# The Roles of Apathy and Depression in Predicting Alzheimer Disease: A Longitudinal Analysis in Older Adults With Mild Cognitive Impairment

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## Abstract

**Objective:** Apathy and depression have each been associated with an increased risk of conversion from mild cognitive impairment (MCI) to Alzheimer disease (AD).These symptoms often co-occur and the contribution of each to risk of AD is not clear.

**Methods:** National Alzheimer's Coordinating Center participants diagnosed with MCI at baseline and followed until development of AD or loss to follow-up (n = 4,932) were included. The risks of developing AD in MCI patients with neuropsychiatric symptoms (NPS) (apathy only, depression only, or both) were compared to that in those without NPS in a multivariate Cox regression survival analysis adjusting for baseline cognitive impairment, years of smoking, antidepressant use, and AD medication use.

**Results:** Thirty-seven percent (N=1713) of MCI patients developed AD (median follow-up 23 months). MCI patients with both apathy and depression had the greatest risk (hazard ratio [HR] = 1.37; 95% confidence interval [CI]: 1.17–1.61; p < 0.0001; Wald $\chi^2$ = 14.70; df=1). Those with apathy only also had a greater risk (HR = 1.24; 95% CI: 1.05 –1.47; p = 0.01; Wald $\chi^2$ = 6.22; df=1), but not those with depression only (HR = 1.08; 95% CI: 0.95–1.22; p=0.25; Wald $\chi^2$ = 1.30; df=1). Post-hoc analyses suggested depression may exacerbate cognitive decline in MCI patients with apathy (odds ratio = 0.70; 95% CI 0.52–0.95; p = 0.02; Wald $\chi^2$ =5.28; df=1), compared to those without apathy.

**Conclusion:** MCI patients with apathy alone or both apathy and depression are at a greater risk of developing AD compared to those with no NPS. Interventions targeting apathy and depression may reduce riskof AD.

## Keywords

Alzheimer disease; apathy; depression; mild cognitive impairment

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## INTRODUCTION

Apathy and depression are two of the most common neuropsychiatric symptoms (NPS) in patients with mild cognitive impairment (MCI), and often co-occur with one another. Although apathy can occur in the context of depression, it can also occur independently and is often underdiagnosed and undertreated.[1] Apathy differs from depression. Although some patients demonstrate loss of motivation or pleasure, depression is characterized by low mood and negative cognitions such as guilt, hopelessness, or suicidal ideation.[2] In contrast, those with apathy demonstrate reduced emotion and reactiveness when stimulated, in addition to reduced goal-directed activities. In recognition of these differences, diagnostic criteria for apathy have now been proposed.[3]

Findings from neuroimaging studies in patients with apathy[4] and depression,[5] and studies that compare apathy and depression,[6] report differences in brain structural volumes, brain hypoperfusion, white matter tract integrity, and white matter hyperintensities. Considering that both apathy and depression have also been linked to cognitive decline, they are each associated with different domains of executive functioning, indicating possible differences in frontal lobe pathology.[7] Furthermore, patients with MCI with apathy demonstrate a lower capacity to carry out activities of daily living compared with patients with depression, suggesting that apathy may have a greater impact on caregiver burden.[8]

A number of studies in cognitively normal elderly individuals and patients with MCI have supported apathy and depression as risk factors for conversion to Alzheimer's disease (AD). Donovan et al.[9] reported that only depression, and not apathy, was a significant predictor of disease progression in patients with MCI. Vicini Chilovi et al.[10] and Palmer et al.[11] reported that apathy was a significant risk factor for conversion to AD. However, Vicini Chilovi et al. [10] reported that depression without apathy was associated with reduced risk of conversion to AD, whereas

Palmer et al.[11] reported that depression did not increase risk of AD. These studies had relatively small sample sizes, with variability in how both depression and apathy were assessed that may have contributed to the conflicting findings. Additional studies with larger sample sizes and standardized assessments are needed to elucidate whether these NPS have an overlapping or additive impact on risk of conversion from MCI to AD.

We therefore wish to determine, in a larger analysis than previously completed, the relative contributions of apathy and depression to the risk of conversion from MCI to AD. We hypothesized that apathy and depression would both individually be associated with increased risk of AD, whereas apathy and depression combined would be associated with a greater risk than either alone.

