Published in final edited form as:

Alzheimers Dement. 2016 March ; 12(3): 225–232. doi:10.1016/j.jalz.2016.01.004.

Impact of Interventions to Reduce Alzheimer's Disease Pathology on the Prevalence of Dementia in the Oldest-Old

Ron Brookmeyer, Ph.D.,

rbrookmeyer@ucla.edu

Claudia H. Kawas, M.D.,

ckawas@uci.edu

Nada Abdallah, M.S.,

nada.a.abdallah@gmail.com

Annlia Paganini-Hill, Ph.D.,

apaganin@uci.edu

Ronald C. Kim, M.D., and

rckim@uci.edu

Maria M. Corrada, Sc.D.

mcorrada@uci.edu

Abstract

Introduction—The number of persons aged over 90 years will grow significantly in coming decades. This group has the highest rates of dementia, most commonly Alzheimer's disease (AD).

Methods—Using The 90+ Study we developed a statistical model for dementia risk based on brain pathologies. Intervention scenarios which reduce or eliminate AD pathology were considered and the numbers of dementia cases among the U.S. oldest-old that could be prevented were estimated.

Results—U.S. dementia prevalence among the oldest-old will increase from 1.35 million in 2015 to 4.72 million in 2050. If interventions eliminate AD pathology, dementia prevalence would be reduced by approximately 50%, averting nearly 2.4 million cases in 2050. However, large numbers of dementia cases would still remain.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Authors Contributions:

RB conceived the study, developed the methods, interpreted the data and drafted the manuscript. CHK conceived the study, interpreted the data and drafted the manuscript. NA carried out statistical analyses, interpreted the data and critically revised the manuscript. APH interpreted the data and critically revised the manuscript. RCK carried out pathological analyses and critically revised the manuscript. MMC conceived the study, carried out statistical analyses, interpreted the data and drafted the manuscript.

Discussion—Reducing AD pathology would significantly decrease the public health burden of dementia. However, other interventions are needed to address the burden associated with other dementing pathologies prevalent in the oldest-old.

Keywords

Alzheimer's Disease; dementia; intervention; oldest-old; pathology; prediction; prevalence; prevention

Introduction

The oldest-old is the fastest growing segment of the population in many countries [1]. Over the next 50 years, the number of persons aged 90 years and older in the United States (U.S.) is expected to grow over six-fold and the resources needed to care for them will increase significantly [2]. The prevalence of dementia among persons 90 and older is high and Alzheimer's disease (AD) is the most significant cause of dementia. Other causes, aside from AD, are also significant contributors to the high prevalence of dementia among the oldest-old [3–5].

Considerable resources and efforts are now focused on developing interventions to reduce risk of AD. Monoclonal antibodies attempt to increase clearance of amyloid- β peptide (A β) and beta secretase inhibitors attempt to limit production. While anti-A β interventions have been largely unsuccessful in symptomatic persons [6], clinical trials are underway to determine if intervening before the development of significant brain damage will be successful [7]. An important public health question is, if such interventions are ultimately successful in reducing AD pathology, including both A β deposits and neurofibrillary tangles, then what is the downstream impact on the total burden of dementia among the oldest-old.

Previous studies have examined the importance of multiple pathologies in explaining the high prevalence rates of dementia among the oldest-old [3–5] as well as among younger segments of the elderly population [8]. Studies have also examined the impact of lifestyle risk factor reduction on AD prevalence [9]. The objective of this study was to estimate the percentages and numbers of total dementia cases among the oldest-old that could be averted if future interventions are successful in reducing AD pathology.

Methods

Study Population

The 90+ Study is a longitudinal study of aging and dementia among persons aged 90 years and older, which was initiated in 2003 [10–12]. Members of the cohort were originally members of the Leisure World Cohort Study (LWCS), an epidemiological study of persons in a California retirement community. Participants in The 90+ Study were assessed at baseline and periodic follow-up visits with neurological examinations and a neuropsychological test battery. If participants were unable to complete a full in-person evaluation, then information was obtained by telephone or with informants. Dementia status at last follow-up visit was determined post-mortem using DSM-IV criteria during a

consensus conference. All available longitudinal information including neurological exams, neuropsychological test scores, informant questionnaires, medical records, and neuroimaging when available, was used for dementia determination. The diagnostic conference was led by one of the authors (CK) with all conferees blinded to the pathological evaluation [5]. Study participants were also invited to be part of an autopsy sub-study [13]. Some additional participants were also recruited for the autopsy sub-study from the same geographic area but who were not members of the original LWCS. As of May 1, 2015, 212 participants in The 90+ Study had been autopsied, of whom 188 were members of the original LWCS. We compared characteristics of persons who participated in the autopsy study to non-autopsy participants who died during the study period using Fisher's exact tests and two sample t-statistics.

