Fruit and vegetable consumption and LDL cholesterol: the National Heart, Lung, and Blood Institute Family Heart Study[1–3]

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ABSTRACT

Background: An elevated LDL-cholesterol concentration is associated with an increased risk of cardiovascular disease. The association between fruit and vegetable consumption and LDL has been inconsistent.

Objective: The objective was to determine whether a high intake of fruit and vegetables is inversely associated with LDL concentrations.

Design: We used data collected from 4466 subjects in the National Heart, Lung, and Blood Institute Family Heart Study to study the association between fruit and vegetable consumption and serum LDL. We used a food-frequency questionnaire to assess fruit and vegetable intakes and regression models to estimate adjusted mean LDL according to fruit and vegetable consumption.

Results: The mean (±SD) age of the men ($n = 2047$) was 51.5 ± 14.0 y and that of the women ($n = 2419$) was 52.2 ± 13.7 y. The average daily serving of fruit and vegetables was 3.2 ± 1.7 for men and was 3.5 ± 1.8 for women. Fruit and vegetable consumption was inversely related to LDL: in the categories 0–1.9, 2.0–2.9, 3.0–3.9, and ≥4 servings/d, multivariate-adjusted mean (95% CI) LDL concentrations were 3.36 (3.28, 3.44), 3.35 (3.27, 3.43), 3.26 (3.17, 3.35), and 3.17 (3.09, 3.25) mmol/L, respectively, for men (P for trend < 0.0001) and 3.35 (3.26, 3.44), 3.22 (3.14, 3.30), 3.21 (3.13, 3.29), and 3.11 (3.04, 3.18), respectively, for women (P for trend < 0.0001). This association was observed across categories of age, education, smoking status, physical activity, and tertiles of Keys score. Exclusion of subjects with prevalent diabetes mellitus or coronary artery disease did not alter these results significantly.

Conclusion: Consumption of fruit and vegetables is inversely related to LDL in men and women. *Am J Clin Nutr* 2004;79:213–7.

KEY WORDS LDL, fruit, vegetables, lipids, National Heart, Lung, and Blood Institute Family Heart Study

INTRODUCTION

An elevated LDL-cholesterol concentration is a risk factor for coronary artery disease (1–5). Plasma concentrations of LDL are influenced by both genetic and environmental factors. Although it is difficult to alter genetic factors, modifiable environmental factors such as smoking or dietary patterns could be targeted in preventive interventions aimed at lowering LDL. The usual guidelines recommend a reduction in dietary saturated fat and cholesterol intakes as a way to prevent hypercholesterolemia; however, only limited data are available on the benefits of fruit and vegetable consumption on plasma concentrations of LDL in a community-based population. Data on the effects of fruit and vegetable intakes on LDL are inconsistent. In the Dietary Approaches to Stop Hypertension (DASH) trial (6), a diet high in fruit and vegetables was not associated with a significant reduction in LDL compared with the control diet, although the trend suggests a decrease in plasma LDL concentrations. In contrast, in the Indian Diet Heart Study (7), fruit and vegetable consumption decreased LDL concentrations by ≈7%. In a randomized trial, fruit and vegetable intake was associated with a reduction in LDL among patients with acute myocardial infarction after 12 wk of intervention (8). Fruit and vegetables are rich in dietary fiber, which has been shown to decrease LDL concentrations (9–11).

In the current study we used data from 4466 adult participants of the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study to evaluate whether higher intakes of fruit and vegetables is inversely related to LDL concentrations in men and women, independent of other risk factors.

SUBJECTS AND METHODS

Study population

The NHLBI Family Heart Study is a multicenter, population-based study designed to identify and evaluate genetic and nongenetic determinants of cardiovascular disease. A detailed description of the methods and design was published previously (12). Subjects in this study are members of families from previously established population-based cohort studies: The Framingham Heart Study in Framingham, MA; the Atherosclerosis Risk in Communities Study cohorts in North Carolina and Minnesota; and the Utah Health Family Tree Study in Salt

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Lake City. Briefly, in 1993–1995, participants (probands) in each of the 4 studies were selected at random and invited to furnish an updated family health history that contained information on their parents, children, and siblings. Of the families who furnished data, 588 were chosen at random and 657 were chosen because of higher than expected coronary artery disease rates among their family members. All members of these families, including the spouses of the probands, were invited to 1 of the 4 study clinics for evaluation. The evaluation included a detailed medical and lifestyle history that was obtained through an interview. Informed consent was obtained from each participant, and the study protocol was reviewed and approved by the institutional review boards of each of the participating institutions.

