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Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study[1–3]

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ABSTRACT

Background: A reduction in dietary cholesterol is recommended to prevent cardiovascular disease (CVD). Although eggs are important sources of cholesterol and other nutrients, limited and inconsistent data are available on the effects of egg consumption on the risk of CVD and mortality.

Objective: We aimed to examine the association between egg consumption and the risk of CVD and mortality.

Design: In a prospective cohort study of 21 327 participants from Physicians' Health Study I, egg consumption was assessed with an abbreviated food questionnaire. Cox regression was used to estimate relative risks.

Results: In an average follow-up of 20 y, 1550 new myocardial infarctions (MIs), 1342 incident strokes, and 5169 deaths occurred. Egg consumption was not associated with incident MI or stroke in a multivariate Cox regression. In contrast, adjusted hazard ratios (95% CI) for mortality were 1.0 (reference), 0.94 (0.87, 1.02), 1.03 (0.95, 1.11), 1.05 (0.93, 1.19), and 1.23 (1.11, 1.36) for the consumption of <1, 1, 2–4, 5–6, and ≥ 7 eggs/wk, respectively (P for trend < 0.0001). This association was stronger among diabetic subjects, in whom the risk of death in a comparison of the highest with the lowest category of egg consumption was twofold (hazard ratio: 2.01; 95% CI: 1.26, 3.20; P for interaction $= 0.09$).

Conclusions: Infrequent egg consumption does not seem to influence the risk of CVD in male physicians. In addition, egg consumption was positively related to mortality, more strongly so in diabetic subjects, in the study population. *Am J Clin Nutr* 2008;87: 964–9.

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of death in the United States. Because elevated LDL cholesterol has been identified as a major risk factor for CAD, dietary guidelines to prevent CAD emphasize the reduction in dietary cholesterol to $<$300 mg/d (1, 2). Egg is a major source of dietary cholesterol with an average egg containing $\approx$200 mg cholesterol. On the other hand, eggs contain other nutrients such as minerals, folate, B vitamins, proteins, and monounsaturated fatty acids (3, 4) that could reduce the risk of CAD. Whereas some studies have shown positive associations between dietary and serum cholesterol (5–9), others did not find any effect (7, 10, 11). There is a large variability in individual response to dietary cholesterol (11–13). In addition, the effect of dietary cholesterol on LDL cholesterol observed in positive studies is modest compared with the LDL-raising effects of saturated and *trans* fatty acids (14, 15).

Limited and inconsistent data have been reported on the association between egg consumption and CAD. Among 514 Australian Aborigines, consumption of $>$2 eggs/wk was associated with a 2.6 times greater risk of CAD in a prospective analysis (16). Mann et al (17) reported a 2.7 times greater risk of death with higher egg consumption ($>$6 eggs/wk) among British persons. In contrast, other large prospective cohorts with longer follow-ups did not observe any association between egg consumption and CAD or mortality (18–21). Because eggs could serve as a good source for vitamins, proteins, and other nutrients in the United States, it is important to determine the net benefit or harm of egg consumption as whole food (as opposed to individual component of eggs such as cholesterol). In the current project, we sought to prospectively assess whether egg consumption was associated with a greater risk of myocardial infarction (MI), stroke, and all-cause mortality. In addition, we assessed the influence of type 2 diabetes and history of hypercholesterolemia as possible effect modifiers of these associations.

SUBJECTS AND METHODS

Study population

The current project used data from the Physicians' Health Study (PHS) I, which was a randomized, double-blind, placebo-controlled trial using a 2×2 factorial design to study low-dose aspirin and β-carotene for the primary prevention of cardiovascular disease (CVD) and cancer among US male physicians. A detailed description of PHS I was previously published (22). Briefly, 261 248 US male physicians aged 40–85 y were invited to participate in the clinical trial in 1981. After exclusion of subjects with a history of stroke, gout, MI, transient ischemic attack, cancer (except nonmelanoma skin cancer), peptic ulcer, current liver or kidney disease, and current use of trial treatments,

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33 223 physicians were enrolled in an 18-wk run-in period. At the end of the run-in period, 22 071 subjects were randomly assigned to 1 of 4 treatment arms: low-dose aspirin, β-carotene, both agents, or placebo. For the current project, after the exclusion of 744 subjects with missing data on egg consumption ($n = 151$) or covariates ($n = 593$), the final sample consisted of 21 327 participants.

