Cholesterol and egg intakes and the risk of type 2 diabetes: The Japan Public Health Center-based Prospective Study

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Abstract

Limited and inconsistent associations between cholesterol and egg consumption and type 2 diabetes risk have been observed in Western countries. In the present study, the association of dietary cholesterol and egg intakes with type 2 diabetes risk was examined prospectively. The study subjects comprised 27 248 men and 36 218 women aged 45–75 years who participated in the second survey of the Japan Public Health Center-based Prospective Study and had no histories of type 2 diabetes or other serious diseases. Dietary cholesterol and egg intakes were estimated using a validated 147-item FFQ. The OR of self-reported, physician-diagnosed type 2 diabetes over 5 years were estimated using multiple logistic regression. A total of 1165 newly diagnosed cases of type 2 diabetes were self-reported. Although dietary cholesterol intake was not associated with type 2 diabetes risk in men, it was found to be associated with a 23 % lower odds of type 2 diabetes risk in women in the highest quartile of intake, albeit not statistically significant, compared with those in the lowest quartile ($P_{trend} = 0.08$). Such risk reduction was somewhat greater among postmenopausal women; the multivariable-adjusted OR for the highest quartile of cholesterol intake compared with the lowest quartile was 0.68 (95 % CI 0.49, 0.94; $P_{trend} = 0.04$). No association between egg intake and type 2 diabetes risk was found in either men or women. In conclusion, higher intake of cholesterol or eggs may not be associated with an increased risk of type 2 diabetes in Japanese populations. The observed association between decreased type 2 diabetes risk and higher dietary cholesterol intake in postmenopausal women warrants further investigation.

Key words: Dietary cholesterol: Eggs: Type 2 diabetes

The prevalence of diabetes is increasing globally, and it is estimated to be 9·9 % by 2030[1]. In Japan, the prevalence of diabetes has been increasing since the 1950s[2], and this increase has generally been ascribed to a Westernised diet that is characterised by high intakes of fat and meat. Dietary cholesterol intake in Japan increased from 57 mg/d in 1947 to approximately 350 mg/d in the 1970s[3]. To date, meta-analyses of the relevant prospective studies have shown that high consumption of meat is associated with an increased risk of type 2 diabetes[4–6]. However, evidence regarding the association between dietary cholesterol intake and type 2 diabetes risk is scarce.

Most[7–10], but not all[11], prospective studies have reported that dietary cholesterol intake is associated with an increased risk of type 2 diabetes in Western populations in which dietary cholesterol is mainly derived from meat[12]. However, most of these Western studies did not consider meat intake when examining the association between dietary cholesterol intake and type 2 diabetes risk[8–10], which may have confounded the results reported. Eggs are rich in cholesterol[13], and the association between egg intake and type 2 diabetes risk has also been examined in Western countries; however, the results are inconsistent. Some studies have found no association[11,14,15], whereas one study has found egg intake to be associated with an increased risk of type 2 diabetes in both men and women[7].

To our knowledge, all the previous prospective studies on this topic have been conducted in Western populations.

Importantly, Western and Asian populations consume similar sources of dietary cholesterol, but contributions of each source differ[12,16]. In addition, Asian populations have relatively lower insulin secretory capacity[17] and body masses[18] than Western populations. Thus, the effect of cholesterol and egg intakes on type 2 diabetes risk in Asian populations may differ from that in Western populations. In the present study, the association of dietary cholesterol and egg intakes with type 2 diabetes risk was investigated prospectively in a large-scale, population-based cohort of Japanese men and women. Furthermore, stratified analyses that included obesity level and menopausal status were conducted.

Materials and methods

Study design

The Japan Public Health Center-based Prospective (JPHC) Study was established in 1990 for cohort I and in 1993 for cohort II[19]. Subjects in cohort I comprised residents of five Japanese public health centre areas (Iwate, Akita, Nagano, Okinawa and Tokyo) aged 40–59 years. Subjects in cohort II included residents of six public health centre areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa and Osaka) aged 40–69 years. A questionnaire survey was conducted at baseline and at the 5-year and 10-year follow-ups. Information on medical histories and health-related lifestyles including smoking, drinking and dietary habits was obtained during each survey. Although written informed consent was not required, the subjects were informed of the objectives of the study, and those who responded to the questionnaire survey were considered to have consented to participating in the survey.

