Chocolate consumption and risk of coronary artery disease: the Million Veteran Program

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ABSTRACT

Background: Although previous studies have suggested cocoa products may promote cardiovascular health in the general population, no public data are available from patients receiving care in a national integrated health care system.

Objectives: We tested the hypothesis that regular chocolate consumption is associated with a lower risk of coronary artery disease (CAD) events among participants of the Million Veteran Program (MVP). Secondary analysis examined if the main hypothesis was observed among participants with type 2 diabetes.

Methods: We analyzed data from MVP participants who completed the food frequency section of the MVP Lifestyle Survey and were free of CAD at the time of survey completion. CAD events during follow-up (International Statistical Classification of Diseases Ninth Revision codes 410–411 and 413–414, and Tenth Revision codes I20–I25 except I25.2) were assessed using electronic health records. We fitted a Cox proportional hazard model to estimate the RR of CAD.

Results: Of 188,447 MVP enrollees with survey data, mean ± SD age was 64 ± 12.0 y and 90% were men. For regular chocolate (28.3 g/serving) consumption of <1 serving/mo, 1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, and ≥5 servings/wk, crude incidence rates (per 1000 person-years) for fatal and nonfatal CAD events or coronary procedures were 20.2, 17.5, 16.7, 17.1, and 16.9, respectively, during a mean follow-up of 3.2 y. After adjusting for age, sex, race, and lifestyle factors, the corresponding HRs (95% CIs) were 1.00 (ref), 0.92 (0.87, 0.96), 0.88 (0.83, 0.93), 0.89 (0.84, 0.95), and 0.89 (0.84, 0.96), respectively (P for linear trend < 0.0001). In a secondary analysis of 47,265 diabetics, we did not observe a decreasing trend in CAD mortality among those who consumed ≥1 serving of chocolate a month compared with those who consumed <1 serving/mo.

Conclusions: Regular chocolate consumption was associated with a lower risk of CAD among veterans, but was not associated with cardiovascular disease risk in veterans with type 2 diabetes. *Am J Clin Nutr* 2021;113:1137–1144.

Keywords: coronary artery disease, nutrition, epidemiology, risk factors, incidence rate, cohort study

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality according to WHO statistics (1), and coronary artery disease (CAD) remains the leading cause of death in the United States (2). It is estimated that by 2035, >130 million adults in the United States will have some form of CVD, and the total cost of care may reach >$1.1 trillion/y (2). Most CVD risk can be lowered by behavioral risk factor modification, and

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

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Abbreviations used: CAD, coronary artery disease; CDW, Corporate Data Warehouse; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; EHR, electronic health record; EPIC, European Prospective Investigation into Cancer; ICD-9, International Statistical Classification of Diseases Ninth Revision; ICD-10, International Statistical Classification of Diseases Tenth Revision; MVP, Million Veteran Program; NHLBI, National Heart, Lung, and Blood Institute; VA, Veteran Affairs; VHA, Veterans Health Administration.

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dietary intake is one of the major modifiable factors (3). Studies have reported an inverse association between consumption of cocoa products and risk of CVD (4–6). Cocoa and cocoa-containing foods, such as chocolate, are rich in flavonoids (7), and trials have shown a favorable effect of flavonoids on CVD risk factors, including blood pressure; total, LDL, and HDL cholesterol; and insulin resistance (8–12). A meta-analysis of randomized controlled trials has shown that chocolate or cocoa consumption reduced insulin resistance, improved endothelial function, and reduced blood pressure in adults (13), whereas other meta-analyses have found that chocolate intake was associated with decreased risks for CAD, stroke, and diabetes (14), and improved blood lipid profile (15). However, little is known about the association of chocolate intake with risk of CAD among patients receiving care in a national health care system and, in particular, among those with type 2 diabetes. Here, we tested the hypothesis that self-reported chocolate intake is inversely related to the incidence of fatal and nonfatal CAD among US veterans participating in the Million Veteran Program (MVP) and conducted a secondary analysis to examine whether the inverse association prevails among diabetics.

