

# Association between serum $\gamma$ -glutamyltransferase and dietary factors: the Coronary Artery Risk Development in Young Adults (CARDIA) Study<sup>1-3</sup>

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## ABSTRACT

**Background:** Diet may be involved in the strong dose-response relation of  $\gamma$ -glutamyltransferase (GGT) concentration with incident diabetes.

**Objective:** We examined dietary correlates of serum GGT activity.

**Design:** Study subjects were 3146 black and white men and women aged 17–35 y in 1985–1986. A diet history was taken at years 0 and 7. Food items were classified into alcohol; breaded, battered, or canned vegetables; fruit; fruit juice; refined grain; whole grain; dairy; legumes; meat; poultry; fish; fresh or frozen vegetables; nuts; and coffee.

**Results:** After adjustment for nondietary factors and other food groups, GGT was positively associated with alcohol consumption and meat intake. Geometric means of year 10 GGT across categories of alcohol consumption (0, 1-9, 10-19, 20-29, and  $\geq 30$  g/d) were 17.7, 18.8, 20.4, 21.8, and 24.8 U/L ( $P$  for trend  $< 0.01$ ); corresponding means across quintiles of meat intake were 19.2, 20.2, 20.5, 21.8, and 21.2 times/wk ( $P$  for trend  $< 0.01$ ). GGT was inversely associated with fruit intake. Among possible meat constituents, dietary heme iron, but not saturated fat, was associated with GGT. Dietary constituents typical of plant foods showed an inverse association. In contrast, vitamin supplements were positively associated with GGT.

**Conclusions:** Serum GGT activity increased in a dose-response manner as alcohol and meat consumption increased and fruit consumption decreased. Heme iron contained in meats and micronutrients contained in fruits may influence GGT metabolism. However, micronutrients taken as supplements had a positive association with GGT. *Am J Clin Nutr* 2004;79:600–5.

**KEY WORDS**  $\gamma$ -Glutamyltransferase, meat, fruit, iron, antioxidants, oxidative stress

## INTRODUCTION

In previous epidemiologic studies (1–7), a serum  $\gamma$ -glutamyltransferase (GGT) concentration within the normal range was associated with most cardiovascular disease (CVD) risk factors and was a predictor of future heart disease, hypertension, stroke, and type 2 diabetes. In particular, serum GGT showed a strong graded relation with diabetes (6, 7), which suggested a role for GGT in the pathogenesis of that disease (6–8). Serum GGT activity has commonly been interpreted as a marker of alcohol consumption or liver disease, yet neither of those possibilities would explain the association of serum GGT with

diabetes (6, 7). At present, the mechanism underlying the above associations remains largely unknown, although we have suggested that GGT may be associated with diabetes through mechanisms related to oxidative stress (7).

Generally, mean GGT increases as the amount of self-reported alcohol consumption increases (9). Nevertheless, considerable variation in GGT concentrations exists among subjects who report the same amount of alcohol consumption and even among those who report no alcohol consumption (10). In addition, although the serum GGT concentration increases in persons with hepatobiliary diseases, GGT actually is widely distributed in the human body, and its highest concentration is in the kidney (11). Some studies have reported inverse associations between the consumption of coffee, fruit, or sucrose and the serum GGT concentration (12–14), but the information on dietary determinants of serum GGT concentrations is limited. Moreover, most prior studies were cross-sectional and did not adjust for demographic factors, health behavior factors, or both. In this study, to help elucidate the nature of GGT, we examined dietary correlates of serum GGT activity.

## SUBJECTS AND METHODS

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a longitudinal, multicenter epidemiologic study of lifestyle and other factors in the evolution of coronary artery disease risk factors during young adulthood. Study design, recruitment of participants, and methods were described elsewhere (15). In 1985 and 1986, black and white men and women aged 17–35 y ( $n = 5115$ ) were recruited and examined at 4 clinical sites in the United States: Birmingham, AL; Chicago;

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Minneapolis; and Oakland, CA. Reexaminations were conducted at 2, 5, 7, 10, and 15 y after baseline, and the reexamination rates among surviving cohort members were 90%, 86%, 81%, 79%, and 74%, respectively.

