Abstract

Background

Whether consumption of egg and cholesterol is detrimental to cardiovascular health and longevity is highly debated. Data from large-scale cohort studies are scarce. This study aimed to examine the associations of egg and cholesterol intakes with mortality from all causes, cardiovascular disease (CVD), and other causes in a US population.

Methods and findings

Overall, 521,120 participants (aged 50–71 years, mean age = 62.2 years, 41.2% women, and 91.8% non-Hispanic white) were recruited from 6 states and 2 additional cities in the US between 1995 and 1996 and prospectively followed up until the end of 2011. Intakes of whole eggs, egg whites/substitutes, and cholesterol were assessed by a validated food frequency questionnaire. Cause-specific hazard models considering competing risks were used, with the lowest quintile of energy-adjusted intake (per 2,000 kcal per day) as the reference. There were 129,328 deaths including 38,747 deaths from CVD during a median follow-up of 16 years. Whole egg and cholesterol intakes were both positively associated with all-cause, CVD, and cancer mortality. In multivariable-adjusted models, the hazard ratios (95% confidence intervals) associated with each intake of an additional half of a whole egg per day were 1.07 (1.06–1.08) for all-cause mortality, 1.07 (1.06–1.09) for CVD mortality, and 1.07 (1.06–1.09) for cancer mortality. Each intake of an additional 300 mg of dietary cholesterol per day was associated with 19%, 16%, and 24% higher all-cause, CVD, and cancer mortality, respectively. Mediation models estimated that cholesterol intake contributed to 63.2% (95% CI 49.6%–75.0%), 62.3% (95% CI 39.5%–80.7%), and 49.6% (95% CI 31.9%–67.4%) of all-cause, CVD, and cancer mortality associated with whole egg consumption, respectively. Egg white/substitute consumers had lower all-cause mortality and mortality from stroke, cancer, respiratory disease, and Alzheimer disease compared with non-consumers. Hypothetically, replacing half a whole egg with equivalent amounts of egg whites/substitutes, poultry, fish, dairy products, or nuts/legumes was related to lower all-cause, CVD, cancer, and respiratory disease mortality. Study limitations include its observational nature, reliance on participant self-report, and residual confounding despite extensive adjustment for acknowledged dietary and lifestyle risk factors.

Conclusions

In this study, intakes of eggs and cholesterol were associated with higher all-cause, CVD, and cancer mortality. The increased mortality associated with egg consumption was largely influenced by cholesterol intake. Our findings suggest limiting cholesterol intake and replacing whole eggs with egg whites/substitutes or other alternative protein sources for facilitating cardiovascular health and long-term survival.

Author summary

Why was this study done?

- The 2015–2020 dietary guidelines for Americans recommend eating as little dietary cholesterol as possible while consuming a healthy eating pattern, but also state cholesterol is not a nutrient of concern for overconsumption.
- There is limited and inconclusive evidence on the associations of egg or dietary cholesterol intake with all-cause and cardiovascular disease mortality.
- Associations of egg or dietary cholesterol intake with mortality from non-cardiovascular causes.

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What did the researchers do and find?

- We used data on 521,120 participants from the NIH-AARP Diet and Health Study with a median follow-up of 16 years to assess the associations of egg and cholesterol intakes with all-cause and cause-specific mortality.
- Whole egg and cholesterol intakes were positively associated with risk of all-cause and major cause-specific mortality, whereas egg white/substitute consumption was inversely associated with mortality.
- Mediation models estimated that the increased mortality associated with whole egg intake was largely influenced by cholesterol intake.
- Replacing half a whole egg with egg whites/substitutes or other protein sources containing less cholesterol is associated with lower overall mortality and mortality from major causes, including cardiovascular disease, cancer, and respiratory disease.

What do these findings mean?

