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ORIGINAL RESEARCH

Dietary Intakes of Eggs and Cholesterol in Relation to All-Cause and Heart Disease Mortality: A Prospective Cohort Study

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BACKGROUND: The aim of this study was to identify associations between dietary intakes of eggs and cholesterol and all-cause and heart disease mortality in a US population.

METHODS AND RESULTS: Data from the National Health and Nutrition Examination Survey 1999–2014 were used in this study, which included 37 121 participants ≥20 years of age. Dietary information was assessed via 24-hour dietary recalls at baseline. Mortality status was documented until December 31, 2015. Cox proportional hazards models were used to examine the associations between dietary intakes of eggs and cholesterol and all-cause and heart disease mortality. During a median follow-up of 7.8 years, 4991 deaths were documented, including 870 deaths from heart disease. No significant association was observed between additional daily consumption of half an egg and all-cause mortality (multivariable-adjusted hazard ratio, 1.04; 95% CI, 0.96–1.13), or heart disease mortality (0.96; 0.80–1.14). Each 50-mg/day increase of cholesterol intake was inversely associated with all-cause mortality among participants with daily intake <250 mg (0.87; 0.77–0.98), but positively associated with all-cause mortality among participants with daily intake ≥250 mg (1.07; 1.01–1.12). No significant association was found between dietary cholesterol intake and heart disease mortality.

CONCLUSIONS: No significant association was found between egg consumption and mortality in US adults. The association between dietary cholesterol intake and all-cause mortality depended on the baseline intake levels, with an inverse association in those with lower intake levels (<250 mg/day) but a positive association in those with higher intake levels (≥250 mg/day).

Key Words: cardiovascular disease ■ cohort study ■ dietary cholesterol ■ egg ■ mortality

Eggs are a major dietary source of cholesterol in daily life. In addition to cholesterol, they contain high-quality protein and several vitamins and minerals.[1] Although they are affordable and nutrient-dense, there are concerns over potential cardiovascular complications associated with high dietary intake of eggs because of the high level of dietary cholesterol in eggs that may lead to worsening of blood cholesterol levels. For decades, it has been advised to restrict consumption of eggs, particularly yolk, but further evidence indicated that eggs were not significantly associated with adverse cardiovascular outcomes.[2–4]

The *2015–2020 Dietary Guidelines for Americans* recommended egg consumption as part of a healthy diet, and abolished the limit of dietary cholesterol intake of 300 mg/day[2] that has been in the American dietary guidelines since 1968.[5] The updated recommendation is based on evidence from some major meta-analyses of observational studies that reported no significant associations between egg consumption, up to 1 per day, and risk of cardiovascular disease (CVD) or coronary heart disease.[6–8] A possible protective association with stroke was even reported.[9] Accordingly, the latest science advisory from the American Heart Association

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CLINICAL PERSPECTIVE

What Is New?

- In this cohort of representative adults in the United States, we did not find a significant association between dietary intake of eggs and all-cause or heart disease mortality.
- Dietary cholesterol intake was not significantly associated with heart disease mortality, but showed a U-shaped association with all-cause mortality: inverse association was found among participants with intake levels <250 mg/day and a positive association was found among individuals with intake levels ≥250 mg/day.

What Are the Clinical Implications?

- Our results indicate that eggs can be a component in a healthy diet as recommended in the recent *2015–2020 Dietary Guidelines for Americans*, but there remain concern with high dietary cholesterol intake.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
CVD	cardiovascular disease
HDL	high-density lipoprotein
LDL	low-density lipoprotein
NHANES	National Health and Nutrition Examination Survey

supported daily consumption of 1 whole egg in healthy individuals with normal cholesterol level.[10] In contrast, in early 2019, a pooled analysis of 6 US prospective cohorts reported positive associations between dietary intakes of egg and cholesterol and risk of incident CVD and all-cause mortality.[11] The reasons for the discrepancy between this study and earlier meta-analyses are unclear, although it is possible that higher risk may only become apparent at higher doses: the average dietary cholesterol intake was 293 mg/day in US adults in 2013–2014,[12] much higher than the global average of 228 mg/day.[13] In addition, the pooled analysis was based on 6 heterogeneous cohorts with substantial differences in baseline characteristics of participants, and generalizability of these findings to the overall US population is unclear. Since the publication of that article, results from several other cohort studies were published and the inconsistent findings further contributed to the ongoing debates on the relationship between dietary eggs and cholesterol and CVD.[14–17] Nevertheless, a comprehensive assessment of the associations in a cohort of US representative population is still needed and may provide valuable evidence for establishment of a general dietary guideline for adults.

In view of these circumstances, we used data from the US National Health and Nutrition Examination Survey (NHANES) to examine dietary intakes of eggs and cholesterol in relation to all-cause and heart disease mortality. We also sought to determine whether such associations vary at different consumption levels and in different subgroups of the population.

METHODS

Study Population

All data were obtained from the NHANES, a complex, multistage, probability sampling designed survey to assess the health and nutritional status of adults and children in the United States.[18] The data are publicly available and can be accessed at https://wwwn.cdc.gov/nchs/nhanes/default.aspx. Detailed descriptions of the planning and operation of each survey have been reported elsewhere.[18] The methods used in the analysis that support the findings of this study are available from the corresponding author upon reasonable request.

A total of 43 793 adults ≥20 years of age were interviewed in 8 cycles (1999–2014) of the NHANES. For the current analyses, we excluded participants with implausible caloric intake (<500 kcal or >6000 kcal/day)[11] or incomplete dietary recalls (n=5073), pregnant or lactating women (n=1542), or when there was lack of mortality status (n=57). A total of 37 121 participants were included in the main analyses (Figure S1). The NHANES was approved by the ethics review board of National Center for Health Statistics Research, and written informed consent was obtained from each participant.

Dietary Assessment

Food and nutrient intakes were assessed via 24-hour dietary recalls by trained interviewers using the US Department of Agriculture Automated Multiple-Pass Method at the Mobile Examination Center. A standard set of measuring guides was used to assist the respondent to report the volume and dimensions of the items. In the 1999–2002 cycle, a single in-person dietary recall was conducted on a randomly chosen day, whereas, beginning in 2003, a second dietary recall was collected by telephone interview approximately 3 to 10 days after the first one. Food intakes were coded and nutrient values were determined according to the US Department of Agriculture Food and Nutrient Database for Dietary Studies, versions 1.0 to 5.0.[19] To account for within-respondent random measurement error and provide estimated dietary intakes over long periods, the usual intakes of foods and nutrients were calculated using a statistical method developed at the National Cancer Institute.[20–22] Consumption of food groups was considered using the Food Patterns Equivalents Database.[23] Egg consumption was defined as intake of whole eggs or egg ingredient in mixed dishes, with the exception of egg substitutes.

Outcome Assessment

Vital status of the NHANES participants was ascertained by probabilistic matching with the National Death Index through December 31, 2015.[24] The cause of death was determined according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*). Total deaths and deaths from heart disease (codes I00–I09, I11, I13, I20–I51) were primary outcomes in our analyses. Due to data availability, we only conducted an exploratory analysis for stroke mortality (codes I60–I69; 191 cases) among 16 556 participants enrolled in 1999–2006. Follow-up time was calculated as person-years from the date of interview to the date of death or December 31, 2015, whichever came first.

Covariate Assessment

Demographic information and lifestyle factors, including age, sex, race/ethnicity, education, family income, marital status, cigarette smoking, and physical activity, were collected at the baseline survey. Alcohol use, weight, and height were assessed during physical examination at the Mobile Examination Center. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The family income–poverty ratio was defined as the total family income divided by the poverty threshold, and a lower ratio indicated lower socioeconomic status. Smokers were defined as participants who reported smoking >100 cigarettes during their lifetime and were current cigarette smokers, and former smokers were defined as those who had quit smoking before the time of the interview. Current smokers were further categorized into 3 groups: <10, 10 to 19, or ≥20 cigarettes per day. Alcohol drinkers were defined as those who consumed ≥12 alcoholic drinks in a given year, and further categorized into low-to-moderate drinkers (<1 [women] or <2 [men] drinks per day) or heavy drinkers (≥1 [women] or ≥2 [men] drinks per day). Diet quality was evaluated using the Healthy Eating Index-2015, which assessed the adherence to the *2015–2020 Dietary Guidelines for Americans*,[25] with a higher score indicating better diet quality. Participants were categorized as having low, medium, and high levels of physical activity if they performed the equivalent of <150, 150 to 300, and >300 minutes of moderate-intensity physical activity per week according to the 2018 *Physical Activity Guidelines for Americans*.[26] Prevalent CVD was defined as self-reported diagnosis of coronary heart disease, stroke, heart attack, or congestive heart failure, and prevalent cancer was defined as self-reported physician diagnosis of cancer or a malignancy of any kind. Diabetes mellitus was defined as fasting glucose ≥7 mmol/L or glycated hemoglobin level ≥6.5%, or taking glucose-lowering medications.[27] Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mm Hg or taking antihypertensive medications.[28] Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/L or taking lipid-lowering medications.[29]

Statistical Analysis

Among the 37 121 eligible participants, there were missing values for education level (n=48; 0.1%), family income–poverty ratio (n=2950; 7.9%), marital status (n=431; 1.2%), cigarette smoking (n=93; 0.3%), alcohol consumption (n=2239; 6.0%), physical activity (n=131; 0.4%), and BMI (n=628; 1.7%). Multiple imputation was done for all missing values.[30]

Characteristics of the participants across intake groups of eggs or dietary cholesterol were compared using analysis of variance for continuous variables and the Rao–Scott chi-square test for categorical variables, accounting for sampling design. Cox proportional hazards models were used to examine the relationship between dietary intake of egg and cholesterol and risk of all-cause and heart disease mortality. The proportional hazards assumption was tested only for the exposure variables by dividing the follow-up period into 3 intervals that held similar numbers of deaths and comparing the associations using the Wald test, and no evidence of departure from the assumption was found. Given the recent inconsistency regarding the association of eggs and cholesterol with mortality risk, we hypothesized that these associations could be nonlinear and depend on level of intake. Therefore, we first used categorical exposures in the analysis, and egg intake was classified into 3 groups (<0.5, ≥0.5 to <1, and ≥1 egg per day), based on the consumption pattern that people usually eat eggs in a predefined unit, whereas dietary cholesterol intake was categorized according to quintiles. We also applied the Cox proportional hazards model based on restricted cubic splines to explore the nonlinear associations. In the presence of nonlinearity, the analysis using continuous exposure (daily increase of 0.5 egg or 50 mg cholesterol) with mortality risk was stratified by intake subgroup levels based on the turning point on the spline curve. The hazard ratios (HRs) and 95% CIs were estimated with adjustment for potential confounders in a stepwise manner. Model 1 was adjusted for age, sex, race/

ethnicity, education, family income–poverty ratio, marital status, and survey cycles. Model 2 was also adjusted for total energy intake, cigarette smoking, alcohol use, and physical activity. Model 3 was further adjusted for BMI, baseline history of hypertension, diabetes mellitus, hypercholesterolemia, CVD, and cancer. Exploratory subgroup analyses were performed by age (<65 and ≥65 years of age), sex (male and female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), smoking status (never, former, and current smoker), BMI (<25.0, 25.0–29.9, and ≥30.0 kg/m^2), and baseline history of comorbidities (yes and no). The significance of the effect modification was examined by the Wald test with addition of a cross-product term of the potential effect modifier and continuous exposure variable to the final model.

