ORIGINAL CONTRIBUTION

Dementia and Alzheimer Disease Incidence

A Prospective Cohort Study

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Context: Age-specific incidence rates for dementia and Alzheimer disease (AD) are important for research and clinical practice. Incidence estimates for the United States are few and vary with the population sampled and study design; we present data that will contribute to a consensus of these rates.

Objectives: To provide age-specific incidence estimates for dementia and AD and to estimate the association of sex, educational level, and apolipoprotein E genotype with onset.

Design: Prospective cohort study; begun in 1994 with follow-up interviews every 2 years.

Setting: Members of community-based, large health maintenance organization with demographics consistent with the surrounding base population; diagnostic evaluation by university-based study clinicians.

Subjects: Random sample of subjects aged 65 years or older from the base population; dementia free, nonnursing home residents. Of 5422 who were eligible, 2581 were enrolled, and 2356 had at least 1 follow-up evaluation (10 591 person-years of observation).

Main Outcome Measure: Dementia and Alzheimer disease diagnoses were based on standard criteria. Age-specific incidence rates were calculated using a person-years approach with Poisson distribution confidence intervals. Cox proportional hazards model analysis was used to examine other factors.

Results: Two hundred fifteen cases of dementia and 151 cases of AD were diagnosed. Incidence rates for dementia and AD increase across the 5-year age groups; AD rates rise from 2.8 per 1000 person-years (age group, 65-69 years) to 56.1 per 1000 person-years in the older than 90-year age group. The rates nearly triple from the 75-to-79-year and 80-to-84-year age groups, but the relative increase is much less thereafter. Sex was not associated with AD onset. Educational level (>15 years vs <12 years) was associated with a decreased risk of AD; however, the association was also dependent on the baseline cognitive screening test score.

Conclusions: Our dementia and AD incidence rates are consistent with recent US and European cohort studies, providing clinicians and researchers new information concerning the reproducibility of incidence estimates across settings. Increased risk was associated with age and the apolipoprotein E genotype; also with a low baseline cognitive screening test score. Educational level was inversely associated with the risk of dementia and positively associated with the baseline cognitive test score; thus, detection of AD by the screening test could also be influenced by educational level.

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THE BURDEN of dementia on the public health is increasing rapidly as our population ages. Dementia occurs more frequently in the older age groups. Prevalence, the proportion of living dementia cases in the population, is the primary frequency measure used to describe the public health burden, but it does not measure disease risk. Prevalence results, roughly, from the product of incidence and disease duration. Incidence, the rate of occurrence of new disease, is critical to assessing risk and to forming causal associations with potential risk factors. Thus, consistent and reliable incidence estimates (along with methods of detecting incident cases) are necessary, both for clinicians evaluating an individual's disease risk and for researchers examining potential risk factors.

Carefully designed cohort studies will provide the best setting in which to estimate the true incidence of dementia and Alzheimer disease (AD) and to identify those factors causally associated with disease onset. Early dementia incidence studies in the United States relied primarily on medical record review.[1,2] Such studies can be powerful but may be limited by changing diagnostic methods, record completeness, or failure to ascertain some types of cases. Long-

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standing cohorts primarily formed for the study of other diseases[3-6] have yielded valuable results and will continue to do so. While some of these studies are limited with regard to dementia and AD ascertainment, they often bring to bear unique methods such as extensive follow-up, serial imaging, or serial laboratory measures. A number of longitudinal incidence studies of dementia and cognitive impairment in US population groups have also been published.[7-12] Case ascertainment and clinical diagnostic criteria may differ somewhat between studies, regardless of whether they are focused on whites or ethnic minorities.[7-12] Non-US investigators have included varying degrees of standardization into study design and diagnosis for their dementia incidence studies.[13-21] To date perhaps the largest cohort study of dementia incidence, with relatively standardized methods, has resulted from a European consortium effort.[18] A 1998 meta-analysis,[22] which included extant US studies and European studies, showed roughly similar incidence patterns.

Although some consistency across studies has emerged regarding the age-specific incidence of dementia and AD, existing figures still lack general acceptance. Consensus may come as more rigorous, well-designed studies accumulate. We conducted a prospective cohort study specifically designed to observe dementia and AD incidence. We used a 2-stage case identification design with full clinical workup of potential cases followed by criteria-based consensus diagnosis. Our results, along with those of similar, recently reported studies should contribute to the formation of consistent estimates that will be of interest to both clinicians and researchers.

METHODS

STUDY DESIGN, SETTING, AND SUBJECTS

"Adult Changes in Thought" (ACT) is a prospective cohort study that focuses on dementia. The base population for ACT was the Seattle area members of Group Health Cooperative of Puget Sound (GHC) who were aged 65 years or older. More than 20 000 persons fit that general description as we began our study. The demographic composition of GHC mirrors that of the surrounding county: primarily white, middle class, and relatively well educated. Thus, observed incidence rates may reflect the dementia experience of a similar demographic population. The GHC enrollment is stable and the organization long lived (established circa 1949). The University of Washington and GHC institutional review boards reviewed and approved this study and all individuals provided written informed consent.

