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Epidemiology of Alzheimer's Disease

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Dementia is emerging as a major health problem; it is an important cause of disability, particularly in the elderly. Dementia is a syndrome that can be caused by many conditions with Alzheimer's disease being numerically the most important. Therefore, etiologic research and intervention studies have mainly concentrated on Alzheimer's disease. In this article we will review the current epidemiologic knowledge concerning this disease and will focus on the results of recent investigations, generally conducted since 1980, since these studies largely conform to contemporary standards of diagnosis. We will successively discuss diagnosis, prevalence, incidence, risk factors, prognosis, and therapy.

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Abbreviations: DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*, third ed.; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, third ed. revised; NINCDS-ADRDA, National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.

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The authors thank all members of the EURODEM work groups on the prevalence of dementia (EURODEM Prevalence), the incidence of dementia (EURODEM Incidence), and risk factors for Alzheimer's disease (EURODEM Risk Factors). Part of this review is based on the EURODEM collaborative reanalyses, and where these results are referred to, the appropriate EURODEM publications and the contributing studies have been referenced. The collaboration with the US National Institute on Aging for the risk factor studies is gratefully acknowledged.

DIAGNOSIS

Diagnostic criteria

The diagnosis of Alzheimer's disease is hampered by insufficient knowledge of its pathogenesis, the lack of biologic markers, and the absence of unique clinical or morphologic features. High clinical and neuropathologic diagnostic accuracy, and valid and standardized criteria, are needed in order to compare the results of various studies. For the clinical diagnosis of Alzheimer's disease, the majority of recent epidemiologic studies conform to the criteria for progressive degenerative dementia as defined in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) (1), to the essentially similar criteria for progressive degenerative dementia of the Alzheimer type presented in the third revised edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R) (2), or to the criteria for possible and probable Alzheimer's disease as developed by a work group of the US National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (3). According to all of these criteria, the clinical diagnosis of Alzheimer's disease is, more or less, a diagnosis by exclusion of other specific causes of dementia. An important difference, however, is that DSM-III and DSM-III-R criteria preclude a diagnosis of Alzheimer's disease when the intellectual decline does not interfere with everyday life, while according to NINCDS-ADRDA criteria, impairment in daily life is

supportive of, but not required for, a diagnosis. In addition, the NINCDS-ADRDA work group recommended, for research purposes, that a single gradually progressive severe cognitive deficit be identified as possible Alzheimer's disease (3).

The diagnosis of definite Alzheimer's disease requires neuropathologic confirmation according to NINCDS-ADRDA criteria (3); however, the neuropathologic hallmarks of neuritic plaques and neurofibrillary tangles are not pathognomonic. At present, there is no universally accepted set of criteria for a pathologic diagnosis of the disorder. Tierney et al. (4) found that, depending on the set of neuropathologic criteria used, the percentage of subjects with a clinical diagnosis of probable Alzheimer's disease, confirmed pathologically, ranged from 64 to 86 percent. The development of uniform criteria permitting consistent neuropathologic assessment of Alzheimer's disease is mandatory (5, 6).

The performance of current clinical criteria has been studied by various researchers. The agreement between several raters applying the same set of diagnostic criteria depends on the specific set of criteria used (7). For DSM-III and NINCDS-ADRDA criteria, among physicians the interrater reliability of Alzheimer's disease diagnosis was found to be comparable and moderate (7, 8). Kukull et al. (9) found NINCDS-ADRDA and DSM-III-R criteria for Alzheimer's disease to have similar overall accuracy, yet NINCDS-ADRDA criteria were more sensitive and DSM-III-R criteria more specific. Several researchers used prospective clinicopathologic studies to investigate the accuracy of a clinical diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA or equivalent criteria and reported percentages of diagnoses that were confirmed at autopsy to range from 85 to 100 percent (10–12), but lower rates have been reported in patients with disease onset before the age of 65 years (13). Although theoretically this high positive predictive value may have come at the cost of low sensitivity, in the study by Wade et al. (12) it was compatible with a sensitivity of 87 percent.

The spectrum of disease severity is an important consideration when making a clinical diagnosis of Alzheimer's disease. Alzheimer's disease presents as a continuum with normal aging, especially in the early stages of the disease which are characterized by an insidious onset and gradual decline. While the extremes of the distribution are easily recognized, the diagnosis of Alzheimer's disease may be arbitrary in mild cases (14, 15), as evidenced by the wide range in prevalence estimates of mild dementia (14, 16). Although this difficulty is unlikely to be resolved without objective markers, further operationalization of diagnostic criteria could limit the extent of varying interpretations (17).

Differential diagnosis

The diagnosis of Alzheimer's disease requires the exclusion of other specific causes of dementia; however, in particular, the distinction between Alzheimer's disease and vascular dementia poses difficulty. The question of how and when vascular disease and infarcts cause dementia is still a matter of debate (18, 19). The characteristics of vascular dementia itself are not unique and may be qualitatively indistinguishable from those seen in Alzheimer's disease (20, 21). The concept of vascular dementia is, in fact, a confusing one since it encompasses a diversity of vascular mechanisms (such as atherosclerosis, cerebral blood flow regulation, and amyloid angiopathy) that alone or in combination may contribute to cognitive impairment (22). Furthermore, Alzheimer's disease itself may have an important vascular component (21). In today's epidemiologic practice, vascular dementia is still simply interpreted as atherosclerotic or multi-infarct dementia, and its diagnosis is largely based on the likelihood that a person has ischemic cerebrovascular disease. The scale that has gained the most use for diagnostic purposes is the Hachinski Ischemic Score (23). Although the reliability and validity of this scale to establish a diagnosis of multi-infarct dementia has been questioned, it tends to rule out possible atherosclerotic

causes of dementia and is, therefore, useful in the diagnosis of Alzheimer's disease by exclusion (12, 24, 25).

Vascular causes, as well as Alzheimer's disease, may contribute independently to dementia in the same patient. This gives rise to the paradoxical diagnosis of mixed dementia (26) which at the same time requires the presence of cerebrovascular disease considered etiologically related to the dementia, as well as a diagnosis of Alzheimer's disease for which cerebrovascular disease has to be excluded. As a pragmatic solution, epidemiologic studies on Alzheimer's disease tend to exclude both mixed and multi-infarct cases. In populations with a high vascular background risk, the diagnostic practice regarding multi-infarct dementia might give a relative underestimation of Alzheimer's disease. For etiologic or intervention studies, where homogeneity of patient groups is of prime importance, this need not be a problem. However, it may bias comparisons of the frequency of Alzheimer's disease across different populations.

There is considerable variation in the proportion of all types of dementia attributed to Alzheimer's disease reported from different geographic regions (27). On average, two out of three demented patients are diagnosed as having Alzheimer's disease in Europe and North America (28, 29), while in Japan and China only one out of three dementia patients is diagnosed as having dementia of the Alzheimer type (27).

PREVALENCE

The relevance of prevalence studies of dementia lies primarily in providing data for local health services planning. Furthermore, comparison of prevalence figures of specific dementing disorders from different populations or at different times might yield etiologic clues to the diseases. In reviews of earlier studies it was recognized that the large variation in prevalence estimates across studies could possibly be due to differences in methodology (30, 31). In this review we will limit ourselves to community-based studies that used currently accepted diagnostic criteria (DSM-III, DSM-III-R, NINCDS-ADRDA, or equivalent) (1–3) for the diagnosis of Alzheimer's disease. We will disregard studies that only reported the overall prevalence of Alzheimer's disease for the population above a certain age (32–35), since these figures are strongly dependent upon the underlying age- and gender-distributions, and for that reason not suitable for comparison with other studies.

Comparison of studies from Europe, the United States, and Japan

Studies that presented age-specific prevalence figures for Alzheimer's disease have been conducted in Europe, the United States, and Japan (tables 1 and 2).

