1   Association of egg consumption and calcified atherosclerotic plaque in the coronary

2   arteries: the NHLBI Family Heart Study

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23   HL56568, and U01 HL56569)

24   Abbreviations: CHD, coronary heart disease; CAC, coronary-artery calcium; CI,

25   confidence interval; CVD, cardiovascular disease; CT, computed tomography; NHLBI

26   FHS, National Hearth, Lung, and Blood Institute Family Heart Study; HDL, high-density

27   lipoprotein; LDL, low-density lipoprotein

28   **ABSTRACT**

29   Background and Aims:

30   Eggs are a ubiquitous and important source of dietary cholesterol and nutrients, yet their

31   relationship to coronary heart disease (CHD) remains unclear. While some data have

32   suggested a positive association between egg consumption and CHD, especially among

33   diabetic subjects, limited data exist on the influence of egg consumption on subclinical

34   disease. Thus, we sought to examine whether egg consumption is associated with

35   calcified atherosclerotic plaques in the coronary arteries.

36   Methods:

37   In a cross-sectional design, we studied 1848 participants of the NHLBI Family Heart

38   Study without known CHD. Egg consumption was assessed by a semi-quantitative food

39   frequency questionnaire and coronary-artery calcium (CAC) was measured by cardiac CT.

40   We defined prevalent CAC using an Agatston score of at least 100 and fitted generalized

41   estimating equations to calculate prevalence odds ratios of CAC.

42   Results:

43   Mean age was 56.5 years and 41% were male. Median consumption of eggs was 1/week.

44   There was no association between frequency of egg consumption and prevalent CAC.

45   Odds ratios (95% CI) for CAC were 1.0 (reference), 0.95 (0.66-1.38), 0.94 (0.63-1.40),

46   and 0.90 (0.57-1.42) for egg consumption of almost never, 1-3 times per month, once per

47   week, and 2+ times per week, respectively (p for trend 0.66), adjusting for age, sex, BMI,

48   smoking, alcohol, physical activity, income, field center, total calories, and bacon.

49   Additional control for hypertension and diabetes mellitus, or restricting the analysis to

50   subjects with diabetes mellitus or fasting glucose >126 mg/dL did not alter the findings.

51   Conclusions:

52   These data do not provide evidence for an association between egg consumption and

53   prevalent CAC in adult men and women.

54   KEYWORDS: egg; diet; epidemiology; subclinical disease; coronary calcium;

55   atherosclerosis

56   **Introduction**

57   Coronary heart disease (CHD) remains the leading cause of death in the United

58   States. Elevated serum non-HDL cholesterol is strongly associated with the risk of CHD[1-

59   2], and thus the role of dietary influences on serum cholesterol has fostered much research

60   attention. The role of egg consumption on CHD is of particular interest because of its

61   unique nutritional qualities. Eggs are an important source of protein, minerals, and fat-

62   soluble vitamins, but also a source of dietary cholesterol with about 200 mg of

63   cholesterol in an average egg.[3]

64   The relationship between egg consumption and CHD remains unclear.[4-5] A meta-

65   analysis of several large, prospective cohorts did not find an association between egg

66   consumption and CHD, however subgroup analysis showed a positive relationship

67   between egg consumption and CHD in diabetic populations.[4] In contrast, a recent meta-

68   analysis involving twelve studies reported a 19% higher risk of cardiovascular disease

69   (CVD) with higher egg consumption (83% higher risk of CVD with egg intake in diabetic

70   individuals).[5]

71   Coronary artery calcification (CAC) is a well-described marker for subclinical

72   atherosclerotic disease.[6-7] The extent of CAC can help in risk stratification and can help

73   predict future CHD events.[8] Despite limited studies of egg intake with CVD, no study has

74   investigated whether egg consumption is associated with subclinical CHD.

75   Hence, the present study sought to determine whether egg consumption was

76   associated with a lower prevalence of CAC in individuals without known coronary heart

77   disease.

