

Egg Consumption and Risk of Type 2 Diabetes in Men and Women

LUC DJOUSSE, MD, DSC¹
J. MICHAEL GAZIANO, MD^{1,2,3}

JULIE E. BURING, SCD^{1,2,4,5}
I-MIN LEE, MBBS, SCD^{2,5}

OBJECTIVE — Whereas limited and inconsistent findings have been reported on the relation between dietary cholesterol or egg consumption and fasting glucose, no previous study has examined the association between egg consumption and type 2 diabetes. This project sought to examine the relation between egg intake and the risk of type 2 diabetes in two large prospective cohorts.

RESEARCH DESIGN AND METHODS — In this prospective study, we used data from two completed randomized trials: 20,703 men from the Physicians' Health Study I (1982–2007) and 36,295 women from the Women's Health Study (1992–2007). Egg consumption was ascertained using questionnaires, and we used the Cox proportional hazard model to estimate relative risks of type 2 diabetes.

RESULTS — During mean follow-up of 20.0 years in men and 11.7 years in women, 1,921 men and 2,112 women developed type 2 diabetes. Compared with no egg consumption, multivariable adjusted hazard ratios for type 2 diabetes were 1.09 (95% CI 0.87–1.37), 1.09 (0.88–1.34), 1.18 (0.95–1.45), 1.46 (1.14–1.86), and 1.58 (1.25–2.01) for consumption of <1, 1, 2–4, 5–6, and ≥ 7 eggs/week, respectively, in men (P for trend <0.0001). Corresponding multivariable hazard ratios for women were 1.06 (0.92–1.22), 0.97 (0.83–1.12), 1.19 (1.03–1.38), 1.18 (0.88–1.58), and 1.77 (1.28–2.43), respectively (P for trend <0.0001).

CONCLUSIONS — These data suggest that high levels of egg consumption (daily) are associated with an increased risk of type 2 diabetes in men and women. Confirmation of these findings in other populations is warranted.

Diabetes Care 32:295–300, 2009

Type 2 diabetes is highly prevalent and is associated with high health care costs and societal burden (1). Therefore, it is important to identify modifiable risk factors that may help reduce the risk of type 2 diabetes. Eggs are not only major sources of dietary cholesterol (~200 mg/egg) but also contain other important nutrients such as minerals, vitamins, proteins, carotenoids, and saturated (~1.5 g/egg), polyunsaturated (~0.7 g/egg), and monounsaturated (~1.9 g/egg) fatty acids (2,3). Whereas

several of these nutrients have been associated with an increased risk of type 2 diabetes (i.e., saturated fat and cholesterol [4,5]), other nutrients may confer a lower risk of type 2 diabetes (i.e., polyunsaturated fat [4]).

Whereas egg consumption was not associated with coronary heart disease (CHD) or stroke overall, Hu et al. (6) reported a twofold increased risk of CHD for egg consumption of more than one per week among men with type 2 diabetes in the Health Professionals' Follow-up

Study and a 49% increased risk of CHD among women in the Nurses' Health Study, compared with intake of less than one per week. Furthermore, we have reported similar findings in U.S. male physicians with type 2 diabetes but not in those without type 2 diabetes (7), suggesting that frequent egg consumption may have negative health effects among individuals with type 2 diabetes. However, it is not known whether egg consumption increases the risk of type 2 diabetes itself. In animal experiments, a diet rich in fat has been shown to induce hyperglycemia and hyperinsulinemia (8). In addition, a diet enriched with egg yolk was associated with elevated plasma glucose compared with a control diet in rats (9). Data from the Zutphen Study (10) have indicated a positive association between egg consumption or dietary cholesterol and fasting glucose. However, in a randomized trial of 28 overweight or obese patients on a carbohydrate-restricted diet, consumption of three eggs per day had no effects on fasting glucose compared with abstinence from eggs (11). Current data on the effects of dietary cholesterol on serum cholesterol have been inconsistent, ranging from positive associations (2,12) to lack of effect (12–14) and may be partly due to a large variability in individual response to dietary cholesterol (14,15).

To our knowledge, no previous study has examined the association between egg consumption and the incidence of type 2 diabetes in a large prospective cohort of men and women. Because eggs can serve as a good source for vitamins, proteins, and other nutrients in the U.S., it is important to determine the net degree of benefit and harm of egg consumption on the risk of type 2 diabetes. The current study examines the association between egg consumption and incident type 2 diabetes among men and women who participated in two large completed randomized control trials.

