Chocolate consumption and risk of diabetes mellitus in the Physicians' Health Study[1–4]

Chisa Matsumoto, Andrew B Petrone, Howard D Sesso, J Michael Gaziano, and Luc Djoussé

ABSTRACT

Background: Previous studies reported beneficial effects of cocoa or chocolate on insulin resistance, oxidative stress, and inflammation, which are important risk factors of type 2 diabetes mellitus (DM). However, it is unclear whether chocolate consumption is associated with risk of DM.

Objective: We tested the hypothesis that chocolate consumption is inversely associated with incident DM in the Physicians' Health Study (PHS).

Design: We prospectively analyzed data on 18,235 PHS participants who were free of DM at baseline (1997–2001). Chocolate consumption was obtained from a baseline food-frequency questionnaire. Incident DM was ascertained via annual follow-up questionnaires and validated in a subsample by a review of medical records. We used Cox proportional hazards models to estimate HRs and 95% CIs of DM.

Results: The mean (±SD) age at baseline was 66.3 ± 9.2 y. During a mean follow up of 9.2 y, 1123 men (6.2%) developed DM. For self-reported chocolate consumption of none, 1–3 servings/mo, 1 serving/wk, and ≥2 servings/wk, multivariable-adjusted HRs (95% CIs) of DM adjusted for lifestyle, clinical, and dietary risk factors including total energy intake were 1.00 (referent), 0.93 (0.79, 1.09), 0.86 (0.72, 1.04), and 0.83 (0.69, 0.99), respectively (P-trend = 0.047). In secondary analyses, the inverse association of chocolate consumption and risk of DM was slightly stronger in subjects without a history of cardiovascular disease or heart failure (P-trend = 0.023). In addition, both age and BMI modified the chocolate-DM relation ($P < 0.05$ each).

Conclusion: Our data support an inverse relation of chocolate intake with incident DM, which appears only to apply in younger and normal–body weight men after controlling for comprehensive life styles including total energy consumption. *Am J Clin Nutr* 2015;101:362–7.

Keywords chocolate, diabetes mellitus, nutrition, epidemiology, risk factors

INTRODUCTION

Type 2 diabetes mellitus (DM)[5] has tremendous worldwide social and economic burden partly because of its complications, including cardiovascular disease (CVD), renal dysfunction, retinopathy, or diabetic cardiomiopathy (1). The prevalence of DM is increasing rapidly and estimated to rise from 171 million cases in 2000 to 366 million cases in 2030 (2). Therefore, it is important to identify modifiable risk factors of DM such as diet and determine beneficial foods that could help reduce risk of DM.

Chocolate contains caffeine, flavonoids (e.g., flavanols and procyanidins), and minerals such as magnesium (3) that could influence risk of DM. An inverse association between the consumption of caffeine, flavonoids, and magnesium with risk of DM has been reported with inconsistent results (4–9). In contrast, cocoa and chocolate have beneficial effects on insulin resistance (10–12), oxidative stress (12–14), and inflammation (15, 16), which play important roles in the pathogenesis of DM, and some observational studies suggested an inverse association of chocolate intake and risk of DM (8, 17). However, it is still unclear whether chocolate consumption is associated with risk of DM and whether this association differs according to characteristics of the study population. Hence, we sought to examine whether chocolate consumption is inversely associated with incident DM in the Physicians' Health Study (PHS).

SUBJECTS AND METHODS

Study population

Study subjects were selected from 29,071 participants in the PHS I (clinicaltrials.gov; NCT00000500) and PHS II (clinicaltrials.gov; NCT00270647). The PHS I is a completed randomized trial of the efficacy of low-dose aspirin and β-carotene

[1]From the Division of Cardiology, Tokyo Medical University, Tokyo, Japan (CM); the Divisions of Aging (ABP, HDS, JMG, and LD) and Preventive Medicine (HDS and JMG), Brigham and Women's Hospital, Boston, MA; the Harvard Medical School, Boston, MA (HDS, JMG, and LD); and the Boston Veterans Affairs Healthcare System, Boston, MA (JMG and LD).

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[3]Study sponsors had no role in the design and conduct of the study, collection, management, analysis, and interpretation of data, and preparation, review, or approval of the manuscript.

[4]Address correspondence to C Matsumoto, Division of Cardiology, Tokyo Medical University, 6-7-1 Nishishinjyuku Shinjyuku-ku, Tokyo, Japan, 160-0023. E-mail: chisamatsumoto@post.harvard.edu.