Of the potential baseline subjects (n 140 420), 113 403 responded to the questionnaire survey at baseline. Of these subjects, 89 947 (79·3 %) responded to the questionnaire survey at the 5-year follow-up (i.e. the second survey) and 76 901 (67·8 %) responded to the questionnaire survey at the 10-year follow-up (i.e. the third survey). Subjects (n 12 872) who reported histories of type 2 diabetes, cancer, stroke, IHD or chronic liver disease during the baseline or second survey, those who reported kidney disease during the baseline survey and those with missing information on cholesterol and egg intakes were excluded from the study. Furthermore, subjects (n 563) who reported extreme total energy intake (outside of the mean (sd 3) for each sex) were excluded. Ultimately, a total of 63 466 subjects (27 248 men and 36 218 women) were included in the study. The present study was approved by the Institutional Review Board of the National Cancer Center of Japan.

FFQ

The subjects completed a self-administered FFQ during the baseline, second and third surveys. Data on 147 food and beverage items and nine frequency categories[20] from the second survey were used as the baseline data for the present analysis because the questionnaire that was used during the second survey more comprehensively provided information on food intake than did the questionnaire that was used during the baseline survey. During the second survey, the subjects were asked details regarding typical consumption of eggs within the past year[20]. For most of the food items, nine response options that described consumption frequencies were available; these options ranged from rarely (<1 time/month) to ≥7 times/d. A standard portion size was specified for each food, and the subjects were asked to indicate their typical portion size from among three options (≤0·5 times, standard or ≥1·5 times). Daily egg intake was calculated by multiplying the daily consumption frequency by the typical portion size and is expressed as g/d.

Dietary intake in terms of energy and selected nutrients, including cholesterol, were estimated based on the Standard Tables of Food Composition in Japan[13]. The validity and reproducibility of the FFQ were examined in a subsample of subjects in cohorts I and II of the JPHC Study. Details of the validation study have been given elsewhere[21–23]. When examining the validity of the FFQ, energy-adjusted Spearman's correlation coefficients for the intake values of cholesterol and eggs derived from the FFQ and those derived from 28- or 14-d dietary records were found to be 0·33 and 0·25, respectively, for men in cohort I and 0·35 and 0·42, respectively, for women in cohort I[23] and 0·47 and 0·47, respectively, for men in cohort II and 0·47 and 0·45, respectively, for women in cohort II[21]. When examining the reproducibility of the FFQ, energy-adjusted Spearman's correlation coefficients for the intake values of cholesterol and eggs derived from the two FFQ that were administered 1 year apart were found to be 0·49 and 0·51, respectively, for men in cohort I and 0·46 and 0·54, respectively, for women in cohort I[22] and 0·50 and 0·55, respectively, for men in cohort II and 0·53 and 0·57, respectively, for women in cohort II[21].

Ascertainment of type 2 diabetes

Physician-diagnosed type 2 diabetes during the 5-year period after the second survey was ascertained via a self-administered questionnaire during the third survey. During the third survey, the study participants were questioned about their histories of major diseases, including diabetes. Because the second survey data were used as the baseline survey data in the present study, only subjects who were diagnosed after this survey were considered as incident cases during the follow-up. In a validation study in a subsample of JPHC Study participants[24], 94 % of the self-reported diabetes cases were confirmed by medical records.

Other variables

Information on other variables including weight, height, smoking status, alcohol consumption, physical activity level, menopausal status and history of hypertension used in the present analysis was derived from the second survey, whereas that on family history of diabetes was derived from the baseline survey. BMI was calculated as weight in kg divided by height in m^2. Average daily ethanol intake from alcoholic beverages was calculated as drinking frequency multiplied

by ethanol consumption per drinking day. Metabolic equivalents (MET) per d were estimated from the average amount of time spent per d engaged in three types of physical activities at work and during leisure time, and this measure has been validated previously[25].