Each participant provided written informed consent. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

Assessment of egg consumption

Information on egg consumption was self-reported by using a simple abbreviated semi-quantitative food-frequency questionnaire. Participants were asked to report their average egg consumption during the past year. Possible response categories included rarely or never, 1–3 times/mo, 1 time/wk, 2–4 times/wk, 5–6 times/wk, daily, and >2 times/d. This information was obtained at baseline and 24, 48, 72, 96, and 120 mo after randomization.

Ascertainment of cardiovascular events and death in the Physicians' Health Study I

A questionnaire was mailed to each participant every 6 mo during the first year and annually thereafter to gather information on compliance with the intervention and the occurrence of new medical diagnoses including MI, stroke, and death. For participants who did not return the follow-up questionnaire within 5–6 wk of the initial mailing, a follow-up questionnaire was sent to them. If necessary, third and fourth questionnaires were sent to nonrespondents, and then they were telephoned in an attempt to obtain the follow-up information if there was still no response to the mailed questionnaires. If the follow-up information was not obtained by questionnaires or telephone call, the vital status of the corresponding participants was ascertained. A letter and return postcard were also mailed to the participants at the 6-mo interval between annual mailings. Participants were asked to return the postcard if they experienced any major problems affecting their participation in the study.

All cardiovascular endpoints were adjudicated by the Endpoint Committee of the PHS, which included cardiologists and neurologists. MI was confirmed on the basis of World Health Organization criteria modified to use cardiac enzyme tests. When participants died, death certificates were obtained for confirmation and review of cause of death. Additional information was obtained from the participants' next of kin and from medical records after the proper permission was obtained from the next of kin. Both the cause of death on death certificates and additional information from the next of kin and medical records were used by the Endpoint Committee. Details on endpoint validation in the PHS were previously published (23–26).

Other variables

Demographic data were collected at baseline. Information on comorbidity (ie, atrial fibrillation, hypertension, and diabetes mellitus) was collected through annual follow-up questionnaires as described above. Data on selected foods such as fruit, vegetables, and breakfast cereals; physical activity; smoking; alcohol consumption; parental history of premature MI; and history of hypercholesterolemia were obtained at baseline.

Statistical analysis

Because there was a reasonable correlation between reported egg consumption at baseline and at 24 mo (weighted kappa: 0.51), we substituted missing values at baseline by using reported egg consumption at 24 mo in 113 subjects. We grouped adjacent categories to allow a sufficient number of person-times per category of egg consumption and to maintain a gradient of exposure. Thus, we classified each subject into one the following categories of egg consumption: <1 egg/wk, 1 egg/wk, 2–4 eggs/wk, 5–6 eggs/wk, and ≥7 eggs/wk. For each endpoint (MI, stroke, or death), we calculated person-time of follow-up from baseline until the first occurrence of an endpoint, death, or a censoring date (ie, the date of receipt of the last follow-up questionnaire). Within each egg consumption group, we calculated the incidence rate of each endpoint by dividing the number of cases by the corresponding person-time. We used Cox proportional hazard models to compute multivariate-adjusted hazard ratios (HRs) (and corresponding 95% CIs) by using subjects in the lowest category of egg consumption as the reference group. We assessed confounding by using a 10% change in HRs. Assumptions for the proportional hazard models were tested (by including main effects and product terms of covariates and a log-transformed time factor) and were met ($P > 0.05$ for all). We obtained the P values for linear trend by assigning the median value of egg consumption in each category to a new variable that was used in the Cox model (we assigned values of 0, 1, 3, 5.5, and 7 for the lowest to the highest egg consumption, respectively). The initial model controlled for age. The parsimonious model also controlled for body mass index (continuous), smoking (never, past, or current smoker), and history of hypertension (yes or no). The final multivariate model also controlled for hypercholesterolemia (yes or no), parental history of premature MI (yes or no), diabetes mellitus (yes or no), atrial fibrillation (yes or no), breakfast cereal consumption (0, 1, 2–6, or ≥7 servings/wk), alcohol consumption (<1, 1–4, 5–6, or ≥7 drinks/wk), vegetable consumption (<3, 3–4, 5–6, 7–13, or ≥14 servings/wk), use of multivitamins (never, past, or current), and physical activity (<1, 1, 2–4, or ≥5 times/wk). Two-way interaction between egg consumption and treatment assignment was evaluated by including main effect and their product term in the regression model ($P > 0.05$ for all).