RESEARCH DESIGN AND METHODS

METHODS — We used data from the Physicians' Health Study (PHS) I and the Women's Health Study (WHS), two completed randomized, double-blind, placebo-controlled trials designed to study the effects of aspirin and β -carotene (PHS) or

From the ¹Division of Aging, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the ²Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; the ³Massachusetts Veterans Epidemiology and Research Information Center (MAVERIC), Boston Veterans Affairs Healthcare System, Jamaica Plain, Massachusetts; the ⁴Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, Massachusetts; and the ⁵Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts.

Corresponding author: Luc Djoussé, ldjouss@rics.bwh.harvard.edu.

Received 9 July 2008 and accepted 8 November 2008.

Published ahead of print at <http://care.diabetesjournals.org> on 18 November 2008. DOI: 10.2337/dc08-1271.

© 2009 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

low-dose aspirin and vitamin E (WHS) in the prevention of cardiovascular disease and cancer. Detailed description of the PHS I and WHS has been published previously (16–18). Briefly, a total of 22,071 U.S. male physicians aged ≥ 40 years at entry (1982) were randomized using a 2 $\times$ 2 factorial design to aspirin (325 mg every other day), β -carotene (50 mg every other day), or their corresponding placebos. Similarly, 39,876 female health professionals aged ≥ 45 years at entry (1992–1995) were randomized to low-dose aspirin (100 mg on alternate days), vitamin E (600 IU on alternate days), or their corresponding placebos. Each participant gave written informed consent, and the institutional review board at Brigham and Women's Hospital approved both study protocols. For the present analyses, we excluded 1,368 men because of prevalent type 2 diabetes ($n = 641$), missing data on egg consumption ($n = 365$), or missing data on potential confounders: smoking, alcohol intake, BMI, exercise, hypertension, and fruits and vegetables ($n = 362$). Among women, we excluded 3,581 because of prevalent type 2 diabetes ($n = 1,171$), missing data on egg consumption ($n = 852$), or missing data on potential confounders: BMI, exercise, smoking, energy intake, fruits and vegetables, nutrients, alcohol consumption, and hypertension ($n = 1,558$). Thus, a final sample of 20,703 men and 36,295 women was used in the current analyses.

Egg consumption

Among men, information on egg consumption was self-reported at baseline using a simple abbreviated semiquantitative food-frequency questionnaire. Participants were asked to report how often, on average, they had eaten one egg during the past year. Possible response categories included “rarely/never,” “1–3/month,” “1/week,” “2–4/week,” “5–6/week,” “daily,” and “2+/day.” This information was obtained at baseline and at 24, 48, 72, 96, and 120 months after randomization. Among women, information on egg consumption was self-reported using a 131-item validated food-frequency questionnaire (19) at baseline. Women were asked to report their average consumption of eggs over the past year. Possible response categories were “Never or <1/month,” “1–3/month,” “1/week,” “2–4/week,” “5–6/week,” “1/day,” “2–3/day,” “4–5/day,” and “6+/day.” Because very few subjects consumed one or more eggs per day (7.8% for men and 1.0% for

women), we combined categories of one per day and beyond for stable estimates. The validity of food-frequency questionnaires in similar populations has been published elsewhere (19,20). The correlation of egg consumption with dietary cholesterol was 0.61 ($P < 0.0001$) and with saturated fat among women was 0.26 ($P < 0.0001$).

Ascertainment of incident type 2 diabetes

Type 2 diabetes was ascertained by self-report on annual follow-up questionnaires in both men and women. Follow-up and ascertainment of type 2 diabetes cases were completed in March 2007. Because all men were physicians, self-report was deemed sufficient. Among the female health professionals, self-reports of type 2 diabetes were validated using American Diabetes Association criteria, for which additional information was obtained using telephone interviews, supplemental questionnaires, or review of medical records from treating physicians (21,22). Overall, the positive predictive value for type 2 diabetes validation was 91% (21).

Other variables

Demographic data were collected at baseline. In addition, information on prevalence of hypertension, hypercholesterolemia, family history of diabetes (WHS only), smoking, exercise, and alcohol consumption was obtained at baseline. Whereas limited data on foods were available in men, detailed dietary information was collected in the WHS, allowing estimation of energy intake and nutrients.