Cohort enrollment occurred between 1994 and 1996. Potential subjects were members of GHC, and aged 65 years or older in 1994. A simple random sample (N=6782) was drawn from the study base. Initial medical record review excluded potential subjects who had an existing diagnosis of dementia or those who were in a skilled nursing facility. We screened the remaining consenting subjects to further exclude existing cases of dementia. Subjects were first administered the Cognitive Abilities Screening Instrument (CASI),[23] supplemented by 2 informant-based measures: the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[24] and a modification of the Blessed Dementia Rating Scale[25,26] (only if subjects failed the CASI screening test). We used a cutoff value of 86 of 100 for the CASI corresponding to a reported sensitivity and specificity of 96.5% and 92%, respectively.[23] Persons scoring less than 80 at baseline were referred for complete diagnostic evaluation. Those scoring lower than 86 on the CASI at baseline but higher than 80 were considered to be in a gray area and were retested within 2 months. The IQCODE and Blessed Dementia Rating Scale scores were also evaluated for informant-reported history of cognitive decline. Those subjects whose scores remained low or in whom acquired cognitive impairment was corroborated by the IQCODE and Blessed Dementia Rating Scale were referred for complete diagnostic evaluation and ruled ineligible because of existing dementia after consensus review (those with no available IQCODE or Blessed Dementia Rating Scale scores were referred for a full examination). Subjects in the gray area at baseline who scored 86 or higher on retesting and whose IQCODE score was normal were included in the cohort. Subjects who did not meet clinical criteria for dementia[27] following examination or review, despite an initial low CASI score were enrolled in the cohort (a total of 203 subjects had an initial low CASI score but were admitted into the cohort). Subjects who scored 86 or higher on the CASI were enrolled directly into the cohort. Additional data concerning demographic, medical history, functional status, and potential epidemiological risk factors were collected at cohort enrollment and updated at follow-up visits. A blood sample was also obtained from consenting subjects to allow apolipoprotein E (*APOE*) genotyping and eventually the analysis of other genetic factors.

We rescreened cohort members every 2 years, following enrollment to identify potential new cases. A similar process (as described earlier) was followed; however, CASI scores lower than 86 at follow-up triggered a full dementia diagnostic evaluation by study physicians (J.D.B., W.C.M., and E.B.L.) and a neuropsychologist (L.T.) (as described in Larson et al[28]). The diagnostic evaluation included a physical and neurological examination with laboratory testing and imaging (if clinically indicated) coupled with a complete battery of neuropsychological tests. The results of each part of the evaluation were discussed at a consensus conference that included the examining physician, a neuropsychologist, other study physicians, and a research nurse. A consensus diagnosis was recorded based on standard criteria.[27,29] Again, those subjects who were evaluated and who did not meet criteria for dementia or AD[29] continued to be followed as subjects without dementia. Subjects who met dementia or AD criteria were considered incident cases. (Incident cases were tested annually to observe the natural history of disease, verify clinical diagnosis, and to obtain autopsy confirmation, whenever possible.) Cohort members who scored at least 86 on the CASI (ie, above the cutoff) were not sampled for diagnostic workup and remained in the cohort. Because of the sensitivity of the CASI and the rarity of dementia, there would likely be few false-negative results on the screening examination; therefore, to detect these cases and meaningfully adjust incidence rates, large numbers of subjects with CASI scores higher than 86 would have to be given a full evaluation, making the study impractical. Furthermore, the longitudinal design of the study alleviates some of the problem of false-negative results since those missed at one screening examination are likely to be discovered at a subsequent examination.

The demographic characteristics of the overall sample, those found ineligible, those found eligible, and those who refused to participate are similar (**Table 1**). Of 5422 eligible subjects, 2841 (52%) refused to participate in the longitudinal ACT study for a variety of medical, personal, and other reasons. Refusal prior to enrollment was somewhat more common among those subjects in the oldest age groups and among women, although the numbers enrolled in these groups were still sufficient to provide relatively stable incidence estimates. Of the eligible subjects, 2581 provided informed consent and were enrolled in the ACT cohort. Of the 2581 subjects enrolled in the ACT cohort, 2356 had a least 1 follow-up examination and, therefore, contributed to the estimation and evaluation of incidence. Their demographic characteristics are also given in Table 1.

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Table 1. Percentage Distributions of Sex, Age, and Race Among Those Initially Sampled, Eligible, and Enrolled in the ACT Cohort*

	Total Sample of Subjects (n = 6782)	Eligible (n = 5422)	Refused Enrollment (n = 2841)	Enrolled (n = 2581)	Subjects Who Had at Least 1 Follow-up Examination (n = 2356)
Sex					
Female	61	61	63	59	60
Male	39	39	37	41	40
Age, y					
65-69	19	20	18	23	23
70-74	27	29	27	30	31
75-79	24	25	25	24	24
80-84	17	17	18	15	15
85+	14	10	12	8	7
Race					
White	90	89	87	91	91
African American	4	5	6	4	4
Other	6	5	6	5	4
No. of subjects missing	2040	922	921	1	1

*Data are given as percentages unless otherwise indicated. ACT indicates Adult Changes in Thoughts.