- The current recommendations for egg and dietary cholesterol intake from the US dietary guidelines might lead to increases in cholesterol intake, which could be detrimental to the prevention of premature death.
- Clinicians and policy makers should continue to highlight limiting cholesterol intake in the US dietary recommendations, considering our results.
- The US dietary guidelines may recommend replacing whole eggs with egg whites/substitutes or alternative protein sources for facilitating cardiovascular health and long-term survival.


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Data Availability: Data cannot be shared publicly because of the sensitive nature of the data collected for this study. Data are available from the US National Cancer Institute Division of Cancer Epidemiology & Genetics (contact via Linda M. Liao, e-mail: liaolm@mail.nih.gov) for researchers who meet the criteria for access to confidential data.

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Abbreviations:
AD, Alzheimer disease; BMI, body mass index; CI, confidence interval; CVD,
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Introduction

Eggs are a good source of high-quality protein, vitamins, and other bioactive nutrients such as lecithins and carotenoids [1], and are recommended as part of a healthy diet in the 2015–2020 US dietary guidelines [2]. However, many people do not consume eggs or egg yolks due to the high amount of cholesterol (approximately 186 mg cholesterol/egg), which might be a dietary risk factor for cardiovascular health [3]. Recently, such public concern has been intensified by a pooled study of 6 prospective US cohorts that linked egg and cholesterol consumption to higher risk of cardiovascular disease (CVD), CVD mortality, and all-cause mortality [4]. In the past decades, limiting dietary cholesterol intake to 300 mg/day was initially recommended for CVD prevention [5]. However, the most recent meta-analysis showed heterogeneous results about the relationship between dietary cholesterol and the risk of CVD death, coronary artery disease, and stroke [6]. Owing to the inadequate evidence, the American Heart Association and American College of Cardiology [7,8] and the 2015–2020 US dietary guidelines [2,9] have not carried forward the upper limit for dietary cholesterol. In addition, cholesterol often coexists with saturated fat and animal protein in foods [2]. The independent effect of cholesterol and the interaction between cholesterol and these nutrients on overall health have yet to be elucidated. With regard to eggs, previous observational studies reported inconsistent results, and most meta-analyses concluded there were not significant associations with CVD or all-cause mortality among the general population [10–14]. However, the studies included in these meta-analyses had relatively small sample sizes or few cases, which may not support robust effect estimates when examining the associations with mortality from various causes. Furthermore, whether the associations differ between whole eggs and egg whites/substitutes, and whether the associations are modified by cooking methods such as frying, remains unclear.

To fill these knowledge gaps, we assessed the associations of egg and dietary cholesterol intake with all-cause and cause-specific mortality in the NIH-AARP Diet and Health Study, which has a large number of participants \( n = 521,120 \) and death cases \( n = 129,328 \). We hypothesized that egg and cholesterol intakes would have significant associations with all-cause, CVD, and other cause-specific mortality.

Methods

Study population

The NIH-AARP study is a large prospective cohort initiated October 1995–May 1996 when a questionnaire was mailed to 3.5 million AARP (formerly the American Association of Retired Persons) members aged 50–71 years living in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 additional metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) [15]. The validated and comprehensive questionnaires covered a broad range of information, including demographics, lifestyle characteristics, and diet history. All participants provided written informed consent.

Among 567,169 participants who completed and returned satisfactory questionnaires at baseline, we excluded duplicate questionnaires, proxy responders, withdrawals, participants who moved out of the cancer registry...
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The final analytic cohort consisted of 521,120 participants (Fig A in S1 Data). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (see S1 STROBE Checklist).