[5]Abbreviations used: CVD, cardiovascular disease; DM, type 2 diabetes mellitus; FFQ, food-frequency questionnaire; PHS, Physicians' Health Study.

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on CVD and cancer in 22,071 US male physicians aged 40–84 y at baseline (1982). The PHS II was a randomized trial designed to assess the effects of β-carotene, vitamin E, vitamin C, and a multivitamin on risk of cancer, CVD, and other chronic diseases in 14,641 US male physicians aged ≥50 y at baseline (1997). Detailed descriptions of both studies have been published previously (18, 19). For the current analysis, we started follow-up when the food-frequency questionnaire (FFQ) was assessed (1997–2001).

In PHS participants free of baseline DM (n = 19,465), we excluded 342 participants with missing data on chocolate consumption and 1105 participants whose reported total energy intakes were implausible (<500 or >3500 kcal/d or missing). Thus, a total of 18,235 men were used for the current analyses.

Ethics

Each participant gave written informed consent, and the Brigham and Women's Hospital Institutional Review Board approved the study protocol.

Ascertainment of DM, chocolate consumption, and other covariates

DM was ascertained by self-reports on annual follow-up questionnaires and validated in a subsample of participants through a review of medical records with a positive predictive value of self-reported DM of 98.3% (20). Chocolate consumption was obtained from a baseline semiquantitative FFQ (1997–2001). In a single question, participants were asked to answer "Please fill in your average use, during the year, of each specified food; chocolate (1 oz)." Possible answers included never or <1 serving/mo, 1–3 servings/mo, 1, 2–4, and 5–6 servings/wk, and 1, 2–3, 4–5, and ≥6 servings/d. Other dietary factors (whole grain, red meat, eggs, nuts, and candies without chocolate) were assessed via the FFQ. Glycemic index, fiber, magnesium, caffeine, and flavonoids were computed for each food item on the FFQ by using the food-composition database from the Harvard School of Public Health and manufacturer information. The validity and reproducibility of the FFQ in health professionals have been reported previously (21, 22). We used the residual method to adjust nutrients for energy intake (23).

Other baseline covariates included cohort status (recruited in 1982 and participated in the PHS II, recruited in 1982 and did not participate in the PHS II, and recruited in 1997), age, BMI, smoking (never, past, and current), vigorous exercise (<1 and ≥1 time/wk), alcohol consumption (rarely or never, 1 drink/mo to 1 drink/wk, 2–6 drinks/wk, and ≥1 drink/d), history of hypercholesterolemia (no or yes), and history of hypertension (no or yes).

Statistics

Chocolate consumption was classified into the following 4 categories: never or rarely (subsequently referred to as "none"), 1–3 servings/mo, and 1 and 2 servings/wk (we merged the last 6 extreme categories because of small sample sizes in these groups). There were missing data on exercise (n = 291), alcohol intake (n = 100), and intakes of whole grain (n = 26), red meat (n = 17), and nuts (n = 172).We created indicator variables for missing variables and included them in the multivariable model.

We presented baseline characteristics across categories of chocolate consumption by using generalized linear models for continuous variables and chi-square tests for categorical variables. The person-time of follow-up was computed from baseline until the first occurrence of DM, death, or the date of last known contact. We used Cox proportional hazards models to estimate HRs with corresponding 95% CIs. An initial model adjusted for age; a second model further controlled for cohort status, smoking status (never, current, and past), vigorous exercise (<1 and ≥1 time/wk), alcohol intake (rarely or never, 1 drink/mo to 1 drink/wk, 2–6 drinks/wk, and ≥1 drink/d), and BMI (continuous) (model 2). The final model adjusted for covariates in model 2 plus total caloric intake (in quartiles), whole grain (in quartiles), red meat (in quartiles), and nut (in quartiles) intakes (model 3). Covariates were selected on the basis of knowledge from previous studies (18, 24, 25) or if the regression coefficient for chocolate consumption (≥2 servings/wk) changed by 10% when adding potential confounders to a model singly or jointly (26). We also considered additional adjustment beyond model 3 for other dietary factors, including nonchocolate candy, eggs, glycemic index, fiber, magnesium, caffeine, and flavonoids. We also considered a multivariable model adjusted for potential mediators such as a history of hypertension and hypercholesterolemia. We tested for a linear trend by using median servings per day in each category of chocolate as a continuous variable.