## METHODS

### Study Sample

The National Alzheimer's Coordinating Center (NACC) database includes data collected annually from past and present Alzheimer's Disease Centers (ADCs) in the United States.

Enrolled participants undergo a physical assessment, in addition to standardized clinical and neuropsychological assessments. Participants may also volunteer to provide imaging and laboratory specimens at specific ADCs. In September 2005, the NACC implemented the uniform dataset (UDS) at all ADCs, which collects longitudinal data prospectively, using standardized clinical evaluations. This article includes data from UDS visits conducted between September 2005 and February 2018. Participants undergo an annual assessment, and information on demographics, neuropsychological testing, and clinical diagnoses are obtained at each visit. Although all participants range in cognitive status (cognitively normal, MCI, or dementia), for the purposes of this article, we included participants with a diagnosis of MCI at baseline, and who had one or more follow-up UDS visits.

### Classification of Apathy and Depression

The subject health history (UDS Form A5) is completed by a clinician or ADC staff based on participant or co-participant report. Apathy and depression are separate items on UDS Form A5, and are characterized as present, absent, or unknown. The Neuropsychiatric Inventory–Questionnaire (NPI-Q) is a behavioral assessment completed by the clinician or other trained health professional and includes an assessment of 12 behaviors: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating. If an NPS is present, the severity of the symptom is rated as 1) mild; 2) moderate; or 3) severe. We identified clinically significant apathy and/or depression as either moderate (score = 2) or severe (score = 3) on the NPI-Q[12] (UDS Form B5). Participants did not have any clinically significant NPS at baseline if each of their NPS were rated as absent, or of mild severity on the NPI-Q (UDS Form B5). Depression was also determined by clinical diagnosis that may include Diagnostic and Statistical Manual of Mental Disorders' criteria for major depressive disorder (UDS Form D1). Finally, a score of 5 or greater on the Geriatric Depression Scale (GDS) was identified as clinically significant depressive symptoms (UDS Form B6).[13] Participants with neither apathy nor depression, and who had other clinically significant NPS were excluded.

### Classification of AD Diagnosis

A consensus team or physician diagnosed dementia using the results of a structured clinical history, neuropsychology testing, and validated assessments of symptoms and function. Dementia of the AD type was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association criteria prior to 2015,[14] and the National Institute on Aging/Alzheimer's Association criteria[15] after 2015. Participants were also identified as having an AD diagnosis, if AD was the primary or contributing cause of cognitive impairment, which included participants who had either probable or possible dementia of the AD type. The accuracy of the clinical diagnoses of AD in the NACC dataset has been validated with neuropathological criteria for AD.[16]

## Medication and Medical Illness History

### Antidepressant, antipsychotic, anxiolytic, and AD medication—A category for U.S. Food and Drug Administration-approved medications for AD symptoms was reviewed; this included current use of memantine and cholinesterase inhibitors. A category of prescribed antidepressants was also examined, which included selective serotonin reuptake inhibitors, tricyclic, monoamine oxidase inhibitors, serotonin-norepi-nephrine reuptake inhibitors, phenylpiperazine, tetracyclic, and miscellaneous antidepressants. Current use of antipsychotic and anxiolytic medications were also examined. Antipsychotics included atypical antipsychotics, miscellaneous antipsychotics, psychotherapeutic combinations, phenothiazine psychotics, and thioxanthenes. Anxiolytics included barbiturates, benzodiazepines, sedative, hypnotics, and miscellaneous anxiolytics.

## Medical Condition and Health Behaviors

A structured health history form was used to collect medical conditions associated with depression and AD. This form was based on reports from the subject or coparticipant. A medical condition was considered present if it was recent/active or remote/inactive. Medical conditions included were heart attack/ cardiac arrest, atrial fibrillation, stroke, transient ischemic attack, diabetes, hypertension, and hypercholesterolemia. The health history form was also used to collect information regarding alcohol abuse. Participants were considered to have alcohol abuse if they reported recent/active or remote/inactive clinically significant impairment over a 12-month period demonstrated in one of the following areas: work, driving, legal, or social. Participants were also asked the total number of years they smoked cigarettes.