Methods

Population

The study population consists of veteran participants of the MVP and receiving health care in the Veterans Health Administration (VHA). The VHA is the largest integrated health system in the United States and provides health care services to 24 million total users across the nation. There are >9 million veteran active users in any given fiscal year. The MVP is a national voluntary research program funded by the Department of Veteran Affairs (VA) Office of Research & Development to study genetic influences on health to improve health care for veterans (16). Since 2012, the MVP has been steadily recruiting active VHA users with invitational mailings that include an MVP Baseline Survey. As of February 2019, 731,424 veterans had been enrolled. For consented veterans, the MVP collects blood samples and information on military exposure, medical history, family history, physical activity status, and lifestyle habits through a Lifestyle Survey. Data for all clinical encounters for VHA service users over the past 20 y are hosted within the VHA's Corporate Data Warehouse (CDW). Merging information from the MVP Baseline and Lifestyle Surveys with electronic health record (EHR) data from the CDW creates a more complete health profile for MVP participants. In this study, we included participants enrolled through September 2018 who had completed the food frequency section of the MVP Lifestyle Survey and were free of prior CAD history or coronary procedures at the time of survey completion. We limited this analysis to participants with complete and validated demographics, dietary information, and CVD risk factor information (**Supplemental Figure 1**). All participants provided informed consent and the study protocol was approved by the VA Central Institutional Review Board.

Assessment of chocolate consumption

Chocolate consumption was self-reported in the FFQ within the MVP Lifestyle Survey. The FFQ was based on the Harvard Willett FFQ which has been previously validated (17). Subjects were asked to report their average consumption of chocolate (28.3 g/serving) in the past year. Possible answers were as follows: "Never or less than once per month," "1–3 per month," "once (1) a week," "2–4 per week," "5–6 per week," "once (1) a day," "2–3 per day," "4–5 per day," and "6+ per day." We collapsed adjacent categories with sparse data to obtain stable estimates of effect, with the final categories of chocolate consumption frequency as follows: "<1/mo," "1–3/mo," "1/wk," "2–4/wk," and "≥5/wk."

Ascertainment of CAD

The primary outcome of CAD was defined as nonfatal myocardial infarction or CAD events using International Statistical Classification of Diseases Ninth Revision (ICD-9) codes 410.x–411.x and 413.x–414.x, and Tenth Revision (ICD-10) codes I20.x–I25.x, except I25.2, within the CDW. The secondary outcome was defined as either nonfatal CAD events or fatal CAD events coded as underlying cause of death using ICD-10 codes I20.x–I25.x from the National Death Index (18); or coronary angioplasty and coronary revascularization using procedural codes (CPT) 33510–33536, 9292x, 9293x, 9294x, 92973, 92974, and 92975 and ICD-9 Procedure codes 36.x and 00.66.

Relevant covariates

Demographics including age, sex, race, and ethnicity were defined using self-reported information supplemented by data from the CDW. BMI, lipids, and blood pressure were extracted from the CDW using data collected closest to the time of MVP Lifestyle Survey completion. Medication use and comorbidity status were also taken from the CDW using dispensed generic drug names and ICD-9 and ICD-10 codes from inpatient and outpatient care (**Supplemental Table 1**) at time of survey completion. Alcohol use, physical activity, and smoking habits were determined by self-reported survey responses (19). We used the Dietary Approaches to Stop Hypertension (DASH) score to characterize overall dietary patterns; details on computation of the DASH score in the MVP have been previously published (20).

