**Trajectories of cognitive function in dementia-free subjects: Radiation
Effects Research Foundation Adult Health Study**

Michiko Yamada, MD, PhD,¹ Reid D. Landes, PhD,¹ Yasuyo Mimori, MD, PhD,²
Yoshito Nagano, MD, PhD,³ Hideo Sasaki, MD, PhD⁴

¹Departments of Clinical Studies and Statistics, Radiation Effects Research
Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732-0815, Japan
(yamada@rerf.or.jp) (rdlandes@rerf.or.jp),

²Department of Physical Therapy, Hiroshima International University, 555-36
Gakuendai, Kurose, Higashi-Hiroshima, 739-2695, Japan
(y-mimori@hs.hirokoku-u.ac.jp)

³Department of Clinical Neuroscience and Therapeutics, Hiroshima University,
1-2-3, Kasumi, Minami-ku, Hiroshima, 734-0037, Japan
(yachtz@hiroshima-u.ac.jp)

⁴Department of Nutritional Sciences, Yasuda Women's University, 6-13-1,
Yasuhigashi, Asaminami-ku, Hiroshima, 731-0153, Japan
(sasaki-h@yasuda-u.ac.jp)

Corresponding author:

Michiko Yamada, MD

Department of Clinical Studies, Radiation Effects Research Foundation

5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan

Telephone: +81-82-261-3131 Fax: +81-82-263-7279 e-mail: yamada@rerf.or.jp

Abbreviated title: Cognitive decline of non-demented subjects

Key words: cognition, cohort study, non-demented subjects, aging, education,
gender

ABSTRACT

Objectives: To investigate associations between age, sex, education, and birth cohort and global cognitive decline among a population that would most likely not progress to dementia.

Methods: 1,538 dementia-free subjects aged 60 to 80 in 1992 were followed up through 2011 without dementia occurrence. We assessed cognitive function using the Cognitive Ability Screening Instrument (CASI). Using stepwise-like model selection procedure, we built mixed-effects models for initial cognition and longitudinal cognition.

Results: Initial CASI scores for younger age and more years of formal education were higher than those for older and less education. Sex did not show a significant effect. In the longitudinal analysis, cognitive decline became more rapid with increasing age. Sex and education did not modify the degree of deterioration with age. CASI scores were higher for younger cohorts and men due to differences in education levels.

Conclusion: Among dementia-free subjects, age is an important predictor of cognitive function level and cognitive decline. Education level affects cognitive function level, but did not affect cognitive decline. The results have implications not only for elucidation of the aging process, but also for reference in dementia screening.

Key words: cognition, cohort study, non-demented subjects, aging, education, gender

INTRODUCTION

Trajectories of cognitive function in later adult life are heterogeneous.¹ Among demented subjects, accelerated decline in cognitive function precedes the onset of dementia by several years,² but little is known about trajectories of cognitive function as an aging phenomenon in the absence of dementia. Trajectories of cognitive function in dementia-free subjects have implications not only for elucidation of the aging process, but also for dementia screening reference values. Several large, long-term studies have estimated actual cognitive decline in aging populations, and most longitudinal studies on cognitive decline include subjects who were demented at baseline.³ Cognitive function reflects prior cognitive ability and the degree of deterioration.⁴ In a study that divided subjects at baseline into categories of no cognitive impairment, mild cognitive impairment, and dementia, those with no cognitive impairment had the slowest rates of cognitive decline during follow-up.⁵ In the Paquid study, the Mini-Mental State Examination score in a large sample of non-demented community residents in France declined very little in 5 years of follow-up.⁶ In a study of 3 subgroups of people aged ≥ 65 years - those with Alzheimer disease (AD) at baseline, those who developed AD during the study, and those who remained unaffected - unaffected persons showed little cognitive decline during a 3.5 year follow-up.⁷

Many studies of relationships between demographic factors such as sex, age, education, and birth cohort to dementia/AD^{8,9} or cognitive decline¹⁰ among aged populations have yielded mixed results. In this study, we evaluate how sex, age, education, and birth cohort affect cognitive aging among a population that would most likely represent those people who would not progress to dementia.

METHODS

Study population

Since 1958, the Adult Health Study of the Radiation Effects Research Foundation (RERF), consisting of atomic bomb survivors and their age- and sex-matched non-exposed controls, has conducted biennial examinations to investigate the health effects of exposure to ionizing radiation from the atomic bombings. In April 1992 in Hiroshima, we initiated the study of cognitive function and dementia incidence for AHS participants who at that time were ≥ 60 years old (those ≥ 13 years old at the atomic bomb) with a pilot study conducted from April to September 1992.¹¹ The RERF institutional review boards (Research Protocol Review Committee and Human Investigation Committee) reviewed and approved this study, and all participants provided informed consent.

