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Dietary cholesterol and egg intake in relation to incident cardiovascular disease and all-cause and cause-specific mortality in postmenopausal women

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ABSTRACT

Background: The potential cardiovascular impact of dietary cholesterol intake has been actively debated for decades.

Objectives: We aimed to evaluate associations of dietary cholesterol and egg intakes with incident cardiovascular disease (CVD) and all-cause and cause-specific mortality.

Methods: We included 96,831 US postmenopausal women aged 50–79 y without known CVD or cancer during baseline enrollment (1993–1998) of the Women's Health Initiative. Dietary information was collected using a validated FFQ. Incident CVD [i.e., ischemic heart disease (IHD) and stroke] and all-cause and cause-specific mortality were ascertained and adjudicated through February 2018.

Results: A total of 9808 incident CVD cases and 19,508 all-cause deaths occurred during a median follow-up of 17.8 y and 18.9 y, respectively. After multivariable adjustment for traditional risk factors and key dietary nutrients including dietary saturated fat, there were modest associations of dietary cholesterol intake with incident CVD (HR$_{Q5versusQ1}$: 1.12; 95% CI: 1.03, 1.21; P-trend < 0.001) and all-cause mortality (HR$_{Q5versusQ1}$: 1.09; 95% CI: 1.02, 1.15; P-trend < 0.001). Significant positive associations were also observed between dietary cholesterol and incident IHD (P-trend = 0.007), incident ischemic stroke (P-trend = 0.002), and CVD mortality (P-trend = 0.002), whereas there was an inverse association for incident hemorrhagic stroke (P-trend = 0.037) and no association for mortality from cancer, Alzheimer disease/dementia, respiratory diseases, or other causes (P-trend > 0.05). Higher egg consumption was also associated with modestly higher risk of incident CVD (P-trend = 0.004) and all-cause mortality (P-trend < 0.001), with

HRs of 1.14 (95% CI: 1.04, 1.25) and 1.14 (95% CI: 1.07, 1.22), respectively, when comparing ≥1 egg/d with <1 egg/wk.

Conclusions: Both higher dietary cholesterol intake and higher egg consumption appeared to be associated with modestly elevated risk of incident CVD and all-cause mortality in US postmenopausal women. *Am J Clin Nutr* 2021;113:948–959.

Keywords: cardiovascular disease, cholesterol, diet, eggs, postmenopausal women

Introduction

The potential cardiovascular impact of dietary cholesterol intake has been actively debated for decades. Accumulative evidence from randomized dietary intervention trials has suggested that increasing intake of dietary cholesterol may increase serum LDL cholesterol (1), an established risk factor for atherosclerotic cardiovascular disease (CVD) (2). However, such increases in LDL cholesterol are typically modest and may be accomplished by increases in HDL cholesterol without meaningful changes in the ratio of LDL to HDL cholesterol (3). Thus, the clinical relevance of possible changes in lipid profile–associated dietary cholesterol remains unclear. Findings from large cohort studies of dietary cholesterol and long-term risk of CVD have been limited and heterogeneous (4).

Eggs are a relatively inexpensive source of high-quality protein and other nutrients, but also a major contributor to dietary cholesterol. The most up-to-date meta-analyses of

prospective cohort studies have found no association between egg consumption and risk of total CVD (5), but instead suggested a possible inverse association between egg consumption and risk of stroke (6). Given the limited evidence supportive of a detrimental association between dietary cholesterol or egg consumption and risk of CVD, the 2015–2020 Dietary Guidelines for Americans no longer listed dietary cholesterol as a "nutrient of concern" (7). Nevertheless, the Guidelines still advised that individuals should eat dietary cholesterol as little as possible while building a healthy eating pattern.

In this context, recent findings from a pooled analysis of 6 US cohorts triggered a call for reconsideration of dietary cholesterol restriction (8, 9). In this analysis including 29,615 US participants (9), it was reported that higher dietary cholesterol intake and higher egg consumption were both associated with modestly elevated risk of CVD and all-cause mortality in a linear dose-response manner. A clearer understanding of any excess disease risk associated with dietary cholesterol intake or egg consumption is highly relevant for dietary recommendations and has significant public health implications. Therefore, we examined associations of dietary cholesterol and egg consumption with incident CVD and all-cause and cause-specific mortality in the Women's Health Initiative (WHI) (10), a large prospective study of US postmenopausal women.

Methods

Study design and population

Details of the WHI design and study population have been reported elsewhere (10). Briefly, between 1993 and 1998, 161,808 women aged 50–79 y were recruited at 40 clinical centers throughout the United States. Participants were either enrolled in the WHI Observational Study (OS) or in ≥1 of the WHI Clinical Trials (CT) that evaluated the health effects of hormone therapy (2 trials), low-fat dietary modification, and calcium and vitamin D supplementation. At the end of the initial WHI study in 2005, the first (2005–2010) and second (2010–2020) WHI Extension Studies continued follow-up of all women who consented. The study was approved by the institutional review boards of all

participating institutions, and all participants provided written informed consent.

Dietary assessment

Information on dietary intake at baseline was collected using a self-administered FFQ adapted from the Block FFQ (11, 12). Questions were added to make the WHI FFQ more sensitive to dietary fat intake. This instrument included 122 composite and single food line items for participants to denote their habitual diets over the past 3 mo. The WHI-FFQ nutrient database was derived from the University of Minnesota Nutrition Coordinating Center food and nutrient database (13), which provides information for >140 nutrients and compounds including dietary cholesterol. Previous validations against 4-d food records and 4 24-h dietary recalls showed that reliable dietary estimates were recorded by the FFQ (11). For example, energy-adjusted Pearson partial correlation coefficients between estimates by the FFQ and those by dietary recalls/food records were 0.49 for dietary cholesterol, 0.58 for total fat, 0.56 for saturated fat, and 0.65 for dietary fiber, with a mean of 0.49 across all assessed major nutrients (11). Using the MyPyramid Equivalents Database, version 2.0 (14), dietary data in units of MyPyramid equivalents were also constructed by translating frequency of food consumption into standardized food quantities. For example, 1 MyPyramid equivalent of egg (including both full egg and egg as ingredients) is an amount equal to 1 oz. equivalent of cooked lean meat, or a large whole egg (14).

Outcome ascertainment

The primary outcomes of interest were all-cause mortality and composite CVD including ischemic heart disease (IHD) and stroke. IHD included possible or definite coronary death, nonfatal myocardial infarction, or coronary revascularization. Stroke included ischemic or hemorrhagic stroke or death due to a cerebrovascular event. Participants were followed up (through 28 February, 2018) semiannually in the WHI CT and annually in the OS using in-person, mailed, or telephone questionnaires to collect information on clinical outcomes. Deaths were ascertained by reviewing death certificates, medical records, or autopsy reports, or by linkage to the National Death Index. Adjudications of CVD and death outcomes have been described in detail previously (15).

Assessment of covariates

Information on demographic characteristics, reproductive and medical histories, exogenous hormone use, family history, smoking, and alcohol drinking was collected at baseline via self-report. Blood pressure including systolic blood pressure (SBP) and diastolic blood pressure (DBP) and anthropometric measures such as weight, height, and waist circumference were measured by trained staff using standard procedures (16). BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Information on previous diagnosis and treatment of hypertension, hyperlipidemia, or diabetes by a physician was collected via questionnaire. Participants were also instructed to bring prescription medication containers during the baseline screening interview. Hypertension was defined as SBP/DBP ≥ 140/90 mm Hg or a self-reported physician's

diagnosis or use of antihypertensive mediations. Dyslipidemia was defined as self-reported hyperlipidemia or recorded statin use. Physical activity was measured using the WHI physical activity questionnaire and the data were summarized in metabolic equivalent (MET)-h/wk (17).

Statistical analysis

Our current analysis considered only participants within the WHO OS or control arms of the WHI CT because all interventions in the WHI CT may lead to subsequent changes in dietary habits and/or blood lipids (18, 19). The following exclusions were applied: *1*) presence of major CVD, heart failure, or cancer at baseline ($n = 18,666$); *2*) missing dietary data ($n = 137$), or extreme values for dietary energy (>5000 or <600 kcal/d; $n = 3189$), dietary cholesterol (>1000 mg/d; $n = 178$), or eggs (>3 eggs/d; $n = 69$); and *3*) participants missing follow-up ($n = 465$), or cases of CVD or death that occurred within the first year of follow-up ($n = 656$). After these exclusions, 96,831 participants remained in the analyses (**Supplemental Figure 1**).

Owing to the substantial correlation between dietary cholesterol and energy intake ($r = 0.72$), energy-adjusted dietary cholesterol (mg · 1000 kcal^{-1} · d^{-1}) was calculated and used in the analyses (20). We created 5 convenient intake categories for eggs based on weekly frequency of consumption (<1, 1 to <2, 2 to <3, 3 to <7, and ≥7 eggs/wk). Baseline characteristics of participants were described by quintile of dietary cholesterol or categories of egg intake. Pearson partial correlation coefficients between dietary cholesterol and egg intakes and intakes of 9 other major food groups and 7 nutrients were calculated, with adjustment for age, region, race/ethnicity, study group, and total energy intake.

