Published in final edited form as:

Alzheimer Dis Assoc Disord. 2014 ; 28(1): 23–29. doi:10.1097/WAD.0b013e3182a2e32f.

Incidence Rates of Dementia, Alzheimer's disease and Vascular Dementia in the Japanese American Population in Seattle, WA: The *Kame* Project

AR Borenstein, PhD¹, Y Wu, PhD¹, JD Bowen, MD², WM McCormick, MD³, J Uomoto, PhD⁴, SM McCurry, PhD⁵, G Schellenberg, PhD⁶, and EB Larson, MD.⁷

¹Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida, Tampa, FL

²Multiple Sclerosis Center, Swedish Neuroscience Institute and University of Washington Medical Center, Seattle, WA

³University of Washington Harborview Medical Center, Seattle, WA

⁴Children's Center for Neuropsychological Rehabilitation, Barrow Neurological Institute, Phoenix, AZ

⁵School of Nursing, University of Washington, Seattle, WA

⁶Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

⁷Group Health Research Institute, Group Health Cooperative, Seattle, WA

Abstract

There are few dementia incidence studies in representative minority populations in the U.S., and no population-based studies of Japanese American women. We identified 3,045 individuals aged 65+ with at least 1 parent of Japanese descent living in King County, WA in 1992–4, of which 1,836 were dementia-free and were examined every two years (1994–2001) to identify incident cases of all dementias, Alzheimer's disease (AD), vascular dementia (VaD) and other dementias. Cox regression was used to examine associations with age, sex, years of education and Apolipoprotein (APOE)-ε4. Among 173 incident cases of dementia, the overall rate was 14.4/1,000/yr, with rates being slightly higher among women (15.9/1,000) than men (12.5/1,000). Rates roughly doubled every 5 years for dementia and AD; the age trend for VaD and other dementias was less consistent. Sex was not significantly related to incidence of dementia or its subtypes in adjusted models. There was a trend for an inverse association with increasing years of education. APOE-ε4 was a strong risk factor for all dementias (HR=2.89, 95% CI 1.88–4.46), AD (HR=3.27, 95% CI 2.03–5.28) and VaD (HR=3.33, 95% CI 1.34–8.27). This study is the first to report population-based incidence rates for both Japanese American men and women.

Corresponding author: Dr. Amy R. Borenstein, Department of Epidemiology and Biostatistics, College of Public Health, MDC-56, University of South Florida, 13201 Bruce B. Downs Blvd, Tampa, FL 33612-3805. Tel: 813-974-6670. Fax: 813-974-4719. aborenst@health.usf.edu.

Conflicts of Interest: The authors have no conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest.

Key words/phrases

Incidence rates; population-based cohort studies; risk factors; Alzheimer's disease; vascular dementia; dementias

INTRODUCTION

Marked geographic differences in the relative proportions of dementia subtypes were thought to exist in the 1980s–1990s between Asia and the West, with Alzheimer's disease (AD) accounting for the majority of cases in the West and vascular dementia (VaD) being more common in Asia¹. The *Ni-Hon-Sea Project* was conducted in Hiroshima, Japan (The Adult Health Study, AHS); Honolulu, Hawaii (Honolulu-Asia Aging Study, HAAS) and Seattle, Washington (*Kame Project*) to examine prevalence and incidence rates and risk factors for dementia and its subtypes among Japanese populations in Japan and among immigrants and U.S.-born individuals, with the goal to discover whether rates of AD increase with migration to the West². Incidence rates for dementia and its subtypes from Japanese American populations have been published from the Honolulu-Asia Aging Study, which included only men³. The *Kame Project* is the first population-based study of dementia among community-dwelling Japanese American men and women.

METHODS

Study population

Identification and recruitment of the baseline population has been described previously¹. A study census was conducted of all Japanese Americans in King County, WA aged 55 and over, representing 90% of all Japanese Americans of this age group as identified by the 1990 US census (1). The study is named *Kame* (pronounced *kah-meh*) after the turtle, the Japanese symbol of longevity. Ninety-six percent of the population had 2 parents of Japanese origin; the remainder had one. Of 3,062 eligible residents, 3,045 were alive and invited and 1,985 (65.2%) agreed to participate in the baseline examination (May 1992–May 1994). Of these, 149 were found to have prevalent dementia (1); the remaining 1,836 were considered dementia-free.

Procedures

Baseline evaluation—Baseline evaluations were conducted from 1992–1994 in English or Japanese (21.6%). Highly-structured interviews were administered in-person by trained interviewers to gather risk factor data from non-demented participants.

