# Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study[1,2]

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**ABSTRACT**

**Background:** Prospective data relating fruit and vegetable intake to cardiovascular disease (CVD) risk are sparse, particularly for women.

**Objective:** In a large, prospective cohort of women, we examined the hypothesis that higher fruit and vegetable intake reduces CVD risk.

**Design:** In 1993 we assessed fruit and vegetable intake among 39 876 female health professionals with no previous history of CVD or cancer by use of a detailed food-frequency questionnaire. We subsequently followed these women for an average of 5 y for incidence of nonfatal myocardial infarction (MI), stroke, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or death due to CVD.

**Results:** During 195 647 person-years of follow-up, we documented 418 incident cases of CVD including 126 MIs. After adjustment for age, randomized treatment status, and smoking, we observed a significant inverse association between fruit and vegetable intake and CVD risk. For increasing quintiles of total fruit and vegetable intake (median servings/d: 2.6, 4.1, 5.5, 7.1, and 10.2), the corresponding relative risks (RRs) were 1.0 (reference), 0.78, 0.72, 0.68, and 0.68 (95% CI comparing the 2 extreme quintiles: 0.51, 0.92; *P* for trend = 0.01). An inverse, though not statistically significant, trend remained after additional adjustment for other known CVD risk factors, with RRs of 1.0, 0.75, 0.83, 0.80, and 0.85 (95% CI for extreme quintiles: 0.61, 1.17). After excluding participants with a self-reported history of diabetes, hypertension, or high cholesterol at baseline, the multivariate-adjusted RR was 0.45 when extreme quintiles were compared (95% CI: 0.22, 0.91; *P* for trend = 0.09). Higher fruit and vegetable intake was also associated with a lower risk of MI, with an adjusted RR of 0.62 for extreme quintiles (95% CI: 0.37, 1.04; *P* for trend = 0.07).

**Conclusion:** These data suggest that higher intake of fruit and vegetables may be protective against CVD and support current dietary guidelines to increase fruit and vegetable intake. *Am J Clin Nutr* 2000;72:922–8.

**KEY WORDS** Fruit, vegetables, cardiovascular disease, myocardial infarction, prospective study, women, Women's Health Study

## INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States (1). Many risk factors for CVD, including high blood cholesterol, hypertension, obesity, and diabetes are substantially influenced by dietary factors. Because these risk factors are modifiable, primary preventive efforts hold much promise (2). The American Heart Association and other national agencies recommend a diet that includes ≥5 servings of fruit and vegetables daily (3, 4). These recommendations are based primarily on the belief that fruit and vegetable intake may reduce CVD risk through the beneficial combinations of micronutrients, antioxidants, phytochemicals, and fiber in these foods. This belief has led to the investigation of individual components of fruit and vegetables as potential preventive agents against CVD (5–9). Several studies relating these constituents of fruit and vegetable intake to CVD risk found that higher intakes of dietary fiber, folate, or antioxidants are associated with lower risk (5–10). It is possible, however, that the combined effects of these and other constituents in fruit and vegetables are best assessed by examining the association between fruit and vegetable intake and CVD risk directly in a prospective setting. A clear understanding of the relation between fruit and vegetable intake and CVD risk will also provide a more direct scientific basis for practical dietary guidance.

Several prospective studies have directly related fruit and vegetable intake to CVD (11). In a 5-y study of 1273 Massachusetts residents aged ≥65 y, Gaziano et al (12) used a 43-item semiquantitative food-frequency questionnaire (SFFQ) to assess participants' average dietary intakes in the previous year and related

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vegetable intake to subsequent cardiovascular death. The authors found that those residents whose reported intake of carotene-containing fruit or vegetables was in the highest quartile had a 46% lower risk of death from CVD than did residents whose reported intake was in the lowest quartile. In a 14-y study of 5133 Finnish adults, Knekt et al (13) assessed vegetable intake with a diet history method and found a relative risk of 0.66 ($P = 0.02$) for coronary mortality when comparing the highest and lowest tertiles of vegetable intake. However, few prospective studies have attempted to relate fruit and vegetable intake to CVD morbidity in general and to the incidence of myocardial infarction (MI) in particular. As pointed out by Ness and Powles (11), the causal link between fruit and vegetable intake and risk of CVD has been more assumed than actually shown.

