

# Mediterranean Diet and Late-Life Cognitive Impairment

## A Taste of Benefit

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**T**HE MEDITERRANEAN-TYPE DIET, A DIET HIGH IN PLANT foods (such as fruits, nuts, legumes, and cereals) and fish, with olive oil as the primary source of monounsaturated 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 mortality.<sup>1</sup> In 2006, Scarmeas et al<sup>2</sup> reported that adherence to the Mediterranean-type diet was associated with a reduced incidence of Alzheimer disease (AD). This study was greeted with a feeding frenzy of media and public attention.<sup>3</sup> However, a single study reporting an association must be replicated to assess its generalizability.

In this issue of JAMA, 2 articles<sup>4,5</sup> report the results of studies designed to replicate and expand that initial report. The article by Scarmeas and colleagues<sup>4</sup> evaluated the association of Mediterranean-type diet adherence and physical activity with risk of incident AD. Mediterranean-type diet 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 Mediterranean-type diet 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 reported,<sup>2</sup> so although it extended the findings of the initial report, it could not address whether these results should be generalized beyond the study population.

In another article, a population-based cohort from Bordeaux, France, Féart and colleagues<sup>5</sup> attempted to replicate the association of Mediterranean-type diet and cognitive decline previously described by Scarmeas et al.<sup>2</sup> The authors used 4 neuropsychological tests to evaluate cognitive decline. Individuals who had high adherence to the Mediterranean-type diet 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 statistically significant associations with changes in other cognitive assessments with only one exception (the Free and Cued Selective Reminding Test) among the several models. Moreover, there was no reduction in incident demen-

tia in those with high adherence to the Mediterranean-type diet, 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 Test 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.<sup>6</sup>

Whether the study by Féart et al should be considered supportive of the protective role of the Mediterranean-type diet for cognitive function is debatable. All 4 cognitive tests constituted their primary outcome measures. Taking into account only the MMSE results, the outcomes could be considered as supportive of the initial findings in the study by Scarmeas et al,<sup>2</sup> but only when the MMSE was analyzed as a continuous variable (not as a categorical variable). The lack of consistent association with the other cognitive measures, especially the Free and Cued Selective Reminding Test, is of concern if pre-AD pathology was the target of the Mediterranean-type diet.

The 2 studies reported in this issue,<sup>4,5</sup> together with the earlier report from the same northern Manhattan cohort,<sup>2</sup> provide moderately compelling evidence that adherence to the Mediterranean-type diet is linked to less late-life cognitive impairment. Given that the Mediterranean-type diet is associated with reductions in cardiovascular disease, cancer, and mortality,<sup>1</sup> the lack of specificity of the apparent effects of adherence to the Mediterranean-type diet is similar to the apparent effects of other health-related behaviors at midlife.<sup>7</sup>

The associations of the Mediterranean-type diet 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,<sup>8</sup> and diet may be more consistent as an individual 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 dis-

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ease in addition to a protective factor. Scarmeas et al<sup>2</sup> controlled for comorbid risk factors using the Charlson index and performed a propensity analysis to try to adjust for such confounding, but it would be difficult to control completely for such factors. 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 al,<sup>4</sup> as in other studies, those with incident dementia tended to have a low body mass index even though obesity is a risk factor in midlife.

In the parent study from which the cohort for the study by Féart et al<sup>5</sup> was derived, the metabolic syndrome and its components were associated with vascular dementia but not with all-cause dementia.<sup>9</sup> The metabolic syndrome<sup>10</sup> and hypertension<sup>11</sup> may appear as protective factors later in life, perhaps because they reflect preserved weight and cardiovascular function, even though in midlife they are consistent risk factors.<sup>12</sup> 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 Mediterranean-type diet 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 Mediterranean-type diet and incident AD<sup>4</sup> or cognitive decline<sup>5</sup> 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 are strongly influenced by diet. Therefore, the Mediterranean-type diet may act on cognition through cerebrovascular mechanisms. Alternatively, AD almost certainly has its pathological origins in midlife,<sup>13</sup> and it is possible that components of the Mediterranean-type diet could affect the metabolism of the  $\beta$ -amyloid or the tau protein. However, cerebrovascular disease often exists in persons diagnosed clinically with AD,<sup>14</sup> 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 Mediterranean-type diet,<sup>8,15</sup> and the association of the Mediterranean-type diet with MMSE performance was attenuated when stroke was added to the analytic model in the study by Féart et al.<sup>5</sup> Whether a reduced accumulation of cerebrovascular pathology may be brought about by some components of the Mediterranean-type diet, by the avoidance of substances not in the Mediterranean-type diet, 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 al<sup>4</sup> and Féart et al<sup>5</sup> 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 frenzy<sup>3</sup> generated by the original study by Scarmeas et al,<sup>2</sup> the nuanced science of the studies by Scarmeas et al<sup>4</sup> and Féart et al<sup>5</sup> 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.

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