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Abstract

Purpose

Eggs are highly nutritious but concerns over their cholesterol content have led to dietary avoidance among many. There are also important international differences in relevant dietary guidance. We conducted the first prospective study in China investigating the association of egg consumption, cardiovascular disease (CVD) mortality, and a meta-analysis.

Methods

We included 28,024 participants without CVD at baseline (2003-8) in Guangzhou Biobank Cohort Study. All-cause and CVD mortality were identified through record linkage. We used Cox proportional hazards regression. We followed the Meta-analysis Of Observational Studies in Epidemiology reporting guidelines.

Results

During 275,343 person-years follow-up (average 9.8 years), we found 2,685 all-cause and 873 CVD deaths. We found no significant difference in all-cause mortality between higher (7+ eggs/week) and low consumption (<1 egg/week) (adjusted hazard ratio (HR) 1.08, 95% confidence interval (CI) 0.93-1.24), and mortality from CVD (0.99, 95% CI 0.76-1.27), ischemic heart disease (IHD) (0.92, 95% CI 0.63-1.36), or stroke (0.88, 95% CI 0.57-1.35). The updated meta-analyses including our results showed that 7+ eggs/week was not associated with all-cause mortality (HR 1.09, 95% CI 0.997-1.200) or IHD (HR 0.97, 95% CI 0.90-1.05), but associated with a small reduction in stroke (HR 0.91. 95% CI 0.85-0.98).

Conclusions

Eating one egg daily is not associated with increase in CVD or all-cause mortality. The small observed reduction in stroke risk need to be confirmed. Our findings support current guidelines recommending eggs as part of a healthy diet, and should be considered in other dietary recommendations. (243 words)

Key words: Egg consumption, cardiovascular disease, ischemic heart disease; mortality, stroke

Introduction

Consumption of dietary cholesterol has been associated with elevated serum cholesterol [1] and thus hypothesized to increase CVD risk.[2] Eggs have been considered highly nutritious but concerns over its high cholesterol content have led to egg avoidance by many people.[3,4] The new 2015 US guidelines no longer include a limit for dietary cholesterol, and recommend eggs as part of a healthy diet.[5] Three meta-analyses (all published in 2013) of prospective cohort studies are cited in the guidelines, but these meta-analyses do not consistently support a null association or beneficial effects.[6-8] While the amount of intake is not specified in the US, the 2016 Chinese Dietary Guidelines recommend to consume 40-50 grams of egg products (about one egg) daily. However, dietary guidelines from the World Health Organization (WHO) (i.e. the WHO Healthy Diet report),[9] Europe [10] or the UK [11] do not mention egg consumption, probably because of the lack of reliable scientific evidence.

One of the 3 meta-analyses above reported a dose-response positive (i.e. harmful) association between egg consumption and CVD risk [8] but the other two reported no association.[6,7] Most of the studies included were from western populations, with only three from Japan which showed no association with IHD risk but a lower risk for stroke mortality in those who consumed eggs daily versus never.[12-14] We have found no prospective evidence on egg consumption and CVD events or mortality in Chinese, or from populations in other low and middle income countries. Results from a Chinese population may contribute important evidence in formulating dietary guidelines regarding egg consumption.

Based on a well-established large cohort of older Southern Chinese people, the Guangzhou Biobank Cohort Study (GBCS), we examined the association between egg consumption and CVD/stroke mortality. Moreover, to better understand the underlying mechanisms, we also examined the cross-sectional association of egg consumption with CVD risk factors using baseline data. We then performed updated meta-analyses on the associations of egg consumptions with all-cause mortality and CVD-specific outcomes including the new GBCS results.

Methods

Study sample

All participants of the Guangzhou Biobank Cohort Study (GBCS) were recruited from 2003 to 2008. The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants gave written, informed consent before participation. Details of the GBCS have been reported previously.[15]

Briefly, the GBCS is a 3-way collaboration among Guangzhou 12th Hospital and the Universities of Hong Kong, China and Birmingham, UK. Recruitment of participants was from "The Guangzhou Health and Happiness Association for the Respectable Elders" (GHHARE), a community social and welfare organization. GHHARE is unofficially aligned with the municipal government. Membership is open to Guangzhou permanent residents aged 50 years or above for a nominal fee of 4 CNY (≈50 US cents) per month. GHHARE included about 7% of Guangzhou residents in this age group, with branches in all 10 districts of Guangzhou, the capital city of Guangdong province in southern China. The baseline examination included a face-to-face computer-assisted interview by trained nurses on lifestyle, family and personal medical history and assessment of anthropometrics, blood pressure, fasting plasma glucose, lipids and inflammatory markers. Reliability and validity of the questionnaire was tested 6 months into recruitment by recalling 200 randomly selected subjects for re-interview.[15]

Exposure

All participants were asked how many eggs they had consumed daily over the past 7 days based on a validated food frequency questionnaire (FFQ).[16] The responses were classified as <1, 1-2, 3-4, 5-6, and 7+ eggs per week.

Outcomes

For the cross-sectional analysis using baseline data, the study outcomes were CVD risk factors including systolic and diastolic blood pressure, lipids (low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides and total cholesterol), fasting glucose, body mass index (kg/m^2) and waist circumference.

Other study outcomes were death from all-causes and cardiovascular diseases. Causes of death were coded according to the 10th revisions of the International Classification of Diseases. The four main outcome measures that were examined were deaths from cardiovascular disease, ischemic heart disease, all stroke, hemorrhagic stroke and ischemic stroke. For those alive, the censored date was 31 January 2016.

Ascertainment of all-cause and cardiovascular disease mortality

Information on cause of deaths up to January 2016 was mostly obtained via record linkage with the Guangzhou Center for Disease Control and Prevention (GCDC). Causes of death were coded according to the 10threvisions of the International Classification of Diseases (ICD) by trained nosologists in each hospital. When the death certificates were not issued by medical institutions (and hence might have quality issue with the coding), the causes of death were verified by GCDC as part of their quality assurance program by cross-checking past medical histories and conducting verbal autopsies. From August 2015 to May 2016, ten verbal autopsy meetings were conducted in the Guangzhou 12th Hospital to clarify the deaths with unclear causes. A physician panel including 5 chief physicians from various disciplines reviewed all available medical records of the individuals and assigned in a standard manner a cause of death, with assistance of several epidemiologists for unsettled cases. The mid-point between the date of recruitment and the date of first censoring (December 31th, 2012) was used for 9 participants confirmed dead at the first follow-up for deaths, but whose exact dates of death were not available. For those alive, as registered by the police, records were censored on 31 January 2016.

Potential confounders

As both the dietary pattern and the CVD prevalence could be influenced by socioeconomic position (education, occupation, family income),[17] lifestyle factors (physical activity, alcohol use and smoking),[18]and chronic disease history (diabetes, hypertension and dyslipidemia), these factors were considered potential confounders and included in the regression model. Moreover, as with other previous cohort studies,[7] we also included daily foods/dietary energy intake insensitivity analysis because it could confound the associations between egg consumption and CVD risk factors/mortality. As from phase 3

(2006), the FFQ was shortened, only participants from the first 2 phases who had a detailed assessment on dietary intake could be assessed for food (vegetables, fruits, nuts and milk) and daily nutrient intake including total dietary energy, and they were included in the sensitivity analysis.[19]

Updated meta-analyses on egg consumption and risk of mortality

We conducted a sensitivity analysis on 12,899 participants with stable egg consumption habit during baseline (September 2003-January 2008) to the 1st follow-up (March 2008-December 2012) (i.e. within about 4 years) to examine the association between egg consumption and CVD risk factors. Moreover, as egg consumption in low-to-middle income countries may be associated with higher socioeconomic position, we conducted another sensitivity analysis to assess whether the results varied by education level.

We then conducted updated meta-analyses on CVD and all-cause mortality incorporating the GBCS results following a review protocol (Meta-analysis Of Observational Studies in Epidemiology).[20] For study selection, we included prospective studies with cohort design investigating the association between egg consumption and risk of IHD, stroke or all-cause mortality. The three recent meta-analyses involved a search of the literature up to March 2012[6], June 2012[7] and December 2012, respectively.[8] Thus, we conducted additional literature searches on PubMed and MEDLINE from January 2013 to August 24, 2016 based on the following main search string: (egg AND (ischemic heart disease OR ischaemic heart disease OR coronary heart disease OR stroke OR myocardial infarction OR coronary artery disease OR all-cause OR all cause) AND (follow up OR mortality)). We retried 10 articles from PubMed and MEDLINE. Of these articles, 8 were excluded for one of the following reasons: 1) was a review article (n=1); 2) did not relate egg consumption to an outcome of interest (n=6); or 3) was conducted in patients with diabetes (n=1). Details of the studies included are shown in Supplementary Table 5.

We used the relative risks comparing the highest (≥1 egg/day) versus lowest categories (≤1 egg /week or never) of egg intake to obtain a summary estimate. The heterogeneity among studies was estimated by the Cochran Q test and I^2 statistic. Heterogeneity was confirmed with a significance level of $P \leq 0.10$. The I^2 statistic describes the percentage of total variation in point estimates that can be attributed to heterogeneity.

We considered heterogeneity to be low if an I^2 values of 40% was found.[21] A fixed effect model was used in the meta-analysis if the heterogeneity was low, otherwise a random effect model was used. We also used funnel plots, Begg adjusted rank correlation test and Egger test to test for the presence of publication bias.

Statistical analysis

Chi-square tests or analysis or variance were used to compare participants' baseline characteristics by egg consumption. Generalized linear modeling was used to assess the association of egg consumption with CVD risk factors at baseline, giving mean differences and 95% confidence intervals (CI). The Cox proportional hazards model was used to calculate adjusted hazard ratios (HRs) with 95% CI. All potential confounders were categorized as in Table 1. Participants who died of any other causes were censored at the date of death.[22] Whether an association varied by sex was assessed from the significance of an interaction term and the heterogeneity of estimates across strata. As no evidence suggested different associations by sex (P values for interaction from 0.45-0.92), all analysis was conducted with both sexes combined, adjusted for sex. All statistical analyses were done with Stata version 14.0 (STATA Corp LP), and all tests were two-sided with a significance level of 0.05.