The pathological evaluations were performed by board-certified neuropathologists blinded to clinical diagnoses. Joshua Sonnen, M.D. performed evaluations pertaining to microinfarcts using the same methodology he applied in other population-based cohorts [14, 15]. Ronald Kim, M.D. performed evaluations for all other pathologies. Further details regarding the protocol for the neuropathological evaluations are provided in an earlier publication [5].

Intervention scenarios for AD

We used AD NIA Reagan criteria for assessing the extent of the neuropathological changes associated with AD [16]. The criteria are based on two main components of AD neuropathological change: neuritic plaques associated with amyloid A β deposits and neurofibrillary tangles. The Braak and Braak tangle stage [17] and the Consortium to Establish a Registry for AD (CERAD) neuritic plaque scoring system [18] were used to construct the AD NIA Reagan criteria. We recognize that revised criteria for assessing plaque accumulation have been developed based on the Thal phase of A β distribution in the brain [19]; however the majority of autopsies we report here were done prior to 2013 before the revised criteria were available. The autopsy results on the participants were classified into four categories: (1) No AD pathology (tangle stage=0 or CERAD plaque=none; (2) Low level of AD pathology defined as plaque=sparse and tangle 1, or plaque=moderate/frequent and tangle =1 or 2; (3) Intermediate level of AD pathology defined as plaque=moderate and tangle 3, or plaque = frequent and tangle=3 or 4; (4) High level of AD pathology defined as plaque=frequent and tangle 5.

We considered four intervention scenarios aimed at reducing AD pathology. Scenario A (modest reduction in AD pathology) is an intervention that reduces high levels to intermediate levels (as defined by AD NIA Reagan criteria). Scenario B (moderate reduction of AD pathology) is an intervention that reduces high levels to intermediate levels and also intermediate levels to low levels. Scenario C (substantial reduction of AD pathology) is an intervention that reduces intermediate and high levels to low levels. Scenario D (complete elimination of AD pathology) is an intervention that succeeds in reducing all levels of AD pathology to no AD pathology.

Statistical Methods

To evaluate the impact of the intervention scenarios on dementia prevalence, we fit a logistic regression model using the data on 212 autopsied participants of The 90+ Study to predict the probability of dementia at the last follow-up prior to death where the predictors of risk were brain pathologies and other covariates such as demographic variables. The model was of the form

$$\text{logit}(p) = \beta_0 + \beta_1 Z_1 + \beta_2 Z_2 + \beta_3 Z_3 + \beta_4 W + \beta_5 X$$

where p is the probability of dementia at last follow-up, and Z are indicator variables indicating AD pathology (using NIA Reagan criteria, $Z_1=1$ if low, $Z_2=1$ if intermediate and $Z_3=1$ if high, and all the Z 's are 0 if no AD pathology); W is a vector of multiple indicator variables that identifies the presence or absence of other brain pathologies including micro-infarcts, hippocampal sclerosis, amyloid angiopathy, white matter disease (subcortical arteriolosclerotic leukoencephalopathy), lacunes or large infarcts, Lewy Body Disease, and other brain pathologies; and X is a vector representing other predictors of dementia including age at death, gender, education (college graduate), and APOE status. Interaction terms between high Alzheimer's disease pathology and other pathologies were also considered.

