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# *Depression and risk of Alzheimer's dementia: A longitudinal analysis to determine predictors of increased risk among older adults with depression.*

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**Highlights**

- Older adults with depression are at increased risk of Alzheimer's dementia (AD) but predictors of increased risk remain incompletely understood
- We followed 1965 older adults with depression and mild cognitive impairment (MCI) until development of AD or loss to follow up.
- Age, baseline cognition, APO E4 genotype, amnestic subtype of MCI and recency of depression (active depression within the last 2 years) were all independently associated with increased risk of AD.
- Individuals with a combination of MCI and recently active depression were at particularly high risk of AD and should be considered for preventive interventions.

***Abstract***

**Objective:** Older adults with depression are at increased risk of Alzheimer's dementia (AD) but predictors of increased risk remain incompletely understood. We aim to identify characteristics of older adults with depression most at most risk of progressing to AD. Identification of high-risk subgroups could facilitate future interventional strategies to reduce risk of AD in older adults with depression. **Methods:** Using data from the National Alzheimer's Coordinating Centre, 1965 participants with clinically defined depression and Mild Cognitive Impairment (MCI) at baseline were followed until development of AD or loss to follow up. **Results:** 780 (39.7%) developed AD over a median follow up duration of 27 months. In survival analyses age (HR 1.04, 95% 1.03 – 1.05), baseline MMSE (HR 0.85, 95% CI 0.83 – 0.87), amnestic subtype of MCI (HR 1.66, 95% 1.30 – 2.12), presence of APOE e4 allele (HR 1.99, 1.69 – 2.36) and presence of active depression within the last 2 years (HR 1.44, 95% CI 1.16 – 1.79) were all independently associated with increased risk of AD. 656 (41.7%) participants with MCI and active depression within the last 2 years developed AD compared to 120 (31.6%) of those with a more remote history of depression. **Conclusion:** Older adults with depression and MCI demonstrated a high rate of progression to AD over a relatively short duration of follow up. Individuals with a combination of MCI and recently active depression are a particularly high-risk subgroup.

## Introduction

Depression in later life has been associated with an approximate two-fold increased risk of Alzheimer's dementia (AD) (1). However, depression is a heterogeneous disorder and it is not clear which clinical characteristics among older adults with depression are most closely associated with risk of AD.

Several mechanisms of association have been proposed to explain the excess risk observed among older adults with depression. It has long been proposed chronic glucocorticoid exposure secondary to stress axis activation in depression may have direct neurotoxic effects. Some support for this proposition has been provided by studies documenting reductions in hippocampal volume among adults with persistent or recurrent depression (2). Inflammatory activation and oxidative stress frequently occur as part of the depressive syndrome and have been associated with accelerated cognitive decline (3, 4). Depression is often associated with a greater burden of vascular risk factors and bidirectional relationships between depression and vascular disease have been well described (5). Alternately it has been proposed that depression is not a true risk factor for AD but occurs as an early symptom of beta-amyloid deposition and neurodegenerative disease. In support of this, it has been observed that depression with first onset in later years is more likely to be associated with cognitive impairment and increased depressive symptoms have been noted in individuals with normal cognition and increased cerebral beta-amyloid burden (6, 7). Conversely several studies, including those with much longer durations of follow up, have reported an increased risk of AD among those with early onset depression. In theses studies an incremental risk has been reported according to number of previous depressive episodes and severity of symptoms (8-10).

In the general population efforts to prevent or delay the onset of AD have largely focused upon individuals with mild cognitive impairment (MCI) and particularly those with amnestic MCI more frequently associated with early Alzheimer's pathology. Depression has been reported to accelerate conversion from MCI to AD in a number population studies and therefore individuals with both depression and MCI potentially represent a high-risk group suitable for preventive interventions (11). However, findings from population studies may not be readily generalized to those attending specialist services as older adults referred to specialist clinics typically have more severe depression & greater co-morbidity (12). A relatively smaller number of studies in clinical samples have reported that between 8 – 85% of adults with depression and MCI may progress to AD (13, 14). The considerable variability observed in clinical studies likely reflects variations in patient samples and clinical processes between centers. To the best of our knowledge no study to date has undertaken a large-scale analysis, specifically focused upon older adults with depression and MCI attending specialized memory services utilizing standardized clinical processes to describe the overall risk of progression to AD. If we are to successfully reduce the incidence of AD in this vulnerable population, it will be critical to determine the overall risk of progression to AD among patients with depression and MCI. It will also be important to characterize subgroups at greatest risk according to characteristics of depression, MCI subtype & medical co-morbidities.