Statistical analysis

Person-time for follow-up was computed from time of FFQ completion until the first occurrence of nonfatal or fatal CAD events, coronary procedures, or censoring time [time of death for deceased subjects, last date of update of medical records in EHRs, or date of closure of the current data set (December 2018)]. For each chocolate consumption frequency category, we computed incidence rates of CAD by using generalized linear models utilizing follow-up time as an offset. We used Cox proportional hazard models to estimate unadjusted and adjusted HRs with 95% CIs, using chocolate intake of "<1/mo" as the reference. We fitted sequential Cox proportional models: *1*) a crude model; *2*) an age-adjusted model; and *3*) a multivariate model including age, race, sex, BMI, smoking, physical activity, alcohol consumption, and DASH score. Because previous trials have shown that cocoa or a high-flavonoid diet has beneficial effects on blood pressure

TABLE 1 Baseline characteristics of 188,447 Million Veteran Program participants by frequency of chocolate consumption[1]

	Chocolate serving consumption frequency					
	<1/mo (n = 43,086)	1–3/mo (n = 54,276)	1/wk (n = 34,840)	2–4/wk (n = 32,711)	≥5/wk (n = 23,534)	P value
Age, y	65.1 ± 11.2	63.7 ± 11.9	63.9 ± 12.3	64.6 ± 12.2	64.8 ± 12.6	<0.001
Male	92.4	90.5	90.0	89.5	86.0	<0.001
Race						<0.001
White	79.6	83.4	86.2	88.0	89.4	
Black	15.3	12.0	9.5	8.3	7.1	
Other	5.1	4.6	4.3	3.7	3.5	
Hispanic	6.0	5.2	4.8	4.2	3.6	<0.001
BMI, kg/m^2	29.3 ± 5.6	29.5 ± 5.5	29.2 ± 5.4	28.8 ± 5.3	28.4 ± 5.4	<0.001
Diabetes	31.6	26.2	23.0	21.0	19.3	<0.001
Cancer	46.2	44.5	44.0	45.1	45.1	<0.001
Hypertension	67.3	61.9	58.9	57.4	54.8	<0.001
Statin, %	53.2	50.4	48.0	47.5	45.8	<0.001
HDL-C, mg/dL	48.4 ± 15.5	47.5 ± 14.5	47.6 ± 14.4	47.9 ± 14.3	48.9 ± 14.6	<0.001
LDL-C, mg/dL	99.1 ± 33.3	101.6 ± 33.2	102.5 ± 33.3	102.6 ± 33.0	103.7 ± 33.1	<0.001
Total cholesterol, mg/dL	173.9 ± 39.6	175.8 ± 38.8	176.3 ± 38.9	176.4 ± 38.3	177.8 ± 38.4	<0.001
Triglyceride, mg/dL	143.2 ± 107.9	144.3 ± 100.6	142.2 ± 101.7	139.5 ± 95.2	136.1 ± 92.3	<0.001
Systolic blood pressure, mm Hg	132.1 ± 16.6	131.7 ± 16.2	131.2 ± 16.2	131.2 ± 16.2	130.6 ± 16.4	<0.001
Alcohol						<0.001
Abstainer	7.6	6.7	6.9	6.9	7.4	
Former	38.7	35.6	34.9	34.8	37.3	
Current	53.7	57.8	58.2	58.2	55.3	
Exercise, times/wk						<0.001
<1	43.3	41.6	39.1	39.1	40.4	
1	13.1	13.9	15.0	14.0	13.0	
2–4	28.2	30.7	31.7	32.5	30.4	
≥5	15.5	13.8	14.2	14.4	16.2	
Smoking						<0.001
Never	27.8	30.0	31.1	31.9	32.7	
Former	54.5	52.0	51.2	50.8	49.5	
Current	17.7	18.0	17.7	17.2	17.8	
DASH score						<0.001
1st–3rd quintile (7–22)	62.9	61.2	58.4	55.0	51.1	
4th quintile (23–25)	18.1	19.3	20.5	21.5	21.2	
5th quintile (26–35)	19.0	19.5	21.1	23.6	27.7	
Candy, g/wk	1.4 ± 7.5	2.4 ± 7.8	3.7 ± 7.9	5.6 ± 9.7	10.7 ± 20.9	<0.001

[1] Values are mean ± SD or percentages unless otherwise indicated. Each serving of chocolate is equivalent to 28.3 g chocolate. DASH, Dietary Approaches to Stop Hypertension; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol.