## Statistical Analyses

Baseline demographics, medication history, and assessments were compared between patients with apathy only, depression only, apathy and depression, and no clinically significant NPS. Bivariate survival analyses were conducted with demographics, medical conditions, health behaviors, medication use, and APOE E4 allele variables to determine predictors associated with an increased risk of conversion to AD. Significant predictors from bivariate analyses were assessed for multicollinearity and included as covariates in the multivariate Cox regression.

Post-hoc analyses were conducted to further investigate the effect of apathy, depression, and both apathy and depression on AD conversion. Specifically, a binary logistic regression was computed to determine the odds of apathy, depression, and apathy x depression interaction term, in predicting conversion to AD from MCI. Subgroup analyses were then conducted within individuals who had and did not have apathy to determine whether depression increased the odds of conversion to AD from MCI. In all post-hoc analyses, significant predictors from previously conducted bivariate analyses were included as covariates.

## RESULTS

This analysis included 4,932 participants with MCI (mean ± standard deviation age = 73.2 ± 9.2; Mini-Mental State Examination = 27.1 ± 2.5; 50% [N = 2,482] male; and 35% [N =

1,713] participants that converted to AD). Of these participants, 8% had apathy only, 31% had depression only, 14% had apathy and depression, and 48% had no NPS. Participants who did not have clinically significant apathy and/or depression, and who had other clinically significant NPS were excluded from analyses (N = 377). Baseline clinical characteristics based on NPS group are included in Table 1.

### Selection of Covariates

Bivariate survival analyses were conducted to determine which clinical characteristics were associated with increased risk of conversion to AD (Table 2). Clinical variables that remained significantly associated with AD included Mini-Mental State Examination, years of smoking, antidepressant use, and AD medication use. These variables were then assessed for multicollinearity and were determined to not be collinear with one another (variance inflation factor cutoff <2.5). As such, all significant predictors were entered into a multivariate Cox proportional hazards regression model.

### Main Outcome

After adjusting for the previous predictors, participants with MCI with both apathy and depression had the greatest risk of conversion to AD. However, participants with MCI with apathy only also had a significantly greater risk of conversion to AD compared with patients with no NPS (Fig. 1, Table 3). Participants with MCI with depression only did not have a significantly greater risk of conversion to AD compared with patients with no NPS. Visual inspection of Kaplan-Meier curves indicated that the proportional hazards assumption was not violated.

### Post-Hoc Analyses

After adjusting for predictors, the presence of apathy, and apathy x depression, were significantly associated with an increased odds of conversion to AD in participants with MCI. The presence of depression only in participants with MCI did not significantly increase the odds of conversion to AD (Table 4).

Subsequent subgroup analyses indicated that the apathy x depression interaction term was significant such that in participants with MCI who had apathy, the presence of depression was significantly associated with conversion to AD, whereas the presence of depression in participants with MCI who did not have apathy was not associated with conversion to AD (Tables 5, 6).

## DISCUSSION

In this longitudinal study, we report that patients with MCI with both apathy and depression have a significantly greater risk of conversion to AD compared with patients with MCI with no NPS, and that this risk is greater compared with patients with MCI with apathy, or depression only. Post-hoc analyses suggest that this may be due to depression exacerbating cognitive decline in patients with apathy.

Interestingly, we report that depression in the absence of clinically significant apathy in MCI was not associated with a greater risk of AD conversion compared with the presence of no NPS. Although previous studies report that a history of depression in elderly individuals and patients with MCI is a significant risk factor for AD conversion,[17] apathy was not considered separately. Longitudinal-cohort studies have reported that apathy and depression are two of the most common and persistent NPS in patients with MCI, occurring in approximately 15% and 20%, respectively.[12] Because of their high prevalence, apathy and depression are likely to co-occur with one another. As such, the impact of apathy should be taken into account when investigating depression as a risk factor for AD conversion.

Underlying AD pathology may be responsible for the additive risk associated with the presence of both apathy and depression in patients with MCI. Specifically, neuropathological, neuroimaging, and neurochemical studies in patients with MCI and AD have reported that AD pathophysiology,[18,19] brain hypo-metabolism,[20,21] and changes in neurotransmitter systems[22,23] are associated with the presence of apathy and depression, independently. These pathologies have also been associated with an increased risk of conversion to AD, and increased AD severity. Therefore, the presence of apathy or depression in patients with MCI may increase the risk of AD conversion through AD pathology, and the increased risk associated with the presence of both symptoms may be because of the combined pathological burden.

