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Mushroom consumption, biomarkers, and risk of cardiovascular disease and type 2 diabetes: a prospective cohort study of US women and men

Dong Hoon Lee,[1] Meng Yang,[1] Edward L Giovannucci,[1,2,3] Qi Sun,[1,3] and Jorge E Chavarro[1,2,3]

Departments of [1]Nutrition and [2]Epidemiology, Harvard TH Chan School of Public Health, Boston, MA; and [3]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

ABSTRACT

Background: Mushrooms are good dietary sources of important vitamins, minerals, and bioactive compounds which may be important in the prevention of chronic diseases. However, studies have not prospectively evaluated the potential health effects of mushrooms with respect to major cardiometabolic diseases.

Objectives: The aim of this study was to examine the association of mushroom consumption with major cardiometabolic diseases and mediating biomarkers in 2 large prospective US cohorts.

Methods: We followed 67,139 women from the Nurses' Health Study (1986–2012) and 43,541 men from the Health Professionals Follow-up Study (1986–2012) who were free of chronic diseases. Mushroom consumption was assessed at baseline through the use of a food-frequency questionnaire. Cardiometabolic biomarkers were collected in subpopulations of the 2 cohorts. Cox proportional hazards models were used to estimate HRs and 95% CIs of cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, and type 2 diabetes (T2D), associated with mushroom consumption.

Results: We identified total 11,894 CVD (7,616 CHD; 4,278 stroke), and 10,206 T2D cases in >2 million person-years of follow-up. In the pooled multivariable-adjusted analysis, participants who consumed ≥5 servings of mushrooms per week had no significantly different risk of total CVD (HR: 1.02; 95% CI: 0.91, 1.14), CHD (HR: 1.00; 95% CI: 0.87, 1.16), stroke (HR: 1.05; 95% CI: 0.87, 1.25), or T2D (HR: 1.04; 95% CI: 0.93, 1.16) than participants who consumed mushrooms <1 time/mo. We consistently found no association between mushroom consumption and the aforementioned cardiometabolic diseases, in subgroups of sex, lifestyle factors, and medical conditions. Moreover, mushroom consumption was not associated with plasma biomarkers of lipids, insulin, and inflammation.

Conclusions: We found no association of mushroom consumption with biomarkers and risks of CVD and T2D in US adults. More large prospective cohort studies are warranted to investigate this association in other racial/ethnic groups. *Am J Clin Nutr* 2019;110:666–674.

Keywords: mushroom, diet, cardiovascular disease, coronary heart disease, stroke, diabetes, biomarkers, prospective study, Nurses' Health Study, Health Professionals Follow-up Study

Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide (1). Moreover, type 2 diabetes (T2D) is a highly prevalent chronic disease with an estimated 415 million people or 8.8% of all adults in the world (2), and is also a major risk

Supported by grants from the National Institute of Health (UM1 CA186107, R01 HL034594, R01 HL088521, UM1 CA167552, R01 HL035464, and DK058845) and a grant from Horticulture Australia Limited (HAL). HAL had no role in study planning, data collection, data analysis, interpretation of the findings, drafting of the manuscript, or decisions regarding where or when to publish study results.

Supplemental Figure 1 and Supplemental Tables 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to JEC (e-mail: jchavarr@hsph.harvard.edu).

Abbreviations used: CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; HPFS, Health Professionals Follow-up Study; MI, myocardial infarction; NHS, Nurses' Health Study; T2D, type 2 diabetes; TG, triglyceride; TNFαR2, TNFα receptor 2.

Received September 10, 2018. Accepted for publication March 18, 2019.

First published online June 7, 2019; doi: https://doi.org/10.1093/ajcn/nqz057.

factor for CVD (3). Thus, CVD and T2D prevention has become an important public health priority in recent decades.

Mushrooms are macrofungi which have distinctive fruiting bodies that can grow above or below ground (4). In many countries, mushrooms are widely consumed as a food or ingredient not only due to their unique taste and flavor but also due to a general understanding that they are a healthful food. Mushrooms are good sources of important vitamins (B-1, B-2, B-12, C, D, and E), minerals (Ca, K, Mg, Na, P, Cu, Fe, Mn, and Se), and bioactive compounds such as polysaccharides and β-glucan (5). A growing body of literature has shown evidence that consumption of mushrooms may protect against the risk of cardiometabolic diseases such as CVD and T2D (6, 7). In in vitro and animal studies, mushroom extracts decrease lipopolysaccharide-induced secretion of proinflammatory cytokines (8–10), and improve lipid profiles (11–13) and glucose uptake in skeletal muscle cell culture. In human studies, limited evidence is available from small studies in patients with a short-term follow-up that have examined the association with intermediate outcomes (e.g., biomarkers) and from a cross-sectional study that is susceptible to many sources of bias (14, 15). To our knowledge, studies have not prospectively evaluated the role of mushroom consumption in the incidence of major cardiometabolic diseases in the healthy population. Therefore, the aim of the study was to examine the association between mushroom consumption and the risk of CVD and T2D in 2 large prospective cohort studies of US women and men. Moreover, we examined whether mushroom consumption is associated with mediating biomarkers of cardiometabolic diseases.

Methods

Study population

We used data from 2 ongoing prospective US cohort studies: the Nurses' Health Study (NHS), which included 121,700 US-registered female nurses aged 30–55 y at enrollment in 1976; and the Health Professionals Follow-up Study (HPFS), which included 51,529 male health professionals aged 40–75 y at enrollment in 1986. Participants completed mailed questionnaires at baseline enrollment and 2 y thereafter to collect demographic, lifestyle, and medical information. Dietary data were collected every 4 y via food-frequency questionnaires (FFQs). The follow-up rates of the 2 cohorts were >90%.

For the current study, we included participants who had reported their mushroom consumption and were free of cancer, CVD, or T2D at baseline in 1986 (**Supplemental Figure 1**). We excluded participants who had implausible calorie intake (<500 or ≥3,500 kcal/d for women; <800 or ≥4,200 kcal/d for men) at baseline. The final sample included 67,139 women and 43,541 men. This study was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard TH Chan School of Public Health.