Our aims therefore are to: (1) Describe the overall risk of progression to AD among a large population of older adults with depression and MCI attending specialized memory services and to (2) Describes clinical characteristics associated with higher risk which might delineate subgroups particularly suited for preventive interventions. We hypothesized that greater severity of depression, more recently active depression,

amnestic subtype and co-morbid vascular risk factors would be associated with increased risk of AD.

## Methods

*Study Sample*

The NACC database includes data collected annually at participating Alzheimer's Disease Centres (ADCs) across the US. Participants provide responses to psychological and cognitive questionnaires and may have a physical examination. Participants may also voluntarily provide imaging and laboratory specimens at some of the participating ADCs. A Uniform Dataset (UDS) was implemented in September 2005 to prospectively gather standardized information from study participants. The UDS is not an epidemiologic sample and is best considered as a case series. It has grown in size to include over 36,500 subjects as of December 2017. This analysis is based upon a subsample of study participants from the UDS who attended from September 2005 through to September 2017. We included participants with clinical defined depression at baseline and MCI who attended for assessment on at least two occasions (n = 2146). We restricted out analysis to those aged 50 yrs and over at baseline (n = 2116) for consistency with previous longitudinal studies that have demonstrated increased risk of AD in late life depression (1). For survival analyses we excluded participants who developed dementia not of Alzheimer's etiology to leave a sample of 1965 for longitudinal survival analyses. Written informed consents were obtained from participants at each ADC and approved by the ADC's Institutional Review Board (IRB). Research using the NACC database was approved by the University of Washington IRB.

*Depression*

Depression was defined as either (1) depression within the last two years or prior to two years as reported by the study participant or co-participant to the assessing clinician (UDS Form A5) or (2) as clinician-reported depression at time of initial assessment according to DSM criteria at the time of assessment (UDS Form D1). The subject health history (Form A5) is completed by a "clinician, based on subject/informant report, medical records, and/or observation" using the clinician's best judgment. A history of depression is documented as present, absent or unknown with instructions to "include depressive disorders for which a clinician was consulted, whether or not treatment (behavioral or drug) was received." Depression includes major depressive disorder and other depressive syndromes for which a clinician was consulted. Assessment can include DSM diagnoses, chart reviews, clinicians' opinion, or whether the subject is taking an SSRI for a depressive mood disorder." This definition of "clinically defined" depression is broadly based on DSM criteria, as that is the typical training for clinicians. Individuals with depression were also asked if they had "depression requiring medical attention within the last two years." Severity of depressive symptoms was assessed with the 15- item Geriatric Depression Scale (GDS) (15).

*Antidepressant medication*

A general antidepressant variable is included in the NACC dataset. This variable includes antidepressant medications from different classes including: SSRI, tricyclic, monoamine oxidase inhibitor, phenylpiperazine, tetracyclic, and serotonin–norepinephrine reuptake inhibitors. This variable allows for a group level analysis of antidepressant medications but does not allow for analysis of individual antidepressant classes.

*Cognition & Alzheimer's Dementia*

Dementia diagnoses were made by a consensus team or the physician conducting the examination using the results of a structured clinical history, neuropsychological testing and validated assessments of symptoms & function as previously described (16). Alzheimer's dementia was diagnosed according to NINCDS/ADRDA criteria (17) prior to 2015 and according to NIA-AA criteria (18) from 2015 onwards when the UDS was updated (version 3). We included all cases of dementia where Alzheimer's disease was considered to be either the primary or contributing etiology. This includes participants considered to have either probable or possible Alzheimer's dementia. Accuracy of clinical diagnoses of AD in the NACC dataset have previously been validated according to neuropathological criteria (19). Normal cognition was defined as having a CDR score of zero and cognitive testing within normal limits. MCI classification included both amnestic and non-amnestic MCI according to international consensus criteria (20). Total Mini Mental Status Examination (MMSE) score (using WORLD) was completed on study participants (versions 1-2) at baseline (21).

*Medical conditions & health behaviors*

A list of common medical conditions was collected using a structured health history form (form A5). The form was completed by a clinician based on participant report, medical records and/or observation. A medical condition was considered to be present if it was active within the last year or occurred in the past. We included several medical conditions known to be associated with both depression and increased risk of cognitive decline including: hypertension, hypercholesterolemia, diabetes, atrial fibrillation, previous heart attack/arrest, previous stroke or TIA. Participants were also asked whether they had a history of alcohol abuse (defined as significant impairment occurring over a 12 month

period in one of the following areas: work, driving legal or social) and the total number of years for which cigarettes were smoked.