Statistical analyses

Analyses were carried out separately for men and women. The subjects were divided into quartiles according to their intake of cholesterol or eggs. The following confounding variables were considered: age (years, continuous); study area (eleven areas); BMI (<21, $21–22\cdot9$, $23–24\cdot9$, $25–26\cdot9$, or $\geq27\,kg/m^2$); smoking status (lifetime non-smoker, former smoker, or current smoker smoking either <20 or ≥20 cigarettes/d); alcohol consumption (non-drinker, occasional drinker, or drinker consuming <150, $150–299$, $300–499$, or $\geq450\,g$ ethanol/week for men and <150 or $\geq150\,g$ ethanol/week for women); total physical activity levels (MET-h/d, quartiles); history of hypertension (yes or no); family history of diabetes mellitus (yes or no); coffee consumption (almost never, <1, 1, or ≥2 cups/d); total energy intake (kJ/d, continuous); Ca intake (mg/d, continuous); Mg intake (mg/d, continuous); rice intake (g/d, continuous); fish and shellfish intake (g/d, continuous); meat intake (g/d, continuous); vegetable intake (g/d, continuous); soft drink intake (g/d, continuous). The dietary factors considered in the present study either have been shown to be associated with type 2 diabetes risk in previous studies or have been found to be associated with type 2 diabetes risk in the present cohort. An indicator variable for missing data was created for each covariate. Age-adjusted means were calculated using ANOVA, and age-adjusted proportions were calculated using logistic regression. Trend associations between confounding factors and dietary cholesterol intake were examined using linear regression analysis for continuous variables and logistic regression analysis for categorical variables.

The association of the energy-adjusted (residual method[26]) intakes of cholesterol and eggs with diabetes risk was assessed by OR, which were estimated by multiple logistic regression. The 95 % CI of the OR were estimated using the Wald method. The first model was adjusted for age and study area, and the second model was further adjusted for BMI, smoking status, alcohol consumption, family history of diabetes mellitus, history of hypertension and total physical activity levels (multivariate model 1). The final model was further adjusted for total energy intake, coffee consumption, and intakes of Ca, Mg, rice, fish and shellfish, meat, vegetables and soft drinks (multivariate model 2). To avoid problems in effect estimation such as variance inflation, all variables of interest were tested for multicollinearity by calculating the variance inflation factor. The variance inflation factor for multivariate model 2 was not significant for multicollinearity (mean variance inflation factor was $1\cdot6$ in men and $1\cdot5$ in women). Tests for linear trends were conducted by assigning a median value for each category and treating that term as a single continuous variable in the model. In addition, dietary variables were included one at a time to multivariate model 1

to identify variables influencing the association between dietary cholesterol and egg intakes and type 2 diabetes risk. Data were also analysed according to BMI (<25 or $\geq25\,kg/m^2$) in both men and women and according to menopausal status (premenopausal or postmenopausal) in women. Interaction terms between dietary intake (continuous) and the above-mentioned stratifying variables (dichotomous) were created and included in the model to assess statistical interactions. Statistical significance was defined by two-sided P values below $0\cdot05$. All analyses were carried out with SAS software (version 9.2; SAS Institute, Inc.).

Results

During the 5-year period after the second survey, 1165 participants (672 men and 493 women) were newly diagnosed as having type 2 diabetes. At baseline (i.e. at the time of the second survey), it was found that men with higher dietary cholesterol intake were more likely to be older and physically inactive and less likely to consume alcohol (Table 1). Furthermore, it was found that women with higher dietary cholesterol intake were less likely to report history of hypertension and postmenopausal status. Both men and women with higher dietary cholesterol intake had higher intakes of protein, fat, Ca, eggs, meat, and fish and shellfish and lower intakes of carbohydrates and rice when compared with those with lower dietary cholesterol intake. Men with higher dietary cholesterol intake consumed higher amounts of Mg and vegetables.

