"The growth of knowledge depends entirely on disagreement."

—Karl R. Popper

NUTRITION CLOSE-UP

Winter 2008 *Volume 25, Number 4*

INSIDE

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Nutrition Close-Up is a quarterly publication of the American Egg Board, written and produced by the Egg Nutrition Center. *Nutrition Close-Up* presents up-to-date reviews, summaries and commentaries on the latest research on the role of diet in health promotion and disease prevention, including the contributions of eggs to a nutritious and healthful diet. Nutrition and healthcare professionals can request a free subscription to the newsletter by visiting the Egg Nutrition Center's website at www.enc-online.org.

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Egg Intake and the Risk of Type 2 Diabetes

Eggs are a convenient and low-calorie source of high-quality protein, vitamin B_{12}, choline, important carotenoid pigments, and many other vitamins and minerals essential during every phase of human life. Although a substantial body of evidence indicates that eggs do not contribute to the risk of CVD, a few epidemiological studies have suggested that egg intake in excess of 7 eggs per week is associated with higher rates of CVD in participants with type 2 diabetes. The Zutphen Study indicated that egg consumption/dietary cholesterol were positively associated with fasting glucose levels; however, in a randomized study of overweight and obese individuals following reduced-carbohydrate diets, intake of up to 3 eggs/day was not associated with changes in fasting glucose. These findings led Djoussé, Gaziano, and colleagues to evaluate data from two large, prospective epidemiological studies (the Health Professional Follow-Up Study and the Nurses' Health Study) to evaluate whether egg intake was associated with the incidence of type 2 diabetes.

Researchers gathered data from the Physicians' Health Study (PHS) and the Women's Health Study (WHS), both of which were randomized, double-blind, placebo-controlled trials. Incident type 2 diabetes was ascertained annually by self-report for both men and women. Because the male participants were all physicians, no additional effort was made to confirm the diagnosis of type 2 diabetes. For women, self-reported diagnoses were validated by review of medical records, supplemental questionnaire, or by the use of American Diabetes Association criteria. Demographic data and information on the prevalence of hypertension and hypercholesterolemia was gathered at baseline for all participants. Information on smoking status, exercise, and alcohol consumption was also collected at baseline for the female cohort.

> *In this analysis, participants who reported frequent egg consumption also had higher BMIs, were older, were more likely to smoke, reported greater consumption of alcohol, were more likely to have hypertension, and—for women—reported higher total calorie, saturated fat, trans fat, and cholesterol intakes. Therefore, it is important to consider that for these health professional populations, egg intake could simply have been a surrogate marker for dietary indiscretion along with other lifestyle choices that were not conducive to overall health . . .*

The PHS included 22,071 US male physicians aged 40 years and older and was designed to determine the effectiveness of beta carotene and aspirin in preventing cancer and CVD. The WHS included 39,876 female health professionals, aged 45 years and older and was designed

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to evaluate the effectiveness of low-dose aspirin and vitamin E on CVD and cancer prevention. In this analysis, 1,368 men were excluded for the presence of type 2 diabetes, missing data on egg consumption, or potential confounders such as smoking, alcohol intake, body mass index, exercise, hypertension, and fruit and vegetable intake. Likewise, 3,581 women were excluded because of the presence of type 2 diabetes, missing data on egg consumption or missing data on potential confounders such as BMI, exercise, smoking, energy intake, fruit and vegetable consumption, intake of other nutrients, alcohol consumption, and hypertension. Information from a total of 20,703 men and 36,295 women was available for this analysis.

For men, egg intake frequency for the past year was self-reported at baseline, and repeated at 24, 48, 72, 96, and 120 months using a simple semi-quantitative food frequency questionnaire (FFQ). For women, egg intake over the year previous to study initiation was self-reported at baseline using a 131-item validated FFQ. While diet information from the WHS was much more comprehensive than was the intake data from the PHS, dietary data collection was gathered only at baseline for the women and was not repeated over the course of the study.

Participants were classified into one of the following categories of egg consumption: 0, <1 per week, 1 per week, 2-4 per week, 5-6 per week, and 7+ eggs per week. Participants in the lowest category of egg consumption served as the reference group for statistical analysis. The multivariable model was adjusted for age, body mass index (BMI), smoking status, alcohol consumption, physical activity, and history of hypercholesterolemia and/or hypertension. More detailed records were available for the WHS cohort, so in this group, the multivariable model was further adjusted for family history of diabetes, energy intake, intake of fruits and vegetables, consumption of red meat, and intake of polyunsaturated fats, saturated fats, trans fats, and cholesterol.

