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Dietary Links to Alzheimer's Disease: 1999 Update*

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ABSTRACT: With the republication of Grant (18), the first paper providing epidemiologic evidence linking diet to the development of Alzheimer's disease (AD), it is an appropriate time to review the findings and hypotheses therein in light of the subsequent literature. The main findings, that dietary fat and energy in old age are high risk factors, while fish and cereals are risk-reduction factors, have been supported in various recent epidemiologic studies. Diet contributes to the development of AD through modulating oxidative stress and inflammation, which is also linked to oxidative stress, but may also arise from series 2 prostaglandins. Thus, as one ages, dietary modifications and additional supplements designed to reduce free radical production and inflammation provide a significant measure of reduction in risk for the development of AD.

When "Dietary links to Alzheimer's disease" (18, reprinted in this issue) was published, it was the first paper showing epidemiologic evidence linking diet to the development of AD. The hypothesized mechanism was a combination of oxidative stress and inflammation arising from arachidonic acid and series 2 prostaglandins (11) arising from excess dietary fat and energy late in life. Since an important test of a hypothesis paper is how good are the predictions of the hypothesis, now is an appropriate time to take stock of what was found, what was hypothesized, and what subsequent research has shown.

The first finding was that total dietary fat was a high risk factor for the development of AD. This point received support in the Zutphen cohort study of Kalmijn et al. (29), although not at a statistically-significant level. It is also supported by the recent report of 1.07% AD prevalence in a rural community of northern India (4). The statistics for dietary fat and fish and AD prevalence improve with the addition of this value along with a dietary fat supply in India in 1993 of 42 g/person/day (15). Khalsa (30,31) had already included a low-fat diet in his program to prevent and reverse memory loss prior to the publication of Grant (18). Walker et al. (53) found that there was cerebral lipid deposition in aged apolipopritein-E-deficient mice, showing that disorders of lipid metabolism can induce significant pathological changes in the central nervous system. On the other hand, Solfrizzi et al. (49) reported that high mono-unsaturated fatty acids, such as commonly found in the Mediterranean diet from olive oil, protects against cognitive decline.

This article is published with permission from the University of Kentucky. It is also published in the online journal Alzheimer's Disease Review; www.coa.uky.edu/ADReview/Second, that total caloric intake is risk factor for the development of AD, although somewhat lower than dietary fat. This finding received support in the case-control study of Smith et al. (46) as well as in another study by Bruce-Keller et al. (3).

Third, that consuming fish reduces the risk of developing AD. This was confirmed in the Zutphen cohort study by Kalmijn et al. (29). Kalmijn et al. (29) also found that linoleic acid, an n-3 fatty acid found in nuts and seeds such as flax seed, was also inversely correlated with AD. This is an important finding, given that fish stocks are being depleted world wide, and that fish tend to bioaccumulate heavy metals and other toxins. Yoshida et al. (55) reviewed a number of studies on n-3/n-6 fatty acid balance

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on brain function, finding that n-3 fatty acids enhance brain function in general. Fernandez et al. (14) reported that fish consumption also reduces the risk of cancer, in addition to heart disease, which was already known. Inflammation is a known risk factor for cancer of a number of organs of the digestive system (1).

Fourth, that diet later in life was much more important than earlier in life. The original study found that diet 4 years prior to prevalence studies gave the best statistical results. Since those with AD live about 7 years after developing the disease, it implies that diet at the time of development has the greatest influence. This point was confirmed in the case-control study of Smith et al. (46). They found that energy intake after the age of 60 years had an impact on risk of AD, but not energy intake in earlier years.

Fifth, that dietary cereals and grains are strongly inversely related to AD. Similar results have been found for most cancers, which are often due to dietary fat, where odds ratios in the range of 0.6–0.9 were found for whole-grain intake (27). The question: Do grains actually have compounds that fight AD and cancer or merely displace dietary components that are risk factors for AD and cancer? is unresolved. Cordain (7) points out that cereals do have some drawbacks including lack of some essential nutrients as well as containing some anti-nutrients that interfere with metabolism.

Sixth, that the prevalence of AD in the U.S. was slightly over 5% of the population aged 65+ years, or slightly more than 2 million of all ages. This finding ran counter to the commonly accepted prevalence at that time of nearly 10% or approximately 4 million, based on the work of Evans et al. (12). The Evans et al. (12) study classified approximately 95% of those with dementia as having AD, a fraction way out of line with all other epidemiologic studies (28). The lower values were confirmed by Brookmeyer et al. (2), who reanalyzed several previous studies and concluded that the AD prevalence in the U.S. was approximately 2.32 million in 1997.

