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Journal

Alzheimer disease and associated disorders, 20(3 Suppl 2)

ISSN

0893-0341

Author

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Publication Date

2006-07-01

DOI

10.1097/00002093-200607001-00014

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Peer reviewed



Published in final edited form as:

Alzheimer Dis Assoc Disord. 2006 ; 20(3 Suppl 2): S89–S96.

Medications and Diet Protective Factors for AD?

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Abstract

In the past decade, studies of Alzheimer disease risk and medication exposures, supplement intake, and dietary factors have grown in number. Typically identified in case-control and cross-sectional studies, many of these exposures have also been replicated in prospective studies. These observational studies have provided the foundation for the development of several prevention trials. This brief review focuses on exposures that have been identified in multiple studies. Observational studies of medications suggesting protection for Alzheimer disease include estrogen hormonal therapy, nonsteroidal anti-inflammatory drugs, and cholesterol-lowering statins. Evidence regarding dietary and supplemental intake of vitamins E, C, and folate, and studies of alcohol and wine intake are also reviewed. At present, there is insufficient evidence to make public health recommendations, but these studies can provide potentially important clues and new avenues for clinical and laboratory research.

Keywords

risk factor; medications; diet; Alzheimer disease

Twenty years ago, the list of potential protective factors for Alzheimer disease (AD) was modest and included neither medications nor dietary factors.¹ In 2006, however, investigations of dietary factors and medications comprise the majority of the published analytical investigations of AD risk. In large measure, dietary intake, nutritional supplements, and medications have received considerable attention because these exposures are potentially modifiable factors, unlike age, family history, and ApoE genotype.

Foods purported to be protective for AD in epidemiologic investigations include vegetables, fish, olive oils, fruits, a low-fat diet, and the composite Mediterranean dietary pattern. In addition, studies have extended beyond food groups to specific foods, such as blueberries, pomegranates, spinach, salmon, mackerel, or to individual vitamins, supplements and other micronutrients, including vitamins E, C, and B, flavonoids, omega 3-fatty acids, ginkgo biloba, and resveratrol. The medication list is equally long with various types of estrogens, steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs), statins, calcium channel blockers, potassium-sparing diuretics, and others.

This review focuses on agents with evidence from multiple studies, especially prospective investigations. In some cases, evidence from these studies has been used to develop experimental randomized trials for the prevention of AD (described in this issue by Thal).

Medications and Risk of AD

Hormonal Therapy

Biologic Plausibility—Estrogens have many effects that could be relevant in the development of AD. Potential mechanisms include effects on vasculature, the cholinergic system, and ApoE levels as well as trophic and antioxidant properties. In the past, the most commonly prescribed form of estrogen replacement therapy consisted of conjugated equine estrogens without progestin. More recently, women without hysterectomy have been prescribed estrogens with progestin.

The Epidemiologic Evidence—Probably more than any other medication, supplement, or dietary factor, estrogen therapy has been associated with a lower risk of AD in numerous observational studies.²⁸ Figure 1 summarizes observational studies of estrogen and risk of AD. Initial case-control investigations were followed by numerous prospective cohort studies, and several studies reported a dose-response relationship with greater protection for longer durations of exposure,^{4,5,7,8} as shown in Figure 2.

With considerable evidence lending support, clinical trials of estrogen were the first prevention studies developed for AD. Unfortunately, these studies (described in this issue by Thal) have not confirmed protective effects for AD. Exposure to conjugated equine estrogens (with or without progestin) in the Women's Health Initiative Memory Study was associated with approximately double the risk of developing AD,^{9,10} and halted several human investigations involving estrogen. However, many questions about hormonal therapy and AD risk remain. In particular, we still do not know if perimenopausal initiation of therapy, more consistent with observational studies, would have the same effects. We also do not know if other dosages or different forms of estrogen, such as estradiol, would have the same effects. And, we are unlikely to attempt replication any time soon.