We screened for dementia using the Cognitive Abilities Screening Instrument (CASI)⁴ over the follow-up period (May 1994–Dec 2001) consisting of four incidence waves: 1994–1996; 1996–1998; 1998–2000 and 2000–2001. Figure 1 shows the numbers of participants alive and those lost to follow-up at each successive wave. At each incidence wave, participants scoring <87/100 on the CASI were invited for proxy, neurologic and neuropsychological evaluations. A cut-point of 87 was selected to provide high sensitivity; at baseline, a CASI score of 86 had a sensitivity of 0.94 and a specificity of 0.94 for dementia⁴. Proxy interviews

included the Clinical Dementia Rating Scale⁵, Blessed Dementia Rating Scale⁶ and Informant Questionnaire on Cognitive Decline in the Elderly⁷. Standard neuropsychological batteries were administered by a trained psychometrist and interpreted by a geriatric neuropsychologist (JU/SM), and clinical and neurologic examinations were performed by a neurologist (JB) or a geriatrician (WC). The Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery was used⁸, excluding the MMSE, which is embedded in the CASI. Additional tests included: the Wechsler Memory Scale-Revised, Verbal Paired Associates (immediate and delayed recall)⁹, Trailmaking Test Parts A and B¹⁰, Digit Span and Digit Symbol subtests of the Wechsler Adult Intelligence Scale—Revised¹¹ and the CES-D¹². Participants suspected of having dementia had standard laboratory evaluations and some of these had non-contrast CT brain scans.

Dementia and subtype diagnoses were made by consensus committee (JB, WC, SM, JU, ARB, NZ), employing the Diagnostic and Statistical Manual IV (DSM-IV)¹³ blinded to CASI scores. The DSM-IV criterion of “impairment in social or occupational function... and decline from a previous level of functioning” was judged by changes in job performance, household responsibilities, hobbies, community and driving ability or personal activities. The NINCDS-ADRDA criteria¹⁴ were used to classify probable/possible AD and the NINDS-AIREN criteria¹⁵ for probable/possible VaD. Possible AD and possible VaD were not mutually exclusive, and some participants received both diagnoses. We report here incidence rates for all dementias (DSM-IV), probable and possible AD, probable and possible VaD, and other dementias.

Between 1994–1996, the cohort was invited to a blood draw to genotype the Apolipoprotein E gene¹⁶; 65.6% participated. Other variables used here (age, sex and years of education) were self-reported from the risk factor questionnaire.

All participants gave written informed consent and the study was approved by the University of Washington and University of South Florida IRBs.

Statistical Analysis—Incidence rates for dementia, AD and VaD were calculated using person-years. Crude rates were determined by dividing the number of new cases by the number of person-years at risk in 5-year age strata beginning at age 65 and ending with age 95+ (expressed per 1,000/year). Age was used as the time scale, such that for each non-demented participant, the number of person-years contributed was the difference between the age at study entry (left-truncation) and the age at last biennial examination. For demented participants, the age at which dementia occurred was the midpoint between the latest exam in which they were considered non-demented and the first exam at which they received a dementia diagnosis. 95% confidence intervals (CI) for incidence rates were derived assuming a Poisson distribution for the number of cases within each age stratum.

Multiple imputation techniques were used to adjust for participants who became demented at the first biennial visit but had missing values on dementia status at baseline due to not being sampled, or who were sampled but did not come in for the baseline diagnostic examination (n=68). The imputations were based on the probability of dementia given CASI

and baseline age¹⁷. The imputations account for any differences in the numerators and denominators in the tables.

Age, sex, level of education (continuous and categorical, analyzed in this population as <8, 9–11, 12 and 13 years) and APOE genotype (presence or absence of an $\epsilon 4$ allele) were examined using Cox proportional hazards regression models with age as the time scale left-truncated at baseline age. Hazard Ratios (HR) are reported with 95% CI and *P*-values. All analyses including multiple imputation macros were conducted using SAS 9.3 (Cary, NC).

RESULTS

From the non-demented cohort (N=1,836), 454 screened below 87 on the CASI during the follow-up period and received full clinical evaluations; 173 of these met criteria for incident dementia. Figure 1 shows the number of incident cases at each wave and those lost to follow-up (1992–2001).

Table 1 depicts the total number of incident cases arising during the follow-up period (1994–2001). As participants could meet either probable or possible NINCDS/ADRDA and probable or possible NINDS-AIREN criteria (e.g., probable AD by NINCDS/ADRDA and possible VaD by NINCDS/AIREN, or possible AD and possible VaD), the numbers shown are not mutually exclusive. There were 17 other dementias, 1 due to vascular disease, 2 to Parkinson's disease, 2 to head trauma, 5 due to other general medical conditions, 1 substance-induced dementia, and 4 due to multiple etiologies, and 2 due to unknown causes.