*Physical Examination*

The majority of participants underwent a brief physical examination by the study clinician who recorded whether there was hearing impairment (without hearing aid) or visual impairment (without corrective lenses). A proportion of participants had genetic testing which usually consisted of either a blood test or a buccal swab according to ADC centre but could also be obtained at autopsy. It was determined whether participants were either homozygous or heterozygous for the e4 allele associated with increased risk of AD.

*Analyses*

We conducted descriptive analyses of baseline clinical characteristics of older adults with depression and MCI according to subsequent progression to AD or not. We then conducted survival analyses to determine which variables were associated with increased risk of AD during follow up. Survival analysis measures the time to an event or outcome of interest and is frequently used to analyze longitudinal data of this type. An event was defined as a diagnosis of AD during follow up, and censoring at the last date of contact was used to account for participants who had not received a diagnosis of AD before loss to follow up. We used Cox proportional hazards regression models which allowed us to adjust for the effects of other covariates on risk of AD. Variables significantly associated with AD in bivariate survival analyses were selected for the multivariable Cox proportional hazards regression model. Prior to running the final model, the variables were assessed for multicollinearity using tolerance statistics (tolerance < 0.4 as a cut-point) to avoid an unstable estimate of regression

coefficients. The assumption of proportionality was examined to ensure that the Cox proportional hazards assumption was met. All analyses were conducted utilizing Stata 12.1 for mac. A $p$ value < 0.05 was considered statistically significant.

## Results

1965 study participants with MCI and clinically defined depression were included in the baseline analysis. 1106 (56.3%) were female with a mean age of 71.8 (SD 8.7). 780 (39.7%) progressed to AD over a median follow up duration of 27 months (range 6 – 138). Clinical characteristics of study participants at baseline according to progression to AD or remaining at MCI during follow up are summarized in table 1.

*Insert table 1 about here*

*Survival analyses*

We initially conducted bivariate survival analyses to determine which clinical characteristics were associated with increased risk of AD (table 2). All significant predictors from bivariate analyses in table 2 were then assessed for multicollinearity prior to being entered into a multivariable Cox proportional hazards regression model. The only variables that remained significantly associated with AD included; age (HR 1.04, 95% 1.03 – 1.05), baseline MMSE (HR 0.85, 95% CI 0.83 – 0.87), amnestic subtype of MCI (HR 1.66, 95% 1.30 – 2.12), presence of APOE e4 allele (HR 1.99, 1.69 – 2.36) and presence of active depression within the last 2 years (HR 1.44, 95% CI 1.16 – 1.79) (table 3).

*Insert table 2 & 3 about here*

In a subgroup analysis comparing participants with active depression within the last two years to those with a more remote history of depression we found that a significantly greater proportion of those with active depression within the last two years developed AD during follow up compared to those with a more remote history of depression. 656 (41.7%) of those with active depression within the last 2 years developed AD compared to 120 (31.6%) of those with a more remote history of depression ($\chi^2$ = 13, $p$ < 0.001). The relationship between active depression within the last two years and increased risk of AD remained significant in a multivariable Cox regression model as outlined in table 3. The disparity in survival is depicted graphically in a Kaplan Meier survival curve (log rank $\chi^2$ = 13.98, $p$ = 0.002) (Fig 1). We conducted further subgroup analyses in those with active depression within the last two years only (n = 1574) to determine if depression severity as measured by GDS (total score) and using cut-off of > 5, previously determined to be optimal cut point for clinical depression, (22) was significantly associated with survival to AD. Only 165 (10%) of this group did not endorse ongoing depressive symptoms (GDS = 0). The mean GDS score in those with active depression within the last two years was 3.86 (SD 3.2) with 394 (25%) reporting a score > 5. Total GDS score (HR 0.98, 95% CI 0.96 – 1.01) and score > 5 (HR 0.87, 95% CI 0.72 – 1.05) were not significantly associated with survival to AD in this subgroup.

