



Self-reported obstructive sleep apnea, amyloid and tau burden, and Alzheimer's disease time-dependent progression

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Abstract

INTRODUCTION: Obstructive Sleep Apnea (OSA) is associated with Alzheimer's disease (AD) biomarkers in cognitive normal (CN) and mild cognitive impaired (MCI) participants. However, independent and combined effects of OSA, A β and tau-accumulation on AD time-dependent-progression risk is unclear.

METHODS: Study participants grouped by biomarker profile, as described by the A/T/N scheme, where "A" refers to aggregated A β , "T" aggregated tau and "N" to neurodegeneration, included 258 CN (OSA+ [A+/TN+ n=10, A+/TN- n=6, A-/TN+ n=10, A-/TN- n=6 and OSA- [A+/TN+ n=84, A+/TN- n=11, A-/TN+ n=96, A-/TN- n=36]) and 785 MCI (OSA+ [A+/TN+ n=35, A+/TN- n=15, A-/TN+ n=25, A-/TN- n=16 and OSA- [A+/TN+ n=388, A+/TN- n=28, A-/TN+ n=164, A-/TN- n=114]) older-adults from Alzheimer's Disease Neuroimaging Initiative cohort.

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Cox proportional hazards regression models estimated the relative hazard of progression from CN-to-MCI and MCI-to-AD, among baseline OSA CN and MCI-patients respectively. Multi-level logistic mixed-effects models with random intercept and slope investigated the synergistic associations of self-reported OSA, A β and Tau burden with prospective cognitive decline.

RESULTS: Independent of TN-status (CN and MCI), OSA+/A β + participants were approximately two to four times more likely to progress to MCI/AD ($p < .001$) and progressed six to eighteen months earlier ($p < .001$), compared to other participants combined (*i.e.* OSA+/A β -, OSA-/A β + and OSA-/A β -). Notably, OSA+/A β - vs. OSA-/A β - (CN and MCI) and OSA+/TN- vs. OSA-/TN- (CN) participants showed no difference in the risk and time-to-MCI/AD progression. Mixed effects models demonstrated OSA synergism with A β (CN and MCI [$\beta = 1.13$, 95%CI, 0.74 to 1.52, and $\beta = 1.18$, 95%CI, 0.82 to 1.54]) respectively, and with tau ([MCI ($\beta = 1.31$, 95%CI, 0.87 to 1.47)], $p < 0.001$ for all).

DISCUSSION: OSA acts in synergism with A β and with tau, and all three acting together result in synergistic neurodegenerative mechanisms especially as A β and tau-accumulation becomes increasingly-abnormal, thus leading to shorter progression time-to-MCI/Alzheimer's disease (AD) in CN and MCI-OSA patients respectively.

Keywords

Obstructive sleep apnea; Alzheimer's disease; Longitudinal study, CSF-biomarkers; Brain amyloid-PET; A β 42; T-tau; P-tau

1. INTRODUCTION

Obstructive Sleep Apnea (OSA) increases Alzheimer's disease (AD) risk¹⁻⁶ and at cross-section, is associated with AD biomarkers, including the presence of significant brain A β and tau burden, measured either by cerebrospinal (CSF) A β 42 or amyloid PET, and CSF levels of tau (*i.e.* total or hyperphosphorylated) or tau-PET, in both cognitive normal (CN) and mild cognitive impaired (MCI) participants.⁷⁻¹⁴ Recently, our group found that this cross-sectional association was not found in participants with PiB-negative scans,¹⁵ suggesting that the presence or absence of amyloid burden might act as a moderator in these relationships. A previous cross-sectional study suggested a similar phenomenon, with associations seen between increased amyloid deposition and higher apnea hypopnea index (AHI) indices in MCI patients but not among CN controls.¹¹ More recently, we expanded the analysis of cross-sectional evaluations to 2-year follow-ups, first, in community-dwelling healthy CN elderly from New York City,¹⁵ and second, from purely CN older individuals to those across the spectrum of dementia, from CN to MCI and to full AD in a large population from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.¹⁶ In the NYU sample, we examined the association between severity of OSA and longitudinal increase in amyloid burden and found that OSA severity was associated with greater CSF A β 42 changes over a 2-year follow-up in CN older-adults.¹⁵ In the ADNI sample, we examined the effect of self-reported clinical diagnosis of OSA on longitudinal changes in brain amyloid-PET and CSF-biomarkers (A β 42, T-tau and P-tau) in CN, MCI and AD older-adults and observed OSA effects on longitudinal increases in amyloid burden by both CSF and PET imaging measures, in the CN and MCI groups.¹⁶

Molecular markers of AD pathology (e.g. amyloid PET uptake and CSF A β 42 levels), are known robust predictors of amyloid burden and of future development of AD,^{17,18} and evidence indicates that A β accumulation starts decades prior to the appearance of the first cognitive symptoms.^{19,20} In previous studies, the lack of longer clinical assessment prevented testing whether amyloid or tau deposition in OSA participants precedes subsequent cognitive decline to MCI or AD. In this study, we tried to overcome this limitation, and hypothesized that OSA's effect on MCI/AD progression risk will be synergistic with A β and tau and this risk will significantly increase, as A β and tau accumulation becomes increasingly abnormal leading to shorter time-to-MCI/AD in CN and MCI participants respectively. Having previously demonstrated a contributory role of OSA on longitudinal increases in amyloid burden by both CSF and PET imaging measures, in CN and MCI patients, our objectives were to (i) to examine whether OSA has a direct neurotoxic and/or neurodegenerative effect that is independent of A β or tau, sufficient to induce a prospective clinical diagnosis of cognitive decline, and (ii) to examine whether OSA's direct neurotoxicity independent of A β or tau, together with OSA's indirect effect that promotes A β or tau accumulation, combine to act synergistically to significantly increase MCI/AD progression risk.

2. METHODS

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). Launched in 2003 as a public-private partnership, and led by Principal Investigator Michael W. Weiner, MD, ADNI's primary goal has been to measure the progression of MCI and early AD using a combination of serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments. Currently, ADNI has recruited over 2,000 adults aged 55-90, consisting of CN, MCI, and early AD. PET and CSF sampling follow-up typically occurs every 1-2 years.

2.1 Study Participants

Participant selection (see supplementary figure) using ADNI data by our group has been previously described.^{2,21} Participants in the current study included 1043 subjects: 258 CN and 785 MCI with one or more clinical follow-up assessments. Subjects for this study must have undergone Florbetapir-PET imaging while carrying a clinical diagnosis of CN or MCI. The primary outcome was time-to-progression from a clinical diagnosis of CN to a clinical diagnosis of MCI for baseline CN patients and, from MCI to a clinical diagnosis of AD, for baseline MCI patients. Neuropsychometric assessments and serial PET-MRI scans were performed at baseline and periodically on participants. Details are available at <http://www.adni-info.org>. Participants were classified as CN or MCI at the time of their baseline visit and remained as CN or MCI up to and including their 12-month visit. Patient diagnosis was recorded at 6 to 12 monthly intervals up until the download date (12/06/2018). CN and MCI subjects were classified as converters if they converted to MCI and AD between 12 months and the download date, respectively.

2.2 Standard protocol approvals, registrations, and patient consent

Written informed consent was obtained from all patients participating in ADNI, as approved by the Institutional Review Board, at each of the ADNI participating centers. ADNI inclusion and exclusion criteria are detailed elsewhere (http://adni.loni.ucla.edu/wp-content/uploads/2010/09/ADNI_GeneralProceduresManual.pdf).

2.3 OSA Diagnosis

As previously described,^{2,16} presence or absence of OSA was based on medical history of a self-reported clinical diagnosis of OSA during the clinical interview. Briefly, participants labeled OSA-positive (OSA+) reported a medical diagnosis of “sleep apnea” “sleep disordered breathing” “OSA” or “SDB” and the remaining participants were considered OSA-negative (OSA-). We ensured proper group allocation from reviewed medical history clinical notes from the ADNI download.

2.4 CN, MCI and AD Diagnosis

ADNI criteria for subject classification are described elsewhere.²² Briefly, CN and MCI subjects scored between 24-30 on the Mini-Mental State Examination (MMSE) while AD subjects scored between 20-26. MCI and AD participants had global Clinical Dementia Rating (CDR) scores of 0.5 and 1, respectively. The diagnosis of AD was made using established clinical criteria.²³

2.5 Florbetapir-PET Imaging Acquisition and Interpretation

Information on florbetapir-pet imaging acquisition and interpretation is available at https://adni.loni.usc.edu/wp-content/uploads/2010/05/ADNI2_PET_Tech_Manual_0142011.pdf, <http://adni.loni.usc.edu/updated-florbetapir-av-45-pet-analysis-results/>. As described previously,²¹ the University of California at Berkeley (UC Berkeley) uploaded ADNI florbetapir summary data to the Laboratory of Neuroimaging (LONI).^{24,25} Calculation of florbetapir standardized uptake value ratios (SUVRs) were done by obtaining means across 4 cortical regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) and dividing this cortical summary region of interest (ROI) by one of the five reference regions (cerebellar grey matter, whole cerebellum, brainstem/pons, eroded subcortical white matter, and a composite reference region). The UC Berkeley team using procedures that involved receiver-operating-characteristic analysis,^{24,25} defined thresholds for A β -positive and -negative status as florbetapir cutoff of >1.11 and <1.11, respectively using the whole cerebellum reference region only.

2.6 Cerebrospinal Fluid Methods (CSF)

CSF bio-specimen data collection details can be found at <http://adni.loni.usc.edu/data-samples/biospecimen-data/> and as previously described²¹. A standardized protocol was implemented to quantify biomarker concentrations in each of the CSF baseline aliquots using a multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3, Ghent, Belgium; for research use only reagents) immunoassay kit-based reagents, validated in Vanderstichele et al.²⁶ and Shaw et al.²⁷ Further details can be found at (<http://www.adni-info.org/index.php>). Using the recently published 2018 NIA-AA

“research framework” for the diagnosis of AD,²⁸ ADNI participant were grouped by biomarker profile, as described by the A/T/N scheme,²⁹ where “A” refers to aggregated A β , “T” aggregated tau and “N” to neurodegeneration. Each biomarker group is dichotomized as negative (–) or positive (+) based on specified biomarkers levels. In the present study, as noted above, florbetapir-PET cutoff of >1.11 and <1.11 defined thresholds for A β -positive and -negative status, respectively because the correlation between ADNI CSF abeta and Florbetapir biomarkers is limited to a middle range of values, is modified by the APOE genotype, and is absent for longitudinal changes.³⁰ Following recent studies that used ADNI data,^{31,32} “T+” individuals had CSF P-tau181 > 21.8 pg/ml and “N+” individuals had T-tau > 245 pg/ml. We merged the aggregated tau (T) and neurodegeneration (N) groups in order to decrease the number of groups to be compared.^{31,32} TN negative (TN–) was defined as having both the aggregated tau (T) and neurodegeneration (N) biomarkers in the normal range (T– and N–, that is P-tau181 < 21.8 pg/ml and T-tau < 245 pg/ml). Participants were classified as TN positive (TN+) if either aggregated tau (T) or neurodegeneration (N) were abnormal (T+ or N+, that is P-tau181 > 21.8 pg/ml or T-tau > 245 pg/ml). None of the individuals of the total differed between the T and N biomarkers groups.

2.7 Data analyses

All analyses were conducted separately for each clinical group (*i.e.* CN, and MCI) in phases. First, survival and cumulative hazard function estimates and their 95% Hall-Wellner bands were populated for both the CN and MCI groups, comparing OSA+ vs. OSA–, A β + vs. A β –, and TN+ vs. TN–patients, respectively. Second, similar survival and cumulative hazard function estimates were populated comparing OSA+ vs. OSA– within dichotomized A β and TN groups (*i.e.* A β + / OSA+ vs. A β + / OSA–, A β – / OSA+ vs. A β – / OSA–, TN+ / OSA+ vs. TN+ / OSA– and TN– / OSA+ vs. TN– / OSA–). The above analyses were also performed comparing A β + vs. A β – and TN+ vs. TN– stratifying by OSA status (*i.e.* OSA+ / A β + vs. OSA+ / A β –, OSA– / A β + vs. OSA– / A β –, OSA+ / TN+ vs. OSA+ / TN– and OSA– / TN+ vs. OSA– / TN–), for both the CN and MCI groups. The analysis comparing CN and MCI OSA+ vs. OSA– among only A β + or TN+ participants examined the combined effects of OSA and A β 42 or OSA, tau accumulation and neurodegeneration on progression risk, respectively. The analysis comparing CN and MCI OSA+ vs. OSA– among only A β – or TN– participants examined whether OSA, independent of A β or tau accumulation and neurodegeneration, was sufficient to induce a prospective clinical diagnosis of cognitive decline respectively. The analysis comparing CN and MCI A β + vs. A β – or TN+ vs. TN–, among only OSA+ participants examined the combined effects of OSA and A β 42 or OSA, tau accumulation and neurodegeneration on progression risk beyond that of OSA. The analysis comparing CN and MCI A β + vs. A β – or TN+ vs. TN– among only OSA– participants examined the individual effect of A β or of tau accumulation and neurodegeneration on AD progression risk among OSA– subjects. Mean and Median time-to-event for all the groups were estimated. Cox proportional hazards regression models estimated the individual and combined effects of OSA and A β load, and OSA and TN burden on the relative hazard of progression from CN to MCI and MCI to AD, among baseline CN and MCI patients respectively. To investigate the additive or synergistic associations of self-reported OSA, A β and Tau burden with prospective cognitive decline, multi-level logistic mixed-effects models with random intercept and slope were used. We

examined interactions of self-reported OSA with time, A β burden with time, and Tau burden with time in a single model (*e.g.* model 1: CN to MCI: OSA \times time + A β \times time + Tau \times time + covariates \times time). Next, we added an interaction term between the OSA, A β burden, and time, and OSA, Tau burden and time, to examine whether these 2 factors increase the likelihood of prospective cognitive decline beyond their separate effects (*i.e.*, synergistic effect; model 2: CN to MCI: OSA \times A β \times time + OSA \times Tau \times time + covariates \times time). Lastly, we added an interaction term between the OSA, A β burden, Tau and time, to examine whether these 3 factors increase the likelihood of prospective cognitive decline beyond their combined effects in model 2 (*i.e.*, synergistic effect; model 3: CN to MCI: OSA \times A β \times Tau \times time + covariates \times time). We operationalized time as years from baseline for each participant. For all analyses, final models adjusted for age, sex, BMI, education, CPAP-use, baseline biomarker data, hypertension, diabetes, history of cardiovascular disease (*e.g.* including ischemic heart disease, heart failure, and stroke/TIA), alcohol use, and history of traumatic brain injury. We also performed sensitivity analyses removing CPAP-users from OSA+ participants. Statistical analyses were performed using SAS (*version 9.4; SAS Institute Inc., Cary, NC*).

3. RESULTS

3.1 Demographic and Clinical Characteristics

Tables 1 and 2 show the demographic and clinical characteristics of study participants at baseline according to their OSA and A β status, and OSA and A/T/N status respectively. Overall, of the 1043 participants, 506 (49%) were women. The overall mean (SD) age was 74.7 (5.0) years and the overall mean (SD) follow-up time was 5.5 (1.7) years (Range: 2.7 - 10.9 years). The mean (SD) follow-up time was 5.3 (1.4) and 5.7 (1.9) for CN and MCI groups, respectively. The mean ages of OSA+ and OSA- (CN and MCI combined) were 72.3 \pm 7.1 and 73.9 \pm 7.3 years, respectively. In the CN group, 31 participants (12% [6% A β + {4% TN+}] and [6% A β - {4% TN+}]) were OSA+, and 91 participants (11% [6% A β + {4% TN+}] and [5% A β - {3% TN+}]) were OSA+ in the MCI group. In both the CN and MCI groups, and in both OSA and non-OSA participants, marked differences existed in AD pathology markers comparing A β + to A β -, with the former having significantly lower CSF-A β 42, and higher levels of CSF T-tau and CSF P-Tau (Table 1). A+/TN+ subjects in both NL and MCI groups were more likely to be APOE4 carriers (Table 2). Participants who were OSA+/A β + had significantly higher BMI in the CN group but not in the MCI group, compared to other participants with varying OSA and A β status. In both CN and MCI, OSA +/A β +/TN+ participants had higher vascular burden (*i.e.* higher rates of hypertension, diabetes and cardiovascular disease) compared to OSA-/A β + participants (*e.g.* 7/10 [70%] vs. 30/84 [36%] for hypertension in CN participants) (Table 2). CN/OSA+/A β + participants had significantly lower educational level (Table 1).

