

Invited Commentary

Dietary flavonoid intake and cardiovascular mortality

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In this issue of the *British Journal of Nutrition*, Mursu *et al.*⁽¹⁾ have reported the association between flavonoid intake, cardiovascular mortality and ischaemic stroke among a group of participants in the Kuopio Ischaemic Heart Disease Risk Factor Study. After following up 1950 Finnish men for an average time of 15.2 years, they ascertained 102 ischaemic strokes and 153 CVD deaths. They found no significant association between total flavonoid intake and risk of ischaemic stroke and cardiovascular mortality; however, individual subclasses of flavonoids were marginally associated with reduced risk of ischaemic stroke and CVD mortality; those in the highest quartile of flavonoid intakes had lower risks for ischaemic stroke and those in the highest quartile of flavanone and flavone intakes were less likely to die of CVD.

Fruit and vegetable intakes have consistently been reported to be inversely associated with cardiovascular mortality^(2–4). Parts of this association might be explained by their higher content of flavonoids. Several epidemiological studies have assessed the association between flavonoid intakes and cardiovascular risk^(5–8), albeit with inconsistent results. Overall, available data suggest that those with higher intakes of flavonoids have modestly lower risks for CVD. However, very few studies considered all flavonoid subclasses^(1,5) and most have used dietary intakes of one or two subclasses^(7,8). The study by Mursu *et al.*⁽¹⁾ is the second that has used updated US Department of Agriculture databases of flavonoids. Investigators from the Iowa Women's Health Study⁽⁵⁾, using updated US Department of Agriculture data, found no significant association between total flavonoid intake and CHD mortality. However, most investigators believe that flavonoids can affect cardiovascular health due to their powerful antioxidant activities⁽⁹⁾. Several reports have shown that flavonoids might reduce LDL-cholesterol susceptibility to oxidation⁽⁹⁾. Because considerable evidence indicates that increased oxidative damage may contribute to the development of CVD, it is logical to expect cardioprotective effects of flavonoids. The potential anti-inflammatory effects, improvement in endothelial function and inhibition

of platelet aggregation have also been suggested as other cardioprotective mechanisms of flavonoids⁽¹⁰⁾.

Dietary intakes of flavonoids

Flavonoids are found in several foods like fruits, vegetables, nuts, seeds, tea and wine. Dietary intakes of flavonoids have been reported in several countries. Mursu *et al.*⁽¹⁾ found a total dietary flavonoid intake of 139.3 mg/d. Mean total flavonoid intake in the recent report from the Iowa Women's Health Study⁽⁵⁾ has been reported to be 603.3 mg/d. Other studies have reported total flavonoid intakes in the range of 20 to <75 mg/d⁽¹¹⁾. Due to lack of comprehensive food composition data on total flavonoids, limited data are available in this regard. However, several studies have calculated intakes of subclasses of flavonoids. For instance, dietary intakes of flavones and flavonols have been reported from Denmark, Finland, Japan, the Netherlands and the USA⁽¹¹⁾. In the study by Mursu *et al.*⁽¹⁾, dietary intake of the flavan-3-ol subclass was 119.7 mg/d (explaining 85.9% of total flavonoid intake). Other subclasses contributed as follows: flavonols 7.2% (10.0 mg/d), anthocyanidins 4.5% (6.2 mg/d), flavanones 2.2% (3.1 mg/d) and flavones 0.2% (0.3 mg/d). Mursu *et al.*⁽¹⁾ have not considered dietary intakes of isoflavones, however, the US Department of Agriculture also has a database on those. In a previous report from Finland⁽¹²⁾, dietary intakes of flavanones, flavones and flavonols have been found to be 20, <1 and 4 mg/d, respectively. These figures are comparable to those reported from Japan, Denmark, the Netherlands and the USA⁽¹¹⁾. Data from NHANES 1999–2002⁽¹³⁾ suggested estimated mean daily total flavonoid intake of 189.7 mg/d, which was mainly from flavan-3-ols (83.5%), followed by flavanones (7.6%), flavonols (6.8%), anthocyanidins (1.6%), flavones (0.8%) and isoflavones (0.6%). The huge discrepancy in total dietary flavonoid intake could be attributed to a lack of a comprehensive database on the flavonoid content of foods, different dietary assessment methods used in different studies, considering limited subclasses to calculate total flavonoid intake, adjustment

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for energy intake in some reports, and different dietary and cultural patterns across populations.

