tive factors against dementia and predementia syndromes. In fact, elevated SFA could have negative effects on age-related cognitive decline and mild cognitive impairment.⁶ Furthermore, at present, epidemiological evidence suggested a possible association among fish consumption, monounsaturated fatty acids, and PUFA (particularly ω -3 PUFA) and reduced risk of cognitive decline and dementia.⁶ Light to moderate alcohol use may be associated with a reduced risk of incident dementia and AD.⁷ Finally, the limited epidemiological evidence available on fruit and vegetable consumption and cognition generally supported a protective role of these macronutrients against cognitive decline, dementia, and AD.⁸

We greatly appreciated this food combination–based analysis from the WHICAP.¹ In fact, notwithstanding the undeniable advantages of the whole-diet approach of previous reports from this study,^{3,5} using such a score in an American and multiethnic population might not adequately represent conformity with the traditional Mediterranean diet, as acknowledged by Gu and colleagues.¹ Furthermore, recent findings from the WHICAP further underlined the possible protective role against cognitive decline of both ω -3 and ω -6 PUFA intake and the detrimental role of SFA.¹ In fact, previous results from the Italian Longitudinal Study on Aging demonstrated that, in an 8.5-year follow-up, high monounsaturated fatty acid, PUFA, and total energy intake were significantly associated with decreased age-related cognitive decline.⁹ Furthermore, in the same sample, high PUFA intake appeared to have a borderline nonsignificant trend toward a protective effect against the development of mild cognitive impairment.¹⁰ However, in a very recent reanalysis from the Italian Longitudinal Study on Aging cohort, high PUFA intake was associated with reduced risk of incident mild cognitive impairment among those who consumed a low monounsaturated fatty acid/SFA ratio of intake.¹¹ In fact, while an increasing body of evidence suggested that elevated fish consumption and high intake of ω -3 PUFA may be protective against age-related cognitive decline and mild cognitive impairment, the traditional Cretan diet, although strongly dependent on high olive oil intake, was never centered on fish consumption.¹² In this context, ω -6 PUFA could also potentially have some health benefits. In fact, in the Mediterranean diet, some foods are rich in ω -6 PUFA (eg, walnuts, almonds, hazelnuts), while other foods, although poor in ω -6 PUFA, are highly consumed such as cereals, legumes, and, in smaller amounts, some types of meat (pork), and poultry. Furthermore, olive oil contains ω -6 and ω -3 PUFA in a ratio of 10:1. Taken together with the recent findings from the WHICAP and the Italian Longitudinal Study on Aging,^{1,9-11} it should be advisable to include elevated PUFA (both ω -3 and ω -6) intake and lower monounsaturated fatty acids/SFA ratio or SFA intake in the food combination presumed to be beneficial against AD and cognitive decline.

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Potential Role of Iron in a Mediterranean-style Diet

Gu and colleagues¹ identified a dietary pattern associated with lower risk of AD. This dietary pattern includes higher intake of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark green leafy vegetables and lower intake of high-fat dairy products, red meat, organ meat, and butter. It is similar to the Mediterranean diet, adherence to which is also associated with reduced risk of developing AD.² Previously, Buijsse et al³ reported that

elderly men from Crete, in the Mediterranean south of Europe, had “consistently lower levels of indicators of oxidative stress and iron status and higher concentrations of major antioxidants” than elderly men from Zutphen in the north of Europe. In particular, serum ferritin levels, a useful marker of body iron stores,⁴ were 2-fold lower in men from Crete (69.8 µg/mL) than in men from Zutphen (134.2 µg/mL). We have proposed that age-associated increase in body iron stores is a pivotal event in AD pathogenesis and progression.⁵ We predict that dietary patterns similar to the Mediterranean diet that reduce the risk of AD will also be associated with lower body iron stores, as indicated by reduced serum ferritin levels. Unfortunately, iron status was not an endpoint in the study of Gu and colleagues.¹ Given the therapeutic interest in iron chelators for neurodegenerative diseases including AD,⁶ and in controlled phlebotomy to safely reduce body iron stores and avoid iron deficiency,⁴ design of future epidemiological studies of diet and AD should consider the potential importance of iron status.