We used Cox proportional hazards models to estimate HRs and 95% CIs of CVD or mortality associated with dietary cholesterol or egg intake. Person-time of follow-up was counted from date of enrollment through date of diagnosis of CVD (for incident CVD), date of death, date of not consenting to the Extension Studies, or date of the end of follow-up, whichever came first. Four Cox models were constructed. Model 1 was adjusted for demographic factors (i.e., age, region, and race/ethnicity), study group, and socioeconomic status (i.e., education, family income, and health insurance). Model 2 was further adjusted for lifestyle behaviors (i.e., smoking status, pack-years of smoking, alcohol consumption, reason for quitting smoking or drinking, recreational physical activity, and frequency of using fat to deep fry/pan fry/sauté), medication use [i.e., aspirin use, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and hormone use], self-rated health status, and total energy intake. Model 3 was further adjusted for diabetes, antihypertensive drug use, SBP, DBP, dyslipidemia, and waist circumference. We used waist circumference as an indicator of adiposity because it has been shown to be more predictive of mortality than BMI in the WHI (21) and many other population studies (22). The full model (model 4) further included 7 key nutrients for the analysis of dietary cholesterol or 9 major food groups for the analysis of egg consumption.

We used restricted cubic splines to examine potential nonlinear relations between dietary cholesterol or egg intake and risk of CVD and all-cause mortality, with 3 knots at the 10th, 50th, and 90th percentiles of the intake distribution. We stratified

analyses and tested interactions between dietary cholesterol (per 100 mg · 1000 kcal^{-1} · d^{-1}) or egg intake (per 0.5 eggs/d) and various demographic, dietary, and lifestyle factors and medical histories on incident CVD or all-cause mortality. For cause-specific mortality, we repeated the analyses by excluding other deaths that were not the outcome of interest because death events may have occurred competingly with each other (9). All statistical analyses were performed using Stata version 15.1 (StataCorp).

Results

Participant characteristics

Median dietary cholesterol intake was 120.9 (IQR: 94.3–153.7) mg · 1000 kcal^{-1} · d^{-1} and median egg intake was 1.3 (IQR: 0.6–2.6) eggs/wk. Baseline participant characteristics by quintiles of dietary cholesterol intake or categories of egg intake are reported in **Table 1** and **Supplemental Table 1**, respectively. Participants with higher dietary cholesterol intake were less likely to be white, had lower levels of education and family income, and a lower rate of health insurance coverage. Higher dietary cholesterol intake was also associated with current smoking, lower levels of physical activity and diet-quality score, and higher BMI, waist circumference, and total energy intake. Furthermore, participants with higher dietary cholesterol intake were more likely to have diabetes and hypertension and to use NSAIDs, but were less likely to have dyslipidemia or to use aspirin or hormones. Distributions of baseline participant characteristics according to categories of egg intake were similar to those according to quintiles of dietary cholesterol (Supplemental Table 1).

Supplemental Figure 2 presents Pearson partial correlation coefficients between intakes of dietary cholesterol and eggs and intakes of 9 other major food groups and 7 nutrients. Correlation between dietary cholesterol and egg consumption was substantial ($r = 0.80$). Dietary cholesterol was moderately and positively correlated with intakes of red and processed meat ($r = 0.35$), organ meat ($r = 0.25$), saturated fat ($r = 0.48$), animal protein ($r = 0.46$), and monounsaturated fat ($r = 0.40$), and was inversely correlated with intakes of fruit and vegetables ($r = -0.22$), whole grains ($r = -0.22$), and dietary fiber ($r = -0.36$).

Dietary cholesterol and incident CVD and mortality

During a median follow-up of 17.8 y, 9808 incident cases of CVD were identified, including 7091 IHD, 2430 ischemic stroke, and 535 hemorrhagic stroke cases. As **Table 2** shows, after full adjustment for potential confounders including key dietary nutrients, higher dietary cholesterol intake was associated with modestly higher risk of CVD (HR$_{Q5versusQ1}$: 1.12; 95% CI: 1.03, 1.21; *P*-trend < 0.001). Higher dietary cholesterol intake was also associated with higher risk of IHD (*P*-trend = 0.007) and ischemic stroke (*P*-trend = 0.002) in the fully adjusted model. Conversely, there was a significant inverse association between dietary cholesterol and risk of hemorrhagic stroke (*P*-trend = 0.037) (Table 2). When cases of hemorrhagic stroke were censored, HRs across quintiles of dietary cholesterol were 1.00, 1.04, 1.07, 1.12, and 1.17 (95% CI: 1.07, 1.27) for incident atherosclerotic CVD (i.e., IHD and ischemic stroke) (*P*-trend < 0.001).

TABLE 1 Baseline participant characteristics according to quintile of dietary cholesterol intake in the Women's Health Initiative[1]

	Dietary cholesterol intake				
	Q1	Q2	Q3	Q4	Q5
Median (range), mg · 1000 kcal^{-1} · d^{-1}	73.1 (3.4–88.1)	100.0 (88.2–110.4)	120.9 (110.5–132.2)	145.4 (132.3–163.4)	193.2 (163.5–722.3)
Participants, n	19,366	19,366	19,366	19,366	19,367
Age, y	63.3 ± 7.4	63.1 ± 7.2	62.9 ± 7.2	62.8 ± 7.2	63.0 ± 7.1
Race/ethnicity, %					
White	86.0	85.8	85.2	82.3	78.9
Black/African American	6.6	6.6	7.2	8.3	10.9
Hispanic/Latino	3.0	3.2	3.4	4.0	5.0
Other/unknown	4.4	4.3	4.2	4.9	5.2
Education ≥ college degree, %	48.6	45.0	41.3	40.2	36.0
Family income ≥$50,000/y, %	46.2	45.3	43.7	42.6	37.5
Any health insurance, %	97.0	97.1	96.5	96.0	94.2
Current smoker, %	3.9	5.1	6.0	7.2	9.6
Moderate drinker (0.5–1.0 drink/d), %	8.8	9.9	10.3	10.1	9.0
Recreational PA, MET-h/wk	16.6 ± 15.7	13.7 ± 13.8	12.5 ± 13.3	11.9 ± 13.1	11.0 ± 13.0
Diabetes, %	3.0	3.6	4.2	5.4	7.8
Hypertension, %	34.0	35.7	37.0	38.7	40.6
Dyslipidemia, %	16.8	13.9	13.0	11.7	10.6
Aspirin use, %	23.5	22.0	21.9	20.6	19.3
NSAID use, %	16.2	19.1	19.2	19.8	19.8
Current hormone use, %	45.7	47.2	46.2	45.5	42.9
BMI, kg/m^2	25.7 ± 5.1	26.8 ± 5.3	27.5 ± 5.6	28.3 ± 6.0	29.1 ± 60.4
Waist circumference, cm	81.1 ± 12.2	83.6 ± 12.6	85.3 ± 13.1	87.1 ± 13.8	89.2 ± 14.6
Very good/excellent health (self-rated), %	67.7	64.1	61.3	58.4	54.0
Fry/sauté foods ≥3/wk, %	11.0	14.5	17.9	20.0	21.6
Total energy intake, kcal/d	1495 ± 542	1597 ± 586	1657 ± 628	1691 ± 660	1620 ± 654
Diet quality score (AHEI-2010)	56.8 ± 10.4	53.8 ± 10.2	52.1 ± 10.2	50.9 ± 10.1	50.3 ± 10.1
Food groups (daily)					
Eggs, oz equivalents[2]	0.08 ± 0.08	0.15 ± 0.11	0.23 ± 0.16	0.35 ± 0.23	0.71 ± 0.40
Fruit and vegetables,[2] cup equivalents	3.09 ± 1.48	2.74 ± 1.32	2.60 ± 1.27	2.48 ± 1.22	2.26 ± 1.19
Whole grain,[2] oz. equivalents	1.55 ± 1.20	1.31 ± 1.00	1.21 ± 0.94	1.09 ± 0.88	0.95 ± 0.81
Refined grain,[2] oz. equivalents	3.66 ± 2.23	3.82 ± 2.15	3.86 ± 2.11	3.87 ± 2.14	3.54 ± 2.03
Potatoes,[2] cup equivalents	0.23 ± 0.20	0.26 ± 0.21	0.28 ± 0.22	0.29 ± 0.23	0.27 ± 0.23
Fish and shellfish,[2] oz. equivalents	0.46 ± 0.45	0.57 ± 0.51	0.64 ± 0.57	0.69 ± 0.62	0.72 ± 0.73
Red meat,[2] oz. equivalents	0.67 ± 0.60	1.20 ± 0.90	1.57 ± 1.15	1.89 ± 1.41	2.00 ± 1.64
Processed meat,[2] oz. equivalents	0.21 ± 0.31	0.35 ± 0.42	0.44 ± 0.50	0.50 ± 0.55	0.51 ± 0.60
Organ meat,[2] oz. equivalents	0.01 ± 0.03	0.01 ± 0.05	0.02 ± 0.07	0.04 ± 0.10	0.08 ± 0.19
Coffee and tea,[3] cups	2.01 ± 1.72	2.12 ± 1.71	2.17 ± 1.76	2.18 ± 1.76	2.13 ± 1.80
Soft drinks and fruit juices,[3] glasses	0.90 ± 1.02	0.85 ± 0.91	0.81 ± 0.85	0.78 ± 0.81	0.71 ± 0.76
Nutrients (daily)					
Dietary fiber, g/1000 kcal	13.2 ± 4.2	11.0 ± 3.3	10.1 ± 3.1	9.4 ± 2.9	8.8 ± 3.0
Saturated fat, % energy	7.5 ± 2.4	9.6 ± 2.5	10.9 ± 2.8	11.8 ± 3.0	12.6 ± 3.3
Polyunsaturated fat, % energy	5.8 ± 2.2	6.4 ± 2.1	6.7 ± 2.1	6.9 ± 2.0	7.2 ± 2.1
Monounsaturated fat, % energy	9.4 ± 3.5	11.2 ± 3.2	12.2 ± 3.1	13.0 ± 3.0	13.9 ± 3.1
Trans fat, % energy	1.8 ± 1.2	2.1 ± 1.1	2.3 ± 1.1	2.4 ± 1.0	2.4 ± 1.0
Animal protein, % energy	9.1 ± 3.2	10.9 ± 2.8	11.9 ± 2.8	12.7 ± 3.0	13.7 ± 3.5
Sodium, mg/1000 kcal	1650 ± 335	1668 ± 293	1679 ± 281	1693 ± 274	1707 ± 280