3.2 Time dependent progression risk and cumulative hazard function estimates in CN group

Figure 1 shows survival and cumulative hazard function estimates and their 95% Hall-Wellner bands populated for the CN group. Compared to OSA- participants, OSA+ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 4.5

± 0.3 [4.0] years vs. 5.0 ± 0.3 [4.8] years, $p = 0.03$), and had a 32% increased hazard risk of developing MCI (adjusted hazard ratio [aHR]:1.32, 95% confidence interval [CI]:1.11–1.65, $p < 0.01$). Compared to A β ⁻ participants, A β ⁺ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 3.6 ± 0.5 [2.6] years vs. 4.2 ± 0.5 [3.0] years, $p < 0.001$), and a significantly higher risk of developing MCI (aHR: 2.44, 95% CI: 1.99 - 2.89, $p < 0.001$). Compared to TN⁻ participants, TN⁺ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 3.4 ± 0.4 [2.5] years vs. 4.7 ± 0.6 [4.3] years, $p < 0.001$), and a significantly higher risk of developing MCI (aHR: 3.52, 95% CI: 1.89 - 5.17, $p = 0.01$). See Table 3.

Stratifying by brain A β or TN burden, A β ⁺/OSA⁺ and TN⁺/OSA⁺ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 3.5 ± 0.4 [2.9] years vs. 3.8 ± 0.3 [3.5] years, $p = 0.04$ and 3.3 ± 0.3 [2.8] years vs. 3.8 ± 0.3 [3.0] years, $p < 0.001$) and a significantly higher risk of developing MCI (aHR: 2.93, 95% CI: 2.17 – 3.69, and aHR: 2.04, 95% CI: 1.11 – 2.97, $p < 0.001$ for both) compared to A β ⁺/OSA⁻ and TN⁺/OSA⁺ participants, respectively. Compared to A β ⁻/OSA⁻ and TN⁻/OSA⁻ participants, A β ⁻/OSA⁺ and TN⁻/OSA⁺ participants showed no significant difference in time-to-progression to MCI (mean \pm SD [median] 3.9 ± 0.6 [3.3] years vs. 4.1 ± 0.5 [4.0] years, and aHR: 1.01, 95% CI: 0.76 – 1.26, $p = 0.11$ and mean \pm SD [median] 4.5 ± 0.4 [4.0] years vs. 5.3 ± 0.6 [4.5] years, and aHR: 1.01, 95% CI: 0.76 – 1.26, $p = 0.06$, respectively). See Table 3.

Stratifying by OSA status, OSA⁺/A β ⁺ participants showed no significant difference in time-to-progression to MCI (mean \pm SD [median] 3.5 ± 0.4 [3.5] years vs. 3.9 ± 0.6 [3.3] years, $p = 0.49$ and aHR: 2.16, 95% CI: 0.87 – 3.45, $p = .12$), relative to OSA⁺/A β ⁻ participants. However, OSA⁺/TN⁺ participants demonstrated significant difference in time-to-progression to MCI (mean \pm SD [median] 3.3 ± 0.3 [2.8] years vs. 4.5 ± 0.4 [4.0] years, and aHR: 3.31, 95% CI: 1.36 – 5.27, $p = .03$), relative to OSA⁺/TN⁻ participants. Relative to OSA⁻/A β ⁻ and OSA⁻/TN⁻ participants, OSA⁻/A β ⁺ and OSA⁻/TN⁺ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 3.8 ± 0.3 [2.9] years vs. 4.1 ± 0.5 [4.0] years, $p = 0.05$ and mean \pm SD [median] 3.8 ± 0.3 [3.0] years vs. 5.3 ± 0.6 [4.5] years, $p = 0.03$, respectively), and a significantly higher risk of developing MCI (aHR: 2.47, 95% CI: 2.06 - 2.88, $p < 0.001$ and aHR: 3.46, 95% CI: 1.78 – 5.14, $p = 0.02$, respectively).

Stratifying by TN status OSA⁺/A β ⁺/TN⁺ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 2.8 ± 0.4 [2.5] years vs. a combined 3.9 ± 0.4 [3.2] years, $p < 0.01$) and a significantly higher risk of developing MCI (aHR: 3.17, 95% CI: 1.19 – 5.15, $p < 0.01$) when compared to other TN⁺ participants combined (*i.e.* OSA⁺/A β ⁻/TN⁺, OSA⁻/A β ⁺/TN⁺ and OSA⁻/A β ⁻/TN⁺). Furthermore, OSA⁺/A β ⁺/TN⁻ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 4.1 ± 0.4 [4.0] years vs. a combined 5.0 ± 0.5 [4.5] years, $p < 0.01$) and a significantly higher risk of developing MCI (aHR: 1.49, 95% CI: 1.06 – 2.84, $p < 0.01$) when compared to other TN⁻ participants combined (*i.e.* OSA⁺/A β ⁻/TN⁻, OSA⁻/A β ⁺/TN⁻ and OSA⁻/A β ⁻/TN⁻).

3.3 Time dependent progression risk and cumulative hazard function estimates in MCI group

Figure 2 shows survival and cumulative hazard function estimates and their 95% Hall-Wellner bands populated for the MCI group. Compared to OSA– participants, OSA+ participants had a significantly shorter time-to-progression to AD (mean \pm SD [median] 4.6 ± 0.3 [4.2] years vs. 6.0 ± 0.3 [5.3] years, $p=0.01$), and a significantly higher risk of developing AD (aHR: 2.47, 95% CI: 1.79 – 3.15, $p=0.01$). Compared to A β – participants, A β + participants had a significantly shorter time-to-progression to AD (mean \pm SD [median] 3.8 ± 0.5 [2.8] years vs. 4.2 ± 0.5 [3.6] years, $p < 0.001$), and a significantly higher risk of developing AD (aHR: 2.62, 95% CI: 2.17 – 3.07, $p < 0.001$). Compared to TN– participants, TN+ participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 4.0 ± 0.3 [3.8] years vs. 4.9 ± 0.4 [4.6] years, $p < 0.001$), and a significantly higher risk of developing MCI (aHR: 3.34, 95% CI: 1.79 – 4.89, $p < 0.001$). See Table 4.

Stratifying by brain A β or TN burden, A β +/OSA+ and TN+/OSA+ participants had a significantly shorter time-to-progression to AD (mean \pm SD [median] 3.6 ± 0.4 [2.8] years vs. 4.7 ± 0.3 [3.6] years, $p = 0.01$ and mean \pm SD [median] 3.8 ± 0.3 [3.7] years vs. 4.9 ± 0.6 [4.5] years, $p < 0.01$) and a significantly higher risk of developing AD (aHR: 2.78, 95% CI: 2.22 – 3.34, and aHR: 2.72, 95% CI: 1.17 – 4.27, $p < 0.001$ for both) compared to A β +/OSA– and TN+/OSA+ participants, respectively. Compared to A β –/OSA– participants, A β –/OSA+ participants showed no significant difference in time-to-progression to AD (mean \pm SD [median] 4.5 ± 0.3 [3.9] years vs. 5.1 ± 0.3 [4.0] years, $p = 0.61$ and aHR: 1.17, 95% CI: 0.86 – 1.48, $p = 0.07$). However, compared to TN–/OSA– participants, TN–/OSA+ participants had significantly shorter time-to-progression to AD and a significantly higher risk of developing AD (mean \pm SD [median] 4.8 ± 0.5 [4.5] years vs. 5.1 ± 0.6 [4.9] years, and aHR: 2.78, 95% CI: 2.22 – 3.34, $p < 0.01$ for both).

Stratifying by OSA status, OSA+/A β + and OSA+/TN+ participants had a significantly shorter time-to-progression to AD (mean \pm SD [median] 3.6 ± 0.4 [2.8] years vs. 4.5 ± 0.3 [3.9] years, and median 3.8 ± 0.6 [3.7] years vs. 4.8 ± 0.5 [4.5] years $p < 0.001$ for both) and a significantly higher risk of developing AD (aHR: 2.16, 95% CI: 2.04 – 2.32, and aHR: 3.37, 95% CI: 1.86 – 4.88, $p < 0.001$ for both), relative to OSA+/A β – and OSA+/TN– participants, respectively. In addition, compared to OSA–/A β – and OSA–/TN– participants, OSA–/A β + and OSA–/TN+ participants had a significantly shorter time-to-progression to AD (mean \pm SD [median] 4.7 ± 0.3 [3.6] years vs. 5.1 ± 0.3 [4.0] years, and mean \pm SD [median] 4.9 ± 0.3 [4.5] years vs. 5.1 ± 0.6 [4.9] years $p < 0.001$ for both), and a significantly higher risk of developing AD (aHR: 2.55, 95% CI: 2.13 – 2.98, and aHR: 2.76, 95% CI: 1.11 – 4.41, $p < 0.001$ for both), respectively.

Stratifying by TN status, OSA+/A β +/TN+ participants had a significantly shorter time-to-progression to AD (mean \pm SD [median] 3.5 ± 0.3 [3.3] years vs. a combined 4.5 ± 0.5 [4.3] years, $p < 0.01$) and a significantly higher risk of developing MCI (aHR: 3.47, 95% CI: 1.96 – 4.98, $p < 0.01$) when compared to other TN+ participants combined (*i.e.* OSA+/A β –/TN+, OSA–/A β +/TN+ and OSA–/A β –/TN+). Furthermore, OSA+/A β +/TN– participants had a significantly shorter time-to-progression to MCI (mean \pm SD [median] 4.4 ± 0.4 [4.1] years vs. a combined 5.5 ± 0.4 [5.1] years, $p < 0.01$) and a significantly higher risk of developing

MCI (aHR: 1.23, 95% CI: 1.03 – 2.43, $p < 0.001$) when compared to other TN– participants combined (*i.e.* OSA+/A β –/TN–, OSA–/A β +/TN– and OSA–/A β –/TN–).

3.4. Interactive Associations of OSA, A β and Tau burden with risk of conversion in CN and MCI

In CN participants, conversion risk from CN to MCI was associated with self-reported OSA ($\beta = 0.42$; 95%CI, 0.13 to 0.70; $p < 0.01$), higher A β burden ($\beta = 0.55$; 95%CI, 0.22 to 0.89; $p < 0.001$), and higher Tau burden ($\beta = 1.2$; 95%CI, 0.63 to 1.77; $P < .001$). The interactions of self-reported OSA and A β burden, and self-reported OSA, A β and Tau burden with time were significant ($\beta = 1.13$, 95%CI, 0.74 to 1.52; $p < 0.001$ and $\beta = 1.38$, 95%CI, 0.99 to 1.76; $p < 0.001$, respectively), suggesting a synergistic effect. However, the interaction of self-reported OSA and Tau burden with time was not significant ($\beta = 0.82$, 95%CI, –0.11 to 1.32; $p = 0.07$) suggesting that the presence of OSA did not modify the relationship between tau and cognitive decline in CN participants. See supplemental table.

In MCI participants, conversion risk from MCI to AD was associated with self-reported OSA ($\beta = 0.84$; 95%CI, 0.49 to 1.18; $p < 0.01$), higher A β burden ($\beta = 1.01$; 95%CI, 0.58 to 1.45; $p < 0.001$), and higher Tau burden ($\beta = 1.23$; 95%CI, 0.57 to 1.68; $P < .001$). The interactions of self-reported OSA and A β burden, self-reported OSA and Tau burden and self-reported OSA, A β and Tau burden with time were significant ($\beta = 1.18$, 95%CI, 0.82 to 1.54; $p < 0.001$, $\beta = 1.31$, 95%CI, 0.87 to 1.47; $p < 0.001$ and $\beta = 1.39$, 95%CI, 0.95 to 1.75; $p < 0.001$, respectively), suggesting a synergistic effect. See supplemental table.

3.4 Sensitivity analysis removing CPAP-users

Sensitivity analysis removing CPAP-users (CN: $n=8$ [A β + = 6, A β – = 2]; MCI: $n=31$ [A β + = 10, A β – = 21]) from OSA+ participants had negligible impact on the estimates (*e.g.* CN OSA+/ A β + vs. OSA+/ A β – aHR: 2.16, 95% CI: 0.87 – 3.45, $p = 0.12$ changed to aHR: 2.21, 95% CI: 0.92 – 3.51, $p = 0.09$ and MCI A β +/OSA+ vs. A β +/ OSA– aHR: 2.78, 95% CI: 2.22 – 3.34, $p < 0.001$ changed to aHR: 2.82, 95% CI: 2.31 – 3.33, $p < 0.001$). We attribute this negligible impact on the findings to data showing low CPAP compliance rates (<50%) with majority of CPAP dropouts occurring early in treatment, and relatively fewer patients discontinuing use as time with CPAP increases.^{33,34} Moreover, the extremely small sample size of history of CPAP users prevented stratified analyses examining the beneficial effects of CPAP especially in the CN group. Subgroup analyses as was conducted in this study precluded testing the effects of CPAP on cognitive deterioration in this ADNI group as some groups had zero participant.

4. DISCUSSION

The major objective of this study was to evaluate the effect of OSA on AD time-dependent progression risk in older CN and MCI elderly participants from the ADNI cohort and to quantify its effect on the risk of progression as A β and Tau accumulation become increasingly abnormal. Our major findings were the following: (i) Both CN and MCI OSA+ participants had a significantly increased risk and shorter time-to-progression to MCI and AD respectively compared to OSA– participants. (ii) Both CN and MCI A β + and TN+

participants respectively, had a significantly increased risk and shorter time-to-progression to MCI and AD compared to A β - and TN- participants. (iii) Among only A β + and TN+ participants respectively, both CN and MCI OSA+ participants had a significantly increased risk and shorter time-to-progression to MCI and AD compared to OSA- participants. (v) Among only A β - and TN- participants respectively, there was no difference in the risk and time-to-progression to MCI between CN OSA+ vs. OSA- participants. This association varied in MCI OSA+ vs. OSA- participants, with significantly increased risk and shorter time-to-progression to AD seen only in TN- participants. (vi) Among only OSA+ participants, only MCI A β + participants had a significantly increased risk and shorter time-to-progression to AD respectively compared to A β - participants. Both CN and MCI TN+ participants had a significantly increased risk and shorter time-to-progression to AD respectively compared to TN- participants. (vii) Among only OSA- participants, both CN and MCI A β + and TN+ participants had a significantly increased risk and shorter time-to-progression to MCI and AD respectively compared to A β - and TN- participants, respectively. (viii) In both CN and MCI participants, the interactions of self-reported OSA and A β burden, and self-reported OSA, A β and Tau burden with time were significant, suggesting a synergistic effect. However, in CN participants, the interaction of self-reported OSA and Tau burden with time was not significant.