Flavonoid intake and risk of stroke

Inconsistent findings are available regarding flavonoid intakes and stroke. Mursu *et al.*⁽¹⁾ found that dietary intakes of flavonols and less strongly flavan-3-ols were inversely associated with the risk of ischaemic stroke while total flavonoid consumption and intakes of other subclasses (namely flavones, flavanones and anthocyanidins) were not found to be associated. In a cross-sectional report from this population, Mursu *et al.*⁽¹⁴⁾ have indicated that flavan-3-ols were inversely associated with common carotid artery intima-media thickness, an early marker of ischaemic stroke and atherosclerosis. They found a marginally significant inverse association between intakes of flavonols and mean common carotid artery intima-media thickness. In line with Mursu *et al.*⁽¹⁾, two other studies^(12,15) have also reached significant inverse association between dietary intake of flavonols and the risk of stroke. However, in a recent prospective study among postmenopausal women, neither total flavonoid intakes nor individual flavonoid subclasses were associated with the risk of stroke⁽⁵⁾. Others have also failed to find any significant association between dietary intakes of flavonols^(16–18), flavones^(15–18), flavanones⁽¹²⁾ or catechins⁽¹⁹⁾ and stroke. Overall, limited data available in this field make judgement very difficult, particularly when the findings are inconsistent. Different findings could be explained by relatively low numbers of stroke incidence during follow-ups, considering different subtypes of stroke, examining stroke mortality instead of stroke incidence as an outcome variable, confinement of the study population to a specific gender or a specific group of participants (e.g. smokers) and using different tools for dietary intake assessments. Although some flavonoid-rich foods have been reported to be protective against stroke, it is not clear whether such protection is conferred by flavonoids, other nutrients and phytochemicals in flavonoid-rich foods, or the whole foods themselves⁽²⁰⁾.

Flavonoids and cardiovascular mortality

The inverse association between intake of individual subclasses of flavonoids and cardiovascular mortality has been suggested by several investigators. However, others have failed to reach such conclusions. Mursu *et al.*⁽¹⁾ found an inverse association between flavanone and flavone intakes, but not total flavonoid intake, and cardiovascular mortality. In the Zutphen Elderly Study, a well-known study in this field, by assessing flavonoid intake of 805 elderly men, Hertog *et al.*⁽²¹⁾ found that those in the highest tertile were 68% less likely to have CHD death compared to those in the lowest tertile. Later, these findings were confirmed in the Seven Countries Study⁽²²⁾. Intake of flavanones and anthocyanidins, but not total flavonoids, were associated with a decreased risk of CHD, CVD and all-cause mortality in a recent study among 34 489 women in the Iowa Women's Health Study with 16 years of follow-up⁽⁵⁾. Previous reports of this cohort have shown decreased risk for CHD mortality with greater flavonol, flavone, catechins and epicatechins (flavan-3-ols) intakes^(16,19). Contrary to these studies, some

data do not support the hypothesis of inverse association between flavonoids and cardiovascular mortality. In the US Health Professionals Follow-up Study, Rimm *et al.*⁽⁸⁾ did not find flavonoid intake (flavonols and flavones) to be associated with the risk of CHD mortality. This finding has recently been confirmed in US women⁽⁷⁾. The Caerphilly Study demonstrated an increased risk of the all-cause mortality by flavonol intakes⁽²³⁾.

It seems that consumption of selected subclasses of flavonoids is more efficacious to human health than total flavonoid intake. A recent meta-analysis of prospective cohort studies showed that high dietary intakes of flavonols might be associated with a modestly decreased risk of CHD mortality⁽²⁴⁾. The inhibition of LDL oxidation and platelet aggregation by flavonoids⁽¹⁰⁾ suggests that higher intakes might protect against cardiovascular mortality. As mentioned earlier, some epidemiological studies have suggested an inverse relation while others demonstrated low or even no relationship between flavonoid intake and the risk of death from CHD. These contradictory findings may be due to various factors such as lifestyle in different populations, lack of control for other dietary components, limitation to estimate total flavonoid intake due to lack of complete flavonoid database etc. Therefore, in the absence of well-designed clinical trials, the possibility of decreased cardiovascular mortality by dietary flavonoids warrants further investigations.

Most investigations assessing flavonoid intakes so far have been limited in their ability to estimate total flavonoid intake due to the lack of a complete flavonoid database. The use of a new database of flavonoids released by the US Department of Agriculture⁽²⁵⁾ might help to clearly define the association between flavonoid intakes and cardiovascular mortality. Just the study by Mursu *et al.*⁽¹⁾ and a recent study in American women⁽⁵⁾ have used these databases to assess total flavonoid intakes in relation to cardiovascular risks. Mursu *et al.*⁽¹⁾ have used five subclasses while the American study has used seven subclasses⁽⁵⁾. Although some countries have assembled databases of flavonoid contents of foods, information on subclasses of flavonoids are lacking in many countries. Because of recent investigations about the health benefits of flavonoids, developing or expanding flavonoid food composition databases is warranted. Accurate and extensive food composition databases, although difficult and time-consuming, are required to clarify the relationships between consumption of flavonoids and incidence of chronic disease.

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