[1]n = 96,831. AHEI, Alternate Healthy Eating Index; MET, metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drug; oz., ounce; PA, physical activity; Q, quintile.

[2]Definitions and determination of what counts as 1 equivalent of food groups can be found at: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/mped/mped2_doc.pdf.

[3]One cup of coffee or tea was 8 fluid oz. (or 236.6 mL), 1 glass of fruit juice was 6 fluid oz. (or 177.4 mL), and 1 glass of soft drink was 12 fluid oz. (or 354.9 mL).

In total, 19,508 all-cause deaths were identified during a median 18.9 y of follow-up, including 5589 CVD deaths, 6228 cancer deaths, 1319 deaths from Alzheimer disease (AD)/dementia, 1448 deaths from respiratory diseases, and 4924 deaths from other causes. As **Table 3** shows, higher dietary cholesterol intake was associated with modestly higher risk of all-cause mortality after the full adjustment (HR$_{Q5versusQ1}$: 1.09; 95% CI: 1.02, 1.15; *P*-trend < 0.001). A significant positive association was also observed between dietary cholesterol and CVD mortality (*P*-trend = 0.002). After multivariable adjustment without adjusting for other dietary nutrients (model

3), dietary cholesterol was not associated with AD/dementia mortality, but was significantly associated with higher risk of cancer, respiratory, and other mortality. However, all these significant associations for non-CVD mortality were no longer significant after the full adjustment (all *P*-trend values > 0.05) (Table 3), with the association for respiratory mortality being most apparently attenuated. Therefore, we performed post hoc analyses with adjustment for dietary nutrients individually, and found that adjustment for saturated fat led to the greatest attenuation of the associations for non-CVD mortality (**Figure 1**).

TABLE 2 Association between dietary cholesterol intake and incident CVD in the WHI[1]

	Dietary cholesterol intake						
	Q1	Q2	Q3	Q4	Q5	P-trend	Per 100 mg · 1000 kcal⁻¹ · d⁻¹
Median (range), mg · 1000 kcal⁻¹ · d⁻¹	73.1 (3.4–88.1)	100.0 (88.2–110.4)	120.9 (110.5–132.2)	145.4 (132.3–163.4)	193.2 (163.5–722.3)		
Participants, n	19,366	19,366	19,366	19,366	19,367		
All CVD							
Cases, n	1769	1884	1925	2061	2169		
Model 1, HR (95% CI)	Reference	1.05 (0.98, 1.12)	1.07 (1.01, 1.15)	1.17 (1.10, 1.25)	1.23 (1.16, 1.32)	<0.001	1.16 (1.12, 1.20)
Model 2, HR (95% CI)	Reference	1.03 (0.96, 1.10)	1.05 (0.98, 1.12)	1.12 (1.05, 1.20)	1.15 (1.08, 1.23)	<0.001	1.11 (1.07, 1.15)
Model 3, HR (95% CI)	Reference	1.03 (0.96, 1.09)	1.02 (0.96, 1.09)	1.07 (1.00, 1.15)	1.08 (1.02, 1.16)	0.004	1.07 (1.03, 1.11)
Model 4, HR (95% CI)	Reference	1.03 (0.96, 1.10)	1.04 (0.96, 1.12)	1.10 (1.02, 1.19)	1.12 (1.03, 1.21)	<0.001	1.09 (1.04, 1.15)
IHD							
Cases, n	1277	1352	1364	1511	1587		
Model 1, HR (95% CI)	Reference	1.04 (0.96, 1.12)	1.05 (0.97, 1.13)	1.18 (1.09, 1.27)	1.24 (1.15, 1.34)	<0.001	1.17 (1.12, 1.22)
Model 2, HR (95% CI)	Reference	1.02 (0.95, 1.10)	1.02 (0.94, 1.10)	1.13 (1.05, 1.23)	1.16 (1.07, 1.25)	<0.001	1.12 (1.07, 1.17)
Model 3, HR (95% CI)	Reference	1.01 (0.93, 1.09)	1.00 (0.92, 1.08)	1.08 (1.00, 1.17)	1.09 (1.01, 1.17)	0.008	1.07 (1.02, 1.12)
Model 4, HR (95% CI)	Reference	1.01 (0.93, 1.10)	1.01 (0.93, 1.10)	1.10 (1.01, 1.21)	1.11 (1.01, 1.23)	0.007	1.09 (1.03, 1.16)
Ischemic stroke							
Cases, n	414	460	521	471	564		
Model 1, HR (95% CI)	Reference	1.10 (0.96, 1.25)	1.25 (1.10, 1.43)	1.15 (1.01, 1.31)	1.38 (1.21, 1.57)	<0.001	1.20 (1.12, 1.29)
Model 2, HR (95% CI)	Reference	1.08 (0.94, 1.23)	1.22 (1.07, 1.39)	1.10 (0.97, 1.26)	1.30 (1.14, 1.48)	<0.001	1.16 (1.07, 1.25)
Model 3, HR (95% CI)	Reference	1.06 (0.93, 1.21)	1.19 (1.04, 1.36)	1.05 (0.92, 1.21)	1.22 (1.07, 1.39)	0.011	1.11 (1.03, 1.20)
Model 4, HR (95% CI)	Reference	1.10 (0.95, 1.26)	1.26 (1.09, 1.46)	1.13 (0.97, 1.33)	1.34 (1.14, 1.59)	0.002	1.18 (1.07, 1.30)
Hemorrhagic stroke							
Cases, n	115	116	106	105	94		
Model 1, HR (95% CI)	Reference	0.99 (0.77, 1.29)	0.90 (0.69, 1.18)	0.92 (0.70, 1.20)	0.82 (0.62, 1.09)	0.14	0.91 (0.76, 1.08)
Model 2, HR (95% CI)	Reference	0.98 (0.76, 1.27)	0.89 (0.68, 1.16)	0.89 (0.68, 1.17)	0.77 (0.58, 1.02)	0.051	0.87 (0.73, 1.03)
Model 3, HR (95% CI)	Reference	0.98 (0.76, 1.27)	0.88 (0.67, 1.16)	0.88 (0.67, 1.16)	0.76 (0.57, 1.01)	0.042	0.86 (0.72, 1.03)
Model 4, HR (95% CI)	Reference	0.94 (0.71, 1.24)	0.83 (0.61, 1.12)	0.81 (0.59, 1.13)	0.69 (0.49, 0.99)	0.037	0.83 (0.66, 1.04)

[1] n = 96,831. Model 1: age (y), region (Northeast, South, Midwest, West), race/ethnicity (white, black/African-American, Hispanic/Latino, other), study group (WHI Observational Study or control of clinical trials), education (at most high school, some college, college or above), annual family income (<$20,000, $20,000 to <$50,000, $50,000 to <$75,000, ≥$75,000), and health insurance (none, prepaid private, other). Model 2: model 1 + smoking status (never, former, current), pack-years of smoking, alcohol consumption (0, <0.5, 0.5 to <1, ≥1 drink/d), quitting smoking/drinking owing to health problems (yes, no), recreational physical activity (metabolic equivalent-h/wk), total energy intake (kcal/d), using fat to deep fry/pan fry/sauté (<1, 1–2, 3–4, 5–6, ≥7 times/wk), aspirin use (yes, no), use of nonsteroidal anti-inflammatory drugs (yes, no), hormone use [never, former, current (<5, 5 to <10, 10 to <15, ≥15 y)], and self-rated health status (very good/excellent, good, fair/poor). Model 3: model 2 + waist circumference (cm), diabetes (yes, no), systolic and diastolic blood pressure (mm Hg), antihypertensive drug use (yes, no), and dyslipidemia (yes, no). Model 4: model 3 + energy-adjusted dietary nutrients (dietary fiber, saturated fat, polyunsaturated fat, monounsaturated fat, *trans* fat, animal protein, sodium). CVD, cardiovascular disease; IHD, ischemic heart disease; Q, quintile; WHI, Women's Health Initiative.