Assessment of cognitive function

We assessed cognitive function using the Cognitive Ability Screening Instrument (CASI), which consists of items identical or similar to those used in the Mini-Mental State Examination, the Modified Mini-Mental State Examination, and the Hasegawa Dementia Screening Scale.¹² The score range of the CASI is 0 to 100, and typical administration time is 15-20 min. We used the full CASI version at baseline.

We selected domains showing large aging effects based on previous CASI analyses¹³ and designated the instruments as CASI-short (CASI-s). The CASI-s tests language (repeat 3 words, name 5 objects), short-term memory (recall 3

words, recall 5 objects), recall digits backward, serial subtraction, orientation (age, time, place), and verbal fluency of animal names. The CASI-s score range is 0 to 49. We used CASI-s at follow-up examinations to reduce the total time required for the health checkup. Using the CASI-s items from baseline and follow-up CASI-s scores, we assessed the trajectories of cognitive function.

Educational attainment

Educational attainment, expressed as years of schooling, was asked at baseline CASI examination. Proportions of participants having ≤ 5 or ≤ 6 years of schooling were 0.5% or 6.6%. Proportions of those with ≥ 13 or ≥ 17 years of schooling were 6.2% or 0.4%.

Radiation dose

Allowance for the effect of radiation dose was necessary because the study population included exposed atomic bomb survivors. We used individual estimates of weighted absorbed brain dose, taking into account survival location and shielding by buildings and terrain, based on the RERF 2002 dosimetry system.¹⁴ In this study, 40.8% of the subjects were unexposed (dose < 5 mGy).

Study subjects without dementia

We used the 2-phase procedure (screening and detail check) established in a US-Japan cross-national study,¹⁵ to determine whether the participants had dementia.¹¹ The consensus panel evaluated the presence of dementia and subtypes using information of cognitive test, questionnaire survey by caregivers

including the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),¹⁶ reported ADL, and Clinical Dementia Rating (CDR)¹⁷ and diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) and other diagnostic criteria.¹⁸ We classified 121 dementia prevalent cases and 441 dementia incident cases and excluded all CASI observations of these cases from the analysis. We also excluded 20 participants for whom we had difficulty differentiating between mild cognitive impairment (MCI) and very mild dementia at the last examination. From April 1992 up to July 2011, we made 6,457 CASI observations of 1,955 dementia-free subjects. Of those, we excluded 249 subjects (817 observations) whose education and radiation data were missing. For 31 participants who had two CASI observations taken within 6 months, we excluded the latter observation. We also excluded 168 subjects (330 observations) whose baseline age was >80 years, and excluded 71 observations from participants who were >90 at the time of observation. After applying the predetermined exclusion criteria, the data contained 1,538 subjects supplying 5,208 observations. Among 1,538 subjects, the 1,161 subjects who supplied 2 or more CASI measures contributed a total of 10,166 person-years. After noting the strong influence on our statistical models by 16 observations from 7 participants (5 females) having 5 years or less of education, we exclude these 16 observations from our main analyses. Hence our final data contained 1,531 subjects supplying 5,192 observations.

Statistical analysis

To arrive at a statistical description of how global cognition changes in

dementia-free elders as they age, we started by building a model for the initial measure of cognition. Using a stepwise model-building algorithm for which the entering p -value was 0.50 and the exiting p -value 0.10, we entered the following variables: female (F), attained age (A), years of education (E), and radiation dose (R), their quadratic terms, and all their 2-way interactions. From attained age, we subtracted 60 (the youngest age of the participants at study-start), and from education, we subtracted 10 (the median education level of all participants in the model).

When building the longitudinal model, we started with the model for initial CASI-s. Since age increases over time, the age terms in the initial CASI model (A and A^2) became longitudinal covariates. To account for the repeated CASI scores coming from the same individual over time, we allowed the intercept and slope on A to depend on the individual. This is sometimes called a random coefficients regression. In the longitudinal model, we added the linear, quadratic, and interaction terms from among A , E , F , and R . We chose a final model in which the terms had $p < .05$, while allowing the possibility for a non-significant linear term to be included when an associated quadratic or interaction term was significant, e.g., including a non-significant A term when A^2 was significant.