Secondary analyses examined the influence of existing hypercholesterolemia, and low vs. high energy intake from carbohydrate in women only. Average egg intake among egg-consuming participants was 1 per week in both men and women. Frequent egg consumption was associated with higher prevalence of hypertension, lower prevalence of hypercholesterolemia, and higher BMI measurements. In men, frequent egg intake was associated with older age and greater alcohol consumption. In women, more frequent egg consumption was associated with higher intakes of total energy, saturated fat, trans fat, and dietary cholesterol.

Men were followed for an average of 20.0 years, in which 1,921 new cases of type 2 diabetes were documented. Women were followed for 11.7 years, on average, with 2,112 new cases documented over the course of follow-up. In the male cohort, crude incidence rates from the lowest to the highest categories of egg consumption were 35.8, 41.3, 42.7, 46.8, 62.4, and 67.0 cases/10,000 person-years. In the female cohort, crude incidence rates were 39.6, 45.8, 43.3, 64.8, 76.8, and 112.7. Consumption of < 1 egg per week was not associated with an increased risk of type 2 diabetes in either cohort, however, compared with no egg consumption, intakes of 7 or more per week were associated with a 58% increased risk of type 2 diabetes in men and a 77% increased risk in women after adjusting for potential confounders. Time-dependent Cox regression analysis resulted in a stronger association between egg consumption and incident type 2 diabetes in men with risk ratios as follows: 1.0 (reference), 1.10 (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). (This analysis could not be completed using data from the women since collection of egg intake information was not repeated for women.)

Dietary cholesterol was also associated with an increased risk of type 2 diabetes, with risk ratios of 1.00 (reference), 0.94 (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 intake. Saturated fat, however, was not associated with type 2 diabetes. After stratifying by prevalent hypercholesterolemia at baseline, similar results were observed in both men and women (*P* for interaction = 0.37 for men and 0.13 for women).

In this analysis using data from two large, randomized, prospective studies, researchers observed an association between consumption of at least 1 egg per day and increased risk of type 2 diabetes in men and women. This observation appears to be independent of the risk factors commonly associated with type 2 diabetes. By definition, statistical associations do not prove cause-and-effect; rather, they show relationships and are best used in guiding the direction of future research. In this analysis, participants who reported frequent egg consumption also had higher BMIs, were older, were more likely to smoke, reported greater consumption of alcohol, were more likely to have hypertension, and—for women—reported higher total calorie, saturated fat, trans fat, and cholesterol intakes. Therefore, it is important to consider that for these health professional populations, egg intake could simply have been a surrogate marker for dietary indiscretion along with other lifestyle choices that were not conducive to overall health. In addition, although consumer and health professional awareness of the health benefits of eggs has improved substantially over the past decade, the time period during which dietary data was gathered for the PHS (1982-2007) and WHS (1992) was characterized by widely-held negative perceptions of eggs' health effects. Thus, motivated health professionals in the PHS and WHS with high health awareness might have avoided eggs as part of their efforts to live overall healthier lifestyles—lifestyles that included making prudent dietary choices, avoiding tobacco and excessive alcohol, and maintaining a healthy weight. The authors note that without repeated data on fasting glucose, fasting insulin, and other biomarkers of glucose metabolism, they are unable to suggest any physiologic mechanism that might explain these observations.

The authors noted that the observational nature of this study introduced factors that could partially or completely explain their unexpected results and acknowledged several weaknesses in the study design, including:

•Limited dietary intake data available for male subjects, which restricted the researchers' ability to control for intake from nutrients associated with an increased risk of type 2 diabetes, such as saturated fat;

•One-time (baseline) estimation of egg consumption for female participants;

•Likelihood of other contributing lifestyle factors that weren't controlled for in the study;

•Lack of generalizability: more than 90 percent of the subjects were Caucasian.

The observations reported in this study were unexpected, given the large body of research supporting the health benefits of egg consumption; however, in light of the importance of this research and its implications, further research is warranted to validate the finding and to identify potential physiological mechanisms if they exist. ■

Djoussé L, Gaziano JM, Buring JE, Lee I. Egg consumption and risk of type 2 diabetes in men and women. *Diabetes Care* 2008; DOI: 10.2337/dc08-1271.