In secondary analyses, we examined the association between egg consumption and types of stroke (ischemic or hemorrhagic) and possible effect modification by diabetes mellitus and hypercholesterolemia with the use of stratified analyses. In addition, we excluded subjects with a follow-up time of ≤2 y. Finally, we repeated the main analysis by using updated egg consumption at 24, 48, 72, 96, and 120 mo in a time-dependent Cox model. All analyses were completed with the use of SAS software (version 9.1; SAS Institute, Cary, NC). Significance was set at 0.05.

RESULTS

Among 21 327 participants in PHS I, the mean ± SD age at randomization was 53.7 ± 9.5 y (range: 40–86 y). The median egg consumption was 1/wk in this population. Baseline characteristics of the study participants are presented in **Table 1**. Frequent consumption of eggs was associated with older age; higher body mass index; higher vegetables and lower breakfast cereal consumption; higher proportions of current drinkers, smokers,

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TABLE 1
Characteristics of 21 327 participants by category of egg consumption in the Physicians' Health Study

	Weekly egg consumption in the Physicians' Health Study					
Variables	<1 (n = 4564)	1 (n = 6627)	2–4 (n = 6983)	5–6 (n = 1421)	≥7 (n = 1732)	P for trend[1]
Age (y)	53.0 ± 9.3[2]	53.4 ± 9.3	53.6 ± 9.5	54.1 ± 9.4	56.8 ± 10.1	<0.0001
BMI (kg/m^2)	24.5 ± 2.6	24.7 ± 2.7	24.9 ± 2.7	25.2 ± 2.9	25.0 ± 3.2	<0.0001
Vegetable intake (servings/wk)	7.9 ± 5.0	8.0 ± 4.6	8.2 ± 4.6	8.2 ± 4.6	8.6 ± 5.1	<0.0001
Breakfast cereal ≥7 times/wk (%)	24.1	24.0	15.9	10.8	11.8	<0.0001
Parental history of premature MI (%)	10.8	9.1	9.5	7.2	7.2	<0.0001
Hypercholesterolemia (%)	13.6	12.2	11.3	10.8	10.5	<0.0001
Current smoking (%)	8.0	9.8	12.0	14.9	16.7	<0.0001
Current alcohol drinking (%)	71.0	75.0	75.5	74.5	73.9	<0.0001
Exercise ≥1 time/wk (%)	71.8	72.6	72.9	72.7	69.9	<0.0001
History of diabetes (%)	1.2	1.8	2.0	2.3	5.2	<0.0001
History of hypertension (%)	21.9	23.8	23.9	25.4	28.5	<0.0001
History of atrial fibrillation (%)	1.3	1.5	1.3	1.8	1.3	0.67
Current use of multivitamins (%)	20.0	18.6	19.9	20.2	24.0	0.001
Aspirin assignment (%)	49.5	49.5	50.3	51.6	50.1	0.22

[1] P for trend values were obtained from ANOVA or a logistic regression model.
[2] $\bar{x}$ ± SD (all such values).

and multivitamin users; higher prevalence of diabetes and hypertension; and lower prevalence of exercise, hypercholesterolemia, and parental history of premature CAD. During an average follow-up of 20 y, 1550 new MIs (7.3%), 1342 incident strokes (6.3%), and 5169 deaths (24.2%) occurred in this cohort. In multivariate Cox regression model, egg consumption was not associated with incident MI (**Table 2**), total stroke (**Table 3**), or types of stroke. From the lowest to the highest category of egg consumption, multivariate-adjusted HRs (95% CI) for ischemic stroke were 1.0; 1.03 (0.86, 1.23); 1.08 (0.91, 1.28); 1.11 (0.86, 1.43); and 0.99 (0.78, 1.26), respectively (P for trend 0.74). Corresponding values for hemorrhagic stroke were 1.0; 0.66 (0.44, 1.00); 0.92 (0.63, 1.36); 1.29 (0.76, 2.20); and 1.07 (0.65, 1.78), respectively (P for trend 0.11). Whereas egg consumption of up to 6 eggs/wk was not associated with the risk of all-cause mortality, consumption of ≥7 eggs/wk was associated with a 23% greater risk of death after control for confounders (**Table 4**). The exclusion of subjects whose follow-up times were ≤2 y, and the use of the time-dependent Cox model with updated egg consumption over time did not alter the results (data not shown).

