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Egg yolk consumption and carotid plaque

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ABSTRACT

Background: Increasingly the potential harm from high cholesterol intake, and specifically from egg yolks, is considered insignificant. We therefore assessed total plaque area (TPA) in patients attending Canadian vascular prevention clinics to determine if the atherosclerosis burden, as a marker of arterial damage, was related to egg intake. To provide perspective on the magnitude of the effect, we also analysed the effect of smoking (pack-years).
Methods: Consecutive patients attending vascular prevention clinics at University Hospital had baseline measurement of TPA by duplex ultrasound, and filled out questionnaires regarding their lifestyle and medications, including pack-years of smoking, and the number of egg yolks consumed per week times the number of years consumed (egg-yolk years).
Results: Data were available in 1262 patients; mean (SD) age was 61.5 (14.8) years; 47% were women. Carotid plaque area increased linearly with age after age 40, but increased exponentially with pack-years of smoking and with egg-yolk years. Plaque area in patients consuming <2 eggs per week ($n = 388$) was 125 ± 129 mm^2, versus 132 ± 142 mm^2 in those consuming 3 or more eggs per week ($n = 603$); ($p < 0.0001$ after adjustment for age). In multiple regression, egg-yolk years remained significant after adjusting for coronary risk factors.
Interpretation: Our findings suggest that regular consumption of egg yolk should be avoided by persons at risk of cardiovascular disease. This hypothesis should be tested in a prospective study with more detailed information about diet, and other possible confounders such as exercise and waist circumference.

1. Introduction

The underpinning of what used to be the step 2 diet and later became the diet recommended for CHD risk reduction by NCEP ATP III was a diet low in saturated fat (<7%) and dietary cholesterol (<200 mg) [1]. This diet if strictly applied tended to drive the consumer towards a more plant based diet with other potential advantages in terms of CHD risk reduction. In addition to saturated fat in meat (especially red meat) and full fat dairy products, eggs were also restricted due to their significant cholesterol content.

Currently, however, serious doubts have been expressed over the relevance of these dietary components to cardiovascular disease [2,3]. In the case of cholesterol much of the debate has been focused on the lack of clear consensus on whether egg consumption consistently raises serum cholesterol [4–8] or impacts negatively on postprandial events, including vascular reactivity [9,10]. Most importantly the association of egg consumption with CHD events in cohort studies has been inconsistent [11–14]. We recently reviewed the evidence that consumption of cholesterol and egg yolk should not be considered benign in patients at risk of vascular disease [15]. Much of the controversy in this area is about effects of egg yolk consumption on fasting lipids; however the main impact of diet is on the post-prandial state, not on the fasting state [15,16].

To address the key issue of whether egg yolk intake relates to vascular damage we report the association of egg consumption with carotid plaque area assessed by ultrasound as an indication of atheromatous change in patients attending vascular clinics at an University Hospital. To provide perspective on the magnitude of the effect, we also analysed the effect of smoking (pack-years).

2. Methods

Patients in the database had been referred to vascular prevention clinics since we routinely began measuring carotid total plaque

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Table 1
Baseline characteristics of the subjects.

	Mean	Std. deviation
Age at first visit	61.50	14.82
Systolic pressure (mmHg)	141.75	23.01
Diastolic pressure (mmHg)	83.37	23.96
Total cholesterol (mmol/L)	4.91	1.21
Triglycerides (mmol/L)	1.90	1.28
HDL cholesterol (mmol/L)	1.33	0.44
Body mass index	27.38	6.44
	Median	Interquartile range
Plaque area (mm^2)	85.0	179.0
Smoking (pack-years)	5.0	25.0
Egg-yolk years	132	133
		Percent
Female		47.1%
Diabetic		13.3%

area (TPA) in 1995 [17,18]. Plaque area was measured as previously described [19]: each plaque identified in the common, external and internal carotid artery on both sides was measured in a longitudinal view, in the plane in which it was biggest. The perimeter of each plaque was traced using a cursor on the screen to measure the area of the plaque, and the sum of all plaque areas was TPA.