Blood samples

Blood samples were collected from subpopulations of 29,611 women between 1989 and 1990 (NHS) and 18,225 men between 1993 and 1994 (HPFS). Details of the procedures, including blood collection, handling, and storage, have been previously described (16, 17). In the current study for the biomarker analyses, we used the data from previous case-control studies nested within the 2 cohorts that measured plasma biomarkers associated with cardiometabolic diseases. We excluded participants with no information on mushroom consumption or prevalent cancer, CVD, or T2D. A total of 9,256 women from the NHS and 6,129 men from the HPFS were included for the biomarker analyses.

Mushroom consumption and covariate assessment

Information on mushroom consumption was collected once in 1986 through the use of FFQs for both the NHS and HPFS. Participants were asked how often, on average, they had consumed mushrooms (fresh, cooked, or canned) during the past year: never or <1 time/mo, 1–3 times/mo, 1 time/wk, 2–4 times/wk, 5–6 times/wk, 1 time/d, 2–3 times/d, 4–6 times/d, or >6 times/d. Other dietary information was assessed repeatedly through the use of FFQs during the follow-up. Diet patterns (i.e., Prudent and Western dietary patterns) were derived based on ∼39 predefined food groups (excluding mushroom) from FFQs by the use of principal component analysis (18, 19). The validity and reproducibility of FFQs have been described in detail elsewhere (20–22). We collected updated information on covariates such as age, race, body weight, physical activity, smoking, medical history, and family history of diseases through the use of biennial questionnaires.

Biomarker assessment

We assessed potential mediating biomarkers of cardiometabolic diseases including LDL cholesterol, HDL cholesterol, total cholesterol, triglyceride (TG), C-peptide, C-reactive protein (CRP), IL6, TNFα receptor 2 (TNFαR2), and adiponectin.

Details of laboratory procedures have been previously described (23–25). Briefly, LDL cholesterol, HDL cholesterol, total cholesterol, and TG were measured by standard methods with the use of reagents from Roche Diagnostics. C-peptide was measured by ELISAs (Diagnostic Systems Laboratories/Beckman Coulter). CRP was measured by highly sensitive immunoturbidimetric assay with reagents and calibrators (Denka Seiken Co.). IL6 and TNFαR2 were measured by ELISAs (R&D Systems). Adiponectin was measured by a competitive radioimmunoassay (Linco Research). The mean intra-assay coefficients of variation for most assays were <10%.

Outcome assessment

The primary outcomes of interest were incident CVD, coronary heart disease (CHD), stroke, and T2D. Participants who reported a new diagnosis from the biennial questionnaires were asked for permission to access their medical records to confirm their diagnosis. Study physicians reviewed the medical records blinded to the exposure status of participants. CVD was defined as CHD [nonfatal myocardial infarction (MI) and fatal CHD] and stroke (nonfatal or fatal). Nonfatal MI was confirmed if WHO criteria of symptoms plus either elevated cardiac enzyme or electrocardiographic changes were met (26). Fatal CHD was confirmed if CHD was listed as the cause of death with prior record of CHD after a review of medical records or autopsy

reports. Strokes were confirmed by the criteria of the National Survey of Stroke, which required evidence of a neurologic deficit with a sudden or rapid onset that persisted for >24 h. We excluded a pathologically confirmed cerebrovascular condition due to infection, trauma, or malignancy. Cases confirmed by interview or letter but without medical records were classified as probable. We considered both ischemic and hemorrhagic stroke.

A supplementary questionnaire was mailed to participants who reported that they had been newly diagnosed with diabetes from the biennial questionnaires. A T2D diagnosis was confirmed if participants reported ≥1 of the following based on the National Diabetes Data Group criteria (27): *1*) ≥1 classic symptoms (excessive thirst, polyuria, weight loss, hunger) plus fasting plasma glucose concentrations ≥140 mg/dL or random plasma glucose concentrations ≥200 mg/dL; *2*) ≥2 elevated plasma glucose concentrations on different occasions (fasting concentrations ≥140 mg/dL, random plasma glucose concentrations ≥11.1 mmol/L, or concentrations ≥200 mg/dL after ≥2 h oral glucose tolerance test, or a combination of these) in the absence of symptoms; or *3*) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). Since 1998, a fasting plasma glucose of 126 mg/dL was used as the threshold following the American Diabetes Association criteria (28). In addition, glycated hemoglobin ≥6.5% was added to the diagnosis criteria after 2010 (29). Only confirmed cases were included in the analysis. In a previous validation study, a high accuracy (98%) was observed comparing our classification against medical records (30).

Deaths were identified from the National Death Index or by reports from next of kin or postal system. More than 98% of deaths were identified over the follow-up.

Statistical analysis

Participants were followed from the date of return of the baseline questionnaire to the date of diagnosis of CVD, T2D, death, or the end of follow-up (June 2012 for the NHS; January 2012 for the HPFS), whichever came first. Mushroom consumption at baseline was categorized into 5 categories: never or <1 per month (almost never), <1 a week, once a week, 2–4 times a week, ≥5 times a week. Mushroom consumption was also used as a continuous variable (per 2 servings/wk increase). The Cox proportional hazards regression model was used to estimate HRs and 95% CIs of developing total CVD, CHD, stroke, and T2D associated with mushroom consumption. Age and calendar time were used as a stratification variable. Multivariable models adjusted for total calorie intake (quintiles), smoking status (never, former, current), BMI (<23, 23–24.9, 25–26.9, 27–29.9, 30–34.9, 35–39.9, ≥40 kg/m^2), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, ≥27 metabolic equivalent of task hours/wk), race (white, nonwhite), family history of MI or T2D (yes, no), baseline high blood cholesterol (yes, no), baseline high blood pressure (yes, no), alcohol intake (quintiles), multivitamin use (yes, no), Prudent dietary pattern (quintiles), and Western dietary pattern (quintiles). For women, menopausal status and postmenopausal hormone use (premenopausal, never, former, current) were additionally adjusted. All covariates were chosen a priori based on the existing literature. We updated the covariates in the model through the use of repeated measures over the follow-up period. Test for linear trend was done by including mushroom consumption as a continuous variable in the models. We tested for proportional hazard assumption by including a cross-product term of mushroom consumption and time variable in the models ($P > 0.05$). We analyzed data stratified by sex and pooled together because we found no significant heterogeneities by sex.

