characteristics which differ between autopsied and non-autopsied subjects and to compare autopsy-based estimates of the frequency of neuropathological diagnoses before and after adjusting for potential verification bias. **Methods:** Subjects were all members of a Seattle-area health maintenance organization between 1987 and 1996, who presented at HMO clinics with new symptoms of previously undiagnosed dementia. Consenting subjects were enrolled in and clinically diagnosed by the UW/GHC Alzheimer's Disease Patient Registry (ADPR). Demographic and clinical characteristics were compared among clinically demented ADPR subjects who, as of October 2003, were autopsied (n = 228), had died but were not autopsied (n = 271), were still alive (n = 71), or had dropped out of the study (n = 82). Logistic regression models were used to identify characteristics associated with likelihood both of autopsy and of specific neuropathological diagnoses. Stratification on these characteristics was used to derive estimates of the frequencies of neuropathological AD and pure vascular disease, adjusted for potential verification bias. **Results:** Compared to non-autopsied subjects, autopsied subjects were more likely to be male, Caucasian, educated beyond high school, and married. They tended to have a lower baseline MMSE score and were more likely to have a clinical diagnosis of AD. Autopsy subjects also demonstrated a lower age at onset and age at study intake than subjects who died but were not autopsied. The frequency of neuropathological AD in the autopsied sample was estimated to be 64% (95% CI = 58–71%). After adjusting for verification bias, this estimate did not change substantially (60%, 95% CI = 53–66%). The frequency of neuropathological pure vascular disease (7%, 95% CI = 4–12%) also did not change appreciably after adjusting for verification bias (9%, 95% CI = 5–13%). **Conclusions:** Although demographic and clinical differences existed between autopsy and non-autopsy samples, these differences did not appreciably affect frequency estimates of several neuropathological diagnoses, suggesting that neuropathological diagnoses in the ADPR subjects provide reasonable dementia frequency estimates among ADPR patients who were clinically demented.

## P2-267 A COMPARISON OF AD BRAIN PATHOLOGY FOR MEN AND WOMEN THROUGHOUT ADULTHOOD

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**Background:** Epidemiologic studies indicate that women are at higher risk for the development of AD compared to men. Clinical studies have not been verified by neuropathologic findings. **Objective(s):** We compared the extent of AD changes for men and women at age 25 and each decade of age thereafter to age 95. **Methods:** Information on Braak staging for SP (none, A to C) and NFT (none, I to VI) was available for more than 5000 subjects ascertained at routine autopsy. About a third of the subjects had APOE genotype information. Linear models were constructed. **Results:** There was on average over all APOE genotypes (n > 5000) a 3-year acceleration of NFT staging for women. In more detail, men and women had the same likelihood for NFT at the initial predilection site in the transentorhinal cortex (I). But, women were more likely to reach stages II (entorhinal) and III (hippocampal) clearly evident at ages 65 (p = 0.01) and 75 (p = 0.01). Isocortical stages IV to VI were also more common for women. Looking at subjects who had APOE information, there was no gender gap for APOE2/3+ subjects. There was a large gender gap for APOE4+ subjects. In addition, women at early NFT stages I to III APOE4+ and in late middle age were much more likely to have extensive SP deposits throughout the brain compared to APOE4+ men. **Conclusions:** APOE4+ women had more brain regions containing NFT and SP compared to APOE4+ men of the same age from about age 55 years onward. The rapid increase in AD neuropathology in late middle age for a subgroup of women argues in favor of development of early interventional strategies to be selectively applied and for better genetic definition of the high-risk subgroup.