In earlier years, data on smoking and egg consumption were recorded by patients into a lifestyle questionnaire at the time of referral. Since 2000, when our referrals were scheduled on an urgent basis soon after transient ischeamic attacks or strokes, a more limited set of lifestyle questions were asked at the time the history was obtained. These data were entered, along with the history, medications, physical examination and recommendations into fields in the database, from which clinic notes were generated. The responses for smoking and egg yolk consumption were used to compute pack-years of smoking (number of packs per day of cigarettes times the number of years of smoking) and egg-yolk years (number of egg yolks per week times number of years consumed). This was not done for alcohol consumption, licorice intake or exercise, because the textual responses were mainly not quantifiable (e.g. “quit drinking six years ago”, “plays golf twice a week”). All patients with complete data for each analysis were included. Egg yolks per week were computed by one observer from text entries in the lifestyle field of the database; for example one whole egg per month was entered as 0.25 eggs per week, consumption of 2 whole eggs per day was entered as 14 eggs per week. Egg whites or egg substitutes were counted as 0 yolks. For example, a person who consumed 3 eggs per week for 50 years would have a score of 150 egg-yolk years. Data were analysed anonymously from electronic medical records; patients provided signed consent to participate in the database, approved by the University of Western Ontario ethics board (review number 12107E).

Data range checks were performed and data entry errors such as decimal errors were identified by scatter plots of age against each continuous variable; outliers were identified using the data label mode in SPSS, and such errors were corrected by re-entering the correct value. Analyses were performed using IBM SPSS 20. Mean and standard deviation were computed for normally distributed baseline variables, median and interquartile range for non-normally distributed variables, and percent for categorical variables. As total plaque area is highly skewed, it was normalized for multiple regression analysis by a cube root transformation (exponent 1/3), as previously described [20,21].

3. Results

There were 2831 patients with data on egg yolk consumption. Of these, consent to use the data, and data on pack-years of smoking and carotid total plaque area were available in 1231 patients. The mean age was 62 years; 47% were women. Baseline characteristics of the patients are shown in Table 1. Table 2 shows the baseline characteristics of the patients grouped by quintiles of egg-yolk years.

Fig. 1A shows that carotid atherosclerotic plaque burden increases linearly after age 40, among Canadian patients referred to cardiovascular prevention clinics. Online Supplemental Fig. 2 shows the distribution of weekly egg yolk consumption, and of pack-years of smoking and egg-yolk years. As 39.9% of patients never smoked, smoking groups were divided for analysis not into quintiles, but into roughly equal groups among those who ever smoked, using groupings that made sense clinically: 0 pack-years (39.9%), >0 < 10 pack-years 17.8%, 10–20 pack-years 13.1%, 20–40 pack-years 17.6%, >40 pack-years 11.6%. Fig. 1B and C shows that compared to age, both tobacco smoking and egg yolk consumption accelerate atherosclerosis, in a similar fashion: the increase in plaque area is linear with age, but it is exponential with smoking history and egg consumption. Curve fitting with the cases that had non-zero values for egg yolks and smoking showed that an exponential fit was better than a linear fit. The total plaque area among people who consumed 2 or fewer eggs per week ($n = 388$) was 125 ± 129.62 mm^2, whereas it was 132.26 ± 142.48 mm^2 in

Table 2
Baseline characteristics of the participants by quintile of egg-yolk years.