Seventh, that genetic predisposition to AD through the apoliprotein E (APOE) and diet are both important in the etiology of AD. Farrer et al. (13) presented model results based on a number of clinical and autopsy studies showing that possession of two epsilon 4 alleles significantly increased the risk of AD, especially prior to age 75 years. Tang et al. (51) found that the prevalence of various APOE alleles in African-American, Hispanic, and white populations in a New York City community was a poor indicator for risk for AD. Grant (19) responded that diet was also important. Practico et al. (42) reported that APOE-deficient mice have a lipid metabolism disorder that can induce an age-dependent increase in brain lipid peroxidation products.

Eighth, that metals such as aluminium and mercury are found in elevated concentrations of the brains of those with AD as a result of an acid forming diet, and while such metals may play a role in oxidative stress, are not significant risk factors for the development of AD. Smith et al. (47) state that aluminium may simply mark alterations in iron metabolism. Gun et al. (25) and Graves et al. (24) did not find chemical exposures in the occupational environment, including aluminium, to be risk factors for the development of AD. Cornett et al. (8) did not find levels of mercury, selenium, iron, rubidium, and zinc in the pituitary glands to be elevated in those with AD in comparison with those without AD. The pituitary gland is a good predictor of environmental mercury exposure. Finally, Roberts et al. (43) found that even with a normal dietary intake, those with AD had increased absorption of aluminium. This finding may support the idea that a long-term diet high in acid-forming foods such as fatty acids and proteins leads to increased absorption of aluminium and transition metals that normally exist in the oxidized state even after the diet may have changed.

Ninth, underscoring the importance of inflammation as a risk factor for AD, especially due to excess dietary fat. Newman (40) also raised the possibility that arachidonic acid could play a role in the inflammation process in AD. The role of inflammation is also consistent with the trend towards use of anti-inflammatory drugs in the treatment of AD (32).

Since inflammation seems to be a risk factor for AD, causes of inflammation other than diet

should also be considered. Grant and Moore (22) suggested that pharmaceutical drugs that are either pro-inflammatory or suppress anti-inflammatory effects of other substances in the body could be risk factors for AD. Miklossy (38) has also suggested that bacterial peptidoglycan should be considered a risk factor for AD since it is a potent inflammatory and amylodogenic factor.

Tenth, underscoring the role of oxidative stress, especially due to excess dietary fat and energy. Recent research has continued to show the importance of oxidative stress in AD (see the reviews in (26,45)). Nunomura et al. (41) reported that RNA oxidation is a prominent feature of vulnerable neurons in AD.

Vitamin E supplementation has been shown to reduce the risk of AD (39). Vitamin E is known to protect lipids against nitric oxide-initiated peroxidative damage (54). NO is also implicated in aging in general (36). Peroxynitrite, a powerful oxidant produced from the reaction of superoxide with nitric oxide, is strongly implicated in oxidative damage of AD (48).

Two more dietary links to AD have been of research interest lately. One is homocysteine (Hcy), which has been implicated in heart disease (37). Serum Hcy is generally elevated when vitamin B6 and B12 and folic acid levels are low. Clarke et al. (6) and McCaddon et al. (35) have found that those with AD have elevated Hcy. Clarke et al. (6) also reported low blood levels of folate and vitamin B12. McCaddon et al. (35) provide evidence that biochemical imbalances, rather than nutritional deficiencies, are responsible.

The second recent dietary link is that elevated levels of low-density lipoprotein are found in the serum of those with AD (33). In fact, Sparks et al. (50) had already shown that feeding rabbits a 2% cholesterol diet led to an increased accumulation of beta-amyloid in their brains.

As a postscript, the results for AD led to the realization that the ecologic approach still has a lot of life in it, despite the near-total abandonment of it by the medical research community in the early 1980s. This probably happened due to some inaccurate results in the 1960s and 1970s and the comments on p. 1218 of Doll and Peto (10). The comparisons made in Grant (18) to the prevalence of other chronic disease showed high correlation for diseases for which dietary fat was thought to be a high-risk factor. However, recent ecologic studies have shown that most of the diseases included in Table 6 of Grant (18) that had values of $r^2 < 0.85$ for prevalence with comparison to AD are no longer considered to be strongly linked to dietary fat. Diabetes among South Asians living in England is strongly linked to highly-processed grains, with minor contributions from sugar for women and animal fat for men (23). Ischemic heart disease (IHD) is linked to lactose for men of all ages and women over about the age of 70 years (20,44), while sweeteners are the high-risk factor for younger women (20). Also, wine, especially red wine, is a risk-reduction factor for IHD (9,23). Lymphoma is linked to the non-fat portion of milk (23,52). Prostate cancer is now strongly linked to the non-fat portion of milk (17,21). Finally, the expression of rheumatoid arthritis seems to be linked to meat through nitrite and fat (23).

Thus, most if not all of the major findings and hypotheses in Grant (18) have been supported by research published subsequently. These works lend further support to the primary hypothesis that diet, especially later in life, plays a major role in the etiology of Alzheimer's disease as well as a number of other chronic diseases.

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