For each scenario, we identified the n_1 dementia cases whose AD pathology is targeted to be changed by the intervention, and the n_2 dementia cases whose AD pathology is not targeted to be changed. For example, for Scenario A (which targets only persons with high levels of AD pathology) n_1 is the number of dementia cases with high level of AD pathology (i.e., $Z_3=1$), and n_2 is the number with no, low or intermediate levels of AD pathology. We calculated the predicted probability of dementia p for each of the n_1 dementia cases targeted by the intervention using the logistic regression model. See Supplementary Material for details. A key assumption we make is that only the AD pathology variables (the Z s) change as a result of the intervention while the other predictors (i.e., W and X) remain fixed. We further discuss the underlying assumptions in the Discussion Section. If the intervention had been successful in reducing AD pathology among the n_1 targeted cases, then the total projected number of dementia cases we would have expected among the study participants is

$$\left(n_2 + \sum_{i=1}^{n_1} \hat{p}_i \right).$$

The estimated fraction (f) of the total number of dementia cases in The 90+ Cohort that could have been averted by an intervention I is the difference between the dementia prevalence rate with intervention ($P(D|I)$) and without the intervention ($P(D)$) divided by the prevalence without the intervention. We have

$$f = \frac{P(D) - P(D|I)}{P(D)} \quad (1)$$

which is estimated by

$$f = \frac{n - \left(n_2 + \sum_{i=1}^{n_1} \hat{p}_i \right)}{n}.$$

where $n = n_1 + n_2$ is the total number of observed dementia cases.

The 90+ Study and the autopsied participants in particular are not representative of all persons over the age of 90 in the U.S. While the gender distributions are similar (69% women among the autopsied participants in The 90+ Study versus 74% in the U.S), the educational levels are very different (50% are college graduates among the autopsied participants in The 90+ Study versus 14% in the U.S [2]). Accordingly, we adjusted f by calculating $P(D|I)$ and $P(D)$ standardized to educational levels in the 90+ population of the U.S. We outline the adjustment method to standardize to strata (e.g., education) as follows. Let N_s represent the numbers of persons in The 90+ Study in stratum s of whom n_s have dementia, and of those, n_{1s} is the number of demented cases with AD pathology targeted by the intervention and n_{2s} is the number of dementia cases not targeted by the intervention ($n_s = n_{1s} + n_{2s}$). Then the prevalence rate of dementia in the absence of intervention adjusted to the U.S population distribution among strata is

$$P(D) = \sum_s w_s \left(\frac{n_s}{N_s} \right) \quad (2)$$

where w_s is the proportion of the oldest-old in the U.S. in stratum s (e.g., $w_1=0.14$ are college grads, $w_2=0.86$ are not college grads).

The projected prevalence rate of dementia adjusted to the U.S. population distribution assuming that intervention scenario I is successful in reducing AD pathology is,

$$P(D|I) = \sum_s w_s \left(\frac{n_{2s} + \sum_{i=1}^{n_{1s}} \hat{p}_i}{N_s} \right) \quad (3)$$

The adjusted f is obtained by inserting equations 2 and 3 into equation 1. Confidence intervals (CI) for $P(D)$, $P(D|I)$ and f were obtained by bootstrapping as follows. For each bootstrap sample we resampled with replacement 212 persons, refit the logistic regression model and recalculated $P(D)$, $P(D|I)$ and f . We performed 2000 bootstraps and used the bias-corrected accelerated method to obtain 95% confidence intervals [20]. The calculations were implemented in the statistical programming language **R**.

We projected the numbers of dementia cases in the absence of an intervention by multiplying U.S. Census Bureau population projections of the 90+ population [21] by equation 2 for $P(D)$ which adjusts for the educational differences between The 90 Study participants and the U.S. population of the oldest old. Similarly, we projected the numbers of dementia cases with each intervention scenario (adjusted for educational differences) by multiplying the U.S. census population projections by equation 3 for $P(D|I)$. We obtained

estimates for 2015, 2030 and 2050. We estimated the numbers of dementia cases that could be averted by the differences between the projected numbers of cases with and without interventions. We also accounted for sources of uncertainty in our projections by considering the low and upper U.S Census projections together with the bootstrapped confidence intervals for the dementia prevalence rates $P(D)$ and $P(D/I)$. Specifically, we obtained plausible lower bounds for the numbers of dementia cases by multiplying the lower U.S census projections by the lower end of the confidence interval for the prevalence rates and an upper bound by multiplying the upper U.S. census projections by the upper end of the confidence interval for the prevalence rates.