Blood collection and assays

Fasting blood samples for lipid measurements were collected into evacuated tubes containing no additives. Blood samples were then spun at 3000 × *g* for 10 min at 4 °C. Sera were stored at −70 °C until shipped periodically to a central laboratory at the Fairview–University Medical Center in Minneapolis for processing. LDL was estimated by using the method of Friedewald et al (13), except for subjects with triacylglycerol concentrations >400 mg/dL, whose LDL concentrations were measured by ultracentrifugation.

Assessment of fruit and vegetable intakes

Trained interviewers obtained information on usual consumption of fruit and vegetables with the use of a 100-item food-frequency questionnaire (FFQ) modified from the FFQ developed by Willett et al (14, 15). The reproducibility and validity of the FFQ was documented elsewhere (16). For fruit consumption, each participant was asked about how often, on average, he or she consumed fruit during the previous year (items 9 through 14 on the FFQ). For vegetable consumption, subjects were asked about their average consumption of vegetables such as beans, broccoli, cabbage, cauliflower, carrots, corn, spinach, squash, and tomatoes (items 15 through 25 on the FFQ). Response categories ranged from almost never, 1–3/mo, 1/wk, 2–4/wk, 5–6/wk, 1/d, 2–3/d, 4–6/d, to >6/d. The portion size of each fruit and vegetable was specified to facilitate determination of the number of typical servings and nutrient content.

Other variables

Information on the dietary consumption of total fat, saturated fat, and cholesterol was obtained by using the same FFQ. Intake of specific nutrients was computed by multiplying the frequency of consumption of an item by the nutrient content of specified portions. Nutrient composition was obtained from the Harvard University FOOD COMPOSITION DATABASE, derived from US Department of Agriculture sources (17), and from manufacturer information.

Anthropometric data were collected while the subjects were wearing scrub suits. A balance scale was used to measure body weight, and height was measured with a wall-mounted vertical ruler. Demographic data and information on alcohol intake, cigarette smoking, and physical activity (minutes per day of leisure activity) were obtained by interview.

Statistical analysis

Because eating habits differ between men and women, we initially analyzed the data stratified by sex and created the following categories of fruit and vegetable consumption: 0–1.9, 2.0–2.9, 3.0–3.9, and ≥4 servings/d. Because the subjects were not independent in this study, we used a general linear model (PROC MIXED; SAS Institute, Cary, NC) to estimate adjusted mean LDL concentrations across categories of fruit and vegetable intake. This method corrects the variance of the point estimates for familial clustering. Adjustment was made for age, age squared, study center, risk group (high risk compared with random), body mass index, energy intake (quintiles), smoking status (never, former, and current smokers), dietary cholesterol (quintiles), history of coronary artery disease, and diabetes mellitus. Additional adjustment for education (high school graduate or less, vocational school, and college or more), physical activity (minutes per day of leisure activity), use of vitamin supplements, consumption of breakfast cereals, and total fat (quintiles), saturated fat (quintiles), and polyunsaturated fat (quintiles) intakes did not alter the results significantly. All sex-specific analyses were initially conducted within the random and high-risk groups separately, but, because the results were similar, we combined the high-risk and random groups.

Subjects with higher intakes of fruit and vegetables were older and had different lifestyle habits and lower Keys score than did those who consumed fewer servings of fruit and vegetables per day. The Keys score correlates changes in fatty acid intake with changes in serum cholesterol and is computed as follows:

$$\text{Keys score} = 1.35 \times (2S - P) + 1.5 \times \sqrt{C} \quad (1)$$

where S and P are percentages of energy from saturated fat and polyunsaturated fat, respectively, and C is dietary cholesterol in mg/1000 kcal. Therefore, in secondary analyses, we conducted stratified analyses according to age (25–39, 40–59, and ≥60 y), tertiles of Keys score, education (high school graduate or less, vocational school, and college or more), smoking status (current nonsmokers and current smokers), physical activity (with the median of total minutes of daily exercise as the cutoff), and use of vitamin supplements. Furthermore, we repeated the analyses after excluding 751 subjects (n = 276 with diabetes mellitus, n = 366 with coronary artery disease, and n = 109 with both diseases). All analyses were performed with the use of SAS software (18).