Ethics statement

The study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

Dietary assessment

Dietary intake was measured using a validated food frequency questionnaire (FFQ) with 124 items developed as the Diet History Questionnaire (DHQ) by the National Cancer Institute [15, 16]. The FFQ inquired about the frequency of food and beverage consumption and portion sizes over the last year. The questionnaire asked the numbers of eggs consumed per day, week, month, or year. The participants were also asked to report the types of eggs (whole eggs, egg whites, or cholesterol-free commercial egg substitutes) and cooking methods for eggs (e.g., fried/sauteed in oil, poached, or boiled). The 1994-1996 USDA Continuing Survey of Food Intakes by Individuals [17] was used to convert frequency of consumption and portion size for each food item into intakes, including intakes of eggs, other foods, and dietary cholesterol. Red meat intake included all types of unprocessed (pork, beef, steak, liver, and hamburger) and processed red meat (bacon, hot dogs, cold cuts, ham, and sausage). Fish intake included all types of finfish and shellfish. Poultry intake included turkey, chicken, ground poultry, and the processed poultry components of turkey or chicken cold cuts. In validation studies, estimated correlation coefficients between true and FFQ-reported energy-adjusted intakes were higher than 0.5 for most of the food groups (0.7 in men and 0.6 in women for eggs) [16] and 0.7 for cholesterol [18]. Based on the 2015–2020 US dietary guidelines, the Healthy Eating Index–2015 (HEI-2015) score was used as previously described [19] to evaluate the adherence to an overall healthy dietary pattern.

Covariates

Information on lifestyle characteristics and potential confounders was collected at baseline (n = 567,169), including age, sex, race, marital status, household income, education, alcohol drinking, cigarette smoking, weight, height, physical activity, and history of hypertension, high blood cholesterol level, and chronic diseases [15]. Data on the use of cholesterol-lowering medications were collected in the resurvey (n = 293,918).

Death ascertainment

All the participants were followed for address changes via the US Postal Service National Change of Address database, responses to study-related mailings, and direct notifications from cohort members. Mortality data were obtained by linkage to the National Death Index Plus maintained by the National Center for Health Statistics. We used the codes of the International Classification of Diseases 9th and 10th revisions to classify cause-specific mortality into 22 categories (Table A in S1 Data). Person-years of follow-up was calculated from the return date of the baseline questionnaire to death or the end date of follow-up (31 December 2011).

Statistical analysis

The analysis plan was developed prospectively (S1 Text), with later adjustments, such as adding restricted-
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We built several models to estimate the changes in mortality risk for hypothetically replacing half an egg/day with equivalent amounts of egg whites/substitutes or alternative protein sources including poultry, fish, dairy products, and nuts/legumes. The substitution models simultaneously included these protein-rich foods as continuous variables, and total energy intake, other major food groups, and non-dietary covariates. The difference between regression coefficients and in variances and covariances was used to derive the HRs and 95% CIs of the substitution analyses.

In secondary analyses, we further separately analyzed the associations for fried eggs and non-fried eggs according to the cooking method, and the associations for egg whites and egg substitutes. Subgroup analyses were also performed according to important potential effect modifiers, and P values for interaction were computed by the likelihood ratio test. We also conducted sensitivity analyses by categorizing whole egg and cholesterol intakes by convenient consumption cutoffs, excluding participants who had extreme BMIs (<18.5 or >40 kg/m²); adjusting for perceived health condition; adjusting for a propensity score to further control potential residual confounding from measured variables; further adjusting for the use of vitamin supplements and aspirin; adjusting for processed meat consumption (processed red meat and processed white meat); adjusting for the use of cholesterol-lowering medications; excluding the initial 5 years of follow-up; excluding those who had CVD, cancer, or diabetes at baseline; or censoring participants at 8 years of follow-up.
Results

Egg and cholesterol intakes and baseline characteristics

The overall median intakes of whole eggs and cholesterol were 8 g/2,000 kcal/day and 208 mg/2,000 kcal/day, respectively. At baseline, participants with higher whole egg consumption had a higher BMI and lower household income. They were less educated, less physically active, more likely to smoke and have a high cholesterol level, and less likely to take aspirin. They also had higher red meat intake; lower intakes of fruit, dairy products, and sugar-sweetened beverages; and lower HEI-2015 score (Table 1). The characteristics of participants according to cholesterol and egg white/substitute consumption are shown in Tables B and C in S1 Data, respectively. The Spearman correlations between egg or cholesterol consumption and a range of dietary factors are shown in Table D in S1 Data.