Results

In 30,430 participants of GBCS, after excluding those with missing information on egg consumption (n=153), CVD risk factors (n=373) and previous CVD history (n=1,520), and 360 lost to follow-up for vital status, 28,024 were included in the main analysis. Of those, 18,707 (67%) with detailed assessment of energy intake were included in the sensitivity analysis (**ESM Figure 1**).

Of the 28,024 participants, 5,868 (21%)reported never or did not consume, and 12,343 (44%), 6,157(22%), 1,361 (5%) and 2,295 (8%) had consumed 1-2, 3-4, 5-6 and 7+ eggs over the past 7 days, respectively. Of those who consumed 7+ eggs/week, 97% consumed an average of one egg per day. During 275,343 person-years of follow-up (average 9.8 years), we found 2,685 deaths, of which 873 were from CVD which included 341 from stroke.

Table 1 shows that participants who were men, had higher socioeconomic position (higher family income and education level, non-manual occupation), and were never smokers, physically active and current alcohol users consumed more eggs (all P<0.01). There was no clear association with sex, age, self-rated health or self-reported hypertension or hyperlipidemia, while more self-reported diabetes was found in those who had more frequent egg consumption (P<0.001). In 18,707 participants with detailed FFQ data, more egg consumption was also associated with higher daily intake of vegetables, fruits, milk and nuts, and total energy, protein, fat, fiber, cholesterol and saturated fatty acid, as well as lower daily intake of carbohydrate, monounsaturated fatty acid and polyunsaturated fatty acid (all P <0.001).

Table 2 shows that higher egg consumption was negatively associated with SBP, DBP, LDL-cholesterol, triglycerides, total cholesterol and BMI, after adjusting for sex, age, education, occupation, family income, smoking status, physical activity, alcohol drinking, self-rated health, chronic disease history (diabetes, hypertension and dyslipidemia) and dietary foods and energy intake (all P for trend <0.01). No association with HDL-cholesterol and waist circumference was found. A sensitivity analysis of 12,899 participants with stable egg consumption habit during the 1st follow-up period (i.e., from 2008 to 2012) showed similar results (**ESM Table 2**).

Table 3 shows that egg consumption was not significantly associated with all-cause mortality or mortality from any CVDs. Compared with those who ate <1 egg per week, the HR (95% CI) in those with egg consumption of 7+/weekwas1.08 (0.93-1.24) for all-cause,0.99 (0.76-1.27) for CVD, 0.92 (0.63-1.36) for IHD, 0.88 (0.57-1.35) for stroke, 0.63 (0.28-1.41) for ischemic stroke and 1.31 (0.60-2.84) for hemorrhagic stroke. Sensitivity analysis adjusting for intake of fruits, vegetables, milk, nuts and total energy showed similarly non-significant results (Table 3), and the results were similar after excluding 61 participants who consumed more than 7 eggs per week (**ESM Table 4**). Moreover, as higher egg consumption was associated with higher education in our sample, to further account for confounding by education, we conducted sensitivity analysis by education and found similar results showing no association between egg consumption and mortality from all-cause, CVD, IHD or stroke (**ESM table 3**).

Our updated search (up to 24th August 2016) on PubMed and MEDLINE found two additional studies[23,24] which met the inclusion criteria, in addition to the studies included in the three 2013 meta-analyses. Therefore, a total of 363,565 participants in nine prospective studies for IHD, 436,088 participants in nine for stroke, and 853,974 participants in four for all-cause mortality were included in our updated meta-analyses, including the present results. The characteristics of the included studies are shown in **ESM Table 5**. The updated meta-analyses showed that frequent egg consumption (7+/week) versus low consumption (<1/week) was associated with a 9% (95% CI 2-15%) lower risk of all stroke (Figure 1). However, no significant association of egg consumption with IHD mortality (pooled HR 0.97, 95% CI 0.90-1.05), ischemic stroke (HR 0.91, 95% CI 0.81-1.02), hemorrhagic stroke (HR 0.88, 95% CI 0.68-1.14) (Figure 1), or all-cause mortality (HR 1.09, 95% CI 0.997-1.20) (**ESM Figure 2**) was found. No evidence for a significant publication bias was found (P values for Begg's test from 0.18 to 0.90, and for Egger's test from 0.36 to 0.86) (**ESM Figure 3**).

Discussion

In a setting with different dietary and cardiovascular disease patterning from the well-studied Western populations, we found no evidence of an association between egg consumption and the risk of CVD or all-cause mortality. In cross-sectional analyses using baseline data, we found an inverse association between egg consumption and LDL-cholesterol, triglycerides and blood pressure, suggesting potential beneficial effects. Similar results were observed in sensitivity analysis restricting to participants with similar level of egg consumption during the follow-up examination. The potential beneficial effect on the CVD risk factors is supported by our updated meta-analyses showing that higher egg consumption was associated with a slightly but significantly lower risk of stroke.

As a rich source of dietary cholesterol, egg consumption has been linked to a moderate increase in CVD risk. One of the 2013 meta-analysis showed that compared to the lowest category of egg consumption, the highest level (7+/week) was significantly associated with a higher risk of CVD by 19%.[8] In contrast, the two other meta-analyses did not show adverse effect on CVD.[6,7] The discrepancy is likely due to the inclusion of different studies of various quality. In the first meta-analysis,[8] no study from Asia was included, while the other two included three studies from Japan, two reporting results on CHD [12,13] and one reporting stroke.[14] These studies from Japan did not support the association of egg intake with the risk of CHD,[12,13] but conversely suggested that higher egg consumption tended to reduce the risk of stroke.[14] However, no other CVD risk factors except for total cholesterol were assessed in those studies.[12-14] Moreover, several trials showed that consumption of 1-2 eggs per day (200-400 mg cholesterol) has little [25] or slightly favourable effect on lipid profiles [26-28]. Such minor effects on plasma cholesterol are unlikely to have substantial overall impact on the risk of CHD or stroke among healthy adults. As most randomized trials had a short follow-up of less than 12 months [29], large cohort studies with longer follow-up are needed to provide clearer and more precise estimates for the long-term effect of egg consumption [30]. However, among individuals with type 2 diabetes, increased egg intake may be associated with higher risks of CHD, although the association varied by study design, diabetes definition, exposure measurement, age, control for confounders and follow-up duration [30,31], suggesting that the underlying mechanisms need to be explored more in depth. Our study provides complementary evidence for the association of egg consumption and other common CVD risk factors in an understudied yet major population with a high incidence of stroke mortality. The potential beneficial effects on CVD risk factors especially blood pressure observed in our cross-sectional analysis warrant further investigation using longitudinal or interventional studies.

Our updated meta-analyses showed a significant negative association of higher egg consumption with the risk of stroke. Such significant inverse association was reported in two previous cohort studies from different settings.[14,32] One is from the Life Span Study in Japan [14] and the other used data from the Third National Health and Nutrition Examination Survey 1988-1994 (NHANES III) in the US.[32] Thus our results are consistent and extend the previous studies. In addition, one of the three 2013 meta-analyses showed that people with higher egg consumption(≥1 egg/day)also showed a 25% lower risk of hemorrhagic stroke.[7] The updated meta-analyses including our results provided a more precise estimate of the association between higher egg consumption and stroke risk, with an effect size being similar with the previous meta-analysis (both pooled HR=0.91). One possible mechanism for this protective association with stroke may be due to the potential negative association between egg consumption, or more specifically protein, and blood pressure,[33] which is supported by the analysis of our baseline data on CVD risk factors.

American Dietary Guidelines, Japanese Dietary Guidelines (2015) and the Chinese Dietary Guidelines (2016) have dropped the recommendation on cholesterol intake limit. But the change in American Dietary Guidelines does not suggest that dietary cholesterol is no longer important to consider when building healthy eating patterns. Such withdrawals of dietary cholesterol limit have led to concerns in both the public and scientific community [34]. As the removal of the dietary cholesterol recommendation from dietary guidelines does not mean that dietary cholesterol is no longer a concern for CVD risk, more evidence for the effects of dietary cholesterol consumption from different foods on cardiovascular disease and other health outcomes is needed. We did not find evidence for a higher risk of all-cause mortality in those who consumed 7+ eggs per week. The HR was attenuated toward the null after further excluding those who ate more than 1 egg per day (or 7+ eggs/week). "7+ eggs/week" in the literature, which has no upper limit of consumption, could have included excessive egg consumers of 2 or more eggs per day (i.e. 14+/week), and the proportion of such people can vary in different populations. More precise categorization is needed for clarifying dose response relationships and dietary recommendations, depending on the numbers of participants and outcome events available.

