



**Seattle Kame Project:
A Community-Based Study of Aging & Dementia in the
Japanese American Community of Seattle and King
County, Washington**

A descriptive tale of published research at the close of the National Institute on Aging Funding
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Introduction:

Many important advances in medical research have been the result of experiments of nature. Today, it is widely accepted that scurvy is caused by a lack of vitamin C. However, the most important observation that led to a means of prevention and, eventually, understanding of scurvy, was not a carefully planned, highly technical experiment in a laboratory at a university, but a rather simple observation from a natural experiment, or so-called experiment of nature. It was widely known for centuries that scurvy was a rather common problem for sailors on long sea journeys. The key observation in the natural experiment occurred when a ship's physician observed that sailors who were given lemons and oranges as part of their food on board ship did not develop scurvy. Those who ate the traditional sailor's diet without citrus fruits were more likely to develop, suffer, and die from scurvy. He went on to prove that lemons and oranges could prevent scurvy in sailors.

The idea for the Kame Project grew from discussions in the early 1980s, when scientists from Japan, Hawaii, Seattle, and the National Institute on Aging met as part of an informal meeting

sponsored by the University of Washington's Alzheimer's Disease Research Center. This group realized that the migration of Japanese Americans who settled in Seattle represented a natural experiment, which might help us understand the mysteries of aging, especially loss of memory, Alzheimer's disease, and other dementias of aging. Previously, studies in Hiroshima, Hawaii, and San Francisco (the Ni-Hon-San study), and especially, the Honolulu Heartwatch study of Japanese American men in Honolulu had made important observations about factors leading to heart disease and stroke. These observations laid the foundations for strategies that have reduced the individual suffering and public health burden of these killer diseases over the past 20 years.

The Kame Project—a collaborative effort of researchers at the University of Washington and the Japanese American community in Seattle—has focused on phenomena associated with the later ages of life, cognitive decline, Alzheimer's disease and related dementia, and other common maladies of old age and the way people are cared for in old age.

Following general discussions in Seattle and Washington, D.C., a series of planning workshops occurred in Honolulu and Japan. These meetings led to the establishment of special measurement tools and common research protocols. At meetings with local leaders and interested persons from the Seattle Japanese American community, we found out that our community would likely be supportive of studies of aging in Japanese Americans.

At the same time, persons in the federal government, and especially an influential federal advisory group, the Department of Health and Human Services/Office of Technology Assessment Advisory Panel on Alzheimer's Disease and Related Disorders were developing position papers on ethnicity and dementia. The Advisory Panel, whose recommendations included dramatically increasing research funding for Alzheimer's disease, announced that studies of special ethnic populations, including so-called migration studies or natural experiments involving minority populations, represented unique opportunities to understand problems of aging and, conversely, so-called successful aging. In Seattle, we realized the remarkable longevity of persons of Japanese ancestry and the cohesiveness of the Japanese American community represented a truly unique opportunity.

Responding to the recommendations of the Advisory Panel on Alzheimer's Disease, the National Institute on Aging, in 1989, issued a request for proposals to study Alzheimer's disease and related disorders in ethnic populations, including migration studies. After consultations with community leaders, University of Washington investigators, led by Eric B. Larson and Amy Borenstein Graves, worked actively to respond to the request, producing in 1990 a proposal to the National Institute of Aging of a project to study "The Epidemiology of Dementia in Elderly Japanese Americans in King County, Washington". The project was funded in 1991 and came to be known as the Kame Project.

The Kame Project—thanks to a remarkable staff, support and cooperation from the local community, and persons who participated in Kame and their families, and the unique opportunity to

study aging in a discrete, stable, and long-lived population (the “experiment of nature”)—is about to complete an 11 year span of its funding by the National Institute on Aging. The purpose of this brief volume is to catalogue the published research that has resulted from our Kame Project. This is a story that will continue to unfold, as we continue to analyze and publish the data over subsequent years. Thus, the story described today should be viewed as our progress to date. As I write this, our team of investigators continues to analyze Kame data to better understand the mysteries of aging, of Alzheimer’s disease and related disorders, and how people, families, and caregiving institutions can best deal with problems of aging.

A large number of people have helped make the Kame Project a success. Heading the list is our outstanding staff and faculty, most of whom have spent years working on this project, many from the start to the end of its funding in April 2002. I also want to acknowledge the tremendous support we have received from the Kame Community Advisory Board and our external scientific advisory panel.