All-cause mortality

During a mean follow-up of 16 years (7,307,097 person-years), overall 129,328 deaths occurred. Whole egg consumption was strongly associated with higher all-cause mortality in the age- and sex-adjusted model (model 1; \(P\) for trend < 0.001). The positive relationship remained significant after further adjusting for other demographic characteristics and dietary factors (models 2, 3, 5, and 6; \(P\) for trend < 0.001) but was not significant after further adjusting for cholesterol (model 4; \(P\) for trend = 0.64; Table 2). In contrast, egg white/substitute consumption was significantly associated with lower all-cause mortality in all models (all \(P\) trend < 0.001; Table E in S1 Data). Egg white/substitute consumers had a 7% (HR 0.93; 95% CI 0.91–0.95; \(P\) < 0.001) lower risk of all-cause mortality compared with non-consumers. Dietary cholesterol intake was positively associated with all-cause mortality in all models (all \(P\) trend < 0.001; Table 3), including the model adjusted for cholesterol-containing foods (model 3), non-cholesterol-containing foods (model 4), overall dietary pattern (model 5), and other nutrients (model 6). Each intake of an additional 300 mg of dietary cholesterol/day was associated with a 19% (HR 1.19; 95% CI 1.16–1.22; \(P\) < 0.001) higher risk of all-cause mortality (Fig 1; Table F in S1 Data). Each additional half a whole egg/day was associated with a 7% (HR 1.07; 95% CI 1.06–1.08; \(P\) < 0.001) higher risk of all-cause mortality. Restricted-cubic-spline regression profiles also show similar results for whole egg and cholesterol intakes (Fig B in S1 Data; not included in the prespecified analysis plan).
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Fig 1. Multivariable-adjusted HRs of all-cause and cause-specific mortality for whole egg, egg white/substitute, and cholesterol consumption.

Forest plots show the multivariable HRs of total and cause-specific mortality associated with each additional half a whole egg/day, egg white/substitute consumption (consumers versus non-consumers), or each additional 300 mg of cholesterol/day. HRs were adjusted for model 6 covariates for whole eggs, egg whites/substitutes, and cholesterol. Horizontal lines represent 95% CIs. CI, confidence interval; HR, hazard ratio.

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CVD mortality and cancer mortality

After multivariable adjustment, intakes of whole eggs and cholesterol were both positively associated with CVD mortality (both $P_{\text{trend}} < 0.001$), whereas the association for egg white/substitute consumption did not appear significant ($P_{\text{trend}} = 0.40$) (Tables 2 and 3; Table E in S1 Data). We observed similar associations with heart disease mortality (Table G in S1 Data). For stroke mortality, we found a positive association for whole egg consumption but inverse association for egg white/substitute consumption. With regard to cancer mortality, we also observed positive associations for the intakes of whole eggs and cholesterol ($P_{\text{for trend}} < 0.001$) and an inverse association for egg white/substitute consumption ($P_{\text{for trend}} = 0.005$). Each additional half a whole egg/day was associated with a 7% higher risk of CVD mortality and cancer mortality. Each intake of an additional 300 mg of dietary cholesterol/day was associated with a 16% and 24% higher risk of CVD mortality and cancer mortality, respectively (Fig 1; Table F in S1 Data). In the mediation analysis, we found that 63.2% (95% CI 49.6%–75.0%), 62.3% (95% CI 39.5%–80.7%), and 49.6% (95% CI 31.9%–67.4%) of increased all-cause, CVD, and cancer mortality associated with whole egg consumption was influenced by cholesterol intake, respectively (all $P < 0.001$; Table H in S1 Data; not included in the prespecified analysis plan).