There are several limitations in our study. First, measurement errors in a study of this kind are inevitable. Random errors in measuring egg consumption and other dietary habits would likely have biased the results toward the null. Second, information on the cooking methods and the amount of oil and salt added to eggs was not available in our study, and some participants might not be aware of the eggs added to other foods. As the nutrient contents of eggs alter depending on the cooking methods,[35] different cooking methods could influence the association between egg consumption and CVD or CVD risk factors. Third, our participants with higher egg intake consumed more protein and fiber but fewer carbohydrates and were more likely to have higher socioeconomic status than those with lower egg intake, suggesting residual confounding may play a role. However this was different from most of the prospective studies in the West that showed higher egg consumption was associated with lower education level.[30,32] Similar results from different settings with different patterns of food consumption may strengthen the causal inference by adding consistency despite different potential patterns of confounding. Moreover, to reduce potential confounding, we firstly adjusted for multiple indicators of socioeconomic position (education, income and occupation), and then conducted sensitivity analysis by stratifying our sample based on education level and found similar results (**ESM table 3**), suggesting education could not fully explain the results. Fourth, during the long follow-up, participants might have changed their diets. In our sensitivity cross-sectional analysis, we restricted to participants with same levels of egg consumption during baseline to the first follow-up and found similar results, suggesting the association between egg consumption and CVD risk factors is unlikely explained by changes in consumption during follow up. However, due to the relative short period of follow-up and small number of CVD deaths, we could not do prospective analysis in those with stable egg consumption habit versus those with changes during follow-up. Fifth, as few participants in our sample consumed more than one egg per day, our results could not be generalized to this group. Similar concerns applied to the earlier meta-analyses.[6-8] Cohort studies including sufficient number of participants with high consumption (i.e. 2+ eggs per day) are warranted. Finally, reverse causality between egg consumption and CVD risk factors cannot be fully ruled out in the cross-sectional analysis. For example, in developed countries, individuals with hypercholesterolemia were provided health services, such as health guidance or education, to prevent further CVD. Eggs have been recognized as a popular media symbol for many of the dietary over consumption by the public, as well as the icon for both dietary and serum cholesterol. Thus, guidelines on dietary cholesterol intake based on recent epidemiological studies that did not find a positive association of egg intake with dietary cholesterol or CVD may not be robust. However, our sensitivity analysis excluding participants with poor health status or including participants with stable consumption habit during follow-up showed similar results, suggesting reverse causality, if any, should not be substantial in our study.

To conclude, egg consumption does not increase CVD and all-cause mortality, and avoiding eggs does not reduce such risks. Eating one egg daily or 7 or more weekly could reduce stroke risk slightly, but the beneficial effects and dose response relationships at high consumption level, if any, need to be confirmed.

Our findings support the US and Chinese guidelines which recommend eggs as part of a healthy diet, and should be taken into account in other dietary recommendations. People who consume about an egg a day can be reassured.

(3261 words)

Conflict of Interest: The authors declare that they have no conflict of interest.

Authorship statement

(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: LX, CQJ, THL, KKC, WSZ, FZ, YLJ, GNT

(2) Drafting the work or revising it critically for important intellectual content: LX, CQJ, THL, KKC, GNT

(3) Final approval of the version to be published: LX, CQJ, THL, KKC, WSZ, FZ, YLJ, GNT

(4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: LX, CQJ, THL, KKC, WSZ, FZ, YLJ, GNT

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Figure 1. Pooled HRs and 95% CIs of ischemic heart disease (IHD), stroke, ischemic stroke and hemorrhagic stroke incorporating results from the Guangzhou Biobank Cohort Study (GBCS).

Note: The pooled estimates were obtained by using a fixed effect model. The dots indicate the adjusted HRs from a comparison of the highest category of egg consumption (≥7 eggs/week) with the lowest (<1 egg/week or never). The size of the square is proportional to the weight of individual study. The horizontal lines represent 95% CI. The diamond data markers indicate the pooled HR.

Table 1 Baseline characteristics by egg consumption levels in 28,024participants of the Guangzhou Biobank Cohort Study first examined from September 2003 to January 2008

	Egg consumption, number per week					
	<1	1-2	3-4	5-6	7+	P-value
Number of participants (row percentage)	5868 (21)	12343 (44)	6157 (22)	1361 (5)	2295 (8)	-
Age, years, mean (SD)	62.4 (7.3)	61.4 (7)	61.8 (7)	61.9 (6.9)	62.6 (7.1)	<0.001
Age group, years, %						
50-59	42.1	47.5	44.9	44.8	40.5	<0.001
60-69	40.0	39.1	40.6	40.3	43.1	
70+	17.9	13.5	14.5	14.9	16.4	
Sex, % men	26.0	26.7	28.1	29.5	29.5	0.002
Family income, CNY/year, %						
<10,000	8.8	4.9	5.3	5.0	4.0	<0.001
10,000-29,999	34.9	31.8	30.7	30.8	33.0	
30,000-49,999	17.9	22.1	21.8	21.6	22.8	
≥50,000	12.8	17.5	18.1	19.0	20.6	
Don’t know	25.7	23.7	24.1	23.6	19.7	
Education, %						
Primary or below	54.6	42.3	39.3	38.0	29.1	<0.001
Secondary	40.4	50.2	50.3	50.0	53.2	
College or above	5.1	7.5	10.4	12.0	17.8	
Occupation, %						
Manual	69.0	62.5	58.5	56.6	49.3	<0.001
Non-manual	16.9	21.7	26.2	28.0	36.6	
Others	14.2	15.8	15.3	15.4	14.1	
Smoking status, %						

Never	79.8	81.7	81.1	80.1	82.6	<0.001
Former	9.4	8.2	9.0	9.8	9.4	
Current	10.8	10.1	10.0	10.1	8.0	
Physical activity, %						
Inactive	10.9	8.6	6.3	5.4	5.3	<0.001
Minimally active	42.9	41.5	38.8	40.8	35.5	
Active	46.3	49.9	54.9	53.8	59.3	
Alcohol use, %						
Never	77.0	71.9	70.0	69.7	69.4	<0.001
Former	3.6	3.7	3.1	2.7	3.6	
Current	19.4	24.4	26.9	27.6	27.0	
Self-rated health, % good	81.6	83.8	83.6	83.5	82.6	0.005
Self-reported diabetes, %	7.1	7.3	7.5	8.2	10.5	<0.001
Self-reported hypertension, %	22.4	21.5	20.9	17.8	20.1	0.001
Self-reported hyperlipidemia, %	9.3	10.5	10.0	7.5	10.8	<0.001
Vegetable intake†, %						
≤100 g/d	13.9	9.5	6.5	4.9	5.4	<0.001
101-150 g/d	19.3	16.9	12.3	11.1	9.6	
151-200 g/d	19.9	21.8	19.2	15.8	12.8	
201-250 g/d	13.9	15.7	14.8	17.2	15.7	
251-300 g/d	9.8	11.5	12.7	12.7	11.4	
>300 g/d	23.3	24.6	34.5	38.3	45.2	
Fruit intake†, %						
≤50 g/d	29.6	22.7	18.3	15.7	15.3	<0.001
51-100 g/d	23.2	22.8	21.2	19.7	17.3	
101-150 g/d	18.9	20.8	19.5	19.6	20.3	

151-200 g/d	12.3	14.2	16.3	17.3	16.1	
201-250 g/d	6.6	8.6	9.4	11.0	11.6	
>250 g/d	9.5	10.9	15.4	16.6	19.4	
Cow milk intake, %						
None	75.8	68.7	68.6	63.5	65.2	<0.001
1-3 portions/week	11.9	16.9	15.0	17.0	8.8	
>3 portions/week	12.3	14.4	16.5	19.5	26.1	
Nut intake, %						
None	67.5	59.5	56.9	55.3	53.3	<0.001
1-3 portions/week	21.9	26.6	28.4	29.4	26.7	
>3 portions/week	10.6	13.9	14.7	15.4	20.0	
Nutrient intakes (energy-adjusted as appropriate)[†]						
Energy, kcal/day, mean (SD)	1694 (524)	1779 (496)	1934 (533)	2065 (553)	2057 (590)	<0.001
Protein[‡], g/day	69.6 (69.2-70.0)	71.5 (71.2-71.8)	73.6 (73.1-73.9)	76.3 (75.5-77.1)	78.9 (78.2-79.6)	<0.001
Carbohydrates[‡], g/day	268 (266-268)	262 (260-262)	261 (259-261)	256 (253-258)	253 (250-255)	<0.001
Fat[‡], g/day	57 (56-57)	58 (57-58)	58 (57-58)	59 (57-60)	59 (58-60)	<0.001
Fiber[‡], g/day	12.6 (12.4-12.7)	12.9 (12.7-12.9)	13.5 (13.3-13.5)	13.7 (13.4-14.0)	15.2 (14.9-15.4)	<0.001
Cholesterol[‡], mg/day	132 (129-134)	144 (142-145)	160 (157-162)	186 (181-189)	160 (156-163)	<0.001
Saturated fatty acid[‡], g/day	9.7 (9.5-9.8)	10.1 (10.0-10.2)	10.0 (9.9-10.1)	10.3 (10.0-10.5)	10.9 (10.6-11.1)	<0.001

Monounsaturated fatty acid‡, g/day	17.6 (7.3-17.8)	17.7 (7.5-17.8)	17.0 (6.8-17.2)	16.7 (6.2-17.1)	16.1 (5.6-16.4)	<0.001
Polyunsaturated fatty acid‡, g/day	13.5 (3.2-13.7)	13.3 (3.1-13.4)	12.5 (2.2-12.6)	11.8 (1.3-12.2)	12.3 (1.9-12.7)	<0.001

†: 18,707 participants with data on daily dietary energy intake

‡: Energy adjusted mean and 95% confidence interval (CI).

Table 2 Cross-sectional analysis of the association of egg consumption with cardiovascular risk factors in 28,024 participants based on baseline information collected from September 2003 to January 2008.