To examine the hypothesis that greater fruit and vegetable intake reduces risk of CVD and MI, we analyzed prospective data collected from 1993 to 1999 as part of the Women's Health Study. Specifically, we examined *1*) whether there is an inverse relation between fruit and vegetable intake and CVD risk and *2*) whether the association between fruit and vegetable intake and CVD risk may be obscured by strong risk factors for CVD such as diabetes, hypertension, and hypercholesterolemia, which often lead to an increase in fruit and vegetable intake.

## SUBJECTS AND METHODS

### Study population

The Women's Health Study is a randomized, double-blind, placebo-controlled trial designed to test the efficacy of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among 39 876 female health professionals who were without heart disease, stroke, or cancer (other than nonmelanoma skin cancer) at baseline. Detailed information on fruit and vegetable intake was provided by 39 127 (98%) of the randomly assigned participants, who completed a 131-item validated SFFQ at baseline in 1993 (14). This study was conducted according to the ethical guidelines of Brigham and Women's Hospital.

### Assessment of fruit and vegetable intake

An SFFQ that included 28 vegetable items and 16 fruit items was administered to all participants. For each fruit or vegetable, a standard unit or portion size was specified and participants were asked how often, on average, during the previous year they had consumed that amount. Nine responses were possible, ranging from "never" to "six or more times per day." Responses to the individual food items were converted to average daily intake of each fruit and vegetable item for each subject. The average daily intakes of individual fruit and vegetables were summed to compute total fruit and vegetable intake. According to criteria established by Smith et al (15) and hypothesized as a priori, we also combined specific vegetables into groups such as cruciferous vegetables (broccoli, cabbage, cauliflower, and Brussels sprouts), dark and yellow vegetables (carrots, yellow squash, yams, and sweet potatoes), green leafy vegetables (spinach, kale, and lettuce), and other vegetables (corn, mixed vegetables, celery, eggplant, mushrooms, and beets). In similar populations, the SFFQ was shown to have high validity as a measure of long-term average dietary intakes (14, 16, 17). For example, the correlations between the SFFQ and detailed 7-d diet records in a sample of women participating in the Nurses' Health Study were 0.80 for apple, 0.84 for grapefruit, 0.74 for tomatoes, and 0.50 for yellow squash (14).

### Outcomes

The primary endpoint for this analysis was incident CVD, which included nonfatal MI or stroke, percutaneous transluminal coronary angioplasty or coronary artery bypass graft (PTCA-CABG), or fatal CVD that occurred during the 6-y period between the return of the 1993 questionnaire and 31 March 1999. Each diagnosis was confirmed by a committee of cardiologists and one neurologist who were unaware of the questionnaire data. For MI, we used criteria proposed by the World Health Organization, ie, symptoms plus either typical electrocardiographic changes or elevation of cardiac enzymes (18). Stroke was diagnosed if the patient had a new neurologic deficit lasting >24 h; computed tomography or magnetic resonance imaging scans were available in most cases. Reported PTCA-CABG was confirmed by hospital records. CVD deaths were confirmed by reviewing medical records, autopsy reports, and death certificates.

### Data analysis

Each participant accumulated follow-up time beginning at baseline and ending in the month of diagnosis of a relevant endpoint or censoring (death from causes other than CVD, PTCA-CABG, or March 1999, whichever came first). We considered fruit and vegetable intake as both a continuous variable (servings/d) and a categorical variable (in quintiles). We calculated incidence rates of CVD for 5 categories of vegetable intake at baseline by dividing the number of incident cases by the person-years of follow-up. The rate ratio was then calculated by dividing the rate among women in each specific intake quintile by the rate among women in the lowest quintile of intake (reference). We used Cox proportional hazards models to estimate the relative risk (RR) of developing CVD, adjusting for age (in y), randomized assignment, body mass index (BMI; $kg/m^2$), smoking, alcohol intake, physical activity, use of multivitamins or vitamin C supplements, and history of high cholesterol, hypertension, or diabetes.

To avoid potential biases that might arise from differential diagnoses or use of medical care, we further excluded "soft" endpoints such as PTCA-CABG and restricted our analyses to the "hard" endpoint of MI, which is less prone to misclassification. In further analyses, we excluded women who reported a history of diabetes, hypertension, or hypercholesterolemia at baseline because of the concern that such diagnoses may lead to changes in fruit and vegetable intake and thus confound and obscure a true association. Tests of linear trend across increasing quintiles of fruit and vegetable intake were conducted by assigning the medians of intakes in quintiles (servings/d) treated as a continuous variable. Data were analyzed with SAS (version 6.12; SAS Institute Inc, Cary, NC).

