Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-240658
IOS Press
CORRECTED PROOF

Review

A Brief History of the Progress in Our Understanding of Genetics and Lifestyle, Especially Diet, in the Risk of Alzheimer's Disease

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Accepted 2 July 2024

Abstract. The two major determining factors for Alzheimer's disease (AD) are genetics and lifestyle. Alleles of the *apolipoprotein E (APOE)* gene play important roles in the development of late-onset AD, with *APOE* ε4 increasing risk, *APOE* ε3 being neutral, and *APOE* ε2 reducing risk. Several modifiable lifestyle factors have been studied in terms of how they can modify the risk of AD. Among these factors are dietary pattern, nutritional supplements such as omega-3 fatty acids, and B vitamins, physical exercise, and obesity, and vitamin D. The Western diet increases risk of AD, while dietary patterns such as the Mediterranean and vegetarian/vegan diets reduce risk. Foods associated with reduced risk include coffee, fruits and vegetables, whole grains and legumes, and fish, while meat and ultraprocessed foods are associated with increased risk, especially when they lead to obesity. In multi-country ecological studies, the amount of meat in the national diet has the highest correlation with risk of AD. The history of research regarding dietary patterns on risk of AD is emphasized in this review. The risk of AD can be modified starting at least by mid-life. People with greater genetic risk for AD would benefit more by choosing lifestyle factors to reduce and/or delay incidence of AD.

Keywords: Alzheimer's disease, APOE, dietary pattern, ecological study, genetic risk, lifestyle, meat, obesity, ultraprocessed foods, Western diet

INTRODUCTION

I am pleased to be invited to submit a review regarding genetic and lifestyle risk factors for AD for the Mark A. Smith JAD 100th Volume. He, and the editor of the *Journal of Alzheimer's Disease*, encouraged me at the beginning of my health research career that started with publishing the first article linking diet to risk of AD in 1997.[1] The two of them wrote the editorial that accompanied my article,[2] and discussed it in a 1998 review.[3] They invited me to write an update on the topic in 1999[4] and to participate in a symposium on AD at Case Western Reserve in 2002: "Challenging Views of Alzheimer's Disease." We debated whether genetics or environment was the more important risk factor for AD. Our topic was the significance of environmental factors in the etiology of AD.[5] We emphasized the effect of diet, aluminum, and infectious agents such as herpes simplex type 1 virus. While aluminum is no longer considered a significant risk factor for AD, infections are.[6,7] Ashford and Mortimer proposed that non-familial AD is mainly due to genetic factors.[8] They estimated that

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ISSN 1387-2877/$35.00

the heritability of AD is about 60%, based on results from twin studies, and the *APOE* genotype accounts for about 50% of AD in many populations.

AD is a devastating disease that strikes many elderly people. In 2020, the number of people in the US with clinical AD was estimated at 6.1 million (95% confidence interval [CI], 5.9 million–6.4 million) people.[9] The US census-adjusted prevalence of clinical AD was 10% among non-Hispanic whites, 14% among Hispanics, and 18.6% among non-Hispanic African Americans.[9] A 2022 article estimated the number of persons worldwide across the AD continuum as 32 million with AD, 69 million with prodromal AD, and 315 million with preclinical AD.[10] This represents 22% of all persons aged 50 and above. However, the impact is much greater, as others have to care for those with AD. It was estimated that in 2016, the cost of formal care per AD patient was $28,100 (95% CI, $25,900–$30,400), and informal care cost of $52,500 (95% CI, $47,000–$58,200).[11]

The risk of developing AD depends on genetics and lifestyle factors, and their interactions. People born with certain genes have greater or lesser risk of developing AD. Lifestyle choices can modify the risk of developing AD. This review will begin with a discussion of the basic findings regarding genetics and the risk of AD. It will then outline the major lifestyle factors affecting the risk of AD. The paper will conclude with a deep discussion of the role of diet and nutrition, followed by a top-line summary of the contribution of physical activity (PA), obesity, and vitamin D. The goal is to have a document useful to AD researchers, healthcare providers, and the general public, as we search for ways to prevent AD.

Recently a major hypothesis in AD research was exposed as based on manipulated images. The hypothesis was that a specific amyloid-β (Aβ) protein assembly, Aβ*56, blocks memory.[12] As outlined in two accounts in *Science*,[13,14] the paper contains manipulated images. As a result, the article was retracted by *Nature* on March 16, 2024 and most of the authors agreed with the retraction in a note published June 24, 2024.[15] As noted in *Nature* on March 16, the article had 65,000 accesses and 2348 citations. It was also the basis for two decades of research in trying to find drugs to remove Aβ from the brain.[13] The research has not led to drugs that effectively reverse AD. Thus, greater emphasis should now be placed on preventing AD. As a result of this retraction, all mention of Aβ in studies discussed in this review have been omitted.

GENETIC RISK FACTORS

The best-known gene that influences late-onset AD (LOAD) (after 60 or 65 years of age) is *apolipoprotein E* (*APOE*). It has three alleles, *APOE* ε2, ε3, and ε4. The *APOE* gene is involved in making a protein that helps carry cholesterol and other types of fat in the bloodstream. Problems in this process are thought to contribute to the development of AD. *APOE* comes in several forms, called alleles (e.g., ε2, ε3, ε4).[16]

- *APOE* ε2 may provide some protection against the disease. If AD occurs in a person with this allele, it usually develops later in life than it would in someone with the *APOE* ε4 gene. About 5% to 10% of people have this allele.
- *APOE* ε3, the most common allele, is believed to have a neutral effect on the disease — neither decreasing nor increasing the risk of AD.
- *APOE* ε4 increases AD risk and is associated with an earlier age of disease onset in certain populations. About 15% to 25% of people have this allele, and 2% to 5% carry two copies.

