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Ascorbic acid, cognitive function, and Alzheimer's disease: a current review and future direction

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Abstract

This narrative review appraises the human and animal studies implicating ascorbic acid (AA) in normal cognitive function and Alzheimer's disease. A research framework for how nutrition affects brain aging is proposed with emphasis on AA intake, status, metabolism, and transport into brain tissue. A final synopsis highlights areas for future research regarding AA nourishment and healthy brain aging.

Keywords

ascorbic acid; vitamin C; cognitive function; Alzheimer's disease; dementia; plasma; CSF; SVCT; blood–brain barrier; blood; CSF barrier; choroid plexus

1. Nutrition and brain aging: Public health perspective and research framework

A surge in the number of people reaching 65 and 85 years of age is placing many more individuals at risk for sporadic Alzheimer's disease (AD) because age is a major risk factor [1]. The global prevalence of AD is projected to reach 100 million by 2050 [2]. Strategies that delay the onset by even 2 years could reduce the global projection by 23 million [2]. Diet and nutrition are reasonable and biologically plausible modes of intervention to promote healthy brain aging, but currently lack a sufficient evidence base to inform such public health practices.

A hypothetical model that describes the natural sequence in which people develop late onset or sporadic AD using biomarkers has recently been proposed [3] and beginning to be validated [4,5]. These prospective studies using clinical and biomarker data suggest disturbances in amyloid-beta (plaque) and tau-protein (tangle) metabolism in the central nervous system (CNS) as early features in people destined to develop dementia of Alzheimer type. Whereas structural changes in the cerebral cortex follow the plaque and tangle changes, and together these observations ultimately increase risk for cognitive and functional decline. These lines of evidence suggest that the plaque and tangle formation precede the cognitive decline by years and even decades [6]. However, more “upstream” factors may exist and have important “downstream” effects on these neuropathologic AD hallmarks and the ultimate clinical manifestation of dementia. Figure 1 is an attempt to capture the role of nutrition, as an environmental factor important to healthy brain aging and

AD prevention. Controlling vascular risk factors through dietary modification may complement cognitive function as well and represent yet another approach for reducing risk for AD [7]. For example, dietary effects on blood pressure and on the blood–brain barrier (BBB) (including the blood–CSF barrier and choroid plexus) may emerge as important mechanisms and therapeutic “targets” in future dementia prevention strategies.

2. Oxidative stress and Alzheimer’s disease

Oxidative stress can induce the protein and DNA damage observed on postmortem examination of brain tissue collected in AD subjects [8]. Lipid peroxidation markers in plasma are also elevated in living subjects with AD compared with age-matched controls [9]. Under conditions of oxidative stress, the highly unsaturated fatty acids in neuronal cell membranes can undergo lipid peroxidation and form reactive products with both cytotoxic and genotoxic properties that modify proteins and DNA [10,11]. Oxidative stress can interact with multiple features observed in AD pathogenesis and risk factors, including amyloid precursor protein processing, mitochondrial function, and metal accumulation [10,12,13]. Thus, a thoughtful antioxidant strategy may operate on multiple pathways in minimizing risk for AD.

3. Ascorbic acid as a potent antioxidant concentrated in the brain

Ascorbic acid (AA; vitamin C) is a remarkable water-soluble antioxidant concentrated predominately in citrus fruits, strawberries, and vegetables (*e.g.*, sweet red pepper and broccoli) and found in many supplement formulations [14]. AA is capable of donating electrons to neutralize a broad variety of free radicals and supports the regeneration of other antioxidants in biological tissues [15–17]. The CSF concentration of AA is about 3–4 times higher (~120 μ M) than plasma (~40 μ M) [18,19] and about 200 times higher in the neurons compared with plasma (~10,000 μ M) [20]. Despite the brains high demand for AA, humans are completely dependent on dietary sources. This is due to the evolutionary process leaving us a gene incapable of producing the enzyme gulonolactone oxidase needed to yield AA from glucose [21]. Thus, humans require a constant stream of AA from the diet and rely on robust “carrier” transport and “barrier” integrity mechanisms to meet the brains demand.

