ORIGINAL ARTICLE

The Relationships Between Age, Sex, and the Incidence of Dementia and Alzheimer Disease

A Meta-analysis

Sujuan Gao, PhD; Hugh C. Hendrie, MB, ChB; Kathleen S. Hall, PhD; Siu Hui, PhD

Background: Prevalence studies on dementia and Alzheimer disease (AD) have reported a positive association with age. However, the trend of the association in the oldest-old categories has been the subject of discussion. The relationship between sex and AD has been inconsistent with these studies. Prevalence rates are influenced by the survival and disease incidence. Incidence rates provide a better measure of disease risk.

Methods: English-language articles identified through a MEDLINE search on "incidence dementia" and "incidence Alzheimer's disease" were examined and references from identified articles were reviewed. Population-based studies using personal interviews, standard clinical diagnosis criteria (*DSM-III* for dementia, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorder Association for AD) and reporting age-specific incidence rates were included in the meta-analysis. Data from the selected studies were extracted and verified. Mixed-effect models were used in the meta-analysis to accommodate the heterogeneity of the studies.

Results: Incident dementia and AD are associated with a significant quadratic age effect indicating that the increase in incidence rates slows down with the increase in age, although there is no sign of a decline in the incidence rates themselves. The odds ratios for women to develop incidence of dementia and AD relative to men are 1.18 (95% confidence interval, 0.95-1.46) and 1.56 (95% confidence interval, 1.16-2.10), respectively.

Conclusions: The acceleration of incidence rates for AD and dementia slows down with the increase in age, although we find no evidence of a rate decline. Women are at higher risk of developing AD than men.

Arch Gen Psychiatry. 1998;55:809-815

From the Departments of Medicine (Drs Gao and Hui) and Psychiatry (Drs Hendrie and Hall), Indiana University School of Medicine, Indianapolis.

As the age distribution of the United States and world population shifts, the dementing disorders, especially Alzheimer disease (AD), are emerging as a major health problem. The assessment of prevalence and incidence of the disease provides crucial input for public health professionals in determining and allocating health care resources as well as identifying critical risk factors that may be amenable to preventive intervention. Many prevalence studies on dementia and AD have been conducted in various populations.[1-24] Reported prevalence rates from those studies vary considerably and the variations, as indicated by Corrada et al,[25] are largely due to methodological differences, namely, clinical diagnostic criteria, sampling strategies, and statistical analysis procedures. Despite the varying magnitude of the reported prevalence rates, all studies show a positive association between age and prevalence rates.[26] However, the trend of the association with age has been subject to considerable discussion. One view is that dementia and AD are age dependent, ie, the inevitable consequence of the aging process. This view predicts that if we live long enough, we would all be demented. The other view is that dementia and AD are age related, as in cancer and aging, where the relationship to age is simply an expression of other biological risk factors. This view implies that the disease can be separated from aging and eliminated with the removal of the risk factors. The latter hypothesis is supported by the evidence that prevalence rates seem to level off or even decline in the very-old age groups.[27]

The relationship between sex and AD has been inconsistent across studies although in many studies women are reported to have higher rates of AD than men even after adjusting for differential survival. Significant differences between sex usually occur, however, in the oldest-age categories where there are few men and even fewer with AD, making estimates unreliable.[6,12,14,16,24,26,28] The association be-

MATERIALS AND METHODS

SELECTION OF STUDIES

A systematic search through MEDLINE (from 1966 to mid 1997) on "incidence dementia" and "incidence Alzheimer's disease" was conducted. Reference lists from identified articles were also reviewed to locate published studies. To minimize methodological variations of the studies in the meta-analysis, studies were selected using the following inclusion criteria: (1) The study is population based using personal interviews and examinations of the study subjects. (2) The study uses standardized clinical diagnotic criteria; specifically, *DSM-III* or *DSM-III-R*[33] for the diagnosis of dementia, National Institutes of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[34] for the diagnosis of AD. (3) Age-specific incidence rates are reported. (4) The study is published in the English language.

Sixty-eight articles were identified as the result of the MEDLINE search, 59 of which were written in English. Twelve studies met the inclusion criteria for the meta-analysis on the incidence of dementia.[28,35-45] Ten of these studies also reported sex- and age-specific incidence rates of dementia. Eight studies met the criteria for the meta-analysis on the incidence of AD, with 7 of them also reporting sex-specific incidence rates of AD.[35,37,40-42,46,47] Most of excluded studies did not report age-specific incidence rates and some were excluded for not using standard diagnostic criteria.

Annual incidence rates were extracted from all included studies. In cases where only sex-specific incidence rates were reported,[40,41] incidence rates combining men and women were calculated using information and methods specified in the articles.

Two well-known incidence studies are excluded for the following reasons: the Rochester, Minn, study[48] which used medical records rather than personal interviews and the Liverpool, England,[13] study which used AGECAT for diagnosis of dementia rather than *DSM-III*.