Standard questionnaires were used to maintain consistency in the assessment of demographic and behavioral information across CARDIA examination visits. Sex, race, date of birth, weekly alcohol consumption, and cigarette smoking were determined by structured interview or by self-administered questionnaire. A physical activity score was derived from the CARDIA Physical Activity History, a simplified version of the Minnesota Leisure Time Physical Activity Questionnaire (16). Alcohol intake (mL/d) was computed from the self-reported frequency of consumption of beer, wine, and liquor per week.

All subjects were asked to fast for  $\geq 12$  h and to avoid smoking and heavy physical activity for  $\geq 2$  h before each examination. Blood was collected with minimal stasis for measurement of the GGT concentration. After plasma or serum separation, aliquots were stored at  $-70^{\circ}\text{C}$  until they were shipped on dry ice to a central laboratory. Serum GGT concentrations were measured at year 0 and year 10 (reference range:  $\leq 40$  U/L in women and  $\leq 50$  U/L in men). At year 0, GGT was measured with the use of a SMAC II continuous-flow analyzer (Technicon Instruments Corp, Tarrytown, NY) at American Bio-science Laboratories [(now Smith-Kline Beecham) King of Prussia, PA]. At year 10, GGT was measured colorimetrically with the use of the nitroanilide method on a Cobas Mira Plus chemistry instrument (Roche Diagnostics, Basel, Switzerland) at Linco Research Inc (St Louis). To identify an appropriate recalibration formula, GGT was remeasured at Linco Research Inc by using the year 10 method in 103 baseline samples whose original GGT values ranged from 3 to 228 U/L and that had been stored at  $-70^{\circ}\text{C}$  for 17 y (since 1985–1986). The correlation between measurements made in year 0 and those made in the baseline samples by using the year 10 method was 0.995; accordingly, the year 0 values reported here are  $2.7618 + 1.9004 \times$  the original year 0 values. Body weight with light clothing was measured to the nearest 0.09 kg, and body height without shoes was measured to the nearest 0.5 cm. Body mass index (BMI) was computed as weight divided by height squared ( $\text{kg}/\text{m}^2$ ).

Diet was measured at years 0 and 7. The CARDIA diet history is an interviewer-administered quantitative food-frequency questionnaire (FFQ) including  $\approx 700$  food items. The validity and reliability of the FFQ were evaluated in a previous study (17). Sex- and energy-adjusted 1-mo test-retest correlations of macronutrients tended to be lower for the blacks (0.27–0.58) than for the whites (0.54–0.82). Validity correlations between mean daily nutrient intakes from the CARDIA diet history and means from 7 randomly scheduled 24-h recalls ranged from 0.50 to 0.86 in the white men and from 0.04 to 0.53 in the black women. The University of Minnesota Nutrition Coordination Center nutrient database was used to estimate nutrient intake. The heme-iron content was calculated by applying a factor of 0.4 to the total iron content of all meat items. Nonheme iron was computed as total iron in nonmeat foods and 0.6 of the total iron content in meats.

For this analysis, we excluded subjects in whom neither year 0 nor year 10 GGT was measured ( $n = 1289$ ), in whom neither year 0 nor year 7 dietary data were obtained ( $n = 1175$ ), who had unusually high or low dietary intake values ( $< 800$  and  $> 8000$  kcal/d for men and  $< 600$  and  $> 6000$  kcal/d for women;  $n = 174$ ), or who reported diabetes at baseline or during follow-up

( $n = 194$ ). Some persons satisfied more than one exclusion criterion, and 3146 study participants remained for analysis. In a sensitivity analysis, we found that inclusion of the 194 people with diabetes had little influence on the findings (data not shown).

This research was reviewed and approved by the institutional review boards of the University of Alabama at Birmingham, Northwestern University (Chicago), the University of Minnesota (Minneapolis), and the Kaiser Permanente Health Care Plan (Oakland, CA).