KEY MESSAGES

- Consumption of at least one egg per day was associated with an increased risk of type 2 diabetes in men and women, independent of the risk factors commonly associated with type 2 diabetes.
- Participants who reported frequent egg consumption had higher BMIs, were older, more likely to smoke, were more likely to have hypertension, consumed more alcohol, and—for women—reported greater consumption of total calories, saturated fat, *trans* fat, and cholesterol.

Dairy, Egg, and Whole Grain Intake and the Risk of Heart Failure

Cardiovascular disease continues to be the leading cause of death in the developed world. Through numerous epidemiological and clinical studies, researchers have attempted to clarify the effects of diet on cardiovascular disease. This research has largely focused on nutrients, rather than on foods and eating patterns. Heart failure (HF), defined as the progressive weakening of the heart muscle, affects millions of people each year, yet little data exists on how dietary intake affects the risk for this cardiovascular disease (CVD) subtype. Researchers at the University of Minnesota designed the Atherosclerosis Risk in Communities (ARIC) study to determine the influence of certain foods previously shown to be significantly associated with heart failure or CVD on the risk of incident HF.

The ARIC study gathered diet and health information from 15,792 white and African-American men and women between the ages of 45 and 64 years from field centers in Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. Records from a total of 14,153 participants were available for these analyses after excluding data from participants of racial groups with limited representation, those with unreasonably high or low reported calorie intakes, and those with established HF at baseline. For the purposes of this study, only first HF hospitalizations and deaths from HF were defined as incident HF.

Medical exams were completed at baseline (1987-1989), with follow-up exams completed in 1990-1992 (Exam 2), 1993-1995 (Exam 3), and 1996-1998 (Exam 4). At baseline and at Exam 3, participants were asked to complete a 66-item semiquantitative food frequency questionnaire (FFQ) designed to assess intake of specific foods and beverages. Researchers chose to assess the relationship between incident HF and specific food groups previously shown to be associated with HF incidence. These food groups included whole grains (oatmeal or grits, whole-grain cold cereal, whole-grain/dark bread), eggs (boiled, poached, fried, scrambled, omelets, egg salad, quiche), fruits and vegetables (fruits and fruit juices; tomatoes; potatoes; cruciferous, carotenoid, green leafy, and other vegetables and legumes), fish (seafood, dark-meat fish, tuna, and other fish), nuts (nuts, peanut butter), high-fat dairy (whole milk, cheese, and ice cream), and red meat (hamburger, meat in sandwiches or mixed dishes, hot dogs, sausage/salami, bacon, liver). There were nine frequency categories ranging from "never or less than one time per month" to "six or more times per day" and standard portion sizes were provided to help participants estimate intake.

Three models were used to determine the associations between dietary intake and incident HF. Model 1 adjusted only for energy intake (kcal/day). Model 2 adjusted for daily energy intake in addition to demographics, lifestyle factors (including smoking status, physical activity level, and alcohol consumption status), and baseline history of diseases such as diabetes and hypertension. Model 3 mutually adjusted intakes of each of the food groups.

With regard to demographic and lifestyle factors, participants who developed HF over the course of follow-up were more likely to be older, male, African-American, less educated, and less physically active. In addition, those who developed HF had greater BMI and waist circumference measurements at baseline and were more likely to be current smokers and less likely to be current drinkers. Diabetes, coronary heart disease (CHD), and stroke were also more common in those who developed HF ($P<0.001$ for all).

After adjustment for total energy intake, consumption of high-fat dairy foods, refined grains, and red or processed meat was significantly greater in those who developed HF, while consumption of whole-grain foods was significantly less compared with that of participants who did not develop HF over the course of follow-up ($P<0.05$ for all).

In Model 1, greater intakes of high-fat dairy, eggs, and red or processed meats were positively associated with the incidence of HF, while whole-grain intake was associated with lower risk ($P<0.05$). In Model 2 (multivariable adjustment), these associations were weakened, but the relationship between HF and intake of eggs and high-fat dairy foods remained significant, as well as the inverse association between whole-grain intake and HF ($P<0.05$ for all). Adjustment for follow-up BMI and incident CVD, diabetes, and hypertension only slightly modified the risk estimates for these food groups. Intake of red meat was no longer associated with HF risk after multivariable adjustment (Models 2 and 3). No significant association was found between consumption of fruits and vegetables, fish, or nuts and incident HF.