Table 2 shows baseline characteristics of the participants who did and did not become demented during follow-up. Women who became cases were older than men who became cases ($p=0.008$). Cohort participants who remained unaffected had more education than those who became cases (1.6 years more education for men and 0.8 years more education for women) ($p<0.0001$). About 20% of the cohort had 1 or 2 APOE- $\epsilon 4$ alleles, with 38.5% of incident cases and 18.8% of unaffecteds possessing an APOE- $\epsilon 4$ allele, with no differences by sex ($p=0.36$).

We imputed incidence rates for 68 individuals who were sampled at baseline for the prevalence phase, but who did not come in for clinical evaluation until the first incidence wave. Of these 68, 18 were found to have incident dementia at the first biennial who had missing data from baseline. Five imputations were conducted, and based on these, 5, 7, 7, 3 and 5 of the 18 subjects were imputed to have had dementia at baseline. We used the first imputation in our incidence analyses to take these cases into account.

Age and sex-specific incidence density rates and 95% CIs are shown in Table 3 for all dementias, AD, VaD, and other dementias. AD was the most common form of incident dementia in this population. The overall incidence rate for all dementias was 14.4/1,000 (95% CI: 12.3, 16.4); for AD, 11.3 (95% CI: 9.4, 13.2) and for VaD, 4.4 (95% CI: 3.2, 5.6). For women, the rates were 15.9 (95% CI: 13.0, 18.8); 13.2 (95% CI: 10.5, 15.9), and 5.3 (95% CI: 3.6, 7.0) for all dementias, AD and VaD; for men, the corresponding rates were 12.5 (95% CI: 9.5, 15.5), 8.8 (95% CI: 6.3, 11.3), and 3.3 (95% CI: 1.8, 4.9), respectively.

The incidence rates for all dementia and AD increased with age in both sexes, approximately doubling every 5 years. A less consistent age trend was evident for VaD. Women had higher incidence rates than men for all dementia and AD in most age groups. Women aged 80–89 had higher rates of vascular dementia compared with men. Rates for ‘other dementias’ were based on very small sample sizes.

When Cox models were constructed, neither sex nor education was associated with any of the outcomes, although there was a trend for education to be inversely associated with dementia and AD (all dementia HR=0.94, 95% CI 0.87–1.02; AD HR=0.92, 95% CI 0.84–1.01; VaD HR=1.07, 95% CI 0.92–1.25). The presence of one or two APOE-ε4 alleles was the sole statistically significant predictor of all dementias (HR= 2.89, 95% CI: 1.88, 4.46), AD (HR=3.27, 95% CI: 2.03, 5.28), and VaD (HR=3.33, 95% CI: 1.34, 8.27), adjusting for sex and years of education.

DISCUSSION

In this population-based study of Japanese Americans living in King County, WA, the overall incidence rate for all dementias was 14.4/1,000 (95% CI: 12.3, 16.5) in 11,638 person-years, with women having an incidence rate of 15.9/1,000 (95% CI: 13.0, 18.8) and men 12.5/1,000 (95% CI: 9.5, 15.5). The overall incidence rate for AD was 11.3/1,000 (13.2/1,000 for women and 8.8/1,000 for men), and for VaD, 4.4/1,000 (5.3/1,000 for women and 3.3/1,000 for men). This is the first time that rates for Japanese Americans can be compared by sex within one population, the only other study of Japanese Americans being the Honolulu-Asia Aging Study, which was conducted among only men.

Comparison with other large population-based studies

Age and sex-specific incidence rates for dementia in the *Kame* Project were generally close to those found in other studies. Our rates were higher in the oldest old (85+) than those in the Rotterdam Study¹⁸, but the small number of cases in this age stratum may obscure true differences. Women aged 85+ in *Kame* had higher rates than those from the Framingham Study¹⁹, but among older men, rates were similar. Incidence rates from France (PAQUID)²⁰ were similar to those in *Kame* for all dementias and AD, except at ages 70–74 and 80–84 where PAQUID’s rates were somewhat higher. Differences in cognitive screening tests, sampling procedures, case definitions and other methodologic applications may hamper the comparison of rates between studies. Our rates were consistent with a meta-analysis of 23 studies²¹. An unexpected finding in our study was the apparent higher rate of vascular dementia seen in women: 5.3 (95% CI: 3.6, 7.0) vs. 3.3 (95% CI: 1.8, 4.9) in men. In Hiroshima²², comparable rates averaged out to be about half that seen in *Kame* women.