Anti-inflammatory Drugs

Biologic Plausibility—Neuritic plaques, a hallmark of AD pathology, have been associated with inflammatory proteins, acute-phase reactants, activated microglia, and complement activation. NSAIDs inhibit cyclooxygenase (COX) enzymes, and could potentially be beneficial by suppressing the inflammatory processes associated with AD. Older NSAIDs inhibit both isoforms of the enzyme: COX 1 and COX 2. Newer drugs primarily inhibit COX 2. It is not clear which isoform (if either) is the proper target in AD. In vitro studies have suggested that a subset of these drugs (ibuprofen, sulindac, and indomethacin) can decrease A β 42 levels in cultured cells and the effect is not mediated by COX inhibition.¹¹

The Epidemiologic Evidence—Steroidal and NSAIDs have been associated with lower AD risk in a variety of study designs, including several prospective investigations. Moreover, data seems to suggest a dose-response relationship for duration with protection after 2 or more years of exposure. Figures 3, 4 summarize observational studies of NSAIDs and AD, and observed effects of duration.

Related to drug availability over time, there are more observational studies, and hence more evidence, for the older nonsteroidal drugs such as ibuprofen and naproxen. In the Rotterdam study, reduction in AD risk among NSAID users was restricted to those who took the subset of NSAIDs that decreased levels of A β 42 peptide in cultured cells as described above.¹² Clinical trials have been initiated with both types of NSAIDs, but the results to date have been disappointing in both prevention and treatment trials.

Statins

Biologic Plausibility—Statins are cholesterol-lowering agents that work by inhibiting 3-hydroxy-3methyl-glutaryl coenzyme A (HMG-CoA) reductase. These compounds could work by lowering cholesterol or by other mechanisms. In animal models, high cholesterol diets increase cerebral amyloid deposition, and elevated cholesterol has been reported to be a risk factor in AD.

The Epidemiologic Evidence—Some cross-sectional and case-control studies have reported statin use to be associated with lower prevalence or risk of AD.¹³⁻¹⁶ Prospective cohort studies, however, have generally not replicated these findings.¹⁷⁻¹⁹ Figure 5 summarizes observational studies of statins and risk of AD.

Dietary Intake, Vitamins, Supplements, and Risk of AD

Investigated frequently, dietary intake and risk of AD has produced an extensive epidemiologic literature, primarily of observational studies. For a more comprehensive review, see Luchsinger and Mayeux.²⁰ In addition to specific mechanisms such as antioxidant effects, and homocysteine-lowering properties, it has been proposed that diet may influence the success of protective mechanisms in the aging brain.²¹ Selected dietary exposures of particular interest are summarized below.

Vitamins E, C, and Other Antioxidants

Biologic Plausibility—Oxidative injury has long been implicated in aging and age-associated diseases such as AD. Laboratory studies and animal models have demonstrated that oxidative processes have effects on mechanisms related to AD including A β aggregation, microglial stimulation, and damage to DNA, proteins and lipids. In addition to vitamins E and C, the list of compounds with antioxidant properties includes β -carotene, Coenzyme Q, α -lipoic acid, and selenium, among others.

The Epidemiologic Evidence—Despite considerable interest in vitamins E, C, and other antioxidants, the epidemiologic evidence remains fairly modest for the prevention of AD. Studies that included vitamin intake from food have been more likely to suggest protection than studies examining pill supplementation only. Figures 6, 7 summarize studies of AD risk and vitamins E and C. In the Cache County study,²² use of vitamin E and C supplements in combination, but not individually, was associated with a lower incidence of AD. Measurement of these intakes from food is challenging and contributes to the difficulties of these studies.

