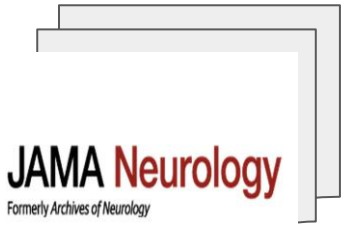
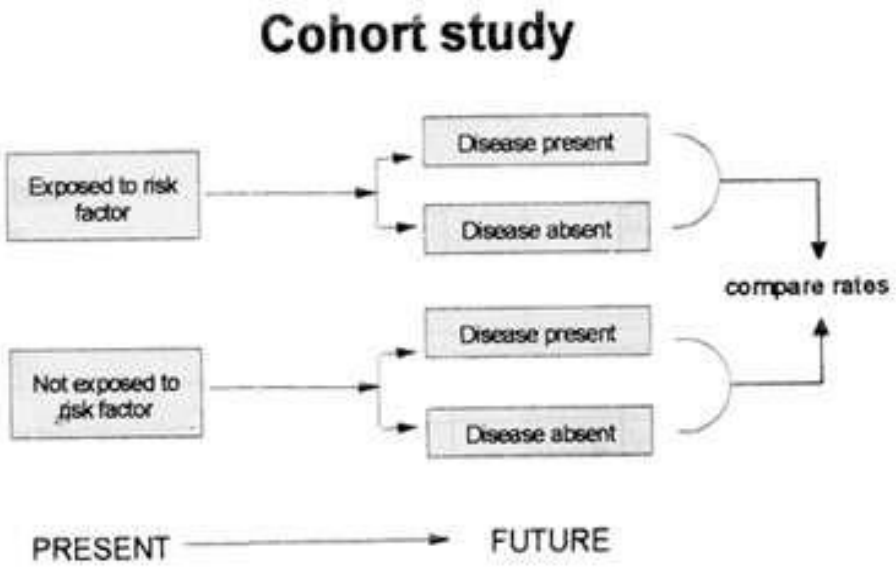
Dementia and Alzheimer Disease Incidence: A Prospective Cohort Study, Kukull, Walter A et al.

Reviewed by Kholoud Mohamed



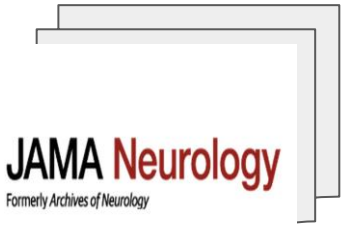
The Data


Cohort study
Exposed to risk factor
Disease present
Disease absent
Not exposed to risk factor
Disease present
Disease absent
compare rates
PRESENT
FUTURE

Introduction

- Dementia and Alzheimer disease incidence: a prospective cohort study, was sourced from the Archives of Neurology/ The Journal of the American Medical Association vol. 59

- Authored by: Walter A Kukull , Roger Higdon, James D Bowen, Wayne C McCormick, Linda Teri, Gerard D Schellenberg, Gerald van Belle, Lance Jolley, Eric B Larson

