesterol:HDL-cholesterol ratio were calculated. Multiple linear and logistic regression models were used for analyses.

Results: Statin usage was 24.9% in all participants (n = 1065), and 31.0% of participants (n = 1327) consumed ≥16 g whole grains/d. After adjustment for demographic and lifestyle factors, the non-HDL-cholesterol concentration was significantly lower in statin users than in nonusers. This difference was greater in participants who consumed ≥16 g whole grains/d (difference: 31 mg/dL; $P <$ 0.001) than in those who consumed <16 g whole grains/d (difference = 20 mg/d; $P < 0.001$) (P-interaction = 0.03). Significant interactions were also observed between whole-grain intake and statin use in relation to the total cholesterol:HDL-cholesterol ratio (P-interaction = 0.04) and elevated total cholesterol concentration (P-interaction = 0.02).

Conclusion: In adults aged ≥45 y, the use of statins was associated with healthier lipoprotein profiles when combined with higher whole-grain intake relative to low whole-grain intake. *Am J Clin Nutr* 2014;100:1149–57.

INTRODUCTION

Hypercholesterolemia, which is characterized by an elevated serum concentration of non-HDL cholesterol, particularly LDL cholesterol, is a major risk factor for cardiovascular disease (CVD)[4] (1, 2). Statin therapy effectively lowers the LDL-cholesterol concentration in most individuals by inhibiting the rate-limiting enzyme in cholesterol biosynthesis, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (2), and lowers CVD risk (3, 4). In the United States, the percentage of adults aged ≥45 y who reported the use of statins in the past 30 d increased from 2.4% in 1988–1994 to 25.1% in 2005–2008 (5).

A lifestyle modification is the cornerstone of CVD risk reduction (2); one of the key components is the consumption of a healthy diet (6). An understanding of the combined benefits of a healthy diet with drug treatments is of increasing interest. Although a healthy diet has been shown to be beneficial in both general and high-risk populations (6, 7), diet alone may not achieve the same level of benefit as a drug treatment. Likewise, drug treatments may not always be balanced in effectiveness, risk, and cost (8, 9). However, little is known about potential diet-drug interactions. Drugs may change people's appetites, tastes, or digestive tract movements and, thus, alter the metabolism of foods and nutrients, whereas foods and nutrients may compete with drugs for absorption sites or metabolic enzymes and, thus, influence the efficacies of drugs.

Whole grains are an important component in a healthy, energy-balanced diet (6, 10). By definition, whole grains contain all of the 3 components of the original kernel (ie, endosperm, bran, and germ) (11). The 2010 Dietary Guidelines for Americans recommended that at least one-half of all grains should be whole grains (10). Whole grains are rich in various nutrients, including fiber, thiamin, niacin, pantothenic acid, and phytochemicals (10). Prospective observational studies and randomized controlled trials (RCTs) have shown an inverse association between whole-grain intake and serum total cholesterol and LDL-cholesterol concentrations (12) as well as CVD risk (12). A limited number of small RCTs have focused on examining the combined effect of dietary fiber and statins on lipid profiles in a manner that indicated potential interactions (13–17). Some of these studies concluded that there were additive (independent) effects of fiber and statins (14–17), whereas one study (13) observed that the daily administration of fiber in addition to lovastatin increased, rather than decreased, LDL-cholesterol concentrations. However,

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[3] Address reprint requests and correspondence to H Wang, Nutritional Epidemiology Laboratory, 711 Washington Street, Boston, MA 02111. E-mail: huifen.wang@tufts.edu.

[4] Abbreviations used: CVD, cardiovascular disease; eq, MyPyramid equivalents; FFQ, food-frequency (propensity) questionnaire; MEC, Mobile Examination Center; MPED, MyPyramid Equivalents Database; NCI, National Cancer Institute; RCT, randomized controlled trial.

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to our knowledge, no previous study has examined the interaction between statin use and whole-grain consumption in relation to serum lipid concentrations.

This cross-sectional study aimed to determine whether there is an interaction between whole-grain intake and statin therapy in relation to serum lipid concentrations in individuals aged ≥45 y who participated in the NHANES. We hypothesized that concentrations of total cholesterol, non-HDL cholesterol, and LDL cholesterol would be lower in statin users with higher compared with lower whole-grain intakes, and the beneficial association of combined statin use and higher whole-grain intake with lipid profiles would be additive.

SUBJECTS AND METHODS

Study population

The NHANES is a long-running study designed to assess the health and nutritional status of noninstitutionalized adults and children in the United States (18). Since 1999, the NHANES was implemented as a continuous survey on a 2-y cycle basis. To produce reliable statistics and obtain estimates that are nationally representative, ~5000 individuals were interviewed and examined annually under a complex, multistage sampling scheme.

Each NHANES cycle included an initial in-person home interview and a subsequent study visit at a specially designed and equipped Mobile Examination Center (MEC). Trained interviewers collected participants' demographic, socioeconomic, dietary, and health-related information (including diabetes and CVD history) during the home interview. Participants were asked to fast 9 h and 6 h for morning and afternoon MEC examination sessions, respectively. At the MEC, a questionnaire was also administered to assess participants' actual fasting times. A 24-h diet recall (ie, day 1 recall) was administered during the MEC examination. A second, telephone-administered 24-h diet recall (ie, day 2 recall) was added in 2003. A computer-assisted personal interview system was used for both home and MEC interviews, and all examinations followed standardized protocols. NHANES protocols were approved by the Institutional Review Board of the National Center for Health Statistics, CDC. Informed consent was obtained from all participants.

