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Association of dietary cholesterol and egg intakes with the risk of incident dementia or Alzheimer disease: the Kuopio Ischaemic Heart Disease Risk Factor Study[1,2]

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ABSTRACT

Background: There is little information about the associations of intakes of cholesterol and eggs, a major source of dietary cholesterol, with the risk of cognitive decline in general populations or in carriers of apolipoprotein E ε4 (*APO-E4*), a major risk factor for dementia.

Objective: We investigated the associations of cholesterol and egg intakes with incident dementia, Alzheimer disease (AD), and cognitive performance in middle-aged and older men from Eastern Finland.

Design: A total of 2497 dementia-free men, aged 42–60 y in 1984–1989 at the baseline examinations of the prospective, population-based Kuopio Ischaemic Heart Disease Risk Factor Study, were included in the study. Information on the apolipoprotein E (Apo-E) phenotype was available for 1259 men. Data on cognitive performance tests at the 4-y re-examinations were available for 480 men. Dietary intakes were assessed with the use of 4-d food records at baseline. Dementia and AD diagnoses were based on Finnish health registers. Cox regression and ANCOVA were used for the analyses.

Results: During the 21.9-y follow-up, 337 men were diagnosed with dementia, and 266 men were diagnosed with AD. Neither cholesterol nor egg intake was associated with a higher risk of incident dementia or AD. For example, when evaluated continuously, each intake of 100 mg cholesterol/d was associated with a multivariable-adjusted HR of 0.90 (95% CI: 0.79, 1.02) for incident dementia, and each additional 0.5 egg (27 g)/d was associated with an HR of 0.89 (95% CI: 0.78, 1.01). However, egg intake was associated with better performance on neuropsychological tests of the frontal lobe and executive functioning, the Trail Making Test, and the Verbal Fluency Test. The Apo-E4 phenotype did not modify the associations of cholesterol or egg intake (P-interactions > 0.11).

Conclusions: Neither cholesterol nor egg intake is associated with an increased risk of incident dementia or AD in Eastern Finnish men. Instead, moderate egg intake may have a beneficial association with certain areas of cognitive performance. *Am J Clin Nutr* doi: 10.3945/ajcn.116.146753.

Keywords: Alzheimer disease, apolipoprotein E4, cholesterol, cognitive function, cognitive performance, dementia, eggs, population study

INTRODUCTION

The prevalence of dementia is expected to triple by the year 2050, when there will be >115 million people in the world who are suffering from dementia (1). A high serum cholesterol concentration is a known risk factor for cardiovascular diseases (CVDs)[5] (2) and for dementia (3). Furthermore, Alzheimer disease (AD) and CVD share the same risk gene, apolipoprotein E ε4 (*APO-E4*) (4). The prevalence of *APO-E4* varies worldwide (5), but in Finland, one-third of the population has ≥1 of the ε4 alleles (6).

Egg has traditionally been stigmatized with warnings because of its high content of cholesterol, but recent studies have challenged the role of dietary cholesterol or egg intake in disease etiology (7, 8). For most people, the effect of dietary cholesterol on plasma cholesterol concentrations is minor (9), and cholesterol or egg intake has not been shown to be associated with CVD risk in general populations (8, 10, 11). The impact of dietary cholesterol on serum cholesterol is enhanced in *APO-E4* carriers (12), but dietary cholesterol or egg intake has not been associated with a higher CVD risk in these carriers either (13). There has been a limited number of studies concerning the impact of dietary cholesterol on dementia risk, and most of the studies have been conducted with the use of animals. These experiments have shown an association between dietary cholesterol and AD-type pathologies (14–18), but such associations have not been shown in human studies (19, 20). To the best of our knowledge, the impact of egg intake on incident dementia risk has not been studied before, although some studies have shown a beneficial association with mild cognitive impairment (21, 22).

[1] The authors reported no funding received for this study.

[2] Supplemental Figure 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[5] Abbreviations used: AD, Alzheimer disease; Apo-E4, apolipoprotein E ε4; CRP, C-reactive protein; ICD, International Classification of Diseases; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; SRR, Special Reimbursement Register.

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In this study we examined the associations of cholesterol and egg intakes with incident dementia in 2497 men from Eastern Finland. In a subset of 1259 men, we investigated whether the Apo-E4 phenotype modified the associations. We also examined the associations of cholesterol and egg intakes with cognitive performance 4 y after the baseline examinations in a subset of 480 men.