Europe. All European studies on the prevalence of dementia conducted or published after 1980 were recently collaboratively reanalyzed under the auspices of EURODEM (28). Using a specified set of criteria developed to enhance validity and comparability, six studies (36–41) were selected that permitted the calculation of age-specific prevalence of Alzheimer's disease (29). One of these studies was restricted to women (36). Results were very similar across these studies (figure 1). The overall prevalence estimates from the EURODEM reanalysis for the age groups 60–69 years, 70–79 years, and 80–89 years were 0.4, 3.6, and 11.2 percent, respectively, for women and 0.3, 2.5, and 10.0 percent, respectively, for men.

United States. Four studies from the United States have reported age-specific prevalence estimates for Alzheimer's disease (figure 2). The Rochester, Minnesota, study reported results which were similar to those of the European studies (42). Although the Rochester study is register-based, the coverage of the register permits the study to be considered community-based. The estimates from the East Baltimore, Maryland, study were somewhat lower (43). The highest prevalence results reported to date were found in the East Boston, Massachusetts, study (44). The study conducted in California by Pfeffer et al. (45) rated cases according to severity ranging from questionable to severe. When

TABLE 1. Population-based prevalence studies of Alzheimer's disease

Site (reference no.)	Diagnostic criteria	Sample size	Institutions	Response rate (%)	Number of cases	% Alzheimer's disease
Europe						
Finland, total country (39)	DSM-III* and NINCDS-ADRDA*	8,000 (aged ≥30 years)	Included	95	67	50
Italy, Appignano (38)	DSM-III and NINCDS-ADRDA	778	Included	95	19	41
Spain, Zaragoza (41)	DSM-III and NINCDS-ADRDA	334	Included	84	13	78
Sweden, Lundby (40)	DSM-III-R*	3,563	Included	Not reported	13	†
United Kingdom, Cambridge (37)	DSM-III and NINCDS-ADRDA	2,311	Included	74	174	75
United States						
East Baltimore, MD (43)	DSM-III	1,230 (aged ≥65 years)	Not included	40	12	44
East Boston, MA (44)	DSM-III-R and NINCDS-ADRDA (excluding functional impairment)	4,485	Not included	53	300	84‡
California (45)	NINCDS-ADRDA	1,367	Not included	60	162 (including questionable)	87
Rochester, MN (42)	DSM-III and NINCDS-ADRDA	23,000 (aged ≥30 years)	Included	Not applicable	206 (aged ≥65 years)	72 (all ages)
Japan						
Kanagawa (47)	DSM-III	1,800	Not included	80	17	24
Miki town (46)	DSM-III-R	3,754	Not included	Not reported	59	39

* DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. revised; NINCDS-ADRDA, National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.

† No prevalence figures for all types of dementia reported. Alzheimer's disease was more frequent than multi-infarct dementia among women, vice versa among men.

‡ Only the relative proportion of Alzheimer's disease among moderate/severe cases was reported.

TABLE 2. Age-specific prevalence (percent) of Alzheimer's disease

Site	Age range (years)						
	60–64	65–69	70–74	75–79	80–84	85–89	≥90
Europe							
Finland, total country*	0.3†		2.5	5.1	11.9§		
Italy, Appignano*	0.6†		2.0‡		10.2§		
Spain, Zaragoza*		0.0	2.8‡		12.1§		
Sweden, Lundby*	0.3†		2.5‡		10.9§		
United Kingdom, Cambridge*				2.3	8.1	15.7	28.0
United States							
East Baltimore, MD		0.3¶		3.7‖		8.2#	
East Boston, MA		3.0¶		18.7‖		47.2#	
California**	0.8	1.2	3.7	8.2		31.7#	
Rochester, MN	0.4	1.1	3.8	7.0		12.7#	
Japan							
Kanagawa	0.2	0.5	0.8	4.0		8.3#	
Miki town	0.2	0.6	1.5	3.9		7.1#	

* Prevalence calculated as a weighted average from the sex-specific figures in the European reanalysis (table 4) (29).
† Age range = 60–69 years.
‡ Age range = 70–79 years.
§ Age range = 80–89 years.
¶ Age range = 65–74 years.
‖ Age range = 75–84 years.
Age range = ≥85 years.
** Prevalence calculated as a weighted average from the sex-specific figures (tables 2 and 6 of reference (45)), excluding questionable dementia.

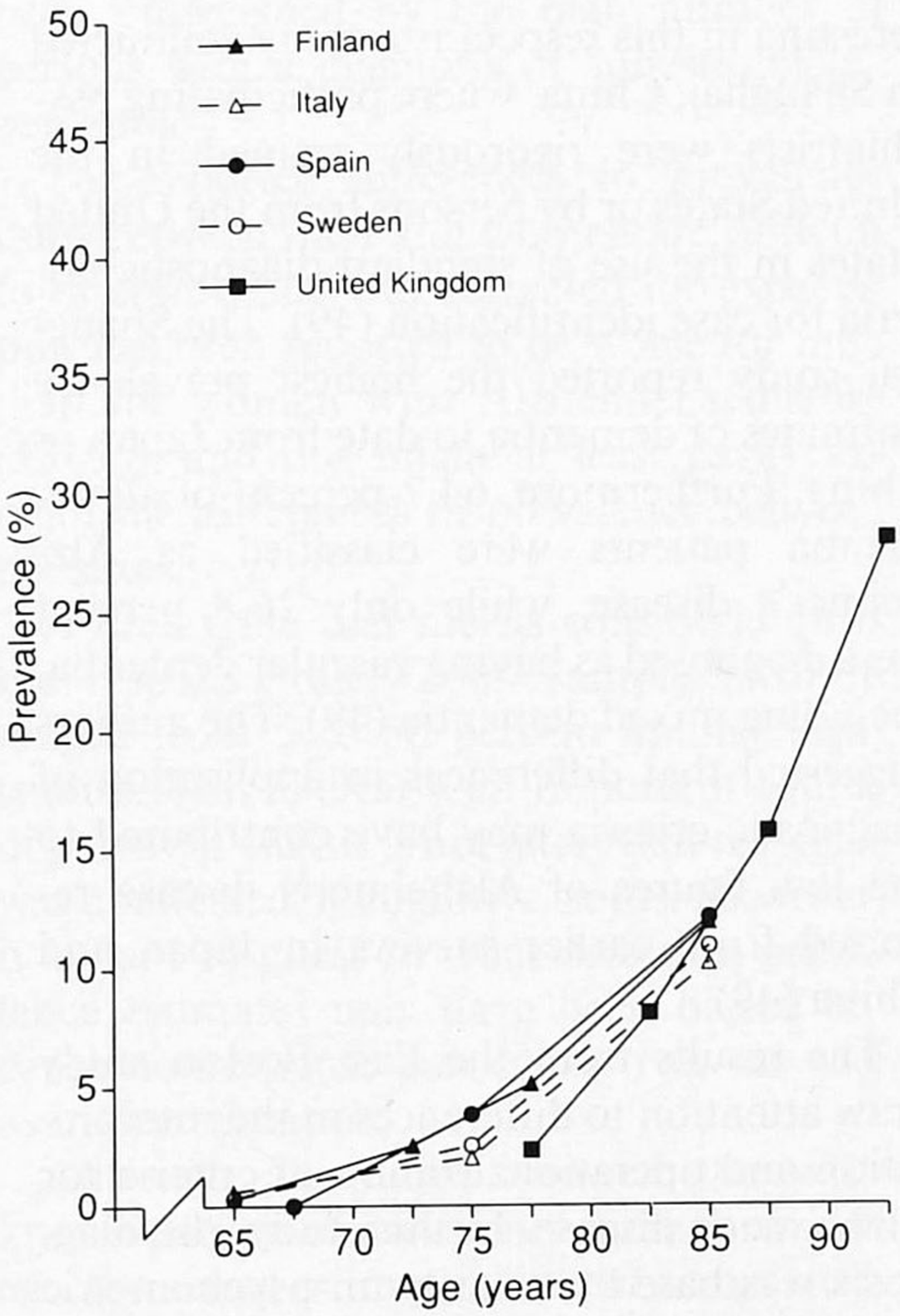

FIGURE 1. Comparison of age-specific prevalence of Alzheimer's disease in the EURODEM studies (37–41).

subjects with a diagnosis of "questionable" dementia were excluded, the prevalence estimates from this study were very similar to the results reported from the Rochester and the European studies, except for the highest age group.