Statins were seldom used by younger adults; only 66 of 3510 adults aged 25–44 y used statins during 2003–2004 and 2005–2006 NHANES cycles. Therefore, for the current study, we combined data from these 2 cycles and restricted analyses to 5501 participants aged ≥45 y. Of these, we excluded subjects with missing (n = 352) or invalid (n = 593) dietary data as defined by NHANES criteria and those with missing serum lipid measurements (n = 576). Exclusion criteria were not mutually exclusive, which left 4386 adults. Because statins were the focus of this study, 102 adults who did not take statins but took other antihyperlipidemic agents (ie, cholestyramine, colesevelam, colestipol, ezetimibe, fenofibrate, gemfibrozil, and probucol) were also excluded, which left 4284 adults for our final analyses. Of note, individuals who took other antihyperlipidemic agents in combination with statins were included in our primary analyses.

Dietary assessment

Both diet recalls were conducted by trained interviewers following a standard set of guidelines and by using the Automated Multiple-Pass Method, which is a computer-assisted dietary data-entry system that records types and amounts of foods that participants consumed in the past 24 h. The telephone-administered diet recall occurred 3–10 d after the day 1 diet recall.

In addition to the 2-day dietary recalls, a nonquantitative food-frequency (propensity) questionnaire (FFQ) was administered during the 2003–2004 and 2005–2006 cycles to ascertain participants' consumption patterns in the previous year.

Estimating usual dietary intake

On the basis of NHANES 24-h diet recalls, the USDA estimated intakes of energy and various nutrients to create the Food and Nutrient Database for Dietary Studies. The USDA also maintains the MyPyramid Equivalents Database (MPED), which translates the amounts of foods reported in 24-h dietary recalls into the number of MyPyramid equivalents (eq) of 32 major food groups or subgroups shown on the USDA Food Guide Pyramid that are present in 100 g food (19). Whole grains are one of the 32 MPED food groups, which, by definition, should contain all of the endosperm, bran, and germ in the same proportion as the original entire grain kernel (11). In contrast, non–whole grains (ie, refined grains) are those with bran and germ removed in milling (20). To estimate the day 1 and day 2 consumption of whole and refined grains for each participant, the MPED database used the food code and ingredient description to identify the proportion of whole- and refined-grain components present in grain-based foods (19). Food specialists also provided guidance for the determination of grain components in foods for which detailed ingredient descriptions were not available (19). The MPED 2.0 (19) provides the day 1 and day 2 dietary intakes for NHANES 2003–2004 participants. The MPED 2.0a (21) is an addendum that includes additional data needed along with the MPED 2.0 to provide day 1 and day 2 dietary intakes for NHANES 2005–2006 participants. For our analyses, we used the Food and Nutrient Database for Dietary Studies to estimate day 1 and day 2 intakes of total energy and nutrients and the MPED 2.0 and 2.0a to estimate day 1 and day 2 intakes of MyPyramid food groups for each adult.

To estimate each participant's usual dietary intake of foods reported in the 2-day recalls, we used the method and macros developed by the National Cancer Institute (NCI), including MIXTRAN, DISTRIB, and INDIVINT macros (22). Briefly, for episodically consumed foods, which are not consumed nearly every day by almost everyone in the population (22, 23), the NCI method recommended a 2-part model that assumed that intake of an episodically consumed food is a function of the probability of consuming the food on a given day and the amount of the food consumed on a consumption day. By contrast, the probability of consumption of ubiquitously consumed foods on any day is assumed to be one for estimating usual intake. Consequently, we categorized the episodically and ubiquitously consumed foods for the current analyses by following the NCI strategy (23), which suggested the use of an amount-only model if <5% of the population had zero intakes of a food, whereas a 2-part model may fit best if ≥5% of the population had zero intakes of a food. The Box-Cox transformation was used to normalize skewed 24-h recall data.

We used MIXTRAN and DISTRIB macros in the amount-only model to estimate the distribution (ie, means, percentiles, and

corresponding SEs) of usual intakes of total energy, added sugar, total grains, refined grains, dietary fiber, discretionary solid fats, and fruit and vegetables. The distribution of usual intakes of whole grains, alcohol, and fish was estimated by using the 2-part model. The NCI macros estimated probabilities and amounts of consumption by using multivariate modeling; all multivariate models included terms, as appropriate, for age, sex, race-ethnicity, educational level, physical activity, a variable that indicated whether the recall day was the first or second day, and a variable that indicated whether intake on the recall day was usual or unusual or a variable that indicated whether the recall day was a weekend day (Friday through Sunday) or a weekday (Monday through Thursday). Models for the probability of consuming fish, whole-grains, and alcohol, all of which are episodically consumed foods, also included a term for the FFQ-estimated consumption frequency as a predictor. FFQ data for whole grains included oatmeal and other cooked cereals, whole-grain cold cereal, whole-grain rice, dark bread, and popcorn. The DISTRIB macro can also produce an estimate of the proportion of the population below specific food- and nutrient-intake cutoffs of interest. The same sets of the previously mentioned covariates were also used in MIXTRAN and INDIVINT macros to generate estimated usual intake of foods and nutrients for each participant in a Box-Cox–transformed scale to be used in the following regression analyses.