## RESULTS

At baseline, the mean ($\pm$SD) daily intake of fruit was $2.2 \pm 1.6$ servings and that of vegetables was $3.9 \pm 2.6$ servings ($6.1 \pm 3.6$ total servings of fruit and vegetables). The median intake of total fruit and vegetables ranged from 2.6 servings/d in the lowest quintile to >10 servings/d in the highest quintile (**Table 1**). Women with high fruit and vegetable intake were older, smoked less, drank and exercised more, and were more likely to use

**TABLE 1**

Baseline distributions of cardiovascular disease risk factors according to quintiles of fruit and vegetable intake in the Women's Health Study[1]

| | Quintile of fruit intake | | | | | | Quintile of vegetable intake | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 (*n* = 7832) | 2 (*n* = 7840) | 3 (*n* = 7806) | 4 (*n* = 7825) | 5 (*n* = 7824) | *P* for trend | 1 (*n* = 7826) | 2 (*n* = 7830) | 3 (*n* = 7824) | 4 (*n* = 7826) | 5 (*n* = 7821) | *P* for trend |
| Servings/d (median) | 0.6 | 1.3 | 1.9 | 2.6 | 3.9 | | 1.5 | 2.5 | 3.4 | 4.6 | 6.9 | — |
| Mean age (y) | 52 ± 6[2] | 53 ± 6 | 54 ± 7 | 55 ± 7 | 55 ± 7 | < 0.001 | 53 ± 6 | 53 ± 7 | 54 ± 7 | 54 ± 7 | 55 ± 7 | < 0.001 |
| Age group (%) | | | | | | < 0.001 | | | | | | < 0.001 |
| 45–54 y | 70.8 | 65.6 | 60.2 | 56.3 | 52.8 | | 65.9 | 63.8 | 60.0 | 59.0 | 57.1 | |
| 55–64 y | 23.5 | 27.2 | 30.1 | 31.2 | 32.4 | | 25.9 | 27.6 | 30.1 | 30.0 | 30.9 | |
| 65–74 y | 5.3 | 6.9 | 9.2 | 11.5 | 13.5 | | 7.7 | 8.0 | 9.2 | 10.4 | 11.1 | |
| ≥75 y | 0.4 | 0.4 | 0.5 | 1.0 | 1.3 | | 0.5 | 0.6 | 0.8 | 0.6 | 0.9 | |
| Smoking (%) | | | | | | < 0.001 | | | | | | < 0.001 |
| Current | 24.4 | 14.9 | 10.9 | 8.2 | 7.2 | | 17.5 | 13.9 | 12.4 | 11.8 | 9.9 | |
| Never | 42.1 | 48.1 | 51.7 | 54.9 | 58.6 | | 49.8 | 51.6 | 51.4 | 50.8 | 51.8 | |
| Past | 33.5 | 37.0 | 37.4 | 37.0 | 34.2 | | 32.8 | 34.5 | 36.2 | 37.4 | 38.3 | |
| Exercise (%) | | | | | | < 0.001 | | | | | | < 0.001 |
| Rarely or never | 50.4 | 41.7 | 36.8 | 32.9 | 29.7 | | 48.5 | 42.7 | 37.6 | 33.6 | 29.2 | |