78   **Materials and methods**

79   *1. Study population*

80   Participants in this study were members of the National Heart, Lung, and Blood

81   Institute Family Heart Study (NHLBI FHS) in whom coronary calcified plaque was

82   measured by cardiac-gated multi-detector computed tomography (cardiac CT). The

83   NHLBI FHS is a multi-center, population-based study designed to identify and evaluate

84   genetic and non-genetic determinants of CHD, preclinical atherosclerosis, and

85   cardiovascular risk factors, and has been described in detail in previous publications.[9-10]

86   Briefly, families in the study had been chosen randomly (random group) or based on a

87   higher than expected risk of CHD (high-risk group) from previously established

88   population-based cohort studies. A total of 588 families were chosen at random (with

89   2673 subjects) and 566 families were selected based on higher than expected risk of CHD

90   (3037 subjects). Of the 5710 subjects, 265 were African-American. The high-risk group

91 was defined based on a family risk score, which compares the family's age and sex-

92 specific incidence of CHD to that expected in the general population.[10] All members of

93 these families were invited for a clinical evaluation (between 1993-1995). Between 2002

94 and 2003, about one-third of the families (the largest families available who also had

95 genome-wide anonymous markers typed by the Mammalian Genotyping Service) of the

96 NHLBI FHS were invited to participate in a clinical examination that included

97 measurement of CAC with cardiac CT. In addition to the initial NHLBI FHS study

98 centers, an African-American center - University of Alabama at Birmingham - was

99 recruited from the Hypertension Genetic Epidemiology Network Study, where subjects

100 underwent cardiac CT but did not have dietary assessments. Of the 3360 subjects who

101 had data on cardiac CT, 1084 subjects did not have data on egg consumption at baseline

102 examination (1993-1995), 286 subjects were excluded for prevalent CHD, 68 subjects

103 had missing data on covariates (56 for income; 5 for diabetes; 3 for hypertension; and 4

104 for physical activity), 18 subjects were non-white, and 56 subjects were excluded for

105 extreme caloric intake (> 4200 and 3500 calories or <800 and 600 calories for men and

106 women, respectively). The final sample size for current analyses was 1848. Each

107 participant gave informed consent and the study protocol was reviewed and approved by

108 each of the participating institutions.

109 *2. Assessment of egg consumption*

110 Dietary information was collected through a staff-administered semi-quantitative

111 food frequency questionnaire developed by Willett et al.[11] The reproducibility and

112 validity of the food frequency questionnaire have been documented elsewhere.[12-13] Each

113 subject was asked the following question: "In the past year, how often on average did you

114 consume eggs?" (Item #21 in the questionnaire forms). Possible responses were: almost

115 never, 1-3/month, 1/week, 2-4/week, 5-6/week, 1/day, 2-3/day, 4-6/day, and >6/day. Due

116 to sparse data, we collapsed adjacent categories while creating final exposure categories

117 of almost never, 1-3/month, 1/week, and 2+/week for stable estimates.

118 *3. Measurement of calcified atherosclerotic plaque in the coronary arteries*

119 Cardiac CT examinations were obtained using General Electric Health Systems

120 LightSpeed Plus and LightSpeed Ultra, Siemens Volume Zoom, or Philips MX 8000

121 machines. Examinations were performed using the same protocol as employed in the

122 NHLBI's Multi-Ethnic Study of Atherosclerosis.[14] The scans were performed using

123 prospective ECG gating at 50% of the cardiac cycle, 120 KV, 106 mAs, 2.5 mm slice

124 collimation, 0.5 s gantry rotation and a partial scan reconstruction resulting in a temporal

125 resolution of between 250 and 300 ms. Images were reconstructed using the standard

126 algorithm into a 35 cm display field-of-view. All subjects were imaged with a calcium

127 calibration standard within the imaging field (Image Analysis, Columbia, KY). The scan

128 through the heart was repeated after a 1-min pause during the same examination,

129 resulting in two sequential scans for measurement of CAC. The effective radiation

130 exposure for the average participant of each coronary scan was 1.5 mSv for men and 1.9

131 mSv for women. CT images from all sites were sent electronically to the central CT

132 reading center located at Wake Forest University Health Sciences, Winston Salem, NC.