Results

As of December 31, 2013, The 90+ Study had enrolled 978 participants who have had at least one in person-visit. Of those participants, 784 had died between January 1, 2003 and December 31, 2013, and among those deceased participants, 212 had completed autopsies and the other 572 either chose not to have an autopsy (N=565) or the full pathological evaluation was not done (N=7). We compared the 212 autopsied participants included in the study to the 572 persons who died during the study period but were not autopsied. The autopsied participants were slightly older at age of death (mean 97.8 versus 97.0 years of age). We compared the autopsied participants, the non-autopsied deceased, and the U.S population of the oldest old ([2], if available) with respect to various attributes (Table 1). The autopsied participants tended to be more highly educated (50% among the autopsied were college graduates vs 38% among the non-autopsied, $p < .002$). The proportion of college graduates in the U.S. aged 90 and older is 14%. There was a trend for men (vs. women), APOE-ε4 carriers (vs. non-carriers) and persons without diabetes (vs. with diabetes) to more likely be autopsy participants ($.05 < p < .10$) than the non-autopsied participants of The 90+ Study. Autopsied and non-autopsied groups did not significantly differ in percentages with reported histories of high cholesterol, stroke, heart disease, or hypertension, or with a diagnosis of dementia at last evaluation.

Of the 212 autopsied patients, 45 (21.2%) had frequent plaques, 28 (13.2%) had tangle stage VI, and 21 (9.9%) had both frequent plaque and tangle stage VI. Of the 212 autopsied participants, 110 had dementia and 102 did not have dementia at last follow-up. Of the 110 dementia cases, 44 were incident cases over the follow-up period. The mean number of years between dementia diagnosis and death was 4.8 and the median was 4.0 years. The mean number of days between last follow-up and death was 156 days and the median was 118 days. The prevalence of dementia increased with level of AD pathology (NIA Reagan criteria) in a dose-response relationship from 30% with no AD pathology to 74% with a high level of AD pathology. Table 2 gives numbers and % of autopsied persons in The 90+ Study with the different pathologies by dementia status. The most frequent pathologies observed other than AD pathology were micro-infarcts and hippocampal sclerosis.

Table 3 presents the results of logistic regression analyses of predictors of dementia prevalence including adjusted odds ratios (OR), confidence intervals (CI) and p-values. Model 1 shows that the significant pathological predictors of dementia included AD pathology, micro-infarcts, hippocampal sclerosis, and white matter disease. Other

pathological variables including amyloid angiopathy, large infarcts, and Lewy Body Disease were not significant when added to the model either individually or when pooled together into an “all other pathology” indicator variable. Gender, education, APOE genotype, and age at death were not significant predictors after accounting for significant brain pathologies. Additionally, whether or not the participant was an original member of the LWCS (versus a recently recruited volunteer) was not a significant predictor. We did not find significant interaction terms between AD pathology and other pathologies although we recognize that our limited samples sizes may limit the statistical power to detect such interactions. Model 2 is a parsimonious reduced model where non-significant variables were removed. The odds ratio from Model 2 associated with low AD pathology was 2.71, for intermediate AD pathology was 3.81, and for high AD pathology was 7.23, relative to no AD pathology. Micro-infarcts (OR=5.19), hippocampal sclerosis (OR=9.95) and white matter disease (OR=5.68) were each significant independent predictors of dementia. We used Model 2 in subsequent calculations.

The dementia prevalence rate (adjusted for education) in the absence of an intervention estimated from equation 2 is 0.55 (95% CI, 0.46–0.66). The dementia prevalence rates (adjusted for education) for the different intervention scenarios estimated from equation 3 are 0.50 (0.41–0.60) for scenario A, 0.43 (0.36, 0.55) for scenario B, 0.42 (0.35, 0.57) for scenario C and 0.27 (0.15, 0.33) for scenario D.

Table 4 shows the percentages of dementia cases that could be prevented by the four intervention scenarios, both unadjusted and adjusted for education levels of the 90+ population in the U.S. We found very small differences between the adjusted and unadjusted percentages and discuss the adjusted rates. Scenario A-modest reduction (decrease only the highest levels of AD pathology to intermediate levels) was associated with only a 9.8% decrease in dementia prevalence (95% CI, 6–16 %). Scenario B-moderate reduction was associated with a 21.9% percentage reduction (95% CI, 17–23%), which was only slightly lower than the 23.7% reduction with scenario C-substantial reduction. Scenario D (complete elimination of AD pathology) was associated with a 50.7% decrease in dementia prevalence among the oldest-old (95% CI, 46–64%).