Folate

Biologic Plausibility—Intake of folate and other B-vitamins is related to serum homocysteine level, a risk factor for vascular disease and, perhaps independently, for AD. Studies in animals have also provided evidence that folic acid deficiency may be related to amyloid toxicity.²³

The Epidemiologic Evidence—Recent observational studies of folate intake and AD are summarized in Table 1. When dietary intake of vitamins C, E, A, B6, B12, and folate were simultaneously analyzed in the Baltimore Longitudinal Study of Aging (BLSA), only intake of folate remained significantly associated with lower risk of AD.²⁴ After a decade of follow-up, BLSA subjects with a total folate intake (diet plus supplements) above the recommended dietary allowance of 400 μ g had a 55% reduction in risk compared with those below the recommended dietary allowance. Recently, investigators in the Netherlands

reported less cognitive decline in nondemented subjects randomized to 800µg folate supplementation in a placebo-controlled randomized clinical trial.²⁵

Wine and Alcohol

Biologic Plausibility—Moderate alcohol intake is associated with cardiovascular benefit, social engagement, and other factors that could be relevant to AD. Wine drinkers may benefit from the alcohol content, or from other nutritional factors. Black grape skin is rich in a variety of nutrients including vitamins E and C, quercetin, and resveratrol, which are all involved in ameliorating oxidative stress. Resveratrol is a naturally occurring polyphenol that reduces Aβ levels in cell lines by promoting intracellular degradation of the amyloid peptide.^{26,27}

The Epidemiologic Evidence—Total alcohol consumption and wine intake has been associated with a reduced risk of AD. It is not clear if red wine consumption has greater benefits when compared with white wine, or if wine is more protective than other alcoholic beverages. Figures 8, 9 summarize observational studies of AD risk and alcohol intake and AD risk and wine intake. The results are somewhat difficult to interpret because these studies were done with different outcomes (all-cause dementia, AD); and different groupings of amounts and types of alcohol.²⁸ For example, the Honolulu Asian Aging Study found protective effects for the risk of vascular dementia, but not for AD. Studies in Canada²⁹ and Copenhagen³⁰ reported a significant reduced risk for all-cause dementia. The Rotterdam Study³¹ had a similar result for all-cause dementia, but not for AD. Similarly, the protective amount of alcohol varied from less than 1 drink per week³² to 3 to 4 glasses of wine per day.³³

Ginkgo Biloba

Biologic Plausibility—Derived from an ancient tree rich in flavonoids, extracts of ginkgo biloba are widely used in the United States, Europe, and Asia for indications related to cognition and memory. In addition to antioxidant and anti-inflammatory properties, ginkgo biloba acts as a vasodilator, and has been shown to inhibit amyloid-β aggregation and caspase-3 activation.

The Epidemiologic Evidence—Published clinical investigations of ginkgo biloba primarily consist of treatment trials in AD patients.³⁴⁻³⁷ A nested case-control study of women participating in an osteoporosis study in Toulouse, France³⁸ found an inverse relationship between use of cerebral and peripheral vasotherapeutics (including ginkgo biloba) for at least 2 years and the development of AD. (Odds ratio = 0.31, 95% confidence interval = 0.12-0.82.) In this investigation, half of the women reported having taken a vasotherapeutic medication, about 1/3 of which was a standardized ginkgo extract. Odds ratio for ginkgo biloba alone was similar but did not reach significance. (OR = 0.38, 95% confidence interval = 0.08-1.76). Randomized clinical trials of ginkgo biloba are in progress and will yield valuable information.

Discussion

Observational studies are one of our most powerful and cost-efficient tools for the identification of putative risk and protective factors. These studies can investigate a wide variety of exposures, dosages, and formulations in diverse groups of subjects over longer periods of time than possible in a randomized trial.³⁹

Moreover, despite several recent high-profile examples of a randomized trial producing discordant results from previous observational studies, both types of studies generally produce results similar in direction and magnitude.^{40,41}

To be considered causal, a risk or protective factor should satisfy criteria including consistency of findings, specificity of the association, proper temporal relationship, dose-response relationship, and biologic plausibility.⁴² Replication of results should ideally be followed by randomized clinical trials to ensure that observed benefits are not due to unrecognized confounders. Clinical trials should also be replicated, although this rarely happens except in novel investigational compounds. Moreover, prevention trials of diet and other lifestyle changes present particular challenges. Subjects cannot be blinded because the intervention requires their participation, and dietary adherence is never ideal even in motivated subjects. Prevention trials require years of participation, and subjects who enroll and complete these studies are likely to reflect many selection biases. Ultimately, causality can only be demonstrated by many studies, observational and experimental, in the laboratory and in living subjects.

