Epidemiology of Alzheimer's Disease: Quantity, Location, Causes, Mechanisms and Intervention/Prevention

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RESUMO

A transição epidemiológica se processa nas diferentes regiões do planeta, envelhecendo as populações. A média de vida aumentará em 5 anos nos países desenvolvildos, e em 10 anos nos países em desenvolvimento. Projeta-se um aumento de 3 vezes nos casos de Alzheimer em países desenvolvidos, e de 8 vezes nos países em desenvolvimento, como o Brasil. Esse artigo utiliza as rúbricas da epidemiologia, proposta por Anthony, como referencial para explorar os diferentes aspectos da distribuição da doença de Alzheimer nas populações humanas. As rúbricas são: quantidade, localização, causas e mecanismos, e intervenções e prevenção. Para cada rúbrica direções futuras para a pesquisa em Alzheimer são apresentadas.

ABSTRACT

The epidemiological transition is unfolding in with different pace in different regions of the globe. The average life span will increase by 5 years in developed economies and by 10 years in developing economies. According to projections the number of Alzheimer's cases will increase by almost 3 times in developed economies, and by 8 times in developing economies, like Brazil. This paper uses the rubrics of epidemiology, as proposed by Anthony, to organize the exploration of different aspects of the distribution of Alzheimer Disease in human populations. The rubrics are: quantity, location, causes and mechanisms, and interventions and prevention. For each rubric future directions are presented in the study of Alzheimer Disease.

INTRODUCTION

Public Health Impact

• Because Alzheimer's disease is a disease of the elderly, prevalence of AD is most affected by increasing life spans.

• The average life span is expected to increase by 5 yrs in more developed countries, and 10 years in less developed countries over the next 50 years.

• This will lead to a profound increase in the number of elderly (especially in the less developed countries) resulting in a 2.7 fold and 8 fold increase in demented individuals in more and less developed countries respectively.

	more developed countries		less developed countries	
year	2000	2050	2000	2050
avg life span	75.3	80.8	65.1	75.5
numbers >65 (in millions)	169	287	245	1132
number demented (in millions)	13.5	36.7	8.5	67.9

Table 1: Expected changes in average life span, and numbers of elderly and demented individuals from 2000 to 2050 in more and less developed nations by UN projections.

QUANTITY

• Reported incidence and prevalence of AD varies in published reports. Methodological difficulties and differing diagnosis criteria, screening methods and thresholds for a definition of a 'case' have been identified as reasons for differences in reported prevalence and incidence of AD (Suh & Shah, 2001).

• In the Baltimore Longitudinal Study of Aging (BLSA), using a neuropsychological clinical assessment, a crude incidence rate of 1.23% per year was observed in participants over the age of 55 (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000). The incidence rates increased from .08% in the 60-64 age group to 6.84% in the 85+ age group, indicating that incidence increases rapidly with age. Logistic regression analyses revealed that the incidence rate of AD in the BLSA doubled approximately every 4.4 years.

• Using a unique stratification method, Hy, & Keller (2000) examined the prevalence of AD in whites by level of disease severity in 21 European and North American studies. Severity of disease has been suggested as a reason for differences in prevalence rates across studies (Corrada, Brookmeyer, & Kawas, 1995; Jorm, Korten, & Henderson, 1987). They found that when disease severity was included in the models much of the variability in incidence rates was accounted for.

• Miech et al. (2002) examined incidence of AD in the Cache County Study, which is known for its sample that ranges well into the oldest old population with participants over the age of 93. For the entire sample (aged 65-93+, the incidence rate of AD (measured using the MMSE, Dementia Questionnaire, and a standardized clinical assessment) and was estimated to be 16.81 (per 1,000 person years). This estimate is higher than usual AD incidence rates because of the wide age range of the sample and increasing incidence rates of AD with increasing age.

• In an attempt to examine the relationship between cardiovascular and cerebrovascular and the incidence of AD in an African American, Hispanic and Caucasian sample Tang et al. (2001) found an overall incidence of 3.0% per person year. See 'Location' section for ethnicity comparisons.

Summary and Future Directions in Quantity

• Because of the great degree of variability in incidence and prevalence rates, likely due in part to varying diagnostic criteria and assessment tools,

nationally and internationally normed measurement batteries and diagnostic criteria are important to decide upon. Such agreement will enable researchers and policy makers to effectively compare large-scale studies.

• More longitudinal prospective epidemiology studies needed to determine antecedents of Alzheimer's Disease.

• Need to distinguish between prospective studies examining incidence, and thus risk and protective factors, from those of prevalence in where correlates may represent associations with length of illness rather than age of onset or vulnerability.

• Examination of prevalence and especially incidence by demographic stratum including severity of diagnosed disease, race, age, education, religion, and region. Some of this work has been done, but little that has combined methods and utilized consistent diagnostic criteria.

LOCATION

Age

• Results from the BLSA (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000) report a trend for women to have higher incidence rates of AD than men (1.43% per year vs. 1.12%, respectively). Logistic regression results, adjusted for age and education, indicated that the odds of developing AD was 10% in women than in men.

• The Canadian Study of Health and Aging reported age-specific incidence rates of AD in their Canadian sample (2000). The rates show an approximate doubling of incidence every five years of age. Age-specific rates were estimated per 1,000 person years and were:

65-69 years: 1.4 (0.1 – 3.3)
70-74 years: 2.9 (1.3 - 4.6)
74-79 years: 4.8 (2.6 – 6.9)
80-84 years: 19.0 (14.5 – 23.5)
85+ years: 49.0 (40.7 – 57.2)

• Tang et al. (2001) examined age specific incidence rates of AD in a sample of African-American, Hispanic, and Caucasians. They found that, in all three ethnic groups, the incidence of AD increased with age. Overall age-specific incidence rates were: 1.3% per person year between the ages of 65 and 74, 4.0% per person year between the ages of 75 and 84, and 7.9% per person year for ages 85 and older.

• Neumann et al. (2001) examined transitional probabilities of stage progression in AD in relation to age of patient. They found that older age groups (aged 66+) had lower probabilities of state-to-stage transitions but had higher ratios for mortality and stage-to-nursing home transitions. These results indicate that younger age is associated with more moderate to severe stage of disease transition in the absence of nursing home placement or death but that older age is associated with more severe stage progressions (into nursing home residence or to death).