Stratified analyses were performed to explore whether the association between mushroom consumption and risk of cardiometabolic diseases differ by potential effect modifiers including age, BMI, physical activity, smoking status, family history of MI or T2D, high blood pressure, high blood cholesterol, and medication use. Tests for interaction were performed by including the cross-product terms for mushroom consumption and stratification variables in the model. Lastly, we further examined the substitution effect of a serving of mushrooms per day for another food (i.e., processed meat, red meat, poultry, fish, whole grain, refined carbohydrate, and vegetable assessed at baseline) by including both as continuous variables in the multivariable model. The differences in their regression coefficients, variances, and covariance were used to estimate the HRs and 95% CIs for the substitution effect (31, 32).

Generalized linear models were used to examine the association between mushroom consumption and potential mediating biomarkers of CVD and T2D. All biomarkers were calibrated according to the method proposed by Rosner et al. (33) to account for variation in sample handling and laboratory drift between batches. Multivariable models were adjusted for the same set of covariates used above. A test for linear trend was performed with the use of a continuous variable of mushroom consumption in the models. Relative difference in mean biomarker concentrations between the highest and lowest categories of mushroom consumption were calculated.

All analyses were performed with SAS software version 9.4 (SAS Institute); all statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

The age-standardized baseline characteristics of participants are shown in **Table 1** and **Supplemental Table 1**. Baseline age and BMI were ∼53 y and ∼25, respectively, for both women and men. Participants who consumed more mushrooms had higher physical activity, alcohol intake, and diet quality (i.e., greater adherence to the Prudent dietary pattern and lower adherence to the Western dietary pattern). Moreover, they tended to have higher blood pressure and blood cholesterol, especially for men. There were fewer current smokers but more past smokers in groups with higher mushroom consumption.

We documented 11,894 incident CVD cases (7,616 CHD cases and 4,278 stroke cases) and 10,206 incident T2D cases in >2 million person-years of follow-up. In the pooled analyses, mushroom consumption was not related to risk of CVD, CHD, stroke, or T2D (**Tables 2** and **3**). Participants who consumed ≥5 servings of mushrooms per week had no significantly different risk of total CVD (HR: 1.02; 95% CI: 0.91, 1.14), CHD (HR: 1.00; 95% CI: 0.87, 1.16), stroke (HR: 1.05; 95% CI: 0.87, 1.25), or T2D (HR: 1.04; 95% CI: 0.93, 1.16) than participants who consumed mushrooms <1/mo. Increasing mushroom consumption by 2 servings/wk was not associated

TABLE 1 Age-adjusted baseline characteristics according to mushroom consumption in 1986[1]