STATISTICAL ANALYSIS

Since all studies reported incidence rates by age groups, we recorded incidence rates using the midpoint of each age category. In an open-ended group such as those 85 years and older, we added the distance between the lower age limit to the midpoint for the other age groups in the same study. The studies with age- and sex- specific incidence rates were first analyzed to test for sex effect. Analyses were then conducted using all studies reporting age-specific incidence rates. Analyses were carried out for the incidence of dementia and for the incidence of AD separately.

It is likely that the relationship between incidence of dementia and/or AD and age is not constant over all ages. To test a level-off effect in incidence rates and a differential increase of incidence rates with age, we included a second order of age as a covariate in the analyses. A significant age squared implies that the increase in incidence rates varies with age. It would also indicate the age of a rate decline, if such decline exists. A meaningful level-off effect, we believe, should occur at an age where there is a considerable proportion of the population still at risk.

A mixed-effect model approach was adopted for the meta-analysis. The model was an extension to the random effect models of DerSimonian and Laird,[49] which allows the studies included in the meta-analysis to be heterogeneous. Details on the mixed-effect models used for the analyses are available from us on request. The modeling was completed in 2 stages. At the first stage, we assumed that the logits of reported incidence rate, ie, log (rate / [1 – rate]), were normally distributed with the logits of true incidence rate as means and variances. At the second stage, we assumed that means from the normal distributions were linearly associated with age, age squared, and sex, with a random study effect. For the analyses on dementia incidence, we assumed that the random study effect increases linearly with age. The underlying assumption for the mixed-effect model is that the effects in the studies included in the meta-analysis can be seen as a random sample of the effects observed in all possible studies meeting the inclusion criteria. The advantages of the mixed-effect model are 2-fold. First, it allows us to model the incidence rates from heterogeneous studies. Second, random measurement errors of the reported incidence rates are taken into consideration in the mixed-effect model.

Likelihood ratio tests were used to test homogeneity of the studies in a mixed-effect model[50] with age and age^2 as continuous variables, and sex as a binary variable if applicable. The difference in the –2 log likelihood functions with a random study effect and the –2 log likelihood function without the random effect was known to follow a 50:50 mixture of 2 χ^2 distributions.[50,51] Tests for the fixed effects (age, age squared, and sex) were performed using F tests.[52] Variance estimates for the random effect parameters were derived using the restricted maximum likelihood method.[53] All analyses were performed using the PROC MIXED procedure found in SAS.[6,12,54] Estimated overall annual incidence rates were derived using the approximation to the logistic function for marginal means in a mixed-effect logistic model proposed by Zeger et al[55] at each medium-age point for various age groups. Confidence intervals for the incidence estimates were obtained using this approximation and the variance-covariance matrices of the fixed-effect parameters from the mixed-effect models.

To demonstrate the effect of age on the estimated incidence rates, we also calculated the *incidence rate ratios*, defined as the incidence rate of an age group divided by the incidence rate of the age group 5 years younger.

tween sex and AD assumes a greater significance as there is now increasing evidence that estrogen replacement therapy in postmenopausal women improves cognitive function and reduces the risk for both cognitive impairment and AD.[29-31]

Prevalence studies, although valuable, have limitations. The changes in observed prevalence estimates with age cannot really answer the question about age dependency or age relatedness because prevalence is influenced by both survival and disease incidence.[32] *Incidence*, which is the rate of new cases in a population, is considered a better measure of disease risk. Since epidemiological studies on incidence of dementia and AD can be expensive and time consuming, only a limited num-

Table 1. Summary on the Studies Included in the Meta-analysis

Source, y	Country	Subject No.	Age Range, y	Sampling for Diagnosis*	Included Institution†	Year of Follow-up	Examination Method‡	Exclusion Method at Baseline§
Aevarsson and Skoos,[35] 1996	Sweden	347	85-88	No	Yes	3	1 Wave	Clinical diagnosis
Aronson et al,[36] 1991	United States	442	75-85	No	No	8	Annually	Screening cut-off
Bachman et al,[37] 1993	United States	2391	60-94	Sampling	Yes	Maximum: 10	Biannual	Screening cut-off
Boothby et al,[38] 1994	United Kingdom	502	65+	Sampling	No	2 y 4 mo	1 Wave	Screening cut-off
Fichter et al,[39] 1996	Germany	358	85-99	No	. . .‖	1	1 Wave	Clinical diagnosis
Fratiglioni et al,[40] 1997	Sweden	1473	75+	Sampling	Yes	3	1 Wave	Clinical diagnosis
Hagnell et al,[41] 1992	Sweden	2596¶	50-109	. . .	. . .	Maximium: 25	2 Waves	. . .
Letenneur et al,[42] 1994	France	2792	65+	Sampling	No	1 and 3	2 Waves	. . .
Li et al,[43] 1991	China	1090	60+	Sampling	NA	3	1 Wave	Clinical diagnosis
Morgan et al,[44] 1993	United Kingdom	970	65+	Sampling	No	4	1 Wave	Screening cut-off
Paykel et al,[28]/Brayne et al,[46] 1994	United Kingdom	1195	75+	Sampling	. . .	2 y 5 mo	1 Wave	Clinical diagnosis
Yoshitake et al,[45] 1995	Japan	826	65+		. . .	8	Daily	Clinical diagnosis
Hebert et al,[47] 1995	United States	2313	65+	Sampling	. . .	4 y 4 mo	1 Wave	Clinical diagnosis

