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International Journal of Epidemiology, 24(5)

0300-5771

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1995

10.1093/ije/24.5.1000

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Peer reviewed
Sources of Variability in Prevalence Rates of Alzheimer’s Disease

MARIA CORRADA,* RONALD BROOKMEYER† AND CLAUDIA KAWAS*


Objective. To investigate potential methodological reasons for the differences in published Alzheimer’s disease (AD) prevalence rates.

Background. Studies reporting prevalence rates of AD have been published worldwide. These rates differ considerably, but may greatly reflect methodological differences.

Methods. All studies published between 1984 and 1993 that reported age-specific AD rates and sample sizes were included. Logistic regression identified variables that contribute to the variation in rates. Estimates of extrabinary variation were also calculated.

Results. Studies characterized by the following features yielded significantly higher rates: inclusion of mild cases, use of laboratory studies, ascertainment of a sample rather than the total population, inclusion of both urban and rural populations, non-use of computerized tomography (CT) scans, non-use of the Hachinski Ischemic Score, and no adjustment for false negatives. The odds of having AD increased 18% for every year of age. The variation in the age-specific prevalence rates of AD was approximately 15 times that expected by sampling variation. However, approximately 76% of this excess variation in rates could be accounted for by methodological differences.

Conclusions. After accounting for age, much of the variability in prevalence rates of AD in the published literature may be explained by differences in methodology. Some unexplained variation in prevalence rates, however, still remains.

Keywords: Alzheimer’s disease, prevalence, epidemiology

Variation in the prevalence of Alzheimer’s disease (AD) across populations may provide insight into the etiology, demographics, and prevention of the disease. Epidemiological studies that report prevalence of AD have been published worldwide, with age-specific prevalence rates varying considerably, ranging from about 7% to 54% over the age of 85. It is likely, however, that some of the variability in previously reported studies is due to differences in methodology, such as case ascertainment, rather than real differences in prevalence rates. For example, in two similar communities only 30 miles apart (Framingham† and East Boston†), up to a sixfold difference in age-specific prevalence has been reported. This disparity would be of great interest except that it probably largely reflects methodological differences.

Attempts to integrate results from the literature on prevalence of dementia and AD are limited by dissimilar methods, which do not allow meaningful comparisons.4-7 There are, for example, differences in case ascertainment procedures, diagnostic criteria, availability of imaging and laboratory studies, and exclusion or inclusion of institutionalized and other special populations. Jorm et al.2 analysed how these and other methodological factors influence the variation between prevalence rates of dementia from several different studies. Our study is different from this previous work in that it focuses specifically on AD instead of all dementias.

In our study, we quantified the extent to which the variation in published prevalence rates of AD can be attributed to methodological differences. We limited our investigations to published studies with age-specific prevalence rates of AD.

METHODS

Selection of Studies
MEDLINE searches and review articles were used to locate studies of AD prevalence published from 1984
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(when NINCDS/ADRDA*-criteria were published) to 1993. A total of 48 studies were located through the search. Studies were selected for analysis if they met the following criteria: (1) AD prevalence rates were reported; (2) NINCDS/ADRDA (or equivalent) criteria were used for the diagnosis of AD; (3) sample size was reported; (4) the article was an original research report (review articles were excluded).

Several well-known studies were excluded for the following reasons: studies in Rochester, Minnesota, used medical records rather than personal examinations to diagnose AD; the Shanghai study and the Copiah County, Mississippi study reported rates for all dementias combined.

Fifteen studies met the inclusion criteria (Table 1). These studies yielded a combined total of 22,091 subjects: 6,553 men, 10,861 women, and 4,677 subjects whose gender was not reported (two studies reported combined rates for men and women). Age-specific rates from these studies vary widely as shown in Figure 1.