	Frequency of mushroom consumption (per serving)									
	NHS ($n = 67,139$ women)					HPFS ($n = 43,541$ men)				
Characteristic	Never or almost never $n = 14,999$	<1/wk $n = 22,170$	1/wk $n = 18,055$	2–4/wk $n = 8984$	≥5/wk $n = 2931$	Never or almost never $n = 9677$	<1/wk $n = 15,714$	1/wk $n = 11,494$	2–4/wk $n = 5563$	≥5/wk $n = 1093$
Age, y	52.8 ± 7.3[2]	52.4 ± 7.2	52.0 ± 7.1	52.3 ± 6.9	52.3 ± 6.9	55.2 ± 9.8	53.6 ± 9.5	52.7 ± 9.2	53.3 ± 9.4	53.2 ± 9.2
BMI, kg/m^2	25.2 ± 4.8	25.1 ± 4.7	25.2 ± 4.6	25.4 ± 4.7	25.2 ± 4.6	25.4 ± 3.2	25.5 ± 3.4	25.5 ± 3.2	25.6 ± 3.6	25.7 ± 3.6
Physical activity, MET-h/wk	12.0 ± 18.8	12.9 ± 18.9	15.2 ± 21.7	16.9 ± 21.6	19.7 ± 26.0	16.9 ± 24.0	18.0 ± 24.8	19.9 ± 27.8	21.7 ± 27.5	25.9 ± 39.2
White, %	97.2	97.7	98.3	97.9	98.1	94.5	94.8	95.6	94.8	95.0
Smoking status, %										
Never smoker	49.7	45.3	41.6	41.0	37.7	53.9	48.8	49.0	48.2	44.5
Past smoker	28.3	33.3	37.2	39.4	44.5	36.0	40.6	41.7	43.6	49.5
Current smoker	22.0	21.4	21.2	19.6	17.8	10.1	10.6	9.3	8.2	6.0
Postmenopausal, %	67.2	66.0	66.1	66.3	67.1	—	—	—	—	—
Postmenopausal hormone use, %	15.8	16.8	17.7	18.8	19.8	—	—	—	—	—
Family history of diabetes, %	29.6	28.9	29.3	28.5	29.1	13.2	14.6	13.5	14.4	17.7
Family history of myocardial infarction, %	35.0	35.8	36.1	36.4	35.4	31.2	31.8	32.7	31.8	36.1
High blood pressure, %	15.0	14.6	15.8	16.0	16.6	21.5	21.6	22.5	24.5	27.1
High blood cholesterol, %	6.9	6.9	7.7	7.7	7.9	9.9	10.4	11.2	12.0	12.4
Current multivitamin use, %	39.9	42.3	43.1	44.6	45.6	40.5	41.1	42.1	44.1	44.3
Medication, %										
Betablocker	8.3	8.3	8.3	8.7	8.5	7.1	7.4	7.8	8.3	10.4
Calcium channel blocker	2.5	2.4	2.5	2.7	2.5	0.7	0.6	0.7	0.9	1.2
ACE inhibitor	2.4	2.2	2.5	2.6	2.4	—	—	—	—	—
Thiazide diuretic	12.2	12.5	13.5	13.8	14.4	—	—	—	—	—
Furosemide-like diuretic	—	—	—	—	—	0.7	0.6	0.9	1.1	0.7
Other antihypertensive drugs	2.0	2.0	1.8	2.1	2.4	3.0	2.8	2.9	3.0	3.7
Antiarrhythmic drug	—	—	—	—	—	0.6	0.5	0.7	0.6	1.0
Cholesterol-lowering drug	1.7	2.0	2.2	2.3	2.1	0.5	0.5	0.4	0.6	0.7
Total calorie intake, kcal/d	1627 ± 453	1625 ± 433	1687 ± 430	1755 ± 443	1795 ± 463	1906 ± 623	1928 ± 597	2046 ± 603	2171 ± 642	2283 ± 664
Alcohol, g/d	4.2 ± 8.3	6.0 ± 9.5	7.4 ± 10.3	8.2 ± 10.6	9.7 ± 11.7	8.5 ± 14.2	11.2 ± 15.2	12.6 ± 15.7	13.7 ± 16.2	14.9 ± 18.5
Food group intake, servings/wk										
Red meat	6.5 ± 3.7	6.4 ± 3.6	6.5 ± 3.6	6.6 ± 3.5	6.4 ± 3.8	4.5 ± 3.5	4.3 ± 3.1	4.3 ± 3.1	4.3 ± 3.3	4.0 ± 3.5
Processed meat	2.1 ± 2.4	2.0 ± 2.2	2.0 ± 2.0	1.9 ± 2.1	1.8 ± 2.3	2.7 ± 3.2	2.6 ± 3.0	2.5 ± 2.8	2.5 ± 2.9	2.2 ± 2.9
Poultry	2.0 ± 1.8	2.1 ± 1.7	2.4 ± 1.7	2.7 ± 1.8	3.0 ± 2.3	2.2 ± 1.9	2.3 ± 1.9	2.5 ± 1.8	2.9 ± 1.9	3.2 ± 2.5
Fish	1.6 ± 1.3	1.6 ± 1.2	1.8 ± 1.2	2.1 ± 1.4	2.2 ± 1.5	2.1 ± 2.1	2.5 ± 2.1	2.9 ± 2.2	3.5 ± 2.6	4.0 ± 3.1
Whole grain	6.5 ± 7.5	7.0 ± 7.3	7.5 ± 7.4	8.1 ± 7.4	8.8 ± 8.1	9.6 ± 10.2	9.5 ± 9.5	9.9 ± 9.2	10.9 ± 9.9	12.5 ± 11.8
Refined carbohydrates	9.9 ± 7.9	9.2 ± 7.2	9.2 ± 6.6	9.1 ± 6.6	8.9 ± 6.5	8.7 ± 8.3	8.4 ± 7.6	8.4 ± 7.0	8.7 ± 7.0	8.6 ± 7.1
Nuts	1.6 ± 2.2	1.5 ± 1.7	1.6 ± 1.8	1.7 ± 1.8	1.8 ± 1.9	3.3 ± 4.9	3.2 ± 4.5	3.5 ± 4.9	3.7 ± 4.7	3.5 ± 4.7
Potatoes	5.5 ± 4.0	5.4 ± 3.9	5.5 ± 3.9	5.6 ± 3.9	5.7 ± 4.2	4.0 ± 3.2	3.8 ± 3.0	3.9 ± 2.8	3.9 ± 2.8	3.8 ± 3.4
Coffee	15.7 ± 12.3	16.3 ± 11.6	16.8 ± 11.5	17.2 ± 11.7	17.6 ± 11.7	12.6 ± 12.6	13.4 ± 12.5	14.1 ± 12.5	14.2 ± 12.6	14.7 ± 12.9
Juice	3.5 ± 3.6	3.3 ± 3.2	3.4 ± 3.2	3.5 ± 3.4	3.4 ± 3.4	5.0 ± 5.9	5.3 ± 5.7	5.7 ± 5.9	6.2 ± 6.5	6.3 ± 6.8
Sugar-sweetened beverages	2.0 ± 2.8	1.7 ± 2.5	1.7 ± 2.3	1.7 ± 2.3	1.7 ± 2.4	2.9 ± 5.1	2.5 ± 4.2	2.3 ± 3.9	2.2 ± 4.0	1.9 ± 3.8
Fruits	10.8 ± 8.4	11.3 ± 8.3	12.8 ± 8.6	14.9 ± 10.1	16.0 ± 10.6	9.9 ± 9.3	10.2 ± 8.2	11.5 ± 8.5	13.6 ± 10.3	16.9 ± 13.1
Vegetables	9.7 ± 6.6	10.7 ± 6.5	13.1 ± 6.9	16.3 ± 8.2	20.7 ± 11.6	8.4 ± 6.4	9.4 ± 6.1	11.6 ± 6.4	15.2 ± 8.0	20.7 ± 12.0
Prudent dietary pattern, % highest quintile	9.2	13.1	22.9	38.9	51.0	11.2	12.6	21.8	43.7	66.4
Western dietary pattern, % highest quintile	22.0	18.9	19.7	19.6	18.4	20.5	19.0	20.1	22.0	20.8

[1] All variables, except for age, were age standardized. ACE, angiotensin-converting enzyme; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study.
[2] Mean ± SD (all such values).

TABLE 2 Hazard ratios (95% CIs) for incident total CVD, CHD, and stroke according to mushroom consumption in women and men[1]