Finch and colleagues discussed the evolution of *APOE* isoforms in two articles. In 1999, they outlined the evidence that *APOE* ε3 evolved from the *APOE* ε4 of primate ancestors in relation to the rapid increase in brain size and the emergence of grandmothering.[17] The importance of grandmothering is that older family members could care for the infants and children while the parents were out hunting and gathering food. They noted that since *APOE* ε4 is associated with more cardiovascular disease (CVD) and cognitive dysfunction, it was not as suitable for long life as was *APOE* ε3. In 2002 they discussed the evolution of *APOE* isoforms in terms of adapting to eating meat.[18] The *APOE* ε3 evolved in the genus Homo to reduce risk of AD and CVD, as well as influencing inflammation, infection, and neuronal growth.

A 2017 review discussed the evolution of *APOE* isoforms.[19] The authors note that the *APOE* ε4 isoform is the archaic hominin *APOE*. They hypothesized that loss of body hair and increased ultraviolet exposure to the skin increases oxidative damage, leading to mutations resulting in the *APOE* ε3 and ε2 isoforms. The ε3 isoform appeared about 300,000 years ago and increased in frequency about 200,000 years ago; the ε2 isoform appeared about 80,000 years ago but has not greatly increased in contrast to the ε2 isoform.[19,20]

Early-onset AD (EOAD) (before 60 or 65 years of age) is mostly related to genes other than *APOE ε4*. EOAD is estimated to affect 5–10% of individuals with AD.[21] The heritability of EOAD is estimated at 90–100%.[21] Elevated low-density lipoprotein cholesterol (LDL-C) levels are also associated with EOAD.[22] It has been suggested that decreasing LDL-C levels could reduce the risk of both EOAD and LOAD.[23]

A 2019 review outlined the previous quarter century of research on *APOE*, the ApoE protein, and AD.[24] *APOE* controls the production of the ApoE protein. ApoE is a protein that shuttles cholesterol and other lipids between cells. *APOE* ε2, ε3, and ε4 code for production of ApoE ε2, ε3, and ε4 proteins [25]. ApoE is a component of very LDL-C particles as they are secreted from the liver [25]. ApoE ε4 increases plasma LDL-C concentrations, compared with ApoE ε3, while ApoE ε2 reduces concentrations compared with ApoE ε3. A 2013 review outlined many more roles of ApoE ε4 in the pathogenesis of AD.[26] Compared with ApoE ε3, ApoE ε4 increases aberrant brain activity, brain atrophy, neuronal toxicity, and tangle formation, while decreasing glucose metabolism, lipid/cholesterol metabolism, mitochondrial function, neurogenesis, synaptic function, and vascular function. This review also notes that a 1997 article[27] reported *APOE* ε2, ε3, and ε4 frequencies in the general population were 8.4%, 77.9%, and 13.7%, respectively, and 3.9%, 59.4%, and 36.7%, respectively, in the AD population.

Allen Roses and coworkers at GlaxoSmithKline Research and Development in North Carolina published three articles in 1993 linking *APOE* genotypes to LOAD.[28,29] He reviewed the discovery in 2006.[30]

A 2021 article reported the race-related association between *APOE* genotype and AD.[31] The review was based on 133 articles comprising 77,402 individuals from 12 countries, with publication years from 1984 to 2020. For Caucasians, having one or two *APOE* ε4 increased risk by a factor of 2.5; having one or two *APOE* ε3 reduced risk by 22%; having one or two *APOE* ε2 reduced risk by 54%. For African and African Americans, having one or two *APOE* ε4 increased risk by a factor of 1.9; having one or two *APOE* ε3 reduced risk by 20%; having one or two *APOE* ε2 reduced risk by 38%. For Hispanics, having one or two *APOE* ε4 increased risk by a factor of 3.1; having one or two *APOE* ε3 reduced risk by 17%; having one or two *APOE* ε2 reduced risk by 2%. For Asians, having one or two *APOE* ε4 increased risk by a factor of 2.4; having one or two *APOE* ε3 reduced risk by 13%; having one or two *APOE* ε2 reduced risk by 31%. Thus, the *APOE* genotype has similar effects for the different races. However, a limitation of this analysis is that it did not differentiate the results for the country of each study. For example, an analysis was reported for AD risk with respect to *APOE* ε4 for African Americans and Yoruba living in Nigeria followed for mean times of 8.5 and 8.9 years, respectively.[32] Possession of one or two copies of *APOE* ε4 was very significant for African Americans ($p < 0.0001$) but only weakly significant for Yoruba people ($p = 0.049$). Differences in dietary factors likely explained the variance.

A 2022 article based on a two-stage genome-wide association study totaling 111,326 clinically diagnosed/'proxy' AD cases and 677,663 controls found 75 risk loci, of which 42 were new at the time of analysis.[33] Gene prioritization in the new loci identified 31 genes that were suggestive of new genetically associated processes, including the tumor necrosis factor alpha pathway through the linear ubiquitin chain assembly complex. They also built a new genetic risk score associated with the risk of future AD/dementia or progression from mild cognitive impairment to AD/dementia. The improvement in prediction led to a 1.6- to 1.9-fold increase in AD risk from the lowest to the highest decile, in addition to effects of age and the *APOE* ε4 allele.