The initial refusal rates appear high relative to other recent cohort studies. However, those who refused may include a number who would have been ruled ineligible if they had existing dementia that had not been noted in the available medical records. This might push the response rate in line with several cohort studies that have reported response rates of between 60% and 70% for eligible subjects.[8,30,31] Refusal to participate (nonresponse) could affect the generalizability of the observed incidence rates if nonparticipants within each age (or exposure) group carried substantially different risk of acquiring dementia over the course of the study than did participants.[32] Otherwise, nonresponse only affects the power of tests and precision of estimates. Regardless of nonresponse, the incidence rates and risk factor associations are reflective of the cohort itself and useful for comparison with cohorts with similar characteristics.[33] The cohort design begins with unaffected individuals and follows them up to observe the onset of disease. It minimizes the potential that self-selection, bias based on the probability of becoming demented, will influence risk factor associations and incidence rates.[33] However, excessive subjects lost to follow-up after the study begins could cause risk factor associations to be biased.[33,34]

STATISTICAL METHODS

Age-specific incidence of dementia and AD are calculated using the person-years approach[35] by dividing the number of cases by the number of person-years at risk given as 5-year age intervals starting at age 65 years (these are multiplied by 1000 to get rates per 1000 person-years). The number of person-years contributed by each subject who had no dementia is calculated by taking the time between their baseline examination and their last follow-up examination. For subjects with dementia the number of person-years is calculated by the time from baseline to the halfway point between diagnosis and the previous follow-up examination. This point is also used as the time of dementia or AD for calculating incidence and for further analysis of relative risks (RRs). The date of the last follow-up examination is also used as the end point for subjects who die or drop out since dementia status is unknown at the time of death or dropout. Confidence intervals (CIs) for incidence rates were calculated assuming a Poisson distribution for the number of cases within each age interval. An adjustment to the incidence rates and CIs to account for 32 subjects failing the CASI screening test but not given a full diagnostic examination was calculated by use of multiple imputation based on the probability of dementia given a failed screening examination.[36]

Risk factors such as sex, level of education (<12 years, 12-15 years, >15 years), *APOE* genotype (presence vs absence of an $\epsilon 4$ allele), and race (white, African American, or other) were examined using Cox proportional hazards regression models.[37] The models adjust for age by using age as the time scale for the regression model, rather than time-in-study, for example, left truncating at the age at baseline. The risk factor results are reported as RRs (ratios of incidence rates).

A sensitivity analysis[34] was conducted to assess the potential influence on incidence if subjects who died or dropped out were likely to have dementia at the time. Imputation of dementia status for those individuals was accomplished by established techniques.[38,39] Hypothetical scenarios are discussed to further describe the stability of the study's observed incidence rates. Dementia risk among subjects who dropped out of the study undiagnosed may have been different from those subjects who completed the study dementia free. One may suspect the factors leading to death or dropout may be linked to the same factors that effect incidence. To assess that possibility, last reported values for risk factors and CASI scores for dropouts and deaths were compared with those of subjects who remained in the study.

RESULTS

ANALYSIS OF INCIDENCE AND RISK FACTORS

Of 2356 subjects with at least 1 follow-up examination, 415 subjects screened positive for dementia and received full examination and consensus diagnosis. After evaluation and consensus diagnosis, 215 of the 415 subjects were diagnosed as having dementia[27] and 146 of those cases were diagnosed as having possible or probable AD.[29] There were an additional 5 subjects (for a total of 151 cases of AD) who were diagnosed as having possible AD by the NINCDS-ADRDA (National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria[29] on the basis of a single severe cognitive deficit, but who did not meet dementia criteria by the *Diagnostic and Statistical Manual of Mental Disorders [DSM]–IV*.[27] The remaining 69 cases con-

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Table 2. Age-Specific Incidence Rates per 1000 Person-years and Poisson-Based 95% Confidence Intervals for Dementia, Alzheimer Disease (AD), and Non-AD Dementia*

Age Group, y	No. of Person-years	All Dementia Cases		AD Cases		Non-AD Dementia Cases	
		No. of Cases	Rate, % (95% CI)	No. of Cases	Rate, % (95% CI)	No. of Cases	Rate, % (95% CI)
65-69	1076	5	4.65 (2.0-10.8)	3	2.78 (1.0-8.2)	2	1.86 (0.5-6.7)
70-74	3203	27	8.43 (5.8-12.3)	14	4.37 (2.6-7.4)	14	4.37 (2.6-7.4)
75-79	3082	37	12.01 (8.7-16.6)	24	7.79 (5.2-11.6)	14	4.54 (2.7-7.7)
80-84	2039	73	35.80 (28.5-45.0)	56	27.46 (21.2-35.7)	19	9.32 (6.0-14.6)
85-89	906	49	54.05 (40.9-71.5)	38	41.92 (30.5-57.6)	12	13.24 (7.6-23.2)
90+	285	24	84.19 (56.5-125.6)	16	56.13 (34.7-91.2)	8	28.06 (14.2-55.6)
Total	**10 591**	**215**	20.30 (17.8-23.2)	**151**	14.26 (12.2-16.7)	**69**	6.51 (5.1-8.3)

*The number of cases of AD and non-AD do not add to the number of cases of dementia because 5 cases were diagnosed as having possible AD but not as having dementia by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. CI indicates confidence interval.