This is the first study showing a shorter progression time-to-MCI/AD in both CN and MCI OSA+ participants respectively. This finding is consistent with our previous study showing that OSA patients had an earlier onset age to MCI or AD.² In this study, both CN and MCI OSA+ participants progressed to MCI and AD respectively, six to eight months earlier than OSA- participants did. In addition, our recent study showed both CN and MCI OSA+ subjects experiencing faster annual increase in florbetapir uptake and decrease in CSF A β 42 levels, as well as increases in CSF T-tau and P-tau compared with OSA- participants.¹⁶ Thereby suggesting that OSA appears to accelerate increases in amyloid deposition, CSF T-tau and P-tau levels over time, both in CN and MCI individuals. Thus possibly significantly reducing the time to MCI or AD progression.² Our results on OSA increasing AD progression risk are consistent with previous prospective studies indicating that individuals with OSA have an elevated risk of developing MCI or AD.^{1,3,4,35,36}

Our results showing A β load increasing MCI or AD progression risk in both CN and MCI participants are consistent with well-established findings from previous studies showing that CN and MCI elderly participants with positive PIB-PET and low CSF A β 42 show associations with cognitive decline,^{37,38} and have an elevated risk of AD progression respectively.³⁹ Our results showing A β load predicting a shorter progression time-to-MCI/AD in both CN and MCI participants are consistent with well-established findings from previous studies showing A β + CN and MCI subjects more likely to progress to MCI^{40,41} and AD,⁴²⁻⁴⁴ in short-term follow-up than A β - CN and MCI individuals respectively. Our tau findings showing tau accumulation and neurodegeneration increasing MCI or AD progression risk and predicting a shorter progression time-to-MCI/AD are in line with established evidence of strong associations between cortical neurofibrillary tangle load and cognitive impairment.⁴⁵

In both A β + CN and MCI participants (*i.e.* with evidence of AD pathologic change), the risk of progression to MCI and AD was approximately two and three times that of A β - participants, respectively. In both TN+ CN and MCI participants (*i.e.* evidence of tau accumulation and neurodegeneration), the risk of progression to MCI and AD was approximately three and four times that of TN- participants, respectively (regardless of OSA status in TN+ CN participants). The combined risk of progressing to MCI and AD in the CN and MCI OSA+/A β + and MCI OSA+/TN+ participants was approximately thrice that of CN and MCI OSA-/A β + participants, and four to five times that of MCI OSA-/TN+ participants, respectively. In addition, the combined risk of progression to MCI and AD amongst CN and MCI OSA+/A β + and OSA+/TN+ participants was approximately three and four times that of OSA-/A β - and OSA-/TN- participants, respectively ($p < .01$). The interactions of self-reported OSA and A β burden and self-reported OSA and TN burden with time were significant. Thereby suggesting that OSA's effect on MCI/AD progression risk is: (i) independently synergistic with A β and Tau, and (ii) significantly increases as A β and Tau accumulation becomes increasingly abnormal. The literature suggests that intermittent hypoxia^{46,47} and sleep fragmentation^{48,49} that are causes for excessive daytime sleepiness (EDS), are two main processes by which OSA may induce neurodegenerative changes and promote the accumulation of A β 42. However, we also know that chronic intermittent hypoxia, hypercapnia and hypertension in OSA can also induce neuronal damage, including axons,⁵⁰ white matter,⁵¹ and reduced diffusion tensor imaging (DTI) based mean diffusivity in multiple brain regions.⁵² This suggests that OSA could promote neurotoxicity that is independent of hypoxia-induced A β 42 accumulation, thereby resulting in possible synergistic neurodegenerative mechanisms with A β 42 accumulation on AD progression risk. Notably, the synergistic effect of being OSA+/TN+ was absent in CN group. However the effect of being either OSA+/A β + or OSA+/TN+ was more marked in the MCI group (*e.g.* median time-to-AD progression of 3 years in A β + vs. 2.8 years in MCI OSA+/A β + and median time-to-MCI progression of 2.6 years in A β + vs. 2.5 years in OSA+/A β + in the CN group, $p < .01$ for all). Thereby lending credence to our hypothesis that OSA's effect on MCI/AD progression risk significantly increases as A β and Tau accumulation becomes increasingly abnormal.

We did not detect significant differences in progression risk when we compared CN and MCI OSA+ vs. OSA- among only A β - participants and CN OSA+ vs. OSA- among only TN- participants. These analyses examined whether established effects of OSA's neurodegenerative effect that is independent of hypoxia-induced A β 42 accumulation was sufficient to induce cognitive decline. We favor a model of AD that implies that one of the contributory role of OSA is the potential for neuronal injury independent of A β in which chronic intermittent hypoxia, and hypercapnia, may induce axonal, glial or white matter damage, in multiple brain regions.^{50,51,53} Plausible explanations for these findings are discussed below. First, this analysis employed the use of self-report for clinical diagnosis of OSA. Possible misclassification of OSA status occurring more frequently in one of the A β or TN groups could lead to fewer OSA patients considered to have progressed to MCI/AD therefore biasing the risk towards the null. Second, our inability to determine OSA severity could also be another reason. In our previous study,¹⁵ it was OSA severity that was associated with increases in brain amyloid burden. Third, our previous study using ADNI

data²¹ showed largely in CN and MCI (early stage subjects) groups that self-reported OSA+ subjects experienced faster annual increase in florbetapir uptake and decrease in CSF-A β 42 levels as well as increases in CSF T-tau and P-tau compared to self-reported OSA- participants. Thereby suggesting that OSA+ subjects are more likely to covert to A β + and TN+ statuses. Therefore, OSA effects may not be specific to the presence of A β or tau; rather it may affect different risk profiles based on the disease stage examined. As such it is not that A β - subjects are protected from progression to MCI or AD, but rather that there is a stepwise progression whereby first, OSA increases risk for transition from A β - to A β +, and, once A β +, increases risk for developing cognitive decline. Fourth, independent of A β and tau pathology, progression to MCI/AD maybe dependent on additional factors such as comorbid hypertension and microvascular changes,^{54,55} all of which were adjusted for in our analyses. Fifth, it could be that OSA's effect on MCI/AD progression risk is only apparent at certain A β or TN threshold levels or that longer follow-up time are needed. As such, CN A β - and TN- participants each, maybe too early in the process and power may have been an issue for this time scale and sample size. Lastly, MCI A β negative participants may represent a less pure population of subjects on an AD trajectory and are generally less likely to progress to clinical AD diagnosis. Since pathological definition of AD requires substantial presence of A β , histopathological examination may actually reveal these individuals may have other diagnoses (e.g. depression) or might be at risk for other forms of dementia, such as a diagnosis of primary age related tauopathy (PART).

Our result showing increased risk and a shorter time-to-progression to AD in MCI A β + participants compared to A β - participants among only OSA+ participants is consistent with well-established findings of MCI A β + elderly participants having elevated risk of AD^{39,56} and in short-term follow-up, being more likely to progress to AD than MCI A β - participants.⁴²⁻⁴⁴ The median time to AD was 2.8 years in OSA+/A β + participants compared to 3.9 years in OSA+/A β - participants. This clearly suggests the effects of OSA on AD progression risk significantly increases as A β accumulation becomes increasingly abnormal. However, these results should be interpreted with caution as A β - MCI ADNI patients have shown a variety of clinical and biomarker features that differ from their A β + counterparts, suggesting that one or more non-AD etiologies (which may include vascular disease and depression) account for their AD-like phenotype.⁵⁷ There was no significant difference in the risk and time-to-progression to MCI in CN A β + participants compared to A β - participants mainly due to lack of statistical power in the subgroup analyses.

The OSA- subset analysis, comparing A β + vs. A β - participants' risk and shorter time-to-progression to MCI and AD respectively in CN and MCI participants revealed findings that are consistent with the OSA+ subset analysis comparing A β + vs. A β - participants. Both eliminate OSA's effect. Our findings from examining A β 's effect independent of OSA positivity (*i.e.* OSA-/A β + vs. OSA-/A β -), and comparing that effect to A β 's effect contingent on OSA positivity (*i.e.* OSA+/A β + vs. OSA+/A β -), helped to further highlight OSA's synergism with amyloid burden with respect to MCI/AD progression risk. For example, the median time-to-MCI/AD progression in MCI OSA-/A β + participants was 3.6 years vs. 4 years in MCI OSA-/A β - participants, while progression time in MCI OSA+/A β + participants was 2.8 years vs. 3.9 years in MCI OSA+/A β - participants.

The analysis showing statistical comparison of progression times of each category (OSA+/A β +, OSA+/A β -, OSA-/A β +, OSA-/A β -) within the two sub-populations (NL and MCI), as well as the respective TN+ and TN- subset analyses, each comparing OSA+/A β + participants to other TN+ and TN- participants combined (*i.e.* OSA+/A β -, OSA-/A β + and OSA-/A β -) further helped to highlight OSA and A β synergism. The latter analysis eliminated the effects of tau. OSA+/A β + participants were approximately two to four times more likely to progress to MCI or AD and had significantly shorter time-to-progression to MCI and AD in CN and MCI participants, respectively depending on whether they were TN+ or TN-. In addition, results from the mixed effects models examining the interactive associations of OSA, A β and Tau burden with risk of conversion to MCI/AD demonstrated that OSA had a synergistic effect with A β in both CN and MCI participants, and with tau only in MCI participants. Thereby suggesting that OSA and tau's synergistic effect is seen and pronounced with an increased susceptibility to tau accumulation.

Strengths of our study include a well-characterized cohort, longitudinal design, relatively long follow-up, objective assessment of amyloid and tau burden and robust statistical analytic methods and large enough sample that allowed subgroup examinations for the most part. As we previously described,^{2,16} measurement of OSA by self-report is an important limitation. Self-reported sleep measures can be impacted by diminished cognition⁵⁸ and in certain situations might not be correlated with objective methods.⁵⁹ The significantly lower than expected prevalence of reported OSA in this elderly cohort, is possibly due to under-diagnosis, as epidemiological and sleep laboratory studies document much higher OSA prevalence in elderly populations. The prevalence of OSA (with or without symptoms) is estimated at 30-50% in older subjects,⁶⁰ therefore, misclassification of some OSA+ subjects into the OSA- group could have occurred; however, this would have driven our findings towards the null, with lower estimates than the true ones, therefore attenuating OSA's true effect. OSA classification by self-report suggests that those with self-reported OSA were more likely to be symptomatic (*i.e.* with excessive daytime sleepiness [EDS]), prompting these subjects to seek diagnosis. Therefore, further research differentiating the risk of OSA for AD with and without associated daytime symptoms is necessary. Notably, a recent study demonstrated that all-cause EDS defined by Epworth sleepiness scores ≥ 10 was associated with longitudinal brain beta amyloid accumulation in elderly subjects.⁶¹

CONCLUSION

Our findings in a cohort of self-reported OSA patients support the hypothesis of an overarching model of late-onset AD with brain amyloid deposition and tau aggregates proceeding at different rates,⁶² influenced by a combination of protective/risk factors of which OSA is part. This model of AD implies a contributory role of OSA, first with the direct potential for neuronal injury independent of A β by inducing intermittent hypoxia, sleep fragmentation, arousal-induced hypertensive surges, systemic inflammation, and impaired glucose handling⁶³ irrespective of MCI/AD progression risk. Second, an indirect contributory role of OSA in which both acute and intermittent hypoxia, sleep fragmentation and EDS may accelerate A β accumulation in the presence of A β plaques via a feedback loop^{8,47,61} and tau accumulation possibly influenced by impaired clearance through the glymphatic pathway.^{64,65} This role of OSA significantly increases MCI/AD progression risk

