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Egg consumption, cholesterol intake, and risk of incident stroke in men: the Kuopio Ischaemic Heart Disease Risk Factor Study

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ABSTRACT

Background: Epidemiologic studies suggest inverse associations between consumption of egg, a major source of dietary cholesterol, and stroke. However, the evidence of the relation remains limited, especially among carriers of apolipoprotein E4 (apoE4), which influences cholesterol metabolism.

Objective: The aim of this study was to investigate associations of egg and cholesterol intakes with risk of stroke and with the major stroke risk factor, blood pressure, in middle-aged and older men from eastern Finland and whether apoE phenotype could modify these associations.

Methods: A total of 1950 men aged 42–60 y in 1984–1989 were included at the baseline examinations of the prospective population-based Kuopio Ischaemic Heart Disease Risk Factor Study. Data on apoE phenotype were available for 1015 men. Dietary intakes were assessed with 4-d food records at baseline and incident stroke events were assessed by record linkage to hospital discharge registries. Cox proportional hazards regression analyses were used to estimate associations with stroke risk. Associations with baseline blood pressure were evaluated with ANCOVA.

Results: During the mean ± SD follow-up of 21.2 ± 7.2 y, there were 217 incidences of any stroke: 166 of ischemic stroke and 55 of hemorrhagic stroke. Comparing the highest egg intake quartile with the lowest, the multivariable-adjusted HRs were 0.81 for total stroke (95% CI: 0.54, 1.23; *P*-trend = 0.32), 0.84 for ischemic stroke (95% CI: 0.53, 1.34; *P*-trend = 0.44), and 0.75 for hemorrhagic stroke (95% CI: 0.32, 1.77; *P*-trend = 0.40). The respective HRs for the highest cholesterol intake quartile compared with the lowest were 0.86 (95% CI: 0.57, 1.32; *P*-trend = 0.42), 0.74 (95% CI: 0.46, 1.20; *P*-trend = 0.32), and 1.10 (95% CI: 0.45, 2.66; *P*-trend = 0.75). Diastolic blood pressure was 1.6 mm Hg (*P*-trend = 0.04) lower in the highest egg intake quartile compared with the lowest, but there were no associations with systolic blood pressure or with cholesterol intake. ApoE phenotype (32% had apoE4 phenotype) did not modify the associations.

Conclusion: Neither egg nor cholesterol intakes were associated with stroke risk in this cohort, regardless of apoE phenotype. This trial was registered at www.clinicaltrials.gov as NCT03221127. *Am J Clin Nutr* 2019;110:169–176.

Keywords: eggs, cholesterol, stroke, apolipoprotein e4, prospective study

Introduction

Stroke is one of the leading causes of global noncommunicable disease mortality and disability (1, 2). Prevention strategies are aimed toward reducing risk from modifiable factors, including dietary habits (3). Dietary recommendations on egg consumption, particularly yolk, have historically been restrictive because of the high amount of cholesterol in egg (~200 mg per medium-sized egg).

Relatively few studies have investigated the associations of egg or cholesterol intakes with risk of stroke, and especially with different types of stroke. Recent meta-analyses controversially indicate there to be either increased (4) or no association (5, 6) between cholesterol intake and stroke risk; however, egg consumption has been associated with both slightly lower (7, 8) and higher (4) risk of total stroke. In contrast, no associations between consumption of up to ~1 egg/d and risk of stroke were found in most earlier meta-analyses (9, 10), with the exception of one (9) reporting inverse associations with hemorrhagic stroke.

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Data described in this article will not be made available, because they contain sensitive personal data of the subjects, which cannot be completely anonymized.

Supplemental Figure 1 and Supplemental Tables 1–4 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: apoE, apolipoprotein E; CAD, coronary artery disease; ICD, International Classification of Diseases; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study.

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High blood pressure is a major risk factor for stroke (11), but few studies have reported on the associations of egg or cholesterol intakes with blood pressure. In 1 study, egg consumption was associated with lower systolic and diastolic blood pressure (8), whereas other studies found that cholesterol intake and systolic blood pressure were positively associated (12, 13).

For the general population, dietary cholesterol has only a modest effect on serum cholesterol concentrations (14). However, the influence of dietary cholesterol on serum LDL cholesterol concentrations is more pronounced among those with genetic susceptibility, such as phenotypic apolipoprotein E (apoE) allele 4 (apoE4) (15). The prevalence of the apoE4 phenotype is exceptionally common among Finns, with about one-third of the Finnish population possessing ≥1 E4 allele (16). The apoE4 phenotype is associated with higher cardiovascular disease and stroke risk (17, 18). We recently reported that higher egg or cholesterol intakes were not associated with less favorable lipid profiles or greater coronary artery disease (CAD) risk, even among apoE4 carriers, among middle-aged and older eastern Finnish men in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) (19). However, there is no information on whether apoE phenotype could modify the associations between egg or cholesterol consumption and stroke risk.

