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Associations of egg consumption with incident cardiovascular disease and all-cause mortality

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Eggs are nutrient-dense while also loaded with abundant cholesterol, thus making the public hesitant about their consumption. We conducted the study to investigate if egg consumption is associated with incident cardiovascular disease (CVD) and all-cause mortality. Using the project of Prediction for Atherosclerotic Cardiovascular Disease Risk in China, we included 102,136 adults free of CVD and assessed their egg consumption with food-frequency questionnaires. CVD endpoints and all-cause mortality were confirmed during follow-ups by interviewing participants or their proxies and checking hospital records/death certificates. The HRs (95% CIs) were calculated using the cohort-stratified Cox regression models. During 777,163 person-years of follow-up, we identified 4,848 incident CVD and 5,511 deaths. U-shaped associations of egg consumption with incident CVD and all-cause mortality were observed. Compared with consumption of 3–<6/week, the multivariable-adjusted HRs (95% CIs) of <1/week and ≥10/week for incident CVD were 1.22 (1.11 to 1.35) and 1.39 (1.28 to 1.52), respectively. The corresponding HRs (95% CIs) for all-cause mortality were 1.29 (1.18 to 1.41) and 1.13 (1.04 to 1.24). Our findings identified that both low and high consumption were associated with increased risk of incident CVD and all-cause mortality, highlighting that moderate egg consumption of 3–<6/week should be recommended for CVD prevention in China.

egg consumption, cardiovascular disease, all-cause mortality, cohort study

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality and disability worldwide. In 2017, CVD accounted for 41.89% of total deaths and 85 million disability-adjusted life years (DALYs) in China (Institute for Health Metrics and Evaluation, 2019). Despite the existence of both hypo- and hyper-responders in the population, dietary cholesterol modestly increases the levels of serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c), both of which are well-established risks factors for CVD (Zhang et al., 2019; Grundy et al., 2019; Jacobson et al., 2015; Vincent et al., 2019). Eggs have been acknowledged as a good source

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of high-quality proteins; they contain bioactive components beneficial for health and abundant cholesterol in the yolks, thus making the public hesitant about consuming whole eggs (The China Nutrition Society, 2016).

Previous studies that explored the association of eggs consumption with incident CVD or all-cause mortality were predominantly conducted in high-income countries and their findings are not representative of the entire population and CVD subtypes (Hu et al., 1999; Key et al., 2019; Nakamura et al., 2006; Qureshi et al., 2007; Sauvaget et al., 2003; Scrafford et al., 2011). As a result, no consensus has been reached on the recommendation of egg consumption. Dietary guidelines from Greece recommended consumption of up to 4 eggs/week (Institute of Preventive Medicine Environmental & Occupational Health, Prolepsis, 2014), while more countries described eggs as a part of a healthy diet, with no limits mentioned (National Health Service, 2018; US Department of Health and Human Services and US Department of Agriculture, 2015). Recently, the American Heart Association recommended the health individuals to consume up to one whole egg daily (Carson et al., 2020). The contemporary Chinese dietary guidelines recommended a weekly consumption of 5–7 eggs for adults; however, these guidelines were mainly based on studies conducted in the US and Japan, where disease constitution and dietary patterns were quite different from those in China (The China Nutrition Society, 2016). Most recent results from the China Kadoorie Biobank (CKB) study suggested significant inverse associations between egg consumption and CVD (Qin et al., 2018), whereas no significant association between egg consumption and CVD was observed in the Guangzhou Biobank study, except for a small reduction in the risk of stroke mortality (Xu et al., 2019). Evidence based on Chinese population has been limited and conflicting. Owing to a limited number of participants, most previous studies failed to clarify the effect of very high level of egg intake.

We have therefore conducted the study based on the project of Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR), which includes 102,136 participants from 15 provinces across the country. The purpose was to explore the associations of egg consumption with incident CVD and all-cause mortality, thus providing population-based evidence for recommendation on CVD prevention.

RESULTS

Baseline characteristics

Among the 102,136 participants included, 40.28% were males and the mean age at enrollment was 51.46 years. Overall, 12,439 (12.18%) participants reported eating <1 egg in a week, and 23,058 (22.58%), 25,647 (25.11%), 16,306 (15.96%) and 24,686 (24.17%) subjects consumed 1–<3, 3–<6, 6–<10 and ≥10 eggs per week, respectively (Table 1). There was no clear difference in egg consumption between men and women. In general, participants with moderate consumption had slightly better cardiometabolic health status (less hypercholesterolemia, hypertension, and diabetes) and economic conditions; however, they were also more likely to be less physically active and to have lower intake of fresh fruit and vegetables. The baseline characteristics of each cohort are shown in Table S1 in Supporting Information.

Primary analyses

During 777,163 person-years of follow-up, 4,848 cases of incident CVD, including 1,273 CHD and 2,919 strokes (ischemic: 1,832, hemorrhagic: 862), and 5,511 all-cause mortality were identified. The associations of egg consumption with CVD endpoints and all-cause mortality are represented in Table 2. Compared with consumption of 3–<6/week, both higher and lower consumptions were associated with increased risk of incident CVD and all-cause mortality. The multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incident CVD across categories of egg consumption were 1.22 (1.11 to 1.35) for <1/week, 1.09 (1.00 to 1.19) for 1–<3/week, 1.25 (1.14 to 1.38) for 6–10/week and 1.39 (1.28 to 1.52) for ≥10/week compared with those participants with egg consumption of 3–<6/week. The corresponding HRs (95% CIs) of all-cause mortality were 1.29 (1.18 to 1.41), 1.07 (0.99 to 1.16), 1.13 (1.04 to 1.24), and 1.13(1.04 to 1.24), respectively. Accordingly, restricted cubic splines indicated nonlinear dose-response relationships between egg consumption and risk of incident CVD as well as all-cause mortality (both $P_{\text{for non-linear relation}}<0.001$, Figure 1), with the lowest risk observed at about 4 eggs/week. We further examined the effects of egg consumption on CVD subtypes. The similar U-shaped association was also observed for overall stroke, while the pronounced increased risk was significantly associated with higher and lower consumptions of eggs for CHD and hemorrhagic stroke, respectively.

