Chocolate intake and heart disease and stroke in the Women's Health Initiative: a prospective analysis

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ABSTRACT

Background: Three recent meta-analyses found significant prospective inverse associations between chocolate intake and cardiovascular disease risk. Evidence from these meta-analyses suggests that such inverse associations may apply only to elderly individuals or those with pre-existing major chronic disease.

Objective: We assessed the association between habitual chocolate intake and subsequent incident coronary heart disease (CHD) and stroke, and the potential effect of modification by age.

Design: We conducted multivariable Cox regression analyses using data from 83,310 postmenopausal women free of baseline pre-existing major chronic disease in the prospective Women's Health Initiative cohort. Chocolate intake was assessed using a food-frequency questionnaire. Physician-adjudicated events or deaths were ascertained up to 30 September 2013.

Results: After exclusions, there were 3246 CHD and 2624 stroke events or deaths, representing incidence rates of 3.9% and 3.2% during 1,098,091 and 1,101,022 person-years (13.4 y), respectively. We found no association between consumption of chocolate and risk of CHD (P for linear trend = 0.94) or stroke ($P = 0.24$). The results for CHD and stroke combined were similar ($P = 0.30$), but were significantly modified by age (P for interaction = 0.02). For women age <65 y at baseline, those who ate 1 oz (28.35 g) of chocolate <1/mo, 1 to <1.5/mo, 1.5 to <3.5/mo, 3.5/mo to <3/wk, and ≥3/wk had HRs (95% CIs) of 1.00 (referent), 1.17 (1.00, 1.36), 1.05 (0.90, 1.22), 1.09 (0.94, 1.25), and 1.27 (1.09, 1.49), respectively (P for linear trend = 0.005). No association was apparent for older women.

Conclusion: We observed no association between chocolate intake and risk of CHD, stroke, or both combined in participants free of pre-existing major chronic disease. The relation for both combined was modified by age, with a significant positive linear trend and an increased risk in the highest quintile of chocolate consumption among women age <65 y. This trial was registered at clinicaltrials.gov as NCT03453073. *Am J Clin Nutr* 2018;108:41–48.

Keywords: coronary heart disease, stroke, postmenopausal women, nutrition, dietary intake and cardiovascular disease, epidemiology

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of mortality worldwide (1) and also in the United States, even though cancer has surpassed CVD in some states and population subgroups (2). A growing body of evidence suggests that chocolate may decrease the risk of CVD via an ability to lower blood pressure, improve endothelial function, and improve insulin sensitivity (3). Three recent meta-analyses (4–6) involving 10 epidemiologic long-term prospective studies found evidence of a negative association between chocolate intake and the risk of CVD, but cautioned that residual confounding or unobserved factors might explain their findings. In fact, none of the studies evaluated in these meta-analyses had excluded participants with pre-existing non-CVD major chronic disease, such as cancer and diabetes. Also, both of the analyzed studies which showed strong inverse associations had a high proportion of participants who were elderly or had pre-existing major chronic disease (7, 8). Such inverse associations may be artefactual if participants with prevalent disease and/or a greater burden of aging-related comorbidities decreased their chocolate consumption following disease diagnosis

prior to follow-up baseline. Based on this empirical evidence, we decided to test the following a priori hypotheses: *1*) the associations between chocolate intake and coronary heart disease (CHD) and stroke risk are inverse for persons free of major chronic disease, including CVD, diabetes, and cancer; *2*) these associations are less strongly inverse at younger age; and *3*) persons decrease their chocolate, energy, and fat intake and their body weight after being first diagnosed with one of these diseases.

We used data from postmenopausal women in the prospective Women's Health Initiative (WHI) cohort to evaluate the association between baseline chocolate intake and subsequent risk of CHD and stroke. We focused on these 2 CVD conditions because they are the 2 major components of CVD, and recent research suggests that the risk of both of these conditions should decrease as chocolate intake increases (3).

METHODS

Participants

Detailed descriptions of the design of the WHI have been published previously (9). In summary, between 1993 and 1998, 161,808 postmenopausal women 50–79 y of age were enrolled into the WHI Observational Study (OS) or one or more overlapping clinical trials (CTs). The OS is a longitudinal cohort study with ongoing collection of data on participant characteristics, lifestyle habits and morbidity and mortality from major chronic disease. The CTs tested: *1*) estrogen plus progestin compared with placebo for women with a uterus; *2*) estrogen-alone compared with placebo for women with hysterectomy; *3*) calcium plus vitamin D supplementation compared with placebo; and *4*) low-fat-dietary intervention compared with usual diet.