Other cause-specific mortality

Whole egg and cholesterol intakes were associated with higher mortality from respiratory disease (RD) and diabetes, but with lower mortality from Alzheimer disease (AD) (Tables I and J in S1 Data). We also observed borderline positive associations between whole egg consumption and kidney disease mortality and between cholesterol intake and chronic liver disease mortality (both $P_{\text{for trend}} = 0.04$). Egg white/substitute consumers had lower RD, AD, and chronic liver disease mortality compared with non-consumers (Table K in S1 Data).

Substitution for whole eggs

In hypothetical substitution analyses, we found 6%, 8%, 9%, 7%, 13%, and 10% lower all-cause mortality when replacing half a whole egg (25 g/day) with equivalent amounts of egg whites/substitutes, poultry, fish, dairy products, nuts, and legumes, respectively (Fig 2). Replacing half a whole egg with an equivalent amount of egg whites/substitutes was associated with reductions of 3% in CVD mortality, 8% in cancer mortality, and 20% in RD mortality. Similarly, substituting an equivalent amount of nuts or legumes for half a whole egg was related to 9%–35% lower mortality from CVD, cancer, and RD. We also found significant changes in CVD, cancer, and RD mortality when replacing half a whole egg with an equivalent amount of poultry, fish, or dairy products.
Fig 2. Multivariable-adjusted hazard ratios of all-cause and cause-specific mortality by replacing 1 whole egg—
with equivalent amounts of other protein sources.

Forest plots show the multivariable HRs of (A) total, (B) CVD, (C) cancer, (D) respiratory disease, (E)
Alzheimer disease, and (F) diabetes mortality associated with replacing half a whole egg/day with an
equivalent amount of egg whites/substitutes, poultry, fish, dairy products, nuts, or legumes. HRs were adjusted
for age; sex; BMI; race; education; marital status; household income; smoking; alcohol; vigorous physical
activity; usual activity at work; history of hypertension, hypercholesteremia, heart disease, stroke, diabetes,
and cancer at baseline; total energy intake; and intakes of fruit, vegetables, potatoes, whole grains, refined
grains, coffee, and sugar-sweetened beverages. Horizontal lines represent 95% CIs. CI, confidence interval;
CVD, cardiovascular disease; HR, hazard ratio.

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Subgroup analyses

In the secondary analysis of egg cooking method, we found similar positive associations with all-cause, CVD,
cancer, and RD mortality for fried egg and non-fried egg consumption (Table L in S1 Data). In the subgroup
analyses, although the associations of whole egg and cholesterol consumption with higher all-cause mortality
persisted in all the subgroups, the positive associations were stronger among men, non-obese participants,
never/former smokers, alcohol drinkers, non-hypertensive participants, non-diabetic participants, those with
higher saturated fat intake, and those with longer duration of follow-up (Table 4).

Sensitivity analyses

We observed similar associations when we further categorized the whole egg and cholesterol intakes by
convenient consumption cutoffs (Tables M and N in S1 Data), excluded participants with extreme BMIs, or
further adjusted for perceived health condition, a propensity score, the use of vitamin supplements and
aspirin, or processed meat (Tables O–S in S1 Data). We also found largely unchanged associations when we
further adjusted for the use of cholesterol-lowering medications; excluded the first 5 years of follow-up;
excluded participants with CVD, cancer, or diabetes at baseline; or censored participants at 8 years of follow-
up (Tables T–W in S1 Data).

Discussion

We comprehensively examined the consumption of eggs and cholesterol in relation to mortality from different
causes in 521,120 participants with a mean follow-up of 16 years. In this large cohort, we showed that whole
egg and cholesterol consumption were both associated with higher all-cause, CVD, and major cause-specific
mortality, whereas egg white/substitute consumption was related to lower mortality. The increased all-cause,
CVD, and cancer mortality associated with egg consumption was largely influenced by cholesterol intake. Egg
white/substitute consumption was related to lower mortality. Replacing whole eggs with an equivalent amount
of egg whites/substitutes or alternative protein sources was associated with lower overall mortality and
mortality from CVD, cancer, and RD.