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In reply

In their letter, Solfrizzi and colleagues¹ interpret our recent findings as evidence supporting “a possible protective

role against cognitive decline of both ω-3 and ω-6 polyunsaturated fatty acids (PUFA) intake and the detrimental role of saturated fatty acid (SFA).” While a dietary pattern representing high intake of both ω-3 and ω-6 PUFA, vitamin E, and folate, and lower intake of SFA and vitamin B₁₂ seems to be associated with lower risk of AD,¹ the isolated role of individual nutrients remains to be understood. We ran additional models in which we individually considered nutrients as possible predictors of AD. After adjustment for recruitment cohort, age, sex, education, and ethnicity, a Cox model including all 7 nutrients used in our reduced rank regression analyses simultaneously showed that none of them had statistically significant individual associations with AD risk; the hazard ratios (HR) and 95% confidence intervals (CI) comparing the highest tertile to the lowest tertile were 1.31 for SFA (95% CI, 0.85-2.03; P for trend=.18); 0.72 for ω-3 PUFA (95% CI, 0.49-1.07; P for trend=.07); 0.89 for ω-6 PUFA (95% CI, 0.59-1.35; P for trend=.52); 1.08 for MUFA (95% CI, 0.66-1.78; P for trend=.74); 1.16 for vitamin E (95% CI, 0.79-1.71; P for trend=.62); 1.23 for vitamin B₁₂ (95% CI, 0.90-1.69; P for trend=.23); and 1.02 for folate (95% CI, 0.71-1.49; P for trend=.76). Therefore, the positive association between ω-3 and ω-6 PUFA and the negative association between SFA and this lower-AD risk dietary pattern may be best considered in aggregation with other nutrients. Overall, from a reductionistic, biological point of view it remains important to understand the individual roles of ω-3 PUFA, ω-6 PUFA, and SFA or the optimal ratio of ω-6 to ω-3 PUFA with regard to cognitive decline or AD development. Progress toward such understanding may shed light on the role of fatty acids in neurodegeneration. Nevertheless, the intercorrelation between various types of fatty acids and nutrients in general and the detection of significant associations only when they are considered in a holistic approach illustrates once more the importance of studying dietary patterns.

In another letter, Dwyer et al proposes that age-associated increase of body iron store might be important in AD pathogenesis and progression. We tested this interesting hypothesis by directly investigating the associations between dietary iron and Mediterranean diet adherence and dietary iron and AD risk. Energy-adjusted dietary iron intake was positively associated with Mediterranean diet score (Spearman $r=0.26$; $P<.001$) but it was not associated with AD risk. Compared with the lowest tertile, multivariable-adjusted hazard ratios were 0.8 (95% CI, 0.5-1.1) and 0.8 (95% CI, 0.6-1.2) for the middle and highest tertile, respectively (P for trend=.31). Overall, to our knowledge, neither association between dietary intake of iron and risk of AD nor therapeutic efficacy of iron chelators for AD have been convincingly demonstrated. Nevertheless, because the hypothesized role of iron in AD mainly involves oxidative stress induced by iron² and iron is likely to interact with other dietary antioxidant, it would be interesting to examine the association between dietary total antioxidant capacity and AD. In our study population, we found that energy-adjusted ferric-reducing antioxidant power values³ as a measure of dietary total antioxidant capacity were not associated with incident AD; the multivariable-adjusted hazard ratio was 0.99 (95% CI, 0.82-1.19), comparing the highest with the lowest quartile. Overall, our data do not seem to

support the notion of an iron-mediating role in the observed Mediterranean diet-AD association.

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Novel Mechanisms and Preventions for Sudden Unexpected Death Related to Medullary Brain Lesions

I read with interest the pathophysiology study of Lipp et al,¹ who found that patients with multiple system atrophy (MSA) and autonomic failure are hemodynamically impaired when stressed with hypercarbia and hypoxia, while maintaining relatively intact ventilatory responses. The authors¹ mentioned a potential relevance to death during sleep in MSA.

A recent neuropathology study² of sudden death in various subpopulations of MSA found that depletion of

medullary serotonergic neurons was associated with sudden death, the leading cause of death in MSA.

Another recent clinical neuropathology review³ described the occurrence of sudden unexpected death in patients with a wide variety of medullary pathology including infarction, demyelination, infection, and inflammation, many of which were small and otherwise asymptomatic in victims who had no other cause for death. All age groups were involved. The authors³ speculated that these lesions triggered a final common pathway involving the autonomic nervous system, resulting in sudden, unexpected death.

Pathophysiology studies like that of Lipp et al¹ contribute significantly to our understanding of how the autonomic nervous system responds after it has become diseased, while other studies^{2,3} sometimes provide a broader context for that work. Additionally, pathophysiology studies can lead to important intermediate milestones such as the Back to Sleep program in the prevention of sudden infant death syndrome. Ultimately, studies of MSA may help us understand the mechanisms of sudden unexpected death related to medullary brain lesions and suggest preventive measures; the utility of these may extend beyond medullary deaths to the many other deaths facilitated by autonomic responses.

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