Excluding 16 observations from 7 participants who had not completed elementary school (≤ 5 years of education) impacted inference on education effects. (Specifically, an interaction of education with gender was significant.) Inference on other effects not involving education changed little; and other analyses confirmed the undue influence of these observations from those with extremely low education. For these reasons, we report the results from the data

set excluding observations from these extremely low education participants as the main results.

For the primary analyses, we used SAS/STAT software, Version 9.3, SAS System for Windows (SAS Institute Inc., Cary, NC, USA), with stepwise regressions performed in the REG procedure, and longitudinal models fitted in the MIXED procedure. We used the Kenward-Roger method to estimate error degrees of freedom in the longitudinal models, as recommended by Littell et al.¹⁹

RESULTS

Table 1 summarizes the participant characteristics by sex. Of the 1,531 participants, 1,054 (68.8%) were women; they were older, had less formal education and lower initial CASI-s scores than the men. The number of exams, length of follow-up, and radiation dose did not statistically differ between men and women.

Table 2 shows the estimates and 95% CIs for effects in the initial model based on the initial observations of the participants and in the longitudinal models based on 5,192 observations from all participants. From the stepwise regression of the initial CASI-s, we selected E , E^2 , and A^2 ($p < .001$ for all three). We also included the (non-significant) linear term A since we had selected A^2 . Radiation and its quadratic and interaction terms did not show significant effects (all $p > .50$). In the longitudinal models, we started by entering the four terms selected in the initial model. We then added, one at a time, sex, radiation, and interactions of each of these with education and with age; none of the terms we added after the initial four were significant (all $p > .08$). In particular there was no evidence

that age effects were modified by another factor, nor was there evidence that radiation impacted cognition. The initial CASI-s scores for those younger in age and with more education were higher than scores from older, less educated participants. Figure 1, a scatter diagram, shows the estimated CASI-s curves as a function of age based on the initial and longitudinal models. The quadratic effects of age (A^2) in the initial and longitudinal models were significant, and the estimated coefficient of A^2 in the initial model was larger than that in the longitudinal model. The steeper slopes on the older ages reflect the acceleration of cognitive decline with age. Figure 2 shows the estimated education effect. Figure 3 shows the estimated CASI-s curves for 5-year-span birth cohorts of men and women at their respective mean education levels to depict actual CASI-s score trend. Younger cohorts had progressively higher CASI-s scores at any given age; this owing to more years of education in younger cohorts. The difference in the estimated cognitive function level between men and women was due to the higher education level in men, and cognitive decline did not differ by sex.

Originally, we included 7 participants who had very low education (≤ 5 years), making up 0.5% of the total number of participants. The data from these participants strongly influenced inferences on education effects. There was a significant interaction between sex and education in the initial and longitudinal models (both $p < .04$). Such an interaction means that differences between men and women depended on the amount of education: specifically, ≤ 9 years of education, men were estimated to fare better than women of the same age, for ≥ 10 years of education, women were estimated to fare better than men of the

1 same age. In the analysis including these participants with very low education,
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3 no significant quadratic effect of education was found in the initial model ($p>.50$).
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5 When excluding these 7 participants, the sex-education interaction was clearly
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7 not significant ($p>.26$ for both initial and longitudinal models).
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10 11 12 13 **DISCUSSION**

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15 Our analyses of initial and longitudinal cognitive function among dementia-free
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17 elders in the AHS revealed that the rate of cognitive decline speeds up with age.
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19 These findings agree with a cross-sectional study of the same cohort²⁰ and
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21 another cross-sectional study that included both demented and dementia-free
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23 subjects.²¹ Additionally, among previous longitudinal analyses of a large
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25 population that included both types of subjects, one reported that the older group
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27 showed significantly faster cognitive decline than the younger group,²² and
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29 another reported that cognitive decline accelerated with age.²³ Although several
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31 long-term follow-up studies on cognitive function have been conducted,²⁴ few
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33 studies have focused on a population that would most likely not progress to
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35 dementia. A longitudinal study of dementia-free subjects with a follow-up period
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37 of 5 years showed a larger cognitive decline among older subjects,⁶ while one
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39 with a follow-up period of 3.5 years did not.⁷ Our results support the likelihood
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41 that among dementia-free elders, cognitive decline accelerates with age.
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49 When we compare the nonlinear effect of age between the initial and
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51 longitudinal models, the effect was notably stronger in the initial model. Perhaps
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53 the difference is akin to those reported in the Rotterdam Study and the Leiden 85
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55 plus Study.²¹ They found that age-related declines were greater when using a
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1 cross-sectional cognitive test compared to restricting their sample to those with
2 complete follow-up.²¹ Further, they found longitudinal decline with various types
3 of follow-up using linear mixed models similar to analyses including those with a
4 complete follow-up.²¹ Excluding those who supplied only one CASI score and
5 re-fitting our chosen models, the age effects in the re-fitting models differed very
6 little from the estimates for the longitudinal model, provided in Table 2 (data not
7 shown).