Dietary cholesterol intake was found to be inversely associated with type 2 diabetes risk in women after adjustment for non-dietary covariates (multivariate model 1) ($P_{trend} = 0\cdot007$; Table 2). This association was attenuated after further adjustment for dietary covariates (multivariate model 2); dietary cholesterol intake was found to be associated with a 23 % lower odds of type 2 diabetes risk in women in the highest quartile of intake compared with those in the lowest quartile, albeit this difference was not statistically significant (OR $0\cdot77$, 95 % CI $0\cdot57$, $1\cdot04$; $P_{trend} = 0\cdot08$). Dietary variables that changed point estimates of multivariate model 1 by ≥3 % were rice ($4\cdot8$ %), fish and shellfish ($11\cdot5$ %), and meat ($-7\cdot7$ %) in men and Ca ($4\cdot3$ %), rice ($7\cdot1$ %), fish and shellfish ($-4\cdot3$ %), and meat ($4\cdot3$ %) in women.

In the analysis stratified by menopausal status, dietary cholesterol intake was found to be significantly associated with the odds of type 2 diabetes risk in the postmenopausal group (multivariate model 2); the multivariate-adjusted OR for type 2 diabetes risk for the lowest quartile through the highest quartile of intake were $1\cdot00$ (95 % CI reference), $0\cdot87$ (95 % CI $0\cdot65$, $1\cdot16$), $0\cdot96$ (95 % CI $0\cdot71$, $1\cdot29$) and $0\cdot68$ (95 % CI $0\cdot47$, $0\cdot94$) ($P_{trend} = 0\cdot04$). In contrast, no such trend association was found among premenopausal women ($P_{trend} = 0\cdot78$; $P_{interaction} = 0\cdot83$). In the analysis stratified by BMI with adjustment for non-dietary covariates (multivariate model 1), high dietary cholesterol intake was found to be significantly associated with a decreased odds of type 2 diabetes risk in both women with BMI <25 and those with $\geq25\,kg/m^2$ ($P_{trend} = 0\cdot03$ in both groups; $P_{interaction} = 0\cdot92$). After further

Table 1. Baseline characteristics of the subjects according to quartiles (Q) of energy-adjusted cholesterol intake

(Mean values and standard deviations; mean values with their standard errors; proportions)

	Men									Women								
	Quartiles of cholesterol intake									Quartiles of cholesterol intake								
	Q1 (low)		Q2		Q3		Q4 (high)			Q1 (low)		Q2		Q3		Q4 (high)		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	P_{trend}*	Mean	SE	Mean	SE	Mean	SE	Mean	SE	P_{trend}*
n	6812		6812		6812		6812			9054		9055		9055		9054		