Variables Studied

Eight study features involving design, characteristics of the sample, and case ascertainment were selected for analysis. Studies were coded on these features as follows: (1) inclusion of mild cases of dementia (included versus excluded); (2) inclusion of institutionalized subjects (included versus excluded); (3) use of CT scans in diagnosing AD (used versus not used or not specified); (4) use of laboratory blood tests in diagnosing AD (used versus not used or not specified); (5) use of the Hachinski Ischemic Score (HIS) to diagnose vascular dementias (used versus not used or not specified); (6) type of sample (random sample versus total population ascertainment); (7) rate adjustment for false negatives (FN) in studies that used a two-stage procedure with a screening phase to identify subjects for full investigation (adjustment or no initial screening versus no adjustment); (8) type of community (urban, rural, or mixed urban/rural). Table 2 shows the classification of the studies on the selected variables. In some cases the information obtained in the original articles was supplemented with previous publications or review articles to identify all necessary information.

Data Analysis

The age-specific prevalence rates of AD are defined as the proportion of individuals in an age category who have AD. The number of AD cases within an age category of a study was assumed to follow a binomial distribution with parameters n and p, where n is the number of individuals in the particular age category, and p is the age-specific prevalence rate. Logistic regression models were used to estimate the parameter p in relation to age and the eight study variables. The first model included only age as an independent predictor of the prevalence of AD, and had the form:

\[
\log \left( \frac{p_{ij}}{1-p_{ij}} \right) = \beta_0 + \beta_1 \text{Age}_{ij},
\]

where \(p_{ij}\) is the proportion of AD cases for the \(j^{th}\) age category of the \(i^{th}\) study. The second logistic regression model, in addition to age, included the eight study

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* National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Country (Area)</th>
<th>Total No. of Subjects</th>
<th>Males</th>
<th>Females</th>
</tr>
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<td>USA1 (Framingham)</td>
<td>2180</td>
<td>853</td>
<td>1327</td>
</tr>
<tr>
<td>B</td>
<td>UK2 (E Cambridgeshire)</td>
<td>365</td>
<td>-</td>
<td>365</td>
</tr>
<tr>
<td>C</td>
<td>San Marino26 (entire republic)</td>
<td>488</td>
<td>237</td>
<td>251</td>
</tr>
<tr>
<td>D</td>
<td>USA27 (Baltimore)</td>
<td>923</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>E</td>
<td>Sweden28 (Stockholm)</td>
<td>1810</td>
<td>432</td>
<td>1378</td>
</tr>
<tr>
<td>F</td>
<td>Japan29 (Miki Town)</td>
<td>3754</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G</td>
<td>China30 (Beijing)</td>
<td>1090</td>
<td>505</td>
<td>585</td>
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<td>H</td>
<td>Spain31 (Zaragoza)</td>
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</tr>
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<td>I</td>
<td>UK32 (Cambridge)</td>
<td>2286</td>
<td>809</td>
<td>1477</td>
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<td>J</td>
<td>USA2 (S California)</td>
<td>817</td>
<td>422</td>
<td>395</td>
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<tr>
<td>K</td>
<td>Italy33 (Appignano)</td>
<td>778</td>
<td>343</td>
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<td>L</td>
<td>Sweden34 (Lundby)</td>
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<td>299</td>
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<tr>
<td>M</td>
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<tr>
<td>N</td>
<td>Finland36 (multiple areas)</td>
<td>2515</td>
<td>982</td>
<td>1533</td>
</tr>
<tr>
<td>O</td>
<td>USA37 East Boston</td>
<td>3623</td>
<td>1382</td>
<td>2241</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22,091</td>
<td>6,553</td>
<td>10,861</td>
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</table>
variables as covariates. The models were fitted using PROC LOGISTIC in the SAS® software package.

Since most studies report prevalence for age ranges rather than for specific ages, the midpoint of the age category was used in the analysis. For the oldest age category, the maximum age reported for the sample or population was used as the upper limit, and the midpoint was calculated accordingly. When a maximum age was not reported, age 95 was used as the upper limit to calculate the midpoint.

To investigate the amount of variation in prevalence that could be explained by the methodological variables in the 15 studies, we calculated the amount of extrabinomial variation for each of the two models described above. Extrabinomial variation is the amount of variation above what would be expected from binomial variation and is characterized by the overdispersion parameter $\phi$ defined below. The square of the Pearson residual is defined as:

$$ r_{ij}^2 = n_{ij} \left( p_{ij} - \hat{p}_{ij} \right)^2 / \hat{p}_{ij} (1 - \hat{p}_{ij}), $$

where $p_{ij}$ and $\hat{p}_{ij}$ are the observed and model fitted prevalence rates, respectively, and $n_{ij}$ is the sample size.