| < 1 time/wk | 20.2 | 20.8 | 20.4 | 19.8 | 18.1 | | 19.2 | 20.2 | 20.2 | 20.6 | 19.2 | |
| 1–3 times/wk | 23.1 | 28.8 | 32.3 | 34.9 | 36.6 | | 25.0 | 28.2 | 32.1 | 34.2 | 36.2 | |
| ≥ times/wk | 6.3 | 8.7 | 10.5 | 12.3 | 15.6 | | 7.3 | 8.9 | 10.1 | 11.7 | 15.5 | |
| Alcohol use (%) | | | | | | < 0.001 | | | | | | < 0.001 |
| Rarely or never | 48.4 | 45.3 | 42.8 | 43.3 | 45.1 | | 52.4 | 45.4 | 42.8 | 41.8 | 42.5 | |
| 1–3 drinks/mo | 12.6 | 13.1 | 13.7 | 13.4 | 13.0 | | 13.5 | 13.9 | 13.5 | 12.5 | 12.5 | |
| 1–6 drinks/wk | 27.8 | 30.5 | 32.9 | 33.6 | 33.2 | | 26.2 | 31.3 | 33.0 | 34.3 | 33.4 | |
| ≥1 drink/d | 11.3 | 11.0 | 10.5 | 9.7 | 8.7 | | 7.9 | 9.3 | 10.7 | 11.5 | 11.7 | |
| Postmenopausal (%) | 47.9 | 51.2 | 55.4 | 58.2 | 61.1 | < 0.001 | 51.3 | 52.3 | 55.0 | 56.7 | 58.4 | < 0.001 |
| Postmenopausal hormone use (%) | | | | | | < 0.001 | | | | | | < 0.001 |
| Never | 51.5 | 48.8 | 47.2 | 46.3 | 46.2 | | 50.7 | 48.9 | 47.4 | 46.9 | 46.0 | |
| Past | 10.3 | 9.8 | 9.7 | 10.1 | 11.4 | | 10.0 | 9.9 | 10.2 | 10.5 | 10.8 | |
| Current | 38.2 | 41.4 | 43.1 | 43.7 | 42.5 | | 39.3 | 41.3 | 42.4 | 42.6 | 43.1 | |
| Mean BMI (kg/m$^2$) | 26.4 ± 5.4 | 26.2 ± 5.0 | 26.1 ± 5.0 | 25.8 ± 4.9 | 25.7 ± 4.9 | 0.43 | 26.1 ± 5.5 | 26.1 ± 5.1 | 25.9 ± 4.9 | 25.9 ± 4.9 | 26.1 ± 5.1 | 0.46 |
| Multivitamin use (%) | 24.2 | 27.7 | 29.3 | 32.4 | 32.4 | < 0.001 | 28.2 | 29.2 | 29.2 | 29.1 | 30.1 | < 0.001 |
| Vitamin C supplement use (%) | 7.0 | 8.9 | 9.4 | 10.4 | 12.0 | < 0.001 | 8.6 | 9.2 | 9.4 | 10.1 | 10.4 | < 0.001 |
| History of diabetes (%)[3] | 2.5 | 2.5 | 2.5 | 2.4 | 2.9 | 0.007 | 2.4 | 2.5 | 2.3 | 2.5 | 3.1 | < 0.001 |
| History of hypertension (%)[3] | 25.9 | 25.0 | 26.0 | 25.8 | 28.1 | < 0.001 | 25.6 | 25.5 | 25.3 | 26.3 | 28.1 | <0.001 |
| History of high cholesterol (%)[3] | 25.8 | 26.3 | 27.4 | 27.6 | 28.8 | 0.01 | 26.2 | 26.8 | 27.7 | 27.2 | 28.0 | 0.01 |
| Parental history of MI (%) | 15.8 | 15.2 | 14.4 | 14.5 | 13.9 | 0.63 | 15.1 | 14.8 | 14.6 | 14.3 | 15.0 | 0.14 |