Statistical analyses

We classified each subject according to the following categories of egg consumption per week: 0, <1, 1, 2–4, 5–6, and ≥ 7 . We computed person-time of follow-up from baseline until the first occurrence of 1) type 2 diabetes, 2) death, or 3) censoring date, the date of receipt of the last follow-up questionnaire (March 2007). Within each egg-consumption group, we calculated the incidence rate of type 2 diabetes by dividing the number of cases by the corresponding person-time. We used Cox proportional hazard models to compute multivariable adjusted hazard ratios (HRs) with corresponding 95% CIs using subjects in the lowest category of egg consumption as the reference group. The initial model adjusted for age, whereas the multivariable model con-

trolled for age (continuous), BMI (<25, 25–29, ≥ 30 kg/m²), smoking (never, former, and current smokers), alcohol consumption (0, 1–3 drinks/month, 1–6 drinks/week, ≥ 1 drinks/day), physical activity (vigorous exercise 0, <1, 1–3, ≥ 4 times per week in men and quintiles of kilocalories per week expended in leisure-time physical activity in women), and history of hypercholesterolemia and hypertension. Because detailed information on diet and family history was available for women, the multivariable model in women also adjusted for family history of diabetes, energy intake (quintiles), intake of fruits and vegetables (quintiles), red meat consumption (<0.5, 0.5–0.9, and ≥ 1 serving/day), and intake of polyunsaturated fats (quintiles), saturated fats (quintiles), and trans fats (quintiles). To examine whether the relation between egg and diabetes was mediated by dietary cholesterol, we evaluated the risk of diabetes associated with dietary cholesterol and also included dietary cholesterol in the multivariable model in women. A similar approach was used for saturated fat. A P value for linear trend was obtained by fitting a continuous variable that assigned the median egg consumption in each egg category in a Cox regression model.

In secondary analyses, we examined possible effect modification by prevalent hypercholesterolemia (yes/no) and amount of energy from carbohydrate (low vs. high), using median energy from carbohydrate as cut point in women only, where data were available. We tested for statistical interaction by including the main effects and the product terms between egg consumption and hypercholesterolemia in a hierarchical Cox regression model (PROC TPHREG in SAS). We also conducted sensitivity analyses by excluding subjects with less than 2 years of follow-up. We repeated the main analysis using updated egg consumption at 24, 48, 72, 96, and 120 months in a time-dependent Cox model in men only, where repeated measures on egg consumption were available. Lastly, we used generalized linear models and polytomous logistic regression to impute missing values for continuous and categorical variables, respectively. All analyses were completed using SAS (version 9; SAS Institute, Cary, NC). Significance level was set at 0.05.

RESULTS — The mean $\pm$ SD age at randomization was 53.5 ± 9.4 years (range 39.7–85.9) in the PHS I and 54.5 ± 7.0 years (38.7–89.9) in the

Table 1—Baseline characteristics of 20,703 men and 36,295 women according to egg consumption