No significant interactions were found between intake of specific food groups and BMI, sex, race, or disease status (presence of CVD, diabetes, or hypertension) at baseline. Since the presence of HF risk factors could have influenced dietary intake over follow-up, an additional analysis was conducted that excluded participants with CVD, diabetes, or hypertension at baseline (n=8,594) to control for recall bias. Although risk ratios remained similar, confidence intervals widened (RR per 1 serving/day of eggs=1.26 [0.99, 1.59]; high-fat dairy=1.05 [0.92, 1.20]; whole grains=0.84 [0.74, 0.95]).

Results from this long-term study in white and African-American men and women suggest that higher intake levels of eggs/egg dishes and high-fat dairy foods might be associated with greater risk of incident HF and that higher intakes of whole grains might reduce HF risk. These findings are consistent with those of several other studies showing whole grains to be associated with decreased risk of CVD, hypertension, inflammation, and poor glycemic control, all of which might contribute to the risk of HF. A recent publication by Djousse and Gaziano evaluating evidence from the Physicians' Health Study also found that greater intake of whole-grain cereal was associated with lower risk of HF.

In a separate analysis of data from the Physicians' Health Study, Djousse and Gaziano showed that while consumption of ≥7 eggs per week was associated with higher incidence of HF, egg consumption up to six times per week had no effect on HF risk. The authors of the current study note that "egg consumption may simply be a marker for a larger dietary pattern that, in total, influences HF risk. Given the long history of debate regarding egg consumption in CVD in general, it is important that these observations be disentangled in studies of varying design…" Indeed, the Djousse and Gaziano study reported that the physicians with the most frequent egg consumption were also more likely to be current smokers, overweight, less physically active, diabetic, hypercholesterolemic, and hypertensive, all of which might indicate general non-compliance with current health recommendations.

The finding that there was no association between fish intake and incident HF is unexpected, given the body of research indicating that fish consumption is cardioprotective. However, the FFQ used in this study did not differentiate between intakes of baked/broiled vs. fried fish. Previous research by Mozzafarian and colleagues showed a decreased incidence of HF in those consuming baked/broiled fish vs. those consuming fried fish.

One limitation of this study is the relative simplicity of the FFQ used to estimate intake. The expected health effects of the foods within certain food groups are not necessarily comparable. For example, whole milk is not comparable to ice-cream with regard to total fat or refined sugar content. Similarly, the nutritional profile of egg salad, omelets, quiche, and fried eggs can deviate widely from that of eggs that are simply boiled or poached. The associations found in this study warrant further research; however, given the degree of nutritional overlap within food groups—and the fact that statistical associations do not indicate causality—it would be premature to develop dietary recommendations based upon these findings. As stated by the authors, further research is needed to validate and clarify the associations observed in this study. ▪

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Djousse L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation*. 2008;117:512-516.

Mozaffarian D, Bryson CL, Lemaitre RN, Burke GL, Siscovick DS. Fish intake and risk of incident heart failure. *J Am Coll Cardiol*. 2005;45:2015-2021.

Influence of Dietary Quality on C-Reactive Protein Concentrations

C-reactive protein, one of a number of inflammatory biomarkers, is receiving increasing attention for its role in identifying those at risk for cardiovascular disease in the absence of other common risk factors such as elevated low-density lipoprotein (LDL) cholesterol. High-sensitivity C-reactive protein (hs CRP) is thought to be an independent predictor of cardiovascular events. Indeed, research has shown that statin therapy effectively lowers hs CRP levels and a recent clinical trial reported that pharmacotherapy with rosvustatin (a statin drug for cholesterol lowering) decreased hs CRP levels by 37% and significantly reduced the incidence of major cardio-vascular events in healthy men and women without hyperlipi-demia, but with elevated hs CRP. With the current focus on educating patients and consumers about dietary and lifestyle modification to improve LDL cholesterol levels, a significant proportion of the at-risk population might be falling through the proverbial "cracks." Can dietary changes modify CRP levels? Findings from a recent study by Fargnoli and colleagues suggest that there are, in fact, dietary components that can reduce circulating levels of C-reactive protein (CRP) and improve other biomarkers of inflammation, endothelial function, and insulin resistance.