133 Trained CT analysts using dedicated hardware (GE Advantage Windows Workstation)

134 and software (GE Smar-Score) identified CAC in the epicardial coronary arteries and an

135 Agatston score modified to account for slice thickness was calculated using a 130 CT

136 number threshold and a minimum lesion size of 0.9 mm (i.e., 2 pixel connectivity filter).

137 Agatston score refers to the amount of calcium detected by the scan and is based on the

138 area and the density of the calcified plaques.[15] In this report, the sum of the vessel plaque

139 is reported as the total CAC score. Total CAC scores from the first and second measured

140 were then averaged.

141 *4. Blood collection and assays*

142   All participants were asked to fast for 12 h before their arrival at the study center.

143 Evacuated tubes without additives were used to collect samples for lipids. Triglyceride

144 concentrations were measured using triglyceride GB reagent on the Roche COBAS

145 FARA centrifugal analyzer (Boehringer Mannheim Diagnostics, Indianapolis). Serum

146 total cholesterol was measured using a commercial cholesterol oxidase method on a

147 Roche COBAS FARA centrifugal analyzer (Boehringer Mannheim Diagnostics,

148 Indianapolis). HDL-cholesterol quantification was performed with the above described

149 cholesterol method after precipitation of non-HDL-cholesterol with magnesium/dextran.

150 For samples with triglyceride concentrations less than 4.5 mmol/L (400 mg/dL), LDL-

151 cholesterol was calculated using the Friedewald formula.[16] For subjects with higher levels

152 of triglycerides, LDL-cholesterol quantitation was performed on EDTA plasma by

153 ultracentrifugation.

154 *5. Other variables*

155   Information on cigarette smoking, alcohol intake, and education was obtained by

156 interview during the clinic visit. Resting blood pressure was measured three times on

157 seated participants after a 5-minute rest using a random zero sphygmomanometer and an

158 appropriate cuff size. For analyses, average systolic and diastolic blood pressures from

159   the second and third measurements were used. We used the seventh Joint National

160   Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

161   classification to define hypertension (stages 1 or 2; systolic blood pressure of at least 140

162   mm Hg or diastolic blood pressure of at least 90 mm Hg) or if the subject reported that,

163   he/she was currently being treated for hypertension. Dietary information was obtained

164   using a food frequency questionnaire. Level of physical activity during the previous year

165   was estimated through self-reports. Anthropometric data were collected with participants

166   wearing scrub suits. Diabetes mellitus was considered present if a subject was taking

167   hypoglycemic agents, if a physician had told the subject that he/she had diabetes mellitus,

168   or if fasting glucose was above 7 mmol/L. Prevalent CHD was defined as a self-reported

169   history of myocardial infarction, percutaneous transluminal coronary angioplasty, or

170   coronary artery bypass graft. All variables used in these analyses were ascertained during

171   the initial examination (1993-1995) except for CAC scores, which were obtained during a

172   follow-up examination (2002-2003).

173   *6. Statistical analysis*

174   CAC was dichotomized into Agatston CAC score of 100+ versus less than 100, as

175   described previously.[17] To correct for the effect of familial clustering, we used

176   generalized estimating equations to calculate the prevalence odds ratios with

177   corresponding 95% confidence interval for the presence of CAC across categories of egg

178   consumption. Model 1 was adjusted for age (continuous) and sex. Model 2 adjusted for

179   age, sex, field center, body mass index (continuous), smoking (current smoker Y/N),

180   alcohol intake (current alcohol intake Y/N), physical activity (quartiles of total MET-

181   min/wk), income (<$25,000, $25,000-<$75,000, ≥$75,000), bacon consumption (almost

182   never, 1-3/month, 1/week, and 2+/week), and caloric intake (continuous). Model 3 was

183   additionally adjusted for history of hypertension (yes/no) and diabetes (yes/no).

184   In secondary analysis, we calculated the odds ratio per SD using different CAC cut-

185   points (CAC >0 and CAC>50) as well as sex-specific analyses. All analyses were

186   completed using SAS, version 9.2 (SAS institute Inc, Cary, NC). All p –values were 2-

187   tailed and significance level was set at an alpha of 0.05.