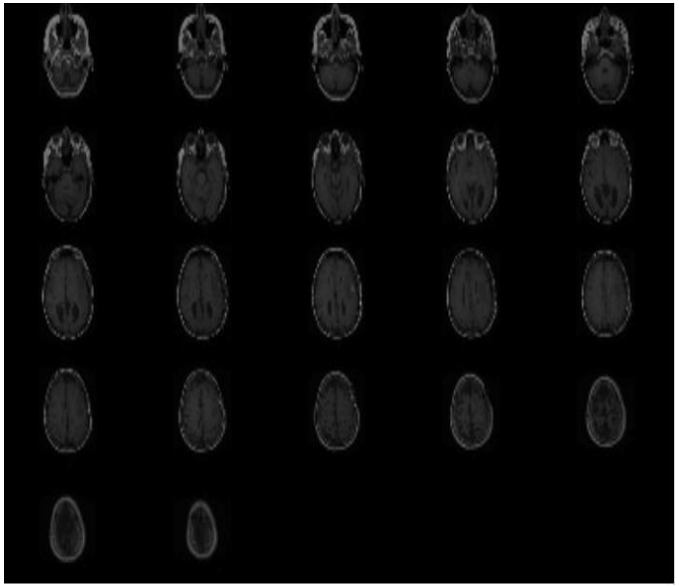


Objective of Study

- **Prospective Cohort study - 1994**
  followed unaffected individuals from the base population of seattle members of Group Health Cooperative (GHC) to observe the onset of dementia and Alzheimer disease (AD). subjects are test in followed up interviews every 2 yrs.

- Obtain age-specific incidence rates estimates for Dementia and Alzheimer's Disease using person-years approach with Poisson distribution confidence intervals.

- Identify factors associated with disease onset using Cox Regression Model analysis; estimate the association of the following factors: sex,education level, race, apolopoprotein E genotype.



Background

Dementia: Dementia is not a specific disease but is rather a general term for the impaired ability to remember, think, or make decisions that interferes with doing everyday activities.

Alzheimer's Disease: Alzheimer’s Disease is the most common type of dementia, it is a chronic neurodegenerative disease that leads to dementia symptoms which worsen gradually over time.

Apolipoprotein E genotype: A genetic risk factor for dementia and Alzheimer's disease

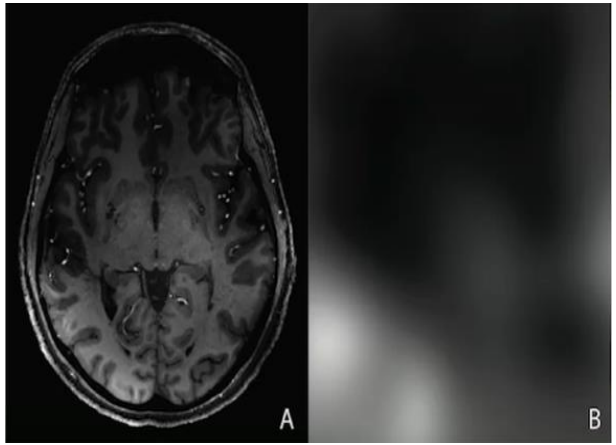
Incidence: Rate of occurrence of a disease

Experimental Methods: Design

- Base population for the study was the seattle members of Group Health Cooperative (GHC) Age 65 or older.
- Cohort enrollment began in 1994 and 1996
- A simple random sample of 6,782 was drawn from the base population.
- Medical records were reviewed existing cases of dementia were excluded.
- Subjects were administered a Cognitive Ability Screening Instrument Test (CASI) with Cut off value of 86/100. Measures cognitive decline in elderly.
- CASI sensitivity = 96.5%
- CASI specificity = 92%
- Subjects who scored less than 80 at baseline were referred for a complete clinical diagnostic evaluation by study physicians, laboratory testing and imaging.
- Subjects who scored higher than 86% on the Cognitive ability test were included in the cohort study.
- Scores between 80 - 86 were considered gray area, subjects were retested within 2 month.

Experimental Methods: Design

- 2,581 individuals were enrolled at start of study.
- Blood samples were collected from consenting subjects for Apolipoprotein E genotyping.
- Screened cohort members every 2 years for potential new cases
- 2,356 had at least one follow up examination
- Subjects who did not meet the criteria for dementia/ AD were continued to be followed
- Subjects who met the criteria for dementia/ AD during those follow ups were considered incidence cases.



Evaluations, Graphs, and Summary Statistics

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

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

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

Statistical Analysis: Part I

*Assumptions:
λ is constant over time

The probability of one event in a short interval is proportional to the interval.