RESULTS

Of the 4466 subjects, 45.8% were men. The average age of the men was 51.5 ± 14.0 y (range: 25.2–91.0 y) and of the women was 52.2 ± 13.7 y (range: 25.2–93.6 y). The mean consumption of fruit and vegetables was 3.2 ± 1.7 servings/d for men (range: 0–15.2 servings/d) and 3.5 ± 1.8 servings/d for women (range: 0–14.1 servings/d). The baseline characteristics of the male and female participants according to their consumption of fruit and vegetables are shown in **Tables 1** and **2**, respectively. For both men and women, a higher intake of fruit and vegetables was associated with older age ($P < 0.0001$), higher energy intake ($P < 0.0001$), a lower percentage of energy from total fat ($P < 0.0001$), lower Keys score ($P < 0.0001$), a higher intake of dairy products ($P < 0.0005$), use of

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TABLE 1
Baseline characteristics of male participants in the National Heart, Lung, and Blood Institute Family Heart Study according to fruit and vegetable intakes

	Mean (range) servings of fruit and vegetables per day				
	1.4 (0–1.9) (n = 552)	2.5 (2.0–2.9) (n = 517)	3.4 (3.0–3.9) (n = 433)	5.4 (4.0–15.2) (n = 545)	P for trend[1]
Age (y)	46.9 ± 13.3[2]	51.0 ± 13.8	52.9 ± 13.8	55.4 ± 13.8	<0.0001
BMI (kg/m^2)	27.9 ± 4.8	27.7 ± 4.1	27.8 ± 4.4	27.6 ± 4.5	0.46
Energy intake (kJ)	7548 ± 2701	7775 ± 2526	7883 ± 2715	8689 ± 2798	<0.0001
Dietary cholesterol (g/d)	0.26 ± 0.13	0.26 ± 0.13	0.26 ± 0.14	0.26 ± 0.15	0.85
Total fat (% of energy)	34.0 ± 7.2	32.5 ± 6.7	31.0 ± 6.6	28.0 ± 7.2	<0.0001
Saturated fat (% of energy)	12.6 ± 3.0	11.8 ± 2.8	11.2 ± 2.8	10.1 ± 3.1	0.024
Monounsaturated fat (% of energy)	13.6	12.9	12.2	10.8	<0.0001
Polyunsaturated fat (% of energy)	4.7	4.8	4.6	4.2	<0.0001
Keys score[3]	45.5 ± 9.6	43.0 ± 9.2	41.5 ± 9.3	38.1 ± 10.1	<0.0001
Intake of ≥2 dairy products/d (%)	40.6	36.4	42.0	50.5	0.0004
Use of vitamin supplements (%)	28.1	32.2	43.3	43.1	<0.0001
Exercise (min/d)	30.0 ± 35.4	33.1 ± 39.1	36.7 ± 42.2	44.4 ± 48.5	<0.0001
Random group (%)	44.0	47.6	46.9	53.8	0.058
College education (%)	51.5	58.4	56.6	65.1	0.003
Current smoking (%)	22.6	16.6	11.6	9.9	<0.0001
Coronary artery disease (%)	11.4	15.7	18.0	23.6	<0.0001
Diabetes mellitus (%)	6.3	7.0	11.6	11.9	0.0002

[1] Values obtained from a general linear model (PROC MIXED in SAS) for continuous variables and from generalized estimating equations (PROC GENMOD in SAS) for categorical variables.
[2] $\bar{x}$ ± SD.
[3] Calculated as $1.35 \times (2S - P) + 1.5 \times \sqrt{C}$, where S is the percentage of energy from saturated fat, P is the percentage of energy from polyunsaturated fat, and C is dietary cholesterol in mg/1000 kcal.

vitamin supplements ($P < 0.0001$), more physical activity ($P < 0.0001$), a lower prevalence of smoking ($P = 0.001$), and a higher prevalence of coronary artery disease ($P < 0.05$) and diabetes mellitus ($P < 0.0002$). In men, a higher consumption of fruit and vegetables was also associated with a lower percentage of energy from saturated fat ($P = 0.024$) and higher educational attainment ($P = 0.003$). In women, a higher intake of fruit and vegetables was also associated with a higher intake of dietary cholesterol ($P < 0.0001$).