### Statistical analysis

Food items were classified into 14 food groups: alcohol; meat, consisting of the subgroups of red, processed, pork, lamb, and organ meats; poultry; fish; fresh or frozen vegetables; fried, breaded or battered, or canned vegetables; fruit, not including juice; fruit juice; refined grain; whole grain; dairy; legumes; nuts; and coffee. The cumulative weekly intake for each food group was obtained by summing the number of times each individual food item in the same group was consumed. We used the average of year 0 and year 7 diets in the present analyses. In a sensitivity analysis, we found that the use as independent variables of year 0 intake only, year 7 intake only, or the 2 in combination resulted in findings similar to those obtained by using the average of year 0 and 7 intakes (data not shown). Regression coefficients for serum GGT concentrations per 1 SD of the corresponding food group were estimated by using linear regression models. Given the skewness in the distribution of serum GGT, we presented geometric means according to quintiles of intake of each food group or nutrient except alcohol (for which the categories were 0, 1–9, 10–19, 20–29, and  $\geq 30$  g/d). First, we adjusted for study center, race, sex, age, BMI, cigarette smoking, physical activity, and total energy intake; all factors except total energy intake were associated with serum GGT concentrations in previous studies (1–7), and, furthermore, dietary behaviors are known to cluster with other health behaviors. Second, we adjusted food groups for each other because of their mutual associations. We repeated the same analyses with the 2 dependent variables, year 10 GGT and changes in serum GGT from year 0 to year 10. We used SAS software (version 8.2; SAS Institute Inc, Cary, NC).

### RESULTS

The subjects were 566 black men, 805 black women, 837 white men, and 938 white women. The average age at baseline was 25.1 y, and the average amount of education completed was 14.1 y. Detailed associations between serum GGT concentrations and nondietary factors have been reported (7). Briefly, the serum GGT concentration was positively associated with black race, male sex, age, intake of alcohol, BMI, and current smoking.

In separate regression analyses for each food group (each adjusted for nondietary factors), alcohol and meat were the only food groups positively and significantly associated with year 10 GGT and change in GGT (**Table 1**). Beer and liquor each were similarly associated with GGT, as was total alcohol, but wine showed only a weak positive trend (data not shown). Among meat subgroups, organ meat and red meat were significantly associated with serum GGT concentrations (data not shown). Various plant foods including fruits, whole grains, and nuts each showed an inverse association with year 10 GGT, a change in GGT, or both. When food groups were simultaneously adjusted

**TABLE 1**Results of regression of serum  $\gamma$ -glutamyltransferase (GGT) on each food group after adjustment for nondietary factors in CARDIA Study subjects<sup>1</sup>

Food group (SD) <sup>4</sup>	log (Year 10 GGT) <sup>2</sup>			log (Year 10 GGT) – log (year 0 GGT) <sup>2,3</sup>		
	Regression coefficients	SE	P	Regression coefficients	SE	P
Alcohol (1.2 g/d)	0.101	0.012	< 0.001	0.052	0.010	< 0.001
Meats (8.4 times/wk)	0.061	0.014	< 0.001	0.034	0.011	0.003
Poultry (1.7 times/wk)	0.001	0.011	0.902	–0.007	0.009	0.449
Fish (1.2 times/wk)	0.001	0.011	0.971	–0.008	0.009	0.383
Dairy (12.2 times/wk)	–0.009	0.012	0.471	–0.004	0.010	0.658
Fresh or frozen vegetables (10.7 times/wk)	–0.021	0.011	0.068	–0.013	0.009	0.160
French-fried, breaded or battered, or canned vegetables (2.6 times/wk)	0.007	0.012	0.570	0.016	0.009	0.088
Fruit, excluding juices (5.6 times/wk)	–0.042	0.011	< 0.001	–0.032	0.009	< 0.001
Fruit juice (6.8 times/wk)	–0.007	0.011	0.503	–0.001	0.009	0.972
Refined grains (9.7 times/wk)	–0.009	0.013	0.498	–0.002	0.011	0.849
Whole grains (6.3 times/wk)	–0.029	0.011	0.010	–0.018	0.009	0.051
Legumes (2.0 times/wk)	–0.002	0.011	0.858	0.001	0.009	0.864
Nuts (3.9 times/wk)	–0.025	0.011	0.019	–0.016	0.009	0.074
Coffee (9.8 times/wk)	–0.015	0.011	0.189	–0.001	0.009	0.887

<sup>1</sup> Adjusted for total energy intake, study center, race, sex, age, BMI, cigarette smoking, and physical activity. A separate regression analysis was done for each food group and dependent variable. CARDIA, Coronary Artery Risk Development in Young Adults.

<sup>2</sup> Dependent variable.

<sup>3</sup> In models with changes in GGT as dependent variable, also adjusted for baseline serum GGT concentration.