METHODS

Study population

The KIHD (Kuopio Ischaemic Heart Disease Risk Factor Study) was designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in a prospective, population-based sample of men from Eastern Finland (23). Baseline examinations were carried out in 1984–1989. A total of 2682 men aged 42, 48, 54, or 60 y at baseline (82.9% of eligible men) were recruited in 2 cohorts (**Supplemental Figure 1**). The first cohort consisted of 1166 men who were 54 y old and were enrolled in 1984–1986, and the second cohort included 1516 men who were 42, 48, 54 or 60 y old and were enrolled in 1986–1989. The baseline examinations were followed by the 4-y examination round in 1991–1993 in which 1038 men from the second cohort (88% of eligible subjects) participated. Baseline characteristics of the entire study population have been described previously (24). The KIHD protocol was approved by the Research Ethics Committee of the University of Kuopio. All subjects gave written informed consent for participation.

Cholesterol and egg intakes and dementia incidence

Subjects with a history of a mental problem (including dementia) at baseline (n = 144) or with missing diet data (n = 41) were excluded, which left 2497 men for the analyses of incident dementia.

Cholesterol and egg intakes and dementia incidence: influence of Apo-E phenotype

The Apo-E phenotype was determined from blood samples of 1033 men who participated in the 4-y examinations and from 307 other men from the baseline examinations for whom blood samples for phenotyping were available. Of these 1340 men, subjects with a history of a mental problem at baseline (n = 70) or with missing diet information (n = 11) were excluded, which left 1259 men for the analyses of incident dementia. Compared with subjects without data on the Apo-E phenotype, subjects with these data were, in general, healthier and had more favorable lifestyles and dietary habits, although their serum lipid and lipoprotein profiles were less favorable (13).

Cholesterol and egg intakes and cognitive performance

Cognitive performance tests at the 4-y examinations in 1991–1993 were performed by 519 of 555 men who belonged to the 2 oldest age groups at the baseline examinations in 1986–1989 (i.e. men who were 54 or 60 y old). Of these men, we excluded individuals with a history of a mental problem (n = 31) or with missing diet (n = 6) or Apo-E phenotype (n = 2) data, which left 480 men for the analyses. We did not have data on cognitive performance tests at baseline.

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 to 5 commonly used portion sizes or could 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 a participant. Nutrient intakes were estimated with the use of NUTRICA 2.5 software (Social Insurance Institution). The databank of the software is mainly based on Finnish values of the nutrient compositions of foods. Nutrient intakes were energy adjusted with the use of the residual method. The egg-consumption variable represented total egg consumption and included the intake of eggs in mixed dishes and recipes.

Measurements

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. Detailed descriptions of the determination of serum lipids and lipoproteins (25) and the assessments of patient medical history and medication use at baseline (25), family history of diseases (25), smoking (25), alcohol intake (25), blood pressure (25), and physical activity (26) were previously published. Serum high-sensitivity C-reactive protein (CRP) was measured with the use of an immunometric assay (Immulite High Sensitivity CRP Assay; DPC). Education was assessed in years with the use of a self-administered questionnaire. The Apo-E 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 Apo-E4 group.

Neuropsychological tests

At the 4-y examinations in 1991–1993, cognitive function was measured with the use of the following 5 neuropsychological tests: the Mini-Mental State Examination, the Trail Making Test, the Verbal Fluency Test, the Selective Reminding Test, and Russell's adaptation of the Visual Reproduction Test (27–31). The tests were administered by interviewers who were trained in neuropsychological assessment. Each of the tests has been validated in the Finnish population (32).

The Mini-Mental State Examination has been widely used in both population-based and clinical research to test for the presence of cognitive impairment and as a screening tool for dementia. The test assesses orientation (10 items), registration (3 items), attention and calculation (5 items), recall (3 items), and language (9 items). A correct response to each item scores 1 (an incorrect response scores 0), and the scores are summed to give a potential maximum score of 30. Higher scores indicate better cognitive function.

The Trail Making Test is a test of frontal lobe functioning as indicated by perceptual motor speed, visual searching and

sequencing, and the ability to make alternating conceptual shifts (33). The original version of the test consisted of 2 parts (A and B), but in the current study, we used part A. Performance was judged in terms of the number of seconds that were required to complete the test.

The Verbal Fluency Test is a test of language performance that assesses an individual's ability to spontaneously produce words under the restrictions of a limited letter category and is also a test of frontal lobe functioning, particularly of the left frontal lobe (33). Participants were asked to generate as many words as possible that began with the letters P, A, and S; 60 s were allocated for each letter. Different forms of the same word and proper names of people or places were not counted as correct. Performance was assessed by counting the number of words produced during the 3-min period with higher scores indicating better language facility.

The Selective Reminding Test examines storage, retention, and the retrieval of information from short- and long-term memory and learning abilities. Participants were initially read 10 unrelated words in ~20 s and were asked to recall the entire list in any order. Participants were read only those words that they failed to recall after the first reading and were again asked to recall the entire list of 10 words. This procedure was repeated 6 times, and the participant's score was the total number of words recalled correctly (potential maximum score of 60).