Japan. The two Japanese studies reported the lowest age-specific prevalence results of Alzheimer's disease (46, 47). Estimates from both studies were very similar (figure 2).

The majority of studies reported a higher prevalence of Alzheimer's disease for women as compared with men (37–39, 42, 43). One study found similar results (40) while in two other studies men had a higher prevalence (41, 45). The higher prevalence among men in the California study was because of the excess number of males with very early disease (45).

Methodological considerations

Despite the apparent similarity in diagnostic inclusion criteria across the recently reported studies, there are still important methodological differences which hamper

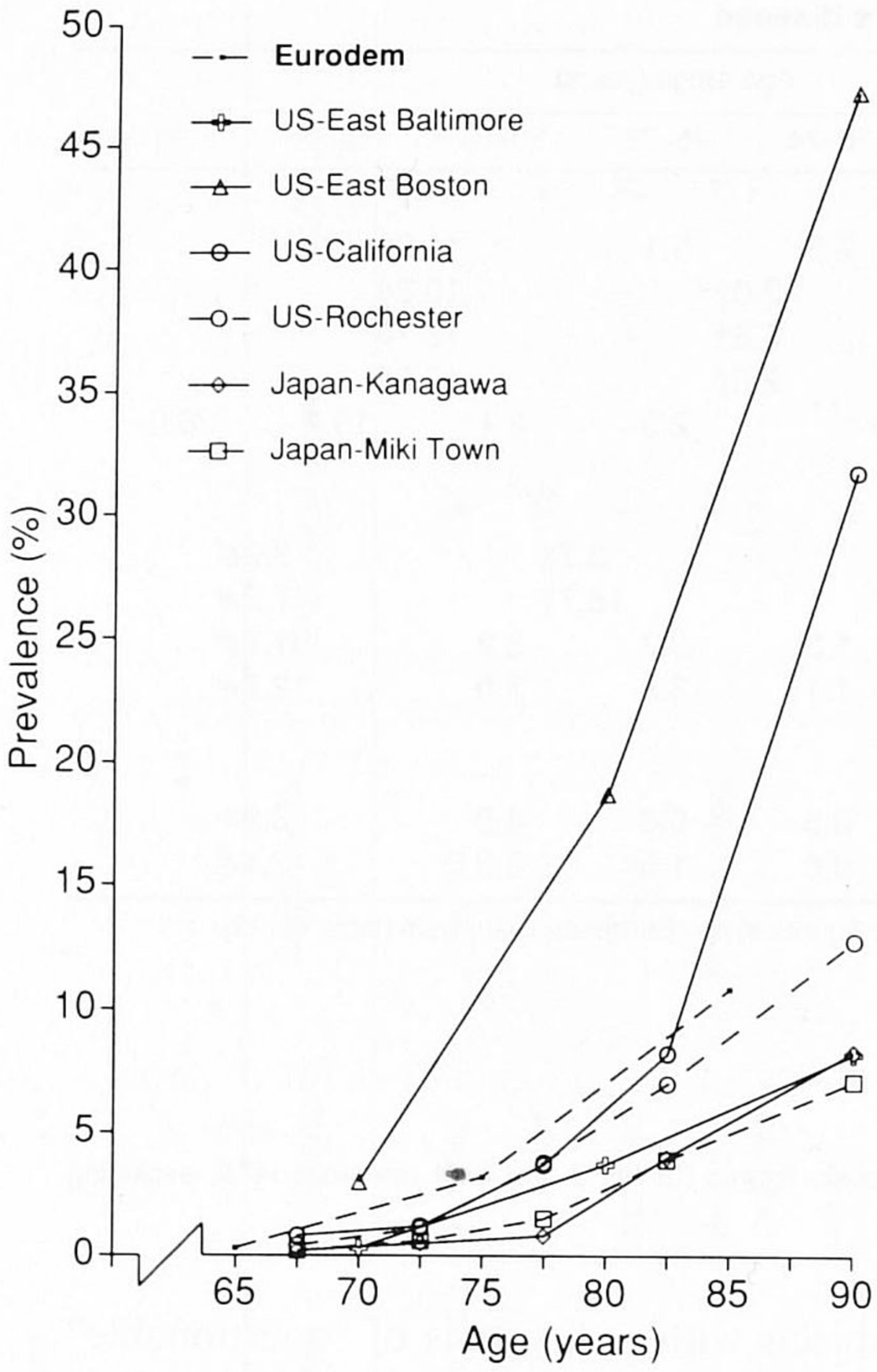

FIGURE 2. Comparison of age-specific prevalence of Alzheimer's disease in the EURODEM reanalysis, and the studies from the United States and Japan (29, 42–47).

direct comparison of prevalence studies of Alzheimer's disease (table 1). Assessment procedures differed substantially between studies. Most surveys used a two phase design, with cognitive screening in the first phase and in-depth clinical examination in the second phase. However, various screening instruments, with presumably different sensitivities, were used. Although the magnitude of the variation introduced by the use of different instruments is hard to assess, it may have been substantial (15). Some studies included a sample of persons in the second stage that had scored above the cut-off in the first phase to be able to correct for false-negatives, but other studies did not. Pfeffer et al. (45) used a composite screening instrument and found that 80 percent of the persons that were considered at least questionably demented in the final analysis had scores above the often used cut-off point of 23/24 on the Mini Mental State Examination. The thoroughness of case ascertainment also varied. Although neurologic examination and informant interview were part of the work-up in all studies, this was not the case for laboratory investigations, and neuroimaging was performed in only a few studies.

In the studies under consideration, reported prevalence of Alzheimer's disease tended to increase with an increasing proportion of total dementia attributed to Alzheimer's disease (tables 1 and 2). The variation in relative frequency of Alzheimer's disease was considerable across studies. Although this may be real, the possibility that it was caused by a different application of diagnostic criteria or varying background risk of vascular disease cannot be excluded. Both Japanese studies found a predominance of vascular dementia. This is in agreement with results from earlier studies from Japan and China that fairly consistently reported a higher prevalence of vascular, compared with Alzheimer's, dementia (48). Interesting in this respect is a study conducted in Shanghai, China, where participating psychiatrists were rigorously trained in the United States or by persons from the United States in the use of standard diagnostic criteria for case identification (49). The Shanghai study reported the highest prevalence estimates of dementia to date from Japan or China. Furthermore, 64.7 percent of all dementia patients were classified as Alzheimer's disease, while only 26.8 percent were diagnosed as having vascular dementia, including mixed dementia (49). The authors suggested that differences in application of diagnostic criteria may have contributed to the low figures of Alzheimer's disease reported from earlier surveys in Japan and China (49).

The results from the East Boston study draw attention to differences in the interpretation and operationalization of criteria for Alzheimer's disease. In this study, the diagnosis was based primarily on psychometric testing (44, 50, 51), and functional impairment in everyday life was not required. Interestingly, the study by Pfeffer et al. (45)

also relied mainly on cognitive tests, and yielded more or less similar prevalence estimates when subjects with a diagnosis of "questionable" dementia were included (in percent by 5-year age groups from 65 to 85 years, then 85 years and over: 0.8, 2.9, 11.9, 27.7, and 47.3, respectively) (45). However, as mentioned above, the prevalence figures for mild to severe dementia in this study were very similar to those reported by others (29, 42, 45).