as suggested by our findings. Third, a contributory role of OSA in which the direct neurotoxicity effect that is independent of A β accumulation together with OSA's indirect effect that promotes A β accumulation, combine to act synergistically to significantly increase MCI/AD progression risk, and possibly affecting and/or accelerating AD biomarker change and leading to shorter time-to-MCI/AD in OSA CN and MCI participants respectively. This OSA-A β synergism related to cognitive decline can be independent of tau as well as synergistic with tau deposition. Future research using objective measures of OSA is needed to replicate these findings and examine OSA's effects on slow wave and rapid eye movement sleep and their mediating role in increasing A β and tau accumulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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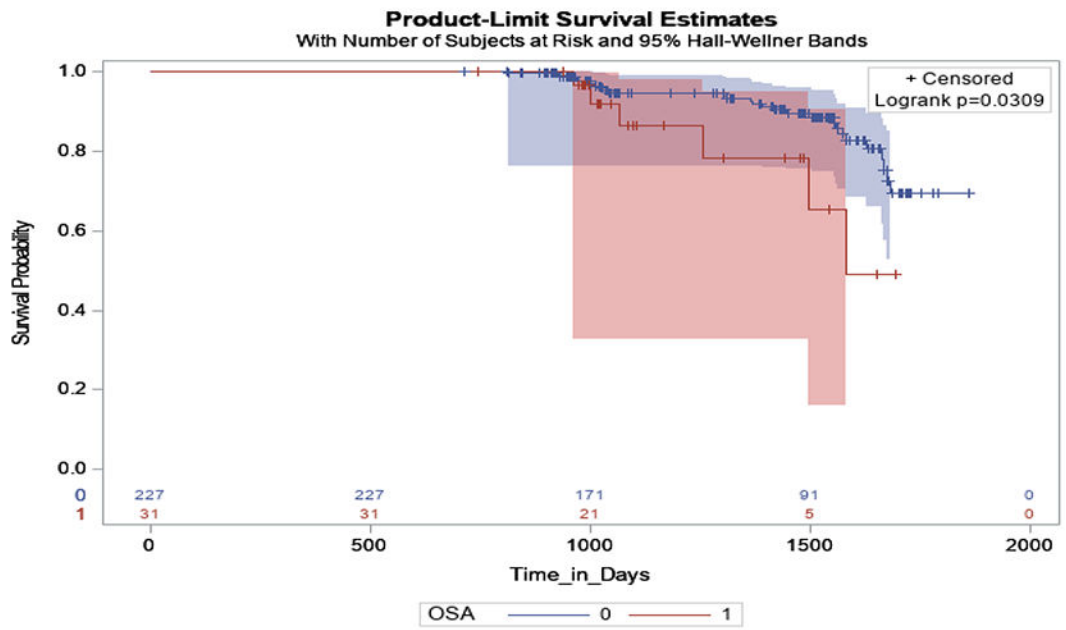
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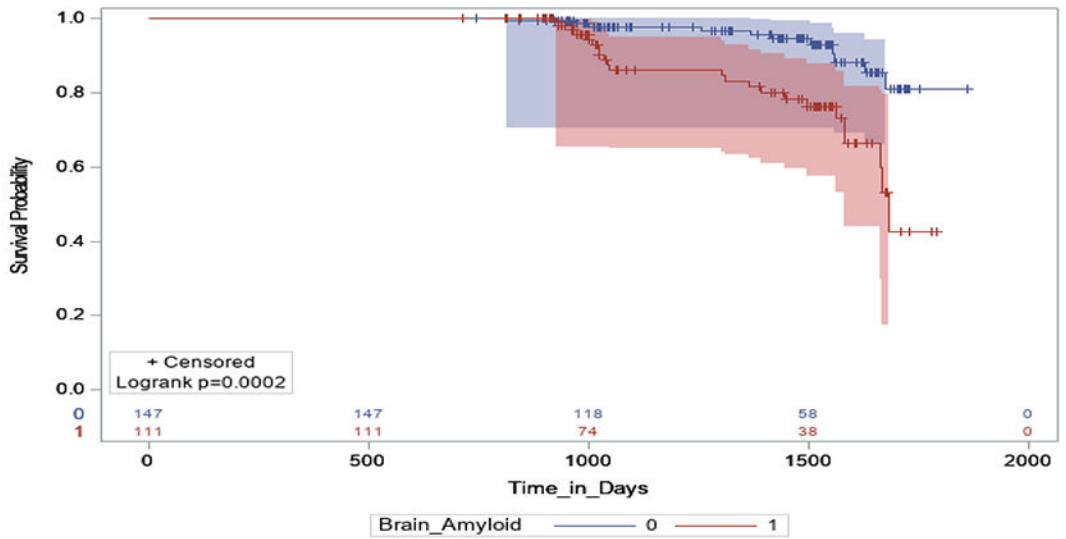
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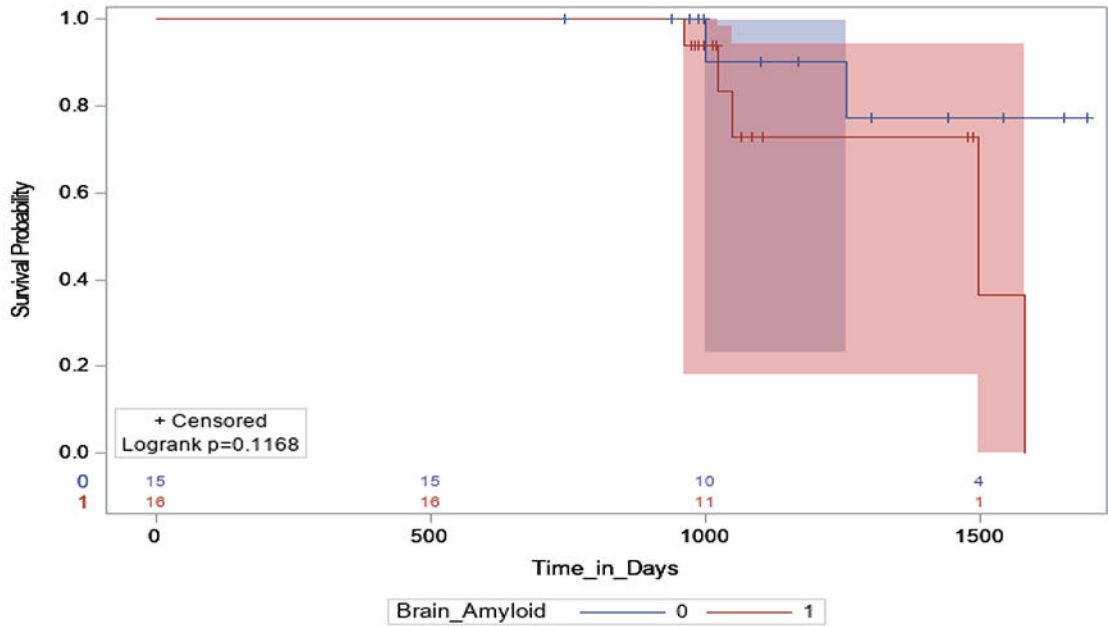
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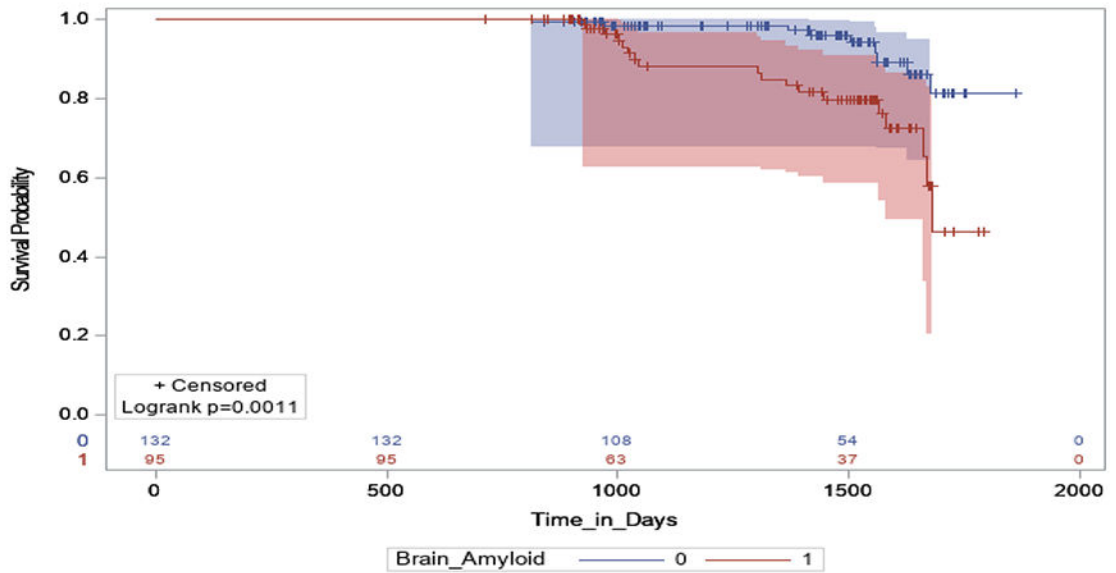
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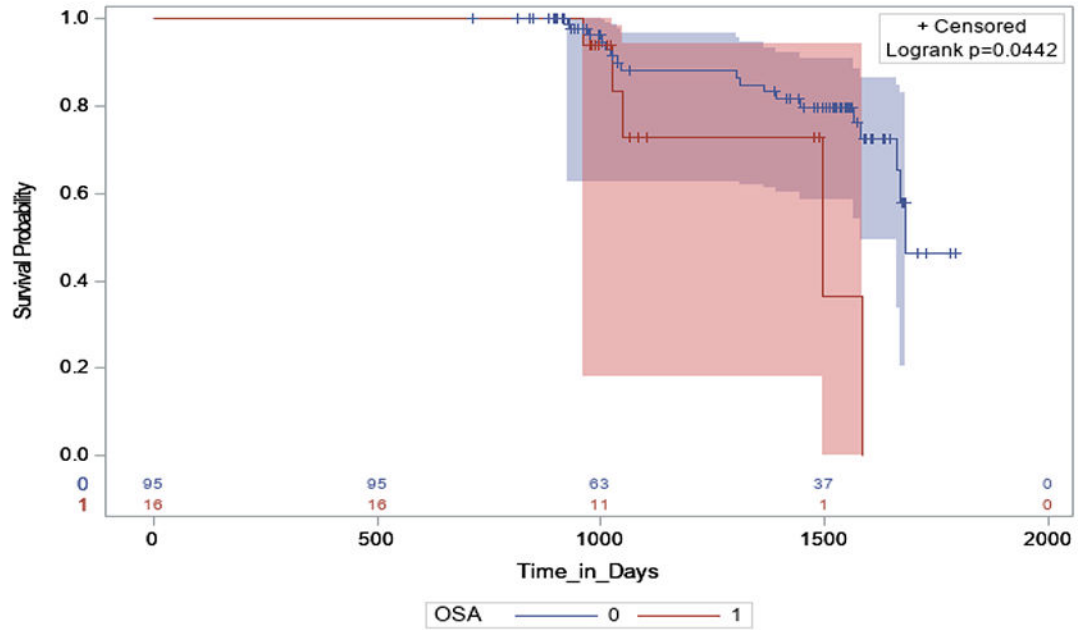
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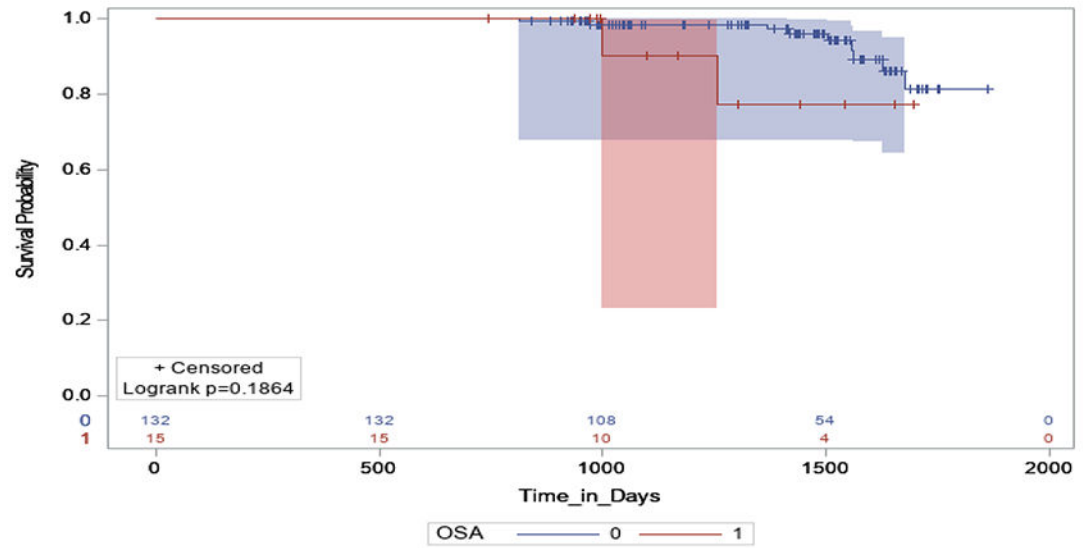
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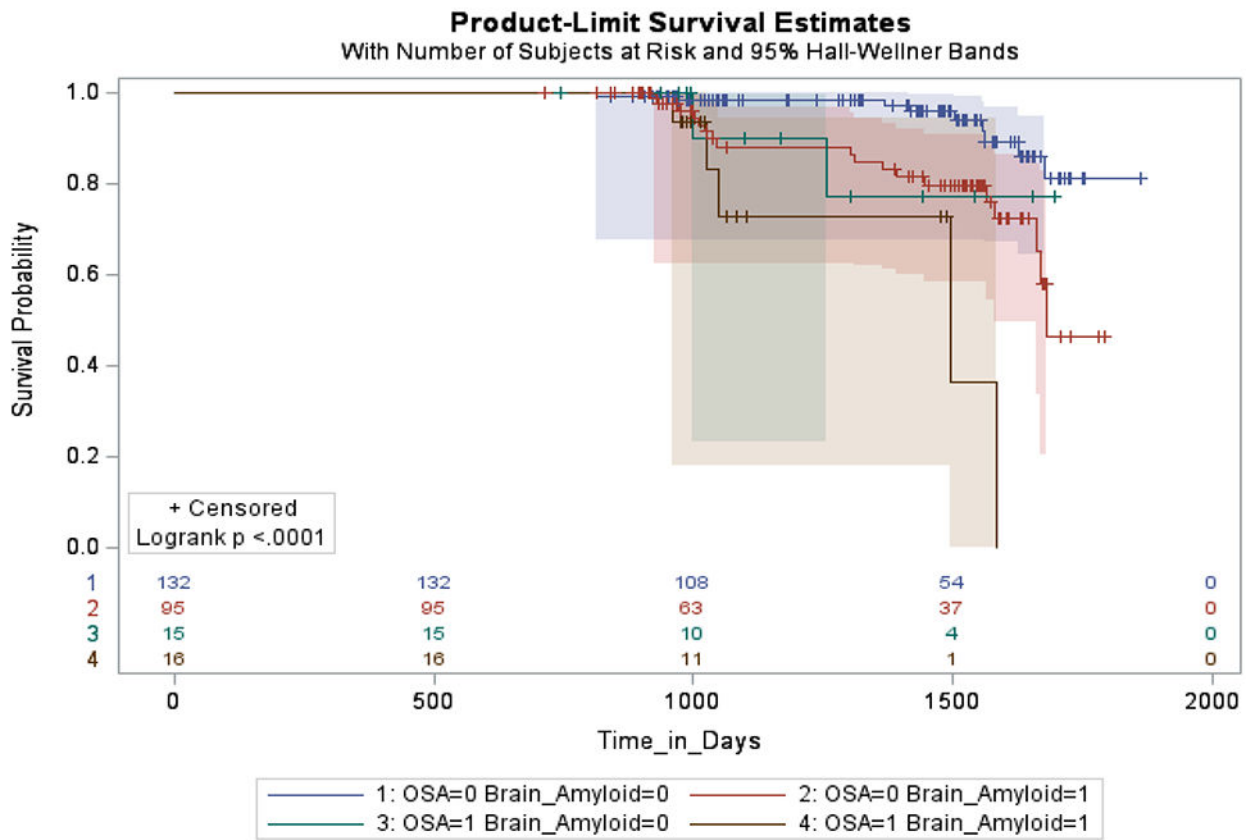
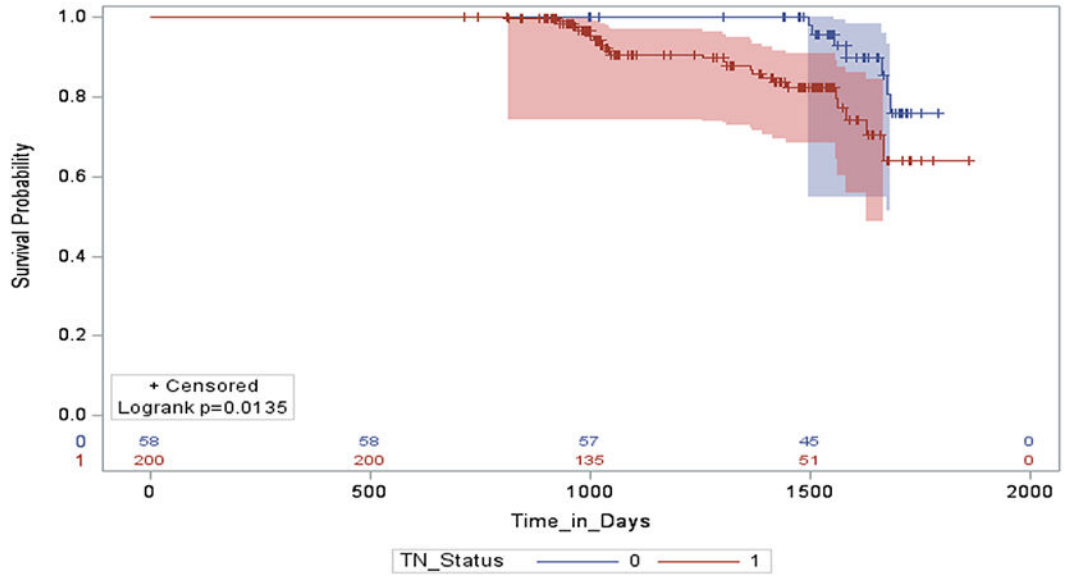


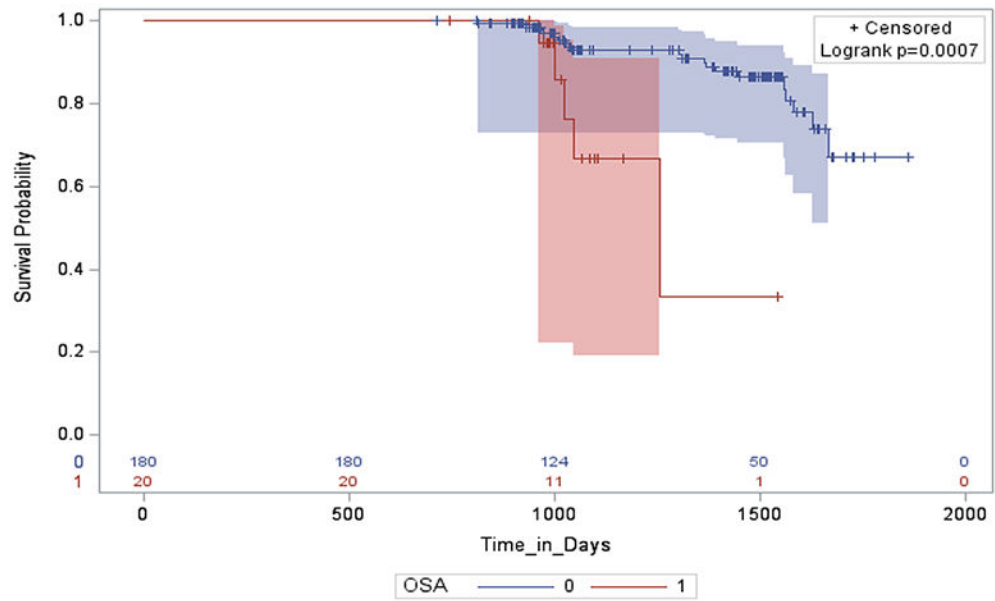
Figure 1a: Kaplan–Meier Product Limit Survival Estimates and time-to-progression from NL to MCI