Assessment of the use of statins and other medications

A questionnaire was administered during the home interview to assess the use of prescription medications during a 1-mo period before examination. Participants who reported in the questionnaire having ever taken a medication were further asked to show the interviewer containers of all medications used, and each product's complete name was recorded. If a container was not available, the name of the medication was reported verbally by participants.

Measurement of serum lipids

Blood specimens were drawn at the MEC, and serum lipids were analyzed at the Johns Hopkins University Lipoprotein Analytic Laboratory. Total cholesterol and HDL cholesterol were measured by using a Hitachi 717 Analyzer (Boehringer Mannheim Diagnostics) in 2003–2005 and Hitachi 717 and 912 Analyzers in 2006. Because of several modifications of the method in 2005–2006, which could have led to a possible bias, a post hoc adjustment (24) was done on HDL-cholesterol measurements for 2005–2006 survey participants. The serum non-HDL-cholesterol concentration was calculated as total cholesterol minus HDL-cholesterol concentrations; a total cholesterol:HDL-cholesterol ratio was also calculated. In both survey cycles, the fasting triglyceride concentration was measured in one-half of the population who attended the morning examination session and with a fasting period ≥8.5 but <24 h. The LDL-cholesterol concentration was then calculated by using Friedewald's formula in subjects with triglyceride concentrations ≤400 mg/dL (25). Other laboratory-test details are shown in the NHANES Laboratory/Medical Technologists Procedures Manual (18).

Assessment of other covariates

Anthropometric measures were collected by trained technicians at the MEC visit. Body weight (kg) and height (m) were measured following standard procedures and used to calculate BMI (in kg/m^2). Systolic and diastolic blood pressures were measured multiple times during one examination, and the average value of ≤3 measurements was used. The physical activity and smoking status of adult participants during the 30 d before the interview were assessed by questionnaires during the home interview. A metabolic equivalent task score was assigned to each individual leisure-time activity as previously described (26). The level of each individual activity for each participant was calculated as a function of the participant's basal energy expenditure and body weight and the duration and metabolic equivalent task score of each activity (27). The total leisure-time physical activity level for each participant was determined by summing up the physical activity level across all individual activities that were done by that participant. Diabetes and CVD history were self-reported at the MEC.

Statistical analysis

All analyses were conducted with SAS 9.3 software (SAS Inc) and SUDAAN 11.0 software (Research Triangle Institute). Appropriate sample weights were used in all analyses to account for the NHANES complex sampling design. A 2-sided $P < 0.05$ was considered significant.

As previously described, estimated usual intake of whole grains for each participant generated from the INDIVINT macro was in a Box-Cox–transformed scale. To facilitate the result interpretation and public health implementation, we identified the proportion of participants who consumed <1 oz eq whole grains (~16 g whole-grain ingredients (28) by using the DISTRIB macro and used that proportion cutoff to group participants on the basis of their Box-Cox–transformed estimates of whole-grain usual intake. Accordingly, participants were categorized into higher-intake (≥16 g) compared with low-intake (<16 g) groups.

Participants' characteristics were described according to statin use and whole-grain intake and presented as means (±SEs) or proportions. Usual intake distributions of dietary factors were estimated on the basis of the NCI method, and corresponding SEs were estimated by using the balanced repeated replication technique (29).

Our primary goal was to determine whether the association between statin use (compared with nonuse) and serum lipid concentrations was modified by whole-grain intake. A high total cholesterol concentration (ie, >200 mg/dL) has been suggested by the National Cholesterol Education Program Expert Panel (2) and American Heart Association (30) as one of the screening factors for an ideal health status. Therefore, we first used logistic regressions to examine the RR of having high total cholesterol. Multiple linear regression analyses were used to examine non-HDL-cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride concentrations as well as the total cholesterol:HDL-cholesterol ratio in separate models.

We tested the interaction between whole-grain intake and statin use by introducing a product term of higher whole-grain intake (≥16 compared with <16 g/d) × statins (users compared with nonusers) in models. Covariates included age; sex; race-ethnicity; educational level; family poverty-income ratio (ie, a ratio of family income to the poverty threshold); smoking status; physical activity level; usual intakes of total energy, fruit,

vegetables, added sugar, discretionary solid fats, fish, alcohol, and refined grains; fasting time; BMI; diabetic status; and CVD history. Two-way interactions between statin use and dietary covariates were also tested, but none of the interactions were statistically significant (all P-interaction > 0.1). No sex or race differences were tested considering insufficient power.

Because whole grains are rich in dietary fiber, we further adjusted for dietary fiber intake to examine the possible underlying mechanism for the interaction between whole-grain consumption and statin use. In addition, it was expected that lifestyle, medication use, and serum lipid concentrations may differ in primary and secondary prevention settings. However, with consideration that the power may have been insufficient to examine the previously detailed associations and interactions stratified by CVD history, we conducted a sensitivity analysis by excluding adults who reported ever having CVD ($n = 861$), and reran the models.

RESULTS

In 1065 statin users, atorvastatin (43.7%) and simvastatin (29.3%) were the statins most commonly used followed by lovastatin (10.1%), pravastatin (7.9%), fluvastatin (2.8%), and rosuvastatin (2.5%). The following 3 combination agents that contained statins were also reported by a small number of participants; ezetimibe plus simvastatin (used by 29 adults), lovastatin plus niacin (used by 3 adults), and amlodipine plus atorvastatin (used by 9 adults). Some participants ($n = 64$; 6.0% of statin users) reported the use of statins as well as other antihyperlipidemic medications, including cholestyramine, colesevelam, colestipol, ezetimibe, fenofibrate, and gemfibrozil. Two adults reported taking simvastatin together with atorvastatin or lovastatin.