In a pharmacological challenge study with dextroamphetamine in AD patients with apathy, apathy was associated with a blunted behavioral response to dextroamphetamine, suggesting that apathy may be associated with an impaired dopaminergic (DA) brain reward system.[24] Following this study, in a small clinical trial with the psychostimulant methylphenidate, Herrmann et al.[25] reported that DA changes predicted therapeutic response, further supporting a link between the DA system and apathy. Interestingly, selective serotonin reuptake inhibitors have been reported to worsen apathy in some patients with depressive symptoms.[26] As such, although the DA brain reward system may be associated with apathy, changes in the serotonergic system in patients that exhibit depressive symptoms may exacerbate symptoms of apathy.

Our findings identified that years of smoking was associated with an increased risk of conversion to AD. A number of studies have demonstrated that smoking is associated with the presence of AD patho-physiology[27] and oxidative stress.[28] Furthermore, as greater oxidative stress has been shown to exacerbate AD pathology,[29] smoking may increase the risk of AD conversion through increasing oxidative stress. In this study, the lack of significant associations between other cardiovascular risk factors and risk of conversion to AD contradicts other studies that have reported that diabetes,[30] history of heart attack,[31] and the presence of an APOE 4 allele[32] increases the risk of AD conversion. However, this may be due to our study sample, in which these risk factors had similar rates of occurrence between patients with MCI with apathy, depression, both apathy and depression, and no NPS.

In our sample we found that antidepressant use was not associated with risk of AD conversion. There are some studies that indicate a protective effect for antidepressants, but

findings have been inconsistent. Specifically, antidepressants for the treatment of depression have demonstrated anti-inflammatory properties that may be beneficial in reducing AD-related proinflammatory processes and pathology.[33] Conversely, some lines of evidence have suggested that in certain instances antidepressants could increase apathy,[34,35] which may be associated with increased risk. Interestingly, in our study sample, approximately 20% of patients with MCI (12% apathy only, 8% no NPS) were prescribed an antidepressant despite not having a past or current diagnosis of depression. These patients may have been prescribed antidepressants for reasons other than depression such as anxiety, insomnia, or anorexia. It is also possible that patients with apathy were misdiagnosed as having depression, or were treated by a physician who chose to treat their apathy with an antidepressant. Unfortunately, as data prior to NACC enrollment are not available, we were unable to study this finding further.

Initial between-group comparisons indicated that patients with MCI with apathy, depression, or both NPS were more often treated with an AD medication compared with patients with MCI with no NPS. The frequency of this medication use may be considered high given the lack of evidence supporting a significant benefit of cholinesterase inhibitors (ChEIs) on cognition in patients with MCI,[36] and on NPS in patients with MCI and AD.[37] Support for their lack of efficacy is further substantiated by our findings as we report that AD medication use was associated with an increased risk of conversion to AD. This finding does not necessarily mean that these medications worsened cognition, but rather did not prevent conversion to AD in a subgroup of patients considered to be high risk. However, the rates of AD medication use reported reflect current prescription practices in the United States of ChEIs in this patient population.[38] It is also possible that ChEIs were prescribed for the treatment of apathy. Previous randomized controlled trials with ChEIs have demonstrated a small benefit for apathy in patients with AD.[39] However, because these studies did not actively recruit patients with apathy, their efficacy on clinically significant apathy is unclear.

Study strengths included a large sample of participants, providing sufficient power to detect between-group differences and predictors of AD conversion. This dataset was also well-characterized, which included AD diagnoses that were completed by experienced clinicians in specialized memory-clinic settings. The inclusion of NPI-Q severity scores allowed us to identify patients who had clinically significant NPS in addition to inclusion of other measures of NPS. Despite several study strengths, these results must also be reviewed in the context of study limitations. The sample included in this analysis may not be considered representative of the general population because patients were attending specialist memory clinics. Another limitation was that depression was not diagnosed with a standardized interview, although assessments were completed by experienced clinicians and informed by Diagnostic and Statistical Manual of Mental Disorders' criteria. In addition, the diagnosis of apathy was not completed with an apathy-specific scale, such as the Apathy Evaluation Scale, which would have allowed us to investigate subdomains of apathy (e.g., behavior, cognition, and emotional domains).[40] However, the assessment of apathy was completed by experienced clinicians as part of a structured assessment. Finally, we did not have data regarding age of first onset of NPS or biomarker data that may have allowed us to disentangle whether NPS caused, exacerbated, or occurred as a consequence of AD pathology.