At present, evidence for many medications and dietary intakes is intriguing but insufficient to make clinical recommendations. It seems likely that a diet rich in fruits and vegetables, unsaturated fats, fish and olive oils, antioxidants, and flavonoids is good for us in general, but more information is needed before we know how helpful these exposures may be for the prevention of AD.

Acknowledgments

The author acknowledges María Corrada, Sc.D. for contributing ideas in the manuscript and compilation of the figures and tables, and Sandy Pittman for help with the manuscript.

Supported by grants from the National Institute on Aging R01 AG-21055 and P50 AG16573 and the Al & Trish Nichols Chair in Clinical Neuroscience.

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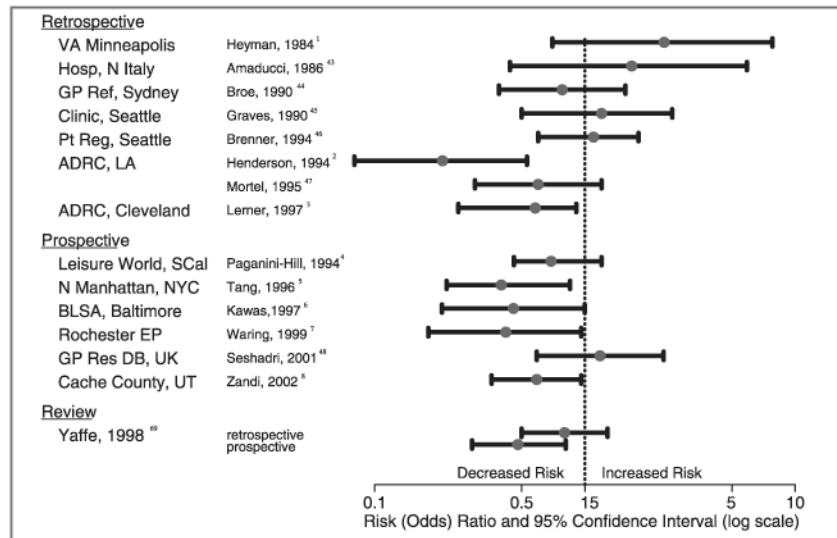


Figure 1. Observational studies of estrogen replacement therapy and AD.

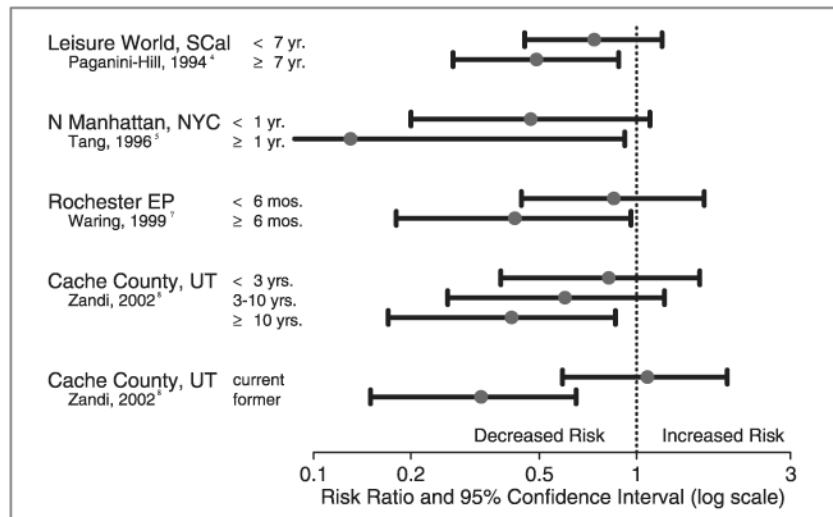


Figure 2. Observational studies of ERT and AD—duration and recency of use.