Sixty-nine percent of subjects reported consuming <16 g whole grains/d (**Table 1**). Regardless of the whole-grain consumption, statin users were older, were less educated, were more likely to self-report diabetes and a history of CVD, had greater BMI and triglyceride concentrations, and had lower total cholesterol, non-HDL-cholesterol, LDL-cholesterol, and HDL-cholesterol concentrations than did nonusers. Irrespective of statin use, adults with greater whole-grain intake were older, more educated, and wealthier, more likely to be white and to consume more fruit, vegetables, dietary fiber, and fish and less added sugar, and less likely to smoke cigarettes. However, lipid profiles were not significantly different between higher– compared with low–whole-grain consumers in statin nonusers. In statin users, subjects who consumed low (compared with higher) whole grains were younger, less educated, more likely to smoke cigarettes, consumed less total calories and fruit and vegetables, had greater BMI, and had higher total cholesterol and non-HDL-cholesterol concentrations.

With adjustment for demographic and lifestyle factors, statin users had 62% (95% CI: 52%, 70%) lower risk of having high total cholesterol than did nonusers if they were in the higher whole-grain intake group (**Figure 1**). Risk was significantly greater (P-interaction = 0.02) than that observed in the adults in the group with low whole-grain intake (44% lower risk in statin users than in nonusers; 95% CI: 31%, 54%).

After adjustment for demographic and lifestyle factors, the non-HDL-cholesterol concentration and total cholesterol:HDL-cholesterol ratio were lower in statin users than nonusers (**Table 2**, model 2). The difference in these variables between users and nonusers was greater in subjects who consumed ≥16 g whole grain/d than in those who consumed <16 g whole grain/d (P-interaction = 0.03 and 0.04 for non-HDL-cholesterol concentration and total cholesterol:HDL-cholesterol ratio, respectively). In subjects who consumed ≥16 compared with <16 g whole grains/d, statin users had 31 and 20 mg/dL lower non-HDL cholesterol, respectively, than did nonusers. The total cholesterol:HDL-cholesterol ratio was 0.56 lower in statin users than nonusers in subjects who consumed ≥16 g whole grains/d and 0.28 lower in subjects who consumed <16 g whole grains/d. However, in the subpopulation whose LDL-cholesterol concentrations were measured, the interaction between whole-grain consumption and statin use in relation to the LDL-cholesterol concentration was not significant (P-interaction = 0.51).

We did not observe a significant interaction between whole-grain intake and statin use in relation to the HDL-cholesterol concentration (P-interaction = 0.19). Regardless of whole-grain consumption, we observed higher triglyceride concentrations in statin users than in nonusers in the subpopulation (P-interaction = 0.61). Further controlling for participants' BMI, diabetes status, and CVD history in all models did not materially change the findings. The statin-triglyceride association was maintained after adjustment for or stratification by total cholesterol or LDL-cholesterol concentration (data not shown).

In the sensitivity analysis (results not tabulated), in which adults who reported ever having CVD were excluded, interactions between whole-grain intake and statin use in relation to risk of having a high total cholesterol or non-HDL-cholesterol concentration were no longer significant (both P-interaction = 0.09). In contrast, the total cholesterol:HDL-cholesterol ratio remained significantly lower in statin users than in nonusers (difference: 0.55; P-difference < 0.001) in the group with higher whole-grain intake, whereas no such difference (difference: 0.18; P-difference = 0.13) was observed in the group with low whole-grain intake (P-interaction = 0.04).

In all models, additional adjustment for dietary fiber intake did not materially change the results (data not shown). Of note, as previously mentioned, ~10% of statin users reported taking combination agents that contained statins or took statins together with other antihyperlipidemic medications. Thus, we conducted a post hoc analysis to account for this potential confounding in the model adjustment but showed no change in the results (data not shown).

DISCUSSION

Statin use leads to both a decrease in hepatic very-low-density cholesterol secretion and increased LDL-cholesterol uptake (32). The rate of intestinal cholesterol absorption is also increased by statin therapy, probably as a compensatory response to the suppression of endogenous cholesterol synthesis rate (33). Some studies have explored the combined effects of statins and a variety of dietary factors including alcoholic beverages, grapefruit juice, fatty acids, phytosterols, or dietary fiber on lipid concentrations (34, 35). However, to the best of our knowledge, there is no such evidence for the joint association of statins and whole grains on lipoprotein concentrations. In NHANES participants, we observed that the non-HDL-cholesterol concentration, total

TABLE 1
Participant characteristics by status of whole-grain intake and statin use[1]

