

The first concerns the validity of the statistical analyses. The EPIC recruited 519,978 men and women in 10 European countries between 1992 and 2000 to investigate the relation between nutrition and ischemic heart disease. In fact, slicing by subgroups (eg, sex or countries) with different sets of variables, and different endpoints, is multiple post hoc analysis, which is a breach of STROBE recommendations (2). For 2009–2010 only, the Journal published 26 original articles from EPIC participants, and the wide range of the hypotheses tested is illustrated by 2 references (3, 4).

The second question concerns the clinical relevance of focusing on the consumption of leafy vegetables, which is very difficult to measure reliably over an 8-y period, whereas smoking, the first cause of both cancer and ischemic heart disease, is present in 24% of EPIC participants. Moreover, no information was provided on salt intake, which tends to be 3 times as high as the recommended allowance due to the epidemic of processed food.

Last, Bendinelli et al (1) reported the relative risk reduction in a composite endpoint. The report of the number needed to treat (ie, with the highest quartile of consumption of leafy vegetables) during 8 y to avoid one death from myocardial infarction is more prosaic but may be of interest for clinicians.

The author did not declare any conflicts of interest.

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## Reply to A Mosher, LH Daugherty, and A Braillon

Dear Sir:

We thank Mosher, Daugherty, and Braillon for their interest in our article (1). We agree with the comments of Mosher about the possible presence of undiagnosed cases of diabetes or hyperlipidemia in our study population. Our decision to exclude only those participants who reported the use of antidiabetic or antihyperlipidemic drugs at baseline had the aim of excluding patients with a clear clinical diagnosis of diabetes or of hyperlipidemia. An additional group of patients with diabetes or hyperlipidemia (not under treatment at the time of enrollment) may have been included in our study

population; this might have led to an underestimation of the inverse association between consumption of leafy vegetables and coronary heart disease (CHD) risk due to the fact that in these subjects at increased risk of CHD because of their conditions, a change toward a more healthy dietary pattern (richer in vegetable foods and poorer in fat-rich foods) might have occurred after diagnosis and before enrollment. Sensitivity analyses carried out after the exclusion of all subjects who reported to be on a specific diet provided the same estimates. In addition, our results were also confirmed in an analysis performed after the exclusion of all patients with prevalent diabetes identified in the frame of InterAct, a large European multicenter study focused on diabetes in participants of most European Prospective Investigation in Cancer and Nutrition (EPIC) cohorts (project LSHM-CT-2006–037197 funded by the European-Community under Framework Program 6), through the linkage with multiple sources of medical information including drug consumption, hospital discharges, death certificates, outpatient services, and exemptions. Unfortunately, in the case of hyperlipidemia, we do not have the same possibility to use other sources of information to integrate data on the use of specific drugs at baseline. We also agree that the prevalence of diabetes and hyperlipidemia in our study population tends to be lower than that expected in the general population, but the enrollment of healthy volunteers is a well-known characteristic of all prospective studies. High body mass index, high waist circumference, and high consumption of alcoholic beverages have been widely recognized as modifiable risk factors for CHD, whereas a protective effect was attributed to low or moderate alcohol consumption (2–4). For this reason, in our analysis, body height, body weight, and alcohol consumption were added to the adjusted model as confounders. Sensitivity analyses (data not shown) were also carried out to evaluate these variables as possible effect modifiers, but no significant interaction with consumption of the several types of vegetables and olive oil emerged.

We also agree with the suggestion of Daugherty about the appropriateness of taking into account mental health factors, and in particular psychosocial risk factors, when studying CHD risk. Unfortunately, this area was not investigated in the original pool of information collected at baseline for the study participants, who were enrolled in the frame of the EPIC study, which originally was planned to investigate mainly cancer risk factors (5, 6). The inclusion of additional data on the presence and severity of depressive disorders in the pool of information to be collected in the next follow-up evaluations of the Italian EPIC participants has been considered, but because of the large size of the cohort, cost estimates are prohibitive.

After reading the comments from Braillon, we would like to point out that the EPIC project is a large European collaborative effort aimed at investigating the association between diet, lifestyle, and cancer, although the possibility of other outcomes of interest has been considered since the beginning of the project. The analyses reported in the article were conducted in the frame of the EPICOR Study, which was set up to investigate the relations between diet and cardiovascular diseases in the Italian EPIC participants. The EPICOR Study is characterized by the accurate definition of the major CHD events, by the availability of systolic and diastolic blood pressure measurements collected at baseline (6, 7), and by the accuracy of the detailed dietary information (8). For these reasons, EPICOR represents a unique opportunity to study determinants of CHD in a Mediterranean population in consideration of the fact that older studies on CHD in the Italian population (including the seminal Seven Countries Study) were often quite small and performed with only aggregated data (9). As reported in our article's Discussion, the collection of information on dietary habits in the year preceding enrollment with a single assessment may be a limitation

of the study. It is possible that some participants may have changed dietary habits during the follow-up period, thus leading to some degree of misclassification and consequently to a weakening of the relative risk estimates. The lack of reliable information about salt intake could be a further limitation. However, processed meats (as pointed out by Braillon), cheese, and salted bread (consumed mainly in southern Italy) are among the major sources of salt intake in Italy (10). Additional analyses were carried out with the addition in the model of a term for processed meat or cereals or dairy products, alternatively. No relevant changes in the estimate of the association between leafy vegetables and olive oil and CHD risk emerged. Finally, we are convinced that our results showing a reduction in risk of CHD with increasing consumption of vegetables, and particularly of leafy vegetables, should be considered in a public health perspective as further evidence of the health benefits of a diet rich in vegetables and poor in animal foods.

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