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Association of egg intake with blood lipids, cardiovascular disease, and mortality in 177,000 people in 50 countries

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ABSTRACT

Background: Eggs are a rich source of essential nutrients, but they are also a source of dietary cholesterol. Therefore, some guidelines recommend limiting egg consumption. However, there is contradictory evidence on the impact of eggs on diseases, largely based on studies conducted in high-income countries.

Objectives: Our aim was to assess the association of egg consumption with blood lipids, cardiovascular disease (CVD), and mortality in large global studies involving populations from low-, middle-, and high-income countries.

Methods: We studied 146,011 individuals from 21 countries in the Prospective Urban Rural Epidemiology (PURE) study. Egg consumption was recorded using country-specific validated FFQs. We also studied 31,544 patients with vascular disease in 2 multinational prospective studies: ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease). We calculated HRs using multivariable Cox frailty models with random intercepts to account for clustering by study center separately within each study.

Results: In the PURE study, we recorded 14,700 composite events (8932 deaths and 8477 CVD events). In the PURE study, after excluding those with history of CVD, higher intake of egg (≥7 egg/wk compared with <1 egg/wk intake) was not significantly associated with blood lipids, composite outcome (HR: 0.96; 95% CI: 0.89, 1.04; *P*-trend = 0.74), total mortality (HR: 1.04; 95% CI: 0.94, 1.15; *P*-trend = 0.38), or major CVD (HR: 0.92; 95% CI: 0.83, 1.01; *P*-trend = 0.20). Similar results were observed in ONTARGET/TRANSCEND studies for composite outcome (HR

0.97; 95% CI: 0.76, 1.25; *P*-trend = 0.09), total mortality (HR: 0.88; 95% CI: 0.62, 1.24; *P*-trend = 0.55), and major CVD (HR: 0.97; 95% CI: 0.73, 1.29; *P*-trend = 0.12).

Conclusions: In 3 large international prospective studies including ~177,000 individuals, 12,701 deaths, and 13,658 CVD events from 50 countries in 6 continents, we did not find significant associations between egg intake and blood lipids, mortality, or major CVD events. The ONTARGET and TRANSCEND trials were registered at clinicaltrials.gov as NCT00153101. The PURE trial was registered at clinicaltrials.gov as NCT03225586. *Am J Clin Nutr* 2020;111:795–803.

Keywords: egg intake, dietary cholesterol, blood lipids, mortality, cardiovascular disease

Introduction

Eggs are a nutrient-dense, rich source of high-quality protein, and bioactive compounds (such as lutein and zeaxanthin) (1). They are widely available, affordable, and their production has low environmental impact compared with other animal sources of protein (2). Despite these advantages, cardiovascular guidelines have long recommended limiting egg consumption to <3 eggs/wk due to concerns that they may adversely affect blood lipids because of their high cholesterol, which could theoretically increase risk of cardiovascular disease (CVD) (2). In recent years, however, randomized trials, animal studies, and mechanistic studies have shown that dietary cholesterol has little effect on blood lipids (3, 4). Eggs are a source of minerals, folate, B vitamins, fat-soluble vitamins, and MUFAs, all of which theoretically may contribute to improved health and CVD (5).

Observational studies and randomized trials have reported contradictory findings on the association of egg consumption with CVD (6–8). Almost all observational studies and meta-analyses found that higher intake of eggs was not associated with risk of CVD (6, 7, 9, 10), although 1 meta-analysis reported a higher risk of heart failure with high egg intake (11). By contrast, a large prospective cohort study of >0.5 million people from

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The external funders and sponsors of the study had no role in study design or conduct; data collection, analysis, or interpretation; the writing, review, or approval of the report; or the decision to submit the manuscript for publication. MD, AM, SR, and SY had full access to the data and were responsible for the decision to submit this manuscript for publication.

PURE: Data described in the article, code book, and analytic code will not be made available as the PURE study is an ongoing study and during the conduct only the investigators who have participated or contributed to the study can have access to the data. Select summary data may be shared with policy makers for specific purposes. The study executive will consider specific requests for data analyses by noncontributing individuals 3 y after the study has been completed (i.e., complete recruitment and a minimum of 10 y follow-up in all) and after the participating investigators have had an opportunity to explore questions that they are interested in. Costs related to data curating and related efforts will need to be met by anybody not contributing to the conduct of the study and requesting analyses.

ONTARGET/TRANSCEND studies: Data described in the article, code book, and analytic code will not be made available for ONTARGET/TRANSCEND studies because they are contractually restricted to the study sponsors and the investigators who have participated or contributed to the study. Select summary data may be shared with policy makers for specific purposes. The study executive will consider specific requests for data analyses by noncontributing individuals after the participating investigators have had an opportunity to explore questions that they are interested in. Costs related to data curating and related efforts will need to be met by anybody not contributing to the study and requesting analyses.

Supplemental Methods, Supplemental Tables 1–4, and Supplemental Figures 1–7 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: ACEI, angiotensin-converting enzyme inhibitor; CAD, coronary artery disease; CVD, cardiovascular disease; MET, metabolic equivalent of task; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial; PURE, Prospective Urban Rural Epidemiology; TC, total cholesterol; TRANSCEND, Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease.

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China (Kadoorie Biobank Study) reported that intake of 1 egg/d was associated with 11% lower risk of CVD (12). However, a recent pooled analysis from 6 prospective US cohorts showed a modest increase (2% in absolute risk) in all-cause mortality for each additional half an egg per day (13) despite directionally lower non-HDL cholesterol and blood pressure with higher egg intake. Further, most studies are from North America, Europe, China, and Japan, with little or no information from South Asia, Africa, the Middle East, and South America.