In stratified analyses, a history of hypercholesterolemia at baseline did not influence the relation between egg consumption and MI, stroke, or total deaths (data not shown). However, when stratified by prevalent diabetes at baseline, there was significantly stronger association between egg consumption and all-cause mortality among subjects with prevalent diabetes than among those without diabetes (**Table 5**). Compared with the lowest category of egg consumption, the intake of ≥7 eggs/wk was associated with a 22% greater risk of death in the absence of prevalent diabetes, whereas the corresponding risk of death in the presence of prevalent diabetes was 100% greater (P for interaction between diabetes and egg consumption = 0.029 in the parsimonious model and 0.09 in the multivariate-adjusted model; Table 5). For MI, multivariate-adjusted HRs (95% CI) were 1.0; 1.07 (0.92, 1.25); 1.16 (0.99, 1.34); 1.13 (0.90, 1.42); and 0.91 (0.73, 1.14) from the lowest to the highest category of egg consumption, respectively (P for trend = 0.97) in the absence of prevalent diabetes. Corresponding values among subjects with diabetes were 1.0; 1.39 (0.61, 3.21); 1.45 (0.64, 3.28); 1.82 (0.66, 5.03); and 1.06 (0.43, 2.64), respectively (P for trend = 0.93; P

TABLE 2
Hazard ratios (and 95% CIs) for myocardial infarction according to egg consumption

		Hazard ratio (95% CI)		
Egg consumption	Cases	Age-adjusted	Model 1[1]	Model 2[2]
	n			
<1/wk	291	1.0	1.0	1.0
1/wk	474	1.10 (0.95, 1.27)	1.05 (0.91, 1.22)	1.12 (0.96, 1.31)
2–4/wk	546	1.21 (1.05, 1.40)	1.14 (0.99, 1.32)	1.16 (1.00, 1.36)
5–6/wk	115	1.24 (1.00, 1.54)	1.12 (0.91, 1.40)	1.18 (0.93, 1.49)
≥7/wk	124	1.02 (0.83, 1.27)	0.92 (0.74, 1.14)	0.90 (0.72, 1.14)
P for linear trend		0.21	0.94	0.88

[1] Adjusted for age, BMI (continuous), smoking (never, past, or current smoker), and history of hypertension.
[2] Adjusted as in model 1 plus vitamin intake, alcohol consumption (<1, 1–4, 5–6, or ≥7 drinks/wk), vegetable consumption (<3, 3–4, 5–6, 7–13, or ≥14 servings/wk), breakfast cereal (0, 1, 2–6, or ≥7 servings/wk), physical activity (<1, 1, 2–4, or ≥5 times/wk), treatment arm (4 groups), atrial fibrillation (yes or no), diabetes mellitus (yes or no), hypercholesterolemia (yes or no), and parental history of premature myocardial infarction (yes or no).

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TABLE 3
Hazard ratios (and 95% CIs) for stroke according to egg consumption

Egg consumption	Cases	Hazard ratio (95% CI)		
		Age-adjusted	Model 1[1]	Model 2[2]
	n			
<1/wk	257	1.0	1.0	1.0
1/wk	386	1.01 (0.86, 1.18)	0.96 (0.82, 1.12)	0.96 (0.82, 1.13)
2–4/wk	459	1.13 (0.97, 1.32)	1.07 (0.92, 1.25)	1.06 (0.91, 1.24)
5–6/wk	103	1.22 (0.97, 1.54)	1.13 (0.90, 1.42)	1.13 (0.89, 1.42)
≥7/wk	137	1.17 (0.95, 1.44)	1.06 (0.86, 1.30)	0.99 (0.80, 1.23)
P for linear trend		0.02	0.14	0.40

[1] Adjusted for age, BMI (continuous), smoking (never, past, or current smoker), and history of hypertension.
[2] Adjusted as in model 1 plus vitamin intake, alcohol consumption (<1, 1–4, 5–6, or ≥7 drinks/wk), vegetable consumption (<3, 3–4, 5–6, 7–13, or ≥14 servings/wk), breakfast cereal (0, 1, 2–6, or ≥7 servings/wk), physical activity (<1, 1, 2–4, or ≥5 times/wk), treatment arm (4 groups), atrial fibrillation (yes or no), diabetes mellitus (yes or no), hypercholesterolemia (yes or no), and parental history of premature myocardial infarction (yes or no).