	Frequency of mushroom consumption (per serving)						
	Never or almost never	<1/wk	1/wk	2–4/wk	≥5/wk	Per 2/wk increase	*P*-trend
Total CVD							
Women (NHS)							
Event	1325	1,822	1,407	704	234		
Person-years	345,767	515,885	423,969	210,536	68,540		
Age-adjusted[2]	1 (ref)	0.96 (0.89, 1.03)	0.94 (0.87, 1.02)	0.92 (0.84, 1.01)	0.94 (0.82, 1.09)	0.98 (0.95, 1.01)	0.16
Multivariate-adusted[3]	1 (ref)	1.01 (0.94, 1.08)	1.01 (0.93, 1.09)	1.02 (0.93, 1.12)	1.08 (0.94, 1.25)	1.00 (0.98, 1.03)	0.78
Men (HPFS)							
Event	1619	2257	1539	844	143		
Person-years	204,253	341,013	253,751	121,284	23,913		
Age-adjusted[2]	1 (ref)	0.93 (0.87, 0.99)	0.91 (0.85, 0.98)	1.00 (0.92, 1.09)	0.88 (0.74, 1.05)	1.00 (0.97, 1.03)	0.89
Multivariate-adusted[3]	1 (ref)	0.97 (0.90, 1.03)	0.96 (0.89, 1.04)	1.07 (0.98, 1.17)	0.93 (0.78, 1.11)	1.01 (0.98, 1.04)	0.50
Pooled results[4]							
Age-adjusted[2]	1 (ref)	0.94 (0.90, 0.99)	0.93 (0.88, 0.98)	0.97 (0.91, 1.03)	0.92 (0.82, 1.02)	0.99 (0.97, 1.01)	0.24
Multivariate-adusted[3]	1 (ref)	0.99 (0.94, 1.03)	0.99 (0.94, 1.04)	1.05 (0.98, 1.12)	1.02 (0.91, 1.14)	1.01 (0.99, 1.03)	0.46
CHD							
Women (NHS)							
Event	736	986	756	371	130		
Person-years	346,193	516,523	424,478	210,810	68,613		
Age-adjusted[2]	1 (ref)	0.92 (0.84, 1.02)	0.90 (0.81, 1.00)	0.87 (0.76, 0.98)	0.93 (0.77, 1.13)	0.97 (0.93, 1.01)	0.09
Multivariate-adusted[3]	1 (ref)	0.98 (0.89, 1.08)	0.98 (0.88, 1.09)	0.97 (0.85, 1.11)	1.09 (0.90, 1.32)	1.00 (0.96, 1.04)	0.83
Men (HPFS)							
Event	1187	1647	1115	589	99		
Person-years	204,582	341,485	254,064	121,481	23,954		
Age-adjusted[2]	1 (ref)	0.93 (0.86, 1.00)	0.89 (0.82, 0.97)	0.95 (0.86, 1.05)	0.82 (0.66, 1.01)	0.98 (0.94, 1.02)	0.30
Multivariate-adusted[3]	1 (ref)	0.98 (0.91, 1.06)	0.96 (0.88, 1.05)	1.05 (0.94, 1.16)	0.89 (0.72, 1.10)	1.00 (0.96, 1.04)	0.91
Pooled results[4]							
Age-adjusted[2]	1 (ref)	0.93 (0.87, 0.98)	0.90 (0.84, 0.96)	0.92 (0.85, 0.99)	0.88 (0.77, 1.01)	0.97 (0.94, 1.00)	0.05
Multivariate-adusted[3]	1 (ref)	0.98 (0.92, 1.04)	0.97 (0.91, 1.04)	1.02 (0.94, 1.11)	1.00 (0.87, 1.16)	1.00 (0.97, 1.03)	0.97
Stroke							
Women (NHS)							
Event	589	836	651	333	104		
Person-years	346,195	516,528	424,436	210,773	68,613		
Age-adjusted[2]	1 (ref)	1.00 (0.90, 1.11)	0.99 (0.89, 1.11)	1.00 (0.87, 1.14)	0.96 (0.78, 1.18)	1.00 (0.96, 1.04)	0.84
Multivariate-adusted[3]	1 (ref)	1.04 (0.94, 1.16)	1.05 (0.93, 1.18)	1.08 (0.94, 1.25)	1.08 (0.86, 1.34)	1.01 (0.97, 1.05)	0.52
Men (HPFS)							
Event	432	610	424	255	44		
Person-years	204,830	341,833	254,318	121,555	23,967		
Age-adjusted[2]	1 (ref)	0.94 (0.83, 1.06)	0.96 (0.84, 1.10)	1.14 (0.98, 1.34)	1.06 (0.78, 1.46)	1.04 (0.99, 1.09)	0.15
Multivariate-adusted[3]	1 (ref)	0.94 (0.82, 1.06)	0.95 (0.82, 1.09)	1.13 (0.95, 1.33)	1.04 (0.75, 1.43)	1.03 (0.98, 1.09)	0.25
Pooled results[4]							
Age-adjusted[2]	1 (ref)	0.97 (0.90, 1.06)	0.98 (0.90, 1.07)	1.05 (0.95, 1.17)	0.99 (0.83, 1.18)	1.01 (0.98, 1.04)	0.53
Multivariate-adusted[3]	1 (ref)	1.00 (0.92, 1.08)	1.01 (0.92, 1.10)	1.10 (0.98, 1.22)	1.05 (0.87, 1.25)	1.02 (0.99, 1.05)	0.28

[1]Mushroom consumption was measured at baseline in 1986 for the NHS and the HPFS. CHD, coronary heart disease; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study.

[2]Age-adjusted models include age (mo) and total calorie intake (quintiles).

[3]Multivariate-adjusted models include age (months), total calorie intake (quintiles), smoking status (never, former, current), BMI (<23, 23–<25, 25–<27, 27–<30, 30–<35, 35–<40, ≥40), physical activity (<3, 3–<9, 9–<18, 18–<27, ≥27 MET-h/wk), race (white, nonwhite), family history of myocardial infarction (yes, no), baseline high blood cholesterol (yes, no), baseline high blood pressure (yes, no), alcohol intake (quintiles), multivitamin use (yes, no), Prudent dietary pattern (quintiles), and Western dietary pattern (quintiles). For women, menopausal status and postmenopausal hormone use (premenopausal, never, former, current) were additionally adjusted.

[4]Pooled results of women (NHS) and men (HPFS). All models were stratified by sex.

with risk of total CVD (HR: 1.01; 95% CI: 0.99, 1.03), CHD (HR: 1.00; 95% CI: 0.97, 1.03), stroke (HR: 1.02; 95% CI: 0.99, 1.05), and T2D (HR: 1.00; 95% CI: 0.98, 1.02). When examined separately in women and men, no associations between mushroom consumption and total CVD, CHD, stroke, or T2D were observed (Tables 2 and 3).