The population over the age of 90 in the U.S. will grow by a factor of nearly 3.5 between 2015 and 2050. In the absence of new prevention interventions, the prevalence of dementia among the oldest-old is expected to increase from 1.35 million in 2015 to 4.72 million in 2050. Table 4 and Figure 1 show the impact of interventions to reduce AD pathology on prevalent dementia cases in 2015, 2030 and 2050; Ranges on the prevalence estimates are presented in Supplementary Table 1. Scenario A which modestly reduces AD pathologies among persons at the highest levels averts about 0.466 million prevalent dementia cases in 2050. Scenarios B and C which reduce but do not eliminate AD pathology avert approximately 1.035 and 1.119 million dementia cases in 2050, respectively. Scenario D (complete elimination of AD pathology) potentially averts 2.392 million cases of prevalent dementia among the oldest-old in 2050. However, 2.323 million prevalent dementia cases will still remain after successful elimination of all AD pathology.

Discussion

We evaluated the potential impact of interventions that reduce AD pathology on dementia prevalence in the oldest-old. Our calculations incorporated reductions in A β deposits and neurofibrillary tangles in defining reductions of AD pathology. In the absence of any prevention interventions, the prevalence of dementia among the oldest-old in the U.S. will approach 5 million by mid-century which is nearly the current burden of dementia prevalence across all ages [22]. Moderate reductions in AD pathology would reduce dementia prevalence by approximately 22% and avert over 1 million dementia prevalent cases in 2050 among the oldest-old. If interventions completely eliminate AD pathology, then dementia prevalence would be reduced by approximately 50% and avert nearly 2.4 million prevalent dementia cases among the oldest-old in 2050. While elimination of AD pathology significantly reduces the burden of dementia, our results underscore that large numbers of dementia cases would still remain.

Our results refer specifically to the oldest-old and the associations between AD pathology and dementia prevalence may differ at younger ages [23]. We used the AD NIA Reagan criteria for AD pathology and it would be interesting to consider other criteria; for example, some criteria do not consider tangles alone as sufficient for AD pathology [24]. Furthermore, our results depend on critical assumptions. First, as with all clinical-pathological studies, the timing between development of AD pathology and dementia cannot be definitively established and we can only assume that pathology indeed leads to dementia. Second, we assumed that the intervention scenarios change only AD pathology and that other variables that predict dementia risk remain constant. While the assumption is reasonable for some variables such as gender and education, which would not change, it is possible that other brain pathologies (such as hippocampal sclerosis, micro-infarcts and amyloid angiopathy) may change in response to interventions. For example, if anti-A β interventions also reduce (or alternatively increase) levels of amyloid angiopathy, then the numbers of averted dementia cases reported here would be an underestimate (or alternatively an overestimate). Since amyloid angiopathy was not a significant predictor in our logistic regression models of prevalent dementia, violation of the assumption may not have a pronounced effect on our results (at least in the case of amyloid angiopathy).

Third, we assumed that regression models from observational studies can be used to predict accurately the risks of dementia among persons who receive interventions. Although similar assumptions underlie most attributable risk calculations [25, 26], regression models from observational studies may be inaccurate for evaluating the impact of intervention scenarios. Consider for example anti-A β interventions. If the amyloid hypothesis of AD [27, 28] is incorrect and if A β deposition and the resulting AD pathology is not the proximate cause of dementia but only a by-product marker of the disease, then an anti-A β intervention that reduces A β burden and AD pathology but does not target the root cause of the disease would not necessarily decrease risks of dementia. We are assuming that the intervention scenarios are “disease modifying” by which we mean that the interventions have an effect both on the underlying patho-physiology of the disease and on the clinical course [29, 30]. The timing of anti-A β interventions appears to be critical [28, 31, 32]. Anti-A β interventions may be ineffective once persons reach symptomatic stages, but may be successful if given during

pre-symptomatic stages before occurrence of significant brain damage. Interventions may be more successful in preventing pathologies rather than in reversing existing pathologies.