In secondary analyses, we repeated analyses in 15,999 men free of prevalent CVD (myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, and stroke) or heart failure at baseline because these comorbidities may have led to a change in dietary habits. We evaluated the effect modification by age (<65 and ≥65 y), BMI (in kg/m^2) (<25 and ≥25), and history of hypercholesterolemia. We performed several sensitivity analyses to assess the robustness of our findings. We excluded men with a history of cancer (except skin cancer) because these men may have changed their dietary habits, and some epidemiologic studies suggested significant association of DM and risk of cancer (27, 28). Furthermore, we excluded men with missing values on the major covariates vigorous exercise, alcohol intake, smoking, and intakes of whole grain, red meat, and nuts. For each of these sensitivity analyses, results were generally similar to main findings and are not presented. All analyses were completed with SAS software (version 9.3; SAS Institute). All statistical tests were 2-sided, and $P < 0.05$ was considered significant.

RESULTS

The mean (±SD) age at baseline was 66.3 ± 9.2 y. Baseline characteristics are summarized in **Table 1** by amount of chocolate consumption. Higher intake of chocolate was not associated with a significant trend for higher intake of energy-adjusted micronutrients such as caffeine and flavonoids. During a mean follow up of 9.2 y, 1123 men (6.2%) developed DM. For self-reported chocolate consumption of none, 1–3 servings/mo, and 1 and ≥2 servings/wk, multivariable-adjusted HRs (95% CI) of DM were 1.00 (reference), 0.93 (0.79, 1.09), 0.86 (0.72, 1.04), and 0.83 (0.69, 0.99), respectively (P-trend = 0.047) (**Table 2**, model 3). Adjustment for other dietary factors did not alter

TABLE 1
Distribution of baseline characteristics of physicians according to chocolate intake assessed by FFQ[1]

	Average frequency of chocolate intake			
Variables	None	1–3 servings/mo	1 serving/wk	≥2 servings/wk
Participants, *n*	4432	5349	3649	4805
Age, y	67.0 ± 8.8	66.0 ± 9.0	66.1 ± 9.2	66.3 ± 9.9[2]
BMI, kg/m^2	25.5 ± 3.2	25.8 ± 3.3	25.7 ± 3.1	25.6 ± 3.2[2]
Smoking status,[2] %				
Past	46.0	42.8	39.3	39.0
Never	50.3	54.2	57.5	57.6
Current	3.5	3.0	3.0	3.3
Vigorous exercise, %				
<1 time/wk	36.8	36.5	35.1	35.9
≥1 time/wk	61.7	62.1	63.3	62.2
Alcohol intake,[2] %				
Rarely, never	15.3	14.6	16.5	18.9
Monthly	6.1	6.9	7.8	8.6
Weekly	35.2	38.5	39.5	39.3
Daily	43.0	39.5	35.6	32.6
Total calories, kcal/d	1528 ± 462	1617 ± 471	1695 ± 481	1863 ± 518[2]
Whole grain, servings/d	1.7 ± 1.7	1.8 ± 1.7	1.8 ± 1.6	1.7 ± 1.6[2]
Red meat, servings/d	0.6 ± 0.6	0.7 ± 0.6	0.7 ± 0.5	0.8 ± 0.6[2]
Eggs, servings/d	1.7 ± 1.4	1.8 ± 1.3	1.9 ± 1.3	2.0 ± 1.3[2]
Nuts, servings/d	1.2 ± 1.3	1.4 ± 1.3	1.6 ± 1.3	1.8 ± 1.4[2]
Candies without chocolate, servings/d	0.4 ± 1.0	1.0 ± 1.1	1.5 ± 1.2	1.7 ± 1.5[2]
Carbohydrate, g/d	216 ± 51	215 ± 43	215 ± 41	211 ± 37[2]
Glycemic index	107 ± 15	107 ± 13	107 ± 14	106 ± 14[2]
Total fat, g/d	47.8 ± 14.4	50.5 ± 12.5	52.3 ± 11.9	55.7 ± 11.5[2]
Fiber, g/d	19.8 ± 7.4	19.3 ± 6.4	18.9 ± 5.9	18.0 ± 5.5[2]
Caffeine, mg/d	195 ± 150	199 ± 151	192 ± 148	185 ± 144[2]
Total flavonoids, mg/d	345 ± 345	312 ± 288	298 ± 277	294 ± 249[2]
Magnesium, mg/d	336 ± 95	325 ± 81	318 ± 73	307 ± 70[2]
History of hypercholesterolemia, %	42.8	39.8	38.4	37.8[2]
History of hypertension, %	44.3	42.3	41.0	39.7[2]
History of cardiovascular disease, %	13.4	11.9	9.9	10.2[2]
History of heart failure, %	1.6	1.7	1.7	2.0
History of cancer, %	11.7	10.7	11.5	11.8