*Indicating if sampling is used to select subjects for clinical diagnosis. Therefore, No means that every subject in the study underwent clinical diagnosis.
†Indicating if the study included subjects institutionalized in nursing homes. NA indicates not available.
‡The number of waves indicates the number of follow-up diagnoses performed; annually, that the study carried out follow-up diagnoses in the study cohort every year; and daily, that the study monitors the subjects in the study cohort daily.
§Method used to exclude the known subjects with dementia at baseline. Clinical diagnosis means that the excluded subjects were identified by clinical diagnosis; screening cut-off, that a screening test was used at baseline and the study cohort excluded those subjects below a certain cut-off point.
‖Ellipses indicate unclear from the study.
¶The study used 2 overlapping cohorts; this sample size contains the number of subjects in the larger cohort.

ber of incidence studies have been published. All incidence studies also report a positive association between age and incidence rates of dementia and AD. However, the trend of association with age and the effect of sex are not clear from individual studies because each study is limited in sample size, especially in the very-old age groups. We conducted a meta-analysis to investigate the relationships between age, sex, and the incidence of dementia and AD using published data.

RESULTS

DESCRIPTION OF DATA

Summary information on the studies included in the meta-analysis is given in **Table 1**. In addition to reporting the sample sizes and age ranges covered by each study, we also included the following information: (1) whether sampling was used for incidence clinical diagnosis; (2) whether the study included institutionalized subjects; (3) length of follow-up; (4) number of follow-up examinations; and (5) methods of excluding putative demented subjects from baseline, eg, using clinical diagnoses, or below a cut-off point of a screening test. Some of these characteristics are highly correlated. For example, the studies with small sample size tend to clinically diagnose everyone while studies with a large sample size used 2-phase sampling.

Because of the inclusion criteria for using standardized diagnostic criteria, all studies included in the meta-analysis were published after 1991. Reported age-specific incidence rates of dementia from the 12 studies are seen in **Figure 1**. (The annual incidence rates of dementia stratified by age and sex along with sample sizes are available from us on request.) The youngest age group studied was the 50- to 59-year-olds and several studies reported incidence rates for the 90 and older groups. Reported age-specific incidence rates of AD from the 8 studies are shown in **Figure 2**. (Annual incidence rates of AD stratified by age and sex along with sample sizes are also available from upon request.)

INCIDENCE OF DEMENTIA

The first set of analyses was performed using the 10 studies reporting both age- and sex-specific incidence rates of dementia. The test for homogeneity indicates the studies are heterogeneous ($c^2_{10,0} = 17.14$,[51] $P = .03$). Both age and age squared are significantly related to the prediction of incident dementia ($F_9 = 43.49$, $P < .001$ and $F_{63} = 26.48$, $P < .001$, respectively). However, female sex is not a significant predictor of incident dementia ($F_{63} = 2.32$, $P = .133$).

All 12 studies with age-specific incidence rates were used to investigate the relationship between age and the incidence of dementia. Both age and age squared are again significant predictors of incidence of dementia ($F_{34} = 40.62$, $P < .001$ and $F_{34} = 25.48$, $P < .001$, respectively). The significance of a quadratic age effect suggests that the increase in incidence rates of dementia varies with the increase in age. The slowing down of the increase in incidence is illustrated in **Figure 3**, where calculated incidence rate ratio is plotted against age. The incidence rate ratio indicates that for every 5-year increase in age, incidence rates of dementia triple before age 63 and double between ages 64 and 75, and the ratio declines to 1.5 at around age 84. However, for the entire age range covered in the meta-analysis, the rate ratio is always above

