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ORIGINAL ARTICLE

Alzheimer's Dementia: Morbidity and Mortality

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Objectives.—To evaluate the morbidity and mortality of Alzheimer's disease in early onset and late onset disease.

Background.—Comprehensive literature review to provide historic and demographic background on the disease as well as to determine the pertinent factors for risk assessment.

Methods.—Abstract mortality methodology is employed to develop mortality ratios and life expectancies on those with early onset as well as late onset disease.

Results.—Mortality ratios and morbidity are high in the early onset disease. The late onset disease has high mortality ratios in the more severe forms of the disease. Mild disease is not associated with high mortality ratios.

Conclusions.—Alzheimer's disease is an important impairment in an elderly individual. Early onset disease is uncommon and associated with high mortality and morbidity. The late onset disease is common and is associated with much less morbidity and mortality. Risk factors are useful in identifying high-risk individuals.

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In 1907, Alois Alzheimer cared for a 51-year-old woman who died from a dementing illness; he subsequently described the disease, which was named after him.[1] The first few subjects described with the disease were relatively young, and the initial assumption was that the disease affected predominantly middle-aged individuals.[2] It is only within the last 25 years that adequate data have accumulated to convince the scientific community that the neurodegenerative disease that Alzheimer described is responsible for the progressive dementia seen in the elderly population.[3] The gross pathology of Alzheimer's disease shows diffuse cortical atrophy, widening of the sulci, narrowing of the gyri, and commonly hydrocephalus. Microscopic changes include neurofibrillary tangles (amyloid, beta-pleated tau protein in twisted helices within neurons) and neuritic plaques in hippocampus and the cortex.[1] The presence of both plaques and tangles have been found in the brains of individuals without evidence of dementia as well as those with other dementing illnesses.[4,5] In Alzheimer's disease, these characteristic gross and microscopic findings must be accompanied by the typical clinical symptoms. The disease occurs as an unrelenting dementia leading from memory loss and emotional lability to errors in judgment to progressive motor and intellectual disability and death.

Interest in Alzheimer's dementia stems from increased concern about the financial and societal burden this disease places on our healthcare system. Estimates of the average cost of home care for an individual with Alzheimer's dementia range from $15,000 to

