Egg consumption and risk of incident type 2 diabetes in men: the Kuopio Ischaemic Heart Disease Risk Factor Study[1–3]

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ABSTRACT

Background: The prevalence of type 2 diabetes (T2D) is increasing around the world. Eggs are a major source of cholesterol, which has been associated with elevated blood glucose and an increased risk of T2D. However, there are limited and conflicting data from prospective population studies on the association between egg consumption and risk of T2D.

Objective: We investigated the association between egg consumption and risk of incident T2D in middle-aged and older men from eastern Finland.

Design: The study included 2332 men aged 42–60 y in 1984–1989 at the baseline examinations of the prospective, population-based Kuopio Ischaemic Heart Disease Risk Factor Study. Dietary intakes were assessed with 4-d food records at baseline. Incident T2D was assessed by self-administered questionnaires; by fasting and 2-h oral-glucose-tolerance-test blood glucose measurement at re-examination rounds 4, 11, and 20 y after baseline; and by record linkage to a hospital discharge registry and reimbursement register of diabetes medication expenses. Cox proportional hazards regression analyses were used to estimate associations with the risk of incident T2D. Associations with the metabolic risk markers at baseline and at the 4-y examinations were analyzed by ANCOVA.

Results: During an average follow-up of 19.3 y, 432 men developed T2D. After adjustment for potential confounders, those in the highest compared with the lowest egg intake quartile had a 38% (95% CI: 18%, 53%; *P*-trend across quartiles <0.001) lower risk of incident T2D. Analyses with metabolic risk markers also suggested an inverse association with fasting plasma glucose and serum C-reactive protein but not with serum insulin. The associations between cholesterol intake and risk of T2D, plasma glucose, serum insulin, and C-reactive protein were mainly nonsignificant, especially after accounting for egg consumption.

Conclusion: Higher egg intake was associated with a lower risk of T2D in this cohort of middle-aged and older men. *Am J Clin Nutr* 2015;101:1088–96.

Keywords: diet, eggs, men, prospective study, type 2 diabetes

INTRODUCTION

With the increasing prevalence of type 2 diabetes (T2D)[4] around the world due mainly to the worsening obesity epidemic (1), there is a need to investigate modifiable factors that are related to the risk of T2D to reduce its individual and societal burden and its comorbidities. Evidence from observational and experimental studies suggests that dietary factors have a major role in the prevention and management of T2D (2).

Among dietary factors, egg consumption has been implicated as one possible risk factor. Egg is a major source of dietary cholesterol (~200 mg/egg), which has been associated with impaired glucose metabolism (3) and increased inflammation (4) in animal models and with elevated fasting glucose (5) and higher risk of T2D (6, 7) in humans. However, in randomized controlled trials, the addition of eggs to the diet has reduced plasma insulin and insulin resistance (8), decreased inflammatory markers (9–11), and increased the formation of larger and less-dense LDL and HDL particles (8, 12). Both inflammation (13) and certain lipoprotein subclasses characterized by small and dense LDL and HDL particles (14, 15) have been shown to predict the risk of T2D. There are, however, no trials of the effect of egg consumption on T2D incidence. In addition, the epidemiologic data on the impact of egg consumption on the risk of T2D are scarce. Five prospective studies evaluated the association between egg consumption and risk of incident T2D and found either no association (16–19) or a direct association (20), whereas 1 cross-sectional (21) and 1 case-control study (22) both found a direct association.

Eggs are a common, affordable, and readily available food item worldwide and, in addition to cholesterol, also a good source of many potentially beneficial nutrients, such as high-quality protein, fatty acids, minerals, and vitamins, so it is important to elucidate their impact on disturbances in glucose metabolism. This is especially important because egg consumption does not appear to increase the risk of cardiovascular disease in the general population but seems to increase the risk among diabetic patients (23, 24). Therefore, because the evidence on the impact of egg consumption on the risk of T2D is limited and mixed, we investigated the association between egg consumption and risk of incident T2D in middle-aged and older men from eastern Finland. We previously showed that egg consumption was not associated with carotid atherosclerosis or risk of myocardial infarction in

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[4] Abbreviations used: *APOE4*, apolipoprotein E4; CRP, C-reactive protein; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; T2D, type 2 diabetes.

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this study population (25). In secondary analyses we also investigated the association of egg consumption with plasma glucose, serum insulin, and serum C-reactive protein (CRP) at baseline and in a subgroup after 4 y of follow-up. We also investigated these associations with cholesterol intake. In the subgroup analysis, we investigated the impact of the apolipoprotein E4 (*APOE4*) phenotype, a major determinant in the response to dietary cholesterol (26), on the association between egg and cholesterol intakes and glucose metabolism.

METHODS

Study population

The Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study was designed to investigate risk factors for cardiovascular disease, atherosclerosis, and related outcomes in a population-based, randomly selected sample of men from eastern Finland (27). The baseline examinations were carried out in 1984–1989 (**Figure 1**). A total of 2682 men who were 42, 48, 54, or 60 y old at baseline (83% of those eligible) were recruited in 2 cohorts. The first cohort consisted of 1166 men who were 54 y old and enrolled in 1984–1986, and the second cohort included 1516 men who were 42, 48, 54, or 60 y old and enrolled in 1986–1989. The baseline examinations were followed by the 4-y examination round (1991–1993) in which 1038 men from the second cohort (88% of those eligible) participated. At the 11-y examination round (1998–2001), all of the men from the second cohort were invited and 854 men (95% of those eligible) participated. During the 20-y examination round, all eligible participants from the first and second cohorts were invited to the study site. A total of 1241 men (80% of those eligible) participated. The baseline characteristics of the entire study population were described previously (27). 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 T2D (n = 167), impaired fasting glucose (n = 127), or unknown diabetes status (n = 38) at baseline or those with missing data on dietary intakes (n = 18) were excluded, which left 2332 men for the analyses of incident T2D. Data on plasma glucose, serum insulin, and CRP were available for 2312 men at baseline and for 880 men at the 4-y examinations. In the analyses with these biomarkers, participants with a diagnosis of T2D at the 4-y examinations were excluded from the analyses with the 4-y data because the use of diabetes treatment could confound the findings. In the subgroup analyses, data for the *APOE4* phenotype were available for 1193 men.