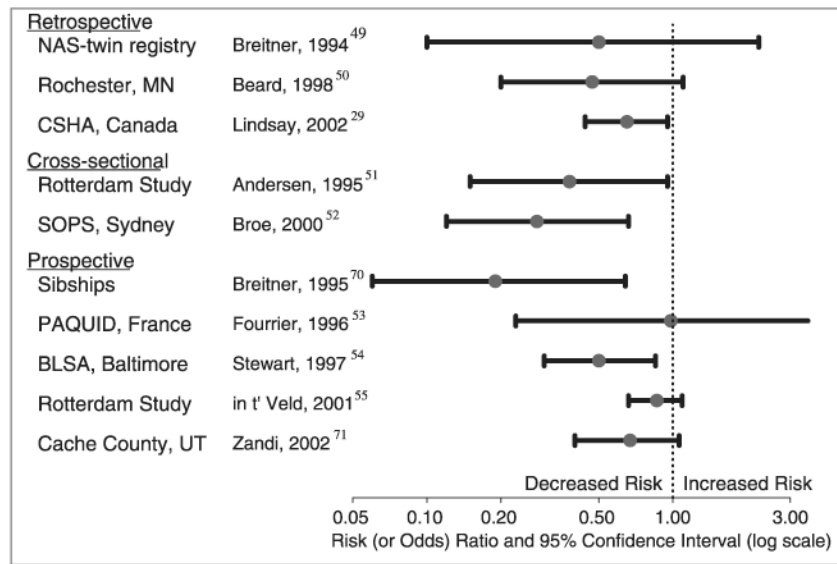


Figure 3.
Observational studies of NSAIDs and AD.

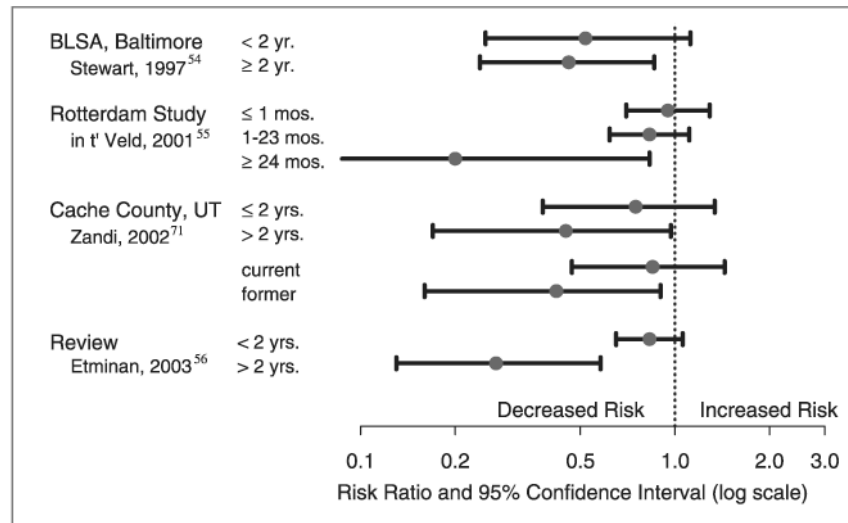


Figure 4. Observational studies of NSAIDs and AD—duration and recency of use.