The goal of Fargnoli's evaluation of existing data from the Nurses' Health Study was to determine whether participants with healthy dietary patterns—as defined by the Alternate Healthy Eating Index (AHEI)—had lower levels of biomarkers of inflammation, endothelial dysfunction, and insulin resistance. For this analysis, researchers gathered data on dietary intake and plasma biomarkers of inflammation, endothelial dysfunction, and insulin resistance from a total of 1922 healthy females (no evidence of cardiovascular disease, cancer, or diabetes) between the ages of 30 and 55 years. Blood samples were obtained twice, once in 1989 and once in 1990 to measure biomarkers of inflammation (CRP and resistin), glycemic control and insulin resistance (HbA1c, insulin, and C-peptide), sE-selectin (an endothelial adhesion molecule), tumor necrosis factor-a receptor II (sTNF-αRII), interleukin-6 (IL-6), soluble intercellular adhesion molecule 1 (sICAM-1), soluble vascular cell adhesion molecule 1 (sVCAM-1), and ferritin. Plasma total adiponectin (a cytokine secreted by adipose tissue that has been shown to help regulate insulin sensitivity, serum glucose and lipid metabolism) was also measured, in addition to high-molecular-weight (HMW) adiponectin, which has been thought to be the most active form of the cytokine.

Demographic, lifestyle, and anthropometric information including age, body weight, smoking status, use of medication, occurrence of hypertension and hypercholesterolemia was gathered by questionnaire in 1990 and was updated every 2 years. Body mass index (BMI) was calculated and waist-to-hip ratio was determined based on waist and hip circumference self-reported in 1986.

Participants completed questionnaires twice a year that assessed lifestyle factors and medical history. Dietary information was gathered using a semiquantitative food-frequency questionnaire (SFFQ) and for this analysis, only data from the 1984, 1986, and 1990 SFFQs were used. Participants reported frequency of food item consumption ranging from "never" to ">6 times/day."

The Alternate Healthy Eating Index (AHEI) is a tool developed by Willett and colleagues at Harvard University to measure adherence to a healthy diet. The AHEI was developed based on the intake levels of 9 dietary components with evidence of association with specific diseases and mortality risk. Specifically, the AHEI includes information on the intake of: fruit, vegetables, ratio of white meat (seafood and poultry) to red meat, trans fat, the ratio of polyunsaturated fat to saturated fat (P:S), cereal fiber, nuts and soy, moderate alcohol consumption (0.5-1.5 servings/day), and long-term multivi-tamin use (<5 or >5 y). Scores range from 2.5-87.5, higher scores representing healthier diets.

AHEI scores for participants were divided into quintiles and simple linear regression models were used to evaluate associa-tions of plasma biomarker concentrations across quintiles. Multiple linear regression was undertaken to adjust for potential confounding factors. Multivariate linear regression analyses were also completed to evaluate associations between plasma biomarkers and quintiles of free and total choline intake.

Women with the highest AHEI scores tended to have lower BMIs and waist-to-hip ratios, higher daily energy intake, and higher weekly physical activity scores. They also tended to be older, more likely to have a history of hypercholesterolemia, and less likely to be current smokers. There were no associa-tions across quintiles with respect to the use of blood pressure and cholesterol-lowering medications. With regard to serum biomarkers of inflammation, women with the highest AHEI scores had higher mean total and HMW adiponectin levels and lower concentrations of resistin, sTNF-αRII, IL-6, CRP, sE-selectin, sICAM-1, sVCAM-1, insulin, and HbA1c. No differ-ences were observed across quintiles for ferritin or C-peptide.

AHEI scores correlated most strongly with physical activity (r = 0.31). There were also positive correlations between AHEI scores and total and HMW adiponectin (r = -0.11) and age (r = 0.18). AHEI scores were inversely associated with BMI (r = -0.12), resistin (r = -0.12), TNF-αRII (r = -0.11), IL-6 (r = -0.08), CRP (r = -0.09), sE-selectin (r = -0.13), sICAM (r = -0.07), C-peptide (r = -0.14), insulin (r = -0.13), and HbA1c (r = -0.10). Women reporting AHEI scores in the highest quintile had 24% higher median total adiponectin concentrations and 32% higher median HMW adiponectin concentrations than those with scores in the lowest quintile after adjustment for age and energy intake. This association remained significant after adjustment for weekly physical activity, smoking status, and BMI.