The major “carrier” mechanisms involve sodium-dependent vitamin C transporters (SVCT) in the gut (absorption, SVCT-1) and kidneys (retention, SVCT-1) and at the blood–CSF barrier that approximates the choroid plexus (SVCT-2) [22–26]. The glucose transporters (GLUT-1) located at the BBB may have a minor role as well [22,23]. In addition to the “carrier” mechanisms, loss of BBB integrity seen in living people of older age and with dementia may cripple the brains ability to retain the CNS AA regardless of successful transport [27–29]. Genetic variation in SVCT-1 in the gut and kidneys may be significant to keep AA readily available to the brain [30]. Perhaps, genetic variants in the SVCT-2 at the choroid plexus and neurons of humans have a significant role as well.

The level of AA that is sufficient to maintain cognitive function and favorably modify brain aging is unknown. However, its strong free radical scavenging properties, well-characterized transport mechanisms, and sheer CNS content provide a strong basis for exploring a role for promoting optimum brain function.

4. Epidemiological studies of AA intake, cognitive function, and AD

Eight large population studies have examined the relationship between the dietary intake of AA and cognitive function or AD incidence. Seven of the cohorts represent US metropolitan areas and another stems from a Dutch population. All of the studies are prospective with the

exception of one case-control analysis. The largest of these studies included 14,968 female participants of the Nurses Health Study (Table 1).

Morris et al. followed 633 dementia-free elder participants of the Chicago Healthy Aging Project for a mean of 4 years [31]. The participants were at least 65 years old and the association between AA supplementation and risk for AD was calculated. The authors used a self-reported questionnaire to assess AA supplementation and directly examined supplementation reported to reduce information bias. None of the subjects supplementing with AA developed AD. The strengths of this study are the direct inspection of the supplementation and the inclusion of a dementia-free study population. In a follow-up study in the same cohort, Morris et al. [36] examined AA dietary intake and was not able to appreciate the same reduced risk for AD. These results may imply that dietary intake of AA alone may not be neuroprotective, but doses achieved through supplementation may reduce risk for AD.

Masaki et al. [32] conducted a case-control study of 3,385 men participating in the Honolulu Asia Aging Study between the ages of 71 and 93 years old. AA intake was associated with a higher likelihood for enhanced cognitive function in the cognitively intact group, but no differences between AD and controls in AA intake were detected. This study also detected an interaction between high AA and vitamin E intake associated with lower likelihood for vascular dementia. These data suggest that AA supplementation may promote cognitive function in dementia free individuals and AA may work in concert with vitamin E to reduce the likelihood of vascular-mediated cognitive impairment.

Engelhart et al. [37] followed 5,395 men and women participants of the Rotterdam Scan Study for 6 years. One hundred and ninety-seven subjects developed dementia, including 146 with AD. Higher AA intake was associated with an 18% reduced relative risk (RR) for AD [RR 0.82, 95% confidence interval (CI) = 0.68–0.99]. This reduction was most dramatic in smokers (RR 0.58). The inclusion of dementia-free at baseline, the large sample size, and the duration of follow-up are strengths of this study. These findings suggest that the magnitude of the association AA intake and risk for AD is most dramatic in people most deplete in AA at baseline (*i.e.*, smokers).

Luchsinger et al. [38] examined 980 dementia-free men and women of the Washington Heights-Inwood Columbia Aging Project. AA intake was self-reported using a semi-quantitative food-frequency questionnaire. Two hundred and forty-two elders developed AD over a mean duration of 4 years. AA intake and supplementation were not associated with AD incidence. These findings suggest that reported AA intake and supplementation does not have a role in reducing risk for AD.

Grodstein et al. [33] examined the relationship between AA supplementation and cognitive function in 14,968 women in the Nurses Health Study between the ages of 70 and 79. This study used a self-reported questionnaire for supplementation use and telephone interview for cognitive testing. The relationship between AA and memory (immediate and delayed recall), verbal fluency, and digit span backward were null. The large sample size is a unique attribute of this study, but the impact of mild cognitive impairment to the reliability and validity of reported supplementation in the cohort is not clear and problematic. These results suggest that AA supplementation in isolation is not associated with cognitive performance.

Zandi et al. [34] studied 4,740 men and women age 65 and older in the Cache County Study cohort. Both cross-sectional and prospective analysis of self-reported AA supplementation and AD prevalence and incidence were conducted. AD was prevalent in 200 cases. Among 3,227 survivors at risk, 104 subjects developed AD over the 3-year period of follow up. AA and vitamin E supplementation in combination were associated with a reduced prevalence

(OR 0.22; 95% CI = 0.05–0.60) and incidence (RR 0.36; 95% CI = 0.09–0.99) of AD, but AA in isolation was not significant. These findings suggest that AA and vitamin E supplementation may have some synergistic effects in reducing risk for AD.