Russell's adaptation of the Visual Reproduction Test examines visual memory for nonrepresentative figures (right temporal lobe functioning) and constructional ability. Participants were initially shown a single geometric figure for 10 s, after which the figure was removed from view, and the participant was required to draw the figure from memory. This procedure was repeated with a figure of greater complexity and then again for a third time, although on this occasion, the participant was asked to draw 2 figures. Scoring was based on the degree to which the participant was able to correctly and accurately replicate the figures (potential maximum score of 21).

Ascertainment of follow-up events

Three national health registers were used to identify incident cases of dementia or AD in the KIHD cohort by the end of the year 2014. Computer linkages to the Care Register (hospital-discharge data) (34) and Causes of Death register (35) were applied with the use of International Classification of Diseases (ICD)-8 code 290, ICD-9 codes 4378A and 290, and ICD-10 codes F00, F01, F02, F03, G30, and G31 to identify persons with dementia and ICD-8 codes 29000 and 29010, ICD-9 codes 290 and 3310A, and ICD-10 codes F00 and G30 were used to identify cases of AD. Since 1999, a few years after the first drugs for symptomatic treatment of AD were launched, a diagnosis of AD was recorded in the Special Reimbursement Register (SRR), which is maintained by the Social Insurance Institution of Finland. The SRR is often used as a clinical epidemiology data source for studies on specific chronic conditions (36, 37) including the prevalence and incidence of AD (38, 39). To receive a special reimbursement right, the patient has to be examined, diagnosed, and given a certificate by a medical doctor, who is usually a specialist. For a diagnosis of AD to be verified and recorded in the SRR, the following conditions are required: the person has *1*) symptoms consistent with AD, *2*) experienced a decrease in social capacity over a period ≥3 mo, *3*) received a computed tomography or MRI scan, *4*) had possible alternative diagnoses excluded, and *5*) received confirmation of the diagnosis by a registered neurologist or geriatrician. Each medical certificate is assessed by the Social Insurance Institution to ensure that a patient meets the diagnostic criteria for AD of the Diagnostic and Statistical Manual Version IV and of the National Institute of Neurological and Communicative Disorders–Alzheimer's Disease and Related Disorders Association for AD (40–42). Persons with mixed dementias of the AD and vascular and AD and Lewy body are also recorded. Linkage to the SRR was also used in the current study, and it proved to be strongest method to identify cases with AD in the KIHD cohort.

Statistical analysis

The univariate relations between cholesterol and egg 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 dementia and AD in quartiles of baseline cholesterol and egg intakes. The validity of the proportional hazards assumption was evaluated with the use of Schoenfeld residuals. The associations of baseline cholesterol and egg intakes with cognitive-performance tests at the 4-y examinations were analyzed with the use of an ANCOVA. Confounders in the analyses were selected on the basis of established risk factors for dementia, previously published associations with dementia (3), or associations with exposures or outcomes in the current analysis. Model 1 included age (years), examination year, and energy intake (kilocalories per day). The multivariable model (model 2) included model 1 variables and education years; smoking (cigarette packs per day multiplied by years of smoking); BMI (in kg/m^2); diabetes (yes or no); leisure-time physical activity (kilocalories per day); history of coronary artery disease (yes or no); use of a lipid-lowering medication during follow-up (yes or no); and intakes of alcohol (grams per week); fruits, berries, and vegetables (grams per day); carbohydrates (percentage of energy); and fiber (grams per day). Model 3 was adjusted as for model 2 and mutually for either egg intake (grams per day) or cholesterol intake (milligrams per day). Further adjustment for history of stroke, systolic or diastolic blood pressure, hypertension medication use, blood glucose, serum long-chain n–3 PUFAs, or intakes of coffee, SFAs, or PUFAs did not appreciably affect the associations (change in estimates: <5%). All quantitative variables were entered as continuous variables.

The cohort mean was used to replace missing values in covariates (<3.4%). 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 21.0 for Windows software (IBM Corp.).