<sup>4</sup> Units of SD are times/wk or g/d.

for each other and for nondietary factors (**Table 2**), alcohol and meat remained significantly and positively associated with year 10 GGT or changes in GGT. Among the food groups that were inversely associated with serum GGT concentrations, fruit was still significantly associated with year 10 GGT and changes in GGT. Most plant foods continued to show inverse associations

with GGT, although the associations were not significant. Additional adjustment for fasting glucose and insulin at baseline did not materially change the results (data not shown). Geometric means of year 10 GGT across categories of alcohol, adjusted as shown in Table 2, were 17.7, 18.8, 20.4, 21.8, and 24.8 U/L (*P* for trend < 0.01); corresponding means across quintiles of meat

**TABLE 2**Results of regression of serum  $\gamma$ -glutamyltransferase (GGT) on food groups after adjustment for nondietary factors and other food groups in CARDIA Study subjects<sup>1</sup>

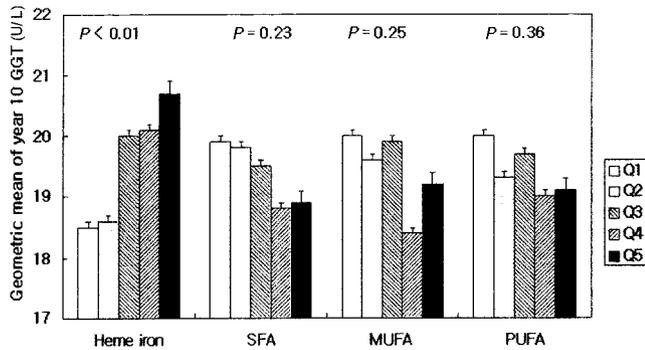
Food group (SD) <sup>4</sup>	log (Year 10 GGT) <sup>2</sup>			log (Year 10 GGT) – log (year 0 GGT) <sup>2,3</sup>		
	Regression coefficients	SE	P	Regression coefficients	SE	P
Alcohol (1.2 g/d)	0.095	0.012	< 0.001	0.049	0.010	< 0.001
Meats (8.4 times/wk)	0.046	0.015	0.002	0.023	0.012	0.057
Poultry (1.7 times/wk)	–0.003	0.012	0.824	–0.008	0.009	0.393
Fish (1.2 times/wk)	–0.002	0.011	0.842	–0.008	0.009	0.375
Dairy (12.2 times/wk)	0.010	0.013	0.462	0.004	0.011	0.704
Fresh or frozen vegetables (10.7 times/wk)	–0.016	0.013	0.218	–0.010	0.010	0.344
French-fried, breaded or battered, or canned vegetables (2.6 times/wk)	0.005	0.012	0.686	0.016	0.010	0.119
Fruit, excluding juices (5.6 times/wk)	–0.024	0.012	0.044	–0.021	0.010	0.031
Fruit juice (6.8 times/wk)	0.004	0.011	0.726	0.009	0.009	0.308
Refined grains (9.7 times/wk)	–0.014	0.014	0.316	–0.005	0.011	0.646
Whole grains (6.3 times/wk)	–0.008	0.012	0.497	–0.005	0.010	0.619
Legumes (2.0 times/wk)	0.014	0.011	0.188	0.010	0.010	0.275
Nuts (3.9 times/wk)	–0.013	0.011	0.240	–0.009	0.009	0.303
Coffee (9.8 times/wk)	–0.020	0.012	0.096	–0.004	0.010	0.719
R <sup>2</sup> (%)	25.7			17.7		

<sup>1</sup> Adjusted for total energy intake, study center, race, sex, age, BMI, cigarette smoking, physical activity, and other food groups. Simultaneous regression analysis included all food groups for each dependent variable. CARDIA, Coronary Artery Risk Development in Young Adults.

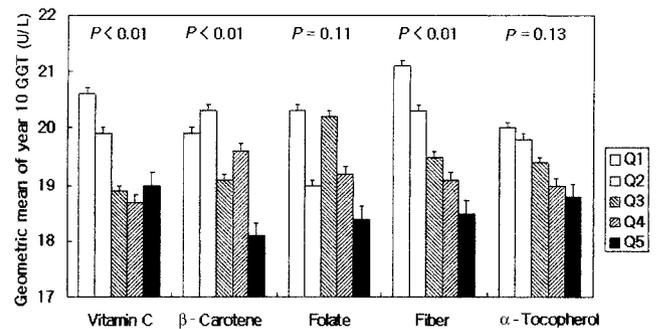
<sup>2</sup> Dependent variable.

