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Sources of variability in estimates of the prevalence of Alzheimer's disease in the United States

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Abstract

Background—The prevalence of Alzheimer's disease in the United States is estimated at 2.3 million in 2002 by the Aging, Demographics, and Memory Study (ADAMS) which is nearly 50% less than the estimate of 4.5 million in 2000 derived from the Chicago Health and Aging Project (CHAP).

Methods—We considered how differences in diagnostic criteria may have contributed to these differences.

Results—We identified several important differences in diagnostic criteria that may have contributed to the differing estimates of AD prevalence. Two factors are especially noteworthy. First, the DSM III-R and IV criteria of functional limitation documented by an informant used in ADAMS effectively concentrates the diagnosis of dementia towards a relatively higher level of cognitive impairment. ADAMS separately identified a category of cognitive impairment not dementia (CIND) and within that group were a substantial number of cases with "prodromal" AD (up to 1.95 million with upweighting). Second, a substantial proportion of dementia in ADAMS

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was attributed to vascular disease (representing up to 0.59 million with upweighting) or undetermined etiology (up to 0.34 million) whereas most dementia, including mixed dementia, was attributed to AD in CHAP.

Conclusion—The diagnosis of AD in population studies is a complex process. When a diagnosis of AD excludes persons meeting criteria for vascular dementia when not all persons with dementia are assigned an etiology, and when a diagnosis of dementia requires an informant report of functional limitations, the prevalence is substantially lower and the diagnosed cases likely have a relatively higher level of impairment.

Keywords

epidemiologic studies; dementia; Alzheimer's disease; vascular dementia; mild cognitive impairment; cognitive impairment no dementia

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia in old age. Because of its devastating impact on cognition and other behaviors and its chronic course, the disease poses enormous public health problems. These problems are projected to increase in the coming decades with the aging of the US population [1–3], underscoring the urgency of developing strategies to prevent the disease or delay the onset of its behavioral symptoms and associated costs.

Knowledge of disease prevalence is critical for public health planning and policy. Most estimates of the prevalence of AD in the US population are based on a single community or group of communities [1,3–5]. By contrast, Plassman et al [6] in the Aging, Demographics, and Memory Study (ADAMS) used data from the ongoing Health and Retirement Study [7] to identify a nationally representative sample of older persons for detailed clinical evaluation. They estimated that in 2002 there were 2.3 million people in the United States with AD. This estimate is comparable to recent estimates from systematic reviews of the dementia prevalence literature [8,9]. However, the ADAMS estimate is only about half of the 4.5 million affected persons estimated by Hebert et al. [3] for the year 2000 using data from the Chicago Health and Aging Project (CHAP). In this article, we consider factors that may have contributed to the differences between these two estimates of the prevalence of AD in the United States, and use ADAMS data to provide some evidence on the cognitive, functional, and genetic characteristics of groups whose diagnostic status would likely differ between the two study protocols.

2. Overview of study differences

The source studies from which the Hebert et al [3] and Plassman et al [6] AD prevalence estimates were derived each involved taking a stratified random sample of older persons from a defined population, inviting them to undergo a uniform evaluation to support clinical classification of dementia and AD, and then using census data to upweight the results to the US population. Because each study involved estimating disease prevalence in millions based on examination of fewer than 1,000 individuals, some difference between the studies would be expected due to random error even if identical methods were used. However, the size of the observed difference suggests that other factors were involved. There were several methodological differences between the source studies with the potential to affect AD prevalence estimates. We begin by noting several differences in methods that might in theory contribute to differences in estimates but that are likely to be of minor importance. We then focus on two issues that we think account for most of the difference.

2.1. National representation

The ADAMS sample was drawn from a nationally representative cohort whereas the CHAP samples were drawn from a single urban community that is not representative of the United States. To the extent that there is regional variation in AD prevalence, ADAMS should provide a more accurate estimate.

2.2. Participation rate

In ADAMS, 56% of the nondeceased target sample completed the clinical evaluation compared to 75% in the most comparable clinical evaluation in CHAP. Because nonparticipation is associated with poorer cognitive performance in some studies, one might be concerned that lower participation in ADAMS could have led to an underestimation of dementia prevalence, as reported by Plassman et al [6]. However, the ADAMS investigators conducted a thorough investigation and found no association between cognitive ability as measured in the HRS either before or after the ADAMS assessment and participation in ADAMS. They also used propensity analyses to adjust for potential bias using data available from the parent HRS. Thus, in this case, the overall impact of differential participation on results is likely to be small.

2.3. Age

The ADAMS estimate of AD prevalence was for individuals age 71 years or older whereas CHAP included 65-to-70-year-olds as well as older individuals. However, only an estimated 26,000 of the 4.5 million individuals in the CHAP estimate were in the age range 65 to 70 years. Thus, the slight difference at the lower end of the age ranges studied is unlikely to have substantially contributed to the differential estimates of disease prevalence.