TABLE 3 Association between dietary cholesterol intake and mortality in the WHI[1]

	Dietary cholesterol intake					P-trend	Per 100 mg · 1000 kcal⁻¹ · d⁻¹
	Q1	Q2	Q3	Q4	Q5		
Median (range), mg · 1000 kcal⁻¹ · d⁻¹	73.1 (3.4–88.1)	100.0 (88.2–110.4)	120.9 (110.5–132.2)	145.4 (132.3–163.4)	193.2 (163.5–722.3)		
Participants, n	19,366	19,366	19,366	19,366	19,367		
All-cause mortality							
Cases, n	3649	3807	3806	4015	4231		
Model 1, HR (95% CI)	Reference	1.05 (1.00, 1.10)	1.09 (1.04, 1.14)	1.21 (1.16, 1.27)	1.34 (1.28, 1.40)	<0.001	1.23 (1.20, 1.26)
Model 2, HR (95% CI)	Reference	1.03 (0.99, 1.08)	1.07 (1.02, 1.12)	1.16 (1.11, 1.22)	1.23 (1.17, 1.29)	<0.001	1.16 (1.13, 1.19)
Model 3, HR (95% CI)	Reference	1.01 (0.97, 1.06)	1.04 (0.99, 1.09)	1.10 (1.05, 1.16)	1.15 (1.10, 1.21)	<0.001	1.12 (1.09, 1.15)
Model 4, HR (95% CI)	Reference	0.99 (0.94, 1.03)	1.00 (0.95, 1.05)	1.05 (1.00, 1.11)	1.09 (1.02, 1.15)	<0.001	1.09 (1.05, 1.13)
CVD mortality							
Cases, n	1009	1112	1053	1148	1267		
Model 1, HR (95% CI)	Reference	1.11 (1.02, 1.21)	1.11 (1.01, 1.21)	1.27 (1.16, 1.38)	1.45 (1.33, 1.57)	<0.001	1.29 (1.23, 1.36)
Model 2, HR (95% CI)	Reference	1.10 (1.01, 1.20)	1.09 (0.99, 1.18)	1.23 (1.12, 1.34)	1.34 (1.23, 1.46)	<0.001	1.23 (1.17, 1.29)
Model 3, HR (95% CI)	Reference	1.07 (0.98, 1.17)	1.04 (0.96, 1.14)	1.14 (1.05, 1.25)	1.23 (1.13, 1.34)	<0.001	1.17 (1.11, 1.23)
Model 4, HR (95% CI)	Reference	1.05 (0.96, 1.15)	1.02 (0.93, 1.12)	1.11 (1.00, 1.23)	1.19 (1.06, 1.33)	0.002	1.17 (1.09, 1.24)
Cancer mortality							
Cases, n	1181	1175	1230	1302	1340		
Model 1, HR (95% CI)	Reference	0.99 (0.91, 1.07)	1.06 (0.97, 1.14)	1.15 (1.06, 1.25)	1.23 (1.14, 1.33)	<0.001	1.16 (1.10, 1.22)
Model 2, HR (95% CI)	Reference	0.98 (0.90, 1.06)	1.04 (0.96, 1.13)	1.11 (1.03, 1.21)	1.14 (1.05, 1.21)	<0.001	1.10 (1.05, 1.16)
Model 3, HR (95% CI)	Reference	0.97 (0.89, 1.05)	1.01 (0.93, 1.10)	1.06 (0.98, 1.15)	1.08 (0.99, 1.17)	0.010	1.06 (1.01, 1.11)
Model 4, HR (95% CI)	Reference	0.94 (0.86, 1.03)	0.98 (0.90, 1.08)	1.03 (0.93, 1.13)	1.03 (0.93, 1.14)	0.16	1.04 (0.97, 1.10)
AD/dementia mortality							
Cases, n	285	298	278	244	214		
Model 1, HR (95% CI)	Reference	1.06 (0.90, 1.24)	1.06 (0.90, 1.25)	1.01 (0.85, 1.21)	0.98 (0.82, 1.17)	0.70	0.91 (0.81, 1.02)
Model 2, HR (95% CI)	Reference	1.05 (0.89, 1.24)	1.05 (0.89, 1.24)	0.99 (0.83, 1.18)	0.95 (0.79, 1.14)	0.47	0.89 (0.79, 1.00)
Model 3, HR (95% CI)	Reference	1.05 (0.89, 1.24)	1.06 (0.90, 1.26)	1.01 (0.85, 1.20)	0.97 (0.81, 1.16)	0.63	0.90 (0.80, 1.01)
Model 4, HR (95% CI)	Reference	1.03 (0.87, 1.23)	1.03 (0.85, 1.24)	0.97 (0.78, 1.19)	0.93 (0.74, 1.18)	0.41	0.84 (0.72, 0.99)
Respiratory mortality							
Cases, n	236	250	268	336	358		
Model 1, HR (95% CI)	Reference	1.05 (0.88, 1.25)	1.17 (0.98, 1.40)	1.54 (1.30, 1.82)	1.71 (1.45, 2.02)	<0.001	1.50 (1.37, 1.63)
Model 2, HR (95% CI)	Reference	1.00 (0.83, 1.19)	1.10 (0.92, 1.31)	1.39 (1.18, 1.65)	1.40 (1.18, 1.65)	<0.001	1.32 (1.21, 1.45)
Model 3, HR (95% CI)	Reference	0.99 (0.83, 1.18)	1.09 (0.91, 1.30)	1.38 (1.16, 1.63)	1.37 (1.15, 1.63)	<0.001	1.31 (1.19, 1.43)
Model 4, HR (95% CI)	Reference	0.91 (0.76, 1.10)	0.96 (0.79, 1.16)	1.16 (0.95, 1.42)	1.13 (0.91, 1.40)	0.057	1.17 (1.04, 1.33)
Other mortality							
Cases, n	938	972	977	985	1052		
Model 1, HR (95% CI)	Reference	1.06 (0.97, 1.16)	1.12 (1.02, 1.22)	1.21 (1.11, 1.33)	1.38 (1.27, 1.51)	<0.001	1.27 (1.20, 1.33)
Model 2, HR (95% CI)	Reference	1.04 (0.95, 1.14)	1.09 (0.99, 1.19)	1.16 (1.06, 1.27)	1.27 (1.16, 1.39)	<0.001	1.20 (1.14, 1.26)
Model 3, HR (95% CI)	Reference	1.01 (0.93, 1.11)	1.06 (0.96, 1.16)	1.09 (1.00, 1.20)	1.18 (1.07, 1.29)	<0.001	1.14 (1.08, 1.20)
Model 4, HR (95% CI)	Reference	0.98 (0.89, 1.07)	1.00 (0.90, 1.11)	1.02 (0.92, 1.13)	1.09 (0.97, 1.23)	0.10	1.10 (1.03, 1.18)

[1] n = 96,831. Model 1: age (y), region (Northeast, South, Midwest, West), race/ethnicity (white, black/African-American, Hispanic/Latino, other), study group (WHI Observational Study or control of clinical trials), education (at most high school, some college, college or above), annual family income (<$20,000, $20,000 to <$50,000, $50,000 to <$75,000, ≥$75,000), and health insurance (none, prepaid private, other). Model 2: model 1 + smoking status (never, former, current), pack-years of smoking, alcohol consumption (0, <0.5, 0.5 to <1, ≥1 drink/d), quitting smoking/drinking owing to health problems (yes, no), recreational physical activity (metabolic equivalent-h/wk), total energy intake (kcal/d), using fat to deep fry/pan fry/sauté (<1, 1–2, 3–4, 5–6, ≥7 times/wk), aspirin use (yes, no), use of nonsteroidal anti-inflammatory drugs (yes, no), hormone use [never, former, current (<5, 5 to <10, 10 to <15, ≥15 y)], and self-rated health status (very good/excellent, good, fair/poor). Model 3: model 2 + waist circumference (cm), diabetes (yes, no), systolic and diastolic blood pressure (mm Hg), antihypertensive drug use (yes, no), and dyslipidemia (yes, no). Model 4: model 3 + energy-adjusted dietary nutrients (dietary fiber, saturated fat, polyunsaturated fat, monounsaturated fat, trans fat, animal protein, sodium). AD, Alzheimer disease; CVD, cardiovascular disease; Q, quintile; WHI, Women's Health Initiative.