We conducted a series of sensitivity analyses to test the robustness of the results, including: (1) additional adjustment for nutrients correlated with dietary cholesterol (saturated fat, total fat, fiber, and sodium) individually or in combination, in addition to covariates in model 3; (2) additional adjustment for cholesterol-containing foods (unprocessed red meat, processed meat, poultry, seafood, and total dairy products) individually or in combination, in addition to covariates in model 3; (3) mutual adjustment for eggs and dietary cholesterol in model 3; (4) additional adjustment for the Healthy Eating Index-2015 in model 3; (5) excluding deaths within 2 years of follow-up; (6) censoring at 10-year follow-up; and (7) excluding participants with major diseases at baseline, such as CVD and cancer. All statistical values were adjusted using sample weights in the NHANES to account for the complex survey design and oversampling of certain subgroups as specified in the instructions.[18] Data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as two-sided *P*<0.05.

RESULTS

Baseline Characteristics

The mean age (SD deviation) of the 37 121 participants was 50.2 (18.1) years, and 49.2% were men. The mean intakes (standard deviation) of eggs and cholesterol were 0.6 (0.3) egg per day and 288.3 (85.9) mg/day, respectively. The distributions of dietary intakes of eggs and cholesterol are plotted in the Figures S2 and S3.

Compared with participants who consumed <0.5 egg per day, those who consumed >1 egg per day were older and had a lower education level and lower family income–poverty ratio, but had higher BMI and physical activity levels. They were also more likely to be male, non-Hispanic black, Mexican American, married, a former smoker, a low-to-moderate alcohol drinker, and have prevalent medical conditions (Table 1). Participants with a higher egg consumption rate also had higher intakes of total energy and dietary cholesterol, but slightly lower Healthy Eating Index-2015 scores. Characteristics patterns for participants with high vs low intakes of dietary cholesterol were generally similar to those for egg consumption, but participants with high dietary cholesterol intakes were younger and less likely to have hypertension, hypercholesterolemia, CVD, and cancer (Table S1). Correlation coefficients between dietary intakes of eggs and cholesterol, and selected nutrients and foods are presented in Table S2. Overall, there were significant and positive correlations between dietary cholesterol intake and certain nutrients, including total and saturated fat and sodium, and foods, including eggs, unprocessed red meat, processed meat, poultry, and seafood (Pearson correlation coefficient ≥0.18 for all).

Association Between Egg and Dietary Cholesterol and Mortality Risk

During 290 698 person-years of follow-up (median, 7.8 years), there were 4991 deaths, including 870 deaths from heart disease. No significant associations were found between egg consumption and either all-cause mortality or heart disease mortality (*P*≥0.18 for overall association, and *P*=0.13 for nonlinearity on the basis of restricted cubic splines; Figure). Consistently, no significant association was observed between each additional 0.5 egg per day and all-cause mortality (HR, 1.04; 95% CI, 0.96–1.13) or heart disease mortality (HR, 0.96; 95% CI, 0.80–1.14; Table 2). There was no evidence of a significant association for all-cause and heart disease mortality when egg consumption was evaluated categorically, comparing those consuming ≥1 vs ≤0.5 egg per day (*P*≥0.47 for trend; Table S3). Results remained stable after additional adjustment for various nutrients (total dietary cholesterol, saturated fat, total fat, fiber, and sodium), potential cholesterol-containing foods, and Healthy Eating Index-2015 score. Excluding events within the first 2 years, censoring at 10 years of follow-up, or excluding participants with baseline CVD did not appreciably change the results (Table 2). Similarly, exploratory analyses also did not identify a significant association between egg consumption and stroke mortality (HR, 0.87; 95% CI, 0.58–1.31; Table S4).

Overall, dietary cholesterol intake was associated with all-cause mortality (*P*=0.01 for overall association, based on the restricted cubic splines), but not with heart disease mortality (*P*=0.35 for overall association; Figure). In addition, the association was U-shaped for all-cause mortality (*P*=0.01 for nonlinearity). We separately assessed the association with

Table 1. Baseline Characteristics of Study Participants Across Egg Consumption Groups in the National Health and Nutrition Examination Survey 1999–2014

Characteristics*	Total (n=37 121)	No. of Eggs per Day			*P* Value
		<0.5 (n=16 501)	0.5– 1 (n=16 818)	>1 (n=3802)	
Age, y	50.2±18.1	47.8±18.3	51.8±17.9	53.9±17.1	<0.001
Sex					
Male	18 634 (49.2)	6368 (39.8)	9253 (55.7)	3013 (79.6)	<0.001
Female	18 487 (50.8)	10 133 (60.2)	7565 (44.3)	789 (20.4)	
Race/ethnicity					
Non-Hispanic white	17 657 (70.2)	9127 (74.8)	7310 (66.8)	1220 (56.3)	<0.001
Non-Hispanic black	7683 (11.1)	2816 (8.6)	3871 (13.1)	996 (17.2)	
Mexican American	6584 (7.9)	2027 (5.6)	3373 (9.2)	1184 (16.5)	
Other	5197 (10.8)	2531 (11.0)	2264 (10.8)	402 (10.1)	
Education					
Less than high school	10 476 (18.4)	4060 (16.6)	5053 (19.8)	1363 (23.7)	<0.001
High school	8689 (24.2)	3982 (24.9)	3857 (23.4)	850 (24.0)	
Some college or above	17 908 (57.4)	8439 (58.5)	7887 (56.9)	1582 (52.4)	
Family income–poverty ratio level					
0 to 1.0	6940 (14.6)	3120 (15.1)	3059 (13.6)	761 (16.2)	0.01
1.1 to 3.0	14 255 (35.9)	6221 (35.6)	6529 (36.2)	1505 (36.2)	
>3.0	12 976 (49.6)	5884 (49.4)	5865 (50.2)	1227 (47.6)	
Marital status					
Married	21 887 (62.1)	9359 (60.5)	10 062 (63.3)	2466 (67.1)	<0.001
Separated	8418 (19.3)	3704 (19.0)	3909 (20.0)	805 (17.9)	
Never married	6385 (18.6)	3238 (20.5)	2642 (16.7)	505 (15.0)	
Smoking status					
Never	19 539 (52.2)	9067 (53.4)	8700 (51.3)	1772 (48.7)	<0.001
Former	9446 (25.0)	3696 (22.5)	4558 (27.2)	1192 (30.7)	
Current <10 cigarettes/day	3327 (8.2)	1451 (8.4)	1485 (7.8)	391 (8.8)	
Current ≥10 to <20 cigarettes/day	2139 (6.1)	1014 (6.8)	938 (5.6)	187 (4.5)	
Current ≥20 cigarettes/day	2577 (8.5)	1231 (8.9)	1099 (8.1)	247 (7.4)	
Drinking status					
Never	10 086 (24.8)	4783 (26.2)	4526 (24.0)	777 (19.2)	<0.001
Low to moderate	21 672 (64.5)	9337 (62.9)	9869 (65.6)	2466 (70.0)	
Heavy	3124 (10.7)	1378 (11.0)	1409 (10.4)	337 (10.7)	
Physical activity					
Low level	17 453 (42.3)	7643 (42.3)	8027 (42.4)	1783 (41.3)	0.04
Moderate level	4756 (13.8)	2233 (14.4)	2099 (13.5)	424 (11.9)	
High level	14 781 (43.9)	6566 (43.3)	6633 (44.1)	1582 (46.8)	
Total energy, kcal/day	2071.2±522.5	1969.1±498.5	2113.6±516.8	2326.6±536.3	<0.001
Total dietary cholesterol intake, mg/day	288.3±85.9	239.7±60.1	305.2±67.2	423.9±80.8	<0.001
Healthy Eating Index-2015	53.1±13.3	53.7±13.9	52.9±12.9	52.0±11.8	0.01
Body mass index, kg/m^2	28.8±6.7	28.7±6.9	28.8±6.6	29.1±6.1	<0.001
Medical conditions					
Hypertension	13 767 (31.7)	5491 (28.3)	6679 (35.0)	1597 (36.9)	<0.001

(Continued)

Table 1. Continued

Characteristics*	Total (n=37 121)	No. of Eggs per Day			*P* Value
		<0.5 (n=16 501)	0.5– 1 (n=16 818)	>1 (n=3802)	
Diabetes mellitus	5503 (10.6)	2007 (8.4)	2692 (12.4)	804 (15.8)	<0.001
Hypercholesterolemia	10 513 (27.5)	4379 (25.5)	4931 (29.4)	1203 (31.4)	<0.001
Cardiovascular disease	4255 (8.9)	1636 (7.5)	2067 (10.2)	552 (12.2)	<0.001
Cancer	3503 (9.5)	1480 (8.7)	1676 (10.3)	347 (10.4)	<0.001

Data are presented as number (%) for categorical variables and mean (standard deviation) for continuous variables.

**P* values calculated by Rao–Scott chi-square test for categorical variables, which is a design-adjusted version of the Pearson chi-square test; analysis of variance adjusting for sampling weights was used to calculate *P* values for continuous variables.

all-cause mortality in participants who consumed <250 mg/day cholesterol and in those who consumed ≥250 mg/day cholesterol. The 250-mg/day cut-off was approximately the turning point of the U-shaped association and the median level of previous recommended upper limit of dietary cholesterol (ranging from 200 to 300 mg). Every 50-mg/day increase of dietary cholesterol was inversely associated with all-cause mortality among participants with daily cholesterol intake <250 mg (HR, 0.87; 95% CI, 0.77–0.98; Table 3), but positively associated with all-cause mortality among participants with daily cholesterol intake ≥250 mg (HR, 1.07; 95% CI, 1.01–1.12). No significant association was found between dietary cholesterol intake and heart disease mortality (HR, 1.00 per 50 mg/day; 95% CI, 0.93–1.08; Table 4). On a consistent basis, there was no evidence of a linear association with all-cause and heart disease mortality when dietary cholesterol intake was assessed in quintiles (*P*≥0.13 for linear trend for both; Table S5). For all-cause mortality, the overall associations were generally similar in various sensitivity analyses in the 2 subgroups of participants on the basis of daily cholesterol intake levels (Table 3). In addition, the association between dietary cholesterol intake and heart disease mortality remained insignificant in all sensitivity analyses (Table 4). Our exploratory analyses also did not show a significant association between dietary cholesterol intake and stroke mortality (Table S6).