	Whole-grain higher-intake consumers (n = 1327)			Whole-grain low-intake consumers (n = 2957)				
	Statin users	Statin nonusers	P^4	Statin users	Statin nonusers	P^4	P^2	P^3
n	388	939		677	2280			
Age (y)	67.5 ± 1.0[5]	61.1 ± 0.6	<0.001	64.3 ± 0.6	57.7 ± 0.3	<0.001	0.004	<0.001
Men (%)	58.1	47.5	0.04	47.6	42.4	0.26	0.07	0.20
Non-Hispanic whites (%)	89.0	88.4	0.17	81.8	74.8	0.03	0.03	<0.001
Education more than high school (%)	55.6	67.9	0.002	44.0	51.7	0.03	0.01	<0.001
Regular cigarette smokers (%)	9.1	11.6	0.18	16.5	24.3	<0.001	0.03	<0.001
Patients with diabetes (%)	30.3	8.6	<0.001	26.5	7.5	<0.001	0.64	0.23
History of CVD (%)	35.4	10.4	<0.001	37.6	9.3	<0.001	0.55	0.43
Income poverty ratio	3.38 ± 0.15	3.42 ± 0.09	0.76	3.02 ± 0.11	3.18 ± 0.08	0.17	0.05	0.005
Physical activity level[6]	0.33 ± 0.04	0.40 ± 0.02	0.23	0.25 ± 0.03	0.31 ± 0.02	0.41	0.47	0.06
BMI (kg/m^2)	29.5 ± 0.4	28.2 ± 0.3	0.003	30.6 ± 0.3	28.5 ± 0.2	<0.001	0.01	0.43
Dietary intake								
Total calories (kcal)	2096 ± 40	2086 ± 35	0.17	1952 ± 27	1937 ± 29	0.19	0.01	0.003
Refined grains (oz eq)	5.2 ± 0.2	5.3 ± 0.1	0.19	5.3 ± 0.1	5.5 ± 0.1	0.80	0.89	0.14
Whole grains (grams)	23.0 ± 0.7	20.8 ± 0.6	0.97	14.3 ± 0.6	5.5 ± 0.3	0.004	<0.001	<0.001
Fruit and vegetables (cup eq)	3.3 ± 0.1	3.1 ± 0.1	0.38	2.7 ± 0.1	2.5 ± 0.1	0.21	<0.001	<0.001
Discretionary solid fats (g)	40.1 ± 1.2	42.1 ± 1.1	0.47	42.2 ± 0.7	43.8 ± 0.7	0.53	0.45	0.45
Fish (oz eq)	0.67 ± 0.07	0.72 ± 0.07	0.38	0.66 ± 0.05	0.70 ± 0.06	0.92	0.04	0.12
Alcohol (drinks)	0.56 ± 0.06	0.67 ± 0.05	0.08	0.59 ± 0.05	0.68 ± 0.06	0.13	0.27	0.69
Added sugar (teaspoon eq)	13.9 ± 0.5	14.8 ± 0.5	0.02	15.2 ± 0.4	16.3 ± 0.5	0.01	0.09	0.15
Dietary fiber (g)	21.6 ± 0.4	18.9 ± 0.4	0.44	15.6 ± 0.2	13.3 ± 0.2	0.04	<0.001	<0.001
Blood lipid concentrations								
Total cholesterol (mg/dL)	180.1 ± 2.5	213.6 ± 1.9	<0.001	188.5 ± 3.1	213.7 ± 1.5	<0.001	0.04	0.95
Non-HDL cholesterol (mg/dL)	127.0 ± 2.2	157.1 ± 1.9	<0.001	135.7 ± 2.9	157.1 ± 1.5	<0.001	0.03	0.99
HDL cholesterol (mg/dL)	53.1 ± 1.1	56.5 ± 0.9	0.01	52.8 ± 0.8	56.6 ± 0.5	<0.001	0.83	0.93
Total cholesterol:HDL-cholesterol ratio	3.6 ± 0.1	4.1 ± 0.1	<0.001	3.8 ± 0.1	4.1 ± 0.1	0.002	0.04	0.42
LDL cholesterol (mg/dL)[7]	95.3 ± 3.2	125.6 ± 2.0	<0.001	99.2 ± 2.7	127.1 ± 1.5	<0.001	0.43	0.52
Triglycerides (mg/dL)[7]	146.8 ± 7.2	121.7 ± 4.2	0.002	150.5 ± 8.3	123.2 ± 2.5	0.003	0.75	0.79

[1] Appropriate sample weights were used in all analyses to account for the NHANES complex sampling design. MyPyramid equivalent serving sizes for food groups or nutrients were defined in a consumer-friendly manner on the basis of the USDA Food and Nutrient Database for Dietary Studies and Nutrient Database for Standard Reference (31). Detailed information is documented in the MyPyramid Equivalents Database User Guide (19). Usual dietary intakes were estimated by using the National Cancer Institute method (23). Whole-grain intake groups were categorized as higher intake [≥1-oz eq (ie, ≥16 g whole-grain ingredients; 28)] compared with low intake (<1-oz eq). Participant characteristics were compared across groups by using the t test for continuous variables and chi-square test for categorical variables. CVD, cardiovascular disease; eq, MyPyramid equivalents.

[2] P values for comparisons of statin users in the whole-grain higher-intake group compared with statin users in the whole-grain low-intake group.

[3] P values for comparisons of statin nonusers in the whole-grain higher-intake group compared with statin nonusers in the whole-grain low-intake group.

[4] P values for comparisons of statin users with nonusers in groups with higher and low whole-grain intakes, respectively.

[5] Mean ± SE (all such values).

[6] Leisure-time physical activity level was calculated according to the method proposed by Ainsworth et al (26) and Gerrior et al (27).

[7] LDL cholesterol and triglycerides were measured only in a subpopulation; the total sample size used in the current analysis was n = 1862 for LDL cholesterol and n = 1913 for triglycerides. Means ± SEs for triglycerides are presented in a geometric scale.

cholesterol:HDL-cholesterol ratio, and risk of elevated total cholesterol concentration were the lowest in statin users who also consumed ≥16 g whole grains/d.