	Egg consumption, number per week					
	<1	1-2	3-4	5-6	7+	P for trend
Systolic blood pressure, mmHg						
Crude	Reference (0)	2.34 (1.66, 3.02)	-0.47 (-1.14, 0.2)	-1.73 (-2.96, -0.51)**	-1.62 (-2.59, -0.65)***	<0.001
Model 1	Reference (0)	1.13 (0.51, 1.76)	-0.54 (-1.15, 0.08)	-1.34 (-2.46, -0.21)*	-1.74 (-2.64, -0.84)***	<0.001
Model 2†	Reference (0)	0.92 (0.16, 1.69)	-0.8 (-1.55, -0.04)*	-1.64 (-2.94, -0.34)*	-2.4 (-3.57, -1.24)***	<0.001
Model 3†	Reference (0)	-0.79 (-1.56, -0.02)*	-1.77 (-2.67, -0.87)*	-2.58 (-3.97, -1.18)*	-3.32 (-4.6, -2.04)***	<0.001
Diastolic blood pressure, mmHg	Reference (0)					
Crude	Reference (0)	0.66 (0.31, 1)	-0.15 (-0.49, 0.19)	-0.76 (-1.39, -0.14)*	-1.07 (-1.57, -0.58)***	<0.001
Model 1	Reference (0)	0.58 (0.24, 0.91)	-0.04 (-0.36, 0.29)	-0.42 (-1.02, 0.18)	-0.69 (-1.16, -0.21)**	<0.001
Model 2†	Reference (0)	0.49 (0.09, 0.9)*	-0.13 (-0.53, 0.27)	-0.51 (-1.2, 0.17)	-1.00 (-1.62, -0.39)***	<0.001
Model 3†	Reference (0)	-0.42 (-0.83, -0.01)*	-0.64 (-1.12, -0.16)*	-0.98 (-1.72, -0.24)*	-1.50 (-2.18, -0.82)***	<0.001
LDL-cholesterol, mmol/l	Reference (0)					
Crude	Reference (0)	-0.01 (-0.04, 0.01)	-0.05 (-0.07, -0.02)***	-0.09 (-0.13, -0.05)***	-0.08 (-0.11, -0.05)***	<0.001
Model 1	Reference (0)	0 (-0.02, 0.02)	-0.04 (-0.06, -0.02)***	-0.07 (-0.11, -0.03)***	-0.07 (-0.1, -0.04)***	<0.001
Model 2†	Reference (0)	-0.01 (-0.04, 0.01)	-0.04 (-0.06, -0.01)**	-0.05 (-0.09, -0.004)$^{*'}$	-0.08 (-0.12, -0.04)***	<0.001

Model 3[†]	Reference (0)	0.01 (-0.02, 0.03)	-0.03 (-0.06, 0.002)	-0.04 (-0.08, 0.01)	-0.07 (-0.11, -0.02)**	<0.001
HDL-cholesterol, mmol/l	Reference (0)					
Crude	Reference (0)	0.0004 (-0.01, 0.01)	0.002 (-0.01, 0.01)	-0.02 (-0.05, -0.001)*	0.002 (-0.02, 0.02)	0.42
Model 1	Reference (0)	-0.001 (-0.01, 0.01)	0.0007 (-0.01, 0.01)	-0.03 (-0.05, -0.004)*	-0.003 (-0.02, 0.01)	0.38
Model 2[†]	Reference (0)	0.002 (-0.01, 0.02)	-0.001 (-0.02, 0.01)	-0.03 (-0.06, -0.01)*	0.005 (-0.02, 0.03)	0.38
Model 3[†]	Reference (0)	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.01)	-0.04 (-0.07, -0.02)*	-0.001 (-0.03, 0.02)	0.32
Triglycerides, mmol/l	Reference (0)					
Crude	Reference (0)	0.06 (0.02, 0.1)**	-0.05 (-0.09, -0.01)**	-0.05 (-0.12, 0.02)	-0.09 (-0.14, -0.03)***	<0.001
Model 1	Reference (0)	0.06 (0.02, 0.1)**	-0.04 (-0.08, -0.003)*	-0.01 (-0.07, 0.06)	-0.07 (-0.12, -0.01)*	<0.001
Model 2[†]	Reference (0)	0.05 (0.01, 0.1)*	-0.04 (-0.08, 0.01)	0.01 (-0.07, 0.09)	-0.08 (-0.15, -0.01)*	0.001
Model 3[†]	Reference (0)	-0.05 (-0.1, -0.002)*	-0.09 (-0.14, -0.03)	-0.04 (-0.13, 0.04)	-0.14 (-0.21, -0.06)*	<0.001
Total cholesterol, mmol/l	Reference (0)					
Crude	Reference (0)	-0.02 (-0.05, 0.02)	-0.06 (-0.09, -0.02)**	-0.1 (-0.16, -0.03)**	-0.14 (-0.19, -0.09)***	<0.001
Model 1	Reference (0)	-0.01 (-0.05, 0.02)	-0.05 (-0.08, -0.01)**	-0.07 (-0.13, -0.005)*	-0.13 (-0.18, -0.08)***	<0.001
Model 2[†]	Reference (0)	-0.01 (-0.06, 0.03)	-0.05 (-0.09, -0.01)*	-0.07 (-0.15, 0.0004)	-0.11 (-0.17, -0.04)**	0.001
Model 3[†]	Reference (0)	0.002 (-0.04, 0.05)	-0.04 (-0.1, 0.01)	-0.07 (-0.15, 0.01)	-0.10 (-0.17, -0.03)**	0.001
Fasting glucose, mmol/l	Reference (0)					
Crude	Reference (0)	0.01 (-0.04, 0.06)	0.02 (-0.03, 0.07)	0.06 (-0.03, 0.16)	0.10 (0.03, 0.18)**	0.02

Model 1	Reference (0)	-0.01 (-0.06, 0.04)	0.01 (-0.04, 0.05)	0.04 (-0.04, 0.12)	0.02 (-0.05, 0.08)	0.27
Model 2†	Reference (0)	0.01 (-0.05, 0.07)	0.04 (-0.02, 0.1)	0.05 (-0.04, 0.15)	0.05 (-0.03, 0.14)	0.15
Model 3†	Reference (0)	0.003 (-0.05, 0.06)	0.03 (-0.04, 0.09)	0.03 (-0.07, 0.14)	0.04 (-0.06, 0.13)	0.24
Body mass index, kg/m^2	Reference (0)					
Crude	Reference (0)	-0.01 (-0.11, 0.09)	-0.21 (-0.31, -0.11)***	-0.24 (-0.43, -0.06)**	-0.32 (-0.46, -0.17)***	<0.001
Model 1	Reference (0)	0.001 (-0.1, 0.1)	-0.18 (-0.27, -0.08)**	-0.09 (-0.28, 0.09)	-0.21 (-0.36, -0.07)**	<0.001
Model 2†	Reference (0)	-0.07 (-0.19, 0.05)	-0.19 (-0.31, -0.07)**	-0.11 (-0.32, 0.1)	-0.28 (-0.47, -0.1)**	0.005
Model 3†	Reference (0)	0.06 (-0.06, 0.19)	-0.17 (-0.32, -0.03)**	-0.07 (-0.29, 0.15)	-0.29 (-0.50, -0.09)**	0.006
Waist circumference, cm	Reference (0)					
Crude	Reference (0)	0.39 (0.11, 0.66)	-0.13 (-0.4, 0.15)	-0.37 (-0.87, 0.13)	-0.07 (-0.47, 0.32)	0.06
Model 1	Reference (0)	0.16 (-0.11, 0.43)	-0.18 (-0.44, 0.08)	-0.23 (-0.71, 0.25)	-0.06 (-0.45, 0.32)	0.08
Model 2†	Reference (0)	0.05 (-0.27, 0.37)	-0.27 (-0.58, 0.05)	-0.40 (-0.94, 0.14)	-0.16 (-0.64, 0.33)	0.08
Model 3†	Reference (0)	-0.002 (-0.32, 0.32)	-0.38 (-0.75, -0.01)	-0.48 (-1.06, 0.10)	-0.35 (-0.89, 0.18)	0.12

Model 1: adjusted for sex, age, education, occupation, family income, smoking status, physical activity, alcohol drinking, self-rated health and chronic disease history (diabetes, hypertension and dyslipidemia).

Model 2 †: Additionally adjusted for daily dietary energy intake

Model 3 †: Additionally adjusted for vegetable, fruit, milk and nut intake

†:18,707participants with data on daily dietary energy intake were included in Model 2&3.

*: P<0.05; **: P<0.01; ***: P<0.001

Table 3.Adjusted hazards ratios (HR) and 95% confidence interval (CI)of all-cause mortality bybaselineeggconsumptionin28,024participants in 2003-2008 and followed up until January 2016

	Egg consumption, number per week					P for trend
	<1	1-2	3-4	5-6	7+	
Person-years	57396	120827	60974	13800	22345	
All-cause						
No. of deaths	611	1119	579	127	244	
Mortality rate, per 10,000 person-year	106.5	92.6	95	92	109.2	
Adjusted HR (95% CI)	1.00	0.99 (0.9, 1.1)	0.99 (0.89, 1.1)	0.89 (0.73, 1.07)	1.08 (0.93, 1.24)	0.73
‡Adjusted HR (95% CI)	1.00	1.01 (0.9, 1.14)	0.98 (0.85, 1.12)	0.94 (0.76, 1.17)	1.11 (0.93, 1.33)	0.89
Cardiovascular disease						
No. of deaths	201	371	185	40	76	
Mortality rate, per 10,000 person-year	35	30.7	30.3	29	34	
Adjusted HR (95% CI)	1.00	0.92 (0.77, 1.1)	0.96 (0.8, 1.14)	0.81 (0.58, 1.14)	0.99 (0.76, 1.27)	0.99
‡Adjusted HR (95% CI)	1.00	1.14 (0.93, 1.4)	1.07 (0.84, 1.35)	0.96 (0.66, 1.41)	1.05 (0.76, 1.45)	0.98
Ischemic heart disease						
No. of deaths	83	166	90	16	33	
Mortality rate, per 10,000 person-year	14.5	13.7	14.8	11.6	14.8	