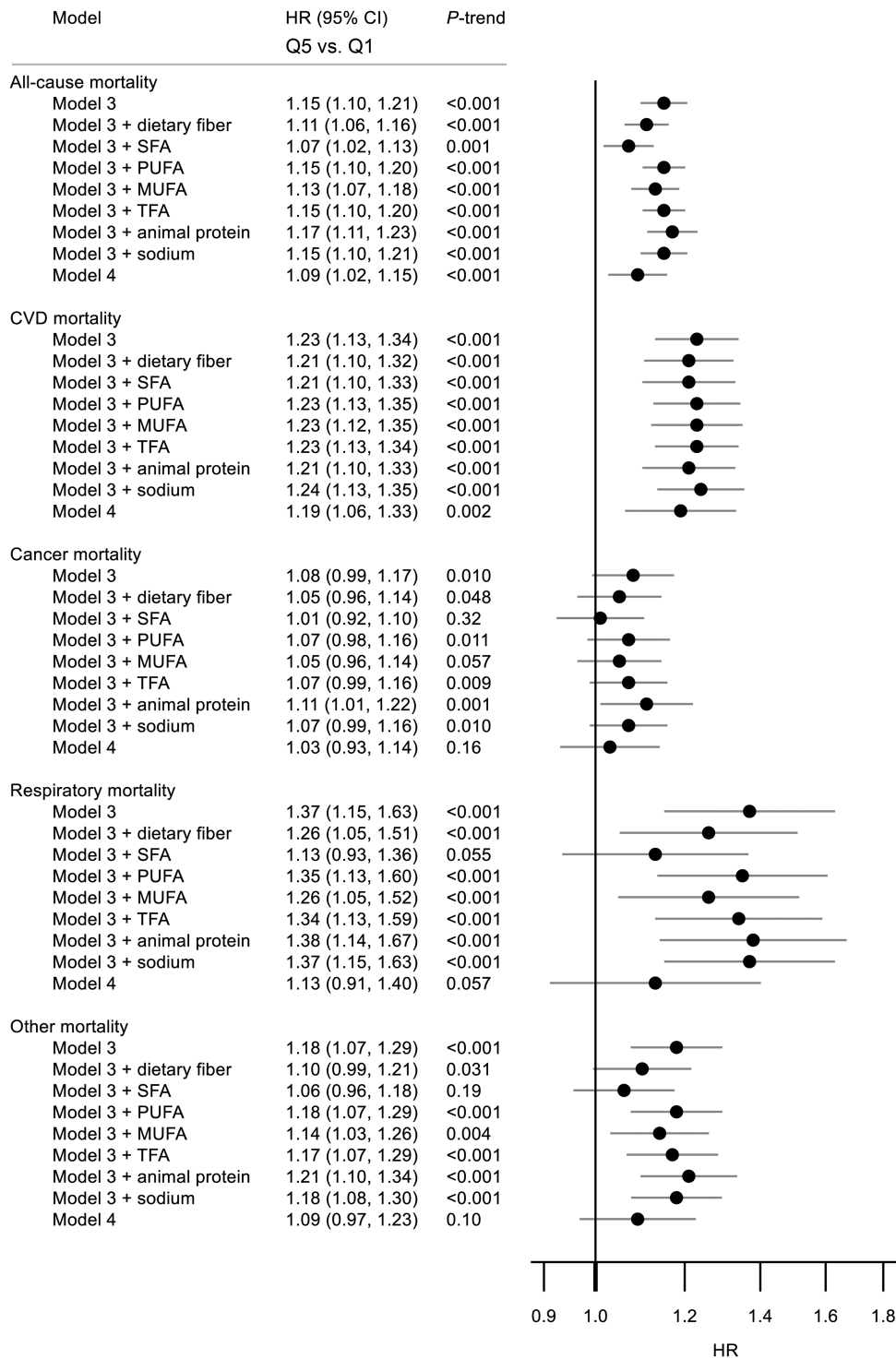| Model	HR (95% CI) Q5 vs. Q1	P-trend
All-cause mortality		
Model 3	1.15 (1.10, 1.21)	<0.001
Model 3 + dietary fiber	1.11 (1.06, 1.16)	<0.001
Model 3 + SFA	1.07 (1.02, 1.13)	0.001
Model 3 + PUFA	1.15 (1.10, 1.20)	<0.001
Model 3 + MUFA	1.13 (1.07, 1.18)	<0.001
Model 3 + TFA	1.15 (1.10, 1.20)	<0.001
Model 3 + animal protein	1.17 (1.11, 1.23)	<0.001
Model 3 + sodium	1.15 (1.10, 1.21)	<0.001
Model 4	1.09 (1.02, 1.15)	<0.001
CVD mortality		
Model 3	1.23 (1.13, 1.34)	<0.001
Model 3 + dietary fiber	1.21 (1.10, 1.32)	<0.001
Model 3 + SFA	1.21 (1.10, 1.33)	<0.001
Model 3 + PUFA	1.23 (1.13, 1.35)	<0.001
Model 3 + MUFA	1.23 (1.12, 1.35)	<0.001
Model 3 + TFA	1.23 (1.13, 1.34)	<0.001
Model 3 + animal protein	1.21 (1.10, 1.33)	<0.001
Model 3 + sodium	1.24 (1.13, 1.35)	<0.001
Model 4	1.19 (1.06, 1.33)	0.002
Cancer mortality		
Model 3	1.08 (0.99, 1.17)	0.010
Model 3 + dietary fiber	1.05 (0.96, 1.14)	0.048
Model 3 + SFA	1.01 (0.92, 1.10)	0.32
Model 3 + PUFA	1.07 (0.98, 1.16)	0.011
Model 3 + MUFA	1.05 (0.96, 1.14)	0.057
Model 3 + TFA	1.07 (0.99, 1.16)	0.009
Model 3 + animal protein	1.11 (1.01, 1.22)	0.001
Model 3 + sodium	1.07 (0.99, 1.16)	0.010
Model 4	1.03 (0.93, 1.14)	0.16
Respiratory mortality		
Model 3	1.37 (1.15, 1.63)	<0.001
Model 3 + dietary fiber	1.26 (1.05, 1.51)	<0.001
Model 3 + SFA	1.13 (0.93, 1.36)	0.055
Model 3 + PUFA	1.35 (1.13, 1.60)	<0.001
Model 3 + MUFA	1.26 (1.05, 1.52)	<0.001
Model 3 + TFA	1.34 (1.13, 1.59)	<0.001
Model 3 + animal protein	1.38 (1.14, 1.67)	<0.001
Model 3 + sodium	1.37 (1.15, 1.63)	<0.001
Model 4	1.13 (0.91, 1.40)	0.057
Other mortality		
Model 3	1.18 (1.07, 1.29)	<0.001
Model 3 + dietary fiber	1.10 (0.99, 1.21)	0.031
Model 3 + SFA	1.06 (0.96, 1.18)	0.19
Model 3 + PUFA	1.18 (1.07, 1.29)	<0.001
Model 3 + MUFA	1.14 (1.03, 1.26)	0.004
Model 3 + TFA	1.17 (1.07, 1.29)	<0.001
Model 3 + animal protein	1.21 (1.10, 1.34)	<0.001
Model 3 + sodium	1.18 (1.08, 1.30)	<0.001
Model 4	1.09 (0.97, 1.23)	0.10

HR axis: 0.9 1.0 1.2 1.4 1.6 1.8

FIGURE 1 Associations of dietary cholesterol with all-cause and cause-specific mortality in the WHI ($n = 96,831$). In addition to multivariable adjustment (model 3), results were further adjusted for other dietary nutrients individually or concordantly. Covariates in model 3 included age (y), region (Northeast, South, Midwest, West), race/ethnicity (white, black/African-American, Hispanic/Latino, other), study group (WHI Observational Study or control of clinical trials), education (at most high school, some college, college or above), annual family income (<$20,000, $20,000 to <$50,000, $50,000 to <$75,000, ≥$75,000), health insurance (none, prepaid private, other), smoking status (never, former, current), pack-years of smoking, alcohol consumption (0, <0.5, 0.5 to <1, ≥1 drink/d), quitting smoking/drinking owing to health problems (yes, no), recreational physical activity (metabolic equivalent-h/wk), total energy intake (kcal/d), using fat to deep fry/pan fry/sauté (<1, 1–2, 3–4, 5–6, ≥7 times/wk), aspirin use (yes, no), use of nonsteroidal anti-inflammatory drugs (yes, no), hormone use [never, former, current (<5, 5 to <10, 10 to <15, ≥15 y)], self-rated health status (very good/excellent, good, fair/poor), waist circumference (cm), diabetes (yes, no), systolic and diastolic blood pressure (mm Hg), antihypertensive drug use (yes, no), and dyslipidemia (yes, no). CVD, cardiovascular disease; TFA, *trans* fatty acid; WHI, Women's Health Initiative.

Egg consumption and incident CVD and mortality

After multivariable adjustment and further adjustment for major food groups including red meat and processed meat, higher egg consumption was associated with modestly higher risk of total CVD, with an HR of 1.14 (95% CI: 1.04, 1.25) when comparing egg intake of daily or above with <1 egg/wk (*P*-trend = 0.004). Higher egg consumption was also associated with higher risk of IHD and ischemic stroke but not associated with risk of hemorrhagic stroke (**Table 4**). For mortality outcomes, higher egg consumption was also associated with higher risk of all-cause mortality (≥7 compared with <1 egg/wk, HR: 1.14; 95% CI: 1.07, 1.22; *P*-trend < 0.001), and mortality from CVD, respiratory diseases, and other causes rather than cancer or AD/dementia (**Table 5**).