We could not conduct a meta-analysis comparing incidence rates from *Kame* with those from Hiroshima²², Honolulu³ and ACT²³ in Seattle, WA due to minor differences in methodologic applications at the four sites, such as using different CASI cut-points and using different clinical criteria in the published incidence papers. Descriptively, age-specific rates for AD were similar in the *Kame* Project and Hiroshima²² and in Caucasians studied in ACT²³. For men, HAAS reported lower rates for AD than the other studies³.

Incidence rates and sex—Whether women are at higher age-specific risk of dementia/AD than men is still not resolved. In this study, no differences were found. One meta-analysis²⁴ found that women are about 50% more likely to develop AD, but no difference by sex was found when the outcome was overall incidence of dementia. Jorm²¹ reported that while the difference in risk by sex is small, women aged 85+ tend to have higher incidence rates than men. In a study focusing on people aged 90+²⁵, there were no differences by sex. The AHS²² and ACT²³ also found no differences by sex.

Incidence rates and education—Education has been shown in many studies to be associated with incident dementia and AD²⁶ but about half show no association, and in *Kame*, education was not statistically significant in the fully-adjusted models. However, in models not adjusted for APOE-ε4, education was inversely associated with the risk of dementia and AD but not VaD. The fact that education lost statistical significance when APOE-ε4 was added to the model may be related to lower statistical power due to reduced sample size (not all participants donated blood). Consistent with this view, the point estimate did not change for AD and increased only slightly for all dementias. Education can be considered in the context of other early-life exposures²⁷, such as perinatal conditions, early-life brain development, body growth and socioeconomic conditions, environmental enrichment and neural reserve as one of many variables that may preserve brain function. Sharp and Gatz²⁶ extended this model to variables that occur during adulthood such as healthy lifestyle and cognitive stimulation and their associations with reduced risk for dementia in late-life. In addition, several studies that consider both intelligence (IQ) and education simultaneously show that including IQ in the predictive model nullifies the significant association with education^{27,28}. In representative autopsy studies, risk factors for disease expression such as education and head circumference are not related to neuropathology^{29,30}. In different populations, variables related to achieved education in childhood and/or adulthood may be surrogates for years of formal education. In the *Kame* Project for example, verbal IQ from the National Adult Reading Test-Revised was correlated with education 0.42 ($p=0.0001$)³¹. The direct measurement of years of education may have different meaning in different cultures and cohorts²⁶.

Incidence rates and APOE—The frequency of APOE-ε4 in *Kame* is similar to that of other Japanese populations³². Table 4 displays the genotypes and isoform frequencies for APOE in *Kame*. *Kame* genotypes were just within Hardy-Weinberg equilibrium ($P=0.053$).

The presence of one or more ε4 alleles strongly predicted vascular dementia as well as AD, and with similar magnitude (HR=3.33, 95% CI: 1.34, 8.27 for VaD and 3.27, 95% CI: 2.03, 5.28 for AD). Studies of the association between APOE-ε4 and VaD are equivocal. A meta-analysis of Chinese Han showed a pooled Odds Ratio (OR) of 2.07 (95% CI: 1.69, 2.53) for VaD³³. However, another study of older Japanese conducted in Hisayama, Japan found no association between ε4 and VaD (RR=1.08, $p=0.86$)³⁴. In HAAS, no association was found between APOE-ε4 and incident VaD (RR=1.27, 95% CI: 0.33, 4.83)³. Among Caucasian populations, the Canadian Study of Health and Aging found an association between ε4 and incident VaD (OR=3.13, 95% CI: 1.76, 5.55)³⁵ and the Cache County study³⁶ also reported a significant HR for 2 alleles (HR=4.4, 95% CI: 1.6, 12.5), with the HR for 1 allele

approaching significance ($p=0.08$). In the Rotterdam Study³⁷, there was also a strong tendency for $\epsilon 4$ to be associated with clinically diagnosed VaD [$(\epsilon 2\epsilon 4$: HR=3.2 (95% CI: 1.0, 10.8); $\epsilon 3\epsilon 4$: HR=1.8 (95% CI: 0.9, 3.4) and $\epsilon 4\epsilon 4$: HR=8.6 (95% CI: 2.9, 25.2)]. We speculate that since the clinical diagnosis of VaD in our study included possible as well as probable VaD, VaD patients could have comorbid AD, strengthening the association with APOE- $\epsilon 4$.

