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## *Invited Commentary*

# The unparalleled benefits of fruit

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Annually, 15 million individuals worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled. Stroke burden is projected to rise from about 38 million disability-adjusted life years in 1990 to 61 million disability-adjusted life years in 2020. Primary prevention of stroke is therefore a major public health priority.

A better diagnosis and treatment of hypertension, together with reduced smoking prevalence, have contributed to the reduction of stroke burden in some developed countries. However, there is still a long way to go. A better knowledge of nutritional factors that may prevent stroke is needed. An increase in the consumption of fruit and vegetables has been advocated for the prevention of stroke.

Two meta-analyses of fruit or vegetable consumption and stroke risk are available[1,2]. One of them[1] included nine cohorts with median follow-up of 13 years (interquartile range 7–18 years). The pooled relative risk was 0·74 (95 % CI 0·69, 0·79) for five *v.* less than three servings per d of total fruits and vegetables. The pooled analysis showed relative risks of 0·72 (95 % CI 0·66, 0·79) for fruits and 0·81 (95 % CI 0·72, 0·90) for vegetables for the highest *v.* the lowest intake.

In the other meta-analysis[2] the risk of stroke was reduced by 11 % (relative risk 0·89; 95 % CI 0·85, 0·93) for each additional serving/d of fruit and by a non-significant 3 % (relative risk 0·97; 95 % CI 0·92, 1·02) for each additional serving/d of vegetables.

Therefore, the cohort study by Mizrahi *et al.* [3], in the current issue of the *British Journal of Nutrition*, assessing the specific roles for different plant foods on stroke risk is of great interest. The authors deserve praise for their perseverance in having successfully completed the follow-up of a prospective cohort during 24 years, thus allowing a long induction period. They started their follow-up in 1968–72. Thus, the follow-up of this cohort is longer than any of those previously published about this issue. In addition they obtained a comprehensive outcome ascertainment through nationwide, population-based registries. They confirmed 625 new cases of stroke during follow-up, more than in most previous cohorts. The use of a validated dietary history interview method for measuring food intake is another strength. The major methodological limitation is that the dietary assessment of participants during follow-up was not repeated. However, the potential bias due to changes in the diet of the Finnish population during the 24-year follow-up would lead to measurement error and would tend to hide any true association. They observed a substantial protection against all types of stroke afforded by a higher consumption of total fruits, but not for total vegetables (only for the subgroup of cruciferous vegetables).

A stronger protection by fruit is in agreement with the available meta-analyses[1,2] and with other recent studies, such as two large Japanese cohorts[4,5] and the Shanghai Women's Health Study[6]. Also, a Mediterranean case–control study observed a significant protection for fruits but not for vegetables against myocardial infarction[7]. Recent studies have reported a protection against atherosclerosis by fruit consumption or by total flavonoid intake using carotid intima thickness as the outcome[8,9].

A protective association, however, for the cruciferous vegetables subgroup was apparent in this latest study[3]. Cruciferous vegetables are characterised by a high content in vitamin C, sinapine and glucosinolates (which can be converted to isothiocyanates). Among the fruit group, the observed inverse association was primarily due to the consumption of citrus fruits. A particular characteristic of citrus fruits is that they are very rich in vitamin C and flavanones (naringenin and hesperetin). Naringenin and hesperetin intake has been associated with a lower incidence of cerebrovascular disease. Synergistic and interactive effects among these phytochemicals naturally present in a complex matrix such as the whole fruit or the natural vegetable cannot be accomplished when these compounds are provided in a pill, because some of these (or other) compounds are not present and some of their mutual interactions are lost[10]. These minor constituents may act jointly via a wide array of mechanisms such as reductions in oxidative stress, inflammation or cytokine production, preservation of endothelium-mediated vasodilatation, inhibition of plaque formation, improvements in adipose tissue and kidney functions, reductions in the thrombotic tendency, or amelioration of lipid levels, among others. In this context, it could be said that the benefits of natural fresh fruits when consumed as the usual dessert are unparalleled.

A cautionary note is, however, needed. Cohort studies, being observational in design, do not assign participants to dietary exposures. Participants instead are free to choose their own diet according to their particular preferences instead of being assigned to a diet by the investigator. It is possible that cohort participants who are otherwise healthier (non-smokers, physically active, more health conscious, etc) might be more likely to self-select themselves to follow what is socially considered as a 'healthy diet'. This means that in cohort studies, as in any observational study, the effect of potential confounding factors needs to be thoroughly considered. The approach followed by Mizrahi *et al.* [3] was the usual in this context, i.e. to measure other aspects of

lifestyle and to control for them using multivariable analyses. This is particularly important for citrus and cruciferous vegetable consumers because they may be more likely to have health-conscious behaviours than non-consumers and may differ in their lifestyle to a great extent from non-users. Not all of these differences can be fully accounted for in multivariable analyses. The question then is what proportion of the protection observed in this cohort study is actually due to the exposure to plant foods and what proportion to lifestyle?

The definitive answer may come from randomised trials testing the effectiveness of a whole food pattern approach in primary cardiovascular prevention, such as the currently on-going Prevención con Dieta Mediterránea (PREDIMED) trial which is testing Mediterranean-type diets[11].

In any case, intervention trials also present some drawbacks, because they can examine only a narrow spectrum of dietary exposures and only for a limited time between exposure and outcome. Hence, epidemiological cohort studies will continue to be extremely important in providing guidance regarding the role of food groups and dietary patterns in stroke prevention. Observational cohort studies and intervention trials should be used in conjunction as complementary tools. The Finnish Mobile Clinic is an important cohort in nutritional epidemiology because participants have been already followed-up for a long time, and this cohort can provide unique knowledge on risks and benefits associated with dietary exposures taking place several decades ago. In this aspect a cohort may even overcome the advantages of a randomised trial. For example, the results of the Boyd Orr cohort[12,13] with over 60 years of follow-up will be almost impossible to be ever replicated by a randomised trial.

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