The aim of this report was to assess the association of egg intake with blood lipids, blood pressure, risk of CVD, and mortality using data on 177,555 people from 50 countries based on 3 large international cohort studies in populations from all continents of the world. The combination of the Prospective Urban Rural Epidemiology (PURE) study, Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ONTARGET), and Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease (TRANSCEND) provides a unique opportunity to study the association of egg intake with blood lipids, CVD events, and mortality in diverse settings.

Methods

Study design and participants

PURE study.

The design and methods of the PURE study (NCT03225586) have been described previously (14, 15). Briefly, the first and second phases of PURE included 146,011 individuals who had provided information on egg intake from 21 countries (Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, occupied Palestine territory, Pakistan, Philippines, Poland, Saudi Arabia, South Africa, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe) and had completed ≥1 follow-up visit. Recruitment began in January 2003. The sampling and recruitment strategy utilized in PURE are described in the **Supplemental Methods** and **Supplemental Figure 1**. The PURE study recruited free-living individuals from the population and the majority (>93%) did not have a history of CVD. Data were collected at the community, household, and individual levels with standardized questionnaires. Standard case-report forms were used to record data on major cardiovascular events and mortality (classified by cause) during follow-up, which were adjudicated centrally in each country by trained physicians using common definitions. For the current analysis, we included all outcome events known to us until 3 July, 2019. The study was approved by the research ethics committee at each participating center and at Hamilton Health Sciences (see the online supplementary material for a list).

ONTARGET and TRANSCEND studies.

Overall, 31,544 individuals [ONTARGET, 25,618 angiotensin-converting enyme inhibitor (ACEI) tolerant; TRANSCEND, 5926 ACEI intolerant] aged ≥55 y with a history of coronary, peripheral, or cerebrovascular disease, or diabetes mellitus with end-organ damage, gave informed consent and were randomly assigned to ramipril, telmisartan, or their combination in ONTARGET and to either telmisartan or placebo in TRANSCEND, following similar protocols, procedures, study forms, and visits. These studies (NCT00153101) were conducted in 733 centers in 40 middle- and high-income countries (for a list of countries see **Supplemental Table 1**). ONTARGET recruitment began in 2002 and was completed in July 2003. TRANSCEND recruitment began in 2001 and was completed in 2004. The median follow-up was 56 mo for these 2 studies. Participants were evaluated at 6 wk and 6 mo after randomization and every 6 mo thereafter until study completion (99.7% follow-up rate). All study protocols were approved by regulatory authorities and the ethics review committee at each participating institution.

All 3 studies were coordinated by the Population Health Research Institute, Hamilton Health Sciences, and McMaster University, Hamilton, Ontario, Canada. Study participants were not involved in the design, conduct, and reporting of research.

Procedures

PURE study.

Each participant's habitual food intake was recorded using country-specific (region-specific in India) validated FFQs at baseline. For countries where a validated FFQ was not available, we developed and validated FFQs using a standard method (**Supplemental Table 2**). Participants were asked, "During the past year, on average, how often have you consumed the following foods or drinks?" and the list of food items was given. For almost all countries, FFQs had the same format and frequencies of consumption, which varied from never to >6 times/d. Standard serving sizes (e.g., an egg, 50 g) were assigned to each food item. To compute the daily food intake, the reported frequency of consumption for each food item was converted to daily intake and then was multiplied by the serving size. Mixed dishes prepared with eggs or dressing (e.g., omelets, cake, mayonnaise) were disaggregated into their constituents and a proportional weight was assigned to each component. The specific weight or amount was then included in the egg group.

ONTARGET and TRANSCEND studies.

We recorded patients' food intake using a qualitative FFQ that contained 20 food items. Participants were asked, "In the last 12 months, how often did you eat foods from each of the following categories?" and a list of food items was given. Because this qualitative FFQ was designed for use in international studies, it contains all the main food groups such as dairy, meats, eggs, fish, fruit, and vegetables and a few food items that were culture-dependent such as tofu and soy sauce. We did not record the serving size of intakes; however, for the present analysis we assigned a standard serving size (e.g., an egg, 50 g). The qualitative FFQ has been validated against 4 dietary recalls and a comprehensive FFQ in Argentina, Brazil, and Colombia (unpublished data), and has been found to be applicable to different countries despite regional differences in dietary constituents (16).

Outcomes

The primary outcome of this analysis was the composite of mortality or major cardiovascular events (defined as death from

cardiovascular causes, and nonfatal myocardial infarction, stroke, or heart failure). Secondary outcomes were total mortality, major CVD, blood lipids [total cholesterol (TC), HDL cholesterol, LDL cholesterol, TC:HDL cholesterol ratio, triglycerides, apoA1, apoB, apoB:apoA1 ratio], and blood pressure.

Statistical analysis

Continuous variables were expressed as means ± SDs and categorical variables as percentages. Education was categorized as none or primary school (first 6 y); secondary school (7–11 y); and college, trade school, or university (>11 y). Smoking was categorized as never, former, or current. These variables were measured in similar fashion across the 3 cohorts. Physical activity was categorized based on the metabolic equivalent of task (MET) per minute per week into low (<600 MET-min/wk), moderate (600–3000 MET-min/wk), and high (>3000 MET-min/wk) activity. In the PURE study, we categorized countries into 7 geographic regions based on similarities in their patterns of food consumption. These regions were Europe and North America, South America, Africa, Middle East, South Asia, South East Asia, and China.

For all 3 cohorts, participants were grouped according to egg consumption into <1 egg/wk, 1 to <3 egg/wk, 3 to <5 egg/wk, 5 to <7 egg/wk, and ≥7 egg/wk; the lowest intake group was used as the reference.

Multivariable linear regression with random intercepts was used to assess the associations of egg and dietary cholesterol with blood lipids and blood pressure. For this analysis we further adjusted models for use of blood cholesterol–lowering or antihypertensive medications.