Because of the limited evidence, we investigated the associations of egg and cholesterol intakes with the risk of incident stroke and with baseline systolic and diastolic blood pressure in men from the KIHD. As a secondary analysis, we elucidated whether these associations differ between apoE4 phenotype carriers and noncarriers within a subgroup of 1015 men.

Methods

Study population

The KIHD was designed to investigate risk factors for cardiovascular disease and related outcomes in a population-based sample of men from eastern Finland (20). The baseline examinations were carried out in 1984–1989. All men who were 42, 48, 54, or 60 y old and living in the city of Kuopio and surrounding rural communities during the baseline examinations were invited to participate in the KIHD. Of the 3235 eligible men, 2682 men (82.9%) participated in the baseline examinations in 2 cohorts. The first cohort consisted of 1166 54-y-old men, enrolled in 1984–1986, and the second cohort included 1516 men aged 42, 48, 54, or 60 y, enrolled in 1986–1989. The baseline characteristics of the entire study population have been described previously (21). The KIHD study protocol was approved by the Research Ethics Committee of the University of Kuopio. All subjects gave written informed consent for participation.

Subjects with history of stroke ($n = 69$) or CAD ($n = 640$) at baseline, or with missing data on dietary intakes ($n = 23$), were excluded, leaving 1950 men for the analyses of incident stroke (**Supplemental Figure 1**). Data for systolic and diastolic blood pressure were available for 99% of men ($n = 1939$) and data for apoE phenotype for 52% of men ($n = 1015$).

Assessment of dietary intakes

The consumption of foods was assessed at baseline in 1984–1989 with the use of a 4-d guided food record, 1 d of which was a weekend day, by using household measures. A picture book of common foods and dishes was used to help in the estimation of portion sizes. The picture book contained 126 of the most common foods and drinks that are consumed in Finland and, for each food item, the participant could choose from 3–5 commonly used portion sizes or describe the portion size in relation to those in the book. To further improve accuracy, instructions were given, and completed food records were checked by a nutritionist together with the participant. Nutrient intakes were estimated with the use of NUTRICA version 2.5 software (Social Insurance Institution, Finland). The databank of the software is mainly based on Finnish values for the nutrient compositions of foods. Nutrient intakes were energy adjusted with the use of the residual method (22). The egg-consumption variable represented total egg consumption and included the intake of eggs in mixed dishes and recipes.

Assessment of stroke

Incident strokes in 1984–1992 were observed through the FINMONICA (Finnish Monitoring Trends and Determinants in Cardiovascular Diseases) stroke register (23). Information regarding the stroke incidence in 1993–2012 was collected through computerized linkage to the National Hospital Discharge Registry. Fatal stroke events were captured through computerized linkage to Statistics Finland's causes of death register. The diagnosis of stroke was based on sudden onset of clinical signs or local or global disturbance of cerebral function lasting ≥24 h (except in the case of sudden death or if interrupted by surgical intervention) with no apparent cause other than a vascular origin. Each suspected stroke [International Classification of Diseases (ICD)-9 codes 430–439 and ICD-10 codes I60–I68 and G45–G46] was classified into the following: a definite stroke, no stroke, or an unclassifiable stroke event. The FINMONICA stroke register data were annually rechecked with the data obtained from the computerized National Hospital Discharge Registry and the cause of death register. Definite strokes and unclassifiable events were included in the group of any stroke. Each definite stroke was classified into an ischemic stroke (ICD-9 codes 433–434; ICD-10 code I63) or a hemorrhagic stroke (ICD-9 codes 430–431; ICD-10 codes I60–I61). If the subject had multiple nonfatal strokes during follow-up, the first stroke was considered as the endpoint. In cases of suspected nonfatal stroke events, computed tomography or MRI was performed in 90% of the patients by 1993 and imaging reached 100% by 1997. All fatal strokes were confirmed with autopsy. Every resident of Finland has a unique personal identifier that is used in registers. There were very few losses to follow-up from subjects who moved abroad ($n = 3$).