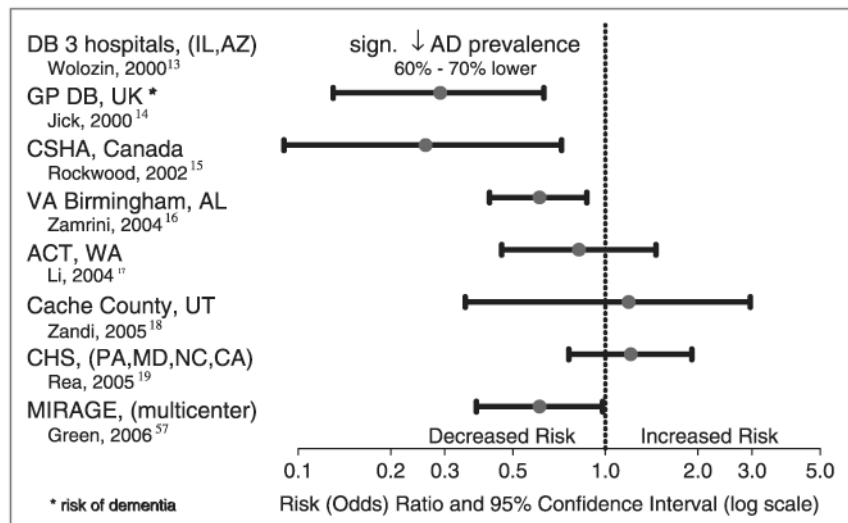


Figure 5.
Observational studies of statins and AD.

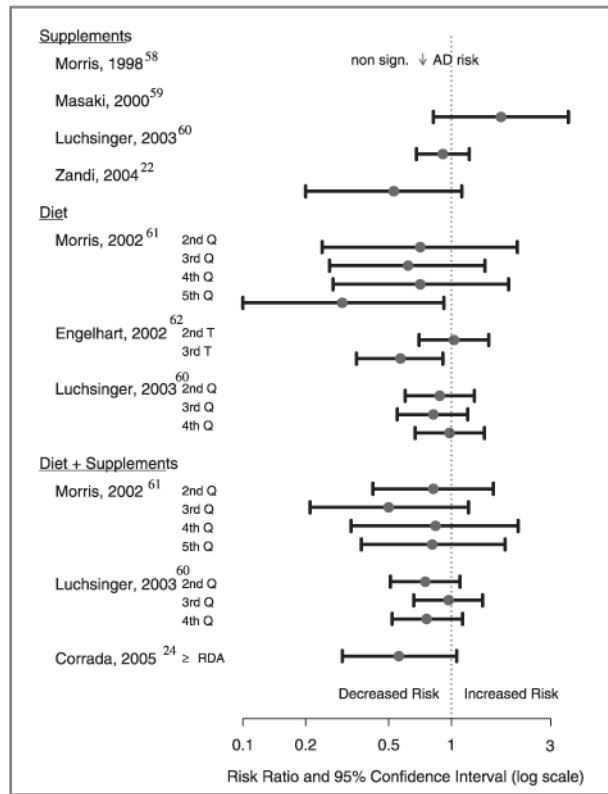


Figure 6. Observational studies of vitamin E and AD.

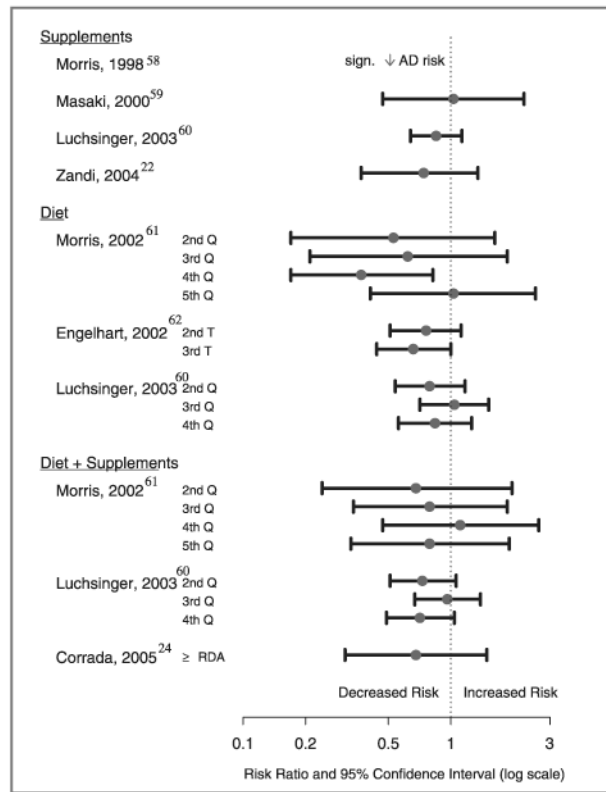


Figure 7.
Observational studies of vitamin C and AD.