Adjusted HR (95% CI)	1.00	0.86 (0.66, 1.13)	1.03 (0.79, 1.34)	0.75 (0.44, 1.27)	0.92 (0.63, 1.36)	0.88
‡Adjusted HR (95% CI)	1.00	1.24 (0.91, 1.69)	1.21 (0.85, 1.72)	0.97 (0.54, 1.76)	1.23 (0.77, 1.97)	0.93
All Stroke						
No. of deaths	84	146	69	16	26	
Mortality rate, per 10,000 person-year	14.6	12.1	11.3	11.6	11.6	
Adjusted HR (95% CI)	1.00	0.99 (0.75, 1.3)	0.9 (0.68, 1.2)	0.81 (0.47, 1.38)	0.88 (0.57, 1.35)	0.38
‡Adjusted HR (95% CI)	1.00	1.14 (0.83, 1.56)	0.99 (0.68, 1.44)	0.86 (0.47, 1.57)	0.82 (0.47, 1.43)	0.39
Ischemic stroke						
No. of deaths	20	52	27	3	7	
Mortality rate, per 10,000 person-year	3.5	4.3	4.4	2.2	3.1	
Adjusted HR (95% CI)	1.00	0.72 (0.43, 1.21)	0.94 (0.59, 1.52)	0.43 (0.13, 1.38)	0.63 (0.28, 1.41)	0.54
‡Adjusted HR (95% CI)	1.00	1.48 (0.81, 2.69)	1.64 (0.85, 3.18)	0.52 (0.12, 2.29)	1.07 (0.40, 2.84)	0.77
Hemorrhagic stroke						
No. of deaths	26	35	24	4	8	
Mortality rate, per 10,000 person-year	4.5	2.9	3.9	2.9	3.6	
Adjusted HR (95% CI)	1.00	1.18 (0.7, 1.99)	1.37 (0.81, 2.3)	0.95 (0.34, 2.68)	1.31 (0.60, 2.84)	0.67
‡Adjusted HR (95% CI)	1.00	1.08 (0.57, 2.04)	1.26 (0.62, 2.55)	1.02 (0.33, 3.14)	0.93 (0.33, 2.67)	0.78
Ischemic heart disease/ischemic stroke						

No. of deaths	103	218	117	19	40	
Mortality rate, per 10,000 person-year	17.9	18	19.2	13.8	17.9	
Adjusted HR (95% CI)	1.00	0.83 (0.65, 1.05)	1.01 (0.8, 1.27)	0.67 (0.41, 1.08)	0.85 (0.60, 1.21)	0.87
‡Adjusted HR (95% CI)	1.00	1.28 (0.97, 1.69)	1.29 (0.95, 1.76)	0.87 (0.5, 1.51)	1.20 (0.78, 1.83)	0.96

†: adjusted for sex, age, education, occupation, family income, smoking status, physical activity, alcohol drinking, self-rated health and chronic disease history (diabetes, hypertension and dyslipidemia).

‡: Adjusted HR in18,707 participants with data on daily dietary energy and vegetable, fruit, milk and nut intake were included in this model with additional adjustment for total energy, vegetable, fruit, milk and nut intake.

ESM Table 1. ICD-10 codes for deaths from cardiovascular disease

Causes of deaths	**ICD-10**
Cardiovascular disease	I00-I25, I28-I99
Ischemic heart disease	I20-I25
Stroke	I60-I69
Ischemic stroke	I63
Hemorrhagic stroke	I61
Ischemic heart disease or ischemic stroke	I20-I25, I63

ESM Table 2 Cross-sectional analysis of the association of egg consumption with cardiovascular risk factors in 28,024 participants based on baseline information collected from September 2003 to January 2008; regression coefficient β, (95% confidence interval).

	Egg consumption, numberper week					
	<1	1-2	3-4	5-6	7+	P for trend
Systolic blood pressure, mmHg						
Crude	Reference (0)	2.34 (1.66, 3.02)**	-0.47 (-1.14, 0.2)	-1.73 (-2.96, -0.51)**	-1.62 (-2.59, -0.65)***	<0.001
Model 1	Reference (0)	-1.07 (-1.69, -0.44)*	-1.45 (-2.17, -0.73)*	-2.44 (-3.62, -1.26)**	-2.56 (-3.54, -1.59)***	<0.001
Model 2†	Reference (0)	-0.94 (-1.7, -0.17)*	-1.57 (-2.45, -0.69)*	-2.62 (-3.99, -1.24)**	-3.05 (-4.3, -1.79)***	<0.001
Model 3†	Reference (0)	-0.86 (-1.63, -0.1)*	-1.58 (-2.46, -0.7)*	-2.52 (-3.9, -1.15)**	-3.01 (-4.27, -1.75)***	<0.001
Diastolic blood pressure, mmHg						
Crude	Reference (0)	-0.64 (-0.99, -0.29)*	-0.79 (-1.19, -0.39)*	-1.42 (-2.09, -0.76)*	-1.67 (-2.22, -1.13)***	<0.001
Model 1	Reference (0)	-0.55 (-0.88, -0.22)*	-0.46 (-0.85, -0.08)*	-0.94 (-1.57, -0.32)*	-1.06 (-1.58, -0.55)*	<0.001
Model 2†	Reference (0)	-0.51 (-0.91, -0.11)*	-0.51 (-0.98, -0.05)*	-0.99 (-1.72, -0.27)*	-1.3 (-1.97, -0.64)**	<0.001
Model 3†	Reference (0)	-0.46 (-0.87, -0.06)*	-0.52 (-0.99, -0.06)*	-0.95 (-1.68, -0.23)*	-1.3 (-1.97, -0.64)**	<0.001
LDL-cholesterol, mmol/l						
Crude	Reference (0)	0.01 (-0.01, 0.03)	-0.03 (-0.06, -0.01)*	-0.07 (-0.12, -0.03)*	-0.07 (-0.1, -0.03)*	<0.001
Model 1	Reference (0)	0.001 (-0.02, 0.02)	-0.04 (-0.06, -0.01)*	-0.06 (-0.1, -0.02)*	-0.07 (-0.1, -0.03)*	<0.001
Model 2†	Reference (0)	0.01 (-0.01, 0.04)	-0.03 (-0.06, 0.004)	-0.03 (-0.08, 0.01)	-0.07 (-0.11, -0.03)*	<0.001

Model 3[†]	Reference (0)	0.01 (-0.02, 0.03)	-0.03 (-0.06, 0.003)	-0.03 (-0.08, 0.01)	-0.06 (-0.11, -0.02)[*]	<0.001
HDL-cholesterol, mmol/l						
Crude	Reference (0)	-0.0005 (-0.01, 0.01)	0.0002 (-0.01, 0.01)	-0.03 (-0.05, -0.002)[*]	-0.004 (-0.02, 0.02)	0.42
Model 1	Reference (0)	0.001 (-0.01, 0.01)	-0.004 (-0.02, 0.01)	-0.03 (-0.05, -0.01)[*]	-0.01 (-0.03, 0.01)	0.38
Model 2[†]	Reference (0)	-0.002 (-0.02, 0.01)	-0.01 (-0.03, 0.009)	-0.04 (-0.07, -0.01)[*]	-0.003 (-0.03, 0.02)	0.38
Model 3[†]	Reference (0)	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.006)	-0.04 (-0.07, -0.02)[**]	-0.01 (-0.03, 0.02)	0.32
Triglycerides, mmol/l						
Crude	Reference (0)	-0.06 (-0.1, -0.02)[*]	-0.11 (-0.15, -0.06)[**]	-0.11 (-0.19, -0.04)[**]	-0.15 (-0.21, -0.09)[**]	<0.001
Model 1	Reference (0)	-0.06 (-0.1, -0.02)[*]	-0.09 (-0.13, -0.05)[**]	-0.06 (-0.13, 0.01)	-0.12 (-0.18, -0.06)[**]	<0.001
Model 2[†]	Reference (0)	-0.06 (-0.1, -0.01)[*]	-0.08 (-0.14, -0.03)[*]	-0.04 (-0.12, 0.04)	-0.12 (-0.2, -0.05)[*]	0.001
Model 3[†]	Reference (0)	-0.05 (-0.1, -0.01)[*]	-0.08 (-0.13, -0.03)[**]	-0.03 (-0.12, 0.05)	-0.12 (-0.19, -0.04)[*]	<0.001
Total cholesterol, mmol/l						
Crude	Reference (0)	0.01 (-0.02, 0.05)	-0.05 (-0.09, 0.001)	-0.08 (-0.15, -0.01)[*]	-0.13 (-0.19, -0.08)[**]	<0.001
Model 1	Reference (0)	0.01 (-0.03, 0.04)	-0.04 (-0.08, 0.001)	-0.05 (-0.12, 0.01)	-0.12 (-0.18, -0.07)[**]	0.002
Model 2[†]	Reference (0)	0.01 (-0.03, 0.05)	-0.04 (-0.09, 0.01)	-0.06 (-0.14, 0.02)	-0.1 (-0.17, -0.03)[*]	0.06
Model 3[†]	Reference (0)	0.002 (-0.04, 0.05)	-0.04 (-0.09, 0.01)	-0.06 (-0.14, 0.02)	-0.1 (-0.17, -0.02)[*]	0.06
Fasting glucose, mmol/l						