There was little evidence of effect modifications for most stratifying variables (Figures S4 through S8). There seemed to be sex differences in the associations between dietary intake of eggs and all-cause mortality: a positive association was observed in men (HR, 1.13; 95% CI, 1.01–1.27), whereas an inverse association was found in women (HR, 0.86; 95% CI, 0.75–0.99; *P*=0.01 for interaction; Figure S4). A similar pattern was found for the association between dietary cholesterol and all-cause mortality for participants with cholesterol intake <250 mg/day (men: HR, 1.12; 95% CI, 0.89–1.42; women: HR, 0.82; 95% CI, 0.71–0.95; *P*=0.02 for interaction; Figure S6). The associations between dietary intake of eggs and all-cause and heart disease mortality differed by baseline hypercholesterolemia status; that is, there seemed to be increased risks in participants with hypercholesterolemia but decreased risk in those without hypercholesterolemia (*P*≤0.03 for interaction; Figures S4 and S5). There were similar opposite associations between dietary cholesterol intake and heart disease mortality in subgroups stratified by hypercholesterolemia (*P*=0.002 for interaction; Figure S8), but such opposite associations for all-cause mortality were restricted to participants with <250 mg/day dietary cholesterol (*P*=0.04 for interaction; Figure S6), but not among those with ≥250 mg/day dietary cholesterol (*P*=0.29 for interaction; Figure S7).

DISCUSSION

In this study of 37 121 US adults with a median follow-up of 7.8 years, we did not find significant associations between egg intake and all-cause or heart disease mortality. No significant association was observed between dietary cholesterol and heart disease mortality. The association between dietary cholesterol and all-cause mortality was nonlinear and the positive association was only observed among participants with daily cholesterol intake ≥250 mg.

Interpretation and Comparison With Previous Studies

As a major source of dietary cholesterol, the association between egg consumption and health outcomes has attracted substantial attention. Several meta-analyses showed no significant associations between egg consumption and cardiovascular events or all-cause mortality.[6–8] For example, the most recent meta-analysis of 9 prospective studies did not demonstrate evidence of association with all-cause mortality (HR, 1.09; 95% CI, 0.997–1.20) or heart disease mortality (HR, 0.97; 95% CI, 0.90–1.05) for egg consumption of ≥1/day vs <1/week.[8] Overall, our findings are consistent with those studies. Most studies

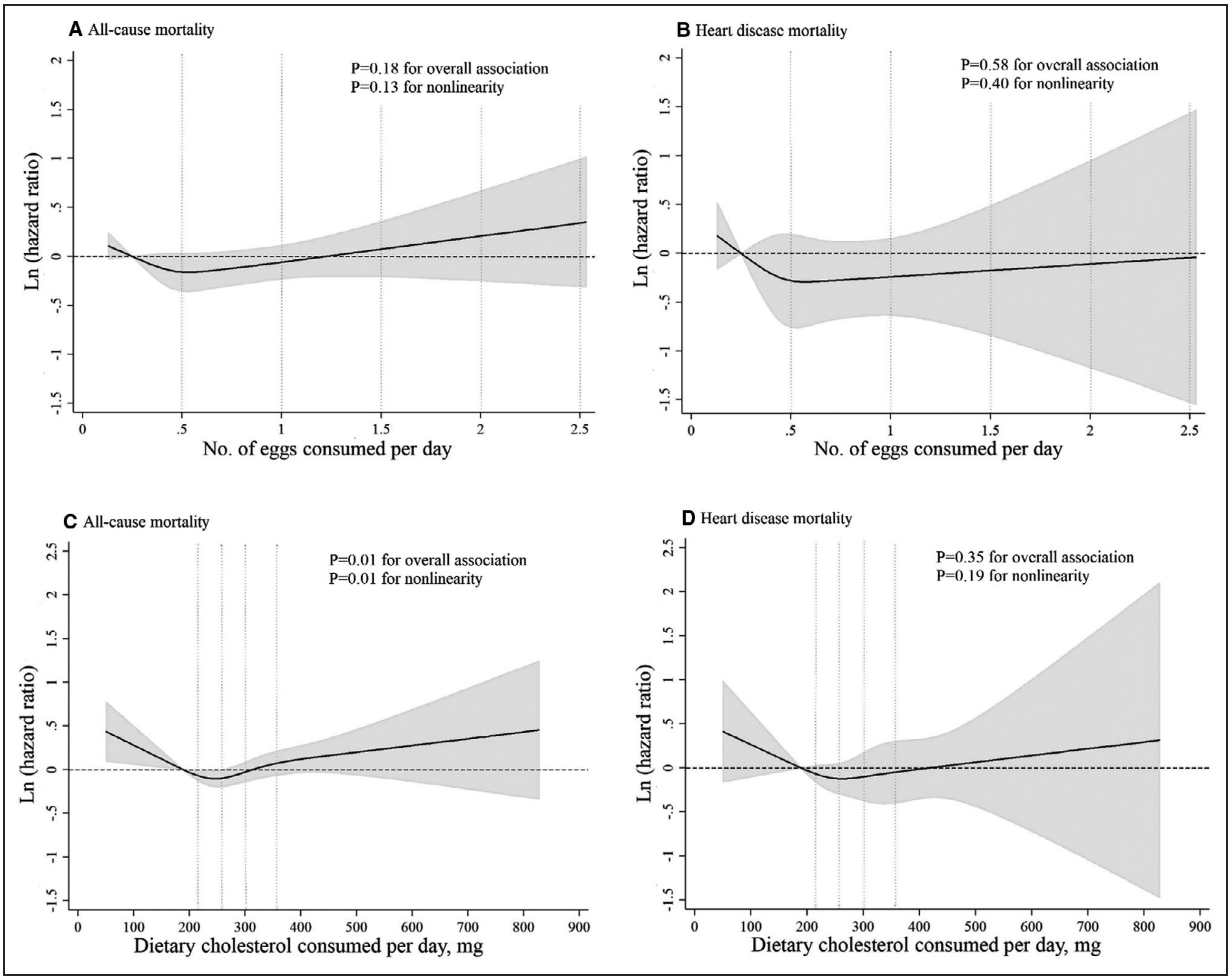

Figure. Associations between dietary intakes of egg and dietary cholesterol and all-cause and heart disease mortality. **A**, Association between dietary intake of egg and risk of all-cause mortality. **B**, Association between dietary intake of egg and risk of heart disease mortality. **C**, Association between dietary intake of cholesterol and risk of all-cause mortality. **D**, Association between dietary intake of cholesterol and risk of heart disease mortality. The solid lines and shaded areas represent the central risk estimates and 95% CIs, respectively, relative to the reference level (0.25 egg consumed per day for **A** and **B**; 10th percentile for **C** and **D**). The dotted vertical lines correspond to 0.5, 1, 1.5, 2, and 2.5 eggs consumed per day for (**A** and **B**), and the 20th, 40th, 60th, and 80th percentiles of dietary cholesterol intake for (**C** and **D**).

in the meta-analysis reported no significant association with all-cause mortality, whereas the Physicians' Health Study with 21 327 US men reported a positive association (HR, 1.23, comparing ≥1/day vs <1/week; 95% CI, 1.11–1.36),[31] and the NIPPON DATA 90 study among Japanese women reported a positive association (HR, 2.05, comparing ≥2/day vs 1/day; 95% CI, 1.20–3.52).[32] In addition, most of these studies reported no significant associations with incident CVD, CVD mortality, or heart disease mortality. A recent large-cohort study with 461 213 Chinese adults reported a linear inverse association for incident CVD (including all CVD subtypes) and CVD mortality.[33] However, a recent pooled analysis of 6 US cohorts indicated that each additional 0.5 egg consumed per day was significantly associated with higher risk of incident CVD (HR, 1.06; 95% CI, 1.03–1.10) and all-cause mortality (HR, 1.08; 95% CI, 1.04–1.11).[11] Despite the large sample size (n=29 615) and long-term follow-up (median, 17.5 years), this study may be subject to several limitations: (1) baseline assessments from included cohort studies spanned from 1985 to 2005, but the secular changes of egg consumption over the years were not taken into account; (2) baseline characteristics varied substantially in individual cohorts in terms of age, race/ethnicity, education level, smoking status, mean BMI, and health status (diabetes mellitus, hypertension, and blood lipid levels), as well as incidence and mortality rates; and (3) the 6 cohorts had different study

Table 2. Associations Between Each Additional 0.5 Egg Consumed per Day and All-Cause and Heart Disease Mortality

Models*	Adjusted Hazard Ratio (95% CI)	
	All-Cause Mortality	Heart Disease Mortality
Model 1	1.04 (0.96–1.12)	0.95 (0.81–1.11)
Model 2	1.05 (0.97–1.14)	0.98 (0.84–1.16)
Model 3	1.04 (0.96–1.13)	0.96 (0.80–1.14)
Model 3 plus nutrients		
Total cholesterol	0.97 (0.85–1.10)	0.88 (0.66–1.17)
Saturated fat	1.04 (0.95–1.13)	0.96 (0.80–1.14)
Total fat	1.05 (0.96–1.15)	0.95 (0.79–1.14)
Fiber	1.01 (0.93–1.10)	0.94 (0.79–1.12)
Sodium	1.05 (0.96–1.14)	0.96 (0.81–1.14)
All previous nutrients	0.97 (0.86–1.10)	0.86 (0.65–1.15)
Model 3 plus cholesterol-containing foods		
Unprocessed red meat	1.04 (0.95–1.13)	0.95 (0.80–1.13)
Processed meat	1.04 (0.96–1.14)	0.96 (0.80–1.14)
Poultry	1.04 (0.95–1.13)	0.95 (0.80–1.13)
Seafood	1.04 (0.96–1.14)	0.96 (0.81–1.14)
Total dairy	1.04 (0.96–1.13)	0.93 (0.78–1.11)
All previous foods	1.04 (0.96–1.13)	0.93 (0.78–1.10)
Model 3 plus Healthy Eating Index-2015	1.03 (0.94–1.12)	0.95 (0.80–1.13)
Model 3 with restrictions		
Excluding events within first 2 years	1.03 (0.93–1.13)	0.95 (0.78–1.16)
Censoring at 10-year follow-up	1.07 (0.98–1.17)	1.00 (0.81–1.24)
Excluding patients with baseline cardiovascular disease	1.03 (0.92–1.15)	0.94 (0.73–1.22)

*Complex survey designs are considered for all estimates. Model 1 was adjusted for age, sex, race/ethnicity, education, family income–poverty ratio, marital status, and National Health and Nutrition Examination Survey cycles. Model 2 was adjusted for total energy intake, cigarette smoking, alcohol drinking, physical activity, and covariates in model 1. Model 3 was adjusted for body mass index, baseline hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular disease, cancer, and covariates in model 2.