In the PURE study, we calculated HRs using a multivariable Cox frailty model with random intercepts to account for center clustering (which also adjusts for region and country). Estimates of HRs and 95% CIs are presented for categories of egg intake. All models were adjusted for age, sex, education, urban or rural location, smoking, physical activity, history of diabetes, fruit and vegetables, red meat, poultry, fish, dairy, percentage of energy from carbohydrates, and total energy intake. To assess the shape of associations between egg intake and outcome events we used restricted cubic splines, fitting a restricted cubic spline to function with 3 knots.

To assess the associations between dietary cholesterol and health outcomes, participants were grouped into <100 mg/d, 100 to <200 mg/d, 200 to <300 mg/d, 300 to 400 mg/d, and >400 mg/d, with the first group used as the reference group.

In ONTARGET and TRANSCEND, because the entry criteria and study conduct were similar between the 2 cohorts, other than ACEI intolerance in the TRANSCEND trial, we pooled the data from both studies in our analysis. As in the analyses with PURE data, we used multivariable Cox frailty models with random intercepts (to account for clustering within centers) to test the associations between egg intake and risk of CVD and mortality. The full model was adjusted for age; sex; education; BMI; current smoking status; physical activity; history of diabetes; history of stroke; history of myocardial infarction; use of statin or antihypertension medication and treatment allocation (ramipril, telmisartan, or both); treatment with statins, β-blockers, diuretic therapy, calcium antagonist, and antidiabetes medication; and intakes of fruit and vegetables, meats, fish, dairy, and refined

TABLE 1 Characteristics of the Prospective Urban Rural Epidemiology study participants at enrollment overall and by regions[1]

	Overall (n = 146,011)	Europe/North America (n = 15,785)	South America (n = 23,721)	Africa (n = 6282)	Middle East (n = 14,337)	South Asia (n = 27,738)	South East Asia (n = 12,587)	China (n = 45,561)
Age, y	50.6 ± 9.9	53.5 ± 9.3	51.4 ± 9.7	49.9 ± 10.6	48.7 ± 9.4	48.2 ± 10.3	52.0 ± 9.9	51.0 ± 9.8
Males	41.9	45.1	38.6	30.0	45.3	45.0	41.0	41.8
Urban	53.4	70.0	57.3	48.9	59.5	45.0	47.2	48.5
Current smoker	20.8	15.2	21.0	24.2	18.4	24.0	15.7	23.0
Energy intake, kcal	2135 ± 812	2258 ± 822	2209 ± 797	2037 ± 951	2313 ± 842	2039 ± 796	2516 ± 1007	1963 ± 667
Dietary intake of main food groups								
Egg, serving/wk	3.9 ± 4.1	3.0 ± 2.5	4.7 ± 4.9	2.9 ± 4.5	4.0 ± 3.1	1.4 ± 2.6	3.8 ± 4.6	5.6 ± 3.9
Dairy, servings/d	1.4 ± 1.7	3.8 ± 2.5	1.7 ± 1.6	0.5 ± 0.7	2.3 ± 1.4	1.0 ± 1.3	0.9 ± 1.2	0.5 ± 0.7
Red meat, servings/d	0.7 ± 0.8	1.2 ± 1.2	0.9 ± 0.7	0.3 ± 0.4	0.8 ± 0.6	0.1 ± 0.2	0.5 ± 0.6	0.7 ± 0.7
Poultry, servings/d	0.3 ± 0.4	0.3 ± 0.3	0.4 ± 0.3	0.2 ± 0.3	0.5 ± 0.6	0.1 ± 0.1	0.8 ± 0.6	0.1 ± 0.1
Fruits, servings/d	2.3 ± 2.5	2.2 ± 1.7	2.0 ± 1.8	3.8 ± 4.2	4.8 ± 3.4	1.3 ± 1.9	1.9 ± 2.2	2.4 ± 2.4
Vegetables, servings/d	4.3 ± 3.0	5.6 ± 4.0	4.6 ± 3.1	5.5 ± 4.5	4.2 ± 2.3	3.6 ± 3.2	3.5 ± 4.6	4.4 ± 1.5
Starchy foods, servings/d	9.0 ± 6.1	5.4 ± 3.0	5.3 ± 2.6	4.7 ± 2.6	5.6 ± 2.6	7.3 ± 3.4	6.6 ± 4.0	15.1 ± 6.3
Dietary cholesterol, mg/d	291 ± 237	265 ± 126	330 ± 196	208 ± 168	337 ± 181	151 ± 307	260 ± 211	371 ± 220

[1] Values are means ± SDs or percentages. Standard servings of each food group are as follows: egg 50 g, dairy milk and yogurt 250 g, cheese 30 g, fruits and vegetables 85 g; for red meat, poultry, and starchy foods local serving sizes were used.

TABLE 2 Adjusted mean ± SE blood lipids and blood pressure by egg intake in the PURE study and ONTARGET/TRANSCEND studies[1]