After adjusting for age and energy intake, women reporting the closest adherence to the AHEI (highest quintile) had 16% lower plasma resistin concentrations than those in the lowest quintile, an association that remained significant after further adjusting for physical activity, smoking status, and BMI. Higher AHEI scores were also associated with lower plasma CRP, sE-selectin, and ferritin levels. After adjustment for age and energy intake, median CRP concentrations were 41% lower, ferritin concentrations were 24% lower, and sE-selectin concentrations were 19% lower for women in the highest quintile of AHEI scores than for those in the lowest quintile. These associations were still significant after adjusting for physical activity, smoking status, BMI, history of hypertension, and history of hypercholesterolemia.

Inverse correlations were observed between AHEI and biomarkers of insulin resistance (C-peptide, insulin, and HbA1c) after adjustment for age and energy intake, but the significance was weakened after adjustment for BMI. After adjustment for age, energy intake, physical activity, and smoking status, AHEI scores were inversely related to sTNF-αRII, IL-6, sICAM-1, and sVCAM-1 concentrations, but did not remain significant after adjusting for BMI.

After multivariate adjustment, biomarkers that were significantly associated with AHEI scores were analyzed in a final model that adjusted for all other significant biomarkers. In this final model, total adiponectin and resistin were significantly associated with the AHEI (P = 0.01 for both), however, the associations between AHEI and sE-selectin (P = 0.08), ferritin (P = 0.08), HMW adiponectin (P = 0.13), and CRP (P = 0.21) were no longer significant.

Total and HMW adiponectin levels were also found to be significantly associated with alcohol consumption and multivitamin use. For the women who used multivitamins for >5 years, plasma total adiponectin was 13% higher and HMW adiponectin levels were 16% higher than for those who did not. In addition, those in the highest quintile of alcohol intake had 28% higher plasma total adiponectin levels and 45% higher HMW adiponectin levels, when compared with those who did not consume alcohol. (Median alcohol intake for those in the highest quintile was ~1 serving/day.) Total adiponectin was inversely associated with daily trans fat intake and both total and HMW adiponectin levels were inversely associated with the P:S ratio. Plasma resistin concentrations were 14% lower for women in the highest quintile of P:S than for those in the lowest. This association remained significant after multivariate adjustment. The ratio of white meat to red meat consumption was also significantly and inversely associated with plasma sE-selectin, CRP, and ferritin concentrations. Those in the highest quintile of white to red meat consumption had 9% lower sE-selectin, 28% lower CRP, and 31% lower ferritin concentrations compared with women in the lowest quintile after adjustment for age and energy intake. These associations remained significant after multivariate adjustment.

Because previous studies have suggested that choline might be one of the protective components of the Mediterranean diet, women in the highest quintile of free choline intake had 20% higher median total adiponectin concentrations, 28% higher HMW adiponectin concentrations, 11% lower resistin concentrations, and 33% lower CRP concentrations than women in the lowest quintile after adjustment for age and energy intake. These observations remained significant after adjusting for physical activity, smoking status, and BMI.

In this sample of 1922 healthy women with no history of CVD or diabetes, higher AHEI scores were associated with higher total and HMW plasma adiponectin levels and lower plasma resistin, sE-selectin, and ferritin levels. With regard to CRP levels, women in the highest quintile of AHEI scores had CRP concentrations 41% lower than women in the lowest quintile. Women with the highest quintile of free choline intake had 20% higher median total adiponectin levels, 28% higher HMW adiponectin levels, 11% lower resistin concentrations, and 33% lower CRP concentrations than those in the lowest quintile of consumption. Those consuming the highest ratio of white to red meat had 28% lower CRP concentrations than those consuming the lowest ratios of white to red meat.

The observations in this study support those of the ATTICA trial, in which Detopoulou et al. reported that a combination of high choline and high betaine intake was associated with lower circulating levels of homocysteine, CRP, IL-6, and TNF-α. Although these associations do not prove causality, they do suggest that consuming a higher-quality diet and including sources of dietary choline might help keep serum CRP and other biomarkers of inflammation and endothelial function in check. ▪

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Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195-207.

Detopoulou P, Panagiotakos D, Antonopoulou S, et al. Dietary choline and betaine intakes in relation to concentrations of inflammatory markers in healthy adults: the ATTICA study. *Am J Clin Nutr* 2008;87:424-30.

EDITORIAL

Good Egg, Bad Egg and Lifestyle Factors

In this issue of *Nutrition Close-Up* there are three studies which seem to say "eggs are good," "eggs are bad" and that egg intake might be a surrogate marker for other lifestyle choices and health behaviors. Why is it so complicated to come to a conclusion regarding egg intake and health? First it was the cholesterol content (eggs = dietary cholesterol = blood cholesterol = heart disease risk). When that didn't pan out, it was eggs and mortality or eggs and diabetes…but then again, what about eggs and choline? The egg just seems to be everything to everyone and it doesn't seem to matter if you think they are a good food or a bad food, eggs can conjure up imagery for both.