Of the original 161,808 women, 93,676 OS and 68,132 CT participants, we included all of the OS and CT control participants except those: *1*) with implausible energy intakes, defined as <600 or >5000 kcal/d; *2*) with implausible BMI (<15 or >50 kg/m^2) or height <122 cm (4 ft); *3*) who at baseline reported pre-existing major chronic disease, including diabetes, angina, myocardial infarction (MI), stroke, heart failure, coronary artery bypass graft, percutaneous coronary intervention, or cancer; and *4*) those with missing values on pre-existing major chronic disease or any exposure, outcome, or confounder variables. The remaining 83,310 women provided data for our analysis (**Figure 1**). The missing data percentage was <1.4% for all variables, except for 2 of our confounder variables, recreational physical activity and income level, for which the missing percentages were 3.3% and 4.3%, respectively.

Chocolate intake

Our exposure variable, chocolate consumption, was assessed using data from the WHI food-frequency questionnaire (FFQ), administered at baseline (year 0) and year 3. On a single line item, the FFQ asked how often over the past 3 mo the participant ate a 1 oz. (28.35 g) portion, referred to as a medium portion, of chocolate candy or candy bars. From the participants' responses, we derived 5 categories of intake frequency of a 1 oz. serving of chocolate: <1/mo, 1 to <1.5/mo, 1.5 to <3.5/mo, 3.5 times/mo to <3 times/wk, and ≥3/wk. We selected cut-off points that resulted in categories corresponding as closely as possible to quintiles, given
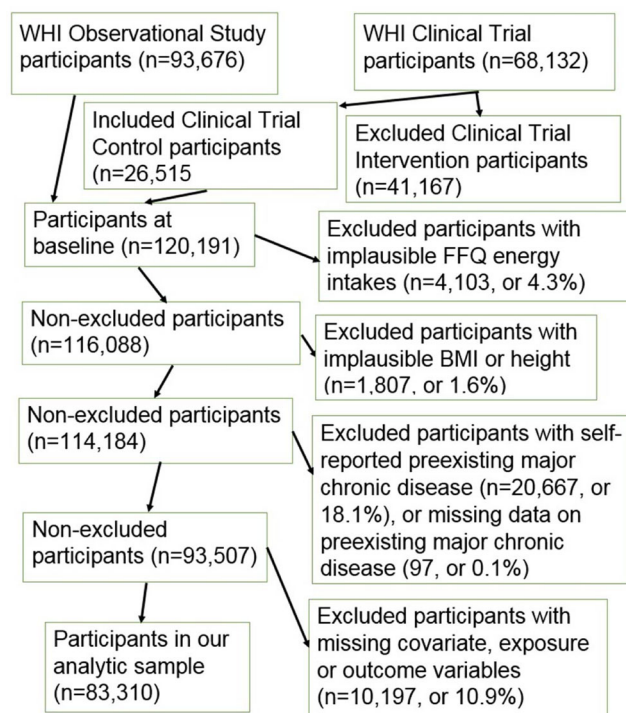
FIGURE 1 Participant flow chart. FFQ, food-frequency questionnaire; WHI, Women's Health Initiative.

that the lowest level (<1 serving/mo) accounted for more than 20% of cases. We also calculated a continuous version of chocolate intake, the number of 1-oz servings consumed/d.

Outcome variables

Our 3 primary outcome events were the first occurrence of, or death due to CHD, stroke, or both combined. For CHD, it was the first occurrence of clinical MI, definite silent MI, or death due to definite or possible CHD. For stroke, it was the first occurrence of ischemic, hemorrhagic. or other stroke, or death due to a cerebrovascular event. Outcomes were ascertained between the baseline survey (1993–1998) and 30 September 2013, and all events were adjudicated by a trained physician adjudicator using available medical records and death certificates. The WHI criteria for cardiovascular endpoints were adapted from standardized criteria, and have been reported elsewhere (10).

Our secondary objective involved assessing whether women free of major chronic disease at baseline decreased their chocolate, energy, and fat intake and their body weight after being diagnosed with a major chronic disease. Our outcome measures were the differences between the year 0 and year 3 assessments of these variables. The first 3 variables were derived from FFQ data, and body weight was measured at both visits.

Covariates

We built 2 regression models. In our basic model, the covariates were age (y), race/ethnicity (white, black or other), and WHI study arm (OS or CT control). Our full model included additional continuous and binary variables. The continuous variables were: the revised Alternative Healthy Eating Index (11); nonchocolate daily energy intake; recreational physical activity; smoking

status; alcohol intake; educational level; and income status. There was one additional binary variable: family history of CVD.

We identified potential covariates using our knowledge of the empirical literature on CVD risk factors (12). We used polynomial or categorical versions of nonbinary variables if they met our inclusion criterion, a >10% change in the regression coefficient for chocolate intake.

Statistical methods

Cox proportional hazards regression was used to estimate the multivariable adjusted HRs for CHD, stroke, and both combined for different levels of chocolate intake frequency and for a 1-oz/d (28.35 g/d) increment in chocolate intake.