## CONCLUSION

In summary, our findings indicate that patients with MCI with either apathy alone or apathy and depression are at a significantly greater risk of conversion to AD compared with patients with no NPS. Future studies focusing on the early detection and treatment of apathy and depression in patients with MCI should be explored to determine if this can reduce risk of AD.

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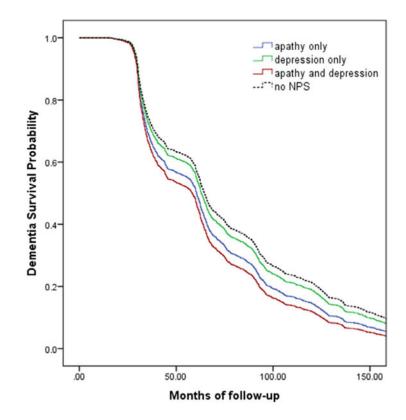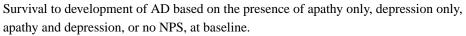
**FIGURE 1.**
Survival to development of AD based on the presence of apathy only, depression only, apathy and depression, or no NPS, at baseline.

**TABLE 1.**

Demographics and Medical History of Study Participants at Baseline

| | Apathy Only N=388 | Depression Only N=1514 | Apathy + Depression N=686 | No NPS N=2344 | Test Statistic and Degrees of Freedom: $\chi^2$(df) or F(df) | p Value |
|---|---|---|---|---|---|---|
| Age (mean, SD) | 73.9 (8.6) | 71.5(9.3) | 70.8(9.3) | 74.9 (8.8) | F(3,4931) = 60.9 | <0.001 |
| Sex (male, %) | 266 (68.6) | 606 (40.0) | 389 (56.7) | 1221 (52.1) | $\chi^2(3) = 129.9$ | <0.001 |
| Education (mean, SD) | 15.4(3.2) | 15.3(3.4) | 15.3(3.3) | 15.3(3.3) | F(3,4914) = 0.2 | 0.90 |
| MMSE (mean, SD) | 26.7(2.6) | 27.3 (2.4) | 27.0(2.6) | 27.2 (2.5) | F(3,4501) = 7.4 | <0.001 |
| Antidepressants (yes, %) | 47(12.2) | 819 (54.5) | 384 (56.2) | 181 (7.8) | $\chi^2(3)= 1272.6$ | <0.001 |
| Antipsychotic (yes, %) | 0 (0.0) | 51 (3.4) | 30 (4.4) | 10 (0.4) | $\chi^2(3)= 76.6$ | <0.001 |
| Anxiolytics (yes, %) | 45(11.7) | 277 (18.4) | 123(18.0) | 159(6.8) | $\chi^2(3)= 136.6$ | <0.001 |
| AD medications (yes, %) | 122(31.8) | 366 (24.3) | 216(31.6) | 461 (19.8) | $X^2(3)= 56.8$ | <0.001 |
| Heart attack (ever, %) | 27 (7.0) | 86 (5.7) | 38 (5.6) | 152(6.5) | $\chi^2(3)\,1.9$ | 0.60 |
| Atrial fibrillation (ever, %) | 25 (6.5) | 120 (8.0) | 47 (6.9) | 188(8.1) | $\chi^2(3)\,2.0$ | 0.58 |
| Stroke (ever, %) | 20 (5.2) | 95 (6.3) | 44 (6.5) | 125 (5.3) | $\chi^2(3)\,2.4$ | 0.50 |
| TIA (ever, %) | 25 (6.5) | 78 (5.2) | 36 (5.3) | 128 (5.5) | $\chi^2(3)\,1.0$ | 0.80 |
| Hypertension (ever, %) | 216(55.7) | 827 (54.8) | 391 (57.2) | 1253 (53.7) | $X^2(3) = 2.8$ | 0.42 |
| Diabetes (ever, %) | 65 (16.9) | 233 (15.4) | 106(15.5) | 325 (13.9) | $\chi^2(3)\,3.4$ | 0.33 |
| Hypercholesterolemia (ever, %) | 223 (57.9) | 827 (55.3) | 391 (57.5) | 1255 (54.2) | $\chi^2(3)\,3.6$ | 0.31 |
| Smoking (years, mean, SD) | 12.47 (21.0) | 14.61 (23.1) | 13.87 (21.8) | 12.37 (20.4) | F(3,4915) = 3.7 | 0.01 |
| Alcohol abuse (ever, %) | 18(4.7) | 128 (8.5) | 56 (8.2) | 77 (3.3) | $\chi^2(3)\,155.8$ | <0.001 |
| APOE4 allele (N, %) | 144(42.7) | 546(44.1) | 240 (42.6) | 813(41.1) | $X^2(3) = 2.9$ | 0.42 |