Nonlinear, stratified, and sensitivity analyses

There was no evidence for nonlinear associations of dietary cholesterol or egg intake with incident CVD or all-cause mortality (**Supplemental Figures 3** and **4**). Because of the relatively fewer participants within the high-intake ranges, we excluded participants in the top 5% of dietary cholesterol or egg intake, and still observed the linear positive associations (**Supplemental Figures 5** and **6**) (all *P* values for nonlinearity > 0.10).

In the analyses stratified by various demographic and lifestyle factors and medical histories, both dietary cholesterol and egg intakes were broadly associated with higher risk of CVD and all-cause mortality after the full adjustment, although the magnitudes of the associations were typically modest (**Supplemental Figures 7** and **8**). Stronger associations between dietary cholesterol or egg intake and incident CVD and/or all-cause mortality were observed in certain groups of the participants, such as participants having younger age, obesity, or diabetes, as compared with the associations in the corresponding opposite groups. However, only the interaction between egg intake and diabetes status on risk of all-cause mortality was marginally significant (*P*-interaction = 0.001) when considering multiple testing correction (at *P* < 0.001). The associations of dietary cholesterol or egg intake with cause-specific mortality were similar after excluding other causes of deaths that may have occurred competing with the outcome of interest (**Supplemental Tables 2** and **3**).

Discussion

In this prospective study of US postmenopausal women, higher dietary cholesterol intake was found to be associated with modestly higher risk of incident CVD and all-cause mortality after multivariable adjustment for traditional risk factors and key dietary nutrients. Significant positive associations were also observed between dietary cholesterol and incident IHD, incident ischemic stroke, and CVD mortality, whereas there was an inverse association for incident hemorrhagic stroke and no association for mortality from cancer, AD/dementia, respiratory diseases, or other causes. The patterns of the associations of egg consumption with incident CVD and mortality were generally comparable with those for dietary cholesterol.

A systematic review and meta-analysis (4) has evaluated 17 prospective studies that examined the association of dietary cholesterol with risk of CVD. Results of the meta-analysis suggested a marginally nonsignificant positive association of dietary cholesterol with risk of ischemic stroke and no association with risk of hemorrhagic stroke; no meta-analysis was performed for fatal and/or nonfatal IHD owing to substantial variations in methodological quality and population characteristics between the evaluated studies (4). More recent results from a pooled analysis of 6 US cohorts (9) suggested modest positive associations of dietary cholesterol with incident CVD and all-cause mortality, similar to findings of the current study. In a nationwide cohort of Chinese individuals (23), however, intake of dietary cholesterol from eggs was inversely associated with all-cause mortality and the intake from nonegg sources was associated with higher risk. There are scant data concerning the association of dietary cholesterol with non-CVD mortality, especially mortality from cancer, AD/dementia, or respiratory diseases.

Our study and the pooled analysis (9) both found modest positive associations of egg consumption with incident CVD and all-cause mortality. However, in a recent meta-analysis (5) that combined 28 prospective studies including the aforementioned pooled analysis, egg consumption was not associated with risk of CVD, which was consistent with more recent findings from an international cohort of individuals from 50 countries (24). In another meta-analysis (6), daily or greater egg consumption, as compared with consumption of <1/wk, was associated with marginally significantly higher risk of all-cause mortality.

Potential explanations for the study-specific differences in the associations of dietary cholesterol and egg consumption with risk of CVD/mortality remain unclear. Differences in methodologic and population characteristics across these studies may have partially contributed to the differences in the observed associations, such as the inclusion of individuals with varying health status, assessment of dietary cholesterol and outcomes using different instruments, use of variable definitions for CVD [e.g., with or without including hemorrhagic stroke (4)], as well as different contributions of individual food groups to total dietary cholesterol. For example, among Chinese individuals aged ≥60 y, eggs contributed to 57.7% of dietary cholesterol during 2010–2012 (25), whereas the corresponding data among US adults in the same age range were ∼28% during 2013–2014 (26).

The potential impact of residual confounding on the associations examined in our study merits discussion. It is notable that dietary cholesterol (or egg consumption) has been shown to be associated with disease risk factors differentially in terms of strength and/or direction across populations. For example, in a large Chinese cohort in which egg consumption was inversely associated with risk of CVD (27), participants with higher egg consumption tended to have higher levels of education and family income and lower prevalence of hypertension, whereas the correlations between egg consumption and BMI and lifestyle factors appeared relatively weak. Conversely, dietary cholesterol was apparently associated with these risk factors in risk-increasing directions in our study [and also in the pooled analysis (9)], such as lower socioeconomic status and diet quality, poorer nutrient profile, excess body weight, and unhealthy lifestyle behaviors. As expected, most examined associations in our study were attenuated moderately after these covariates were added to the models. It is unclear to what extent residual confounding may have biased the associations examined in our and other previous studies. In the current study, for example, the multivariable-adjusted associations between dietary cholesterol

TABLE 4 Association between egg consumption and incident CVD in the WHI[1]

	Intake categories, eggs/wk						
	<1	1 to <2	2 to <3	3 to <7	≥7	P-trend	Per 0.5 eggs/d
Participants, n	34,503	23,525	16,217	16,690	5896		
All CVD							
Cases, n	3337	2283	1649	1851	688		
Model 1, HR (95% CI)	Reference	0.99 (0.94, 1.05)	1.03 (0.97, 1.10)	1.12 (1.06, 1.18)	1.28 (1.18, 1.39)	<0.001	1.11 (1.08, 1.15)
Model 2, HR (95% CI)	Reference	0.99 (0.94, 1.04)	1.03 (0.97, 1.10)	1.09 (1.03, 1.16)	1.20 (1.10, 1.30)	<0.001	1.08 (1.05, 1.12)
Model 3, HR (95% CI)	Reference	0.98 (0.92, 1.03)	1.00 (0.94, 1.07)	1.06 (0.99, 1.12)	1.15 (1.05, 1.25)	0.003	1.06 (1.03, 1.10)
Model 4, HR (95% CI)	Reference	0.97 (0.92, 1.03)	1.00 (0.94, 1.07)	1.05 (0.99, 1.12)	1.14 (1.04, 1.25)	0.004	1.06 (1.03, 1.10)
IHD							
Cases, n	2412	1668	1160	1357	494		
Model 1, HR (95% CI)	Reference	1.00 (0.94, 1.06)	0.99 (0.93, 1.07)	1.13 (1.05, 1.20)	1.25 (1.14, 1.38)	<0.001	1.11 (1.07, 1.15)
Model 2, HR (95% CI)	Reference	1.00 (0.94, 1.06)	1.00 (0.93, 1.08)	1.10 (1.02, 1.18)	1.17 (1.05, 1.29)	0.001	1.07 (1.03, 1.12)
Model 3, HR (95% CI)	Reference	0.98 (0.92, 1.05)	0.98 (0.91, 1.05)	1.06 (0.99, 1.14)	1.12 (1.01, 1.24)	0.028	1.05 (1.01, 1.10)
Model 4, HR (95% CI)	Reference	0.98 (0.92, 1.05)	0.97 (0.91, 1.05)	1.06 (0.99, 1.14)	1.11 (1.00, 1.23)	0.040	1.05 (1.01, 1.09)
Ischemic stroke							
Cases, n	793	555	439	450	193		
Model 1, HR (95% CI)	Reference	1.03 (0.92, 1.15)	1.16 (1.03, 1.31)	1.16 (1.03, 1.31)	1.54 (1.31, 1.80)	<0.001	1.17 (1.10, 1.24)
Model 2, HR (95% CI)	Reference	1.02 (0.92, 1.14)	1.16 (1.03, 1.31)	1.13 (1.01, 1.28)	1.46 (1.24, 1.73)	<0.001	1.15 (1.08, 1.22)
Model 3, HR (95% CI)	Reference	1.01 (0.90, 1.12)	1.13 (1.00, 1.27)	1.09 (0.97, 1.24)	1.40 (1.19, 1.66)	0.001	1.13 (1.06, 1.20)
Model 4, HR (95% CI)	Reference	1.00 (0.90, 1.12)	1.13 (1.00, 1.27)	1.09 (0.97, 1.24)	1.40 (1.18, 1.66)	0.001	1.13 (1.06, 1.20)
Hemorrhagic stroke							
Cases, n	203	127	86	87	32		
Model 1, HR (95% CI)	Reference	0.92 (0.74, 1.15)	0.89 (0.69, 1.14)	0.88 (0.68, 1.13)	0.98 (0.68, 1.43)	0.40	0.94 (0.82, 1.09)
Model 2, HR (95% CI)	Reference	0.93 (0.74, 1.16)	0.90 (0.70, 1.17)	0.89 (0.68, 1.15)	0.99 (0.67, 1.47)	0.47	0.95 (0.82, 1.11)
Model 3, HR (95% CI)	Reference	0.92 (0.73, 1.15)	0.89 (0.68, 1.15)	0.87 (0.67, 1.14)	0.98 (0.67, 1.14)	0.41	0.95 (0.81, 1.10)
Model 4, HR (95% CI)	Reference	0.93 (0.74, 1.16)	0.90 (0.69, 1.16)	0.89 (0.68, 1.15)	0.98 (0.66, 1.46)	0.46	0.95 (0.81, 1.11)