LDL-cholesterol and non-HDL-cholesterol concentrations are important predictors of CVD risk (2, 36, 37), with non-HDL-cholesterol concentrations having been shown to be as good or a better predictor as LDL cholesterol (36, 37). It has been clearly established that the management of LDL-cholesterol and non-HDL-cholesterol concentrations leads to a significant reduction in CVD risk (2). For example, RCTs have shown a 1–2% reduction in risk of coronary heart disease with every 1% reduction in the LDL-cholesterol concentration (2). Consistent with statin's mode of action, statin users compared with nonusers in the current study had lower LDL-cholesterol and non-HDL-cholesterol concentrations and a total cholesterol:HDL-cholesterol ratio as well as lower risk of having a high total cholesterol concentration.

A multifaceted diet intervention termed the Portfolio Diet has been shown to result in cholesterol-lowering effects similar to those with statin therapy (38–40). However, a dietary modification overall tends to yield more-modest changes in plasma lipid concentrations (2), particularly when fewer beneficial dietary components are combined, and participant compliance to the dietary modification is low (41). We did not observe a significantly independent, inverse association between whole-grain intake and serum lipid concentrations. This result may have been due to the low whole-grain intake in this NHANES cohort whose median intake was 7.1 g/d (<0.5-oz eq), whereas the 2010 Dietary Guidelines for Americans recommended average daily intake ≥3-oz eq whole grains for adults (10).

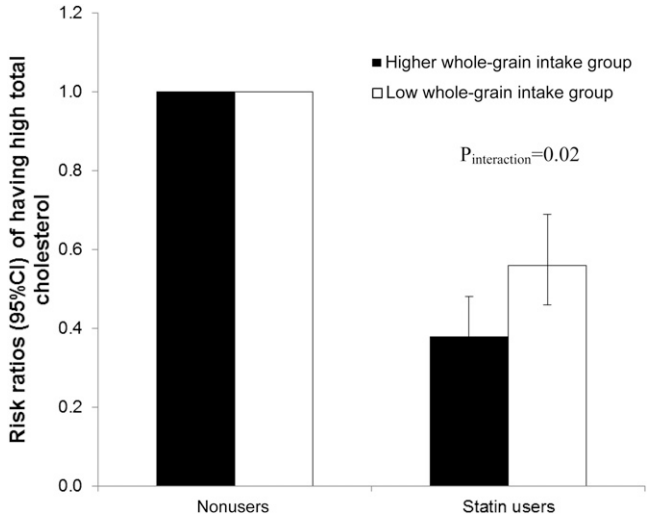

FIGURE 1. Risk ratios (95% CIs) of having high total cholesterol (>200 mg/dL) by status of statin use and whole-grain consumption (n = 4284). The logistic regression model was adjusted for age; sex; race-ethnicity; smoking status; educational level; family poverty income ratio; physical activity level; dietary intakes of total calories, fruit and vegetables, discretionary solid fats, fish, alcohol, added sugar, and refined grains; and fasting time. The interaction was tested by including the product term of statin group (users compared with nonusers) × whole-grain intake group (≥16 compared with <16 g).

However, in this adult population, we observed that higher whole-grain intake combined with statin use had an effect size on the non-HDL-cholesterol concentration and total cholesterol:HDL-cholesterol ratio that was greater than the sum of effect sizes attributed to higher intake of whole grains or use of statins alone. This interaction between statins and whole-grain intake was significant, which suggested a potential synergism between higher whole-grain intake and statin use; and it remained significant after relevant covariates were controlled for. However, we could not rule out the possibility that whole-grain intake may have been a marker for other heart-healthy dietary components or lifestyles that we failed to identify.

A potential mechanism for this effect may be related to a higher amount of nondigestible intestinal contents that causes a reversible nonspecific binding of statins or dilution of the intestinal stain concentration, in either case causing a slower rate of absorption and, hence, prolonging the elevated plasma concentrations of the drug. Dietary fiber, rather than whole grains, has been primarily studied in this regard. In a 12-wk trial in patients with hypercholesterolemia, psyllium (a soluble fiber supplement) plus 10 mg simvastatin lowered concentrations of LDL cholesterol, apolipoprotein B, and total cholesterol significantly more than 10 mg simvastatin alone and had comparable effects to 20 mg simvastatin alone (14). In contrast, other studies have reported that dietary fiber lowered statin efficacy by inhibiting its intestinal absorption (13, 42). After additional adjustment of our data for dietary fiber, the statin–whole-grain interaction was not materially attenuated, which suggested that fiber alone did not account for all of the differences observed. Types and dosages of statins and dietary fiber as well as the relative timing of administering these 2 treatments might be critical (42). Although it is also possible that both the pharmacodynamics and pharmacokinetics of statins may be enhanced by the various nutrients in whole grains, it is still too early to speculate the mechanisms because of the very little existing evidence.

In our sensitivity analysis in which adults who reported any CVD history were excluded, the strength of the whole grain–statin interaction on total cholesterol and non-HDL cholesterol were both attenuated (both P-interaction = 0.09). In contrast, the interaction between whole-grain consumption and statin use on the total cholesterol:HDL-cholesterol ratio remained significant. Possible explanations for such changes included the smaller sample size and smaller variation of serum lipid concentrations in the low-risk population. The sample-size issue may also explain the lack of a significant interaction for the LDL-cholesterol concentration. We originally expected similar findings for LDL cholesterol and non-HDL cholesterol because LDL cholesterol accounted for >80% of the non-HDL cholesterol. However, LDL-cholesterol concentrations were only measured in a subpopulation (approximately one-half of subjects with a non-HDL-cholesterol measurement). In a post hoc analysis of non-HDL cholesterol in the same subpopulation with LDL-cholesterol measurements, the interaction originally shown in our primary analysis for non-HDL cholesterol was no longer significant (data not shown).