In the categories 0–1.9, 2.0–2.9, 3.0–3.9, and ≥4 servings of fruit and vegetables per day, adjusted mean (±SE) LDL concentrations were 3.36 ± 0.04, 3.35 ± 0.04, 3.26 ± 0.04, and

TABLE 2
Baseline characteristics of female participants in the National Heart, Lung, and Blood Institute Family Heart Study according to fruit and vegetable intakes

	Mean (range) servings of fruit and vegetables per day				
	1.4 (0–1.9) (n = 426)	2.5 (2.0–2.9) (n = 614)	3.4 (3.0–3.9) (n = 562)	5.5 (4.0–14.1) (n = 817)	P for trend[1]
Age (y)	47.4 ± 13.4[2]	51.0 ± 13.1	53.6 ± 13.6	54.7 ± 13.6	<0.0001
BMI (kg/m^2)	26.7 ± 6.2	27.4 ± 6.2	27.5 ± 6.0	27.1 ± 5.1	0.39
Energy intake (kJ)	5945 ± 2240	6387 ± 2230	6753 ± 2187	7433 ± 2253	<0.0001
Dietary cholesterol (g/d)	0.20 ± 0.11	0.22 ± 0.10	0.22 ± 0.10	0.23 ± 0.11	<0.0001
Total fat (% of energy)	33.6 ± 7.9	31.2 ± 6.4	29.5 ± 6.8	26.8 ± 6.8	<0.0001
Saturated fat (% of energy)	12.6 ± 3.6	11.8 ± 2.9	10.9 ± 2.9	10.0 ± 2.9	0.43
Monounsaturated fat (% of energy)	13.2	12.4	11.4	10.2	<0.0001
Polyunsaturated fat (% of energy)	4.8	4.7	4.4	4.1	<0.0001
Keys score[3]	45.3 ± 11.3	43.3 ± 9.5	40.6 ± 9.1	37.8 ± 9.5	<0.0001
Intake of ≥2 dairy products/d (%)	28.6	35.5	38.1	42.0	<0.0001
Use of vitamin supplements (%)	40.9	45.7	48.5	55.0	<0.0001
Exercise (min/d)	18.3 ± 36.2	20.4 ± 26.0	23.4 ± 30.9	30.7 ± 33.6	<0.0001
Random group (%)	44.4	46.6	48.0	48.0	0.16
College education (%)	43.2	48.2	47.3	49.8	0.50
Current smoking (%)	23.9	16.1	10.0	8.3	<0.0001
Coronary artery disease (%)	2.4	6.0	3.7	6.3	0.024
Diabetes mellitus (%)	5.2	6.5	8.0	10.5	<0.0001

[1] Values obtained from a general linear model (PROC MIXED in SAS) for continuous variables and from generalized estimating equations (PROC GENMOD in SAS) for categorical variables.
[2] $\bar{x}$ ± SD.
[3] Calculated as $1.35 \times (2S - P) + 1.5 \times \sqrt{C}$, where S is the percentage of energy from saturated fat, P is the percentage of energy from polyunsaturated fat, and C is dietary cholesterol in mg/1000 kcal.

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TABLE 3
Adjusted LDL cholesterol according to fruit and vegetable intakes in the National Heart, Lung, and Blood Institute Family Heart Study[1]

Mean (range) servings of fruit and vegetables per day	Model 1[2]	Model 2[3]
	mmol/L	
Men		
1.4 (0–1.9), $n = 552$	3.36 ± 0.04	3.36 ± 0.04
2.5 (2.0–2.9), $n = 517$	3.35 ± 0.04	3.35 ± 0.04
3.4 (3.0–3.9), $n = 433$	3.26 ± 0.04	3.26 ± 0.04
5.4 (4.0–15.2), $n = 545$	3.17 ± 0.06	3.17 ± 0.06
P for trend	<0.0001	0.0002
Women		
1.4 (0–1.9), $n = 426$	3.35 ± 0.05	3.36 ± 0.05
2.5 (2.0–2.9), $n = 614$	3.22 ± 0.04	3.23 ± 0.04
3.4 (3.0–3.9), $n = 562$	3.21 ± 0.04	3.20 ± 0.04
5.5 (4.0–14.1), $n = 817$	3.11 ± 0.04	3.11 ± 0.04
P for trend	<0.0001	<0.0001

[1] $\bar{x}$ ± SE.