Subgroup and sensitivity analysis

The subgroup analyses indicated that the association of egg consumption with incident CVD was consistent across age, gender, cardiometabolic health status, and dietary factors, while there was a significant interaction effect between egg consumption and per-capita household income ($P_{\text{for interaction}}$=0.01). For participants with better economic condition, there seemed to be a J-shaped association between egg consumption and risks of CVD; on the contrary, a U-shaped dose-response relationship among less affluent sub-

Table 1 Baseline characteristics of participants according to egg consumption[a)]

	Habitual egg consumption (number per week)				
	<1 (*N*=12,439)	1–<3 (*N*=23,058)	3–<6 (*N*=25,647)	6–<10 (*N*=16,306)	≥10 (*N*=24,686)
Age (year)	51.48±0.10	51.55±0.08	51.00±0.08	50.95±0.10	52.17±0.08
Male (%)	37.36	39.83	40.43	41.97	40.89
Urban resident (%)	13.15	10.64	9.49	16.92	1.17
Per-capita household income ≥6,000 CNY/year (%)	22.21	37.96	43.56	32.63	26.96
Education attainment >9 years (%)	10.92	15.57	18.45	21.45	19.20
Tobacco smoking (%)	23.73	21.20	21.80	19.67	16.66
Alcohol consuming (%)	14.53	16.55	17.91	14.70	16.29
Family history of CVD (%)	10.69	9.66	9.51	12.39	9.54
BMI (kg m^{-2})	23.36±0.03	23.38±0.03	23.34±0.03	23.91±0.03	24.04±0.03
Ideal physical activity (%)	68.77	61.68	56.57	58.95	60.61
Red meat intake ≥75 g d^{-1} (%)	15.46	15.10	16.86	22.04	43.58
Fresh fruit and vegetable intake ≥500 g d^{-1} (%)	53.09	51.05	50.60	62.34	73.65
Waist circumference (cm)	78.98±0.09	79.05±0.07	79.06±0.07	80.51±0.08	80.48±0.08
Hypercholesterolemia (%)	7.83	6.12	5.40	8.47	8.43
Hypertension (%)	27.12	27.40	26.74	31.72	35.96
Diabetes (%)	5.36	4.41	4.45	5.85	5.94

a) Values (except for age, gender and urban resident) according to the egg consumption were represented by mean±standard error (for continuous variables) or percentage (for categorical variables) with adjustment for age at recruitment, gender, and cohort. Abbreviations: CVD, cardiovascular disease; BMI, body mass index; CNY, Chinese Yuan.

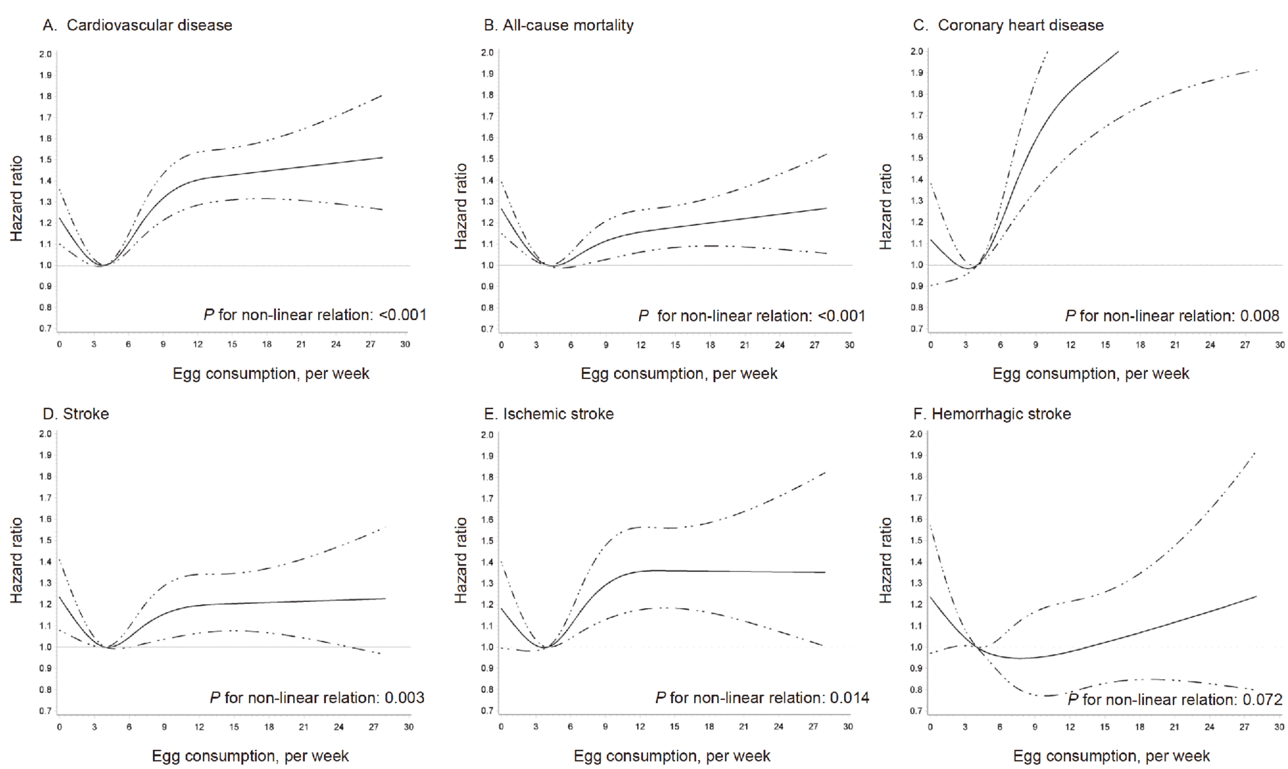

Figure 1 Restricted cubic spline curves of the associations between egg consumption and risk of incident cardiovascular disease and all-cause mortality. A, Cardiovascular disease. B, All-cause mortality. C, Coronary heart disease. D, Stroke. E, Ischemic stroke. F, Hemorrhagic stroke. Adjusted for age, gender, cohort, urban or rural resident, per-capita household income, education attainment, tobacco smoking, alcohol consumption, family history of CVD, physical activity, BMI, and dietary factors (red meat intake, fresh fruit and vegetable intake). Hazard ratios were estimated by comparing to a reference consumption of 4 eggs/week. Solid lines represented point estimates of the hazard ratios and dashed lines represented 95% confidence intervals.