and cholesterol, we considered hypertension and cholesterol as potential mediators in the causal pathway between chocolate and CAD and therefore did not control for them in multivariable analyses (21–23). We repeated the multivariate model with competing risk by other causes of death using Fine and Gray (24). In secondary analyses, we tested effect modification by age, sex, BMI (<25 compared with ≥25 kg/m^2), diabetes, hypertension, statin use, and smoking status (ever compared with never) using a product term between each potential effect modifier and the chocolate categories in a multivariable-adjusted hierarchical model. We also computed multivariable-adjusted models stratified by median age, sex, BMI (<25 compared with ≥25 kg/m^2), diabetes, hypertension, statin use, and smoking status. We used chocolate consumption frequency as an ordinal term to assess possible linear or nonlinear trends in all models. All statistical analyses used SAS Enterprise Guide version 7.1 (SAS Institute Inc.). The significance level was set at 0.05.

Results

Of 188,447 MVP enrollees included in the current analyses, mean ± SD age was 64 ± 12.0 y and 90% were men. Frequent chocolate consumption was associated with female sex, white race, lower BMI, lower systolic blood pressure, lower prevalence of diabetes and hypertension, and more desirable dietary patterns characterized by higher DASH scores (**Table 1**). Veterans with high chocolate consumption also consumed more candy (P < 0.001). Over a mean follow-up time of 3.2 y, 10,224 new CAD events and 10,856 secondary events were recorded. Crude incidence rates (per 1000 person-years) for primary CAD events were 19.0, 16.5, 15.8, 16.1, and 15.7 for chocolate serving consumption frequency of <1/mo, 1–3/mo, 1/wk, 2–4/wk, and ≥5/wk, respectively (**Table 2**).

After adjusting for age, sex, race, BMI, and lifestyle factors, the corresponding HRs (95% CIs) for primary CAD events were 1.00 (ref), 0.92 (0.87, 0.97), 0.88 (0.83, 0.94), 0.89 (0.84, 0.95), and 0.89 (0.83, 0.95), respectively (P linear trend

TABLE 2 HRs (95% CIs) for fatal and nonfatal coronary artery disease according to chocolate consumption in the Million Veteran Program[1]

	Chocolate serving consumption frequency						
	<1/mo (n = 43,086)	1–3/mo (n = 54,276)	1/wk (n = 34,840)	2–4/wk (n = 32,711)	≥5/wk (n = 23,534)	P value for linear trend	P value for quadratic trend
Primary cases, n	2636	2901	1774	1710	1203		
Deaths, n	1748	1807	1238	1187	966		
Crude incidence rate, /1000 PY	19.0 (18.3, 19.7)	16.5 (15.9, 17.1)	15.8 (15.1, 16.5)	16.1 (15.4, 16.9)	15.7 (14.9, 16.6)		
Crude death rate, /1000 PY	12.1 (11.5, 12.7)	9.9 (9.5, 10.4)	10.6 (10.1, 11.3)	10.8 (10.2, 11.4)	12.2 (11.5, 13.0)		
Model 1, HR (95% CI)	Ref.	0.87 (0.82, 0.92)	0.83 (0.78, 0.88)	0.85 (0.80, 0.90)	0.83 (0.77, 0.89)	<0.0001	0.0001
Model 2, HR (95% CI)	Ref.	0.91 (0.86, 0.96)	0.86 (0.81, 0.92)	0.87 (0.82, 0.92)	0.85 (0.79, 0.91)	<0.0001	0.0088
Model 3, HR (95% CI)	Ref.	0.92 (0.87, 0.97)	0.88 (0.83, 0.94)	0.89 (0.84, 0.95)	0.89 (0.83, 0.95)	<0.0001	0.0069
Model 4, HR (95% CI)	Ref.	0.92 (0.87, 0.97)	0.88 (0.83, 0.94)	0.90 (0.84, 0.95)	0.89 (0.83, 0.95)		

[1]Model 1: unadjusted; Model 2: age-adjusted; Model 3: multivariate-adjusted for age, race, sex, BMI, smoking, physical activity, and alcohol consumption; Model 4: multivariate-adjusted for age, race, sex, BMI, smoking, physical activity, and alcohol consumption, competing risk model. PY, person-years.