RESULTS

Baseline characteristics

Mean ± SD energy-adjusted cholesterol intake was 401 ± 107 mg/d, and mean ± SD egg intake was 32 ± 25 g/d

TABLE 1
Baseline characteristics according to cholesterol and egg intakes in 2497 men in the KIHD[1]

	Cholesterol intake quartile, mg/d				Egg intake quartile, g/d			
	1 (<331)	2 (331–387)	3 (388–458)	4 (>458)	1 (<14)	2 (14–25)	3 (26–43)	4 (>43)
Age, y	53.1 ± 5.5[2]	53.0 ± 5.1	53.4 ± 5.1	52.8 ± 4.9	53.6 ± 5.2	52.9 ± 5.2	52.9 ± 5.1	52.8 ± 5.0*
Education, y	8.8 ± 3.6	8.9 ± 3.5	8.5 ± 3.5	8.4 ± 3.3*	8.4 ± 3.4	8.9 ± 3.6	8.6 ± 3.3	8.6 ± 3.4
Married, %	88	86	88	86	82	89	91	87
Leisure-time physical activity, kcal/d	158 ± 200	142 ± 161	137 ± 172	128 ± 162*	133 ± 164	139 ± 165	155 ± 206	138 ± 160
BMI, kg/m^2	26.7 ± 3.7	26.6 ± 3.3	27.0 ± 3.7	27.1 ± 3.6*	27.0 ± 3.7	26.8 ± 3.6	26.8 ± 3.5	26.8 ± 3.5
Systolic blood pressure, mm Hg	133 ± 16	135 ± 19	135 ± 17	134 ± 16	135 ± 17	133 ± 17	135 ± 17	133 ± 16
Diastolic blood pressure, mm Hg	88 ± 10	89 ± 11	89 ± 10	89 ± 11	90 ± 11	88 ± 10	89 ± 10	88 ± 11*
Serum total cholesterol, mmol/L	5.79 ± 1.06	5.89 ± 1.07	5.94 ± 1.13	6.02 ± 1.04*	5.98 ± 1.16	5.93 ± 1.05	5.83 ± 1.10	5.90 ± 0.99
Serum LDL cholesterol, mmol/L	3.92 ± 0.97	4.03 ± 1.01	4.09 ± 1.07	4.15 ± 0.99*	4.08 ± 1.08	4.08 ± 1.00	4.01 ± 1.04	4.03 ± 0.94
Serum HDL cholesterol, mmol/L	1.26 ± 0.28	1.29 ± 0.31	1.29 ± 0.30	1.32 ± 0.31*	1.28 ± 0.31	1.28 ± 0.31	1.29 ± 0.28	1.32 ± 0.31*
Serum triglycerides, mmol/L	1.43 ± 0.87	1.32 ± 0.76	1.25 ± 0.71	1.25 ± 0.93*	1.43 ± 0.91	1.31 ± 0.75	1.28 ± 0.72	1.23 ± 0.90*
Current smoker, %	22	29	31	35*	37	28	24	28*
Diabetes, %	5	6	6	7	8	4	5	6
Coronary artery disease, %	26	23	26	24	31	25	22	21*
Stroke, %	3	2	2	3	3	3	2	2
Hypertension, %	63	62	59	57*	66	59	60	55*
Lipid-lowering medication use, %								
At baseline	1.4	0.5	0.2	0.5*	1.0	0.8	0.5	0.3
During follow-up	53	51	49	50	49	53	50	51
Blood glucose, mmol/L	4.7 ± 1.0	4.8 ± 1.4	4.8 ± 1.2	4.8 ± 1.2*	4.9 ± 1.3	4.8 ± 1.4	4.7 ± 0.8	4.8 ± 1.2
Serum CRP, mg/L	2.40 ± 5.43	2.40 ± 4.19	2.48 ± 3.30	2.43 ± 3.35	2.93 ± 5.09	2.39 ± 4.86	2.20 ± 2.94	2.18 ± 3.25*
Alcohol intake, g/wk	78 ± 194	72 ± 106	67 ± 104	79 ± 111	83 ± 151	63 ± 97	66 ± 102	83 ± 170
Serum long-chain n–3 PUFAs, %	4.3 ± 1.4	4.7 ± 1.6	4.7 ± 1.5	5.0 ± 1.7*	4.7 ± 1.7	4.6 ± 1.6	4.6 ± 1.5	4.7 ± 1.6
Dietary intakes								
Energy, kcal/d	2517 ± 622	2381 ± 572	2356 ± 642	2508 ± 634	2207 ± 587	2385 ± 566	2485 ± 579	2684 ± 656*
Protein, E%	15.1 ± 2.3	15.7 ± 2.4	16.0 ± 2.7	16.4 ± 2.6*	16.0 ± 2.8	15.7 ± 2.5	15.8 ± 2.3	15.7 ± 2.5
Carbohydrates, E%	46.9 ± 6.2	43.7 ± 5.5	41.4 ± 5.6	38.9 ± 5.7*	42.5 ± 6.9	43.7 ± 6.5	43.3 ± 5.9	41.4 ± 6.5*
Fiber,[3] g/d	28.6 ± 8.5	25.3 ± 6.2	23.9 ± 5.8	22.4 ± 6.2*	23.8 ± 9.0	25.2 ± 8.5	25.5 ± 8.3	25.7 ± 8.5*
SFAs, E%	15.6 ± 3.3	17.8 ± 3.5	19.1 ± 3.9	20.2 ± 4.1*	18.0 ± 4.6	17.7 ± 4.0	18.1 ± 3.7	19.0 ± 3.9*
PUFAs, E%	4.9 ± 1.5	4.4 ± 1.4	4.4 ± 1.4	4.3 ± 1.3*	4.6 ± 1.5	4.6 ± 1.5	4.4 ± 1.3	4.4 ± 1.2*
MUFAs, E%	11.3 ± 2.4	11.3 ± 2.1	11.9 ± 2.1	12.3 ± 2.0*	11.5 ± 2.3	11.7 ± 2.4	11.5 ± 2.0	12.1 ± 2.1*
trans Fatty acids, E%	1.1 ± 0.5	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.3*	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.3	1.1 ± 0.4
Cholesterol,[3] mg/d	280 ± 47	361 ± 16	421 ± 20	543 ± 79*	338 ± 73	356 ± 77	403 ± 72	507 ± 110*
Eggs, g/d	17 ± 12	22 ± 14	30 ± 16	57 ± 29*	7 ± 4	20 ± 3	34 ± 5	65 ± 23*
Processed red meat, g/d	63.1 ± 55.3	62.9 ± 52.3	74.3 ± 64.9	79.4 ± 65.7*	70.4 ± 60.2	68.2 ± 63.2	66.9 ± 56.7	74.2 ± 60.6
Fruits, berries, and vegetables,[4] g/d	293 ± 173	251 ± 151	237 ± 149	220 ± 134*	236 ± 172	256 ± 153	259 ± 146	250 ± 145
Dairy, g/d	732 ± 359	689 ± 349	681 ± 343	744 ± 384	673 ± 362	682 ± 345	714 ± 348	775 ± 376*
Tea, g/d	106 ± 196	94 ± 167	88 ± 165	88 ± 163	86 ± 166	97 ± 169	96 ± 181	99 ± 176
Coffee, g/d	550 ± 286	568 ± 290	559 ± 299	578 ± 292	542 ± 288	547 ± 291	574 ± 282	591 ± 304*