Age (years)									<0·0001									0·001
Mean	50·5		50·6		51·1		52·0			52·1		51·2		51·1		51·7		
SD	7·7		7·5		7·6		7·8			7·7		7·7		7·6		8·0		
BMI (kg/m²)†‡	23·5	0·03	23·5	0·03	23·6	0·03	23·5	0·03	0·78	23·5	0·03	23·4	0·03	23·4	0·03	23·4	0·03	0·04
Current smoker (%)†§	47·4		46·5		45·2		45·8		0·04	4·9		4·3		4·1		4·4		0·12
Alcohol consumption ≥1 d/week (%)	71·3		70·4		68·9		59·9		<0·0001	10·7		12·2		11·7		11·5		0·19
Total physical activity levels (MET-h/d)†	34·2	0·09	34·1	0·09	34·0	0·09	33·5	0·09	<0·0001	32·9	0·07	33·0	0·07	32·9	0·07	32·6	0·07	0·001
History of hypertension (%)	15·8		15·5		15·7		14·1		0·007	17·3		15·8		16·0		15·4		0·001
Family history of diabetes (%)	8·3		8·3		7·6		8·2		0·65	8·1		8·8		8·8		8·8		0·12
Postmenopausal status (%)	–		–		–		–		–	81·7		81·8		80·5		78·6		<0·0001
Food and nutrient intakes‖																		
Energy (kJ/d)	9134	36·8	9740	36·8	9699	36·8	8983	36·8	<0·0001	1872	6·77	2000	6·76	2010	6·76	1808	6·76	<0·0001
Protein (g/d)	62	0·13	70	0·13	75	0·13	84	0·13	<0·0001	61	0·09	67	0·09	70	0·09	76	0·09	<0·0001
Carbohydrate (g/d)	302	0·57	287	0·57	276	0·56	258	0·57	<0·0001	278	0·33	258	0·33	247	0·33	231	0·33	<0·0001
Fat (g/d)	43	0·17	53	0·17	58	0·17	66	0·17	<0·0001	48	0·12	55	0·12	58	0·12	63	0·12	<0·0001
Saturated fat (g/d)	13	0·07	16	0·07	18	0·07	20	0·07	<0·0001	14	0·05	17	0·05	17	0·05	19	0·05	<0·0001
Monounsaturated fat (g/d)	15	0·07	18	0·07	20	0·07	23	0·07	<0·0001	16	0·05	19	0·05	20	0·05	22	0·05	<0·0001
Polyunsaturated fat (g/d)	10	0·04	12	0·04	13	0·04	14	0·04	<0·0001	12	0·03	12	0·03	13	0·03	14	0·03	<0·0001
Fish and shellfish (g/d)	63	0·61	83	0·61	97	0·61	119	0·61	<0·0001	63	0·48	81	0·47	93	0·47	109	0·47	<0·0001
Ca (mg/d)	431	2·61	492	2·61	514	2·61	561	2·62	<0·0001	508	2·2	546	2·2	549	2·2	588	2·2	<0·0001
Mg (mg/d)	267	0·65	276	0·65	282	0·65	289	0·65	<0·0001	272	0·52	270	0·52	271	0·52	273	0·52	0·07
Rice (g/d)	485	2·02	449	2·02	418	2·02	377	2·03	<0·0001	377	1·4	352	1·4	337	1·4	309	1·4	<0·0001
Vegetables (g/d)	181	1·49	194	1·49	201	1·49	204	1·49	<0·0001	241	1·37	228	1·37	225	1·37	221	1·37	<0·0001
Meat (g/d)	45	0·49	61	0·49	68	0·49	79	0·49	<0·0001	43	0·39	54	0·39	59	0·39	66	0·39	<0·0001
Eggs (g/d)	11	0·31	21	0·31	33	0·31	64	0·31	<0·0001	10	0·21	19	0·21	29	0·21	56	0·21	<0·0001
Soft drinks (g/d)	73	3·12	52	3·12	52	3·11	65	3·12	0·16	22	0·76	16	0·76	15	0·76	16	0·76	0·0001
Coffee consumption ≥1 cup/d (%)†	32·3		34·3		34·1		33·7		0·16	35·2		37·4		37·0		35·3		0·79