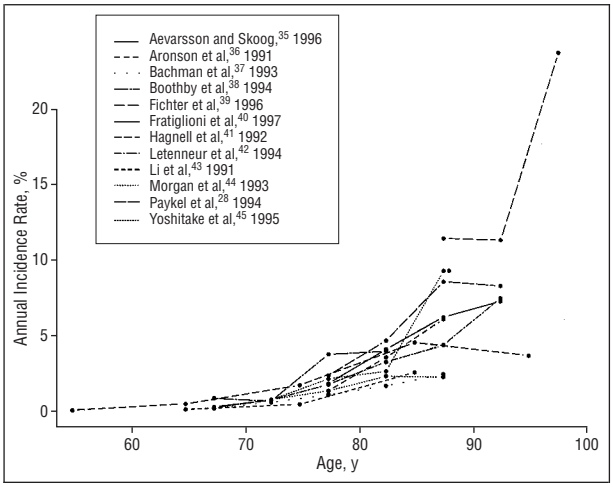

Figure 1. *Reported annual incidence rates of dementia.*

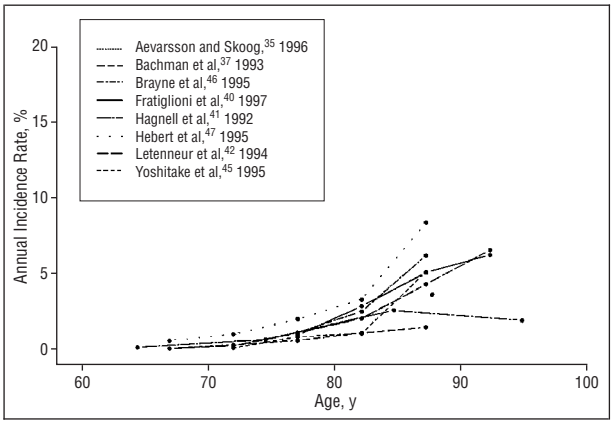

Figure 2. *Reported annual incidence rates of Alzheimer disease.*

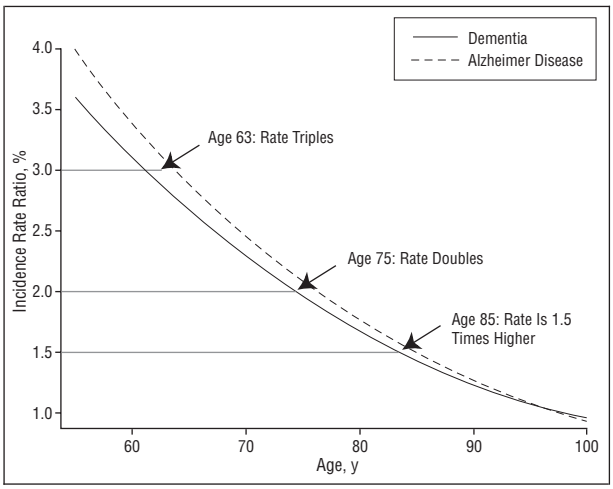

Figure 3. *Incidence rate ratio with 5-year increase in age. The* incidence rate ratio *is defined as the incidence rate of an age group divided by the incidence rate of the age group that is 5 years younger. For example, the incidence rate ratio of dementia for the 75-year-old age group is approximately 2, according to the figure, indicating that the incidence rate for the 75-year-old age group is twice as high as the incidence rate for the group at age 70.*

1, showing no sign of a rate decline. The phenomenon of a differential increase in incidence rates can also be observed from **Table 2**, which gives the estimated annual incidence rates and 95% confidence intervals.

Table 2. Estimated Overall Annual Incidence of Dementia From 12 Studies*

Age Group, y	Annual Rate, %	95% Confidence Intervals	
		Lower Limit	Upper Limit
55-59	0.033	0.019	0.056
60-64	0.112	0.079	0.158
65-69	0.330	0.255	0.427
70-74	0.838	0.649	1.080
75-79	1.817	1.383	2.383
80-84	3.364	2.522	4.474
85-89	5.333	3.874	7.299
90-94	7.289	4.873	10.77
95+	8.678	4.973	14.72

**Because some studies did not report the number of study subjects by age group (some reported person-year at risk, which is affected by the length of follow-up and mortality rates in addition to the sample sizes), we are unable to include total sample sizes for each age group in this table. However, the total sample sizes from the studies are included in Table 1.*

The maximum point of predicted incidence rates from this model is at age 98. Theoretically, the model predicts a rate decline after age 98. However, since age 98 is at the upper bound of our data, any prediction beyond this point is not reasonable.

INCIDENCE OF AD

The analysis on the incidence of AD parallels those on the incidence of dementia. The first set of analyses was performed using the 7 studies with age- and sex-specific incidence rates of AD. Age and age squared are shown to be significant predictors of incident AD (F_{42}=15.6, P=.0003 and F_{42}=10.68, P=.002, respectively). Female gender is also significantly related to the prediction of incidence of AD (F_{42}=9.37, P=.004). Specifically, parameter estimates indicate that women are at greater risk of developing incidence of AD with an estimated odds ratio of 1.56 (95% confidence interval, 1.16-2.10).

When all 8 studies with age-specific incidence rate for AD are analyzed, both age and age squared are again significant predictors of incidence of AD (F_{22}=10.07, P=.004 and F_{22}=6.20, P=.021, respectively). The significance of the age squared term again indicates a differential increase in incidence rates of AD with increasing age. It is interesting to observe from Figure 3 that the patterns on the incidence rate changes are almost identical for dementia and AD. Estimated annual incidence rates of AD are presented along with 95% confidence intervals in **Table 3**.