Table 3. Associations Between Each Additional 50 mg of Dietary Cholesterol Consumed per Day and All-Cause Mortality

Models*	Hazard Ratio (95% CI)	
	Daily Consumption <250 mg	Daily Consumption ≥250 mg
Model 1	0.90 (0.80–1.02)	1.04 (0.99–1.08)
Model 2	0.91 (0.80–1.03)	1.07 (1.02–1.12)
Model 3	0.87 (0.77–0.98)	1.07 (1.01–1.12)
Model 3 plus nutrients		
Saturated fat	0.87 (0.77–0.99)	1.06 (1.00–1.12)
Total fat	0.89 (0.78–1.01)	1.07 (1.01–1.13)
Fiber	0.83 (0.73–0.94)	1.06 (1.00–1.11)
Sodium	0.89 (0.78–1.00)	1.07 (1.02–1.13)
All previous nutrients	0.86 (0.75–0.98)	1.05 (0.99–1.12)
Model 3 plus cholesterol-containing foods		
Egg	0.90 (0.79–1.04)	1.07 (1.00–1.14)
Unprocessed red meat	0.85 (0.75–0.96)	1.07 (1.01–1.12)
Processed meat	0.87 (0.77–0.99)	1.07 (1.01–1.13)
Poultry	0.88 (0.77–1.00)	1.07 (1.02–1.12)
Seafood	0.87 (0.77–0.99)	1.07 (1.02–1.13)
Total dairy	0.87 (0.77–0.98)	1.07 (1.02–1.12)
All previous foods	0.94 (0.79–1.11)	1.11 (1.04–1.20)
Model 3 plus Healthy Eating Index-2015	0.85 (0.75–0.96)	1.06 (1.01–1.12)
Model 3 with restrictions		
Excluding events within first 2 y	0.88 (0.76–1.01)	1.05 (0.99–1.11)
Censoring at 10-year follow-up	0.95 (0.82–1.10)	1.09 (1.04–1.14)
Excluding patients with baseline cardiovascular disease	0.84 (0.70–1.00)	1.08 (1.02–1.14)

*Complex survey designs are considered for all estimates. Model 1 was adjusted for age, sex, race/ethnicity, education, family income–poverty ratio, marital status, and National Health and Nutrition Examination Survey cycles. Model 2 was adjusted for total energy intake, cigarette smoking, alcohol drinking, physical activity, and covariates in model 1. Model 3 was adjusted for body mass index, baseline hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular disease, cancer, and covariates in model 2.

designs and data collection procedures. Pooling individual data from these heterogeneous cohorts could be problematic if confounding patterns differed among studies, but effect sizes for individual studies were not estimated separately. In addition, the combined results may not be generalizable to the whole US population; therefore, our study has the unique advantage of representative sampling of the US population and standard and consistent data collection procedures. The inconsistent findings across previous studies may be because of different population characteristics, differential adjustments for confounders (such as lack of adjustment for other foods in certain studies), various egg consumption levels in different countries (eg, 25.5 g/day in 2011–2012 in the United States[34] vs 16.2 g/day [rural] and 28.8 g/day in 2012 [urban] in China[35]), and different cooking methods for eggs (eg, mostly fried eggs in the United States, and boiled eggs or mixed dishes with vegetables in China). Taken together, the current evidence indicates that egg consumption of up to 1 per day should not be a concern for the general public, although relationships with very high intake levels (eg, ≥2/day) still need to be confirmed. However, the proportion of people with such a high intake level is small in the population.

Table 4. Associations Between Each Additional 50 mg of Dietary Cholesterol Consumed Per Day and Heart Disease Mortality

Models*	Hazard Ratio (95% CI)
Model 1	0.97 (0.91–1.04)
Model 2	1.02 (0.95–1.09)
Model 3	1.00 (0.93–1.08)
Model 3 plus nutrients	
Saturated fat	1.01 (0.93–1.09)
Total fat	1.00 (0.92–1.08)
Fiber	0.99 (0.92–1.08)
Sodium	1.01 (0.93–1.08)
All previous nutrients	1.00 (0.92–1.09)
Model 3 plus cholesterol-containing foods	
Egg	1.05 (0.93–1.19)
Unprocessed red meat	0.99 (0.92–1.06)
Processed meat	1.00 (0.93–1.08)
Poultry	1.01 (0.93–1.09)
Seafood	1.01 (0.93–1.08)
Total dairy	1.00 (0.93–1.08)
All previous foods	1.07 (0.92–1.25)
Model 3 plus Healthy Eating Index-2015	1.00 (0.93–1.07)
Model 3 with restrictions	
Excluding events within first 2 years	1.00 (0.92–1.08)
Censoring at 10-year follow-up	1.01 (0.92–1.12)
Excluding patients with baseline cardiovascular disease	1.03 (0.92–1.14)

*Complex survey designs are considered for all estimates. Model 1 was adjusted for age, sex, race/ethnicity, education, family income–poverty ratio, marital status, and National Health and Nutrition Examination Survey cycles. Model 2 was adjusted for total energy intake, cigarette smoking, alcohol intake, physical activity, and covariates in model 1. Model 3 was adjusted for BMI, baseline hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular disease, cancer, and covariates in model 2.

In our study, we did not find a significant association between dietary cholesterol intake and heart disease mortality. The results are consistent with those of several previous studies on CVD mortality and also in a systematic review of 19 studies with 361 923 participants, which did not identify significant associations with incident coronary heart disease, ischemic stroke, or hemorrhagic stroke.[36] Although increased dietary cholesterol intake was thought to modestly increase serum total and low-density lipoprotein (LDL) cholesterol as well as LDL/high-density lipoprotein (HDL) cholesterol ratio,[37] such an effect may not substantially increase the risk of CVD. This was demonstrated in a meta-analysis of 17 trials, where 100 mg/day dietary cholesterol only increased total cholesterol by 0.056 mmol/L (2.2 mg/dL) and the LDL/HDL cholesterol ratio by 0.020 unit.[37] Cholesterol homeostasis is maintained constant through a compensatory mechanism,[38] and increased intake of dietary cholesterol is associated with decreased synthesis of endogenous cholesterol. In the pooling study of 6 US cohorts, Zhong et al[11] reported positive and monotonic associations between dietary cholesterol intake and risk of all-cause mortality and incident CVD, even after adjustment for saturated fat, red meat, and other nutrients or foods consistently found to be related to risk of CVD and premature death.[39–42] However, we observed a nonlinear U-shaped association between dietary cholesterol and all-cause mortality, and the weakly positive association was only restricted to participants with a daily intake ≥250 mg. The result raises concerns over whether the association between dietary cholesterol and increased all-cause mortality depends on the baseline cholesterol consumption levels. Although our results among individuals with high consumption levels are in part consistent with those of Zhong et al,[11] there is still a possibility of residual confounding from foods and nutrients that may increase risk of mortality. Our findings need to be validated in other similar prospective studies to achieve consensus about the optimal intake levels of dietary cholesterol.

The findings for all-cause and heart disease mortality were generally consistent in subgroups according to demographic characteristics, risk factors, and baseline medical conditions. In a recent study among 6 cohorts, the association between dietary cholesterol intake and all-cause mortality was significantly stronger among women than men.[11] However, our study showed opposite associations between egg consumption (and lower dietary cholesterol) and all-cause mortality among men and women. Egg consumption was associated with higher risk in men, consistent with some earlier reports from the United States[43,44] and Sweden.[45] Some studies suggested that dietary intake of eggs was associated with higher risk of CVD mortality among participants with diabetes mellitus,[6,7] but our study did not show any significant association between intake of eggs or cholesterol and mortality outcomes in patients with diabetes mellitus. However, we found divergent associations with all-cause and heart disease mortality in participants with and without hypercholesterolemia. The higher risk observed among participants with hypercholesterolemia may imply that dietary cholesterol needs to be controlled in individuals with high blood cholesterol levels, whereas, in those without hypercholesterolemia, the inverse associations may suggest that dietary cholesterol intake is not a concern. Of note, a feeding trial identified limited rise in LDL cholesterol levels among hypercholesterolemic participants after feeding with 2 eggs per day, which was also assumed to be similar to that reported among normocholesterolemic participants.[46] Because we conducted multiple exploratory subgroup analyses, positive results in the stratified analyses should be interpreted with caution.