Table 2 Associations of egg consumption with risk of CVD endpoints and all-cause mortality

	Habitual egg consumption (number per week)				
	<1	1–<3	3–<6	6–<10	≥10
CVD					
No. of cases	736	1,048	1,003	868	1,193
Incidence rate (per 100,000 person-years)	671.03	606.02	533.08	690.48	818.45
HR (95% CI), Model 1[a)]	1.29 (1.17 to 1.42)	1.12 (1.02 to 1.22)	Ref	1.33 (1.22 to 1.46)	1.51 (1.38 to 1.64)
HR (95% CI), Model 2[b)]	1.21 (1.09 to 1.34)	1.09 (1.00 to 1.20)	Ref	1.30 (1.18 to 1.42)	1.45 (1.33 to 1.59)
HR (95% CI), Model 3[c)]	1.22 (1.11 to 1.35)	1.09 (1.00 to 1.19)	Ref	1.25 (1.14 to 1.38)	1.39 (1.28 to 1.52)
All-cause mortality					
No. of cases	985	1,271	1,226	912	1,117
Mortality rate (per 100,000 person-years)	886.06	727.81	645.40	714.09	758.86
HR (95% CI), Model 1[a)]	1.40 (1.29 to 1.53)	1.11 (1.02 to 1.20)	Ref	1.12 (1.02 to 1.22)	1.16 (1.07 to 1.27)
HR (95% CI), Model 2[b)]	1.29 (1.18 to 1.41)	1.07 (0.98 to 1.16)	Ref	1.12 (1.03 to 1.22)	1.12 (1.03 to 1.22)
HR (95% CI), Model 3[c)]	1.29 (1.18 to 1.41)	1.07 (0.99 to 1.16)	Ref	1.13 (1.04 to 1.24)	1.13 (1.04 to 1.24)
CHD					
No. of cases	175	238	243	259	358
Incidence rate (per 100,000 person-years)	158.12	136.54	128.29	203.98	243.76
HR (95% CI), Model 1[a)]	1.08 (0.88 to 1.32)	1.01 (0.85 to 1.21)	Ref	1.47 (1.23 to 1.75)	2.07 (1.75 to 2.45)
HR (95% CI), Model 2[b)]	1.05 (0.86 to 1.29)	1.01 (0.84 to 1.21)	Ref	1.39 (1.16 to 1.67)	2.00 (1.68 to 2.37)
HR (95% CI), Model 3[c)]	1.07 (0.88 to 1.32)	1.01 (0.85 to 1.21)	Ref	1.34 (1.12 to 1.61)	1.86 (1.57 to 2.22)
Stroke					
No. of cases	457	681	630	506	645
Incidence rate (per 100,000 person-years)	414.48	392.31	333.74	399.98	440.49
HR (95% CI), Model 1[a)]	1.36 (1.20 to 1.54)	1.17 (1.05 to 1.31)	Ref	1.29 (1.14 to 1.45)	1.26 (1.13 to 1.41)
HR (95% CI), Model 2[b)]	1.25 (1.10 to 1.42)	1.14 (1.02 to 1.27)	Ref	1.25 (1.11 to 1.41)	1.21 (1.08 to 1.36)
HR (95% CI), Model 3[c)]	1.27 (1.12 to 1.44)	1.13 (1.01 to 1.26)	Ref	1.21 (1.07 to 1.36)	1.18 (1.05 to 1.33)
Ischemic stroke					
No. of cases	263	407	395	328	439
Incidence rate (per 100,000 person-years)	237.94	233.90	208.91	258.72	299.30
HR (95% CI), Model 1[a)]	1.28 (1.09 to 1.50)	1.13 (0.99 to 1.30)	Ref	1.37 (1.19 to 1.59)	1.40 (1.22 to 1.60)
HR (95% CI), Model 2[b)]	1.19 (1.01 to 1.40)	1.10 (0.96 to 1.27)	Ref	1.32 (1.13 to 1.53)	1.35 (1.17 to 1.55)
HR (95% CI), Model 3[c)]	1.20 (1.02 to 1.42)	1.09 (0.95 to 1.26)	Ref	1.28 (1.10 to 1.49)	1.33 (1.15 to 1.54)
Hemorrhagic stroke					
No. of cases	152	218	181	142	169
Incidence rate (per 100,000 person-years)	137.04	124.90	95.40	111.37	114.80
HR (95% CI), Model 1[a)]	1.48 (1.19 to 1.85)	1.28 (1.05 to 1.56)	Ref	1.18 (0.95 to 1.47)	1.13 (0.91 to 1.40)
HR (95% CI), Model 2[b)]	1.31 (1.04 to 1.64)	1.23 (1.01 to 1.51)	Ref	1.18 (0.94 to 1.47)	1.09 (0.88 to 1.35)
HR (95% CI), Model 3[c)]	1.34 (1.07 to 1.68)	1.23 (1.01 to 1.50)	Ref	1.13 (0.90 to 1.41)	1.03 (0.83 to 1.28)

a) Model 1: Cox proportional hazard model, stratified by cohort, adjusted for age and gender. b) Model 2: Further adjusted for urban or rural resident, per-capita household income, education attainment, tobacco smoking, alcohol consumption and family history of CVD. c) Model 3: Further adjusted for physical activity, BMI and dietary factors (red meat intake, fresh fruit and vegetable intake). Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio; CI, confidence interval.

jects was observed. No significant interaction was found for all-cause mortality (Figure 2). In addition, replacing baseline exposures with egg consumption records collected uniformly for each cohort during the 2007–2008 survey did not considerably alter the significant associations. Other sensitivity analyses also had no substantial influence on the original results (Table S2 in Supporting Information). The results of cohort-specific analyses were also generally consistent with the overall findings (Table S3 in Supporting Information).

DISCUSSION

Benefiting from a wide range of egg intake (from <1/week to ≥10/week) and a large sample size, the current cohort study indicated that both higher and lower consumptions of eggs were associated with increased risk of incident CVD and all-cause mortality compared with consumption of 3–<6 eggs/week. A moderate level of egg consumption was beneficial and worth of recommendation for the general Chinese and probably other populations in the low and middle-income countries.