The overdispersion parameter is:

$$ \sum \frac{r_{ij}^2}{m-k}, $$

where $m$ is the total number of prevalence rates and $k$ is the number of fitted parameters in the regression model. The per cent reduction of the extrabinomial variation between the model with only age and the multiple logistic regression model with age and the study variables, represents the amount of extrabinomial variation that the additional covariates can explain.

### RESULTS

In the regression model that included only age, as expected, age had a significant effect in predicting prevalence of AD (odds ratio [OR] = 1.17, 95% confidence interval [CI]: 1.16-1.18, $P < 0.001$). However, variation in age-specific AD prevalence rates from this model was 14.9 times more than would be expected based on binomial variation. The second regression model included all the methodological variables and age. By using all methodological variables to predict prevalence of AD, a significant improvement in the fit...
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Table 3 Results of multiple logistic regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coding</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>per year</td>
<td>1.18</td>
<td>1.17-1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild cases</td>
<td>excluded</td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>included</td>
<td>2.06</td>
<td>1.61-2.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>excluded</td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>included</td>
<td>0.98</td>
<td>0.78-1.23</td>
<td>0.86</td>
</tr>
<tr>
<td>CT scans</td>
<td>not used</td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>used</td>
<td>0.26</td>
<td>0.20-0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory studies</td>
<td>not used</td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>used</td>
<td>7.79</td>
<td>5.47-11.08</td>
<td>&lt;0.001</td>
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<tr>
<td>Hachinski</td>
<td>not used</td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ischemic Score</td>
<td>used</td>
<td>0.50</td>
<td>0.39-0.64</td>
<td>&lt;0.001</td>
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<tr>
<td>Type of sample</td>
<td>whole</td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sample</td>
<td>2.02</td>
<td>1.67-2.44</td>
<td>&lt;0.001</td>
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<tr>
<td>Adjustment for</td>
<td>not done</td>
<td>1.00</td>
<td>-</td>
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<tr>
<td>false negatives</td>
<td>done</td>
<td>0.55</td>
<td>0.44-0.70</td>
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<td>Type of community</td>
<td>urban</td>
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<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rural</td>
<td>0.99</td>
<td>0.68-1.44</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>mixed urban/rural</td>
<td>1.71</td>
<td>1.28-2.28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The model with all the covariates and age, but was not significant (OR = 1.04, 95% CI: 0.90-1.20, P > 0.2). Therefore, we found no significant difference in the prevalence rates of males and females after adjusting for all the other covariates.

A striking feature in Figure 1 is the very high prevalence rates associated with two of the studies, namely the Southern California2 and East Boston3 studies. The main source of variation in the rates that remained after accounting for the methodological variables were from these two studies. A separate analysis was performed deleting these two studies. We found that when these studies were deleted, the amount of extrabinomial variation is much less than when the studies are included. The variation in prevalence rates is reduced from 3.1 times binomial variation in the model with only age, to 1.3 times binomial variation in the model with all the variables and age.

DISCUSSION

This study suggests that much of the variation in AD prevalence rates reported in the worldwide literature is due to methodological differences. After adjusting for age and all other covariates, higher rates tended to occur in studies that included mild cases, used laboratory tests to aid in the diagnosis, ascertained a sample rather than the entire population, or included mixed urban/rural communities. Studies that used CT scans, used the Hachinski Ischemic Score, or adjusted for false negatives during screening were associated with lower rates of AD.

There are several plausible explanations for these findings. Studies that include mild cases would be expected to have higher prevalence rates than studies that only report moderate and severe cases of AD. The choice of diagnostic criteria has a similar effect. The two studies with the highest rates2,3 did not require clear evidence of functional decline and therefore may have included milder cases. In contrast, a study with relatively low rates1 used the criteria specified by Cummings and Benson,19 which tend to exclude mild cases since deficits in three cognitive domains are required.