2.4. Estimating prevalence from incidence data

Another difference underlying the two estimates of AD prevalence is that the estimate of Hebert et al [3] is based on AD incidence in the source study (CHAP) whereas the estimate of Plassman et al [6] is based on AD prevalence in the source study (ADAMS). Prevalence projections based on incidence studies can overstate prevalence if there is overdiagnosis in the assessment because false positives in the follow-up wave will inflate the incidence rates, while overdiagnosis for the calculation of mortality ratios will increase estimated survival of people with AD in the projections. Prevalence studies can understate prevalence if they underdiagnose disease or if they underestimate persons with rapidly progressive disease and death [10]. There is no evidence that these concerns are of substantial quantitative importance in this comparison.

3. Possible modifiers of prevalence estimates

In this section, we consider further differences between the source studies used to estimate AD prevalence. In addition, we provide a quantitative estimate of the impact of each factor on AD prevalence.

3. 1. Diagnostic criteria for dementia

Clinical classification of AD requires that dementia be present or absent, and the criteria used to make that determination can strongly affect estimates of the prevalence of dementia [11]. Diagnostic criteria for dementia in ADAMS and CHAP differed. In ADAMS, the diagnosis of dementia was based on clinical judgment anchored by the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) III-R and IV [12,13] whereas the diagnosis in CHAP was based on clinical judgment anchored by the criteria of the National Institutes of Neurological and Communicative Disorders and Stroke and the

Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA [14]). Both criteria require a history of cognitive decline and impairment in multiple cognitive domains. An important difference is that the DSM criteria require that the cognitive decline be of sufficient severity to impair daily function. The latter is typically documented by an interview with an informant. By contrast, in the NINCDS-ADRDA criteria for dementia, evidence of cognitive decline is obtained by medical history from the participant and an informant, if available, with decline documented by cognitive performance testing. The DSM requirement of both functional impairment and evidence of cognitive impairment on neuropsychological tests will likely identify persons with a greater degree of cognitive impairment compared to just using performance on neuropsychological tests alone. Therefore, all other things being equal, more people would be expected to meet NINCDS-ADRDA criteria for dementia than DSM criteria.

3.2. Separating dementia from normality

The primary clinical manifestation of dementia is accelerated cognitive decline over the course of many months to years. However rates of cognitive decline in old age more closely approximate a normal distribution than a bimodal one [15], so, it is often not immediately clear where to place the line between normal aging and dementia. One response to this problem has been to create a new syndrome, most commonly referred to as mild cognitive impairment (MCI) [16] or cognitive impairment not dementia (CIND) [17], for individuals with cognitive impairment not severe enough to warrant a diagnosis of dementia. Although these intermediate syndromes have proven useful, there is no secure agreement on how best to implement diagnostic criteria or distinguish them from dementia. Moreover, to the extent that impairment in daily function is measured with error, that error compounds the measurement error in cognitive assessments.

In ADAMS 241 cases of CIND were identified, which translates to a national estimate of 5.4 million persons with upweighting. Of this group, the ADAMS assigned a diagnosis of prodromal AD (defined as "a pattern of clinical symptoms or performance on neuropsychological testing suggestive of prodromal AD and no other medical or neuropsychiatric conditions present to preclude an eventual diagnosis of AD" [17]) to 98 individuals (1.9 million persons with upweighting). Thus, shifting the threshold for dementia towards that of CIND could account for very large differences in AD prevalence.

3.3. Differential diagnosis of dementia

A diagnosis of AD requires additional criteria besides the diagnosis of dementia. Both ADAMS and CHAP used NINCDS-ADRDA criteria for AD. These criteria require progressive loss of cognitive abilities one of which must be memory. The studies differed in how they approached differential diagnosis in the presence of co-morbidities and atypical disease presentation.

3.3.1. Comorbidity—AD is widely recognized as the leading cause of dementia, but other pathologic factors contribute to cognitive impairment as well, particularly cerebrovascular disease and Lewy bodies which can cause vascular dementia and Lewy body disease but can also contribute to mixed dementia [18]. Clinical classification of the cause of dementia is difficult, however. In fact, community-based clinical-pathologic studies indicate that most dementia arises from mixed pathologic processes, most commonly AD pathologic changes (i.e., neuritic plaques, neurofibrillary tangles) in conjunction with cerebrovascular disease and often Lewy bodies; and, further, most cases of dementia meeting NINCDS/ADRDA criteria for clinical AD arise from mixed pathologic processes [19,20]. Finally, both cortical and subcortical cerebral vascular disease, in addition to AD pathology, contribute to impaired episodic memory and other domains of cognition suggesting that cognitive profiles