	Eggs per week					
	0	<1	1	2–4	5–6	≥7
Men						
<i>n</i>	1,430	3,025	6,466	6,792	1,378	1,612
Age (years)	53.1 ± 9.2	52.8 ± 9.3	53.2 ± 9.3	53.4 ± 9.4	53.8 ± 9.3	56.4 ± 10.0
BMI (kg/m ²)	24.1 ± 2.7	24.6 ± 2.6	24.7 ± 2.7	24.9 ± 2.7	25.1 ± 2.9	24.9 ± 3.1
Fruits and vegetables per week	15.2 ± 8.4	14.1 ± 7.4	14.8 ± 7.1	15.3 ± 6.9	15.8 ± 7.4	17.0 ± 8.5
Whole milk	16.7	31.1	37.1	42.8	50.9	54.2
Skim milk	60.8	61.9	67.7	65.9	61.4	53.5
Nut intake*	72.2	77.9	80.4	81.8	82.7	77.8
Breakfast cereal	60.7	62.1	74.2	77.7	74.2	58.9
Smoking	6.4	8.8	9.8	12.0	14.6	16.8
Never smokers	56.9	51.0	51.1	48.6	46.9	41.6
Exercise	84.4	86.2	87.4	87.6	87.4	84.9
Current drinkers of ≥1 per day	21.5	23.3	23.9	25.8	26.4	30.7
Hypertension	22.8	20.3	22.8	22.9	24.7	26.2
High cholesterol	14.6	12.9	12.0	11.1	10.4	10.4
Women						
<i>n</i>	6,381	10,758	9,222	8,921	647	366
Age (years)	55.2 ± 7.2	54.3 ± 7.0	54.4 ± 6.9	54.5 ± 7.0	54.6 ± 7.0	55.1 ± 7.2
BMI (kg/m ²)	25.1 ± 4.6	25.7 ± 4.8	25.8 ± 4.8	26.6 ± 5.2	27.4 ± 6.0	26.9 ± 6.0
Fruits and vegetables per week	6.2 ± 3.6	5.7 ± 3.2	6.0 ± 3.1	6.3 ± 3.1	6.4 ± 3.5	6.4 ± 3.8
Red meat (servings/day)	0.45 ± 0.45	0.62 ± 0.46	0.75 ± 0.49	0.93 ± 0.59	1.15 ± 0.76	1.26 ± 0.83
Energy intake (kcal/day)	1,547 ± 506	1,614 ± 498	1,758 ± 503	1,925 ± 530	2,043 ± 585	2,072 ± 605
Exercise (kcal/week)	1,078 ± 1,282	931 ± 1,172	911 ± 1,145	882 ± 1,104	833 ± 1,073	800 ± 1,040
Dietary cholesterol (g/day)†	0.17 ± 0.06	0.20 ± 0.05	0.22 ± 0.05	0.28 ± 0.05	0.35 ± 0.07	0.44 ± 0.15
Trans fat (g/day)†	1.95 ± 1.11	2.28 ± 1.08	2.35 ± 1.01	2.40 ± 1.00	2.55 ± 1.11	2.41 ± 0.98
Polyunsaturated fat (g/day)†	10.6 ± 3.2	11.0 ± 2.9	11.2 ± 2.7	11.4 ± 2.7	11.8 ± 2.8	11.9 ± 3.1
Saturated fat (g/day)†	17.3 ± 5.2	19.4 ± 4.7	20.0 ± 4.40	20.9 ± 4.4	22.4 ± 4.8	23.1 ± 5.5
Smoking	10.8	12.1	11.8	15.3	19.8	23.5
Current drinkers of ≥1 per day	10.2	9.8	10.8	11.5	10.5	10.4
Hypertension	24.7	23.6	23.4	26.6	29.5	27.1
High cholesterol	38.0	28.9	26.4	25.3	26.1	19.1
Family history of diabetes	24.6	24.2	24.1	25.9	27.5	23.5

Data are mean ± SD or %. *Nut consumption assessed 1 year after randomization. †Energy adjusted.

WHS. Among egg consumers, the median egg consumption was approximately one egg per week in men and women. Table 1 presents baseline characteristics of the study participants. Frequent consumption of eggs was associated with higher BMI, higher proportion of current smoking, higher prevalence of hypertension, and lower prevalence of hypercholesterolemia. In addition, frequent consumption of eggs was associated with older age and more alcohol consumption in men and higher energy intake, as well as intakes of saturated and *trans* fatty acids, and dietary cholesterol in women.

A total of 1,921 new cases of type 2 diabetes were documented in men during a mean follow-up of 20.0 years. Among

women, 2,112 new cases of type 2 diabetes occurred during a mean follow-up of 11.7 years. From the lowest to the highest category of egg consumption, crude incidence rates of diabetes were 35.8, 41.3, 42.7, 46.8, 62.4, and 67.0 cases per 10,000 person-years in the PHS I. A similar increase in rates of type 2 diabetes with egg consumption was observed in women, with corresponding crude incidence rates of 39.6, 45.8, 43.3, 64.8, 76.8, and 112.7 cases per 10,000 person-years, respectively. Whereas consumption of up to one egg per week was generally not associated with an increased risk of type 2 diabetes in either sex in multivariate analyses, more frequent consumption of eggs was associated with an

increased risk of type 2 diabetes (Table 2). Compared with subjects who did not report egg consumption, intake of seven or more eggs per week was associated with a 58% increased risk of type 2 diabetes in men and a 77% increased risk of type 2 diabetes in women after adjustment for potential confounders (Table 2). Updating egg consumption using time-dependent Cox regression (PHS I) yielded a stronger relation between egg consumption and incident type 2 diabetes in men with HRs of 1.0 (reference), 1.10 (95% CI 0.99–1.23), 1.31 (1.16–1.47), 1.40 (1.10–1.77), 1.77 (1.39–2.26), and 1.99 (1.23–3.23), from the lowest to the highest category of egg consumption, respectively, using a multivariable model as

