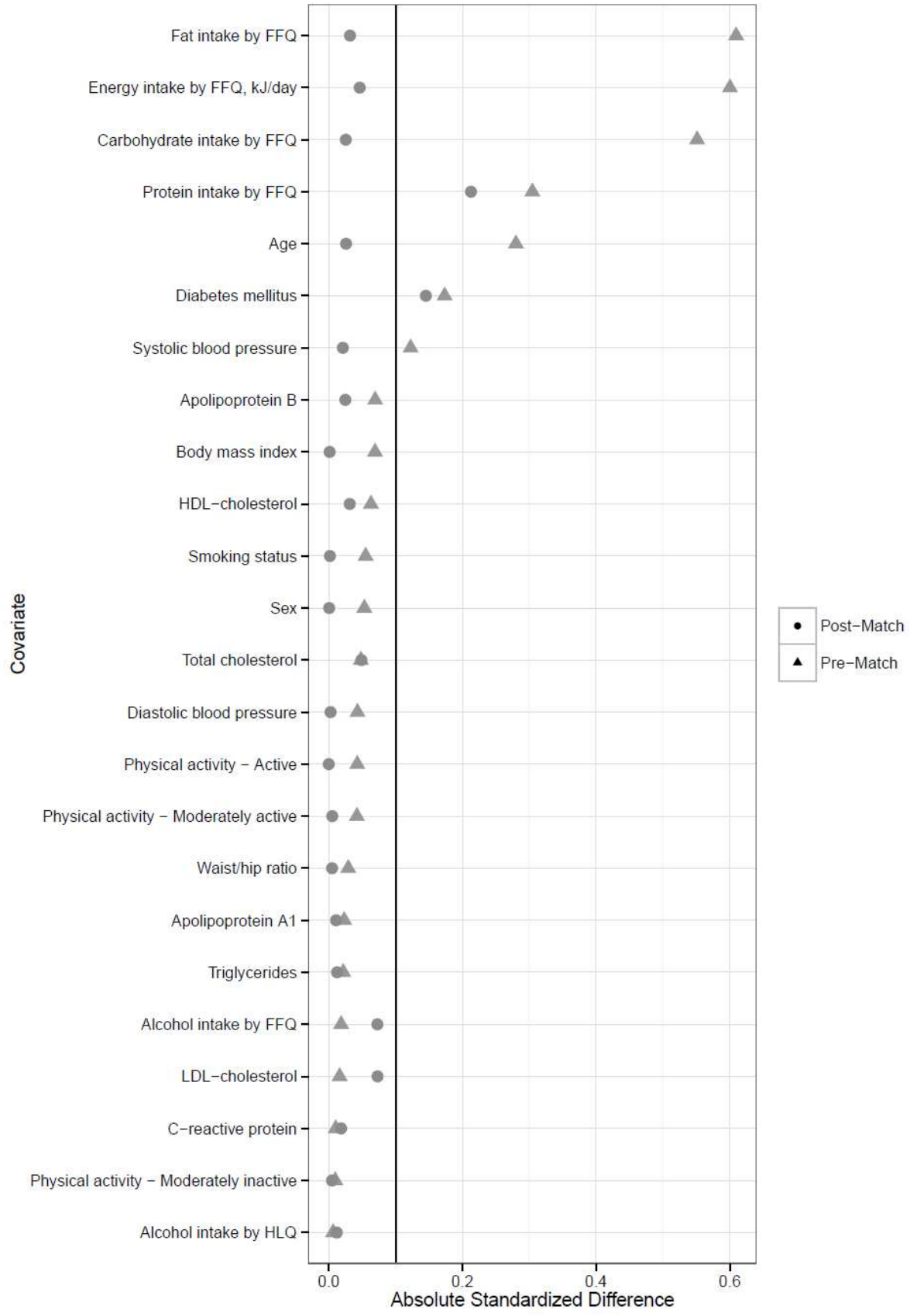
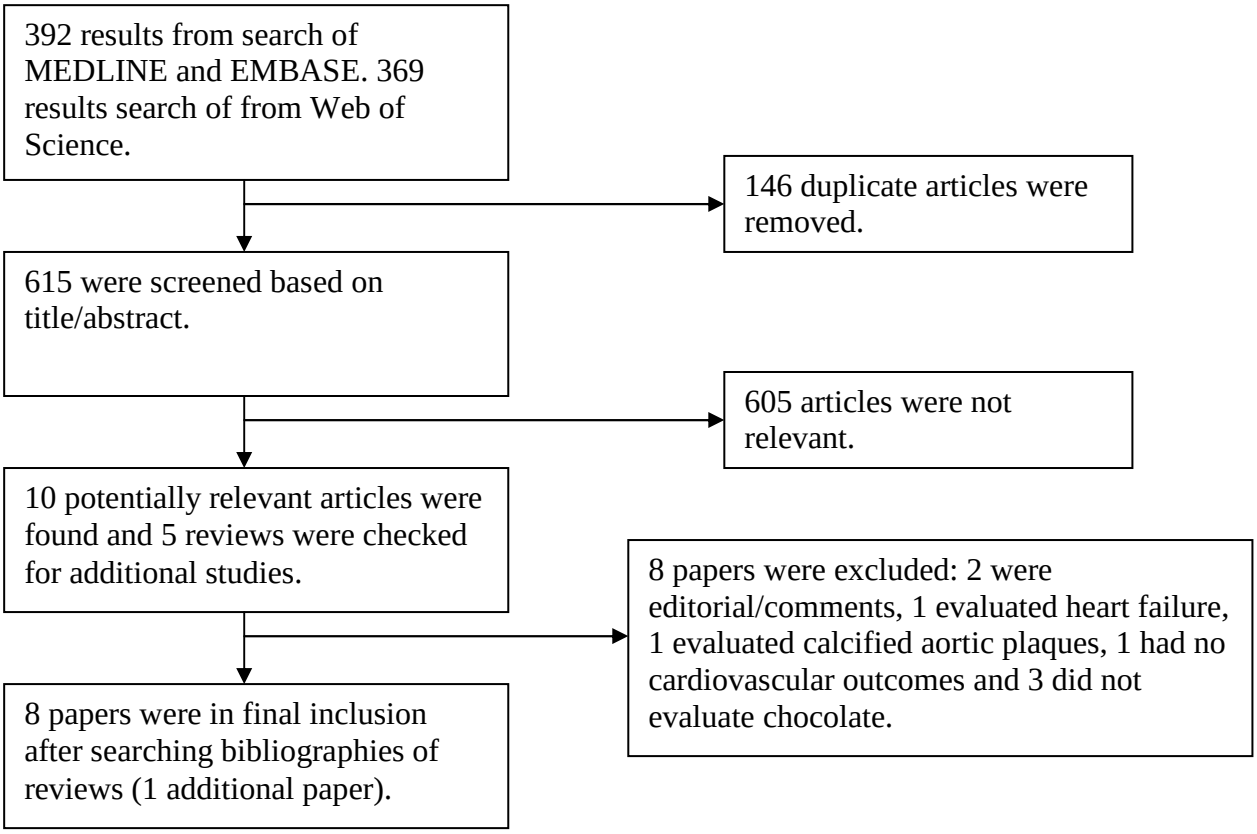
**Supplementary Figure 1: Love plot examining the standardized difference in covariates before and after propensity score adjustment.**



