Dear Sir:

In a prospective study of 38,445 women, Sesso et al (1) reported that flavonoid intake was not strongly associated with reduced mortality from cardiovascular disease (CVD). Significant inverse correlations with CVD were observed for broccoli, apples, and tea, although Sesso et al concluded that the observed relations were not mediated by flavonoids. I am concerned that the terminology used in their article was not specific enough and that their conclusions may be premature. It may be useful for readers of the Journal to properly understand the terminology used to describe the types of flavonoids in foods.

Hundreds of flavonoids are consumed regularly within the food supply. They are divided into subclasses with different physiochemical and biological properties. There are 5 major subclasses of flavonoids: flavonols, flavones, catechins (flavanols), anthocyanins, and flavanones (2). Sesso et al determined the dietary intakes of 2 of the major flavonoid subclasses: flavonols and flavones. Although these 2 subclasses have received more attention than have other subclasses because of reports of specific biological activities, these 2 subclasses are the least abundant subclasses of flavonoids in the diet (3). Flavonols are ubiquitous in fruit and vegetables but are present in fairly low concentrations in common foods, with the notable exception of yellow onions. Flavones are abundant in only a few select foods, such as parsley, celery, and certain types of sweet peppers.

Sesso et al concluded that the inverse relations between CVD and the consumption of broccoli, apples, and tea were not due to the flavonoids present in these foods (1). Although broccoli, apples, and tea are sources of at least one of the subclasses measured in the study, apples and tea contain significantly higher amounts of catechins than of flavonols or flavones (Table 1). Catechins and other important subclasses of flavonoids were not measured in Sesso et al’s study, so the conclusion that the inverse relations observed for tea and apples were not mediated by flavonoids may be incorrect. In a prospective cohort study, Arts et al (6) showed that the intake of monomeric catechins is inversely associated with ischemic heart disease mortality, and the major dietary sources of catechins in that study were tea and apples. Dietary intervention studies indicate that catechins modulate platelet activity and other risk factors for CVD (7, 8).

Sesso et al also concluded that “total flavonoid” intake was not related to the incidence of CVD in women. Although the term total flavonoids was defined in the Subjects and Methods section as the sum of the major compounds from the flavonol and flavone subclasses, the term was also used in the abstract and throughout the text. Because the Journal attracts a diverse group of readers in all areas of nutrition and the health sciences, it is possible that some readers will take the use of the term total flavonoids literally. I am not aware of any studies that have measured the consumption of total flavonoids including all subclasses. On the basis of the amounts of flavonoids in common foods, the average dietary intake of total flavonoids from a typical Western diet was estimated to be as high as 650 mg/d (3). Although total flavonoid intake may arguably be much lower than 650 mg/d in the United States, Sesso et al based their conclusions on mean consumption values of only 25 mg/d, a small proportion of the intake of total flavonoids.

Because this important research is likely to stimulate further investigation, it is necessary for readers to understand that Sesso et al have shown that the intake of flavonols and flavones is not correlated with the incidence of CVD in women. We do not know whether other abundant flavonoid subclasses have effects or whether there are additive effects of consuming several or all flavonoid subclasses together. The inverse relations for tea and apples that were observed in the study by Sesso et al may have been due to catechins, a subclass of flavonoids that were not measured. Future epidemiologic reports must be specific when referring only to particular flavonoid subclasses to avoid the possibility of misleading readers who are not familiar with this diverse group of biologically active compounds.

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TABLE 1
Flavonoid concentrations in foods that have been shown to be inversely correlated with cardiovascular disease mortality in women

<table>
<thead>
<tr>
<th>Flavonoids</th>
<th>Catechins</th>
<th>Percentage of total flavonoids in the flavonol and flavone subclasses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monomers</td>
<td>Oligomers</td>
</tr>
<tr>
<td>Broccoli, 200 g</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Apples, 200 g</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Green tea, 250 mL</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Black tea, 250 mL</td>
<td>10</td>
<td>—</td>
</tr>
</tbody>
</table>

*Data obtained from references 2–5.