For decades, the association of egg consumption with incident CVD and all-cause mortality remains controversial worldwide. Evidence from cohort studies and meta-analyses primarily focused on the potential effect of high intake of eggs as compared with low or rare intake and most of them reported insignificant associations with CVD endpoints or all-cause mortality (Hu et al., 1999; Nakamura et al., 2006; Qureshi et al., 2007; Rong et al., 2013). However, only a few participants in the aforementioned studies had a very high intake of eggs; thus, the highest category to a large extent represented those with slightly higher consumption. For example, only 8.03% of the participants consumed ≥1 egg/day in the previous study based on two large US population-based cohorts (Hu et al., 1999). In contrast, the China Health and Nutrition Survey (CHNS) observed that 25.8% of the participants consumed >1 egg/day (Jia et al., 2016). Our study suggested, based on a population with higher egg consumption, that the relationships of egg consumption with incident CVD and all-cause mortality were more likely to be U-shaped rather than monotone linear. Therefore, there is a potential concern that previous studies, which included a limited number of participants with very high intake of eggs and chose the lowest category as reference, may overlook the real associations, thus leading to the nonsignificant conclusion (Díez-Espino et al., 2017; Nakamura et al., 2006).

Recently, the Lifetime Risk Pooling Project conducted in the US indicated a positive linear relationship between egg consumption and incident CVD as well as all-cause mortality, with significantly elevated risks observed among those consuming ≥7 eggs/week compared with non-consumers of eggs (Zhong et al., 2019). These results generally supported our findings on the comparison between moderate and high consumption of eggs, and the discrepancy of low consumption was potentially attributed to the differences of disease constitution and dietary patterns between two countries. IHD remains the major subtype of CVD as well as the leading cause of mortality in the US. In China, stroke has always been the most cause of mortality, and the incidence of hemorrhagic stroke is relatively higher (Institute for Health Metrics and Evaluation, 2019; Wang et al., 2017). According to our study, higher consumption of eggs was significantly associated with increased risk of CHD and ischemic stroke. However, the elevated risk of hemorrhagic stroke was only found among participants with lower consumption, which was consistent with previous published meta-analyses (Rong et al., 2013; Sauvaget et al., 2003). Therefore, the association observed in China was more akin to a U-shaped relationship rather than J-shaped or linear. Moreover, the average intake of high-quality protein among Chinese population was generally insufficient and much lower than that of the US (Ju et al., 2018; Pasiakos et al., 2015), where multiple sources of high-quality protein might cover up the adverse effects of low egg consumption. This explanation was further ascertained in our subgroup analyses according to per-capita household income, in which low intake of eggs was only significantly associated with increased risk of CVD among those less affluent individuals.

Results from our study provided critical evidence for the general Chinese and probably other populations with similar characteristics. With the wide range of egg intake, the current study confirmed the beneficial effect of moderate consumption and further indicated the potential adverse effects of too much egg intake. The CKB study with participants with low to moderate intake of eggs indicated that daily egg consumption (about 0.76 egg/day) was significantly associated with lower risk of CVD, IHD, and stroke compared with no or rare consumption (Qin et al., 2018). This primarily represented the left side of the U-shaped curve observed in our study. Results from the Guangzhou Biobank cohort study also suggested U-shaped relationships between egg consumption and CVD or all-cause mortality, although the difference was not statistically significant, probably due to the relatively short period of follow-up and the limited number of participants consuming more than seven eggs per week (Xu et al., 2019).

The potential explanations for the beneficial effects of moderate egg consumption observed in our study are as follows. Elevated serum TC and LDL-c levels are acknowledged as the primary risk factors of CVD. Recently, a series of Mendelian randomization studies have further established the causal relationship between LDL-c and the risk of CHD (Hu et al., 2019). On the other hand, excessively low TC or LDL-c concentration has also been reported to increase the risk of hemorrhagic stroke (Gu et al., 2019).