[1] Fruit was defined as a composite score of all the fruit items on the questionnaire, including apple, pear, orange, grapefruit, peach, banana, strawberry, blueberry, cantaloupe, raisin, prune, and fruit juices. Vegetable was defined as a composite score of all the vegetables items, including cruciferous vegetables, dark-yellow vegetables, tomatoes, green leafy vegetables, legumes, and other vegetables such as corn, mixed vegetables, celery, eggplant, mushroom, and beet.

[2] $\bar{x}$ ± SD.

[3] History of hypertension was defined as ever having received a diagnosis by a physician or self-reported blood pressure >140/90 mm Hg; history of high cholesterol and history of diabetes were self-reported.

postmenopausal hormones or supplements of multivitamins or vitamin C than were women with low fruit and vegetable intake. Greater fruit and vegetable intake was also associated with a higher prevalence of diabetes, hypertension, and high cholesterol. BMI and history of parental MI before 60 y of age did not vary appreciably across quintiles of fruit and vegetable intake.

During an average of 5 y of follow-up (195 647 person-years), 418 incident cases of CVD (including 126 MIs, 43 CABGs, 74 PTCAs, 160 strokes, and 15 CVD deaths not related to stroke and MI) were confirmed. We observed a significant inverse association between fruit and vegetable intake and subsequent occurrence of CVD (**Table 2**). The RR of CVD adjusted for age and randomized treatment was 0.68 (95% CI: 0.51, 0.92) when the highest and lowest quintiles were compared. In multivariate models, smoking was the strongest confounding factor. A similar inverse trend was observed both after smoking was added to the model and after adjustment for other CVD risk factors. When we considered fruit and vegetable intake as a continuous variable and adjusted for the same covariates, we found an RR of 0.94 (95% CI: 0.85, 1.02) for CVD risk for each additional daily serving of fruit and vegetables. Adding red meat to the model did not significantly alter the magnitude of the RRs for fruit and vegetable intake.

To minimize potential biases that may arise from differential diagnoses or use of medical care, we next restricted our analyses to the endpoint of MI. As expected, the inverse relation of fruit and vegetable intake with MI risk was stronger than that with

**TABLE 2**
Relative risk (95% CI) of cardiovascular disease (CVD) according to quintiles of fruit and vegetable intake in the Women's Health Study, 1993–1999[1]

| | Quintile of intake | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | *P* for trend |
| All fruit and vegetables | | | | | | |
| Servings/d (median) | 2.6 | 4.1 | 5.5 | 7.1 | 10.2 | |
| Cases of CVD | 95 | 79 | 80 | 80 | 84 | |
| Person-years of follow-up | 39 270 | 39 311 | 39 245 | 38 961 | 38 860 | |
| Age- and treatment-adjusted risk | 1.0 | 0.78 (0.57, 1.05) | 0.72 (0.53, 0.97) | 0.68 (0.50, 0.92) | 0.68 (0.51, 0.92) | 0.01 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.85 (0.63, 1.15) | 0.82 (0.61, 1.11) | 0.80 (0.59, 1.08) | 0.82 (0.60, 1.10) | 0.18 |
| Multivariate-adjusted risk | 1.0 | 0.75 (0.54, 1.04) | 0.83 (0.60, 1.14) | 0.80 (0.57, 1.10) | 0.85 (0.61, 1.17) | 0.45 |
| All fruit | | | | | | |
| Servings/d (median) | 0.6 | 1.3 | 1.9 | 2.6 | 3.9 | |
| Cases of CVD | 101 | 65 | 71 | 86 | 95 | |
| Person-years of follow-up | 39 177 | 39 376 | 39 189 | 39 082 | 38 879 | |
| Age- and treatment-adjusted risk | 1.0 | 0.58 (0.42, 0.79) | 0.58 (0.43, 0.79) | 0.65 (0.48, 0.87) | 0.66 (0.49, 0.88) | 0.03 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.66 (0.48, 0.91) | 0.72 (0.52, 0.97) | 0.82 (0.61, 1.11) | 0.84 (0.63, 1.13) | 0.67 |
| Multivariate-adjusted risk | 1.0 | 0.73 (0.52, 1.01) | 0.70 (0.50, 0.99) | 0.91 (0.66, 1.26) | 0.96 (0.70, 1.33) | 0.69 |
| All vegetables | | | | | | |
| Servings/d (median) | 1.5 | 2.5 | 3.4 | 4.6 | 6.9 | |
| Cases of CVD | 89 | 95 | 75 | 81 | 78 | |
| Person-years of follow-up | 39 285 | 39 336 | 39 161 | 39 049 | 38 873 | |
| Age- and treatment-adjusted risk | 1.0 | 1.03 (0.77, 1.38) | 0.76 (0.56, 1.04) | 0.81 (0.60, 1.10) | 0.75 (0.55, 1.02) | 0.02 |
| Age-, treatment- and smoking-adjusted risk | 1.0 | 1.08 (0.80, 1.44) | 0.81 (0.60, 1.11) | 0.88 (0.65, 1.19) | 0.84 (0.61, 1.14) | 0.11 |
| Multivariate-adjusted risk | 1.0 | 1.07 (0.78, 1.46) | 0.83 (0.59, 1.16) | 0.91 (0.66, 1.27) | 0.85 (0.61, 1.19) | 0.21 |

[1] CVD was defined as incidence of death due to cardiovascular disease, nonfatal myocardial infarction, stroke, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft. Fruit and vegetable were defined as in Table 1. The multivariate model was adjusted for all the covariates described in Table 1.

CVD risk (**Table 3**). Compared with the lowest quintile of intake, the age- and treatment-adjusted RR for the highest quintile of intake was 0.47 (95% CI: 0.28, 0.79). After further adjustment for CVD risk factors, an inverse trend was still observed, although this trend was not statistically significant.