This study had some limitations. The FFQ data, which were used as one of the covariates to predict the intake of episodically consumed foods, did not contain detailed information of foods. For example, the FFQ data for predicting whole-grain consumption included "oatmeal" and "other cooked cereals" in one question item, whereas some "other cooked cereals" may not have been whole grains but were misclassified as whole grains. For other episodically consumed foods that have been used as covariates in the current analyses, such a misclassification may have introduced residual confounding. Because the statin dosage was not collected in the NHANES 2003–2006, we were not able to determine whether subjects in the group with lower whole-grain intake used lower-dose statins or were less compliant in the use of their prescribed statins than their counterparts with higher whole-grain intake . However, there was no significant difference between groups with low compared with higher whole-grain intakes in terms of types of statins they used (data not shown). Because NHANES data are cross-sectional, causality could not be inferred, and we do not intend to advocate any changes to clinical practice or nutritional policies. In our cohort, statin users had lower HDL-cholesterol and higher triglyceride concentrations, which likely reflected clinical characteristics of individually prescribed statin drugs.

Several strengths of this study should be highlighted. To our knowledge, this study is the first to examined the interaction between whole-grain consumption and statin use in relation to serum lipid concentrations. Both older individuals and minority populations were oversampled in the NHANES surveys. We have combined data of 2 survey cycles for analyses, which increased the statistical power of testing the statin–whole grain interaction. We applied the NCI methodology to estimate the usual dietary intake from 2-day diet recalls, which allowed us to reduce the potential bias because of day-to-day variations of 24-h diet recalls. In addition, the current nationally representative sample facilitated the generalization of our findings to at least the US population aged ≥45 y.

Associations identified in this study were of an observational nature; hence, cause-and-effect relations could not be determined. The associations do raise the issue of whether there are clinically important and as yet recognized diet-statin interactions

TABLE 2
Association between combined statin use and whole-grain consumption in relation to serum lipid profiles[1]

		Statin use								
		Users		Nonusers						
	Whole-grain intake groups	*n*	Mean (95% CI)	*n*	Mean (95% CI)	Dif_1[2]	*P*-dif_1[2]	Eff_2[3]	Eff_3[4]	Eff_4[5]
Non-HDL cholesterol (mg/dL) (*P*-interaction = 0.03)[6]										
Model 1	Higher intake	388	128.1 (123.5, 132.7)	939	157.2 (153.3, 161.0)	−29.1	<0.001	—	—	—
	Low intake	677	136.5 (130.3, 142.7)	2279	156.6 (153.5, 159.8)	−20.2	<0.001	−24.9	−28.5	−8.9
Model 2	Higher intake	365	127.9 (122.7, 133.1)	892	159.1 (155.0, 163.3)	−31.2	<0.001	—	—	—
	Low intake	642	136.0 (129.8, 142.1)	2158	156.1 (152.5, 159.7)	−20.1	<0.001	−23.6	−28.2	−11.1
Model 3	Higher intake	357	128.6 (123.5, 133.8)	871	159.2 (155.0, 163.4)	−30.5	<0.001	—	—	—
	Low intake	632	136.3 (130.2, 142.5)	2121	156.1 (152.6, 159.6)	−19.8	<0.001	−23.0	−27.5	−10.8
Total cholesterol:HDL-cholesterol ratio (*P*-interaction = 0.04)										
Model 1	Higher intake	388	3.56 (3.44, 3.68)	939	4.05 (3.93, 4.18)	−0.49	<0.001	—	—	—
	Low intake	677	3.82 (3.66, 3.99)	2279	4.11 (4.02, 4.21)	−0.29	0.004	−0.47	−0.55	−0.20
Model 2	Higher intake	365	3.56 (3.43, 3.70)	892	4.13 (3.97, 4.28)	−0.56	<0.001	—	—	—
	Low intake	642	3.81 (3.64, 3.97)	2158	4.09 (3.99, 4.18)	−0.28	0.006	−0.41	−0.53	−0.28
Model 3	Higher intake	357	3.53 (3.40, 3.66)	871	4.15 (3.99, 4.30)	−0.62	<0.001	—	—	—
	Low intake	632	3.75 (3.58, 3.92)	2121	4.11 (4.01, 4.20)	−0.36	<0.001	−0.47	−0.58	−0.26
HDL cholesterol (mg/dL) (*P*-interaction = 0.19)										
Model 1	Higher intake	388	53.5 (51.5, 55.4)	939	56.4 (54.8, 57.9)	−2.93	0.01	—	—	—
	Low intake	677	52.8 (51.4, 54.2)	2279	56.6 (55.7, 57.5)	−3.85	<0.001	—	—	—
Model 2	Higher intake	365	53.8 (52.1, 55.6)	892	56.0 (54.5, 57.5)	−2.16	0.04	—	—	—
	Low intake	642	52.8 (51.3, 54.3)	2158	56.7 (55.9, 57.5)	−3.89	<0.001	—	—	—
Model 3	Higher intake	357	55.3 (53.6, 57.0)	871	55.4 (54.0, 56.9)	−0.15	0.87	—	—	—
	Low intake	632	54.4 (52.5, 56.3)	2121	56.2 (55.4, 57.1)	−1.84	0.07	—	—	—
LDL cholesterol (mg/dL) (*P*-interaction = 0.51)										
Model 1	Higher intake	156	96.1 (89.3, 102.8)	402	125.4 (121.4, 129.4)	−29.3	<0.001	—	—	—
	Low intake	307	99.5 (93.5, 105.5)	997	127.0 (124.0, 129.9)	−27.4	<0.001	—	—	—
Model 2	Higher intake	149	96.1 (89.9, 102.2)	382	126.1 (122.2, 130.1)	−30.1	<0.001	—	—	—
	Low intake	294	100.0 (93.9, 106.0)	942	127.4 (124.3, 130.4)	−27.4	<0.001	—	—	—
Model 3	Higher intake	148	97.2 (91.1, 103.3)	375	125.8 (121.8, 129.8)	−28.6	<0.001	—	—	—
	Low intake	290	100.5 (94.5, 106.5)	923	127.5 (124.5, 130.4)	−27.0	<0.001	—	—	—
Triglycerides (mg/dL) (*P*-interaction = 0.61)										
Model 1	Higher intake	160	147.0 (131.7, 164.0)	413	121.7 (113.8, 130.1)	25.3	0.002	—	—	—
	Low intake	319	149.9 (133.6, 168.2)	1021	123.4 (118.5, 128.5)	26.6	0.003	—	—	—
Model 2	Higher intake	153	143.7 (129.6, 159.3)	391	123.7 (115.6, 132.4)	20.0	0.02	—	—	—
	Low intake	306	149.3 (133.1, 167.4)	964	123.6 (118.0, 129.5)	25.6	0.005	—	—	—
Model 3	Higher intake	152	140.1 (125.6, 156.2)	384	124.9 (116.6, 133.9)	15.1	0.09	—	—	—
	Low intake	302	143.3 (127.3, 161.4)	945	125.6 (120.2, 131.2)	17.8	0.04	—	—	—