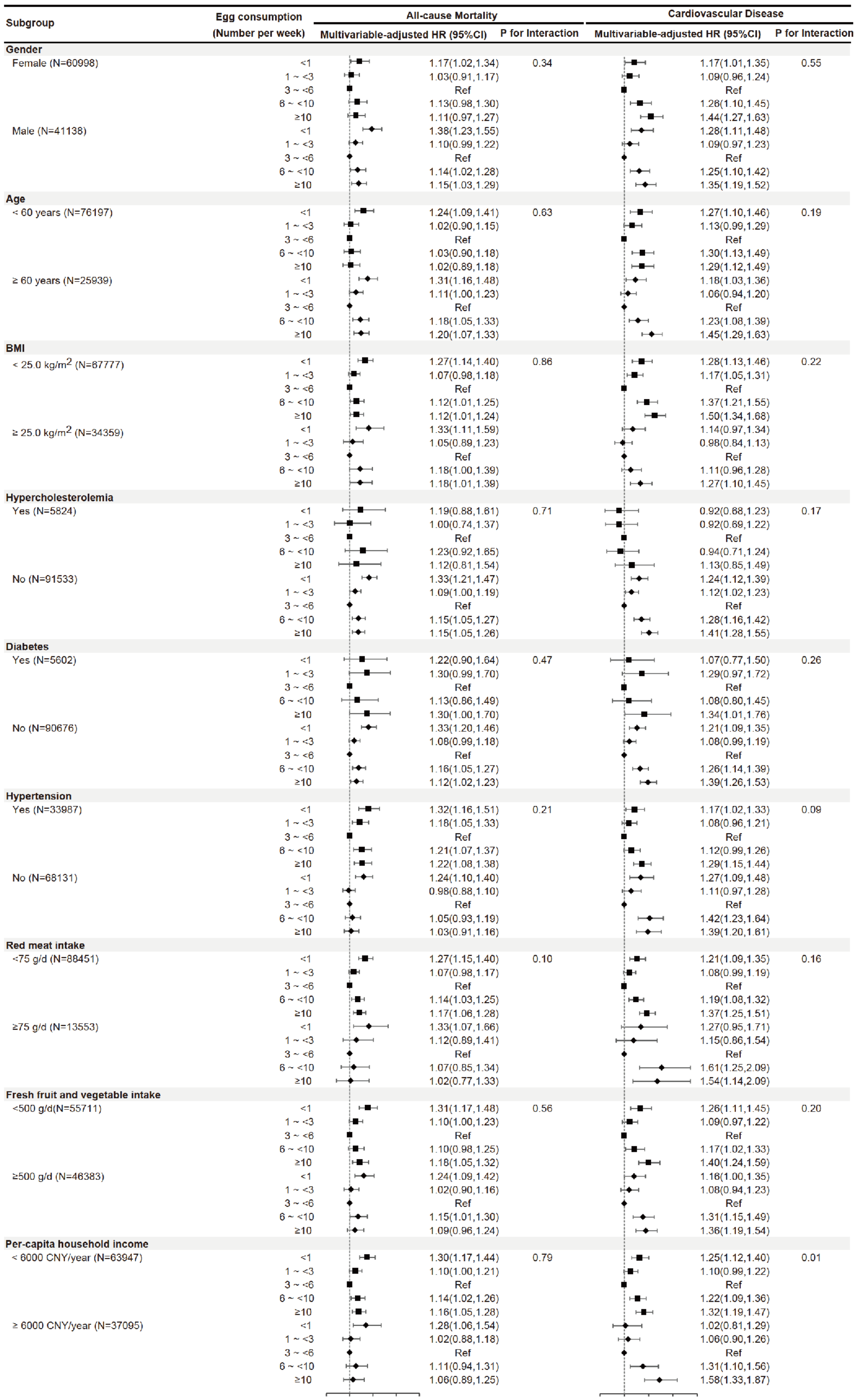

Figure 2 Subgroup analyses for the associations of egg consumption with risk of incident cardiovascular disease and all-cause mortality. The squares and diamonds represented point estimates of the hazard ratios and the horizontal lines represented 95% confidence intervals. Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CNY, Chinese Yuan.

Cholesterol intake could also increase oxidation susceptibility of LDL and enhance the adverse effects of saturated fatty acids (Spence et al., 2010). Previous studies suggested that egg consumption was significantly associated with higher serum TC and LDL-c concentrations and further increased the carotid plaque areas as well as the prevalence of coronary artery calcium (Choi et al., 2015; Rouhani et al., 2018; Spence et al., 2012). In the current study, the increased risks of CHD and ischemic stroke were also found to be more obvious in the high consumption categories. On the other hand, eggs are considered as a low-cost and highly accessible source of high-quality proteins. They also contain abundant antioxidant carotenoids like lutein and zeaxanthin, which may reduce LDL oxidation. Furthermore, moderate intake of egg phospholipids was proved to be beneficial for lipid metabolism without significantly increasing the level of trimethylamine N-oxide (TMAO) (Miller et al., 2014).

The primary advantages of our study include the prospective cohort design, the wide range of egg intake and the sufficient number of cases, which enable us to distinguish the effect of moderate intake with very high level of consumption and to provide more precise estimates for CVD subtypes. Inevitably, our study also has several limitations to address. First, since egg consumption was assessed by cohort-specific food-frequency questionnaires (FFQs), the measurement error of self-reported diet data as well as the heterogeneity across cohorts should be concerned. However, results of each cohort were generally in accordance with the main findings and no substantial change was observed when replacing the baseline exposure with egg consumption uniformly collected during the 2007–2008 survey. Secondly, the existing data were insufficient for us to calculate either the total energy intake or the intake of dietary cholesterol. However, according to the China Health and Nutrition Survey, egg and red meat consumption contributed to about 80% of dietary cholesterol intake among general Chinese (Su et al., 2015) and several bioactive components of fruits and vegetables (such as soluble fiber and phytosterols) were proved to reduce the intestinal absorption of cholesterol (Cohn et al., 2010). Thus, we adjusted the daily intake of red meat, fresh fruits, and vegetables in the analyses. Furthermore, we adjusted BMI and physical activity to approximately represent the level of total energy intake. However, residual confounding may still exist due to other food intake as well as the cooking methods of eggs. Finally, reverse causality might also bias the results. Health conditions of individuals could have an influence on their consumption of eggs. However, subjects with severe chronic diseases were excluded and exclusion of deaths or incidences identified in the first three years during follow-up did not considerably alter the associations. Moreover, subgroup analyses showed consistent results among participants without preexisting hypertension, diabetes, or hypercholesterolemia.

CONCLUSION

The current study indicated U-shaped relationships between egg consumption and the incident CVD and all-cause mortality among Chinese adults. Both low and high consumptions of eggs were significantly associated with increased risk. These findings supported a moderate egg consumption of 3–<6 /week in CVD prevention and the novel evidence should be considered in the update of guidelines on dietary cholesterol and cardiovascular risk for the general Chinese and probably other populations with similar disease constitution and dietary patterns.

MATERIALS AND METHODS

Study population

The China-PAR project is a nationwide prospective study; it is aimed at estimating the epidemic of CVD and identifying the related risk factors in general Chinese population. Three cohorts with dietary records from the China-PAR project were included in the present study, namely the China Multi-Center Collaborative Study of Cardiovascular Epidemiology (China MUCA) 1998, the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA), the Community Intervention of Metabolic Syndrome in China, and Chinese Family Health Study (CIMIC). The detailed description of the cohorts has been published elsewhere (Yang et al., 2016).

Briefly, the China MUCA (1998) was established in 1998 by cluster random sampling. About 1,000 participants aged 35–59 were selected from each of the 15 clusters across China. The InterASIA conducted baseline survey during 2000–2001, employing a four-stage stratified sampling method to recruit a representative sample of the general population aged 35–74. The CIMIC, a large community-based cohort study, was established in 2007–2008 by three-stage cluster random sampling. A total of 86,428 adults were recruited from four survey sites representing different levels of economic development in China. All the three cohorts were followed up under a unified protocol from 2012 to 2015. Before that, the China MUCA (1998) and the InterASIA were followed up once during 2007–2008, along with the baseline survey of the CIMIC.

In total, 113,448 participants were enrolled at baseline, among which 105,263 were followed up successfully. The lost rate of follow-up was 7.2%. After excluding 1,271 subjects with missing information on egg consumption at baseline, 1,712 with preexisting CVD, six lacking information of age at recruitment and 138 having cancer or end-stage renal diseases at baseline, a total of 102,136 adults were finally included in the current analysis (Figure 3).

The project was approved by the Institutional Review

Board at Fuwai Hospital (Beijing, China) and all the participants had provided written informed consent before data collection.