Other measurements

Fasting venous blood samples were collected between 0800 and 1000 at baseline and at the follow-up examinations. Subjects were instructed to abstain from ingesting alcohol for 3 d and from smoking and eating for 12 h before providing the sample. Detailed descriptions of the determination of serum lipids and lipoproteins (28) and serum fatty acids (29) and the assessment of medical history and medications (28), family history of diseases (28), smoking (28), alcohol consumption (28), blood pressure (28), and physical activity (30) at baseline have been published. Education was assessed in years by using self-administered questionnaires. Annual income was obtained from a self-administered questionnaire. Family history of diabetes was defined as positive if a first-degree relative of the participant had a history of diabetes. A diagnosis of hypertension was defined as systolic/diastolic blood pressure >140/90 mm Hg or the use of hypertension medication. BMI was computed as the ratio of weight in kilograms to the square of height in meters. *APOE4* phenotype was determined from plasma with isoelectric focusing and immunoblotting techniques. Subjects with 1 or 2 apolipoprotein ϵ4 alleles were included in the *APOE4* group. The diagnosis of metabolic syndrome was based on the definition by the National Cholesterol Education Program Adult Treatment Panel III.

Assessment of dietary intakes

The consumption of foods at baseline was assessed with a guided food record of 4 consecutive days, one of which was a weekend day, by household measures. A picture book of common foods and dishes was used to help in the estimation of portion sizes and contained 126 of the most common foods and drinks consumed in Finland during the 1980s. For each food item, the participant could choose from 3 to 5 commonly used portion sizes or describe the portion size in relation to those shown 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 by using NUTRICA 2.5 software (Social Insurance Institution). The software's databank is mainly based on Finnish values of nutrient composition of foods. The egg consumption variable used in this study represents total egg consumption, including eggs in mixed dishes and recipes.

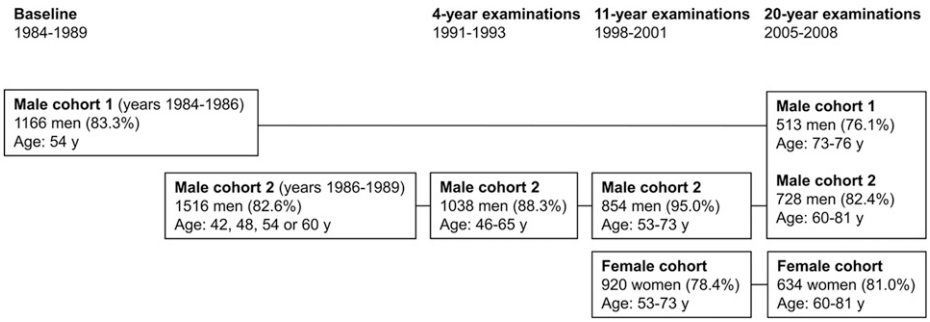

FIGURE 1 Timeline of the Kuopio Ischaemic Heart Disease Risk Factor Study. The percentages in parentheses indicate the proportion of eligible participants who participated in the study visits.

Measurement of plasma glucose, serum insulin, and serum CRP

Both at baseline and at the 4-y examinations, plasma glucose was measured by using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. The serum samples for insulin determination were stored frozen at –80°C. Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk). Serum CRP was measured with an immunometric assay (Immulite High Sensitivity CRP Assay; Diagnostic Products Corporation).

Diagnostic criteria for T2D

T2D was defined as a self-reported physician diagnosis of T2D and/or fasting plasma glucose ≥7.0 mmol/L or 2-h oral-glucose-tolerance-test plasma glucose ≥11.1 mmol/L at the re-examination rounds 4, 11, and 20 y after baseline and by record linkage to the national hospital discharge registry and to the Social Insurance Institution of Finland register for reimbursement of medicine expenses used for T2D for the entire study period until the end of the follow-up on 31 December 2010.

Impaired fasting glucose at baseline was defined by using the WHO criterion: fasting plasma glucose of 6.1–6.9 mmol/L. The 2-h oral-glucose-tolerance test was not performed at study baseline.