MET, metabolic equivalents.

* On the basis of the logistic regression analyses for categorical variables and linear regression analysis for continuous variables, each category of intake was weighted against the median intake for that category.

† Subjects with missing information were excluded (BMI (kg/m²): 496 men and 794 women; smoking status: 579 men and 2161 women; total physical activity levels: 4400 men and 6086 women; coffee consumption: 1241 men and 1602 women).

‡ Age-adjusted means and standard errors.

§ Age-adjusted proportion.

‖ Energy-adjusted by the residual method except energy intake and coffee consumption.

Table 2. Association between dietary cholesterol intake and type 2 diabetes risk according to quartiles (Q) of energy-adjusted cholesterol intake
(Odds ratios and 95 % confidence intervals; medians, number of cases and subjects)

	Quartiles of cholesterol intake									
	Q1 (low)		Q2		Q3		Q4 (high)		P_{trend}*	$P_{interaction}$
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI		
Men										
Cases (*n*)		167		168		160		177		
Subjects (*n*)		6812		6812		6812		6812		
Median (mg)		168·5		247·6		316·7		423·3		
Age and area adjusted†	1·00	Reference	1·01	0·82, 1·26	0·96	0·77, 1·20	1·06	0·86, 1·32	0·65	
Multivariate model 1‡	1·00	Reference	1·01	0·81, 1·26	0·95	0·76, 1·19	1·04	0·83, 1·29	0·83	
Multivariate model 2§	1·00	Reference	1·04	0·83, 1·30	1·00	0·79, 1·28	1·12	0·86, 1·44	0·44	
Men with BMI < 25 kg/m² ‖										
Cases (*n*)		83		89		91		83		
Subjects (*n*)		4827		4846		4863		4802		
Multivariate model 1‡	1·00	Reference	1·08	0·79, 1·46	1·09	0·81, 1·48	0·99	0·73, 1·36	0·95	0·58
Multivariate model 2§	1·00	Reference	1·13	0·82, 1·54	1·18	0·85, 1·64	1·09	0·75, 1·56	0·69	0·59
Men with BMI ≥ 25 kg/m² ‖										
Cases (*n*)		80		77		69		92		
Subjects (*n*)		1848		1859		1850		1856		
Multivariate model 1‡	1·00	Reference	0·96	0·69, 1·33	0·82	0·59, 1·15	1·11	0·81, 1·52	0·60	
Multivariate model 2§	1·00	Reference	0·99	0·71, 1·39	0·87	0·60, 1·25	1·21	0·83, 1·76	0·34	
Women										
Cases (*n*)		145		128		120		100		
Subjects (*n*)		9054		9055		9055		9054		
Median (g)		166·8		236·5		296·5		389·6		
Age and area adjusted†	1·00	Reference	0·90	0·71, 1·15	0·85	0·67, 1·09	0·70	0·54, 0·90	0·005	
Multivariate model 1‡	1·00	Reference	0·94	0·74, 1·20	0·87	0·68, 1·11	0·70	0·54, 0·91	0·007	
Multivariate model 2§	1·00	Reference	0·99	0·77, 1·28	0·94	0·72, 1·22	0·77	0·57, 1·04	0·08	
Women with BMI < 25 kg/m² ‖										
Cases (*n*)		63		63		57		42		
Subjects (*n*)		6287		6524		6490		6391		
Multivariate model 1‡	1·00	Reference	0·99	0·70, 1·42	0·90	0·62, 1·29	0·66	0·44, 0·98	0·03	0·92
Multivariate model 2§	1·00	Reference	1·09	0·75, 1·57	0·996	0·67, 1·48	0·74	0·47, 1·15	0·15	0·94
Women with BMI ≥ 25 kg/m² ‖										
Cases (*n*)		80		65		62		51		
Subjects (*n*)		2549		2383		2393		2407		
Multivariate model 1‡	1·00	Reference¶	0·89	0·63, 1·24	0·83	0·59, 1·17	0·67	0·47, 0·97	0·03	
Multivariate model 2§	1·00	Reference	0·91	0·64, 1·29	0·85	0·59, 1·23	0·71	0·47, 1·07	0·097	
Premenopausal women										
Cases (*n*)		30		37		21		29		
Subjects (*n*)		2335		2567		2701		2754		
Multivariate model 1‡	1·00	Reference	1·29	0·78, 2·13	0·65	0·37, 1·16	0·88	0·52, 1·48	0·26	0·88
Multivariate model 2§	1·00	Reference	1·61	0·95, 2·73	0·88	0·48, 1·64	1·32	0·71, 2·45	0·78	0·83
Postmenopausal women										
Cases (*n*)		115		91		99		71		
Subjects (*n*)		6719		6488		6354		6300		
Multivariate model 1‡	1·00	Reference	0·86	0·65, 1·13	0·94	0·72, 1·24	0·66	0·49, 0·90	0·02	
Multivariate model 2§	1·00	Reference	0·87	0·65, 1·16	0·96	0·71, 1·29	0·68	0·47, 0·94	0·04	

* Linear trends across quartiles of cholesterol intake were tested using the median consumption value for each quartile as an ordinal variable.
† Adjusted for age and public health centre area.
‡ Additionally adjusted for BMI, smoking status, alcohol consumption, total physical activity levels, history of hypertension and family history of diabetes.
§ Additionally adjusted for Mg intake, Ca intake, coffee consumption, rice intake, fish and shellfish intake, meat intake, vegetable intake, soft drink intake and energy intake.
‖ Subjects with missing information (496 men and 794 women).

adjustment for dietary covariates (multivariate model 2), the significant inverse associations disappeared in both normal-weight (BMI < 25 kg/m²) and overweight (BMI ≥ 25 kg/m²) women ($P_{trend} = 0.15$ and 0·10, respectively; $P_{interaction} = 0.94$). No significant association between dietary cholesterol intake and type 2 diabetes risk was found in men.