Independence

Age-specific incidence rates estimates for Dementia and Alzheimer's Disease using person- years approach with Poisson distribution confidence intervals per 1,000 person yrs

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

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

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

R code for Incidence rates estimates for each age Group

```
library(epitools)
#for age 65-69
5/1076 *1000
pois.approx(5, pt = 1076*1000, conf.level = 0.95)
# for Age70-74
27/3203 *1000
pois.approx(27, pt = 3203*1000, conf.level = 0.95)
# for Age75-79
37/3082 *1000
pois.approx(37, pt = 3082*1000, conf.level = 0.95)
# for Age80-84
73/2039 *1000
pois.approx(73, pt = 2039*1000, conf.level = 0.95)
# for age Age85-89
49/906 *1000
pois.approx(49, pt = 906*1000, conf.level = 0.95)
# fo age 90 above
24/285 *1000
pois.approx(24, pt = 285*1000, conf.level = 0.95)
```

R code output for Incidence rates estimates for each age Group

```
[1] 4.64684
[1] 8.429597
[1] 12.00519
[1] 35.80186
[1] 54.08389
[1] 84.21053
```

All Dementia Cases	
No. of Cases	Rate, % (95% CI)
5	4.65 (2.0-10.8)
27	8.43 (5.8-12.3)
37	12.01 (8.7-16.6)
73	35.80 (28.5-45.0)
49	54.05 (40.9-71.5)
24	84.19 (56.5-125.6)

Results I

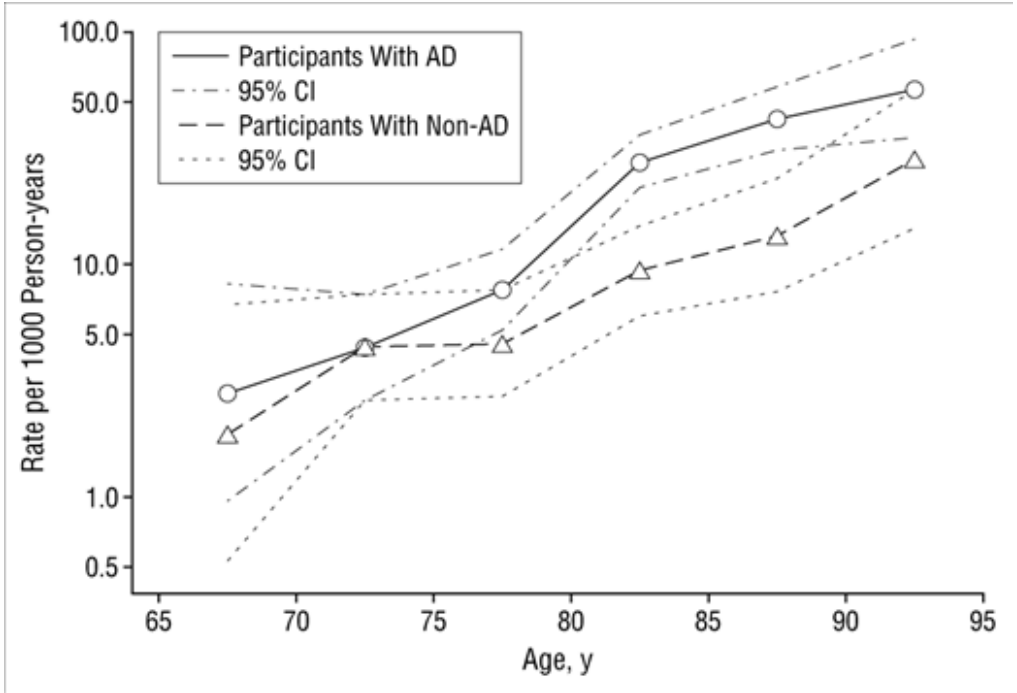
- Of 2,356 subjects 415 subjects screened positive for dementia. (by CASI metric)
- After clinical evaluation of 415 subjects 215 subjects were diagnosed as having dementia. And 146 diagnosed as having probable AD by *Diagnostic and Statistical Manual of Mental Disorders criteria*
- 5 subjects diagnosed as having possible AD by *The National Institute of Neurological Disorders and Stroke-Alzheimer's Disease Related Disorders Association criteria*
- Remaining 69 cases non-AD dementia