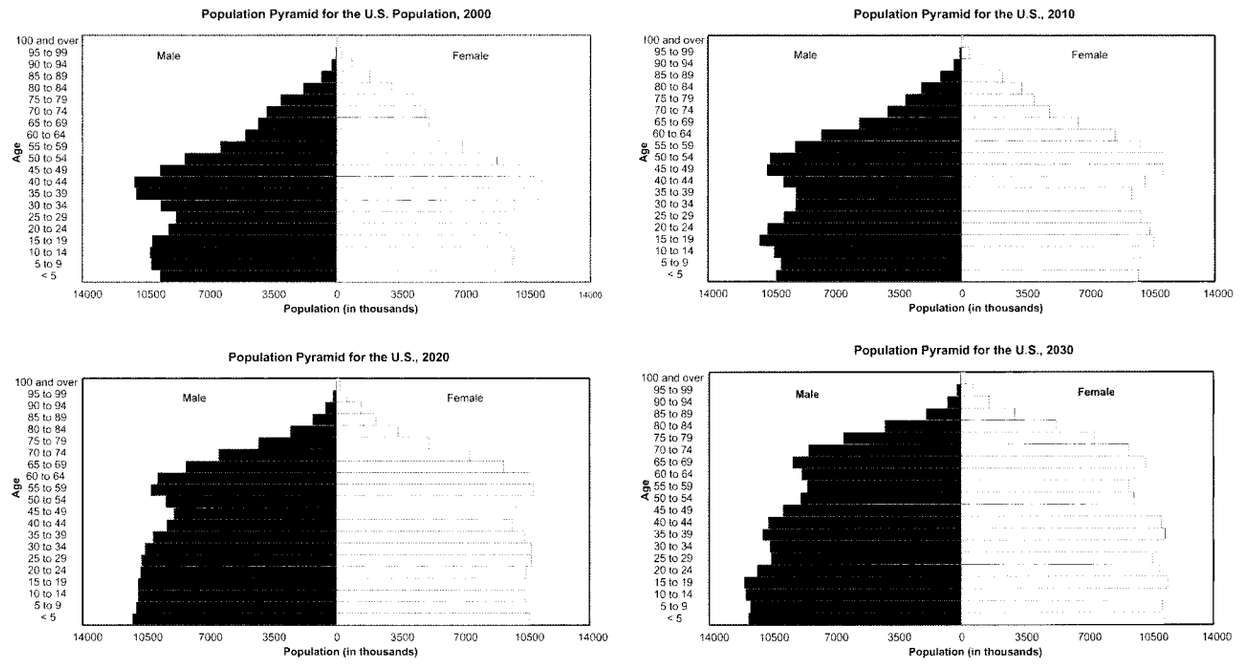

Figure 1. Population pyramids for individuals in the US, 2000–2030.

$47,000 per year,[6] while the total cost of care averages $174,000 from time of diagnosis to death.[5] In addition to the financial costs of caring for cognitively impaired persons, there are societal implications, particularly when older individuals are in positions of responsibility or decision making.

DEMOGRAPHY OF THE AGING POPULATION AND ALZHEIMER'S DISEASE

A graphic representation of the population in 5-year age increments for both males and females is pyramid-like (Figure 1). The baby boomers are those individuals that are now turning 50; future demographic trends show increasing numbers of individuals between the ages of 65 and 100. Growth of the population over age 65 is rapid, in contrast with the very low growth in the overall population, reflecting the presence of the aging baby boomers.[7,8]

A significant incidence of Alzheimer's dementia begins at age 65, and the prevalence increases, doubling every 5 years. The prevalence rates for Alzheimer's dementia range from 3/1000 for ages 60–69 to 108/1000 for ages 80–89.[5]

METHODS

To determine the magnitude of the excessive mortality associated with Alzheimer's disease, abstract methodology is used to determine the excess death rate.[9] Cumulative survival (P_x) curves from Aeversson et al[10] and a cumulative mortality (Q_x) curve from Heyman et al[11] supplied the data from which observed interval mortality (q_x) rates were derived.[9]

The 2 studies capture the mortality experience of a wide range of ages. The Aeversson article focuses on females aged 85 in the years 1989–91 and describes survival experience of nondemented, mildly demented, moderately demented, and severely demented males and females.[10] To eliminate random fluctuations with the data, the rates were smoothed by using an exponential function.

The Heyman study focuses on younger ages, including men and women, with individuals aged 62.4 on average and took place around 1980. Factors predictive of institution-

alization and death were the major endpoints of the study.[11]

Two sets of comparison data were utilized to most closely match the study populations. Expected mortality for the old age cohort is from the US decennial life table 1989–91 for women aged 85[12]; the other is obtained from the US decennial life tables for 1979–81, total population.[13]

Mortality methodology is applied to the curves to derive observed interval survival from which interval mortality can then be calculated.[9] Mortality ratios and excess death rates are computed according to the equations set forth in the abstract methodology and are briefly summarized in the tables.[9]

MORTALITY AND MORBIDITY OF ALZHEIMER'S DISEASE

The medical literature is filled with research that has been conducted to determine which factors associated with Alzheimer's disease increase the risk of death. The list varies somewhat among different research groups. Nevertheless, there are 2 variables that are common to the studies reviewed. The first is severity of dementia, as manifested by cognitive impairment, and the second is age at onset of disease, both of which are correlated with extra mortality.[10,14,15]

Aeversson et al conducted a 7-year longitudinal study to examine survival rates in individuals aged 85 with Alzheimer's dementia. The study population consisted of 494 individuals, with a predominance of women. The number of men in each category (mild, moderate, and severe dementia) was so small that statistically significant conclusions could not be drawn from that subset of the population studied.

Selection criteria used to determine the presence of Alzheimer's dementia consisted of both objective (neuropsychiatric evaluation) and subjective data (phone interview with close informant). Classification of disease into mild, moderate, and severe categories was based on functional capacity determined through interviews.

Both people living in the community and those in institutions were included in the study—the distribution of each is not known.

Occurrence of both vascular dementia and Alzheimer's dementia were similar. It is difficult to differentiate between vascular dementia and Alzheimer's dementia either on clinical grounds or on autopsy findings, and coexistence of both forms of dementia are common.[10] The existence of both forms of dementia could impact mortality unfavorably, although this was not specifically addressed in the Aeversson et al. article.