**Supplementary Figure 2: Search results and study selection for meta-analysis of chocolate consumption and risk of cardiovascular disease.**



**Supplementary Table 1: Baseline cardiovascular risk factors by quintiles of chocolate intake in 20,951 men and women of EPIC-Norfolk with 8,373 matched and unmatched on the propensity score (quintile 1 vs quintile 5), mean (sd) or percentage**

| | Unmatched | | | Matched | | |
|---|---|---|---|---|---|---|
| | Quintile 1 | Quintile 5 | p-value | Quintile 1 | Quintile 5 | p-value |
| Age | 60.71(9.00) | 57.07(9.39) | <0.001 | 58.64(8.91) | 58.98(9.40) | 0.19 |
| Body mass index | 26.34(4.05) | 25.96(3.70) | <0.001 | 26.00(4.03) | 26.00(3.63) | 0.95 |
| C-reactive protein | 3.01(5.84) | 2.91(7.45) | 0.55 | 2.85(4.99) | 3.03(8.10) | 0.41 |
| Diabetes mellitus (%) | 7.31% | 0.26% | <0.001 | 1.14% | 1.25% | <0.001 |
| Alcohol intake by HLQ | 7.08(10.13) | 6.99(9.14) | 0.67 | 7.07(9.46) | 6.91(9.00) | 0.54 |
| Carbohydrate intake by FFQ | 231.78(76.06) | 295.71(87.60) | <0.001 | 259.56(76.58) | 257.01(64.72) | 0.20 |
| Protein intake by FFQ | 78.88(20.89) | 88.14(22.05) | <0.001 | 85.63(20.96) | 79.74(18.14) | <0.001 |
| Fat intake by FFQ | 66.31(26.83) | 91.43(31.29) | <0.001 | 76.36(27.32) | 77.51(23.76) | 0.11 |
| HDL-cholesterol | 1.43(0.43) | 1.40(0.41) | <0.001 | 1.44(0.44) | 1.42(0.41) | 0.11 |
| LDL-cholesterol | 3.97(1.04) | 3.94(1.02) | 0.29 | 3.89(1.01) | 4.00(1.03) | <0.001 |
| Physical activity - Moderately inactive | 26.76% | 27.51% | 0.53 | 28.41% | 28.84% | 0.80 |
| Physical activity - Moderately active | 20.60% | 24.48% | 0.006 | 23.30% | 24.06% | 0.79 |
| Physical activity - Active | 16.91% | 21.65% | 0.006 | 19.39% | 18.74% | 1.00 |
| Sex (% men) | 44.9% | 52.1% | 0.001 | 43.2% | 42.5% | 0.98 |
| Smoking status (% current) | 9.47% | 14.1% | <0.001 | 11.8% | 11.6% | 0.93 |
| Systolic blood pressure | 136.75(18.61) | 133.66(17.14) | <0.001 | 135.13(17.79) | 134.61(17.65) | 0.29 |

[a] propensity score based on the covariates used in Model 2: age, sex, smoking status, physical activity, FFQ energy and HLQ alcohol
[b] for comparison of characteristics before and after matching, derived by t-test

**Supplementary Table 2: Hazard ratios of coronary heart disease, stroke and cerebrovascular disease (all and fatal) by quintiles of cocoa intake in 20,951 men and women of EPIC-Norfolk using propensity score analyses**