Genes associated with early onset AD include *APP*, *PSEN1*, and *PSEN2*.[34] A 2023 review described 45 new genes that affect the risk of neuropathophysiological events in AD and provided a figure indicating their actions.[35]

LIFESTYLE RISK-MODIFYING FACTORS

Many lifestyle or environmental factors have been linked to the risk of AD. A 2014 review from the 9th Key Symposium: Updating Alzheimer's Disease Diagnosis[36] listed a number of modifiable risk factors for AD and dementia: CVDs; cerebrovascular lesions; diabetes mellitus (DM) and pre-diabetes; midlife high BMI, high cholesterol, and hypertension; high alcohol intake and smoking; low B vitamins, high homocysteine (Hcy); saturated fats; depression; several infective agents; occupational exposure to heavy metals; and traumatic brain injury. Modifiable risk-reduction factors were: high educational level; high level of complexity of work; a rich social network and social engagement; mentally

stimulating activity; PA; moderate alcohol intake; antioxidant vitamins (A, C, and E); Mediterranean diet (MeDi); polyunsaturated fatty acids (PUFAs) and fish-related fats; vitamins B_6, B_{12}, and folate; vitamin D; and the use of antihypertensive drugs, hormone replacement therapy (HRT), non-steroidal anti-inflammatory drugs, and statins.

A 2015 review summarized results from clinical trials regarding some of these factors including HRT, Hcy-lowering vitamins, fish oil or omega-3 fatty acids, cognitive activity or training, physical exercise, and multidomain interventions.[37] Several trials testing the effects of PA, cognitive training, or antihypertensive interventions showed some evidence of efficacy on a primary cognitive endpoint.

Twenty-eight members of The Lancet Commission helped draft their 2020 report on dementia prevention, intervention, and care.[38] They identified 12 potentially modifiable risk factors for dementia and population attributable fractions (PAFs) for each: 1) early life: low education, 2%; 2) midlife: hearing loss, 8%; traumatic brain injury, 3%; hypertension, 2%; high alcohol consumption, 1%; obesity, 1%; and 3) later life: smoking, 5%; depression, 4%; social isolation, 4%; physical inactivity, 2%; air pollution, 2%, and DM, 2%, for a total of 40% PAF. Although the report was for dementia, there are many references to AD in the report. From my perspective, with only 5% of the PAF related directly to dietary factors, the results of this report do not align with my understanding of the main modifiable risk factors for AD. As discussed later in this review, AD rates in different countries correlate well with dietary macronutrients, and AD rates increase dramatically when countries undergo nutrition transitions from their indigenous diet to the Western diet (WD). These changes cannot be explained by the non-dietary factors considered by the Lancet Commission.

Another 2020 review summarized findings for some lifestyle modifications and nutritional interventions in aging-associated cognitive decline and AD.[39] Among the topics included were PUFAs, curcumin, flavonoids, resveratrol, minerals, B vitamins, the MeDi, PA, and caloric restriction.

A 2023 umbrella review and Delphi study updated the analysis of 12 modifiable and protective factors for dementia risk reduction.[40] The 12 risk factors in the Lifestyle for BRAin health (LIBRA) score were somewhat different from the 12 in the Lancet Commission study. They are, in descending order of number of studies included in the analysis by 18 dementia experts: DM, depression, midlife hypertension, high leisure –time PA, high alcohol consumption, chronic kidney disease (CKD), high cognitive activity, healthy diet/MeDi, coronary heart disease, smoking, midlife obesity, and high midlife cholesterol. Seven of the 12 are directly related to diet. CKD, for example, is linked to high consumption of animal protein.[41]

A 2024 report from the UK, also published in the *Lancet*,[42] included the same 12 modifiable factors for dementia. This time, the pooled unweighted PAFs for dietary-related factors were higher: hypertension, 15.8%; and obesity, 9.4%; while the weighted PAFs for dietary-related factors were higher as well: hypertension, 7.1%; and obesity, 5.3%. When these and other factors, including DM, were summed, the pooled unweighted and weighted PAFs were 55.5% and 32%, respectively. Again, these figures seem low, no doubt because of the approach used in the analysis.

Opinions on some of these factors have changed, such as the benefits of HRT. A recent review pointed out that HRT can reduce risk of AD, but its use has to be carefully considered on an individual basis.[43] As for DM, it shares many risk factors with AD, including insulin resistance, inflammation, oxidative stress, mitochondrial dysfunction, advanced glycation end products, and amyloid deposition.[44] However, the vastly different relative mortality rates for DM and AD in different countries indicate that risk factors probably related to diet play different roles for the two diseases. For example, in 2016, the estimated age-adjusted mortality rates for DM and AD in India were 32.6/100,000 and 17.0/100,000, respectively, while in France they were 6.8/100,000 and 19.3/100,000; in the US they were 15.3/100,000 and 32.4/100,000.[45] In the period 1992–94, there were only 20 kCal/day from meat but 1511 kCal/day from cereals in the Indian dietary supply versus 455 kCal/day and 833 kCal/day in the US dietary supply.[46] The high rate of DM in India has been attributed to elevated intake of refined cereal and low intake of dietary fiber, fruit, and vegetables.[47] In the US, risk of DM mortality rates as been associated with several dietary habits: total dietary pattern, 45.4% (95% CI, 43.6–47.0%); <20.2 g/day nuts, 7.0% (95% CI, 5.5–8.4%); <125 g/day whole grains, 17.1% (95% CI, 14.9–19.4%); red meats >14.3 g/day, 4.2% (95% CI, 3.1–5.4%); and processed meats, 17.5% (95% CI, 14.8–20.4%).[48] Thus, the different dietary links to DM in India and the US help explain the different amounts of AD in the two countries and why DM is not a risk factor for AD.

Diet and dietary patterns

Diet has been extensively studied as a risk-modifying factor for AD. As of May 14, 2024, 3,153 entries at Pubmed.gov were found with a search of "diet and Alzheimer or Alzheimer's." From the perspective of how AD prevalence changes between countries with respect to diet (e.g., [1,49,50]) or in response to dietary changes in single countries,[49] it seems that diet is the most important modifiable risk factor for AD.