Tests of interaction were conducted by inserting a cross product of the continuous version of chocolate intake (number of 1-oz servings consumed/d) and the variable being tested (age in years or BMI in kg/m^2) into our full model. Our interaction variables were selected a priori.

Tests for linear trend across quintiles of chocolate intake used the median value in each quintile as a continuous variable.

We used the t test for 2 independent samples with the Satterthwaite method to test the hypothesis that the prospective changes in chocolate, energy, and fat intake and body weight between year 0 and year 3 were different for women who experienced a first incidence of major chronic disease before year 3 and those who did not.

A 2-sided P value of <0.05 was considered significant. SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for all analyses. The WHI study is registered at CLINICTRIALS.gov as NCT00000611. Our manuscript was prepared using the STROBE guidelines for observational studies (13).

Ethics

The WHI study protocol (available at www.whi.org) was approved by institutional review boards at each participating institution, and all participants provided written informed consent. The study was conducted in accordance with the Helsinki Declaration of 1975 as revised in 1989.

RESULTS

Participant baseline characteristics

More frequent chocolate intake was associated with: *1*) higher BMI, higher energy intake, and greater likelihood of being white and smoking >15 cigarettes/d; and *2*) lower levels of recreational physical activity, healthy eating, and prevalence of major chronic disease, especially diabetes and revascularization (**Table 1**).

Prospective association between chocolate consumption and CVD risk

After exclusions, there were 83,310 participants. There were 3246 CHD, 2624 stroke, and 5563 combined CHD and stroke events or deaths, representing incidence rates of 3.9%, 3.2%, and 6.7%, respectively. The person-years of follow-up were 1,098,091, 1,101,022 and 1,087,545, respectively. The mean ± SD follow-up period was 13.4 ± 4.3 y for uncensored participants in our full-model survival analyses.

As shown in **Table 2**, there were no significant associations between chocolate intake and risk of CHD, stroke, or both combined in our full-model analyses for participants without major chronic disease at baseline.

There was a significant interaction for age (P = 0.02) but not for BMI (P = 0.93) in the analysis with CHD and stroke combined as the outcome variable. We therefore performed survival analyses in 2 subgroups, defined by age <65 y and ≥65 y. **Table 3** shows that there was no significant association for age ≥65 y, but there was a significant positive linear association (β = +0.27) with an increased risk of CVD in the highest quintile of chocolate intake for age <65 y.

Incidence of major chronic disease and prospective changes in chocolate, energy, and fat intake and body weight

Table 4 shows that women free of major chronic disease at year 0 decreased their chocolate, energy, and fat intake and body weight between year 0 and year 3 to a greater extent if they were diagnosed with a major chronic disease during the 3-y period compared with those without incident disease. The decrease was noticeably larger for chocolate intake than for energy and fat intake and body weight. Specifically, women who developed a major chronic disease had a percentage reduction in chocolate intake, energy intake, fat intake, and body weight that was larger by about 15%, 2.8%, 5%, and 1.9%, respectively, than those women who remained free of these conditions during follow-up. The percentage reduction for each characteristic was estimated as the "Yes-no year 3–year 0 difference" divided by the mean of the 2 "Year 0" values.

The decrease in chocolate intake after diagnosis of a major chronic disease prior to baseline could bias the association between chocolate and CHD or stroke to become more inverse. We therefore investigated whether a possible difference in this effect at different ages could explain the age modification we found in the association between chocolate intake and CHD and stroke combined. We repeated our full-model survival analyses for women aged <65 y and those aged ≥65 y who had major chronic disease at baseline. For women aged <65 y, the HRs (95% CI) for those who ate 1 oz. (28.35 g) of chocolate <1/mo, 1 to <1.5/mo, 1.5 to <3.5/mo, 3.5/mo to <3/wk and ≥3/wk were 1.00 [referent; n (number of events) = 293], 0.89 (0.72, 1.11; n = 113), 0.75 (0.59, 0.95; n = 97), 0.82 (0.67, 1.01; n = 143), and 0.75 (0.58, 0.96; n = 90), respectively (P for linear trend = 0.07). For women aged ≥65 y, the equivalent HRs were 1.00 (referent; n (number of events) = 747), 0.96 (0.84, 1.10; n = 283), 0.92 (0.80, 1.06; n = 277), 0.89 (0.78, 1.01; n = 369), and 0.76 (0.65, 0.89; n = 197), respectively (P for linear trend = 0.0008). Comparison of these results with those in Table 3 shows that for women aged <65 y, those without pre-existing major chronic disease exhibited a significant positive association whereas those with such a disease showed no significant association. For women aged ≥65 y, those without a pre-existing disease exhibited no significant association whereas those with one had a significant inverse association.