Kame Project Faculty & Staff:

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A Brief Summary of Research Findings:

1. Rates of Dementia and Related Disorders:

- A. Prevalence of Dementia and its Subtypes in the Japanese American Population of King County, Washington State: The Kame Project. Authors: Graves A. Borenstein, Larson EB, Edland SD, Bowen MD, McCormick WC, McCurry SM, Rice MM, Wenzlow A, Uomoto JM. American Journal of Epidemiology, 1996, Volume 144, pages 760-771.

This paper was one of the first major publications on the Kame Project. Previous studies of Asian populations had reported prevalence rates for dementia that were similar to those of predominantly Caucasian populations. However, the relative rates of Alzheimer's disease and vascular dementia (dementia related to strokes) differed, with vascular dementia being more common than Alzheimer's disease in Asian populations. The Kame Project studied the overall rates of dementia, Alzheimer's disease, and vascular dementia between May 1, 1992 and May 1, 1994 in 1,985 individuals who participated in our baseline examination. A total of 107 persons were judged to have met criteria for dementia. Fifty-eight of these persons were diagnosed with Alzheimer's disease, and 24 with vascular dementia. The overall rate for dementia was 6.3%. The rates increased continuously with age, and increased dramatically above age 85. The rates were 30% for persons aged 85-89, 50% for those aged 90-94, and 74% for persons 95 years and older. We concluded that the rates of dementia in this King County population of Japanese Americans were somewhat higher than prevalence rates reported from Japan. In addition, the distribution of dementia types (Alzheimer's disease and vascular dementia) most closely resembled those found in Caucasian populations in North America and Europe, compared to rates reported previously in Asian populations. The important observation of this study was the fact that the rate of dementia continued to increase, even above 50% in the oldest aged persons. The fact that the patterns of dementia and the rates were more like those of Caucasian populations in North America and Europe suggests there may be some environmental factors affecting these rates in different geographic areas.

- B. Incidence of Dementia in the Japanese American Population of King County, Washington State: The Kame Project. Authors: Graves A. Borenstein.

This is a new analysis that will be presented at the 10th International Conference on Alzheimer's Disease and Related Disorders in Stockholm, Sweden in July 2002.

While the prevalence enumeration gave us some idea of what percent of the King County Japanese American elder population had a dementia and what subtypes were most common, scientists studying these disorders prefer to enumerate new cases, or incidence rates of disease occurring over a specified time period. This is the main reason that the Kame Project was designed as a prospective study, i.e., we followed the population over time to document prevalent cases (who had the diseases of interest at baseline) and then, among a dementia-free cohort, we documented new cases, which are more important for studies looking at causes of disease. We are then able to look at information (risk factors) that we collected at baseline when the population was free of dementia and able to report about their own life histories and understand how these histories differ among individuals who later developed or did not develop dementia. After our prevalence cycle was finished, we followed 1,869 Kame participants who were free of dementia in 1992-1994. Every two years, we administered a cognitive test, the Cognitive Abilities Screening Instrument (CASI), which also is being used in our sister studies in Honolulu, Hawaii and Hiroshima, Japan. The CASI is scored from 0 to 100, with 100 being the highest score. Kame participants who screened 87 or below on the CASI received an in-depth neurological and neuropsychological examination. In the period between baseline and July 1, 2001, Kame investigators documented 163 new cases of dementia (15.7 per 1,000 person years). Eighty cases were attributed to Alzheimer's disease (7.7 per 1,000 person-years); 35 to vascular dementia (3.4 per 1,000) and 48 to other causes (4.6 per 1,000) (DSM-IV). As we had expected, the incidence rates rose exponentially with age, doubling every five years from 1.7 per 1,000 person-years for ages 65-69 to 206.7 in those aged 95+. In 1993, Kame asked participants to donate blood because a new finding that was published in the journal, *Science*, reported that a cholesterol-carrying protein, Apolipoprotein E-e4, was a strong risk factor for Alzheimer's disease. Of 1,985 participants in the study, 1,111 (56%) agreed to donate blood samples. Dr. Jerry Schellenberg's laboratory at the Veteran's Administration agreed to genotype these blood samples. In Kame, participants who carry one of these alleles were two and a half times more likely to develop a dementing illness than those who did not. And this relation was stronger for participants who developed Alzheimer's disease (who were over three times more likely to develop Alzheimer's disease if they carry this allele), but was not present for participants who developed a vascular (stroke-related) dementia. Women were at a slightly higher risk of developing dementia compared with men, and this propensity was somewhat stronger

for Alzheimer's disease (70% increase over men). Our results for the incidence study show strong associations of dementia and Alzheimer's disease with age, gender, education and ApoE-4. We also found that Alzheimer's disease was more than twice as common as vascular dementia, which again reflected our findings in the prevalence study. Japanese Americans in Seattle-King County were more like their Caucasian counterparts in terms of the occurrence of Alzheimer's and vascular type dementias, which supports the view that these diseases have strong environmental influences.