Egg consumption assessment

Baseline egg consumption was assessed by trained research staff through face-to-face interviews, using cohort-specific FFQs. In the China MUCA (1998), five predefined categories (<1, 1–<3, 3–<6, 6–<10 and ≥10 eggs/week) of habitual egg consumption were offered to participants and the usual amount of each category was estimated by the midpoint value. Participants in the InterAISA were asked how many times they consumed eggs per day, per week or per month during the previous 12 months, setting one-time intake as one egg. For CIMIC, we adopted a quantitative FFQ to investigate the portion size and frequency of consumption over the past year. In the current analyses, responses of the latter two cohorts were further harmonized in accordance with the China MUCA (1998).

In addition, egg consumptions during the 2007–2008 follow-up visits of the InterAISA and the China MUCA (1998) were also collected using the same questionnaire of CIMIC baseline survey and utilized in the sensitivity analyses.

Outcomes ascertainment

The primary outcomes were incident CVD and all-cause mortality. The incident CVD was a composite of nonfatal acute myocardial infarction, unstable angina (UA), stroke, heart failure, and death due to circulatory diseases (*ICD-10* I00-I99). The secondary outcomes included CHD, stroke, ischemic stroke, and hemorrhagic stroke. CHD was defined as nonfatal acute myocardial infarction, unstable angina, or death due to CHD (*ICD-10* I20-I25). Stroke was defined as nonfatal or fatal (*ICD-10* I60-69), including hemorrhagic stroke (*ICD-10* I60-62), ischemic stroke (*ICD-10* I63), and unspecified stroke.

During follow-up surveys, subjects were invited to participate in questionnaire surveys and physical examinations,

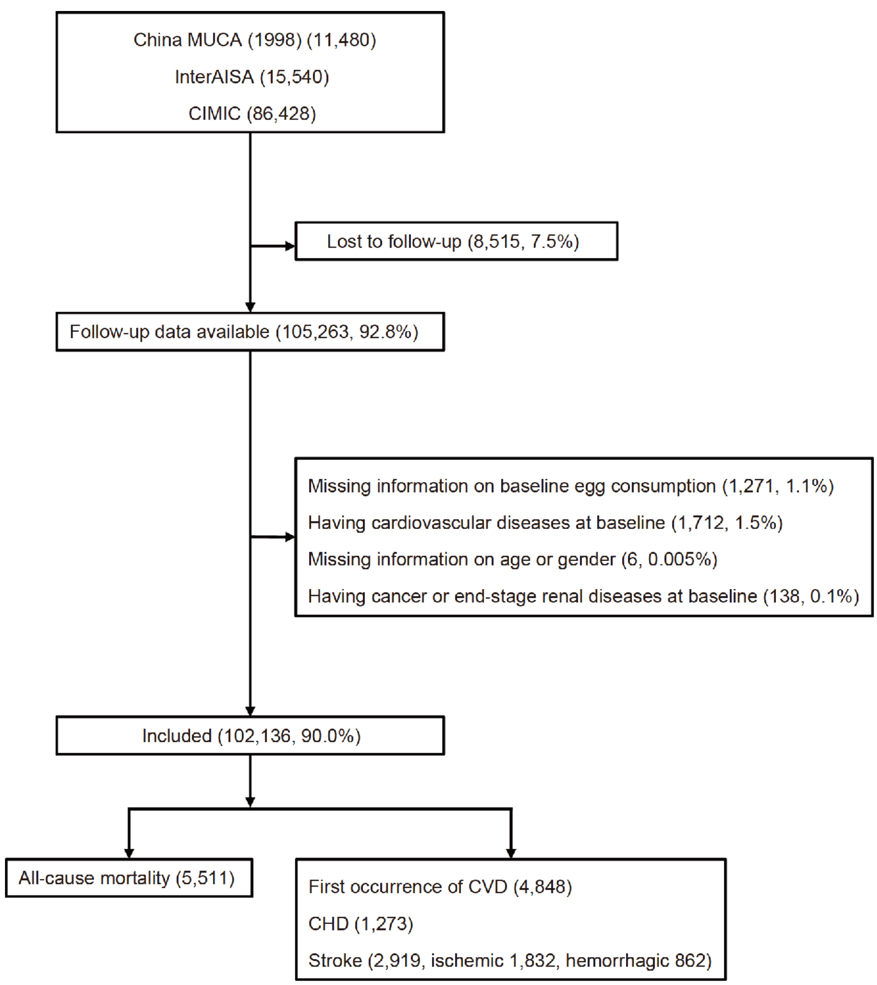

Figure 3 Flow chart of participants included and excluded in the analyses. Abbreviations: China MUCA (1998), China Multi-Center Collaborative Study of Cardiovascular Epidemiology (1998); InterASIA, International Collaborative Study of Cardiovascular Disease in Asia; CIMIC, Community Intervention of Metabolic Syndrome in China & Chinese Family Health Study; CVD, cardiovascular disease; CHD, coronary heart disease.

and they or their proxies were interviewed to update their latest disease information and vital status. Hospital records or death certificates were also checked to validate the diagnosis. All the outcomes were initially recorded by well-trained local investigators and further adjudicated by the outcome assessment committee at Fuwai Hospital. Two committee members verified the outcomes independently. Any discrepancies were resolved through discussion with additional committee members.

Covariates assessment

Baseline information on socio-demographic characteristics (age at recruitment, gender, per-capita household income, urban or rural resident, education attainment), lifestyles (tobacco smoking, alcohol consumption, physical activity), personal medical histories (self-reported antihypertensive, antidiabetic and lipid-lowering medications), family history of CVD and dietary factors were collected by trained staff using standard questionnaire. Ideal physical activity was defined as ≥150 min/week of moderate aerobic activity or ≥75 min/week of vigorous aerobic activity, or an equivalent combination of both (Piercy et al., 2018). Dietary intake of red meat, fresh fruits and vegetables was recorded under the same way of egg consumption and then classified based on both the recommendations of the current dietary guideline (The China Nutrition Society, 2016) and the ideal diet defined in the cardiovascular health metrics of Chinese population (Han et al., 2018). Waist circumference was measured at 1 cm above the navel at the end of a normal expiration. Three blood pressure (BP) measurements were taken in a seated position with 30 s intervals. Overnight fasting blood samples were drawn to measure serum lipid and glucose concentrations. Hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or current (within two weeks) antihypertensive medication. Diabetes was defined as fasting glucose level ≥7.0 mmol L^{-1} or current treatment with oral hypoglycemic agents or insulin injection. Hypercholesterolemia was defined as serum TC concentration ≥6.2 mmol L^{-1} or current lipid-lowering treatment.