Statistical analysis

The univariate relations between egg consumption and baseline characteristics were assessed by means and linear regression (for continuous variables) or by chi-square tests (for categorical variables). Cox proportional hazards regression models were used to estimate HRs in quartiles of egg and cholesterol intakes, with the lowest category as the reference. The validity of the proportional hazards assumption was evaluated by using Schoenfeld residuals. Absolute risk reduction was calculated by multiplying the absolute risk in the reference group by the multivariable-adjusted HR reduction in the comparison group. The mean values of plasma glucose and serum insulin and CRP in quartiles of egg consumption were analyzed by using ANCOVA, with adjustments for potential confounders. The confounders were selected on the basis of established risk factors for T2D, previously published associations with T2D in the KIHD study (29, 31, 32), or on associations with exposures or outcomes in the present analysis. Model 1 included age (y), examination year, and energy intake (kcal/d). The multivariate model (model 2) included the variables in model 1 and BMI (kg/m^2), family history of T2D (yes or no), hypertension (yes or no), smoking (never smoker; previous smoker; current smoker, <20 cigarettes/d; and current smoker, ≥20 cigarettes/d), education years, leisure-time physical activity (kcal/d), serum long-chain omega-3 PUFAs (percentage of all serum fatty acids), and intakes of alcohol (g/d), linoleic acid (18:2n−6; % of energy), fiber (g/d), and fruit, berries, and vegetables (g/d). Model 3 included the variables in model 2 and either cholesterol intake (mg/d) in the analyses with egg consumption or egg consumption (g/d) in the analyses with cholesterol intake. All quantitative variables were entered in the models as continuous variables. Further adjustments for waist-to-hip ratio, serum 25-hydroxyvitamin D, glycemic load, or intakes of carbohydrates, saturated, monounsaturated, or *trans* fatty acids, processed or unprocessed red meat, dairy, coffee, or magnesium had no appreciable impact on the associations (<5% change in estimates). The cohort mean was used to replace missing values in covariates (<0.5%) (33). Tests of linear trend were conducted by assigning the median values for each category of exposure variable and treating those as a single continuous variable. The statistical significance of the interactions with BMI, *APOE4* phenotype, and metabolic syndrome status on a multiplicative scale was assessed by likelihood ratio tests with the use of a cross-product term. All *P* values were 2-tailed ($\alpha = 0.05$). Correlations were estimated by Spearman correlation coefficients. Data were analyzed by using SPSS 21.0 for Windows (IBM Corporation).

RESULTS

At baseline, men with a higher egg intake were more likely to be younger and to have lower serum triglyceride and higher serum apolipoprotein A-I concentrations (**Table 1**). They were also less likely to smoke and less likely to have ischemic heart disease and hypertension. They also had higher intakes of energy, unprocessed red meat, dairy, SFAs and MUFAs, linoleic acid, fiber, coffee, and cholesterol and lower intake of carbohydrates.

The average egg intake was 33 g/d [median (SD): 27 (26) g/d]. Among participants, 377 (16.2%) consumed at least 55 g/d (equivalent to ∼1 medium egg). Only 22 participants did not consume eggs at all during the 4-d food recording period and only 2 subjects reported using egg whites. The average cholesterol intake was 396 mg/d [median (SD): 372 (153) mg/d]. The correlation coefficient between egg consumption and cholesterol intake was 0.66.

During the average follow-up of 19.3 y (SD: 6.6 y; minimum–maximum: 0.2–26.8 y; 45,008 person-years) a total of 432 T2D events occurred. After adjustment for age, examination year, and energy intake in the Cox regression model (**Table 2**, model 1), there was a lower risk of T2D with increasing egg intake (*P*-trend across quartiles <0.001). However, the lowest risk was observed already in the third egg intake quartile (median intake: 35 g/d or a little more than half a medium egg), and higher egg intake did not provide further reductions in risk. Compared with the lowest quartile (median intake: 9 g/d or ∼1 medium egg/wk), the relative risk reduction in the third quartile was 37% (95% CI: 17%, 52%; absolute risk in the lowest quartile: 21.0%; absolute risk reduction in the third quartile: 13.2%). When evaluated continuously, each additional egg per day (55 g) was associated with a 30% lower risk (HR: 0.70; 95% CI: 0.55, 0.90). Further multivariate adjustments for potential confounders (model 2) did not have a major impact on the associations, but further adjustment for cholesterol intake (model 3) slightly strengthened the association.

Cholesterol intake was not associated with the risk of T2D after adjustment for age, examination year, and energy intake (**Table 3**, model 1). However, after further multivariate adjustment (model 2), cholesterol intake showed a pattern with risk similar to what was observed with egg consumption—that is, the risk was significantly lower already in the third tertile and little change was observed with a higher cholesterol intake. However, further adjustment for egg consumption (model 3) attenuated the association.

In the analyses with glucose metabolism markers, higher egg intake was associated with modestly lower plasma glucose concentrations both at baseline and at the 4-y examinations, especially after cholesterol intake was accounted for (**Table 4**,

TABLE 1
Baseline characteristics according to dietary egg intake[1]