[1] *P-trend across quartiles ≤ 0.05. P-trend was assessed with the use of linear regression (for continuous variables) or the chi-square test (for bivariate relations). CRP, C-reactive protein; E%, percentage of energy; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study.

[2] Mean ± SD (all such values).

[3] Energy adjusted.

[4] Excludes potatoes.

(~4 medium-sized eggs/wk). Cholesterol intake from eggs (mean ± SD: 110 ± 81 mg/d) accounted for 27% of total cholesterol intake. Forty-eight percent of subjects (n = 1199) consumed ≥0.5 eggs (27 g)/d. Only 27 subjects (1.1%) did not consume eggs at all, and 3 subjects reported consuming egg whites only.

Men with a higher cholesterol intake were less physically active, less educated, more likely to smoke, and less likely to have hypertension (**Table 1**). They had higher total-, LDL-, and HDL-cholesterol concentrations but lower serum triglyceride concentrations. Their serum long-chain n–3 PUFA concentrations were higher. They also had higher intakes of protein, SFAs, MUFAs, and processed red meat and lower intakes of carbohydrates, fiber, PUFAs, *trans* fatty acids, and fruit, berries, and vegetables. Men with higher egg intakes were younger and less likely to smoke, have hypertension, or have a history of a coronary artery disease, and their serum CRP concentrations and diastolic blood pressures were lower (Table 1). They had higher serum HDL-cholesterol concentrations and lower serum triglyceride concentrations. They also had higher intakes of energy, fiber, SFAs, MUFAs, cholesterol, dairy, and coffee and lower intakes of carbohydrates and PUFAs.

Cholesterol and egg intakes and risk of any incident dementia

During a mean ± SD follow-up of 21.9 ± 7.9 y, 337 men (13.5%) were diagnosed with any incident dementia. Cholesterol intake was not associated with risk of incident dementia (**Table 2**). Egg intake had a trend toward lower risk after multivariable adjustments (HR for highest compared with lowest quartiles: 0.74; 95% CI: 0.53, 1.02; P-trend across quartiles = 0.04) (model 2), but the association was NS after adjustment for cholesterol intake (P-trend = 0.20) (model 3). When evaluated continuously, each intake of an additional 100 mg cholesterol/d was associated with a multivariable-adjusted HR of 0.90 (95% CI: 0.79, 1.02) (model 2). After further adjustment for egg intake, the HR was 0.97 (95% CI: 0.79, 1.19) (model 3). Each additional 0.5 eggs (27 g)/d was associated with an HR of 0.89 (95% CI: 0.78, 1.01) (model 2) with little impact after further adjustment for cholesterol intake (HR: 0.91, 95% CI: 0.74, 1.13) (model 3).