COMMENT

Results from the meta-analysis indicate that the increase in incidence rates of both dementia and AD slows down with increasing age, although the incidence rates themselves do not decline. For every 5-year increase in age, both dementia and AD incidence rates triple before age 64, double before age 75, and drop down to an increase of 1.5 times around age 85. This slowing down of age-related increase in incidence rates lends support to the hypothesis that both dementia and AD are age re-

Table 3. Estimated Overall Annual Incidence Rates of Alzheimer Disease From 8 Studies*

Age Group, y	Annual Rate, %	95% Confidence Intervals	
		Lower Limit	Upper Limit
60-64	0.058	0.026	0.129
65-69	0.186	0.113	0.305
70-74	0.506	0.346	0.741
75-79	1.174	0.808	1.703
80-84	2.310	1.609	3.306
85-89	3.858	2.705	5.474
90-94	5.488	3.409	8.72
95+	6.685	3.031	14.10

**Since some studies did not report the number of study subjects by age group (some reported person-year at risk, which is affected by the length of follow-up and mortality rates in addition to the sample sizes), we are unable to include total sample sizes for each age group in this table. However, the total sample sizes for these studies are included in Table 1.*

lated rather than age dependent, with the hopeful corollary that it is possible that preventable risk factors can be identified. Most authorities would already agree that at least one major cause of dementia, cerebrovascular disease, is amenable to preventive strategies.[56] However, while incidence studies are less influenced by differential mortality than prevalence studies, they do not entirely eliminate the possibility that the oldest subjects with cognitive impairment are more likely to die of comorbid causes before they reach the criteria threshold for dementia, thus influencing rates in the oldest-old category.

Although we do not rule out completely the possibility that the slowing down in the increase of incidence rates is because of small sample sizes for the older age groups, we believe that this is unlikely. If we restricted our analyses only to the large studies (ie, with >1000 subjects), the slowing down effect is still apparent.

Whether or not there is a leveling off of actual rates of incidence with age, as has been suggested by Ritchie and Kildea,[27] is not so clear, however. Although the increase in incidence rates slows down with increasing age, there is no evidence of a rate decline at least to age 98 which is the upper limit of our data.

It is important to note that previous studies on dementia and AD have mostly assumed logistic models linear in age when modeling the relationship between age and the disease. Our results demonstrate that a more complicated relationship between age and dementia and/or AD exists.

In contrast to the age effect, the sex effect seemed to be confined to AD with women being at a significantly higher risk for developing an incidence of AD. The differences in the sex effect between dementia and AD are most likely explained by the fact that men are at a higher risk than women for vascular dementia. The reasons for the apparent higher risk for women to develop AD are still uncertain. It has been proposed that there is a sex apolipoprotein genotype interaction, with women who are ϵ3 ϵ4 heterozygotes being at greater risk for AD than men who are ϵ3 ϵ4 heterozygotes.[57-59] The results of the meta-analysis by the APOE and Alzheimer Disease MetaAnalysis Consortium[60] suggest, however, that women have a higher degree of susceptibility than men regardless of apolipoprotein genotype. It has also been suggested that lack of estrogen or other hormonal changes in postmenopausal women either by themselves or in association with other factors account for the increased risk. Our results are consistent with this hypothesis.[29-31]

The significant female effect on incidence of AD may be due to selection bias in that the studies not reporting sex-specific rates may not have found a significant difference between men and women. However, this is unlikely because the meta-analyses on dementia studies with reported sex-specific rates did not find women at significantly higher risk for incidence of dementia. Furthermore, the difference in sex effect on dementia and AD remains even after we restrict the analysis to only the 7 studies that reported sex-specific rates for both dementia and AD.

It is possible that both our findings, the slowing down of increase in incidence with age and the higher risk of AD for women, are due to survival effects, ie, older subjects are biologically different (harder) than younger subjects. However, this hypothesis can only be tested by longitudinal studies where baseline characteristics may be compared between survivors and the subjects who died.

Meta-analysis was developed as a systematic approach to identify, abstract, and integrate the results of different studies. If performed correctly, a meta-analysis can answer questions that may not be answered from each individual study because of the small sample sizes. However, there are methodological limitations to all meta-analyses. Ideally, a weighted analysis with each reported rate weighted by its precision is preferred.[61] However, since some studies did not report SEs or confidence intervals, the results reported here are based on unweighted analyses. Nevertheless, when we used approximate SEs derived for these studies to perform a weighted analysis, the results changed very little and our conclusions remained the same.

Results from meta-analysis using summarized data can be different from those obtained from using individual subject data.[62] However, in the studies of dementia and AD, synthesis would be difficult even if data on individual subjects were available because different studies used different sampling and estimation methods. For example, the Cambridge study[28,46] and the East Boston study[47] both used complex sampling designs at baseline prevalence and at incidence waves. The Cambridge study used weighting from stratified sampling to estimate incidence rates, while the East Boston study derived incidence rates using logistic models. The Framingham study[37] had unequal numbers of follow-up times for the study subjects and survival analysis techniques were used for the estimation of incidence rates. Therefore, synthesis of individual subject data would be difficult, if not impossible.