Statistical analysis

Participants were classified into five predefined categories of egg consumption in accordance with the China MUCA (1998): <1/week, 1–<3/week, 3–<6/week, 6–<10/week and ≥10/week. Baseline characteristics were presented as means or percentages by category, with adjustment for age, gender, and cohort as appropriate, by means of general linear regression (continuous variables) and logistic regression (categorical variables).

Person-years of follow-up were calculated from the completion of baseline survey till the incidence of any CVD endpoints, death, or last follow-up, whichever came first. Cohort-stratified Cox proportional hazard regression model was employed to estimate the HRs (95% CIs), using 3–<6/week as reference. For each outcome, three sets of models were fitted. In model 1, we adjusted age at recruitment and gender; in model 2, urban or rural resident, per-capita household income, education attainment, tobacco smoking, alcohol consumption, and family history of CVD were added; in model 3, physical activity, BMI, red meat intake, and fresh fruit and vegetable intake were further adjusted. Restricted cubic splines with four knots were adopted to explore the potentially non-linear dose-response relationship. Subgroup analyses by baseline characteristics were conducted for primary outcomes and the interaction terms with egg consumption were tested in model 3 to investigate the potential effect modifications.

Five sensitivity analyses were conducted: (1) participants were regrouped by egg consumption recorded during the 2007–2008 survey, when all cohorts employed the same questionnaire (participants who died or were diagnosed with CVD before this survey were excluded); (2) mortality or incidence identified during the first three years of follow-up were excluded; (3) baseline cardiometabolic risk factors including waist circumference, hypertension, diabetes and hypercholesterolemia were further adjusted; (4) incident CVD and CHD were redefined by excluding the incidence of UA; (5) participants from one survey site of CIMIC where egg consumption was obviously higher than average were excluded. In addition, we performed cohort-specific analyses to further assess the robustness of our findings.

Statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc, Cary, NC, USA). A two-tailed P value of <0.05 was regarded as statistically significant.

Compliance and ethics *The author(s) declare that they have no conflict of interest. This study was approved by the institutional review board at Fuwai Hospital in Beijing, China.*

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References

Carson, J.A.S., Lichtenstein, A.H., Anderson, C.A.M., Appel, L.J., Kris-Etherton, P.M., Meyer, K.A., Petersen, K., Polonsky, T., and Van Horn, L. (2020). Dietary cholesterol and cardiovascular risk: a science