Evidence regarding egg consumption in relation to CVD or mortality has been limited and inconclusive
[10–12]. Recent meta-analyses showed that frequent egg consumption (>7 eggs/week) compared to low
consumption (<1 egg/week) was not significantly associated with higher all-cause mortality, due to seemingly
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Our findings are consistent with a recent joint study of 6 prospective US cohorts ($n = 29,615$) reporting that each additional half an egg/day was associated with 6%, 8%, and 8% higher risk of incident CVD, CVD mortality, and all-cause mortality, respectively [4]. Meanwhile, we reported a similar pattern for the associations for fried and non-fried egg consumption and found an inverse association of egg white/substitute consumption with mortality, underscoring the adverse role of egg yolk or cholesterol in premature deaths. These consistent results were further supported by our mediation model analyses, indicating that the associations of whole egg consumption with higher all-cause and CVD mortality were largely influenced by the cholesterol content. We also observed reductions in all-cause and major cause-specific mortality when replacing eggs with other alternative protein sources such as dairy, nuts, and legumes. Our results from the substitution analysis also suggested that meat containing less cholesterol was comparatively healthier than eggs, which is in line with the recent joint study, showing positive relationships between dietary cholesterol and all-cause and CVD mortality [4]. Correspondingly, avoiding 200 mg of dietary cholesterol per day decreased blood total cholesterol levels by 0.13 mmol/l and low-density lipoprotein cholesterol (LDL-c) levels by 0.10 mmol/l [32], although dietary cholesterol was not shown to significantly change serum triglyceride or very-low-density lipoprotein concentrations [6]. We observed that the positive associations were slightly weakened after adjusting for high blood cholesterol, which indicated high blood cholesterol might at least in part contribute to the adverse associations for egg/cholesterol. The latest meta-analysis summarizing results from 17 randomized controlled trials (RCTs) showed that egg consumption increased LDL-c and LDL-c/high-density lipoprotein cholesterol (HDL-c) ratio among healthy populations [33]. In addition, evidence from Mendelian randomization studies and RCTs of LDL-lowering therapies consistently demonstrate that any mechanism of lowering LDL-c levels decreases the risk of atherosclerotic CVD, suggesting a causal role of LDL-c in atherosclerotic CVD development [34]. Together, accumulating evidence support the hypercholesterolemic effect (high LDL-c) as the biological mechanism for the effect of egg consumption and dietary cholesterol on CVD. The latest science advisory from the American Heart Association, developed after a review of human studies, highlighted that it remained advisable to limit cholesterol intake to current levels and that healthy individuals could include up to 1 whole egg per day [35]. Collectively, our findings strengthen the significance of minimizing dietary cholesterol intake among general populations for the management of cardiovascular health, and more clinical trials are warranted to collaborate our findings [36].

Regarding other cause-specific mortality, we found associations of whole egg and cholesterol consumption with higher cancer mortality. Dietary cholesterol has been reported to increase the incidence of breast and pancreatic cancers [37,38], while egg consumption is related to higher incidence of ovarian cancer [39]. For putative mechanisms, elevated total cholesterol and LDL-c levels have been linked with increased levels of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α [40]. In animal models, cholesterol may increase the generation of secondary bile acids and enhance cancer incidence [41,42]. Our finding of positive associations of whole egg and cholesterol intakes with diabetes mortality was consistent with a previous meta-analysis reporting higher risk of diabetes for those eating ≥3 eggs/week in US populations [43]. In addition, we detected adverse associations with risk of death from RD. A cross-sectional study reported that serum cholesterol level was positively associated with airway resistance in patients with chronic obstructive pulmonary disease [44]. In a murine model of asthma, dietary cholesterol enhanced pulmonary allergic inflammation [45]. Interestingly, we detected inverse associations of egg and cholesterol intakes with AD mortality, which was in accordance with the Spanish European Prospective Investigation into Cancer and
Nutrition showing an inverse relationship between egg consumption and risk of death from nervous system causes [46]. Moderate egg consumption may have beneficial effects on certain areas of cognitive performance [47]. The protective effect on neurodegenerative diseases is potentially related to the content of dietary choline [48], zeaxanthin, and lutein [49], which may be beneficial to cognitive performance across the lifespan [50]. Excess cholesterol intake appears to be one of the main factors for the development of nonalcoholic fatty liver disease [51], which was supported by our current study showing a positive relationship between cholesterol intake and chronic liver disease mortality. Moreover, we detected associations of egg white/substitute consumption with lower stroke, cancer, RD, AD, and all-cause mortality, supporting that egg substitute intake instead of whole egg or egg yolk consumption should be encouraged for overall health [52].