In summary, in this meta-analysis of published incidence studies of both dementia and AD, it would appear that the age-related increase in incidence rates slows down with increasing age, although the incidence rates themselves do not show a decline. Women are at significantly greater risk for developing AD.

Accepted for publication June 11, 1998.

Supported by grants PHS RO1 AGO9956-06 and P30 AG10133-06 from the National Institute on Aging, Rockville, Md.

We would like to acknowledge Taketo Yoshitake, MD, DMSc, Medical Corporation, Department of Japan International Cooperation Agency (JICA) for providing us with the Hisayama Study of Dementia incidence data.

Reprints: Hugh C. Hendrie, MB ChB, Professor and Chairman, Department of Psychiatry, Indiana University School of Medicine, 541 Clinical Dr, Room 298, Indianapolis, IN 46202-5111.

REFERENCES

1. Livingston G, Sax K, Willison J, Blizard B, Mann A. The Gospel Oak Study stage II: the diagnosis of dementia in the community. *Psychol Med*. 1990;20: 881-891.
2. Dartigues JF, Gagnon M, Michel P, Letenneur L, Commenges D, Barberger-Gateau P, Auriacombe S, Rigal B, Bedry R, Alperovitch A, Orgogolo JM, Henry P, Loiseau P, Salamon R. The Paquid research program on the epidemiology of dementia: methods and initial results. *Rev Neurol (Paris)* 1991;147: 225-230.
3. Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH, Taylor JO. Prevalence of Alzheimer's disease in a community population of older persons: higher than previously reported. *JAMA*. 1989; 262:2551-2556.
4. Folstein MF, Bassett SS, Anthony JC, Romanoski AJ, Nestadt GR. Dementia: case ascertainment in a community survey. *J Gerontol*. 1991;46:132-138.
5. Canadian Study of Health and Aging. Canadian Study of Health and Aging: study methods and prevalence of dementia. *CMAJ*. 1994;150:899-913.
6. Heeren TJ, Lagaay AM, Hijmans W, Rooymans HG. Prevalence of dementia in the "oldest old" of a Dutch community. *J Am Geriatr Soc*. 1991;35:755-759.
7. O'Connor DW, Pollitt PA, Hyde JB, Fellows JL, Miller ND, Brook CP, Reiss BB, Roth M. The prevalence of dementia as measured by the Cambridge Mental Disorders of the Elderly Examination. *Acta Psychiatr Scand*. 1989;79:190-198.
8. Aronson MK, Ooi WL, Geva DL, Masur D, Blau A, Frishman W. Dementia: age-dependent incidence, prevalence, and mortality in the old old. *Arch Intern Med*. 1991;151:989-992.
9. Hendrie HC, Osuntokun BO, Hall KS, Ogunniyi AO, Hui SL, Unverzagt FW, Gureje O, Baiyewu O, Rodenberg CS, Musick BS, Farlow MR, Class CA, Brashear A, Burdine VE, Oyewole S, Raji SO, Komolafe O. Prevalence of Alzheimer's disease and dementia in two communities: Nigerian Africans and African Americans. *Am J Psychiatry*. 1995;152:1485-1492.
10. White L, Petrovitch H, Ross W, Masaki KH, Abbott RD, Teng EL, Rodriguez BL, Blanchette PL, Havlik RJ, Wergowske G, Chiu D, Foley DJ, Murdaugh C, Curb JD. Prevalence of dementia in older Japanese-American men in Hawaii: the Honolulu-Asia Aging Study. *JAMA*. 1996;276:955-960.
11. Graves AB, Larson EB, Edland SD, Bowen JD, McCormick WC, McCurry SM, Rice MM, Wenzlow A, Uomoto JM. Prevalence of dementia and its subtypes in the Japanese American population of King County, Washington State: the Kame Project. *Am J Epidemiol*. 1996;144:760-771.
12. Bachman DL, Wolf PA, Linn R, Knoefel JE, Cobb J, Belanger A, D'Agostino RB, White LR. Prevalence of dementia and probably senile dementia of the Alzheimer type in the Framingham study. *Neurology*. 1992;42:115-119.
13. Copeland JRM, Davidson IA, Dewey ME, Gilmore C, Larkin BA, McWilliam C, Saunders PA, Scott A, Sharma V, Sullivan C. Alzheimer's disease, other dementias, depression and pseudo dementia: prevalence, incidence and three-year outcome in Liverpool. *Br J Psychiatr*. 1992;161:230-239.
14. Fratiglioni L, Grut M, Forsell Y, Viitanen M, Grafstrom M, Holmén K, Ericsson K, Backman L, Ahlbom A, Winblad B. Prevalence of Alzheimer's disease and other dementias in an elderly urban population: relationship with age, sex, and education. *Neurology*. 1991;41:1886-1892.
15. Hofman A, Rocca WA, Brayne C, Breteler MM, Clarke M, Cooper B, Copeland JR, Dartigues JF, da Silva Droux A, Hagnell O, Heeren TJ, Engedal K, Jonker C, Lindesay J, Lobo A, Mann AH, Mölsä PK, Morgan K, O'Connor DW, Sulkava R, Kay DWK, Amaducci L, for the EURODEM Prevalence Research Group. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings: Eurodem Prevalence Research Group. *Int J Epidemiol*. 1991;20:736-748.