Gender

• The incidence of AD was found to differ by gender across age ranges in the Cache County study (Miech, et al., 2002). Miech and his colleagues found that although there were gender differences in incidence rates of AD across all ages investigated, sex-differences varied with age. Small, but significant, gender differences were seen before age 80. However, in the oldest old, aged 85 and older, the incidence of AD was higher in women than in men.

• Miech, et al. (2002) also found a decline in the incidence of AD for men and women in extremely old age. Moreover, incidence rates began to decline at different ages by sex. Incidence rates begin to decline for men earlier (at age 93) than for women (age 97). Overall, after age 85 the incidence rate for dementia was twice as high in women as in men.

• The Canadian Study of Health and Aging examined incidence rates of AD by gender in Canada (2000). Consistent with previous findings, they found that overall age-standardized incidence rates varied significantly by gender. Women had an incidence rate of 21.8 per 1,000 person years while men had a rate of 19.1 per 1,000 person years.

• Hy and Keller (2000) examined gender differences in prevalence rates of AD among whites. They found gender differences, favoring women, only when the disease was classified as moderate or severe. When the AD was classified as questionable or mild, prevalence rates were higher among men, a finding that is in contrast to a majority of the work examining gender differences in AD. These results suggest that men may not live long enough to enter the more severe stages of AD and thus gender comparisons favoring women may be accounted for by shorter life expectancies in males.

• Ganguli et al. (1999) found 10-year incidence rates of AD to be 1.3 times higher in men than women in their sample of rural elders. Similar to Hy and Keller (2000), Ganguli and her colleagues (1999) examined gender differences in the 10-year incidence of AD by severity of diagnosis. Ganguli et al. found non-significant gender differences when examining more severe AD (CDR = .5) and higher rates among men in cases where disease severity was high (CDR >= 1). These results by disease severity suggest that gender difference in the overall sample can be accounted for by severity subgroup.

• Neumann et al. (2001) examined the transitional probabilities for stage-to-stage disease transitions as well as state-to-death and stage-to-nursing home placement transitions in relation to a number of covariates, including gender.

• Results showed that disease progression was faster in men than women. In an aged controlled analysis, men were 1.6 times more likely to transition from a mild to a moderate stage of disease, and were significantly more likely to die at all three stages of the disease (mild, moderate, and severe).

Education

• The BLSA also examined the relationship between education and odds of developing AD. Logistic regression analyses, adjusted for age and gender, revealed that the odds of developing AD were 27% less for participants with some college education and 36% less for participants with some graduate school compared to participants with a high school education or less.

• Ganguli et al. (1999) examined the association between education and ten-year incidence rates of AD by severity of disease (CDR classification) in a rural US sample. They found that participants with less than a high school education had incidence rates 1.5 times as high as those with more education for moderate AD (CDR = .5), adjusted for age and gender. Education was not significantly associated with incidence of more severe AD (CDR >= 1). There were also no significant interactions between gender and education in either of the disease severity models.

Ethnicity

• Gurland, et al. (1999) examined the prevalence of AD among African-Americans, Hispanics, and Caucasians in a case registry probability sample. They found higher prevalence rates among African Americans and Hispanics compared to Caucasians.

• Tang et al. (2001) examined the incidence of AD in African Americans, Hispanics, and Caucasians in a 7-year longitudinal study. The overall incidence rate for white individuals was 1.9% per person year, 4.2% per person year for African-Americans, and 3.7% in Hispanics (Figure 1). All incidence rates were controlled for age, education, gender, and health status.

• A typical confounder in the relationship between race and AD incidence in the US is the presence of

cerebrovascular and cardiovascular disease. Because ethnic differences in these health conditions have been identified, ethnicity comparisons require examination of incidence rates by differential health statuses. Tang and his colleagues (2001) examined the association between clinically apparent cerebrovascular and cardiovascular disease and incident AD in a sample of African Americans, Hispanics, and Caucasians. Interestingly, they found that neither disease contributed to the increased risk of disease in the three ethnic groups.

diagnostic criteria, and cultural norms preventing true reports of incidence and prevalence of AD (Chandra, Ganguli & Pandav, 1998).

· The Indo-US Study compared incidence rates of AD in rural, population-based, studies in India and the US (Chandra, Pandav, Dodge, Johnson, Belle, DeKosky, & Ganguli, 2001). This group developed a rigorous process to assure comparability of assessment methods used in India and rural US. They found the crude incidence rate of 1.74 (per 1000 person years) in participants in India over the

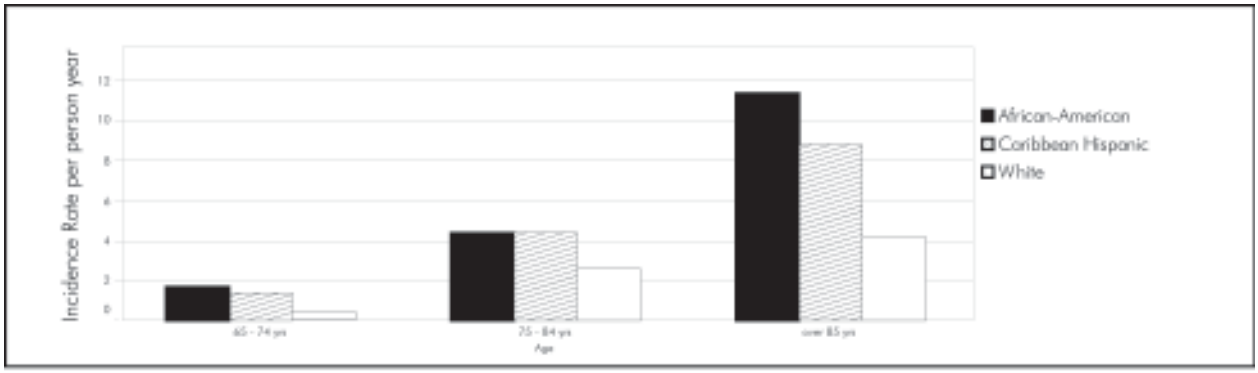

Figure 1. *Annual age-specific rates for AD among African-Americans, Caribbean Hispanics, and White elderly*

• Cross-national comparisons of prevalence of AD have often examined prevalence and incidence trends of AD in comparison to vascular dementia (VaD). Wide variability in the reported prevalence of both AD and VaD have lead to numerous epidemiological investigations of transition in dementia.