Other measurements

Fasting venous blood samples were collected between 0800 and 1000 at the baseline examinations in 1984–1989. Subjects were instructed to abstain from ingesting alcohol for 3 d and from smoking and eating for 12 h before giving the sample. Resting blood pressure was measured 6 times with a random-zero mercury sphygmomanometer: 3 times in a supine position after a rest of 5 min before each measurement, 1 time in a standing position after a standing rest of 1 min, and 2 times in a sitting position after 5 min rest before both measurements. The mean

of each respective 6 values was used in the present analyses as the systolic and diastolic blood pressure. Detailed descriptions of the determination of serum lipids and lipoproteins (21) and the assessments of patient medical history and medication use (21), family history of diseases (21), smoking (21), alcohol intake (21), and leisure-time physical activity (24) have been previously published. Education in years and marital status were assessed with the use of a self-administered questionnaire. BMI was computed as kg/m^2. The apoE phenotype was determined from plasma with the use of isoelectric focusing and immunoblotting techniques. Subjects who had the phenotype 3/4 or 4/4 were included in the apoE4 group.

Statistical analysis

The univariate relations between egg and cholesterol intakes and baseline characteristics were assessed with the use of means and linear regression (for continuous variables) or chi-square tests (for bivariate relations). Cox proportional hazards regression models were used to estimate HRs for incident stroke in quartiles or tertiles of baseline egg and cholesterol intakes. Tertiles were used in the subgroup analyses stratified by the apoE4 phenotype owing to the lower number of incident events. The associations of egg and cholesterol intakes with systolic and diastolic blood pressure at baseline were analyzed with the use of ANCOVA.

Two statistical models were used to investigate the associations. Model 1 included age (years), examination year, and energy intake (kilocalories per day). The multivariable model (model 2) included the model 1 variables and BMI; pack-years of smoking (cigarette packs per day multiplied by years of smoking); leisure-time physical activity (kilocalories per day); use of hypertension medication; and intakes of alcohol (grams per week) and fruits, berries, and vegetables (grams per day). All quantitative variables were entered in the models as continuous variables. Further adjustment for education years, income, lipid-lowering medication, or intake of total meat, red meat, processed red meat, dairy, fiber, *trans* fatty acids, SFAs, MUFAs, or PUFAs did not appreciably change the associations (<5% change in estimates).

The cohort mean was used to replace missing values in covariates (<2.1% of the values). The significance of interactions on a multiplicative scale was assessed with the use of a stratified analysis and likelihood ratio tests with a cross-product term. Tests of linear trend were conducted by assigning the median values of each category of exposure variable and treating these as a single continuous variable. All P values were 2-tailed ($\alpha = 0.05$). Data were analyzed with the use of SPSS version 25.0 for Windows software (IBM Corp.).

Results

The mean ± SD consumption of eggs was 33 ± 26 g/d. The mean ± SD cholesterol intake was 408 ± 150 mg/d; 114 ± 87 mg/d (27.9%) of cholesterol intake was derived from eggs. Egg consumption and cholesterol intake had a correlation coefficient of 0.70 (P value <0.001). A total of 22 participants did not consume any eggs, and only 3 participants reported consumption of egg whites instead of whole eggs. About 16% of men ($n = 306$) consumed ≥1 egg (55 g)/d.

Participants that consumed more eggs were less likely to use hypertension-lowering medication, have hypertension, or smoke at baseline (**Table 1**). They were also more likely to have higher intakes of energy and SFAs, MUFAs, and dairy and lower intakes of PUFAs.

Men with higher cholesterol intake had fewer education years and were less physically active (Table 1). Their concentrations of serum total and LDL cholesterol were higher and they were more likely to smoke at baseline. They also had higher intakes of protein, SFAs, and MUFAs, and lower intakes of carbohydrates, PUFAs, and fruits, berries, and vegetables.

During the mean ± SD follow-up of 21.2 ± 7.2 y, 217 incident stroke events occurred, with 166 men diagnosed with ischemic stroke and 55 men with hemorrhagic stroke. Four men were diagnosed with both ischemic and hemorrhagic stroke events. We did not find any statistically significant associations between egg consumption and risk of total, ischemic, or hemorrhagic stroke (**Table 2**). No statistically significant associations were observed with cholesterol intake, either (**Table 3**). When evaluated continuously, each 1 egg/d higher consumption was associated with an HR of 0.89 (95% CI: 0.64, 1.22) for total stroke, 0.90 (95% CI: 0.62, 1.29) for ischemic stroke, and 0.73 (95% CI: 0.37, 1.44) for hemorrhagic stroke. The HRs of each 100 mg/d higher cholesterol intake were 0.98 (95% CI: 0.86, 1.12), 0.97 (95% CI: 0.83, 1.13), and 0.94 (95% CI: 0.71, 1.23) for total, ischemic, and hemorrhagic stroke, respectively.