[1]All values for continuous variables are means ± SDs, and all values for categorical variables are proportions. All nutrients are presented as energy adjusted values. Data were missing for BMI (*n* = 3), vigorous exercise (*n* = 291), alcohol intake (*n* = 100), history of hypercholesterolemia (*n* = 439), history of hypertension (*n* = 89), and intake of whole grain (*n* = 26), red meat (*n* = 17), eggs (*n* = 95), nuts (*n* = 172), and candies without chocolate (*n* = 280). FFQ, food-frequency questionnaire.

[2]$P < 0.05$, across categories of chocolate. A generalized linear model was used for continuous variables, and the chi-square test was used for categorical variables.

the main results (data not shown). As expected, after additional adjustment for potential intermediate factors (history of hypertension and hypercholesterolemia), there was a slight attenuation of the HR (95% CI) from 0.83 (0.69, 0.99) to 0.86 (0.72, 1.03) for ≥2 chocolate servings/wk compared with nonconsumers (*P*-trend = 0.11).

In secondary analyses, the exclusion of men without history of CVD or heart failure led to a slightly stronger inverse association

TABLE 2
HRs (95% CIs) for DM by category of chocolate intake in 18,235 male physicians[1]

				HRs (95% CIs) for DM		
Frequency of chocolate intake	*n*	Cases, *n* (%)	Incidence rate/1000 PY	Age-adjusted model 1	Multivariate model 2	Multivariate model 3
None	4432	275 (6.2)	6.9	Referent	Referent	Referent
1–3 servings/mo	5349	345 (6.5)	7.0	1.02 (0.87, 1.19)	0.97 (0.83, 1.14)	0.93 (0.79, 1.09)
1 serving/wk	3649	217 (6.0)	6.4	0.93 (0.78, 1.11)	0.91 (0.76, 1.08)	0.86 (0.72, 1.04)
≥2 servings/wk	4805	286 (6.0)	6.5	0.94 (0.80, 1.11)	0.89 (0.75, 1.05)	0.83 (0.69, 0.99)
P-linear trend	—	—	—	0.39	0.17	0.047

[1]Cox proportional hazards models were used to estimate HRs (95% CIs). Model 1 was adjusted for age. Model 2 was adjusted as for model 1 and for cohort status, BMI, smoking status, exercise, and alcohol consumption. Model 3 was adjusted as for model 2 and for total caloric intake and intakes of whole grains, nuts, and red meat. DM, type 2 diabetes mellitus; PY, person-years.

TABLE 3
HRs (95% CIs) for DM by category of chocolate intake in 15,999 physicians without cardiovascular disease or heart failure at baseline[1]

				HRs (95% CIs) for DM		
Frequency of chocolate intake	*n*	Cases, *n* (%)	Incidence rate/1000 PY	Age-adjusted model 1	Multivariate model 2	Multivariate model 3
None	3806	240 (6.3)	6.8	Referent	Referent	Referent
1–3 servings/mo	4672	280 (6.0)	6.3	0.93 (0.79, 1.11)	0.88 (0.74, 1.05)	0.85 (0.72, 1.02)
1 serving/wk	3250	182 (5.6)	5.9	0.86 (0.71, 1.05)	0.84 (0.69, 1.02)	0.81 (0.66, 0.98)
≥2 servings/wk	4271	241 (5.6)	6.0	0.88 (0.73, 1.05)	0.82 (0.68, 0.98)	0.77 (0.63, 0.93)
P-linear trend	—	—	—	0.21	0.07	0.02

[1]Cox proportional hazards models were used to estimate HRs (95% CIs). Model 1 was adjusted for age. Model 2 was adjusted as for model 1 and for cohort status, BMI, smoking status, exercise, and alcohol consumption. Model 3 was adjusted as for model 2 and for total caloric intake and intakes of whole grains, nuts, and red meat. DM, type 2 diabetes mellitus; PY, person-years.

between chocolate consumption and risk of DM [HR (95% CI) for ≥2 chocolate servings/wk: 0.77 (0.63, 0.93)] (**Table 3**). No significant association between chocolate consumption and DM was observed in 2236 men with CVD or heart failure (*P*-trend = 0.43).