• A Western trend in the transition of higher rates of VaD to higher rates of AD over the past decade has also been identified in cross-cultural comparison studies in Far Eastern countries (Korea, Japan, & China; Li, Shen, & Chen, 1989, Shibayama, Kashara, & Kobayashi, 1986, Suh & Shah, 2001), Africa (Hendrie, Osuntokun, & Hall, 1995) and Canada (McDowell, et. l., 2000).

• Cross-national studies have also offered reasons for differing prevalence and incidence rates in various nations including: differing age structures and life expectancies across nations, differing age of 55. Comparing rates, standardized to the age distribution of the 1990 US Census, cross-culturally, the incidence of AD in India in participants over the age of 65 was 4.7 (per 1000 person years), substantially lower than the rate in the US of 17.5. These findings for the US are consistent with previous studies reporting the prevalence of dementia in Western Populations to be approximately 5% and the incidence to be 1% per year in persons aged >65 years (Kukull & Ganguli, 2000).

Future Directions in Location

• Examination of incidence and prevalence by severity of disease. Studies that have begun to adapt this approach (Hy & Keller, 2000; Ganguli, et al., 1999) have found differing prevalence rates and correlates in the different severity groups. These results indicate the need to further examine this variable in the location and quantity of AD.

In addition differing rates and correlates, studies of severity have reported contrasting findings highlighting the need for further investigation.

• Further employment of latent transition analysis, inducing demographic and disease severity and stage covariates, is important to elucidate the trajectory of AD progression overtime. In addition, an LTA approach may be useful for the development and evaluation of intervention and prevention efforts similar to efforts currently underway in drug and addiction research (Collins, Graham, Fidler, & Hansen, 1994).

• Long-standing gender differences in incidence and prevalence of AD have begun to be questioned with recent work (Hy & Keller, 2000; Miech, et al, 2002) suggesting that gender differences in AD may vary by age and disease severity. Findings for higher rates of AD in men only at younger ages and in earlier, less severe, stages of the disease suggest that differences in life expectancies between men and women may be responsible for many of the gender differences seen in earlier work and studies examining overall cohorts of older adults rather than age or disease severity stratified samples. Further work is needed to confirm recent findings and to extend this work to more fully describe the cross-over effects in gender differences in AD rates.

CAUSE AND MECHANISMS

Risk Factors/ Suspected Causes

Genetics

Early onset AD

• Although early onset familial form (FAD) only accounts for a small percentage of those with the disease, the discovery of the genes that cause the disease in these families has allowed for the generation of animal models. Because of this, tremendous strides in neuroscience have been made in understanding the progression of the disease.

• Only about 5% of those with Alzheimer's disease have the familial autosomal dominant form. They usually show symptoms before age 65 (Cruts et al., 1998)

• The 3 mutations that have been discovered and are widely corroborated are: APP on chromosome 21, presenlin 1 (PS1) on chromsome 14 and presenilin 2 (PS2) on chromosome 1.

• Mutations in the b-amyloid precursor protein (APP) comprise less than 0.1%, while presenilin (PS) mutations comprise 6% (PS-1) and 1% (PS-2) of familial early onset Alzheimer's disease (Selkoe, 1999).

Late onset

• Late onset AD accounts for 90-95% of all cases (Tol et al., 1999). The most widespread genetic risk currently known is the APOE genotype, which accounts for 17% of the late onset cases (Tol et al., 1999).

• Those with at least 1 APOE4 allele have a 25-40% chance of developing the disease (Mayeux, 1999), and the APOE2 allele is reported by some to have a protective effect (Saunders et al., 1993).

· The Cache County workgroup has shown that the more APOE4 alleles, the earlier the onset of AD. They also showed that if a person remains disease free by age 95, they are unlikely to get the disease. This paper refutes the idea that APOE4 increases the risk of the disease and says that instead, it lowers the onset of AD (Meyer et al., 1998).

• The susceptibility of a person with an APOE4 allele also varies with other factors such as Downs syndrome (Schupf et al., 1996), head injury (Mayeux et al., 1995), or NSAID (non-steroidal anti-inflammatory drug) usage (Breitner et al., 1995).

Other candidate genes

• Other possible genes that have found to be linked to late onset AD include the a2-macroglobulin (Blacker et al., 1998; Liao et al., 1998; Myllykangas et al., 1999), HLA-A2 allele (Payami et al., 1997),

VLDL-R, a-1-antichymotrypsin and LRP-1. However, the association of these genes with AD has not been confirmed consistently across different studies.

Genetic Mechanisms

Mechanisms of Ab

• All of the gene mutations known to be linked to early onset AD are associated with the processing of the amyloid precursor protein (APP) into Ab.

• APP is a transmembrane protein which is normally cleaved by a-secretase to release soluble APP, or the b- and g-secretase to generate Ab (Figure 2) (DeKosky, 2001; Selkoe, 1999).

• All of the known mutations in APP that are responsible for the Alzheimer's phenotype are located near the a, b or g-secretase sites, and no other APP mutations have been found that are associated with AD.

• Ab is generated into either a 40 (Ab_{40}) or 42 (Ab_{42}) amino acid peptide, of which the former represents about 90% of the secreted peptide (Selkoe, 1999).

• APP mutations generated in mice and found in humans are both found to increase levels of Ab_{42}.

• In humans, presenilin mutations result in an increased secretion of Ab_{42} (Scheuner et al., 1996). Presenilin 1 directly regulates g-secretase activity, and may even be the enzyme itself (Haass and De Strooper, 1999).

• Ab_{42} has been shown to aggregate far more rapidly than Ab_{40} into amyloid fibrils, which are the basis for formation of amyloid plaques (Jarrett et al., 1993).

• Most of the strains of transgenic mice that express the FAD mutant APP or overexpress APP, not only have an increased AB_{42} load and plaques, but also have reactive astrocytosis, changes in neuronal morphology or number, and/or have learning deficits (Seabrook and Rosahl, 1999).

Mechanisms of APOE

• APOE redistributes cholesterol, promoting the formation of membranes, sprouting and regeneration (Vickers et al., 2000)

• High plasma cholesterol is correlated with increased b-amyloid deposition in the human brain. In transgenic AD mice, high cholesterol increases b-amyloid production (Poirier, 2000).

• APOE knockout mice have significantly less synaptic remodeling after injury than controls (Fagan et al., 1998), and reintroduction of APOE3 and APOE4 in the knockout mice drastically reduces synaptic loss and improves cognitive functioning (Poirier, 2000).

