Cocoa Intake, Blood Pressure, and Cardiovascular Mortality

The Zutphen Elderly Study

Brian Buijsse, MSc; Edith J. M. Feskens, PhD; Frans J. Kok, PhD; Daan Kromhout, PhD

Background: Small, short-term, intervention studies indicate that cocoa-containing foods improve endothelial function and reduce blood pressure. We studied whether habitual cocoa intake was cross-sectionally related to blood pressure and prospectively related with cardiovascular mortality.

Methods: Data used were of 470 elderly men participating in the Zutphen Elderly Study and free of chronic diseases at baseline. Blood pressure was measured at baseline and 5 years later, and causes of death were ascertained during 15 years of follow-up. Habitual food consumption was assessed by the cross-check dietary history method in 1985, 1990, and 1995. Cocoa intake was estimated from the consumption of cocoa-containing foods.

Results: One third of the men did not use cocoa at baseline. The median cocoa intake among users was 2.11 g/d. After adjustment, the mean systolic blood pressure in the highest tertile of cocoa intake was 3.7 mm Hg lower (95% confidence interval [CI], −7.1 to −0.3 mm Hg; $P = .03$ for trend) and the mean diastolic blood pressure was 2.1 mm Hg lower (95% CI, −4.0 to −0.2 mm Hg; $P = .03$ for trend) compared with the lowest tertile. During follow-up, 314 men died, 152 of cardiovascular diseases. Compared with the lowest tertile of cocoa intake, the adjusted relative risk for men in the highest tertile was 0.50 (95% CI, 0.32-0.78; $P = .004$ for trend) for cardiovascular mortality and 0.53 (95% CI, 0.39-0.72; $P < .001$) for all-cause mortality.

Conclusion: In a cohort of elderly men, cocoa intake is inversely associated with blood pressure and 15-year cardiovascular and all-cause mortality.

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Author Affiliations: Center for Nutrition and Health, National Institute for Public Health and the Environment, Bilthoven (Mr Buijsse and Drs Feskens and Kromhout), and Division of Human Nutrition, Wageningen University, Wageningen (Mr Buijsse and Drs Feskens, Kok, and Kromhout), the Netherlands.

COCOA HAS A RICH HISTORY, covering a period of more than 2600 years.[1] In ancient history, numerous positive properties to human health have been ascribed to cocoa and chocolate. Already in the 18th century, cocoa was believed to strengthen the heart and reduce angina pectoris,[2] but these benefits were not based on scientific evidence. After the finding that cocoa and chocolate contain phenolic compounds,[3] scientific interest was triggered. Cocoa is a rich source of flavan-3-ols, also known as flavanols or catechins, a subclass of flavonoids. The flavan-3-ols in cocoa are present as monomers,[4] and as oligomers and polymers, better known as procyanidins.[5]

In the past few years, the results of several small randomized trials were published in which the effects of cocoa-containing foods were studied on intermediate end points of cardiovascular diseases (CVDs). Consumption of chocolate or cocoa drinks rich in flavan-3-ols lowered blood pressure[6-8] and improved endothelial function[8-11] and insulin sensitivity.[7,8] Although these results are promising, most studies[6-10] used chocolate or cocoa that contained much higher amounts of flavan-3-ols than commercially available products. Furthermore, the question remains whether the observed effects are long-standing or transitory, and whether they extend to clinical CVDs.

To our knowledge, observational studies examining the association of cocoa intake with blood pressure or CVD have not been published. We, therefore, have estimated the intake of cocoa from the habitual consumption of cocoa-containing foods and evaluated whether cocoa intake was inversely related to blood pressure and cardiovascular mortality in elderly men living in Zutphen, the Netherlands.

METHODS

STUDY POPULATION

The Zutphen Elderly Study is the continuation of the Zutphen Study, the Dutch contribution to the Seven Countries Study.[12] Base-

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line examinations took place between March 9 and June 25, 1985, and repeated examinations took place in the same period in 1990 and 1995. At baseline, 367 of the 555 men in the original cohort who were still alive participated. In addition, a random sample of 711 other men of the same age and also living in Zutphen was selected. In total, 1266 men aged 65 to 84 years were invited, of whom 939 (74.2%) participated in the study. In 876 men, dietary intake was estimated. Information on risk factors and chronic disease prevalence was available for 790 men. Men with a history of CVDs, diabetes mellitus, or cancer at baseline (n=266) or those who were taking antihypertensive medication (n=54) were excluded from the analysis. Therefore, our study population consisted of 470 men.