Product-Limit Survival Estimates with number at risk and 95 % Hall-Wellner bands

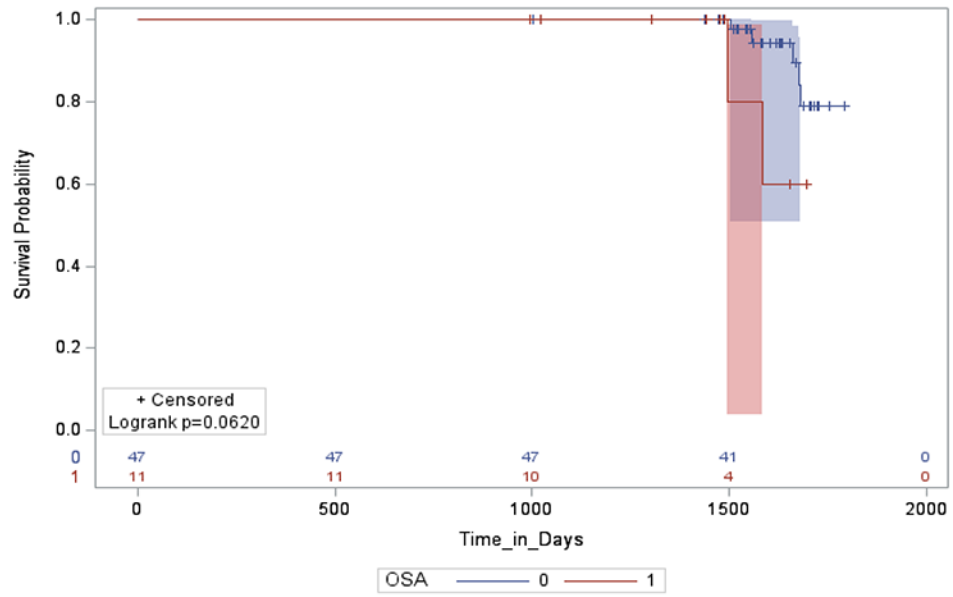
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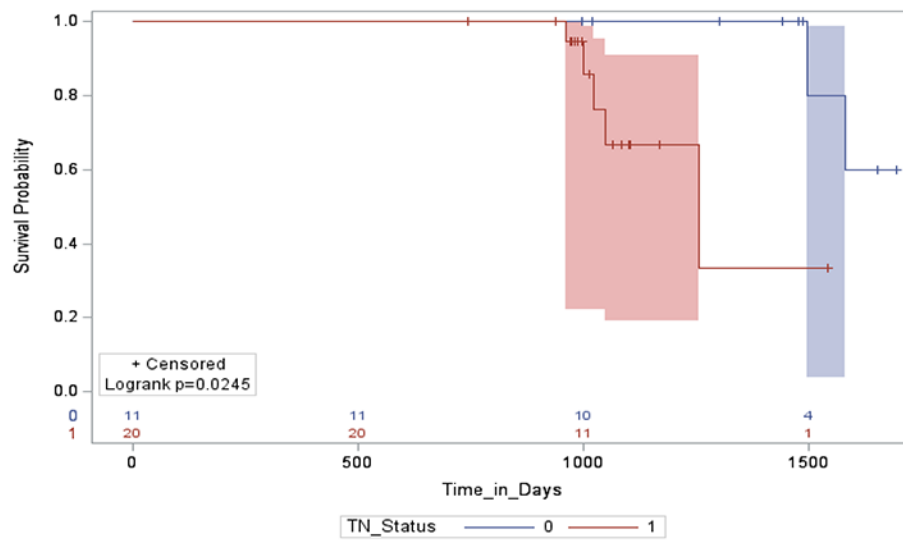
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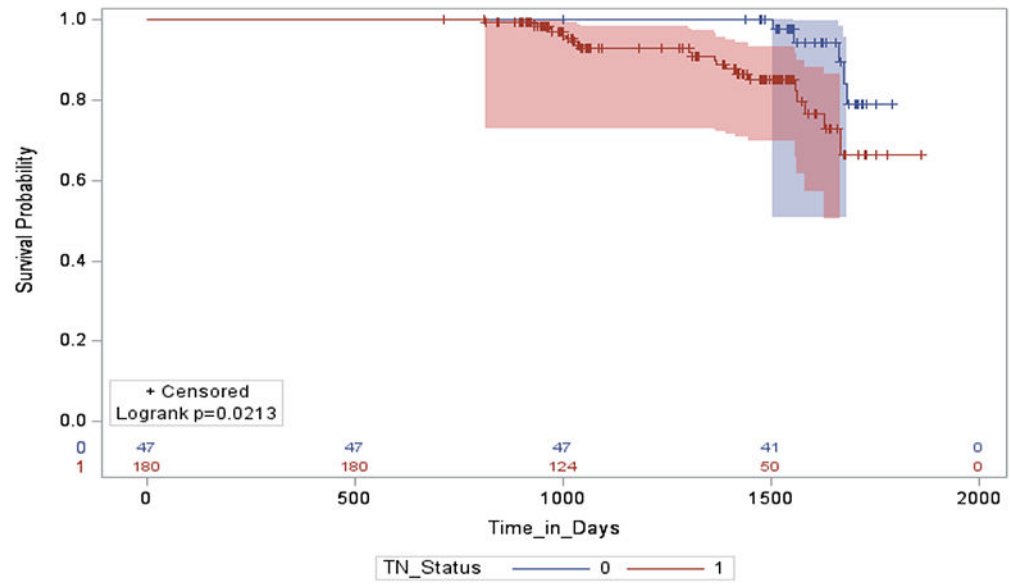
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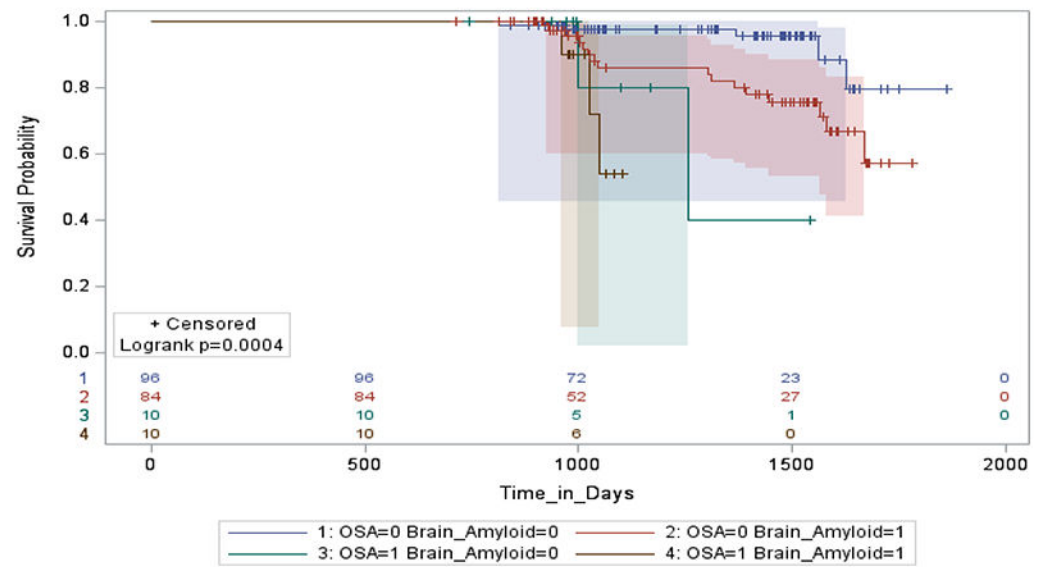
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(ALL TN+ PARTICIPANTS COMPARED BY OSA & BRAIN AMYLOID STATUS)



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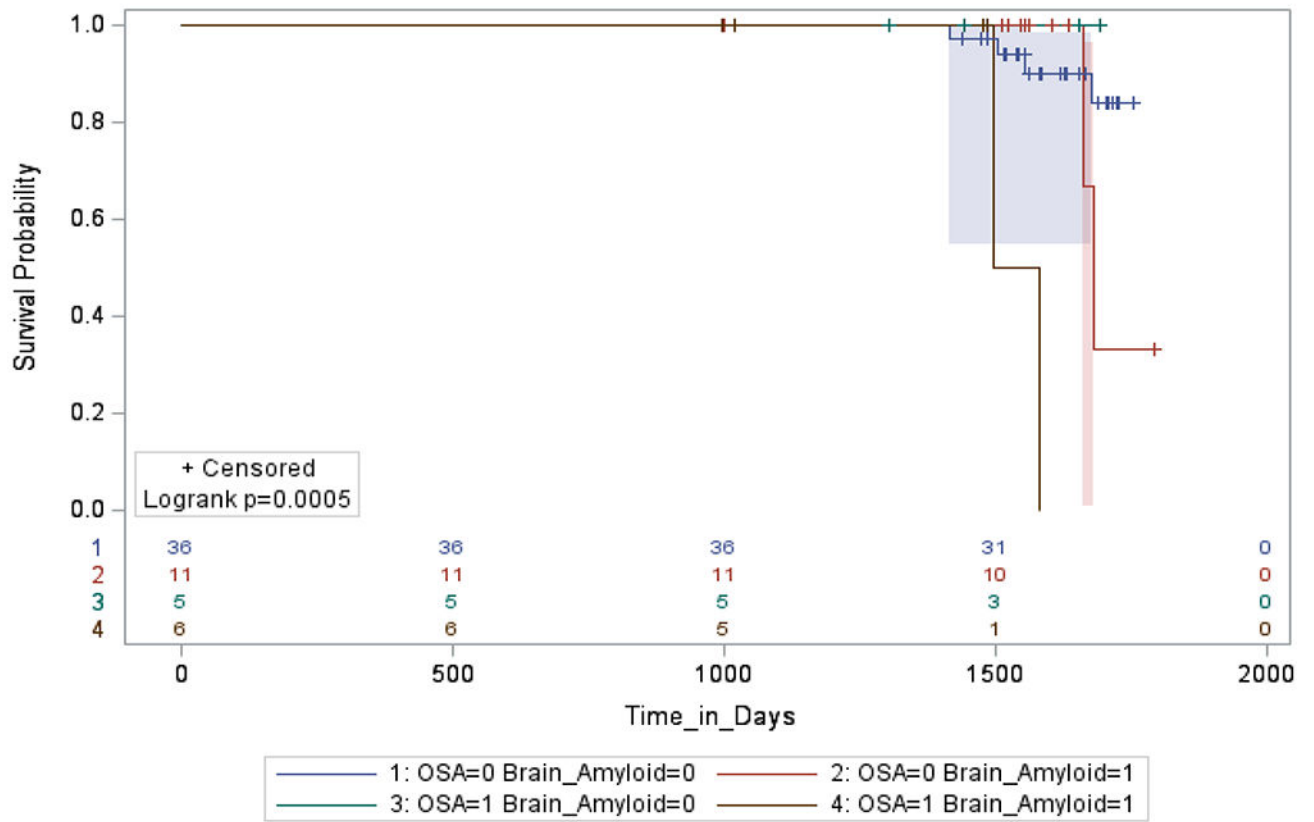
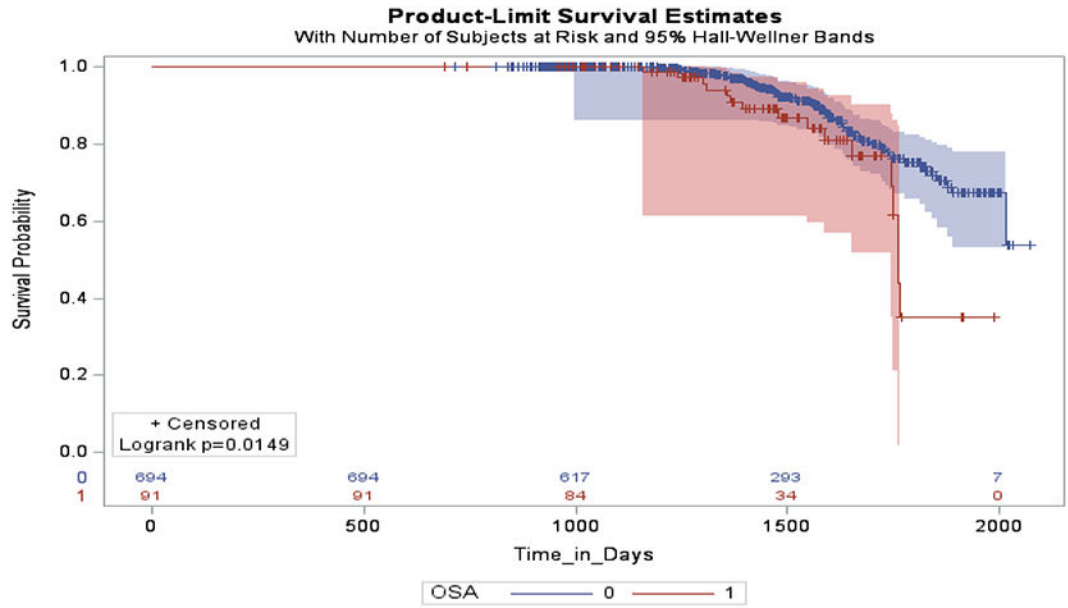
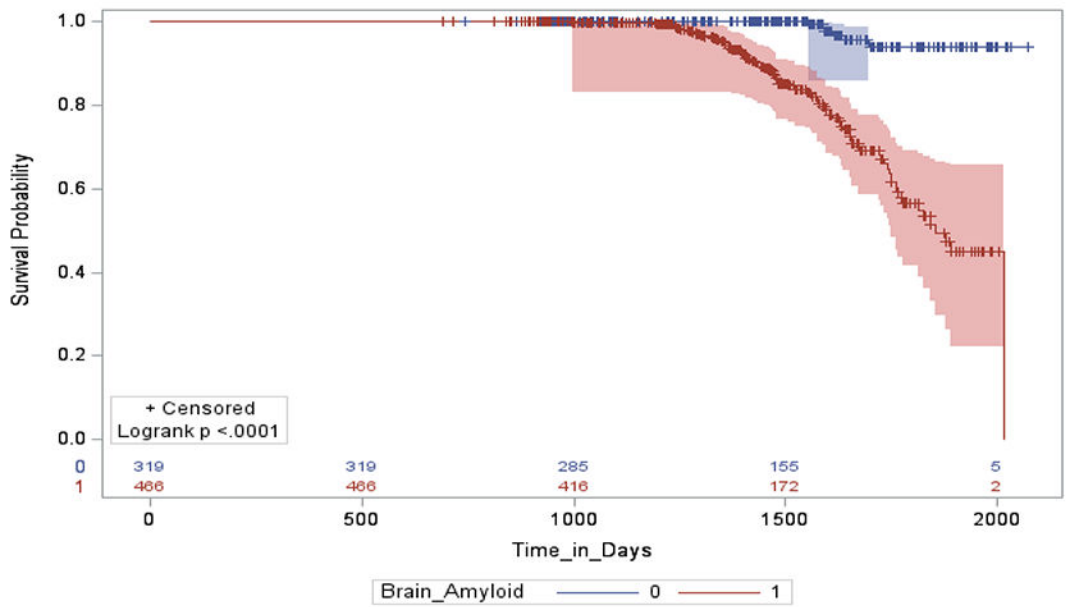


Figure 1b: Kaplan–Meier Product Limit Survival Estimates and time-to-progression from CN to MCI
Product-Limit Survival Estimates with number at risk and 95% Hall-Wellner bands