TABLE 1
Baseline characteristics of postmenopausal women with different levels of chocolate consumption in the WHI[1]

| | Frequency of consumption of a 1-oz (28.35 g) serving of chocolate | | | | |
Characteristics	<1/mo (n = 31,332)	1 to <1.5/mo (n = 15,093)	1.5 to <3.5/mo (n = 16,774)	3.5/mo to <3/wk (n = 22,925)	≥3/wk (n = 14,468)
Chocolate, 1-oz servings/d	0.00 ± 0.01	0.03 ± 0.00	0.07 ± 0.01	0.20 ± 0.07	0.79 ± 0.53
Age, y	64.0 ± 7.2	63.6 ± 7.2	63.4 ± 7.2	63.5 ± 7.3	63.4 ± 7.3
BMI, kg/m^2	26.9 ± 5.5	27.2 ± 5.3	27.5 ± 5.4	27.7 ± 5.5	28.4 ± 5.8
Physical activity,[2] MET-h/wk	14.6 ± 15.1	13.7 ± 14.1	13.0 ± 13.5	12.1 ± 13.2	11.1 ± 12.9
Total dietary calories, kcal/d	1424.2 ± 539.6	1483.6 ± 533.0	1576.3 ± 558.5	1704.8 ± 610.9	2016.3 ± 724.0
Nonchocolate calories, kcal/d	1423.8 ± 539.6	1479.1 ± 533.0	1566.8 ± 558.6	1679.3 ± 610.7	1913.4 ± 711.8
Healthy Eating Index[3]	51.4 ± 10.0	50.0 ± 9.6	49.2 ± 9.6	48.2 ± 9.6	46.3 ± 9.6
Family income[2]	4.2 ± 1.9	4.3 ± 1.9	4.3 ± 1.8	4.3 ± 1.8	4.3 ± 1.8
Race/ethnicity, %					
White	80.2	84.9	86.4	89.2	89.3
Black	10.6	8.1	7.7	5.6	6.0
Other	9.2	6.9	6.0	5.2	4.7
Education,[2] %					
Less than high school	21.8	20.6	20.5	20.4	21.3
High school to less than college	36.9	36.4	36.9	37.2	38.0
College to less than postgraduate study	22.8	24.0	24.0	23.4	23.2
Postgraduate study/degree or higher	18.6	19.0	18.7	19.1	17.5
Family history of CVD, %	66.1	67.4	66.9	66.6	66.5
Pre-existing major chronic disease,[4] %	21.6	18.3	16.3	16.5	16.3
Pre-existing diabetes, %	7.0	3.9	2.9	2.6	2.3
Pre-existing heart attack, %	2.8	2.3	1.9	2.0	1.9
Pre-existing stroke, %	1.6	1.4	1.1	1.2	1.2
Pre-existing heart failure, %	1.3	0.9	0.9	0.9	0.9
Pre-existing revascularization, %	2.4	2.0	1.5	1.3	1.3
Pre-existing cancer, %	11.5	11.4	10.8	11.2	11.1
Alcohol, %					
Nondrinker	12.5	10.7	9.6	9.5	9.6
Former drinker	21.0	16.9	16.6	16.8	19.0
<1 drink/mo	11.4	11.1	11.8	12.2	14.1
1 drink/mo to <1 drink/wk	18.0	21.0	21.3	20.9	21.7
1 drink/wk to <1 drink/d	23.2	27.4	28.0	28.8	25.8
≥1 drink/d	13.9	13.0	12.8	11.8	9.8
Smoking, %					
Never	50.6	51.3	50.0	51.1	50.0
Former	43.5	42.6	43.5	42.0	42.2
Current, <15/d	3.2	3.4	3.6	3.5	3.5
Current, ≥15/d	2.7	2.7	2.8	3.4	4.3

[1] All characteristics showed significant differences between levels of chocolate intake ($P < 0.05$) except for family history of CVD, based on analysis of variance, the Kruskal-Wallis test, or the chi-square test. Data are given as means ± SDs for continuous variables and as percentages for categorical variables. Data are for observational study and clinical trial control participants without: *1)* implausible FFQ energy intakes (defined as mean intakes <600 or >5000 kcal/d), BMI (kg/m^2; <15 or >50), or height <122 cm (4 ft); and *2)* no missing values for any of the characteristics in this table. CVD, cardiovascular disease; FFQ, food-frequency questionnaire; MET, metabolic equivalent; WHI, Women's Health Initiative.

[2] Educational level, physical activity, and family income were quantified by WHI researchers. Physical activity was total energy expended in recreational physical activity. Family income ranged from 1 to 9.

[3] The Modified Alternative Healthy Eating Index (10).

[4] Pre-existing serious chronic disease [yes/no—diabetes, heart attacks, stroke, heart failure, coronary artery bypass graft, revascularization (percutaneous transluminal coronary angioplasty), or cancer].