Fourth, our risk model was developed from the autopsied participants in The 90+ Study and may not accurately describe dementia risks of the entire 90+ population in the U.S. While the gender distributions were comparable, significant educational differences were observed. Accordingly, we adjusted for education. It may also be important to account for other differences such as the prevalence of vascular risk factors for dementia. Furthermore, participants in our study were almost exclusively Caucasian compared with 88% of the oldest-old in the entire U.S. As in all pathological studies, our data comes from autopsied participants, which are a selected subset. If certain brain pathologies are particularly lethal then those pathologies may be over-represented in the autopsied sample. Nevertheless, since our study is conducted among the oldest-old, who have very high death rates from many different causes, the impact of that potential source of bias may not be significant.

Fifth, we have not attempted to refine U.S. census projections to account for the fact that the interventions scenarios designed to reduce AD pathology may also increase the numbers of persons surviving to age 90. While census projections do attempt to model the calendar time trends of declining mortality rates, if those models overestimate future mortality rates then our estimates of the absolute numbers of oldest-old with dementia (as shown in Figure 1) will be too low. Furthermore, our calculations of the prevalence rates of dementia assume that the future populations of persons over age 90 would have the same distributions of brain pathologies as we have predicted from The 90+ Study with the various intervention scenarios.

Our estimates are also subject to sources of uncertainty in dementia case definition. Previous work has discussed the uncertainties in dementia prevalence estimates due to variation in case definition [33, 34]. It will also be helpful to replicate our study and to combine with other cohorts of the oldest old. Larger sample size will also increase power in the logistic regression modeling of dementia prevalence to aid in identifying interaction terms and other subtle effects.

We focused on the impact of AD interventions on total dementia prevalence in the oldest-old. It would be useful to extend the work to assess the broader potential public health impact of AD interventions across all ages such as by calculating changes in the total disability adjusted life years associated with different intervention scenarios. In our study, we find that while AD interventions would significantly reduce by half the prevalence of dementia, other clinical and public health interventions need to address the burden associated with other dementing pathologies prevalent among the oldest-old.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the participants and their relatives, testers, and examiners of The 90+ Study, and the staff of the UCI brain repository.

Role of Funding Source:

This research was funded by grants from the National Institutes of Health (R01AG21055, P50AG16573, and R01AG042444). The study sponsor had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Declaration of Interests:

RB serves on a data safety monitoring board for Takeda, Inc.

References

1. United Nations. Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2010 Revision, Volume II: Demographic Profiles. ST/ESA/SER.A/317. 2011 Available at http://www.un.org/en/development/desa/population/publications/trends/population-prospects_2010_revision.shtml.
2. He, W.; Muenchrath, MN. Washington, DC: U.S. Census Bureau, American Community Survey Reports, AC-17, U.S. Government Printing Office; 2011. 90+ in the United States: 2006–2008.
3. James BD, Bennett DA, Boyle PA, Leurgans S, Schneider JA. Dementia from Alzheimer disease and mixed pathologies in the oldest old. JAMA. 2012; 307:1798–1800. [PubMed: 22550192]
4. White L, Small BJ, Petrovitch H, Ross GW, Masaki K, Abbott RD, et al. Recent clinical-pathologic research on the causes of dementia in late life: update from the Honolulu-Asia Aging Study. Journal of geriatric psychiatry and neurology. 2005; 18:224–227. [PubMed: 16306244]
5. Kawas CH, Kim RC, Sonnen JA, Bullain SS, Trieu T, Corrada MM. Multiple pathologies are common and related to dementia in the oldest-old: The 90+ Study. Neurology. 2015; 85:535–542. [PubMed: 26180144]
6. Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. New England Journal of Medicine. 2014; 370:311–321. [PubMed: 24450890]
7. Watt AD, Crespi GA, Down RA, Ascher DB, Gunn A, Perez KA, et al. Do current therapeutic anti-Aβ antibodies for Alzheimer's disease engage the target? Acta neuropathologica. 2014; 127:803–810.
8. Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. PLoS medicine. 2009; 6:e1000180. [PubMed: 19901977]
9. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurology. 2011; 10:819–828. [PubMed: 21775213]
10. Kawas CH. The oldest-old and the 90+ Study. Alzheimer's Dement. 2008; 4:S56–S59. [PubMed: 18632002]
11. Corrada MM, Brookmeyer R, Berlau D, Paganini-Hill A, Kawas CH. Prevalence of dementia after age 90: Results from The 90+ Study. Neurology. 2008; 71:337–343. [PubMed: 18596243]
12. Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest-old: the 90+ study. Annals of neurology. 2010; 67:114–121. [PubMed: 20186856]
13. Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: the 90+ study. Current Alzheimer Research. 2012; 9:709. [PubMed: 22471863]
14. White L, Petrovitch H, Hardman J, Nelson J, Davis DG, Ross G, et al. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann NY Acad Sci. 2002; 977:9–23. [PubMed: 12480729]

15. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg G, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol*. 2007; 62:406–413. [PubMed: 17879383]
16. Hyman BT, Trojanowski JQ. Editorial on consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *Journal of Neuropathology & Experimental Neurology*. 1997; 56:1095–1097. [PubMed: 9329452]
17. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta neuropathologica*. 1991; 82:239–259.
18. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Part II. Standardization of the neuropathological assessment of Alzheimer's disease. *Neurology*. 1991; 41:479–479. [PubMed: 2011243]
19. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathological assessment of Alzheimer's disease: a practical approach. *Acta neuropathologica*. 2012; 123:1–11.
20. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. *Statistics in medicine*. 2000; 19:1141–1164. [PubMed: 10797513]
21. U.S. Census Bureau. [accessed June 15, 2015] Population Division Table 9. Projections by Sex and Age for the United States: 2015 to 2015–2016 (NP2014-T9). /release December 2014. Available at www.census.gov/population/projections/data/national/2014/summarytables.html
22. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology*. 2007; 29:125–132. [PubMed: 17975326]
23. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, Neuropathology and Dementia. *N Eng J Med*. 2009; 360:2302–2309.
24. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta neuropathologica*. 2014; 128:755–766.
25. Benichou J. Biostatistics and Epidemiology: measuring the risk attributable to an environmental or genetic factor. *C.R. Biologies*. 2007; 330:281–298. [PubMed: 17502285]
26. Walter SD. The estimation and interpretation of attributable risk in health research. *Biometrics*. 1976; 32:829–849. [PubMed: 1009228]
27. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002; 297:353–356. [PubMed: 12130773]
28. Jack CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *The Lancet Neurology*. 2010; 9:119–128. [PubMed: 20083042]
29. Cummings JL. Defining and labeling disease modifying treatments for Alzheimer's disease. *Alzheimer's & Dementia*. 2009; 5:406–418.
30. Mani RB. The evaluation of disease modifying therapies in Alzheimer's disease: a regulatory viewpoint. *Stat Med*. 2004; 23:305–314. [PubMed: 14716731]
31. Schneider LS. Quantifying an amyloid β model for Alzheimer's disease. *The Lancet Neurology*. 2013; 12:327–328. [PubMed: 23477990]
32. Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *The Lancet Neurology*. 2013; 12:357–367. [PubMed: 23477989]
33. Corrada M, Brookmeyer R, Kawas C. Sources of Variability in Age Specific Prevalence Rates of Alzheimer's Disease, *International Journal of Epidemiology*. 1995; 24:1000–1005. [PubMed: 8557432]
34. Brookmeyer R, Evans D, Hebert L, Langa K, Heeringa S, Plassman B, Kukull W. National Estimates of the Prevalence of Alzheimer's disease in the United States. *Alzheimer's and Dementia*. 2011; 7:1–13.

Research in Context

Systematic Review

The authors searched PubMed for articles addressing dementia in the oldest-old. No study has quantified the impact of reducing Alzheimer's disease (AD) pathology on dementia prevalence among this group.

Interpretation

The prevalence of dementia among the oldest-old in the U.S. will approach 5 million by mid-century which is nearly the current burden of dementia across all ages. Moderate reductions in AD pathology would reduce dementia prevalence by 22% averting 1 million dementia prevalent cases in the U.S. in 2050. Complete elimination of AD pathology would reduce dementia prevalence among the oldest-old by 50% averting 2.4 million prevalent dementia cases in the U.S. in 2050.

Future Directions

While elimination of AD pathology would significantly reduce the dementia burden, our results underscore that large numbers of dementia cases would still remain. Interventions are needed to address the burden associated with dementias other than AD prevalent among the oldest-old.