*Notes:* One-way analysis of variance for continuousvariables and the $\chi^2$test for categorical variables.df: degrees of freedom; MMSE: Mini-Mental State Examination; SD: standard deviation; TIA: transient ischemic attack.

**TABLE 2.**

Hazard Ratios for Development of AD for Each Predictor Variable in Bivariate Analyses

| Predictor Variable | N | Hazard Ratios (95% CI) | Wald $\chi^2$ | df, p Value |
|---|---|---|---|---|
| | | Demographics | | |
| Age | 4,932 | 1.00(0.99–1.00) | 1.47 | 1, 0.23 |
| Sex (male compared to female) | 4,932 | 1.06(0.97–1.17) | 1.66 | 1, 0.20 |
| Education (years) | 4,915 | 1.01(0.99–1.03) | 2.04 | 1, 0.15 |
| MMSE | 4,502 | 0.91 (0.89–0.92)[b] | 115.63 | 1, <0.001 |
| | Medical Conditions (Presence versus Absence) | | | |
| Diabetes | 4,915 | 1.01 (0.87–1.16) | 0.01 | 1, 0.91 |
| Hypercholesterolemia | 4,878 | 0.98(0.89–1.07) | | |
| Hypertension | 4,917 | 0.98(0.89–1.07) | 0.24 | 1, 0.62 |
| Heart attack | 4,921 | 0.99(0.81–1.21) | 0.004 | 1, 0.95 |
| Atrial fibrillation | 4,910 | 1.04(0.88–1.25) | 0.02 | 1, 0.63 |
| Stroke | 4,914 | 1.01 (0.82–1.25) | 0.01 | 1, 0.92 |
| TIA | 4,880 | 0.99(0.80–1.21) | 0.02 | 1, 0.89 |
| | Health Behaviors | | | |
| Smoking (years) | 4,919 | 1.00 (1.00–1.01)[a] | 7.56 | 1, 0.006 |
| Alcohol abuse (presence versus absence) | 4,919 | 1.03 (0.82–1.28) | 0.05 | 1, 0.82 |
| | Medications (Use versus No Use) | | | |
| Antidepressants | 4,894 | 1.20 (1.08–1.33)[b] | 11.02 | 1, 0.001 |
| Antipsychotics | 4,894 | 1.26(0.80–1.98) | 1.001 | 1, 0.32 |
| Anxiolytic | 4,894 | 0.98(0.83–1.15) | 0.07 | 1, 0.79 |
| AD medications | 4,894 | 1.50 (1.36–1.65)[b] | 63.29 | 1, <0.001 |
| | Other Risk Factors | | | |
| APOE4 allele (presence versus not) | 4,117 | 1.06(0.96–1.17) | 1.19 | 1, 0.28 |

CI: confidence interval; df: degrees of freedom; MMSE: Mini-Mental State Examination; TIA: transient ischemic attack.

[a] p<0.05.

[b] p<0.001.