8 In this study, inclusion of the CASI of MCI subjects may have influenced the
9 results by contributing to age-associated cognitive decline, especially among old
10 aged subjects. The incidence of MCI increases with age,²⁵ cognitive decline is
11 steeper among subjects who develop MCI during follow-up than among
12 non-demented and non-MCI subjects,² and significant cognitive decline
13 accompanying MCI is found even in individuals in their 60s.²⁶ We did not exclude
14 MCI subjects due to the following difficulties. The concept of MCI developed by
15 Petersen et al. came at the end of the 1990s.²⁷ Diagnostic criteria of MCI was
16 not defined at baseline and underwent revisions during follow-up.²² Moreover,
17 sometimes MCI is sustained, sometimes it progresses to dementia, and
18 sometimes normalcy returns.²⁸

19 Reported differences between the sexes from both cross-sectional and
20 longitudinal studies are controversial. Karlamangla et al. reported women had
21 higher scores than men at initial assessment and faster decline in the Study of
22 Assets and Health Dynamics Among the Oldest Old.²² Although sex differences
23 disappeared after adjusting for education and age in initial level and trend in the
24 Religious Orders Study²⁹ and the Paquid study,⁶ sex differences in cognitive

1 decline were found in the Betula project in Sweden after adjustment for
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3 education.³⁰ We found no evidence that men and women differed, nor that sex
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5 modified age or education effects in our main analyses. Though originally, we
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7 found a significant interaction effect between sex and education when including
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9 the 7 participants who had 5 or less years of schooling. Excluding these
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11 participants, however, resulted in a substantial attenuation in the sex-education
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13 effect. Whether these low-education participants were in or out, the main effect
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15 of sex was not significant. For men and women of the same age, men tended to
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17 have higher actual CASI-s score than women, this owing to higher levels of
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19 education in men. Sex differences in raw cognition level might be modified by
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21 sex differences in other covariates, such as education, income, occupation, and
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23 longevity.
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30 Among dementia-free AHS subjects with relatively low proportions of very low
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32 or very high levels education, those with a higher education level had higher
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34 cognition at initial examination. A similar educational effect on cognition has
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36 been reported in cross-sectional studies^{20,31} and at the initial examination in
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38 longitudinal studies,^{6,23} with and without demented subjects. Whether and how
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40 education affects cognitive aging when examined in longitudinal studies,
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42 however, has been inconsistent.^{10,23} The effect in longitudinal analysis is
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44 weak³² or not significant in studies including dementia subjects^{22,33} and
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46 significant albeit a small association in a study not including demented subjects.⁶
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50 One study including dementia subjects with 12-years follow-up indicated that
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52 high levels of education led to slightly increased cognition during earlier years of
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54 follow-up but slightly decreased cognition in later years when compared to low
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1 levels of education.²³ That is, increasing levels of education robustly boosts
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3 cognitive function by a certain amount, but at best, education has been found to
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5 have no more than subtle effects in one's ability to hold on to cognitive function.
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8 Our study found no education modification of age effects on cognitive decline
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10 over a long follow-up period. This lack of an education effect follows Wilson's
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12 prediction that the studies best equipped to assess changes in cognitive function,
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14 by virtue of measuring it more often during a longer period of time, were the least
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16 likely to find an association with education.²³
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20 Cohort differences of cognitive decline are recognized, but the findings of
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22 several recent longitudinal studies were mixed.³⁴ In the Paquid study, with 5
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24 years follow-up, the aging effect in the cross-sectional study was larger than in
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26 the longitudinal study, which may be explained by a cohort effect, but the
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28 follow-up was too short to examine it.⁶ The Seattle Longitudinal Study reported
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30 favored cognition in the later-born cohort (1914-1948 vs. 1886-1913).^{34,35}
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33 Although we did not include birth cohort indicator as a variable in the model, we
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35 depicted cognitive decline by birth cohort by substituting average education level
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37 for each cohort in Figure 3; the younger birth cohorts showed higher CASI levels
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39 due to higher education levels.
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44 We found no radiation effects on initial cognition level or cognitive decline.
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46 Previous cross-sectional studies among the AHS that included dementia-free
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48 and demented subjects also found no radiation effect on cognition,²⁰ nor did
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50 sub-group analysis comparing exposed to non-exposed subjects in this study
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52 (data not shown). Another study of subjects exposed at or after adolescence
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54 also found no radiation effect on dementia occurrence.³⁶
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1 Some limitations of this study need to be noted. Cognitive measure other than
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3 CASI was not investigated in this study. The CASI examination was not always
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5 conducted biennially even if the health checkup was. The most common reason
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7 given was lack of time, and the irregular intervals of CASI examinations might
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9 have affected the accuracy of the estimated rate of cognitive decline. Some
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11 factors affecting cognition, such as diseases and socioeconomic factors,
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13 including occupation and income, were not considered in this analysis.
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16 Additionally, the fact that the CASI-short is unique to the AHS should also be
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18 considered when wanting to generalize to other populations. Lastly, the
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20 distribution of age and educational levels for the specific population should be
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22 considered.
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27 The advantages of this study included our investigation of the effects of
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29 demographic factors on cognition level and cognitive decline among a
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31 population that would most likely represent those people who would not
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33 progress to dementia. The subjects consisted of a relatively large number of
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35 men and women, a broad age range starting at 60 years, and a relatively long
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37 follow-up.
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42 In conclusion, our long-term longitudinal study of global cognitive function
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44 among dementia-free subjects shows that age is an important predictor of
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46 cognitive function level and cognitive function declines without a sex difference.
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48 Education level affects initial cognitive function, but not cognitive decline. The
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50 results will offer useful information for dementia screening.
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FIGURE LEGENDS