Sensitivity analyses

In order to assess the effects of using different definitions for stroke and CHD, we repeated our main full-model analyses with: *1)* stroke defined as the first occurrence of ischemic or hemorrhagic stroke, or death due to a cerebrovascular event; and *2)* CHD defined as the first occurrence of coronary revascularization, clinical MI, definite silent MI, or death due to coronary revascularization or definite or possible CHD. The results were essentially the same as those in Table 2. For instance, the HRs (95% CI) for ischemic or hemorrhagic stroke or death due to a cerebrovascular event for women who ate 1 oz. (28.35 g) of chocolate <1/mo, 1 to <1.5/mo, 1.5 to <3.5/mo, 3.5/mo to <3/wk, and >3 times/wk were 1.00 (referent; n (number of events) = 664), 1.11 (0.98, 1.26; n = 373), 1.05 (0.93, 1.19; n = 400), 1.00 (0.89, 1.13; n = 539), and 1.08 (0.94, 1.23; n = 371), respectively (P for linear trend = 0.50). Using the

TABLE 2
Chocolate intake, HRs, and 95% CIs for incident CHD, stroke, or both in the WHI[1]

Covariates in the model	Frequency[2] of chocolate consumption [1-oz (28.35 g) servings]					P for linear trend[4]
	<1/mo[3]	1 to <1.5/mo	1.5 to <3.5/mo	3.5/mo to <3/wk	≥3/wk	
Incident coronary heart disease events or death						
Age, race, and WHI study arm (n = 91,815)						
HR (95% CI)[5]	1.00	1.06 (0.95, 1.17)	1.08 (0.98, 1.19)	1.01 (0.92, 1.11)	1.08 (0.98, 1.20)	0.27
Women,[6] n	27,506	13,734	15,609	21,332	13,634	91,815
Events,[6] n	1052	555	635	835	562	3639
Full model[7] (n = 83,310)						
HR (95% CI)	1.00	1.07 (0.96, 1.19)	1.06 (0.96, 1.18)	0.98 (0.89, 1.08)	1.03 (0.92, 1.15)	0.94
Women, n	24,958	12,501	14,212	19,377	12,262	83,310
Events, n	923	502	566	745	510	3246
Incident stroke events or death						
Age, race, and WHI study arm (n = 91,815)						
HR (95% CI)	1.00	1.07 (0.95, 1.20)	1.05 (0.94, 1.17)	1.02 (0.92, 1.13)	1.20 (1.07, 1.35)	0.002
Women, n	27,506	13,734	15,609	21,332	13,634	91,815
Events, n	845	446	488	664	490	2933
Full model (n = 83,310)						
HR (95% CI)	1.00	1.07 (0.95, 1.21)	1.04 (0.92, 1.17)	0.97 (0.87, 1.09)	1.09 (0.96, 1.23)	0.24
Women, n	24,958	12,501	14,212	19,377	12,262	83,310
Events, n	752	406	446	593	427	2624
Incident coronary heart disease or stroke events or death						
Age, race, and WHI study arm (n = 91,815)						
HR (95% CI)	1.00	1.07 (0.99, 1.16)	1.06 (0.98, 1.15)	1.03 (0.96, 1.11)	1.14 (1.06, 1.24)	0.003
Women, n	27,506	13,734	15,609	21,332	13,634	91,815
Events, n	1789	950	1054	1435	998	6226
Full model (n = 83,310)						
HR (95% CI)	1.00	1.08 (0.99, 1.17)	1.05 (0.96, 1.13)	0.99 (0.92, 1.07)	1.07 (0.98, 1.16)	0.30
Women, n	24,958	12,501	14,212	19,377	12,262	83,310
Events, n	1584	860	949	1279	891	5563

[1] Incident CHD was the first occurrence of, or death due to, CHD between the baseline survey (1993–1998) and 30 September 2013. Incident stroke was the first occurrence of, or death due to, stroke in the same time period. Our sample included observational study and clinical trial control participants without: *1*) implausible FFQ energy intakes (defined as mean intakes <600 or >5000 kcal/d) or extreme energy intake (<600 or >5000 kcal/d), BMI (kg/m²; <15 or >50), or height <122 cm (4 ft); or *2*) any of the following pre-existing major chronic conditions at follow-up baseline: diabetes, angina, myocardial infarction, stroke, heart failure, coronary artery bypass graft, percutaneous coronary intervention, or cancer. CHD, coronary heart disease; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; MET, metabolic equivalent; WHI, Women's Health Initiative.
[2] Frequency of chocolate intake was assessed by means of a semi-quantitative FFQ.
[3] Referent chocolate consumption category.
[4] Tests for linear trend were performed by using the median for each chocolate intake level as the sole predictor in the model.
[5] HRs and 95% CIs were determined by means of Cox regression.
[6] Women, *n* is the number of participants at year 0 (baseline) without pre-existing serious chronic disease at year 0 who provided data on all variables at year 0. Events, *n* is the number of incident events or deaths of the condition during the 13.4-y follow-up period. *n* for the full model is lower than for the model with age, race, and WHI study arm as covariates because of missing values for some of the extra covariates in the full model.
[7] Basic model covariates were age (years), race/ethnicity (white, black, other), and WHI study arm. The full model included additional continuous and categorical variables. The continuous variables were: the revised Alternative Healthy Eating Index ([10]); nonchocolate daily energy intake (derived from FFQ data); physical activity (total energy expended from recreational physical activity in MET-h/wk); smoking status (0 = never, 1 = past, 2 = current); alcohol intake (1 = nondrinker, 2 = past drinker, 3 = <1 drink/mo, 4 = <1 drink/wk, 5 = 1 to <7 drinks/wk, 6 = ≥7 drinks/wk), educational level (11 levels), and income status (9 levels). The one additional categorical variable was family history of CVD (yes/no).