Crude	Reference (0)	-0.01 (-0.06, 0.05)	0.01 (-0.05, 0.07)	0.06 (-0.04, 0.15)	0.1 (0.02, 0.18)*	0.02
Model 1	Reference (0)	0.02 (-0.03, 0.06)	0.03 (-0.02, 0.09)	0.06 (-0.03, 0.15)	0.05 (-0.02, 0.12)	0.27
Model 2†	Reference (0)	0.001 (-0.06, 0.06)	0.05 (-0.02, 0.11)	0.05 (-0.05, 0.16)	0.08 (-0.02, 0.17)	0.15
Model 3†	Reference (0)	0.003 (-0.06, 0.06)	0.04 (-0.03, 0.1)	0.04 (-0.06, 0.14)	0.05 (-0.04, 0.15)	0.24
Body mass index, kg/m^2						
Crude	Reference (0)	-0.01 (-0.11, 0.09)	-0.21 (-0.31, -0.11)***	-0.24 (-0.43, -0.06)**	-0.32 (-0.46, -0.17)***	<0.001
Model 1	Reference (0)	0.001 (-0.1, 0.1)	-0.18 (-0.27, -0.08)**	-0.09 (-0.28, 0.09)	-0.21 (-0.36, -0.07)**	<0.001
Model 2†	Reference (0)	-0.07 (-0.19, 0.05)	-0.19 (-0.31, -0.07)**	-0.11 (-0.32, 0.1)	-0.28 (-0.47, -0.1)**	0.005
Model 3†	Reference (0)	0.06 (-0.06, 0.19)	-0.17 (-0.32, -0.03)**	-0.07 (-0.29, 0.15)	-0.29 (-0.50, -0.09)**	0.006
Waist circumference, cm						
Crude	Reference (0)	-0.36 (-0.64, -0.08)*	-0.49 (-0.81, -0.16)*	-0.71 (-1.24, -0.18)*	-0.42 (-0.86, 0.01)	0.06
Model 1	Reference (0)	-0.13 (-0.29, 0.03)	0.06 (-0.12, 0.25)	-0.15 (-0.45, 0.15)	0.25 (0.0001, 0.5)*	0.08
Model 2†	Reference (0)	-0.175 (-0.36, 0.01)	-0.03 (-0.24, 0.19)	-0.33 (-0.67, 0.001)	0.24 (-0.07, 0.55)	0.08
Model 3†	Reference (0)	-0.14 (-0.32, 0.05)	-0.01 (-0.23, 0.2)	-0.31 (-0.64, 0.03)	0.26 (-0.05, 0.56)	0.12

Model 1: adjusted for sex, age, education, occupation, family income, smoking status, physical activity, alcohol drinking, body mass index (except for BMI above) , self-rated health and chronic disease history (diabetes, hypertension and dyslipidemia), as appropriate.

Model 2 †: Additionally adjusted for daily dietary energy intake

Model 3 †: Additionally adjusted for vegetable, fruit, milk and nut intake

†:18,707participants with data on daily dietary energy intake were included in Model 2&3.

*: P<0.05; **: P<0.01; ***: P<0.001

ESM Table 3. Cross-sectional analysis of the association of egg consumption with cardiovascular risk factors in 12,899 participants with stable egg consumption habit during the 1st follow-up

	Egg consumption, number per week					P for trend
	<1 (n=2,208)	1-2 (n=6,761)	3-4 (n=3,033)	5-6 (n=441)	7+ (n=456)	
Systolic blood pressure, mmHg						
Crude	Reference (0)	2.05 (1.02, 3.07)[**]	-0.96 (-1.88, -0.05)[*]	-2.68 (-4.74, -0.63)[*]	-1.88 (-3.89, 0.14)	<0.001
Model 1[†]	Reference (0)	0.77 (-0.18, 1.72)	-0.78 (-1.62, 0.06)	-1.9 (-3.79, -0.01)[*]	-2.25 (-4.09, -0.4)[*]	<0.001
Diastolic blood pressure, mmHg						
Crude	Reference (0)	0.65 (0.12, 1.18)[*]	-0.31 (-0.78, 0.16)	-1.28 (-2.35, -0.22)[*]	-1.32 (-2.36, -0.28)[*]	<0.001
Model 1[†]	Reference (0)	0.54 (0.03, 1.05)[*]	-0.16 (-0.61, 0.3)	-0.80 (-1.82, 0.22)	-0.86 (-1.85, 0.14)	0.001
LDL-cholesterol, mmol/l						
Crude	Reference (0)	-0.02 (-0.06, 0.01)	-0.02 (-0.05, 0.01)	-0.08 (-0.14, -0.01)[*]	-0.09 (-0.15, -0.02)[*]	<0.001
Model 1[†]	Reference (0)	-0.01 (-0.04, 0.03)	-0.03 (-0.06, 0.001)	-0.07 (-0.13, 0.001)	-0.07 (-0.13, -0.002)[*]	0.008
HDL-cholesterol, mmol/l						
Crude	Reference (0)	-0.004 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0.01 (-0.03, 0.05)	0 (-0.04, 0.03)	0.48
Model 1[†]	Reference (0)	-0.002 (-0.02, 0.02)	0.01 (-0.01, 0.02)	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	0.87
Triglycerides, mmol/l						
Crude	Reference (0)	0.07 (0.01, 0.13)[*]	-0.06 (-0.11, -0.004)[*]	-0.08 (-0.19, 0.04)	-0.10 (-0.22, 0.01)	<0.001
Model 1[†]	Reference (0)	0.06 (0.0009, 0.12)[*]	-0.05 (-0.1, 0.003)	-0.02 (-0.14, 0.10)	-0.09 (-0.21, 0.02)	0.001
Total cholesterol, mmol/l						
Crude	Reference (0)	-0.02 (-0.08, 0.03)	-0.02 (-0.07, 0.02)	-0.05 (-0.16, 0.06)	-0.11 (-0.22, -0.002)[*]	0.15
Model 1[†]	Reference (0)	-0.01 (-0.07, 0.04)	-0.03 (-0.08, 0.02)	-0.03 (-0.14, 0.08)	-0.1 (-0.21, 0.005)	0.10
Fasting glucose, mmol/l						
Crude	Reference (0)	0.01 (-0.06, 0.09)	0.01 (-0.05, 0.08)	0.02 (-0.13, 0.16)	0.16 (0.01, 0.30)[*]	0.20
Model 1[†]	Reference (0)	-0.02 (-0.08, 0.05)	0 (-0.05, 0.06)	0.03 (-0.1, 0.16)	0.04 (-0.09, 0.17)	0.36
Body mass index, kg/m^2						
Crude	Reference (0)	0.1 (-0.06, 0.25)	-0.25 (-0.39, -0.11)[***]	-0.17 (-0.48, 0.14)	-0.11 (-0.41, 0.2)	0.001
Model 1[†]	Reference (0)	0.06 (-0.1, 0.21)	-0.2 (-0.33, -0.06)[**]	-0.02 (-0.32, 0.29)	0.04 (-0.26, 0.34)	0.08
Waist circumference, cm						
Crude	Reference (0)	0.67 (0.25, 1.1)	-0.32 (-0.7, 0.05)	-0.47 (-1.32, 0.37)	0.16 (-0.67, 0.99)	0.002
Model 1[†]	Reference (0)	0.25 (-0.16, 0.66)	-0.28 (-0.64, 0.08)	-0.16 (-0.97, 0.65)	0.18 (-0.61, 0.97)	0.16

[†]: adjusted for sex, age, education, occupation, family income, smoking status, physical activity, alcohol drinking, self-rated health and chronic disease history (diabetes, hypertension and dyslipidemia).

ESM Table 4. Adjusted hazards ratios (HR) and 95% confidence interval (CI) of all-cause mortality for baseline egg consumption in 27,963 participants (61 participants consuming more than 1 egg/day were excluded)

	Egg consumption, number per week				
	<1	1-2	3-4	5-6	7
Person-years	57402	120820	60979	13800	21770
All-cause					
No. of deaths	614	1120	580	127	234
Mortality rate, per 10,000 person-year	107	92.7	95.1	92	107.5
Adjusted HR (95% CI)†	1.00	1.00 (0.91, 1.11)	0.99 (0.88, 1.12)	0.89 (0.73, 1.08)	1.07 (0.91, 1.25)
Cardiovascular disease					
No. of deaths	201	371	185	40	73
Mortality rate, per 10,000 person-year	35	30.7	30.3	29	33.5
Adjusted HR (95% CI)†	1.00	1.09 (0.91, 1.3)	1.04 (0.85, 1.28)	0.88 (0.62, 1.26)	1.06 (0.8, 1.4)
Ischemic heart disease					
No. of deaths	83	166	90	16	32
Mortality rate, per 10,000 person-year	14.5	13.7	14.8	11.6	14.7
Adjusted HR (95% CI)†	1.00	1.16 (0.89, 1.53)	1.20 (0.88, 1.63)	0.87 (0.5, 1.51)	1.07 (0.7, 1.65)
All Stroke					
No. of deaths	84	146	69	16	24
Mortality rate, per 10,000 person-year	14.6	12.1	11.3	11.6	11
Adjusted HR (95% CI)†	1.00	1.01 (0.77, 1.33)	0.91 (0.66, 1.27)	0.82 (0.47, 1.43)	0.85 (0.53, 1.35)

†: adjusted for sex, age, education, occupation, family income, smoking status, physical activity, alcohol drinking, self-rated health and chronic disease history (diabetes, hypertension and dyslipidemia).