• Poirier thinks that APOE normally acts as a scavenger for aggregated Ab (Poirier, 2000). APOE4 supposedly has a higher affinity (than other APOE isoforms) for b-amyloid 4 peptide and thus transports Ab into brain cells (Nemetz et al., 1999; Nicoll et al., 1995; Poirier et al., 1993).

• APOE4 subjects had less APOE and increased levels of b-amyloid aggregation than non-apoE4 AD patients (Beffert et al., 1999).

• APOE3 may also be protective in the formation of tangles. APOE3 has been shown to bind and stabilize microtubules more efficiently than APOE4.

• APOE4 is not as good an antioxidant as APOE3 or 2 (Miyata and Smith, 1996).

• Alzheimer's patients with the APOE4 allele showed a loss of neurons that express acetylcholinesterase (required for local synthesis of acetylcholine which is depleted in AD patients – See drug interventions below) compared to other AD patients (Guenette and Tanzi, 1999).

Future directions in genetics

• There are more genes to be found for both the early onset and late sporadic form of AD. It may be wise to target specific proteins, like the complement proteins and PPARg, as well as proteins involved in regeneration of synapses, and lipid transport in the CNS. More work needs to be done to clear up the discrepancies in genetic associations already found.

Down Syndrome

• Those with trisomy 21 (Down's syndrome) inevitably develop Alzheimer's disease if they live to the age of 40 (Mann and Esiri, 1989).

• The APP gene on chromosome 21 is thought to be responsible for the early appearance of Ab_{42} in their teens. The pathological progression of Down's syndrome is thought by many to be similar to the sequence seen in conventional AD (Selkoe, 1999).

• Meta-analysis also shows significant increase in association of APOE4 (vs. other alleles) and AD in adults with Down syndrome (Deb et al., 2000).

• There is an increased frequency of Down syndrome births in families with AD, and increased frequency of AD with Down syndrome probands. (van Duijn et al., 1991; Yatham et al., 1988)

• Mayeux found a statistically significant increase in AD of mothers who bore Down syndrome children before age 35, but not with mothers who bore Down syndrome children later in life. After 35, the risk of bearing a child with Down syndrome increases with increasing age, but bearing a child with Down's syndrome before then suggests a genetic susceptibility of non-disjunction of chromosome 21 (Schupf et al., 2001).

Cholesterol

• A cross sectional study from Rotterdam showed higher odds of AD with higher severity of arteriosclerosis. Furthermore the odds increased with increasing number of APOE4 alleles (Hofman et al., 1997).

• A couple of cross sectional studies show decreases in serum cholesterol or HDL levels in AD patients (Hoshino et al., 2002; Siest et al., 2000).

• However two prospective studies showed that those with higher total cholesterol or HDL levels in later life had an increasing risk of AD (Kivipelto et al., 2001; Launer et al., 2001). Furthermore, the study by Launer et al. showed that levels of HDL cholesterol correlated with increasing number of neuritic plaques and tangles (Launer et al., 2001).

• HMG-CoA reductase is the rate-controlling enzyme for the synthesis of cholesterol. A cross sectional study showed a significantly reduced risk of AD for those who took the HMG-CoA reductase inhibitors lovastatin and pravastatin, but not simvastatin (Wolozin et al., 2000).

· These studies suggest that increasing levels of cholesterol increase the risk of AD, and that cholesterol levels may drop after onset of the disease.

Mechanism of Cholesterol

• APOE is involved in redistributing cholesterol in the brain from regions of high to low cholesterol (Mahley, 1988).

• Cholesterol is an essential in membrane compartmentalization. Studies show that generation of the amyloidogenic Ab occurs in cholesterol rich areas of the membrane, whereas non-amyloidogenic Ab is created in areas of the membrane with less cholesterol (Figure 3) (Lee et al., 1998; Simons et al., 1998).

• APOE4 allele is associated with higher cholesterol levels (Isbir et al., 2001; Sing and Davignon, 1985). APOE2 and 3 are better at removing cholesterol from membranes than APOE4 (Michikawa et al., 2000). Thus APOE4 patients probably synthesize more Ab due to increased levels of cholesterol in their membranes (Simons et al., 2001).

Future directions for Cholesterol

• It would be of benefit to do a prospective study that looked to see if increases in cholesterol increased the risk of AD, and if cholesterol levels subsequently dropped after clinical expression of the disease. This should help clarify the discrepancies in findings between the prospective and case control studies.

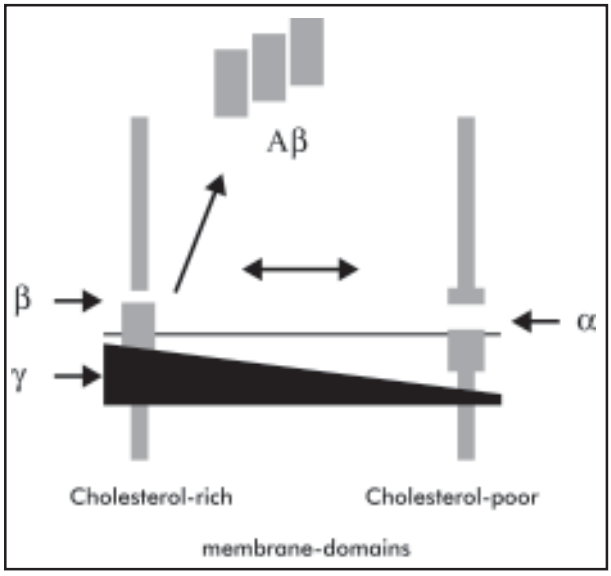

Figure 2. Generation of amyloidogenic Ab occurs in cholesterol-rich regions of the membrane.

Homocysteine, folate and B12

• Plasma total homocysteine is a major cardiovascular risk factor, which can be lowered by supplementation with folic acid.

• A case control study showed that while homocysteine blood levels were significantly higher, folate and vitamin B12 were significantly lower in AD patients than controls (Clarke et al., 1998).

• Framingham longitudinal study showed that elevated homocysteine levels measured 8 yrs prior to development of disease, still increased the risk of AD. This demonstrated that elevated levels were not due to poor nutrition after onset of the disease (Seshadri et al., 2002).

• Mechanism: Homocysteine binds NMDA receptors, inducing influx of Ca^{+2}, and increasing oxidative stress. Ho et al. found that homocysteine enhances Ab- induced excitotoxic cell death, and that the anti-oxidant vitamin E blocks the effect.