Characteristic	Egg consumption quartile				*P*-trend
	1 (<14 g/d)	2 (14–26 g/d)	3 (27–45 g/d)	4 (>45 g/d)	
Subjects, *n*	585	579	586	582	
Age, y	53.4 ± 5.2[2]	52.9 ± 5.3	53.0 ± 5.1	52.7 ± 5.0	0.03
BMI, kg/m^2	26.7 ± 3.6	26.5 ± 3.2	26.6 ± 3.3	26.6 ± 3.3	0.83
Leisure-time physical activity, kcal/d	135 ± 166	138 ± 166	158 ± 210	131 ± 148	0.79
Income, €	12,840 ± 9675	13,635 ± 9060	13,545 ± 8265	13,170 ± 8755	0.80
Education, y	8.4 ± 3.4	8.9 ± 3.6	8.8 ± 3.4	8.7 ± 3.5	0.43
Serum EPA + DPA[3] + DHA, %	4.67 ± 1.64	4.61 ± 1.55	4.66 ± 1.52	4.76 ± 1.60	0.21
Serum LDL cholesterol, mmol/L	4.07 ± 1.09	4.09 ± 1.02	4.03 ± 1.01	4.00 ± 0.96	0.16
Serum HDL cholesterol, mmol/L	1.30 ± 0.32	1.29 ± 0.31	1.28 ± 0.27	1.33 ± 0.31	0.16
Serum apolipoprotein B, g/L	1.04 ± 0.25	1.04 ± 0.24	1.03 ± 0.24	1.02 ± 0.24	0.06
Serum apolipoprotein A-I, g/L	1.33 ± 0.27	1.33 ± 0.26	1.33 ± 0.24	1.36 ± 0.26	0.02
Serum triglycerides, mmol/L	1.34 ± 0.79	1.30 ± 0.76	1.24 ± 0.66	1.19 ± 0.79	<0.001
Systolic blood pressure, mm Hg	134 ± 17	133 ± 17	133 ± 17	133 ± 16	0.80
Diastolic blood pressure, mm Hg	89 ± 10	88 ± 10	88 ± 10	88 ± 10	0.40
Alcohol intake, g/wk	83 ± 145	63 ± 94	60 ± 92	85 ± 176	0.35
Current smoker, %	39	32	27	30	0.002
Hypertension, %	63	57	58	55	0.02
Ischemic heart disease, %	30	23	22	19	<0.001
Stroke, %	3	3	2	2	0.24
Family history of type 2 diabetes, %	24	27	30	26	0.58
Dietary intakes					
Energy, kcal/d	2151 ± 582	2348 ± 592	2414 ± 554	2619 ± 674	<0.001
Cholesterol, mg/d	291 ± 110	342 ± 106	406 ± 107	545 ± 148	<0.001
Protein, % of energy	15.7 ± 2.9	15.4 ± 2.5	15.7 ± 2.7	15.5 ± 2.5	0.30
SFAs, % of energy	17.9 ± 4.9	17.7 ± 4.1	18.0 ± 4.0	18.8 ± 4.0	<0.001
PUFAs, % of energy	4.5 ± 1.6	4.6 ± 1.6	4.5 ± 1.5	4.4 ± 1.3	0.06
Linoleic acid, % of energy	3.3 ± 1.4	3.5 ± 1.5	3.3 ± 1.2	3.2 ± 1.2	0.02
MUFAs, % of energy	10.7 ± 2.3	10.9 ± 2.3	10.9 ± 2.3	11.2 ± 2.0	<0.001
trans Fatty acids, % of energy	1.1 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	1.1 ± 0.4	0.96
Carbohydrates, % of energy	43.6 ± 7.0	44.4 ± 6.6	44.1 ± 6.0	42.1 ± 6.7	<0.001
Glycemic load	140 ± 30	144 ± 30	139 ± 35	142 ± 31	0.43
Glycemic index	56 ± 8	56 ± 7	56 ± 7	56 ± 7	0.15
Fiber, g/d	23.7 ± 9.0	25.7 ± 8.8	25.7 ± 8.5	25.9 ± 9.0	<0.001
Unprocessed red meat, g/d	62 ± 46	69 ± 49	68 ± 44	72 ± 51	0.001
Processed red meat, g/d	70 ± 61	69 ± 63	67 ± 56	73 ± 61	0.33
Dairy, g/d	727 ± 378	733 ± 363	745 ± 352	806 ± 382	<0.001
Fruit, berries, and vegetables, g/d	232 ± 161	261 ± 156	260 ± 147	253 ± 147	0.11
Coffee, mL/d	545 ± 285	545 ± 292	585 ± 290	592 ± 311	0.001

[1] *P*-trend was assessed by using linear regression (continuous variables) or by chi-square test (categorical variables). 1 medium egg weighs ~55 g.
[2] Mean ± SD (all such values).
[3] DPA, docosapentaenoic acid (22:5n–3).

model 3). No association was found with serum insulin (Table 4). Higher egg intake was also associated with lower CRP, but the association was significant only with the 4-y examination data (Table 4) and was attenuated after further adjustment for cholesterol intake. Dietary cholesterol intake was associated with higher glucose and insulin concentrations at baseline, especially after adjustment for egg intake (**Table 5**, model 3). No significant associations were observed with glucose or insulin at the 4-y examinations. The associations with CRP were generally nonsignificant, except for the inverse association at the 4-y examinations after multivariate adjustment (model 2). However, further adjustment for egg intake attenuated the association (model 3).

In the sensitivity analyses, we evaluated the associations of egg and cholesterol intakes with T2D incidence after 10 y of follow-up, because the associations with a single measurement at baseline may be attenuated by a long follow-up period. The multivariate-adjusted HRs for T2D (72 cases) in quartiles of egg consumption were 1, 0.79, 0.69, and 0.41 (95% CI: 0.19, 0.89; *P*-trend = 0.02; model 2). After further adjustment for cholesterol intake, HRs were 1, 0.76, 0.58, and 0.29 (95% CI: 0.11, 0.74; *P*-trend = 0.01). For cholesterol intake, the multivariate-adjusted HRs were 1, 1.20, 1.16, and 0.76 (95% CI: 0.29, 1.97; *P*-trend = 0.54; model 2), and after further adjustment for egg consumption HRs were 1, 1.48, 1.72, and 1.62 (95% CI: 0.52, 5.07; *P*-trend = 0.41). We also investigated the impact of excluding participants with coronary heart disease at baseline (n = 545), because those who had experienced a coronary heart disease event might have changed their dietary habits. This could explain the lower frequency of participants with a history of coronary heart disease among those with a higher egg intake (Table 1). After exclusion, the associations

TABLE 2
Incident type 2 diabetes in 2332 men according to egg consumption at baseline in 1984–1989[1]

	Egg consumption quartile				
	1 (<14 g/d)	2 (14–26 g/d)	3 (27–45 g/d)	4 (>45 g/d)	*P*-trend
Subjects, *n*	585	579	586	582	
Incidence rate/1000 person-years	12.0	10.9	8.0	7.9	
Model[2]					
1	1	0.86 (0.67, 1.11)	0.63 (0.48, 0.83)	0.63 (0.47, 0.83)	<0.001
2	1	0.91 (0.71, 1.18)	0.63 (0.48, 0.83)	0.62 (0.47, 0.82)	<0.001
3	1	0.90 (0.69, 1.16)	0.59 (0.44, 0.80)	0.55 (0.38, 0.79)	0.001

[1]One medium egg weighs ~55 g.