## P2-268 GENETICS, PATOPHYSIOLOGY AND Aβ PROTOFIBRIL FORMATION IN ALZHEIMER'S DISEASE

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Analysis of families with a distinct inheritance pattern of dementia has shown to be a powerful approach for the identification of disease genes. We have used 12 extended families with Alzheimer's disease (AD) and several hundred sib-pairs to investigate disease susceptibility regions. We performed a genome wide screen using microsatellite markers and linkage and haplotype analysis. Shared haplotypes in individual families were observed on chromosomes 2, 4 and 20. On chromosome 8 a nonparametric LOD score of 3.7 (p = 0.004) was obtained in one family. All affected individuals in this family shared a seven markers haplotype spanning approximately 50 cM. This haplotype was also found in affected individuals in other families. Amyloid β-protein (Aβ) accumulation is central in AD pathogenesis. Aβ protofibrils, an intermediate in Aβ fibril formation, have been shown to mediate neurotoxicity and disrupt neuronal electrophysiological parameters. Aβ with the Arctic mutation (Aβ E22G) enhances formation of protofibrils *in vitro*. We are investigating the fibrillization of Aβ1-42wt and Aβ1-42Arc with size exclusion chromatography by measuring decline in peaks of monomers and protofibrils. Thus, aggregation phases can be separately examined. The Arctic Aβ1-42 protofibrils forms fibrils ~18× faster than wild type protofibrils. The two phases, the monomer oligomerization and the fibrillization of protofibrils, can be influenced differently in response to physio-chemical changes. We are currently developing Aβ conformation specific monoclonal antibodies (mAb) for Aβ monomers, Aβ protofibrils and Aβ fibrils. Such monoclonal antibodies will provide an opportunity to assay these differently aggregated Aβ forms. Several mAbs have been isolated and characterized. It has been suggested that Aβ aggregates inside neurons, raising the issue whether Aβ accumulation is initiated at an intracellular, rather than extracellular, site. The Arctic mutation affects the APP processing, resulting in decreased Aβ levels as measured by ELISA, both in plasma of mutation carriers and in cell media of transfected cells. These findings has lead to the assumption that an abnormal accumulation of Aβ inside cells might occur in Arctic cells due to high levels of intracellular Aβ. Preliminary results indicate increased intracellular levels of Arctic Aβ peptides.

## P2-269 HOMOCYSTEINE IS NOT ASSOCIATED WITH MEMORY AND LANGUAGE IN THE NONDEMENTED OLDEST OLD

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**Background:** Elevated homocysteine levels have been associated with cognitive impairment and dementia in the elderly. Few studies have examined these relationships in the oldest old. **Objective(s):** To examine the association between homocysteine levels and cognitive function in nondemented oldest old. **Methods:** 104 community dwelling nondemented (CDR = 0) subjects 85 years old and above, participating in a longitudinal study of cardiovascular risk factors for Alzheimer's disease in the oldest old, were assessed by a cognitive battery and on levels of serum total homocysteine, vitamin B12, creatinin and serum folate. **Results:** Factor analysis yielded three cognitive factors: memory (immediate recall, delayed recall, and recognition), language (fluency, shipley, and Boston), and psychomotor (digit symbol, Trails A, and Trails B). Controlling for age, education, vitamin B12, creatinin, and folate, memory (r = 0.12; p = 0.22) and language (r= −0.09; p = 0.39) performance were not significantly correlated with homocysteine level. The inverse association of homocysteine levels with psychomotor performance (r= −0.19) approached significance (p = 0.054). **Conclusions:** Elevated homocysteine levels were not associated with memory and language performance in a sample of nondemented oldest old. The trend level association with psychomotor function is consistent

with some results in the nondemented elderly suggesting that homocysteine is associated with psychomotor rather than memory impairment.

## P2-270 DEMENTIA PREVALENCE IN VERY LONG-TERM USERS OF ESTROGEN ALONE VERSUS ESTROGEN PLUS PROGESTIN

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**Background**: In the Women's Health Initiative Memory Study (WHIMS), the risk of dementia in women assigned to PERT was increased compared with those assigned to placebo. We previously reported on dementia risk in users of hormone replacement therapy, combining users of estrogen alone (ERT) and estrogen plus progestin (PERT). **Objective:** We reanalyzed our data to assess the risk of dementia in ERT and PERT users separately. **Methods**: The study involved 3,924 women 75+ years who were members of the Southern California Kaiser Permanente Medical Care Program in 1998. Hormone use was determined based on computer-stored prescription data for 1992-1998. Cognitive function and dementia were assessed using the Telephone Interview of Cognitive Status supplemented by the Telephone Dementia Questionnaire and medical record review. **Results**: There were a total of 300 dementia cases; 207 were probable Alzheimer's Disease (AD) and 93 were dementia with known cause, mostly vascular dementia. The mean duration of hormone use was 29.1 years (± 11.8 SD) for ERT users and 21.6 years (± 11.1 SD) for PERT users. PERT users (N = 569) differed from ERT users (N = 1375) in age and education but not ethnicity. After adjustment for age, education, ethnicity, and medical history variables, the odds ratio (OR) for all dementia in ERT users compared with non-hormone users was 0.78 (95% C.I. 0.59,1.03); for PERT users compared with non-users of hormones, it was 0.90 (95% C.I. 0.61,1.32). The adjusted OR for probable AD in ERT users compared with non-users of hormones was 0.73 (95% C.I. 0.52, 1.02); for PERT users compared with non-users of hormones, it was 0.92 (95% C.I. 0.58, 1.44). The adjusted ORs for dementia with known cause, were 0.93 (95% C.I. 0.58, 1.49) in ERT users and 0.85 (95% C.I. 0.42, 1.72) in PERT users. **Conclusions**: In this study, unlike WHIMS, the ORs for all dementia, AD dementia, and dementia with known cause were not increased in PERT users. There was some hint that the OR for probable AD might be lower in ERT users but not in PERT users, but the confidence limits for the OR estimates for ERT and PERT overlapped.