Future directions for Homocysteine, folate and B12

• Perform an epidemiological study looking at people that take vitamin E supplements and other anti-oxidants, and have elevated homocysteine levels, and ascertain if their risk of AD is lower than others with elevated homocysteine levels.

Head Injury

Case-control studies:

• Although individual studies don't have enough power, Mortimer et al . (Mortimer, 1995; Mortimer et al., 1991) did meta-analysis and found highly statistical association with case-control studies after controlling for other risk factors. (Lye and Shores, 2000)

• Some studies have looked at association with APOE4. Mayeux found that people with at least 1 APOE4 allele had a 10x increase risk of AD! (Mayeux et al., 1995) Yet another paper found a greater association of head injury and AD for those without the APOE4 allele. (Guo et al., 2000)

Cohort studies – more inconsistent

• One showed that increased risk of AD if had loss of consciousness for 5 minutes or more. (Schofield et al., 1997)

• Recent cohort study found greater AD with moderate and severe head injury (defined by loss of consciousness or post-traumatic amnesia for > 30 min and or skull fracture). They found a non-significant increase w/APOE4. (Plassman et al., 2000)

• Another showed that with traumatic brain injury, there was no greater risk of AD, but an earlier onset (Nemetz et al., 1999).

• Weiner et al. (longitudinal cohort) looked at a variety of risk factors to determine if they differed by APOE status. They did not find significant increases in AD for APOE4 individuals with head injury (Weiner et al., 1999).

• The Rotterdam study found no increase in risk of AD with head injury, nor did it change with APOE4 status. Head injury was assessed by self-report, and they recorded the duration of unconsciousness, the number of head traumas and time since injury.

(Mehta et al., 1999)

Mechanism of Head Injury

• There are many similar neuropathological characteristics between dementia pugilistica (dementia caused by brain injury) and AD. They both have neurofibrillary tangles (Allsop et al., 1990; Roberts, 1988) and although dementia pugilistica doesn't have classical AD plaques, like AD, it does have diffuse b-amyloid plaques with substantial tangle formation (Roberts et al., 1990).

• One third of individuals dying after severe brain injury had cortical b-amyolid deposits post mortem, vs. controls (Roberts et al., 1994).

• There is good biological plausibility for an association of head injury with APOE4:

• Jordan looked at 30 boxers. He found that the amount of exposure to boxing was associated with a higher chronic brain injury (CBI) score (measures neurological and behavioral outcomes – the higher the score, the more brain injury). Within the high exposure group, CBI scores were significantly higher for those with APOE4 (Jordan et al., 1997).

• APOE is responsible for cholesterol and lipid transport which is necessary for dendritic remodeling and synaptogenesis (Poirier, 1994). There are isoform specific differences in synaptic repair, remodeling and regeneration. APOE4 AD patients have less dendritic arborization (Arendt et al., 1997), and people with APOE4 have lower concentrations of APOE (Poirier and Sevigny, 1998). Thus those with APOE4 are less able to recover from any injury (ie. traumatic brain injury) that causes neuronal damage.

Future directions for Head Injury

• How do we explain that APOE4 seems to increase risk of AD w/head injury, yet APOE4 status doesn't increase risk, but lowers age of onset. Maybe head injury studies and other studies that incorporate APOE4 into their analysis should ask if APOE4 lowers onset of AD with their respective risk factor.

Herpes Simplex Virus 1

• About 80% of the elderly have serological evidence of HSV-1 infection. It is usually latent, but under stress, emotional disturbances or hormonal imbalance the virus is reactivated and causes cold sores.

• Acute HSV1 encephalitis targets same regions of the central nervous system as those most affected in AD (Ball, 1982).

• Itzhaki's group detected HSV1 DNA in brain of elderly people, but not young, which suggested that the decline in immune function in old age may permit the entry of HSV1 into the CNS (Jamieson et al., 1991; Jamieson et al., 1992).

• They postulated that people with HSV1 might more susceptible to AD due to other factors. They found a significant association of APOE4 and HSV1 with AD patients vs. controls, but not either APOE4 or HSV-1 alone.

Mechanism of HSV-1

• Virus particles can enter into axons of sensory neurons and are transported to the cell bodies. Reactivation of HSV-1 can reactivate virus in the neuronal cell bodies, but only a few neurons are likely to be destroyed at a time.

• APOE is involved in repair of neurological insult, and several studies have shown the APOE4 allele is not as effective as the other isoforms (Slooter et al., 1997; Sorbi et al., 1995). Perhaps APOE4 genotypes are less effective at repairing damage caused by HSV-1.

• Cribbs et al. found that an internal sequence of HSV-1 closely resembles the toxic portion of Ab in form and ability to aggregate. It even is toxic to primary cortical neurons at doses comparable to Ab.

• The same sequence in HSV-1 has been shown to bind to APOE (Huemer et al., 1988).

• Maybe APOE is interacting with the HSV-1 DNA in a similar way to how it interacts with Ab, leading to degradation and aggregation of the protein.

Future directions of HSV-1

• Prospective studies should be carried out to see if people who get cold sores (the most common manifestation of HSV-1 infection) have a higher risk of AD.

• Experiments should be carried out using cell cultures to determine if APOE is able to degrade HSV-1 DNA, and whether this leads to its subsequent aggregation

CAUSE AND MECHANISMS

Protective Correlates

NSAIDs

• The discoveries that people with inflammatory diseases (such as arthritis) had a reduced risk of Alzheimer's disease (1994; Broe et al., 1990; Jenkinson et al., 1989; Li et al., 1992; McGeer et al., 1990), and that postmortem AD brains have activated microglia and astrocytes (McGeer and McGeer, 1998), led to the hypothesis that anti-inflammatories may be effective in prevention of the disease.

• Patients with rheumatoid arthritis (RA) are frequently treated with NSAIDs, and most case-control and case-cohort studies showed a significant inverse relationship between RA and AD (Zandi and Breitner, 2001).

• Traditionally it has been thought that NSAIDs inhibit inflammation via their inhibition of cyclooxygenase (the rate-limiting enzyme involved in converting arachadonic acid into prostaglandins). However recent cross-sectional studies found that there was a protective effect even with lower doses of aspirin and NSAIDs than normally required for inhibition of cycloxygenase (Anthony et al., 2000; Broe et al., 2000).