Strengths and Limitations

Because the NHANES has a large sample size with systematic surveys of dietary factors and a representative sampling of the US population, our analyses can facilitate quantitative delineation of the impact of dietary intake of eggs and cholesterol in the US population. However, there are certain limitations to be acknowledged. First, the 24-hour dietary recalls may not represent long-term exposure levels and participants may have changed their dietary habits during the follow-up. Second, although we adjusted for certain lifestyle and dietary factors, residual confounding cannot be entirely dismissed. Third, we could not examine the associations of dietary intake of eggs and cholesterol with incident CVD and their subtypes because of the lack of available data. Fourth, the average follow-up was 7.6 years, which may not be long enough for assessing the long-term dietary impact on mortality outcomes in a relatively young population. Fifth, information was available on apolipoprotein E gene polymorphism, which has been shown to affect variations of serum cholesterol in response to dietary cholesterol[43]; therefore, further study is needed to determine whether the association between dietary cholesterol intake and health outcomes can be modified by genetic background.[47,48]

CONCLUSIONS

In this study we did not find a significant association between dietary intake of eggs and all-cause and heart disease mortality in US adults, whereas total dietary cholesterol intake at high levels seemed to be associated with higher risk of all-cause mortality. Our findings are generally supportive of the recommendation from the *2015–2020 Dietary Guidelines for Americans* that moderate consumption of up to 1 egg per day may be included in a healthy dietary pattern. However, caution should be taken for high-risk individuals, such as those with hypercholesterolemia and those already with high dietary cholesterol intake levels. Our analyses should be replicated in other populations with different intake levels of eggs and cholesterol. In addition, further prospective studies are warranted to investigate the relationships between of high dietary egg and cholesterol intake and other major health outcomes such as incident CVDs and their subtypes.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S6
Figures S1–S8

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of study participants in the NHANES 1999-2014 across dietary cholesterol consumption groups.*

	Total (n=37 121)	Quintile 1 (n=7424)	Quintile 2 (n=7424)	Quintile 3 (n=7425)	Quintile 4 (n=7424)	Quintile 5 (n=7424)	***P* values**
Dietary cholesterol, mg/day	288.3±85.9	183.5±24.7	235.4±11.9	277.3±12.6	325.5±16.1	419.5±56.9	< 0.001
Age, years	50.2±18.1	55.1±18.5	52±18.4	50.4±18	47.8±17.6	45.9±16.7	< 0.001
Sex							
Male	18 634 (49.2)	772 (8.5)	2050 (25.5)	3777 (53)	5357 (74.3)	6678 (90.7)	< 0.001
Female	18 487 (50.8)	6652 (91.5)	5374 (74.5)	3648 (47)	2067 (25.7)	746 (9.3)	
Race/ethnicity							
Non-Hispanic White	17 657 (70.2)	3965 (74.2)	3720 (71.7)	3536 (70.6)	3435 (69.4)	3001 (64.4)	< 0.001
Non-Hispanic Black	7683 (11.1)	1149 (7.7)	1419 (10.4)	1610 (11.6)	1604 (11.8)	1901 (14.5)	
Mexican American	6584 (7.9)	920 (4.7)	1173 (6.5)	1275 (7.4)	1463 (9.3)	1753 (12.1)	
Other	5197 (10.8)	1390 (13.4)	1112 (11.4)	1004 (10.5)	922 (9.6)	769 (9.0)	

Education							
Less than high school	10 476 (18.4)	2142 (18.8)	2048 (18.4)	2021 (17.6)	2072 (17.7)	2193 (19.5)	0.16
High school	8689 (24.2)	1706 (24.0)	1710 (24.2)	1724 (24.0)	1725 (23.7)	1824 (25.1)	
Some college or above	17 908 (57.4)	3566 (57.1)	3654 (57.5)	3672 (58.4)	3616 (58.5)	3400 (55.5)	
Family income-poverty ratio level							
0-1.0	6940 (14.6)	1425 (15.6)	1462 (16.1)	1323 (13.5)	1324 (13.2)	1406 (14.2)	< 0.001
1.1-3.0	14 255 (35.9)	2965 (38.4)	2845 (36.1)	2810 (35.6)	2804 (34.0)	2831 (35.0)	
>3.0	12 976 (49.6)	2390 (46.1)	2532 (47.7)	2692 (50.9)	2711 (52.8)	2651 (50.8)	
Marital status							
Married	21 887 (62.1)	3935 (58.9)	4180 (60.5)	4422 (62.6)	4624 (64.1)	4726 (64.8)	< 0.001
Separated	8418 (19.3)	2413 (26.7)	1966 (22.5)	1624 (18.3)	1307 (15.4)	1108 (12.7)	
Never married	6385 (18.6)	983 (14.3)	1189 (17.0)	1298 (19.0)	1395 (20.5)	1520 (22.6)	
Smoking status							

Never	19 539 (52.2)	4513 (58.3)	4156 (54.7)	3833 (51.1)	3663 (48.6)	3374 (47.6)	< 0.001
Former	9446 (25.0)	1661 (22.6)	1796 (23.6)	1971 (25.9)	1998 (26.9)	2020 (26.5)	
Current <10 cigarettes/day	3327 (8.2)	483 (6.7)	586 (7.7)	643 (8.0)	718 (8.4)	897 (10.3)	
Current ≥10 to <20	2139 (6.1)	364 (5.6)	401 (6.3)	428 (6.0)	465 (6.5)	481 (6.2)	
Current ≥20/d	2577 (8.5)	390 (6.9)	463 (7.8)	532 (9.0)	562 (9.5)	630 (9.4)	
Drinking status							
Never	10 086 (24.8)	3030 (36.8)	2358 (29.3)	2005 (23.3)	1535 (18.2)	1158 (14.8)	< 0.001
Low-to-moderate	21 672 (64.5)	3450 (54.6)	4038 (60.8)	4367 (66.1)	4777 (69.7)	5040 (72.3)	
Heavy	3124 (10.7)	450 (8.6)	544 (9.9)	613 (10.6)	691 (12.1)	826 (12.8)	
Physical activity							
Low level	17 453 (42.3)	3876 (47.1)	3694 (45.7)	3572 (42.5)	3277 (38.8)	3034 (36.4)	< 0.001
Medium level	4756 (13.8)	1022 (15.0)	1004 (13.9)	948 (14.4)	927 (13.4)	855 (12.4)	
High level	14 781 (43.9)	2501 (37.9)	2700 (40.4)	2879 (43.1)	3199 (47.7)	3502 (51.2)	
Total energy, kcal/d	2071.2±522.5	1602.3±297.7	1835.7±325.1	2041.7±387.5	2289±439.5	2587.3±487.3	< 0.001

Healthy eating index-2015	53.1±13.3	57.5±14.4	54.4±13.5	52.7±13	51.3±12.4	49.6±11.4	< 0.001
BMI[‡], kg/m2	28.8±6.7	28.4±6.6	28.9±7	29.0±6.8	28.9±6.6	28.9±6.3	< 0.001
Medical conditions							
Hypertension	13 767 (31.7)	3216 (35.2)	2968 (34.0)	2812 (32.0)	2412 (28.0)	2359 (28.5)	< 0.001
Diabetes	5503 (10.6)	1137 (10.0)	1103 (10.9)	1130 (11.2)	1025 (9.7)	1108 (11.3)	0.02
Hypercholesterolemia	10 513 (27.5)	2423 (30.5)	2207 (28.2)	2077 (27.0)	1910 (25.6)	1896 (25.9)	< 0.001
CVD[§]	4255 (8.9)	969 (10.3)	945 (10.0)	885 (9.0)	767 (7.7)	689 (7.4)	< 0.001
Cancer	3503 (9.5)	861 (11.3)	836 (11.7)	717 (9.8)	593 (7.7)	496 (6.4)	< 0.001

[*] Data are presented as no. (%) for categorical variables and mean (standard deviation, SD) for continuous variables

[†] For categorical variables, *P* values were calculated by Rao-Scott chi-square test, which is a design-adjusted version of Pearson Chi-square test; for continuous variables, ANOVA adjusting for sampling weights were used to calculate *P* values.

[‡] BMI, body mass index.

[§] CVD, cardiovascular disease.

Table S2. Correlation coefficients between consumption of eggs or cholesterol, and selected nutrients and foods. *

	Dietary cholesterol		**Eggs**	
	Coefficients	***P* values**	**Coefficients**	***P* values**
Total fat	0.30	<0.001	0.18	<0.001
Saturated fat	0.29	<0.001	0.07	<0.001
Fiber	-0.21	<0.001	-0.02	0.009
Sodium	0.22	<0.001	0.07	<0.001
Eggs	0.76	<0.001	1.00	<0.001
Unprocessed red meat	0.30	<0.001	0.09	<0.001
Processed meat	0.18	<0.001	0.05	<0.001
Poultry	0.23	<0.001	-0.004	0.57
Seafood	0.21	<0.001	0.16	<0.001
Dairy	-0.11	<0.001	-0.17	<0.001

[*] Correlation coefficients were estimated through the Pearson's correlation test after adjustment for sampling weights and total energy consumption.

Table S3. Associations between egg consumption levels and all-cause and heart disease mortality.

Mortality	Cases	Person years	HR (95% CI) *	*P* values for trend†
All-cause				
<0.5 egg/day	1871	130 518	1.00	0.82
≥0.5 to <1	2472	132 029	0.96 (0.88 to 1.05)	
≥1	648	28 151	1.05 (0.90 to 1.23)	
Heart Disease				
<0.5 egg/day	308	130 518	1.00	0.47
≥0.5 to <1	450	132 029	0.97 (0.81 to 1.17)	
≥1	112	28 151	0.89 (0.64 to 1.23)	

* Complex survey designs are considered for all estimates. Adjusted for age, sex, race/ethnicity, education, family income poverty ratio, marital status, NHANES cycles, total energy intake, cigarette smoking, alcohol drinking, physical activity, BMI, hypertension, diabetes, hypercholesterolemia, CVD, and cancer.

† *P* values for trend were estimated by modelling the egg consumption level as an ordinal variable.

Table S4. Association between each additional half an egg consumed per day and stroke mortality.

Models*	HR (95% CI)
Model 1	0.86 (0.59 to 1.26)
Model 2	0.89 (0.60 to 1.31)
Model 3	0.87 (0.58 to 1.31)
Model 3 plus nutrients	
Saturated fat	0.87 (0.45 to 1.69)
Total fat	0.88 (0.58 to 1.32)
Fiber	0.93 (0.60 to 1.42)
Sodium	0.86 (0.57 to 1.27)
All previous nutrients	0.88 (0.58 to 1.32)
Model 3 plus cholesterol-containing foods	0.86 (0.45 to 1.65)
Egg	
Unprocessed red meat	0.86 (0.58 to 1.28)
Processed meat	0.87 (0.58 to 1.30)
Poultry	0.86 (0.57 to 1.29)

Seafood	0.88 (0.59 to 1.30)
Total dairy	0.86 (0.57 to 1.30)
All previous foods	0.84 (0.56 to 1.26)
Model 3 plus Healthy Eating Index-2015	0.84 (0.56 to 1.25)
Model 3 with restrictions	
Excluding events within first 2 years	0.84 (0.52 to 1.35)
Censoring at 10 years follow-up	0.85 (0.56 to 1.29)
Excluding baseline CVD[§]	0.81 (0.48 to 1.37)

[*] Complex survey designs are considered for all estimates. Model 1 was adjusted for age, sex, race/ethnicity, education, family income poverty ratio, marital status, and NHANES cycles. Model 2 was adjusted for total energy intake, cigarette smoking, alcohol drinking, physical activity, and covariates in Model 1. Model 3 was adjusted for BMI, hypertension, diabetes, hypercholesterolemia, CVD, cancer, and covariates in Model 2.

[§] CVD, cardiovascular disease.

Table S5. Associations between dietary cholesterol intake in quintiles and all-cause and heart disease mortality.