<0.0001) (Table 2, Model 3). The corresponding HRs (95% CIs) for secondary CAD events were 1.00 (ref), 0.92 (0.87, 0.96), 0.88 (0.83, 0.93), 0.89 (0.84, 0.95), and 0.89 (0.84, 0.96), respectively (**Table 3**). The results for primary CAD events and secondary CAD events remained significant after sensitivity analyses were conducted to exclude participants with a short onset time of CAD (<1 y) (**Supplemental Tables 2**, **3**). In secondary analyses, the chocolate–CAD relation was not modified by age, BMI, race, sex, diabetes, or hypertension (all P for interaction > 0.05) (**Supplemental Table 4**). However, in stratified analyses, we observed statistically significantly lower risks of nonfatal and fatal CAD events among veterans who were male, nonsmokers, younger, had higher BMI, or had hypertension (**Table 4**). HRs across chocolate consumption groups were similar regardless of diabetes status, smoking status, or statin use (Table 4). Consuming chocolate servings at frequencies of 1–3/mo, 1/wk, 2–4/wk, or ≥5/wk was not associated with a lower risk of nonfatal or fatal CAD events among diabetics ($P = 0.19$).

Discussion

In this large patient population receiving care in a national integrated health care system, we showed, to our knowledge for the first time, that chocolate consumption was associated with a lower risk of CAD and that such relation was not modified by age, BMI, race, sex, diabetes, or hypertension.

Our overall findings are consistent with other cohort studies that examined the association between cardiovascular health and chocolate consumption. The EPIC (European Prospective Investigation into Cancer)-Norfolk study analyzed data from 20,915 men and women and observed a 12% lower risk of CAD (HR: 0.88; 95% CI: 0.77, 1.01) when comparing consumption of 16–99 g chocolate/d with no chocolate consumption (25). The lower risk of CAD observed in the EPIC-Norfolk study is similar to what we observed among veterans consuming any consistent amount of chocolate compared with those who consumed <28.3 g/mo. In addition, our results support those observed in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study where there was an inverse relation between chocolate intake and prevalence of CAD for chocolate consumption of 0, 1–4, and ≥5 oz/wk (equivalent to 0, 28.3–113.4, and ≥141.7 g/d, respectively) (26). The NHLBI study did not observe a lower CAD prevalence among those reporting chocolate consumption of 1–3 oz/mo (equivalent to 28.3–85.0 g/mo), whereas our study found an 8% lower CAD risk among veterans consuming 28.3 g/mo. With respect to fatal and nonfatal CAD events, we observed an ∼10% lower risk of CAD among our predominantly male population, whereas the Zutphen Elderly Study found a 50% lower risk of CVD death (RR: 0.50; 95% CI: 0.32, 0.78) when comparing >2.25 g cocoa/d (approximately equivalent to the cocoa contents in 8.5 g dark chocolate per day) with <0.5 g cocoa/d (approximately equivalent to the cocoa contents in 1.4 g dark chocolate per day) (27). While the Zutphen study focused mostly on healthy participants that were free of CVD, diabetes mellitus, or cancer at baseline, the high prevalence of long-term comorbidities among veterans could have contributed to a lower effect size in our study owing to a higher rate of CAD among subjects not consuming any chocolate.