[1] n = 96,831. Model 1: age (y), region (Northeast, South, Midwest, West), race/ethnicity (white, black/African-American, Hispanic/Latino, other), study group (WHI Observational Study or control of clinical trials), education (at most high school, some college, college or above), annual family income (<$20,000, $20,000 to <$50,000, $50,000 to <$75,000, ≥$75,000), and health insurance (none, prepaid private, other). Model 2: model 1 + smoking status (never, former, current), pack-years of smoking, alcohol consumption (0, <0.5, 0.5 to <1, ≥1 drink/d), quitting smoking/drinking owing to health problems (yes, no), recreational physical activity (metabolic equivalent-h/wk), total energy intake (kcal/d), using fat to deep fry/pan fry/sauté (<1, 1–2, 3–4, 5–6, ≥7 times/wk), aspirin use (yes, no), use of nonsteroidal anti-inflammatory drugs (yes, no), hormone use [never, former, current (<5, 5 to <10, 10 to <15, ≥15 y)], and self-rated health status (very good/excellent, good, fair/poor). Model 3: model 2 + waist circumference (cm), diabetes (yes, no), systolic and diastolic blood pressure (mm Hg), antihypertensive drug use (yes, no), and dyslipidemia (yes, no). Model 4: model 3 + food groups (fruit/vegetables, red meat, processed meat, organ meat, fish/shellfish, whole grain, refined grain, potatoes, soft drinks/fruit juices, coffee/tea). CVD, cardiovascular disease; IHD, ischemic heart disease; WHI, Women's Health Initiative.

TABLE 5 Association between egg consumption and mortality in the WHI[1]

	Intake categories, eggs/wk						
	<1	1 to <2	2 to <3	3 to <7	≥7	P-trend	Per 0.5 eggs/d
Participants, n	34,503	23,525	16,217	16,690	5896		
All-cause mortality							
Cases, n	6619	4747	3300	3578	1264		
Model 1, HR (95% CI)	Reference	1.06 (1.02, 1.10)	1.06 (1.01, 1.10)	1.16 (1.11, 1.21)	1.32 (1.25, 1.41)	<0.001	1.13 (1.10, 1.15)
Model 2, HR (95% CI)	Reference	1.06 (1.02, 1.10)	1.07 (1.02, 1.11)	1.13 (1.09, 1.18)	1.23 (1.16, 1.31)	<0.001	1.10 (1.07, 1.12)
Model 3, HR (95% CI)	Reference	1.04 (1.00, 1.08)	1.04 (0.99, 1.08)	1.09 (1.04, 1.14)	1.17 (1.10, 1.25)	<0.001	1.07 (1.05, 1.10)
Model 4, HR (95% CI)	Reference	1.03 (1.00, 1.07)	1.03 (0.98, 1.07)	1.08 (1.03, 1.12)	1.14 (1.07, 1.22)	<0.001	1.06 (1.03, 1.09)
CVD mortality							
Cases, n	1878	1330	939	1054	388		
Model 1, HR (95% CI)	Reference	1.05 (0.98, 1.13)	1.06 (0.98, 1.15)	1.21 (1.11, 1.30)	1.45 (1.30, 1.62)	<0.001	1.18 (1.13, 1.23)
Model 2, HR (95% CI)	Reference	1.06 (0.99, 1.14)	1.08 (1.00, 1.17)	1.18 (1.09, 1.28)	1.35 (1.20, 1.51)	<0.001	1.14 (1.10, 1.20)
Model 3, HR (95% CI)	Reference	1.03 (0.96, 1.11)	1.04 (0.96, 1.12)	1.12 (1.04, 1.21)	1.27 (1.13, 1.42)	<0.001	1.11 (1.06, 1.16)
Model 4, HR (95% CI)	Reference	1.03 (0.96, 1.11)	1.03 (0.95, 1.12)	1.11 (1.02, 1.20)	1.23 (1.10, 1.39)	0.001	1.10 (1.05, 1.15)
Cancer mortality							
Cases, n	2126	1517	1054	1138	393		
Model 1, HR (95% CI)	Reference	1.04 (0.97, 1.11)	1.04 (0.96, 1.12)	1.12 (1.04, 1.20)	1.19 (1.07, 1.32)	<0.001	1.10 (1.04, 1.12)
Model 2, HR (95% CI)	Reference	1.03 (0.96, 1.10)	1.04 (0.97, 1.12)	1.09 (1.01, 1.18)	1.11 (0.99, 1.25)	0.010	1.05 (1.01, 1.10)
Model 3, HR (95% CI)	Reference	1.01 (0.95, 1.09)	1.02 (0.95, 1.10)	1.06 (0.98, 1.14)	1.06 (0.95, 1.19)	0.14	1.03 (0.99, 1.07)
Model 4, HR (95% CI)	Reference	1.01 (0.94, 1.08)	1.01 (0.94, 1.09)	1.05 (0.97, 1.13)	1.04 (0.93, 1.17)	0.26	1.02 (0.98, 1.07)
AD/dementia mortality							
Cases, n	501	356	206	193	63		
Model 1, HR (95% CI)	Reference	1.06 (0.92, 1.21)	0.88 (0.74, 1.03)	0.87 (0.74, 1.03)	1.00 (0.77, 1.30)	0.093	0.94 (0.85, 1.03)
Model 2, HR (95% CI)	Reference	1.05 (0.91, 1.20)	0.87 (0.73, 1.02)	0.85 (0.71, 1.01)	0.94 (0.72, 1.24)	0.055	0.91 (0.82, 1.01)
Model 3, HR (95% CI)	Reference	1.05 (0.91, 1.21)	0.87 (0.74, 1.03)	0.86 (0.72, 1.02)	0.95 (0.72, 1.25)	0.062	0.92 (0.83, 1.02)
Model 4, HR (95% CI)	Reference	1.05 (0.91, 1.20)	0.87 (0.73, 1.02)	0.85 (0.72, 1.02)	0.93 (0.71, 1.23)	0.054	0.91 (0.82, 1.01)
Respiratory mortality							
Cases, n	433	364	247	290	114		
Model 1, HR (95% CI)	Reference	1.22 (1.06, 1.40)	1.17 (1.00, 1.37)	1.39 (1.20, 1.62)	1.77 (1.44, 2.18)	<0.001	1.25 (1.16, 1.35)
Model 2, HR (95% CI)	Reference	1.20 (1.05, 1.39)	1.20 (1.02, 1.41)	1.33 (1.14, 1.56)	1.57 (1.26, 1.96)	<0.001	1.19 (1.10, 1.29)
Model 3, HR (95% CI)	Reference	1.19 (1.03, 1.37)	1.18 (1.00, 1.38)	1.30 (1.11, 1.52)	1.54 (1.24, 1.92)	<0.001	1.18 (1.09, 1.28)
Model 4, HR (95% CI)	Reference	1.17 (1.01, 1.35)	1.15 (0.98, 1.35)	1.27 (1.08, 1.48)	1.46 (1.17, 1.82)	<0.001	1.15 (1.06, 1.25)
Other mortality							
Cases, n	1681	1180	854	903	306		
Model 1, HR (95% CI)	Reference	1.06 (0.98, 1.14)	1.11 (1.02, 1.20)	1.20 (1.11, 1.30)	1.35 (1.19, 1.52)	<0.001	1.15 (1.10, 1.20)
Model 2, HR (95% CI)	Reference	1.06 (0.98, 1.14)	1.12 (1.03, 1.22)	1.17 (1.08, 1.28)	1.27 (1.11, 1.44)	<0.001	1.12 (1.07, 1.18)
Model 3, HR (95% CI)	Reference	1.04 (0.96, 1.12)	1.08 (1.00, 1.18)	1.12 (1.03, 1.22)	1.20 (1.05, 1.36)	0.001	1.09 (1.04, 1.15)
Model 4, HR (95% CI)	Reference	1.03 (0.95, 1.11)	1.07 (0.99, 1.17)	1.11 (1.02, 1.21)	1.16 (1.02, 1.32)	0.004	1.08 (1.03, 1.13)

[1] n = 96,831. Model 1: age (y), region (Northeast, South, Midwest, West), race/ethnicity (white, black/African–American, Hispanic/Latino, other), study group (WHI Observational Study or control of clinical trials), education (at most high school, some college, college or above), annual family income (<$20,000, $20,000 to <$50,000, $50,000 to <$75,000, ≥$75,000), and health insurance (none, prepaid private, other). Model 2: model 1 + smoking status (never, former, current), pack-years of smoking, alcohol consumption (0, <0.5, 0.5 to <1, ≥1 drink/d), quitting smoking/drinking owing to health problems (yes, no), recreational physical activity (metabolic equivalent–h/wk), total energy intake (kcal/d), using fat to deep fry/sauté (<1, 1–2, 3–4, 5–6, ≥7 times/wk), aspirin use (yes, no), use of nonsteroidal anti-inflammatory drugs (yes, no), hormone use [never, former, current (<5, 5 to <10, 10 to <15, ≥15 y)], and self-rated health status (very good/excellent, good, fair/poor). Model 3: model 2 + waist circumference (cm), diabetes (yes, no), systolic and diastolic blood pressure (mm Hg), antihypertensive drug use (yes, no), and dyslipidemia (yes, no). Model 4: model 3 + food groups (fruit/vegetables, red meat, processed meat, organ meat, fish/shellfish, whole grain, refined grain, potatoes, soft drinks/fruit juices, coffee/tea). AD, Alzheimer disease; CVD, cardiovascular disease; WHI, Women's Health Initiative.

and all-cause mortality and some cause-specific mortality were apparently attenuated after further adjustment for saturated fat alone. This observation may highlight the importance of accurate measurement and adequate adjustment for key dietary nutrients, especially saturated fat which shares food sources with dietary cholesterol, although the potential impact of over-adjustment on these fully adjusted associations cannot be completely excluded.