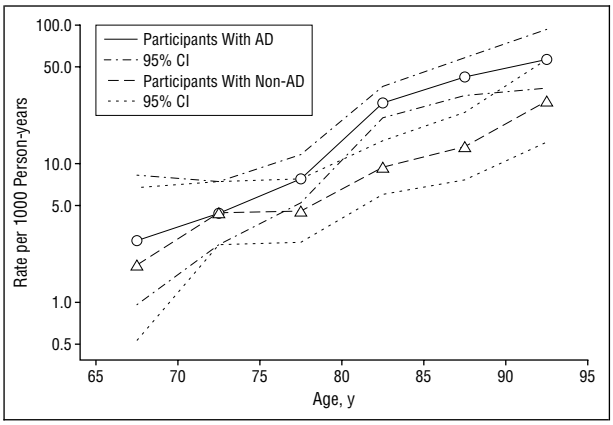

Figure 1. Age and the incidence of Alzheimer disease (AD) and non-AD dementia; rates per 1000 person-years and Poisson-based 95% confidence intervals for each.

stituted the cases of non-AD dementia of which most (39) were vascular dementia as indicated by *DSM-IV* criteria; however, more detailed study of subjects with non-AD dementias will be the subject of later articles. There were 195 subjects who failed the screening examination but whose conditions were diagnosed as nondemented and 32 others who failed the screening examination but who were not given a full diagnostic evaluation because they died, were lost to follow-up, or were still awaiting a full evaluation. In addition, over the course of the study, 430 subjects died and 180 were lost to follow-up.

Table 2 gives the age-specific rates for dementia, AD, and non-AD dementias. The greatest number of AD cases occurred between the ages of 80 and 89 years. The trend of increasing age-specific incidence rates is shown in **Figure 1**. The rates of dementia and AD increase 3.5-fold from the 75- to 79-year age group to the 80- to 84-year age group. The relative increase in other successive age groups is 1.5- to 1.8-fold, except that the older than 90-year age group shows only a 1.3-fold increase over the 85- to 89-year age group. The 95% CIs (shown) provide a gauge for the estimates' precision and an indication of the effect of smaller numbers of cases within some of the age groups.

To adjust for the 32 subjects who failed the screening examination but did not have a full evaluation, multiple imputation was carried out based on the proportion of subjects being diagnosed as having dementia after failing the screening examination. In the ACT cohort 53% of subjects failing the screening examination were diagnosed as having dementia; of those, 69% were diagnosed as having possible or probable AD. Multiple imputation has a negligible influence on the estimation of RRs or inference on risk factors. The estimates of incidence rates based on this multiple imputation are given in **Table 3**.

Table 4 lists the point estimates of age- and gender-specific rates. Point estimates for AD in men and women are similar across all but the oldest age group. Small numbers of cases and person-years occur in the upper age stratum. Examination of 95% CIs in the older than 90 years age stratum show marked overlap for AD indicating that the point estimates are not significantly different (men, 3.2-88.9 per 1000 person-years; women, 40.8-111.5 per 1000 person-years). For non-AD dementias, the age-specific rates for men are consistently elevated across age strata compared with the point estimates shown for women.

We examined the strength of association between dementia onset and sex, educational level, race, and *APOE* genotype using Cox regression models.[37] **Table 5** gives the RR estimates (rate ratios)for sex, *APOE* genotype, educational level, and race adjusted for age only and for age, sex, *APOE* genotype, and educational level. The numbers of cases and person-years represent unadjusted breakdowns for each risk factor. When adjusting for *APOE* genotype only, 2124 of the 2356 subjects who underwent *APOE* genotyping with at least 1 follow-up were included in the analysis.

When all these terms were included in the same regression model, with age used as the time axis, sex was not significantly associated with AD or dementia. However, the RRs indicate that the occurrence of non-AD dementia was significantly less frequent in women than in men (RR, 0.58; 95% CI, 0.34-0.97). Ethnicity showed no discernible effect, perhaps because the number of nonwhite cases was small.

There was a clear association between *APOE* genotype and dementia. This association occurred and was similar in magnitude for both AD and non-AD dementia. While the risk for dementia was increased in both subjects with a single *APOE* ϵ*4* allele and 2 *APOE* ϵ*4* alleles, the increase in risk was, as expected, much greater for the homozygous subjects. There is evidence of an in-

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Table 3. Age-Specific Incidence Rates per 1000 Person-years Adjusted by Multiple Imputation to Account for 32 Subjects Failing Cognitive Abilities Screening Instrument but Not Receiving a Full Diagnostic Examination*

Age Group, y	All Dementia Cases	AD Cases	Non-AD Dementia Cases
	Rate, % (95% CI)	Rate, % (95% CI)	Rate, % (95% CI)
65-69	5.39 (1.8-10.8)	3.53 (0.8-8.1)	1.86 (0.2-5.3)
70-74	9.69 (6.5-13.5)	5.88 (3.4-9.0)	4.63 (2.6-7.3)
75-79	13.52 (9.7-18.0)	9.36 (6.0-13.4)	5.14 (2.9-8.1)
80-84	38.00 (29.9-47.1)	29.63 (22.3-38.0)	10.04 (5.9-15.2)
85-89	58.58 (43.6-75.8)	46.38 (33.0-62.0)	15.53 (8.2-25.2)
90+	89.39 (57.8-127.9)	61.01 (35.4-93.5)	31.22 (13.8-55.6)

*CI indicates confidence interval; AD, Alzheimer disease.