Fish intake was identified as a risk-reduction factor for AD in 1997.[51] Saturated fat intake was identified as a risk factor for AD in 2003.[52] The MeDi pattern was the first identified dietary factor that reduced AD risk.[53] This dietary pattern is characterized by "high monounsaturated/saturated fat ratio; ethanol consumption at moderate levels and mainly in the form of wine; high consumption of vegetables, fruits, legumes, and grains; moderate consumption of milk and dairy products, mostly in the form of cheese; and low consumption of meat and meat products."[54]

I published the first article linking diet to risk of AD.[1] I was working at that time as an atmospheric scientist at NASA Langley Research Center in Hampton, VA. In September 1996, I learned of the Honolulu-Asia Aging Study,[55] which found that Japanese-American men in Hawaii had 2.5 times the prevalence of AD, relative to native Japanese. I was aware of some risk factors, such as aluminum.[56] While at NASA, I spent three years after hours working on a project for the Sierra Club, examining the effects of acid rain and ozone on eastern hardwood forests. I joined with forestry professor Orie Loucks of Miami University, Oxford, Ohio, who taught me how to use the ecological-study approach. We used that method to explore state-averaged data for oak decline, with respect to acid rain and tropospheric ozone concentrations, to show that red oaks declined due to ozone, while white oaks declined due to acid deposition.[57] In that process, I learned that acid deposition reduced soil solution concentrations of base cations, such as calcium, magnesium, and potassium, and increased concentrations of aluminum and transition metal ions.

Thus, with that background, as soon as I learned the results of the Honolulu-Asia Aging Study, I hypothesized that the American diet was the reason the Japanese-American men had the increased AD prevalence rate. Using a dietary-cancer ecological study[58] as a guide, I set about to do an ecological study of AD prevalence in various countries, focusing on macro-dietary factors. I obtained AD prevalence data for 11 countries from journal articles and dietary supply date from the Food and Agriculture Organization of the United Nations,[59] including Canada, China, Finland, Italy, Japan, Nigeria, Singapore, Spain, Sweden, UK, and USA.[1] The dietary component with the highest correlation in my study was total fat ($r = 0.97$), followed by total caloric supply ($r = 0.94$). The percentage of cereals in the diet was the dietary component with an inverse relationship to AD prevalence ($r = -0.83$). In a regression analysis with the seven European and North American countries, the correlation with fish was $r = -0.75$ ($p = 0.054$).

The advantages of the ecological-study approach include the large number of participants, the ability to incorporate many risk-modifying factors, and the very low cost of conducting the study when publicly-available data can be used. The disadvantages include the potential for overlooking some important risk-modifying factors and the fact that data for risk-modifying factors may not apply directly to those who develop the health outcome of interest.

During the preparation of the manuscript, I became aware of research at the University of Kentucky regarding the distribution of trace minerals in the brains of people with AD.[60] The distributions were very similar to those in soil solutions impacted by acid deposition. Since I was a novice in health studies, I contacted James Geddes at the University of Kentucky regarding my study, and he invited me to give a seminar to the AD group. The group liked the findings, and Dr. Geddes invited me to submit the paper to their electronic journal, *Alzheimer's Disease Review*. I hired a press agent who organized a press conference at the National Press Club in Washington, DC, on June 17, 1997. The Alzheimer's Association issued a press release disputing the findings, pointing out that it was known that *APOE* ε4 was an important risk factor for AD. Nonetheless, the finding did make the evening national TV news on both the Dan Rather program and CNN evening news.

Shortly thereafter, results from the prospective Rotterdam Study[51] were published. A total of 5386 nondemented participants aged 55 years or older completed food-frequency questionnaires (FFQs) and were followed for an average of 2.1 years. During that time, 58 developed dementia, of which 37 were AD without cerebrovascular disease. A significantly reduced risk of AD was found for fish intake of >18.5 g/day versus <3.0 g/day (relative risk [RR] = 0.3 [95% CI, 0.1–0.9]). A significant correlation with total fat (>0.85 g/day versus <75.5 g/day)

was found for total dementia [RR = 2.4 (95% CI, 1.1–5.2)], but the reduction in risk was only 1.6 (95% CI, 0.6–3.9) for AD without cerebrovascular disease. The findings for saturated fat and cholesterol were non-significantly increased for both total dementia and AD.

Hcy was confirmed as a significant risk factor for AD in 2002 in an analysis of data from the Framingham Study.[61] A recent meta-analysis found that higher Hcy concentrations were a significant risk factor for AD [RR = 1.07 (95% CI, 1.04–1.11)] and that a 5 μmol/L increase in Hcy was associated with a $12 \pm 4\%$ increased risk of AD.[62]

A June 2002 article from the Rush Institute for Healthy Aging reported the results from a prospective cohort study of the intake of antioxidant nutrients and risk of incident AD.[63] The study was conducted with 815 residents near the south side of Chicago aged 65 years or older who were free of AD at baseline and followed for a mean of 3.9 years. Fifty-one percent were African Americans. They completed a FFQ an average of 1.7 years after baseline. Increasing vitamin-E intake from foods was associated with a decreased risk of developing AD, after adjusting for age, education, sex, race, *APOE* ε4, and length of follow-up. Relative risks from the lowest to highest quintiles of intake were 1.00, 0.71 (95% CI, 0.24–2.07), 0.62 (95% CI, 0.26–1.45), 0.71 (95% CI, 0.27–1.88), and 0.30 (95% CI, 0.10–0.92) (p for trend = 0.05). The protective association of vitamin E was observed only among persons who were *APOE* ε4 negative. The hazard ratios (HRs) of AD for the highest quartiles of calorie and fat intake, compared with the lowest quartiles, in individuals without the *APOE* ε4 allele were close to 1 and were not statistically significant ($p = 0.83$ and $p = 0.61$, respectively).