<sup>3</sup> In models with changes in GGT as dependent variable, also adjusted for baseline serum GGT concentration.

<sup>4</sup> Units of SD are times/wk or g/d.



**FIGURE 1.** Geometric  $\bar{x}$  ( $\pm$  SE) of year 10  $\gamma$ -glutamyltransferase (GGT) concentrations according to quintile (Q) of heme iron (cutoffs were 0.53, 0.58, 0.63, and 0.71 mg/d for Q2, Q3, Q4, and Q5, respectively), saturated fatty acids (SFA; cutoffs were 24.8, 33.8, 44.5, and 62.0 g/d, respectively), monounsaturated fatty acids (MUFA; cutoffs were 25.5, 34.5, 45.2, and 62.1 g/d, respectively), and polyunsaturated fatty acids (PUFA; cutoffs were 12.9, 17.3, 22.5, and 31.4 g/d, respectively), after adjustment for alcohol consumption, total energy intake, study center, race, sex, age, BMI, cigarette smoking, and physical activity, in CARDIA Study subjects. A separate regression was done for each set of bars. Shown is the *P* for trend. CARDIA, Coronary Artery Risk Development in Young Adults.



**FIGURE 2.** Geometric  $\bar{x}$  ( $\pm$  SE) of year 10  $\gamma$ -glutamyltransferase (GGT) concentrations according to quintile (Q) of constituents contained in plant foods or antioxidants, after adjustment for alcohol consumption, total energy intake, study center, race, sex, age, BMI, cigarette smoking, and physical activity, in CARDIA Study subjects. A separate regression was done for each set of bars. Shown is the *P* for trend. Cutoffs were 91, 134, 178, and 250 mg/d for Q2, Q3, Q4, and Q5, respectively, for vitamin C; 1864, 2863, 4157, and 6433  $\mu$ g/d for  $\beta$ -carotene; 219, 295, 377, and 503  $\mu$ g/d for folate; 6.2, 9.8, 13.2, and 17.9 g/d for fiber; and 6.3, 8.3, 10.7, and 14.9 mg/d for  $\alpha$ -tocopherol. CARDIA, Coronary Artery Risk Development in Young Adults.

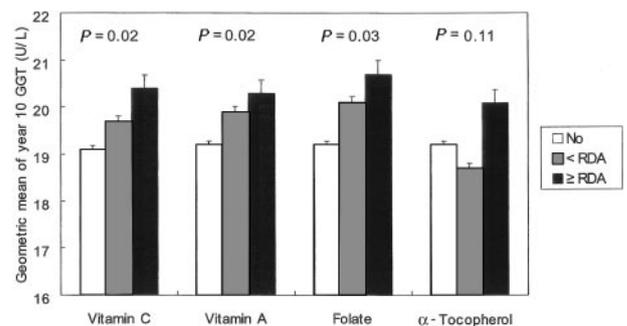
intake (cutoffs: 7.4, 11.4, 15.5, and 21.9 times/wk) were 19.2, 20.2, 20.5, 21.8, and 21.2 U/L (*P* for trend < 0.01).

