Published in final edited form as:
J Rural Health. 2009 ; 25(3): 320–325. doi:10.1111/j.1748-0361.2009.00237.x.

Exceptional Brain Aging in a Rural Population-Based Cohort

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Abstract

Context—The 2000 US census identified 50,454 Americans over the age of 100. Increased longevity is only of benefit if accompanied by maintenance of independence and quality of life. Little is known about the prevalence of dementia and other disabling conditions among rural centenarians although this information is important to clinicians caring for them.

Purpose—To determine the prevalence of disabling conditions, including cognitive impairment, among the very elderly in a rural setting to guide clinicians in their care.

Methods—We performed a population-based cohort study of all residents 97 years and older in the Klamath Basin, a rural region in southern Oregon. The prevalence of disabling conditions was determined by in-person examination.

Findings—100% of the target sample was identified. Of the eligible 67 individuals ≥ 97 years old, 31 were evaluated in-person. The prevalence of dementia (probable or possible Alzheimer's disease or vascular dementia) was 61.3% (95% CI: 43.8, 76.2), mild cognitive impairment was 29.0% (95% CI: 16.1, 46.6), and no dementia was 9.7% (95% CI: 3.4, 25.0). Parkinsonism and the APOEe4 allele were rare. Systemic vascular disease was almost universally present.

Conclusions—While cognitive impairment was nearly universal in this rural population of very elderly persons, almost 40% had not progressed to full dementia. Determining risk factors for dementia in this population can identify strategies to prevent progression to dementia among younger elderly populations.

Keywords

brain; aging; centenarian; dementia; Alzheimer's disease; rural

INTRODUCTION

In less than 50 years a projected 2.2 million people will reach the century mark, a 15-fold increase in centenarians compared to today[1]. Increased longevity is beneficial if

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Financial Disclosure: None reported.

Author Contributions: *Study concept and design*: Kaye, Kramer, *Acquisition of data*: Kaye, Leahy, Calvert, Crawford, Kramer, *Analysis and interpretation of data*: Kaye, Michael, Leahy, Kramer, *Drafting of the manuscript*: Kaye, Michael, Leahy, Calvert, Crawford, Kramer, *Critical revision of the manuscript for important intellectual content*: Kaye, Kramer, *Obtained funding*: Kaye, Leahy, *Administrative, technical, and material support:* Kaye, *Study supervision*: Kaye, Calvert, Kramer.

accompanied by maintenance of independence and quality of life. Information about health status after age 90, especially among rural elderly, is limited.

The majority of population-based studies of the oldest-old have been conducted among urban or mixed rural-urban populations[2]. The majority of studies regarding the prevalence and impact of dementia in rural elderly have focused on younger elderly (65–85 years). The very elderly in rural communities represent an isolated population that, because of differing environments and limited access to resources, might have different outcomes from their urban peers[3][4].

We assessed the prevalence of disabling conditions, with an emphasis on the dementias, in a well-characterized, population-based sample of individuals 97 years old or older, (97+) residing in a large rural area of southern Oregon. The study was conducted among participants in the Klamath Exceptional Aging Project (KEAP), a community study of health in the oldest-old in rural eastern Oregon. This study is unusual because of its focus on describing brain aging and accompanying co-morbidities in the oldest-old living in rural communities.

METHODS

The research area for KEAP comprises the Klamath Basin watershed, a rural area in Eastern Oregon. The region includes the county seat, Klamath Falls, 20 small towns, and a large frontier area with a population density under five persons per square mile. This region was selected for study because: 1) most inhabitants obtained their primary medical care from local medical practices and tertiary care at one small hospital, the Sky Lakes Medical Center (SLMC); 2) there were existing computer registries of seniors receiving care from the local hospital, and 3) a close relationship existed between the investigators and local physicians and hospital administration.