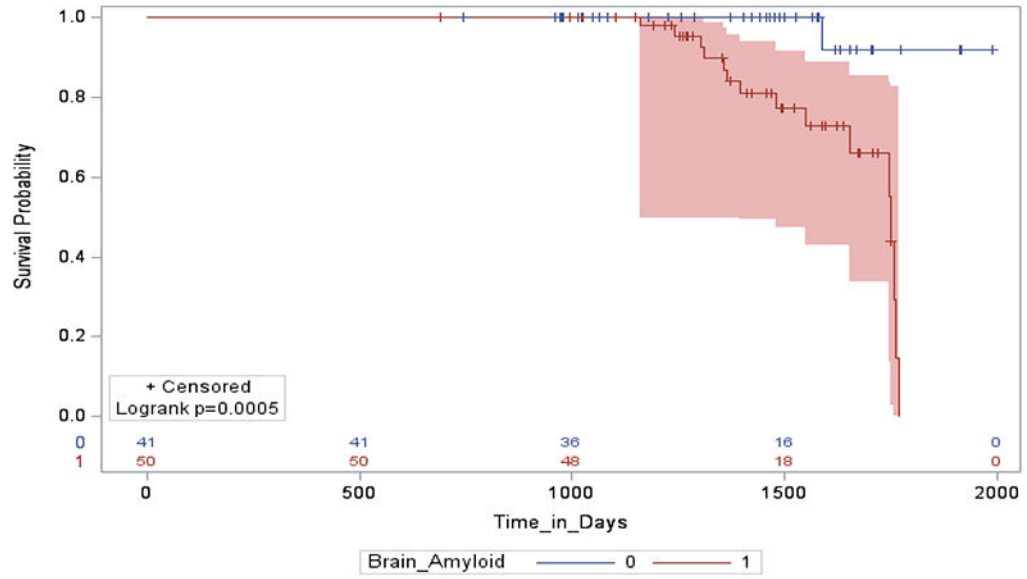
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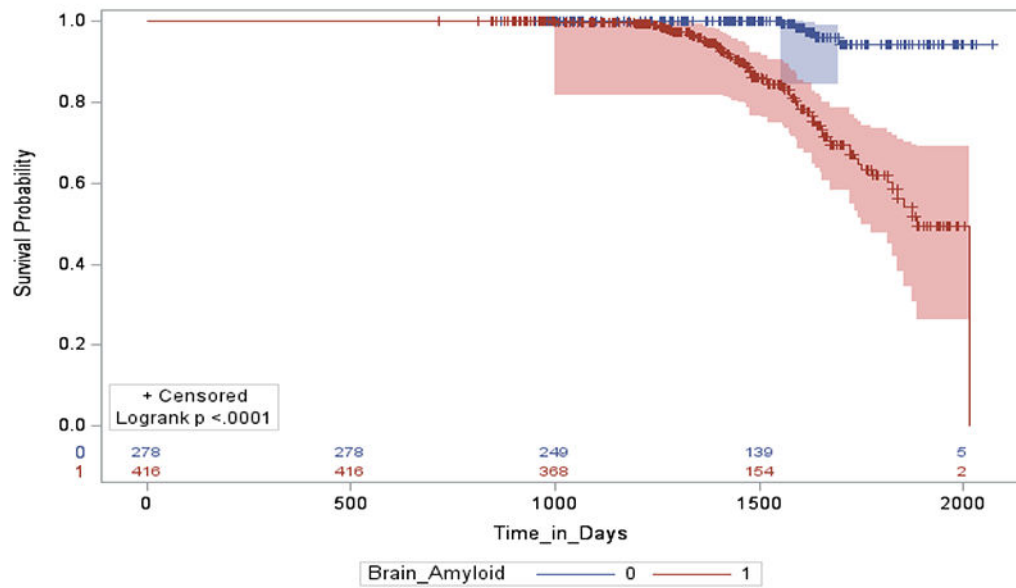
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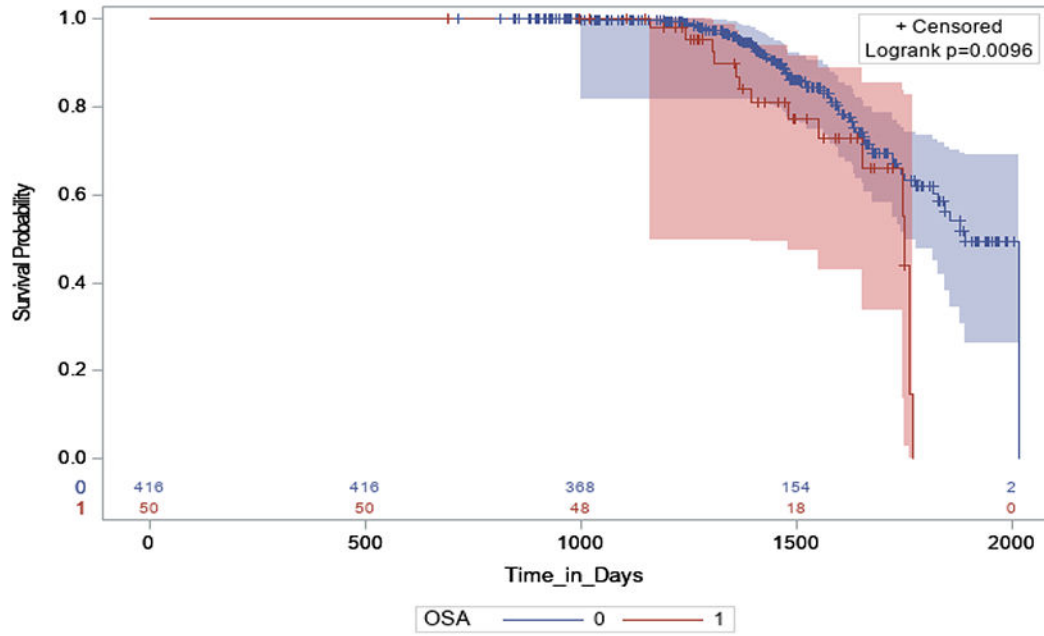
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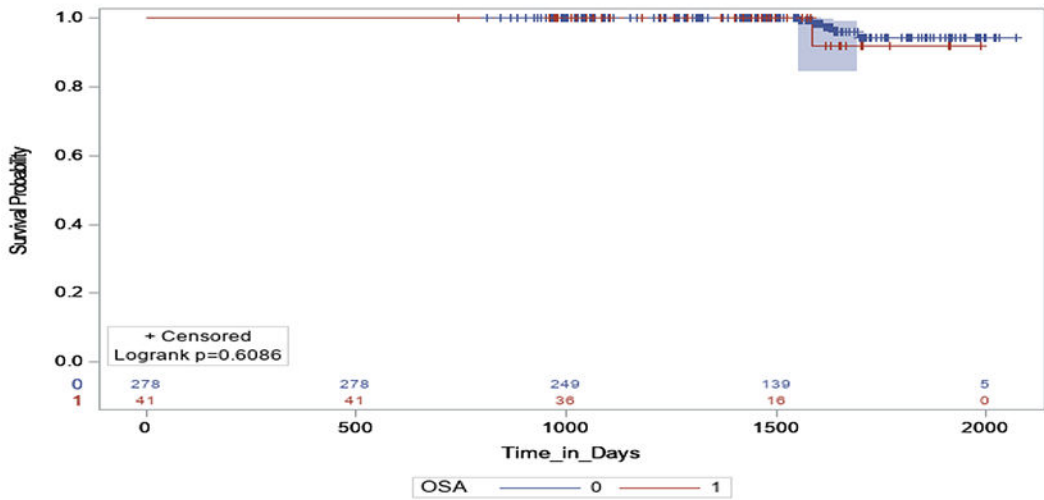
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(ALL A β +: OSA+ vs. OSA- PARTICIPANTS)



(ALL A β -: OSA+ vs. OSA- PARTICIPANTS)



(ALL MCI PARTICIPANTS COMPARED BY OSA & BRAIN AMYLOID STATUS)

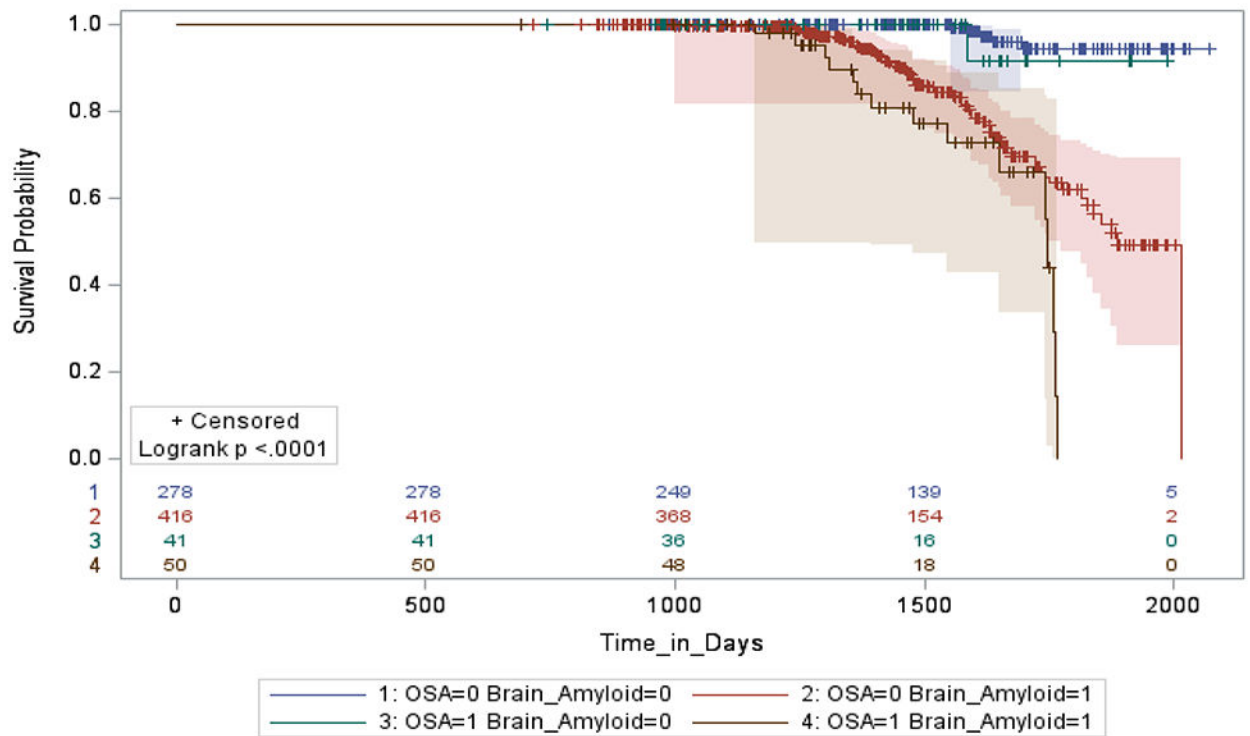
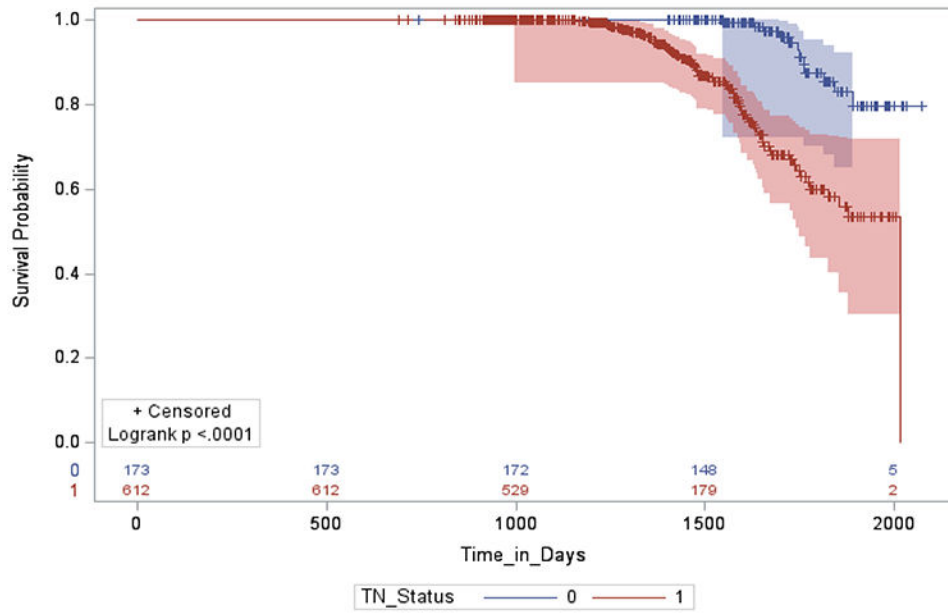
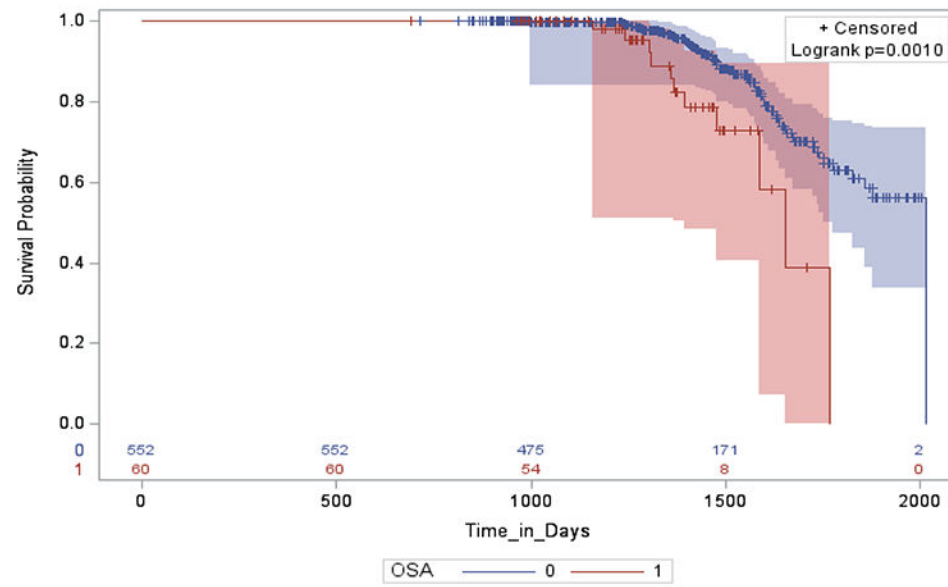


Figure 2a: Kaplan–Meier Product Limit Survival Estimates and time-to-progression from MCI to AD
 Product-Limit Survival Estimates with number at risk and 95% Hall-Wellner bands