*Including catechin, epicatechin, and their gallate esters.

*Including the proanthocyanidins present in apples and the oxidized forms present in black tea (ie, theaflavins and thearubigins).
REFERENCES
5. Hamsteronje F, Lazarus SA, Schmitz HH. Proanthocyanidin content and variation in some commonly consumed foods. J Nutr 2000;130:2085S–92S.

Reply to JL Donovan
Dear Sir:

We appreciate Donovan’s comments regarding our recent article on dietary flavonoids and the risk of cardiovascular disease (CVD) in women (1). We agree that the terminology used not only in our article but in all articles on flavonoids in their various forms suffers from varying degrees of inconsistency. This is not surprising because thousands of different flavonoids are found in foods and beverages, and, at least until recently, there was no single nutrient database that included all of the subclasses of flavonoids in sufficient detail. In our article, we explicitly stated that “total flavonoids represent the sum of the individual selected flavonols and flavones.” Still, in the interests of avoiding any possible misinterpretation of our conclusions, we wish to clarify our statements on flavonoid food sources and “total” flavonoid intake.

First, a more specific conclusion from our data would be that the observed relations between various flavonoid food sources and CVD were not mediated by the flavonols and flavones that composed our limited flavonoid database. Whether our findings extend to other major flavonoid subclasses is a critical research question that needs to be answered in future studies on flavonoid food sources and CVD.

The recent release of an expanded flavonoid database by the Nutrient Data Laboratory of the US Department of Agriculture, Agricultural Research Service has created potentially important opportunities for research on flavonoids and health (2). In 2002 the US Department of Agriculture, Agricultural Research Service also released data on the isoflavone content of foods, including the amounts of daidzein, genistein, glycitein, and total isoflavones (3), but these data have yet to be fully integrated into analyses examining soy-based food products and chronic disease. Questions surrounding the specific roles of these various flavonoid subclasses in the associations of tea, yellow onions, apples, chocolate, red wine, soy products, and other common flavonoid food sources with the risk of CVD and other chronic diseases await clarification. The study by Arts et al (4) on dietary catechins and ischemic heart disease mortality is an important first step; however, the reported strong correlation between catechins and tea intake (r = 0.98) illustrates how researchers must be careful to distinguish food-specific effects from flavonoid-specific effects when interpreting the results of any study.

The notion of total flavonoid intake is therefore a work in progress as the new databases begin to be incorporated into data analyses. With thousands of different flavonoids found in fruit, vegetables, and beverages, all studies on flavonoids inherently underestimate true total flavonoid intake. This parallels the challenges involved in quantifying dietary carotenoids, of which > 600 have been identified (5).

The hypothesis that dietary flavonoids reduce the risk of CVD offers tremendous potential based upon the total evidence to date. Future studies on the various subclasses of flavonoids will hopefully shed new light on whether particular subclasses have more prominent roles in CVD prevention than do other subclasses.

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REFERENCES

Dietary patterns and chronic disease
Dear Sir:

The September 2003 issue of the Journal featured a series of articles on vegetarian diets, health, and prevention. This issue as well as the September 1999 and January 2000 issues discuss vegetarian diets, essential fatty acids, and optimal ratios of n−6 to n−3 essential fatty acids in the diet.

Simopoulos (1) wrote, “Studies indicate that a high intake of n−6 fatty acids shifts the physiologic state to one that is prothrombotic and proaggregatory, characterized by increases in blood viscosity, vasospasm, and vasoconstriction and decreases in bleeding time. n−3 Fatty acids, however, have antiinflammatory, antithrombotic, antiarrhythmic, hypolipidemic, and vasodilatory properties.” A few recommended optimal ratios of n−6 to n−3 fatty acids are given in the article by Davis and Kris–Etherton (2). They wrote, “The World Health Organization/Food and Agriculture Organization suggests a ratio of 5:1–10:1. Sweden recommends a ratio of 5:1, Canada recommends 4:1–10:1, and Japan recently changed its recommendation from 4:1 to 2:1. Another research group suggested that the...