	<1 egg/wk	1 to <3 egg/wk	3 to <5 egg/wk	5 to <7 egg/wk	≥7 egg/wk	*P*-trend
PURE study (n = 114,615)						
n	23,321	31,096	23,329	14,498	22,371	
Total cholesterol, mmol/L	4.90 ± 0.05	4.92 ± 0.05	4.90 ± 0.05	4.91 ± 0.05	4.89 ± 0.05	0.24
LDL-C, mmol/L	3.07 ± 0.05	3.09 ± 0.05	3.08 ± 0.05	3.07 ± 0.05	3.08 ± 0.05	0.44
HDL-C, mmol/L	1.21 ± 0.02	1.21 ± 0.02	1.21 ± 0.02	1.21 ± 0.02	1.20 ± 0.02	0.25
TC:HDL-C ratio	4.27 ± 0.06	4.27 ± 0.06	4.27 ± 0.06	4.28 ± 0.06	4.30 ± 0.06	0.90
Triglycerides, mmol/L	1.57 ± 0.04	1.57 ± 0.04	1.55 ± 0.04	1.56 ± 0.04	1.54 ± 0.04	0.90
ApoA1,[2] mmol/L	1.49 ± 0.02	1.49 ± 0.02	1.50 ± 0.02	1.50 ± 0.02	1.50 ± 0.02	0.21
ApoB,[2] mmol/L	1.01 ± 0.02	1.01 ± 0.02	1.00 ± 0.02	1.01 ± 0.02	1.02 ± 0.02	0.06
ApoB/apoA1,[2] mmol/L	0.71 ± 0.02	0.71 ± 0.02	0.70 ± 0.02	0.70 ± 0.02	0.71 ± 0.02	0.86
Systolic blood pressure, mm Hg	132.7 ± 0.74	132.7 ± 0.73	132.1 ± 0.74	131.9 ± 0.75	131.4 ± 0.75	<0.001
Diastolic blood pressure, mm Hg	83.6 ± 0.62	83.6 ± 0.62	83.3 ± 0.62	83.1 ± 0.62	82.6 ± 0.62	<0.001
ONTARGET/TRANSCEND studies (n = 31,410)						
n	10,731	16,831	1217	2322	309	
Total cholesterol, mmol/L	4.99 ± 0.04	5.0 ± 0.04	5.0 ± 0.05	5.0 ± 0.04	5.08 ± 0.07	0.68
LDL-C, mmol/L	2.99 ± 0.04	2.98 ± 0.04	2.97 ± 0.04	2.96 ± 0.04	3.05 ± 0.06	0.77
HDL-C, mmol/L	1.26 ± 0.01	1.27 ± 0.01	1.28 ± 0.02	1.28 ± 0.02	1.25 ± 0.03	0.50
TC:HDL-C ratio	4.23 ± 0.12	4.21 ± 0.10	4.21 ± 0.32	5.17 ± 0.25	4.44 ± 0.63	0.05
Systolic blood pressure	142.0 ± 0.4	142.1 ± 0.4	142.8 ± 0.60	141.8 ± 0.56	144.3 ± 1.0	0.03
Diastolic blood pressure	82.2 ± 0.3	82.4 ± 0.3	83.2 ± 0.4	82.1 ± 0.4	83.7 ± 0.6	0.02

[1]PURE study: means are adjusted for age; sex; smoking; location; education; physical activity; history of diabetes; daily intakes of fruits, vegetables, dairy, red meat, poultry, and fish; percentage energy from carbohydrate; total daily energy; and center as a random effect. ONTARGET/TRANSCEND studies: means are adjusted for age; sex; smoking; location; BMI; education; physical activity; history of diabetes; history of myocardial infarction; history of stroke; medication; trial allocation; daily intakes of fruit, vegetables, red meat, poultry, fish, and dairy; and regions as a random effect. HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial; PURE, Prospective Urban Rural Epidemiology; TC, total cholesterol; TRANSCEND, Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease.

[2]Apolipoproteins were available for 19,685 individuals.

grains. Data were analyzed with the Stata software package, version 14 (StataCorp).

Results

In the PURE study, during 9.5 y of follow-up, 14,700 (10.1%) individuals had either died or had a major CVD event (3410 cardiovascular deaths, 5932 noncardiovascular deaths, 3664 myocardial infarction, 3916 stroke, and 939 heart failure). Overall, the median egg intake was 3.9/wk among the PURE participants. Egg intake was higher in China (5.6 egg/wk) and lower in South Asia (1.4 egg/wk) than in other regions (**Table 1**).

Table 2 shows the adjusted means of blood lipids and blood pressure by categories of egg intake. For the PURE study and after adjustment for covariates, higher intake of egg was not associated with concentrations of TC, LDL cholesterol, or HDL cholesterol, TC:HDL cholesterol ratio, or apoB:apoA1 ratio (*P*-trend > 0.20 for all comparisons). But higher intake of egg was associated with lower systolic (*P*-trend < 0.0001) and diastolic blood pressure (*P*-trend < 0.0001). Similarly, higher dietary cholesterol intake was not associated with blood lipids (**Supplemental Table 3**).

Supplemental Table 1 shows characteristics of ONTARGET and TRANSCEND participants at enrollment overall and by regions. For ONTARGET/TRANSCEND studies, we found no significant association between egg intake and blood lipids but significant associations between egg intake and lower systolic and diastolic blood pressure (Table 2).

Table 3 shows estimates of the associations of egg intake with risks of various clinical outcomes from the PURE study. After excluding those with history of CVD, higher intake of egg (≥7 egg/wk compared with <1 egg/wk) was not significantly associated with composite outcome events (HR: 0.96; 95% CI: 0.89, 1.04; *P*-trend = 0.74), total mortality (HR: 1.04; 95% CI: 0.94, 1.15; *P*-trend = 0.38), cardiovascular mortality (HR: 1.00; 95% CI: 0.85, 1.19; *P*-trend = 0.93), noncardiovascular mortality (HR: 1.06; 95% CI: 0.94, 1.20; *P*-trend = 0.21), major CVD (HR: 0.92; 95% CI: 0.83, 1.01; *P*-trend = 0.20), stroke (HR: 0.97; 95% CI: 0.84, 1.13; *P*-trend = 0.65), or heart failure (HR: 1.24; 95% CI: 0.90, 1.70; *P*-trend = 0.20). We found that higher egg intake was associated with a lower risk of myocardial infarction (HR: 0.84; 95% CI: 0.72, 0.98; *P*-trend = 0.02) but this should be interpreted with caution because this is one of the many outcomes examined and the results are not observed in ONTARGET or TRANSCEND (see below). The association was found to be similar in all participants irrespective of history of CVD. Further adjustment for blood cholesterol did not alter the association between egg intake and health outcomes (**Supplemental Table 4**).