2. Risk Factors for Cognitive Decline and Alzheimer's Disease:

One of the specific aims of our project has been to determine what factors might contribute to cognitive decline and, more specifically, to the development of Alzheimer's disease. Much of our work has been related to the so-called "brain reserve" hypothesis. This theory implies that, with age, there is a natural decline in cognitive function and accumulation of degenerative changes in the brain. The more brain reserve a person has, the longer it takes to develop significant symptoms, and, in particular, symptoms that are strong enough to impair function, and, which, in many instances, are associated with Alzheimer's disease and other dementias. Of course, as people age, the risk of Alzheimer's and dementia, overall, increases—as we and others have demonstrated in studies of rates of Alzheimer's in various populations.

One set of studies used the marker of head circumference as an indicator of brain reserve.

- A. Head circumference as a measure of cognitive reserve: Association with severity of impairment in Alzheimer's disease. Authors: Graves A, Borenstein, Mortimer JA, Larson EB, Wenzlow A, Bowen JD, McCormick WC. *British Journal of Psychiatry*, 1996, Volume 169, pages 86-92.

This study looked at all persons with so-called prevalent dementia in the original Kame survey (1992-94). The analysis found that those persons with Alzheimer's disease and smaller head circumference had more cognitive impairment. However, in persons who did not have dementia, there was no association between the circumference of the head and the level of cognitive ability, as measured by our screening test, the CASI. Other prevalence studies, in particular, one conducted in Northern Manhattan in New York City, subsequently reported that persons in the lowest one-fifth of the population distribution, with regard to their head circumference, had an increased risk of Alzheimer's disease. The increase in risk, after adjustment for age, education, and ethnicity, was about three-fold for women and 2.3 fold for men.

Overall, these studies seem to indicate there may be a relationship to head circumference as a measure of brain reserve and dementia.

- B. Head circumference and incident Alzheimer's disease: Modification by Apolipoprotein E. Authors: Graves A, Borenstein, Mortimer JA, Bowen JD, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. *Neurology*, 2001, Volume 57, pages 1453-1460.

This study further explored the relationship between head circumference and Alzheimer's disease on the premise that the accumulation of degeneration in the brain leads to a descent below a critical threshold of brain reserve, below which, normal cognitive function cannot be maintained. In this study, the outcome of interest was the number of persons in the Kame Project who had been normal at enrollment who developed dementia while they were being followed-up every two years. After four years of follow-up, there were 59 new cases of Alzheimer's disease among approximately 1,870 persons originally seen and found to not be demented. The incident cases were significantly older, less educated, shorter in stature, and lighter in weight. They were also more likely to have at least one apolipoprotein E-e4 (apoE 4) allele. This genetic marker has been associated in other studies, including our own, with increased risk of late-life Alzheimer's disease. What was unique about this study was that it looked at head circumference and the genetic marker, apoE -e4 together. As in other studies, the apoE -e4 marker was associated with a significantly increased risk of Alzheimer's disease. However, a combination of a small head circumference and the apoE -e4 marker predicted earlier onset of Alzheimer's disease and a much higher risk in this study, or the so-called hazard ratio was increased almost 14 fold for the combination.

The conclusion of this study was that the results support the idea that Alzheimer's disease occurs when two conditions are met: first, the accumulation of neuropathologic, degenerative diseases of the brain, a process that is accelerated by the genetic marker, the apoE-e4 allele, and second, the descent below a critical threshold of brain reserve. The study's marker for brain reserve was represented by an indirect measure of premorbid brain size, the head circumference. Studies in other populations that have tried to replicate our findings have done so successfully thus far.

3. Risk Factors for Cognitive Decline in the Kame Population

The Kame Project allowed us to measure change in cognitive abilities over time. By dividing persons into groups of those who declined more and those who declined less, it was possible to test different markers and risk factors for decline.

- A. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: The Kame Project. Authors: Graves A, Borenstein, Rajaram L,

Bowen JD, McCormick WC, McCurry SM, Larson EB. *The Journal of Gerontology: Social Sciences*, 1999, Volume 54B, pages S154-S161.

This study tested the idea that, since studies of Japanese living in Japan show generally lower rates of Alzheimer's disease when compared to studies of Caucasians living in North America and Europe, there could be something about Japanese lifestyle that might protect against or delay progression to Alzheimer's disease. Thus, persons who had a more characteristically Japanese lifestyle might be expected to show slower cognitive decline.