Table 2—HR (95% CI) of type 2 diabetes according to egg consumption in men and women

	Men			Women		
	n	Age adjusted	Model 1*	n	Age adjusted	Model 1†
Egg intake per week						
0	104	1.0	1.0	295	1.0	1.0
<1	254	1.16 (0.92–1.45)	1.09 (0.87–1.37)	576	1.16 (1.01–1.34)	1.06 (0.92–1.22)
1	560	1.19 (0.96–1.46)	1.09 (0.88–1.34)	470	1.10 (0.95–1.27)	0.97 (0.83–1.12)
2–4	637	1.30 (1.06–1.61)	1.18 (0.95–1.45)	669	1.65 (1.44–1.89)	1.19 (1.03–1.38)
5–6	169	1.73 (1.36–2.21)	1.46 (1.14–1.86)	56	1.97 (1.48–2.63)	1.18 (0.88–1.58)
≥7	197	1.82 (1.44–2.31)	1.58 (1.25–2.01)	46	2.88 (2.11–3.94)	1.77 (1.28–2.43)
P for trend		<0.0001	<0.0001		<0.0001	<0.0001

n = cases of type 2 diabetes. *Adjusted for age (continuous), BMI (<25, 25–29.9, and ≥30 kg/m²), smoking (never, former, and current smokers), alcohol consumption (0, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), vigorous exercise (0, <1, 1–3, and ≥4 times per week), and history of hypercholesterolemia and hypertension. †Adjusted for age (continuous), BMI (<25, 25–29.9, and ≥30 kg/m²), smoking (never, former, and current smokers), alcohol consumption (0, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), exercise (quintiles of kilocalories per week), red meat intake (<0.5, 0.5–0.9, and ≥1 servings/day), quintiles of energy intake, fruits and vegetables, saturated fatty acids, *trans* fatty acids, polyunsaturated fatty acids, family history of diabetes, and history of hypercholesterolemia and hypertension.

above (this was not done for women due to lack of updated information on egg consumption). Lastly, exclusion of subjects with follow-up time <2 years in either cohort did not alter the results (P for trend <0.0001 in men and 0.0001 in women).

Dietary cholesterol was positively associated with the risk of diabetes (multivariable adjusted HR 1.00 [reference], 0.94 [95% CI 0.80–1.11], 1.03 [0.88–1.21], 1.07 [0.91–1.25], and 1.28 [1.10–1.50], from the lowest to the highest quintile of dietary cholesterol, respectively (P for trend <0.0001). Additional adjustment for dietary cholesterol in women attenuated the point estimates in the multivariable model with corresponding HRs of 1.00 (reference), 1.05 (0.91–1.21), 0.94 (0.80–1.10), 1.07 (0.90–1.27), 1.00 (0.73–1.37), and 1.49 (1.06–2.09), respectively (P for trend = 0.10). However, saturated fat was not as-

sociated with type 2 diabetes (multivariable adjusted HR 1.0, 1.03 [0.87–1.21], 1.00 [0.84–1.19], 1.00 [0.84–1.20], and 1.10 [0.92–1.33], from the lowest to highest quintile of energy-adjusted saturated fat, respectively). Additional control for saturated fat did not alter the results (e.g., HR of 1.78 [1.30–2.45] without and 1.77 [1.28–2.43] with additional control for saturated fat, comparing the highest with the lowest egg consumption categories). Imputing missing data did not change the findings (online appendix Table A1, available at <http://dx.doi.org/10.2337/dc08-1271>).