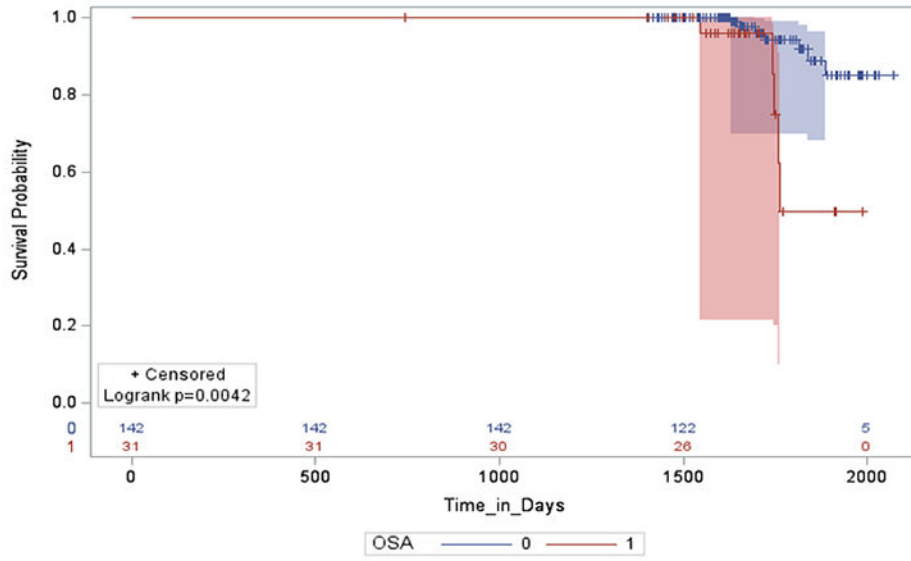
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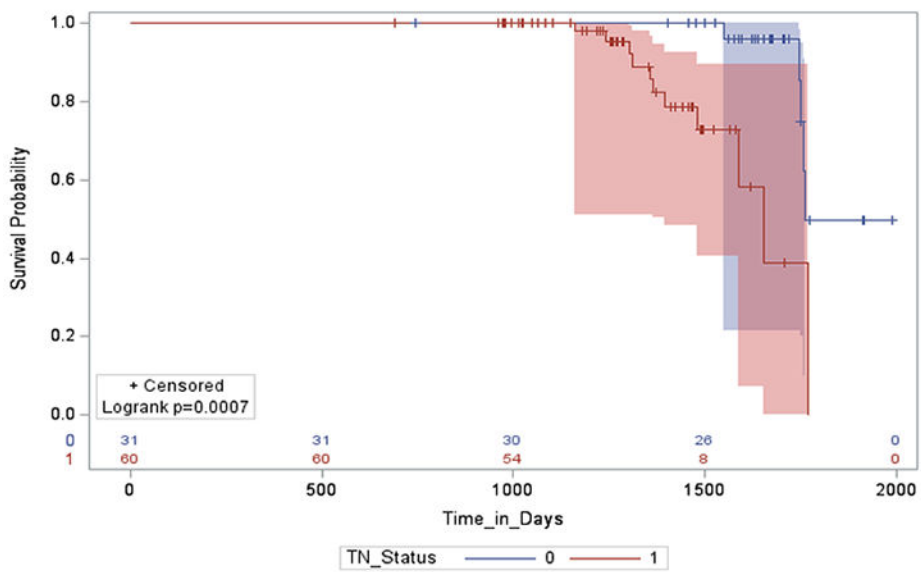
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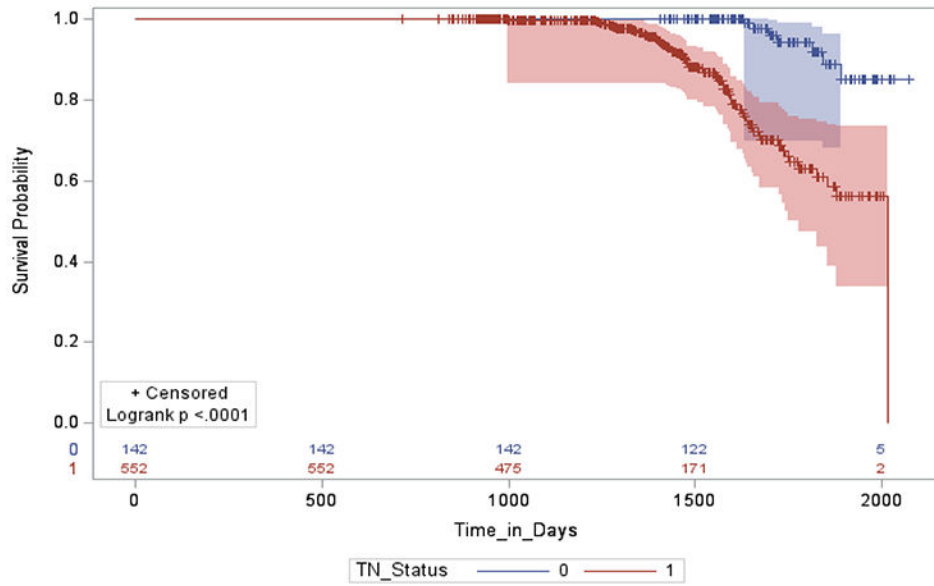
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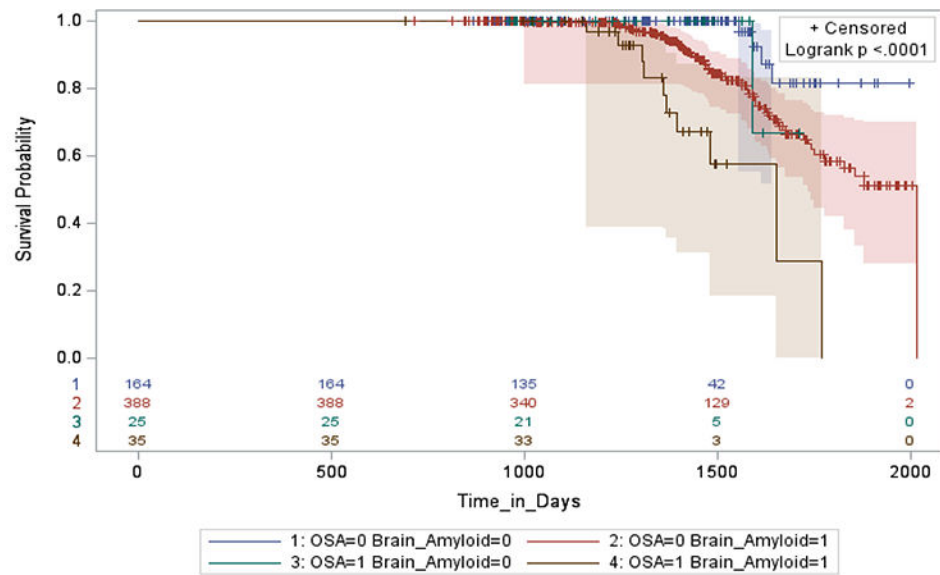
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(ALL TN+ PARTICIPANTS COMPARED BY OSA & BRAIN AMYLOID STATUS)



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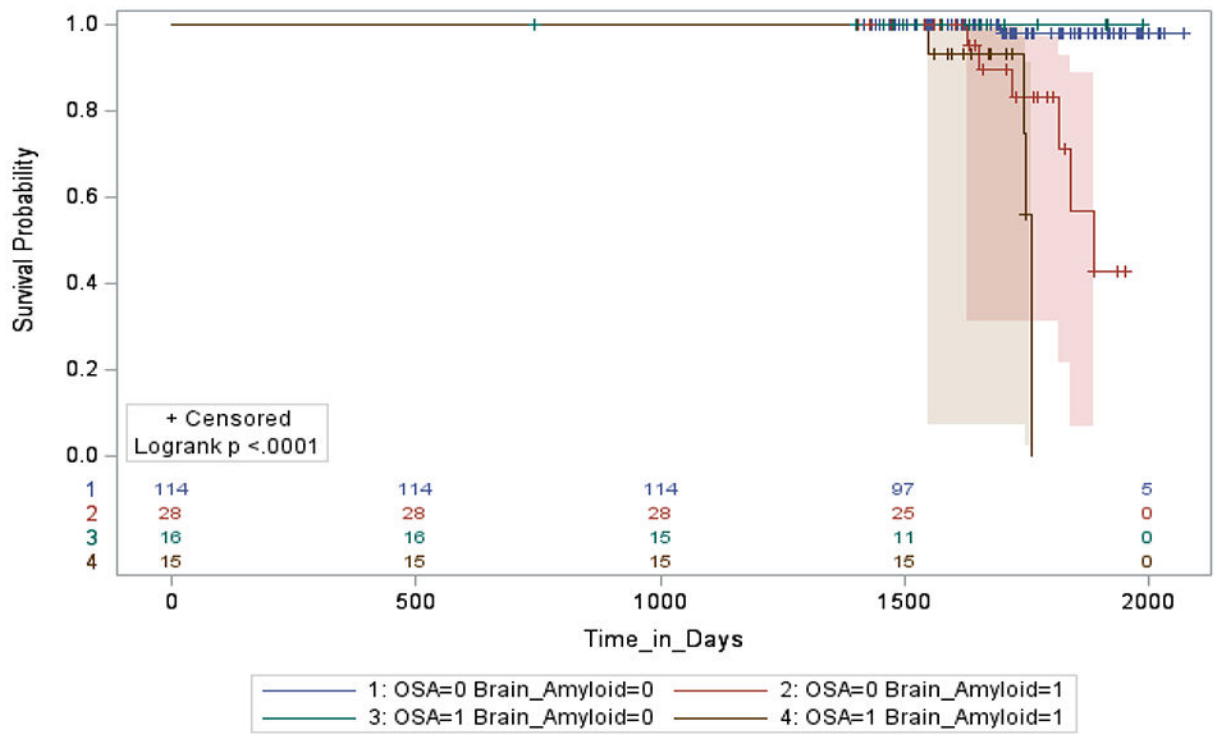


Figure 2b: Kaplan–Meier Product Limit Survival Estimates and time-to-progression from MCI to AD
Product-Limit Survival Estimates with number at risk and 95% Hall-Wellner bands

Table 1:

Baseline Descriptive Characteristics of Participants by Obstructive Sleep Apnea and A β load Status

Table 1a: Characteristics of Cognitively Normal Participants by Obstructive Sleep Apnea Status and by A β load Status; and Converters from Cognitive Normal to Mild Cognitive Impairment

Characteristics	All	Without OSA		With OSA		Stable	Converters
		A β +	A β -	A β +	A β -		
Number of participants (%)	258 (100)	95 (37)	132 (51)	16 (6)	15 (6)	187 (72)	71 (28)
Follow-up time, mean (SD), years	5.3 (1.4)	5.7 (1.1)	5.2 (1.5)	4.9 (1.7)	5.4 (1.4)	5.6 (1.1)	5.1 (1.9)
Female gender, number (%)	121 (47)	52 (43)	58 (48)	2 (1)	9 (8)	92 (76)	29 (24)
Age, years, median (interquartile range)	74 (71, 78)	75 (71, 79)	71 (68, 76)	70 (70, 86)	71 (68, 75)	71 (68, 76)	74 (70, 79)
APOE positive, number (%) [*]	80 (31)	37 (46)	32 (41)	10 (12)	1 (1)	38 (48)	42 (52)
Education, years, median (interquartile range)	16 (14, 18)	16 (14, 18)	17 (16, 19)	12 (12, 12)	16 (16, 18)	17 (16, 19)	16 (12, 16)
BMI (kg/m ²) [*]	27.2 \pm 4.8	27.1 \pm 4.8	27.7 \pm 5.2	36.5 \pm 10.5	29.7 \pm 4.5	28.7 \pm 7.2	31.5 \pm 7.8
Hypertension, number (%) [*]	124 (48)	38 (31)	68 (55)	9 (7)	9 (7)	84 (68)	40 (32)
Diabetes, number (%) [*]	28 (11)	8 (29)	13 (46)	5 (18)	2 (7)	18 (64)	10 (36)
Thyroid Disease, number (%)	59 (23)	25 (43)	28 (47)	5 (9)	1 (1)	41 (69)	18 (31)
Respiratory Disease, number (%)	57 (22)	16 (28)	23 (40)	5 (9)	13 (23)	38 (67)	19 (33)
Cardiovascular Disease, number (%) [*]	173 (67)	82 (47)	75 (44)	9 (5)	7 (4)	114 (66)	59 (33)
TBI, number (%)	10 (4)	6 (58)	4 (42)			5 (50)	5 (50)
Alcohol use, number (%)	18 (7)	7 (39)	8 (44)	1 (6)	2 (11)	12 (67)	6 (33)
CPAP use, number (%)	8 (3)			6 (70)	2 (30)	6 (70)	2 (30)
MMSE median (interquartile range)	29 (28, 29)	29 (28, 30)	29 (28, 29)	29 (27, 30)	29 (28, 29)	29 (28, 29)	29 (28, 30)
CDR median (interquartile range)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
CSF-ABETA pg/ml median (interquartile range) [*]	210 (155, 241)	149 (132, 173)	221 (200, 245)	112 (93, 123)	229 (213, 268)	198 (188, 245)	132 (120, 164)
TAU pg/ml median (interquartile range) [*]	59 (45, 84)	71 (49, 105)	53 (43, 69)	141 (126, 156)	56 (42, 63)	61 (42, 89)	109 (86, 140)
PTAU pg/ml median (interquartile range) [*]	27 (20, 40)	41 (30, 55)	27 (21, 38)	91 (46, 137)	27 (21, 29)	31 (21, 48)	65 (33, 117)
A β , median (interquartile range) [*]	1.1 (1.0, 1.2)	1.3 (1.2, 1.4)	1.0 (1.0, 1.1)	1.2 (1.2, 1.3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.2)	1.3 (1.2, 1.4)

Table 1a: Characteristics of Cognitively Normal Participants by Obstructive Sleep Apnea Status and by Aβ load Status; and Converters from Cognitive Normal to Mild Cognitive Impairment

Characteristics	All	Without OSA		With OSA		Stable	Converters
		Aβ +	Aβ -	Aβ +	Aβ -		
Table 1b: Characteristics of Mild Cognitive Impairment Participants by Obstructive Sleep Apnea Status and by Aβ load Status; and Converters from Mild Cognitive Impairment to Alzheimer's disease							
Characteristics	All	Without OSA		With OSA		Stable	Converters
		Aβ +	Aβ -	Aβ +	Aβ -		
Number of participants (%)	785 (100)	416 (53)	278 (35)	50 (6)	41 (5)	487 (62)	298 (38)
Follow-up time, mean (SD), years	5.7 (1.9)	5.6 (1.4)	6.1 (1.1)	5.5 (1.6)	5.6 (1.5)	5.9 (1.7)	5.5 (1.7)
Female gender, number (%)	385 (49)	236 (61)	102 (27)	27 (7)	20 (5)	250 (65)	135 (35)
Age, years, median (interquartile range)	74 (68, 79)	74 (69, 78)	71 (65, 76)	72 (69, 77)	72 (68, 75)	71 (68, 75)	74 (68, 79)
APOE positive, number (%) *	395 (50)	288 (73)	55 (14)	32 (8)	20 (5)	125 (58)	89 (42)
Education, years, median (interquartile range) *	16 (14, 18)	16 (14, 18)	16 (14, 18)	16 (12, 19)	17 (15, 19)	16 (14, 18)	16 (14, 18)
BMI (kg/m2) *	26.9 ± 4.6	26.8 ± 4.8	27.8 ± 4.6	30.5 ± 6.1	29.6 ± 5.6	28.7 ± 4.8	30.4 ± 5.8
Hypertension, number (%) *	369 (47)	192 (52)	118 (32)	30 (8)	29 (8)	196 (53)	173 (47)
Diabetes, number (%) *	79 (10)	30 (38)	21 (27)	16 (20)	12 (15)	54 (68)	25 (32)
Thyroid Disease, number (%)	165 (21)	81 (49)	56 (34)	17 (10)	11 (7)	125 (76)	40 (24)
Respiratory Disease, number (%)	188 (24)	83 (44)	42 (22)	24 (13)	39 (21)	137 (73)	51 (27)
Cardiovascular Disease, number (%) *	502 (64)	226 (45)	201 (40)	45 (9)	30 (6)	377 (75)	125 (25)
TBI, number (%)	31 (4)	10 (33)	14 (44)	5 (17)	2 (6)	14 (44)	17 (56)
Alcohol use, number (%)	63 (8)	23 (37)	32 (51)	2 (3)	6 (9)	42 (66)	21 (34)
CPAP use, number (%)	31 (4)			10 (31)	21 (69)	23 (75)	8 (25)
MMSE median (interquartile range)	27 (24, 28)	26 (25, 28)	28 (25, 29)	26 (24, 28)	27 (24, 29)	28 (25, 29)	26 (24, 28)
CDR median (interquartile range)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)
CSF-ABETA pg/ml median (interquartile range) *	153 (130, 209)	134 (120, 154)	219 (199, 243)	147 (134, 167)	212 (190, 240)	179 (159, 243)	134 (120, 154)
TAU pg/ml median (interquartile range) *	80 (54, 116)	97 (70, 140)	52 (36, 72)	93 (66, 114)	55 (42, 78)	62 (46, 82)	97 (66, 140)
PTAU pg/ml median (interquartile range) *	36 (23, 51)	50 (36, 67)	23 (17, 32)	40 (32, 59)	27 (19, 38)	25 (20, 38)	50 (33, 67)
Aβ ₄₂ median (interquartile range) †	1.2 (1.0, 1.4)	1.4 (1.3, 1.5)	1.0 (1.0, 1.1)	1.3 (1.2, 1.4)	1.0 (1.0, 1.0)	1.1 (1.0, 1.2)	1.3 (1.2, 1.4)

Abbreviation: OSA: Obstructive Sleep Apnea, A β : amyloid beta, MCI: Mild Cognitive Impairment, ApoE4: Apolipoprotein epsilon4, BMI: body mass index, CDR: Clinical Dementia Rating, CPAP: continuous pulmonary airway pressure; CSF: cerebrospinal fluid, MMSE: Mini Mental State Exam; TAU: tau protein, PTAU: phosphorylated tau, TBI: traumatic brain injury. All columns show column percent where indicated. OSA and A β columns show row percent where indicated.

Superscript *: indicates significant differences between groups. A β + participants had significantly lower CSF-A β 42, and higher levels of CSF T-tau and CSF P-Tau. Amyloid positive subjects in both NL and MCI groups were more likely to be APOE4 carriers. Participants who were OSA+/A β + had significantly higher BMI in the NL group but not in the MCI group, compared to other participants with varying OSA and A β status. In both NL and MCI, OSA+/A β + participants had higher vascular burden (*i.e.* higher rates of hypertension, diabetes and cardiovascular disease) compared to OSA-/A β + participants (*e.g.* 9/15 [60%] vs. 38/95 [40%] for hypertension in NL participants). NL/OSA+/A β + participants had significantly lower educational level. Significance level $p < .05$.