AD researchers at Columbia University published in 2002 findings from a prospective cohort study regarding diet and the incidence of AD.[64] There were 980 elderly individuals (mean age 75 ± 6 years) of Caucasian, African American, and Hispanic race/ethnicity, who were followed for a mean period of four years, during which time 242 developed AD. They completed a 61-item FFQ early in the follow-up period. Among the 263 individuals with the *APOE* ε4 allele, the HRs 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. The HRs for the 667 participants without the *APOE* ε4 allele were not significantly different from 1.0. This paper seems to be the first to report that the risk of AD was dependent on both genetics and diet/lifestyle.

A 2003 article from the Rush Institute for Healthy Aging reported the results for dietary fats.[52] Persons in the upper quintile of saturated-fat intake had 2.2 times the risk of incident AD, compared with persons in the lowest quintile, using a multivariable model adjusted for age, sex, race, education, and *APOE* ε4 allele status [RR = 2.3 (95% CI, 1.1–4.7)]. Risk also increased with consumption of trans-unsaturated fats, beginning with the second quintile of intake [RR, 2.4 compared with the lowest fifth; (95% CI, 1.1–5.3)]. They observed linear inverse associations between AD and vegetable fat ($p = 0.002$), and, after further adjustment for other types of fat, marginally significant associations with intake of omega-6 polyunsaturated fat ($p = 0.10$ for trend) and monounsaturated fat ($p = 0.10$ for trend). Intakes of total fat, animal fat, and dietary cholesterol were not associated with AD.

AD researchers at Columbia University published an article in 2006 discussing findings regarding the MeDi and risk of AD.[53] The paper included 2258 community-based, nondemented individuals, who were followed for a median of 4 ± 3 years. During this period, 262 developed AD. The authors provided data on the average diet for the year preceding enrollment and scored the diet according to a framework identified by Trichopoulou et al.[65] Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a HR = 0.85 (95% CI, 0.63–1.16) and those at the highest tertile had a HR = 0.60 (95% CI, 0.42–0.87) for AD (p for trend = 0.007).

A 2021 meta-analysis of AD risk with respect to the MeDi, which included 11 studies with 12,458 participants, found that higher adherence to the MeDi resulted in a RR for AD = 0.89 (95% CI, 0.84–0.93).

A 2014 analysis of several ecological studies of national dietary supply data and prevalence of AD indicated that, in Japan, alcohol consumption, animal product, meat and rice supply, and lung cancer rates correlated highly with AD prevalence data, with the strongest correlation for a lag of 15–25 years.[49] In the eight-country study, overall, total energy and animal fat correlated highly with AD prevalence data, with a lag of 15–20 years, likely related to increased prevalence of obesity.

Barnard and colleagues published dietary and lifestyle guidelines for the prevention of AD in 2014.[66] They included minimizing intake of saturated fats and trans fats and recommended that vegetables, legumes, fruits, and whole grains should replace

meats and dairy products as primary staples of the diet.

AD researchers at Rush University Medical Center published their study of the MIND (MeDi-DASH Intervention for Neurodegenerative Delay), a hybrid of the MeDi-DASH diets, and risk of AD in 2015.[67] Table 1 in that article[67] compares the three dietary patterns (see, also[68]). The MIND diet score has 15 components, including 10 brain-healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). This study included 1545 persons enrolled in the Rush Memory and Aging Project. From 2004 to February 2013, participants were invited to complete FFQs. A total of 923 participants were included in the analysis, of whom 144 developed AD over a 4.5-year follow-up period. In adjusted proportional hazards models, the second [HR = 0.65 (95% CI, 0.44–0.98)] and highest tertiles [HR = 0.47 (95% CI, 0.26–0.76)] of MIND-diet scores had lower rates of AD, versus tertile 1, whereas only the third tertiles of the DASH [HR = 0.61 (95% CI, 0.38–0.97)] and MeDi [HR = 0.46, (95% CI, 0.26, 0.79)] diets were associated with lower AD rates.

In a related study, the risk of AD was evaluated with respect to the MIND diet and other healthy lifestyle factors using data from two cohort studies.[69] The other four factors were smoking, PA, alcohol consumption, and late-life cognitive activities. Compared to participants with 0 to 1 healthy lifestyle factor, the risk of AD was 37% lower [pooled HR 0.63 (95% CI < 0.47–0.84)] in those with 2-to-3 healthy lifestyle factors and 60% lower [pooled HR 0.40 (95% CI < 0.28–0.56)] in those with 4-to-5 healthy lifestyle factors.

Perrone and Grant published a review of the effect of advanced glycation end products (AGEs) on risk of AD in 2015.[70] Meat had the largest contribution to national diets, according to our calculations, accounting for about 30% for Nigeria in 1973 and 80% for Canada and the US in 1972. AGEs are formed when food, especially meat, is cooked at high temperature, such as by frying. Mechanisms whereby AGEs can increase risk of AD are thought to include oxidative stress and increased tau phosphorylation.[71]