Increasing severity of disease differentiated the 3 categories (mild, moderate, severe disease) into progressively higher mortality ratios.

Statistical analysis of the data shows significance in death rates between mild and moderate dementia as well as mild and severe dementia. There is no statistical significance between moderate and severe dementia as demonstrated in the graphic representation of the survival curves comparing levels of severity (Figure 2).

Table 2 is a summary of the life expectancy of the general population in comparison with the life expectancies of those with different degrees of Alzheimer's. There is little reduction in life expectancy with mild dementia, particularly at ages 85 and 86. Moderate and severe dementia have a more negative influence on survival.[10]

Heyman's study of early onset of Alzheimer's dementia, before the age of 65, is associated with high morbidity and mortality. Ninety-two individuals (30 men and 62 women) with early onset disease were studied prospectively to determine factors predictive of institutionalization or death. All participants were screened for other diseases that may simulate Alzheimer's dementia; thus, there was a low prevalence of chronic conditions in the selected cohort. At onset, all levels of disease severity were represented—mild, moderate, and severe; average duration of disease among all subjects evaluated was 3.4 years. There was no correlation established

Table 1. Observed and Expected Mortality from Alzheimer's Disease by Severity, Females*

Age	Years	Observed Interval $q(o)$	Expected US Females 1989–91 $q(e)$	Comparative Experience: Mortality Ratio $100\ q(o)/q(e)$	Comparative Experience: Excess Death Rate $1000\ [q(o) - q(e)]$
Mild					
85	0–1	0.04851	0.08446	57.4	−35.9
86	1–2	0.06922	0.09376	73.8	−24.5
87	2–3	0.09878	0.10379	95.2	−5.0
88	3–4	0.14094	0.11442	123.2	26.5
89	4–5	0.20111	0.12590	159.7	75.2
90	5–6	0.28697	0.13918	206.2	147.8
91	6–7	0.40947	0.15417	265.6	255.3
Moderate					
85	0–1	0.14700	0.08446	174.0	62.5
86	1–2	0.18693	0.09376	199.4	93.2
87	2–3	0.23771	0.10379	229.0	133.9
88	3–4	0.30227	0.11442	264.2	187.9
89	4–5	0.38438	0.12590	305.3	258.5
90	5–6	0.48879	0.13918	351.2	349.6
91	6–7	0.62156	0.15417	403.2	467.4
Severe					
85	0–1	0.16153	0.08446	191.3	77.1
86	1–2	0.20858	0.09376	222.5	114.8
87	2–3	0.26932	0.10379	259.5	165.5
88	3–4	0.34776	0.11442	303.9	233.3
89	4–5	0.44904	0.12590	356.7	323.1
90	5–6	0.57982	0.13918	416.6	440.6
91	6–7	0.74868	0.15417	485.6	594.5

* Source: Observed mortality derived from Aeversson, Svanborg, and Skoog.[10] Note: Observed mortality smoothed through an exponential function.

between duration of disease and severity of disease within the study design. Findings indicate a decline in functional status leading to institutionalization in 54 of the 92 participants in the 6-year follow-up period.[11] Mortality ratios for the group are shown in Table 3.

Mortality ratios are better than standard in the first 2 intervals, which may be related to the elimination of competing causes of death in the study design. Alzheimer's disease is a chronic illness culminating in disability and death over a period of years.[14,15]

Seltzer and Sherwin's study, done on a group of patients with disease onset before age 65, found the mean survival from symptom onset to death was 9.1 years.[16] In comparison, the life expectancy of a 65-year-old male in the general population, based on life table data from 1979 to 1981, is 17.5 years.[13] The 1979–81 life table is used for comparison because the study was conducted in 1980.[16]

Molsa, in his study comparing causes of death in those with and without Alzheimer's dementia, demonstrated the most common cause of death (54%) was lower-respiratory system infection. The second and third (9 and 4%, respectively) were cerebrovascular and cardiovascular disease. In an age-matched population without Alzheimer's disease, cardiovascular and cerebrovascular disease were the predominant causes of death, with infection causing only 1% of deaths in the group without Alzheimer's.[15]