ESM Table 5. Adjusted hazards ratios (HR) and 95% confidence interval (CI) of all-cause mortality for baseline egg consumption by education[‡] in 28,024 participants

	Egg consumption, number per week				
	<1	1-2	3-4	5-6	7+
Low education (Illiterate or primary school)					
Person-years	31,294	51,451	24,172	5,258	6,588
All-cause					
No. of deaths	410	613	286	63	76
Mortality rate, per 10,000 person-year	131	119	118	120	115
Adjusted HR (95% CI)	1.00	1.00 (0.88, 1.14)	0.97 (0.83, 1.13)	0.9 (0.69, 1.19)	0.94 (0.73, 1.2)
Cardiovascular disease					
No. of deaths	150	225	98	21	25
Mortality rate, per 10,000 person-year	48	44	41	40	38
Adjusted HR (95% CI)	1.00	1.06 (0.85, 1.31)	0.95 (0.73, 1.24)	0.85 (0.53, 1.36)	0.82 (0.52, 1.27)
Ischemic heart disease					
No. of deaths	60	95	47	8	14
Mortality rate, per 10,000 person-year	19	18	19	15	21
Adjusted HR (95% CI)	1.00	1.1 (0.79, 1.53)	1.11 (0.75, 1.65)	0.75 (0.34, 1.65)	1.11 (0.61, 2.04)
All Stroke					
No. of deaths	61	93	36	11	10
Mortality rate, per 10,000 person-year	19	18	15	21	15
Adjusted HR (95% CI)	1.00	1.05 (0.75, 1.46)	0.84 (0.55, 1.28)	1.1 (0.57, 2.09)	0.77 (0.38, 1.56)
Relatively high education (secondary school, and college or above)					
Person-years	135,877	142,459	139,507	134,424	136,831
All-cause					
No. of deaths	1,040	1,098	1,089	1,021	1,054
Mortality rate, per 10,000 person-year	77	77	78	76	77
Adjusted HR (95% CI)	1.00	1.01 (0.86, 1.19)	1.03 (0.86, 1.23)	0.88 (0.66, 1.17)	1.2 (0.98, 1.47)
Cardiovascular disease					
No. of deaths	300	318	313	294	304
Mortality rate, per 10,000 person-year	22	22	22	22	22
Adjusted HR (95% CI)	1.00	1.13 (0.83, 1.54)	1.15 (0.82, 1.62)	1.03 (0.61, 1.74)	1.41 (0.96, 2.06)
Ischemic heart disease					
No. of deaths	141	153	150	139	142
Mortality rate, per 10,000 person-year	10	11	11	10	10
Adjusted HR (95% CI)	1.00	1.31 (0.82, 2.09)	1.36 (0.82, 2.26)	1.16 (0.54, 2.51)	1.33 (0.74, 2.4)

All Stroke					
No. of deaths	109	114	114	105	111
Mortality rate, per 10,000 person-year	8	8	8	8	8
Adjusted HR (95% CI)	1.00	0.92 (0.57, 1.49)	0.96 (0.56, 1.62)	0.56 (0.21, 1.48)	0.97 (0.52, 1.82)

[†]: adjusted for sex, age, occupation, family income, smoking status, physical activity, alcohol drinking, self-rated health and chronic disease history (diabetes, hypertension and dyslipidemia).

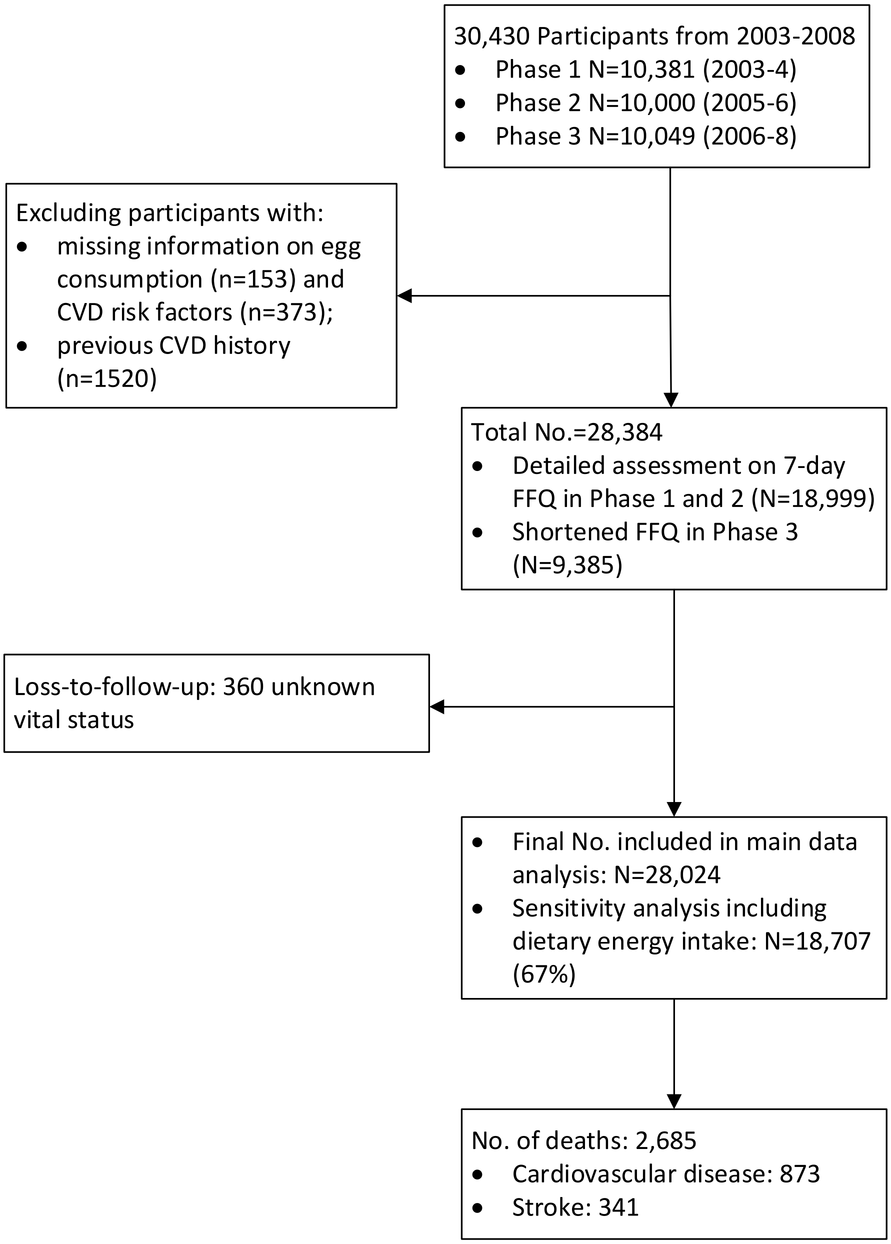
[‡]: P for interaction between egg consumption and education ranged 0.65 to 0.97

ESM Table 6 Details of studies in the meta-analysis

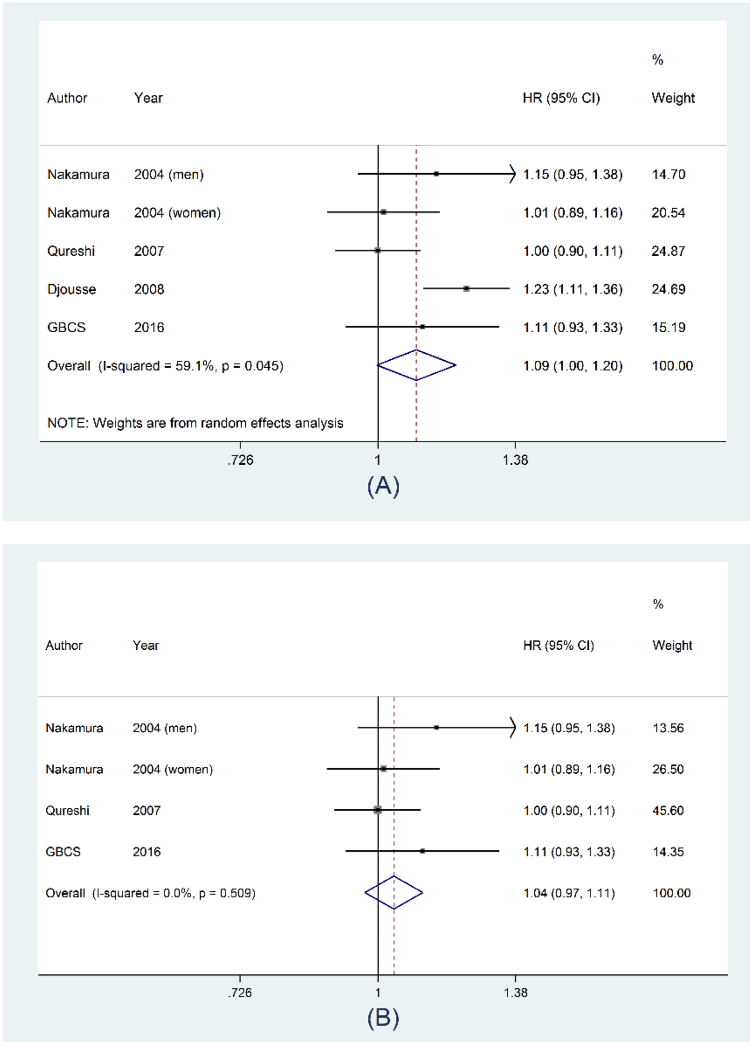
Study	First author (year)	Setting	Total sample	Events(number)	Age range of participants	Main findings HR (95% CI)
1	Hu 1999[30]	USA	37,851 men and 80,082 women	CHD (866 in men and 939 in women) Stroke (258 in men and 563 in women)	Men: 40-75 Women: 34-59	***IHD:*** Men HR=1.08 (0.79-1.48) Women HR=0.82 (0.60-1.13) ***All stroke:*** Men HR=1.07 (0.66-1.75) Women HR=0.89 (0.60-1.31) ***Ischemic stroke:*** Men HR=0.93 (0.46-1.87) Women HR=0.81 (0.46-1.42) ***Haemorrhagic stroke:*** Men HR=1.07 (0.66-1.75) Women HR=1.07 (0.56-2.03)
2	He 2003[36]	USA	43,732 men	455 ischemic strokes; 125 haemorrhagic stokes	40-75	***Ischemic stroke:*** HR=1.09 (0.69-1.71) ***Haemorrhagic stroke:*** HR=0.32 (0.07-1.37)
3	Sauvaget 2003[14]	Japan	37,130	Stroke (1462)	34-103	HR=0.70 (0.51-0.95)
4	Nakamura 2004[13]	Japan	5,186 women and 4,077 men	IHD (39 in men and 41 in women) Stroke (112 in men and 107 in women)	30+	***IHD:*** Men HR=0.93 (0.50-1.87) Women HR=0.86 (0.62-1.40) ***All stroke:*** Men HR=1.03 (0.67-1.53) Women HR=1.11 (0.74-1.48) ***All cause*** Men HR=1.15 (0.88-1.28) Women HR=1.01 (0.88-1.15)
5	Nakamura 2006[12]	Japan	90,735	IHD (462)	40-69	HR=0.93 (0.84-1.11)
6	Qureshi 2007□[37]	USA	9,734	IHD (1584) Stroke (655)	25-74	***IHD:*** HR=1.1 (0.90-1.30) ***All stroke:*** HR=0.9 (0.70-1.10)