In a secondary analysis stratified by prevalent hypercholesterolemia at baseline (Table 3), similar patterns were observed in subjects of either sex with and without hypercholesterolemia (P for interaction 0.37 for men and 0.13 for women). Similar relations were observed between egg consumption and type 2 di-

abetes when data were stratified by low energy from carbohydrate (P for linear trend = 0.0004 for low energy from carbohydrate and 0.12 for high energy from carbohydrate) in women only (data were not available to estimate carbohydrate intake in men), and these findings were not altered when restricted to overweight or obese subjects (online appendix Table A2).

CONCLUSIONS — In this large prospective study, we have demonstrated that daily consumption of at least one egg is associated with an increased risk of type 2 diabetes in both men and women, independently of traditional risk factors for type 2 diabetes. Furthermore, the observed association between egg consumption and incident type 2 diabetes was not modified by prevalent hypercholesterolemia in either sex.

To the best of our knowledge, this is the first study to examine prospectively

Table 3—Hazard ratios of diabetes according to prevalent hypercholesterolemia and egg consumption

	Men		Women	
	Normal cholesterol	High or treated cholesterol	Normal cholesterol	High or treated cholesterol
Egg consumption per week				
0	1.0	1.0	1.0	1.0
<1	1.09 (0.84–1.42)	1.11 (0.70–1.74)	1.11 (0.91–1.37)	1.02 (0.83–1.25)
1	1.03 (0.80–1.31)	1.28 (0.84–1.94)	1.00 (0.80–1.24)	0.98 (0.79–1.22)
2–4	1.16 (0.92–1.48)	1.19 (0.79–1.81)	1.26 (1.02–1.55)	1.14 (0.92–1.42)
5–6	1.34 (1.01–1.79)	1.78 (1.11–2.87)	0.88 (0.57–1.36)	1.68 (1.13–2.51)
≥7	1.47 (1.11–1.94)	1.96 (1.23–3.12)	1.84 (1.24–2.75)	1.72 (0.98–3.02)
P for trend	<0.0001	0.0001	0.0045	0.0028

*Adjusted for age (continuous), BMI (<25, 25–29.9, and ≥30 kg/m²), smoking (never, former, and current smokers), alcohol consumption (none, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), vigorous exercise (0, <1, 1–3, and ≥4 times per week), and history of hypertension. †Adjusted for age (continuous), BMI (<25, 25–29.9, and ≥30 kg/m²), smoking (never, former, and current smokers), alcohol consumption (none, 1–3 drinks/month, 1–6 drinks/week, and ≥1 drink/day), exercise (quintiles of kilocalories per week), red meat intake (<0.5, 0.5–0.9, and ≥1 serving/day), quintiles of energy intake, fruits and vegetables, saturated fatty acids, *trans* fatty acids, polyunsaturated fatty acids, family history of diabetes, and history of hypertension.

the association between egg consumption and incident type 2 diabetes in a large population of men and women. Before the current study, limited and inconsistent data (mainly from animal models) have been reported in the literature on the effects of eggs or dietary cholesterol on glucose metabolism. In an animal experiment, a diet rich in fat was shown to induce hyperglycemia and hyperinsulinemia (8). Furthermore, Adamopoulos et al. (9) demonstrated that a diet enriched with egg yolk resulted in elevated plasma glucose compared with a control diet in male Wistar albino rats. Data from the Zutphen Study (10) showed a positive association between egg consumption or dietary cholesterol and fasting glucose. These animal studies and data from the Zutphen Study are consistent with our findings. In contrast, in a randomized trial of 28 overweight or obese subjects on a carbohydrate-restricted diet, consumption of three eggs per day had no effects on fasting glucose compared with no egg consumption (11). Because the positive associations described above were observed in studies without restricted consumption of carbohydrates, it is possible that the hyperglycemic effect of frequent egg consumption might only occur with a diet rich in carbohydrates. However, our secondary data analysis provided no evidence for such a hypothesis in that we observed similar increased risk of type 2 diabetes with consumption of one or more eggs per day in women with low or high energy intake from carbohydrate. Further restriction to women with BMI ≥ 25 kg/m², to mimic the above trial of 28 overweight or obese subjects on restricted carbohydrate diet (11), did not alter these findings. Under the premise that our observed findings were driven by dietary cholesterol contained in eggs, one possible explanation for the inconsistency in reported data on the association between egg consumption and glucose metabolism could be the large variability of individual response to dietary cholesterol (14,15,23). Whereas dietary cholesterol has been shown to increase plasma cholesterol in hyperresponders (2,12,24), no effect was documented among hyporesponders (12–14). Second, the lack of an effect of egg consumption on fasting glucose among obese or overweight subjects in the only human randomized trial (11) may imply differential physiological effects of eggs in lean versus overweight or obese subjects. However, the lack of re-

peated data on fasting glucose in men and women in the present study prevented us from further exploring the relation between adiposity, egg consumption, and fasting glucose.