There was a significant effect modification by BMI (*P*-interaction = 0.04) (**Table 4**), age, and chocolate intake on DM risk (*P*-interaction = 0.03) (Table 4). In subgroup analysis, only men with normal BMI (<25) or aged <65 y showed an inverse association of chocolate consumption and risk of DM. A history of hypercholesterolemia did not modify the association between chocolate and DM (*P*-interaction = 0.65).

DISCUSSION

In this prospective study, self-reported chocolate intake was significantly and inversely associated with incident DM and such relation appeared to be limited to normal–body weight and younger men after comprehensive adjustment for lifestyle, clinical, and dietary risk factors.

Other studies supported our finding that chocolate consumption may lower risk of DM (8, 17). In a Japanese observational study, the consumption of ≥1 serving chocolate/wk compared with none was inversely associated with risk of DM in men [HR (95% CI): 0.65 (0.43, 0.97)] (8). The Japanese population was

TABLE 4
HRs (95% CIs) for DM by category of chocolate intake stratified by BMI and age[1]

				HRs (95% CIs) for DM		
Frequency of chocolate intake	*n*	Cases, *n* (%)	Incidence rate/1000 PY	Age-adjusted model 1	Multivariate model 2	Multivariate model 3
BMI <25 kg/m^2 (*n* = 8218)[2]						
None	2059	78 (3.8)	4.2	Referent	Referent	Referent
1–3 servings/mo	2332	80 (3.4)	3.7	0.88 (0.65, 1.21)	0.86 (0.63, 1.17)	0.84 (0.61, 1.15)
1 serving/wk	1620	55 (3.4)	3.6	0.87 (0.62, 1.23)	0.82 (0.58, 1.16)	0.81 (0.57, 1.15)
≥2 servings/wk	2207	57 (2.6)	2.8	0.67 (0.47, 0.94)	0.62 (0.44, 0.87)	0.59 (0.42, 0.85)
P-linear trend	—	—	—	0.02	0.007	0.005
BMI ≥25 kg/m^2 (*n* = 10,014)[2]						
None	2373	197 (8.3)	9.1	Referent	Referent	Referent
1–3 servings/mo	3016	265 (8.8)	9.5	1.05 (0.87, 1.26)	1.02 (0.85, 1.23)	0.97 (0.81, 1.18)
1 serving/wk	2028	162 (8.0)	8.6	0.94 (0.77, 1.16)	0.94 (0.76, 1.16)	0.90 (0.72, 1.11)
≥2 servings/wk	2597	229 (8.8)	9.6	1.06 (0.87, 1.28)	1.01 (0.83, 1.22)	0.93 (0.76, 1.15)
P-linear trend	—	—	—	0.64	0.97	0.57
Age <65 y (*n* = 8736)[3]						
None	2019	139 (6.9)	7.0	Referent	Referent	Referent
1–3 servings/mo	2601	179 (6.9)	6.9	1.01 (0.81, 1.26)	0.98 (0.79, 1.23)	0.93 (0.74, 1.17)
1 serving/wk	1808	114 (6.3)	6.3	0.91 (0.71, 1.17)	0.91 (0.71, 1.17)	0.87 (0.68, 1.13)
≥2 servings/wk	2308	134 (5.8)	5.7	0.84 (0.66, 1.06)	0.78 (0.61, 0.99)	0.73 (0.57, 0.94)
P-linear trend	—	—	—	0.08	0.02	0.01
Age ≥65 y (*n* = 9499)[3]						
None	2413	136 (5.6)	6.7	Referent	Referent	Referent
1–3 servings/mo	2748	166 (6.0)	7.0	1.04 (0.83, 1.30)	0.99 (0.79, 1.24)	0.96 (0.76, 1.21)
1 serving/wk	1841	103 (5.6)	6.5	0.96 (0.74, 1.24)	0.93 (0.72, 1.21)	0.90 (0.69, 1.17)
≥2 servings/wk	2497	152 (6.1)	7.3	1.09 (0.87, 1.38)	1.06 (0.84, 1.33)	0.98 (0.77, 1.25)
P-linear trend	—	—	—	0.44	0.54	0.96

[1]Cox proportional hazards models were used to estimate HRs (95% CIs). Model 1 was adjusted for age. Model 2 was adjusted as for model 1 and for cohort status, BMI, smoking status, exercise, and alcohol consumption. Model 3 was adjusted as for model 2 and for total caloric intake and intakes of whole grains, nuts, and red meat. DM, type 2 diabetes mellitus; PY, person-years.