TABLE 3 HRs (95% CIs) for fatal and nonfatal coronary artery disease and coronary revascularization according to chocolate consumption in the Million Veteran Program[1]

	Chocolate serving consumption frequency						
	<1/mo (n = 43,086)	1–3/mo (n = 54,276)	1/wk (n = 34,840)	2–4/wk (n = 32,711)	≥5/wk (n = 23,534)	P value for linear trend	P value for quadratic trend
Secondary cases, n	2798	3069	1881	1817	1291		
Deaths, n	1748	1807	1238	1187	966		
Crude incidence rate, /1000 PY	20.2 (19.4, 20.9)	17.5 (16.8, 18.1)	16.7 (16.0, 17.5)	17.1 (16.4, 17.9)	16.9 (16.0, 17.8)		
Crude death rate, /1000 PY	12.1 (11.5, 12.7)	9.9 (9.5, 10.4)	10.6 (10.1, 11.3)	10.8 (10.2, 11.4)	12.2 (11.5, 13.0)		
Model 1, HR (95% CI)	Ref.	0.87 (0.82, 0.91)	0.83 (0.78, 0.88)	0.85 (0.80, 0.90)	0.84 (0.78, 0.89)	<0.0001	<0.0001
Model 2, HR (95% CI)	Ref.	0.90 (0.86, 0.95)	0.86 (0.81, 0.92)	0.87 (0.82, 0.92)	0.86 (0.80, 0.91)	<0.0001	0.004
Model 3, HR (95% CI)	Ref.	0.92 (0.87, 0.96)	0.88 (0.83, 0.93)	0.89 (0.84, 0.95)	0.89 (0.84, 0.96)	0.0001	0.0037
Model 4, HR (95% CI)	Ref.	0.92 (0.87, 0.97)	0.88 (0.83, 0.93)	0.90 (0.84, 0.95)	0.89 (0.84, 0.96)		

[1]Model 1: unadjusted; Model 2: age-adjusted; Model 3: multivariate-adjusted for age, race, sex, BMI, smoking, physical activity, and alcohol consumption; Model 4: multivariate-adjusted for age, race, sex, BMI, smoking, physical activity, and alcohol consumption, competing risk model. PY, person-years.

The amount of chocolate consumption needed to confer a lower risk of CAD varies across studies. We observed that any consistent chocolate intake among veterans was associated with a significantly lower risk of CAD, but a recent meta-analysis of 14 studies found that only chocolate consumption <100 g/wk was associated with a lower risk of CVD; higher amounts suggested increased risk of adverse health effects with higher sugar consumption (28). In addition, a dose-response meta-analysis observed a small inverse association between a 10-g daily increase in chocolate consumption and risk of CAD (RR: 0.96; 95% CI: 0.93, 0.99) (29). The discrepancy in the minimum and maximum amounts of chocolate needed to observe an association with health effect might be clarified with future studies that focus on cocoa content and flavonoid amounts in the types of chocolate consumed because these compounds can vary widely across different chocolates.

Studies have examined chocolate consumption and risk of CAD among postmenopausal women and have found no association (30, 31). Among our older female population (n = 18,636), we did not observe a significantly lower risk of fatal and nonfatal CAD events when comparing women who consumed ≥28.3 g/mo with those consuming <1 serving/mo, supporting the findings observed in the Women's Health Initiative.

Beneficial effects of chocolate consumption on CAD risk factors have been reported in randomized clinical trials, as well as in observational and experimental studies. Chocolate and cocoa have been associated with enhanced insulin sensitivity (32, 33), reduced risk of type 2 diabetes (34), and decreased blood pressure (35, 36). We were able to detect a 12% lower risk of fatal and nonfatal CAD events among diabetic veterans who consumed chocolate up to once a week when comparing with those who consumed less than once per month. Unfortunately, we did not have sufficient power to detect significant associations among other consumption frequency categories owing to insufficient numbers of participants with diabetes.

Our study has some limitations. The MVP survey did not differentiate between white, milk, or dark chocolate consumption. A standard chocolate bar is ∼42.5 g, and cocoa contents could range from 10% for milk chocolate to >35% for dark chocolate. Lack of information on precise flavonoid contents, sugar and dairy content, and source or preparation of chocolate consumed might lead to bias. Data on chocolate consumption were self-reported, which could lead to recall bias. Although there is also the possibility of misclassification due to self-reported data, such misclassification is likely nondifferential and might have biased the results toward the null. The fact that our population consists primarily of white male veterans may limit the generalizability of our findings. Lastly, chocolate consumption was ascertained only at baseline and we did not have data on nutrients to further control for energy intake and other dietary variables. Despite these limitations, the large sample size, >15 y of patient history and >3 y of follow-up, and availability of data on CAD risk factors are strengths of this study.