[2] Adjusted for age, age squared, field center, risk group (random compared with high risk of coronary artery disease), BMI, energy intake (quintiles), smoking status (never, former, and current smokers), dietary cholesterol (quintiles), and history of coronary artery disease and diabetes mellitus with the use of a general linear model (PROC MIXED in SAS).

[3] Adjusted for variables controlled for in model 1 and for education (high school graduate or less, vocational school, and college or more), physical activity, and saturated fat (quintiles), polyunsaturated fat (quintiles), and total fat (quintiles) intakes.

3.17 ± 0.06 mmol/L, respectively, in men (P for trend < 0.0001) and 3.35 ± 0.05, 3.22 ± 0.04, 3.21 ± 0.04, and 3.11 ± 0.04 mmol/L, respectively, in women (P for trend < 0.0001) in a model that adjusted for age, age squared, field center, risk group, body mass index, energy intake, smoking status, dietary cholesterol, and prevalence of diabetes mellitus and coronary artery disease (**Table 3**). Additional adjustment for education, physical activity, and saturated, polyunsaturated, and total fat intakes did not alter the results significantly. Furthermore, exclusion of 751 subjects with diabetes mellitus, coronary artery disease, or both did not change the results (data not shown). We also looked at HDL, LDL:HDL, and triacylglycerol as endpoints. Although the consumption of fruit and vegetables was not associated with HDL (P for trend = 0.57 for men and 0.97 for women) or triacylglycerol (P for trend = 0.83 for men and 0.60 for women) concentrations, fruit and vegetables consumption was inversely related to LDL:HDL. From the lowest to the highest category of fruit and vegetable consumption, multivariate-adjusted mean LDL:HDL values were 3.21 ± 0.05, 3.19 ± 0.05, 3.16 ± 0.05, and 3.03 ± 0.05, respectively, for men (P for trend = 0.006). Corresponding values for women were 2.52 ± 0.05, 2.40 ± 0.04, 2.42 ± 0.04, and 2.36 ± 0.04 (P for trend = 0.020). Because the intake of fruit and vegetables was inversely related to the intake of energy from saturated fat, we conducted subanalyses that were restricted to subjects above the 75th percentile of energy intake from saturated fat; we found an inverse relation between fruit and vegetable consumption and LDL cholesterol concentration (P for trend < 0.0001; data not shown).

To assess residual confounding by dietary fat intake, we stratified by tertiles of Keys score. From the lowest to the highest category of fruit and vegetable consumption, multivariate-adjusted mean (±SE) LDL-cholesterol concentrations were 3.43 ± 0.07, 3.37 ± 0.06, 3.26 ± 0.06, and 3.19 ± 0.05 mmol/L, respectively, for the lowest tertile of Keys score (P for trend = 0.0004); 3.31 ± 0.05, 3.28 ± 0.05, 3.24 ± 0.05, and 3.11 ± 0.05 mmol/L, respectively, for the second tertile of Keys score (P for trend = 0.002); and 3.38 ± 0.05, 3.24 ± 0.05, 3.23 ± 0.06, and 3.14 ± 0.06 mmol/L, respectively, for the third tertile of Keys score (P for trend = 0.0008). In addition, when stratified by age, education, smoking status, physical activity, and use of vitamin supplements, the relation between fruit and vegetable intakes and LDL-cholesterol concentrations persisted (data not shown).