[2]Values are HRs (95% CIs) derived by Cox proportional hazards regression models. Model 1 was adjusted for age, examination year, and energy intake (kcal/d). Model 2 was adjusted as for model 1 plus BMI (kg/m^2), family history of type 2 diabetes (yes or no), hypertension (yes or no), smoking (never smoker; previous smoker; current smoker, <20 cigarettes/d; current smoker, ≥20 cigarettes/d), education years, leisure-time physical activity (kcal/d), serum long-chain omega-3 PUFAs (percentage of all serum fatty acids), and intakes of alcohol (g/d), linoleic acid (% of energy), fiber (g/d), and fruit, berries, and vegetables (g/d). Model 3 was adjusted as for model 2 and dietary cholesterol intake (mg/d).

with egg consumption remained similar but were attenuated with cholesterol intake. The multivariate-adjusted HR in the highest vs. the lowest egg intake quartile was 0.69 (95% CI: 0.50, 0.96; *P*-trend = 0.01; model 2) and after further adjustment for cholesterol intake the HR was 0.58 (95% CI, 0.38, 0.90; *P*-trend = 0.01; model 3). For cholesterol intake, the multivariate-adjusted HR in the highest vs. the lowest quartile was 0.81 (95% CI: 0.53, 1.24; *P*-trend = 0.15) and after further adjustment for egg consumption the HR was 0.95 (95% CI: 0.56, 1.61; *P*-trend = 0.54). We also excluded from the analyses the T2D events that occurred during the first 2 y of follow-up (n = 3) but that had no effect on the associations (data not shown). Finally, because adiposity is a major risk factor for T2D, and weight gain could potentially have an effect on glucose metabolism markers such as plasma glucose, we also investigated whether higher egg intake was associated with better weight management between the baseline and the 4-y examinations. However, the 4-y change in BMI was greater in those with a higher baseline egg intake [unadjusted difference between the highest and the lowest quartile (in kg/m^2): 0.26, 95% CI: −0.05, 0.58; *P*-trend = 0.03]. Furthermore, although the inverse association between egg consumption and risk of T2D was stronger in those with a baseline BMI below the median of 26.3 (multivariate-adjusted extreme quartile HR: 0.43; 95% CI: 0.26, 0.72; *P*-trend = 0.001; model 2) than in those with a BMI equal to or greater than the median (extreme quartile HR: 0.74; 95% CI: 0.52, 1.04; *P*-trend = 0.03), there was no evidence for statistical interaction (*P*-interaction = 0.21). There was also no evidence for effect modification by baseline BMI in the analyses with plasma glucose, serum insulin, and serum CRP (*P*-interaction > 0.05). Adjustment of the models for the 4-y change in BMI instead of the baseline BMI did not have an appreciable effect on the associations (data not shown). Cholesterol intake showed a similar direct, but weaker, association with the 4-y change in BMI (unadjusted difference between the extreme quartiles: 0.12; 95% CI: −0.43, 0.20; *P*-trend = 0.84). Adjustment for the 4-y change in BMI instead of the baseline BMI in the analyses with glucose metabolism markers (Table 5) did not appreciably change the associations (data not shown). Baseline BMI also did not modify the association between cholesterol intake and risk of T2D (*P*-interaction = 0.84) or glucose metabolism markers (*P*-interaction > 0.05). Because participants with metabolic syndrome (n = 156) are more likely to develop T2D during follow-up, we also evaluated whether metabolic syndrome could modify the associations between egg or cholesterol intake and risk of T2D. However, we found no evidence for effect modification by metabolic syndrome status (*P*-interaction > 0.05). Finally, in the subgroup of 1193 men for whom *APOE4* phenotype

TABLE 3
Incident type 2 diabetes in 2332 men according to cholesterol intake at baseline in 1984–1989

	Cholesterol intake quartile				
	1 (<291 mg/d)	2 (291–371 mg/d)	3 (372–478 mg/d)	4 (>478 mg/d)	*P*-trend
Subjects, *n*	583	583	583	583	
Incidence rate/1000 person-years	10.3	11.4	8.2	8.7	
Model[1]					
1	1	1.13 (0.86, 1.47)	0.78 (0.58, 1.06)	0.84 (0.59, 1.20)	0.12
2	1	1.06 (0.81, 1.39)	0.67 (0.49, 0.91)	0.66 (0.46, 0.96)	0.01
3	1	1.12 (0.85, 1.49)	0.75 (0.53, 1.05)	0.84 (0.53, 1.34)	0.20

[1]Values are HRs (95% CIs) derived by Cox proportional hazards regression models. Model 1 was adjusted for age, examination year, and energy intake (kcal/d). Model 2 was adjusted as for model 1 plus BMI (kg/m^2), family history of type 2 diabetes (yes or no), hypertension (yes or no), smoking (never smoker; previous smoker; current smoker, <20 cigarettes/d; current smoker, ≥20 cigarettes/d), education years, leisure-time physical activity (kcal/d), serum long-chain omega-3 PUFAs (percentage of all serum fatty acids), and intakes of alcohol (g/d), linoleic acid (% of energy), fiber (g/d), and fruit, berries, and vegetables (g/d). Model 3 was adjusted as for model 2 and egg consumption (g/d).