Egg consumption was not associated with systolic blood pressure. Among those in the highest egg intake quartile compared with the lowest, there was a trend toward a 1.6 mm Hg lower diastolic blood pressure (95% CI: −0.1, 3.3 mm Hg, P value = 0.09) (P value for trend across the quartiles = 0.04, model 2, **Table 4**). Each additional 1 egg/d consumed was associated with a trend toward a 0.8 mm Hg lower diastolic blood pressure (95% CI: −1.8, 0.1 mm Hg, P value = 0.09). Cholesterol intake was not associated with blood pressure (Table 4).

Among the 1015 men with available apoE phenotype data, 287 (28.3%) were carriers of allele 3/4 and 40 (3.9%) of allele 4/4 (**Supplemental Table 1**). Those with the apoE4 phenotype were not at increased stroke risk when compared with noncarriers for total (multivariable-adjusted HR: 0.78; 95% CI: 0.50, 1.20; 29 events among apoE4 carriers and 75 among noncarriers), ischemic (HR: 0.80; 95% CI: 0.49, 1.30; 23 events among carriers, 58 among noncarriers), or hemorrhagic stroke (HR: 0.46; 95% CI: 0.17, 1.24; 5 events among carriers, 21 among noncarriers). There was no statistically significant difference in the risk of total stroke or ischemic stroke associated with egg or cholesterol intake between carriers and noncarriers, although higher cholesterol intake was associated with lower risk of ischemic stroke among noncarriers (**Supplemental Tables 2** and **3**). For each 1 egg/d higher consumption, HR for total stroke was 0.73 (95% CI: 0.24, 2.16) for carriers and 0.58 (95% CI: 0.30, 1.11) for noncarriers of apoE4 (P for interaction = 0.91), in the multivariable model (model 2). For ischemic stroke, the respective HRs were 0.73 (95% CI: 0.22, 2.46) and 0.51 (95% CI: 0.24, 1.08) (P for interaction = 0.85). For each 100-mg/d higher cholesterol intake, the HRs for total stroke were 1.15 (95% CI: 0.79, 1.69) and 0.83 (95% CI: 0.65, 1.06) for apoE4 carriers and noncarriers, respectively (P for interaction = 0.19), and for ischemic stroke they were 1.13 (95% CI: 0.73, 1.73) and 0.76 (95% CI: 0.57, 1.01), respectively (P

TABLE 1 Baseline characteristics according to egg and cholesterol intakes in 1950 men from the Kuopio Ischaemic Heart Disease Risk Factor Study[1]