have limited utility in separating these common conditions [21,22]. Although cerebrovascular disease is common in the brains of old people with dementia, it is rarely the only pathologic finding. That is, dementia is rarely due to cerebrovascular disease in isolation. Of 308 individuals with dementia in ADAMS, 48 (16%) were diagnosed with vascular dementia based on a combination of reported temporally related stroke and cognitive decline, medical record documentation of stroke, and a cognitive profile consistent with cerebrovascular disease. When results were upweighted to the population, these 48 people represented approximately 0.59 million affected persons in the United States. By contrast, in CHAP, vascular disease was often recognized as contributing to cognitive impairment in people diagnosed with AD. Thus, persons meeting criteria for both AD and vascular dementia were included as cases of AD and pure vascular dementia was rarely diagnosed [23].

3.3.2. Indeterminate dementia—In some cases, clinical classification of dementia subtype is particularly difficult, usually because of insufficient or conflicting data or atypical presentation. The DSM-IV allows for this possibility with the category of "dementia not otherwise specified" [13]. In ADAMS, 23 of 308 dementia cases (7%) received a diagnosis of "dementia, undetermined etiology" when the clinical presentation was too atypical to permit a diagnosis of possible AD, but there was no other apparent cause for dementia. When upweighted to the population, these 23 individuals represented 0.34 million persons. In CHAP, the study design required that at least one contributing factor be assigned to all dementia cases. Because AD is by far the most common cause of late life dementia, it is likely that many persons who would have been classified as having dementia of undetermined etiology in ADAMS were classified as AD in CHAP despite meager or conflicting data. This may have slightly inflated the number of AD cases in CHAP.

4. Characteristics of persons diagnosed differently by different criteria

We reviewed above the two major diagnostic differences, the use of the criterion for the presence of functional impairment, identified by an informant, to distinguish dementia from CIND in ADAMS, and the attribution of dementias of primarily vascular or potentially mixed etiology to AD in CHAP, that could account for most of the difference in AD prevalence estimates. In Table 1 we show, using ADAMS data, how these differentially diagnosed groups compare on some key indicators of cognitive function, functional impairment, and genetics.

The bottom row of Table 1 describes persons diagnosed with prevalent AD in ADAMS. Their average scores on the MMSE and the Dementia Rating Severity Scale indicated moderate dementia; the average CDR scores were consistent with mild to moderate dementia. In the two rows above them are the groups who were identified in ADAMS as demented but with non-AD etiology, and as CIND with prodromal AD. Taken together with the bottom row, these groups add up to 5.3 million persons—slightly higher than the CHAP estimate of AD. It is likely that the CHAP diagnostic criteria would have classified most of the individuals in these three rows as AD. While the cognitive and functional level of the vascular and other dementia group was quite similar to that of the AD group, the CIND prodromal AD category had much better global cognitive and functional performance, though it was much worse than the normal group (mean MMSE=24.28, mean CDR=0.49), and delayed recall intermediate between the dementia group and the remaining CIND group (mean 3.18) consistent with the procedures used to classify these persons. We find it interesting that while the prodromal AD subgroup within the CIND category had cognitive function very similar to CIND cases with other etiologies, their episodic memory was more impaired and the presence of any APOE ε4 allele in this group was nearly three times higher than the other CIND cases and actually higher than the AD dementia group. Moreover, the

combined group of vascular and other dementia also had an ε4 allele frequency comparable to the AD dementia group. While this is a very limited genetic profile, the ε4 allele is strongly related to AD pathology [24]. Thus, these data suggest that the prodromal AD group may be exhibiting the early signs of cognitive impairment related to the pathology of AD.

5. Discussion

Estimating the prevalence of AD in the United States is a complex process that requires many assumptions and decisions. So it is not surprising that estimates have previously been noted to be variable [25]. We reviewed several differences between the Hebert et al [3] and Plassman et al [6] studies that could have affected results. In some cases, we were able to quantitatively estimate the effects of different decisions. The results suggest that the difference between the two prevalence estimates could be entirely accounted for by two factors. First, a diagnosis of dementia in ADAMS required functional impairment reported by an informant and as a result was likely associated with a higher level of cognitive impairment than a dementia diagnosis in CHAP. By lowering the threshold for dementia to classify all individuals with prodromal AD as demented, one could account for up to two million cases and much of the difference between the prevalence estimates. This observation is consistent with previous analyses of the impact of dementia criteria on estimates of its prevalence [11].