16. Jorm AF, Korten AE, Henderson AS. The prevalence of dementia: a quantitative integration of the literature. *Acta Psychiatr Scand*. 1987;76:465-479.
17. Kokmen E, Beard CM, Offord KP, Kurland LT. Prevalence of medically diagnosed dementia in a defined United States population: Rochester, Minnesota, January 1, 1975. *Neurology*. 1989;39:773-776.
18. Li G, Shen YC, Chen CH, Zhao YW, Li SR, Lu M. An epidemiological survey of age-related dementia in an urban area of Beijing. *Acta Psychiatr Scand*. 1989; 79:557-563.
19. Liu H-C, Lin K-N, Teng EL, Wang S-J, Fuh J-L, Guo N-W, Chou P, Hu H-H, Chiang BN. Prevalence and sub. types of dementia in Taiwan: a community survey of 5297 individuals. *J Am Geriatr Soc*. 1995;43:144-149.
20. Meneghini F, Rocca WA, Grigoletto F, Morgante L, Reggio A, Savettieri G, Di Perri R, Anderson DW. Door-to-door prevalence survey of neurological diseases in a Sicilian population: background and methods: the Sicilian Neuro-Epidemiologic Study (SNES) Group. *Neuroepidemiology*. 1991;10(2):70-85.
21. Rocca WA, Bonaiuto S, Lippi A, Luciani P, Turtu F, Cavarzeran F, Amaducci L. Prevalence of clinically diagnosed Alzheimer's disease and other dementing disorders: a door-to-door survey in Appignano, Macarata Province, Italy. *Neurology*. 1990;40:626-631.
22. Shibayama H, Kasahara Y, Kobayashi H. Prevalence of dementia in a Japanese elderly population. *Acta Psychiatr Scand*. 1986,74:144-151.
23. Skoog I, Nilsson L, Palmertz B, Andreasson L-A, Svanborg A. A population-based study of dementia in 85-year-olds. *N Engl J Med*. 1993;328:153-158.
24. Zhang M, Katzman R, Salmon D, Jin H, Cai G, Wang Z, Qu G, Grant I, Yu E, Levy P, Klauber M, Liu WT. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. *Ann Neurol*. 1990;27: 428-437.
25. Corrada M, Brookmeyer R, Kawas C. Sources of variability in prevalence rates of Alzheimer's disease. *Int J Epidemiol*. 1995;24:1000-1005.
26. Graves AB, Kukull WA. The epidemiology of dementia. In: Morris JC, ed. *Handbook of Dementing Illnesses*. New York, NY: Marcel Decker Inc. In press.
27. Ritchie K, Kildea D. Is senile dementia "age-related" or "ageing-related"? evidence from meta-analysis of dementia prevalence in the oldest old. *Lancet*. 1995; 346:931-934.
28. Paykel ES, Brayne C, Huppert FA, Gill C, Barkley C, Gehlhaar E, Beardsall L, Girling DM, Pollitt P, O'Connor D. Incidence of dementia in a population older than 75 years in the United Kingdom. *Arch Gen Psychiatry*. 1994;51:325-332.
29. Schmidt R, Fazekas F, Reinhart B, Kapeller P, Fazekas G, Offenbacher H, Eber B, Schumacher M, Freidl W. Estrogen replacement therapy in older women: a neuropsychological and brain MRI study. *J Am Geriatr Soc*. 1996;44:1307-1313.
30. Henderson VW, Paganini-Hill A, Emmanuel CK, Dunn ME, Buckwalter JG. Estrogen replacement therapy in older women: comparison between Alzheimer's disease cases and non-demented control subjects. *Arch Neurol*. 1994;51: 896-900.
31. Paganini-Hill A, Henderson VM. Estrogen replacement therapy and risk of Alzheimer disease. *Arch Intern Med*. 1996;156:2213-2217.
32. McGee MA, Brayne C. The impact on prevalence of dementia in the oldest age groups of differential mortality patterns: a deterministic approach. *Int J Epidemiol*. In press.
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
34. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan M. 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.
35. Aevarsson O, Skoog I. A population-based study on the incidence of dementia disorder between 85 and 88 years of age. *J Am Geriatr Soc*. 1996;44:1455-1460.
36. Aronson MK, Ooi WL, Geva DL, Masur D, Blau A, Frishman W. Age-dependent incidence, prevalence and mortality in the old old. *Arch Intern Med*. 1991;51: 989-992.
37. 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.
38. Boothby H, Blizard R, Livingston G, Mann AH. The Gospel Oak study stage III: the incidence of dementia. *Psychol Med*. 1994;24:89-95.
39. Fichter MM, Schroppel H, Meller I. Incidence of dementia in a Munich community sample of the oldest old. *Eur Arch Psychiatry Clin Neurosci*. 1996;246: 320-328.
40. Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen project, Stockholm. *Neurology*. 1997;48:132-138.
41. Hagnell O, Ojesjo, L, Rorsman, B. Incidence of dementia in the Lundby study. *Neuroepidemiology*. 1992;11(suppl):61-66.
42. Letenneur L, Comenges D, Dartigues JF, Darberger-Gateau P. Incidence of de-

