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Review

Using Multicountry Ecological and Observational Studies to Determine Dietary Risk Factors for Alzheimer's Disease

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Key words: Alzheimer's disease, diet, ecological studies, meat, Mediterranean diet, observational studies, vascular dementia, Western diet

Rates of Alzheimer's disease (AD) are rising worldwide. The most important risk factors seem to be linked to diet. For example, when Japan made the nutrition transition from the traditional Japanese diet to the Western diet, AD rates rose from 1% in 1985 to 7% in 2008. Foods protective against AD include fruits, vegetables, grains, low-fat dairy products, legumes, and fish, whereas risk factors include meat, sweets, and high-fat dairy products. The evidence comes from ecological and observational studies as well as investigations of the mechanisms whereby dietary factors affect risk. The mechanisms linking dietary risk factors to AD are fairly well known and include increased oxidative stress from metal ions such as copper as well as from advanced glycation end products associated with high-temperature cooking, increased homocysteine concentrations, and cholesterol and its effects on amyloid beta, insulin resistance, and obesity. Lower 25-hydroxyvitamin D concentrations also are associated with increased risk of AD. In addition to reviewing the journal literature, a new ecological study was conducted using AD prevalence from 10 countries (Brazil, Chile, Cuba, Egypt, India, Mongolia, Nigeria, Republic of Korea, Sri Lanka, and the United States) along with dietary supply data 5, 10, and 15 years before the prevalence data. Dietary supply of meat or animal products less milk 5 years before AD prevalence had the highest correlations with AD prevalence in this study. Thus, reducing meat consumption could significantly reduce the risk of AD as well as of several cancers, diabetes mellitus type 2, stroke, and, likely, chronic kidney disease.

Teaching points:

- Single-country ecological data can be used to find links between diet and AD because the national diet changes, such as during the nutrition transition to a Western diet.
- Multicountry ecological studies can be used to find links between dietary factors and risk of AD.
- Prospective observational studies are useful in linking dietary components and patterns to risk of AD.
- The most important dietary link to AD appears to be meat consumption, with eggs and high-fat dairy also contributing.
- Diets high in grains, fruits, vegetables, and fish are associated with reduced risk of AD, but these factors cannot counter the effects of meat, eggs, and high-fat dairy.
- Higher vitamin D status is associated with reduced risk of AD.

INTRODUCTION

Alzheimer's disease (AD) is characterized by neurofibrillary tangles and senile plaques in the brain, which Alois Alzheimer first described in 1907 [1]. AD is the most common type of dementia in Western developed countries. In the United States, an estimated 3.1 million people have AD (updated from

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Abbreviations: 25(OH)D = 25-hydroxyvitamin D, AD = Alzheimer's disease, Aβ = amyloid-β, AGE = advanced glycation end product, DASH = dietary approaches to stop hypertension, DRCD = diet-related chronic disease, *DSM-IV* = *Diagnostic and Statistical Manual*, FAO = United Nations Food and Agriculture Organization; Hcy = homocysteine, MeDi = Mediterranean diet, MIND = MeDi-DASH intervention for neurodegenerative delay, MMSE = Mini-Mental State Examination, MOWN = metabolically obese normal weight, NL = normal, OR = odds ratio, PHR = proportional hazard ratio, PMASRs = pooled/meta-analyses and systematic reviews, RR, relative risk, VaD = vascular dementia.

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Brookmeyer et al. [2]). Globally, about 42 million people now have dementia [3]. AD is the most common type of dementia, accounting for at least 60% of dementia in developing countries [4] and 67% in the United States [5]. Thus, approximately 27 million people have AD globally. On the basis of the age distribution in the U.S. population in 2010, the estimates of dementia prevalence in the United States by 5-year groups, and the fraction of dementia attributed to AD [5], each person in the United States has about a 4% chance of developing AD. Thus, examining primary approaches to prevent AD seems worthwhile.

Researchers have used multicountry ecological studies to link dietary factors to risk of various diseases. For example, such studies found that, for men, animal fat was an important risk factor for coronary heart disease and that the Mediterranean diet (MeDi) reduced that risk [6]. A more recent study found that animal fat was an important risk factor for men, whereas added sugars were for women [7]. Other studies have recognized both factors as important risk factors [8,9]. Multicountry ecological studies also have linked dietary animal products to risk of many cancers, especially those common in Western developed countries [10]. That study was criticized for 3 decades because observational studies did not support the findings. Eventually it was realized that such studies integrate the effect of diet starting early in life. Indeed, a Harvard cohort study enrolling younger women confirmed that meat was a risk factor for breast cancer [11]. More recently, ecological studies linked Japan's nutrition transition to the Western diet to increased risk of breast, colon, and ovarian cancers [12], and a recent multicountry ecological study largely confirmed the results of the 1975 Armstrong and Doll study [13]. Numerous case–control studies in Uruguay found significant links between meat consumption and risk of many cancers [14]. An ecological study also linked meat consumption with risk for exacerbated rheumatoid arthritis. That study compared exacerbations of rheumatoid arthritis expressed as time lost from work and hospital admissions in several European countries over the 1965–1975 period, relating the increased rate of exacerbations after 1970 to increased consumption of meat, which had been low up until then due to rebuilding after World War II [15]. A multicountry ecological study also identified consumption of milk protein as a risk factor for Parkinson's disease [16]. That study is supported by a meta-analysis of prospective observational studies [17]. Thus, the literature includes many examples showing that single- and multicountry ecological studies are useful in determining dietary links to chronic diseases.