for interaction = 0.48). Finally, from the lowest to the highest category of egg consumption, multivariate-adjusted HRs (95% CI) for stroke were 1.0; 0.94 (0.80, 1.11); 1.07 (0.91, 1.25); 1.12 (0.88, 1.42); and 0.96 (0.77, 1.21), respectively, for subjects without diabetes (*P* for trend = 0.42) and 1.0; 1.95 (0.89, 4.30); 1.61 (0.72, 3.56); 1.69 (0.58, 4.91); and 1.83 (0.71, 4.23), respectively, for people with diabetes (*P* for trend = 0.52; *P* for interaction = 0.52).

DISCUSSION

In this prospective cohort, we showed that infrequent egg consumption (ie, ≤6 eggs/wk) was not associated with MI, stroke, or total mortality in healthy US male physicians. In addition, consumption of ≥7 eggs/wk was associated with a modestly but significantly greater risk of total mortality in this population. In contrast, egg consumption was associated with a greater risk of all-cause mortality in a dose-response fashion among physicians with diabetes (2 times the risk of death in people consuming ≥7 eggs/wk than in those consuming <1 egg/wk). Furthermore, our data provided suggestive evidence for a greater risk of MI and stroke with egg consumption among male physicians with diabetes. In contrast, baseline hypercholesterolemia status did not influence the relation between egg consumption and CVD or mortality.

Because eggs are rich in dietary cholesterol, metabolic studies have focused on the effects of dietary cholesterol in eggs on serum cholesterol or other intermediate phenotypes. In particular, limited and inconsistent data are available on the effect of egg consumption (not just cholesterol content of eggs) on incident CVD and mortality in a community setting. To the best of our knowledge, only 2 studies have reported a positive association between egg consumption and CAD. Data from 514 Western Australian Aborigines showed a risk of CAD that was 2.6 times greater with the consumption of ≥2 eggs/wk than with that of <2 eggs/wk after ≈14 y of follow-up (16). Unfortunately, that study did not evaluate the influence of diabetes on the reported association, and data on baseline characteristics of that population suggested a lower prevalence of diabetes (4% for both men and women). It is notable that egg consumption in that population was higher than that reported among male physicians**.** Mann et al (17) reported a graded association between egg consumption and mortality after 13 y of follow-up in 10 802 healthy men and women in the United Kingdom. Compared with the consumption of <1 egg/wk, the incidence rate ratio for total mortality was 1.23 and 2.68 in subjects consuming 1–5 and ≥6 eggs/wk, respectively, after adjustment for age, sex, smoking, and social class. It is notable that subjects in that study were younger than those in the present study (median ages: 34 and 54 y, respectively).

TABLE 4
Hazard ratios (and 95% CIs) for all-cause mortality according to egg consumption

Egg consumption	Cases	Hazard ratio (95% CI)		
		Age-adjusted	Model 1[1]	Model 2[2]
	n			
<1/wk	1000	1.0	1.0	1.0
1/wk	1469	0.98 (0.90, 1.06)	0.93 (0.85, 1.00)	0.94 (0.87, 1.02)
2–4/wk	1685	1.06 (0.98, 1.15)	1.01 (0.93, 1.09)	1.03 (0.95, 1.11)
5–6/wk	366	1.11 (0.98, 1.25)	1.03 (0.91, 1.16)	1.05 (0.93, 1.19)
≥7/wk	649	1.41 (1.28, 1.55)	1.27 (1.15, 1.40)	1.23 (1.11, 1.36)
P for linear trend		<0.0001	<0.0001	<0.0001

[1] Adjusted for age, BMI (continuous), smoking (never, past, or current smoker), and history of hypertension.
[2] Adjusted as in model 1 plus vitamin intake, alcohol consumption (<1, 1–4, 5–6, or ≥7 drinks/wk), vegetable consumption (<3, 3–4, 5–6, 7–13, or ≥14 servings/wk), breakfast cereal (0, 1, 2–6, or ≥7 servings/wk), physical activity (<1, 1, 2–4, or ≥5 times/wk), treatment arm (4 groups), atrial fibrillation (yes or no), diabetes mellitus (yes or no), hypercholesterolemia (yes or no), and parental history of premature myocardial infarction (yes or no).