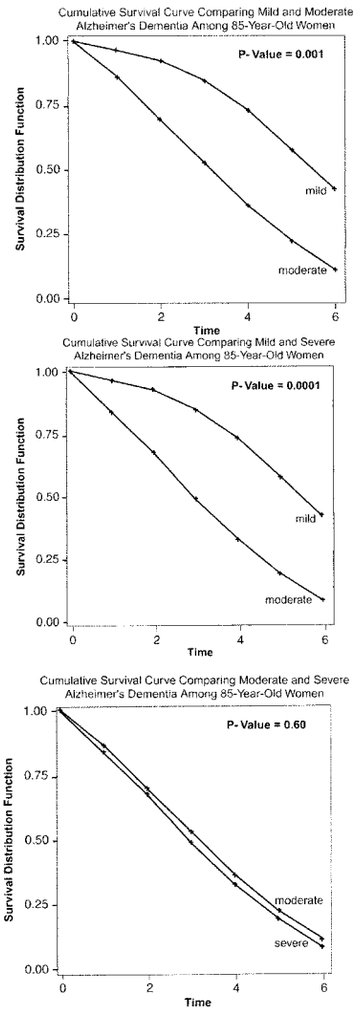

Figure 2. Comparative survival curves of women with mild, moderate and severe degrees of dementia.

RISK ASSESSMENT IN ALZHEIMER'S DEMENTIA

The risk assessment of an individual with cognitive deficits presents a challenge because there is only a brain biopsy to confirm a diagnosis of Alzheimer's dementia.[5]

The characteristics of the disease associated with extra mortality risk are discussed in the preceding section. The severity of dementia and behavioral disturbances are 2 areas that can be stratified into mild, moderate, or severe disease.

Dementia can be diagnosed and followed with cognitive tests. The mini-mental status exam is the most popular screening test used by geriatric health care providers and researchers.[5] The test is divided into 2 sections. The first requires verbal responses and covers orientation, memory, and attention with a maximum score of 21. The second portion tests the ability to name common objects, follow commands, write a sentence, and copy a complex polygon with a maximum score of 9. The maximum total score for the 2 sections is thus 30.[17] The original article, written by Folstein in 1975, evaluated the test to ascertain whether it could be used as a tool to determine the presence or absence of cognitive impairment in patients admitted to a psychiatric unit.

The mean score was 9.7 for demented patients, 19 for depressed patients with cognitive impairment, and 25 for depressed patients without cognitive impairment. The mean score for individuals without cognitive impairment or depression was 27.6.[17] The mini-mental status exam is a good screening tool; although it is insensitive in detecting early dementia and is biased in regard to age and education, it can be used as a measure for progressive impairment when performed serially. Scores below 23 suggest some degree of dementia.[5]

Behavioral disturbances in Alzheimer's disease may be identified on physical examination and may predispose individuals to accidents and institutionalization. These disturbances are commonly seen in the more advanced stages of disease. As Table 4 indicates, staging of disease correlates disease duration and clinical symptomatology.[5]

Risk factors identified as significant in disease development include age and family history. Other factors linked to the disease are lack of formal education and possibly head trauma.[4]

Age is consistently reported as the most important risk factor for disease development.[3–5] The prevalence of disease increases with age over 65 and is constant in all countries.[4]

Family history in a first-degree relative with Alzheimer's increases risk from 2 to 6 times.[4,18–21] Genetic factors are involved in the inheritance of the disease and differ in the nature of the genetic disorder that is trans-

Table 2. Observed and Expected Mortality Rates, Mortality Ratios, and Excess Death Rates from Alzheimer's Disease: Males and Females Combined

				Comparative Experience	
Age	Interval	Observed $q(o)$	Expected $q(e)$	Mortality Ratio 100 $q(o)/q(e)$	Excess Death Rate 1000 $[q(o) - q(e)]$
62	0–1	0.01613	0.01613	100.0	0.0
63	1–2	0.01913	0.01639	116.7	2.7
64	2–3	0.04735	0.02083	227.3	26.5
65	3–4	0.04678	0.01844	253.7	28.3
66	4–5	0.13190	0.02890	456.4	103.0