We conducted a dose-response analysis for each additional half an egg per day intake and further adjusted models for dietary cholesterol, animal protein, total fiber, or various types of fatty acids. There was no significant association between each additional half an egg and composite outcome events, total mortality, and major CVD (**Figure 1**), or other outcomes (**Supplemental Figure 2**). Also, we assessed the association of egg intake >7/wk by increments of 2 eggs. The numbers of

TABLE 3 Associations between egg consumption and clinical outcomes, Prospective Urban Rural Epidemiology study[1]

	<1 egg/wk ($n = 35,028$)	1 to <3 egg/wk ($n = 39,152$)	3 to <5 egg/wk ($n = 28,099$)	5 to <7 egg/wk ($n = 16,767$)	≥7 egg/wk ($n = 26,965$)	*P*-trend[2]
Eggs/wk	0.2 [0–0.6]	1.8 [1.3–2.3]	3.7 [3.3–4.2]	6.3 [5.7–6.9]	8.6 [7.6–12.5]	
Composite outcome events						
Events ($n = 14,700$)	4845 (14.0)	3730 (9.5)	2336 (8.3)	1516 (9.1)	2273 (8.4)	
All individuals	1 (ref)	0.91 (0.87, 0.96)	0.89 (0.84, 0.96)	0.95 (0.88, 1.02)	0.93 (0.87, 1.00)	0.19
Those without history of CVD	1 (ref)	0.92 (0.87, 0.98)	0.91 (0.85, 0.97)	0.97 (0.89, 1.05)	0.96 (0.89, 1.04)	0.74
Total mortality						
Events ($n = 8932$)	3333 (9.5)	2218 (5.7)	1384 (4.9)	797 (4.7)	1200 (4.5)	
All individuals	1 (ref)	0.95 (0.89, 1.02)	0.94 (0.87, 1.02)	0.99 (0.90, 1.09)	0.99 (0.91, 1.09)	0.85
Those without history of CVD	1 (ref)	0.98 (0.91, 1.06)	0.96 (0.87, 1.05)	1.02 (0.92, 1.14)	1.04 (0.94, 1.15)	0.38
Cardiovascular mortality						
Events ($n = 3410$)	1259 (3.6)	845 (2.2)	522 (1.9)	299 (1.8)	485 (1.8)	
All individuals	1 (ref)	0.92 (0.82, 1.02)	0.91 (0.80, 1.03)	0.88 (0.76, 1.03)	0.93 (0.80, 1.07)	0.29
Those without history of CVD	1 (ref)	0.95 (0.84, 1.08)	0.91 (0.78, 1.06)	0.92 (0.77, 1.10)	1.00 (0.85, 1.19)	0.93
Noncardiovascular mortality						
Events ($n = 5932$)	2227 (6.4)	1470 (3.8)	933 (3.3)	525 (3.1)	777 (2.9)	
All individuals	1 (ref)	0.97 (0.89, 1.05)	0.96 (0.87, 1.06)	1.04 (0.93, 1.18)	1.04 (0.93, 1.17)	0.28
Those without history of CVD	1 (ref)	0.98 (0.89, 1.08)	0.97 (0.87, 1.08)	1.06 (0.93, 1.21)	1.06 (0.94, 1.20)	0.21
Major CVD						
Events ($n = 8477$)	2387 (6.8)	2232 (5.7)	1384 (4.9)	989 (6.0)	1485 (5.5)	
All individuals	1 (ref)	0.90 (0.84, 0.96)	0.87 (0.80, 0.94)	0.91 (0.84, 1.00)	0.89 (0.82, 0.97)	0.04
Those without history of CVD	1 (ref)	0.92 (0.85, 0.99)	0.88 (0.80, 0.96)	0.94 (0.84, 1.04)	0.92 (0.83, 1.01)	0.20
Myocardial infarction						
Events ($n = 3664$)	1243 (3.5)	984 (2.5)	568 (2.0)	346(2.1)	523 (1.9)	
All individuals	1 (ref)	0.85 (0.77, 0.94)	0.77 (0.68, 0.87)	0.81 (0.70, 0.93)	0.83 (0.72, 0.95)	0.004
Those without history of CVD	1 (ref)	0.83 (0.74, 0.93)	0.78 (0.68, 0.89)	0.79 (0.67, 0.93)	0.84 (0.72, 0.98)	0.02
Stroke						
Events ($n = 3916$)	867 (2.5)	1025 (2.6)	627 (2.2)	565 (3.4)	832 (3.1)	
All individuals	1 (ref)	0.99 (0.89, 1.09)	0.94 (0.83, 1.06)	1.01 (0.89, 1.15)	0.93 (0.82, 1.05)	0.34
Those without history of CVD	1 (ref)	1.03 (0.91, 1.16)	0.97 (0.85, 1.12)	1.05 (0.90, 1.21)	0.97 (0.84, 1.13)	0.65
Heart failure						
Events ($n = 939$)	223 (0.6)	271 (0.7)	200 (0.7)	89 (0.5)	156 (0.6)	
All individuals	1 (ref)	0.95 (0.77, 1.16)	1.06 (0.85, 1.32)	0.94 (0.71, 1.24)	1.00 (0.77, 1.30)	0.92
Those without history of CVD	1 (ref)	1.08 (0.83, 1.39)	1.10 (0.82, 1.46)	1.14 (0.81, 1.61)	1.24 (0.90, 1.70)	0.20

[1] $n = 146,011$. Values are median [IQR], *n* (%), or HR (95% CI). Cox hazard multivariable model adjusted for age; sex; smoking; location; education; physical activity; history of diabetes; daily intakes of fruits, vegetables, dairy, red meat, poultry, and fish; percentage energy from carbohydrate; total daily energy; and center as a random effect. CVD, cardiovascular disease.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous variable.

individuals were small in the high-intake groups and we did not find a statistically significant increase in risk by higher egg intake (**Supplemental Figure 3**). **Supplemental Figure 4** shows restricted multivariable cubic spline plots for composite outcome events. We found no associations between egg intake and clinical events.