Gray et al. [35] followed 2,969 dementia-free men and women age 65 and older in the Adult Changes in Thought Study over a mean of 5.5 years. Self-reported AA supplementation and AD incidence was assessed. Over this period, 289 subjects developed AD. The authors found no association between AA supplementation (with or without vitamin E) and AD incidence. This study suggests that AA supplementation together with vitamin E or in isolation have no association with risk for AD.

In summary, the large population-based studies using self-reported measures of intake and supplementation have produced mixed results. The majority of the studies were unable to appreciate any benefit from AA intake or supplementation on risk for AD (2 positive and 6 negative). The primary limitation of these studies is the characterization of AA exposure using a self-reported questionnaire. This approach to dietary assessment has reliability and validity aspects sensitive to even mild cognitive deficits, which are frequent in older populations [39]. When the reported intake is equally misclassified in those that do and do not develop dementia, the measure of association can be attenuated running the risk of type II error. On the other hand, when the intake misclassification is different among those that do and do not develop dementia, the direction of bias in the measure of association can swing either direction (under or over-estimated risk estimate). One approach to circumvent these potential sources of measurement error is to use reliable biological markers of diet.

5. Epidemiological studies of AA status, cognitive function, and AD

Eleven studies examined the relationship between plasma AA and cognitive function. Four of these analyzed CSF AA and CSF-to-plasma AA ratio. Most of the studies are cross sectional, but two have prospective aspects. The largest of the studies included 921 subjects (Tables 2 and 3).

Goodwin et al. [40] studied 260 noninstitutionalized men and women age 60 and older to determine the relationship between nutritional status (including intake) and cognitive function. The subjects in the highest percentile of plasma AA performed best on verbal memory (delayed recall) and calculation tests. Besides the limitation of the cross-sectional design, the plasma AA concentrations were not available to compare the consistency across other studies. In a separate cross-sectional study, Gale et al. [41] examined the relationship between plasma AA and cognitive function in 921 men and women age 65 and older from England, Scotland, and Wales. Although the primary outcome was 20-year mortality, the authors detected 1.6 higher odds of cognitive impairment in elders with plasma AA under 12 $\mu\text{M/L}$ and 1.7 higher odds of cognitive impairment in those consuming less than 28 g/day of AA. These findings suggest the effects of plasma AA may be best appreciated in memory and calculation, and that plasma AA less than 12 μM or 28 g/day is a risk factor for cognitive impairment.

Perrig et al. [45] conducted a cross-sectional and prospective analysis in 442 Swiss men and women, age 65 and older (mean age 75, 312 males). In both analyses, higher plasma AA was associated with better free recall, recognition, and vocabulary, but not working memory. This association was independent of age, gender, and education. This study suggests that changes in plasma AA precede cognitive decline in community dwelling elder Swiss men and women.

6. Epidemiological studies of CSF AA, cognitive function, and AD

The CSF contains the nutrients with direct access to the brain parenchyma. This is the closest direct representation of the brain's nourishment in living subjects [26]. Three cross-sectional studies have examined CSF AA and CSF-plasma AA ratios in elders with and without AD. Another study investigated the relationship between CSF AA and longitudinal rates of decline, and interaction with BBB integrity in AD (Table 3).

The first study reviewed was a cross-sectional analysis of age and gender-matched subjects with and without a neurodegenerative disease (*e.g.*, AD and ALS) [46]. There were no differences in mean plasma, CSF, and CSF-to-plasma AA ratio between cases and controls. The authors state that all subjects were hospitalized, free of supplementation, and similar in dietary intake although the raw intake data was not provided. The inability to gain a detailed understanding of how the investigators classified cases from controls is another major limitation of this study.

The second study conducted by Quinn et al. [19], examined the cross-sectional differences in CSF and plasma AA between 10 cases with AD versus 10 healthy controls. Subjects were age and gender-matched and all cases met the NINCDS-ADRDA criteria for AD. The mean plasma AA (58 ± 42 vs. 86 ± 39 μ M) and CSF AA (207 ± 64 vs. 238 ± 48) were lower in AD subjects, but did not achieve statistical significance. However, the mean CSF-to-plasma AA ratio was significantly higher in AD compared with controls. A third cross-sectional study conducted by Glaso et al. [47], examined the mean differences between plasma and CSF AA in women with and without dementia of AD type. The cases met the Diagnostic and Statistical Manual of Mental Disorders, Third Edition–Revised criteria for dementia of AD type. The mean plasma (44 ± 25 vs. 80 ± 28 , $P = 0.002$) and CSF AA (140 ± 37 vs. 167 ± 23 , $P = 0.038$) were lower and the CSF-to-plasma AA ratio (3.3 ± 1.4 vs. 2.1 ± 0.7 , $P = 0.001$) was higher in AD versus controls. These findings were not explained by age, BMI, skin-fold measurements or meals consumed.