According to the 2000 US census, there were 71,479 inhabitants in the Klamath Basin. We targeted all adults 97+ years old. We chose the 97-year cut-off in order to obtain a meaningful sample of oldest-old subjects, and to establish a basis for follow-up studies into centenarian years in this cohort. All people 97+ years were eligible for the study if they resided in the research area on January 1, 2001. In order to ensure the most comprehensive sample, additional subject identification included in-person surveys of all nursing homes, foster care homes, and assisted living or residential care facilities in the region.

The study was approved by the Institutional Review Boards of the SLMC and the Oregon Health and Science University (IRB# 5473). Informed consent was obtained for all subjects.

Study subjects were visited at their homes every six months to perform neuropsychiatric testing and update their medical and social histories. Individuals were evaluated using a standardized protocol conducted during a comprehensive examination by a geriatric research nurse. Standardized medical history, physical and neuropsychological examinations were performed as previously described[5]. Clinical evaluation included a collateral interview with at least one person who had close contact with each subject. Self-reported conditions were verified with the subject's medical chart at their primary care physician's office.

Information on education, current living arrangement, alcohol and tobacco use, residence history, and acute and chronic co-morbid conditions was gathered by an interview-administered questionnaire and verified by a collateral source. Functional impairment was assessed using a modified Older Americans Resources and Services Multidimensional Functional Assessment and Questionnaire [6] that assessed Activities of Daily Living

(ADLs) [7] and Instrumental Activities of Daily Living (IADLs) [8]. Subjects donated blood for ApolipoproteinE (APOE) genotyping using standard methods[9].

Cognitive function was summarized using the Mini Mental State Examination (MMSE) [10] and dementia was staged with the Clinical Dementia Rating Scale (CDR) [11]. Cognitive function was further assessed with a standardized battery of tests: word list recall, category fluency, naming and constructions[12]. The Unified Parkinson's Disease Rating Scale [13] was used to assess motor function. Those with a CDR of 0 and MMSE of 24 or higher were considered not demented. Mild cognitive impairment (MCI) was defined as a CDR of 0.5 regardless of MMSE. For those with CDR 1 or higher a dementia diagnosis was made based on standardized criteria, using a consensus conference approach by a research team. The diagnosis of probable or possible AD was made according to NINCDS-ADRDA criteria[14]. Vascular dementia was diagnosed according to the California criteria[15]. Other dementias (Lewy body dementia (LBD), fronto-temporal dementia (FTD) and relevant neurological conditions were assessed. The Cumulative Illness Rating Scale (CIRS) [16], which gives a numeric rating from 0 to 56 for the burden of chronic illness present in an individual was also calculated.

One-way analysis of variance was used to determine differences in the groups of interest. The prevalence of dementia was estimated directly from the data using the formula: p = (number of subjects with possible/probable dementia, for example)/n, where n is the total number of subjects included in the assessment beginning January 1, 2001 and ending December 31, 2001. The 95% confidence interval was calculated for each prevalence estimate [17] for use with small samples. Statistical analyses were conducted using SAS9.1 and JMP5.0.

RESULTS

A total of 67 individuals aged 97+ years living in the Klamath Basin in 2001 were identified. The Census 2000 figures within the study area listed 62 people ≥ 97 years the previous year, five less than we found. Of the 67 eligible subjects, 31 (46%) received a full assessment, 15 (22%) died before the assessment and 21 (32%) refused to participate.

Participant refusal or death before study completion are problems common to all published studies involving direct contact with centenarians. Our participation rate of 46% is consistent with the published literature. The Japan Centenarian study had a 57% refusal rate [18] and the Swedish Centenarian Study a 31% refusal rate [19]. While most published studies do not include information about subjects who died after consenting but before being studied, the Finnish Centenarian Study reported that 32% of subjects died before being seen[20], which compares with 22% in our study.

Participating subjects were not different in age, sex or living arrangement from those who declined or died before assessment, as shown in Table 1. The majority of subjects were female (87%). These rural adults were well-educated; 19 (63%) completed at least a high school education. Subjects had engaged primarily in lifetime occupations related to agriculture, teaching and homemaking (*data not shown*). Nearly half of the participants lived on a farm during their adult years plus at least one other period in their life (childhood, teen years or retirement).