TABLE 4
Markers of glucose homeostasis and inflammation at baseline and after 4 y of follow-up according to egg consumption at baseline in 1984–1989[1]

	Egg consumption quartile				
	1	2	3	4	*P*-trend
Fasting plasma glucose, mmol/L					
Baseline number of participants (intake, g/d)	579 (<14)	577 (14–26)	578 (27–45)	578 (>45)	
Model 1	4.55 (4.52, 4.58)	4.51 (4.48, 4.57)	4.50 (4.47, 4.54)	4.52 (4.49, 4.56)	0.40
Model 2	4.55 (4.52, 4.58)	4.52 (4.49, 4.55)	4.50 (4.47, 4.54)	4.52 (4.49, 4.55)	0.27
Model 3	4.57 (4.54, 4.61)	4.53 (4.50, 4.57)	4.50 (4.47, 4.53)	4.48 (4.44, 4.52)	0.002
Number of participants at 4 y (intake, g/d)	220 (<14)	222 (14–25)	218 (25–41)	220 (>41)	
Model 1	4.88 (4.83, 4.95)	4.85 (4.79, 4.91)	4.83 (4.77, 4.89)	4.80 (4.74, 4.85)	0.03
Model 2	4.88 (4.83, 4.94)	4.86 (4.81, 4.92)	4.82 (4.77, 4.88)	4.79 (4.74, 4.85)	0.02
Model 3	4.90 (4.83, 4.96)	4.87 (4.81, 4.93)	4.82 (4.77, 4.88)	4.78 (4.71, 4.84)	0.02
Fasting serum insulin, mU/L					
Baseline number of participants (intake, g/d)	579 (<14)	577 (14–26)	578 (27–45)	578 (>45)	
Model 1	10.95 (10.44, 11.45)	10.84 (10.35, 11.34)	10.62 (10.12, 11.11)	11.07 (10.56, 11.57)	0.73
Model 2	10.96 (10.53, 11.40)	10.91 (10.48, 11.34)	10.57 (10.14, 11.00)	11.03 (10.59, 11.47)	0.88
Model 3	11.12 (10.64, 11.60)	11.00 (10.56, 11.45)	10.55 (10.13, 10.98)	10.79 (10.26, 11.33)	0.35
Number of participants at 4 y (intake, g/d)	220 (<14)	222 (14–25)	218 (25–41)	220 (>41)	
Model 1	7.66 (6.98, 8.33)	6.98 (6.31, 7.64)	7.42 (6.75, 8.09)	7.36 (5.58, 8.05)	0.86
Model 2	7.31 (6.73, 7.89)	7.30 (6.73, 7.87)	7.33 (6.76, 7.91)	7.47 (6.88, 8.06)	0.68
Model 3	7.52 (6.89, 8.15)	7.42 (6.83, 8.00)	7.32 (6.75, 7.89)	7.15 (6.45, 7.85)	0.49
C-reactive protein, mg/L					
Baseline number of participants (intake, g/d)	579 (<14)	577 (14–26)	578 (27–45)	578 (>45)	
Model 1	2.54 (2.21, 2.87)	2.37 (2.04, 2.70)	2.18 (1.85, 2.50)	2.17 (1.84, 2.51)	0.13
Model 2	2.40 (2.07, 2.73)	2.43 (2.11, 2.75)	2.28 (1.96, 2.60)	2.14 (1.81, 2.47)	0.20
Model 3	2.42 (2.06, 2.79)	2.45 (2.11, 2.78)	2.28 (1.96, 2.60)	2.11 (1.71, 2.51)	0.26
Number of participants at 4 y (intake, g/d)	220 (<14)	222 (14–25)	218 (25–41)	220 (>41)	
Model 1	3.38 (2.50, 4.26)	3.93 (3.06, 4.79)	3.15 (2.28, 4.02)	2.27 (1.38, 3.17)	0.03
Model 2	3.21 (2.33, 4.09)	4.09 (3.23, 4.95)	3.14 (2.30, 4.03)	2.26 (1.36, 3.15)	0.04
Model 3	3.07 (2.11, 4.03)	4.01 (3.12, 4.90)	3.17 (2.30, 4.04)	2.47 (1.41, 3.54)	0.26

[1]Values are means (95% CIs) obtained by using ANCOVA unless otherwise indicated. Model 1 was adjusted for age, examination year, and energy intake (kcal/d). Model 2 was adjusted as for model 1 plus BMI (kg/m^2), family history of type 2 diabetes (yes or no), hypertension (yes or no), smoking (never smoker; previous smoker; current smoker, <20 cigarettes/d; current smoker, ≥20 cigarettes/d), education years, leisure-time physical activity (kcal/d), serum long-chain omega-3 PUFAs (percentage of all serum fatty acids), and intakes of alcohol (g/d), linoleic acid (% of energy), fiber (g/d), and fruit, berries, and vegetables (g/d). Model 3 was adjusted as for model 2 and dietary cholesterol intake (mg/d). One medium egg weighs ~55 g.

data were available, *APOE4* phenotype (n = 394) did not modify the associations with either egg or cholesterol intake (P-interaction > 0.05).

DISCUSSION

In this prospective, population-based cohort study in middle-aged and older men, higher egg intake was associated with lower risk of incident T2D. The analyses with metabolic risk markers for T2D suggested an inverse association with fasting plasma glucose and serum CRP but not with serum insulin. The association between cholesterol intake and risk of T2D was similar to that of egg consumption but was attenuated after adjusting for egg consumption. Cholesterol intake also had an unfavorable association with plasma glucose and serum insulin, although most associations were not significant.