Our subgroup analyses showed that the positive associations of whole egg and cholesterol consumption with mortality remained significant among all subgroups, including participants with a higher or lower quality diet, healthy participants, and those with a history of hypertension, high cholesterol level, CVD, cancer, or diabetes, although previous studies suggested the harmful effect of egg consumption might be restricted to diabetic patients [12,14]. The interaction between sex and egg/cholesterol intake on mortality could be due to sex dimorphisms in cholesterol catabolism and modulation [53]. Although alcohol drinkers are known to have higher HDL-c and lower LDL-c compared with non-drinkers [54], our results showed more pronounced positive associations of egg/cholesterol intake with mortality among alcohol drinkers. Smoking has been evidenced to exacerbate the effect of cholesterol on CVD risk [55]. However, we found slightly stronger positive associations among non-smokers. Future research is needed to verify and elucidate these observed interactions. We noted that a few associations, such as for CVD and diabetes mortality, appeared stronger for non-fried eggs compared with fried eggs, which may be due to the type of fat used for frying [24]. For example, plant-sourced cooking oil consumption has been linked with lower risk of mortality in a nationwide cohort study [56].

The current investigation is to our knowledge the largest cohort study on this topic, with a large number of deaths from various causes and long-term follow-up with a high follow-up rate (>99%). In addition, when we excluded the first 5 years of follow-up or patients with major chronic diseases at baseline, the associations did not change materially, indicating the robustness of our results, with minimized reverse causality. Several limitations should also be noted. First, measurement errors of egg and cholesterol intakes assessed through postal surveys were inevitable despite our using a validated FFQ. However, such errors could have diluted real associations of egg and cholesterol intakes with mortality owing to the prospective study design. Second, egg and cholesterol intakes were assessed at baseline and could have potentially changed during the long-term follow-up. However, this might not appreciably affect our results because we detected similar associations when censoring participants at a shorter duration (8 years) of follow-up. Third, we could not specifically analyze the mediation of egg-sourced cholesterol for eggs due to the perfect correlation between egg-sourced cholesterol and eggs. Fourth, findings from this study might not be generalizable to non-US populations due to different nutrition and dietary patterns and different prevalence of chronic diseases. In addition, despite extensive adjustment for acknowledged diet and lifestyle risk factors, we cannot exclude the possibility of residual confounding from other unmeasured confounders. Lastly, a causal relationship cannot be established, given the study’s observational nature.

Conclusions

Among the US population, intakes of whole egg and cholesterol were associated with higher all-cause mortality and mortality from major causes including CVD, cancer, RD, and diabetes. Dietary cholesterol intake largely influenced all-cause, CVD, and cancer mortality associated with whole egg consumption. Replacing whole eggs with equivalent amounts of egg whites/substitutes or alternative protein sources was associated with lower all-cause, CVD, and major cause-specific mortality. Our findings support limiting cholesterol intake and suggest replacing whole eggs with egg whites/substitutes or other alternative protein sources for facilitating long-term survival and health. The 2015-2020 US dietary guidelines recommend eggs as part of a
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