Diabetes, hypertension, hypercholesterolemia, and other high-risk conditions for CVD may lead to changes in fruit and vegetable intake and may thus confound the association between fruit and vegetable intake and CVD risk. We therefore examined the association between fruit and vegetable intake and

**TABLE 3**
Relative risk (95% CI) of myocardial infarction (MI) according to quintiles of fruit and vegetable intake in the Women's Health Study, 1993–1999[1]

| | Quintile of intake | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | *P* for trend |
| All fruit and vegetables | | | | | | |
| Servings/d (median) | 2.6 | 4.1 | 5.5 | 7.1 | 10.2 | |
| Cases of MI | 39 | 18 | 26 | 19 | 24 | |
| Person-years of follow-up | 39 404 | 39 478 | 39 380 | 39 099 | 39 018 | |
| Age- and treatment-adjusted risk | 1.0 | 0.43 (0.24, 0.76) | 0.57 (0.35, 0.94) | 0.39 (0.23, 0.68) | 0.47 (0.28, 0.79) | 0.004 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.49 (0.28, 0.85) | 0.69 (0.42, 1.14) | 0.50 (0.28, 0.86) | 0.62 (0.37, 1.04) | 0.07 |
| Multivariate-adjusted risk | 1.0 | 0.45 (0.24, 0.83) | 0.78 (0.46, 1.33) | 0.51 (0.27, 0.94) | 0.63 (0.38, 1.17) | 0.21 |
| All fruit | | | | | | |
| Servings/d (median) | 0.6 | 1.3 | 1.9 | 2.6 | 3.9 | |
| Cases of MI | 39 | 24 | 16 | 24 | 23 | |
| Person-years of follow-up | 39 323 | 39 495 | 39 319 | 39 232 | 39 009 | |
| Age- and treatment-adjusted risk | 1.0 | 0.55 (0.33, 0.92) | 0.34 (0.19, 0.61) | 0.45 (0.27, 0.77) | 0.40 (0.24, 0.68) | 0.0006 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.66 (0.40, 1.10) | 0.45 (0.25, 0.81) | 0.64 (0.38, 1.09) | 0.57 (0.34, 0.98) | 0.04 |
| Multivariate-adjusted risk | 1.0 | 0.76 (0.44, 1.34) | 0.58 (0.32, 1.09) | 0.82 (0.46, 1.47) | 0.66 (0.36, 1.22) | 0.26 |
| All vegetables | | | | | | |
| Servings/d (median) | 1.5 | 2.5 | 3.4 | 4.6 | 6.9 | |
| Cases of CVD | 32 | 26 | 18 | 25 | 25 | |
| Person-years of follow-up | 39 427 | 39 512 | 39 308 | 39 179 | 39 006 | |
| Age- and treatment-adjusted risk | 1.0 | 0.79 (0.47, 1.32) | 0.52 (0.29, 0.92) | 0.70 (0.41, 1.18) | 0.67 (0.40, 1.14) | 0.13 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.84 (0.50, 1.41) | 0.57 (0.32, 1.01) | 0.78 (0.46, 1.32) | 0.79 (0.47, 1.35) | 0.36 |
| Multivariate-adjusted risk | 1.0 | 0.94 (0.54, 1.63) | 0.55 (0.29, 1.05) | 0.87 (0.49, 1.55) | 0.88 (0.50, 1.58) | 0.60 |

[1] MI included fatal and nonfatal MI confirmed by medical records. Fruit and vegetable were defined as in Table 1. The multivariate model was adjusted for all the covariates described in Table 1.

**TABLE 4**
Relative risk (95% CI) of cardiovascular disease (CVD) according to quintiles of fruit and vegetable intake in the Women's Health Study (excluding women with self-reported diabetes, history of hypertension, or history of high cholesterol at baseline), 1993–1999[1]