The average egg intake in our study was similar to the average intake in another study population from Finland (16) and in studies from China (21) and Japan (19) and in the Adventist Health Studies in the United States (17) but was higher than in other study cohorts from the United States—the Cardiovascular Health Study (18) and the Physicians' Health Study and the Women's Health Study (20). Our finding of a lower T2D risk with higher egg intake is in contrast with these studies, which found either a direct association (20–22) or no association (16–19) with higher intake. However, one of these studies was a cross-sectional analysis (21) and one was a case-control study (22). The limitations of case-control and cross-sectional study designs in nutrition research, such as reverse causation and recall and selection biases, warrant caution in interpreting the results from these studies. These limitations are largely avoided with a prospective study design, in which the information on dietary intakes is collected before the occurrence of disease. The association between egg consumption and risk of T2D has been investigated in 5 prospective studies (16–20) and only one found a direct association (20).

Most studies have assessed egg intake by using food-frequency questionnaires, which do not usually contain detailed information about egg consumption, such as eggs in mixed dishes or eggs used in baking. However, this would add random error to the estimates of egg intake, which would attenuate the true associations. One potential explanation for the opposite findings is that eggs are seldom consumed in isolation but are usually eaten as part of a mixed dish. For example, in many countries, eggs are commonly consumed with processed red meat, such as bacon, sausages, or burgers, and processed red meat has been associated with a higher risk of T2D (34). Also, in many studies that found a positive association between higher egg intake and risk of T2D

TABLE 5
Markers of glucose homeostasis and inflammation at baseline and after 4 y of follow-up according to cholesterol intake at baseline in 1984–1989[1]

	Cholesterol intake quartile				
	1	2	3	4	*P*-trend
Fasting plasma glucose, mmol/L					
Baseline number of participants (intake, mg/d)	578 (<291)	578 (291–371)	578 (372–478)	578 (>478)	
Model 1	4.51 (4.47, 4.55)	4.49 (4.46, 4.52)	4.51 (4.47, 4.54)	4.58 (4.54, 4.62)	0.01
Model 2	4.52 (4.49, 4.56)	4.50 (4.47, 4.53)	4.50 (4.47, 4.53)	4.56 (4.52, 4.60)	0.13
Model 3	4.51 (4.46, 4.55)	4.49 (4.46, 4.52)	4.50 (4.47, 4.54)	4.59 (4.54, 4.63)	0.03
Number of participants at 4 y (intake, mg/d)	220 (<277)	220 (277–347)	220 (348–455)	220 (>455)	
Model 1	4.88 (4.82, 4.94)	4.82 (4.77, 4.88)	4.84 (4.78, 4.90)	4.83 (4.76, 4.89)	0.45
Model 2	4.90 (4.83, 4.96)	4.83 (4.77, 4.89)	4.83 (4.78, 4.89)	4.81 (4.74, 4.87)	0.16
Model 3	4.88 (4.81, 4.95)	4.82 (4.76, 4.88)	4.83 (4.78, 4.89)	4.83 (4.75, 4.91)	0.56
Fasting serum insulin, mU/L					
Baseline number of participants (intake, mg/d)	578 (<291)	578 (291–371)	578 (372–478)	578 (>478)	
Model 1	10.45 (9.89, 11.02)	10.47 (9.97, 10.97)	10.99 (10.49, 11.49)	11.56 (10.98, 12.14)	0.01
Model 2	10.54 (10.04, 11.04)	10.65 (10.21, 11.08)	10.91 (10.48, 11.34)	11.38 (10.86, 11.90)	0.03
Model 3	10.35 (9.78, 10.92)	10.56 (10.12, 11.01)	10.93 (10.50, 11.35)	11.63 (11.00, 12.26)	0.01
Number of participants at 4 y (intake, mg/d)	220 (<277)	220 (277–347)	220 (348–455)	220 (>455)	
Model 1	6.99 (6.23, 7.74)	6.82 (6.14, 7.50)	7.73 (7.06, 8.40)	7.88 (7.10, 8.65)	0.07
Model 2	7.04 (6.27, 7.71)	6.96 (6.38, 7.54)	7.65 (7.08, 8.22)	7.76 (7.07, 8.45)	0.12
Model 3	7.05 (6.31, 7.78)	6.96 (6.36, 7.55)	7.65 (7.08, 8.22)	7.75 (7.07, 8.57)	0.19
C-reactive protein, mg/L					
Baseline number of participants (intake, mg/d)	578 (<291)	578 (291–371)	578 (372–478)	578 (>478)	
Model 1	2.25 (1.88, 2.63)	2.37 (2.03, 2.70)	2.17 (1.84, 2.50)	2.46 (2.08, 2.85)	0.60
Model 2	2.40 (2.02, 2.78)	2.42 (2.10, 2.75)	2.19 (1.87, 2.51)	2.24 (1.85, 2.63)	0.49
Model 3	2.25 (1.82, 2.68)	2.36 (2.02, 2.70)	2.20 (1.88, 2.53)	2.44 (1.97, 2.91)	0.75
Number of participants at 4 y (intake, mg/d)	220 (<277)	220 (277–347)	220 (348–455)	220 (>455)	
Model 1	3.34 (2.36, 4.32)	3.76 (2.87, 4.64)	2.91 (2.03, 3.78)	2.73 (1.72, 3.73)	0.27
Model 2	3.69 (2.67, 4.71)	3.95 (3.06, 4.83)	2.80 (1.93, 3.66)	2.30 (1.25, 3.35)	0.05
Model 3	3.48 (2.37, 4.60)	3.85 (2.95, 4.76)	2.80 (1.93, 3.66)	2.60 (1.36, 3.84)	0.24

[1]Values are means (95% CIs) obtained by using ANCOVA unless otherwise indicated. Model 1 was adjusted for age, examination year, and energy intake (kcal/d). Model 2 was adjusted as for model 1 plus BMI (kg/m^2), family history of type 2 diabetes (yes or no), hypertension (yes or no), smoking (never smoker; previous smoker; current smoker, <20 cigarettes/d; current smoker, ≥20 cigarettes/d), education years, leisure-time physical activity (kcal/d), serum long-chain omega-3 PUFAs (percentage of all serum fatty acids), and intakes of alcohol (g/d), linoleic acid (% of energy), fiber (g/d), and fruit, berries, and vegetables (g/d). Model 3 was adjusted as for model 2 and egg consumption (g/d).