The final study reviewed [28] was a prospective analysis of CSF AA, rates of cognitive decline, and BBB function over 1 year in 32 subjects with mild to moderate AD. Neither plasma nor CSF AA predicted rates of decline. However, a higher CSF-to-plasma AA ratio was associated with a slower rate of decline. The relationship between CSF AA ratio and rate of decline was attenuated when CSF Albumin Index (a validated measure of BBB integrity) was added to the regression model. These findings suggest that maintenance of high CSF-to-plasma AA ratio may be important to preventing cognitive decline in AD and that BBB impairment unfavorably alters this ratio. This study was unable to distinguish whether “carrier” mechanisms for AA (*i.e.*, SVCT-2) were disturbed as well as the integrity of the BBB because the CSF albumin index reflects only barrier disturbances to our knowledge. How much of this barrier impairment is also accompanied by carrier dysfunction is one area for future research pursuits.

7. Animal studies of ascorbic acid, behavior, and neuropathology

AA is clearly concentrated in the human brain; however, the mechanisms by which AA affects cognitive function and neurodegeneration are not entirely clear. Three animal studies have attempted to elucidate some of the biological mechanisms.

Murakami et al. [48] conducted a study in APP transgenic mice. They show that AA administration attenuates A β oligomerization, but not the total volume of A β plaques. This implies that AA affects A β peptide formation to oligomers, but not the final fertilization of the plaques in the extracellular space. Although somewhat difficult to interpret, these observations may be explained by the ability of these mice to retain AA through *de novo*

synthesis. This stream of AA might be adequate to delay the accumulation of the plaques and may require longer study duration to appreciate significant plaque accumulation. Rodents deplete in AA may be incapable of halting the later stages of the amyloid cascade, because they would represent human primates unable to synthesize any AA.

Harrison et al. [49] studied APP/PSEN1 and wild type mice at middle and very old age to test the hypothesis that short-term high-dose AA infusion (125 mg/kg) affects behavior. Both the wild type and APP/PSEN1 mice treated with AA had better Y-maze alternation rates and swim accuracy in the water maze (markers of spatial learning and memory). These effects were independent of any long-term effects on lipid peroxidation, acetylcholine esterase activity, and neuropathological hallmarks of AD. In another study by the same group [50], the authors crossed APP/PSEN1 transgenic mice with gulonolactone oxidase knockout mice to replicate more closely the human condition. Experimental mice were maintained on 0.33 g/L or 0.099 g/L of AA from week 6 of age to assess for changes in behavior and neuropathology. Long-term AA decreased the altered locomotion habituation and increased omission errors in the Barnes maze in the transgenic mice. The authors interpret their findings as indicative of an interaction between AA and the cholinergic system. These findings need to be confirmed.

8. Summary of ascorbic acid studies

The literature implicating AA in the promotion of cognitive function and prevention of AD remains controversial. The large prospective studies of dietary intake and supplementation are predominantly negative, but difficult to form firm conclusions because they rely on subjective measures of AA. The studies of plasma AA are mostly positive, but limited by the cross-sectional design. For example, lower plasma AA in a dementia subject could be explained by changes in diet after the dementing illness has set in. Most of the plasma AA studies controlled for dietary intake, but these measures have the same limitations experienced by the large prospective studies of AA intake. Some of the studies did provide more objective measures of potential confounders, but without a prospective analysis the inferences for causality remain futile.

A synopsis of the literature provides some fabric of notable consistency: 1) Plasma AA is apparently lower in AD compared with controls and does not appear to be explained by age, gender, BMI, or diet, 2) CSF AA may be moderately lower and the CSF-to-plasma AA ratio higher in AD, but only the CSF-to-plasma AA ratio appears to predict cognitive decline over 1 year in mild-to-moderate AD. BBB impairment may cripple that brain's ability to retain a high CSF-to-plasma AA ratio regardless of the robust “carrier” mechanisms in place for AA.