Overall, the observed increased risk of type 2 diabetes with daily consumption of eggs in the current study raises the possibility of undesirable health effects with high rates of egg consumption and may help explain previously reported increased risk of CHD that was restricted to individuals with type 2 diabetes in the Health Professional Follow-up Study (6), the Nurses' Health Study (6), and in our earlier publication from the PHS I showing an increased risk of mortality (and suggesting increased risk of CHD and stroke) with frequent egg consumption by subjects with prevalent type 2 diabetes (7). It is possible that frequent egg consumption may potentiate the risk of cardiovascular disease by inducing impaired glucose metabolism and insulin resistance. Future investigations into underlying physiological mechanisms are warranted.

Besides dietary cholesterol, eggs contain other important nutrients that have been shown to increase (i.e., saturated fat and cholesterol [4,5,25]) or decrease (i.e., polyunsaturated fat [4]) the risk of type 2 diabetes. It is possible that the individual contribution from each of these components as derived not just from eggs but also from other foods may play a role in determining the net effect of egg consumption. Unfortunately, as noted above, we did not have repeated data on fasting glucose, fasting insulin, and other biomarkers of glucose metabolism in either cohort to comprehensively examine possible physiological mechanisms by which egg consumption might influence the risk of type 2 diabetes in our cohort. However, in women, where we had data on dietary cholesterol, there was attenuation of the association after additional adjustment for dietary cholesterol. This suggests that the observed relation between egg intake and diabetes may be partially explained by the cholesterol content of eggs. In contrast, saturated fat was not associated with type 2 diabetes, and adjustment for this did not attenuate the results.

Additional limitations of the present study include the observational nature of the study design in which residual confounding or unmeasured confounding could partly or completely explain our results. In addition, because egg consumption was self-reported, we cannot exclude

reporting bias in the present study. However, because information on egg consumption was collected before the occurrence of type 2 diabetes, such reporting bias is more likely to be nondifferential and thus bias the results toward the null. We did not collect information on whether participants consumed egg yolk (rich in cholesterol) to further examine the contribution of dietary cholesterol from eggs on type 2 diabetes risk in this study. In addition, we had limited dietary data for men to further assess the interplay of eggs and other foods, energy, and nutrients with the risk of type 2 diabetes. The generalizability of our finding is limited as both PHS I and WHS consist of homogeneous groups (male physicians and female health professionals, respectively) with the possibility that their behaviors may differ from those of the general population. Furthermore, over 90% of the study participants were Caucasian. Given the self-report nature of type 2 diabetes, we cannot exclude misclassification of the outcome in these data, especially in the WHS where not all participants were physicians, as was the case in the PHS. However, in the WHS, we had a 91% positive predictive value in a validation study of self-reported type 2 diabetes using American Diabetes Association criteria, for which data were attained by telephone interview, supplemental questionnaire, or review of medical records from treating physicians (21). Moreover, egg consumption was collected before the diagnosis of diabetes; thus, it is likely that any misclassification of diabetes would be nondifferential and bias the results toward the null. Nevertheless, the large sample size, the long duration of follow-up, the repeated and standardized methods for data collection in both cohorts, and the robustness of the findings in sensitivity analyses are major strengths of this study.

In conclusion, our data are consistent with possible detrimental effects of daily consumption of eggs on the risk of type 2 diabetes in both men and women. Because the median egg consumption in this population (one egg per week for men and women) fell within a range not associated with an increased risk of type 2 diabetes, dietary advice to reduce egg consumption may target individuals who consume one or more eggs per day if these findings are confirmed in other studies. Given the societal burden of type 2 diabetes, confirmation of these findings in other populations and exploration of pos-

sible underlying biological mechanisms are warranted.

Acknowledgments—This study was supported by grants CA-34944, CA-40360, CA-047988, and CA-097193 from the National Cancer Institute and grants HL-26490, HL-43851, HL-080467, and HL-34595 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

No potential conflicts of interest relevant to this article were reported.