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TABLE 5
Hazard ratios (and 95% CIs) for all-cause mortality according to baseline prevalent diabetes and egg consumption[1]

	Subject without prevalent diabetes			Subjects with prevalent diabetes		
Egg consumption	Cases	Model 1[2]	Model 2[3]	Cases	Model 1[2]	Model 2[3]
	n			*n*		
<1/wk	971	1.0	1.0	29	1.0	1.0
1/wk	1408	0.92 (0.85, 1.00)	0.93 (0.85, 1.01)	61	1.20 (0.77, 1.87)	1.30 (0.82, 2.07)
2–4/wk	1605	0.99 (0.92, 1.08)	1.01 (0.93, 1.10)	80	1.30 (0.85, 1.99)	1.49 (0.95, 2.33)
5–6/wk	341	0.99 (0.88, 1.12)	1.00 (0.88, 1.13)	25	2.48 (1.44, 4.27)	2.27 (1.28, 4.03)
≥7/wk	581	1.23 (1.11, 1.37)	1.22 (1.09, 1.35)	68	1.55 (1.00, 2.40)	2.01 (1.26, 3.20)
P for linear trend		<0.0001	<0.0001		0.009	0.0005

[1] Difference in effect between diabetic and nondiabetic subjects: *P* for interaction = 0.029 (model 1) and 0.09 (model 2).
[2] Adjusted for age, BMI (continuous), smoking (never, past, or current smoker), and history of hypertension.
[3] Adjusted as in model 1 plus vitamin intake, alcohol consumption (<1, 1–4, 5–6, or ≥7 drinks/wk), vegetable consumption (<3, 3–4, 5–6, 7–13, or ≥14 servings/wk), breakfast cereal (0, 1, 2–6, or ≥7 servings/wk), physical activity (<1, 1, 2–4, or ≥5 times/wk), treatment arm (4 groups), atrial fibrillation (yes or no), hypercholesterolemia (yes or no), and parental history of premature myocardial infarction (yes or no).

In contrast, data from the Framingham study showed no association between egg consumption and CAD among 912 men and women after 16 y of follow-up (18). The average consumption in the Framingham study was ≈6 eggs/wk in men and 4 eggs/wk in women. In a case-control study among 936 Italian women, egg consumption was not associated with MI: age-adjusted odds ratios were 1.0, 1.2, and 0.8 for intakes of <1, 1–2, and >2 eggs/wk, respectively (27). In a large Japanese cohort of 5186 women and 4077 men, Nakamura et al (20) reported no association between egg consumption and all-cause mortality or CVD deaths in men after 14 y of follow-up. Little effect was also observed in women in that study. Other large cohorts reported no association between egg consumption and CAD, stroke, or mortality (19, 28). However, in these later studies, there was suggestive evidence for a greater risk of CVD among subjects with diabetes. Qureshi et al (28) reported a 2 times greater risk of CAD in persons reporting an intake of ≥6 eggs/wk than in those reporting an intake of <1 egg/wk. In addition, Hu et al (19) reported a 2 times greater risk of CAD with consumption of >1 egg/wk than with that of <1 egg/wk in 37 851 diabetic men from the Health Professionals Follow-up Study after adjustment for potential confounders; In the same report, the corresponding risk of CAD was 49% greater in diabetic women from the Nurses' Health Study. These findings in persons with diabetes are consistent with our report of a dose-response association between egg consumption and all-cause mortality in PHS I participants with prevalent diabetes at baseline. Could a biological mechanism help explain the positive association between egg consumption and CVD or mortality in persons with diabetes?