expanded version of CHD, the equivalent HRs were 1.00 (referent; *n* (number of events) = 1533), 1.01 (0.93, 1.10; *n* = 796), 1.03 (0.94, 1.11; *n* = 918), 0.97 (0.90, 1.05; *n* = 1235), and 1.01 (0.93, 1.11; *n* = 843), respectively (*P* for linear trend = 0.85).

We included the second FFQ assessment of chocolate intake, which was made at the third visit, into our predictor by averaging the 2 estimates. We then repeated our full-model analyses in Tables 2 and 3. The HRs were similar to those in Tables 2 and 3. For instance, for CHD and stroke combined, the HRs for healthy women aged <65 y who ate 1 oz. (28.35 g) of chocolate <1/mo, 1 to <1.5/mo, 1.5 to <3.5/mo, 3.5/mo to <3/wk, and >3 times/wk were 1.00 (referent; *n* (number of events) = 434), 1.02 (0.86, 1.21; *n* = 199), 1.01 (0.87, 1.16; *n* = 334), 0.91 (0.79,

1.04, *n* = 396), and 1.19 (1.01, 1.40; *n* = 265), respectively (*P* for linear trend = 0.047).

We tested the effects of including 2 variables (one at a time) that could be in the causal pathway between our predictor and outcome variable as covariates in our main full-model analyses in Tables 2 and 3. The variables were pre-existing hypertension (yes/no) and BMI. The results were essentially the same as those presented in Tables 2 and 3. For instance, after including pre-existing hypertension as a covariate in the model for women <65 y of age, the HRs (95% CI) for CHD and stroke combined for those who ate 1 oz. (28.35 g) of chocolate <1/mo, 1 to <1.5/mo, 1.5 to <3.5/mo, 3.5/mo to <3/wk, and >3 times/wk were 1.00 (referent; *n* (number of events) = 422), 1.16 (1.00,

TABLE 3
Chocolate intake, HRs, and 95% CIs for incident CHD or stroke showing the effects of age (P for interaction = 0.02) in the WHI[1]

Covariates in the model	Frequency[2] of chocolate consumption [1-oz (28.35 g) servings]					P for linear trend[4]
	<1/mo[3]	1 to <1.5/mo	1.5 to <3.5/mo	3.5/mo to <3/wk	≥3/wk	
Women aged <65 y						
Age, race, and WHI study arm (n = 52,173)						
HR (95% CI)[5]	1.00	1.14 (0.98, 1.32)	1.06 (0.92, 1.22)	1.10 (0.96, 1.25)	1.34 (1.17, 1.54)	<0.0001
Women,[6] n	15,027	7871	9082	12,253	7940	52,173
Events,[6] n	482	292	317	439	347	1877
Full model[7] (n = 47,506)						
HR (95% CI)	1.00	1.17 (1.00, 1.36)	1.05 (0.90, 1.22)	1.09 (0.94, 1.25)	1.27 (1.09, 1.49)	0.005
Women, n	13,733	7189	8287	11,148	7149	47,506
Events, n	423	264	281	401	319	1688
Women aged ≥65 y						
Age, race, and WHI study arm (n = 39,642)						
HR (95% CI)	1.00	1.04 (0.95, 1.15)	1.07 (0.97, 1.17)	1.01 (0.93, 1.09)	1.06 (0.97, 1.17)	0.35
Women, n	12,479	5863	6527	9079	5694	39,642
Events, n	1307	658	737	996	651	4349
Full model (n = 72,988)						
HR (95% CI)	1.00	1.04 (0.95, 1.15)	1.05 (0.96, 1.16)	0.95 (0.87, 1.04)	0.99 (0.89, 1.10)	0.49
Women, n	11,225	5312	5925	8229	5113	35,804
Events, n	1161	596	668	878	572	3875

[1]Incident CHD was the first occurrence of, or death due to, CHD between the baseline survey (1993–8) and 30 September 2013. Incident stroke was the first occurrence of, or death due to, stroke in the same time period. Our sample included observational study and clinical trial control participants without: *1*) implausible FFQ energy intakes (defined as mean intakes <600 or >5000 kcal/d) or extreme energy intake (<600 or >5000 kcal/d), BMI (kg/m^2; <15 or >50), or height <122 cm (4 ft); or *2*) any of the following pre-existing major chronic conditions at follow-up baseline: diabetes, angina, myocardial infarction, stroke, heart failure, coronary artery bypass graft, percutaneous coronary intervention, or cancer. CHD, coronary heart disease; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; MET, metabolic equivalent; WHI, Women's Health Initiative.