The percentage of persons with Alzheimer's disease living in institutions varies widely from place to place (52) but may exceed half of all cases with severe Alzheimer's disease (34, 39). Exclusion of institutionalized persons can, therefore, result in an underestimation of prevalence rates, and this may have contributed to the relatively low rates reported in the East Baltimore study and the Japanese studies (43, 46, 47). All other studies included institutionalized persons except for the East Boston and California studies (44, 45). A possible underestimation in the latter studies has possibly been outweighed by the high number of persons with a diagnosis of "questionable" dementia.

The reported differences in prevalence rates between men and women are difficult to interpret. Survival corrected for expectation has been reported to be worse for men than for women with Alzheimer's disease (53–56), and this might at least partly explain the differences in prevalence between the sexes.

A final issue that merits consideration is the response rate. Total sample attrition ranged from 5 to 60 percent among these studies. This is clearly an important source of potential bias. It is not likely that response was unaffected by cognitive status. However, it is hard to guess in what direction prevalence estimates may have been biased because nonresponse can cause over- as well as underestimation.

Although all studies showed the well-known pattern of prevalence increasing with age, the actual estimates differed across studies. Part of the variation is likely to be a reflection of the small sample size in some of the studies. Several other methodological differences may be underlying the variation, as previously discussed. It is remarkable that studies that were methodologically most comparable yielded the most similar results (29, 42). This stresses the importance of the universal adaptation of comparable methods of case ascertainment in well-defined populations for epidemiologic research on Alzheimer's disease.

INCIDENCE

Comparison of incidence rates is of etiologic interest since these are theoretically not affected by differences in survival rates. A limited number of studies have reported the results to date of age-specific incidence of Alzheimer's disease (40, 57–64). To enhance comparability, we will concentrate on community surveys based on random or total samples of geographically-defined populations (40, 59, 63, 64). As with the prevalence studies, we include the register-based studies from Rochester (57, 58) because these can be considered community-based.

Comparison of studies from Europe and the United States

Four studies from Europe and two studies from the United States, based on the same population but covering different time periods, reported age-specific incidence rates for Alzheimer's disease (tables 3 and 4). All studies showed an exponential increase in the incidence rate with age (figure 3). Several studies found that the proportion of incident dementia patients attributable to Alzheimer's disease increased with age. In the Rochester study over the period 1965–1974, 47 percent of all dementia patients aged 60–69 years, 66 percent of all dementia patients aged 70–79 years, and 80 percent of all dementia patients aged 80 years or older were the result of Alzheimer's disease (57). The data from France and the United Kingdom showed the same trend: for the age groups 65–74 years, 75–84 years, and 85 years and older the proportion of Alzheimer's disease was 14, 86, and 86 percent, respectively, in Bordeaux, France (J.-F. Dartigues, INSERM U330, Université de

TABLE 3. Population-based incidence studies of Alzheimer's disease

Site (reference no.)	Sample size	Length of study (years)	Incidence interval (years)	Free of disease	Disease onset	Nonresponse information
Europe						
France,* Bordeaux (64)	4,134	8	2	Absence of dementia by DSM-III-R† criteria	Diagnosis	General practitioner informant
Sweden, Gothenburg (59)	652	10	5 and 4	Absence of dementia by DSM-III-R criteria	Diagnosis	Medical records searched for deceased and lost to follow-up
Sweden. Lundby (40)	3,563	≥53	15	Clinical interview	Diagnosis	Medical record information
United Kingdom,* Liverpool (63)	1,070	6	3	GMS-AGECAT† ≤ 2	First symptoms	Demographic information informant
United States						
Rochester, MN, 1960–1964 (58)	18,991 (aged ≥30 years)	5	Not applicable	Documented evidence of previously normal function	First symptoms	Mayo Clinic records-linkage system
Rochester, MN, 1965–1974 (57)	22,976 (aged ≥30 years)	10	Not applicable	Documented evidence of previously normal function	First symptoms	Mayo Clinic records-linkage system

* Ongoing study.
† DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. revised; GMS-AGECAT, Geriatric Mental State-Automated Geriatric Examination for Computer Assisted Taxonomy.

TABLE 4. Age-specific incidence of Alzheimer's disease (per 100,000 person-years)

Site	Age range (years)					
	60–64	65–69	70–74	75–79	80–84	≥85
Europe						
France, Bordeaux			106*		868†	3,333
Sweden, Gothenburg			358	1,326		
Sweden, Lundby, 1957–1972‡	115§		600¶		2,230‖	
United Kingdom, Liverpool			187*		824†	2,424
United States						
Rochester, MN, 1960–1964	96§		530¶		1,432‖	
Rochester, MN, 1965–1974	66§		409¶		1,480‖	

* Age range = 65–74 years.
† Age range = 75–84 years.
‡ Incidence rate calculated as a weighted average from the gender-specific incidence rates.
§ Age range = 60–69 years.
¶ Age range = 70–79 years.
‖ Age range = ≥80 years.

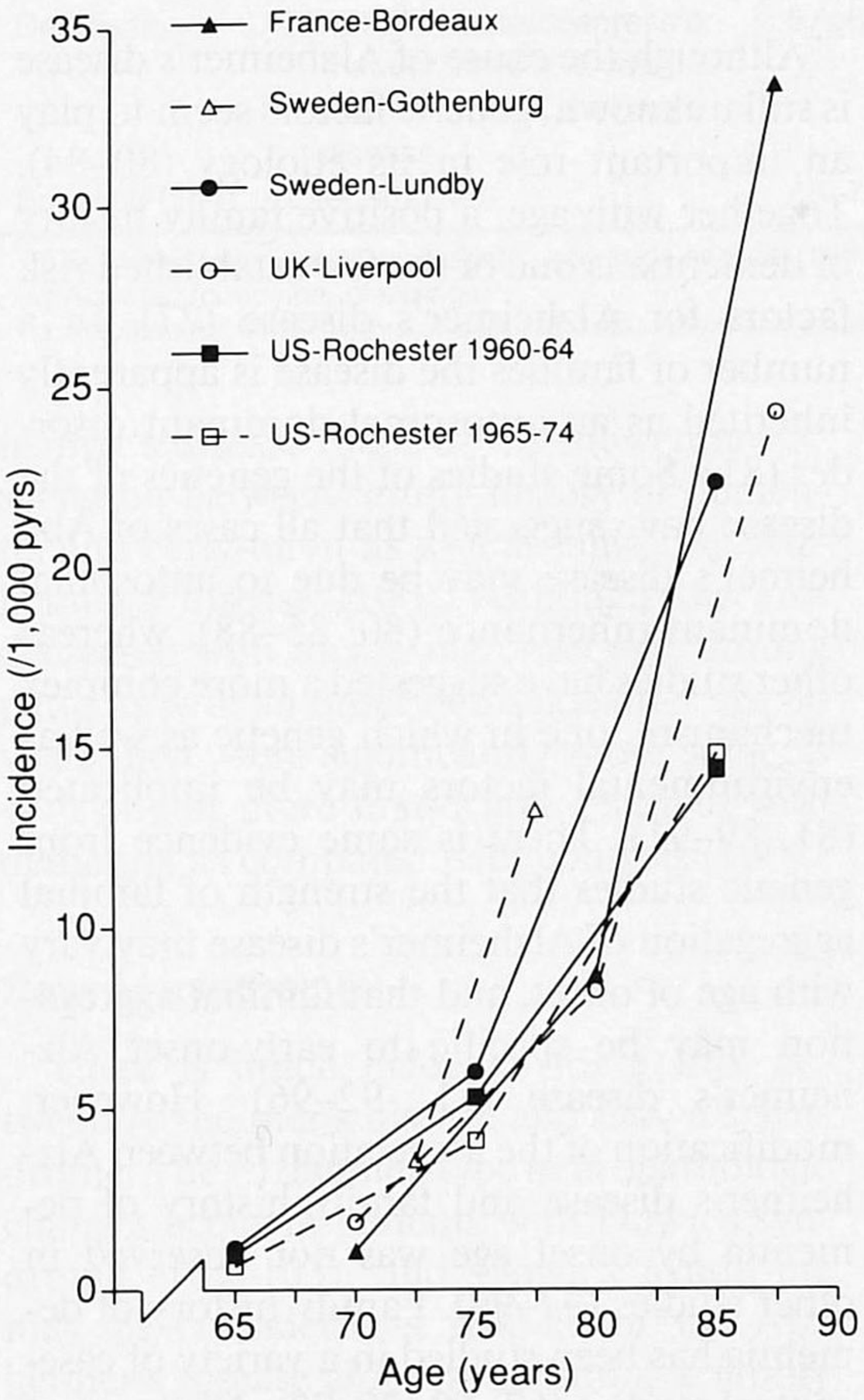

FIGURE 3. Comparison of age-specific incidence of Alzheimer's disease in community-based studies (41, 57–59, 63, 64).