Strengths and limitations—The *Kame* Project is representative of the Japanese American population of King County aged 65 and over and is the first population-based study of dementia to include Japanese American women. Our study had a high cut-point on the CASI for screening for incident dementia ($<87/100$), so it is likely that most of the incident cases that occurred during the follow-up period were captured. We asked the cohort for blood during the first incidence wave, and 39.5% refused. Participants in the study who refused blood donation and were missing APOE genotypes ($n=725$) were older (mean= 72.9 years) ($p<.001$), more likely to be women ($p=<0.001$), and somewhat less educated (mean=12.3 years) ($p<0.001$) than those who agreed. Therefore, those with complete APOE data in our study may have fewer risk factors for dementia, and analyses using APOE may be biased toward the null. A limitation is that we have no autopsy results and the associations with risk factors depend on the accuracy of the clinical diagnosis of dementia subtypes. The likelihood of misclassification is minimized by following strict, clinical diagnostic criteria that are standardly used in large epidemiologic studies and adjudicating all cases by consensus committee and monitoring dementia cases annually for disease progression. Further analyses will delineate Asian vs. Western dietary and cultural patterns that may be associated differentially with incident dementia in this cohort; we have previously published, among others, associations examining acculturation and early-life exposures^{38–41}, estrogen and dietary soy isoflavones⁴², alcohol consumption⁴³ and consumption of fruit and vegetable juices⁴⁴.

Acknowledgments

Source of Funding: This study was supported by NIH (AG09769-10).

We thank *Kame* Project coordinators Nina Chinn and Nancy Z. Quan, as well as the interviewers and psychometrists. We also acknowledge the assistance of Dr. Madeline M. Rice, Patti Tsubota Boorkman and Greta Hoshibata. We are grateful for the help of our colleagues in Japan and the United States: Drs. Kazuo Hasegawa, Akira Homma, Hideo Sasaki, Michiko Yamada, Yuki Imai, Lon White, Helen Petrovitch, Web Ross, Kamal Masaki, David Curb, James Mortimer, and Evelyn Teng. Finally, we thank our Community Advisory Board members for their support.

References

1. Graves AB, Larson EB, Edland SD, et al. Prevalence of dementia and its subtypes in the Japanese American population of King County, Washington state. The Kame Project. *Am J Epidemiol.* 1996; 144(8):760–771. [PubMed: 8857825]
2. Larson EB, McCurry SM, Graves AB, et al. Standardization of the clinical diagnosis of the dementia syndrome and its subtypes in a cross-national study: the Ni-Hon-Sea experience. *J Gerontol A Biol Sci Med Sci.* 1998; 53(4):M313–319. [PubMed: 18314572]
3. Havlik RJ, Izmirlian G, Petrovitch H, Ross GW, Masaki K, Curb JD, Saunderson SM, Foley DJ, Brock D, Launer LJ, White L. APOE- $\epsilon 4$ predicts incident AD in Japanese-American men: The Honolulu-Asia Aging Study. *Neurology.* 2000; 54:1526–1529. [PubMed: 10751272]

4. Teng ELHK, Homma A, Imai Y, Larson E, Graves A, Sugimoto K, Yamaguchi T, Sasaki H, Chiu D, White LR. The Cognitive Abilities Screening Instrument (CASI): A Practical Test for Cross-Cultural Epidemiological Studies of Dementia. *International Psychogeriatrics*. 1994; 6(1):45–58. [PubMed: 8054493]
5. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *British Journal of Psychiatry*. 1982 Jun;140:566–572. [PubMed: 7104545]
6. Blessed GTB, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*. 1968; 114:797–811. [PubMed: 5662937]
7. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. *Psychological Medicine*. 1989; 19:1015–1022. [PubMed: 2594878]
8. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish A Registry for Alzheimer's Disease (CERAD). I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989; 39:1159–1165. [PubMed: 2771064]
9. Wechsler, D., editor. Wechsler Memory Scale-Revised. New York: Psychological Corp; 1987.
10. Reitan, RM.; Wolfson, D., editors. The Halstead-Reitan Neuropsychological Test Battery. Tempe, AZ: Neuropsychology Press; 1985.
11. Wechsler, D., editor. Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corporation; 1981.
12. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measures*. 1977; 3:385–401.
13. American Psychiatric Association. Diagnostic and statistical manual of mental health disorders. 4. Washington, D.C: 1994.
14. McKhann G, Drachman D, Folstein MF, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]
15. Roman GC, Tatemichi TK, Erkinjuntii T, et al. Vascular demetnia: diagnostic criteria for research studies. report of the NINDS-AIREN International Workshop. *Neurology*. 1993; 42:250–260. [PubMed: 8094895]
16. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *Journal of Lipid Research*. 1990; 31(3):545–548. [PubMed: 2341813]
17. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res*. 1999; 8:3–15. [PubMed: 10347857]
18. Ott A, Breteler MM, van Harskamp F, et al. Incidence and risk of dementia. The Rotterdam Study. *American journal of epidemiology*. 1998; 147(6):574–580. [PubMed: 9521184]
19. Bachman DL, Wolf PA, Linn RT, Knoefel JE, Cobb JL, Belanger AJ, White LR, D'Agostino RB. Incidence of dementia and probable Alzheimer's disease in a general population: The Framingham Study. *Neurology*. 1993; 43:515–519. [PubMed: 8450993]
20. Letenneur L, Commenges D, Dartigues JF, Barberger-Gateau P. Incidence of dementia and Alzheimer's disease in elderly community residents of SouthWestern France. *International Epidemiological Association*. 1994; 23(4):1256–1261.
21. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology*. 1998; 51(3):728–733. [PubMed: 9748017]
22. Yamada M, Kasagi F, Mimori Y, et al. Incidence of dementia among atomic-bomb survivors — Radiation Effects Research Foundation Adult Health Study. *Journal of the Neurological Sciences*. 2009; 281(1–2):11–14. [PubMed: 19327783]
23. Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, van Belle G, Jolley L, Larson EB. Dementia and Alzheimer disease incidence: a prospective cohort study. *Archives of Neurology*. 2002; 59(11):1737–1746. [PubMed: 12433261]
24. Gao S, Hendrie HC, Hall KS, et al. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Archives of General Psychiatry*. 1998; 55(9): 809–815. [PubMed: 9736007]