We found that dietary cholesterol was positively and inversely associated with risk of ischemic and hemorrhagic stroke, respectively. Higher serum total and LDL cholesterol are both associated with higher risk of ischemic stroke, whereas lower concentrations have been found to be associated with higher risk of intracerebral hemorrhage (28). Thus, there might be plausible mechanisms underlying the differences in the associations of dietary cholesterol with stroke subtypes. However, it is also possible that the differences in the associations were driven by residual confounding factors that are differentially associated with stroke subtypes.

The WHI study is notable for its specifically designed and validated FFQ that was sensitive to dietary habits, especially dietary fat intake, in this ethnically diverse sample of postmenopausal women. Additional strengths of our study include its large sample size, prospective design, long-term follow-up, careful adjustment for multiple potential confounders including key dietary nutrients, and the adjudication of outcome events. In addition to the aforementioned problems of residual confounding, there are other limitations to our study. Information on dietary intake was collected using an FFQ that asked about participants' usual intake during the 3 mo before the baseline recruitment, such that the FFQ may not well capture the average intake for those whose diets were not stable. However, validation results for the WHI FFQ have been found to be highly comparable with those for FFQs used in other cohort studies of US older women (11), including the Nurses' Health Study (29) in which the FFQ was repeatedly used to ask about participants' diets over the year before the dietary assessment. Further, our findings were derived in postmenopausal women and are yet to be assessed in men and in younger populations.

In a broad sample of US postmenopausal women, higher dietary cholesterol intake and higher egg consumption were both associated with modestly higher risk of incident CVD and all-cause mortality. Our findings indicate that limiting dietary cholesterol intake while building a healthy eating pattern might be beneficial for human health. However, given the limited and inconsistent epidemiologic evidence concerning the potential cardiovascular impact of dietary cholesterol, additional prospective studies conducted in other populations with different demo-socioeconomic and lifestyle backgrounds are still needed for more definite conclusions.

Data Availability

Data described in the article, code book, and analytic code will be made available upon request pending application and approval.

References

1. Vincent MJ, Allen B, Palacios OM, Haber LT, Maki KC. Meta-regression analysis of the effects of dietary cholesterol intake on LDL and HDL cholesterol. Am J Clin Nutr 2019;109(1):7–16.
2. Wilson PWF, Polonsky TS, Miedema MD, Khera A, Kosinski AS, Kuvin JT. Systematic review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139(25):e1144–e61.
3. Rouhani MH, Rashidi-Pourfard N, Salehi-Abargouei A, Karimi M, Haghighatdoost F. Effects of egg consumption on blood lipids: a systematic review and meta-analysis of randomized clinical trials. J Am Coll Nutr 2018;37(2):99–110.
4. Berger S, Raman G, Vishwanathan R, Jacques PF, Johnson EJ. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr 2015;102(2):276–94.
5. Drouin-Chartier JP, Chen S, Li Y, Schwab AL, Stampfer MJ, Sacks FM, Rosner B, Willett WC, Hu FB, Bhupathiraju SN. Egg consumption and risk of cardiovascular disease: three large prospective US cohort studies, systematic review, and updated meta-analysis. BMJ 2020;368: m513.
6. Xu L, Lam TH, Jiang CQ, Zhang WS, Zhu F, Jin YL, Woo J, Cheng KK, Thomas GN. Egg consumption and the risk of cardiovascular disease and all-cause mortality: Guangzhou Biobank Cohort Study and meta-analyses. Eur J Nutr 2019;58(2):785–96.
7. US Department of Health and Human Services (US DHHS), US Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th ed. [Internet]. Washington (DC): USDHHS and USDA; 2015 [cited August 20, 2019]. Available from: http://www.health.gov/DietaryGuidelines.
8. Eckel RH. Reconsidering the importance of the association of egg consumption and dietary cholesterol with cardiovascular disease risk. JAMA 2019;321(11):1055–6.
9. Zhong VW, Van Horn L, Cornelis MC, Wilkins JT, Ning H, Carnethon MR, Greenland P, Mentz RJ, Tucker KL, Zhao L, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. JAMA 2019;321(11):1081–95.
10. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19(1):61–109.
11. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health

Initiative food frequency questionnaire. Ann Epidemiol 1999;9(3):178–87.

12. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. J Clin Epidemiol 1990;43(12):1327–35.

13. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nutrient database. J Am Diet Assoc 1988;88(10):1268–71.

14. Bowman SA, Friday JE, Moshfegh A. MyPyramid Equivalents Database, 2.0 for USDA survey foods, 2003–2004: documentation and user guide [Internet]. Beltsville, MD: Food Surveys Research Group, Beltsville Human Nutrition Research Center, USDA Agricultural Research Service; 2008 [cited August 20, 2019]. Available from: https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/mped/mped2_doc.pdf.

15. Curb JD, McTiernan A, Heckbert SR, Kooperberg C, Stanford J, Nevitt M, Johnson KC, Proulx-Burns L, Pastore L, Criqui M, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. Ann Epidemiol 2003;13(9 Suppl):S122–8.

16. Chen GC, Arthur R, Iyengar NM, Kamensky V, Xue X, Wassertheil-Smoller S, Allison MA, Shadyab AH, Wild RA, Sun Y, et al. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. Eur Heart J 2019;40(34):2849–55.

17. Meyer AM, Evenson KR, Morimoto L, Siscovick D, White E. Test-retest reliability of the Women's Health Initiative physical activity questionnaire. Med Sci Sports Exerc 2009;41(3):530–8.

18. Prentice RL, Aragaki AK, Van Horn L, Thomson CA, Beresford SA, Robinson J, Snetselaar L, Anderson GL, Manson JE, Allison MA, et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. Am J Clin Nutr 2017;106(1):35–43.

19. Schnatz PF, Jiang X, Aragaki AK, Nudy M, O'Sullivan DM, Williams M, LeBlanc ES, Martin LW, Manson JE, Shikany JM, et al. Effects of calcium, vitamin D, and hormone therapy on cardiovascular disease risk factors in the Women's Health Initiative: a randomized controlled trial. Obstet Gynecol 2017;129(1):121–9.

20. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(4 Suppl):1220S–8S; discussion 1229S–31S.

21. Sun Y, Liu B, Snetselaar LG, Wallace RB, Caan BJ, Rohan TE, Neuhouser ML, Shadyab AH, Chlebowski RT, Manson JE, et al. Association of normal-weight central obesity with all-cause and cause-specific mortality among postmenopausal women. JAMA Netw Open 2019;2(7):e197337.

22. Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD. Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obes Rev 2011;12(9):680–7.

23. Zhuang P, Jiao J, Wu F, Mao L, Zhang Y. Egg and egg-sourced cholesterol consumption in relation to mortality: findings from population-based nationwide cohort. Clin Nutr 2020;39(11):3520–7.

24. Dehghan M, Mente A, Rangarajan S, Mohan V, Lear S, Swaminathan S, Wielgosz A, Seron P, Avezum A, Lopez-Jaramillo P, et al. Association of egg intake with blood lipids, cardiovascular disease, and mortality in 177,000 people in 50 countries. Am J Clin Nutr 2020;111(4):795–803.

25. Pang SJ, Jia SS, Man QQ, Song S, Li YQ, Song PK, Zhao WH, Zhang J. Dietary cholesterol in the elderly Chinese population: an analysis of CNHS 2010–2012. Nutrients 2017;9(9):934.

26. Xu Z, McClure ST, Appel LJ. Dietary cholesterol intake and sources among U.S adults: results from National Health and Nutrition Examination Surveys (NHANES), 2001–2014. Nutrients 2018;10(6):771.

27. Qin C, Lv J, Guo Y, Bian Z, Si J, Yang L, Chen Y, Zhou Y, Zhang H, Liu J, et al. Associations of egg consumption with cardiovascular disease in a cohort study of 0.5 million Chinese adults. Heart 2018;104(21):1756–63.

28. Hackam DG, Hegele RA. Cholesterol lowering and prevention of stroke. Stroke 2019;50(2):537–41.

29. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122(1):51–65.