Conclusion I

- Incidence rates for AD and dementia increases across age groups
- Dementia rates increase from 4.65 (65-69) to 84.1 per 1000 person-years for (Age group, > 90)
- AD rates increase from 2.8 (65-69) to 56.1 per 1000 person-years for(Age group, > 90)

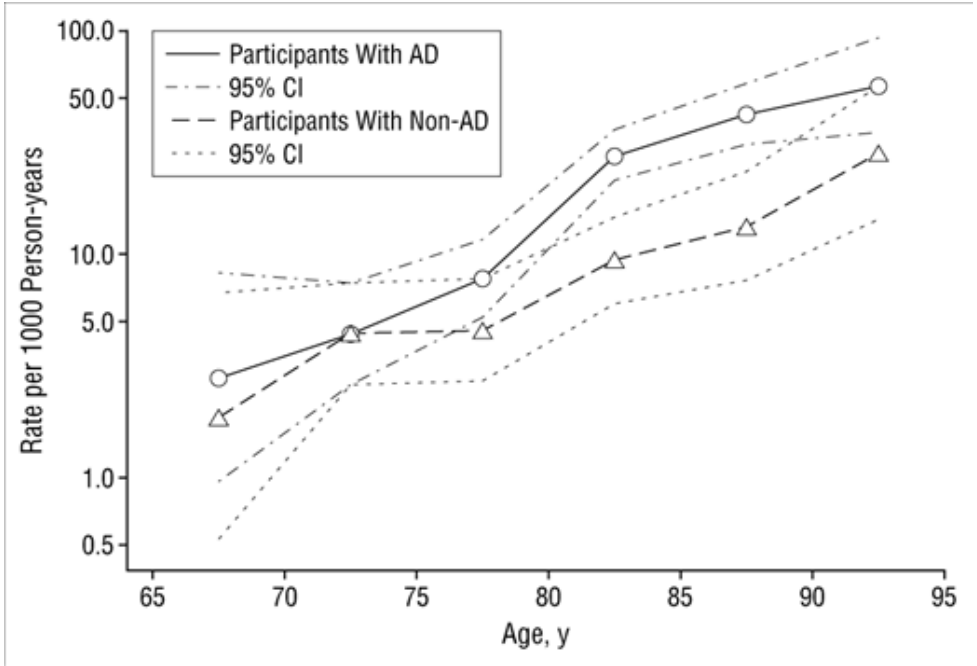
Conclusion I

The greatest number of AD cases occurred between the ages of 80 and 89 years. There is a trend of increasing age-specific incidence rates shown below.



Conclusion I

The rates of dementia and AD increase 3.5-fold from the (75-79) age group to the (80-84) age group.



Statistical Analysis Part I I : Cox Proportional Hazards Regression Model

- Cox proportional hazards regression model is a regression model commonly used in medical research for investigating the association between the survival time of patients and one or more predictor variables.

- Survival analysis corresponds to a set of statistical approaches used to investigate the time it takes for an event of interest to occur. (**onset of dementia**)

- Here Cox model allows the examination of how specific factors influence the rate of a developing dementia/AD.

- Outcome is Event time which is subject to Right Censor
  - ≥1 (event(s) happened) or 0 (no event at the end of the study, i.e. "**right censored**").

- The hazard, denoted by h(t), is the probability that an individual who is under observation at a time t has an event at that time.