• The three prospective studies from the Baltimore Longitudinal Study of Aging, the Rotterdam study and Cache County all suggest that the most significant inverse association is with prior use of NSAIDs, at least 2 years before age of onset (in t' Veld et al., 2001; Stewart et al., 1997; Zandi and Breitner, 2001). Two of the three studies also showed that the longer the duration of use of NSAIDs, the more significant the effect (in t' Veld et al., 2001; Stewart et al., 1997).

• Breitner et al. examined monozygotic twins and showed that those who had one year of exposure to NSAIDs had a 7-10 year delay of AD, and those without the APOE4 allele showed the greatest benefit. They also examined the effects of histamine blockers (H2) and showed that they in contrast to NSAIDs, had the greatest benefit for those with APOE4 (Breitner et al., 1994; Breitner et al., 1995)

• There have been several treatment trials with NSAIDs, and all have failed to find any statistically significant reversal of cognitive decline (Zandi and Breitner, 2001).

• There are several randomized control trials currently underway to test the effects of NSAIDs on preventing AD. Three are designed to determine if NSAIDs can benefit at the prodromal phase (during mild cognitive impairment), and one (the ADAPT study) is aimed at primary prevention (non-cognitively impaired) (Zandi and Breitner, 2001).

Mechanism of NSAIDs

• There are 2 isoforms of cycloxygenase (COX), both which are inhibited by NSAIDs. COX-1 is expressed constitutively for homeostatic purposes, while COX-2 is upregulated by pro-inflammatory cytokines, inhibited by glucocorticoids, and generates prostanoids in response to many pathological conditions. Because of these separate roles, it was believed that the protective effect of NSAIDs was primarily via its ability to inhibit COX-2 (O'Banion, 1999).

• Several reports have found increases in COX-2 in AD brain in neurons in regions susceptible in Alzheimer's disease (ie. hippocampus and frontal cortex) (Ho et al., 1999; Kitamura et al., 1999; Oka and Takashima, 1997; Pasinetti and Aisen, 1998; Yasojima et al., 1999).

• Ho found increasing COX-2 immunoreactivity in CA2 and CA3 of hippocampus with increasing CERAD dementia ratings (Ho et al., 2001), and Oka and Takashima saw increasing COX-2 immunoreactivity with increasing age and NFTs (Oka and Takashima, 1997).

• The outcome of these studies are surprising. One would expect that if COX-2 levels did increase with severity of dementia, that NSAIDs would be somewhat effective in treating AD, but this has not been confirmed by clinical trials.

• Yermakova et al. on the other hand, found a decrease in the percentage of COX-2 positive neurons in the hippocampus of advance AD as measured by the CERAD dementia score. Since significant cell loss has already occurred in advance AD, and since the expression of COX-2 is activity dependent (Kaufmann et al., 1997), the loss of COX-2 was thought to be due to the loss of neuronal activity (Yermakova and O'Banion, 2001).

• A common hypothesis regarding inflammation in Alzheimer's disease is that secreted Ab activates the microglia and astrocytes as demonstrated in vitro (Kopec and Carroll, 1998; Meda et al., 1995), and more so with the help of cytokines (Gitter et al., 1995; Hu et al., 1998; Rossi and Bianchini, 1996). While Ab activates the complement cascade (Webster et al., 1997), cytokines increase APP expression and alter Ab processing (Brugg et al., 1995; Donnelly et al., 1990; Goldgaber et al., 1989), thus forming a vicious loop which contributes to the production of toxic products, such as oxygen species, proinflammatory cytokines, excitotoxins and proteases (Eikelenboom et al., 1998; O'Banion, 1999).

• Lim et al. have further substantiated this hypothesis by showing that Ibuprofen, administered beginning at the normal time of plaque formation (10 months) suppresses plaque and dystrophic neurite formation and inflammation in a transgenic mouse model of AD (Lim et al., 2000).

• Interestingly enough, Thomas et al. showed that aspirin and other NSAIDs are able to inhibit b-amyloid aggregation in vitro (Thomas et al., 2001).

• Lue et al. (Lue et al., 1996) compared AD brains to those without cognitive impairment, but had significant AD pathology (high pathology controls). The AD brains and high pathology controls had about equal numbers of plaques, but the high pathology controls had significantly less tangles and C5b-9 (a complement protein) immunoreactivity.

• Another study examined the differences in postmortem tissue between elderly who had been taking NSAIDs vs those who had not. They found the same degree of plaques and tangles, but significant differences in activation of microglia (Mackenzie and Munoz, 1998). Thus inflammation may be a requirement for the clinical expression of AD.

• The amount of NSAIDs required for an effective theraputic dose is much higher than what is required to inhibit cyclooxygenases, and the use of acetaminophen, which is an effective inhibitor of the cyclooxygenases, does not lead to a reduction in AD risk (Landreth and Heneka, 2001).

• NSAIDs also directly bind to the peroxisome proliferator-activated receptor gamma (PPARg) and activate its transcriptional activities. Other PPARg agonists include a number of long chain polyunsaturated fatty acids, eicosaniods, the cyclopentone prostaglandin, 15-deoxy-D-12, 14 PGJ2, and the thiazolidinediones (TZDs) developed for the treatment of type II diabetes (Landreth and Heneka, 2001).

• PPARg is normally expressed in microglia. PPARg agonists can block microglia activation, the

expression of COX-2 (Combs et al., 2000), nitric oxide (NO) dependent cell death (Ogawa et al., 2000), the complement receptor CR3/Mac1 and subsequent generation of toxins induced by b-amyloid (Combs et al., 2000).

Future directions in NSAIDs

• More studies should be done to see if COX-2 increases or decreases through the various stages of the disease. Maybe COX-1 should be analyzed in a similar manner.

• We may also need to carry out epidemiological studies, which address the question of whether NSAIDs have any effect on the entire course of the disease. Currently, studies do not look at long term effects of NSAIDs after disease onset.

• It would be interesting to carry out studies to determine if there is a common mechanism of action of H2-blockers with NSAIDs and aspirin. H2-blockers are currently not known to inhibit COX. It would be interesting to see if they may act at PPARg, or via an alternative pathway that may reveal a new inflammatory pathway that contributes to AD.