In 2016, Grant published a new ecological study of diet and AD prevalence based on data for ten countries for which such findings were available following his 1997 ecological study.[72] The countries were Brazil, Chile, Cuba, Cyprus, Egypt, Republic of Korea, Inner Mongolia (misidentified as Mongolia), Sri Lanka, and the US. Dietary-supply data for 5, 10, and 15 years prior to the prevalence data were obtained from FoodStat at the Food and Agriculture Organization of the United Nations.[73] Data five years prior to the AD prevalence data had the highest correlation with prevalence. The highest correlation was with meat and fish ($r = 0.95$, $p < 0.001$). Cereals had the strongest inverse correlation ($r = -0.56$, $p = 0.10$). The equation for meat and AD prevalence was AD prevalence (%) = 1.7 +0.014 × kCal/cap/day, $r = 0.95$. A table of mechanisms to explain dietary risk factors for AD was included. In addition, an examination of how meat consumption serves as a risk factor for AD was supported by an analysis using Hill's criteria for causality.[74]

A 2019 review presented a systematic review of dietary pattern in relation to the risk of AD.[75] Of the 26 studies included in the review, eight studies assessed unhealthy diet (e.g., high-fat, high-glycemic, sweetened sugary beverage diets). Healthy diet included MeDi, DASH, MIND, and seafood-rich diet. The authors indicated that adherence to a healthy dietary pattern has neuroprotective effects on AD prevention, while an unhealthy diet can cause neurodegenerative effects in AD etiology. Dietary flavonols were shown to significantly reduce the risk of AD in an observational study conducted by the Rush Memory and Aging Project.[76] A total of 921 participants (75% female) with a mean age of 81 years were followed for a mean of 6.1 years, during which time 220 developed AD. The adjusted HR for high versus lowest quintile of flavonols was 0.52 (95% CI, 0.33–0.84).

A randomized trial investigated the effect of MeDi and WDs on AD biomerkers, cerebral perfusion, and cognition in mid-life.[77] Participants were between the ages of 45 and 65 years, of whom 56 had normal-cognition (NC) and 31 had mild cognitive impairment (MCI). MeDi or WD pattern foods were consumed for four weeks. The main differences between the two were the WD had 25% saturated fat and 3200 mg/day sodium per 2000 calories, while the MeDi had 7% saturated fat and 1600 mg/day sodium per 2000 calories. For NC participants, the MeDi increased and the WD decreased cerebral perfusion, a measure of blood flow in the brain.

A 2022 review of supplemental long-chain omega-3 fatty acids found they were most effective in reducing AD risk when consumed prior to, or in the early stages of, cognitive decline.[78]

A 2023 review of 38 studies (17 RCTs and 21 systematic reviews and/or meta-analyses) indicated the WD increases the risk of AD, while the MeDi, ketogenic diet, and supplementation with omega-3 fatty acids and probiotics reduce the risk of AD.[79]

In 2023, Blake and Grant published a review of dietary risk factors for AD.[50] The review was based on the Harvard study of optimal diet for reducing risk of chronic disease.[80] That study used findings regarding dietary components and health outcomes in 205,852 healthcare professionals from three US cohorts, who were followed for up to 32 years. Dietary assessments related to 37 food groups were compiled every four years to determine the components that best explain the empirical dietary hyperinsulinemia and dietary inflammatory patterns. Red meat, processed meats, and french fries had the highest adverse association, while fruit, coffee, wine, and green leafy vegetables had the highest beneficial relationship. These two dietary patterns had the strongest inverse correlation with DM: the HR, which adjusted for many factors, including socioeconomic status and BMI, was 0.57 (95% CI, 0.54–0.59) for reversed empirical dietary index for hyperinsulinemia and 0.57 (95% CI, 0.55–0.59) for reversed empirical dietary inflammatory pattern. We justified use of the findings for these two dietary patterns, in part because the contemporary understanding was that DM is a significant risk factor for AD[81] and red meat and processed meat had the highest negative ratings for reversed empirical dietary index for hyperinsulinemia. In addition, data for the ecological study in 1997[1] were reanalyzed, finding that total meat had the highest correlation with AD prevalence. In this regard, a 2021 review discussed inflammation and insulin resistance as potential therapeutic targets for AD.[82] We also discussed the great important of obesity and how the obesity trends likely foreshadowed continued increases in AD rates in the US.

A 2020 review outlined how dietary patterns affect gut microbiota, and, thereby, the risk of AD.[83] In clinical studies, researchers have found that people with AD have lower abundances of *Eubacterium rectale* and *Bacteroides fragilis*, which have an anti-inflammatory activity. An important benefit of good gut microbiota is the production of short-chain fatty acids. Figure 3 in reference[84] shows that short-chain fatty acids are involved in several processes: intestinal gluconeogenesis; maturation and function of microglia, vagal nerve, and calcium-ion signaling; and neurotransmission (glutamate, gamma-aminobutyric acid). A comparison of the WD with the MeDi is discussed, and it shows how the WD increases IR and system inflammation, in contrast to the MeDi.

LDL-C is a dietary risk factor for AD. A meta-analysis of 26 studies found that the standard mean difference for levels of LDL-C in people with AD, compared with non-demented controls, was 0.35 (95% CI, 0.12–0.58)[85]. An LDL-C concentration >121 mg/dl (3.13 mmol/L) was suggested as the value associated with the risk for AD in people aged 60–70 years. Age and BMI had some impact on the correlation. A meta-analysis of previous meta-analyses of cholesterol and AD risk found that only LDL-C increased the risk.[86] The random effect OR for high versus low LDL-C from three meta-analyses was 2.55 (95% CI, 1.25–5.22). A later article reported that the effect of LDL-C on AD neuropathy burden is independent of the *APOE* allele.[87]

A 2021 review and meta-analysis tabulated the effect of various foods on LDL-C levels.[88] With high evidence, most of the foods that reduce LDL-C levels are plant-based foods, such as n-6 PUFA and/or MUFA, and foods high in soluble fiber, such as psyllium and oats, soy protein, tomatoes, and almonds. Foods associated with increased levels are those high in saturated fats or trans fatty acids, and unfiltered coffee. Moderate evidence suggests that nuts, legumes, and whole grains, reduce concentrations, while and marine oils high in long-chain n-3 PUFA (a very small increase), free sugars, and coffee rather than tea increase levels. Foods with a low degree of evidence that reduce LDL-C levels include cumin, ginger, and high polyphenol olive oil, while eggs increase levels a small amount.