Figure 1.
U.S. prevalence of dementia among persons aged 90 and over in calendar years 2015, 2030 and 2050 with no intervention and with four intervention scenarios

Table 1

Percentages of persons with each attribute among autopsied participants in the 90+ Study, persons in The 90+ Study who died without autopsy and U.S population of persons aged 90 and older [2]

Attribute	90+ Study Autopsied (%)	90+ Study Not Autopsied (%)	90+ in the U.S. [2] (%)
College education	50	38	14
Women	69	75	74
White race	99	99	88
Widowed	75	79	75
Married	15	12	16
Reported history of diabetes	5	9	-
Reported history of high cholesterol	27	29	-
Reported history of heart disease	56	56	-
Reported history of stroke	17	17	-
Reported history of hypertension	57	59	-
Reported history of diabetes	5	8	-
APOE-e4 carrier	23	17	-
Dementia	52	54	-

Table 2

Numbers (%) of autopsied persons in The 90+ Study with the different pathologies stratified by dementia status

Pathology	Dementia (N=110) N (%)	No Dementia (N=102) N (%)
AD Pathology		
No	16 (15)	38 (37)
Low	29 (26)	27 (26)
Intermediate	36 (33)	27 (26)
High	29 (26)	10 (10)
Microinfarcts (3 or more)	29 (26)	7 (7)
Hippocampal Sclerosis	31 (28)	4 (4)
White Matter Disease	14 (13)	2 (2)
Cerebral Amyloid Angiopathy (moderate/severe)	17 (15)	9 (9)
Lacunes or Large infarcts (2 or more)	9 (8)	3 (3)
Lewy Body Disease	7 (6)	1 (1)
Other Pathologies	1 (1)	1 (1)

Table 3

Logistic regression models for dementia at last follow-up based on 212 autopsied participants of The 90+ Cohort Study; odds ratios with 95% confidence intervals and p-values

	Model 1 ^a			Model 2		
	OR	95% CI	p	OR	95% CI	p
AD Pathology						
None	1.0			1.0		
Low	2.56	(1.04, 6.52)	.042	2.71	(1.12, 6.8)	.029
Intermediate	3.57	(1.49, 8.97)	.005	3.81	(1.62, 9.44)	.003
High	6.75	(2.45, 20.00)	<.001	7.23	(2.65, 21.24)	<.001
Micro-infarcts						
<3	1.0			1.0		
3+	4.94	(1.90, 14.36)	.002	5.19	(2.04, 14.9)	.001
Hippocampal sclerosis						
No	1.0			1.0		
Yes	9.65	(3.31, 36.00)	<.001	9.95	(3.47, 36.61)	<.001
White matter disease						
No	1.0			1.0		
Yes	5.86	(1.33, 41.5)	.035	5.68	(1.31, 39.96)	.037
Any other pathology						
No	1.0					
Yes	1.48	(0.64, 3.45)	.356			
Original LW cohort						
Yes	1.0					
No	0.76	(0.266, 2.07)	.593			
Gender						
Male	1.0					
Female	1.18	(0.58, 2.40)	.641			

^aNot shown is another model in which each specific individual pathology (amyloid angiopathy, large infarcts, Lewy Body Disease, and other pathologies) was included as a separate indicator variable (instead of grouping them together in the single variable "any other pathology" as in Model 1. However, none of these pathologies was individually statistically significant ($p > .15$). In addition, age at death, education (college), APOE2 carrier and APOE4 carrier were included (not shown) but were non-significant in Model 1 ($p > .20$). The mean number of days between death and last follow-up was 156 days (median=118 days).

Table 4

Percentages of dementia cases prevented among the oldest-old by interventions that reduce levels of Alzheimer's disease pathology (high, intermediate and low) with 95% confidence intervals (CI). Unadjusted and adjusted for differences in educational levels (college education) between The 90+ Study and the U.S. population over age 90.

<u>Intervention Scenario</u>	Unadjusted % prevented (95% CI)	Adjusted % prevented (95% CI)
A: Modest Reduction (High → Intermediate)	7.9 (5, 12)	9.8 (6, 16)
B: Moderate Reduction (High → Intermediate, & Intermediate → Low)	21.8 (17, 23)	21.9 (17, 23)
C: Significant Reduction (High & Intermediate → Low)	23.3 (13, 27)	23.7 (13, 28)
D: Complete Elimination (High, Intermediate & Low → None)	49.0 (44, 64)	50.7 (46, 64)