ASSESSMENT OF DIET AND COCOA INTAKE

The habitual dietary intake of the subjects in the month preceding the interview was estimated in 1985, 1990, and 1995 by experienced dieticians using a cross-check dietary history method adapted to the Dutch situation.[13] All subjects were interviewed at home for about 1 hour in the presence of the person who usually prepared the meals. The habitual consumption of foods during the whole week was determined, and verified with the quantities of foods bought per week. Also, information on the type of diet prescribed by a physician was collected.

The intake of calories (energy) and nutrients in 1985, 1990, and 1995 was calculated using the Netherlands' food composition table from 1987/1988, 1989/1990, and 1996, respectively. The most recent version of this table[14] was used to calculate the intake of magnesium, vitamin E, beta carotene, and folate in all examination years, because only this version contains information on these nutrients. Earlier collected information on *trans* fatty acids in foods consumed in the Zutphen Elderly Study was used to calculate the intake of these fatty acids.[15]

We identified 24 cocoa-containing foods that were reported by the Zutphen elderly subjects. For each examination year, the consumption of these foods was multiplied with their individual cocoa content, which was derived from the Conversion Model for Consumer Foods to Primary Agricultural Products[16] or from food labels. The intake of cocoa from individual foods was summed to yield actual cocoa in grams per day for each subject.

The reproducibility of the dietary history method was tested 3 and 12 months after the start of the study in a sample of the present study.[13] For the consumption of sugar confectionary, which is the most important source of cocoa in the present study, the 3- and 12-month reproducibility was $r=0.72$ and $r=0.76$, respectively.[13] Baseline cocoa intake correlated with the cocoa intake that was estimated 5 and 10 years later (Spearman $r=0.45$ and $r=0.43$, respectively; $P<.001$ for both). The reproducibility of total calorie intake was about $r=0.80$ after 3 and 12 months.[13]

COLLECTION OF RISK FACTOR AND MORBIDITY DATA

Systolic and diastolic blood pressure (Korotkoff phase V) were measured twice at the end of the physical examination by 1 of 5 physicians using a random-zero sphygmomanometer (Hawksley & Sons Ltd, West Sussex, United Kingdom) while participants were in the supine position. The mean values of the 2 blood pressure measurements are presented herein. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Total and high-density lipoprotein cholesterol levels were measured in nonfasting serum samples using standard validated methods.[17] Remaining serum samples were stored at −20°C. Serum homocysteine levels were determined in stored samples 10 years after the examination.[18]

The history of myocardial infarction, angina pectoris, and intermittent claudication was ascertained using the Dutch translation of the questionnaire formulated by Rose and Blackburn.[19] For history of heart failure, diabetes mellitus, and cancer, a standardized questionnaire was developed and the physicians' conclusion was used in the present analyses. Physical activity was estimated using a validated questionnaire originally designed for retired men.[20] This questionnaire asks about the frequency and duration of different activities, such as walking, cycling, and gardening. The time spent on each activity was summed to yield minutes of physical activity. Information on cigarette smoking, socioeconomic status, and the use of antihypertensive drugs, aspirin, and anticoagulants was also collected by questionnaire.

ASCERTAINMENT OF FOLLOW-UP EVENTS

Municipal registries provided information on vital status and were checked at 5-year intervals. Two men were lost to follow-up during the study and were censored after their last physical examination. Information on the cause of death was obtained from hospital discharge data and/or general practitioners, and up to 1990 also from Statistics Netherlands, Voorburg. The final causes of death were ascertained by one clinical epidemiologist and coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*. Cardiovascular diseases refer to *ICD-9* codes 390 to 459. Because the underlying cause of death in elderly people is often difficult to ascertain, we included CVDs coded as primary (n=118), secondary (n=30), and tertiary (n=4) cause of death in our analysis. Information on the cause of death was lacking for 1 man, and his follow-up was censored at the date of death.