25. Corrada MM, Brookmeyer R, Paganini-Hill A, et al. Dementia incidence continues to increase with age in the oldest old: The 90+ study. *Annals of Neurology*. 2010; 67(1):114–121. [PubMed: 20186856]
26. Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. *Alzheimer Dis Assoc Disord*. 2011; 25(4):289–304. [PubMed: 21750453]
27. Borenstein AR, Copenhaver CI, Mortimer JA. Early-life risk factors for Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006; 20(1):63–72. [PubMed: 16493239]
28. Plassman BL, Welsh KA, Helms M, et al. Intelligence and education as predictors of cognitive state in late life: a 50-year follow-up. *Neurology*. 1995; 45(8):1446–1450. [PubMed: 7644038]
29. Mortimer JA, Snowdon DA, Markesbery WR. Head circumference, education and risk of dementia: findings from the Nun Study. *Journal of Clinical and Experimental Neuropsychology*. 2003; 25(5):671–679. [PubMed: 12815504]
30. Bennett DA, Wilson RS, Schneider JA, et al. Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology*. 2003; 60(12):1909–1915. [PubMed: 12821732]
31. Borenstein Graves AR, Mortimer JA, Bowen JD, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Head circumference and incident Alzheimer's disease: modification by apolipoprotein E. *Neurology*. 2001; 57(8):1453–1460. [PubMed: 11673588]
32. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1988; 8(1):1–21.
33. Liu X, Li L, Liu F, et al. ApoE gene polymorphism and vascular dementia in Chinese population: a meta-analysis. *Journal of Neural Transmission*. 2012; 119(3):387–394. [PubMed: 21984189]
34. Ohara T, Ninomiya T, Kubo M, et al. Apolipoprotein genotype for prediction of Alzheimer's disease in older Japanese: the Hisayama Study. *J Am Geriatr Soc*. 2011; 59(6):1074–1079. [PubMed: 21649613]
35. Hsiung GY, Sadovnick AD, Feldman H. Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. *Canadian Medical Association Journal*. 2004; 171(8):863–867. [PubMed: 15477624]
36. Chuang YF, Hayden KM, Norton MC, et al. Association between APOE epsilon4 allele and vascular dementia: The Cache County study. *Dementia and Geriatric Cognitive Disorders*. 2010; 29(3):248–253. [PubMed: 20375505]
37. Slooter AJ, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study. *Neurology*. 2004; 62(7):1196–1198. [PubMed: 15079025]
38. Graves AB, Mortimer JA, Larson EB, Wenzlow A, Bowen JD, McCormick WC. Head circumference as a measure of cognitive reserve: association with severity of impairment in Alzheimer's disease. *British Journal of Psychiatry*. 1996; 169:86–92. [PubMed: 8818374]
39. Graves A, Borenstein, Mortimer JA, Bowen JD, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Head circumference and incident Alzheimer's disease: modification by Apolipoprotein E. *Neurology*. 2001; 57:1453–1460. [PubMed: 11673588]
40. Graves AB, Rajaram L, Bowen JD, McCormick WC, McCurry SM, Larson EB. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: The *Kame* Project. *Journals of Gerontology: Social Sciences*. 1999; 54B:S154–S161.
41. Borenstein AR, Wu Y, Mortimer JA, Schellenberg GD, McCormick WC, Bowen JD, McCurry S, Larson EB. Developmental and vascular risk factors for Alzheimer's disease. *Neurobiology of Aging*. 2005; 26(3):325–334. [PubMed: 15639310]
42. Rice MM, LaCroix AZ, Lampe JW, van Belle G, Kestin M, Sumitani M, Graves A, Borenstein, Larson EB. Dietary soy isoflavone intake in older Japanese American women. *Public Health Nutrition*. 2001; 4(5):943–952. [PubMed: 11784407]
43. Bond GE, Burr R, McCurry SM, Rice MM, Borenstein AR, Kukull WA, Teri L, Bowen JD, McCormick WC, Larson EB. Alcohol, gender, and cognitive performance: A longitudinal study comparing older Japanese and non-Hispanic White Americans. *Journal of Aging and Health*. 2004; 16(5)(26):615–640. [PubMed: 15448275]