Co-morbid conditions, many of which are associated with increased risk of dementia, are described in Table 2. Approximately 75% of subjects reported a current or prior diagnosis of vascular disease. Cancer and diabetes were not particularly prevalent, and Parkinsonian syndromes were notably absent.

The prevalence of dementia (probable or possible AD or vascular dementia), MCI and no dementia are presented in Table 3. Three subjects, all female, exhibited no cognitive impairment. Cognitive screening tests or psychometric testing were within non-impaired ranges for these three individuals. Nine subjects were diagnosed with MCI. Of the 19 demented study participants, 11 were diagnosed with probable AD, 7 with possible AD and one with vascular dementia. No cases of LBD or FTD were diagnosed. Five subjects with probable AD came to autopsy and met post-mortem AD criteria[21].

Clinical characteristics of the population according to cognitive status are summarized in Table 3. Age was not significantly different among groups. Education levels were higher in the MCI and no dementia groups compared to the demented group. Comparison of the demented and MCI groups indicated significant differences on measures of functional disability and cognitive performance in a pattern consistent with an AD syndrome.

DISCUSSION

A rich literature over the last two decades addresses the question of cognitive health among the oldest-old. Although subject ascertainment strategies and methods for assessing cognitive function differ, most studies have used standard assessment tools for differentiating “no or cognitive impairment without dementia” from “mild, moderate or severe AD”. Estimates of dementia prevalence in the oldest-old range from 48–71%[2], [22], [23], [24]. A notable exception is a large Swedish study in which only 25–40% of subjects over 90 years of age were found to have dementia[25].

The dementia prevalence estimate of 61% obtained in our rural cohort falls within the typical range reported for oldest-old populations. We used direct assessment with psychometric testing and a collateral informant rather than only screening tool, a method that may yield higher prevalence rates for dementia than studies using only screening instruments or information from relatives. While cognitive impairment was nearly universal among our subjects, three individuals (9.7%) remained non-demented and nine (29.0%) had only MCI. [26] Individuals with MCI can often continue to live independently and appear intact in casual social interactions. Because there were only three cognitively intact subjects we did not perform statistical comparisons between them and the MCI or demented subjects; however, inspection of the data suggested that the MCI group was primarily an amnestic MCI when contrasted to the cognitively intact subjects

Variation in dementia prevalence rates across studies can result from various factors, including the use of different assessment methods. This is the basis for determining the numerator in the prevalence ratio. An equally problematic issue is that of calculating the denominator, namely the total number of individuals in the population of interest. We identified virtually all adults, aged 97+, in our defined study area.

Once identified, the ensuing issue is that of enlisting participation. This is a significant problem among the very elderly, in which high mortality rates, perceptions that the individual is “too frail” to undergo testing and dispersed geography prevail. The fact that half our sample was not available for direct evaluation is typical for field studies of this kind. Rates of refusal and death vary widely, from 16–58% in other studies [2], and are not easily comparable because of study design.

Although those who refused to participate in this study were not noticeably different in age, gender or living arrangement from those who chose to participate, it is not clear that their cognitive health status was similar. In a five-year follow-up in 2006, we obtained mortality data for all of the original 67 eligible subjects who had died in the last 5 years. The distributions of age at death for participants and non-participants, presented in Table 1, are

similar (p=0.6). Those who refused tended to live as long as those who participated. If the prevalence of dementia was increased among those who refused, one would expect earlier mortality rates in these individuals, given the decreased interval between onset of dementia and time to death in the oldest-old[27]. Thus, these data provide additional evidence that subjects who refused to participate were not significantly different from participants in terms of cognitive health, and substantiates our estimates of dementia prevalence in this population.

Systemic vascular disease (hypertension, heart disease) was almost universal in this cohort; only four (13%) individuals had no symptoms of heart or vascular disease. Interestingly, only one subject was diagnosed with vascular dementia by current clinical criteria. Additional cases of vascular dementia may have been identified by neuropathological assessment; however, among the five subjects with autopsy all had predominantly AD pathology.