The effect of red meat on LDL-C levels depends on the foods with which it is compared. A summary of meta-analyses of RCTs of red-meat consumption in comparison with various diets included calculated expected reductions in LDL-C for several foods.[89] The reported reductions in LDL-C (mmol/L) ranged from 0.053 (peanuts) to 0.060 and 0.062 (for mixed nuts and soybeans, respectively). Assuming a range of LDL-C of 0–2.56 mmol/L, these values represent about 4–5% of the midpoint of the range.

A randomized cross-over trial was conducted to compare the MeDi and low-fat vegan diet in improving cardiometabolic risk factors.[90] Among participants with no changes in lipid-lowering medications, LDL-C decreased 0.5 mg/dL (0.01 mmol/L) during the 16-week Mediterranean phase, compared with 15.3 mg/dL (0.4 mmol/L) during the vegan phase.

In 2024, results of a lifestyle and nutrition intervention clinical trial were published.[91] Fifty-one early-stage AD patients from San Francisco with a mean age 73.5 years were enrolled. The dietary intervention during the 20-week study for half of the participants included a whole foods, minimally-processed plant-based (vegan) diet, which contained 14–18% of calories from fat, 16–18% protein, and 63–68% mostly complex carbohydrates. Other interventions included exercise, stress management, and group support. Additional supplements included omega-3 fatty acids with curcumin, multivitamin and minerals, coenzyme Q10, vitamins C and B12, magnesium, hericium erinaceus (Lion's Mane), and a probiotic. The most significant change in biomarkers was LDL-C (–31%). Other significant changes were found, in ascending order of the p value, for glycoprotein acetylation, beta-hydroxybutyrate (ketones), and insulin. Results of the primary analysis showed statistically significant differences between the intervention group and the randomized control group in cognition and function, as measured by the Clinical Global Impression of Change ($p = 0.001$), Clinical Dementia Rating–Sum of Boxes ($p = 0.03$), and Clinical Dementia Rating Global ($p = 0.04$) tests. Borderline significance was seen in the AD Assessment Scale-Cog test ($p = 0.053$). Thus, this clinical trial provides evidence that an intensive lifestyle intervention with a low-fat vegan diet can yield significantly reduced measures of early-stage AD.

Finally, an analysis of RCTs for AD prevention found that PE and Hcy-lowering treatment seem more promising than eight other interventions.[92]

Physical activity

Regular PA is a good way to reduce the risk of AD adverse-health outcomes, including the overall risk.[93] A 2017 review reported that PA, especially during leisure time, significantly reduced AD risk in observational studies.[94] A total of 24 observational studies were included. Reductions in the incidence of AD were near 50% in many of the studies. It appeared that midlife PA was more important than late life, and leisure-time PA was more important than occupational PA. A study from Japan reported that aerobic PA, especially open-skill exercise, was useful in preventing dementia.[95] The likely reason is that open-skill exercise uses the cognitive functions of the brain more than does closed-skill exercise.

PA appears to modulate inflammation, synthesis and release of neurotrophins, and improvements in cerebral blood flow.[96] A 2021 review outlined the effects of exercise on a number of molecular pathways and biological processes dysregulated in AD. They include: endothelial function and cerebrovascular insufficiency; metabolism, oxidative stress and neurotoxicity; DNA damage and repair; and synaptic plasticity.[97] Exercise was found to inhibit many of these pathways.

Obesity

Obesity in midlife is an important risk factor for AD.[98] However, as people with midlife obesity age, they often lose weight. As a result, low BMI in old age is a risk factor for dementia,[99,100,101] and late-life obesity is protective.[102] Researchers with the Whitehall II Study in the UK followed 10,308 adults aged 35-to-55 years enrolled in 1985.[103] BMI was assessed six times. A total of 329 developed dementia. At 28 years prior to the diagnosis, the difference in BMI between dementia cases and matched controls was 0.79 kg/m^2. At eight-to-nine years, the difference was near zero. At the time of diagnosis, the difference was –0.79 kg/m^2. Thus, it appears better to avoid becoming obese in midlife than to reduce weight later in life.

A 2017 review noted that several neurodegenerative mechanisms are involved in the link between obesity and AD risk.[104] They include oxidative stress, mitochondrial dysfunction, and inflammation. Also, damage to the blood-brain barrier can lead to infiltration of cells into the brain, thereby increasing inflammation. Another 2017 review outlined the evidence that insulin resistance, for which obesity is a primary driver, is an important risk factor.[105] The suggested pathways were decreased brain-glucose metabolism and dysfunctional brain insulin signaling, resulting in reduced brain volume.

Two subsequent reviews outlined the role of obesity-induced leptin in the risk of AD. The first pointed out that leptin concentrations are elevated in obesity, leading to leptin resistance.[106] Leptin has both neurotrophic and neuroprotective properties, so leptin-signaling deficits can lead to AD. This review also discussed the role of the obesity-increased neurotransmitter glutamate, which overexcites *N*-methyl-D-aspartate receptors. The second outlined the role of additional key players involved in leptin resistance and how their activity increases inflammation.[107]

Neuroinflammation has been proposed as a modifiable pathway linking obesity to risk of AD.[108]

However a commentary regarding that hypothesis suggested that a better explanation is an attack on neuroplastic mechanisms in the brain.[109] Steps were proposed to reduce obesity included weight loss, PE, diet, statins, use of recombinant form of leptin, metformin, good sleep, and some non-steroidal anti-inflammatory drugs.