In the subset of 1259 men, 29.6% of subjects had the Apo-E3/4 phenotype, and 3.6% of subjects had the 4/4 phenotype (**Table 3**). After adjustment for age and examination year, men with the Apo-E4 phenotype had 97% (HR: 1.97, 95% CI: 1.46, 2.65) higher risk of any incident dementia compared with that of Apo-E4 noncarriers. After multivariable adjustments (model 2), the HR was 1.97 (95% CI: 1.45, 2.68). However, the Apo-E4 phenotype did not modify the association of either cholesterol intake (P-interaction = 0.62) (model 2) or egg intake (P-interaction = 0.95) with risk of incident dementia.

Cholesterol and egg intakes and risk of AD

In the analyses with the incident AD diagnosis as the outcome (266 events), HRs were 0.79 (95% CI: 0.53, 1.19; P-trend = 0.29) for highest compared with lowest cholesterol-intake quartiles and 0.85 (95% CI: 0.59, 1.23; P-trend = 0.34) for highest compared with lowest egg-intake quartiles (Model 2). The associations were again attenuated after mutual adjustments (data not shown).

In the subset of 1295 men, the Apo-E4 phenotype did not modify the associations of either cholesterol intake (P-interaction = 0.87) (model 2) or egg intake (P-interaction = 0.52) with incident AD although subjects with the Apo-E4 phenotype had 127% higher risk of developing AD (140 AD events; HR: 2.27; 95% CI: 1.62, 3.18).

Cholesterol and egg intakes and cognitive performance

In the subset of 480 men, there were no significant associations between baseline cholesterol intake and cognitive performance at

TABLE 2
Risk of incident dementia in quartiles of cholesterol and egg intakes in 2497 men in the KIHD[1]

	Intake quartile				
	1	2	3	4	P-trend
Cholesterol intake,[2] mg/d	<331 (291)	331–387 (360)	388–458 (420)	>458 (522)	—
Events/participants, n (%)	91/624 (14.6)	84/624 (13.5)	82/625 (13.1)	80/624 (12.8)	—
Model[3]					
1	1	0.90 (0.67, 1.21)	0.87 (0.64, 1.17)	0.89 (0.65, 1.21)	0.47
2	1	0.83 (0.61, 1.13)	0.77 (0.55, 1.07)	0.78 (0.54, 1.12)	0.20
3	1	0.87 (0.63, 1.19)	0.85 (0.60, 1.22)	1.00 (0.62, 1.61)	0.95
Egg intake,[2] g/d	<14 (8)	14–25 (20)	26–43 (34)	>43 (59)	—
Events/participants, n (%)	83/625 (13.3)	88/624 (14.1)	83/624 (13.3)	83/624 (13.3)	—
Model[3]					
1	1	0.90 (0.67, 1.22)	0.81 (0.59, 1.11)	0.75 (0.54, 1.03)	0.07
2	1	0.97 (0.71, 1.32)	0.82 (0.60, 1.13)	0.74 (0.53, 1.02)	0.04
3	1	0.98 (0.72, 1.33)	0.84 (0.60, 1.18)	0.78 (0.51, 1.19)	0.20

[1] Model 1 was adjusted for age, examination year, and energy intake. Model 2 was adjusted as for model 1 and for education; smoking; BMI; diabetes; leisure-time physical activity; coronary artery disease history; use of lipid-lowering medication during follow-up; and intakes of alcohol, carbohydrates, fiber, and fruits, berries, and vegetables. Model 3 was adjusted as for model 2 and for either egg or dietary cholesterol intake. KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study.

[2] Medians shown in parentheses.

[3] HR; 95% CI in parentheses (all such values). Values were obtained from Cox proportional hazards regression models.

TABLE 3
Frequencies of the apolipoprotein E phenotypes in 1259 men in the KIHD[1]

Phenotype	Frequency, *n*	Proportion, %
2/2	4	0.3
2/3	75	6.0
3/3	745	59.2
2/4	17	1.4
3/4	373	29.6
4/4	45	3.6

[1] KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study.

the 4-y follow-up examinations, whereas higher egg intake was associated with better performance in the Trail Making Test and Verbal Fluency Test (**Table 4**). Further adjustment for cholesterol intake had little impact on the results of the Trail Making Test (*P*-trend = 0.04) or the Verbal Fluency Test (*P*-trend = 0.03). Each additional 0.5 eggs/d was associated with a 1.9-s better performance on the Trail Making Test (95% CI: 0, 3.8 s) (model 2) and with a better score of 1.2 words (95% CI: −0.1, 2.4 words) on the Verbal Fluency Test. Again, the Apo-E4 phenotype did not modify the association of cholesterol intake (*P*-interaction > 0.11) or egg intake (*P*-interaction > 0.24).