STATISTICAL ANALYSIS

Cocoa intake was related to blood pressure cross-sectionally, combining data from 470 men at baseline and data from 324 men who were repeatedly examined in 1990, composing 794 total observations. A random intercept model (SAS Proc Mixed; SAS Institute Inc, Cary, NC) was used to calculate adjusted means and 95% confidence intervals (CIs) of blood pressure for each tertile of cocoa intake. In addition to an age-adjusted model, we used 3 multiple regression models to adjust for other factors that are associated with cocoa intake or are well-known determinants of blood pressure. Dietary covariates were adjusted for total calorie intake according to the residual method.[21]

Relative risks (RRs) and 95% CIs for the association between cocoa intake and cardiovascular and all-cause mortality were estimated using Cox proportional hazards models in which the middle and the highest tertiles of cocoa intake were compared with the lowest tertile. In the time-dependent analyses, mortality between 1985 and 1990 was related to cocoa intake estimated in 1985; mortality between 1990 and 1995 was related to the mean cocoa intake in 1985 and 1990; and mortality between 1995 and 2000 was related to the mean cocoa intake in 1985, 1990, and 1995.[22] Besides an age-adjusted model, we used a multivariate-adjusted model that included lifestyle factors related to CVD risk and BMI as an indicator of calorie balance (model A). This model was extended with diet prescription, total calorie intake, and calorie-adjusted consumption of foods (model B). In model C, we also adjusted for dietary intake using calorie-adjusted intake of nutrients instead of foods. Adjustment for continuous distributed covariates was

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done time dependently; for discrete variables, we used baseline data. Stratified analyses were performed for major cardiovascular risk factors. All statistical tests were 2-sided.

RESULTS

COCOA INTAKE AND BASELINE CHARACTERISTICS

In 1985, one third of the study population did not use cocoa. The median intake in the middle tertile was 0.92 g/d; in the highest tertile, this was 4.18 g/d. All cocoa-containing foods that were consumed at baseline are listed in **Table 1**. Plain chocolate and chocolate bars contributed two thirds to the total intake of cocoa. Men who consumed cocoa-containing foods used more low- and medium-fat dairy foods, sugar confectionary foods, and cookies and savory foods, and were more likely to consume alcohol and nuts and seeds (**Table 2**). Cocoa intake was inversely associated with the consumption of meat and coffee. Furthermore, cocoa intake was positively related with calorie intake, and with intake of calcium (P=.03) and magnesium (P=.04). The median cocoa intake among users was 2.11 g/d in 1985, 2.30 g/d in 1990, and 2.36 g/d in 1995.

COCOA INTAKE AND BLOOD PRESSURE

After adjustment for potential confounders, cocoa intake was inversely associated with systolic and diastolic blood pressure (**Table 3**). The mean systolic blood pressure was 3.7 mm Hg lower (95% CI, –7.1 to –0.3 mm Hg; P=.03) in the highest tertile of cocoa intake compared with the lowest tertile after multivariate adjustment, including consumption of foods (model B). This difference was –3.1 mm Hg (95% CI, –6.5 to 0.2 mm Hg; P=.07) after adjustment according to model C, which included intake of nutrients rather than foods. The mean diastolic blood pressure was 2.1 mm Hg lower in the highest tertile of cocoa intake compared with the lowest tertile (95% CI, –4.0 to –0.2 mm Hg; P=.03; model B). Adjustment for covariates in model C yielded similar estimates.

Additional multivariate-adjusted analysis showed that neither systolic nor diastolic blood pressure was related to the consumption of sugar confectionary (P=.84 and P=.16 for linear trend, respectively), and to the consumption of cookies and savory foods (P=.31 and P=.20 for linear trend, respectively). After multivariate adjustment, the mean systolic blood pressure did not differ between consumers and nonconsumers of nuts and seeds (P=.44), whereas the diastolic blood pressure was higher among consumers (P=.02).