In conclusion, our findings indicate that regular chocolate consumption is associated with an 8%–12% lower risk of CAD among veterans. Future studies are needed to confirm these findings and to explain the mechanism by which chocolate reduces CAD risk.

TABLE 4 Multivariable-adjusted HRs (95% CIs) for coronary artery disease stratified by age, BMI, diabetes, sex, hypertension, statin use, and smoking status[1]

	Chocolate serving consumption frequency						
	<1/mo	1–3/mo	1/wk	2–4/wk	≥5/wk	*P* value for linear trend	*P* value for quadratic trend
Age < 66 y ($n = 92,175$)							
Crude incidence rate, /1000 PY	16.1 (15.2, 17.1)	13.5 (12.8, 14.3)	13.4 (12.5, 14.3)	12.8 (11.9, 13.8)	11.3 (10.3, 12.4)		
HR (95% CI)	Ref.	0.86 (0.79, 0.93)	0.86 (0.79, 0.94)	0.83 (0.76, 0.91)	0.76 (0.68, 0.85)	<0.0001	0.2307
Age ≥ 66 y ($n = 96,272$)							
Crude incidence rate, /1000 PY	24.1 (23.0, 25.3)	22.0 (21.0, 23.1)	20.5 (19.3, 21.7)	21.6 (20.4, 22.9)	22.7 (21.2, 24.2)		
HR (95% CI)	Ref.	0.92 (0.87, 0.99)	0.87 (0.80, 0.94)	0.92 (0.86, 1.00)	0.97 (0.90, 1.06)	0.2099	0.0003
BMI < 25 ($n = 38,992$)							
Crude incidence rate, /1000 PY	18.5 (17.0, 20.2)	16.2 (14.9, 17.7)	15.9 (14.3, 17.6)	16.0 (14.4, 17.7)	15.6 (14.0, 17.5)		
HR (95% CI)	Ref.	0.93 (0.83, 1.05)	0.91 (0.79, 1.04)	0.91 (0.79, 1.04)	0.90 (0.78, 1.04)	0.1206	0.4006
BMI ≥ 25 ($n = 149,455$)							
Crude incidence rate, /1000 PY	20.6 (19.7, 21.4)	17.7 (17.1, 18.4)	16.9 (16.1, 17.8)	17.5 (16.6, 18.4)	17.3 (16.3, 18.4)		
HR (95% CI)	Ref.	0.91 (0.86, 0.96)	0.87 (0.82, 0.93)	0.89 (0.83, 0.95)	0.89 (0.83, 0.96)	0.0003	0.0045
Nondiabetic ($n = 141,182$)							
Crude incidence rate, /1000 PY	16.1 (15.3, 17.0)	14.4 (13.8, 15.1)	14.3 (13.5, 15.1)	14.6 (13.8, 15.5)	14.6 (13.7, 15.6)		
HR (95% CI)	Ref.	0.94 (0.88, 1.00)	0.93 (0.86, 1.00)	0.93 (0.86, 1.00)	0.94 (0.86, 1.02)	0.0968	0.1204
Diabetic ($n = 47,265$)							
Crude incidence rate, /1000 PY	28.9 (27.3, 30.5)	26.0 (24.6, 27.5)	25.0 (23.1, 26.9)	26.6 (24.5, 28.8)	26.6 (24.1, 29.4)		
HR (95% CI)	Ref.	0.93 (0.86, 1.00)	0.88 (0.80, 0.97)	0.95 (0.86, 1.04)	0.95 (0.85, 1.07)	0.1904	0.0281
Nonhypertensive ($n = 73,660$)							
Crude incidence rate, /1000 PY	11.8 (10.8, 12.9)	10.2 (9.5, 11.0)	9.9 (9.0, 10.8)	10.1 (9.2, 11.0)	10.0 (9.0, 11.1)		
HR (95% CI)	Ref.	0.93 (0.83, 1.05)	0.90 (0.80, 1.03)	0.90 (0.79, 1.02)	0.90 (0.78, 1.03)	0.0726	0.3478