Looking at 1,604 older Japanese American persons in King County who were tested and retested after two years, the variables related to reading, writing, and speaking Japanese, being born or having lived in Japan in early life, and having only or mostly Japanese friends were less likely to be associated with cognitive decline—that is, they seemed to be protective against decline. The two strongest protecting factors were knowledge of the Japanese language and having spent one's early years in Japan. We speculated that the greater social support characteristic of Japanese culture, as well as the role that Japanese language may play in building up more nerve connections in the brain and more stimulation in adult life, might also explain the findings.

- B. Postmenopausal estrogen and estrogen-progestin use and two-year rate of cognitive change in a cohort of older Japanese American women: The Kame project. Authors: Rice MM, Graves A, Borenstein, McCurry SM, Gibbons L, Bowen J, McCormick W, Larson EB. *Archives of Internal Medicine*, 2000, Volume 160, pages 1641-49.

The relationship between estrogen and cognition among elderly and postmenopausal women is controversial. This study used the women participants in the Kame Project to determine whether unopposed estrogen and combined estrogen-progestin use are associated with rate of cognitive decline. Eight hundred thirty-seven women who participated in the baseline evaluation (1992-1994) and the two-year follow-up were studied. Approximately half of the cohort had never used any estrogen since menopause. One hundred eighty-six were past users, 132 were current users of estrogen alone, and 64 currently used both estrogen and progestin. After adjustment for other factors known to affect cognitive performance, persons using estrogen alone had the greatest improvement in cognitive testing, whereas, those who used estrogen and progestin together performed significantly worse than those who had never used any postmenopausal hormones, like estrogen or progestin.

We concluded that these findings supported a beneficial association between current unopposed estrogen use and rate of cognitive change, and suggested that the addition of progestin had a modest detrimental association. These findings are

currently being tested in a more rigorous fashion as part of the large national study called the Women's Health Initiative.

- C. Alcohol, aging, and cognitive performance in a cohort of Japanese Americans aged 65 and older: The Kame project. Authors: Bond GE, Burr R, McCurry SM, Graves A. Borenstein, Larson EB. *International Journal of Psychogeriatrics*, 2001, Volume 13(2), pages 207-223.

This study was designed to investigate the effects of light to moderate alcohol consumption on cognitive performance. It has been known for many years that low to moderate alcohol consumption is associated with improved survival. Many of these observations were findings from the original Honolulu Heart Watch study. This study looked at cognitive performance during the screening phase of the Kame Project by studying 1,836 participants who did not display dementia at the time they were enrolled. Overall, the test scores were lower for men who were either abstinent or heavy drinkers. Men in the light to moderate alcohol consumption group scored better. For women, a similar protective effect was seen for some measures of cognitive function, but not for all. These results suggest that there was a possible positive relationship between light to moderate drinking and cognitive performance in this aging, Japanese American population. Since studies conducted over time are the best way to determine the relationship between variables such as alcohol and cognition, the following study was done.

- D. A prospective study of alcohol and cognitive performance in a cohort of Japanese American older adults. Authors: Bond GE, Burr R, McCurry SM, Graves A. Borenstein, Larson EB. (Abstract) *The Gerontologist*, Volume 40 (Special Issue I), 2000, page 43.

This study looked at the effects of light to moderate alcohol consumption on cognitive performance over time. A total of 1,416 persons who completed the baseline and 2 and 4 year follow-up interviews were included. Findings showed that light to moderate drinking for men under the age of 76 resulted in better cognitive tests scores than for non-drinkers. In contrast, older women (≥ 76 years) who were light to moderate drinkers showed higher cognitive performance than non-drinkers. These findings, conducted over time, suggest that light to moderate alcohol consumption in this Japanese American population did not have a negative effect on certain tests of cognitive performance, and that gender and age differences represent important variables when studying the relationship between light to moderate drinking and cognitive performance in older adults.

Since there have been no published studies comparing the role of ethnicity in

relationship to alcohol and cognitive performance, the following study was done, comparing this older Japanese American population with older Caucasians.

- E. Alcohol, aging, and cognitive performance: A cross-cultural comparison. Authors: Bond, GE, Burr R, Rice MM, McCurry SM, Graves, AB, Teri, L, Bowen JD, McCormick WC, Larson EB. *Journal of Aging & Health*, 2002 (in press).