44. Dai Q, Borenstein AR, Wu Y, Jackson JC, Larson EB. Consumption of fruit and vegetable juice and risk of Alzheimer's disease. *American Journal of Medicine*. 2006; 119:751–9. [PubMed: 16945610]

Figure 1.

Flowchart of *Kame* Project non-demented participants from baseline through four incidence waves, 1992–2001.

TABLE 1

Number of Incident Cases in the *Kame* Project, King County, WA from May 1994–Dec 2001, by Outcome Type (not Mutually Exclusive).

Diagnosis	Number of Cases
All Dementias	173
Probable AD	79
Possible AD	56
(Probable + possible AD)	135
Probable VaD	32
Possible VaD	20
(Probable + Possible VaD)	52
Other (DSM-IV)	17
Vascular	1
General medical conditions	9
Parkinson's	2
Head trauma	2
Other	5
Substance-induced	1
Multiple Etiologies	4
Head trauma	2
Other	2
Other, unknown	2

TABLE 2

Baseline Characteristics of 173 Incident Dementia Participants and 1,663 Unaffected Participants Enrolled in the *Kame* Project, King County, WA, May 1992–Dec 2001.

	All Dementias			Unaffected			<i>p</i> ^a
	Men	Women	Total (%)	Men	Women	Total (%)	
Number (%)	65 (37.6%)	108 (62.4%)	173	743 (44.7%)	920 (55.3%)	1,663	
Mean Age (SD)	75.6 (7.0)	078.0 (7.4)	77.1 (7.4)	71.2 (4.8)	71.5 (5.8)	71.4 (5.4)	< 0.0001
Age group							
65–69	12	10	22 (12.7%)	314	399	713 (42.9%)	
70–74	22	32	54 (31.2%)	257	315	572 (34.4%)	
75–79	19	26	45 (26.0%)	128	121	249 (15.0%)	
80–84	7	18	25 (14.5%)	34	52	86 (5.2%)	
85–89	1	14	15 (8.7%)	7	16	23 (1.4%)	
90–94	2	4	6 (3.5%)	3	12	15 (0.9%)	
95+	2	4	6 (3.5%)	0	5	5 (0.3%)	< 0.0001
Average years of education (SD)	12.0 (3.0)	11.6 (2.9)	11.7 (2.9)	13.6 (3.0)	12.4 (2.6)	13.0 (2.9)	< 0.0001
Education group							
8 years	8	21	29 (16.8%)	36	73	109 (6.6%)	
9–11 years	9	16	25 (14.5%)	66	129	195 (11.7%)	
12 years	29	45	74 (42.8%)	278	437	715 (43.0%)	
13 years	19	24	43 (24.9%)	363	276	639 (38.4%)	< 0.0001
APOE-ε4							
1 or 2 alleles	14	21	35 (38.5%)	91	101	192 (18.8%)	
0 alleles	31	25	56 (61.5%)	408	420	828 (81.2%)	< 0.0001

^a *p*-values for comparison between “All dementias” and “unaffected”.

TABLE 3

Age- and Sex-Specific Incidence Density Rates per 1,000 Person-Years in the *Kame* Project, King County, WA, May 1992–Dec 2001 After Multiple Imputation to Account for 68 Subjects who were Sampled at Baseline but not Clinically Evaluated.