Statistical Analysis Part I I : Cox Proportional Hazards Regression Model

- The Cox model is expressed by the hazard function h(t). The hazard function can be interpreted as the risk of dying at time t. It can be estimated as follow:

$$h(t) = h_0(t) \times exp(b_1 x_1 + b_2 x_2 + \ldots + b_p x_p)$$

- t represents the survival time
- **h(t)** is the hazard function determined by a set of p covariates ($\mathbf{x_1}$,$\mathbf{x_2}$,...,$\mathbf{x_p}$)
- the coefficients ($\mathbf{b_1}$,$\mathbf{b_2}$,...,$\mathbf{b_p}$) measure the impact (i.e., the effect size) of covariates.
- the term $\mathbf{h_0}$ is called the baseline hazard. It corresponds to the value of the hazard if all the $\mathbf{x_i}$ are equal to zero (the quantity exp(0) equals 1).
- The 't' in h(t) reminds us that the hazard may vary over time.
- The quantities $\mathbf{exp(b_i)}$ are called hazard ratios (HR)

Statistical Analysis Part I I : Cox proportional hazards regression model

- Hazard Ratio

  HR = 1: No effect
  HR < 1: Reduction in the hazard
  HR > 1: Increase in Hazard

- Assumptions

  The hazard for any individual is a fixed proportion of the hazard for any other individual.
  (i.e., *proportional* hazards)

  The relationship between the log hazard and each covariate is linear,

Statistical Analysis Part I I : Cox Proportional Hazards Regression Model

- Used to estimate the association of the following factors:
  - Sex
  - Education level (<12yrs, 12-15 yrs, <15 yrs)
  - Race
  - Apolipoprotein E genotype.
- The regression model used age as time scale
- Risk factors are reported as RRs (ratios of incidence rates)

Statistical Analysis Part I I : Cox proportional hazards regression model Results

- Sex showed no significance association with AD or Dementia
  - However, RR indicated that Non- AD dementia was less frequent in women than in men.
- Race showed no discernible effect.
- Association between Apolipoprotein E (APOE) genotype and dementia
  - Risk of dementia increased in subjects with single APOE ϵ4 Allele and 2 APOE ϵ4 allele.
  - Increased risk among homozygous subjects
- Higher education level is associated with decreased risk of both AD and Non-AD dementia

- There is evidence of an interaction between age and APOE ϵ4 in the incidence of dementia and AD. Subjects with a single copy of APOE ϵ4 experienced roughly a 3-fold increased risk in successive 5-year age groups (70-85 years old) but showed an RR less than 1 in the oldest age group (90+ years old).
- Baseline CASI score was also strongly associated with dementia and with educational level.

Cox proportional hazards regression model Results

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

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

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

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

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

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

Part III : Multiple Imputation for handling missing data

- 195 failed CASI test, diagnosed as not -demented
- 32 failed CASI test, no definitive diagnosis - participants died
- 430 subjects died
- 180 were lost to follow up

Multiple Imputation was carried out to adjust for the **32 subjects** who failed CASI test but died before receiving a definitive clinical diagnosis.

Multiple imputation fills in missing data with multiple values and runs regression analysis with the completed data set in all different entries then averages the final results for a unbiased estimate.

Used known proportion of subjects who were diagnosed as having dementia after failing CASI test as a substitute.

53% of those who failed CASI test were diagnosed as having dementia

69% were diagnosed as having probable AD

Multiple Imputation

- Multiple Imputation had negligible effect on the estimation of RR or inference on risk factors.

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

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

*CI indicates confidence interval; AD, Alzheimer disease.

Limitations with the study

- Since Alzheimer's disease and Dementia are rare, need to ensure lower false negative cases during CASI testing. Increase specificity.
- Not many extensive follow up
- Allow for a uniform/ standard case detection procedure and diagnostic.
- CASI scores a consequence of education or a proxy for dementia?
- Risk factor association could be biased due to the excessive subjects lost.

Appendix

Kukull, Walter A et al. “Dementia and Alzheimer disease incidence: a prospective cohort study.” Archives of neurology vol. 59,11 (2002): 1737-46. doi:10.1001/archneur.59.11.1737