Overall, epidemiologic studies suggest that, among hyperresponders, dietary cholesterol from egg leads to a modest increase in serum LDL- and HDL-cholesterol concentrations and to no effect on the ratio of LDL to HDL cholesterol (8, 29–32). It is estimated that each additional 100-mg intake of dietary cholesterol results in an increase of 1.9 mg/dL in LDL and of 0.4 mg/dL in HDL (32). It is notable that this estimation does not take into account the effects of saturated fat or the type of response to dietary cholesterol. In addition, in randomized trials, consumption of eggs was associated with an increase in LDL peak diameter and a decrease in smaller LDL subfraction, which suggests that egg consumption may lead to a less atherogenic lipoprotein profile (13, 33). In the same study, 5 of the children with LDL phenotype B shifted to pattern A (low-risk pattern) (13). However, other investigators did not report an effect of egg consumption on LDL subfraction (29). Because of the wide variability in individual responses to dietary cholesterol (hyperresponders or hyporesponders), it is not known whether such differential responses to egg consumption could selectively influence glucose metabolism and thus help understand our findings of increased risk of death among people with diabetes in particular. Furthermore, it has been shown that baseline cholesterol influences individual response to dietary cholesterol (with higher baseline serum cholesterol leading to little effects of dietary cholesterol) (34). At present, we can only speculate that, among diabetic subjects, dietary cholesterol may perhaps lead to a less favorable lipoprotein profile in terms of serum concentration and particle size, with a shift to smaller and dense LDL particle size, which may lead to accelerated atherosclerosis and its complications. Testing of such a hypothesis in an experimental design among persons with diabetes is warranted.

The present study had additional limitations. We did not exclude unmeasured confounding or residual confounding as a possible explanation of the observed positive association among persons with diabetes. In particular, we were not able to examine the effects of saturated fat, markers of insulin resistance, lipids, and other nutrients or relevant biomarkers on the observed association. Whereas the lack of a detailed dietary questionnaire in the present study prevented control for energy and other major nutrients, the Nurses' Health Study and the Health Professionals' Follow-up Study (19) accounted for total energy intake. Changes of dietary patterns may lead to a spurious association between baseline exposure and incident outcome. In the data in the present study, we used time-dependent Cox regression model to update reported egg consumption at 24, 48, 72, 96, and 120 mo after randomization. Such an exposure update over time led to similar conclusions, which suggests that these findings are robust. The fact that the sample in the current study consisted of male physicians who may have different behaviors than the general population limits the generalizability of these findings. In addition, the fact that these physicians were knowledgeable about the dietary cholesterol content of eggs may have led to a higher probability of adopting other healthful behaviors, which would attenuate any unfavorable effect of egg consumption. However, this hypothesis is not consistent with the lower frequency of

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exercise and intake of breakfast cereals and the higher proportion of smokers among frequent egg consumers. Similar data were reported in the Health Professionals' Follow-up Study (19). Because we had few cases of CAD and stroke, we did not have sufficient power to detect an interaction between prevalent diabetes and egg consumption for the risk of MI or total stroke and subtypes of stroke. Nevertheless, the large sample size, the longer duration of follow-up, and the robustness of the findings in sensitivity analyses are strengths of the present study.

In conclusion, these data suggest that the consumption of ≤6 eggs/wk has no major effect on the risk of CVD and mortality and that the consumption of ≥7 eggs/wk is associated with a modestly greater risk of total mortality in US male physicians. However, among male physicians with diabetes, any egg consumption is associated with a greater risk of all-cause mortality, and there was suggestive evidence for a greater risk of MI and stroke. Confirmation of these findings in the general population and among diabetic subjects, along with the investigation of possible biologic mechanisms, is warranted.