*Insert figure 1 about here*

**Discussion**

In this longitudinal evaluation of older adults with depression and MCI, we found that a large proportion of patients (39.7%) progressed to AD over a relatively short median follow up duration of 27 months. This compares to an annual conversion rate of approximately 15% in a previous analysis of all participants with MCI in the NACC dataset (23). We also found that risk of progression to AD was significantly elevated in those who reported an active history of depression within the last two years compared to those with a more remote history of depression. Late onset depression has previously been associated with greater cognitive impairment (7, 24) but depression with earlier onset has also been associated with increased risk of AD (8, 10). With the advent of molecular imaging techniques a number of studies have demonstrated a positive correlation between increasing cerebral beta-amyloid and tau burden and depressive symptoms in individuals with normal cognition, supporting the proposition that depression may be one of the earliest symptoms Alzheimer's pathology (6, 25, 26). In this sample it is likely that individuals with active depression within the last two years includes a combination of those with late onset depression (first onset > 50 – 60yrs of age) & those with earlier onset depression that has persisted or recurred at the time of baseline assessment. Therefore, the association between elevated risk and recency of depression does not preclude the possibility that depression with earlier onset remains a risk factor for AD. However, in this population at least, it appears that the presence of active depression within the last two years should be considered a marker of even greater risk, possibly reflecting more aggressive progression of underlying Alzheimer's pathology. It is also possible that physiologic and behavioral changes associated with the depressive state accelerate cognitive decline at a time of increased vulnerability. Physical inactivity, inflammatory activation and oxidative stress have all been associated with cognitive decline (3, 4) while both endogenous and exogenous glucocorticoids have been associated with increased production of beta-amyloid in animal models (27).

We replicate findings reported in previous analyses indicating that baseline cognition, age & APOE4 status are important predictors of increased risk of AD (28). We found that the amnestic subtype of MCI was associated with greater risk of progression reflecting the closer association between amnestic MCI and underlying Alzheimer's pathology (29). We did not find an independent association between vascular risk factors and increased risk of AD in this sample. This likely reflects the overall increased risk of AD once MCI has become established, the fact that vascular risk factors have been closely associated with non-amnestic MCI and the relatively short duration of follow up (30).

It remains to be determined whether treatment of depression in MCI, in addition to providing symptomatic relief, can slow progression to AD. There are several plausible mechanisms by which antidepressant treatment might reduce risk of AD both indirectly through changes in behaviour (e.g. increased activation) & more directly through impact on patho-physiological mechanisms associated with AD. For example SSRIs are known to have anti-inflammatory effects and there is some evidence to suggest that escitalopram may reduce production of beta-amyloid (31). In a recent longitudinal analysis in MCI patients with a history of depression, SSRI treatment for more than 4 years was significantly associated with delayed progression to Alzheimer's dementia (32). Conversely, tricyclic antidepressants have anti-cholinergic properties and so may have a deleterious effect upon cognition. In this analysis we did not find a significant effect for antidepressant treatment as a whole but note that we were unable to examine for the effects of specific classes of medication, as all antidepressants were included within the antidepressant variable in this dataset.

The strengths of this study include use of a well-characterized dataset with diagnosis of AD by experienced clinicians in specialist memory clinic settings. We were able to identify a

subgroup of older adults with depression at increased risk of progression to AD & suitable for novel interventional strategies requiring further study. Limitations include lack of diagnostic interview for depression in addition to more detailed information regarding number, severity and age of onset of previous depressive episodes. However, diagnosis of depression was overseen by clinicians & informed by usual DSM diagnostic criteria as part of a structured assessment. The study sample is best considered to be a convenience sample of those attending specialist memory services and is not representative of the general population where conversion rates from MCI to dementia are generally lower (33). Findings should be replicated in a general population sample to determine generalizability. We tested for multiple associations inflating chances of a type 1 error but note that variables associated with AD in the final multivariable model all displayed highly significant associations. Finally, the median follow up duration was relatively short with loss to follow up and likely progression of participants to AD beyond the timeframe captured here.

In conclusion, we found that a large proportion of older adults with clinically defined depression & MCI progressed to AD over a relatively short follow up duration. The combination of MCI with active depression within the last 2 years was associated with even greater risk & should alert clinicians to heightened risk of AD in such cases. Future studies should explore potentially modifiable risk factors & test novel interventions to reduce risk of AD in this vulnerable population.

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Figure 1: Survival to development of AD according to presence or absence of active depression within the last two years.