Table 4. Age- and Sex-Specific Rates of Dementia, Alzheimer Disease (AD), and non-AD Dementia Cases per 1000 Person-years of Observation*

Age Group, y	Person-years	All Dementia Cases		AD Cases		Non-AD Dementia Cases	
		No. of Cases	Rate, %	No. of Cases	Rate, %	No. of Cases	Rate, %
Female							
65-69	585	2	3.42	1	1.71	1	1.71
70-74	1855	14	7.55	9	4.85	6	3.23
75-79	1844	18	9.76	13	7.05	6	3.25
80-84	1231	45	36.57	39	31.69	8	6.50
85-89	638	36	56.41	28	43.88	9	14.10
90+	222	19	85.42	15	67.44	4	17.98
Male							
65-69	491	3	6.11	2	4.07	1	2.04
70-74	1347	13	9.65	5	3.71	8	5.94
75-79	1237	19	15.35	11	8.89	8	6.46
80-84	809	28	35.63	17	21.03	11	13.60
85-89	268	13	48.45	10	37.27	3	11.18
90+	63	5	79.84	1	15.97	4	63.87

*The number of cases of AD and non-AD do not add to the number of cases of dementia because 5 cases were diagnosed as having possible AD but not as having dementia by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. CI indicates confidence interval.

teraction between age and *APOE* ϵ*4* in the incidence of dementia and AD. Persons with a single copy of *APOE* ϵ*4* experienced roughly a 3-fold increased risk in successive 5-year age groups (70-85 years old) but showed an RR less than 1 in the oldest age group (90+ years old). There were too few homozygous subjects with *APOE* ϵ*4* to effectively assess that interaction with age. Incidence rate continues to increase with age past 80 years for subjects with non–*APOE* ϵ*4* but apparently levels or declines for subjects with *APOE* ϵ*4* as shown in **Figure 2**.

Initial analysis given in Table 5 indicates that a higher educational level is associated with decreased risk of both AD and non-AD dementia, or, conversely, a lower educational level is associated with an increased risk. Subjects who have more than 15 years of education were at nearly half the risk of subjects with less than 12 years of education (RR, 0.48; 95% CI, 0.27-0.84) after adjusting for the effects of age, sex, and *APOE* genotype. Each additional year of education over 11 years the RR decreased approximately 9%. Further analysis revealed that the baseline CASI score was also strongly associated with dementia and with educational level. Of subjects included in this analysis, 203 had an initial CASI score lower than 86; 57 of these subjects later had dementia. The subjects with a low CASI score were also older at enrollment (78.5 vs 74.7 years) and less educated (11.3 vs 14.0 years). **Table 6** gives 3 different ways of examining the association between dementia and education based on the initial CASI score. First, when the CASI score is treated as a confounder and adjusted for, the association between education and dementia or AD reduces to the null. Second, examining the effect of a low CASI score as a risk factor for dementia and AD, a low CASI score is associated with a 3-fold increase in risk. Third, we excluded subjects with a low CASI score and calculated the association between AD and educational level. The RRs for each educational category were not significantly different from 1.0, although the point estimates suggest slight reduction in RR with a higher educational level.

SENSITIVITY ANALYSIS

Table 7 gives a comparison of subjects who died or were lost to follow-up with subjects who were active and had dementia. Subjects who died or were lost to follow-up after cohort enrollment were more similar in age at enrollment and educational level to persons who became demented than to subjects who had no nondementia and who

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Table 5. Relative Risks (RRs) and 95% Confidence Intervals (CIs)*

Variable	Person-years	All Dementia Cases		AD Cases		Non-AD Dementia Cases	
		No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
Adjusted for Age Only							
Sex							
Male	4215	81	1.0	46	1.0	35	1.0
Female	6375	134	0.91 (0.69-1.20)	105	1.24 (0.88-1.77)	34	0.55 (0.34-0.89)
Apolipoprotein level							
No ϵ4	7264	116	1.0	75	1.0	41	1.0
Single ϵ4	2221	61	1.85 (1.35-2.53)	45	2.12 (1.46-3.08)	17	1.46 (0.83-2.57)
ϵ4/ϵ4	126	8	5.06 (2.47-10.4)	6	5.93 (2.57-13.7)	3	5.33 (1.64-17.4)
Educational level, y							
<12	1419	45	1.0	38	1.0	11	1.0
12-15	5751	122	0.79 (0.56-1.12)	85	0.66 (0.45-0.97)	38	0.98 (0.50-1.92)
>15	3407	48	0.63 (0.42-0.95)	28	0.45 (0.27-0.74)	20	0.97 (0.46-2.04)
Linear 1-y effect			0.94 (0.90-0.98)		0.91 (0.86-0.96)		0.99 (0.91-1.07)
Race							
White	9689	200	1.0	140	1.0	64	1.0
African American	399	9	1.33 (0.68-2.59)	7	1.54 (0.72-3.29)	2	0.85 (0.21-3.47)
Other	498	6	0.91 (0.40-2.07)	4	0.92 (0.34-2.51)	3	1.25 (0.39-4.02)
Adjusted for Age, Sex, Apolipoprotein Level, and Educational Level							
Sex							
Male			1.0		1.0		1.0
Female			0.83 (0.62-1.13)		1.04 (0.71-1.53)		0.58 (0.34-0.97)
Apolipoprotein level							
No ϵ4			1.0		1.0		1.0
Single ϵ4			1.83 (1.34-2.51)		2.07 (1.42-3.01)		1.48 (0.84-2.60)
ϵ4/ϵ4			5.47 (2.65-11.3)		6.31 (2.72-14.6)		5.97 (1.82-19.6)
Educational level, y							
<12			1.0		1.0		1.0
12-15			0.85 (0.58-1.24)		0.73 (0.47-1.14)		0.98 (0.48-2.02)
>15			0.64 (0.40-1.00)		0.48 (0.27-0.84)		0.92 (0.42-2.02)
Linear 1-y effect			0.94 (0.90-0.99)		0.91 (0.86-0.97)		0.99 (0.91-1.07)
Race							
White			1.0		1.0		1.0
African American			1.30 (0.63-2.67)		1.40 (0.60-3.23)		0.98 (0.24-4.10)
Other			0.82 (0.30-2.23)		0.65 (0.16-2.65)		1.10 (0.27-4.59)