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REFERENCES

1. Krauss RM, Deckelbaum RJ, Ernst N, et al. Dietary guidelines for healthy American adults. A statement for health professionals from the Nutrition Committee, American Heart Association. Circulation 1996; 94:1795–800.
2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285:2486–97.
3. Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. J Am Coll Nutr 2001;20:5–19.
4. Song WO, Kerver JM. Nutritional contribution of eggs to American diets. J Am Coll Nutr 2000;19(suppl):556S–62S.
5. Mattson FH, Erickson BA, Kligman AM. Effect of dietary cholesterol on serum cholesterol in man. Am J Clin Nutr 1972;25:589–94.
6. Keys A. Serum cholesterol response to dietary cholesterol. Am J Clin Nutr 1984;40:351–9.
7. Chakrabarty G, Manjunatha S, Bijlani RL, et al. The effect of ingestion of egg on the serum lipid profile of healthy young Indians. Indian J Physiol Pharmacol 2004;48:286–92.
8. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. Am J Clin Nutr 2001;73:885–91.
9. Sacks FM, Salazar J, Miller L, et al. Ingestion of egg raises plasma low density lipoproteins in free-living subjects. Lancet 1984;1:647–9.
10. Fernandez ML. Dietary cholesterol provided by eggs and plasma lipoproteins in healthy populations. Curr Opin Clin Nutr Metab Care 2006;9:8–12.
11. Chakrabarty G, Bijlani RL, Mahapatra SC, et al. The effect of ingestion of egg on serum lipid profile in healthy young free-living subjects. Indian J Physiol Pharmacol 2002;46:492–8.
12. Pyorala K. Dietary cholesterol in relation to plasma cholesterol and coronary heart disease. Am J Clin Nutr 1987;45:1176–84.
13. Ballesteros MN, Cabrera RM, Saucedo MS, Fernandez ML. Dietary cholesterol does not increase biomarkers for chronic disease in a pediatric population from northern Mexico. Am J Clin Nutr 2004;80:855–61.
14. Howell WH, McNamara DJ, Tosca MA, Smith BT, Gaines JA. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. Am J Clin Nutr 1997;65:1747–64.
15. Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. BMJ 1997;314:112–7.
16. Burke V, Zhao Y, Lee AH, et al. Health-related behaviours as predictors of mortality and morbidity in Australian Aborigines. Prev Med 2007; 44:135–42.
17. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. Heart 1997;78: 450–5.
18. Dawber TR, Nickerson RJ, Brand FN, Pool J. Eggs, serum cholesterol, and coronary heart disease. Am.J. Clin Nutr 1982;36:617–25.
19. Hu FB, Stampfer MJ, Rimm EB, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. JAMA 1999;281:1387–94.
20. Nakamura Y, Okamura T, Tamaki S, et al. Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80). Am J Clin Nutr 2004;80:58–63.
21. Nakamura Y, Iso H, Kita Y, et al. Egg consumption, serum total cholesterol concentrations and coronary heart disease incidence: Japan Public Health Center-based prospective study. Br J Nutr 2006;96:921–8.
22. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989;321:129–35.
23. Muntwyler J, Hennekens CH, Manson JE, Buring JE, Gaziano JM. Vitamin supplement use in a low-risk population of US male physicians and subsequent cardiovascular mortality. Arch Intern Med 2002;162: 1472–6.
24. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n–3 fatty acids and the risk of sudden death. N Engl J Med 2002;346: 1113–8.
25. Kurth T, Gaziano JM, Berger K, et al. Body mass index and the risk of stroke in men. Arch Intern Med 2002;162:2557–62.
26. Bowman TS, Gaziano JM, Kase CS, Sesso HD, Kurth T. Blood pressure measures and risk of total, ischemic, and hemorrhagic stroke in men. Neurology 2006;67:820–3.
27. Gramenzi A, Gentile A, Fasoli M. Association between certain foods and risk of acute myocardial infarction in women. BMJ 1990;300:771–3.
28. Qureshi AI, Suri FK, Ahmed S, Nasar A, Divani AA, Kirmani JF. Regular egg consumption does not increase the risk of stroke and cardiovascular diseases. Med Sci Monit 2007;13:CR1–8.
29. Knopp RH, Retzlaff BM, Walden CE, et al. A double-blind, randomized, controlled trial of the effects of two eggs per day in moderately hypercholesterolemic and combined hyperlipidemic subjects taught the NCEP step I diet. J Am Coll Nutr 1997;16:551–61.
30. Katz DL, Evans MA, Nawaz H, et al. Egg consumption and endothelial function: a randomized controlled crossover trial. Int J Cardiol 2005;99: 65–70.
31. Herron KL, Vega-Lopez S, Conde K, et al. Pre-menopausal women, classified as hypo- or hyperresponders, do not alter their LDL/HDL ratio following a high dietary cholesterol challenge. J Am Coll Nutr 2002;21: 250–8.
32. McNamara DJ. The impact of egg limitations on coronary heart disease risk: do the numbers add up? J Am Coll Nutr 2000;19(suppl):540S–8S.
33. Herron KL, Lofgren IE, Sharman M, Volek JS, Fernandez ML. High intake of cholesterol results in less atherogenic low-density lipoprotein particles in men and women independent of response classification. Metabolism 2004;53:823–30.
34. Hopkins PN. Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. Am J Clin Nutr 1992;55:1060–70.

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