In the stratified analyses, the results were consistent in the overall population when events occurring after 24 mo were separately examined and in those with prior diabetes (**Figure 2**). However, there was a lower risk of incident CVD in those with prevalent CVD at baseline but not in those without CVD at baseline (*P*-interaction = 0.24). Overall, results were consistent in different geographic regions (**Supplemental Figure 5**).

In PURE, the association between dietary cholesterol (per 100 mg/d increase) and health outcomes was nonsignificant (**Figure 3**, **Supplemental Figure 6**).

In ONTARGET and TRANSCEND studies (patients with vascular disease), we observed higher intake of egg was not significantly associated with composite outcome events (HR: 0.97; 95% CI: 0.76, 1.25; *P*-trend = 0.09), total mortality (HR: 0.88; 95% CI: 0.62, 1.24; *P*-trend = 0.55), cardiovascular mortality (HR: 0.87; 95% CI: 0.56, 1.37; *P*-trend = 0.81), noncardiovascular mortality (HR: 0.86; 95% CI: 0.50, 1.47; *P*-trend = 0.76), major CVD (HR: 0.97; 95% CI: 0.73, 1.29; *P*-trend = 0.12), myocardial infarction (HR: 1.12; 95% CI: 0.68, 1.82; *P*-trend = 0.70), or stroke (HR: 0.97; 95% CI: 0.58, 1.64; *P*-trend = 0.16) but was associated with increased risk of heart failure (HR: 1.25; 95% CI: 0.74, 2.11; *P*-trend = 0.01) (**Table 4**).

Pooling the data from all 3 cohorts, using a random-effects model showed a marginal decrease in risk of the composite outcome with higher egg intake (HR: 0.98; 95% CI: 0.95, 1.00) (**Supplemental Figure 7**).

Discussion

In 3 large international prospective studies including ~177,000 individuals, 12,701 deaths, and 13,658 CVD events from 50 countries in 6 continents, we did not find significant associations between egg intake and blood lipids, mortality, or major CVD events. Our findings indicate that moderate egg intake (1 egg/d) does not increase the risk of CVD or mortality

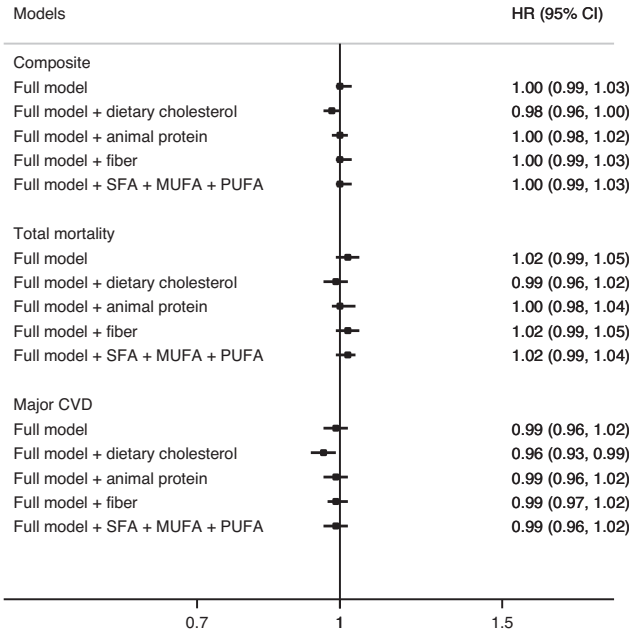

FIGURE 1 Association between each additional half an egg intake per week and health outcomes (Prospective Urban Rural Epidemiology study, $n = 146{,}011$). P trend > 0.10 for all comparisons. Multivariable model adjusted for age; sex; smoking; location; education; physical activity; history of diabetes; daily intakes of fruits, vegetables, dairy, red meat, poultry, and fish; percentage energy from carbohydrate; total daily energy; and center as a random effect. CVD, cardiovascular disease.

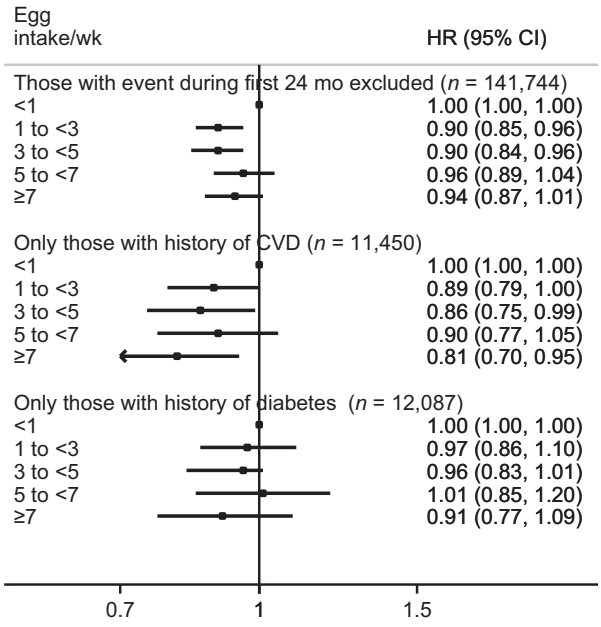

FIGURE 2 Association between egg intake per week and composite outcome (Prospective Urban Rural Epidemiology study). Multivariable model adjusted for age; sex; smoking; location; education; physical activity; history of diabetes; daily intakes of fruits, vegetables, dairy, red meat, poultry, and fish; percentage energy from carbohydrate; total daily energy; and center as a random effect. CVD, cardiovascular disease.

among those with or without a history of CVD or diabetes. Also, no significant association was found between egg intake or dietary cholesterol and blood lipids. In the PURE study, we found that higher egg intake was associated with a lower risk of myocardial infarction, but this was not observed in the other 2 studies and should therefore be viewed with considerable caution.