• It might be possible to carry out some epidemiological studies to address whether the mechanism of action is primarily through NSAIDs or PPARg. We could compare NSAIDs that inhibit COX-1 and 2 and activate PPARg with those that just activate PPARg. Some of the ligands that activate PPARg include the long chain polyunsaturated fatty acids (could look for people who get a lot in their diet), and the thiazolidinediones, developed for the treatment of type II diabetes. The problem however, is that diabetes itself may increase the risk of AD, so one would have to control for that.

Estrogen

• An observational study done by Robinson and colleagues (1994) have shown that women on estrogen replacement therapy (ERT) have a reduced risk of AD. A series of investigations in the Baltimore Longitudinal Study of Aging (BLSA) resulted in positive correlation between ERT and reduced risk for AD (Kawas, C., Resnick, S., & Morrison, A. et al., 1997).

• Some studies have observed a dose-response relationship either between the amount or duration of estrogen use, and its protective effect (Henderson, 1999; Brenner, 1994)

• Its presumed biological mechanism is that is improves cognitive functioning via promoting the growth of cholinergic neurons, and thereby increasing acetylcholine (Brinton, 1997; Toran-Allerand, 1991)

• Increasing blood flow in the CNS and protecting against vascular risk factors for AD (Belfort, 1995)

• Moderating inflammatory processes (Josefsson, 1992; Pacifici, 1991)

• Decreasing amyloid deposition (Xu, 1998)

• Protecting neurons from dying due to oxidative stress (Behl, 1997; Goodman, 1996; Regan and Guo, 1997)

• Maki, P., Zonderman, A., and Resnick, S., (2001), have found that ERT protects against age-associated decline in visual memory, associated with better encoding, retrieval and recognition of verbal items.

• However, the longest and largest double blind placebo control study, which was carried out for one year with 120 subjects, showed that ERT was not beneficial for women with mild to moderate AD (Mulnard, 2000)

• Other investigators have proposed that ERT is beneficial if taken during a "critical window" of time, e.g. if taken during the latent stage of AD. This may explain the contradicting results from prior studies. (Resnick, 2001)

• ERT may be effective for preventing or delaying the onset of the disease, but has little effect once symptoms have already begun. Explained in biological terms, neurons and pathways involved in cognitive functioning may have already been damaged or lost due to the neuropathology of the disease.

Vitamin E

• There is pathological evidence that AD patients have higher levels of oxidized proteins in their brain tissue, and lower concentrations of vitamins C and E in cerebrospinal fluid (CSF) (Smith, C. & Carney J. et al. 1991; Kontush, A. et al, 2001). It is therefore logical to speculate that supplemental antioxidants such as Vitamin E and Vitamin C may delay the development of AD.

• Free-radicals, which are oxygen compounds that may attack and damage lipids, proteins and DNA, are responsible for inducing oxidative damage.

• The brain is especially sensitive to oxidative damage because of its high content of readily oxidized fatty acids and low levels of antioxidants.

• á-Tocopherol (the main form of Vitamin E), exists in humans as a major lipophilic antioxidant. It has been shown to reduce the neurotoxicity of Aß, the major component of plaques (Behl, C. et al, 1992).

• A first large clinical trial of á-tocopherol showed a beneficial effect by delaying the time to clinical decline by administering 1000 IU twice daily. (Sano, M., Ernesto, C., Thomas, R. et. al. 1997).

• The exact molecular basis for á-Tocopherol supplementation in AD still needs to be revealed. Several studies suggest that vitamin E protects neurons against oxidative stress by scavenging free radicals and interrupting oxidative redox chain reactions (Goodman and Mattson, 1994; Behl, 1999; Butterfield et al., 1999).

Activity

• Hultsch, Hammer, Small, and Dixon (1993) cross-sectionally examined the relationship between self-reported activity and cognitive performance. Their results confirmed previous work (Arbuckle, Gold, & Andres, 1986; Schaie, 1996) reporting that there was a positive relationship between everyday cognitively stimulating activity and cognitive performance. However, the relationship between lifestyle and cognition is complicated by a number of factors including age, gender, education, health, and personality. These factors may influence activity or cognition itself.

• In an attempt to examine the lifestyle/cognition relationship and further investigate the role of possible confounders, a number of prospective longitudinal studies have been conducted.

• Hultsch, et al. (1999) examined the relationship between cognitively stimulating activity and decline in cognitive ability. In contrast to cross-section findings, longitudinal investigations did not yield a significant relationship between activity and cognitive decline.

• Wilson, et al. (2002) examined the relationship between cognitive activity and the risk of incident AD. They found that a 1-point increase in cognitive activity score (measured as participation in 7 common activities that involve cognitive stimulation or processing) was associated with a 33% reduction in the 6-year incidence of AD. Results were comparable when adjusted for age, education, baseline level of cognitive performance, and apolipoprotein E4 allele and other medical conditions.

• Scarmeas, Levy, Tang, Manly, and Stern (2001) examined the influence of leisure activity on the 7-year incidence of AD. They examined both overall activity (total hours) and participation in three separate domains of activity (intellectual, social, and physical) in an attempt to disentangle the specific mechanism of influence between activity and risk of AD.

• For overall activity, Scarmeas and his colleagues (2001) found that higher activity was associated with a reduced risk of AD (RR = 0.88; 95% CI = .83 - .93) in an age-stratified Cox model. Similar results were found when ethnicity, education, and occupation were controlled.

• When activities were examined separately by category (intellectual, social, and physical) all three domains of activity were associated with a decreased

risk of AD (Intellectual: RR = .76; CI, .61 - .94; Physical: RR = .80; CI, .66 - .97; Social: RR = .85; CI, .77 - .94). These results indicate that while intellectual activities provide the greatest decrease in risk for AD, physical and social activities also provide a significant buffer against the disease.

Future Directions in Activity work:

• Although the consensus across studies is that cognitive activity provides a reserve against the risk of AD, different studies of activity and cognitive performance and the risk of AD use varying measures of cognitively stimulating activity. These differential classification methods have resulted in varying results across studies. In order to accurately compare across studies and offer recommendations to the general public on the effects of cognitive activity and risk of AD standardized measures of 'activity' need to be agreed upon. A gold standard of cognitively stimulating activity measurement needs to be identified.

PREVENTION / INTERVENTION

Behavioral Interventions

• Although there have been a number of cognitive intervention efforts, both in the US (Blieszner, Willis, & Baltes, 1981; Kelly & Hayslip, 2000; Rebok, Rasmusson, & Brandt, 1997;Schaie & Willis, 1986; Willis & Schaie, 1986) and abroad (Baltes, & Kliegl, 1992; Raykov, 1997) few of these large-scale intervention efforts have targeted patients with Ad because of the severely degenerative and seemingly irreversible nature of this disease.