Among meat constituents, total dietary heme iron but not saturated fat was positively associated with the serum GGT concentration; saturated fat showed a nonsignificant inverse trend (Figure 1). Neither monounsaturated nor polyunsaturated fat was significantly associated with serum GGT (Figure 1). Protein, zinc, or B group vitamins—nutrients that are obtained mostly by eating meat—were not associated with the serum GGT concentration (data not shown). There are 2 other sources of iron: iron from supplements and naturally occurring nonheme iron. Iron from supplements (1–29 mg/d: *n* = 1135;  $\geq$  30 mg/d: *n* = 75) was not associated with the serum GGT concentration (data not shown). Participants who were taking an iron supplement tended to have lower values of hemoglobin at baseline than did those who were not taking an iron supplement. The mean ( $\pm$  SD) hemoglobin concentration at baseline among subjects taking  $\geq$  30 mg iron supplement/d was  $13.1 \pm 1.2$  mg/dL (15% of the subjects in this group were clinically anemic: ie, hemoglobin was < 12 mg/dL in the women and < 13 mg/dL in the men), but the concentration among subjects who were not taking an iron supplement was  $14.3 \pm 1.7$  mg/dL (6.5% of the subjects in this group were clinically anemic; *P* < 0.01). Nonheme iron (96% of total dietary iron) derived primarily from plant foods was not associated with the serum GGT concentration (data not shown). In a separate analysis, we found that the consumption of breakfast cereals, which often are iron fortified, was not associated with GGT (data not shown). Vitamin C,  $\beta$ -carotene, folate, and fiber—constituents that are typical of plant foods—were inversely associated with the serum GGT concentration (Figure 2).  $\alpha$ -Tocopherol also showed a nonsignificant inverse trend with the serum GGT concentration (Figure 2). The positive association with heme iron and the inverse association with micronutrients from plant foods were observed among most race and sex subgroups, although some of the associations were not significant (data not shown). However, vitamin A, vitamin C, folate, and  $\alpha$ -tocopherol from supplements were positively associated with the serum GGT concentration (Figure 3). Further adjust-

ment for nonheme and supplemental iron did not change the findings shown in Figure 3.

## DISCUSSION

This study was motivated by a consistent finding that the serum GGT concentration is predictive of future diabetes and hypertension (6, 7) and of other CVD risk factors and CVDs (1–5). Therefore, it is important to understand better the dietary correlates of GGT. In this prospective study of young black and white men and women, alcohol and meat were the only food groups whose consumption was positively associated with the serum GGT concentration, after adjustment for lifestyle factors and other dietary factors. When nutrients in meat were examined, heme iron was strongly associated with the serum GGT concen-



**FIGURE 3.** Geometric  $\bar{x}$  ( $\pm$  SE) of year 10  $\gamma$ -glutamyltransferase (GGT) concentrations according to intake of micronutrients from vitamin and mineral supplements, after adjustment for alcohol consumption, heme iron, vitamin C from food,  $\beta$ -carotene from food, folate from food, fiber from food,  $\alpha$ -tocopherol from food, total energy intake, study center, race, sex, age, BMI, cigarette smoking, and physical activity in CARDIA Study subjects. *P* for trend is based on logarithmic transformations of the continuous micronutrient variables. Cutoffs of micronutrients from supplements were the recommended dietary allowances (RDA; 46) among men and women aged 19–30 y (vitamin C: 90 mg for men, 75 mg for women; vitamin A: 900  $\mu$ g for men, 700  $\mu$ g for women; folate: 400 mg for men, 400 mg for women; and  $\alpha$ -tocopherol: 15 mg for men, 15 mg for women). CARDIA, Coronary Artery Risk Development in Young Adults.

tration. On the other hand, saturated, monounsaturated, and polyunsaturated fats showed a nonsignificant inverse association with GGT. Consumption of various plant foods appeared to be inversely associated with the serum GGT concentration. Consistent with an inverse association of plant foods and GGT, several nutrients typical of plant foods, including vitamin C,  $\beta$ -carotene, folate, and fiber, had inverse associations with the serum GGT concentration. However, the same nutrients consumed as isolated compounds in supplements had positive associations with the serum GGT concentration.

There are few reports of studies that examined dietary factors and serum GGT (12–14). An inverse association between fruit intake and serum GGT (13, 14) was consistent with our findings. In those 2 studies, meat intake was not associated with the serum GGT concentration. It is possible that those studies did not subdivide meat sufficiently. In our study, the association between poultry or fish intake and serum GGT was inverse (though not significant), whereas the association with mammalian meat intake was positive; combining all meat subgroups might lead to a null association. In addition, coffee and sucrose intakes were inversely associated with the serum GGT concentration in the previous studies (12–14). However, in our study, both coffee and sucrose intakes (data not shown) showed only a weak inverse trend. Limitations of the previous studies are that most were cross-sectional and did not adjust for demographic and health behavior factors, despite strong associations of both diet and GGT with these factors.

One experimental study supported our finding that iron intake may lead to higher GGT concentrations. In that study (18), rats consumed iron mixed in rat chow for 10 wk. Hepatic GGT activity increased 6-fold and was colocalized with iron; GGT mRNA also increased. Two population-based studies (14, 19) found a positive association between serum GGT and ferritin, a marker of stored body iron, regardless of alcohol consumption. In addition, patterns of serum GGT and serum ferritin are similar across age and sex groups (20–26).