Figure 1. Estimated CASI as a function of attained age from the initial (dashed line) and longitudinal (solid line) models at the mean education level of 9.6 years. Points represent a randomly drawn 10% of the available data.

Figure 2. Estimated effect of education at the mean age of 69.6 years

Figure 3. Estimated CASI as a function of attained age for 5-year-span birth cohorts of men (solid lines) and women (dashed lines) at their respective mean education level.

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Table 1. Collected variables for all participants, and comparisons between women and men. Means (SD) and {25th percentile, 75th percentile} are presented for quantitative variables, counts (percent) for categorical variables.

	Overall <i>N</i> = 1531	Women <i>N</i> = 1054	Men <i>N</i> = 477	Test Statistic	<i>p</i>-value
Age at First Exam (yrs)	69.6 (5.5) {65.4, 73.1}	70.3 (5.3) {66.0, 73.8}	68.1 (5.1) {64.6, 69.9}	7.69 ^a	<.001
CASI score	43.3 (3.9) {41.2, 46.2}	43.1 (4.0) {40.7, 46.2}	43.7 (3.7) {41.7, 46.7}	3.13 ^a	.001
Number of exams	3.4 (2.4) {2, 5}	3.5 (2.3) {2, 5}	3.4 (2.4) {2, 5}	0.11 ^a	.91
Those with ≥2 Exams (%)	1158 (75.6%)	798 (75.7%)	360 (75.5%)	0.00 ^b	.97
Follow-up length ≥2 Exams (yrs)	8.8 (5.3) {4.0, 14.0}	8.8 (5.3) {4.0, 14.0}	8.6 (5.5) {4.0, 14.0}	0.83 ^c	.41
Education (yrs)	9.6 (1.9) {8, 11}	9.4 (1.6) {8, 10}	10.2 (2.4) {8, 11}	7.60 ^a	<.001
Radiation (Gy)	0.44 (0.74) {0, 0.56}	0.42 (0.73) {0, 0.56}	0.47 (0.77) {0, 0.60}	1.09 ^a	.27
Those with <.005 Gy (%)	627 (41.0%)	432 (41.0%)	195 (40.9%)	0.00 ^b	.97

^a *t*-statistic, *df* = 1529. ^b χ^2 -statistic, *df* = 1. ^c *t*-statistic, *df* = 1156.

Table 2. Estimates and 95% CIs for effects in the chosen model of initial CASI, Model 0, and the chosen longitudinal CASI model. All estimates are $\times 10^{-3}$.

Effect	Model	Estimate	95% CI	p-value
<i>Education</i>	Initial	520	(422, 617)	<.001
	Longitudinal	568	(485, 651)	<.001
<i>Education</i> ²	Initial	-50	(-78, -22)	<.001
	Longitudinal	-66	(-90, -41)	<.001
<i>Age</i>	Initial	27	(-107, 161)	.691
	Longitudinal	-19	(-71, 33)	.571
<i>Age</i> ²	Initial	-10	(-16, -4)	<.001
	Longitudinal	-5	(-7, -3)	<.001

Figure 1

Figure 2

Figure 3