This study looked at alcohol and cognitive performance at the screening phase of the Kame and the ACT studies. There were 1,836 Japanese American and 2,581 Caucasians who did not display dementia at the screening phase of these two projects. Findings showed that Caucasian drinkers scored higher than Japanese American drinkers on one test of overall cognitive performance. In contrast, Japanese-American drinkers scored faster than Caucasian drinkers on a test that measured speed. The results indicated that current drinking behavior was not related with poor cognition in either the Caucasian or Japanese American groups.

- F. Ethnicity and cognitive performance among older African Americans, Japanese Americans, and Caucasians: The role of education. Authors: Shadlen MF, Larson EB, Gibbons LE, Rice MM, McCormick WC, Bowen J, McCurry SM, Graves AB. *Journal of the American Geriatric Society*, 2001, Volume 49, pages 1371-1378.

This study used the screening data from the Kame Project and a companion study in Group Health—the so-called Adult Changes in Thought study of the UW/ Group Health Alzheimer’s Disease Patient Registry. The purpose of the study was to evaluate whether there is an association between ethnicity and cognitive performance, and whether education modifies the association. A total of 103 African Americans, 1,388 Japanese Americans, and 2,306 Caucasians were evaluated. Overall, African Americans scored significantly lower than either Japanese Americans or Caucasians on the Cognitive Abilities Screening Instrument (CASI). However, education affected the scores differently within the groups. The gap between ethnic groups decreased for African Americans in the high education group compared with Japanese Americans and Caucasians. The conclusion was that the increased ethnic discrepancy in cognitive test scores is largely related to differences found in persons with low levels of education and may reflect differential education quality. Much of this education quality difference may relate to, not only generally low educational attainment as a risk factor for Alzheimer’s disease, but also, the likelihood that less-educated African Americans had qualitatively inferior educational experiences than less-educated Japanese Americans and Caucasians. This difference may relate to the fact that many African Americans in Seattle come from the South, where segregated schools, for this generation, generally had inferior education and were a proxy for low

socio-economic status during early life.

- G. Impaired olfaction as a clinical marker for cognitive decline. Interaction with apolipoprotein E ϵ 4 status. Authors: Graves A, Borenstein, Bowen JD, Rajaram L, McCormick WC, McCurry SM, Schellenberg GD, Larson EB *Neurology*, 1999, Volume 53, pages 1480-1487.

It has been known that patients with Alzheimer's disease have difficulty detecting and identifying odors. It is felt that this problem might be related to the disease affecting parts of the brain where the sensation of smell (olfaction) is processed. This part of the brain is typically involved early in the course of Alzheimer's disease.

As part of the Kame Project, all subjects were asked to complete a twelve-item cross-cultural smell identification test. This study analyzed the relationship of cognitive decline to the sense of smell at enrollment and the apolipoprotein E ϵ 4 status. Compared with persons who had normal smell sense (so-called normosmics), persons with impaired smell sense or no smell sense were at increased risk for cognitive decline. The increase in risk was relatively modest—from 25% to 90% (1.25-1.9 fold). However, persons who had no smell sense at enrollment and at least one apoE ϵ 4 allele were at nearly five times the risk for cognitive decline—the risk was especially large in women compared to men.

We concluded that unexplained dysfunction in smell in the presence of one or more apoE ϵ 4 alleles is a high risk factor for cognitive decline. It will be important to determine if this relationship continues as persons go on to develop full-blown Alzheimer's disease.

4. Long Term Care Studies

The Kame Project provided a unique opportunity to study preferences, attitudes, and patterns of long-term care in the Japanese American community. It will also, eventually, allow us to compare these patterns between the Japanese American population and the general population in Seattle, which is largely Caucasian.

- A. Attitudes toward use of nursing homes and home care in older Japanese-Americans. Authors: McCormick WC, Uomoto J, Young H, Graves A, Borenstein, Vitaliano P, Mortimer JA, Edland SD, Larson EB. *Journal of the American Geriatrics Society*, 1996, Volume 44, pages 769-777.

This study was designed to identify preferences and attitudes regarding use of long-term care, either nursing home or home care. One thousand one hundred forty-two older Japanese American subjects were asked to consider hypothetical situations in which they were temporarily disabled by hip fracture, or permanently disabled by

dementing illness. Of persons fracturing a hip, only 12% intended to use a nursing home, 29% intended to recover at home, and another 54% intended to use paid home health care. However, if they became demented, the majority (53%) intended to use a nursing home. Only 11% intended to rely on family and friends for care, and another 29% intended to use paid home health care. There was good agreement between the responses of subjects and what the subjects believed their family or friends wished them to do. The preferences of family and friends were more important than the perceived wishes of religious figures or the Japanese American community at large. The factors that correlated with the intention to enter a nursing home were a lack of social support (unmarried, few or no close relatives), female gender, and higher levels of acculturation into American society. Age and female gender were predictors of intention to use home care.