COCOA INTAKE AND MORTALITY

During the 4908 person-years of follow-up between 1985 and 2000, 314 (66.8%) of the 470 men died. Cardiovascular diseases were the cause of death for 152 men. The results of the time-dependent Cox proportional hazards regression model showed that cocoa intake was inversely related to cardiovascular mortality (**Table 4**).

Table 1. Cocoa-Containing Food Items Consumed by Elderly Men in Zutphen, the Netherlands*

Cocoa-Containing Foods	Cocoa Content, g/100 g	Contribution to Total Cocoa Intake, %
Chocolate confectionary		
Plain chocolate		
Dark	43.0	28.4
Milk	30.0	21.8
Chocolate bar with nuts	22.5	3.3
Chocolate candy bar†	15.0	9.5
Chocolates (bonbons)	18.0	2.3
M&Ms		
Chocolate	28.5	<0.1
Peanut	16.5	0.4
Chocolate cookies	9.0	1.1
Cocoa sandwich filling		
Chocolate spread	13.5	0.6
Chocolate nut spread	6.0	0.6
Chocolate confetti		
Dark	38.7	10.9
Milk	27.0	4.3
Cocoa desserts		
Chocolate custard	8.3	4.4
Chocolate pudding	2.5	0.6
Chocolate pudding with sauce	2.1	<0.1
Chocolate mousse	22.6	<0.1
Drinks		
Cocoa drink		
Full fat	1.5	2.4
Skimmed	1.5	1.9
Miscellaneous		
Cocoa powder	100	5.9
Cocoa powder sweetened	25.0	0.3
Nutritional supplement‡	42.0	1.2

*Data are given for men free of chronic diseases and not using antihypertensive drugs at baseline.
†Bounty, Mars, Milky Way (Mars Inc, Mclean, Va), and Nuts (Nestlé, Vevey, Switzerland).
‡Ovomaltine (cocoa flavor) (Novartis, Basel, Switzerland).

After adjustment for age, BMI, lifestyle factors, drug use, and food and calorie intake (model B), the RR for cardiovascular mortality for men in the highest tertile of cocoa intake was 0.50. Adjustment for intake of nutrients (model C) instead of foods resulted in similar risk estimates. Analyzing baseline cocoa intake rather than cumulative average cocoa intake in time-dependent analysis yielded similar results (multivariate-adjusted RR of cardiovascular death for the highest vs the lowest tertile, 0.51; 95% CI, 0.33-0.78; P=.006 for linear trend).

The association between cocoa intake and cardiovascular mortality did not differ significantly between strata of BMI, cigarette smoking, physical activity, calorie intake, alcohol consumption, or socioeconomic status (P>.30 for all) (**Table 5**).

The consumption of sugar confectionary was not significantly associated with cardiovascular mortality (P=.54 for linear trend), nor was the consumption of cookies and savory foods (P=.45 for linear trend), nor the consumption of nuts and seeds (P=.12).

To explore whether blood pressure contributed to the lower cardiovascular mortality risk observed in cocoa users, we also adjusted for baseline blood pressure in model

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Table 2. Selected Characteristics of Elderly Men in 1985 in Zutphen, the Netherlands, by Tertiles of Cocoa Intake*