advisory from the American Heart Association. Circulation 141, e39–e53.
Choi, Y., Chang, Y., Lee, J.E., Chun, S., Cho, J., Sung, E., Suh, B.S., Rampal, S., Zhao, D., Zhang, Y., et al. (2015). Egg consumption and coronary artery calcification in asymptomatic men and women. Atherosclerosis 241, 305–312.
Cohn, J.S., Kamili, A., Wat, E., Chung, R.W.S., and Tandy, S. (2010). Reduction in intestinal cholesterol absorption by various food components: mechanisms and implications. Atherosc Suppl 11, 45–48.
Díez-Espino, J., Basterra-Gortari, F.J., Salas-Salvadó, J., Buil-Cosiales, P., Corella, D., Schröder, H., Estruch, R., Ros, E., Gómez-Gracia, E., Arós, F., et al. (2017). Egg consumption and cardiovascular disease according to diabetic status: The PREDIMED study. Clin Nutrition 36, 1015–1021.
Grundy, S.M., Stone, N.J., Bailey, A.L., Beam, C., Birtcher, K.K., Blumenthal, R.S., Braun, L.T., de Ferranti, S., Faiella-Tommasino, J., Forman, D.E., et al. (2019). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 139, e1082–e1143.
Gu, X., Li, Y., Chen, S., Yang, X., Liu, F., Li, Y., Li, J., Cao, J., Liu, X., Chen, J., et al. (2019). Association of lipids with ischemic and hemorrhagic stroke. Stroke 50, 3376–3384.
Han, C., Liu, F., Yang, X., Chen, J., Li, J., Cao, J., Li, Y., Shen, C., Yu, L., Liu, Z., et al. (2018). Ideal cardiovascular health and incidence of atherosclerotic cardiovascular disease among Chinese adults: the China-PAR project. Sci China Life Sci 61, 504–514.
Hu, F.B., Stampfer, M.J., Rimm, E.B., Manson, J.E., Ascherio, A., Colditz, G.A., Rosner, B.A., Spiegelman, D., Speizer, F.E., Sacks, F.M., et al. (1999). A prospective study of egg consumption and risk of cardiovascular disease in men and women. JAMA 281, 1387–1394.
Hu, Q., Hao, P., Liu, Q., Dong, M., Gong, Y., Zhang, C., and Zhang, Y. (2019). Mendelian randomization studies on atherosclerotic cardiovascular disease: evidence and limitations. Sci China Life Sci 62, 758–770.
Institute for Health Metrics and Evaluation. (2019). Global Burden of Disease Study 2017 (GBD 2017) data resources. http://ghdx.healthdata.org/gbd-2017.
Institute of Preventive Medicine Environmental & Occupational Health, Prolepsis. (2014). National Dietary Guidelines for Adults. http://www.diatrofikoiodigoi.gr/?Page=summary-adults.
Jacobson, T.A., Maki, K.C., Orringer, C.E., Jones, P.H., Kris-Etherton, P., Sikand, G., La Forge, R., Daniels, S.R., Wilson, D.P., Morris, P.B., et al. (2015). National lipid association recommendations for patient-centered management of dyslipidemia: Part 2. J Clin Lipidol 9, S1–S122.e1.
Jia, X., Su, C., Wang, Z., Wang, H., and Zhang, B. (2016). Study on the relationship between egg food intake and dyslipidemia in Chinese adults (in Chinese). Food Nutr China 22, 72–75.
Key, T.J., Appleby, P.N., Bradbury, K.E., Sweeting, M., Wood, A., Johansson, I., Kühn, T., Steur, M., Weiderpass, E., Wennberg, M., et al. (2019). Consumption of meat, fish, dairy products, and eggs and risk of ischemic heart disease. Circulation 139, 2835–2845.
Ju, L.H., Yu, D.M., Fang, H.Y., Guo, Q.Y., Xu, X.L., Li, S.J., and Zhao, L. Y. (2018). Trends and food sources composition of energy, protein and fat in Chinese residents, 1992–2012 (in Chinese). J Hygiene Res 47, 689–694, 704.
Miller, C.A., Corbin, K.D., da Costa, K.A., Zhang, S., Zhao, X., Galanko, J. A., Blevins, T., Bennett, B.J., O'Connor, A., and Zeisel, S.H. (2014). Effect of egg ingestion on trimethylamine-N-oxide production in humans: a randomized, controlled, dose-response study. Am J Clin Nutr 100, 778–786.
Nakamura, Y., Iso, H., Kita, Y., Ueshima, H., Okada, K., Konishi, M., Inoue, M., and Tsugane, S. (2006). Egg consumption, serum total cholesterol concentrations and coronary heart disease incidence: Japan Public Health Center-based prospective study. Br J Nutr 96, 921–928.
National Health Service. (2018). The healthy way to eat eggs—Eat well. https://www.nhs.uk/live-well/eat-well/eggs-nutrition/.
Pasiakos, S.M., Agarwal, S., Lieberman, H.R., and Fulgoni, V.L. (2015). Sources and amounts of animal, dairy, and plant protein intake of US adults in 2007–2010. Nutrients 7, 7058–7069.
Piercy, K.L., Troiano, R.P., Ballard, R.M., Carlson, S.A., Fulton, J.E., Galuska, D.A., George, S.M., and Olson, R.D. (2018). The Physical Activity Guidelines for Americans. JAMA 320, 2020–2028.
Qin, C., Lv, J., Guo, Y., Bian, Z., Si, J., Yang, L., Chen, Y., Zhou, Y., Zhang, H., Liu, J., et al. (2018). Associations of egg consumption with cardiovascular disease in a cohort study of 0.5 million Chinese adults. Heart 104, 1756–1763.
Qureshi, A.I., Suri, F.K., Ahmed, S., Nasar, A., Divani, A.A., and Kirmani, J.F. (2007). Regular egg consumption does not increase the risk of stroke and cardiovascular diseases. Med Sci Monit 13, CR1–8..
Rong, Y., Chen, L., Zhu, T., Song, Y., Yu, M., Shan, Z., Sands, A., Hu, F.B., and Liu, L. (2013). Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. BMJ 346, e8539.
Rouhani, M.H., Rashidi-Pourfard, N., Salehi-Abargouei, A., Karimi, M., and Haghighatdoost, F. (2018). Effects of egg consumption on blood lipids: a systematic review and meta-analysis of randomized clinical trials. J Am College Nutrition 37, 99–110.
Sauvaget, C., Nagano, J., Allen, N., Grant, E.J., and Beral, V. (2003). Intake of animal products and stroke mortality in the Hiroshima/Nagasaki Life Span Study. Int J Epidemiol 32, 536–543.
Scrafford, C.G., Tran, N.L., Barraj, L.M., and Mink, P.J. (2011). Egg consumption and CHD and stroke mortality: a prospective study of US adults. Public Health Nutr 14, 261–270.
Spence, J.D., Jenkins, D.J., and Davignon, J. (2010). Dietary cholesterol and egg yolks: not for patients at risk of vascular disease. Can J Cardiol 26, e336–e339.
Spence, J.D., Jenkins, D.J.A., and Davignon, J. (2012). Egg yolk consumption and carotid plaque. Atherosclerosis 224, 469–473.
Su, C., Jia, X., Wang, Z., Wang, H., and Zhang, B. (2015). Trends in dietary cholesterol intake among Chinese adults: a longitudinal study from the China Health and Nutrition Survey, 1991–2011. BMJ Open 5, e007532.
The China Nutrition Society. (2016). The Chinese Dietary Guidelines (2016). (Beijing: People's Medical Publishing House).
US Department of Health and Human Services and US Department of Agriculture. (2015). 2015–2020 Dietary Guidelines for Americans. 8th ed. https://health.gov/dietaryguidelines/2015/guidelines/.
Vincent, M.J., Allen, B., Palacios, O.M., Haber, L.T., and Maki, K.C. (2019). Meta-regression analysis of the effects of dietary cholesterol intake on LDL and HDL cholesterol. Am J Clin Nutr 109, 7–16.
Wang, W., Jiang, B., Sun, H., Ru, X., Sun, D., Wang, L., Wang, L., Jiang, Y., Li, Y., Wang, Y., et al. (2017). Prevalence, incidence, and mortality of stroke in China. Circulation 135, 759–771.
Xu, L., Lam, T.H., Jiang, C.Q., Zhang, W.S., Zhu, F., Jin, Y.L., Woo, J., Cheng, K.K., and Thomas, G.N. (2019). Egg consumption and the risk of cardiovascular disease and all-cause mortality: Guangzhou Biobank Cohort Study and meta-analyses. Eur J Nutr 58, 785–796.
Yang, X., Li, J., Hu, D., Chen, J., Li, Y., Huang, J., Liu, X., Liu, F., Cao, J., Shen, C., et al. (2016). Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese population. Circulation 134, 1430–1440.
Zhang, X., Liu, H., Gao, J., Zhu, M., Wang, Y., Jiang, C., and Xu, M. (2019). Metabolic disorder in the progression of heart failure. Sci China Life Sci 62, 1153–1167.
Zhong, V.W., Van Horn, L., Cornelis, M.C., Wilkins, J.T., Ning, H., Carnethon, M.R., Greenland, P., Mentz, R.J., Tucker, K.L., Zhao, L., et al. (2019). Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. JAMA 321, 1081–1095.

SUPPORTING INFORMATION

Table S1 Baseline characteristics of included participants by cohorts

Table S2 Sensitivity analyses for the associations of egg consumption with risk of CVD endpoints and all-cause mortality

Table S3 HRs (95% CIs) for associations of egg consumption with risk of CVD endpoints and all-cause mortality by cohorts

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