Hypertensive ($n = 114,787$)							
Crude incidence rate, /1000 PY	24.1 (23.1, 25.1)	21.7 (20.9, 22.6)	21.4 (20.3, 22.5)	22.2 (21.1, 23.4)	22.4 (21.0, 23.9)		
HR (95% CI)	Ref.	0.93 (0.87, 0.98)	0.90 (0.84, 0.96)	0.93 (0.87, 0.99)	0.94 (0.87, 1.01)	0.0453	0.0084
Female ($n = 18,636$)							
Crude incidence rate, /1000 PY	8.3 (6.7, 10.2)	6.9 (5.8, 8.3)	6.7 (5.3, 8.4)	5.5 (4.3, 7.1)	6.8 (5.4, 8.5)		
HR (95% CI)	Ref.	0.94 (0.71, 1.23)	0.94 (0.69, 1.28)	0.78 (0.56, 1.08)	0.92 (0.67, 1.25)	0.3319	0.5494
Male ($n = 169,811$)							
Crude incidence rate, /1000 PY	21.2 (20.4, 22.0)	18.6 (17.9, 19.3)	17.8 (17.0, 18.7)	18.5 (17.7, 19.4)	18.6 (17.6, 19.6)		
HR (95% CI)	Ref.	0.92 (0.87, 0.96)	0.88 (0.83, 0.93)	0.90 (0.85, 0.96)	0.89 (0.83, 0.96)	0.0002	0.0042
Non–statin user ($n = 95,106$)							
Crude incidence rate, /1000 PY	14.9 (14.0, 15.8)	13.0 (12.3, 13.8)	12.3 (11.4, 13.2)	12.8 (11.9, 13.8)	12.6 (11.6, 13.8)		
HR (95% CI)	Ref.	0.95 (0.87, 1.04)	0.89 (0.81, 0.98)	0.91 (0.83, 1.01)	0.90 (0.81, 1.01)	0.0259	0.2457
Statin user ($n = 93,341$)							
Crude incidence rate, /1000 PY	24.6 (23.5, 25.8)	21.6 (20.7, 22.6)	21.4 (20.2, 22.6)	21.7 (20.5, 23.1)	21.7 (20.2, 23.2)		
HR (95% CI)	Ref.	0.90 (0.85, 0.96)	0.89 (0.83, 0.96)	0.90 (0.84, 0.97)	0.91 (0.84, 0.99)	0.0113	0.0077
Nonsmoker ($n = 57,218$)							
Crude incidence rate, /1000 PY	15.8 (14.6, 17.1)	12.7 (11.8, 13.7)	12.8 (11.7, 14.1)	11.9 (10.8, 13.2)	11.8 (10.6, 13.3)		
HR (95% CI)	Ref.	0.88 (0.78, 0.98)	0.88 (0.78, 1.00)	0.80 (0.71, 0.91)	0.82 (0.71, 0.94)	0.001	0.204
Former or current smoker ($n = 131,229$)							
Crude incidence rate, /1000 PY	21.8 (20.9, 22.8)	19.5 (18.7, 20.3)	18.5 (17.5, 19.5)	19.5 (18.5, 20.6)	19.4 (18.2, 20.6)		
HR (95% CI)	Ref.	0.93 (0.88, 0.98)	0.88 (0.83, 0.94)	0.93 (0.87, 0.99)	0.92 (0.86, 1.00)	0.0153	0.0076

[1]All *P* values for interaction are >0.05 and not statistically significant. BMI in kg/m^2. PY, person-years.

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Data Availability

Data described in the article, code book, and analytic code will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, in order to comply with current VA privacy regulations pursuant to the US Department of Veterans Administration policies on compliance with the confidentiality of US veterans' data.

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