Characteristic	Tertile of Cocoa Intake: Lowest (n = 165)	Middle (n = 149)	Highest (n = 156)	*P* Value†
Cocoa intake, g/d‡	0 (0-0)	0.92 (0.60-1.45)	4.18 (2.90-6.10)	NA
Demographics, lifestyle, risk factors, and drug use				
Age, y	72.1 (5.6)	72.0 (5.4)	71.3 (4.4)	.38
High socioeconomic status§	55 (33.3)	45 (30.2)	49 (31.4)	.83
Positive family CVD history§	28 (17.0)	29 (19.5)	28 (17.9)	.85
Leisure time physical activity, h/wk‡	10.5 (4.5-20.5)	9.8 (4.5-18.9)	10.7 (6.3-20.4)	.40
Current cigarette smoking§	59 (35.8)	47 (31.5)	52 (33.3)	.73
Alcohol consumer§	117 (70.9)	115 (77.2)	130 (83.3)	.03
Prescribed diet§	25 (15.2)	19 (12.8)	14 (9.0)	.24
Use of vitamin supplements§	25 (15.2)	19 (12.8)	22 (14.1)	.83
Body mass index‖	25.9 (3.2)	25.4 (3.0)	25.3 (2.7)	.24
Resting heart rate, beats/min¶	70.7 (10.8)	70.9 (11.9)	70.8 (10.6)	.97
Serum cholesterol, mg/dL				
Total	237.1 (40.5)	232.0 (44.8)	236.7 (41.7)	.53
HDL	45.2 (13.5)	44.4 (11.2)	43.6 (9.7)	.46
Serum homocysteine, mg/L	2.0 (1.1)	2.0 (0.8)	2.0 (1.1)	.96
Aspirin use§	23 (13.9)	18 (12.1)	12 (7.7)	.20
Anticoagulant use§	25 (15.2)	16 (10.7)	17 (10.9)	.39
Food intake, g/d				
Bread and cereal products	165 (72)	162 (61)	158 (63)	.66
Potatoes	182 (96)	165 (84)	181 (88)	.17
Vegetables	181 (77)	173 (65)	169 (61)	.27
Fruits‡	157 (100-243)	189 (116-271)	167 (112-263)	.13
Low- and medium-fat dairy products‡	250 (124-461)	321 (165-493)	330 (212-490)	.03
Meat	122 (50)	113 (40)	109 (37)	.02
Fish	18 (21)	20 (23)	19 (24)	.82
Butter and hard margarine	49 (37)	55 (39)	54 (35)	.35
Vegetable oil and soft margarine‡	5 (0-22)	2 (0-23)	3 (0-21)	.26
Sugar confectionery other than chocolate	47 (37)	53 (34)	61 (38)	<.001
Cookies and savory foods	31 (29)	40 (29)	50 (34)	.003
Coffee‡	428 (288-624)	396 (226-496)	400 (284-517)	.05
Tea‡	372 (201-590)	392 (180-600)	400 (223-610)	.60
Nuts and seeds consumers§	53 (32.1)	60 (40.3)	86 (55.1)	<.001
Calorie intake, kcal#	2104 (528)	2236 (458)	2395 (514)	<.001

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; NA, data not applicable.
SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert homocysteine to micromoles per liter, multiply by 7.397.
*Data are given as mean (SD) unless otherwise indicated. Data are given for men free of chronic diseases and not using antihypertensive drugs at baseline.
†Based on the analysis of variance, Kruskal-Wallis test, or χ^2 test.
‡Data are given as median (interquartile range).
§Data are given as number (percentage) of each group.
‖Calculated as weight in kilograms divided by the square of height in meters.
¶Based on 461 observations because of missing data.
#Calories contributed by alcohol are not included.

B. Neither systolic nor diastolic blood pressure, however, affected our risk estimates.

Cocoa intake was also inversely related to all-cause mortality in time-dependent analysis (Table 4). Similar results were obtained when baseline cocoa intake was related to 15-year all-cause mortality (multivariate-adjusted RR for the highest vs the lowest tertile, 0.59; 95% CI, 0.44-0.79; *P*=.003 for trend).

COMMENT

In the present study, usual daily cocoa intake was inversely related to blood pressure in cross-sectional analysis. In prospective analysis, usual cocoa intake was associated with a 45% to 50% lower risk of cardiovascular and all-cause death.

To our knowledge, the present study is the first epidemiological study reporting inverse relationships of cocoa intake with blood pressure and with cardiovascular and all-cause mortality. In the Harvard Alumni Study,[23] consumers of candy had a lower risk of all-cause mortality compared with subjects who almost never consumed candy. However, the investigators were not able to differentiate between consumption of chocolate and sugar candy. In the Nurses' Health Study, the frequency of consumption of chocolate bars and chocolate pieces was not associated with a lower risk of coronary heart disease after 14 years of follow-up.[24] Because cocoa is not only present in chocolate, this association may have been underestimated in this study.