Use of the Hachinski Ischemic Score (HIS) was associated with lower prevalence rates. The HIS, a codification of features associated with cerebrovascular disease, was used in some studies to diagnose multi-infarct dementia (MID) or mixed AD and vascular dementia (MIX). Pathological correlations in subjects with MID/MIX as assigned by the HIS, suggest that about half of these subjects have Alzheimer's pathology in addition to vascular disease.20 Exclusion of these subjects with...
mixed disease may have contributed to the lower AD prevalence estimates observed in studies that used the HIS. Similarly, the use of CT scans probably identified cerebrovascular disease in some patients with AD, thereby changing their diagnostic classification.

It is not immediately apparent why the use of laboratory tests or sampling would result in higher prevalence estimates. It is possible that studies with sufficient resources to include laboratory studies were able to conduct more thorough investigations and therefore ascertain more cases. Similarly, selection of a sample for study may have allowed concentration of resources and more thorough ascertainment of a smaller group. It is of interest that Jorm obtained a similar result in his study in which investigations with total population assessments had lower rates than studies with random samples.7

We do not have an explanation for the finding that studies conducted in mixed urban/rural areas had higher rates when compared to urban studies. However, no significant difference was found between solely urban and solely rural studies. It is worth noting that Jorm reported a similar result when using an age-specific model for all dementias.7 Similarly, it is not clear to us why adjusting for false negatives during screening, contrary to what one would expect, resulted in lower rates when compared to studies that did not adjust. This variable was often difficult to define and encompasses a variety of methods used for adjustment. Further studies would be useful to understand this finding better.

Inclusion of institutionalized subjects, contrary to what would be expected, did not significantly affect the prevalence rates in our model. One reason for this result may be that other significant factors in the model, such as age and severity of dementia, could be accounting for this effect.

An exponential model has been used by many researchers for modelling age-specific prevalence of dementia and AD. Although the model seems to hold well for certain age ranges (65–85 years) it assumes that prevalence rates increase at a constant rate across ages and thus may not apply to the entire age spectrum. 21 The logistic regression model used in this paper and discussed by Dewey,22 permits a slower increase in prevalence rates in the very young and at very old ages, an observation that has been clearly documented in younger subjects. Although data in the very old are limited, some studies have also reported a slower increase in prevalence rates in subjects >90 years.23

Ideally, the present analysis should have been performed with incident cases since there are many factors such as life expectancy, competing morbidities and mortalities, and other socio-cultural features that affect the duration of the disease and thus influence prevalence rates. At present, however, the small number of incidence studies limits the utility of such an analysis.

In our study, methodological features from the published literature were codified from information provided in the studies. There was, however, some variation in the rates that remained unexplained in our analysis, after accounting for these methodological factors. This variation could be due to additional methodological variables that we were unable to identify and code, or that were not reported. More importantly, it could also be due to factors other than methodology that may be relevant for disease pathogenesis or expression in various populations or subgroups. It is precisely these factors that require study with uniform methodology in order to obtain a better understanding of AD.

It is likely that real differences in prevalence rates of AD do exist. Studies that use similar methodologies, however, are necessary to distinguish substantive differences from those due to dissimilar methods. In the absence of a biological marker for AD, it is not possible to assess the accuracy of different field methods. Generally, studies with more resources (particularly laboratory and radiological) are likely to assign more accurate diagnoses but may not be financially feasible for large-scale field investigations. It is, however, possible for investigators worldwide to minimize a substantial source of variability by agreeing on definitions of dementia particularly in mild cases without obvious functional impairment. By standardizing these definitions across studies, comparisons are more likely to yield important demographic and biological differences in cross-cultural settings. Fortunately some studies (EURODEM14 and WHO24) are currently underway to address these issues by using common methodology and diagnostic criteria in geographically widespread populations.

ACKNOWLEDGEMENTS
This project was supported in part by grants AG08325 and AG05146 from the National Institutes of Health. We wish to thank Dr Pamela Talalay for her editorial guidance.

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(Revised version received March 1995)