National diets can be considered uncontrolled experiments examining diet's role in disease risk. National diets can change for several reasons. One way is related to increased prosperity, generally leading to more energy content and a larger fraction of the diet derived from animal products. Several countries have made the transition from their traditional diet to the Western diet, leading to such outcomes as increased mean adult height, as observed in Japan [18] and Thailand [19], and obesity in developing countries [20]. Other times, national diets are changed to improve health. For example, reducing consumption of animal fat in Finland significantly reduced the rate of coronary heart diseases [9]. On the other hand, the *Dietary Goals for the United States* [21] recommended that Americans reduce their consumption of fat. That report, prepared by the U.S. Senate Select Committee on Nutrition and Human Needs, led food manufacturers to replace fat in processed foods with sugar to maintain flavor and energy content. The release of that report may have precipitated the obesity epidemic in the United States [22].

In this article, findings are reviewed regarding major risk-modifying factors for AD in relation to diet through a combination of ecological and observational studies coupled with an understanding of how various factors affect the risk of developing AD.

METHOD

As just discussed, multicountry ecological studies can be used to identify and quantify diet's role in risk of disease by comparing various dietary supply factors with disease incidence, prevalence, or mortality data for various countries. Values for large components of diet such as total energy or energy derived from animal products can be used first, followed by values for smaller components as warranted. Because chronic diseases take years to develop and knowing which lag would be optimal is hard to presume, the lag between dietary supply values and health outcomes should be varied to determine the interval that yields the strongest correlation. If other risk-modifying factors are known and suitable data are available, they should also be included in the analysis.

The approach includes a combination of ecological and observational studies along with studies designed to determine the mechanisms of risk-modifying factors to elucidate diet's role in risk of AD. The ecological studies reviewed were by me; the other studies were found by searching the National Library of Medicine's PubMed database and Google Scholar.

New 10-Country Ecological Study

While preparing the article, the idea arose to do another ecological study of AD prevalence with respect to dietary factors. Data were used from 10 countries with age-adjusted prevalence data published in peer-reviewed journals after 1995: Brazil [23,24], Chile [25], Cuba [26], Egypt [27], India [4], Mongolia [28], Nigeria [29], the Republic of Korea [30], Sri Lanka [31], and the United States [2].

The year of the prevalence data was assumed to be 2 years before the publication date unless indicated otherwise. Dietary supply data came from the Food and Agriculture Organization (FAO) of the United Nations [32]. The values reported are for the food supply available to consumers. Not all food in the

supply is consumed. According to FAO, up to one third of all food is spoiled or squandered before people can consume it [33]. It is assumed that the same reduction factor applies to all countries in this study. Values of dietary supply factors likely to be associated with both increased and decreased risk of AD were obtained for 5, 10, and 15 years before the prevalence data. Table 1 gives the AD prevalence and dietary supply factors for 5 years before the prevalence data.

Using IBM SPSS Statistics for Windows, version 20.0 (IBM, Armonk, NY), regression analyses were run for each factor in linear regression analysis. After finding dietary factors with the strongest correlation with AD prevalence, those factors were used in multiple linear regression analysis pairing the strongest factors with the other factors. With only 10 countries, it was not expected that both components of any pair would prove statistically significant. However, doing so would indicate whether the minor factors might be significant. Combinations of energy supply from eggs, fish, and meat were also used in linear regression analyses.

RESULTS

Ecological Studies

Several ecological studies have linked dietary to risk of AD, starting with a multicountry study in 1997 [34]. That study was based on prevalence of AD in 11 countries and dietary supply values near the time of the prevalence data from FAO [32]. Total fat and total energy were highly correlated with AD prevalence, with some reduction associated with fish and low rates associated with cereals (grain) consumption. The findings in that study regarding total energy, total fat, and fish were subsequently supported in some of the first prospective cohort studies regarding diet and risk of AD [35–38].

An ecological study of AD prevalence in Japan associated the nutritional transition from the traditional Japanese diet to the Western diet with increased AD rates 20–25 years after the transition [39]. AD rates increased from 1% for those older than 65 years in 1985 to 7% in 2008, whereas rates of vascular dementia (VaD) remained near 3.5% for the entire period [40]. The factors most strongly correlated with changes in AD rates in Japan were lung cancer ($R = 0.95$ at 25 years' lag), rice ($R = -0.95$ at 25 years' lag), meat ($R = 0.94$ at 15 years' lag), alcohol supply ($R = 0.93$ at 20 years' lag), and animal product energy ($R = 0.92$ at 15 years' lag). Results for 8 developing countries also were presented. Changes in total energy ($R = 0.87$ at 20 and 25 years' lag) and animal fat ($R = 0.62$ at 15 and 20 years' lag) were most highly correlated with the changes. Lung cancer is an index of smoking combined with dietary saturated fat [41].