Bordeaux II, personal communication, 1991), and 50, 70, and 80 percent, respectively, in Liverpool, United Kingdom (J. R. M. Copeland, University of Liverpool, personal communication, 1991).

Differences between men and women were minor within studies and inconsistent across studies. Two studies suggested that women have a greater risk then men for Alzheimer's disease (40, 57), while two other studies reported higher risks among men in most age categories (58, 59).

Methodological considerations

In addition to several of the methodological problems already discussed in the "Prevalence" section above, there are some issues that, in particular, pertain to incidence studies.

In a cohort study there is inevitably loss to follow-up. Since it cannot be assumed that this occurs randomly, the intensity of follow-up and the documentation of, and adjustment for, persons who died and persons who withdrew from the cohort will affect the observed incidence rates. Most studies reviewed here sought medical records or information from general practitioners for deceased and lost persons (table 3).

The insidious onset of Alzheimer's disease makes it difficult to specify a specific point in time of disease occurrence. Definition of the time of disease onset influences the calculation of person-years of follow-up. The length of the follow-up interval can also affect the results. Studies with an interval

shorter than the longest lead time gained by the first screening will have a lower apparent rate than a study with a longer interval (65).

The reported estimates of the incidence density of Alzheimer's disease do not permit conclusions concerning differences across populations that have been studied thus far. Estimates were derived from a small number of studies with a restricted geographic spread. Furthermore, some of these studies have only recently been started and follow-up time is, therefore, limited. A new generation of incidence studies of Alzheimer's disease in Europe and North America is likely to provide us with ample data in the near future (66).

RISK FACTORS

Methodological issues

Given the high frequency of Alzheimer's disease, remarkably little epidemiologic research has focused on the etiology of the disease. A number of relatively small case-control studies have been performed (57, 67–77), all of which had little statistical power individually (78). Moreover, the validity of these studies has been limited. First, all studies comprised a mixture of prevalent and incident Alzheimer patients. It is well known that, if prevalent cases are studied, selection bias may result from mortality and migration related to the disease. Second, there has been substantial opportunity for information bias in most epidemiologic studies of Alzheimer's disease, with the exception of one follow-up study (57) which was based on medical records. An important source of nondifferential bias may have been the use of surrogate informants in the retrospective studies which were based on interviews. Differential misclassification in exposure status between cases and controls may possibly have resulted from recall bias, since exposures may have occurred decades before onset of disease and informants of cases may have been more willing to recollect such historical data than informants of controls. Therefore, the risk factors that emerged in the various case-control studies, as will be discussed below, remain to be confirmed in studies of incident cases in which the exposure status is measured before onset of disease.

The putative risk factors of Alzheimer's disease that will be discussed below are family history of dementia, Down's syndrome, Parkinson's disease, parental age, head trauma, medical history, smoking, aluminum, and education. Many of these risk factors have recently been collaboratively reanalyzed by the EURODEM Risk Factors Research Group (79). The main overall results of this reanalysis are presented in table 5.

Family history of dementia

Although the cause of Alzheimer's disease is still unknown, genetic factors seem to play an important role in its etiology (80–84). Together with age, a positive family history of dementia is one of the few established risk factors for Alzheimer's disease (27). In a number of families the disease is apparently inherited as an autosomal dominant disorder (81). Some studies of the genetics of the disease have suggested that all cases of Alzheimer's disease may be due to autosomal dominant inheritance (80, 85–88), whereas other studies have suggested a more complex mechanism, one in which genetic as well as environmental factors may be implicated (81, 89–91). There is some evidence from genetic studies that the strength of familial aggregation of Alzheimer's disease may vary with age of onset, and that familial aggregation may be specific to early-onset Alzheimer's disease (71, 92–96). However, modification of the association between Alzheimer's disease and family history of dementia by onset age was not observed in other studies (97–99). Family history of dementia has been studied in a variety of case-control studies (67, 68, 70–77). Nine out of 10 studies reported a significantly higher risk of Alzheimer's disease for relatives of patients with dementia. The only study that failed to show an association was of late-onset Alzheimer's disease (71). A reanalysis of all formal case-control studies of Alz-

TABLE 5. Risk factors for Alzheimer's disease; results from the Eurodem reanalysis of case-control studies of Alzheimer's disease

Risk factor (reference no.)	Definition of exposure	Studies included	Relative risk*	95% confidence interval	Exposure frequency	
					Cases	Controls
Family history of dementia (100)	Dementia of any kind in at least one first degree relative	68, 70–75	3.5†	2.6–4.6	305/814	140/894
Family history of Parkinson's disease (100)	Parkinson's disease in at least one first degree relative	70, 73	2.4†	1.0–5.8	20/312	8/294
Family history of Down's syndrome (100)	Down's syndrome/mental retardation in at least one first degree relative	68, 70, 71, 73, 75	2.7†	1.2–5.7	20/588	7/615
Head trauma (126)	Head trauma with loss of consciousness ≥ 1 year before onset of Alzheimer's disease	57, 69–71, 73–75	1.8‡	1.3–2.7	87/1,059	50/1,059
Hypothyroidism (127)	History of hypothyroidism ≥ 1 year before onset of Alzheimer's disease	57, 72, 75	2.3	1.0–5.4	17/655	8/732
Depression (131)	Medically-treated depression that occurred ≥ 1 year before onset of Alzheimer's disease	57, 69, 72, 75	1.8	1.2–2.9	55/743	34/818
Smoking (144)	Ever smoked	68–75	0.8	0.6–1.0	477/899	563/955

* Estimated using conditional logistic regression analysis, taking into account matching on age and sex.
† Adjusted for number of siblings.
‡ Adjusted for family history of dementia, education, and alcohol consumption.

heimer's disease (68, 70–75) showed an association between family history of dementia and early-onset as well as late-onset Alzheimer's disease (100). Although the risk decreased with increasing onset age, among patients with an onset of disease after age 80 years there were significantly more subjects with one or more first-degree relatives with dementia as compared with controls (100).

Down's syndrome

There is much evidence for a link between Alzheimer's disease and Down's syndrome. The Alzheimer-type neuropathologic changes occur in patients with Down's syndrome (101–103), and Down's syndrome may be considered a risk factor for Alzheimer's disease (27). In addition, a family history of Down's syndrome has been associated with Alzheimer's disease, suggesting a genetic link between these disorders. A family history of Down's syndrome has been evaluated in 10 studies (68, 70, 71, 75, 85, 86, 92, 96, 99, 104). Although in seven studies more patients were observed with a positive family history of Down's syndrome as compared with controls (68, 70, 71, 75, 92, 96, 99), a significant association was established in only three studies (68, 75, 92). It can be argued that the negative findings of the other studies may be explained by the low rate of occurrence of Down's syndrome in the general population. A significant increase in the risk of Alzheimer's disease for those with a first-degree relative with Down's syndrome was shown in a reanalysis of case-control studies (68, 70, 71, 73, 75, 100) (table 5). A genetic link between Alzheimer's disease and Down's syndrome would lead one to expect that familial aggregation of Alzheimer's disease with Down's syndrome is found predominantly in familial cases. Indeed, the risk of Alzheimer's disease for those with a family history of Down's syndrome tended to be higher for those with a positive family history of dementia when pooling the data of all case-control studies (100). However, familial aggregation of Down's syndrome and Alzheimer's disease was also observed in the absence of a first-degree relative with dementia (100).