| | Quintile of intake | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | *P* for trend |
| All fruit and vegetables | | | | | | |
| Servings/d (median) | 2.2 | 4.1 | 5.4 | 7.0 | 10.0 | |
| Cases of CVD | 30 | 19 | 20 | 28 | 13 | |
| Person-years of follow-up | 22 365 | 22 420 | 22 381 | 22 175 | 22 154 | |
| Age- and treatment-adjusted risk | 1.0 | 0.60 (0.34, 1.06) | 0.57 (0.32, 1.01) | 0.76 (0.46, 1.28) | 0.33 (0.17, 0.64) | 0.005 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.67 (0.38, 1.20) | 0.67 (0.38, 1.20) | 0.92 (0.55, 1.57) | 0.41 (0.21, 0.80) | 0.04 |
| Multivariate-adjusted risk | 1.0 | 0.68 (0.37, 1.22) | 0.77 (0.43, 1.37) | 0.95 (0.55, 1.65) | 0.45 (0.22, 0.91) | 0.09 |
| All fruit | | | | | | |
| Servings/d (median) | 0.6 | 1.3 | 1.9 | 2.6 | 3.8 | |
| Cases of CVD | 31 | 19 | 20 | 21 | 19 | |
| Person-years of follow-up | 22 531 | 22 136 | 22 548 | 22 145 | 22 165 | |
| Age- and treatment-adjusted risk | 1.0 | 0.56 (0.32, 0.99) | 0.53 (0.30, 0.93) | 0.52 (0.30, 0.93) | 0.43 (0.24, 0.78) | 0.007 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.66 (0.37, 1.16) | 0.66 (0.37, 1.16) | 0.68 (0.39, 1.21) | 0.57 (0.32, 1.04) | 0.09 |
| Multivariate-adjusted risk | 1.0 | 0.71 (0.39, 1.26) | 0.67 (0.37, 1.23) | 0.79 (0.44, 1.42) | 0.57 (0.30, 1.09) | 0.15 |
| All vegetables | | | | | | |
| Servings/d (median) | 1.5 | 2.5 | 3.4 | 4.5 | 6.8 | |
| Cases of CVD | 32 | 19 | 17 | 27 | 15 | |
| Person-years of follow-up | 22 408 | 22 418 | 22 353 | 22 194 | 22 152 | |
| Age- and treatment-adjusted risk | 1.0 | 0.58 (0.33, 1.02) | 0.49 (0.27, 0.88) | 0.76 (0.45, 1.27) | 0.39 (0.22, 0.74) | 0.02 |
| Age-, treatment-, and smoking-adjusted risk | 1.0 | 0.61 (0.35, 1.08) | 0.53 (0.29, 0.95) | 0.85 (0.50, 1.41) | 0.45 (0.24, 0.84) | 0.06 |
| Multivariate-adjusted risk | 1.0 | 0.63 (0.35, 1.14) | 0.59 (0.33, 1.09) | 0.96 (0.54, 1.61) | 0.45 (0.24, 0.89) | 0.11 |

[1] CVD was defined as incidence of death due to cardiovascular disease, myocardial infarction, stroke, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft. Fruit and vegetable were defined as in Table 1. The multivariate model was adjusted for all the covariates described in Table 1.

CVD risk only among participants who reported no history of these high-risk conditions at baseline. In this analysis, the inverse association between fruit and vegetable intake and CVD risk became even stronger (**Table 4**): the age- and treatment-adjusted RR was 0.33 (95% CI: 0.17, 0.64) and the multivariate-adjusted RR was 0.45 (95% CI: 0.22, 0.91) when the 2 extreme quintiles were compared.

## DISCUSSION

In this 5-y prospective study of female health professionals, we found an inverse association between fruit and vegetable intake and risk of CVD. This association appeared to be more evident for MI and among those who did not report a history of diabetes, hypertension, or hypercholesterolemia at baseline. It is possible that the inverse association is explained by other heart-healthy lifestyle factors associated with fruit and vegetable intake (19). Smoking appeared to be an important confounding factor, yet the protective effect of fruit and vegetable intake persisted after adjustment for smoking and other CVD risk factors, although the association was attenuated. In addition, the relative homogeneity in educational attainment and socioeconomic status of the study participants should minimize the possibility that other unknown confounding factors distorted the primary association between fruit and vegetable intake and CVD risk.

The inverse association between fruit and vegetable intake and CVD risk may also have been confounded by other dietary factors, such as intake of saturated fat and red meat. However, adjustment for intake of saturated fat or total fat did not change the relation between fruit and vegetable intake and CVD risk. In our data, neither saturated fat nor total fat was related to CVD endpoints, findings that are consistent in large epidemiologic studies (20, 21). Thus, differences in intakes of saturated fat or total fat were not likely to account for the inverse association between fruit and vegetable intake and CVD risk.