The association between egg intake and type 2 diabetes risk is summarised in Table 3. In multivariate model 1 with adjustment for non-dietary covariates, type 2 diabetes risk was found to be 21 % lower among women (OR 0·79, 95 % CI 0·61, 1·02; $P_{trend} = 0.047$) in the highest quartile of egg intake than among those in the lowest quartile. This association was attenuated after additional adjustment for dietary covariates (multivariate model 2); the multivariate-adjusted OR for type 2 diabetes risk for the lowest quartile through the highest quartile of intake were 1·00 (95 % CI reference), 1·01 (95 % CI 0·79, 1·29), 0·94 (95 % CI 0·73, 1·21) and 0·82 (95 % CI 0·63, 1·06) ($P_{trend} = 0.098$). No significant association between egg intake and type 2 diabetes risk was found in men. Similar results were obtained when crude egg intake instead of the energy-adjusted intake was included in the model. Fully adjusted OR of type 2 diabetes risk for the

Table 3. Association between egg intake and type 2 diabetes risk according to quartiles (Q) of energy-adjusted egg intake

(Odds ratios and 95 % confidence intervals; medians, number of cases and subjects)

	Q1 (low)		Q2		Q3		Q4 (high)		
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}*
Men									
Cases (n)		174		160		156		182	
Subjects (n)		6812		6812		6812		6812	
Median (g)		7·7		19·4		32·6		55·0†	
Age and area adjusted‡	1·00	Reference	0·92	0·74, 1·14	0·90	0·72, 1·12	1·04	0·84, 1·29	0·61
Multivariate model 1§	1·00	Reference	0·91	0·73, 1·14	0·91	0·73, 1·13	1·04	0·84, 1·29	0·58
Multivariate model 2‖	1·00	Reference	0·93	0·74, 1·15	0·93	0·74, 1·16	1·06	0·85, 1·32	0·50
Women									
Cases (n)		137		131		119		106	
Subjects (n)		9054		9055		9055		9054	
Median (g)		6·9		17·5		29·4		50·3†	
Age and area adjusted‡	1·00	Reference	0·97	0·76, 1·24	0·89	0·69, 1·14	0·77	0·60, 0·996	0·03
Multivariate model 1§	1·00	Reference	0·99	0·78, 1·26	0·91	0·71, 1·17	0·79	0·61, 1·02	0·047
Multivariate model 2‖	1·00	Reference	1·01	0·79, 1·29	0·94	0·73, 1·21	0·82	0·63, 1·06	0·098

* Linear trends across quartiles of egg intake were tested using the median consumption value for each quartile as an ordinal variable.
† Corresponded to approximately one egg.
‡ Adjusted for age and public health centre area.
§ Additionally adjusted for BMI, smoking status, alcohol consumption, total physical activity levels, history of hypertension and family history of diabetes.
‖ Additionally adjusted for Mg intake, Ca intake, coffee consumption, rice intake, fish and shellfish intake, meat intake, vegetable intake, soft drink intake and energy intake.

lowest quartile through the highest quartile of crude egg intake were 1·00 (95 % CI reference), 0·96 (95 % CI 0·78, 1·18), 1·15 (95 % CI 0·88, 1·49) and 1·10 (95 % CI 0·89, 1·36), respectively, in men (P_{trend} = 0·24) and 1·00 (95 % CI reference), 1·54 (95 % CI 1·05, 2·27), 0·88 (95 % CI 0·71, 1·11) and 0·91 (95 % CI 0·70, 1·17), respectively, in women (P_{trend} = 0·49).

Discussion

In the present large-scale, population-based prospective study of Japanese adults, high dietary cholesterol intake was found to be not associated with an increased risk of type 2 diabetes in either men or women overall. Conversely, it was found to be associated with a reduced risk of diabetes in postmenopausal women. Egg intake was found to be not associated with type 2 diabetes risk in either men or women. This is the first prospective study to be carried out on this topic in Asia.