Sensitivity analyses

We investigated the impact of excluding men with coronary artery disease at baseline (n = 613) because they might have changed their dietary habits after the coronary artery disease event, which could explain the lower number of men with a history of coronary artery disease in subjects with higher egg intakes (Table 1). However, this factor did not have any major impact on the associations with incident events. For example, in these analyses (254 events), each intake of an additional 100 mg cholesterol/d was associated with a multivariable-adjusted HR of 0.89 (95% CI: 0.77, 1.03) (model 2) and each additional 0.5 eggs (27 g)/d was associated with an HR of 0.90 (95% CI: 0.78, 1.05) (model 2) for incident dementia. In the cognitive-performance tests (n = 335), the inverse associations of egg intake with the Trail Making Test and the Verbal Fluency Test were attenuated and no longer significant. Each additional 0.5 eggs/d was associated with a 1.4-s better performance on the Trail Making Test (95% CI: −0.9, 3.6 s) (model 2) and with a better score of 0.7 words (95% CI: −0.9, 2.3 words) on the Verbal Fluency Test (model 2).

DISCUSSION

In this population-based cohort study in middle-aged and older men from Eastern Finland, we showed that higher cholesterol or egg intake was not associated with higher risk of incident dementia. Instead, we showed that higher egg intake was associated with better performance in 2 cognitive tests (i.e., Trail Making Test and Verbal Fluency Test) that assessed frontal lobe and executive functioning.

The evidence about the association between dietary cholesterol intake and risk of dementia is controversial. In animal studies in mice, rats, and rabbits, the association between high cholesterol intake and AD-type pathologies has been shown systematically (14–18). However, the association has not been shown in humans (19, 20). As regards the association between dietary cholesterol and lower cognitive performance, ≥3 studies have been published of which 2 studies showed an association (43, 44) and 1 study did not (45). In our study, higher intake of dietary cholesterol had, in general, no association with cognitive performance or risk of incident dementia.

It is not clear why the associations between dietary cholesterol and dementia seem incoherent between animal and human studies. One explanation could be the different lipoprotein metabolism of rats, mice, rabbits, and humans (46), and thus, results obtained from animal studies are possibly not directly applicable to humans. Although the lipid metabolism of rabbits is more comparable to that of humans than is the metabolism of rodents, there are still some differences. For instance, rabbits are sensitive

TABLE 4
Cognitive performance after 4 y of follow-up in tertiles of baseline cholesterol and egg intakes in 480 men in the KIHD[1]

	Intake tertile			
	1 (n = 160)	2 (n = 160)	3 (n = 160)	*P*-trend
Cholesterol intake,[2] mg/d	<339 (284)	339–406 (370)	>406 (456)	—
Mini-Mental State Examination score	27.1 (26.8, 27.5)[3]	27.0 (26.7, 27.3)	27.1 (26.8, 27.5)	0.96
Trail Making Test, s	51.5 (48.5, 54.4)	53.5 (50.8, 56.2)	52.3 (49.4, 55.2)	0.75
Verbal Fluency Test words, *n*	31.1 (29.2, 33.0)	33.3 (31.5, 35.0)	33.0 (31.1, 34.9)	0.22
Selective Reminding Test words, *n*	34.5 (33.1, 35.9)	34.4 (33.1, 35.6)	34.0 (32.7, 35.4)	0.66
Visual Reproduction Test, *n* correct	11.3 (10.7, 11.9)	11.3 (10.8, 11.8)	11.3 (10.7, 11.9)	0.95
Egg intake,[2] g/d	<16 (8)	16–32 (23)	>32 (45)	—
Mini-Mental State Examination score	27.0 (26.7, 27.3)	27.1 (26.7, 27.4)	27.2 (26.9, 27.5)	0.29
Trail Making Test, s	54.2 (51.5, 56.9)	53.0 (50.3, 55.7)	50.0 (47.3, 52.8)	0.03
Verbal Fluency Test words, *n*	31.0 (29.2, 32.8)	32.3 (30.5, 34.1)	34.1 (32.3, 35.9)	0.02
Selective Reminding Test words, *n*	34.0 (32.7, 35.2)	34.0 (32.8, 35.3)	34.9 (33.7, 36.2)	0.27
Visual Reproduction Test, *n* correct	11.2 (10.6, 11.7)	11.1 (10.6, 11.7)	11.6 (11.0, 12.1)	0.30