DISCUSSION

In this cross-sectional study, we found that consumption of fruit and vegetables was inversely related to LDL-cholesterol concentrations in men and women, independent of age, Keys score, smoking status, exercise, educational attainment, and use of vitamin supplements. Subjects in the highest fruit and vegetable intake groups had LDL concentrations that were ≈6–7% lower than those in the lowest fruit and vegetable intake groups. Although several clinical trials and observational studies have assessed the effects of dietary fat on LDL concentrations, limited data are available on the association between the consumption of fruit and vegetables and LDL concentrations in a community-based population. In the DASH trial, LDL-cholesterol concentrations in 146 subjects assigned to consume a fruit and vegetable diet—a diet increased in fruit, vegetables, and whole grains and lower in sweets—were not significantly lower than concentrations in the control group after an 8-wk intervention period (6). In that study, although the DASH diet—which is rich in fruit, vegetables, and low-fat dairy products and low in saturated fat, total fat, and cholesterol—resulted in a reduction in LDL cholesterol (mmol/L) in men [$\bar{x}$ change: −0.43 (95% CI: −0.60, −0.26)] and in women [−0.14 (−0.31, 0.03)], a diet high in fruit and vegetables indicated a nonsignificant reduction in LDL cholesterol (mmol/L) in men [−0.12 (−0.29, 0.05)] and no effect in women [0.05 (−0.12, 0.23)]. In contrast, the Indian Diet Heart Study showed that fruit and vegetable consumption was associated with a 7.3% decrease in LDL after 12 wk of intervention (7). However, this study did not analyze the data stratified by sex; of the 621 participants, only 14% were women. Neither the DASH trial (6) nor the Indian Diet Heart Study (7) assessed a dose-response effect between fruit and vegetable consumption and LDL-cholesterol concentrations. Fornes et al (19) reported in a cross-sectional study that the intake of fruit and vegetables was inversely correlated with LDL-cholesterol concentrations, and other investigators reported beneficial effects of fruit and vegetable intakes on LDL-cholesterol concentrations (20, 21). Our findings are consistent with these reports.

Diets rich in fruit and vegetables are good sources of dietary fiber. In a randomized trial, a fiber-multivitamin combination resulted in a reduction in LDL cholesterol of ≈8% from baseline after 8 wk (22). Other epidemiologic studies (9, 11) and a meta-analysis (23) showed LDL-cholesterol lowering effects of dietary fiber.

Our study has some limitations. Given the cross-sectional design, we cannot infer causality between fruit and vegetable consumption and lower concentrations of LDL cholesterol. However, dietary patterns in adults are relatively stable, and the exclusion of those with prevalent coronary artery disease and

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diabetes mellitus did not alter the results significantly, making it more likely that dietary intakes reported over the past year may reflect the subjects' usual diets. Frequencies of fruit and vegetable consumption were self-reported; thus, reporting bias might have affected our estimates of the effect.

Could the observed inverse association between fruit and vegetable consumption and LDL-cholesterol concentrations simply be attributed to a lower intake of saturated fat and dietary cholesterol in subjects with higher fruit and vegetable intakes? Our data indicate that a higher intake of fruit and vegetables was associated with lower Keys score and a lower percentage of energy from saturated fat, especially in men. This suggests that residual confounding by saturated fat could have biased our estimates. However, dietary cholesterol did not differ across categories of fruit and vegetable intakes in men and was in the opposite direction in women, because a higher intake of fruit and vegetables was related to higher dietary cholesterol in women (Table 2). In addition, the inverse association between fruit and vegetable consumption and LDL-cholesterol concentrations was observed across all tertiles of Keys score and among subjects whose energy intake from saturated fat was above the 75th percentile of the total population. This finding is not consistent with the fact that subjects with a higher intake of fruit and vegetables were more likely to eat less saturated fat and dietary cholesterol. Thus, our findings are less likely to be attributable to the effect of substituting saturated fat and dietary cholesterol with fruit and vegetables. The wide age range, the availability of data across many centers, and the large sample size are strengths of the study. In conclusion, our data show that the consumption of fruit and vegetables is associated with lower concentrations of LDL cholesterol in a dose-response manner.

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LD designed the project, completed the data analyses, and drafted the manuscript. DKA and MAP participated in the study design, the data collection, and the critical review of the manuscript. HC and LLM participated in the data analyses and the critical review of the manuscript. RCE participated in the study design, the data collection, the data analyses, and the critical review of the manuscript. None of the authors had a conflict of interest to disclose.

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