A recent ecological study concluded that the observational data do not yet indicate a significantly increased rate of AD prevalence in China but that given the increasing trend of meat and animal products in the national diet, increases in AD prevalence are expected soon [42]. Another recent study based on 6357 cases of AD found that AD prevalence increased from 1.93 million in 1990 to 5.69 million in 2010. However, that study did not give age-adjusted prevalence rates [43]. Thus, although AD prevalence rates in China may or may not have increased by 2015, they are certain to rise soon.

Although studies have not linked trends of AD prevalence in the Republic of Korea to the nutrition transition, they probably are as well. A review of prevalence and trends of dementia for people older than 65 years in Korea was published in 2014 [30]. When data for AD and VaD were plotted, the regression fit found that AD prevalence increased from 4.9% in 1998 to 6.5% in 2012

Table 1. Dietary Supply Values 5 Years before Prevalence Data (kcal/capita/d; g/capita/d for Animal Fat and Protein)

Country	India	Nigeria	Sri Lanka	Egypt	Cyprus[a]	Chile	Cuba	Korea	U.S.	Brazil	Mongolia
AD prevalence	1.3 (0.88–1.8)	1.4 (0.6–2.2)	2.9	2.9	—	4.1	4.3	5.8	6.9	7.6	7.8
Year of prevalence	2001	1995	2003	1998	(1962)	1995	2006	2011	2000	2002–2008	2008–2009
Energy	2343	2192	2298	3197	2385	2569	3076	3080	3580	2880	2221
Vegetable product energy	2167	2117	2154	2992	2031	2099	2735	2642	2583	2237	1480
Cereals	1466	1082	1204	2137	954	1170	1141	1470	841	643	1033
Animal product energy	176	75	144	205	353	470	341	439	997	643	741
Animal product fat	11.8	4.6	7.7	15.9	25.1	33.9	21.9	29.2	65.7	45.3	53.7
Animal product protein	9.6	7.1	13.4	12.8	22.2	28.7	22.0	41.9	71.9	41.3	43.8
Meat	17	34	19	72	165	236	147	197	428	357	398
Vegetable oils	190	302	62	170	298	198	162	301	556	402	129
Sugar and sweeteners	199	45	316	290	221	378	607	332	618	390	123
Milk	107	8	54	50	134	140	127	42	397	189	234
Eggs	5	11	9	8	21	22	19	42	51	27	4
Fish	8	13	50	14	13	28	22	84	31	10	1
Alcoholic drinks	11	69	4	1	40	80	48	127	153	85	45

AD = Alzheimer's disease.

[a]Dietary supply data for Cyprus are for 1962.

Table 2. Regression Results for Alzheimer's Disease Prevalence for 10 Countries with Respect to Dietary Supply Factors 5, 10, and 15 Years before the Prevalence data

Factor	5 Years (R, p)	10 Years (R, p)	15 Years (R, p)
Meat, fish	0.95*	0.91*	0.88, 0.001
Meat	0.95*	0.89, 0.001	0.86, 0.001
Meat, fish, eggs	0.94*	0.92*	0.89, 0.001
Animal product energy less milk	0.94*	0.92*	0.86, 0.001
Meat, eggs	0.94*	0.91*	0.88, 0.001
Animal product fat	0.91*	0.89, 0.001	0.83, 0.003
Animal product energy	0.90, 0.001	0.90*	0.82. 0.003
Animal product protein	0.87, 0.001	0.89*	0.81, 0.004
Milk	0.69, 0.03	0.71, 0.02	0.57, 0.08
Alcoholic drinks	0.57, 0.08		
Eggs	0.52, 0.12	0.50, 0.15	0.47, 0.18
Vegetable oils	0.44, 0.20		
Energy total	0.39, 0.26		
Sugar and sweeteners	0.38, 0.29		
Cereals	−0.56, 0.10		

*$p < 0.001$.

($R = 0.57$), whereas VaD rates decreased from 3.1% to 1.2% during the same period. According to FAO [32], the per capita meat supply was below 7.2 kg/y up to 1974–1976, increasing to 14.1 kg/y in 1979–1981 and 36.5 kg/y in 1992–1994.

New Ecological Study

In the new ecological study involving 10 countries, linear regression analyses were run for the factors shown in Table 1 for 5 years before the AD prevalence data as well as for 10 and 15 years before for factors with the highest regression coefficients. Table 2 gives those regression results and Figure 1 shows the relation between Alzheimer's disease prevalence by country for dietary meat supply five years prior to the prevalence data. The strongest correlation between single dietary factors and AD prevalence data was for meat supply 5 years before the prevalence data. Four combinations—meat, fish and eggs, meat and fish, and animal product energy less milk—had similar regression coefficients. However, meat supply was highly correlated with energy supply from eggs, fish, and meat ($R = 0.97$, 0.99, and 0.98 for lags of 5, 10, and 15 years, respectively) so that no additional information is obtained from the combinations with meat.