*The number of cases of Alzheimer disease (AD) and non-Alzheimer disease do not add to the number of cases of dementia because 5 cases were diagnosed as having possible AD but not as having dementia by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.

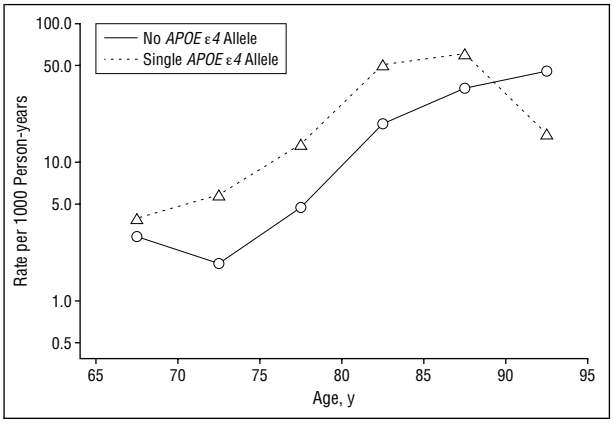

Figure 2. Age and the incidence of Alzheimer disease for persons with an apolipoprotein E ϵ4 allele compared with persons without an apolipoprotein E ϵ4 allele. Person-years were calculated by dividing the number of cases by the number of person-years of exposure within 5-year intervals starting at the age of 65 years (these are multipled by 1000 to get rates per 1000 person-years).

remained in the cohort. Subject's last CASI score, prior to the CASI at diagnosis (for cases), showed an average age-adjusted decline of 5.4 points relative to active subjects with no dementia for subjects with dementia, and declines of 2.7 and 2.1 points, respectively, for those who were lost to follow-up or died. Simple listwise deletion of these subjects, intuitively regarded as "conservative" in the past, can lead to biased incidence estimates when the data are not missing "completely at random."[38,39] **Table 8** gives the imputed age-specific dementia incidence rates that would result if deaths and dropouts were included in the analysis and if they had experienced rates 1.5 to 3 times higher than those subjects who did not drop out or die. The relative influence is greatest in the oldest age groups since they suffer most deaths.

COMMENT

The rates of dementia and AD reported in this study were comparable to the rates reported in other contemporary cohort studies (Figure 1). The rates fall approximately midway between those of the East Boston study[7] and the Framingham study.[3] Interstudy incidence rate differences could have resulted from variations in case detection and diagnosis. Nevertheless, there is still a great deal of consistency among most recent cohort studies.

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Table 6. Effect of Education as Influenced by Baseline Cognitive Abilities Screening Instrument (CASI) Score*

Variable	Person-years	All Dementia Cases		AD Cases	
		No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
Adjusting for Age, Sex, Apolipoprotein E Level, and CASI at Baseline					
Educational level, y					
<12	1419	45	1.0	38	1.0
12-15	5751	122	1.47 (0.96-2.25)	85	1.27 (0.77-2.11)
>15	3407	48	1.44 (0.86-2.44)	28	1.13 (0.59-2.16)
Linear 1-y effect			1.03 (0.98-1.09)		1.01 (0.94-1.08)
Low (<86) vs High Baseline CASI Score Adjusting for Age, Sex, and Apolipoprotein E Level					
CASI score					
High	9680	152	1.0	104	1.0
Low	743	57	3.68 (2.56-5.27)	42	3.58 (2.32-5.55)
Excluding Subjects With Low Baseline CASI Score (<86)					
Educational level, y					
<12			1.0		1.0
12-15			1.07 (0.61-1.86)		0.94 (0.49-1.80)
>15			0.88 (0.47-1.62)		0.66 (0.31-1.40)
Linear 1-y effect			0.97 (0.91-1.03)		0.94 (0.87-1.02)

*AD indicates Alzheimer disease; RR, relative risk; and CI, confidence interval.

Table 7. Characteristics of Subjects Deceased and Lost to Follow-up*

Variable	Subjects Lost to Follow-up (n = 180)	Subjects Deceased (n = 430)	Subjects With Dementia† (n = 220)	Subjects With Active Non-Dementia (n = 1719)	Subjects Who Failed CASI‡ but Had No Examination (n = 32)
No. of follow-ups					
0	72	153	0	0	0
1	65	117	84	11	18
2	43	137	72	857	9
3	0	23	64	851	5
Female, %	61	47	63	61	75
Years of education	12.7	13.5	12.8	13.9	11.9
Apolipoprotein ϵ4 level, %	27	21	38	24	29
Age at enrollment, y	75.6	78.5	79.4	74.0	78.1
White, %	89	92	93	91	84
CASI score at baseline	91.8	92.2	88.9	93.8	87.9
Difference in last CASI relative to active subject adjusting for age	−2.7	−2.1	−5.4		−4.9

*CASI indicates Cognitive Abilities Screening Instrument.