Evert et al [28] conducted a study of co-morbidity profiles in centenarians, based on the New England Centenarian study (NECS). Although the rural vs. urban composition of the study sample was not reported or differentiated in the results, comparison of rates with this study is noteworthy. The occurrence of non-skin cancers, diabetes and Parkinson's disease were similar, and relatively low, in both studies. However, the occurrence of heart disease was 65% in this rural cohort, but 40–42% (depending on gender) in the NECS; rates of hypertension were similarly elevated in our study: 63% (combined genders) compared with 19% and 35% in males and females, respectively, in the NECS. Occurrence of stroke in the NECS was 14–15%, but 79% in the current study. Differences in diagnostic regimens may account for the wide variation in co-morbidity profiles across these studies. However, these results exemplify the importance of differentiating rural vs. urban components of study samples.

Presence of the ε4 variant of the APOE gene is a major risk factor for development of late-onset (65–85 years of age) AD[29]. However, it is not clear whether APOEε4 continues to exert a major influence on the occurrence of AD in the oldest-old populations. The frequency of APOEε4 in this rural population was noticeably rare (5%), compared with established estimates of 15% in the general adult population[29]. This reduction of APOEε4 in a very elderly population is most likely a function of its deleterious effect on cognitive health and consequent mortality earlier in life (and thus its gradual disappearance). Nonetheless, our data support the view that the association of ε4 with risk of dementia changes with advancing age, since the large majority of demented subjects in this study did not carry the ε4 variant (Table 2). It is likely that other age-associated genetic susceptibilities are present that promote long-life and dementia-free survival[30]. In fact, five subjects in this study reported a family history of longevity, defined as having five or more first-degree relatives who lived at least 85 years. These observations underscore the need for population-based studies to identify genetic and environmental factors that protect against dementia among the oldest-old.

Differences between populations in the prevalence of dementia may also reflect differences in locality or environment. The definition of rural status is based on population density and distance from population centers. This definition has traditionally had implications for factors that characterize rural communities, including occupation, education levels and access to health care. No consistent evidence has emerged of the extent to which any of these factors is involved in increased (or decreased) risk of dementia in the oldest-old, with the notable exception of education levels.

Rural residents may have limited access to health care. The fact that the subjects reported in this study exceeded human life expectancy suggests that health care access may not be as prominent a factor at advanced ages. Very few subjects reported a history of smoking or drinking. Persons living in a rural, agrarian area might have greater levels of physical activity as part of the daily routine, which has been shown to be protective against dementia. [31]

Our goal was to evaluate the prevalence of dementia and related conditions among the extreme elderly in a geographically defined rural community. Retention of cognitive capacity is essential for sustaining independence. Our study supports the idea that a substantial number of oldest-old do not progress to dementia, although the majority do not escape some level of cognitive impairment that could affect their ability to live independently.

Acknowledgments

Funding/Support: Northwest Health Foundation; Merle West Center for Medical Research; Alzheimer's Research Alliance of Oregon; Oregon Partnership for Alzheimer's Research Award; National Institute on Aging, National Institutes of Health (AG08017).

We would like to thank the research volunteers and the staff of the Layton Aging and Alzheimer's Disease Center at OSHU in Portland, Oregon, and the Merle West Center for Medical Research in Klamath Falls, Oregon.

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Biographies

Dr. Kaye is the Director of the Layton Aging and Alzheimer Disease Center at Oregon Health and Science University (OHSU). His interests include longitudinal studies of healthy aging and the application of technology to help the aging.

Dr. Michael is a social epidemiologist with an interest in healthy aging, cancer prevention, and community-based approaches to improving health.

Dr. Calvert is a family physician with an interest in research in healthy aging. He and Dr. Kaye are co-directors of the Klamath Exceptional Aging Project (KEAP), a longitudinal study of very old rural people.