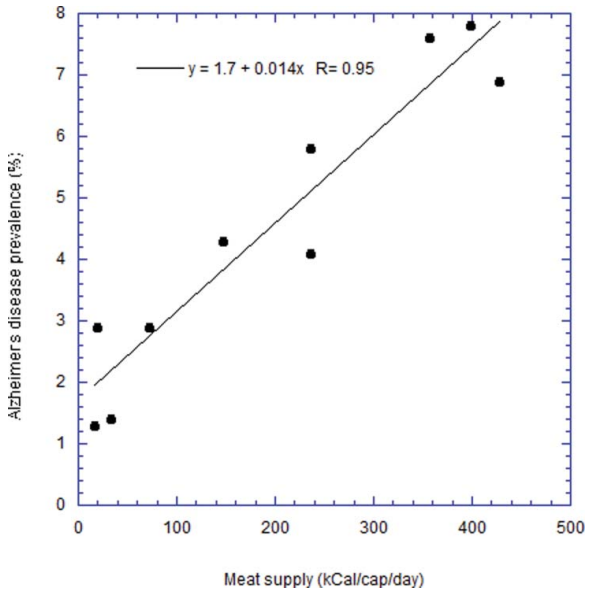

Fig. 1. Linear regression results for AD prevalence with respect to dietary supply of meat 5 years prior to the prevalence data.

Limitations of Ecological Studies

One limitation of ecological studies using AD or dementia prevalence is the variable quality of observational studies of prevalence. Limitations include differences in clinical application of dementia diagnosis, which can change over time and by country [44], and the racial mixture of the population sampled [45]. For example, a recent estimate of AD prevalence in the United States that used a mixed black–white population incorporated the assumption that race did not matter, resulting in an estimate of AD prevalence in 2010 of 4.7 million [46]—twice that in an estimate using a primarily white population [2]. Because black Americans have rates of AD incidence about 64% higher than those of whites [47], the 4.7 million estimate is too high.

Another limitation is that dietary supply values are correlated with population mean dietary intake, although larger fractions of the supply will be eaten in some countries than in others. In addition, dietary habits vary within a country, so there will be people with much more of some foods and less of others.

A third limitation is that ecological studies generally do not include nondietary factors such as smoking and genetic risk factors. Despite those limitations, ecological studies have made important contributions to the study of dietary risk factors for chronic diseases, as outlined in the Introduction.

Observational Studies

Observational studies of diet and risk of AD are generally prospective cohort studies. In such studies, researchers monitor a defined group of people for several years. Dietary data are collected several times by using a food frequency questionnaire, and diagnosis of AD is determined from a medical examination.

The first observational study to identify dietary links to AD was from the Adventist Health Study [48]. "The first [45] enrolled 272 California residents matched for age, sex, and zip code (1 vegan, 1 lacto-ovo-vegetarian, and 2 'heavy' meat eaters in each of 68 quartets)." It found that "the matched subjects

who ate meat (including poultry and fish) were more than twice as likely to become demented as their vegetarian counterparts (relative risk 2.18, $p = 0.065$) and the discrepancy was further widened (relative risk 2.99, $p = 0.048$) when past meat consumption was taken into account" [p. 28]. Because two thirds of dementia in the United States is AD, it is assumed that AD represented two thirds of those with dementia in that study. In their second study involving unmatched subjects living in Loma Linda, no difference in incidence between vegetarians and meat eaters was apparent [48].

The Rotterdam Study involving 5386 nondemented participants at baseline followed for an average of 2.1 years found these nutrients associated with increased risk of dementia (AD plus VaD): total fat (relative risk [RR] = 2.4; 95% confidence interval [CI], 1.1–5.2), saturated fat (RR = 1.9; 95% CI, 0.9–4.0), and cholesterol (RR = 1.7; 95% CI, 0.9–3.2). Fish consumption was inversely correlated with risk of AD (RR = 0.3; 95% CI, 0.1–0.9) [35].

Columbia University has conducted several observational studies of diet and incidence of AD. Columbia researchers made one of the early confirmations that diet was a risk factor for AD, finding that "among individuals with the apolipoprotein E ε4 allele, the hazard ratios of AD for the highest quartiles of calorie and fat intake were 2.3 (95% CI, 1.1–4.7) and 2.3 (95% CI, 1.1–4.9), respectively, compared with the lowest quartiles" [37; p. 1258]. That group also studied the MeDi, finding that people in the highest tertile of compliance with that diet had a 34% reduction ($p_{trend} = 0.04$) in risk of AD compared to those in the lowest tertile [49]. A meta-analysis associated the MeDi with about 64% (95% CI, 0.46%–0.89%) of the risk of developing AD as the Western diet [50].

A recent paper presented results of a cohort study involving 923 participants who provided information on diet and had at least 2 neuropsychological assessments between 2004 and February 2013 [51]. The food frequency questionnaires were scored according to the guidelines for 3 diets: dietary approaches to stop hypertension (DASH), MeDi, and MeDi-DASH intervention for neurodegenerative delay (MIND). The MIND diet scored 10 healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). The other 2 diets had similar lists of healthy and unhealthy food groups but used different scoring methods. People who scored in the middle and highest tertile of the MIND diet had significantly lower risk of developing AD than those in the lowest tertile (proportional hazard ratio [PHR] = 0.64, 95% CI, 0.42–0.97 and PHR = 0.48, 0.29–0.79 for tertiles 2 and 3, respectively), but only participants in the highest tertile of the other 2 diets did so (PHR = 0.60, 95% CI, 0.37–0.96 for the DASH diet; PHR = 0.49, 95% CI, 0.29–0.85 for the MIND diet).

Risk Factors for AD Related to the Western Diet

The literature describes several risk factors for AD related to the Western diet. Table 3 gives the findings.