Table 1: Clinical characteristics of study participants at baseline according to development of AD during follow-up, (t test for continuous & $\chi^2$ test for categorical variables).

| | AD (n = 780) | MCI (n = 1185) | $t/\chi^2$ | *df* | *p* |
|---|---|---|---|---|---|
| Age (mean, SD) | 74.1 (8.3) | 70.3 (8.7) | - 9.6 | 1963 | < 0.001 |
| Sex (female, %) | 455 (58.3) | 651 (54.9) | 2.2 | 1 | 0.138 |
| Education (mean, SD) | 15.4 (3.4) | 15.1 (3.4) | - 1.6 | 1957 | 0.115 |
| MMSE (mean, SD) | 26.5 (2.6) | 27.8 (2.1) | 11.8 | 1808 | < 0.001 |
| MCI (amnestic, %) | 696 (89.2) | 894 (75.4) | 57.9 | 1 | < 0.001 |
| APOE (e4 allele, %) | 369 (57.4) | 357 (37.1) | 64.2 | 1 | < 0.001 |
| **Depression** | | | | | |
| Active in last 2yrs (%) | 656 (84.5) | 918 (77.9) | 13.0 | 1 | < 0.001 |
| Severity (GDS, mean, SD) | 3.46 (2.9) | 3.79 (3.2) | 2.3 | 1895 | 0.023 |
| Antidepressant (yes, %) | 418 (53.8) | 670 (57.0) | 1.97 | 1 | 0.160 |
| **Medical conditions** | | | | | |
| Hypertension | 437 (56.1) | 668 (56.6) | 0.1 | 1 | 0.823 |
| Hypercholesterolemia | 414 (53.2) | 668 (56.6) | 3.0 | 1 | 0.081 |
| Diabetes | 102 (13.1) | 213 (18.1) | 8.5 | 1 | 0.004 |
| Atrial fibrillation | 64 (8.2) | 85 (7.2) | 0.6 | 1 | 0.417 |
| Heart attack/arrest | 39 (5.0) | 79 (6.7) | 2.4 | 1 | 0.124 |
| Stroke/TIA | 80 (10.4) | 119 (10.2) | 0.1 | 1 | 0.876 |

| | | | | | |
|---|---|---|---|---|---|
| **Health Behaviors** | | | | | |
| Smoking (yrs, mean, SD) | 10.8 (15.7) | 12.1 (16.6) | 1.65 | 1 | 0.100 |
| Alcohol abuse (ever, %) | 56 (7.2) | 109 (9.2) | 2.52 | 1 | 0.113 |
| **Physical examination** | | | | | |
| Hearing impairment (%) | 189 (24.7) | 271 (23.3) | 0.49 | 1 | 0.486 |
| Visual impairment (%) | 521 (68.4) | 813 (69.5) | 0.29 | 1 | 0.585 |

Table 2: Hazard ratios for development of AD for each predictor variable in bivariate survival analyses. SE, Standard Error *Statistical significance at $p < 0.05$, ** $p < 0.001$

| Predictor variable | Analytic Sample size | SE | z-value | Hazard ratio (95% CI) |
|---|---|---|---|---|
| Age (yrs) | 1965 | 0.004 | 9.3 | 1.04 (1.03 – 1.05)** |
| Sex (female) | 1965 | 0.071 | - 0.16 | 0.99 (0.86 – 1.14) |
| Education (yrs) | 1959 | 0.011 | 1.62 | 1.01 (0.99 – 1.04) |
| MMSE score | 1810 | 0.010 | - 14.67 | 0.84 (0.82 – 0.86)** |
| **Depression** | | | | |
| Active in last 2yrs (yes) | 1954 | 0.144 | 3.72 | 1.45 (1.19 – 1.76)** |
| Severity (Total GDS score) | 1897 | 0.012 | - 0.27 | 0.99 (0.97 – 1.02) |
| Antidepressant (yes) | 1952 | 0.071 | - 0.13 | 0.99 (0.86 – 1.14) |
| **Medical Conditions** | | | | |
| Hypertension | 1959 | 0.071 | - 0.31 | 0.98 (0.9 – 1.13) |
| Hypercholesterolemia | 1943 | 0.062 | - 2.14 | 0.86 (0.7 – 0.99)* |
| Diabetes | 1962 | 0.084 | - 2.25 | 0.79 (0.64 – 0.97)* |
| Atrial fibrillation | 1956 | 0.149 | 1.06 | 1.15 (0.89 – 1.48) |
| Heart attack/arrest | 1959 | 0.143 | - 0.83 | 0.87 (0.63 – 1.20) |
| Stroke/TIA | 1935 | 0.117 | - 0.06 | 0.99 (0.79 – 1.25) |
| **Health Behaviors** | | | | |