(20, 21) or cardiovascular disease (35–37), those who consumed more eggs were also more likely to smoke and have lower leisure-time physical activity. This was not observed in our study cohort (Table 1). On the other hand, higher egg intake was also not uniformly associated with healthier lifestyle or dietary factors (Table 1), and adjustment for potential risk factors in the multivariate-adjusted model did not have a major impact on the associations. This suggests that, in our study cohort, egg consumption was not just a surrogate for some other factors that could explain the inverse association between egg intake and risk of T2D.

Several small randomized trials that investigated the effect of additional egg intake on various risk markers support our findings. In these trials, compared with a yolk-free substitute, the consumption of 3 eggs/d for 12 wk as a part of a carbohydrate-restricted diet reduced plasma insulin concentrations and insulin resistance among subjects with metabolic syndrome (8), although no effect was found on fasting glucose among overweight men (38). Also, the consumption of 3 eggs/d was found to decrease inflammatory markers (9–11). The opposite was observed in another trial, in which the addition of 4 eggs/d for 4 wk increased inflammatory markers in lean insulin-sensitive subjects, although this was not observed in lean or obese insulin-resistant subjects (39). Although egg intake may increase the total- to HDL-cholesterol ratio (40), the addition of eggs has also been found to increase the formation of larger and less-dense LDL and HDL particles, at least when accompanied with a low-carbohydrate diet (8, 12). Egg intake may also increase plasma adiponectin concentrations (9), and low plasma adiponectin has been suggested as a risk factor for insulin resistance and T2D (41). Although we did not find an association between egg consumption and serum insulin, we did find an inverse association with plasma glucose and a suggestive inverse association with serum CRP, which provide possible mechanisms for the observed lower risk of T2D. Unfortunately, we did not have data on lipoprotein particle sizes or plasma adiponectin.

One medium egg contains ~200 mg cholesterol, so eggs are a major contributor to cholesterol intake. In rats, an egg yolk–enriched diet increased plasma glucose (3); and in studies in humans, egg or cholesterol intakes correlated with elevated fasting glucose (5). Higher cholesterol intake was also associated with increased risk of incident T2D in some (6, 7, 42) but not all (18, 19) studies. In our analyses, both egg and cholesterol intakes had a similar inverse association with T2D risk after multivariate adjustment. However, the association with cholesterol intake was attenuated after further adjustment for egg intake, suggesting that the inverse association with cholesterol intake mainly reflected the inverse association of egg consumption. This

is also supported by the mainly negative associations between cholesterol intake and plasma glucose and serum insulin (Table 5) and by the lack of association with T2D with a shorter (10-y) follow-up or after the exclusion of participants with coronary heart disease at baseline.

In addition to cholesterol, eggs and especially egg yolks are also a rich source of many nutrients that could have a beneficial impact on health. The change in the risk estimates after mutual adjustment for egg and cholesterol intakes (model 3) may reflect the impact of these nutrients on glucose metabolism. In addition to high-quality protein, PUFAs, vitamins, and minerals, these nutrients include several bioactive compounds such as phosphatidylcholine and other phospholipids and carotenoids such as lutein and zeaxanthin (43), which have been found to have anti-inflammatory properties (44–46). The inverse association between egg consumption and T2D risk could also be explained by foods that eggs replace in the diet, such as low-quality carbohydrates. However, adjustment for carbohydrate intake or glycemic load, an indicator of carbohydrate quality, did not have an effect on the associations.

Strengths of our study include the assessment of egg consumption with a dietary record and the inclusion of eggs in mixed dishes and recipes in the egg intake estimates. However, we did not have information on the food preparation methods, so we could not investigate whether the associations would be similar with fried and boiled eggs. Also, because few subjects consumed only egg whites, we could not differentiate the associations with egg whites from the associations with whole eggs. Other strengths include the population-based recruitment, prospectively collected data, extensive examinations for potential confounders, a long follow-up period with a large number of events, and no loss to follow-up. A potential limitation is the single-exposure measurement at baseline, which may cause random error due to misclassification, therefore possibly underestimating the observed associations. This is supported by the analyses with a shorter (10-y) follow-up, which showed stronger associations between egg intake and the risk of T2D. However, the average egg consumption in Finland has remained relatively stable during the past 40 y (47). Margarines and other products that contain plant sterols and stanols can lower the absorption of dietary cholesterol (48) and could therefore confound the associations with egg and cholesterol intakes. However, we did not have information on the use of these products. Finally, the findings may not be generalizable to other age groups or to women, because our study population included only middle-aged and older men.

In conclusion, our study did not show any adverse effects of moderate egg intake (up to 1 egg/d) on the risk of T2D in middle-aged and older men from eastern Finland but rather suggested an inverse association. Some population groups are still advised to limit their egg intake, such as those who already have T2D (23, 24). However, these findings suggest that the recommendations to limit the consumption of eggs (or any food) in a general healthy population should not be based on a single component in a food, such as the cholesterol in eggs.

The authors' responsibilities were as follows—JKV, JM, T-PT, and SV: acquired data and designed and conducted the research; JKV: analyzed data, drafted the manuscript, and had primary responsibility for final content; JM, T-PT, HEKV, and SV: critically revised the manuscript for important intellectual content; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

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