	Egg consumption in quartiles				Cholesterol intake in quartiles			
Characteristics	1 (<15 g/d)	2 (15–26 g/d)	3 (27–45 g/d)	4 (>45 g/d)	1 (<333 mg/d)	2 (333–387 mg/d)	3 (388–459 mg/d)	4 (>459 mg/d)
Participants	487	488	487	488	487	488	488	487
Median intake[2]	9	21	35	61	296	361	421	523
Age, y	52.8 ± 5.5	52.2 ± 5.4	52.1 ± 5.3	52.1 ± 5.1	52.3 ± 5.6	52.4 ± 5.4	52.7 ± 5.3	52.2 ± 5.1
Education, y	8.9 ± 3.7	9.3 ± 3.8	8.9 ± 3.5	8.9 ± 3.6	9.1 ± 3.8	9.3 ± 3.6	9.0 ± 3.7	8.6 ± 3.5*
Married or living as a couple, %	82	90	90	86*	88	86	88	85
Leisure-time physical activity, kcal/d	131 ± 158	132 ± 153	156 ± 204	135 ± 151	158 ± 206	141 ± 155	133 ± 159	122 ± 144*
BMI, kg/m^2	26.7 ± 3.5	26.6 ± 3.6	26.7 ± 3.4	26.6 ± 3.5	26.5 ± 3.5	26.5 ± 3.2	26.8 ± 3.7	26.9 ± 3.6
Serum total cholesterol, mmol/L	5.9 ± 1.2	5.9 ± 1.0	5.8 ± 1.1	5.9 ± 1.0	5.8 ± 1.1	5.9 ± 1.0	5.9 ± 1.1	6.0 ± 1.0*
Serum LDL cholesterol, mmol/L	4.1 ± 1.1	4.0 ± 1.0	4.0 ± 1.0	4.0 ± 0.9	3.9 ± 1.0	4.0 ± 1.0	4.0 ± 1.0	4.1 ± 1.0*
Serum HDL cholesterol, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3*
Serum triglyceride, mmol/L	1.3 ± 0.7	1.2 ± 0.7	1.3 ± 0.7	1.2 ± 0.8*	1.3 ± 0.8	1.3 ± 0.7	1.2 ± 0.7	1.2 ± 0.8*
Alcohol intake, g/wk	86.2 ± 133.0	62.6 ± 92.2	64.7 ± 101.9	76.1 ± 125.6	75.4 ± 139.2	73.1 ± 109.5	65.4 ± 94.5	75.7 ± 111.2
Hypertension medication at baseline, %	19	14	12	11*	17	15	13	12
Lipid-lowering medication at baseline, %	0.4	0.4	0.2	0.2	0.6	0.2	0.0	0.2
Hypertension, %	61	54	55	52*	56	59	54	53
Current smoker, %	37	31	25	26*	24	31	32	33*
Diabetes, %	6	4	5	4	3	5	5	5
Family history of stroke, %	22	19	22	18	20	21	20	18
Family history of coronary heart disease, %	49	48	42	47	47	46	47	45
Dietary intakes								
Energy, kcal/d	2260 ± 591	2417 ± 588	2503 ± 577	2711 ± 641*	2564 ± 596	2405 ± 575	2393 ± 660	2528 ± 633
Protein, E%	16.0 ± 2.7	15.6 ± 2.5	15.7 ± 2.4	15.7 ± 2.5	15.0 ± 2.3	15.7 ± 2.3	15.8 ± 2.6	16.4 ± 2.7*
Carbohydrates, E%	42.7 ± 6.8	43.5 ± 6.4	43.5 ± 5.8	42.0 ± 6.1*	46.7 ± 6.1	43.8 ± 5.6	41.6 ± 5.5	39.5 ± 5.6*
SFAs, E%	17.8 ± 4.4	17.9 ± 3.8	18.1 ± 3.7	18.7 ± 3.7*	15.8 ± 3.3	17.8 ± 3.4	19.0 ± 3.7	19.9 ± 4.0*
PUFAs, E%	4.6 ± 1.5	4.7 ± 1.6	4.4 ± 1.3	4.4 ± 1.2*	13.5 ± 4.6	11.6 ± 4.2	11.5 ± 4.3	11.8 ± 4.1*
MUFAs, E%	11.5 ± 2.1	11.8 ± 2.5	11.5 ± 1.2	12.0 ± 2.0*	11.2 ± 2.3	11.3 ± 2.0	11.9 ± 2.2	12.2 ± 2.1*
Trans fatty acids, E%	1.0 ± 0.4	1.1 ± 0.4	1.0 ± 0.3	1.0 ± 0.4	1.1 ± 0.5	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3*
Cholesterol, mg/d	337 ± 71	361 ± 73	405 ± 73	508 ± 110*	—	—	—	—
Egg, g/d	—	—	—	—	18 ± 12	23 ± 14	32 ± 17	59 ± 31*
Processed red meat	70 ± 61	70 ± 64	67 ± 55	73 ± 61	64 ± 57	63 ± 52	75 ± 66	77 ± 65*
Fruit, berries, and vegetables[3]	247 ± 178	260 ± 153	260 ± 147	268 ± 151	303 ± 180	254 ± 148	247 ± 153	232 ± 138*
Dairy	674 ± 381	666 ± 338	715 ± 345	772 ± 380*	721 ± 369	688 ± 351	679 ± 347	739 ± 384

[1]Values are means ± SDs unless otherwise indicated. *P*-trend was assessed with linear regression (continuous variables) or chi-square test (bivariate relations). *P-trend ≤ 0.05 across quartiles. E%, percent of energy.

[2]Median intakes are in grams per day for egg consumption and milligrams per day for cholesterol intake.

[3]Excluding potatoes.

TABLE 2 Risk of incident total stroke in 1950 men according to egg consumption at baseline in 1984–1989[1]

	Egg consumption in quartiles				
	1 (<15 g/d)	2 (15–26 g/d)	3 (27–45 g/d)	4 (>45 g/d)	*P*-trend
Participants	487	488	487	488	
Total stroke					
Events, *n* (%)	54 (11.1)	56 (11.5)	62 (12.7)	45 (9.2)	
Model 1[2]	1	0.95 (0.65, 1.38)	1.05 (0.72, 1.52)	0.77 (0.51, 1.16)	0.23
Model 2	1	1.01 (0.69, 1.47)	1.10 (0.76, 1.61)	0.81 (0.54, 1.23)	0.32
Ischemic stroke					
Events, *n* (%)	40 (8.2)	43 (8.8)	46 (9.5)	37 (7.6)	
Model 1	1	0.96 (0.63, 1.49)	1.02 (0.66, 1.57)	0.81 (0.51, 1.30)	0.39
Model 2	1	0.99 (0.64, 1.54)	1.04 (0.67, 1.60)	0.84 (0.53, 1.34)	0.44
Hemorrhagic stroke					
Events, *n* (%)	15 (3.1)	17 (3.5)	14 (2.9)	9 (1.8)	
Model 1	1	1.10 (0.55, 2.23)	0.95 (0.45, 2.01)	0.66 (0.28, 1.56)	0.31
Model 2	1	1.29 (0.63, 2.62)	1.09 (0.52, 2.31)	0.75 (0.32, 1.77)	0.40