[2]*P*-interaction = 0.04.

[3]*P*-interaction = 0.03.

younger (mean age: 57 y) than our population (mean age: 66 y); furthermore, BMI was lower in Japanese subjects (mean BMI: 22.3) than the PHS cohort (mean BMI: 25.7). A stronger association observed in PHS subjects who were <65 y old and those with normal BMI was consistent with Japanese results.

A recent prospective analysis of the Atherosclerosis Risk in Communities cohort showed that, in men, consumption of chocolate was associated with 29% (95% CI: 10%, 64%) lower risk of DM for <1 serving/mo, 44% (24%, 59%) lower risk of DM for 1–4 servings/wk, and 32% (95% CI: −6%, 56%) lower risk of DM for ≥2 servings/wk (17). As with the Japanese study, this relation was stronger than in our study, possibly explained by a younger population (mean age: 53–54 y across categories of chocolate consumption). However, BMI was higher in the Atherosclerosis Risk in Communities study (mean BMI: 27.2–27.8), and results did not change after adjustment for BMI (17).

What might explain a slightly stronger inverse association between chocolate consumption and risk of DM after the exclusion of men with CVD and heart failure? CVD or heart failure may lead to dietary changes that confound the association of chocolate consumption with risk of DM. It is also possible that competing causes of death or different risk factors in overweight or obese men might have increased the background rate of DM, thereby making it more difficult to detect a small increase in risk. In fact, the incidence rate of DM in men with BMI ≥25 was almost 3 times higher than that of men with normal BMI, especially in the higher chocolate-consumption group (Table 4). In our study, potential benefits of chocolate consumption were limited to individuals with BMI <25 and age <65 y, which suggested that the benefits of chocolate could be limited to this specific subgroup. Lastly, the inverse association of chocolate consumption and risk of DM was only significant when it was controlled for comprehensive life style factors including total energy consumption.

Possible mechanisms by which chocolate consumption may influence DM risk

Beneficial effects of cocoa and chocolate on risk factors related to DM were consistently reported in short-term randomized clinical trials as well as long-term observational and experimental studies. For example, cocoa or chocolate improves insulin resistance (12–14), oxidative stress (14–16), and inflammation (17, 18). Whether these results and possible mechanisms extend to an inverse association between chocolate consumption and risk of DM remains unclear.

Also uncertain is which substances in chocolate are responsible for any potential inverse association. Results from previous observational studies that evaluated the association of flavonoids or caffeine with risk of DM have been inconsistent (5–9). Adjustment for these and other key dietary components of chocolate did not greatly affect HRs of DM (data not shown).

Strengths and limitations

Our study has several strengths, including a large sample size, long follow-up, and valid ascertainment of DM. Our cohort study has some limitations. First, we were not able to differentiate types of chocolates consumed. Nevertheless, dark chocolate contains greater amounts of cocoa and higher flavonoid concentrations than does milk or white chocolate (29). Also, cocoa concentrations of chocolate in the market has a wide range [i.e., the required cocoa concentration of milk chocolate produced in the United States is lower (>10%) than for milk chocolate produced in European countries (>25%)] (30, 31). And, this could have led to an underestimation or overestimation of the true association between chocolate consumption and risk of DM. Second, our sample consisted of highly educated male physicians, possibly limiting the generalizability of our findings to other socioeconomic or ethnic groups and women. Additional studies are needed in other ethnic groups and people with lower socioeconomic status to confirm the current findings. Third, unmeasured and residual confounding could have partially explained our findings. Fourth, chocolate was self-reported in this cohort, and we could not exclude a reporting bias in our data.

In conclusion, our data are consistent with an inverse association between chocolate consumption and incident DM, which appeared only to apply in younger and normal–body weight men after controlling for comprehensive lifestyle factors.

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