References

- American Diabetes Association: Economic costs of diabetes in the U.S. in 2007. *Diabetes Care* 31:596–615, 2008
- Herron KL, McGrane MM, Waters D, Lofgren IE, Clark RM, Ordovas JM, Fernandez ML: The ABCG5 polymorphism contributes to individual responses to dietary cholesterol and carotenoids in eggs. *J Nutr* 136:1161–1165, 2006
- Song WO, Kerver JM: Nutritional contribution of eggs to American diets. *J Am Coll Nutr* 19:556S–562S, 2000
- Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC: Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr* 73:1019–1026, 2001
- Song Y, Manson JE, Buring JE, Liu S: A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the women's health study. *Diabetes Care* 27:2108–2115, 2004
- Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, Rosner BA, Spiegelman D, Speizer FE, Sacks FM, Hennekens CH, Willett WC: A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA* 281:1387–1394, 1999
- Djoussé L, Gaziano JM: Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. *Am J Clin Nutr* 87:964–969, 2008
- Wu L, Vikramadithyan R, Yu S, Pau C, Hu Y, Goldberg IJ, Dansky HM: Addition of dietary fat to cholesterol in the diets of LDL receptor knockout mice: effects on plasma insulin, lipoproteins, and atherosclerosis. *J Lipid Res* 47:2215–2222, 2006
- Adamopoulos PN, Papamichael CM, Zampelas A, Mouloupoulos SD: Cholesterol and unsaturated fat diets influence lipid and glucose concentrations in rats. *Comp Biochem Physiol B Biochem Mol Biol* 113:659–663, 1996
- Feskens EJ, Kromhout D: Habitual dietary intake and glucose tolerance in euglycaemic men: the Zutphen Study. *Int J Epidemiol* 19:953–959, 1990
- Mutungi G, Ratliff J, Puglisi M, Torres-Gonzalez M, Vaishnav U, Leite JO, Quann E, Volek JS, Fernandez ML: Dietary cholesterol from eggs increases plasma HDL cholesterol in overweight men consuming a carbohydrate-restricted diet. *J Nutr* 138:272–276, 2008
- Chakrabarty G, Manjunatha S, Bijlani RL, Ray RB, Mahapatra SC, Mehta N, Lakshmy R, Vashisht S, Manchanda SC: The effect of ingestion of egg on the serum lipid profile of healthy young Indians. *Indian J Physiol Pharmacol* 48:286–292, 2004
- Fernandez ML: Dietary cholesterol provided by eggs and plasma lipoproteins in healthy populations. *Curr Opin Clin Nutr Metab Care* 9:8–12, 2006
- Chakrabarty G, Bijlani RL, Mahapatra SC, Mehta N, Lakshmy R, Vashisht S, Manchanda SC: The effect of ingestion of egg on serum lipid profile in healthy young free-living subjects. *Indian J Physiol Pharmacol* 46:492–498, 2002
- 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* 80:855–861, 2004
- Steering Committee of the Physicians' Health Study Research Group: Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 321:129–135, 1989
- Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE: Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 294:56–65, 2005
- Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE: A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352:1293–1304, 2005
- Willett W: *Nutritional Epidemiology*. New York, Oxford University Press, 1998
- Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC: Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol* 18:858–867, 1989
- Ding EL, Song Y, Manson JE, Pradhan AD, Buring JE, Liu S: Accuracy of administrative coding for type 2 diabetes in children, adolescents, and young adults: response to Rhodes et al. (Letter). *Diabetes Care* 30:e98, 2007
- Liu S, Lee IM, Song Y, Van Denburgh M, Cook NR, Manson JE, Buring JE: Vitamin E and risk of type 2 diabetes in the Women's Health Study randomized controlled trial. *Diabetes* 55:2856–2862, 2006
- Pyorala K: Dietary cholesterol in relation to plasma cholesterol and coronary heart disease. *Am J Clin Nutr* 45:1176–1184, 1987
- Sacks FM, Salazar J, Miller L, Foster JM, Sutherland M, Samonds KW, Albers JJ, Kass EH: Ingestion of egg raises plasma low density lipoproteins in free-living subjects. *Lancet* 1:647–649, 1984
- Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR: Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care* 24:1528–1535, 2001