[1] KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study.
[2] Medians shown in parentheses.
[3] Mean; 95% CI in parentheses (all such values). Values were obtained with the use of an ANCOVA and were adjusted for age; examination year; education; smoking; BMI; diabetes; leisure-time physical activity; coronary artery disease history; use of lipid-lowering medication during follow-up; and intakes of energy, alcohol, carbohydrates, fiber, and fruits, berries, and vegetables.

to cholesterol, and the consumption of a long-lasting diet that contained >1% cholesterol resulted in abnormally high cholesterol concentrations in plasma, which have not been shown in humans (46). Another explanation could be that dietary cholesterol does have an effect on the human brain, but the pathologic changes are so minor that they cannot be seen on MRI or on clinical status. This possibility could explain why there have been some indications of the associations between dietary cholesterol and lower cognitive performance (43, 44). However, this connection cannot be applied to eggs as such.

To the best of our knowledge, there has been no previous evidence concerning the impact of egg intake on the risk of dementia. However, a few studies have investigated the association between egg intake and mild cognitive impairment and have shown either no association (47) or that eggs have had a beneficial association (21, 22), as was the case in our study. Nevertheless, all of these previous publications covered a more limited number of tests than in our study.

Eggs are a major source of dietary cholesterol because 1 egg contains ~200 mg cholesterol. However, the effects of eggs on health are difficult to determine only by their cholesterol content. Dietary cholesterol has only a minor effect on plasma cholesterol concentration in the majority of people (9), and eggs are a source of many other nutrients and bioactive compounds than just cholesterol (48). Eggs contain high-quality protein, unsaturated fatty acids, chelators, and all necessary minerals and vitamins, with the exception of vitamin C. The nutrient-dense form of eggs may be a good source of energy for individuals who are at risk of malnutrition, such as the elderly (49). The bioactive compounds, such as lutein, zeaxanthin, (50) and choline (51), may have some beneficial effects on inflammation (52) and intestinal cholesterol absorption (53). High intake of choline has also been associated with fewer errors in a test that measured cognitive capacity (21), and in the current study population, eggs have been associated with a lower risk of type 2 diabetes (54). Overall, egg intake does not appear to be associated with elevated risk of CVD (8, 10, 11) or mortality (11) in general populations. The results have been similar even in hyperresponders to dietary cholesterol (i.e., in *APO-E4* carriers) (13). Our results indicate that a moderate intake of ≤1 egg/d does not seem to increase the risk of cognitive decline either.

In some studies, egg intake has been associated with unhealthy lifestyle factors such as smoking, high intake of processed red meat, and low intake of vegetables (55, 56), which may have influenced the conclusions that were made on the health effects of eggs. In our study population, such associations were not observed (Table 1). On the contrary, higher intake of eggs was associated with some favorable health factors, such as lower serum CRP, and a lower likelihood to have hypertension.

A strength of our study is the detailed information about dietary intakes, which were assessed with the use of a 4-d food record and included data about eggs in mixed dishes and recipes. We also had detailed information about incident dementia diagnoses. The other strengths are the population-based recruitment, extensive database of potential confounders, and virtually no loss to follow-up in the analyses with incident dementia.

A potential limitation of the study is the lack of data on the Apo-E4 phenotype for all participants. We also had information on the performance in the cognitive tests for only a small proportion of the participants, which limited the generalizability of the findings to the whole study population. The number of subjects was further reduced in the sensitivity analyses after the exclusion of men with coronary artery disease at baseline, which may at least partly explain the attenuated associations between egg intake and the performance on the Trail Making Test and Verbal Fluency Test in those analyses. Dietary habits were assessed only at baseline, which may have attenuated the associations with incident dementia during the long follow-up. Because the majority of dementia events occurred toward the end of the follow-up as the men were getting older, we were unable to investigate the associations with a shorter follow-up without losing a significant number of events. For example, only 11 events occurred during the first 10 y of follow-up. However, cholesterol or egg intake was not associated with worse performance in the cognitive tests at the 4-y examinations either, which supports the lack of an association with incident events. Scores on the cognitive performance tests at the 4-y examinations were relatively good, which indicated the good cognitive ability of participants at baseline. Therefore, our results may not be generalizable to study populations who already exhibit cognitive declines.

In conclusion, there are no indications of a relation of dietary cholesterol intake or moderate egg consumption with an increased risk of incident dementia in the current study. Instead, our results suggest that moderate egg intake may have a positive association with certain areas of cognitive performance. More studies in diverse populations are needed to elucidate the impact of egg and cholesterol intakes on cognitive decline.

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