A high intake of ultra-processed foods (UPFs) has been found to increase the risk of dementia in adults. In a 2024 review, 10 observational studies involving 867,316 individuals were included in the analysis.[110] High versus low intake of UPF was associated with increased risk of dementia [pooled RR = 1.44 (95% CI, 1.09–1.90)], while moderate versus low intake of UPF did not significantly elevate the risk [pooled RR = 1.12 (95% CI, 0.96–1.31)]. The link here is that UPF is associated with a risk of obesity. An observational study involving 110,260 middle-aged adults in France determined that an increase of 10% of UPF in the diet led to a HR for overweight = 1.11 (95% CI, 1.08–1.14) and obesity = 1.09 (95% CI, 1.05–1.13).[111]

Vitamin D

Vitamin D is a secosteroid hormone that accomplishes most of its genetic effects though the binding of the hormonal metabolite, 1,25-dihydroxyvitamin D (calcitriol) to vitamin D receptors coupled to cell nuclei.[112,113] The benefits of vitamin D extend to many health outcomes, including autoimmune diseases, cancer, DM, infectious diseases, pregnancy and birth outcomes. Supplementation of 2000 IU/day (50 mcg/day) to achieve a 25(OH)D concentration of 75 nmol/L (30 ng/mL) is recommended.[114] Thus, it would be expected, and has been demonstrated, that vitamin D also reduces risk of AD.

By 2019, five prospective studies and one cross-sectional study of serum 25(OH)D concentration and incidence of AD had been conducted. A total of 10,884 participants were included. The meta-analysis HR of AD for <25 ng/mL versus >25 ng/mL was 1.59 (95% CI, 1.09–2.33). However, since the apparent effect of outcomes related to serum 25(OH)D concentration decreases with increasing follow-up time,[115] the actual HR is higher.

An RCT investigating the effects of vitamin D supplementation on cognitive function and was conducted in China.[116] Half of the 210 AD patients in the trial were given 800 IU/d vitamin D. During the 12-month trial, mean serum 25(OH)D concentration increased from 18.8 ± 2.9 ng/mL to 23.5 ± 3.1 ng/mL. Significant improvements in many cognitive function tests were found in the treatment group, but significant decreases were found in the control group. In addition, modeled full-scale IQ increased from 91.4 ± 8.5 to 92.3 ± 7.9 in the treatment group but declined from 88.4 ± 9.3 to 82.5 ± 8.4 in the control group ($p < 0.001$).

Another way to determine whether vitamin D has an effect on health outcomes is through Mendelian randomization studies. A 2016 article reported the Mendelian randomization analysis for 17,008 AD cases and 37,154 controls.[117] Using four single-nucleotide polymorphisms that described 2.44% of the variance in 25(OLH)D, a one-standard deviation decrease in the natural log-transformed 25(OH)D increased AD risk by 25% [OR = 1.25 (95% CI, 1.03–1.51)].

Finally, a comprehensive review of the role of vitamin D in reducing Alzheimer's type neurodegeneration was published in *Journal of Alzheimer's Disease* in 2023.[113] In it, Gezen-Ak and Dursun emphasized the importance of maintaining adequate vitamin D levels throughout life to reduce the risk of neurodegeneration, particularly with respect to AD.

DISCUSSION

Genetics plays an important role in the risk of AD. However, many lifestyle choices also play a part. It might be said that genetics loads the gun and lifestyle/nutrition pulls the trigger. Those with one or two *APOE* ε4 allele would benefit most from reducing risk through such lifestyle choices as adopting a vegan diet. However, even those without *APOE* ε4 could benefit through judicious lifestyle choices.

The effect of lifestyle and nutritional choices on risk of AD has been studied primarily through observational and ecological studies, while studies of mechanisms and a few RCTs have supported many of the findings from those studies. However, more RCTs would help move the understanding forward.

The role of meat in the risk of AD seems to be very important but not fully appreciated. The strongest evidence seems to come from ecological studies (e.g., [49,50,72]). There is evidence that the *APOE* ε3 allele arose in Homo to reduce the risk of AD and CVD and increase life expectancy.[18] Strong evidence also comes from the Harvard observational study examining diet patterns that reduce inflammation and IR.[80] Additional support comes from comparing the vegan diet with the MdDi with respect to LDL-C.[90] Meat

cooked at high temperatures is an important source of AGEs.[70] Also, meat increases hypertension in midlife,[118] an important risk factor for AD.[119] Meat consumption is also an important risk factor for CKD.[41] Thus, limiting or omitting meat consumption might be the most important dietary approach to reducing risk of AD.

CONCLUSION

For more than 30 years, researchers have identified and quantified genetic and lifestyle factors for AD and other dementias. In early-to-midlife, and perhaps later life as well, people can reduce their risk of LOAD through lifestyle and dietary choices. EOAD can also be reduced in the same way, but more research is required regarding the interaction between genetic risk and lifestyle/dietary factors. Given the large impact AD and dementia have on individuals, their care givers, and society as a whole, more effort should be expended to revise public-health guidelines regarding lifestyle/dietary factors to reduce risk of AD.

AUTHOR CONTRIBUTIONS

William B. Grant (Conceptualization; Investigation; Writing – original draft).

ACKNOWLEDGMENTS

The author has no acknowledgments to report.

FUNDING

The author has no funding to report in the preparation of this review. However, Dr. Grant received funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR, USA).

CONFLICT OF INTEREST

William B. Grant is an Editorial Board Member of this journal but was not involved in the peer-review process of this article nor had access to any information regarding its peer-review.

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