The conclusion of this study was that older Japanese Americans in the Pacific Northwest often intend to enter nursing homes if they become disabled by dementing illness. The actual use is similar to the general U.S. older population. We believe that this is attributable largely to the existence of an ethnically appropriate nursing home (Keiro), which is strongly supported by and familiar to the Japanese American community and King County. The intention to use long-term care services appears to be dependent primarily on the level of social supports and acculturation into American society.

- B. Advance directive preferences among subpopulations of Asian nursing home residents in the Pacific Northwest. Authors: Vaughn G, Kiyasu E, McCormick WC. *Journal of the American Geriatrics Society*, 2000, Volume 48, pages 554-557.

The purpose of this study was to determine how different populations in Asian nursing homes address end-of-life issues—specifically, so-called advance directives. Advance directives describe a person's wishes with regard to cardiopulmonary resuscitation (CPR), artificial nutrition, intravenous fluids for hydration, and mechanical ventilation for breathing assistance. The study compared residents belonging to Chinese, Japanese, and other Asian ethnic groups (Korean, Philippino, South East Asian). The majority of patients in these nursing homes were “no code”, indicating that they preferred not to have any resuscitation efforts made were they to die unexpectedly in the nursing home. Japanese Americans were more likely to be no code (85%), compared with Chinese Americans (62%). Higher age and more comorbid illness were also associated with no code status.

This demonstrated that code status differs among Asian subgroups in these ethnic nursing homes in Seattle. This research indicates the importance of identifying and understanding cultural factors that influence people's views of life and death, and

feelings about medical interventions at the end of life.

5. **Successful Aging and Other Topics**

The Kame Project afforded an opportunity to study other aspects of aging, including the oft-expressed preference for “successful aging”. These studies spanned a broad array of topics, ranging from performance in cognitive tests, to maintenance of musculoskeletal function, especially as it relates to osteoporosis and osteoarthritis, frailty, sleep disturbance, depression, and general attitudes towards successful aging.

- A. Neuropsychological test performance in a cognitively intact sample of older Japanese American adults. Authors: McCurry SM, Gibbons LE, Uomoto JM, Thompson ML, Graves A, Borenstein, Edland SD, Bowen J, McCormick WC, Larson EB. Archives of Clinical Neuropsychology, 2001, Volume 16, pages 447-459.

This study was designed to present population based data, showing the effects of age on cognitive test performance in older Japanese American adults. Two hundred one Japanese American subjects, aged 70 and older, without dementia, were studied. These persons completed a large, neuropsychological assessment battery testing an array of skills, including arithmetic skills, concentration, and psychomotor speed, among others. Older age was associated with significantly lower scores on all tests. Less than high school education was associated with lower scores on most tests, except those associated with psychomotor tasks. Women and English-speaking participants scored higher than men and Japanese speakers on various tests of memory, attention, and visual motor ability. The study reinforces the importance of using appropriately corrected norms when interpreting results of cognitive screening tests.

- B. Dietary soy isoflavone intake in older Japanese American women. Authors: Rice MM, LaCroix AZ, Lampe JW, van Belle G, Kestin M, Sumitani M, Graves A, Borenstein, Larson EB. Public Health Nutrition, 2001, Volume 4(5), pages 943-952.

Our co-investigator, Madeline Murguia Rice, made many contributions to the Kame Project. Her PhD project involved the study of dietary soy and its relationship to musculoskeletal health, especially osteoporosis. This study was designed to describe the most commonly consumed soy foods and a general estimate of dietary soy isoflavone (a natural plant estrogen) to compare these with previously published estimates of diet in other Japanese samples. Two hundred seventy-four women over age 65 were recruited from the Kame Project. The soy foods most commonly consumed were tofu, miso and aburaage. Mean intake of dietary soy isoflavones was estimated to be about one-quarter to one-half that of published estimates in Japanese samples in Japan. Increased consumption of dietary soy was associated with

speaking Japanese, a more traditional Japanese diet, vitamin E supplement use, and walking several blocks per day. The study concluded that the Japanese American women in King County have adopted a soy intake that is considerably less than persons living in Japan, but more than the average Caucasian diet. Dietary soy intake was associated with speaking Japanese, and a healthy lifestyle and dietary habits.