We then evaluated whether the relation between mushroom consumption and cardiometabolic diseases differed by strata

TABLE 3 Hazard ratios (95% CIs) for type 2 diabetes according to mushroom consumption in women and men[1]

	Frequency of mushroom consumption (per serving)						
	Never or almost never	<1/wk	1/wk	2–4/wk	≥5/wk	Per 2/wk increase	*P*-trend
Women (NHS)							
Participants	14,999	22,170	18,055	8984	2931		
Event	1529	2221	1907	1004	285		
Person-years	324,332	487,325	400,677	197,843	64,770		
Age-adjusted[2]	1 (ref)	0.96 (0.90, 1.03)	1.01 (0.94, 1.08)	1.05 (0.97, 1.13)	0.91 (0.80, 1.03)	0.99 (0.96, 1.01)	0.26
Multivariate-adusted[3]	1 (ref)	1.03 (0.96, 1.10)	1.10 (1.02, 1.18)	1.18 (1.08, 1.28)	1.04 (0.91, 1.19)	1.00 (0.98, 1.03)	0.79
Men (HPFS)							
Participants	9677	15,714	11,494	5563	1093		
Event	773	1274	939	463	95		
Person-years	185,304	311,248	232,119	111,257	21,796		
Age-adjusted[2]	1 (ref)	1.00 (0.91, 1.10)	0.99 (0.90, 1.10)	1.02 (0.91, 1.15)	1.09 (0.88, 1.35)	1.00 (0.95, 1.04)	0.83
Multivariate-adusted[3]	1 (ref)	1.03 (0.94, 1.13)	1.02 (0.92, 1.13)	1.01 (0.89, 1.14)	1.04 (0.83, 1.31)	0.98 (0.94, 1.03)	0.52
Pooled results[4]							
Age-adjusted[2]	1 (ref)	0.97 (0.92, 1.03)	1.00 (0.95, 1.06)	1.04 (0.97, 1.11)	0.95 (0.85, 1.06)	0.99 (0.97, 1.01)	0.27
Multivariate-adusted[3]	1 (ref)	1.03 (0.97, 1.08)	1.07 (1.01, 1.13)	1.12 (1.04, 1.20)	1.04 (0.93, 1.16)	1.00 (0.98, 1.02)	0.98

[1]Mushroom consumption was measured at baseline in 1986 for the NHS and the HPFS. HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study.

[2]Age-adjusted models include age (mo) and total calorie intake (quintiles).

[3]Multivariate-adjusted models include age (mo), total calorie intake (quintiles), smoking status (never, former, current), BMI (<23, 23–<25, 25–<27, 27–<30, 30–<35, 35–<40, ≥40 kg/m^2), physical activity (<3, 3–<9, 9–<18, 18–<27, ≥27 MET-h/wk), race (white, nonwhite), family history of type 2 diabetes (yes, no), baseline high blood cholesterol (yes, no), baseline high blood pressure (yes, no), alcohol intake (quintiles), multivitamin use (yes, no), Prudent dietary pattern (quintiles), and Western dietary pattern (quintiles). For women, menopausal status and postmenopausal hormone use (premenopausal, never, former, current) were additionally adjusted.

[4]Pooled results of women (NHS) and men (HPFS). All models were stratified by sex.

of risk factors for these conditions. Consistently, we observed no significant association between mushroom consumption and risk of CVD, CHD, stroke, or T2D across subgroups of age, BMI, physical activity, smoking status, family history of MI/T2D, high blood pressure, high blood cholesterol, or medication use (**Supplemental Tables 2–4**). Moreover, we estimated the effect of consuming mushrooms instead of other foods including processed meats, red meats, poultry, fish, whole grains, refined carbohydrates, and vegetables (**Supplemental Table 5**). Consuming 1 serving of mushrooms per day instead of 1 serving of processed meat, poultry, and fish per day was associated with 11% (HR: 0.89; 95% CI: 0.80, 0.98), 10% (HR: 0.90; 95% CI: 0.81, 1.00), and 15% (HR: 0.85; 95% CI: 0.76, 0.95) lower risk of T2D, respectively. Consuming mushrooms as a replacement for the aforementioned foods was not associated with risk of total CVD, CHD, or stroke.

Lastly, we examined whether mushroom consumption is associated with mediating biomarkers of CVD and T2D (**Table 4**). Overall, we found no association between mushroom consumption and plasma biomarkers of lipids (LDL cholesterol, HDL cholesterol, total cholesterol, and TG), C-peptide and inflammation (CRP, IL6, TNFαR2, and adiponectin). Multivariable-adjusted mean concentrations of all biomarkers were not significantly different across the categories of mushroom consumption.

Discussion

In the 2 large cohorts of US women and men studied here, higher mushroom consumption was not associated with risk of total CVD, CHD, stroke, and T2D. We consistently found no association between mushroom consumption and risk of major cardiometabolic diseases across subgroups of major risk factors for these diseases. Moreover, mushroom consumption was not associated with potential mediating biomarkers of CVD and T2D.

Current evidence on the effect of mushroom consumption on cardiometabolic diseases is largely generated from in vitro and animal studies (34). These studies have shown some promising evidence that mushroom consumption may improve risk factors for CVD and T2D, but data from human studies are sparse (35, 36). Only a limited number of epidemiologic studies are currently available and results have been inconsistent. A cross-sectional study of 13,770 Italian nondiabetic adults showed no association between mushroom consumption and fasting glucose concentrations in women but an increase of 1 portion (30 g) per week of mushroom consumption was associated with a 0.47-mmol/L increase in fasting glucose concentrations in men after adjusting for confounders (15). Moreover, women and men consuming >28 g mushroom/wk was associated with higher prevalence of diabetes compared to those consuming <14 g/wk. The observed positive associations may be due to reverse causation and residual/unmeasured confounding. In a retrospective study of 37 adults with metabolic syndrome who participated in a diet intervention, 16 wk of daily consumption (100 g) of white button mushroom (the most commonly consumed type of mushroom) was associated with a significant increase in adiponectin and antioxidant markers (ergothioneine and oxygen radical absorption capacity), and a decrease in circulating oxidative stress markers (carboxymethyllysine and methylglyoxal), although this study did not have a parallel

TABLE 4 Multivariate-adjusted biomarker concentrations of cardiometabolic diseases according to mushroom consumption in women and men[1]