Egg-yolk years	Quintile of egg-yolk years					*p*
	<50	50–110	110–150	150–200	≥200	
Normally distributed variables: mean ± SD						
Age at first visit	55.70 ± 17.03	57.97 ± 16.32	56.82 ± 12.35	64.55 ± 12.00	69.77 ± 11.38	0.0001
Eggs per week	0.41 ± 0.44	1.37 ± 0.54	2.30 ± 0.53	2.76 ± 0.59	4.68 ± 3.03	0.0001
Systolic pressure (mmHg)	141 ± 24	139 ± 24	142 ± 22	144 ± 22	145 ± 23	0.001
Diastolic pressure (mmHg)	83 ± 12	82 ± 12	85 ± 13	82 ± 13	80 ± 13	0.001
Total cholesterol (mmol/L)	4.93 ± 1.16	4.94 ± 1.17	5.0 ± 1.14	4.90 ± 1.16	4.81 ± 1.19	0.47
Triglycerides (mmol/L)	1.88 ± 1.41	1.84 ± 1.08	1.96 ± 1.31	1.94 ± 1.40	1.85 ± 1.17	0.77
HDL cholesterol (mmol/L)	1.34 ± 0.48	1.33 ± 0.42	1.33 ± 0.42	1.29 ± 0.42	1.35 ± 0.45	0.58
LDL cholesterol (mmol/L)	2.76 ± 1.04	2.75 ± 1.02	2.81 ± 1.09	2.73 ± 1.19	2.67 ± 1.06	0.62
Body mass index	27.62 ± 5.62	27.42 ± 5.53	28.71 ± 9.91	27.00 ± 4.81	26.31 ± 4.48	0.001
Plaque area (mm^2)	101.45 ± 125.64	110.35 ± 129.02	113.58 ± 138.82	135.76 ± 137.67	175.77 ± 147.61	0.0001
Age-dependent variables: age-adjusted marginal mean ± SE						
Smoking (pack-years)	14.14 ± 1.37	14.37 ± 1.40	16.57 ± 1.25	13.88 ± 1.30	17.00 ± 1.20	0.24
Categorical variables: percent						
Female	48.6%	51.7%	44.8%	45.0%	46.7%	0.56
Diabetic	11.8%	14.5%	11.8%	13.4%	14.6%	0.80

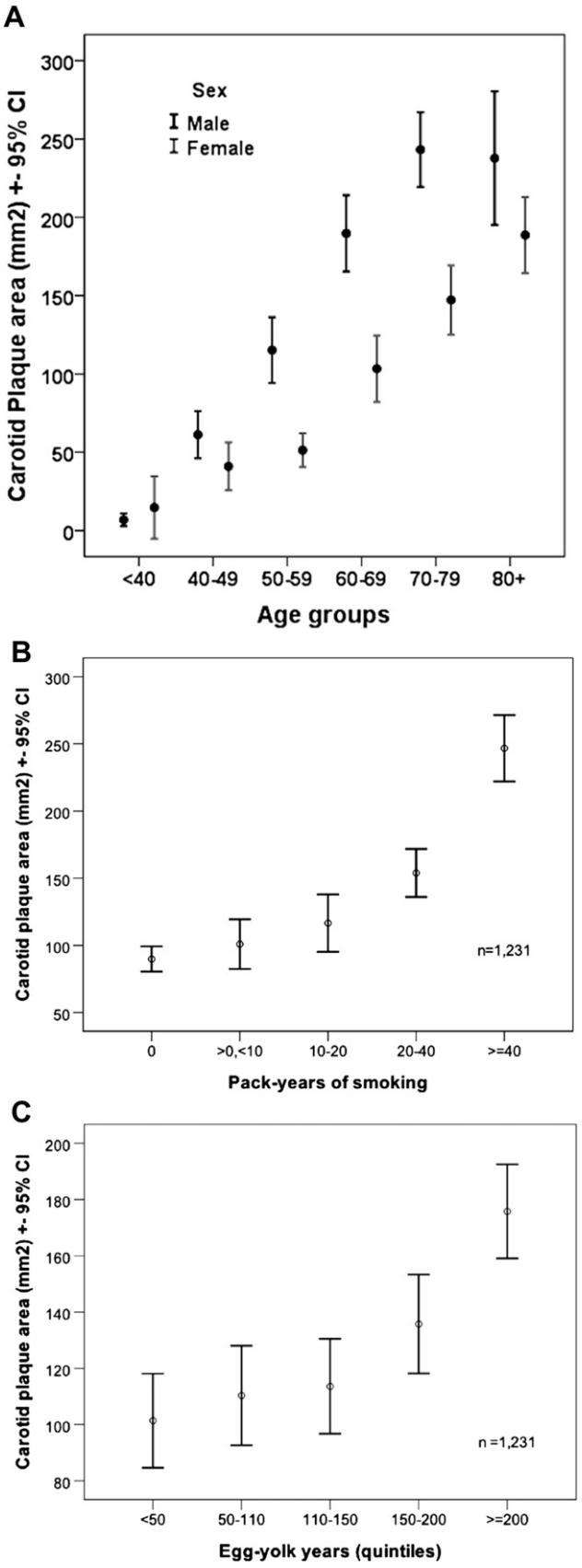

Fig. 1. Carotid total plaque area: effect of age, smoking (pack-years) and egg yolks (egg-yolk years) panel A shows how plaque area increases by age groups in all patients, including smokers and eaters of eggs; panel B shows plaque area by pack-years of smoking (number of packs of cigarettes per day times number of years smoked); panel C shows plaque area by quintiles of egg-yolk years (number of eggs per week times number of years consumed). Plaque area increases linearly with age, but exponentially with smoking and egg yolk consumption.