• Studies that have focused on AD patients have been small intervention trials.

• Cherry, Simmons, and Camp examined the effectiveness of spaced retrieval training on performance and duration of training session with in AD patients. Spaced retrieval is a memory training method often used with AD patients where participants are trained to remember and recall information over increasingly longer periods of time. They found that in addition to increased memory performance following training, intervention subjects were able to endure longer training sessions over the intervention period.

• These results indicate that in addition to improving memory performance in AD patients, traditional spaced retrieval intervention efforts may also lead to increased attention span. Findings for increased duration of attention have implications for quality of life issues for both the AD patients and their caregivers.

• McKitrick and Camp (1993) examined the effects of spaced retrieval training on ammonia (the inability to recall the names of objects or people) in AD patients. They found that trained subjects were able to relearn the names of a number of objects in their immediate environment. In a later study, McKitrick (1993) examined t a similar intervention where caregivers administered the intervention. Findings from this study were similar to those of the traditional behavioral intervention.

• Camp, Foss, Stevens, and O'Hanlon (1995) examined the use of external memory aides, such as calendars, following spaced retrieval memory intervention. They found that significantly more participants in the training group than controls used the external aides at immediate posttest, as well as six months later at follow-up.

• These results suggest that traditional memory training can improve prospective memory performance as well as strategic behavior. The long-term effects of behavioral intervention reported by camp and his colleagues are particularly important for quality of life issues and are especially impressive in a demented population.

• Rapp, Bernes, and Marsh (2002) examined the immediate and long-term effectiveness of memory enhancement training in patients with mild cognitive impairment (MCI). MCI patients arte an interesting

group to study in relation to Ad because this group is at a heightened risk for developing AD. Previous research (Peterson et al., 1999) has suggested that within an MCI population 10-15% of individuals develop AD per year, compared with an incidence rate of 1-2% in the general population of normal elders.

• Results from this MCI intervention trial found that although there was no difference in cognitive performance between the intervention and control groups at immediate follow-up, six months later participants receiving the memory enhancement intervention were performing at a significantly higher level than controls.

• These results indicate that in a mildly impaired population intervention effects, although not immediately apparent, may provide more of a long-term buffer against the risk of further decline.

• Taken together with less impressive long-term effects from studies of full AD patients (rather than mildly impaired individuals) indicate that targeting patients in the early stages of decline is critical for long-term results of behavioral intervention efforts.

Future Directions in Behavioral Intervention/ Prevention

• Although there are many studies of cognitive intervention in normal, non-demented elders, none to date have prospectively followed their participants over time to quantify the reduction in risk of AD with cognitive intervention. The reduced risk is approximated by studies of the relationship between education and reduced risk AD. Although the relationship between education and incident AD may be similar to that of behavioral interventions, cognitive training efforts aim to provide additional buffers against cognitive deterioration beyond that attainable by education and cognitive stimulation alone. These studies provide specific strategies aimed to improve performance on everyday activities and improve quality of life beyond that of the buffer of education alone.

• An important future direction in intervention work is follow-up assessments of cohorts of participants who received behavioral intervention for prevalence and incidence of AD compared to the general population of similar age and education. A number of studies currently underway have the potential to examine such a relationship including the ACTIVE (Advanced Cognitive Training in Independent and Vital Elders) Study, a six-site clinical trial on the effects of several cognitive interventions.

• Although studies of the effects of cognitive intervention in AD patients have yielded consistent findings for improved performance on various cognitive tasks, little work has been done to examine the affect of training gains on the overall quality of life of AD patients and their caregivers. Investigation of the long-term effects of behavioral intervention on day-to-day behavior and the experience of the caregiver are important in designing future intervention efforts for individuals suffering from AD.

• Follow-up on early studies where caregivers of AD patients administer the intervention should be conducted. Comparisons of traditional intervention efforts and those where caregivers act as the intervention agent can be examined for development of optimal future intervention designs.

Drug Interventions

Treatment of AD Symptoms

• Because no cure for AD currently exists, psychiatrists and neurologists use pharmacological means to subside symptoms of progressing cognitive decline.

• Nearly all of the drugs available for the treatment of AD symptoms exert their effects based upon the cholinergic hypothesis.

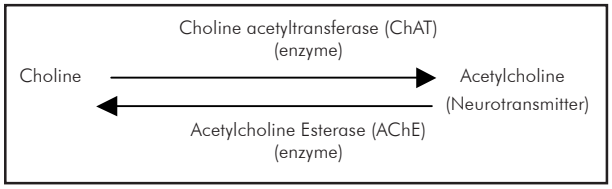

Figure 3. The cholinergic hypothesis links AD to the deficiency of acetylcholine, a neurotransmitter responsible for memory and cognitive functioning at the hippocampal and cortical levels. This loss is also because of the decrease in cholinergic neuronal projections to the neocortex and hippocampus. Acetylcholine esterase (AChE) serves to maintain the chemical equilibrium between choline and acetylcholine. But this effect is offset by the reduction of the enzyme choline acetyltransferase (ChAT) in AD patients.

• What the current drug treatments aim to do is replace the amount of the neurotransmitter acetylcholine by inhibiting AChE. The following drugs (not comprehensive) have been FDA-approved and are (or were) used to treat mild to moderate AD symptoms (Bullock, 2002):

Tacrine
Donepezil (Aricept)
Rivastigmine (Exelon)
Galanthamine (Reminyl)

• There are numerous other drugs being used to treat AD symptoms that work by other mechanisms. A number of them have been hypothesized to prevent AD symptoms from arising before a diagnosis is even made. At a recent American Medical Association conference, experts observed that acetylcholine esterase inhibitors appear to stabilize or improve mild to moderate symptoms in up to 80% of patients (Johns Hopkins Medical Letter, Health After 50). The problem with these drugs, as with any inorganic drugs, are the side-effects patients experience when taking them for extended periods of time. Thus, researchers are increasingly focusing their interests on intervention with other forms of drugs or behavioral modalities. One of the more recent studies is the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) study, conducted by Breitner and colleagues (2002). This prevention trial compares two NSAIDS against placebo (Martin, B.K, Meinert, C.L., Breitner, J.C.S., 2002).

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