mentia and Alzheimer's disease in elderly community residents of southwestern France. *Int J Epidemiol*. 1994;23:1256-1261.
43. Li G, Shen YC, Chen CH, Zhau YW, Li SR, Lu M. A three-year follow-up study of age-related dementia in an urban area of Beijing. *Acta Psychiatr Scand*. 1991; 83:99-104.
44. Morgan K, Lilley JM, Arie T, Byrne EJ, Jones R, Waite J. Incidence of dementia in a representative British sample. *Br J Psychiatry*. 1993;163: 467-470.
45. Yoshitake T, Kiyohara Y. Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, Sueishi K, Tsuneyoshi M, Fujishima M. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama study. *Neurology*. 1995;45: 1161-1168.
46. Brayne C, Gill C, Huppert FA, Barkley C, Gehlhaar, Girling DM, O'Connor DW, Paykel ES. Incidence of clinically diagnosed subtypes of dementia in an elderly population: Cambridge project for later life. *Br J Psychiatry*. 1995;167:255-262.
47. Hebert LE, Scherr PA, Beckett LA, Albert MS, Pilgrim DM, Chown MJ, Funkenstein HH, Evans DA. Age-specific incidence of. Alzheimer's disease in a community population. *JAMA*. 1995;273:1354-1359.
48. Kokmen E, Beard CM, O'Brien PC, Offord KP, Kurland LT. Is the incidence of dementing illness changing? a 25-year time trend study in Rochester, Minnesota (1960-1984). *Neurology*. 1993;43:1887-1892.
49. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177-188.
50. Stram DO. Meta-analysis of published data using a linear mixed-effects model. *Biometrics*. 1996;52:536-544.
51. Stram DO, Lee JW. Variance components testing in the longitudinal mixed effects model. *Biometrics*. 1994;50:1171-1177.
52. McLean RA, Sanders WL, Stroup WW. A unified approach to mixed linear models. *Am Statistician*. 1991;45:54-64.
53. Patterson HD, Thompson R. Recovery of inter-block information when block sizes are unequal. *Biometrika*. 1974;58:545-554.
54. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. *SAS System for Mixed Models*. Cary, NC: SAS Institute Inc; 1996.
55. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988;44:1049-1060.
56. Hachinski V. Preventable senility: a call for action against the vascular dementias. *Lancet*. 1992;340:645-648.
57. Duara R, Barker WW, Lopez-Alberola R, Loewenstein DA, Grau LB, Gilchrist D, Sevush S, d St George-Hyslop S. Alzheimer's disease: interaction of apolipoprotein E genotypes, family history of dementia, gender, education, ethnicity, and age of onset. *Neurology*. 1996;46:1575-1579.
58. Payami H, Zareparsi S, Mentee KR, Sexton GJ, Kaye JA, Bird TD, Ys CE, Wijsman EM, Heston LL, Litt M, Schellenberg GD. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: a possible clue to the higher incidence of Alzheimer disease in women. *Am J Hum Genet*. 1996;58:803-811.
59. Bickeboller H, Campion D, Brice A, Amouyel P, Hannequin D, Didierjean O, Penet C, Martin C, Perez-Tur J, Michon A, Dubois B, Ledoze F, Thomas-Anterion C, Pasquier F, Puel M, Demonet JF, Moreaud O, Babron MC, Meulien D, Guez D, Chartier-Harlin MC, Frebourg T, Agid Y, Martinez M, Clerget-Darpoux F. Apolipoprotein E and Alzheimer disease: genotype-specific risks by age and sex. *Am J Hum Genet*. 1997;60:439-446.
60. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N. The effects of age, sex and ethnicity on the association between apolipoprotein e genotype and Alzheimer disease: a meta-analysis. *JAMA*. 1997;278:1349-1356.
61. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol*. 1994;140:90-296.
62. Jeng GT, Scott JR, Brumeister LF. A comparison of meta-analytic results using literature vs individual patient data: paternal cell immunization for recurrent miscarriage. *JAMA*. 1995;274:830-836.