188   **Results**

189   Of the total 1848 subjects, 41% were men and the mean age was 56.5 years.

190   **Table 1** shows the baseline characteristics by categories of egg consumption. Egg

191   consumption was associated with younger age, higher body mass index, larger waist

192   circumference, male sex, current smoking status; higher intake of dietary fiber, dietary

193   cholesterol, saturated fat, magnesium, and total calories; and lower HDL. Subjects

194   reporting egg consumption were less likely to exercise, and more likely to have diabetes

195   mellitus. Of the 496 patients who consumed 2 eggs or more per week: 394 (79%)

196   consumed 2-4/week; 10.1% consumed 5-6 eggs/wk; 7.9% consumed 1egg/day; 2.4%

197   consumed 2-3 eggs/day; 0.2% consumed 4-6 eggs/day; and 0% consumed 6+ eggs/day.

198   There was no association between egg consumption and prevalent CAC.

199   Compared to subjects reporting almost no egg consumption, multivariable adjusted odds

200   ratio (95% CI) for CAC of 100+ were 1 (reference), 0.95 (0.66-1.38), 0.94 (0.63-1.40),

201   and 0.90 (0.57-1.42) among subjects reporting egg consumption of <1/month, 1-3/month,

202   1/week, and 2+/week, respectively (p for linear trend 0.66, **Table 2**), adjusting for age,

203   sex, BMI, smoking, alcohol, physical activity, income, field center, total calories, and

204 bacon. Further adjustment for hypertension and diabetes in the same model did not alter

205 the conclusion: adjusted odds ratios were 1 (reference), 0.93 (0.64-1.34), 0.88 (0.58-1.32),

206 and 0.90 (0.57-1.42) from the lowest to highest category of egg consumption,

207 respectively (p for linear trend, 0.62, Table 2). Analysis restricted to individuals with

208 diabetes mellitus or fasting glucose > 126 mg/dL did not show a significant association

209 between egg consumption and prevalent CAC: adjusted odds ratios were 1 (reference),

210 1.28 (0.44-3.74), 1.29 (0.45-3.64), and 1.21 (0.36-4.09) among increasing categories of

211 egg consumption, respectively (p for linear trend 0.76).

212   In a sensitivity analysis, there was no evidence of association between egg

213 consumption and prevalent CAC when CAC cut points of 0 and 50 were used. Using

214 CAC cut point of 0 to define prevalent CAC, the fully adjusted model showed adjusted

215 odds ratios of 1 (reference), 0.97 (0.67-1.39), 0.99 (0.68-1.45), and 0.77 (0.52-1.14) from

216 the lowest to highest category of egg consumption, respectively (p for linear trend, 0.22).

217 Corresponding values with CAC cutpoint of 50 were 1 (reference), 1.23 (0.56-1.76), 1.05

218 (0.71-1.57), and 0.95 (0.62-1.45), respectively (p for linear trend, 0.62). Further

219 adjustments for hypertension and diabetes and analyses restricted to diabetic individuals

220 did not change the conclusions.

221 **Discussion**

222   In this study, we did not find an association between egg consumption and prevalent

223 CAC in adult subjects free of prevalent CHD. The fully adjusted model and an additional

224 model controlling for both hypertension and diabetes did not show an association. The

225 lack of association was also observed when using CAC cut points of 0 and 50 and when

226   analyses were restricted to individuals with diabetes mellitus.

227   There has been a significant research interest in egg consumption as a possible

228   mediator for cardiovascular disease owing to the large amount of dietary cholesterol in

229   eggs. Other studies have investigated the effects of egg consumption on coronary heart

230   disease[18-20], stroke[21], and carotid artery plaque burden.[22] More recently, Chagas et al.

231   found an inverse association between egg consumption and coronary atherosclerotic

232   burden as determined by angiography. [23] To our knowledge, this is the first study to

233   examine whether egg consumption is associated with prevalent CAC.