Ms. Leahy and Ms. Crawford are research nurses who work with Dr. Calvert in KEAP.

Dr. Kramer is a geneticist in the Department of Neurology at OHSU with an interest in the genetics of aging.

Table 1

Selected characteristics of total population ≥ 97 years by participation. Differences between groups are not statistically significant.

	Assessed (n=31)	Declined (n=21)	Died (n=15)
Age (mean, standard deviation)	98.4 (1.1)	98.1 (1.6)	98.7 (1.8)
Age at death	100.7 (2.3)	100.6 (2.1)	98.6 (1.8)
Gender (%)			
Female	27 (87%)	18 (86%)	12 (80%)
Male	4 (13%)	3 (14%)	3 (20%)
Living arrangement (%)			
Independent	6 (19%)	4 (19%)	2 (13%)
With family	9 (29%)	5 (24%)	6 (40%)
Assisted living facility	4 (13%)	5 (24%)	3 (20%)
Nursing home/foster care	12 (39%)	7 (33%)	4 (27%)

Table 2

Medical conditions and risk factors for dementia

Medical Condition or Risk Factor	Combined Gender n (%)
Heart Disease	20 (65%)*
CAD/Angina	*6 (19%)*
Cardiac Arrhythmia	*12 (39%)*
Myocardial infarction	*5 (16%)*
Hypertension	17(63%)*
Cerebrovascular Disease	23 (74%)*
Stroke	*9 (29%)*
TIAs	*9 (29%)*
Non-skin Cancer	7 (23%)
Diabetes	3 (10%)
Parkinson's disease	0
Alcohol Use	
currently use weekly	1
ever use weekly	4 (13%)
Tobacco Use	
currently smoke	0
ever smoke > 100 cigarettes	5 (16%)
APOE genotype (n=21)	
APOE ε4-ε4	0
APOE ε4-ε3	1 (5%)
APOE ε4-ε2	1 (5%)
APOE ε3-ε3	15 (70%)
APOE ε2-ε3	4 (20%)
APOE ε2-ε2	0

*numbers in clear rows represent overall rates; specific Conditions are given in italics in shaded rows; individuals may have >1 specific condition, but are tabulated only once in the general category.

Table 3

Demographic, functional, and neurocognitive characteristics (mean, standard deviation) according to cognitive status

	No Dementia (n=3)	MCI (n=9)	Dementia[1] (n=19)
Age	98.8(.6)	98.7(1.1)	98.5(1.4)
Age range (years)	98–99	97–100	97–102
% Female:	100%	89%	84%
n:	3 of 3	8 of 9	16 of 19
Education:	12.3 (4.7)	12.3 (2.3)	10.4 (3.6)
range:	7–16	8–16	4–16
MMSE	27.3 (0.6)	25.7(1.3)	18 (4.6)**
ADL	3.0 (2.6)	4.6 (2.5)	10.3 (5.0)*
IADL	3.7 (2.1)	6.1 (3.8)	11.7 (2.8)**
CESD	0.7 (1.2)	1.6 (1.5)	1.8 (1.3)
UPDRS	1.3 (2.7)	5.2 (1.8)	8.9 (1.30
CIRS	28.7 (6.7)	29.8 (4.4)	30.2 (4.3)
Word List Acquisition	17.3 (4.7)	11.6 (3.0)	9.0 (3.4)
Word List Delayed Recall	6.0 (1.0)	3.5 (1.2)	1.4 (1.5)*
Word List Recognition	20 (1.8)	18.5 (1.1)	14 (0.9)*
Category Fluency (Animals)	16.7 (4.5)	11.3 (4.2)	7.9 (3.8)
Boston Naming	12.3 (1.6)	13.4 (1.1)	9.6 (1.7)**
Constructions	10.0 (1.0)	9.5 (1.7)	6.2 (3.3)*

[1]ANOVA comparing Dementia and MCI groups only (too few non-demented subjects for analysis):

*p < .01;

**p < .001