Mortality	Cases	Person years	HR (95% CI) *	*P* values for trend†
All-cause				
Quintile 1	1179	55 612	1.00	0.13
Quintile 2	1058	58 501	0.89 (0.80 to 0.98)	
Quintile 3	992	58 409	0.90 (0.80 to 1.01)	
Quintile 4	935	59 300	1.04 (0.92 to 1.18)	
Quintile 5	827	58 877	1.07 (0.89 to 1.28)	
Heart Disease				
Quintile 1	187	55 612	1.00	0.77
Quintile 2	193	58 501	0.99 (0.77 to 1.28)	
Quintile 3	177	58 409	0.87 (0.67 to 1.13)	
Quintile 4	169	59 300	1.06 (0.77 to 1.48)	
Quintile 5	144	58 877	1.01 (0.70 to 1.46)	

* Complex survey designs are considered for all estimates. Adjusted for age, sex, race/ethnicity, education, family income poverty ratio, marital status, NHANES cycles,

total energy intake, cigarette smoking, alcohol drinking, physical activity, BMI, hypertension, diabetes, hypercholesterolemia, CVD, and cancer.

[†] *P* values for trend were estimated by modelling the cholesterol intake using the median value of each quintile as a continuous variable.

Table S6. Association between each additional 50 mg dietary cholesterol consumed per day and stroke mortality.

Models*	HR (95% CI)
Model 1	0.93 (0.83 to 1.06)
Model 2	0.96 (0.81 to 1.13)
Model 3	0.96 (0.81 to 1.13)
Model 3 plus nutrients	
Saturated fat	0.96 (0.80 to 1.13)
Total fat	1.00 (0.83 to 1.20)
Fiber	0.94 (0.79 to 1.12)
Sodium	0.96 (0.81 to 1.14)
All previous nutrients	0.95 (0.79 to 1.13)
Model 3 plus cholesterol-containing foods	
Egg	1.00 (0.76 to 1.33)
Unprocessed red meat	0.93 (0.78 to 1.11)
Processed meat	0.94 (0.79 to 1.12)
Poultry	0.96 (0.81 to 1.14)

Seafood	0.97 (0.82 to 1.14)
Total dairy	0.95 (0.80 to 1.13)
All previous foods	1.01 (0.74 to 1.39)
Model 3 plus Healthy Eating Index-2015	0.92 (0.77 to 1.10)
Model 3 with restrictions	
Excluding events within first 2 years	0.92 (0.75 to 1.13)
Censoring at 10 years follow-up	0.92 (0.78 to 1.08)
Excluding baseline CVD[§]	1.02 (0.85 to 1.23)

[*] Complex survey designs are considered for all estimates. Model 1 was adjusted for age, sex, race/ethnicity, education, family income poverty ratio, marital status, and NHANES cycles. Model 2 was adjusted for total energy intake, cigarette smoking, alcohol drinking, physical activity, and covariates in Model 1. Model 3 was adjusted for BMI, hypertension, diabetes, hypercholesterolemia, CVD, cancer, and covariates in Model 2.

[§] CVD, cardiovascular disease.

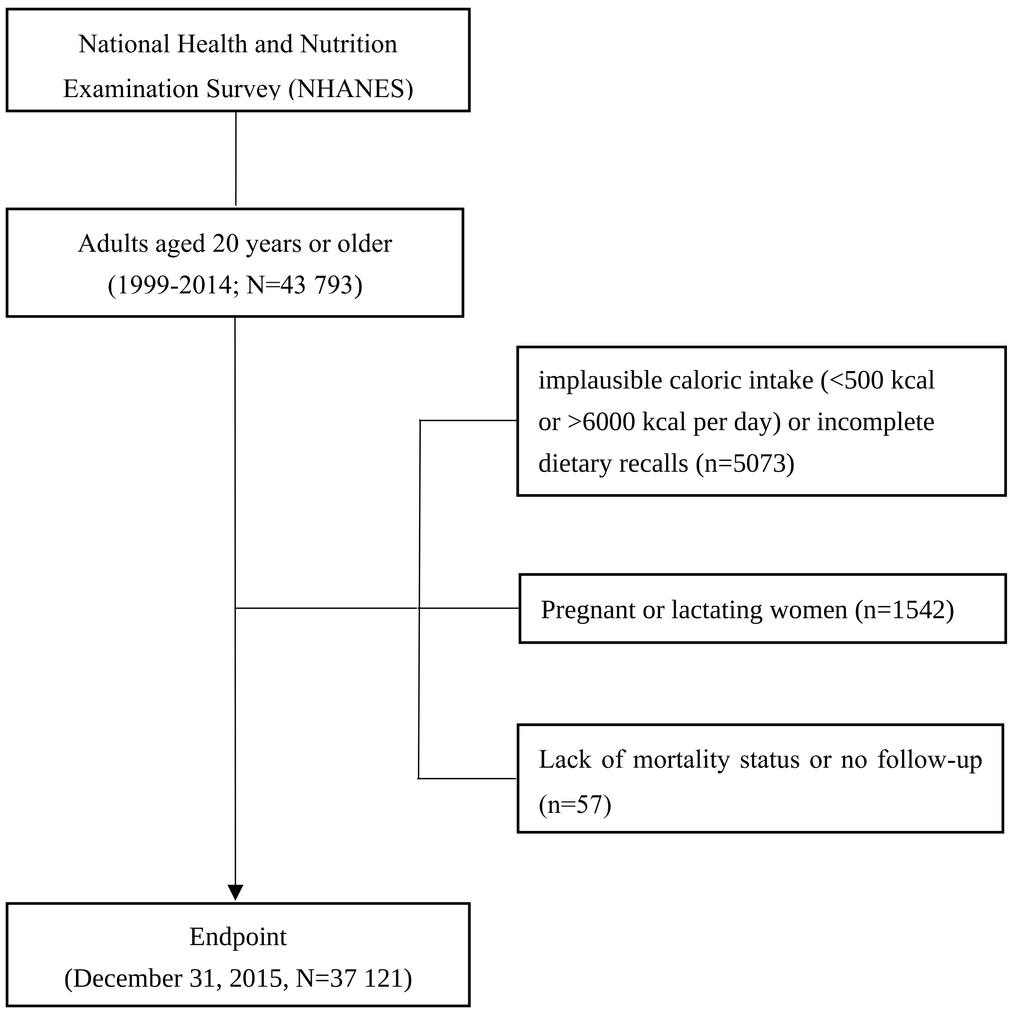

Figure S1. Flowchart of the study population in the NHANES.

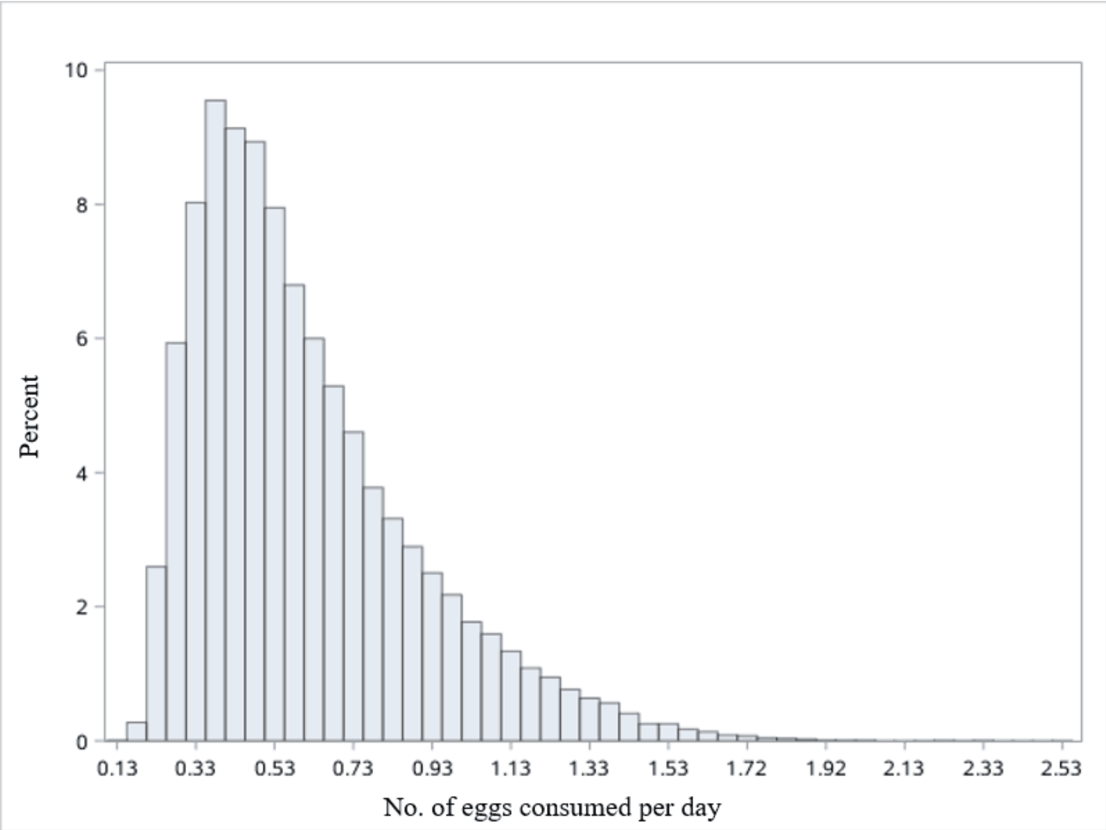

Figure S2. Distribution of usual intake of eggs in the US population in 1999-2014.