Table 3. Dietary Factors and Cognitive Decline or AD: Findings from Observational Studies

Location	Study	Findings Risk	Risk Reduction	Reference
Poland	71 people diagnosed with AD according to guidelines in *DSM-IV*	Meat, butter, high-fat dairy products, eggs, and refined sugar	Grains and vegetables	[52]
New York	253 subjects developed AD during 3.9 years	High-fat dairy products, red meat, organ meat, and butter	Salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables	[49]
	Review	Meats, high-fat dairy, and sweets	Fruits, vegetables, fish, nuts and legumes	[53]
New York	Brain biomarkers of AD in cognitively normal individuals with and without AD risk factors	High-fat dairies, meat, and sweets	Vegetables, fruit, whole grains, fish, and legumes	[54]
New York	52 normal individuals (age 54 ± 12 years, 70% women; Clinical Dementia Rating = 0, MMSE > 27; looked at biomarkers of AD	Sweets, fried potatoes, high-fat dairies, processed meat, and butter	Fresh fruit and vegetables, whole grains, fish, and low-fat dairy products	[55]
Ireland	Community-dwelling subjects (n = 208; 94 males and 114 females; aged 64–93 years);cognitive performance	Western dietary pattern (high in red meat and white bread and low in fruit and vegetables)	Prudent dietary patterns (high in fruit, vegetables, fish, low-fat dairy, and salad dressings and low in red meat and white bread)	[56]
Taiwan	Cognitive decline in Taiwanese aged 65 years and older	Meat/poultry and eggs	Fish, beans/legumes, and vegetables and fruits	[57]

DSM-IV = *Diagnostic and Statistical Manual*, AD = Alzheimer's disease, MMSE = Mini-Mental State Examination.

Beans/legumes, low-fat dairy, fish, fruits, grains, nuts, and vegetables protected against cognitive decline or AD, whereas white bread, high-fat dairy products, eggs, meat, fried potatoes, and sweets were risk factors. Those results are similar to those of ecological studies but with greater specificity for some of the minor dietary factors.

Mechanisms Linking Animal Products to Risk of AD

Many studies have reported dietary animal products such as meat and eggs as risk factors for AD; therefore, exploring the mechanisms is worthwhile.

One factor is that nondairy animal products lead to concentrations in the brain of trace minerals that promote oxidative stress. The first paper on dietary and risk of AD noted that in the brains of people with AD, concentrations of base cations (calcium, magnesium, and potassium) were lower than those of controls, whereas concentrations of aluminum and transition metals such as copper, iron, and mercury were higher [34]. Nondairy animal products seem to be the most important source of transition metal ions. A dietary intervention study found that going from a mixed to a lactovegetarian diet decreased levels of cadmium, copper, lead, mercury, selenium, and zinc in the hair but increased magnesium concentrations after 3 months [58]. A study involving children in Austria found that meat was the most important source of dietary copper [59]. Excess levels of copper are seen as a risk factor for AD [60,61]. As pointed out by Brewer, it is divalent copper that is the problem, and it can come from drinking water delivered by copper pipes or diet [62,63]. In addition, meat, as a source of saturated fat increases the absorption of copper similar to drinking water delivered via copper pipes [64]. Heme iron from red meat is a risk factor for AD through its ability to generate free radicals and cause oxidative stress [65].

Homocysteine (Hcy) is a risk factor for AD. A meta-analysis of cross-sectional and cohort studies associated high Hcy levels with AD (RR = 1.93; 95% CI, 1.50–2.49) [66]. Hcy is strongly related to diet. A study in Pakistan found a significantly lower Hcy levels for a diet high in plant protein diet and significantly higher Hcy levels associated with a diet high in animal products:

> The high plant-protein diet pattern was inversely related to hyperhomocysteinemia, with a higher intake being protective. Compared with the 1st quartile, the adjusted OR was 0.42 (95% CI = 0.25–0.69; $p = 0.001$) for the 4th quartile. The high animal-protein diet was positively associated with hyperhomocysteinemia, with participants in the highest quartile of intake having the greatest increase in risk [OR = 2.10 (95% CI = 1.22–3.60); $p = 0.007$]. [67; p. 1261]

Meat consumption is also linked to increased risk of insulin resistance. A study in Iran found the following:

> Fat and meat consumption and energy intake in subjects with metabolically obese normal weight (MONW) were more than subjects without MONW. Each serving of meat consumption was associated with three times increased risk of MONW (OR [odds ratio]: 3.06), while each serving of dairy consumption was associated with 56% lower risk of MONW with borderline significance (OR: 0.64)" [68; first page (epub)]

Insulin resistance is a risk factor for AD and may help explain the link between obesity and risk of AD [69].

Dietary animal products increase production of insulin-like growth factor-I [70]. Insulin-like growth factor-I has been associated with increased risk of dementia and AD [71].

A hypothesis has been proposed to explain some of the link between the Western diet and risk of AD related to disruption of the blood–brain barrier [72]. That paper presents evidence supporting the Western diet as a cause of elevated secretion of amyloid-β (Aβ) from the small intestines. That process elevates Aβ in the vasculature system, leading to blood–brain barrier damage by reducing gene expression of tight junction proteins. That scenario leaves the hippocampal formation vulnerable to damage by excessive Aβ accumulation and other circulating toxins such as heavy metals and inflammatory markers.