GGT is known to play an important role in antioxidant defense systems at the cellular level (27–29). Our findings regarding dietary correlates of GGT support GGT's role as a marker of oxidative stress. Free iron is an important catalyst in generating oxidative stress (30). In the present study, GGT is positively related to the intake of heme iron (a prooxidant) and inversely related to  $\beta$ -carotene and vitamin C obtained from food (antioxidants). The view of GGT as a marker of oxidative stress is further supported by observations in our previous study (7). There, serum GGT concentrations within the normal range at baseline predicted the values for inflammatory marker C-reactive protein and the oxidative damage product F<sub>2</sub>-isoprostanes measured after 15 y. The well-known elevation of serum GGT after alcohol drinking might also be interpreted as a mechanism of oxidative stress: acute and chronic ethanol treatment increases the production of reactive oxygen species (31). The association between wine consumption and GGT, which was weaker than the associations between beer or liquor consumption and GGT, might be related to a counteracting effect of the polyphenols contained in red wine, which can exert antioxidant effects (32).

It is surprising that vitamin A, vitamin C, folate, and  $\alpha$ -tocopherol from supplements were positively associated with serum GGT; these findings were not confounded by iron, which is commonly consumed together with other micronutrients in the

form of a multivitamin. Different effects of supplemental micronutrients from the same micronutrients in food are in agreement with the concept of an antioxidant paradox: people with diets rich in fruits and vegetables have a decreased risk of getting chronic diseases, especially CVD and cancer, but vitamin supplements do not have a clear beneficial effect—rather, the effect is the opposite among some groups (33). This paradox can be explained by food synergy: ie, the additive or more than additive influence of foods and food constituents in the human body (34, 35). Our finding is similar to the unexpected positive associations with disease outcomes in large clinical trials of vitamin supplements (36, 37). Antioxidants naturally present in food usually are balanced biochemically—ie, they are part of a mixture of redox agents in oxidized form and in reduced form—whereas supplement pills lack this balance (38). The body's defense against oxidative stress requires interconnecting systems of antioxidant micronutrients with a range of physical properties, and therefore the use of high doses of a single antioxidant could perturb the antioxidant-prooxidant balance (39).

Although heme-iron intake was positively related to serum GGT concentrations, neither dietary nonheme iron nor iron from supplements was associated with serum GGT concentration. Even though most dietary iron comes from nonheme iron, the absorption of heme iron is about 5–10 times greater than that of nonheme iron (40, 41). The absorption of heme iron is less sensitive to body iron stores than is the absorption of nonheme iron, and it is not influenced by other dietary factors (40, 41). Some population studies showed a positive association between meat or heme-iron intake and serum ferritin, a marker of stored body iron, but the association of nonheme-iron intake and serum ferritin was negligible (14, 42). Low bioavailability of nonheme iron might explain the lack of association between nonheme-iron intake and the serum GGT concentration. However, the reported associations of iron and serum ferritin have not been totally consistent (43–45). In addition, it is possible that antioxidants simultaneously contained in plant food sources (vegetables, fruits, or grains) of nonheme iron might counteract the oxidative stress that is due to nonheme iron and, in turn, result in no association with the serum GGT concentration, although this possibility has not been specifically studied. The absence of an association between iron from supplements and the serum GGT concentration might be explained by the possibility that subjects who take supplemental iron are likely to do so because of conditions associated with low iron stores, such as iron deficiency anemia, pregnancy, or lactation, as suggested by our observation of reduced hemoglobin in participants who took an iron supplement.

In conclusion, in addition to its well-known relation with alcohol intake, serum GGT concentrations mostly within the normal range were positively associated with meat intake, especially meats high in heme iron, and were inversely associated with fruit intake. Heme iron contained in meats and dietary micronutrients contained in fruits may influence GGT metabolism. However, micronutrients taken as supplements did not show a consistent relation with the serum GGT concentration. 

D-HL was responsible for the conception of the study, the analysis and interpretation of data, and the writing of the final draft of the manuscript. LMS was responsible for the interpretation of data and revision of the manuscript. DRJ was responsible for obtaining grant funding, the analysis and interpretation of data, and revision of the manuscript. None of the authors had any personal or financial conflicts of interest.



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