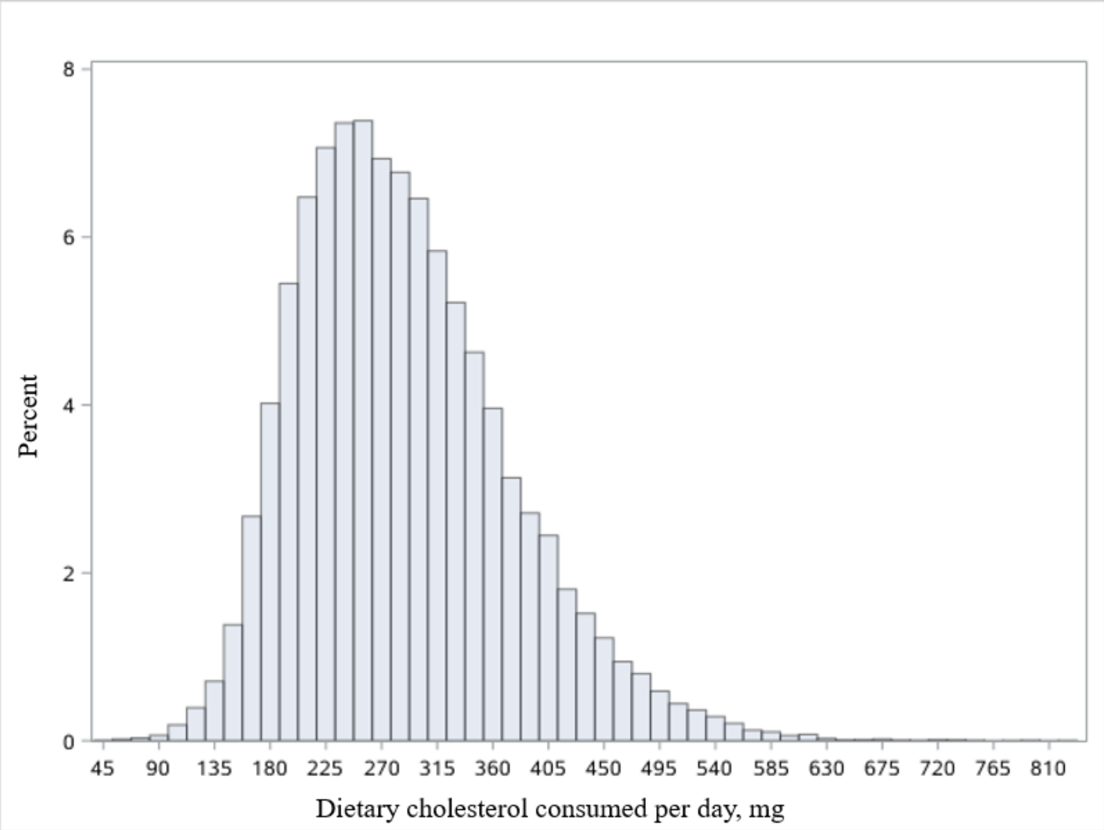

Figure S3. Distribution of usual intake of dietary cholesterol in the US population in 1999-2014.

Subgroups	Cases	Person years	HR (95% CI)	P values for interaction
Age, years				
<65	1 492	225 532	1.04 (0.90 to 1.19)	0.44
≥65	3 499	65 166	1.05 (0.96 to 1.16)	
Sex				
Male	2 834	144 572	1.13 (1.01 to 1.27)	0.01
Female	2 157	146 126	0.86 (0.75 to 0.99)	
Race/ethnicity				
Non-Hispanic White	2 937	140 031	1.03 (0.92 to 1.16)	0.59
Non-Hispanic Black	938	58 738	1.22 (1.04 to 1.42)	
Mexican American	792	58 708	0.99 (0.82 to 1.19)	
Other	324	33 221	0.97 (0.75 to 1.25)	
Smoking status				
Nonsmoker	2 033	152 961	0.93 (0.83 to 1.05)	0.15
Former smoker	1 960	72 446	1.16 (1.01 to 1.33)	
Current smoker	992	65 002	1.05 (0.89 to 1.22)	
Dietary cholesterol, mg/day				
<250	2 091	105 291	0.74 (0.58 to 0.94)	0.02
≥250	2 900	185 407	1.12 (1.00 to 1.25)	
Body mass index, kg/m2				
<25	1 492	87 231	1.09 (0.93 to 1.29)	0.25
≥25 to <30	1 730	100 143	0.99 (0.88 to 1.13)	
≥30	1 445	99 163	1.04 (0.91 to 1.19)	
Hypertension				
Yes	3 265	100 734	1.03 (0.93 to 1.13)	0.15
No	1 726	189 964	1.07 (0.93 to 1.22)	
Diabetes				
Yes	1 394	37 770	1.06 (0.94 to 1.19)	0.45
No	3 597	252 928	1.03 (0.93 to 1.14)	
Hypercholesterolemia				
Yes	1 857	78 232	1.17 (1.04 to 1.31)	0.03
No	3 134	212 465	0.97 (0.87 to 1.07)	
Cardiovascular disease				
Yes	1 679	27 782	1.06 (0.93 to 1.20)	0.32
No	3 312	262 916	1.03 (0.92 to 1.15)	
Cancer				
Yes	1 075	23 495	1.15 (0.99 to 1.33)	0.26
No	3 916	267 203	1.02 (0.93 to 1.11)	
Overall	4 991	290 698	1.04 (0.96 to 1.13)	

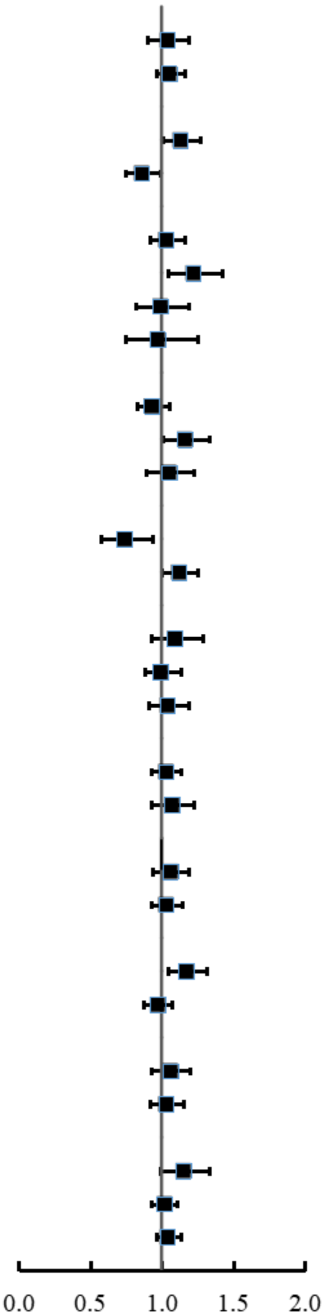

Figure S4. Subgroup analyses of each additional half an egg consumed per day for all-cause mortality. ***P*** **values for interaction were estimated by adding a product term between the stratified variables and egg consumption, and statistical significance was assessed by the Wald test.**

Subgroups	Cases	Person years	HR (95% CI)	P values for interaction
Age, years				
<65	205	225 532	0.81 (0.54 to 1.22)	0.98
≥65	665	65 166	1.02 (0.83 to 1.27)	
Sex				
Male	550	144 572	1.07 (0.88 to 1.30)	0.15
Female	320	146 126	0.70 (0.48 to 1.03)	
Race/ethnicity				
Non-Hispanic White	527	140 031	0.95 (0.77 to 1.18)	0.98
Non-Hispanic Black	167	58 738	1.07 (0.73 to 1.57)	
Mexican American	129	58 708	1.32 (0.81 to 2.15)	
Other	47	33 221	0.79 (0.47 to 1.31)	
Smoking status				
Nonsmoker	336	152 961	0.92 (0.65 to 1.29)	0.76
Former smoker	366	72 446	1.18 (0.92 to 1.53)	
Current smoker	167	65 002	0.74 (0.52 to 1.06)	
Dietary cholesterol, mg/day				
<250	350	105 291	0.73 (0.38 to 1.38)	0.38
≥250	520	185 407	1.03 (0.84 to 1.26)	
Body mass index, kg/m2				
<25	238	87 231	0.79 (0.53 to 1.19)	0.94
≥25 to <30	307	100 143	1.12 (0.77 to 1.63)	
≥30	257	99 163	0.97 (0.73 to 1.30)	
Hypertension				
Yes	640	100 734	0.90 (0.75 to 1.09)	0.15
No	230	189 964	1.06 (0.75 to 1.51)	
Diabetes				
Yes	282	37 770	0.78 (0.58 to 1.04)	0.07
No	588	252 928	1.06 (0.85 to 1.31)	
Hypercholesterolemia				
Yes	365	78 232	1.25 (0.92 to 1.70)	0.01
No	505	212 465	0.76 (0.61 to 0.95)	
Cardiovascular disease				
Yes	389	27 782	0.94 (0.74 to 1.20)	0.19
No	481	262 916	0.94 (0.73 to 1.22)	
Cancer				
Yes	165	23 495	0.93 (0.64 to 1.37)	0.92
No	705	267 203	0.95 (0.77 to 1.17)	
Overall	870	290 698	0.96 (0.80 to 1.14)	

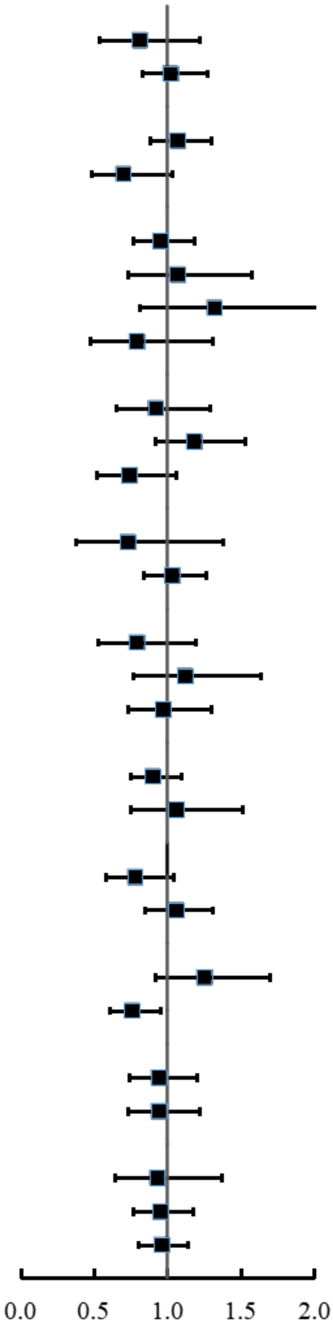

Figure S5. Subgroup analyses of each additional half an egg consumed per day for heart disease mortality. *P* values for interaction were estimated by adding a product term between the stratified variables and egg consumption, and statistical significance was assessed by the Wald test.