Table 4 summarizes the mechanisms linking dietary risk factors to AD.

Hill's Criteria for Causality

Hill's criteria for causality in a biological system [86] can be used to evaluate whether meat consumption can be considered causally linked to risk of AD. Not all criteria need be satisfied to claim causality, but the more that are, the stronger the claim. Table 5 lists the applicable criteria and evaluates whether they are satisfied.

Vitamin D

Evidence is mounting that low 25-hydroxyvitamin D [25 (OH)D] concentrations are associated with risk of developing AD. The evidence is of several types: observational with respect to AD, observational with respect to conditions and diseases linked to AD, and mechanistic.

Three observational studies have examined vitamin D and incidence of AD. A study in France involved 498 community-dwelling women with mean age at enrollment of 80 years who were monitored for 7 years. The highest quartile of vitamin D intake (mean = 600 IU/d) was associated with a fully adjusted risk of developing AD of 0.23 (95% CI, 0.08–0.69; $p = 0.009$) [89]. Sun exposure at midday was associated with a fully adjusted risk of developing AD of 0.45 (95% CI, 0.24–0.85; $p = 0.01$).

A study in Denmark involved 10,186 white individuals from the Danish general public with a mean age of 48 years at enrollment. A total of 418 of participants developed AD over a

Table 4. Mechanisms to Explain Dietary Risk Factors for AD

Link	Dietary Link	Mechanisms	Reference
Trace minerals	Animal products have more zinc, copper, and selenium as well as mercury, lead, and cadmium and less magnesium		[58]
	Meat as the most important dietary source of copper		[59]
		Copper and iron stimulate free radical formation (e.g., hydroxyl radicals via Fenton reaction)	[65]
		Copper increases oxidative stress	[60–63]
Homocysteine	Dietary deficiency of vitamin B6 and folic acid and absorptive deficiency of vitamin B12		[73]
		Folic acid deficiency and homocysteine impair DNA repair in neurons, which sensitizes them to oxidative damage induced by Aβ)	[74]
Saturated fat	Animal products are a source of saturated fat		[75]
		Increases absorption of copper	[64]
Cholesterol	Midlife total cholesterol is a risk factor for dementia/AD		[76]
		Enzymatic production of the Aβ peptide, the peptide thought to play a major role in AD pathogenesis, is affected by membrane cholesterol levels	[77]
		APOE4 allele, which modulates LDL metabolism, increases free radical formation, and reduces plasma antioxidant concentrations. Together, those risk factors support a mechanism for increased LDL circulation time and free radical modification of LDL	[78]
Insulin resistance	Insulin resistance seems to make the link between obesity, diabetes mellitus, and AD		[69]
		Deterioration of synapses	[79]
Obesity	For obesity assessed by body mass index, the pooled effect size for AD was 1.59 (95% CI, 1.02–2.5; $z = 2.0$; $p = 0.04$)		[80]
		Leptin, which is neuroprotective, is reduced. Adiponectin, which is normally beneficial, also is reduced. However, high levels may induce adiponectin resistance	[81]
		Systemic and chronic presence of proinflammatory cytokines	[82]
AGEs	High levels of dietary AGEs are associated with faster rate of decline in memory in 49 initially nondemented young elderly ($p = 0.01$ in mixed regression models)		[83]
		Suppression of deacetylase survival factor Sirtuin 1, a key host defense and a central feature of AD	[84]
		AGEs elicit oxidative stress and inflammatory reactions through the interaction with the receptor for AGEs	[85]

AD = Alzheimer's disease, Aβ = amyloid-β; APOE4 = apolipoprotein E ε4, LDL = low-density lipoprotein, CI = confidence interval, AGEs = advanced glycation end products.

30-year period. That study found a nonsignificant increased incidence of AD for those with 25(OH)D <50 nmol/L at enrollment [90]. The problem with that study is that 25(OH)D concentrations change with time, reducing the predictive power of the values as follow-up time increases [91,92].

Another study was based on 1658 elderly community-dwelling inhabitants of the United States with a mean age at enrollment of 74 years and monitored for a mean time of 5.6 years. A total of 102 developed AD, with hazard ratios of 1.53 (95% CI, 1.06–2.21) for 25(OH)D concentrations between 25 and 50 nmol/L and 2.25 (95% CI, 1.23–4.13) for 25(OH)D <25 nmol/L [93]. Thus, observational studies offer good evidence that low 25(OH)D concentration is a risk factor for developing AD.

Vitamin D could reduce risk of AD through several mechanisms. One is by reducing inflammation. C-reactive protein, a marker of systemic inflammation, is modestly associated with increased risk of developing AD [94], and

Table 5. Evidence That Meat Consumption Is Causally Linked to Risk of AD Using Hill's Criteria for Causality in a Biological System

Criterion	Finding
Strength of association	Very strong in the new ecological study; also strong in some observational studies
Consistency of findings	Found in both ecological and observational studies
Temporality	Increase in AD in Japan following the nutrition transition
Biological gradient	Found in the new ecological study
Plausibility (e.g., mechanisms)	Mechanisms linking meat to risk of AD are discussed in this paper
Coherence with known facts	It is well known that diet affects risk of disease and that environmental factors affect risk of AD
Experiment	There are some animal model experiments of dietary fat showing increased risk of AD; human experiments are uncontrolled such as when national diets change
Analogy	Meat is also a risk factor for other chronic diseases
Ruling out confounding factors [87]	Most other dietary factors were not significantly associated with AD prevalence in the new ecological study. Genetic risk for AD varies for the countries in the new ecological study [88]. However, adding genetic factors is not expected to change the findings.