[1] Model 1 was adjusted for age and sex. Model 2 was adjusted as for model 1 and for race-ethnicity, smoking status, education level, family poverty income ratio, and physical activity level, dietary intakes of total calories, fruit and vegetables, discretionary solid fats, fish, alcohol, added sugar, refined grains, and fasting time. Model 3 was adjusted as for model 2 and for BMI, diabetic status, and cardiovascular disease history. Sample sizes differed across models because of missing data on some covariates or outcome variables. Multiple linear regressions were used for analyses. The non-HDL-cholesterol concentration was calculated by subtracting HDL-cholesterol from total cholesterol concentrations. Triglyceride concentrations are presented in a geometric scale. Dif, difference; Eff, effect size.

[2] Differences in the lipoprotein concentrations (or ratio) between statin users and nonusers in each of the whole-grain intake groups by using statin nonusers as the reference group. *P*-dif is for testing if the difference was significantly different from zero.

[3] Additive effect [ie, the difference in the lipoprotein concentration (or ratio) if the interaction between whole-grain intake and statin use was not significant]. It equals the sum of the independent effects of whole-grain intake and statin use and was calculated as the sum of the regression coefficient for the whole-grain intake group and the regression coefficient for the statin group in the regression model without the interaction term.

[4] Observed effect [ie, the difference in the lipoprotein concentration (or ratio) when there was a significant interaction between whole-grain intake and statin use and was calculated as the difference between statin users with higher whole-grain intake and statin nonusers with low whole-grain intake (reference group)].

[5] Magnitude of the interaction [ie, the additional difference in lipoprotein concentration (or ratio) attributed to the interaction]. It equals the difference between groups with higher compared with low whole-grain intakes (low-intake group as the reference) of differences in the lipoprotein concentration (or ratio) between statin users and nonusers (nonusers as the reference). Significant interactions as shown in the table indicate the synergism of higher whole-grain intake and statin use in relation to both the non-HDL-cholesterol concentration and total cholesterol:HDL-cholesterol ratio.

[6] Interactions were tested in model 2 by including a product term of statin group (users compared with nonusers) × whole-grain intake group (≥16 compared with <16 g). The nature of the interaction (antagonism or synergism) was further elaborated by comparing the observed effect size with the additive effect size as shown in the table.

that need to be assessed, particularly because an increasing proportion of the population are treated with this class of drugs. The resolution of this issue will await results of clinical intervention studies.

In conclusion, this study in US adults aged ≥45 y revealed that statin users who also consumed ≥16 g (ie 1-oz eq) whole grains/d had lower non-HDL-cholesterol concentrations, lower risk of having high total cholesterol, and a lower total cholesterol:HDL-cholesterol ratio than those of their counterparts who consumed less whole grain or who did not use statins. Despite the relatively modest magnitude of interactions, our findings suggested that combining whole grains, a healthy dietary component, with statin treatment should not antagonize and may improve the efficacy of statins in adults aged ≥45 y. Longitudinal studies and trials are needed to confirm our findings, which could potentially lead to the use of a lower dose of statins, resulting in such benefits as lower drug costs, higher compliance rates, and lower adverse event rates. Underlying mechanisms for whole-grain foods to enhance cholesterol-lowering efficacies of statins are also worth exploration.

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