Parkinson's disease

Alzheimer's disease and Parkinson's disease share several neuropathologic characteristics (105). Lewy bodies, one of the hallmarks of Parkinson's disease, are frequently observed in Alzheimer's disease, while the Alzheimer type pathology is found more often in patients with advanced idiopathic Parkinson's disease than in the general population (105, 106). These findings have led to the hypothesis that Alzheimer's disease and Parkinson's disease may have a common etiology (107). Two case-control studies of Alzheimer's disease have investigated family history of Parkinson's disease (70, 73). In both studies there were more Alzheimer patients with a first-degree relative with Parkinson's disease as compared with age- and sex-matched population controls (100) (table 5). In the largest study, a significant association with family history of Parkinson's disease was observed (73). These findings support the view that Alzheimer's disease and Parkinson's disease may have a common pathogenesis, which perhaps is genetically determined.

Parental age

The role of parental age in Alzheimer's disease is subject to debate. To date, 13 studies have reported on this issue yielding contradicting results (70, 104, 108–118). Five studies have reported a significant association to late maternal age (70, 104, 108, 114, 118), while two studies reported a significant increase in risk for young maternal age as well as young paternal age (112, 117). Of the latter studies, the most recent showed that the association with young maternal age disappeared when adjusting for paternal age, while the association with paternal age was specific for late-onset Alzheimer's disease (117). As a corollary to these contradictory findings, there are two competing hypotheses on the underlying mechanism. For late maternal age, the association has been explained by the link with Down's syndrome. This hypothesis predicts that the risk of Alzheimer's disease follows the risk of Down's syndrome, which increases slowly with increasing maternal age until age 30 years and rapidly thereafter (118). According to the second hypothesis, the association of late-onset Alzheimer's disease with young paternal age may be explained by genetic imprinting, i.e., patients have inherited an increased predisposition to the disease through a particular parent (117). These two potential mechanisms may outbalance each other and, therefore, it is conceivable that their effects can only be shown at both extremes of the parental age distribution, which in most studies comprised only a limited number of subjects.

Head trauma

Repeated head trauma in boxers has been linked to dementia pugilistica (punch-drunk syndrome) (119). In patients with this syndrome, neurofibrillary tangles, indistinguishable from those seen in Alzheimer's disease, are found (120). These findings have led to the hypothesis that head trauma may be implicated in Alzheimer's disease. In four case-control studies a significant increase in risk of Alzheimer's disease was observed for those with a history of head trauma (68, 77, 121, 122). With the exception of two small studies (67, 76), each of the case-control studies reported an excess of head trauma in patients with Alzheimer's disease, although no significant association could be established (69–72, 75, 123–125). Pooling of the data from all formal case-control studies of head trauma with loss of consciousness (69–71, 75, 121–123, 125) showed a significant association (126) (table 5). Although the association was strongest for head trauma that occurred within 10 years before disease onset, a significant elevation in risk was also observed for head trauma that occurred more than 10 years before the onset of disease (126). In this reanalysis the association between Alzheimer's disease and head trauma could only be established in men (126).

Despite the apparently consistent findings of epidemiologic studies, there are some reasons to challenge the interpretation of a causal relation. The only prospective follow-

up study based on data obtained from medical records of the Rochester register (123) showed only a slight nonsignificant elevation in risk. In case-control studies there is considerable opportunity for recall bias for events that occurred long before disease onset. For head trauma occurring close to disease onset, we cannot exclude the possibility that the head trauma may be a consequence of an early stage of the dementia. Finally, there is as yet no biologic explanation for the effect modification by sex.

Medical history

A great variety of disorders have been linked with Alzheimer's disease, but many of these associations appeared in one or two studies and were not replicated in other investigations (127). Caution is warranted when interpreting these studies since exposures were usually rare and the precision in assessing the disease history or previous treatment was generally low.

There is some evidence of an association between Alzheimer's disease and history of thyroid disease. In the Rochester study (57), an increase in risk was observed for history of hypothyroidism, albeit nonsignificant. However, exposure frequency was low in cases and controls. When reanalyzing the data of all formal case-control studies (57, 72, 75), a significant association could be shown (127) (table 5). Although the association between Alzheimer's disease and hypothyroidism may be of interest because of the direct and indirect role of the thyroid hormone on the nervous system (127–130), there are several arguments pleading for cautious interpretation: 1) earlier studies yielded contradicting results; 2) the classification for type of thyroid disorder may be criticized because it was based on functional status as reported by informants who, with the exception of the Rochester study, were not medically trained; 3) although an association could be shown with hypothyroidism, from a statistical point of view skepticism on this relation results from the lack of an association with all thyroid diseases combined; and 4) hypothyroidism can be a cause of secondary dementia and cases may not have been recognized as such (127).

In a reanalysis of case-control studies (57, 69, 72, 75), history of medically treated depression emerged as a risk factor for Alzheimer's disease, particularly for the late-onset form (131) (table 5). There were two findings that overruled concern of bias with regard to this relation: first, the association was present in the Rochester follow-up study (57) (since this study was based on medical records, there was no recall bias), and second, a significant association was observed for episodes of depression that occurred more than 10 years before disease onset, suggesting a causal relation rather than the depression being an early symptom of Alzheimer's disease. There are several possible explanations for an association between history of depression and Alzheimer's disease (131). One explanation is that antidepressant treatment may alter neurotransmitter functioning. Another explanation may be a joint etiology of both disorders, i.e., systems disrupted in depression may also be involved in Alzheimer's disease. It is also conceivable that, as patients with depression may already have subtle cognitive deficits, they may reach the threshold for the diagnosis of Alzheimer's disease more quickly.

Smoking

There is some evidence from clinical trials that nicotine may improve information processing and attention in Alzheimer patients, and this would suggest a protective effect of smoking for Alzheimer's disease (132, 133). The mechanism underlying this association may be related to decreased nicotinic receptor binding, which has been linked to Alzheimer-type pathology (134, 135). Nicotine has been reported to increase the density of nicotinic receptors in the brain (136). It has been suggested that nicotine from cigarette smoke may compensate for the loss of nicotinic receptors in Alzheimer's disease and may thus delay the progression of Alzheimer's disease (137). Indirectly, this hypothesis derives support from the fact that a decrease in nicotinic receptor binding has

also been observed in patients with Parkinson's disease, while the majority of studies of Parkinson's disease have reported a protective effect of smoking (138).

Epidemiologic studies of the association between Alzheimer's disease and smoking have yielded equivocal results (69–72, 75, 76, 137, 139–144). In two studies a significant positive association between smoking and Alzheimer's disease was reported (72, 143), but in four studies a significant inverse relation was suggested (76, 137, 139, 142). Pooling of the data of all formal case-control studies (68–72, 74, 75, 137), however, resulted in a significant inverse association (144) (table 5). An inverse relation between smoking and Alzheimer's disease could only be shown among patients with a positive family history of dementia in the Dutch case-control study (137) and in the reanalysis of case-control studies (144), suggesting that smoking may interact with a genetically determined process. The main problem in the interpretation of these findings is that all studies were based on a mixture of prevalent and incident cases. Thus, it cannot be excluded that selection bias has occurred due to smoking-related mortality, and the findings remain to be confirmed in a follow-up study.