	Frequency of mushroom consumption (per serving)						
	Never or almost never	<1/wk	1/wk	2–4/wk	≥5/wk	*P*-trend	Percentage difference ≥5/wk vs never or almost never
LDL cholesterol (mg/dL)							
Women (NHS)[2]	142 (133, 151)	141 (132, 150)	137 (129, 146)	140 (131, 150)	141 (131, 152)	0.61	−0.7
Men (HPFS)[2]	130 (119, 141)	131 (120, 142)	128 (118, 139)	129 (118, 140)	121 (109, 133)	0.16	−7.4
Pooled results[3]	136 (130, 142)	136 (130, 142)	133 (127, 139)	135 (128, 141)	132 (125, 140)	0.54	−3.0
HDL cholesterol (mg/dL)							
Women (NHS)[2]	56 (53, 60)	56 (53, 59)	56 (53, 59)	58 (55, 61)	58 (54, 62)	0.11	3.4
Men (HPFS)[2]	45 (42, 48)	45 (42, 49)	46 (43, 50)	47 (44, 51)	44 (41, 49)	0.24	−2.3
Pooled results[3]	51 (48, 53)	50 (48, 53)	51 (49, 53)	52 (50, 55)	51 (49, 54)	0.05	0
Total cholesterol (mg/dL)							
Women (NHS)[2]	201 (192, 210)	200 (191, 209)	196 (187, 205)	202 (192, 212)	203 (192, 214)	0.19	1.0
Men (HPFS)[2]	177 (166, 189)	178 (167, 190)	177 (166, 189)	179 (167, 191)	168 (155, 182)	0.37	−5.4
Pooled results[3]	189 (182, 196)	189 (183, 196)	186 (180, 193)	190 (183, 197)	186 (178, 194)	0.75	−1.6
TG (mg/dL)							
Women (NHS)[2]	127 (114, 142)	128 (115, 142)	130 (116, 144)	123 (110, 138)	124 (109, 141)	0.45	−2.4
Men (HPFS)[2]	147 (126, 171)	146 (125, 169)	145 (124, 169)	145 (124, 170)	145 (120, 175)	0.49	−1.4
Pooled results[3]	140 (129, 153)	140 (129, 152)	141 (130, 153)	137 (126, 150)	138 (124, 153)	0.84	−1.4
C-peptide (ng/mL)							
Women (NHS)[2]	2.33 (2.15, 2.54)	2.43 (2.25, 2.64)	2.48 (2.29, 2.69)	2.41 (2.21, 2.63)	2.35 (2.12, 2.59)	0.57	0.9
Men (HPFS)[2]	2.74 (2.43, 3.10)	2.82 (2.51, 3.17)	2.84 (2.52, 3.19)	2.74 (2.42, 3.11)	2.73 (2.34, 3.19)	0.99	−0.4
Pooled results[3]	2.42 (2.29, 2.57)	2.51 (2.38, 2.66)	2.56 (2.41, 2.71)	2.47 (2.33, 2.63)	2.43 (2.25, 2.62)	0.68	0.4
CRP (mg/L)							
Women (NHS)[2]	1.55 (1.29, 1.87)	1.50 (1.26, 1.80)	1.59 (1.33, 1.90)	1.72 (1.42, 2.08)	1.72 (1.38, 2.16)	0.04	9.9
Men (HPFS)[2]	1.06 (0.80, 1.41)	1.04 (0.79, 1.37)	1.04 (0.79, 1.37)	1.07 (0.80, 1.42)	1.07 (0.77, 1.48)	0.50	0.9
Pooled results[3]	1.42 (1.22, 1.65)	1.38 (1.19, 1.60)	1.41 (1.22, 1.64)	1.49 (1.28, 1.74)	1.50 (1.25, 1.80)	0.40	5.3
IL6 (pg/mL)							
Women (NHS)[2]	1.41 (1.23, 1.60)	1.42 (1.25, 1.61)	1.37 (1.21, 1.56)	1.43 (1.25, 1.64)	1.31 (1.12, 1.53)	0.52	−7.6
Men (HPFS)[2]	1.46 (1.12, 1.90)	1.45 (1.12, 1.88)	1.38 (1.06, 1.79)	1.37 (1.05, 1.79)	1.52 (1.13, 2.05)	0.63	3.9
Pooled results[3]	1.42 (1.26, 1.59)	1.40 (1.25, 1.56)	1.36 (1.22, 1.52)	1.39 (1.24, 1.56)	1.36 (1.18, 1.56)	0.52	−4.4
TNFαR2 (ng/mL)							
Women (NHS)[2]	2.47 (2.34, 2.60)	2.41 (2.29, 2.53)	2.40 (2.28, 2.53)	2.39 (2.26, 2.52)	2.40 (2.25, 2.56)	0.40	−2.9
Men (HPFS)[2]	2.55 (2.37, 2.75)	2.50 (2.32, 2.69)	2.49 (2.31, 2.69)	2.45 (2.27, 2.65)	2.46 (2.25, 2.68)	0.15	−3.7
Pooled results[3]	2.51 (2.41, 2.61)	2.45 (2.35, 2.54)	2.44 (2.34, 2.54)	2.42 (2.32, 2.52)	2.42 (2.30, 2.55)	0.10	−3.7
Adiponectin (μg/mL)							
Women (NHS)[2]	9.19 (8.37, 10.1)	8.84 (8.09, 9.67)	8.89 (8.13, 9.72)	9.05 (8.22, 9.96)	9.76 (8.72, 10.9)	0.15	5.8
Men (HPFS)[2]	5.57 (4.88, 6.36)	5.58 (4.91, 6.35)	5.64 (4.94, 6.43)	5.67 (4.96, 6.48)	5.61 (4.81, 6.54)	0.67	0.7
Pooled results[3]	7.25 (6.74, 7.79)	7.13 (6.64, 7.64)	7.17 (6.68, 7.69)	7.26 (6.74, 7.82)	7.57 (6.93, 8.27)	0.18	4.2

[1] Values are adjusted means (95% CIs). Mushroom consumption was measured at baseline in 1986 for the NHS and the HPFS. Biomarkers were collected between 1989 and 1990 for the NHS and between 1993 and 1994 for the HPFS. Number of participants: LDL cholesterol (2677 women, 2465 men), HDL cholesterol (2677 women, 2465 men), total cholesterol (2677 women, 2465 men), TG (2677 women, 2465 men), C-peptide (5122 women, 3088 men), CRP (3075 women, 3641 men), IL6 (3075 women, 2341 men), TNFαR2 (3075 women, 2755 men), adiponectin (3075 women, 2964 men). CRP, C-reactive protein; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; NHS, Nurses' Health Study; TG, triglyceride; TNFαR2, TNFα receptor 2.