[2]Frequency of chocolate intake was assessed by means of a semi-quantitative FFQ.

[3]Referent chocolate consumption category.

[4]Tests for linear trend were performed by using the median for each chocolate intake level as the sole predictor in the model.

[5]HRs and 95% CIs were determined by means of Cox regression.

[6]Women, *n* is the number of participants at year 0 (baseline) without pre-existing serious chronic disease at year 0 who provided data on all variables at year 0. Events, *n* is the number of incident events or deaths of the condition during the 13.4-y follow-up period. *n* for the full model is lower than for the model with age, race, and WHI study arm as covariates because of missing values for some of the extra covariates in the full model.

[7]Basic model covariates were age (years), race/ethnicity (white, black, other), and WHI study arm. The full model included additional continuous and categorical variables. The continuous variables were: the revised Alternative Healthy Eating Index ([10]); nonchocolate daily energy intake (derived from FFQ data); physical activity (total energy expended from recreational physical activity in MET-h/wk); smoking status (0 = never, 1 = past, 2 = current); alcohol intake (1 = nondrinker, 2 = past drinker, 3 = <1 drink/mo, 4 = <1 drink/wk, 5 = 1 to <7 drinks/wk, 6 = ≥7 drinks/wk), educational level (11 levels), and income status (9 levels).The one additional categorical variable was family history of CVD (yes/no).

1.36; *n* = 262), 1.05 (0.90, 1.22; *n* = 281), 1.10 (0.96, 1.27; *n* = 400), and 1.29 (1.11, 1.51; *n* = 317), respectively (*P* for linear trend = 0.003).

In order to test the ability of the revised Alternative Healthy Eating Index to fully capture the effects of dietary factors on the association between chocolate and CHD and stroke risk combined, we added sodium intake, saturated fat intake, and total sugar intake, one at a time, as extra covariates in our full-model analysis in Table 2. Sodium intake was expressed in g/d. We used the residual method for saturated fat and sugar intake. None of these factors had a significant coefficient, or changed any of the chocolate HRs by more than one unit in the second decimal place.

DISCUSSION

Among postmenopausal US women in the WHI aged 50–79 y without CVD, diabetes, or cancer at baseline, chocolate intake was not associated with risk of incident CHD or stroke, both combined, or death. However, the relation for both conditions combined, the 2 major components of CVD, was modified by baseline age, with a significant positive linear trend

and an increased risk in the highest quintile of chocolate consumption among women below age 65 y, but not among older women. Women below age 65 y constituted 52.4% of our sample. These findings were not changed by any of 8 sensitivity analyses. The fact that an elevated risk only occurred among the younger women is unlikely to be explained by higher levels of any of the factors for which risk was adjusted, such as smoking, BMI, physical activity, or alcohol intake. All of our risk factor estimates were adjusted for the same factors. It seems more likely that a decrease in chocolate intake after the first diagnosis of a serious chronic illness among women in both age groups could explain why we only found an elevated risk among the younger women, as explained below. However, all of our findings require confirmation owing to the limitations inherent in our study, including the fact that we had no data on the types of chocolate consumed by our participants, as outlined below.

Previous findings of significant inverse associations between chocolate consumption and CVD may be at least partially attributable to decreases in chocolate intake that can occur after disease diagnosis/onset. We found some evidence to support this hypothesis. WHI participants initially free of major chronic

TABLE 4
Changes in characteristics of participants with and without incidence of serious chronic disease between year 0 and year 3 in the WHI cohort[1]

| | Diagnosis of serious chronic disease between year 0 and year 3 | | | | | | |
| | No (n = 56,374) | | | Yes (n = 3536) | | | |
Characteristic	Year 0	Year 3	Year 3–year 0 difference	Year 0	Year 3	Year 3–year 0 difference	Yes-no year 3–year 0 difference
Chocolate intake, oz/mo	5.19 ± 9.65	5.56 ± 9.89	0.37 ± 10.04	5.40 ± 9.79	4.95 ± 9.62	−0.44 ± 10.33	−0.81 ± 10.06****
Energy intake, kcal/d	1590.8 ± 578.7	1525.4 ± 558.2	−65.5 ± 519.2	1647.9 ± 622.4	1537.5 ± 575.4	−110.4 ± 556.0	−44.98 ± 521.4****
Fat intake, kcal/d	54.32 ± 28.84	54.71 ± 28.00	0.39 ± 24.98	58.47 ± 31.70	56.00 ± 29.57	−2.47 ± 26.81	−2.86 ± 25.09****
Body weight, kg	69.82 ± 14.04	70.83 ± 15.56	1.01 ± 7.70	73.95 ± 16.02	73.63 ± 17.21	−0.32 ± 8.42	−1.33 ± 7.74****