The totality of observational studies, randomized trials, and animal studies indicate little effect of dietary cholesterol on lipids, CVD, or mortality (17). The 2015–2020 Dietary Guidelines for Americans and the American Heart Association removed the previous limit of 300 mg/d dietary cholesterol (18). Recently, the EAT–*Lancet* commission on a healthy diet recommended consuming 1.5 eggs/wk, but the report stated that higher consumption of egg may be beneficial for individuals with poor dietary quality, particularly among low-income populations (2). Our findings indicate that egg intake of 1 serving/d is not harmful, and so can be consumed safely by most populations.

Our results of no association between moderate egg intake and health outcomes are generally consistent with the majority of previous studies. A comprehensive review of randomized trials and observational studies (19) found that egg intake did not adversely affect serum cholesterol and CVD among healthy individuals and patients with type 2 diabetes. The Health Professionals Follow-Up Study ($n = 37{,}851$) and the Nurses' Health Study ($n = 80{,}082$) reported that consuming $\leq$1 egg/d did not increase the risk of coronary artery disease (CAD) or stroke (20). Similarly, meta-analyses of observational studies showed no significant association between egg intake and CVD events or mortality (6, 7).

In addition, in the China Kadoorie Biobank study, higher egg consumption was associated with a lower risk of CVD (12). By contrast, in a recent study on 29,615 people from 6 cohorts in the United States, higher egg consumption was associated with higher risk of CVD and mortality (13). In that study, however, egg intake was associated with lower blood non-HDL cholesterol and systolic blood pressure, which is not consistent with an increased risk of CVD, raising questions about the internal coherence of findings from this report. The reason for the different results in this recent study compared with the collective data from other cohort studies which include ~1 million people (including PURE and the Kadoorie Biobank) is not known. Possible factors include the play of chance or selection biases that led to the inclusion of some but not other US studies in the analyses. It is also possible that the health effects of eggs could depend on the background diet, with eggs providing different effects depending on the quality of protein in the diet. For instance, PURE includes regions of the world (e.g., China, South Asia, and Africa) that consume high-carbohydrate diets (mostly as refined carbohydrates) in which eggs are least likely to be harmful. However, in the ONTARGET, TRANSCEND, and PURE studies no adverse associations were observed in populations from high-income countries, which is consistent with the Health Professionals Follow-Up Study and the Nurses' Health Studies.

In the PURE study, when stratified by prevalence of CVD, we found that higher egg intake was associated with a lower risk of composite outcome, but this was not observed in the 2 populations with prior CVD (ONTARGET and TRANSCEND). Therefore, the apparent protective association of eggs with CVD risk in subgroup analyses in PURE may be due to chance.

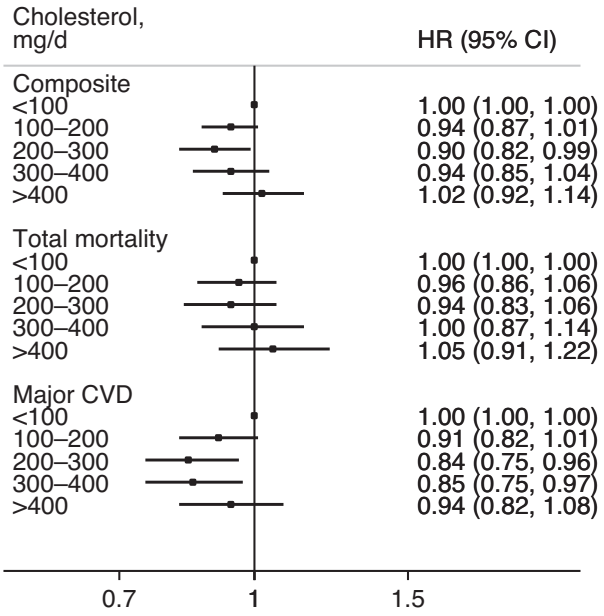

FIGURE 3 Association between dietary cholesterol and outcomes (Prospective Urban Rural Epidemiology study, $n = 134,597$). P-trend > 0.10 for all comparisons. Multivariable model adjusted for age; sex; smoking; location; education; physical activity; history of diabetes; blood cholesterol; daily intakes of fruits, vegetables, dairy, red meat, poultry, and fish; percentage energy from carbohydrate; total daily energy; and center as a random effect. Those with a history of CVD ($n = 11,414$) were excluded. CVD, cardiovascular disease.

Our findings are robust and widely applicable because for both healthy individuals and patients with vascular disease, results are consistent. Among those with vascular disease (ONTARGET/TRANSCEND studies), we assessed the associations of egg intake with health outcomes in addition to the proven drugs. We did not find a significant association, regardless of the type or combination of medications, with the CVD outcomes. Our study has a large number of events (>20,000 composite outcomes) and so high statistical power to detect even modest excess in risk of CVD or death. Whereas participants in PURE were mainly from low- and middle-income countries (which reflects the global population distribution), the majority of participants in ONTARGET/TRANSCEND studies were from middle- and high-income countries. Therefore, our study covers a broad range of dietary quality, socioeconomic status, and lifestyle behaviors and so our findings are applicable globally.

We did not observe a graded effect of increasing egg consumption either on blood lipids or on clinical events. Our observations are consistent with a meta-analysis of 8 cohort studies comprising a total of 263,938 participants with 5847 incident cases of CAD and 7579 cases of stroke, which reported no associations with CAD or stroke (6).

The neutral association between egg intake and health outcomes may be due to several competing factors. Dietary cholesterol has a relatively modest effect on blood TC and LDL cholesterol (21), but the phospholipid in egg raises HDL cholesterol which may offset the adverse effect of egg on LDL cholesterol (22). The effects of egg consumption may also vary across populations with varying diet quality (such as a low- or high-carbohydrate diet). In addition, substitution of carbohydrate with protein improves blood lipid profile (15), lowers blood pressure, and consequently reduces risk of CVD (23). Also, egg-derived phospholipids have pro- and anti-inflammatory properties (1) but the effect varies among individuals. It is associated with a reduction in inflammatory markers among overweight and obese individuals, whereas it has a proinflammatory response in healthy individuals.