| | Quintile 1 vs 5 | |
|---|---|---|
| | Events/N | Hazard ratio (95% CI) |
| **CHD (fatal and non-fatal)** | | |
| Model 1 | 577/3618 vs 407/3771 | 0.85 (0.75-0.97) |
| Model 2 | 577/3618 vs 407/3771 | 0.88 (0.77-1.00) |
| Model 3 | 577/3618 vs 407/3771 | 0.91 (0.80-1.04) |
| Model 4a | 435/2816 vs 280/2903 | 0.83 (0.71-0.97) |
| Model 4b | 435/2816 vs 280/2903 | 0.82 (0.70-0.97) |
| Propensity score adjusted | 435/2816 vs 280/2903 | 0.88 (0.76-1.01) |
| Matched by propensity score | 307/2273 vs 283/2297 | 0.91 (0.77-1.07) |
| **Stroke (fatal and non-fatal)** | | |
| Model 1 | 226/3969 vs 131/4047 | 0.78 (0.63-0.96) |
| Model 2 | 226/3969 vs 131/4047 | 0.78 (0.62-0.98) |
| Model 3 | 226/3969 vs 131/4047 | 0.80 (0.64-1.00) |
| Model 4a | 168/3083 vs 99/3084 | 0.81 (0.63-1.05) |
| Model 4b | 168/3083 vs 99/3084 | 0.81 (0.63-1.06) |
| Propensity score adjusted | 168/3083 vs 99/3084 | 0.78 (0.62-0.99) |
| Matched by propensity score | 125/2455 vs 94/2486 | 0.75 (0.57-0.99) |
| **CVD (fatal and non-fatal)** | | |
| Model 1 | 729/3466 vs 500/3678 | 0.84(0.75-0.94) |
| Model 2 | 729/3466 vs 500/3678 | 0.86(0.76-0.97) |
| Model 3 | 729/3466 vs 500/3678 | 0.89(0.79-1.00) |
| Model 4a | 548/2703 vs 350/2833 | 0.82(0.72-0.95) |
| Model 4b | 548/2703 vs 350/2833 | 0.82(0.71-0.95) |
| Propensity score adjusted | 548/2703 vs 350/2833 | 0.86(0.75-0.97) |
| Matched by propensity score | 397/2183 vs 348/2232 | 0.87(0.75-1.00) |
| **CVD (fatal)** | | |
| Model 1 | 308/3887 vs 162/4016 | 0.73(0.60-0.89) |

| | | |
|---|---|---|
| Model 2 | 308/3887 vs 162/4016 | 0.76(0.62-0.92) |
| Model 3 | 308/3887 vs 162/4016 | 0.79(0.65-0.97) |
| Model 4a | 231/3020 vs 113/3070 | 0.73(0.57-0.92) |
| Model 4b | 231/3020 vs 113/3070 | 0.72(0.57-0.91) |
| Propensity score adjusted | 231/3020 vs 113/3070 | 0.81(0.65-1.00) |
| Matched by propensity score | 160/2420 vs 118/2462 | 0.77(0.60-0.97) |

Model 1 adjusted for sex and age.
Model 2 adjusted for sex, age, smoking, physical activity, energy intake and alcohol consumption.
Model 3: as model 2 and diabetes, body mass index, systolic blood pressure, LDL-cholesterol and HDL-cholesterol.
Model 4a: as model 3, but restricted to number of participants for whom C-reactive protein is available.
Model 4b: as model 3 and C-reactive protein.

[a] Propensity scores are based on the covariates included in Model 2

## Supplementary Table 3: Quality assessment of studies which evaluated chocolate consumption and cardiovascular disease.