A major concern in observational studies is the possibility of residual confounding. In our study, cocoa us-

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Table 3. Systolic and Diastolic Blood Pressure According to Cocoa Intake Among Elderly Men in Zutphen, the Netherlands*

Blood Pressure	Tertile of Cocoa Intake†			*P* Value for Trend
	Lowest (<0.36 g/d)	Middle (0.36-2.30 g/d)	Highest (>2.30 g/d)	
Systolic				
Crude	149.7 (147.3-152.2)	148.8 (146.5-151.1)	147.0 (144.6-149.5)	.08
Age adjusted	149.6 (147.2-152.0)	148.8 (146.4-151.1)	147.0 (144.6-149.5)	.09
Model‡				
A	149.9 (147.4-152.4)	148.9 (146.6-151.2)	146.9 (144.4-149.4)	.07
B	150.2 (147.7-152.8)	149.0 (146.7-151.3)	146.5 (144.0-149.1)	.03
C	150.0 (147.5-152.6)	148.8 (146.5-151.2)	146.9 (144.4-149.4)	.06
Diastolic				
Crude	84.4 (82.9-85.8)	83.6 (82.3-85.0)	82.2 (80.8-83.6)	.02
Age adjusted	84.5 (83.1-85.9)	83.7 (82.3-85.0)	82.2 (80.8-83.6)	.01
Model‡				
A	84.2 (82.8-85.6)	83.8 (82.5-85.1)	82.5 (81.1-83.8)	.05
B	84.4 (83.0-85.8)	83.8 (82.5-85.1)	82.3 (80.9-83.7)	.03
C	84.3 (82.9-85.7)	83.8 (82.5-83.7)	82.3 (80.9-83.7)	.03

*Data are given for men free of chronic diseases and not using antihypertensive drugs at baseline.
†Data are given as mean (95% confidence interval) blood pressure, measured in millimeters of mercury.
‡Model A was adjusted for age (continuous), body mass index (continuous), alcohol intake (yes or no), physical activity (continuous), cigarette smoking (yes or no), diet prescription (yes or no), aspirin use (yes or no), anticoagulant use (yes or no), and the physician who measured blood pressure (categorical); B, those variables given for model A and adjustment for consumption of vegetables (continuous), fruit (continuous), meat (continuous), low- and medium-fat dairy (continuous), nuts and seeds (continuous), sugar confectionary other than chocolate (continuous), cookie and savory foods (continuous), coffee (continuous), and total calorie intake (continuous); and C, those variables given for model A and adjustment for intake of potassium (continuous), sodium (continuous), calcium (continuous), magnesium (continuous), and total calories (continuous).

Table 4. Relative Risks for the Association Between Cocoa Intake and 15-Year Mortality Among Elderly Men in Zutphen, the Netherlands*

Mortality Data	Tertile of Cocoa Intake			*P* Value for Trend
	Lowest (<0.50 g/d)	Middle (0.50-2.25 g/d)	Highest (>2.25 g/d)	
No. of subjects	161	147	162	NA
Person-time, person-years	1481	1573	1854	NA
Total cardiovascular mortality				
No. (%) of cases	58 (36.0)	50 (34.0)	44 (27.2)	NA
Mortality (per 1000 person-years)	39.2	31.8	23.7	NA
RR (95% CI)				
Age adjusted	1.00	0.79 (0.54-1.15)	0.58 (0.39-0.86)	.008
Models†				
A	1.00	0.84 (0.57-1.24)	0.67 (0.45-1.01)	.05
B	1.00	0.70 (0.47-1.05)	0.50 (0.32-0.78)	.004
C	1.00	0.79 (0.53-1.19)	0.50 (0.32-0.78)	.002
All-cause mortality				
No. (%) of cases	122 (75.8)	100 (68.0)	92 (56.8)	NA
Mortality (per 1000 person-years)	82.4	63.6	49.6	NA
RR (95% CI)				
Age adjusted	1.00	0.76 (0.58-0.99)	0.57 (0.43-0.75)	<.001
Models†				
A	1.00	0.81 (0.62-1.05)	0.65 (0.49-0.86)	<.001
B	1.00	0.73 (0.55-0.97)	0.53 (0.39-0.72)	<.001
C	1.00	0.79 (0.60-1.05)	0.52 (0.38-0.71)	<.001