AD = Alzheimer's disease.

clinical trials have associated 25(OH)D concentrations below 50 nmol/L with increased risk of elevated levels of C-reactive protein [95]. The hormonal metabolite of vitamin D, 1,25-dihydroxyvitamin D, stimulates clearance of Aβ, a marker of AD, by macrophages in AD patients [96]. A mouse model also was used to show that vitamin D protects neurons by preventing cytotoxicity and apoptosis and upregulating vitamin D receptors [97]. Most effects of vitamin D are mediated by 1,25-dihydroxyvitamin D entering vitamin D receptors. Those receptors are bound to chromosomes, thereby affecting gene expression, upregulating some genes and downregulating others [98]. Vitamin D also can maintain tight junctions [99].

A review stated,

> Vitamin D supplements appear to have a beneficial clinical effect on AD by regulating micro-RNA, enhancing toll-like receptors, modulating vascular endothelial factor expression, modulating angiogenin, and advanced glycation end products. Vitamin D also exerts its effects on AD by regulating calcium-sensing receptor expression, enhancing amyloid-β peptides clearance [and] interleukin 10, downregulating matrix metalloproteinases, upregulating heme oxygenase 1, and suppressing the reduced form of nicotinamide adenine dinucleotide phosphate expression. [100, p. 126]

Experts on vitamin D and cognitive decline at a meeting in July 2013 reached agreement that hypovitaminosis D increases the risk of cognitive decline and dementia in older adults and that older adults should be screened for hypovitaminosis D and treated with vitamin D supplements if needed for better health in general [101]. It was agreed that more research is required to confirm that vitamin D benefits brain health and whether there is a critical period of life when it has the greatest impact.

DISCUSSION

The new ecological study results presented here have some similarities and some differences with respect to other studies. In this study, dietary supply values 5 years before AD prevalence values had the strongest correlation with AD prevalence values. The ecological study for Japan found that dietary supply 20–25 years before prevalence data had the highest correlation [39]. It was noted in that paper that many risk factors for AD are apparent in midlife. A recent study using positron emission tomography found that changes in the brain indicative of AD can be observed 17 years prior to expected symptom onset [102]. Thus, dietary changes to reduce risk of AD should begin in midlife.

Vegetable oils apparently do not contribute significantly to risk of AD, as suggested in the ecological study based on dietary advanced glycation end products (AGEs) [103]. One reason could be that vegetable oils are mostly used in cooking but are not actually consumed. Meat was identified as the most important contributing factor to dietary AGEs, which is consistent with the findings of that study.

Milk seems to reduce risk of AD. A study in Japan found that milk and dairy consumption was significantly associated with reduced risk of developing AD over a 17-year period [104]. There is also good evidence that milk consumption reduces risk of cardiovascular disease [105].

The diet of midcentury Cyprus is considered a prototypical MeDi [106]. As shown in Table 1, the dietary supply values for Cyprus in 1962 place it between Egypt of 1998 and Chile of 1995, suggesting that AD prevalence rates in Cyprus around 1967 would be about 3.5%—about half of that for the United States in 2000. That finding is consistent with the finding that adherence to the MeDi is associated with about a 35%–50% reduction in AD risk [50,51]. By that logic, further reducing eggs and meat in the diet would further reduce risk of AD.

Meat consumption is a risk factor for other chronic diseases. For example, observational studies in Uruguay have linked dietary meat as a risk factor for many cancers [14]. A review lists the cancers linked to eating meat [75]. A remarkable increase in mortality rates of breast, colon, and prostate cancers has been observed in southeast Asia, lagging the nutrition transition to the Western diet by 10 or more years [107]. Observational studies

have linked dietary meat to risk of type 2 diabetes [108,109] stroke [110], and, likely, chronic kidney disease [111] Consuming red and processed meat is also associated with increased risk of obesity [112]. Westernized dietary patterns have been associated with higher risk of metabolic syndrome [113].

In addition, a recent review of 304 pooled/meta-analyses and systematic reviews published between 1950 and 2013 confirmed that plant food groups are more protective than animal food groups against diet-related chronic disease. Within plant food groups, grain products are more protective than fruits and vegetables. Among animal food groups, dairy/milk products have a neutral effect on the risk of diet-related chronic diseases, whereas red/processed meats tend to increase the risk. Overweight/obesity, type 2 diabetes, and various types of cardiovascular disease and cancer accounted for 289 of the pooled/meta-analyses and systematic reviews [114]. Thus, eating meat is linked to many adverse health outcomes.

One of the implications of the findings reported in this article is that because there are many mechanisms linking meat in particular and diet in general to risk of AD, it is unlikely that simple approaches to reducing risk of AD other than dietary modification will be found.