Aluminum

Aluminum silicates are found in the cores of senile plaques and in neurons containing neurofibrillary tangles (145). However, it remains to be established if the presence of aluminum is a cause, a consequence, or an epiphenomenon of the disease. Case reports of subjects exposed to high doses of aluminum leading to high concentrations in the brain suggest that the exposure does not lead to pathologic changes specific for Alzheimer's disease (146–148). However, several studies reported an association between aluminum intake through drinking water and the risk of Alzheimer's disease despite the fact that water contributes only a small percentage of aluminum intake (149–151). However, there is considerable opportunity for bias in these observational studies. In the earliest study, dementia was assessed by death certificates (149), a method that has been shown to be unreliable (152, 153). The study by Martyn et al. (150) can be criticized because the diagnosis of Alzheimer's disease was based on computed tomography scan readings without clinical examination of the patients. Furthermore, the association was mainly due to an increase in risk for the highest exposure category without showing convincing evidence for a dose-response relation. Finally, the findings of a relation in the most recent study (151) could not be replicated after remeasurement of the aluminum content of the drinking water.

A role of aluminum in Alzheimer's disease was supported by the finding of a higher risk of Alzheimer's disease for miners who were treated with aluminum powder, albeit the diagnosis was based on informant reports and was not clinically confirmed for all cases (154). Also, a case-control study based on informant interviews reported an increase in the risk of Alzheimer's disease for subjects using aluminum containing antiperspirants (155). On the other hand, three case-control studies that investigated the role of aluminum-containing antacids failed to show an association (68, 70, 75). One can, therefore, not escape the conclusion that the etiologic significance of these findings remains to be proven.

Education

Education has been linked to cognitive decline and dementia in several studies (27, 49, 156). However, the interpretation of these findings has been hampered by the possibility of assessment bias (27, 156). When the ascertainment of patients is accomplished through screening for cognitive impairment, an association with education may result from the fact that the scores of the screening tests may in part be determined by the subject's level of education. To date, only one study, conducted in Shanghai, China, specifically showed an association between education and Alzheimer's disease (49). The interpretation of this finding is not straightforward as

education-dependent cut-off points for the screening instrument were used.

Education may be related to Alzheimer's disease through several mechanisms (27). It is conceivable that highly educated subjects have greater cognitive or neuronal reserves than poorly educated subjects and, therefore, can lose more neurons due to Alzheimer's disease before showing symptoms of the disease. It is also possible that highly educated subjects practice their cognitive skills more intensively during their lives than do subjects with less education, and it has been suggested that lack of intellectual stimulation may lead to an increased risk of neuronal loss and Alzheimer's disease (157). Another possibility is that level of education is merely related to socioeconomic status, and life-style and occupational exposures may underlie the possible association with Alzheimer's disease.

Interaction between genetic and environmental risk factors

Little is known about the interaction between genetic and environmental risk factors for Alzheimer's disease. Several models can be hypothesized that describe the relations between genetic and environmental factors (158). Genetic and environmental risk factors may increase the risk of Alzheimer's disease independently (158). It is also conceivable that a genetic factor exacerbates the effect of an environmental risk factor (or vice versa), or that the presence of both a genetic and an environmental risk factor are required to increase the risk of disease (158). In the EURODEM reanalysis of case-control studies, the interaction among genetic and other putative risk factors was studied using family history of dementia in first-degree relatives as an indicator for genetic susceptibility (79, 159). Seven case-control studies had examined family history of dementia and other risk factors for Alzheimer's disease (68, 70–75). For family history of Down's syndrome and Parkinson's disease, late maternal age, history of head trauma, and history of depression, an association with Alzheimer's disease was observed regardless of the presence or absence of a first-degree relative with dementia (159). Family history of dementia remained strongly associated with Alzheimer's disease in the absence of these other risk factors (159). These findings suggest that genetic and environmental risk factors may independently increase the risk for Alzheimer's disease. As to the interaction between history of cigarette smoking and family history of dementia, an inverse association between Alzheimer's disease and smoking was only found in subjects with a positive family history of dementia. The risk of family history of dementia tended to be lower in smokers compared with nonsmokers. This effect was most pronounced in subjects with two or more affected relatives, suggesting that smoking may interact specifically with a genetically determined process (159).

PROGNOSIS

Survival

There is much evidence for reduced life expectancy of patients with Alzheimer's disease compared with the life expectancy in the general population (57, 60, 160–162). Studies based on hospital-based case series or on prevalent cases are difficult to interpret since there may have been large differences in study populations, in particular in severity of disease. Two studies were based on incident population-based cases even though in both investigations the case series were register-based (57, 60). Treves et al. (60) studied survival in 71 patients with early-onset Alzheimer's disease (onset before age 60 years). Patients were derived from the Israeli National Neurologic Disease Register. Survival was significantly reduced when compared with expected survival in the general population of Israel after adjustment for age and sex. The median survival in cases with early-onset Alzheimer's disease was 8.1 years (60). Kokmen et al. (57) studied survival in Alzheimer patients derived from the Rochester register. In this study of 296 Alzheimer patients with primarily late-onset disease, there was evidence for reduced survival after the diagnosis of disease compared

with expected survival. The median survival was 6 years in men and 5 years in women. In these studies, survival from the moment of diagnosis or hospitalization was studied. Although these data may be of interest for health care planning, survival from the age of onset would give more insight into the course of the disease. Such studies have not been conducted to date on a community basis.

Up until now, no specific treatment is available that can positively alter the clinical course of Alzheimer's disease. Advances in understanding the pathophysiology of Alzheimer's disease may eventually lead to interventions that slow the progression of disease, as will be discussed later. The most common causes of death in patients with Alzheimer's disease are respiratory disease (163) and bronchopneumonia (160). It has been argued that survival with dementia has increased due to improvement in treatment of infections (164). There is some evidence for an improvement in prognosis in the Lundby study, a population-based study of incidence of dementing disorders that covered the period from 1947 to 1972 (40, 162). Survival was worse in the period until 1962 when compared with survival thereafter; however, the difference was not significant.

Predictors of survival

There is a wide variation in the number of years of survival following a diagnosis of Alzheimer's disease. As expected, the prognosis is associated with the severity of the dementia at diagnosis (161, 162). Better survival has been reported for women with Alzheimer's disease compared with men when adjusted for the higher mortality among men in the general population (53–56). The sex difference in survival may explain the predominance of women among prevalent cases with Alzheimer's disease that has been observed in a number of studies. It has been suggested that patients with early-onset Alzheimer's disease have a worse prognosis than patients with a late-onset disease (165). Again, these results must be adjusted for differences in life expectancy. Although crude survival rates suggest a worse survival in late-onset Alzheimer's disease (53, 55, 60, 166), the results that are adjusted for age-related differences in life-expectancy show a worse survival in early-onset Alzheimer's disease (54, 55, 166, 167). To date there is no evidence for ethnic differences in survival (60). A number of clinical features (i.e., extrapyramidal signs, aphasia, psychosis, seizures, and tremors) have been associated with a poor prognosis (166, 168).

INTERVENTION

There is clearly a need for treatment of symptoms related to Alzheimer's disease; however, poor understanding of the pathogenetic mechanisms involved has impeded the development of effective treatment. Endeavors to develop therapies for Alzheimer's disease have largely focused on alleviation of symptoms by neurotransmitter substitution or by stimulation of neuronal metabolism. Recent advancements in molecular neuroscience have generated several hypotheses about mechanisms of neuronal death. Although at this stage these hypotheses remain highly speculative, they lead one to expect that specific interventions, that can modify the natural history of the disease by directly approaching the causative abnormality, may become available in the foreseeable future. Palliative therapeutic strategies will be briefly reviewed, and then the areas of current research that hold promise for potentially causal therapies will be delineated.