Table 3. Life Expectancies by Severity of Alzheimer's Disease, Females*

		Alzheimer's Disease		
Age	US Population	Mild	Moderate	Severe
85	6.9	6.9	3.5	3.1
86	6.5	5.9	3.0	2.4
87	6.1	5.3	2.5	1.8
88	5.7	4.6	2.4	1.4
89	5.4	3.7	2.2	1.3
90	5.1	3.6	1.6	0.7
91	4.8	2.9	1.2	0.6

* Source: Observed life expectancies derived from Aeversson, Svanborg, and Skoog.[10]

mitted.[3] Mendelian inheritance of an autosomal dominant mutation is the method of transmission among the familial forms of early onset Alzheimer's dementia.[22] This form of the disease is represented by less than 5% of all individuals developing Alzheimer's dementia.[22]

Genetic predisposition for sporadic Alzheimer's involves at least 3 possible alleles for the apo E gene on chromosome 19. Inherited and/or sporadic Alzheimer's disease involves genes on at least 4 chromosomes, namely 1, 2, 14, and 19, and possibly chromosome 12. The apo E 4 genotype is associated with the highest risk for the disease—this genotype is found in 60% of individuals with late onset disease and in 50% of the cases of sporadic Alzheimer's with age of onset between 65 and 80 years.[4,23]

Numerous studies have substantiated that there is a relationship between no formal education and increased risk of dementia. Relative risk ratios are 2–4 times higher in those without an education.[4,24,25] As a risk factor for dementia development, head trauma is debatable. Some researchers find a strong association and others find no association.[4]

CONCLUSION

Alzheimer's dementia is an important condition to consider in the evaluation of cognitive deficit in an elderly individual. Because the disease onset is sutble and difficult to detect, it goes relatively unrecognized for 2–3 years before deficits become apparent. Progression varies widely. It is often slow, and cognitive impairment may be the dominant feature until the later stages of disease, when motor signs may develop.

Mortality caused by the disease is related to duration of the disease and age of onset. High mortality ratios are seen among younger individuals, under age 65. The pattern seen with the older age cohort suggests a minimal influence on mortality in mild early disease, but moderate and severe disease are associated with high mortality ratios and reduced life expectancy.

Risk assessment presents a challenge in recognizing both the disease and its severity. Mental status testing is used as screening for detection of cognitive impairment and for following progression of disease. Behavioral and psychiatric symptoms suggest significant

Table 4. Clinical Stages Typical of Alzheimer's Disease*

Stage I (1–3 years)	
Memory	New learning defective, remote recall mildly impaired
Visuospatial skills	Topographic disorientation, poor complex construction
Language	Poor word list generation, anomia
Personality	Indifference, occasional irritability
Psychiatric features	Sadness or delusions in some
Motor system	Normal
EEG	Normal
CT/MRI	Normal
PET/SPECT	Bilateral posterior parietal hypometabolism/hypoperfusion
Stage II (2–10 years)	
Memory	Recent and remote recall more severely impaired
Visuospatial skills	Poor construction, spatial disorientation
Language	Fluent aphasia
Calculation	Acalculia
Praxis	Ideomotor apraxia
Personality	Indifference or irritability
Psychiatric features	Delusion in some
Motor system	Restlessness, pacing
EEG	Slowing of background rhythm
CT/MRI	Normal or ventricular dilatation and sulcal enlargement
PET/SPECT	Bilateral parietal and frontal hypometabolism/hypoperfusion
Stage III (8–12 years)	
Intellectual function	Severely deteriorated
Motor	Limb rigid and flexion posture
Sphincter control	Urinary and fecal incontinence
EEG	Diffusely slow
CT/MRI	Ventricular dilatation and sulcal enlargement
PET/SPECT	Bilateral partial and frontal hypometabolism/hypoperfusion

* Modified from Cummings JL, Benson DF. *Dementia: A Clinical Approach.* Boston: Butterworth-Heinemann; 1992, with permission.

cognitive involvement and may be used to determine severity of disease.

Risk factors for the development of disease include family history and age. Head trauma history and lack of formal education have also been associated with increased risk for the development of Alzheimer's. The interaction between genetic and environmental influences is still unclear. Once the relationship between the two factors is elucidated, this information will further differentiate individuals at high risk for development of disease.