A second factor that affected estimates of AD prevalence in the two studies was differential diagnosis. In CHAP, more than 90% of dementia was classified as AD. This includes those judged to have AD plus one or more other conditions contributing to cognitive impairment such as vascular cognitive impairment. In ADAMS, similar to other epidemiological studies of dementia, a substantial subset of dementia was classified as vascular dementia, which was very rare in CHAP. An additional proportion of dementia cases in ADAMS was classified as etiology unknown, which was not an option in CHAP. Together, these factors could have accounted for a difference of up to one million cases in the prevalence estimates.

So which prevalence number is correct—the 2.4 million from ADAMS or the 4.5 million from CHAP? The answer is that the choice of prevalence estimate must be matched to the specific question it is used to answer. For example, if the question is how many people with AD are dependent in activities of daily living, it seems appropriate to exclude the highly functioning early AD cases in that count. In fact, such a question was a focus of some early prevalence studies that were restricted to persons with moderate to severe dementia [26,27]. If the question is how many people might benefit from an effective therapy aimed at the underlying pathology of AD such as an anti-amyloid agent, it seems appropriate to include those persons with mild forms of cognitive dysfunction due to the underlying disease pathology. Further, since recent clinical-pathologic studies suggest that AD pathology and cerebrovascular pathology have additive effects on the odds of dementia and cognitive impairment [19–22], it is possible that persons with mixed pathologies might also benefit from an agent that affects the underlying pathology of AD making it important to identify the contribution of AD pathology to cognition in persons who also meet criteria for vascular dementia.

An important evolving debate is whether the definition of dementia and AD should shift from dependence on a level of cognitive impairment that leads to moderate disability in daily life to much milder levels of cognitive impairment, or even criteria that depend on the presence of biomarkers or imaging findings associated with AD pathology that may not yet have caused significant cognitive or functional impairment. Many persons had MCI in CHAP [28,29] and CIND in ADAMS [17]. In fact, Plassman et al. [17] estimated that 5.4

million people in the United States had CIND in 2002. Recent data suggest that persons with this syndrome have mild limitations in daily living [30] and are at greater risk of cognitive decline [29,31] and death [28,31]. In addition, clinical-pathologic research suggests that many old people without dementia meet pathologic criteria for AD [20,32–38]. In one study, for example, nearly two thirds of those who died with MCI and one third of those who died with no apparent cognitive impairment met pathologic criteria for the disease [37]. Further, the correlation of the pathologic findings with cognitive impairment was similar in those with and without dementia. It is not surprising, therefore, that some investigators suggest that many of those with MCI or CIND already have AD [39] or that a recent panel recommended revising AD criteria to include a subset of MCI with memory impairment supplemented by a biomarker of AD pathology [40]. In fact, the National Institute on Aging and the Alzheimer's Association recently established three working groups to (1) revise the NINCDS–ADRDA criteria for AD, (2) better define MCI, and (3) define persons with preclinical AD referring to persons with AD pathology who do not meet clinical criteria for dementia or MCI. Draft reports were presented at the 2010 International Conference on Alzheimer's Disease, in Honolulu, Hawaii. Thus, persons with dementia may only represent a fraction of those who have the underlying disease pathology and whose cognition and behavior may already show some subtle changes due to this pathology. While there are ongoing efforts to make the diagnosis of AD even earlier in the disease process, in the absence of clearer evidence of which cognitively impaired individuals will progress to dementia and of robust therapy for the treatment or prevention of cognitive decline, one should also be cautious about the potential risks and "clinical cascade" that might result from labeling as "disease" pathologic changes in the brain or subtle cognitive changes that might not impact the daily lives, or life expectancy, of older adults [41].

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Table 1

Descriptive information from ADAMS weighted to the US population*

Diagnosis	Etiology	Weighted N	Age	MMSE	CDR	DSRS	Blessed	IADLs	Del Recall	ε4
Normal		15,557,113	77.84	27.84	0.12	1.67	0.31	0.22	6.34	23.5%
CIND	Other	3,381,975	80.67	25.03	0.43	6.46	1.17	1.25	4.62	16.0%
CIND	Prodromal AD	1,947,924	82.08	24.28	0.49	5.45	1.26	0.73	3.18	46.3%
Dementia	Vascular/ other	1,004,790	82.15	16.41	1.50	21.19	5.55	3.60	1.64	39.7%
Dementia	AD	2,301,398	85.71	13.78	1.85	22.28	6.94	3.20	0.58	38.8%

Weighted using ADAMS sampling weight.

Acronyms

ADAMS Aging, Demographics, and Memory Study

AD Alzheimer's disease

CIND Cognitive impairment not dementia

CDR Clinical Dementia Rating Scale

DSRS Dementia Severity Rating Scale

Blessed Blessed Dementia Scale

IADLs Number (out of 6) of impaired instrumental activities of daily living

ε4 any apolipoprotein E ε4 allele

Del Recall: Word List Recall