Age	All Dementias				Alzheimer's Disease				Vascular Dementia				Other Dementias			
	N	P-Y	IDR [†] (95% CI)	N	P-Y	IDR [†] (95% CI)	N	P-Y	IDR [†] (95% CI)	N	P-Y	IDR [†] (95% CI)	N	P-Y	IDR [†] (95% CI)	
Men																
65–69	1	642	1.6 (0.0–4.6)	0	643		0	643		1	642	1.6 (0.0–4.6)				
70–74	7	1822	3.8 (0.1–6.6)	3	1828	1.6 (0.0–3.5)	3	1824	1.6 (0.0–3.5)	3	1825	1.6 (0.0–0.35)				
75–79	27	1628	16.8 (10.7–22.8)	20	1631	12.3 (7.1–17.5)	8	1643	4.7 (1.4–8.1)	4	1652	2.4 (0.1–4.8)				
80–84	15	772	19.4 (9.9–28.9)	11	780	14.1 (6.0–22.2)	5	785	5.9 (0.4–1.4)	2	792	2.5 (0.0–6.0)				
85–89	6	164	34.1 (6.2–62.0)	6	167	36.0 (8.5–63.5)	1	172	4.7 (0.0–16.2)	0	177					
90–94	2	25	96.8 (0.0–224.7)	2	27	75.1 (0.0–171.9)	1	28	28.0 (0.0–96.2)	0	31					
95+	3	18	168.9 (48.0, 289.7)	3	18	168.9 (48.0, 289.7)	0	21		0	21					
Overall	61	5,071	12.5 (9.5, 15.5)	45	5,094	8.8 (6.3, 11.3)	18	5,116	3.3 (1.8, 4.9)	10	5,139	1.9 (0.7–3.1)				
Women																
65–69	0	810		0	811		0	811		0	811					
70–74	14	2363	5.9 (2.9–8.9)	10	2371	4.2 (1.7–6.8)	4	2373	1.9 (0.1–3.6)	2	2377	0.8 (0.0–2.0)				
75–79	26	2004	13.1 (8.2–18.0)	23	2015	11.4 (6.9–15.9)	11	2030	5.3 (2.2–8.5)	1	2047	0.5 (0.0–1.4)				
80–84	27	898	30.1 (19.3–40.9)	22	910	24.6 (14.7–34.5)	10	926	10.8 (4.2–17.4)	2	940	2.1 (0.0–5.1)				
85–89	19	353	53.3 (31.0–75.5)	18	358	49.7 (28.5–70.9)	7	368	19.0 (5.4–32.6)	1	381	2.6 (0.0–7.7)				
90–94	9	101	89.1 (37.7, 140.6)	7	104	67.6 (21.9, 113.4)	1	113	8.9 (0.0, 26.0)	1	118	8.4 (0.0, 24.8)				
95+	8	38	212.9 (105.5, 320.2)	7	40	176.5 (72.9, 280.0)	2	51	39.6 (0.0, 92.2)	0	54					
Overall	103	6,567	15.9 (13.0, 18.8)	87	6,609	13.2 (10.5, 15.9)	35	6,672	5.3 (3.6, 7.0)	7	6,727	1.0 (0.3–1.8)				
Total																
65–69	1	1,452	0.69 (0–2.0)	0	1,454	0	0	1,454	0	1	1,452	0.7 (0–2.0)				
70–74	21	4,185	5.0 (2.9–7.1)	13	4,199	3.1 (1.4–4.7)	7	4,197	1.8 (0.5–3.1)	5	4,201	1.2 (0.2–2.2)				
75–79	53	3,632	14.7 (10.9–18.5)	43	3,646	11.8 (8.4–15.2)	19	3,673	5.1 (2.8–7.4)	5	3,699	1.4 (0.2–2.5)				
80–84	42	1,670	25.2 (17.9–32.4)	33	1,690	19.8 (13.2–26.3)	15	1,711	8.5 (4.2–12.9)	4	1,732	2.3 (0.1–4.6)				
85–89	25	517	47.2 (29.5–64.9)	24	525	45.4 (28.3–62.4)	8	540	14.5 (4.4–24.5)	1	558	1.8 (0–5.3)				
90–94	11	126	90.8 (42.1–139.6)	9	131	69.2 (27.7–110.6)	2	141	12.8 (0.0–32.3)	1	149	6.7 (0–19.7)				
95+	11	56	198.7 (115.7–281.8)	10	58	174.1 (91.9–256.3)	2	72	28.0 (0.0–65.5)	0	75					
Overall	164	11,638	14.4 (12.3, 16.5)	132	11,703	11.3 (9.4, 13.2)	53	11,788	4.4 (3.2, 5.6)	17	11,866	1.4 (0.8–2.1)				

TABLE 4

Apolipoprotein E Genotypes in the *Kame* Project (Men and Women), King County, WA, May 1994–May 1996.

Genotype	<i>Kame</i> Project	
	Number	Percent
$\epsilon 2\epsilon 2$	6	0.50
$\epsilon 2\epsilon 3$	107	8.9
$\epsilon 3\epsilon 3$	849	70.5
$\epsilon 2\epsilon 4$	8	0.66
$\epsilon 3\epsilon 4$	223	18.5
$\epsilon 4\epsilon 4$	12	1.0
Frequency		
$\epsilon 2$	0.053	
$\epsilon 3$	0.841	
$\epsilon 4$	0.106	