Together, these findings suggest an AA “sink” hypothesis in AD—where the brain draws upon the peripheral pools of AA at all cost to shore the antioxidant capacity of the CNS to battle the oxidative stress seen in AD. Factors that affect the brain's ability to achieve this innate demand for AA may be important considerations for future research (*e.g.*, intake, carrier, and barrier mechanisms).

9. Future direction

To verify a “sink” hypothesis and substantiate a significant role for AA in promoting brain health, large prospective studies using plasma and CSF AA as predictors of cognitive decline should be conducted (Fig. 1). This could be achieved by taking advantage of existing clinical datasets with the appropriate measures to reasonably assess a role for AA in maintaining brain health. The analysis of plasma, CSF, and DNA in dementia-free elders or AD would permit studies of a putative interaction between tissue AA, cognitive decline, and “carrier” and “barrier” mechanisms at the blood-CSF and BBBs. Neuroimaging measures

may be a useful alternative to lumbar puncture for CSF analysis and may offer new insights into structural, metabolic, or connectivity mechanisms for which AA plays a significant role.

Animal studies might consider data-driven analysis of the proteome and metabolome to identify novel mechanisms of action for AA related to brain function. For example, the gulonolactone oxidase knockout mice used by Harrison et al. [50] would reflect the metabolic profile of animals depleted in AA. That information may help confirm and generate novel mechanisms of action for AA in the CNS.

In summary the priorities for future research in this area include: 1) Prospective studies of the association of CSF and plasma AA with rates of cognitive decline/brain atrophy in elders with and without AD, and 2) exploratory studies of CSF and plasma AA, CSF albumin index, and SVCT-2 SNPs to examine “barrier” and “carrier” mechanisms for AA in elders destined to develop AD.

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Fig. 1.

Hypothetical framework for nutrition and brain aging research. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Epidemiological studies of ascorbic acid intake, cognitive function, and Alzheimer's disease

Cohort and authors	Study sample	Design and methods	Conclusion
Chicago Healthy Aging Project [31]	633 dementia-free Men/women Age 65 years Mean duration of follow up 4.3 years	Prospective Self-reported and direct inspection of AA supplementation AD incidence	AA supplementation associated with lower AD incidence compared with nonusers
Honolulu Asia Aging Study [32]	3,385 men Age 71–93 years	Case-control Self-reported supplementation	AA supplementation associated with higher likelihood for superior cognitive function in the cognitively intact subset (OR 1.25, 95% CI = 1.04–1.50) AA supplementation not associated with likelihood for AD
Nurses Health Study [33]	2,999 NIE 47 AD, 35 VD, 50 mixed/other dementia, 254 low cognitive function without dementia 14,968 women Age range 70–79 years	Cognitive abilities screening instrument Prospective Self-reported supplementation Cognitive battery by telephone	AA supplementation not associated with cognitive parameters.
The Cache County Study [34]	4,740 men/women Mean age 75 years	Cross sectional and prospective Self-reported supplementation AD incidence	AA supplementation not associated with AD prevalence or incidence
Adult changes in thought study [35]	2,969 dementia-free men/women Age 65 years followed for 5.5 years	Prospective Self-reported supplementation AD incidence	AA supplementation not associated with AD incidence or all cause dementia
Chicago healthy aging project [36]	815 dementia-free, men/women Age 65 Mean duration of follow up 3.9 years	Prospective Self-reported intake AD incidence	AA intake was not associated with AD incidence
Rotterdam scan study [37]	5,395 dementia-free men/women age 55 years Mean duration of follow up 6 years 197 developed dementia (146 AD)	Prospective Self-reported intake AD incidence	AA intake was associated with reduced risk for AD (RR 0.82, 95% CI = 0.68–0.99); more dramatic in smokers RR 0.58 (95% CI: 0.30–1.12)
Washington heights-inwood Columbia aging project [38]	980 dementia free men/women Mean duration of follow up 4 years Mean age 75 years 242 developed AD	Prospective Self-reported intake AD incidence	AA intake and supplementation not associated with AD incidence

AD, Alzheimer's disease; VD, vascular dementia; NIE, nonimpaired elders; AA, ascorbic acid; OR, odds ratio; RR, relative risk; CI, confidence interval.

