Published in final edited form as:

JAMA. 2009 August 12; 302(6): 686–687. doi:10.1001/jama.2009.1149.

Mediterranean Diet and Late-Life Cognitive Impairment: A Taste of Benefit

David S. Knopman, MD

Department of Neurology, Mayo Clinic, Rochester, MN

The Mediterranean-type diet (MeDi), a diet high in plant foods (such as fruits, nuts, legumes, and cereals) and fish, with olive oil as the primary source of mono-unsaturated fat and low-to-moderate intake of wine, as well as low intake of red meat and poultry, has been associated with a number of healthful outcomes including reduced risk of cardiovascular disease, cancer, and mortality⁵. In 2006, Scarmeas et al³ reported that adherence to the MeDi was associated with a reduction in incident dementia. This study was greeted with a feeding frenzy of media and public attention.¹⁵ However, a single study reporting an association must be replicated to assess its generalizability. In this issue of JAMA, 2 articles^{1,2} report results of studies designed to replicate and expand that initial report. The first article, by Scarmeas and colleagues,¹ evaluated the association of MeDi adherence and physical activity with risk of incident Alzheimer disease (AD). MeDi adherence and physical activity were both independently associated with reduced risk for AD in the analytic models, and the authors concluded that the associations of AD with MeDi adherence and physical activity were distinct from a general tendency to adhere to a healthier lifestyle. This analysis was performed in the same cohort that Scarmeas et al originally reported³ so could not address whether these results should be generalized beyond the study population.

In the second article, Feart and colleagues² attempted to replicate the association of MeDi and cognitive decline previously described by Scarmeas et al³ in a population-based cohort from Bordeaux, France. The authors used 4 neuropsychological tests to evaluate cognitive decline. Individuals who had high adherence to the MeDi in this study had higher Mini-Mental State Examination (MMSE) scores at the end of the 5-year follow-up period in some of the analytic models, but there were no associations with changes in other cognitive assessments with only one exception (the Free and Cued Selective Reminding) among the several models. Moreover, there was no reduction in incident dementia in those with high adherence to the MeDi, although the study was underpowered for this outcome. In addition, the neuropsychological tests used in the study may not have been ideal; while the Free and Cued Selective Reminding Task used by the authors was an excellent choice for detecting changes in short-term memory associated with pre-AD, other tests of executive function such as the Digit-Symbol Substitution test or the Trailmaking test might have been more sensitive to subtle cognitive differences associated with cerebrovascular disease.⁴

Address correspondence and reprint requests to D.S. Knopman, MD, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905 (telephone: 507-538-1038; fax: 507-538-6012; knopman@mayo.edu).

Disclosures: DSK has served on a Data Safety Monitoring Board for Sanofi-Aventis Pharmaceuticals (completed 10-08) and received personal compensation, will serve on a Data Safety Monitoring Board for Lilly and will receive personal compensation, and is an investigator for clinical trials sponsored by Baxter Pharmaceuticals, Elan Pharmaceuticals and Forest Pharmaceuticals. He served as one time consultant to GlaxoSmithKline for an anti-Alzheimer agent. He is an Associate Editor of Neurology for which he receives compensation from the American Academy of Neurology.

Whether the study by Feart et al should be considered supportive of the protective role of the MeDi for cognitive function is debatable. All 4 cognitive tests constituted their primary outcome measures. Considering only the MMSE results, the results could be considered as supportive of the initial findings of the study by Scarmeas et al, but only when the MMSE was analyzed as a continuous variable, not as a categorical variable. The lack of consistent association with the Cued Selective Reminding Test is of concern if pre-Alzheimer pathology was the target of the MeDi.

The 2 studies reported in this issue,^{1,2} together with the earlier report from the same North Manhattan cohort,³ provide moderately compelling evidence that adherence to the MeDi is linked to less late-life cognitive impairment. Given that the MeDi is associated with reductions in cardiovascular disease, cancer, and mortality,⁵ the lack of specificity of the apparent effects of adherence to the MeDi is similar to the apparent effects of other health-related behaviors at midlife.⁶ MeDi adherence is likely correlated with other healthy activities.

The associations of the MeDi with cognition, heart disease, cancer, and mortality probably reflect a lifetime of exposure both to the diet and to other healthy behaviors. An elderly person's diet is shaped by a life-long set of preferences,⁷ and diet may be more consistent as one ages than is physical activity. For example, while food preferences may be preserved after an individual develops age-related illnesses, preserved physical activity in older individuals might be a marker of freedom from disease in addition to a protective factor. In addition, late-life diabetes, hypertension, obesity and other health problems do not necessarily reflect what was happening at midlife. For example, in the study by Scarmeas et al¹, as in other studies, those with incident dementia tended to have low BMI even though obesity is a risk factor in midlife. In the parent study from which the cohort for the Feart et al³ was derived, metabolic syndrome and its components were associated with vascular dementia but not with all-cause dementia.⁸ Metabolic syndrome⁹ and hypertension¹⁰ may appear as protective factors in later life, perhaps because they reflect preserved weight and cardiovascular function, even though in mid-life they are consistent risk factors.¹¹ While both studies controlled for a number of conditions that reflected general health and other risk factors as measured in late life, the much longer time frame of exposure represented by adherence to the MeDi and the shorter exposure to other factors and their potential to be protective in late life raise the possibility of residual confounding. Although the persistence of the associations between the MeDi and incident AD¹ or cognitive decline² with inclusion of vascular risk factors in the models is noteworthy, controlling for late life risk factors is not equivalent to controlling for a lifetime of exposure to vascular risk factors.

Midlife obesity, diabetes and hypertension are all vascular risk factors for late life dementia and strongly influenced by diet. Therefore, MeDi may act on cognition through cerebrovascular mechanisms. Alternatively, AD almost certainly has its pathological origins in midlife,¹² and it is possible that components of the MeDi could affect the metabolism of β -amyloid or the tau protein. However, cerebrovascular disease often exists in persons diagnosed clinically with AD,¹³ and small changes in cerebrovascular disease burden could affect the clinical expression of the cognitive disorder of AD. Consistent with this hypothesis, reduced risk of cardiovascular disease is associated with adherence to the MeDi,^{7, 14} and the association of the MeDi with MMSE performance was attenuated when stroke was added to the analytic model. Whether a reduced accumulation of cerebrovascular pathology may be brought about by some of the substances contained in the MeDi, by the avoidance of substances not in the MeDi, or by an adherence to a broader set of healthy behaviors cannot be resolved with the current analyses.

A variety of approaches to mitigating cerebrovascular disease in midlife exist, including diet, exercise, treatment of hypertension, treatment of diabetes, avoidance of obesity, and avoidance of smoking. The findings of Scarmeas et al¹ and Feart et al² fit into a larger and potentially optimistic view of prevention of late life cognitive impairment through application, at least by midlife, of as many healthy behaviors as possible, including diet. Based on these 2 studies, diet may play a supporting role, but following a healthy diet does not occur in isolation.

Rather than the feeding frenzy¹⁵ generated by the original study by Scarmeas et al,³ the nuanced science of the studies by Scarmeas et al³ and Feart et al² should not be consumed so unabashedly. The scientific value of these studies cannot be disputed, but whether and how they can or should be translated into recommendations for the public is the question. For now, it is reasonable to nibble on these findings and savor them, but not to swallow them whole.

Acknowledgments

Supported by grants U01 AG 06786 (Mayo Alzheimer's Disease Patient Registry), P50 AG 16574 (Mayo Alzheimer's Disease Research Center) from the National Institute on Aging, and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program

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