## P2-271 AMYLOID MEDIATES THE ASSOCIATION OF APOLIPOPROTEIN E ε4 ALLELE TO COGNITIVE FUNCTION IN OLDER PERSONS

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**Background:** We previously provided evidence consistent with a sequence of pathological events whereby the effect of amyloid deposition on cognitive function is mediated by neurofibrillary tangles. **Objective(s):** Test the hypothesis that amyloid mediates the association of the apolipoprotein E ε4 allele with level of cognition. **Methods:** Subjects were 44 persons with clinical AD and 50 without dementia, who participated in the Religious Orders Study, underwent apolipoprotein E allele determination, cognitive testing about eight months prior to death, and brain autopsy. Percent area of cortex occupied by amyloid-beta and the density of tau-positive neurofibrillary tangles were quantified from six brain regions and averaged to yield summary measures of amyloid load and neurofibrillary tangles. Multiple regression analyses were used to simultaneously examine the effects of allele status on amyloid load and neurofibrillary tangles, and level of global cognition, controlling for age, sex, and education. **Results:** The apolipoprotein E ε4 allele was associated with the density of tangles ($p = 0.002$) in a regression model. When a term for amyloid was added to the model, the effect of the ε4 allele was reduced by more than 50% and was no longer significant ($p = 0.12$) consistent with amyloid mediating the effect of allele status on tangles. In subsequent regression analyses, the ε4 allele was associated with amyloid load ($p < 0.001$). However, when a term for tangles was added to the model, the effect of the ε4 allele was reduced but remained significant ($p = 0.02$). To confirm that amyloid mediates the effect of allele status on level of cognition proximate to death, we added a term for amyloid to a regression model examining cognition as a function of the ε4 allele. The ε4 allele was associated with a lower cognitive function score ($p = 0.04$). When a term for amyloid load was added to the model, the effect of the ε4 allele was reduced by nearly 60% and was no longer significant ($p = 0.41$) while the effect of amyloid was significant ($p = 0.001$). **Conclusions:** These findings are consistent with a sequence of pathologic events whereby amyloid deposition comes prior to tangles in the sequence linking the apolipoprotein E ε4 allele to level of cognition.

## P2-272 PUBLICATION TRENDS IN ALZHEIMER DISEASE

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**Background:** For more than sixty years since its first description by Alois Alzheimer in 1906 neurodegenerative disease named after him had not been attracting attention of researchers. However over the last four decades there has been a significant increase in both basic and clinical research on the subject. There are many causes for such renewed and growing interest. Better understanding of the underlying causes can help in predicting future developments. **Objective:** Documentation of publication trends in Alzheimer disease related articles in biomedical literature covering the period from 1962 to 2003. **Methods:** Search of The National Institute of Health MEDLINE database was conducted to retrieve the papers published between 1962 and 2003 containing MeSH keywords *"Alzheimer disease"* and its derivatives. Frequency of search terms in keywords and titles was analyzed by bibliometrics. **Results:** Over last four decades the number of publications concerning Alzheimer disease has rapidly increased. From single number of publications per year in 1950' it increased to 2611 papers in 2002. At the same time the number of papers with MeSH keyword *'dementia'* grew steadily from 57 in 1965 to 3957 in 2002. We also found that the nature of publications on Alzheimer disease has changed over this period of time from basic research to definition and criteria seeking papers and to analysis of diagnostic approach, therapeutic options and clinical trials. Pace of growth of Alzheimer publications compared to the rest of publications on dementia syndromes is substantially higher. **Conclusions:** We consider the

Abstract P2-272 – Table 1. Total publication count in 5 year periods

| Year of publication | ACHEI in any and Alzheimer Disease in MeSH keyword | Alzheimer in MeSH keyword and Publication Type: Review | Dementia in MeSH keyword without Alzheimer Disease in MeSH keyword | Alzheimer in MeSH keyword | Dementia in MeSH keyword |
|---|---|---|---|---|---|
| 65–69 | 0 | 0 | 620 | 2 | 622 |
| 70–74 | 0 | 0 | 1033 | 19 | 1052 |
| 75–79 | 0 | 26 | 1152 | 271 | 1423 |
| 80–84 | 0 | 84 | 1724 | 1148 | 2872 |
| 85–89 | 47 | 591 | 2856 | 4088 | 6944 |
| 90–94 | 181 | 1225 | 4157 | 6608 | 10756 |
| 95–99 | 385 | 1970 | 5423 | 9714 | 15137 |
| 00–02 | 361 | 1707 | 3964 | 7405 | 11369 |