The null findings recorded for both men and women overall are inconsistent with those reported for US populations. Most[7–10], but not all[11], studies have consistently reported positive associations between dietary cholesterol intake and diabetes. This discrepancy may be due differences in the dietary sources of cholesterol and not due to differences in cholesterol intake levels. In the present study population, the median cholesterol intake of those in the highest quartile of intake (423·0 mg/d in men and 389·6 mg/d in women) was similar to that reported in the Women's Health Study carried out in the USA (382 mg/d)[10]. Dietary cholesterol is mainly derived from eggs (47 %), shellfish (22 %) and meat (19 %) in Japan[16], whereas it is mainly derived from meat (35 %), eggs (29 %), and cheese and milk (11 %) in the USA[12]. Meat intake makes a notably higher contribution to cholesterol intake in the USA than in Japan, and three

meta-analyses have consistently shown that high consumption of meat is associated with an increased risk of diabetes[4–6]. Meat intake was not considered in three of the US studies[8–10], and other relevant studies that did adjust for meat intake reported inconsistent results[7,11]. Thus, it is unclear whether dietary cholesterol per se is independently associated with the risk of type 2 diabetes.

An inverse association between dietary cholesterol intake and type 2 diabetes risk was found in postmenopausal women in the present study. This finding was unexpected and is not in agreement with those of the three previously mentioned US studies carried out in women aged ≥45 years, which reported that an increased risk of type 2 diabetes is associated with high dietary cholesterol intake[7,9,10]. However, one US study carried out in elderly women has reported a decreased risk of type 2 diabetes in women in the highest quartile of cholesterol intake (albeit this association was not statistically significant)[11]. There are some possible explanations for our finding of a protective association. In an animal study, ovariectomised mice on high-cholesterol diets had higher serum oestrogen concentrations than those on a control diet[27]. High intake of fat/cholesterol has been reported to be associated with higher serum oestrogen concentrations in Japanese postmenopausal women[28]. Furthermore, postmenopausal therapy with oestrogen and progestin has been found to reduce the incidence of diabetes in a large-scale intervention study[29,30]. These data suggest that dietary cholesterol in postmenopausal women could be beneficial in the prevention of diabetes via the induction of sex hormones.

No significant association between egg intake and type 2 diabetes risk was found in either men or women in the present study. This is in line with those of most[11,14,15], but not all[7], studies on this topic in both men and women in

Western countries. Thus, the majority of these studies did not detect an association between an increased risk of type 2 diabetes and egg intake[11,14,15]. Eggs not only contain SFA, which have been reported to be associated with an increased risk of type 2 diabetes[8–10], but also contain MUFA, PUFA, antioxidants, including lutein and zeaxanthin, and folate. MUFA, PUFA and antioxidants can improve insulin sensitivity[31,32]. Taken together, egg intake may not be detrimental to glucose metabolism.

The major strengths of the present study include a large number of subjects comprising men and women, a population-based prospective design, the use of a validated FFQ, and the adjustments for potentially important confounding variables. Despite these strengths, the present study has several limitations that warrant mention. First, the incidence of diabetes was ascertained based on self-reported information. However, it was confirmed that 94 % of the cases of self-reported diabetes were correctly documented in medical records of the sample of a validation study[24]. Furthermore, any under-reporting is unlikely to have varied with cholesterol or egg intake. Second, only data collected during the second survey were used to assess dietary intake. This could have led to non-differential misclassification of cholesterol and egg intakes and thus attenuated the risk estimates towards null. Third, the validity of the FFQ used in the present study was moderate for cholesterol and egg intakes (r 0·33–0·47 and r 0·25–0·47, respectively[21,23]), and resulting measurement errors might have attenuated the associations. Fourth, circulating concentrations of oestrogen, which might play a role in the association between dietary cholesterol intake and type 2 diabetes risk, were not measured. Fifth, the follow-up period was relatively short (5 years). Sixth, participants with pre-diabetes at baseline might have been instructed to decrease their egg or cholesterol intake. If so, risk estimates would be attenuated towards null. Lastly, the possibility of bias due to residual confounding or unmeasured confounders cannot be entirely excluded. Specifically, the observed inverse association between dietary cholesterol intake and type 2 diabetes risk in postmenopausal women could be ascribed to the differences in unmeasured lifestyles between women in the lowest quartile of intake and those in the highest quartile of intake.

In conclusion, higher intake of cholesterol or eggs may not be associated with an increased risk of type 2 diabetes in Japanese populations. The observed association between decreased type 2 diabetes risk and higher dietary cholesterol intake in postmenopausal women warrants further investigation.

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