TABLE 4 Associations between egg consumption and clinical outcomes, ONTARGET/TRANSCEND studies[1]

	<1 egg/wk ($n = 10,766$)	1 to <3 egg/wk ($n = 16,859$)	3 to <5 egg/wk ($n = 1218$)	5 to <7 egg/wk ($n = 2329$)	≥7 egg/wk ($n = 311$)	P-trend[2]
Eggs per week	0.23 [0–0.46]	2.0 [1.0–2.0]	4.0 [4.0–4.1]	6.96 [6.96–6.96]	14 [14.0–21.0]	
Composite outcome events						
Events ($n = 6448$)	2084 (19.4)	3516 (20.9)	260 (21.4)	522 (22.4)	66 (21.2)	
Multivariable adjusted	1 (ref)	1.05 (0.99, 1.10)	1.05 (0.92, 1.20)	1.11 (1.00, 1.24)	0.97 (0.76, 1.25)	0.09
Total mortality						
Events ($n = 3769$)	1235 (11.5)	2058 (12.2)	155 (12.7)	286 (12.3)	35 (11.2)	
Multivariable adjusted	1 (ref)	1.03 (0.96, 1.11)	1.09 (0.92, 1.29)	1.05 (0.91, 1.21)	0.88 (0.62, 1.24)	0.55
Cardiovascular mortality						
Events ($n = 2264$)	746 (6.9)	1238 (7.3)	92 (7.6)	167 (7.2)	21 (6.8)	
Multivariable adjusted	1 (ref)	1.04 (0.94, 1.14)	1.07 (0.86, 1.34)	1.02 (0.85, 1.23)	0.87 (0.56, 1.37)	0.81
Noncardiovascular mortality						
Events ($n = 1505$)	489 (4.5)	820 (4.9)	63 (5.2)	119 (5.1)	14 (4.5)	
Multivariable adjusted	1 (ref)	1.00 (0.90, 1.13)	1.09 (0.83, 1.42)	1.05 (0.85, 1.30)	0.86 (0.50, 1.47)	0.76
Major CVD						
Events ($n = 5181$)	1664 (15.5)	2835 (16.8)	208 (17.1)	421 (18.1)	53 (17.1)	
Multivariable adjusted	1 (ref)	1.06 (0.99, 1.13)	1.04 (0.90, 1.21)	1.11 (0.98, 1.25)	0.97 (0.73, 1.29)	0.12
Myocardial infarction						
Events ($n = 1554$)	524 (4.9)	848 (5.0)	55 (4.5)	108 (4.6)	19 (6.1)	
Multivariable adjusted	1 (ref)	1.00 (0.89, 1.11)	0.91 (0.69, 1.21)	1.07 (0.86, 1.35)	1.12 (0.68, 1.82)	0.70
Stroke						
Events ($n = 1394$)	415 (3.9)	754 (4.5)	61 (5.0)	149 (6.4)	15 (4.8)	
Multivariable adjusted	1 (ref)	1.10 (0.97, 1.24)	1.12 (0.85, 1.47)	1.17 (0.95, 1.45)	0.97 (0.58, 1.64)	0.16
Heart failure						
Events ($n = 1337$)	407 (3.8)	758 (4.5)	52 (4.3)	105 (4.5)	15 (4.8)	
Multivariable adjusted	1 (ref)	1.14 (1.00, 1.29)	1.09 (0.81, 1.47)	1.33 (1.05, 1.68)	1.25 (0.74, 2.11)	0.01

[1] $n = 31,544$. Values are median [IQR], n (%), or HR (95% CI). Cox hazard multivariable model adjusted for age; sex; smoking; location; BMI; education; physical activity; history of diabetes; history of myocardial infarction; history of stroke; medication; trial allocation; daily intakes of fruit, vegetables, red meat, poultry, fish, and dairy; and regions as a random effect. CVD, cardiovascular disease; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial; TRANSCEND, Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease.

[2] P-trend was calculated by assigning median values to each quintile and was treated as a continuous variable.

To the best of our knowledge, our study represents one of the largest studies assessing the association of egg intake with blood lipids and blood pressure, as well as mortality and cardiovascular events in different regions of the world. The large numbers of participants and events (>20,000 composite outcome events), the high completeness of the data, and the availability of detailed covariates used for adjustment are major strengths of our study. For all 3 cohorts, standardized methods were used to record events and in >95% of events, supporting documentation was available permitting central adjudication of the events. For the PURE study, we used standardized methods to measure diet using a country-specific validated FFQ.

Our study has a few potential limitations. First, although for the PURE study validated FFQs were used, some measurement error is inevitable. FFQ is not the method of choice for measuring individuals' absolute intake but it is useful in categorizing individuals based on their intake and so comparisons across categories of intakes are valid. For ONTARGET/TRANSCEND studies we used a qualitative FFQ and our estimates are not adjusted for energy intake but adjusted for BMI and physical activity which are closely related to energy balance (24). Second, as with any other observational cohort study, residual confounding is possible; however, we adjusted for established and potential risk factors for CVD as well as for the intake of other dietary variables.

In conclusion, we found that moderate egg intake (1/d) was not associated with an increased risk of mortality or major CVD.

See the online supplementary material for a list of PURE Project Office Staff, National Coordinators, Investigators, and Key Staff.

The authors' responsibilities were as follows—SY: conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct, and reviewed and commented on the draft; MD, AM, and SY: had primary responsibility for writing the report; SR: coordinated the worldwide study and reviewed and commented on drafts; MD: coordinated the entire nutrition component of the PURE study and did all data analyses; all other authors: coordinated the study in their respective countries and provided comments on drafts of the manuscript; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

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