[1]Values are HRs (95% CIs) derived by Cox proportional hazards regression models unless otherwise indicated.
[2]Model 1 was adjusted for age, examination year, and energy intake (kilocalories per day). Model 2 was adjusted as for model 1 plus BMI (kg/m^2), pack-years of smoking, leisure-time physical activity, hypertension medication, and intakes of alcohol and fruit, berries, and vegetables.

for interaction = 0.17). There were too few cases of hemorrhagic stroke for these stratified analyses. We did not find statistically significant differences in the associations of egg or cholesterol intakes with systolic or diastolic blood pressure between carriers and noncarriers of the apoE4 phenotype, either (**Supplemental Table 4**).

To assess whether the associations with stroke incidence were attenuated by a long follow-up period, we evaluated associations with events during the first 10 y of follow-up. During this midway follow-up, there were no statistically significant associations between egg or cholesterol intake and risk of total stroke ($n = 86$), ischemic stroke ($n = 62$), or hemorrhagic stroke ($n = 21$) cases, either. For each 1 egg/d higher consumption, the multivariate-adjusted HRs were 0.72 (95% CI: 0.41, 1.25) for total stroke, 0.70 (95% CI: 0.36, 1.37) for ischemic stroke, and 0.60 (95% CI: 0.19, 1.97) for hemorrhagic stroke. For each 100 mg/d higher cholesterol intake, the multivariate-adjusted HRs were 0.95 (95% CI: 0.76, 1.18) for total stroke, 0.93 (95% CI: 0.72, 1.21) for ischemic stroke, and 0.94 (95% CI: 0.60, 1.48) for hemorrhagic stroke.

Finally, the associations were not appreciably different if the analyses included only those men with complete data on all variables ($n = 1866$ men in the analyses with incident stroke, $n = 1861$ in the analyses with blood pressure, and $n = 967$ in the analyses with apoE4 phenotype). For example, the multivariable-adjusted (model 2) HRs were 0.81 (95% CI: 0.53, 1.25) for total stroke, 0.83 (95% CI: 0.51, 1.34) for ischemic stroke, and 0.75 (95% CI: 0.30, 1.88) for hemorrhagic stroke in the highest egg consumption quartile compared with the lowest, and 0.84 (95% CI: 0.54, 1.28) for total stroke, 0.73 (95% CI: 0.44, 1.18) for ischemic stroke, and 1.13 (95% CI: 0.44, 2.87) for hemorrhagic stroke in the highest cholesterol intake quartile compared with the lowest (other data not shown).

TABLE 3 Risk of incident total stroke in 1950 men according to cholesterol consumption at baseline in 1984–1989[1]

	Cholesterol intake in quartiles				
	1 (<333 mg/d)	2 (333–387 mg/d)	3 (388–459 mg/d)	4 (>459 mg/d)	*P*-trend
Participants	487	488	488	487	
Total stroke					
Events, *n* (%)	47 (9.7)	60 (12.3)	66 (13.5)	44 (9.0)	
Model 1[2]	1	1.22 (0.83, 1.79)	1.34 (0.92, 1.96)	0.91 (0.60, 1.34)	0.59
Model 2	1	1.22 (0.83, 1.79)	1.32 (0.90, 1.93)	0.86 (0.57, 1.32)	0.42
Ischemic stroke					
Events, *n* (%)	40 (8.2)	42 (8.6)	53 (10.9)	31 (6.4)	
Model 1	1	1.02 (0.66, 1.57)	1.28 (0.85, 1.95)	0.75 (0.47, 1.21)	0.34
Model 2	1	1.04 (0.67, 1.60)	1.28 (0.84, 1.95)	0.74 (0.46, 1.20)	0.32
Hemorrhagic stroke					
Events, *n* (%)	9 (1.8)	19 (3.9)	15 (3.1)	12 (2.5)	
Model 1	1	1.88 (0.84, 4.17)	1.43 (0.62, 3.10)	1.24 (0.52, 2.98)	0.99
Model 2	1	1.82 (0.82, 4.05)	1.38 (0.59, 3.22)	1.10 (0.45, 2.66)	0.75

[1]Values are HRs (95% CIs) derived by Cox proportional hazards regression models unless otherwise indicated.
[2]Model 1 was adjusted for age, examination year, and energy intake (kilocalories per day). Model 2 was adjusted as for model 1 plus BMI (kg/m^2), pack-years of smoking, leisure-time physical activity, hypertension medication, and intakes of alcohol and fruit, berries, and vegetables.