Abbreviations: CI, confidence interval; NA, data not applicable; RR, relative risk.
*Data are given for men free of chronic diseases and not using antihypertensive drugs at baseline.
†Model A was adjusted for age (continuous), body mass index (continuous), cigarette smoking (yes or no), alcohol consumption (yes or no), physical activity (continuous), use of aspirin (yes or no), and use of anticoagulants (yes or no); B, those variables given for A and adjustment for diet prescription (yes or no), consumption of vegetables (continuous), fruit (continuous), low- and medium-fat dairy (continuous), meat (continuous), sugar confectionary other than chocolate (continuous), cookies and savory foods (continuous), nuts and seeds (continuous), coffee (continuous), and total calorie intake (continuous); and C, those variables given for A and adjustment for diet prescription (yes or no), dietary cholesterol (continuous), and intake of *trans* fatty acids (continuous), saturated fat (continuous), folic acid (continuous), vitamin C (continuous), vitamin E (continuous), beta carotene (continuous), potassium (continuous), sodium (continuous), calcium (continuous), magnesium (continuous), and total calories (continuous).

ers consumed less meat and coffee; consumed more dairy, sugar confectionary, cookies, and savory foods; and were more likely to use alcoholic drinks and nuts and seeds. Consequently, cocoa intake was positively associated with calorie intake. However, we did not observe a positive association of cocoa intake with BMI or physical activ-

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Table 5. Relative Risks for the Association Between Cocoa Intake and 15-Year Cardiovascular Mortality Among Elderly Men in Zutphen, the Netherlands, Stratified by Major Risk Factors*

Variable	Tertile of Cocoa Intake: Lowest (<0.50 g/d)	Medium (0.50-2.25 g/d)	Highest (>2.25 g/d)	*P* Value for Trend
Body mass index†				
≥25	1.00	0.90 (0.53-1.51)	0.55 (0.31-0.98)	.03
<25	1.00	0.63 (0.31-1.25)	0.40 (0.20-0.79)	.01
Cigarette smoking				
Yes	1.00	0.59 (0.29-1.22)	0.42 (0.18-0.95)	.06
No	1.00	0.76 (0.45-1.30)	0.52 (0.30-0.92)	.03
Physical activity				
High	1.00	1.31 (0.41-4.20)	0.40 (0.11-1.54)	.07
Low	1.00	0.67 (0.42-1.05)	0.50 (0.31-0.81)	.009
Calorie intake				
High	1.00	0.54 (0.28-1.06)	0.48 (0.26-0.87)	.04
Low	1.00	0.95 (0.56-1.63)	0.54 (0.28-1.05)	.06
Alcohol consumption				
Yes	1.00	0.65 (0.41-1.02)	0.51 (0.32-0.84)	.02
No	1.00	1.29 (0.45-3.74)	0.18 (0.04-0.73)	.01
Socioeconomic status				
High	1.00	0.59 (0.23-1.48)	0.42 (0.16-1.13)	.12
Low	1.00	0.75 (0.46-1.21)	0.46 (0.27-0.78)	.004

*Data are given as multivariate-adjusted relative risk (95% confidence interval) unless otherwise indicated. Data are given for men free of chronic diseases and not using antihypertensive drugs at baseline. Data were adjusted for age (continuous), cigarette smoking (yes or no), alcohol consumption (yes or no), physical activity (continuous), use of aspirin (yes or no), use of anticoagulants (yes or no), body mass index (continuous), diet prescription (yes or no), consumption of vegetables (continuous), fruit (continuous), low- and medium-fat dairy (continuous), meat (continuous), sugar confectionary other than chocolate (continuous), cookies and savory foods (continuous), nuts and seeds (continuous), and coffee (continuous), and total calorie intake (continuous).

†Calculated as weight in kilograms divided by the square of height in meters.

ity. Because BMI was measured accurately, we cannot rule out that residual confounding by physical activity, and by dietary factors, may partly explain our results.