- C. Diagnosing osteoporosis in Japanese American women. Authors: Rice MM, Larson EB, LaCroix AZ, Drinkwater BL. *American Journal of Medicine*, 2001, Volume 110, pages 241-242.

This important study looked at the difference in bone mineral density in Asian and Caucasian women. The study demonstrated that the average values in the 273 Japanese American women studied obtained with a commonly used bone density measuring system were very different than the “normal” Caucasian American reference values provided by the manufacturer of the system. This could lead to an over-diagnosis of osteoporosis in Japanese American women. This is important because Japanese American women generally have a lower rate of hip and vertebral fractures. The paper suggests that it will be important to determine the longitudinal risk of future fractures in this population, and likely, create ethnically appropriate control values.

- D. Soy consumption and bone mineral density in older Japanese American women in King County, Washington. Authors: Rice MM, LaCroix AZ, Lampe JW, van Belle G, Kestin M, Drinkwater BL, Graves AB, Larson EB. Abstract presented at the annual meeting of the North American Menopause Society and the International Symposium on the Role of Soy in Preventing and Treating Chronic Diseases, 2001.

Estrogen replacement therapy is a common therapy used in postmenopausal women to slow the progression of bone loss. An important related question is whether the naturally occurring plant estrogens found in soy (isoflavones) may also influence bone mineral density. This study examined the relationship between dietary soy isoflavone intake and bone mineral density in 267 women participating in the Kame Project. After adjustment for other factors known to be associated with bone mineral density (such as age, weight, and estrogen use) women who consumed the highest amounts of soy isoflavones had the highest bone mineral density. These data suggest that soy may be good for the bones, however it is important that future studies address whether soy can reduce the risk of fractures, especially hip and vertebral fractures.

- E. A prospective study of depression in a cohort of Japanese American older adults.

Authors: Bond GE, Burr R, McCurry SM, Rice MM, Graves A, Borenstein, Larson EB. (Abstract) *The Gerontologist*, 2000, Volume 41 (Special Issue I), page 177.

This study looked at depression over a six year period with 1,836 Japanese American men and women. This study showed that study participants who were born in Japan and migrated to the U.S. (Issei) had higher ratings of depression at baseline but much lower ratings at the two and four year follow-up times than Nisei (U.S. born and educated) or Kibei (individuals who were born in the U.S. and spent part or all of their education in Japan). These findings demonstrate very low rates of depression for this group of aging Japanese Americans, and that migrant status may represent an important variable contributing to successful aging.

- F. Older adults and functional decline: A cross-cultural comparison. Authors: McCurry SM, Gibbons LE, Bond GE, Rice MM, Graves A, Borenstein, Kukull WA, Teri L, Higdon R, Bowen JD, McCormick WC, Larson EB. *International Psychogeriatrics*, 2002, manuscript under review.

This study looked at the relationship between functional independence in common activities of daily living and a variety of medical conditions and life style practices in Japanese-American adults enrolled in the Kame study, and compared results to those from Caucasian older adults who were enrolled in another study of aging, the Adult Changes in Thought (ACT) study. The study looked at data from 1,083 Kame subjects and 1,011 ACT subjects who had no functional limitations when they entered their respective studies. After four years of follow-up, 70% of all subjects still had no problems with their daily activities, and fewer than 5% had developed five or more problems. Factors that were associated with functional decline over the follow-up period included a number of medical risk factors such as a history of cerebrovascular disease, arthritis, diabetes, high blood pressure, obesity, and smoking. Older participants and women were more likely to decline over the follow-up period. Depression and poor self-perceptions of health were also predictors of decline. There was some evidence that Japanese-speaking Kame subjects had slower decline than English-speaking Kame or ACT subjects. Future studies will be needed to examine whether this is due to differences in persons who maintain a more traditional Japanese life-style, or because Japanese-speakers were somewhat more likely to discontinue participation over time or minimize their complaints of functional difficulty in follow-up interviews.

6. Methodologic Studies

Finally, there are a number of published studies that contribute to the scientific method as it relates to the study of dementia, aging, and related topics. Even before the

Kame Project was launched, preliminary work was accomplished to develop the Cognitive Abilities Screening Instrument (CASI) by a group that included Evelyn Teng from Los Angeles, Kasuo Hasegawa and Akira Homma from Japan, Lon White, Kasahiro Yano and others from Honolulu, and Amy Borenstein Graves and Eric Larson from Seattle. The measure has enjoyed widespread use in trans-Pacific research, including projects in Taiwan, Guam, Japan, Honolulu, Seattle, and Los Angeles, in addition to projects with Spanish-speaking populations.