234   While one prospective cohort of 514 Australian Aborigines with ~14 years of follow-

235   up showed an increased risk of CHD in subjects consuming >2 eggs per week[18], the

236   majority of prospective cohort studies have found no association between egg

237   consumption and risk of CHD.[19-20] The latter finding was further supported by a recent

238   meta-analysis of six studies between 1999-2011.[4] However, another recent systematic

239   meta-analysis found a dose-response relationship between egg consumption and both

240   cardiovascular disease (CVD) and diabetes.[5] In the analysis by Li et al[5], twelve relevant

241   papers were selected using coronary heart disease, ischemic heart disease, and congestive

242   heart failure as CVD outcomes. Their findings of increased risk of CVD with increasing

243   egg consumption contrasts with the majority of findings in recent literature, while the

244   positive association between egg consumption and risk of CVD in both diabetic men and

245   women in the US has been supported by few studies.[19-20] Indeed, in a prospective cohort

246   study of Greek adult diabetics, consumption of one egg (~40gm) was associated with a

247   fivefold increased risk of death by CHD.[24]

248   The relationship between egg nutrient components, namely cholesterol, and their

249   cardiometabolic effects remains unclear. Physiologic evidence has supported individual

250   variation (hyperresponders vs. hyporesponders) in fasting lipid responses to dietary

251   cholesterol.[25] Epidemiological data from a meta-analysis that included over 500 patients

252   across three continents, however, showed that dietary cholesterol significantly increased

253   the total to HDL- cholesterol ratio, suggesting the increase in protective HDL is offset by

254   a greater rise in LDL and other non-HDL cholesterol.[26] More recent evidence suggests

255   that postprandial oxidative stress and inflammation from dietary cholesterol may confer

256   risk independent of lipid profiles.[27] Furthermore, the phosphatidylcholine (lecithin)

257   content of eggs may confer CVD risk independently of changes in lipid profile; recent

258   research has demonstrated that its pro-atherosclerotic metabolite, trimethylamine-N-oxide

259   (TMAO), is associated with increased incident risk of major CVD events.[28]

260   Individuals with diabetes have demonstrated abnormal cholesterol profiles and may

261   have impaired cholesterol transport. [29-30] The influence of egg on the cholesterol profile in

262   an abnormal host could help explain the increased risk of CHD in diabetic populations.

263   Our analysis, however, did not reveal a significant association between increasing egg

264   consumption and prevalent CAC in individuals with diabetes mellitus, suggesting that the

265   development of atherosclerotic coronary artery disease may not be significantly

266   influenced by egg consumption. Alternatively, egg consumption might be associated with

267   other healthful factors that could offset any detrimental effects of dietary cholesterol or

268   glycerolipid species contained in eggs.

269   Limitations of the current study include its observational design, self-reported egg

270   consumption that could have been inaccurate, and a lack of details on how eggs were

271   consumed (e.g. egg with or without yolk, fried egg, boiled egg). Furthermore, eggs are

272   often consumed in conjunction with other food items, including processed red meats and

273   breadstuffs; thus egg consumption may be a marker of specific dietary patterns. We only

274   had baseline dietary assessment and were unable to capture changes in dietary habits that

275   may have occurred over time and could affect CAC outcomes. It is also possible that a

276   lack of an association between egg consumption and CAC may be partially due to a

277   younger age of our population and the fact that coronary calcium assessment may only

278   identify calcified plaques. The subgroup analysis of diabetic individuals had a small

279   sample size and thus our ability to draw conclusions is limited. Furthermore, we had one

280   single measurement of CAC and cannot account for change in CAC over time nor

281   distinguish CAC development unrelated to egg intake.

282   Strengths of this study include the detailed dietary questionnaire; a large sample size;

283   and robustness of findings in sensitivity analyses using various cut points to define

284   prevalent CAC.