those consuming 3 or more eggs per week ($n = 603$). Because plaque area increases steeply with age, as shown in Fig. 1, it was important to adjust for age; this difference was statistically significant after adjustment for age in a General Linear Model ($p < 0.0001$). In linear multiple regression analysis (Table 3), egg-yolk years remained a significant predictor of baseline TPA after adjustment for sex, serum total cholesterol, systolic blood pressure, diabetes, body mass index and pack-years of smoking. As reflected in the Beta (proportion of explained variance), egg-yolk years was more predictive than fasting cholesterol or BMI. Triglycerides, HDL cholesterol and LDL cholesterol were not significant predictors of baseline TPA in stepwise linear regression (Online Supplemental Table 4).

There was no significant correlation between egg yolk consumption and smoking history: $R = 0.046$; $p = 0.10$; the partial correlation, adjusted for age, was also not significant: $R = 0.01$; $p = 0.70$.

4. Interpretation

Our data suggest a strong association between egg consumption and carotid plaque burden. The exponential nature of the increase in TPA by quintiles of egg consumption follows a similar pattern to that of cigarette smoking. The effect of the upper quintile of egg consumption was equivalent in terms of atheroma development to 2/3 of the effect of the upper quintile of smoking. In view of the almost unanimous agreement on the damage caused by smoking, we believe our study makes it imperative to reassess the role of egg yolks, and dietary cholesterol in general, as a risk factor for CHD.

At present many jurisdictions include no consideration of cholesterol in their guidelines including the European Union, Canada, India, Korea, New Zealand [3]. Part of the reason is the inconsistency in the data relating change in cholesterol intake to change in blood levels. Early on, analysis of the data at the time, independently by Keys and Hegsted, lead to the development of predictive equations in which dietary cholesterol was recognized to determine a proportion, albeit limited, of the change in serum cholesterol [22,23]. These equations formed the basis for subsequent dietary advice. Since then the data have been mixed with some studies supporting an increase in serum cholesterol with cholesterol feeding [7,8,24] while others have not [4,6]. Notably egg consumption has resulted in divergent effects on serum cholesterol. In some studies raising serum cholesterol [24–26] and in other studies being without effect [3,4,9,27,28]. In addition, similarly to saturated fat, dietary cholesterol has also been shown to raise HDL-C [26,29,30]. Part of the explanation for the differences in lipid responses may relate to genetic differences, such as in the apo-E4 polymorphism with carriers of apoE4 showing higher fasting LDL-C levels [31] and differences in the ABCG 5/8 sterol transporter where ABCG 5 polymorphism increasers sterol absorption [32–34]. This situation is further complicated by the fact that cholesterol feeding may reduce the efficiency of cholesterol absorption [35] and depress hepatic cholesterol biosynthesis [36] so confounding a clear dose response. However none of these considerations negate the possible existence of significant vulnerable populations. Indeed a meta-analysis involving 395 experiments among 129 groups of individuals demonstrated that avoiding 200 mg/d dietary cholesterol, the amount similar to that found in a large egg, reduced LDL-C by 0.10 mmol/L [37].

Table 3
Multiple regression analysis. Egg-yolk years remained a significant predictor of carotid plaque area after adjustment for sex, total cholesterol, pack-years of smoking, systolic blood pressure, diabetes and body mass index. (Age is incorporated into pack-years and egg-yolk years).