- A. Standardization of the clinical diagnosis of dementia syndrome and its subtypes in a cross-national study: The Ni-Hon-Sea experience. Authors: Larson EB, McCurry SM, Graves A. Borenstein, Bowen JD, Rice MM, McCormick WC, Zee N, Homma A, Imai Y, White L, Masaki K, Petrovitch H, Ross W, Yamada M, Mimori Y, Sasaki H. *Journal of Gerontology, Medical Sciences*, 1998, Volume 53A(4), pages M313-M319.

This study demonstrated that fifteen clinicians from four participating sites could develop good levels of agreement for the diagnosis of dementia in 85 patients. This occurred after clinicians had agreed to follow common standards for diagnosis. The study demonstrated that use of common criteria to classify dementia cases would make cross-national research possible. However, to achieve good agreement, the investigators had to have clear-cut guidelines for interpretation, and the guidelines needed to be followed.

- B. Estimation and sample design in prevalence surveys of dementia. Authors: Edland SD, Graves A. Borenstein, McCormick WC, Larson EB. *Journal of Clinical Epidemiology*, 1999, Volume 52, pages 399-403, 1999.

Blomqvist revisited: How and when to test the relationship between level and longitudinal rate of change. Author: Edland SD. *Statistics in Medicine*, 2000, Volume 19, pages 1441-1452.

Mixed effect models of longitudinal Alzheimer's disease data: A cautionary note. Authors: Milliken JK, Edland SD. *Statistics in Medicine*, 2000, Volume 19, pages 1617-1629.

Estimating reference ranges from stratified two-stage samples. Authors: Thompson ML, Edland SD, Gibbons LE, McCurry SM. *Journal of the Royal Statistical Society*, 2001, Volume 164, part 3, pages 505-516.

These four studies were published in statistics and epidemiology journals.

They discuss the lessons learned from how we selected our sample, the nature of measuring change, the rate of change in studies that make repeated measurements over time, and the effect of sampling on the reference ranges of tests, like the CASI. All the studies used data from the Kame Project and should be helpful to investigators around the world who are working on studies of dementia and other age-related illnesses.

7. **The Future**

The Kame Project's database is a rich resource that will be used by Kame and other investigators over the years to come, for up to fifteen years. In addition to genetic data, we have a great deal of information from participants about their lives, their health behaviors, their diagnoses and medications, their social support, migration status, acculturation, diet, exercise and other factors. Scientific papers will continue to be written and the Kame Project will live on for many more years in this way.

In addition, we have a new NIH grant proposal that is pending review. This proposal will seek to combine the data obtained from the three sites: Hiroshima, Japan, Honolulu, Hawaii, and Seattle, Washington to answer the cross-national questions we set forth in the late 1980s and early 1990s, namely: (1) do prevalence and incidence rates of Alzheimer's disease really increase as Japanese populations move from Japan to Hawaii, where there is a real admixture of cultures, to Seattle, where there is a great deal of acculturation to Western society? Do the rates for vascular dementias show the reverse trend, with higher stroke rates in Japan being translated into higher dementia rates due to stroke there, with lower rates in Hawaii and still lower ones in Seattle? (2) What is the constellation of risk factors that predispose individuals to Alzheimer's disease, vascular dementia, or a mixture of these two conditions, and do they differ by study site? (3) What is the clinical presentation of prevalent and incident cases at the three sites and how do they differ? (4) Do individuals live longer with Alzheimer's disease than with vascular dementia, and does this vary by study site, and finally, (5) given that Japanese have the greatest longevity of any population in the world, do Japanese Americans in Seattle-King County live longer than Japanese Americans in Honolulu or Japanese in Japan? Does American lifestyle and education increase the ability to survive to extreme old ages? Only using the combined data from the three sites will these questions be answered. Dr. Amy Borenstein Graves has written this proposal and submitted it for review (February 1, 2002). It will be reviewed in June 2002 by the NIH study section and we should have information regarding its funding by October. This project brings together the principal investigators from each of the sites to coordinate data analyses and writing of manuscripts to address the five questions above. We hope that the scientific papers resulting from this project will be published as a series in a special issue of a top-notch journal such as *Neurology* or the *International Journal of Epidemiology*. This project

is the natural culmination of many years of effort to carry out standardized studies of Japanese populations in three geographical regions. These three studies provide a wealth of information in genetically homogeneous populations that migrate from the East to the West. The information from these three studies will allow us to sort out whether environmental and lifestyle changes associated with migration are accompanied by changes in risk factors and rates of specific types of dementia.