†Subjects with dementia includes the 215 cases diagnosed as having dementia plus the 5 cases of possible Alzheimer disease diagnosed as possible Alzheimer disease but not as having dementia by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.

‡Of the 32 subjects failing their CASI examination who did not have a full diagnostic examination, 12 are dead, 17 were lost to follow-up, and 3 are still active awaiting a full diagnostic examination.

Dementia and AD risk factors have not yet been fully explored by cohort studies. Many studies, including ours, have examined the strength of association between dementia onset and sex, education, and *APOE* genotype, and some have included other risk factors as well (eg, the EURODEM study[18]). We pooled available ethnic groups in this analysis; although our cohort was more than 90% white (this was consistent with the demographics of the area). Ethnicity was included also as a potential confounder of the risk factor associations. Unfortunately, we were unable to examine relationships within ethnic groups because of the sparse number of cases at this time.

The incidence rates for AD and overall dementia in the ACT cohort were similar to those reported by the EURODEM study[18] and the Baltimore Longitudinal Study of Aging,[5] except for appearing slightly higher in the 65-to-74-year age groups and slightly lower in the very oldest age group. While the point estimates at the extremes appear different (**Figure 3**), there is likely to be inherent instability in the calculated rates owing to small numbers of cases. Higher incidence rates were reported by the East Boston study[7] and the Monongahela Valley study (MoVIES Project)[10](when MoVIES included mildly impaired cases) across all ages. The ACT cohort age-specific incidence rates were consistently higher than those reported by either the Rochester, Minn, study[1,2] or, the Framingham study.[3] The Framingham study only included moderate and severe AD cases, and it was not originally designed as a dementia study, perhaps explaining

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Table 8. Imputed Age-Specific Dementia Incidence Rates Including Deaths and Dropouts*

	Age Groups, y					
k	65-69	70-74	75-79	80-84	85-89	90+
1.0	4.64	8.43	12.0	35.8	54.0	84.2
1.5	4.89	8.74	12.5	37.4	57.8	92.0
2.0	4.93	9.04	13.0	39.0	61.3	99.1
3.0	5.21	9.65	13.9	41.8	67.7	111.1

*Values are calculated assuming the rate for deaths and dropouts is k times higher than for the remaining cohort members.

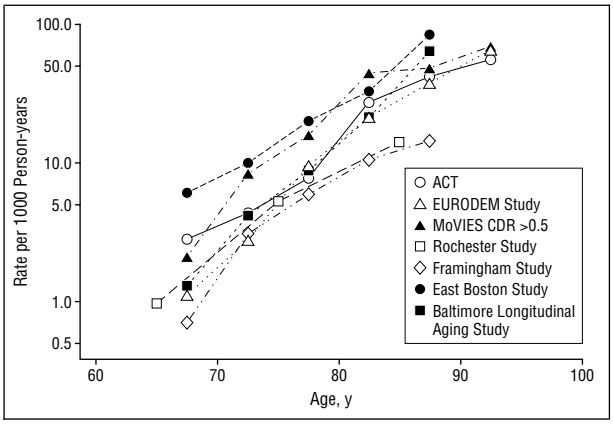

Figure 3. Age and the incidence of Alzheimer disease in 6 studies compared with the Adult Changes in Thought (ACT) cohort study. EURODEM indicates European Studies of Dementia[18]; MoVIES CDR >0.5, MoVIES Clinical Dementia Rating 0-5 or greater, Monongahela Valley Study[10]; Rochester, Rochester, Minn, study[2]; Framingham, Framingham, Mass, study[3]; East Boston, East Boston, Mass, study[41]; and Baltimore Longitudinal Aging Study, the Baltimore Longitudinal Study of Aging,[5] Baltimore, Md.

its lower observed rates. The Rochester study based its case finding and diagnosis on extensive medical record review. While this strategy was timely when first applied, it may have captured primarily the more severe or clinically recognized cases whose diagnosis of dementia was obtained through their general medical care provider.

There is striking similarity between the ACT rates and those reported by the EURODEM study.[18] Reasons for this similarity include the use of a common study design, similar case detection procedures, similar diagnostic evaluation and use of relatively standard diagnostic criteria, and similar methods of statistical analysis. The incidence rates were consistent despite the different populations being studied. Studies with uniformly higher rates may have been conducted with more "sensitive" methods, that is, including more very mild or questionable cases. Studies with consistently lower rates may have had higher "specificity," emphasizing the reduction in false-positive diagnoses. There is some evidence for that line of reasoning; for example, one study has shown that fewer cases are diagnosed as dementia using the *DSM-IV* criteria vs the *DSM-III-R* and both criteria diagnose fewer cases than the *DSM-III* criteria.[40] But, the differences could also be due in part to variability in the details of study design, case ascertainment, and analysis.

When the rates of AD and dementia are plotted on the log scale vs age, the rates of nearly all of these cohort studies seem to increase in a roughly linear fashion indicating exponential growth in incidence with age (Figure 2). The slopes of these lines are similar for each of the cohort studies. The ACT study showed a somewhat flatter slope than the comparison studies owing to its relatively high rates in the 65-to-74-year age groups; still, the incidence rate of AD doubled every 5.3 years. A steeper slope of the incidence curve was seen in the Baltimore Longitudinal Study of Aging[5] where the incidence rate of AD doubled every 3.6 years. Compared with AD incidence (except the Rochester study[2]), the incidence rate of non-AD dementias increased more slowly with age. In the ACT cohort the incidence rate of non-AD dementias doubled every 8.5 years (Figure 2).