| Study ID | Ascertaining Chocolate Consumption | Determining Cardiovascular Outcome | Adjustment for Confounders |
|---|---|---|---|
| Buijsse 2006 | The habitual dietary intake of the subjects was determined by interview conducted by experienced dieticians (using a cross-check dietary history method adapted to the Dutch situation). A total of 24 cocoa-containing foods and the intake of cocoa from individual foods was summed to yield actual cocoa in grams per day for each subject. | Information on the cause of death was obtained from hospital discharge data, general practitioners, and Statistics Netherlands. The final causes of death were ascertained by one clinical epidemiologist and coded according to the ICD-9. | Age; body mass index; smoking status; alcohol consumption; physical activity; aspirin use; anticoagulant use; diet prescription (Y/N); consumption of: vegetables, fruit, low and medium fat dairy, meat, sugar confectionery other than chocolate, cookies, savoury foods, nuts, and coffee; and total calorie intake |
| Buijsse 2010 | Usual food intake in the year before baseline was assessed by a self administered 148-item food-frequency questionnaire. Chocolate consumption was asked by how frequent a chocolate bar of 50 g was consumed. Participants could indicate whether they consumed half, one, two, or three bars of chocolate. | Possible cases of MI or stroke were identified by self-reports or death certificates. Self-reported information was obtained by at least one of the four follow-up questionnaires, which contained questions about physician-diagnosed CVD and the use of medication. All possible cases were verified by reviewing medical records from the hospital, by contacting the patients' physician, or by review of the death certificate. | Age, sex, alcohol intake, employment status, body mass index, waist circumference, smoking status, occupational physical activity, sports cycling, education, and total energy intake |
| Djousse 2011 | Dietary information collected through a staff-administered semi-quantitative food frequency questionnaire. Each subject was asked the following question: "In the past year, how often on average did you consume chocolate bars or pieces, such as Hershey's Plain, M & M, Snickers, Reeses; 1 ounce?". Possible answers were: ">6 per day, 4-6 per day, 2-3 per day, 1 per day, 5-6 per week, 2-4 per week, 1 per week, 1-3 per month, and almost never". | Prevalent CHD was assessed from the medical history and a 12-lead electrocardiogram. Individuals were defined as a case of CHD if there was a self-reported history of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft that could be validated by review of medical records, or if abnormal Q waves detected on a resting 12-lead electrocardiogram. | Age, sex, dietary linoleic acid intake, education, exercise, smoking status, alcohol intake, fruit and vegetables intake, energy intake, non-chocolate candy intake |
| Janszky 2009 | Questionnaire distributed few days after AMI regarding the number of usual (50 g) portions of chocolate that participants usually consumed per day, per week or per month during the last 12 months. The original consumption categories included: never, less than once per month, 1–3 times per month, once per week, twice per week, 3–4 times per week, 5–6 times per week, once per day, twice per day and 3 times or more per day. | All-cause and cardiac mortality (ICD-9 and -10) were used as primary end-points as provided by the National Cause of-death Register. Patients were also followed for nonfatal AMI using the Swedish Myocardial Infarction Register. Information on hospitalization for stroke was derived from the Swedish Hospital Discharge Register. | Age, sex, smoking status, obesity, physical inactivity, alcohol consumption (g/day), filtered coffee intake (cups/day), educational attainment, sweet score |
| Larsson 2011 | Validated self-administered food-frequency questionnaire regarding how often on average they had consumed chocolate and 95 other foods during the previous year. There were 8 pre-defined consumption categories ranging from never to ≥3 times a day. | Incident cases of first stroke were ascertained by linkage with the Swedish Hospital Discharge Registry. The stroke events were classified by ICD-10 code. Information on dates of death was obtained from the Swedish Cause of Death Registry. | Age, education (less than high school, high school, or university), smoking status and pack-years of smoking (never; past <20, 20 to 39, or ≥40 pack-years; or current <20, 20 to 39, or ≥40 pack-years), body mass index (<20, 20 to 24.9, 25 to 29.9, or ≥30 kg/m2), total physical activity (metabolic equivalent of energy expenditure hours/day, quartiles), aspirin use (never, 1 to 6, ≥7 tablets/week), self-reported history of hypertension (yes or no), diagnosis of atrial fibrillation (yes or no), family history of myocardial infarction before |