TABLE 4 Systolic and diastolic blood pressure according to egg and cholesterol intakes[1]

	Egg consumption quartile (g/d)					Cholesterol intake quartile (mg/d)				
	1 (<14) (n = 485)	2 (14–26) (n = 486)	3 (27–45) (n = 485)	4 (>45) (n = 484)	P-trend	1 (<333) (n = 485)	2 (333–387) (n = 487)	3 (388–459) (n = 485)	4 (>459) (n = 483)	P-trend
Systolic blood pressure, mm Hg										
Model 1[2]	135.1 (133.6, 136.5)	134.2 (132.7, 135.6)	134.0 (132.6, 135.5)	133.4 (131.9, 134.9)	0.17	133.8 (132.3, 135.3)	135.5 (134.0, 137.0)	133.9 (132.4, 135.3)	133.5 (132.0, 135.0)	0.45
Model 2	134.9 (133.5, 136.4)	134.3 (132.9, 135.7)	134.0 (132.6, 135.4)	133.4 (132.0, 134.9)	0.15	133.7 (132.3, 135.2)	135.7 (134.3, 137.1)	134.0 (132.6, 135.4)	133.3 (131.9, 134.7)	0.30
Diastolic blood pressure, mm Hg										
Model 1	90.2 (89.3, 91.2)	88.6 (87.6, 89.5)	88.6 (87.6, 89.5)	88.6 (87.7, 89.6)	0.06	88.8 (87.9, 89.7)	89.7 (88.8, 90.6)	88.8 (87.9, 89.7)	88.7 (87.7, 89.6)	0.51
Model 2	90.2 (89.3, 91.0)	88.7 (87.8, 89.5)	88.6 (87.7, 89.5)	88.6 (87.7, 89.5)	0.04	88.8 (88.0, 89.7)	89.8 (89.0, 90.7)	88.9 (88.0, 89.7)	88.4 (87.6, 89.3)	0.23

[1] Values are means (95% CIs) obtained by using ANCOVA unless otherwise indicated.
[2] Model 1 was adjusted for age, examination year, and energy intake (kilocalories per day). Model 2 was adjusted as for model 1 plus BMI (kg/m^2), pack-years of smoking, leisure-time physical activity, hypertension medication, and intakes of alcohol and fruit, berries, and vegetables.

Discussion

In this prospective cohort study of middle-aged and older eastern Finnish men, we did not find statistically significant associations between egg or cholesterol intake and risk of incident stroke. In addition, we found no evidence that the risk would be increased among apoE4 carriers, who are more susceptible to effects of dietary cholesterol. Furthermore, we did not find evidence that egg or cholesterol intakes were associated with elevated blood pressure, a major risk factor for stroke.

Our findings are consistent with most results from previous research examining egg consumption and stroke risk. Two meta-analyses from 2013 reported no association between egg consumption and overall stroke risk (9, 10), although one (9) reported a 25% lower risk of hemorrhagic stroke associated with higher egg consumption. An updated meta-analysis with 3 additional cohort studies from China (8) and Sweden (25) showed a slightly reduced risk (9%) in total stroke when consuming ≥1 egg/d (8). Similarly to our study, no associations were found with either ischemic or hemorrhagic stroke risk in this most recent meta-analysis. A recent pooled analysis of cohorts from the United States reported a modest increase in the risk of total stroke with higher egg intake; however, ischemic and hemorrhagic stroke were not separately analyzed (4).

The mean amount of egg consumed in the present cohort was comparable with the consumption in the previous meta-analyses, and thus probably does not explain the differences in results. An interesting contrast is observed between egg consumption and risk of stroke compared with risk of type 2 diabetes. Prospective studies of egg consumption and risk of type 2 diabetes have observed an increased risk primarily in studies conducted in the United States (26–28). This is hypothesized to reflect the unfavorable lifestyle factors often associated with higher egg consumption in studies from the United States, including higher consumption of red meat, smoking, and less physical activity (26–28). However, in the case of stroke risk, 1 meta-analysis found an inverse association between egg consumption and stroke risk mainly in the studies conducted in the United States (7), although this was not confirmed in the most recent pooled analysis of 6 studies from the United States (4). More research is undoubtedly needed to elucidate the impact of egg consumption on cardiovascular diseases.