[2] All models include age (mo), total calorie intake (quintiles), smoking status (never, former, current), BMI (<23, 23–<25, 25–<27, 27–<30, 30–<35, 35–<40, ≥40 kg/m^2), physical activity (<3, 3–<9, 9–<18, 18–<27, ≥27 MET-h/wk), race (white, nonwhite), family history of myocardial infarction and type 2 diabetes (yes, no), baseline high blood cholesterol (yes, no), baseline high blood pressure (yes, no), alcohol intake (quintiles), multivitamin use (yes, no), Prudent dietary pattern (quintiles), and Western dietary pattern (quintiles). For women, menopausal status and postmenopausal hormone use (premenopausal, never, former, current) were additionally adjusted.

[3] Pooled results of women (NHS) and men (HPFS). All models were stratified by sex.

control group with no mushroom consumption (14). Our findings are inconsistent with the previous studies. We found no association of mushroom consumption with mediating biomarkers and incidence of major cardiometabolic diseases in 2 large prospective cohorts of healthy US women and men. The major difference is that previous studies have only examined the effect of mushroom consumption on intermediated outcomes. Previous studies suggested that mushroom consumption may be associated with short-term changes in biomarkers, but we consistently found no association for both short-term and long-term outcomes. Moreover, the effect of mushroom can be biologically different in people with pre-existing medical conditions compared with healthy people.

However, there are several points worthy of note when interpreting our findings. First, the distributions of mushroom consumption for women and men were right-skewed, meaning

that the majority of participants had low mushroom consumption. Approximately half of participants consumed mushrooms <1 time/wk. Low variation of mushroom consumption may have masked the potential effect of mushroom consumption on cardiometabolic diseases. Nevertheless, our study included >4,000 individuals consuming mushrooms ≥5 times/wk who were followed for >86,000 person-years. Second, diets generally have high correlations over time but mushroom consumption assessed once at baseline may not be sufficient to represent long-term mushroom consumption. Previous studies that have examined the association between diet and risk of chronic diseases often showed stronger associations when they used cumulative average of repeated diets, instead of a diet at baseline, partially due to reduced measurement error, but the results were generally consistent between the 2 approaches (37). Although we did not have repeated measures of mushroom consumption, we consistently found no associations between mushroom consumption at baseline and risk of major cardiometabolic diseases regardless of follow-up periods (i.e., 0–5.9, 6–11.9, 12–17.9, and 18–24 y) (data not shown). Third, there are many kinds of edible mushrooms, which are known to vary in different nutritional value and medicinal properties. In the United States, only a few types of mushrooms are commonly consumed, and thus it is difficult to examine the association between specific types of mushroom consumption and cardiometabolic diseases. However, the therapeutic properties of certain mushrooms, so-called medicinal mushrooms, are well understood in other countries, particularly in Asia. Several small randomized controlled trials have been conducted to examine the clinical effect of medicinal mushrooms in patients. For example, studies have shown evidence that specific mushrooms (*Agaricus blazei* Murill, *Pleurotus* spp., and *Ganoderma lucidum*) may improve insulin resistance, glycemic control, and lipid profiles in patients with diabetes, hypertension, or dyslipidemia (38–40). On the other hand, several studies reported no beneficial effect of mushrooms (*G. lucidum* and *A. blazei* Murrill) for treatment of CVD risk factors (41, 42).

Interestingly, we found some evidence that consuming mushrooms instead of processed meat, poultry, or fish may be inversely related to risk of T2D. Previous studies have shown that high consumption of meat, particularly processed meat, was associated with increased risks of CVD and T2D (43, 44). In contrast, fish consumption was associated with reduced risks of CVD (45) but not of T2D (46). It is possible that the results of these substitution analyses may be more reflective of the relative hazards of these specific foods, especially of red and processed meats, rather than of absolute benefits of mushroom consumption itself. In fact, we found similar inverse associations with risk of T2D when substituting vegetables with the aforementioned meats (data not shown). Further, it is also important to consider that these relations may represent chance findings. This substitution effect of mushroom needs to be further investigated in future studies as it could provide meaningful dietary recommendations.

This study has several limitations. First, mushroom consumption was measured once at baseline. We did not have repeated measures to evaluate the association of long-term mushroom consumption with risk of cardiometabolic diseases. Second, different types of mushrooms were not assessed in the FFQs, and therefore we may have missed the effect of specific mushrooms on cardiometabolic diseases. Moreover, FFQs require participants to remember and report many food items. However, FFQs are useful for estimating usual dietary intakes and for ranking participants by intake amounts, especially in large epidemiologic studies (20–22). Third, although we had detailed information on potential confounders, we cannot rule out residual or unmeasured confounding in an observational study. Lastly, our cohorts consisted predominantly of white health professionals, which may limit the generalizability of the findings, albeit strengthening the internal validity.

To our knowledge, this is the first prospective cohort study that has examined the association between mushroom consumption and risk of major cardiometabolic diseases. We found that mushroom consumption is not associated with risk of CVD and T2D in healthy US adults. Given the wide popularity of mushrooms and the growing interest in their potential clinical effects, more prospective cohort studies addressing the limitations of the present study are warranted to further evaluate the relation between mushroom consumption and health. First of all, studies with repeated measures of diet can help understand the role of long-term mushroom consumption on health. Second, frequency and amount of mushroom consumption can vary by culture and race/ethnicity. Thus, more studies are needed to examine the potential dose–response association of mushroom consumption in other populations with different characteristics. Lastly, large studies, preferably randomized controlled trials, are required to investigate the potential beneficial effect of medicinal mushrooms and cultivation methods on cardiometabolic diseases in general and patient populations.

In conclusion, we found no association of mushroom consumption with the risk of major cardiometabolic diseases and mediating biomarkers in 2 large prospective US cohorts.

The authors' contributions were as follows—DHL, MY, ELG, QS, and JEC: designed and conducted research; DHL: analyzed data; DHL and JEC: wrote the paper; JEC: had primary responsibility for final content; and all authors: read and approved the final manuscript. All authors declare no conflicts of interest.

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