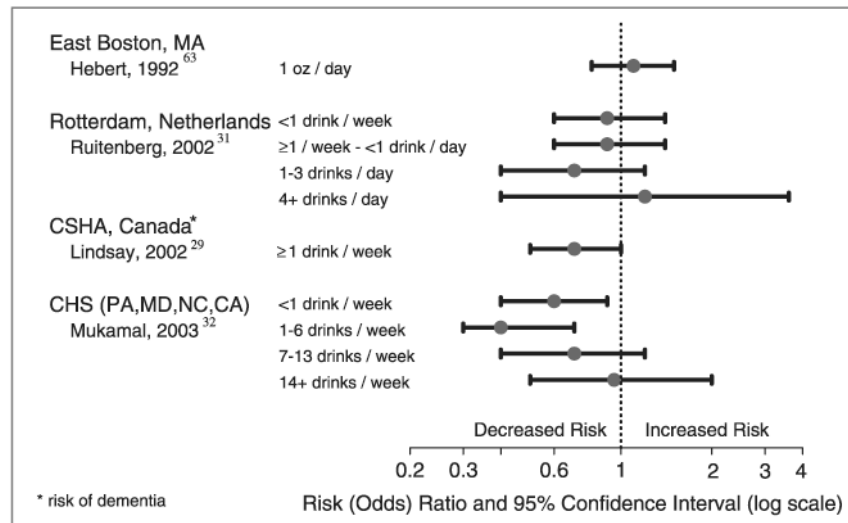


Figure 8.
Observational studies of alcohol intake and risk of AD.

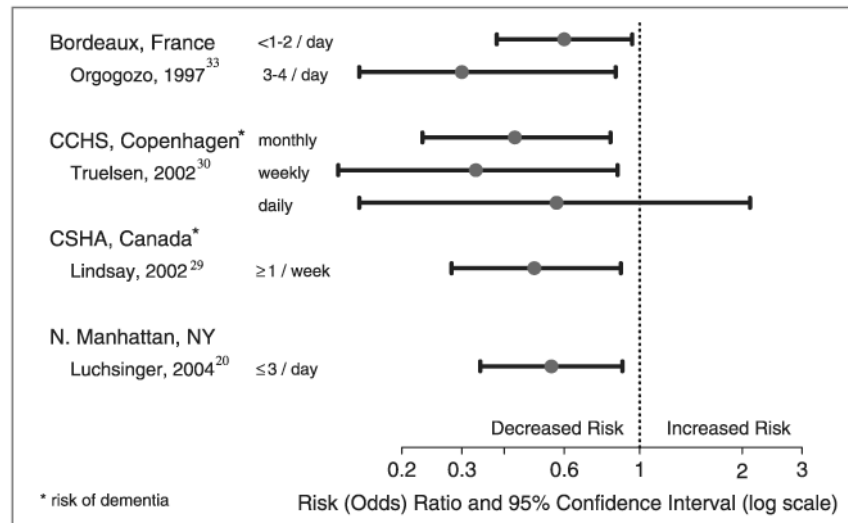


Figure 9. Observational studies of wine intake and risk of AD.

Table 1
Studies of Folate and AD Risk or Cognition

Type	Study	AD/N	Result
Folate levels			
CC	OPTIMA (Clarke ⁶⁴)	76/164	↑ levels, ↓ AD risk
CC	N. Wales (McCaddon ⁶⁵)	30/30	NS
PROSP	Kungsholmen (Wang ⁶⁶)	60/370	NS*
Folate intake			
CC	Case Western (Mizrahi ⁶⁷)	64/128	↑ intake, ↓ AD risk
PROSP	BLSA (Corrada ²⁴)	57/579	↑ intake, ↓ AD risk
PROSP	CHAP (Morris ⁶⁸)	3718	↑ intake, faster cognitive decline
RCT	Netherlands (Durga ²⁵)	818	↑ intake, better cognition

* Normal or high levels of folate and B12, ↓ AD risk.

CC indicates case control; PROSP, prospective; RCT, randomized clinical trial.