285   In conclusion, we found no relationship between egg consumption and prevalent

286   CAC in this population.

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297   **Conflict of interest:**

298   None of the authors has a conflict of interest to disclose.

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397

398   **Table 1**

399   Characteristics among 1848 participants of the NHLBI Family Heart Study according

400   to egg consumption

		Frequency of Egg Consumption				
		Almost Never (n = 361)	1-3/month (n = 476)	1/week (n = 515)	2+/week (n = 496)	p for linear trend
Age (y)		58.4 ± 12.8	55.6 ± 12.8	56.6 ± 13.0	55.7 ± 12.8	0.0110
BMI (kg/m^2)		28.0 ± 5.4	28.5 ± 5.4	28.8 ± 5.7	29.6 ± 5.9	<0.0001
Male (%)		38.0	38.5	39.6	48.2	0.0017
Current Smoker (%)		8.0	6.9	9.3	12.3	0.0096
Current Drinker (%)		50.1	54.6	51.3	49.2	0.4502
History of hypertension (%)		32.4	35.9	40.8	34.9	0.3046
History of diabetes (%)		7.8	7.8	10.9	11.1	0.0345
Income (%)						
	<$25,000	12.7	12.8	11.8	11.5	0.4874
	$25,000 - <$75,000	51.8	49.6	55.2	59.9	0.0031
	≥$75,000	35.5	37.6	33.0	28.6	0.0083
Almost never eats bacon (%)		80.3	55.3	38.8	25.0	<0.0001
LDL (mg/dl)		114.3 ± 32.2	112.3 ± 31.5	114.2 ± 33.8	112.7 ± 34.7	0.6964
HDL (mg/dl)		50.2 ± 13.4	50.1 ± 14.9	49.9 ± 15.0	47.9 ± 14.3	0.0220
Waist Circumference (cm)		95.8 ± 15.4	97.4 ± 16.0	98.3 ± 16.0	100.9 ± 16.1	<0.0001
Exercise (MET-min/week)		825.7 ± 1294.7	760.0 ± 874.1	661.0 ± 895.9	684.8 ± 1060.2	0.0191
Fruit and Veg (s/day)		4.7 ± 2.4	4.2 ± 2.4	4.0 ± 2.3	4.0 ± 2.5	0.0873
Dietary Fiber (g/d)		16.4 ± 7.8	16.0 ± 7.2	16.1 ± 7.3	18.0 ± 8.3	0.0021
Calories (kcal/d)		1545.1 ± 555.7	1639.9 ± 7.2	1726.3 ± 569.4	2008.5 ± 636.8	<0.0001
Saturated fat (g/d)		17.9 ± 9.8	20.5 ± 9.8	22.2 ± 9.5	27.7 ± 11.1	<0.0001
Dietary Magnesium (mg/d)		241.2 ± 87.8	250.0 ± 91.4	255.7 ± 89.4	283.2 ± 102.2	<0.0001
Dietary Cholesterol (g/d)		162.8 ± 83.8	196.0 ± 86.1	223.3 ± 89.4	344.5 ± 131.7	<0.0001

401

402

403   **Table 2**

404   Prevalence odds ratios (95% confidence intervals) of calcified atherosclerotic plaque

405   in the coronary arteries according to egg consumption in 1848 participants in the

406   NHLBI Family Heart Study.

407

Frequency of Egg Consumption	Cases/n	Crude	Age and Sex adjusted	Model 2 [a]	Model 3 [b]
Almost never	97/361	1.00	1.00	1.00	1.00
1-3/month	104/476	0.76 (0.57-1.02)	0.96 (0.58-1.37)	0.95 (0.66-1.38)	0.93 (0.64-1.34)
1/week	124/515	0.86 (0.64-1.17)	0.98 (0.67-1.42)	0.94 (0.63-1.40)	0.88 (0.58-1.32)
2+/week	110/496	0.78 (0.57-1.06)	0.79 (0.54-1.16)	0.90 (0.57-1.42)	0.90 (0.57-1.42)
p for trend		0.2410	0.2639	0.6600	0.6213

408

409   [a] Adjusted for age, sex, BMI, smoking, alcohol, physical activity, income, field center,

410   total calories, bacon

411   [b] Adjusted as in model 2 plus additional adjustment for hypertension and diabetes

412   mellitus

413