Women may increase their intake of fruit and vegetables if they perceive themselves to be at elevated risk of CVD. For example, greater fruit and vegetable intake was associated with a higher prevalence of diabetes, hypertension, and high cholesterol, which would lead to an underestimation of the inverse association between fruit and vegetable intake and CVD risk. As expected, when women with diabetes, hypertension, or high cholesterol at baseline were excluded from our analyses, we observed a much stronger inverse association between fruit and vegetable intake and CVD risk in this cohort, possibly reflecting better control of residual confounding by these risk factors.

As in any epidemiologic study of diet, misclassification is a major concern because fruit and vegetable intake was reported through a self-administered SFFQ. In addition, because we assessed diet only at baseline, misclassification could have occurred if the participants changed their dietary practices during follow-up, particularly after receiving a diagnosis of such intermediate endpoints as diabetes, hypertension, and hypercholesterolemia (22). In a prospective study, however, measurement error in the assessment of fruit and vegetable intake is unlikely to be associated with the assessment of CVD endpoints, and random and nondifferential misclassification would tend to underestimate any association between fruit and vegetable intake and CVD risk. Therefore, the ≈20–30% reduction in risk associated with high intake of fruit and vegetables observed in our study may be a conservative estimate. It can be argued that if the true intake of fruit and vegetables could be assessed precisely, the inverse association with CVD and MI risk would be of even greater magnitude.

Findings from ecologic studies show that populations with lower intakes of animal products and higher intakes of fruit and vegetables have lower prevalences of CVD than do populations with higher intakes of animal products (23). Comparing variations in dietary and disease patterns among populations is problematic, though, because this approach cannot fully adjust for other important confounding factors such as physical inactivity, obesity, and smoking (14). Moreover, because the diagnosis of CVD is often followed by alterations in diet and other lifestyle practices, the value of retrospective studies is limited.

Prospective cohort studies are best suited to evaluate the role of fruit and vegetables in the development of CVD because dietary assessment is conducted before the outcome and reporting of intake is not biased by a recent CVD diagnosis. Several prospective studies have related higher fruit and vegetable intake to lower CVD mortality (12, 13) and morbidity (24, 25). During an average of 12 y of follow-up of 15 220 men in the Physicians' Health Study, incidence of coronary heart disease (CHD) was ≈25% lower in those who consumed ≥2.5 servings of vegetables daily than in those who consumed <1 serving/d. The inverse relation between vegetable intake and CHD risk was also more evident among men with a BMI > 25 (RR: 0.71; 95% CI: 0.51, 0.99) and among current smokers (RR: 0.40; 95% CI: 0.18, 0.86).

The inverse association of fruit and vegetable intake with CVD risk in the present cohort of women is generally consistent with findings from the cohort of men in the Physicians' Health Study, in which a much simpler FFQ was used to assess vegetable intake (24). In our subgroup analyses, the inverse association between fruit and vegetable intake appeared to be more evident among women with a BMI > 25 and among current smokers (data not shown). These observations were not significant because of the small sample sizes in these subgroups. In light of the existing literature, however, these findings support the hypothesis that fruit and vegetable intake is associated with reduced risk of CVD, even though the trends presented generally were not significant at the conventional level of $\alpha = 0.05$.

It has been estimated that the average American consumes only ≈0.7 servings of vegetables (1.5 servings when potatoes and salads are included) and 0.7 servings of fruit per day (26). The median intake of fruit and vegetables in this cohort of highly selected women was 6.1 servings/d, which is similar to intake reported previously in the Nurses' Health Study (25). This intake is considerably higher than that of the general population, and also higher than the US Department of Agriculture recommendation of 5 servings/d (3, 27, 28). Although the dose-response relation between fruit and vegetable intake and CVD risk in our study was not entirely linear, intake beyond the highest quintile (median: 10 servings/d) appeared to afford the greatest reduction in risk of CVD (Table 4). In addition, the reduction in CVD risk was associated with each of the different types of vegetables except potatoes, suggesting that increased intake of fruit and vegetables could have a significant effect on reducing risk of CVD in the general population. Thus, our data generally support the current dietary guideline, although the recommendation for inclusion of potatoes as a vegetable may not be warranted.

In conclusion, in this large-scale prospective cohort of women, higher intakes of fruit and vegetables were associated with lower risk of CVD, especially MI. These findings support current dietary recommendations to increase the intake of fruit and vegetables as a primary preventive measure against CVD.

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