| | | | |
|---|---|---|---|
| | | | 60 years of age (yes or no), and intakes of total energy (kcal/day), alcohol (non-drinkers or <3.4, 3.4 to 9.9, or ≥10.0 g/day), coffee (<1, 1 to 2, 3 to 4, or ≥5 cups/day), tea (0, <1, 1 to 1.9, 2 to 3.9, ≥4 cups/day), and quartiles (g/day) of fresh red meat, processed red meat, fish, fruits, and vegetables. |
| Larsson 2012 | Validated self-administered food-frequency questionnaire that included 96 foods and beverages. Participants reported how often on average they had consumed chocolate based on 8 pre-specified consumption categories, ranging from never to 3 or more times per day. | Incident cases of first stroke were identified by linkage of the study population to the Swedish Hospital Discharge Registry and ICD-10 codes were used to identify stroke events in the cohort. Information on dates of death was obtained from the Swedish Death Register. | Age, education, smoking status, and pack-years of smoking, body mass index, total physical activity, aspirin use, history of hypertension, atrial fibrillation, family history of myocardial infarction, and intakes of total energy, alcohol, coffee, tea, fresh red meat, processed meat, fish, fruits, and vegetables. |
| Lewis 2010 | At baseline, information on food and beverage consumption frequency was verified by their general practitioner and previously validated questionnaires. The frequency of chocolate consumption was collapsed into the following 3 categories: less than 1 serving/wk (rarely), 1 to 6 servings/wk (weekly), and 7 or more servings/wk (daily). | The Western Australian Data Linkage System (WADLS) was used to assess clinical outcomes. Atherosclerotic vascular disease events were defined using diagnosis codes from the ICD-10-AM. | Age, body mass index, socioeconomic status, and energy intake at baseline. |
| Mink 2007 | Dietary assessment was performed using a 127-item food-frequency questionnaire was adapted from the questionnaire used in the 1984 Nurses' Health Study survey which had detailed information on fruit (15 items) and vegetables (29 items) and included information on individual foods with high flavonoid content (eg, chocolate). | Women were followed annually through the State Health Registry of Iowa and identified through the 4 follow-up questionnaires by linking women who did not respond to the questionnaire with the National Death Index. The ICD-9 was used to classify the reported cause of death. | Age, energy consumption, marital status, education, blood pressure, diabetes, body mass index, waist to hip ratio, physical activity, smoking, oestrogen use |
| Current study | Three questions from a food frequency questionnaire were considered indicative of chocolate consumption namely "Chocolates singles or squares" (average portion size of 8 g), "Chocolate snack bars, e.g. Mars, Crunchie" (average portion size of 50 g) and "Cocoa, hot chocolate (cup)" (average portion size of 12 g powder weight). Frequency categories were multiplied by the portion size to derive the amount of chocolate products eaten (g/day). The sum of the weights of these food items consumed, rather than their flavonoid or cocoa content, formed the measure of exposure. | Patients admitted to hospital were identified using their National Health Service number by data linkage with ENCORE. All participants were flagged for death certification at the UK Office of National Statistics, ascertaining vital status for the entire cohort. Diagnosis of CHD, stroke and CVD (combination of CHD and stroke) was based on ICD-10 codes. | Age, sex, smoking status, body mass index, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, C-reactive protein, physical activity, protein intake, total fat intake, total carbohydrate intake and alcohol intake. |

**Supplementary Table 4: Use of adjustments or exclusions in studies which evaluated chocolate consumption and cardiovascular disease.**

| Study ID | Diabetes mellitus | Body Mass Index | Total Energy Intake | Smoking | Blood Pressure | Cholesterol |
|---|---|---|---|---|---|---|
| Buijsse 2006 | Y (excluded patients with diabetes) | Y | Y | Y | N | N |
| Buijsse 2010 | Y | Y | Y | Y | N | N |
| Djousse 2011 | Y | N | Y | Y | N | N |
| Janszky 2009 | Y (excluded patients with diabetes) | N | N | Y | N | N |
| Larsson 2011 | Y (excluded patients with diabetes) | Y | Y | Y | N | N |
| Larsson 2012 | Y (excluded patients with diabetes) | Y | Y | Y | Y (hypertension) | N |
| Lewis 2010 | N | Y | Y | N | N | N |
| Mink 2007 | Y | Y | Y | Y | Y | N |
| Current study | Y | Y | Y | Y | Y (systolic blood pressure)* | Y* |

*Although these factors were included in the study, the model without these risk factors were included in the meta-analysis.

**Data Supplement 1: Search strategy for chocolate consumption and risk of cardiovascular disease**

EMBASE,MEDLINE; Duplicate filtered: [((cacao OR chocolate OR cocoa) AND ((cardiovascular disease) OR (coronary heart disease) OR (ischaemic heart disease) OR (ischemic heart disease) OR stroke OR (brain vascular accident) OR (cerebrovascular accident) OR (cerebral vascular accident))).ti,ab]; 392 results.