Symptomatic therapy

Acetylcholine. The most widely employed strategy for symptomatic treatment of Alzheimer's disease dementia is the replacement of neurotransmitters found to be deficient in clinical and neuropathologic examinations. In the last decade, the cholinergic hypothesis of cognitive functioning in Alzheimer's disease has attracted the most attention in the attempt to alleviate symptoms. This hypothesis is based on the consistent finding that cholinergic projec-

tions from the nucleus basalis of Meynert and other brain stem nuclei are lost and that this deficiency appears to be related to cognitive decline (169). Three conceptually different approaches are used to improve cholinergic function: metabolic precursor therapy to stimulate acetylcholine synthesis (170, 171), inhibition of the enzyme acetylcholinesterase that metabolizes acetylcholine (172–178), and receptor agonists to directly stimulate postsynaptic cholinergic receptors (179–181). None of these strategies has been shown to provide symptomatic benefit to Alzheimer patients.

Monoamines. Deficiencies in noradrenergic, serotonergic, and, possibly, dopaminergic central indices have been documented in Alzheimer's disease (182). Although noradrenalin and serotonin have a well established role in memory and learning in preclinical studies, their relation to cognitive functions in Alzheimer's disease is less clear. Therapy with the antihypertensive drug clonidine, an α-2 adrenergic receptor agonist, yielded no improvement in a trial with Alzheimer's disease patients (183). Serotonergic therapy, through blockade of synaptic uptake, has no effect on cognitive function or mood (184, 185). Adverse effects were even reported for a serotonergic receptor agonist (186). Replacement with levodopa has no effect on Alzheimer's disease symptoms (187), but short-term treatment with deprenyl (selegeline), a selective inhibitor of monoamine oxidase-B, showed some improvement in memory and attention (188, 189).

Neuropeptides. Changes in several central neuropeptides have been reported in Alzheimer's disease (190, 191). These neuropeptides have been implicated in learning and memory in preclinical models of dementia. Treatment with various neuropeptides, including synthetic vasopressin-related peptides (192), adrenocorticotropin-related compounds (193), and a synthetic somatostatin analogon (194) were not successful. Endorphins and enkephalins may have a deleterious effect on memory functions, but trials with opiate antagonists were without clinical benefit (195, 196).

Metabolic enhancers. In clinical dementia trials, a multitude of efforts have been directed toward the evaluation of metabolic enhancers, compounds with mostly unknown mechanisms of action that are believed to stimulate neuronal metabolism. Dihydroergotoxine (hydergine), for example, has been widely investigated but without consistent positive results. Indeed, a recent study concluded that hydergine is ineffective for the treatment of Alzheimer's disease (197). Nootropics are a group of psychotropic drugs of which piracetam was first discovered as a derivative of γ-aminobutyric acid. In animal models for dementia these drugs are effective in the reversal of amnesia induced by scopolamine or hypoxia. Although piracetam enhances cerebral metabolism in Alzheimer's disease patients (198), the therapeutic effect is minimal (199) or absent (200). The same disappointing results were found with other nootropics (201, 202).

New areas of intervention research

There are several new areas of intervention research that are based on recent pathophysiologic insights. We will briefly mention four of these research fields: amyloid deposition, excitotoxic mediated neurotoxicity, oxidative stress, and growth factors.

Amyloid metabolism. The inhibition of abnormal protein deposition in the brains of Alzheimer's disease patients as a potentially therapeutic strategy is currently under study. It remains unknown whether the formation of neurofibrillary tangles and senile plaques arises as a consequence of a primary degenerative process or as a by-product of some other underlying mechanism of the disease. In senile plaques the β-amyloid protein is found which is probably released through abnormal cleavage by protease activity from the amyloid precursor protein. One of the proteins found in the intracellular accumulated neurofibrillary tangles is tau (203). Abnormal phosphorylation of tau may contribute to the formation of neurofibrillary tangles, but the precise mechanisms remain elusive. Further biochemical understanding of the complex cascade of events leading to

senile plaques and neurofibrillary tangles may yield specific intervention strategies in the future.

Excitotoxin hypothesis. Excitotoxic amino acids, including glutamate and aspartate, are neurotransmitters of pyramidal neurons in the cerebral cortex and hippocampus and have a function in learning and memory (204). These neurons are specifically involved in the neuropathology of Alzheimer's disease and form neurofibrillary tangles (205). Excitotoxic amino acids can act as neurotoxins by overactivation of postsynaptic glutamergic receptors, and it is hypothesized that this process plays a role in the neurodegeneration in Alzheimer's disease (206). Some evidence that excitatory amino acid antagonists may offer neuroprotection is derived from the ability of these drugs to inhibit neuronal death resulting from ischemia or hypoglycemia (207). Several antagonists are available now but these agents have limited clinical use because of their potential toxicity.

Oxidative stress. Under normal conditions the cell produces free oxy radicals, superoxides, and peroxides. Several scavenger systems, including superoxide dismutase, act to protect against their potential toxicity. A defect in these scavenger systems or an intracerebral excess of oxy radicals may result in damage to the cell membrane. The hypothesis that oxidative stress plays a role in the neuronal degeneration of Alzheimer's disease is currently under evaluation by the long-term administration of deprenyl (208). Several other compounds that could afford neuroprotection according to this mechanism are being developed.

Growth factors. Neurotrophic factors have a function in neuronal regeneration and survival, and several studies suggested that nerve growth factor has a trophic function for cholinergic neurons in the basal forebrain (209–211). Administration of nerve growth factor in an early phase of Alzheimer's disease could possibly prevent neuronal cell loss (212). Other growth-stimulating compounds are currently being investigated but without definitive results (213).

CONCLUSIONS

Alzheimer's disease is the most important cause of dementia; it is emerging as a major problem for the patients and their families as well as in terms of public health. The main epidemiologic findings of Alzheimer's disease concerning its frequency, risk factors, prognosis, and treatment have been reviewed.

In most recent epidemiologic studies, the diagnosis of Alzheimer's disease has been based on sets of criteria like those of DSM-III, DSM-III-R, and NINCDS-ADRDA. It remains essentially a clinical diagnosis in the majority of population studies arrived at through a multistage approach.

Prevalence estimates of Alzheimer's disease rise exponentially with age. Typical estimates are about 0.5 percent in subjects aged 65 years, 3 percent in subjects aged 75 years, and 10 percent in subjects aged 85 years. On the basis of currently available data, there is little evidence to suggest that other than methodological factors contribute importantly to the variation in Alzheimer prevalence. This applies to incidence estimates as well. A recent generation of incidence studies has been initiated and the evidence from these studies, combined with earlier ones, suggest relatively similar incidence rates of Alzheimer's disease across populations.

Risk factors for Alzheimer's disease have been investigated in a number of generally small case-control studies. Recently, all formal case-control studies have been reanalyzed collaboratively, and except for age and a positive family history of dementia, no definite risk factors for Alzheimer's disease have yet been established. There is, however, interesting evidence to suggest that a positive family history of Parkinson's disease or Down's syndrome, a history of depression, severe head trauma, and smoking may be associated with Alzheimer's disease.

There is general agreement that the prognosis of Alzheimer patients in terms of life expectancy is compromised, although there is a wide variation in survival time among patients. Survival is worse in early-onset

cases and in men, and it appears to be related to the initial severity of the disease. Improvement of prognosis through intervention has been unsuccessful until now; this applies to both symptomatic and potentially causal treatment.

New epidemiologic approaches to Alzheimer's disease will focus on studies of the incidence of the condition in prospective follow-up studies that have recently been initiated in Europe and North America. These investigations will enable nested case-control studies of risk factors, and they are likely to emphasize gene-environment interaction in the etiology of Alzheimer's disease. As to prevention and treatment of the disease, new pathophysiologic leads in concert with epidemiologic evidence will in the near future hopefully result in improvement in the prognosis of Alzheimer patients.

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