Chocolate confectionary contributed about two thirds to the total intake of cocoa in our study. We considered the possibility of reverse causation, ie, that healthy subjects consume more chocolate confectionary than those who are not healthy. However, we limited our study to subjects without chronic diseases and to those not using antihypertensive drugs at baseline. Also, the association between cocoa intake and cardiovascular mortality did not differ between subjects with a high and low level of physical activity, which can also be considered as a marker of general health. Finally, the consumption of sugar confectionary other than chocolate, cookies and savory foods, and nuts and seeds, which were all strongly related to cocoa intake, was not associated with cardiovascular mortality, suggesting a specific effect of cocoa on cardiovascular mortality.

A few small short-term intervention studies have evaluated the effect of dark chocolate consumption on blood pressure. In hypertensive and normotensive persons, daily consumption of 100 g of dark chocolate for 2 weeks reduced the average systolic blood pressure between 4.1 and 11.9 mm Hg and the average diastolic blood pressure between 1.8 and 8.5 mm Hg.[6,8] However, daily consumption of 46 g of dark chocolate did not affect blood pressure after 2 weeks in healthy subjects.[10] In summary, these studies suggest that large amounts of dark chocolate lower blood pressure, whereas a smaller amount appears to have no effect.

The present study indicates that men with a usual daily cocoa intake of about 4.2 g, which is equal to 10 g of dark chocolate per day, had a lower systolic and diastolic blood pressure compared with men with a low cocoa intake. Although this amount is one tenth of the dose that is used in most intervention studies, it suggests that long-term daily intake of a small amount of cocoa may lower blood pressure.

Mechanistic studies suggest that the flavan-3-ols in cocoa-containing foods are likely to be responsible for the reduction in blood pressure and the improvement of endothelial function. Consumption of flavan-3-ol–rich chocolate or cocoa is shown to increase arterial[9,11] and peripheral vasodilation,[10] whereas this effect is less[10] or absent[9,11] after consumption of flavan-3-ol–low chocolate or cocoa. An increased activity of nitric oxide is likely to play a major role in this process.[9,10] This is supported by the observation that polymeric procyanidins increased endothelial nitric oxide synthase activity in cultured endothelial cells.[25] Although there is little doubt that flavan-3-ols have a beneficial effect on endothelial function and blood pressure, other bioactive substances in cocoa, including theobromine,[26] may also contribute to its effects.

The lower cardiovascular mortality risk associated with cocoa intake could not be attributed to the lower blood pressure observed with cocoa use. An explanation may be that blood pressure itself was not a risk factor for cardiovascular and all-cause mortality in the Zutphen Elderly Study.[27] Our findings, therefore, suggest that the lower cardiovascular mortality risk related with cocoa intake is mediated by mechanisms other than lowering blood pressure. The improvement of endothelial function by flavan-3-ols in cocoa may be a plausible candidate.[8-11] Dark chocolate also exhibits several metabolic effects.[7,8] Daily 100 g of dark chocolate for 2 weeks reduced fasting insulin and glucose levels and decreased glucose and insulin responses after an oral glucose load.[7,8] Cocoa-containing foods and flavan-3-ols may also reduce cardiovascular risk by the inhibition of platelet function[28-30] and low-density lipoprotein oxidation,[31-33] the modulation of cytokine production,[34-36] and the beneficial effect on serum cholesterol levels.[8,33,37]

To explore whether possible misclassification of cardiovascular mortality occurred in our study, we also studied the association of cocoa intake with all-cause mortality. We observed a similar risk for all-cause mortality as for cardiovascular mortality. This may implicate that cocoa intake is also associated with noncardiovascular mortality. Because cocoa is a rich source of antioxidants, it may also be related to other diseases that are linked to oxidative stress (eg, pulmonary diseases, including chronic obstructive pulmonary disease,[38] and certain types of cancer).[39] However, this merits further investigation.

In conclusion, to our knowledge, this is the first observational study that found that habitual cocoa intake was inversely associated with blood pressure in cross-

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sectional analysis and with cardiovascular and all-cause mortality in prospective analysis. Before drawing conclusions, confirmation by other observational and experimental studies is needed.

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Correspondence: Brian Buijsse, MSc, Center for Nutrition and Health, National Institute for Public Health and the Environment, PO Box 1, 3720 BA Bilthoven, the Netherlands (brian.buijsse@rivm.nl).
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