[1] Serious chronic disease was defined as incidence of heart attack, stroke, heart failure, revascularization, diabetes, or cancer. *P* values (****<0.0001) are based on the 2-independent sample *t* test, with the Satterthwaite method, of the difference between participants with and without incident serious chronic disease in the difference in the characteristic between year 0 and year 3. Values are means ± SDs. Data are for participants who at baseline had no self-reported pre-existing serious chronic disease, nonextreme self-reported energy intake (<600 or >5000 kcal/d) derived from an FFQ, nonextreme values of measured BMI (kg/m^2; <15 or >50) and height (<122 cm), and with no missing values for any of the characteristics in this table at year 0 or year 3. FFQ, food-frequency questionnaire; WHI, Women's Health Initiative.

disease showed a prospective 3-y 25.1% decrease in chocolate intake if they were diagnosed with a major chronic disease during the 3-y period. These women also showed significant but smaller decreases in their energy and fat intake and body weight during the 3-y period. Therefore, it seems likely that some of the significant inverse associations between chocolate intake and CVD risk observed in prior studies among those with pre-existing major chronic disease and/or a greater burden of aging-related comorbidities may be because of post-illness decreases in chocolate intake prior to the baseline assessment. Chocolate is a discretionary nutritional item with high energy and fat density. Whether intake is modified in an attempt to lose weight and decrease risk of disease progression or because serious illness directly affects food intake, the inclusion of participants with prevalent major chronic disease at baseline may introduce bias.

To our knowledge, our finding of a positive association between a high level of chocolate consumption and the risk of CHD or stroke has not been reported previously. However, a positive association is consonant with the available empirical evidence. Two prior epidemiologic analyses (14, 15) found that higher levels of chocolate consumption were followed by prospective significant increases in body weight, with a significant linear trend; and elevated body weight is a major CVD risk factor (12). The possibility that long-term chocolate consumption can cause an increase in adiposity is not surprising given the high energy and fat density of chocolate.

We tested the possibility that high levels of chocolate intake were positively associated with the risk of CHD or stroke for women aged <65 y, but not for those aged ≥65 y, could be explained by a difference in a decrease in chocolate consumption after disease diagnosis/onset in these 2 age subgroups. We found that among women aged ≥65 y, those without pre-existing major chronic disease exhibited no association, whereas those with these pre-existing conditions had a significant inverse association. For age <65 y, those without pre-existing major chronic disease exhibited a significant positive association at high levels of intake, whereas those with such a pre-existing condition demonstrated no significant association. This result suggests that, for

women in both age groups, the effect of disease diagnosis/onset was probably similar: a decrease in chocolate intake that changed the chocolate-CVD association to appear more inverse or less positive. We did not find any evidence suggesting that a difference in a decrease in chocolate consumption after disease diagnosis/onset in the 2 age subgroups could explain the difference between the chocolate-CVD association for women aged <65 y and those aged ≥65 y. Further research is needed to confirm and/or explain these observations.

One of the limitations of our study is that heavier WHI participants tend to underreport the intake of energy on the FFQ to a greater extent than lighter persons (16), and this could have affected our results. Another limitation is that the FFQ only asked about chocolate candy or candy bars, so we had no data on the types of chocolate consumed by our participants. Dark chocolate may have yielded different results in our analysis, as many of the phytochemicals in dark chocolate are at higher concentrations than in milk chocolate (17). There is evidence suggesting that dark chocolate or cocoa containing higher levels of cocoa compounds (such as flavanols) than regular milk chocolate might decrease CVD risk, by decreasing blood pressure (18), body weight (19), or diabetes risk (3, 20). Nonetheless, high levels of consumption of dark chocolate may also be associated with elevated energy intake.

In summary, we found no overall association between chocolate intake and risk of CHD, stroke, or both combined among postmenopausal women in the WHI who were free of major chronic disease at baseline. The results for both conditions combined were modified by age, with a significant positive linear trend and increased risk in the highest quintile of chocolate consumption among women below age 65 y, but not among women aged 65 y or above. Inverse associations found in previous studies that included participants with pre-existing major chronic diseases or comorbidities may be at least partially attributable to disease-induced decreases in chocolate intake. Randomized clinical trials are needed to establish the effects of chocolate or cocoa flavanol intake on incident CVD. Our results do not support any changes in chocolate intake when giving dietary advice.

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