First, the good news! Egg yolks are rich in choline; and choline intake, according to the study by Fargnoli et al., lowers biomarkers of inflammation and endothelial dysfunction. That should be a good thing.

Now the bad news. According to the studies by Djoussé et al., egg intake is associated with increased risk of type 2 diabetes. In addition, Nettleton et al. reported that egg intake was associated with increased heart failure. Neither study could provide a feasible biological mechanism for the observed relationship. But overall, clearly not so good.

All of this leads me to an obvious question—Why would a large portion of this group of health professionals consume 7 or more eggs per week during a period of time when everyone knew the recommendation was "no more than three eggs yolks per week." These participants also had higher BMIs, were older, were more likely to smoke, reported greater consumption of alcohol, were more likely to have hypertension, and—for women—reported higher total calorie, saturated fat, and trans fat, and cholesterol intakes. My guess is that these are the same physicians who would go without seat belts and ride motorcycles without helmets! So was the increased diabetes incidence due to eggs or due to an overall unhealthy lifestyle that is associated with higher egg intake?

The Coronary Drug Project[1] reported an interesting observation about behavioral factors and mortality that might be applicable here. Using data from the trial's placebo group, they found that participants taking <80% of the per-protocol placebo dose had a 5-year total mortality rate nearly 90% higher than that of participants taking 80% of the dose[1]. That meant that for nonadherers (those not taking the placebo as advised), risk of mortality was actually higher than for those who did adhere to the study protocol and took the placebo as instructed. What was the difference? The only plausible explanation is that there were other factors associated with noncompliance with the prescribed placebo regimen that contributed to mortality.

Adherence	Subjects (N)	Mortality (%)
Low (<80%)	882	28.2
High (≥80%)	2695	15.1
Relative Risk		1.87 (95% CI 1.60,2.17)

[2]Kritchevsky, SB. "Adherence bias" in nutritional epidemiology. *Am J Clin Nutr* 2008; 88: 1448 - 1449.

In a recent Letter to the Editor[2] in the American Journal of Clinical Nutrition, Kritchevsky noted the following about the earlier Djoussé and Gaziano[3] report:

"The problem of nonadherer bias comes to mind in an interpretation of the recent findings of Djoussé and Gaziano that link the consumption of > 7 eggs/wk to total mortality risk in physicians with diabetes who were enrolled in the Physicians' Health Study. The result is hard to understand on its own because of the lack of association between egg consumption and myocardial infarction and stroke risk in that study, which suggests that high egg consumption is associated with noncardiovascular causes of death, an association for which there is no apparent biologic basis…it is not a stretch to think that, among physicians with diabetes, a group that should have the knowledge, motivation, and resources to minimize the adverse consequences of diabetes through both dietary and nondietary means, the consumption of high-cholesterol foods could be considered nonadherent behavior."

Similarly, the time period during which dietary data was gathered for the Physicians Health Study (1982-2007) and Womens' Health Study (1992) (current analysis by Djoussé and Gaziano) was characterized by widely-held negative perceptions of eggs' health effects. Thus, motivated health professionals with high health awareness might have minimized egg intake as part of their efforts to live overall healthier lifestyles—lifestyles that included making prudent dietary choices, avoiding tobacco and excess alcohol, and maintaining a healthy weight. Likewise, health professionals who did not adhere to the precautionary guidelines of that time to minimize cholesterol intake likely had many other health habits that could have contributed to the development of type 2 diabetes or heart failure.

In light of the importance of this preliminary research and its potential implications, further research must be done in order to find out whether the findings can be replicated and to identify potential mechanisms if any exist. However, let's not forget that decades of research and numerous trials have failed to show an independent relationship between egg intake and cardiovascular disease. Given the large body of research supporting the health benefits of egg consumption, the findings reported by Nettleton, Djoussé and Gaziano are unexpected. By nature, statistical associations cannot prove causation. They simply indicate relationships between variables and outcomes and—if viable physiological mechanisms are available—can provide a framework for future research. Therefore, further studies must be undertaken before any conclusion can be reached with regard to egg intake in special populations. As such research moves forward, the potential for "adherence bias" must also be taken into account.

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