**TABLE 3.**

Hazard Ratios for Development of AD for Each Predictor Variable in Multivariate Cox Proportional Hazard Survival Analyses

| Predictor Variables | Hazard Ratio (95% CI) | Wald $\chi^2$ | df, p Value |
|---|---|---|---|
| Apathy only | 1.24(1.05–1.47)[a] | 6.22 | 1, 0.013 |
| Depression only | 1.08 (0.95–1.22) | 1.30 | 1, 0.25 |
| Apathy and depression | 1.37(1.17–1.61)[b] | 14.70 | 1, <0.001 |
| Neither apathy nor depression (ref) | – | – | – |
| MMSE score | 0.91 (0.89–0.93)[b] | 104.70 | 1, <0.001 |
| Years of smoking | 1.003 (1.00–1.01)[a] | 8.98 | 1, 0.003 |
| Antidepressant use | 1.04 (0.92–1.18) | 0.46 | 1, 0.50 |
| No antidepressant use (ref) | – | – | – |
| AD medication use | 1.42 (1.28–1.58)[b] | 43.41 | 1, <0.001 |
| No AD medication use (ref) | – | – | – |

CI: confidence interval; df: degrees of freedom; MMSE: Mini-Mental State Examination; ref: reference group.

[a] p<0.05.

[b] p<0.001.

**TABLE 4.**

Odds Ratios for Development of AD for Each Predictor Variable in Binary Logistic Regression

| Predictor Variables | Odds Ratio (95% CI) | Wald $\chi^2$ | df, p Value |
|---|---|---|---|
| Apathy only | 1.48 (1.16–1.88)[a] | 10.02 | 1, 0.002 |
| Depression only | 1.09 (0.92–1.23) | 1.07 | 1, 0.30 |
| Apathy by depression | 0.66 (0.48–0.91)[a] | 6.60 | 1, 0.01 |
| MMSE score | 0.84 (0.82–0.86)[b] | 165.64 | 1, <0.001 |
| Years of smoking | 0.998(0.995–1.001) | 1.63 | 0.20 |
| Antidepressant use | 0.85 (0.72–1.01) | 3.50 | 0.06 |
| No antidepressant use (ref) | – | – | – |
| AD medication use | 2.89 (2.49–3.34)[b] | 199.06 | 1, <0.001 |
| No AD medication use (ref) | – | | |

CI: confidence interval; df: degrees of freedom; MMSE: Mini-Mental State Examination; ref: reference group.

[a] p<0.05.

[b] p<0.001.

**TABLE 5.**

Odds Ratios for Development of AD for Each Predictor Variable in Binary Logistic Regression in MCI Patients With Apathy

| Predictor Variables | Odds Ratio (95% CI) | Wald $\chi^2$ | df, p Value |
|---|---|---|---|
| Depression only | 0.70 (0.52–0.95)[a] | 5.28 | 1, 0.02 |
| MMSE score | 0.86 (0.82–0.91)[b] | 27.91 | 1, <0.001 |
| Years of smoking | 1.001 (0.995–1.01) | 0.19 | 1, 0.67 |
| Antidepressant use | 0.91 (0.67–1.23) | 0.36 | 1, 0.55 |
| No antidepressant use (ref) | – | – | – |
| AD medication use | 2.52 (1.90–3.35)[b] | 40.56 | 1, <0.001 |
| No AD medication use (ref) | – | – | – |

CI: confidence interval; df: degrees of freedom; MMSE: Mini-Mental State Examination; ref: reference group.

[a]
p<0.05.

[b]
p<0.001.

**TABLE 6.**

Odds Ratios for Development of AD for Each Predictor Variable in Binary Logistic Regression in MCI Patients With No Apathy

| Predictor Variables | Odds Ratio (95% CI) | Wald $\chi^2$ | df, p Value |
|---|---|---|---|
| Depression only | 1.11 (0.93–1.32) | 1.31 | 1, 0.25 |
| MMSE score | 0.83 (0.80–0.86)[a] | 138.64 | 1, <0.001 |
| Years of smoking | 0.997 (0.994–1.001) | 2.67 | 1, 0.10 |
| Antidepressant use | 0.83 (0.68–1.01) | 3.42 | 1, 0.06 |
| No antidepressant use (ref) | – | – | – |
| AD medication use | 3.02 (2.55–3.59)[a] | 159.22 | 1, <0.001 |
| No AD medication use (ref) | – | – | – |

CI: confidence interval; df: degrees of freedom; MMSE: Mini-Mental State Examination; ref: reference group.

[a] p<0.001.