Table 2

Epidemiological studies of ascorbic acid status in dementia and nonimpaired elders (NIE)

Authors	Sample	Design and methods	Conclusion
Goodwin et al. [40]	260 dementia-free men/women Age 60 years Community-dwelling	Cross sectional Plasma, 3-day diet recall Halstead-Reitan categories Test, WMS-R delayed	Plasma AA associated with higher verbal memory; elders in the 90th percentile of plasma AA had better calculating ability and delayed recall
Gale et al. [41]	921 men/women Age 65 years English-Scottish-Welsh	Cross sectional Plasma Hodkinson test	Plasma AA 11.91 μ M was associated with 1.6 higher odds of cognitive impairment (95% CI: 1.1–2.3). Less than 27 mg of AA intake per day was associated with 1.7 higher odds for impairment
Riviere et al. [42]	19 Ctls MMSE 24–30 20 severe AD MMSE 0–9 24 mod AD MMSE 10–23	Cross sectional Plasma Mini-nutritional assessment	Plasma AA was incrementally lower by degree of cognitive impairment in AD, this observation was not explained by lower intake of AA
Charlton et al. [43]	93 men/women 50 Ctls 43 dementia Age 65	Cross sectional Plasma Mini-nutritional assessment	Plasma AA was lower in subjects with dementia compared with controls, this observation was not explained by lower intake of AA
Polidori and Mecocci [9]	75 women 40 Ctls (85.4 $\pm$ 4.4 years) 35 AD (85.9 $\pm$ 5.5 years) Age-matched Mean age 85 years	Cross sectional Plasma NINCDS-ADRDA criteria	Plasma AA was lower in AD than controls (18 $\pm$ 6 μ M vs. 36 $\pm$ 6, P < 0.001) AD subjects had increased plasma lipid peroxidation and less resistance to peroxy-radical
Polidori et al. [44]	141 55 Ctls 63 AD 23 VD	Cross sectional Plasma	Plasma AA was lower in AD and VD versus NIE, no differences between AD and VD
Perrig et al. [45]	442 men/women (n = 312/132) Community-dwelling Age 65 (mean 75)	Prospective, cross sectional Plasma Memory, WAIS-R vocabulary test	Plasma AA in 1971 associated with better cognitive performance in 1993; plasma AA associated with better free recall, recognition, and vocabulary, but not priming and working-memory in cross-sectional analysis

AD, Alzheimer's disease; VD, vascular dementia; Ctls, control subjects; NIE, nonimpaired elders; AA, ascorbic acid; MMSE, mini-mental state exam (Folstein); NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; WAIS-R, Wechsler Adult Intelligence Scale—revised.

Epidemiological studies of CSF ascorbic acid, cognitive function, and Alzheimer's disease^a

Table 3

Authors	Sample and design	Plasma (μM)		CSF (μM)		Ratio		Conclusion
		Ctls	AD	Ctlxx	AD	Ctls	AD	
Puraskavas et al. [46]	32 15 Ctls (58 ± 12 years) 17 AD (62 ± 7 years) Men/women Age-gender matched Cross sectional	43 ± 13	45 ± 19	166 ± 45	156 ± 38	3.6 ± 0.5	4.1 ± 1.6	No differences between cases and controls
Quinn et al. [19]	20 10 Ctls (MMSE 29 ± 1), 10 AD (MMSE 19 ± 7) Age-gender matched Mean age 66 years Cross sectional	86 ± 39	58 ± 42	238 ± 48	207 ± 64	3.1 ± 1.1	5.0 ± 2.6	CSF: plasma AA ratio higher in AD ($P = 0.048$). Mean plasma and CSF AA were lower in AD (not statistically significant).
Glaso et al. [47]	38 18 Ctls (MMSE 27), 20 AD (MMSE 16) Women Age-matched (75–85 years) Cross sectional	80 ± 28	44 ± 25	167 ± 23	140 ± 37	2.1 ± 0.7	3.3 ± 1.4	CSF: serum ratio higher in AD versus controls ($P = 0.001$) and plasma ($P = 0.002$) and CSF ($P = 0.038$) were lower in AD. All subjects were well-nourished and without vascular disease
Bowman et al. [28]	32 AD (MMSE 19 ± 5) Men/women Mean age 71 years Prospective		41 ± 30		129 ± 52		4.0 ± 1.6	Higher CSF: plasma AA ratio associated with slower cognitive decline over 1 year (age, gender, education, apoE4, and cognitive function at baseline adjusted $P = 0.025$). Interaction between CSF AA ratio and BBB integrity identified

Ctls, control subjects; AD, Alzheimer's disease subjects; MMSE, mini-mental state exam.

^aTotal of 79 AD and 43 controls with CSF AA analysis.