REFERENCES

1. Rainulf A, Stelzmann H, Schnitzlein N, et al. An English translation of Alzheimer's 1907 paper, ''Uber eine eigenartige Erkankung der Hirnrinde.'' *Clin Anat.* 1995;8:429–431.
2. Salyer K. Historical perspectives. In: Hamdy RC, Turnbull JM, Clark W, Lancaster MM, eds. *Alzheimer's Disease: A Handbook for Caregivers.* 2nd ed. St. Louis, Mo: Mosby Yearbook; 1994.
3. Warshaw G, Gwyther L, Phillips L, Koff T. *Alzheimer's Disease: An Overview for Primary Care.* Tucson, AZ: University of Arizona Health Sciences Center; 1996.
4. Katzman R, Kawas C. The epidemiology of dementia and Alzheimer disease. In: Terry R, Kutmann R, Bick K, eds. *Alzheimer Disease.* New York: Raven Press; 1994;105–122.
5. Green R. Alzheimer's disease and other dementing disorders in adults. In: Joint R, ed. *Clinical Neurology.* New York: Raven Press; 1995:1–84.
6. Rice DP, Fox PJ, Max W. The economic burden of Alzheimer's disease care. *Health Aff.* 1993;12:164–176.
7. Day J. Populations of the United States, by age, sex, race, and Hispanic origin: 1992–2050. *Current Population Report Series* no. 1130. Washington, DC: USGPO.
8. *Mortality Research Review.* ING Reinsurance. July 1999; Vol 2.
9. Pokorski RJ. Mortality methodology and analysis seminar. *J Insur Med.* 1988;20:20–45.
10. Aeversson O, Svanborg A, Skoog I. Seven year survival rate after 85 years. *Arch Neurol.* 1998;55:1226–1232.
11. Heyman A, Wilkinson WE, Hurwitz BJ, et al. Early onset Alzheimer's disease; clinical predictors of institutionalization and death. *Neurology.* 1987;37: 980–984.
12. US Department of Health and Human Services. *U.S. decennial life tables for 1989–1991.* 1997;1:1–33.

13. US Department of Health and Human Services. *U.S. decennial life tables for 1979–1981.* 1985;1:1–33.
14. Burns A, Lewis G, Jacoby R, Levy R. Factors affecting survival in Alzheimer's disease. *Psychol Med.* 1991;21:363–370.
15. Molsa PK, Marttila RJ, Rinne UK. Survival and cause of death in Alzheimer's disease and multi infarct dementia. *Acta Neurol Scand.* 1996;74:103–107.
16. Seltzer B, Sherwin I. A comparison of clinical features in early- and late-onset primary degenerative dementia one entity or two? *Arch Neurol.* 1983;40: 143–146.
17. Folstein M, Folstein S, McHugh P. ''Mini-mental state'' a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–198.
18. Payami H, Montee K, Kaye J. Evidence for familial factors that protect against dementia and outweigh the effect of increasing age. *Am J Hum Genet.* 1994; 54:650–657.
19. Mohs RC, Breitner JCS, Siverman JM, Davis KD. Alzheimer's disease: morbid risk among first degree relatives approximates 50% by 90 years of age. *Arch Gen Psychiatry.* 1987;44:405–408.
20. Shalat SL, Seltzer B, Pidcock C, Baker EL. Risk factors for Alzheimer's disease: a case control study. *Neurology.* 1987;37:1630–1633.
21. Breitner JCS, Siverman JM, Mohs RC, Davis KL. Familial aggregation in Alzheimer's disease: comparison of risk among male and female relatives in successive generations. *Neurology.* 1988;30:207–212.
22. Roses A. Alzheimer's disease and the dementias. In: Dale D, Federman D, Alpert J, eds. *Scientific American Medicine.* New York: Scientific American Inc; 1997:1–10.
23. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of aplipoprotein E allele e4 with late onset familial and sporadic Alzheimer's disease. *Neurology.* 1993;43:1467–1472.
24. Dortigues JF, Gagnon M, Michel P. Le programme de recherche pasquid sur l'epidemiologie de la demence methodes et resultats initiaux. *Rev Neurol (Paris).* 1991;147:225–230.
25. Zhang M, Katzman R, Jin H, et al. The prevalence of dementia and Alzheimer's disease (AD) in Shanghai, China: impact on age, gender, and education. *Ann Neurol.* 1990;27:428–437.