In the present study, egg intake was associated with a modestly lower diastolic blood pressure, but not with systolic blood pressure. Likewise, observational studies have found higher egg consumption to be associated with lower blood pressure (8) and lower risk of hypertension incidence (29, 30). One randomized crossover intervention reported lack of association (31), whereas another nonrandomized crossover intervention reported an inverse association between egg consumption and diastolic blood pressure (32).

One possible mechanism for this beneficial effect on blood pressure may be egg white–derived ovotransferrin peptides that work similarly to antihypertensive medication, preventing vascular smooth muscle remodeling via inhibition of angiotensin type 1 receptors (33). Another explanation could be attributed to phospholipids found in egg yolk that have been associated with enhanced endothelial vasodilatory function (34). A third explanation may relate to antioxidants in egg, which could ameliorate oxidative stress and vascular function and consequently

reduce blood pressure (35). The evidence is still inconclusive, and more research is necessary to explicate the association of egg consumption with blood pressure and, therefore, stroke risk (7–9).

We did not find associations between cholesterol intake and stroke risk, a finding that corroborates most previous studies. For example, 2 meta-analyses indicated no statistically significant associations between cholesterol intake and ischemic or hemorrhagic stroke risk (5, 6). On the other hand, another recently published pooled analysis found cholesterol intake to be associated with higher total stroke risk (4). In addition, a few observational studies have found higher cholesterol intake to be associated with higher systolic blood pressure (12, 13), an observation that we did not find. Owing to the scarce epidemiological and experimental evidence, the role of dietary cholesterol in blood pressure regulation remains largely uncertain.

To our knowledge, no other study has investigated the relation of egg consumption with stroke risk among those more sensitive to dietary cholesterol intake, i.e., apoE4 carriers. Our results showed no evidence that egg or cholesterol intakes would be associated with higher stroke risk or with high blood pressure among apoE4 carriers. These findings are in accordance with our previous observations in this study population, where we found that higher egg or cholesterol intakes were not associated with risk of CAD, carotid atherosclerosis, or hypercholesterolemia among apoE4 carriers (19).

Strengths of this study include the prospective design, very little loss to follow-up, and information on several potential confounders. Limitations of the study include the inherent bias and random error associated with dietary assessment methods; also, the dietary intakes, being assessed only at baseline, may not reflect accurate or long-term intake. Even though these limitations provide opportunity for misclassification that can potentially attenuate associations in analyses with long follow-up periods, the similar results we observed in the midway 10-y follow-up corroborate our findings. Furthermore, the average egg consumption in Finland has been fairly consistent over the past 40 y (36). Although egg intakes in mixed dishes and baked goods were collected, different preparation methods not accounted for could influence associations with stroke risk. In addition, there may also be residual confounding by unmeasured or incompletely measured factors that may have influenced the findings. The median intakes in the highest quartile were 61 g/d for egg and 523 mg/d for cholesterol, therefore our results may not be applicable to populations with higher intakes. The variability in egg consumption might have been too low to observe significant associations. However, we have previously reported that egg consumption was associated with lower fasting plasma glucose and serum C-reactive protein and with lower risk of type 2 diabetes (37) and with better performance on neuropsychological tests (38) in this study population, suggesting sufficient variability for finding associations also with stroke risk. The number of hemorrhagic stroke events was low, so these results should be interpreted with caution. Similarly, the data on the apoE phenotype were available only for a part of the study population, so the findings may not represent the whole study population. The associations between egg and cholesterol intakes and blood pressure were cross-sectional and therefore by design do not infer temporal associations. Because this study only consisted of middle-aged and older men from eastern Finland, the results cannot be extrapolated to women or other ethnicities.

In conclusion, neither egg nor cholesterol intakes were associated with stroke risk in this cohort, regardless of apoE phenotype.

The authors' responsibilities were as follows—HEKV, SV, T-PT, SK, and JKV: acquired the data and designed and conducted the research; AMA and JKV: analyzed the data; AMA: drafted the manuscript; JKV: had primary responsibility for the final content; HEKV, SV, SK, T-PT, JTS, and JKV: critically revised the manuscript for important intellectual content; and all authors: read and approved the final manuscript. JKV reports that he received a speaker's fee from the Finnish egg producer company Munax Ltd. None of the other authors reported a conflict of interest related to the study.

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