Another reason to reduce consumption of meat is to slow climate change. A report from the Johns Hopkins Center for a Livable Future made that case [115]. The draft version of the *Dietary Guidelines for Americans* also stated that reducing meat consumption would be good for environmental sustainability, but that statement was removed under pressure from the meat industry [116].

Because 25(OH)D concentrations have been found inversely correlated with risk of AD, those wishing to reduce risk with AD might consider the recommendations of the Endocrine Society. It recommended 1500–2000 IU/d vitamin D_3 for those at risk of vitamin D deficiency to raise 25(OH)D concentrations above 30 ng/mL (75 nmol/L) [117]. The Institute of Medicine's recommendation of 600 IU/d vitamin D (800 IU/d for those over the age of 70 years) was based solely on the evidence they found for bone health [118].

This article did not review VaD, in part because no change in VaD rates was observed in Japan after it underwent the nutrition transition. VaD has a different pathophysiology from that of AD, with vascular factors being the primary cause [119,120]. Nonetheless, seeing whether the literature includes any information regarding dietary risk factors is worthwhile. A review in 2012 concluded:

> Fourteen articles were found that proposed a potential role of specific nutritional components in VaD. These components included antioxidants, lipids, homocysteine, folate, vitamin B12, and fish consumption. Antioxidants, specifically vitamin E and C, and fatty fish intake were found to be protective against VaD risk. Fried fish, elevated homocysteine, and lower levels of folate and vitamin B12 were associated with increased VaD. Evidence for dietary lipids was inconsistent, although elevated midlife serum cholesterol may increase risk, while late-life elevated serum cholesterol may be associated with decreased risk of VaD. [121, p. 319]

Of course, many factors affect national diets, including relative cost of various food items, taste preferences, per capita income, national dietary guidelines, food distribution systems, food storage, convenience, and personal evaluations of current pleasure vs risk of future disease. For example, the U.S. government subsidizes grain production and hence livestock production. Grain production is correlated with overweight and obesity by affecting consumer food costs for subsidized compared with unsubsidized foods [122]. With the strong political pressure for such subsidies, it is unlikely that they will be reduced any time soon.

One might hope that national disease organizations would encourage people to eat healthful diets to reduce risk of chronic disease. The American Cancer Society recommends nutritional guidelines generally consistent with the information presented here, although still accepting meat consumption [123]:

- Choose vegetables, whole fruits, and other low-calorie foods instead of calorie-dense foods.
- Limit consumption of processed meats and red meats.
- Prepare meat, poultry, and fish by baking, broiling, or poaching rather than by frying or charbroiling.
- Eat at least 2.5 cups of vegetables and fruits each day.
- Choose whole grains instead of refined grains.

Neal Barnard of the Physicians Committee for Responsible Medicine organized a paper with leading AD researchers on dietary and lifestyle guidelines for the prevention of AD. The 2 guidelines related to diet were (1) minimize intake of saturated fats and trans fats and (2) vegetables, fruits, and whole grains should replace meats and dairy as primary staples in the diet [124]. These recommendations are generally consistent with the findings of the present study, although milk was not identified as a risk factor.

A paper showed maps of the United States to indicate AD or all-cause dementia–related mortality rates in 2002 by state of birth [125]. For blacks, rates for AD were highest in the traditional South, from Texas to West Virginia; for whites, rates were highest not only in the traditional South but also in the Northwest and Maine. The south is also known for high rates of stroke [126] and lung cancer [127]. A survey of 114 blacks living in the rural south found that "frequent consumption of fried foods; fast foods; sugary, carbonated beverages; processed, high-fat and high-sodium foods; and low fruit and non-starchy vegetable intake were evident" [128, p. 57].

A recent paper presented findings on inequalities in dementia incidence between 6 racial and ethnic groups over 14 years [129]. The hazard ratios for the model based on age, sex, and health care utilization were as follows: African American, 1.73 (95% CI, 1.66–1.81); Latino, 1.29 (95% CI, 1.23–1.35); white, 1.25 (95% CI, 1.21–1.29);

Asian American, 1.00. The authors did not provide any explanation for the inequalities but plan to investigate life course determinants. The findings regarding diet in the present study can provide some insight. According to data from the National Health and Nutrition Examination Survey, 2003–2004, blacks consume 140.2 g/d meat; Hispanics, 128.6 g/d; and whites, 124.4 g/d [130]. The dementia vs meat consumption data are perfectly fit by the equation

$$\text{Dementia } (\%) = -33\ \% + 0.51 \times [\text{meat consumption } (\text{g/d})]\ \%.$$

The zero intercept is about 65 g/d. Asian Americans probably eat less meat than the other ethnic groups based on national diets in their ancestral lands and the generally shorter stature of elderly Asian Americans. Thus, investigating dietary practices of those in the study should help explain the findings.

CONCLUSION

Mounting evidence from ecological and observational studies, as well as studies of mechanisms, indicates that the Western dietary pattern—especially the large amount of meat in that diet—is strongly associated with risk of developing AD and several other chronic diseases. Although the traditional Mediterranean diet is associated with about half the risk for AD of the Western diet, the traditional diets of countries such as India, Japan, and Nigeria, with very low meat consumption, are associated with an additional 50% reduction in risk of AD. Lowering meat consumption would also help to achieve environmental sustainability. Keeping 25(OH)D concentrations above 75 nmol/L would also help lower the risk of AD.

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