7	Djousse 2008[38]	USA	21,327 men	MI (1550) Stroke (1342)	40-85	***All cause*** HR=1.0 (0.90-1.10) ***MI:*** HR=0.90 (0.72-1.14) ***All stroke:*** HR=0.99 (0.80-1.20)
8	Scrafford 2011[32]	USA	6,833 men and 8,113 women	IHD (366) Stroke (137)	17+	***All cause*** HR=1.23 (1.11-1.36) ***IHD:*** Men HR=1.13 (0.61-2.11) Women HR=0.92 (0.27-3.11) ***All stroke:*** Men HR=0.27 (0.10-0.73) Women HR=1.03 (0.25-4.22)
9	Bernstein 2012[39]	USA	84,010 women and 43,150 men	Stroke (2633 in women and 1397 in men)	Men: 40-75 years Women: 30-55	***All stroke:*** Men HR=0.84 (0.68-1.04) Women HR=0.91 (0.80-1.04) ***Ischemic stroke:*** Men HR=0.79 (0.61-1.04) Women HR=0.95 (0.79-1.14) ***Haemorrhagic stroke:*** Men HR=0.53 (0.22-1.25) Women HR=0.76 (0.47-1.23)
10	Larsson 2015[24]	Sweden	37,766 men and 32,805 women	MI (3,262 in men &1,504 in women); ischemic strokes (2,039 in men and 1,561 in women); haemorrhagic strokes (405 in men and 294 in women)	men 45-79y and women 49-83 y	***MI:*** Men HR=1.03 (0.84-1.27) Women HR=0.85 (0.59-1.23) ***Ischemic stroke:*** Men HR=0.87 (0.66-1.14) Women HR=1.06 (0.76-1.47) ***Haemorrhagic stroke:*** Men HR=1.05 (0.59-1.88) Women HR=0.96 (0.44-2.12)
11	Virtanen 2016[23]	Finland	1,032 men	230 IHD	42-60	HR=1.18 (0.85-1.66)

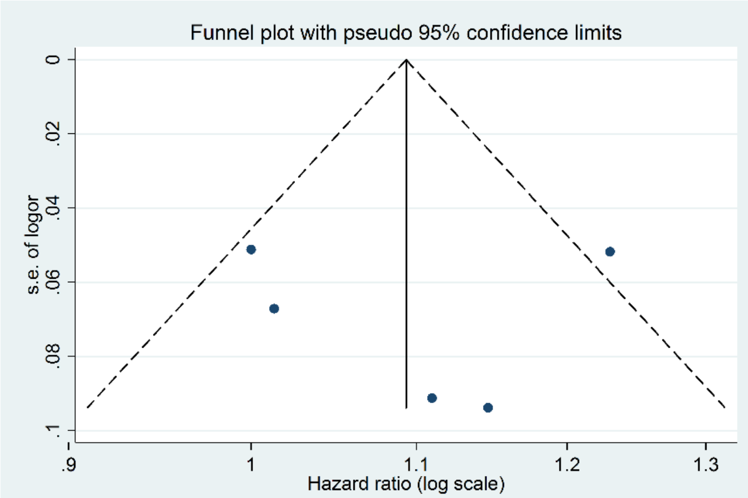
HR=hazard ratio; CI=confidence interval; USA=United States of America; IHD=ischemic stroke; MI=myocardial infarction



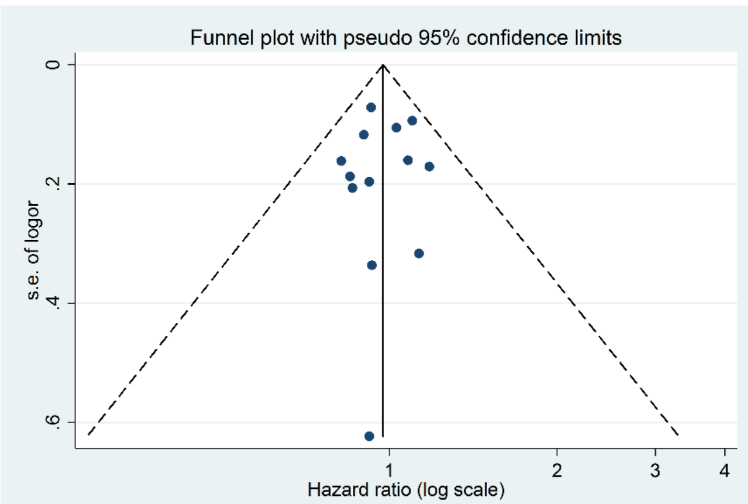
ESM Figure 1. Study sample selection.



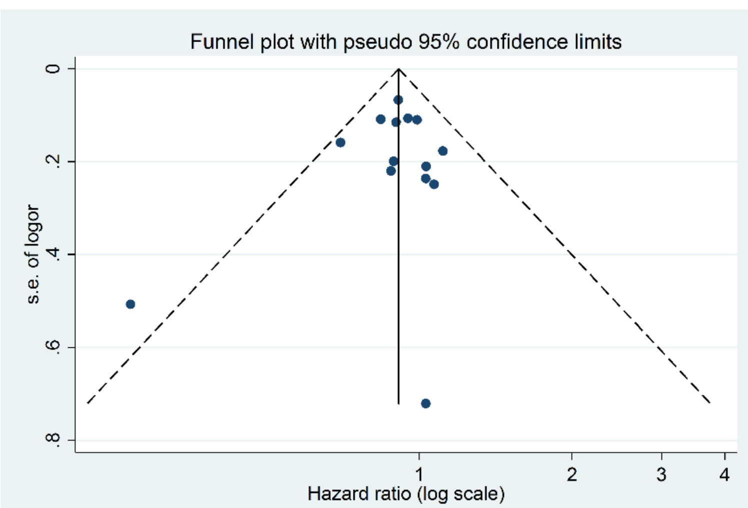
ESM Figure 2. Pooled HRs and 95% CIs of all-cause mortality including results from the Guangzhou Biobank Cohort Study (GBCS). The pooled estimates were obtained by using a random effect model for model (A), and fixed effect model for model (B). The study by *Djousse et al. 2008[38]* which contributed most to heterogeneity were excluded in model (B). The dots indicate the adjusted HRs from a comparison of the highest category of egg consumption (≥7 eggs/week) with the lowest (<1 egg/week or never). The size of the square is proportional to the weight of individual study. The horizontal lines represent 95% CI. The diamond data markers indicate the pooled HR.



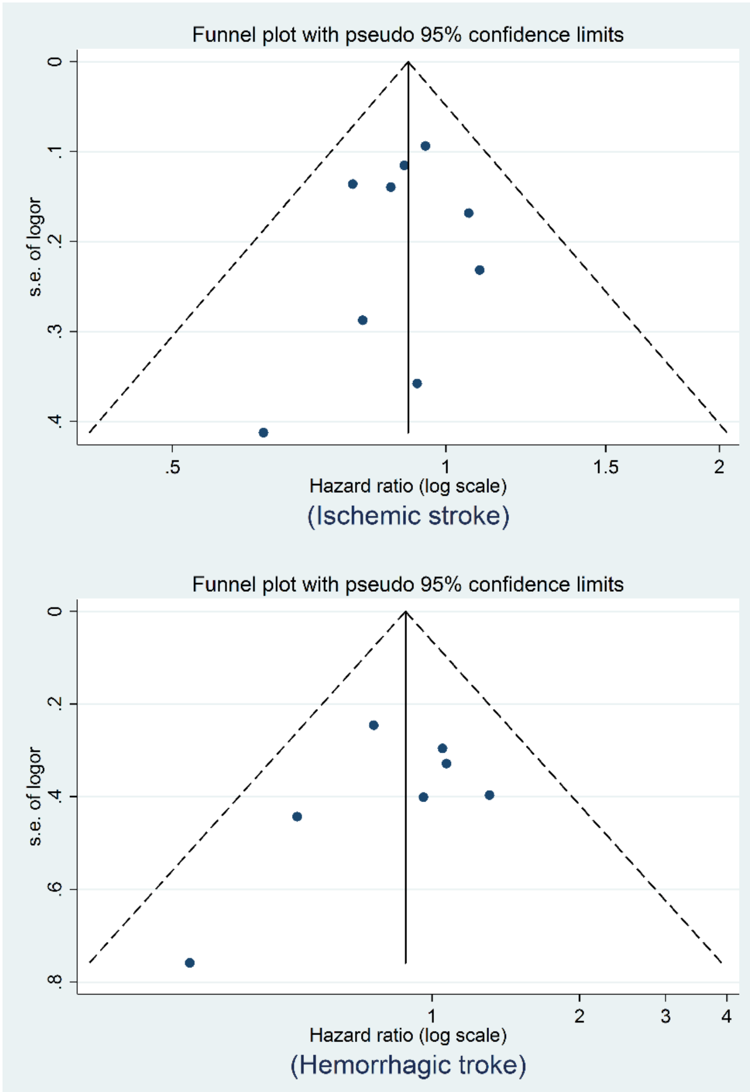
(All-cause)



(IHD)



(Stroke)



ESM Figure 3: Test for publication bias for the association between egg intake and all-cause mortality, ischemic heart disease, and stroke and its subtypes

Note: Tests for publication bias: (1) Begg's test, P=0.33, 0.90, 0.87, 0.53 and 0.18 for all-cause mortality, IHD, stroke, ischemic stroke and hemorrhagic stroke, respectively; (2) Egger's test, P=0.74, 0.86, 0.57, 0.61, 0.36 for all-cause mortality, IHD, stroke, ischemic stroke and hemorrhagic stroke, respectively.

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1. Hopkins PN (1992) Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. Am J Clin Nutr 55 (6):1060-1070
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