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### Author

Kawas, Claudia H

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## Diet and the Risk for Alzheimer's Disease

**Claudia H. Kawas, MD**

Institute for Brain Aging and Dementia, University of California, Irvine, Irvine, CA

For centuries, the role of diet in the causation and prevention of disease has engaged scientific and lay interest. The hope, presumably, is that by identifying (and consuming) significant amounts of a single nutrient or set of nutrients, we can prevent disease and promote longevity. Clinical studies of vitamins and other micro-nutrients are published regularly in support of this notion, and the results are highlighted routinely in newspapers, magazines, and popular media.

In this issue of *Annals of Neurology*, Scarmeas and colleagues<sup>1</sup> report an observational study of the Mediterranean diet and risk for Alzheimer's disease (AD) in a multiethnic population sample in northern Manhattan. The Mediterranean diet is characterized by high intake of foods and nutrients that have been reported to be beneficial in AD, including fruits, vegetables, fish, unsaturated fatty acids, and modest amounts of wine. After adjustment for numerous potential confounders, individual food groups were not significantly associated with risk for AD, but the composite Mediterranean dietary pattern (highest tertile) was associated with a 40% reduction in AD risk when compared with the lowest tertile (hazard ratio, 0.60; confidence interval, 0.42–0.87). The results of Scarmeas and colleagues' study<sup>1</sup> are consistent with other studies that show benefit of the composite Mediterranean diet on cognitive performance,<sup>2</sup> as well as mortality cardiovascular disease, and cancer outcomes.<sup>3–5</sup>

The work of Scarmeas and colleagues<sup>1</sup> extends the approach in the study of diet and AD risk from individual foods and nutrients to a composite dietary pattern. As they emphasize, "defining diet by dietary patterns has the ability to capture its multi-dimensionality... because patterns can integrate complex or subtle interactive effects..." It makes scientific sense to consider dietary patterns because this conception more closely approximates the way people consume our nutrients. Defining diet by dietary patterns, of course, also has limitations. In particular, we can only speculate on the key mechanisms and interactive effects underlying any observed benefits of a dietary pattern. Some components of the diet may actually be antagonistic or even harmful, and these effects would be difficult to detect.

### Causality

To be considered causal, a risk or protective factor should satisfy criteria including consistency or replication of findings, specificity of the association, proper temporal relation, dose–response relation, and biological plausibility.<sup>6</sup> First, Scarmeas and colleagues' study<sup>1</sup> requires replication, preferably in a variety of settings, study designs, and subjects. If successfully replicated, randomized clinical trials (RCTs) should ideally follow. Randomized experimental studies could best demonstrate that the diet, rather than unknown confounders, is responsible for the reduction in AD risk.

A prevention study with dietary intervention would present many challenges. Obviously, subjects could not be blinded, because the intervention requires their participation. People who volunteer and successfully complete a decade-long study involving diet will undoubtedly reflect subject selection biases. Finally, even in motivated people, dietary adherence can be problematic, as recently demonstrated in the Women's Health Initiative

study of a low-fat dietary intervention and the development of heart disease and cancer. Adherence to a dietary intervention is always far from ideal, which provides fodder for critics who do not believe the results of a trial that does not adhere to their notions.

## Strengths and Weaknesses of Observational Studies and Randomized Trials

Observational studies are one of our most powerful and cost-efficient tools for the identification of putative risk and protective factors. They are able to investigate a wide variety of exposures, dosages, and formulations in diverse groups of subjects over much longer periods than is possible with a randomized trial. Moreover, despite the ascendancy of the RCT as the gold standard, observational studies generally produce results similar in direction and magnitude to randomized trials.<sup>7,8</sup> In all observational studies, however, it is impossible to control for unknown confounders. People in northern Manhattan who adhere to a “Mediterranean diet” are probably more health conscious and different in other ways compared with people with other dietary histories. These differences could potentially account for the observed difference in AD risk.

A recent spate of investigations has heightened awareness that randomized trials and observational studies can provide discordant results. Well-known examples include results from the Women’s Health Initiative with an apparent increase in AD and stroke in women receiving hormonal replacement therapy<sup>9,10</sup> and a lack of cardiovascular or cancer benefits from a low-fat diet.<sup>11–13</sup> But these results should be interpreted with caution because randomized trials also have limitations: only one formulation and dosage can be investigated, participants can be poorly representative of the population (selection bias), and the trial can investigate only relatively short-duration exposures at a particular stage in life. For example, in the Women’s Health Initiative study of estrogen, women who were randomized to conjugated estrogens (with or without progestin) were typically long past menopause. Exposure to hormonal therapy in these women was associated with approximately double the risk for development of AD and an increase in cerebrovascular events. However, we still do not know whether the results would be similar with earlier initiation of therapy during the perimenopausal period, which was the beneficial exposure period suggested by most of the observational studies.<sup>14–19</sup> We also do not know whether other dosages or different forms of estrogen, such as estradiol, would have the same effects. We do not even know whether the results of the trial would be replicated if the study were to be repeated.

The results of randomized trials and observational studies must be interpreted with caution. The results of a single randomized trial or a single observational study should be interpreted *very* cautiously. Although observational studies often are replicated, RCTs rarely are repeated because of cost and potential ethical concerns. When we think we know the answer, it is difficult to conduct additional clinical research. A single RCT, however, can only answer a modest number of questions. To advance our understanding of the complex relations between diet and risk for disease, we need to integrate a comprehensive variety of studies from the laboratory, the clinic, and the population.

## Conclusion

Evident to all biologists, farmers, and parents, diet and nutrition have effects on living organisms, and these effects are likely to include susceptibility to disease. But it is unlikely that a single nutrient or food group is causal. It is also unlikely that only one dietary pattern is beneficial. From the plethora of current studies of diet and health, we can probably reasonably conclude that a varied diet, rich in vegetables, fruits, fish, and saturated fatty

acids and modest in meat and dairy, is good for us in general; however, additional research may tell us whether it is specifically good for lowering our risk for AD.

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