| | | | | |
|---|---|---|---|---|
| Smoking (yrs) | 1893 | 0.002 | - 0.61 | 0.99 (0.99 – 1.01) |
| Alcohol abuse (ever) | 1961 | 0.121 | - 1.01 | 0.87 (0.66 – 1.14) |
| **Physical examination** | | | | |
| Hearing impairment | 1927 | 0.088 | 0.61 | 1.05 (0.89 – 1.24) |
| Visual impairment | 1931 | 0.081 | 0.52 | 1.04 (0.89 – 1.21) |
| Amnestic subtype | 1965 | 0.271 | 7.34 | 2.34 (1.86 – 2.93)** |
| APOE (e4 allele) | 1606 | 0.156 | 8.38 | 1.96 (1.67 – 2.29)** |

Table 3: Clinical characteristics with significant associations with AD in multivariable Cox regression model. SE, Standard Error *Statistical significance at $p < 0.05$, ** $p < 0.001$

| Predictor variable | SE | z-value | Hazard ratio (95% CI) |
|---|---|---|---|
| Age (yrs) | 0.005 | 7.88 | 1.04 (1.03 – 1.05)** |
| MMSE score | 0.012 | - 11.56 | 0.85 (0.83 – 0.87)** |
| Amnestic subtype | 0.207 | 4.09 | 1.66 (1.30 – 2.12)** |
| APOE (e4 allele) | 0.167 | 8.3 | 1.99 (1.69 – 2.36)** |
| Active in last 2yrs (yes) | 0.161 | 3.25 | 1.44 (1.16 – 1.79)** |

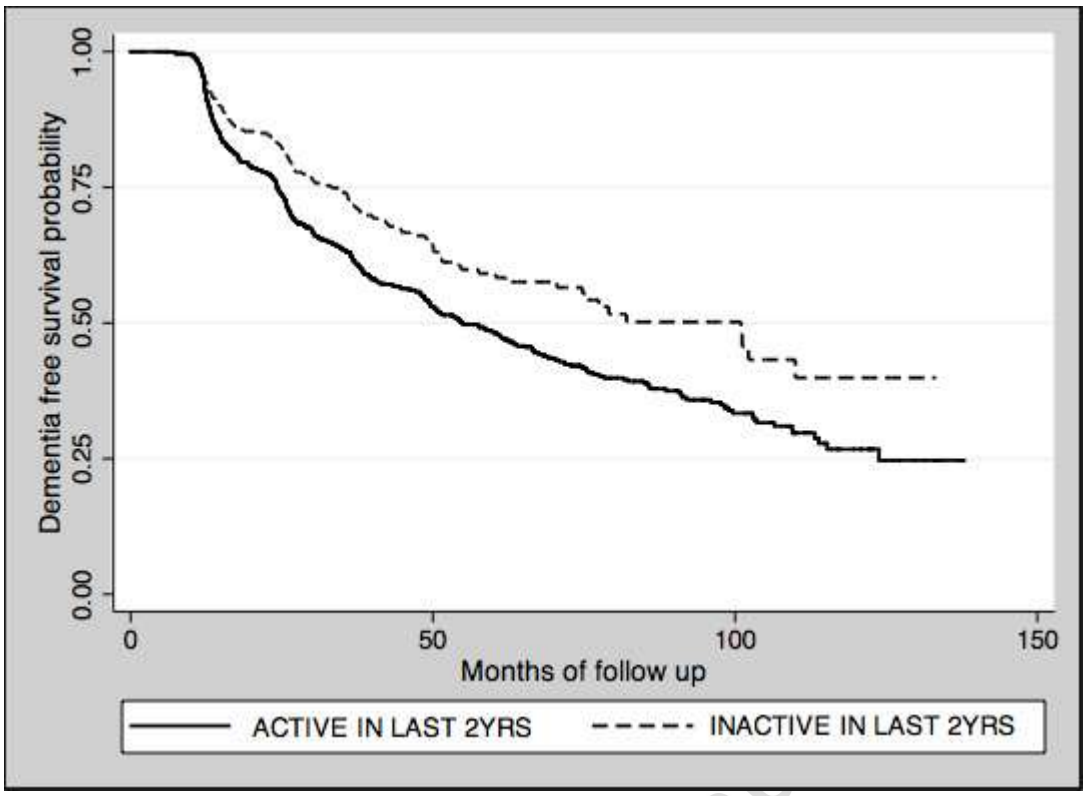


Fig1.tif