Coefficients[a]						
Model		Unstandardized coefficients		Standardized coefficients	*t*	Sig.
		B	Std. error	Beta		
1	(Constant)	2.073	0.460		4.502	0.000
	Female sex	−0.803	0.113	−0.184	−7.110	0.000
	Total cholesterol	−0.171	0.046	−0.095	−3.712	0.000
	Systolic blood pressure	0.023	0.002	0.247	9.767	0.000
	Smoking (pack-years)	0.031	0.003	0.280	10.930	0.000
	Diabetes	0.914	0.161	0.144	5.669	0.000
	Body mass index	−0.033	0.009	−0.097	−3.828	0.000
	Egg-yolk years	**0.002**	**0.000**	**0.124**	**4.897**	**0.000**

$R^2 = 0.277$.
[a] Dependent variable: baseline plaque area (normalized by a cube root transformation).

The outcome of increased vascular damage as demonstrated in the present study, or hard outcomes, including CHD events or deaths, assessed in relation to eggs, remains the critical issue. Here again the literature which is derived from cohort studies is divided. Analysis of the Health Professionals and Nurses Health studies by Hu and colleagues noted no overall effect of egg consumption on CHD events and mortality after 8 years of follow up, among participants who remained non-diabetic [11]. However, among participants who became diabetic during follow-up, daily egg consumption doubled CHD mortality [11]. The same pattern was seen in another large population-based study: among participants who became diabetic during follow-up, intake of eggs was associated with a doubling of cardiovascular risk [38]. Extending these findings further, a later assessment of the Physicians Health Study demonstrated a relation of egg consumption to total mortality and confirmed an even stronger relation to mortality in those with diabetes [13], and a Greek study in diabetics showed that daily egg consumption increased coronary risk more than 5-fold [39]. In view of the predicted increase in the incidence of diabetes both in western cultures and in the developing world the deleterious effect of egg consumption in diabetes is of particular concern. Furthermore there is also emerging evidence that egg consumption itself may be related to increased diabetes incidence [40]. Therefore egg yolk consumption remains a public health concern.

The study weakness includes its observational nature, the lack of data on exercise, waist circumference and dietary intake of saturated fat and sources of cholesterol other than eggs, and the dependence on self-reporting of egg consumption and smoking history, common to many dietary studies. Study strengths include the large number of patients on whom data were available, the significant egg consumption despite recommendations to high risk individuals to limit egg consumption and most importantly the use of carotid plaque burden as the study end point rather than risk factors such as fasting cholesterol levels.

Carotid plaque area strongly predicts cardiovascular risk. We reported in 2002 [19] that after adjustment for age, sex, systolic blood pressure, diabetes, serum total cholesterol, plasma total homocysteine and treatment of blood pressure and cholesterol, patients in the top quartile of plaque area had 3.4 times higher 5-year risk of stroke, death or myocardial infarction compared to patients in the lowest quartile. These findings were corroborated in the Tromsø study [41], a population-based study in Norway. A meta-analysis by Inaba et al. in this journal [42] confirmed that plaque area is a stronger predictor of cardiovascular events than carotid intima-media thickness.

We conclude that the prevailing tendency to ignore dietary cholesterol as a risk factor for coronary heart disease requires reassessment, including the consumption of cholesterol from eggs. Although low fat egg dishes may be less harmful than meals high in both saturated fat and cholesterol (even if the latter have somewhat lower cholesterol content), meals high in cholesterol should not be consumed regularly by those at risk for cardiovascular diseases, as dietary cholesterol itself is harmful, and potentiates the effect of saturated fats [15]. Increasingly studies are showing that vegetable oils and plant protein sources low in cholesterol and saturated fats confer benefits in terms of heart disease risk and diabetes incidence [43,44] with improvements in the blood lipid profile [45]. This approach to diet has been captured in the idealized description of the Mediterranean diet now considered by many as the ideal diet for CHD risk reduction. Ansel Keys, who first drew attention to the Mediterranean diet, commented that “the heart of this diet is mainly vegetarian, and differs from the American and Northern European diets in that it is much lower in meat and dairy products and uses fruit for dessert” [46]. Our study supports a return to earlier concepts of the therapeutic diet, including a continued prohibition on high dietary cholesterol intakes.

5. Conclusion

Our findings suggest that regular consumption of egg yolk should be avoided by persons at risk of cardiovascular disease. This hypothesis should be tested in a prospective study with more detailed information about diet, and other possible confounders such as exercise and waist circumference.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.atherosclerosis.2012.07.032.

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