Subgroups	Cases	Person years	HR (95% CI)	P values for interaction
Age, y				
<65	465	74 073	0.78 (0.57 to 1.06)	0.57
≥65	1626	31 218	0.93 (0.82 to 1.07)	
Sex				
Male	527	16 595	1.12 (0.89 to 1.42)	0.02
Female	1564	88 696	0.82 (0.71 to 0.95)	
Race/ethnicity				
Non-Hispanic White	1340	55 771	0.79 (0.68 to 0.90)	0.001
Non-Hispanic Black	325	17 597	1.18 (0.92 to 1.52)	
Mexican American	263	16 842	1.29 (0.97 to 1.70)	
Other	163	15 081	1.26 (0.93 to 1.70)	
Smoking status				
Nonsmoker	1090	61 600	0.91 (0.72 to 1.14)	0.62
Former smoker	716	23 814	0.90 (0.74 to 1.09)	
Current smoker	283	19 759	0.83 (0.65 to 1.06)	
Body mass index, kg/m2				
<25	660	34 475	0.92 (0.79 to 1.07)	0.51
≥25 to <30	704	33 286	0.96 (0.78 to 1.17)	
≥30	574	35 591	0.86 (0.74 to 1.00)	
Hypertension				
Yes	1503	41 560	0.90 (0.80 to 1.01)	0.71
No	588	63 732	0.79 (0.59 to 1.05)	
Diabetes				
Yes	561	13 915	0.91 (0.75 to 1.11)	0.93
No	1530	91 376	0.85 (0.74 to 0.97)	
Hypercholesterolemia				
Yes	839	31 198	1.05 (0.88 to 1.26)	0.04
No	1252	74 093	0.77 (0.65 to 0.92)	
Cardiovascular disease				
Yes	720	11 441	0.94 (0.82 to 1.09)	0.79
No	1371	93 850	0.84 (0.70 to 1.00)	
Cancer				
Yes	473	10 767	0.83 (0.66 to 1.03)	0.23
No	1618	94 524	0.91 (0.77 to 1.06)	
Overall	2091	105 291	0.87 (0.77 to 0.98)	

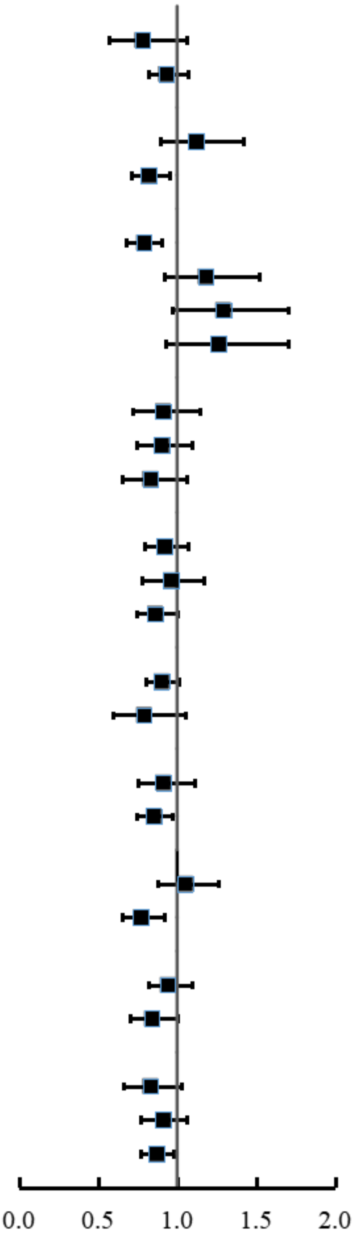

Figure S6. Subgroup analyses of each additional 50 mg dietary cholesterol consumed per day for all-cause mortality among participants with <250 mg daily cholesterol consumption. *P* values for interaction were estimated by adding a product term between the stratified variables and dietary cholesterol intake, and statistical significance was assessed by the Wald test.

Subgroups	Cases	Person years	HR (95% CI)	P values for interaction
Age, y				
<65	1027	151 459	1.06 (0.99 to 1.12)	0.34
≥65	1873	33 948	1.09 (1.02 to 1.16)	
Sex				
Male	2307	127 976	1.07 (1.02 to 1.14)	0.26
Female	593	57 430	0.99 (0.85 to 1.16)	
Race/ethnicity				
Non-Hispanic White	1597	84 260	1.09 (1.02 to 1.16)	0.62
Non-Hispanic Black	613	41 141	1.04 (0.95 to 1.13)	
Mexican American	529	41 866	1.00 (0.92 to 1.10)	
Other	161	18 139	1.03 (0.85 to 1.26)	
Smoking status				
Nonsmoker	943	91 361	1.02 (0.95 to 1.09)	0.56
Former smoker	1244	48 632	1.14 (1.05 to 1.24)	
Current smoker	709	45 243	1.03 (0.95 to 1.12)	
Body mass index, kg/m2				
<25	832	52 756	1.12 (1.03 to 1.22)	0.65
≥25 to <30	1026	66 857	1.07 (0.99 to 1.15)	
≥30	871	63 572	1.03 (0.96 to 1.11)	
Hypertension				
Yes	1762	59 174	1.08 (1.02 to 1.15)	0.36
No	1138	126 232	1.05 (0.98 to 1.13)	
Diabetes				
Yes	833	23 855	1.05 (0.98 to 1.13)	0.82
No	2067	161 552	1.07 (1.01 to 1.14)	
Hypercholesterolemia				
Yes	1018	47 035	1.11 (1.02 to 1.19)	0.29
No	1882	138 372	1.05 (0.99 to 1.10)	
Cardiovascular disease				
Yes	959	16 341	1.05 (0.97 to 1.14)	0.53
No	1941	169 066	1.08 (1.02 to 1.14)	
Cancer				
Yes	602	12 728	1.17 (1.06 to 1.29)	0.11
No	2298	172 679	1.04 (0.99 to 1.10)	
Overall	2900	185 407	1.07 (1.01 to 1.12)	

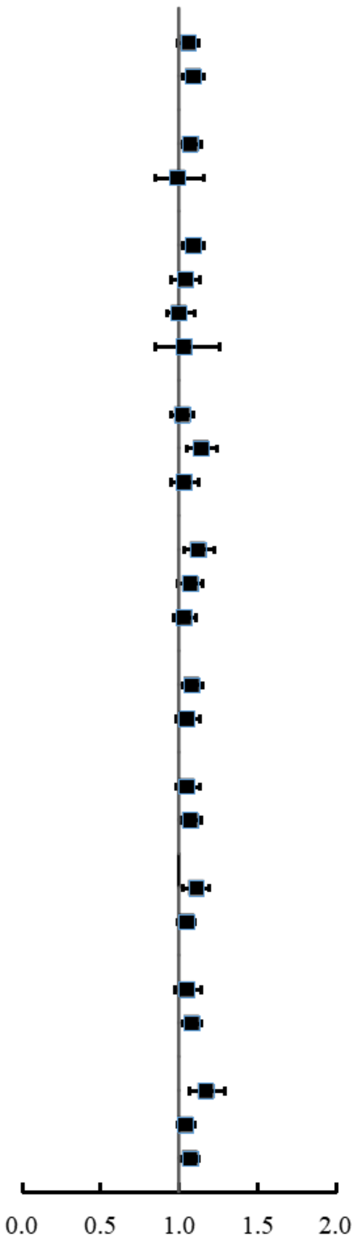

Figure S7. Subgroup analyses of each additional 50 mg dietary cholesterol consumed per day for all-cause mortality among participants with ≥250 mg daily cholesterol consumption. *P* values for interaction were estimated by adding a product term between the stratified variables and dietary cholesterol intake, and statistical significance was assessed by the Wald test.

Subgroups	Cases	Person years	HR (95% CI)	P values for interaction
Age, y				
<65	205	225 532	0.95 (0.81 to 1.11)	0.44
≥65	665	65 166	1.02 (0.92 to 1.13)	
Sex				
Male	550	144 572	1.04 (0.97 to 1.13)	0.06
Female	320	146 126	0.88 (0.74 to 1.05)	
Race/ethnicity				
Non-Hispanic White	527	140 031	1 (0.91 to 1.1)	0.30
Non-Hispanic Black	167	58 738	0.99 (0.84 to 1.17)	
Mexican American	129	58 708	1.14 (0.95 to 1.36)	
Other	47	33 221	1.08 (0.87 to 1.34)	
Smoking status				
Nonsmoker	336	152 961	0.99 (0.86 to 1.13)	0.52
Former smoker	366	72 446	1.09 (0.97 to 1.22)	
Current smoker	167	65 002	0.93 (0.8 to 1.08)	
Body mass index, kg/m2				
<25	238	87 231	0.97 (0.83 to 1.15)	0.59
≥25 to <30	307	100 143	1.05 (0.91 to 1.22)	
≥30	257	99 163	0.98 (0.87 to 1.11)	
Hypertension				
Yes	640	100 734	0.98 (0.9 to 1.06)	0.90
No	230	189 964	1.06 (0.92 to 1.23)	
Diabetes				
Yes	282	37 770	0.88 (0.77 to 1)	0.24
No	588	252 928	1.07 (0.98 to 1.17)	
Hypercholesterolemia				
Yes	365	78 232	1.13 (1 to 1.27)	0.002
No	505	212 465	0.91 (0.83 to 1)	
Cardiovascular disease				
Yes	389	27 782	0.96 (0.87 to 1.06)	0.42
No	481	262 916	1.03 (0.92 to 1.14)	
Cancer				
Yes	165	23 495	0.91 (0.79 to 1.05)	0.36
No	705	267 203	1.02 (0.94 to 1.11)	
Overall	870	290 698	1 (0.93 to 1.08)	

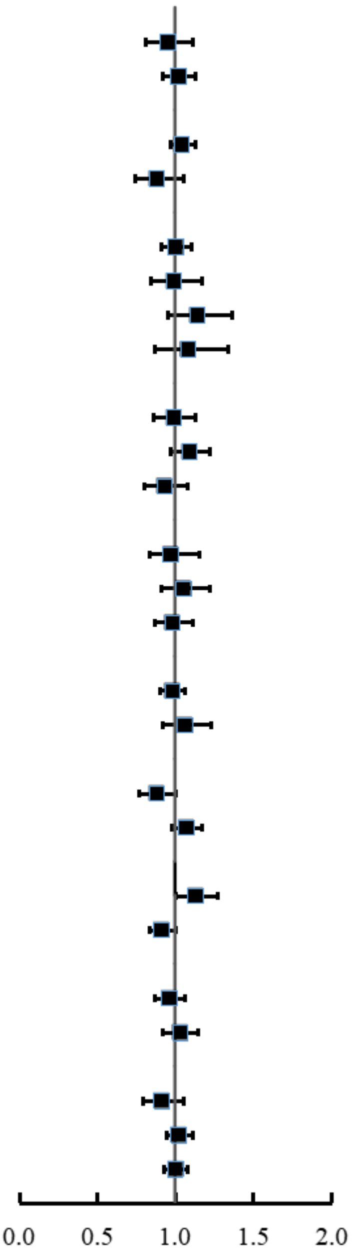

Figure S8. Subgroup analyses of each additional 50 mg dietary cholesterol consumed per day for heart disease mortality. *P* values for interaction were estimated by adding a product term between the stratified variables and dietary cholesterol intake, and statistical significance was assessed by the Wald test.