Previous reports of the association between sex and AD or dementia have been equivocal. Generally, variation in sex-specific rates is seen at the upper end of the age distribution where few subjects and cases occur and where there are correspondingly wide CIs around the estimated rate. Treating sex as a risk factor in analysis, the EURODEM study[18] reported a 1.5-fold increased risk of AD among women. Similarly, Fillenbaum et al[11] reported a higher, though not statistically significant, rate of AD for white women vs white men. The MoVIES study,[10] the Rochester study,[2] the Framingham study,[3] the Baltimore Longitudinal Study of Aging,[5] the East Boston study,[41] and the ACT cohort provided no support for an increased RR of dementia or AD specific to sex. The ACT cohort women, however, had a decreased risk of non-AD dementias (RR, 0.58; 95% CI, 0.34-0.97).

A lower educational level has been a more consistently reported risk factor for AD and dementia, with the risk of AD and dementia decreasing with increasing education. The EURODEM study,[18] MoVIES study,[10] Baltimore Longitudinal Study of Aging,[5] Framingham study,[42] East Boston study,[43] and others[16,44] showed associations of educational level with AD and/or dementia incidence that were somewhat similar to those in the ACT cohort.

In the ACT study the association between educational levels and AD is potentially complex. For example, in our crude analysis a lower educational level was associated with increased risk of AD. However, CASI score at baseline is associated with both dementia diagnosis and educational level. The CASI and other cognitive screening tests are likely to have an education bias. This bias would make it more likely for a highly educated person to have a false-negative result on the screening test. Thus, part of the observed effect of education could be due to under detection of highly educated subjects on screening tests. Analysis of CASI scores, education, and de-

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mentia is difficult because of how they might be interrelated. Different analyses would be indicated if CASI scores were considered a consequence of education or if CASI scores were considered a proxy for dementia. The analyses we presented generally show that inclusion of this initial cognitive test score in the analysis tends to reduce the observed effect of education on dementia incidence. Racial and ethnic differences could also influence the observed association with education. Although we computed adjusted RRs for education (to account for confounding by race, age, sex, and *APOE* genotype), strata were too sparse to allow adequate determination of potential effect modification by race of the association between AD and educational level. Future studies should consider evaluating the effect of education not only within ethnic strata but also within strata of the initial cognitive screening examination. Perhaps a clearer specification of the potential for a causal association between education and AD will result.

The ACT cohort has observed an elevated risk of dementia and AD associated with *APOE* ϵ*4* allele of roughly similar magnitude to that observed in other cohort studies.[12,45-48] For example, the cohort shows elevated risk for both AD and non-AD dementia when an *APOE* ϵ*4* allele is present. The risk is much greater when there are 2 *APOE* ϵ*4* alleles present for both AD and non-AD dementia. The association between *APOE* ϵ*4* genotype and non-AD dementias is similar to some other studies[45,47]; however, others have had inconclusive associations.[12,48] The AD RR associated with the *APOE* ϵ*4* allele seems to decrease dramatically in the oldest age group while the AD incidence in subjects with non-*APOE* ϵ*4* continues to increase.

The ACT cohort dementia and AD incidence rates are most similar to those of the EURODEM consortium, but are also consistent with other US-based incidence studies. Some may argue that our observed rates are not "representative" because of initial nonparticipation or because our study base was not a statistical sample of some other larger population. We acknowledge that nonparticipation could have affected the observed incidence rates (as described earlier); however, the similarity between our rates and those of other studies indicates that the resulting potential bias may not have been dramatic. Representativeness of the chosen base population with regard to the US population, for example, is also not a requisite for validity unless the task was specifically to provide accurate incidence estimates for the US population as a whole. Cohort studies are often established within specific so-called unrepresentative groups,[33,34] such as the Nurses Health Study[6] or Framingham, Mass[3]; Baltimore Longitudinal Study of Aging,[5] Baltimore, Md; or the MoVIES Project,[10] Monongehela Valley.[10] Much has been learned from these studies that has been generalizable to the population-at-large, despite their purported lack of statistical representativeness. Dementia incidence in nonwhite ethnic groups is in need of much greater study; it is not well addressed by our ACT cohort because of small numbers of nonwhite subjects. Other studies are underway (elsewhere) to address the effects of ethnicity on incidence. Choice of a particular study base for a cohort may be done to increase the likelihood of subject retention and complete follow-up, thus, maximizing the study's internal validity.[49] Study results that lack internal validity (eg, resulting from loss to follow-up) are not generalizable regardless of sample representativeness. The effect of ACT loss to follow-up was small. Thus, results contributed by ACT and the several other cohort studies should be viewed as providing multiple, imperfect estimates. The extent to which these estimates converge is additional evidence for their representativeness, generalizability and validity. The addition of the ACT data to the existing pool will contribute to the converging consensus. While much remains to be done, especially in ethnic populations, age-specific incidence estimates are becoming more consistent as studies accumulate; consensus is being approached. Researchers and clinicians now have a stronger foundation from which to address age-associated risks of dementia and AD.

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