Table 2: Baseline Descriptive Characteristics of Participants by Obstructive Sleep Apnea and A/T/N Status

Characteristics	All	Without OSA				With OSA			
		A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -	A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -
Number of participants (%)	258 (100)	84 (33)	11(4)	96 (37)	36 (14)	6 (2)	10 (4)	5 (2)	
Follow-up time, mean (SD), years	5.3 (1.4)	5.9 (1.3)	5.4 (1.9)	5.6 (1.5)	5.4 (1.5)	4.7 (1.8)	5.2 (1.6)	5.3 (1.7)	
Female gender, number (%)	121 (47)	35 (28)	17 (14)	36 (30)	22 (18)	1 (1)	4 (4)	5 (4)	
Age, years, median (interquartile range)	74 (71, 78)	75 (71, 79)	75 (70, 79)	73 (68, 77)	72 (68, 75)	78 (70, 86)	70 (70, 70)	72 (66, 75)	
APOE positive, number (%) [*]	80 (31)	28 (35)	9 (11)	24 (30)	8 (11)	8 (11)	2 (1)	1 (1)	
Education, years, median (interquartile range) [*]	16 (14, 18)	16 (14, 18)	16 (14, 20)	17 (16, 19)	17 (16, 18)	12 (12, 12)	12 (12, 12)	17 (16, 19)	
BMI (kg/m2) [*]	27.2 ± 4.8	26.7 ± 4.5	28.5 ± 6.1	27.7 ± 5.4	27.5 ± 4.8	32.4 ± 11.2	34.5 ± 4.8	30.0 ± 5.5	
Hypertension, number (%) [*]	124 (48)	30 (24)	8 (7)	47 (38)	21 (17)	7 (6)	2 (1)	6 (5)	
Diabetes, number (%)	28 (11)	6 (21)	2 (7)	7 (25)	6 (21)	4 (14)	1 (4)	1 (4)	
Thyroid Disease, number (%)	59 (23)	19 (32)	6 (11)	18 (30)	10 (17)	1 (2)	4 (7)	1 (1)	
Respiratory Disease, number (%)	57 (22)	12 (21)	4 (7)	13 (23)	10 (17)	4 (7)	1 (2)	7 (12)	
Cardiovascular Disease, number (%) [*]	173 (67)	65 (38)	17 (10)	52 (30)	23 (14)	7 (4)	2 (1)	5 (3)	
TBI, number (%)	10 (4)	6 (58)	4 (42)						
Alcohol use, number (%)	18 (7)	5 (28)	2 (11)	7 (38)	1 (6)	1 (6)		2 (11)	
CPAP use, number (%)	8 (3)			5 (70)	1	1		1 (30)	
MMSE median (interquartile range)	29 (28, 29)	28 (27, 30)	29 (28, 30)	29 (28, 29)	29 (28, 30)	27 (27, 29)	29 (28, 29)	29 (28, 29)	
CDR median (interquartile range)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
CSF-ABETA pg/ml median (interquartile range) [*]	210 (155, 241)	151 (132, 166)	179 (161, 184)	224 (203, 248)	210 (188, 232)	112 (93, 132)	159 (131, 172)	246 (226, 269)	
TAU pg/ml median (interquartile range) [*]	59 (45, 84)	86 (60, 106)	36 (27, 46)	65 (47, 81)	42 (35, 49)	141 (126, 156)	46 (37, 53)	61 (54, 69)	
PTAU pg/ml median (interquartile range) [*]	27 (20, 40)	48 (34, 57)	16 (12, 19)	35 (26, 43)	17 (15, 20)	91 (46, 137)	17 (17, 19)	29 (27, 32)	

Table 2a: Characteristics of Cognitively Normal Participants by Obstructive Sleep Apnea Status and by A/T/N Status from Cognitive Normal to Mild Cognitive Impairment

Characteristics	Without OSA				With OSA			
	A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -	A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -
Aβ, median (interquartile range)*	1.1 (1.0, 1.2)	1.1 (1.1, 1.1)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.2 (1.2, 1.3)	1.2 (1.1, 1.3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)

Table 2b: Characteristics of Mild Cognitive Impairment Participants by Obstructive Sleep Apnea Status and by A/T/N Status from Mild Cognitive Impairment to Alzheimer's disease

Characteristics	Without OSA				With OSA			
	A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -	A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -
All	16 (14, 18)	16 (14, 20)	16 (14, 18)	16 (14, 18)	16 (12, 19)	13 (11, 17)	17 (14, 19)	17 (16, 19)
Number of participants (%)	785 (100)	28 (4)	164 (20)	114 (15)	35 (4)	15 (2)	25 (3)	16 (2)
Follow-up time, mean (SD), years	5.7 (1.9)	5.6 (1.3)	6.0 (1.3)	5.9 (1.1)	5.5 (1.7)	5.7 (1.3)	5.6 (1.5)	5.7 (1.2)
Female gender, number (%)	385 (49)	210 (55)	63 (16)	39 (10)	20 (5)	7 (2)	11 (3)	9 (2)
Age, years, median (interquartile range)	74 (68, 79)	76 (71, 80)	71 (66, 76)	70 (65, 76)	71 (68, 77)	76 (71, 82)	72 (68, 76)	70 (63, 75)
APOE positive, number (%) *	395 (50)	254 (64)	32 (8)	23 (6)	30 (6)	2 (1)	10 (3)	10 (3)
Education, years, median (interquartile range) *	16 (14, 18)	16 (14, 20)	16 (14, 18)	16 (14, 18)	16 (12, 19)	13 (11, 17)	17 (14, 19)	17 (16, 19)
BMI (kg/m ²)	26.9 ± 4.6	26.6 ± 4.7	28.0 ± 5.3	27.5 ± 4.5	30.9 ± 6.4	28.0 ± 2.4	30.0 ± 5.9	29.0 ± 5.2
Hypertension, number (%)	369 (47)	164 (44)	61 (17)	57 (15)	26 (7)	4 (1)	18 (5)	11 (3)
Diabetes, number (%)	79 (10)	24 (30)	11 (14)	10 (13)	12 (15)	4 (5)	6 (8)	6 (7)
Thyroid Disease, number (%)	165 (21)	73 (44)	39 (24)	17 (10)	12 (7)	5 (3)	9 (6)	2 (1)
Respiratory Disease, number (%)	188 (24)	75 (40)	19 (10)	23 (12)	22 (12)	2 (1)	25 (14)	14 (7)
Cardiovascular Disease, number (%)	502 (64)	193 (38)	140 (28)	61 (12)	39 (8)	5 (1)	21 (4)	9 (2)
TBI, number (%)	31 (4)	10 (32)	14 (45)	8 (13)	4 (14)	1 (3)	2 (6)	
Alcohol use, number (%)	63 (8)	18 (29)	5 (8)	24 (38)		2 (3)	6 (9)	
CPAP use, number (%)	31 (4)				8 (26)	2 (5)	18 (58)	3 (11)
MMSE median (interquartile range)	27 (24, 28)	26 (24, 28)	27 (25, 29)	28 (25, 29)	26 (24, 28)	26 (24, 28)	28 (25, 28)	27 (24, 29)
CDR median (interquartile range)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)	0.5 (0.5, 0.5)
CSF-ABETA pg/ml median (interquartile range) *	153 (130, 209)	156 (136, 169)	178 (131, 214)	221 (202, 249)	219 (202, 239)	145 (138, 151)	227 (214, 245)	206 (189, 229)
TAU pg/ml median (interquartile range) *	80 (54, 116)	115 (77, 143)	47 (36, 57)	66 (50, 79)	103 (66, 114)	46 (37, 55)	71 (46, 83)	44 (29, 51)

Table 2a: Characteristics of Cognitively Normal Participants by Obstructive Sleep Apnea Status and by A/T/N Status from Cognitive Normal to Mild Cognitive Impairment

Characteristics	Without OSA				With OSA				
	All	A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -	A+(TN) +	A+(TN) -	A-(TN) +	A-(TN) -
PTAU pg/ml median (interquartile range)*	36 (23, 51)	55 (37, 68)	19 (15, 20)	32 (25, 38)	16 (13, 19)	51 (32, 58)	20 (19, 21)	41 (31, 44)	18 (15, 20)
Aβ ₄₂ median (interquartile range)*	1.2 (1.0, 1.4)	1.4 (1.3, 1.5)	1.3 (1.1, 1.3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)	1.4 (1.2, 1.4)	1.3 (1.1, 1.4)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)

Abbreviation: OSA: Obstructive Sleep Apnea, Aβ₄₂: amyloid beta, MCI: Mild Cognitive Impairment, ApoE4: Apolipoprotein epsilon4, BMI: body mass index, CDR: Clinical Dementia Rating, CPAP: continuous pulmonary airway pressure; CSF: cerebrospinal fluid, MMSE: Mini Mental State Exam; TAU: tau protein, PTAU: phosphorylated tau, TBI: traumatic brain injury. All columns show column percent where indicated. OSA and Aβ₄₂ columns show row percent where indicated.

Superscript *: indicates significant differences between groups. Aβ₄₂ + participants had significantly lower CSF-T-tau and CSF P-Tau. Amyloid positive subjects in both NL and MCI groups were more likely to be APOE4 carriers. Participants who were OSA+/Aβ₄₂+ had significantly higher BMI in the NL group but not in the MCI group, compared to other participants with varying OSA and Aβ₄₂ status. In both NL and MCI, OSA+/Aβ₄₂+ participants had higher vascular burden (i.e. higher rates of hypertension, diabetes and cardiovascular disease) compared to OSA-/Aβ₄₂+ participants (e.g. 9/15 [60%] vs. 38/95 [40%] for hypertension in NL-participants). NL/OSA+/Aβ₄₂+ participants had significantly lower educational level. Significance level $p < .05$.

Cox proportional hazard models' estimates of the effect of Obstructive Sleep Apnea and Aβ load on Alzheimer's Disease time-dependent progression risk in older CN and MCI elderly participants from ADNI

Table 3:

Characteristics N	Mild Cognitive Impairment n (%)	Mean time-to-MCI		Median time-to-MCI Days (Years)	Model 1		Model 2		
		Days ± SD (Years)	Days (Years)		HR 95% CI	P-value	HR 95% CI	P-value	
Cox proportional relative hazard of progression from Cognitive Normal to Mild Cognitive Impairment.									
OSA+ vs. OSA- Participants									
OSA+ (N=31)	11 (35)	1638 ± 105 (4.5)	1462 (4.0)	1.78 (1.58, 1.98)	1.32 (1.11, 1.65)	0.007	REF	<0.01	
OSA- (N=227)	60 (26)	1833 ± 181 (5.0)	1745 (4.8)	REF	REF		REF		
Aβ+ vs. Aβ- Participants									
Aβ+ (N=111)	47 (42)	1325 ± 183 (3.6)	956 (2.6)	2.96 (2.71, 3.22)	2.44 (1.99, 2.89)	<.001	REF	<.001	
Aβ- (N=147)	24 (16)	1543 ± 170 (4.2)	1084 (3.0)	REF	REF		REF		
Amyloid Positive (Aβ+) Participants by OSA status									
OSA+ (N=16)	8 (49)	1288 ± 151 (3.5)	928 (2.5)	3.61 (3.24, 3.97)	2.93 (2.17, 3.69)	<.001	REF	<.001	
OSA- (N=95)	39 (41)	1402 ± 125 (3.8)	1275 (3.5)	REF	REF		REF		
Amyloid Negative (Aβ-) Participants by OSA status									
OSA+ (N=15)	3 (17)	1421 ± 207 (3.9)	1206 (3.3)	1.05 (0.31, 1.79)	1.01 (0.76, 1.26)	0.11	REF	0.11	
OSA- (N=132)	21 (16)	1497 ± 167 (4.1)	1475 (4.0)	REF	REF		REF		
OSA Positive (OSA+) Participants by Aβ load									
Aβ+ (N=16)	8 (49)	1288 ± 151 (3.5)	928 (2.5)	2.55 (0.98, 4.12)	2.16 (0.87, 3.45)	0.12	REF	0.12	
Aβ- (N=15)	3 (17)	1421 ± 207 (3.9)	1206 (3.3)	REF	REF		REF		
OSA Negative (OSA-) Participants Aβ load									
Aβ+ (N=95)	39 (41)	1402 ± 125 (3.8)	1275 (3.5)	2.98 (2.66, 3.30)	2.47 (2.06, 2.88)	<.001	REF	<.001	
Aβ- (N=132)	21 (16)	1497 ± 167 (4.1)	1475 (4.0)	REF	REF		REF		
Cox proportional relative hazard of progression from Mild Cognitive Impairment to Alzheimer's Disease.									
Alzheimer's disease									
Characteristics N		Mean time-to-MCI		Model 1		Model 2		P-value	
		Days ± SD (Years)	Days (Years)	HR 95% CI	HR 95% CI	P-value	HR 95% CI	P-value	
OSA+ (N=91)	39 (43)	1678 ± 117 (4.6)	1521 (4.2)	2.78 (2.25, 3.31)	2.47 (1.79, 3.15)	0.01	2.47 (1.79, 3.15)	0.01	0.01

Characteristics N	Mild Cognitive Impairment n (%)	Mean time-to-MCI Days ± SD (Years)	Median time-to-MCI Days (Years)	Model 1		Model 2	
				HR 95% CI	P-value	HR 95% CI	P-value
Cox proportional relative hazard of progression from Cognitive Normal to Mild Cognitive Impairment.							
Aβ+ vs. Aβ- Participants							
OSA- (N=694)	259 (37)	2196 ± 109 (6.0)	1937 (5.3)	REF	REF	REF	REF
Aβ+ (N=466)	210 (43)	1381 ± 171 (3.8)	1096 (3.0)	3.03 (2.61, 3.46)	<.001	2.62 (2.17, 3.07)	<.001
Aβ- (N=319)	88 (28)	1526 ± 169 (4.2)	1268 (3.5)	REF	REF	REF	REF
Amyloid Positive (Aβ+) Participants by OSA status							
OSA+ (N=50)	27 (54)	1323 ± 141 (3.6)	1008 (2.8)	3.53 (3.12, 3.94)	0.001	2.78 (2.22, 3.34)	<.01
OSA- (N=416)	183 (44)	1720 ± 136 (4.7)	1316 (3.6)	REF	REF	REF	REF
Amyloid Negative (Aβ-) Participants by OSA status							
OSA+ (N=41)	12 (29)	1637 ± 102 (4.5)	1416 (3.9)	1.25 (0.67, 1.83)	0.07	1.17 (0.86, 1.48)	0.07
OSA- (N=278)	76 (27)	1872 ± 117 (5.1)	1468 (4.0)	REF	REF	REF	REF
OSA Positive (OSA+) Participants by Aβ load							
Aβ+ (N=50)	27 (54)	1323 ± 141 (3.6)	1008 (2.8)	2.21 (2.06, 2.36)	<.001	2.16 (2.04, 2.32)	<.001
Aβ- (N=41)	12 (29)	1637 ± 102 (4.5)	1416 (3.9)	REF	REF	REF	REF
OSA Negative (OSA-) Participants by Aβ load							
Aβ+ (N=416)	183 (44)	1720 ± 136 (4.7)	1316 (3.6)	3.05 (2.64, 3.46)	<.0001	2.55 (2.13, 2.98)	<.001
Aβ- (N=278)	76 (27)	1872 ± 117 (5.1)	1468 (4.0)	REF	REF	REF	REF

Model 1: Adjusted for age, sex, education, body mass index, baseline biomarker data and ApoE4 status

Model 2: Adjusted for age, sex, BMI, education, CPAP-use, ApoE4 status, alcohol use, baseline biomarker data, hypertension, diabetes, history of cardiovascular disease (e.g. including ischemic heart disease, heart failure, and stroke/TIA), and history of traumatic brain injury. Significance level $p < .05$.

Cox proportional hazard models' estimates of the effect of Obstructive Sleep Apnea, Tau and Neurodegeneration load on Alzheimer's Disease time-dependent progression risk in older NL and MCI elderly participants from the ADNI cohort

Table 4:

Characteristics N	Mild Cognitive Impairment n (%)	Mean time-to-MCI	Median time-to-MCI	Model 1		Model 2	
				Days (Years)	HR 95% CI	Days (Years)	HR 95% CI
Cox proportional relative hazard of progression from Cognitive Normal to Mild Cognitive Impairment.							
TN+ vs. TN- Participants							
TN+ (N=200)	64 (32)	1254 ± 128 (3.4)	914 (2.5)	3.75 (2.12, 5.35)	0.001	3.52 (1.89, 5.17)	0.013
TN- (N=58)	7 (12)	1754 ± 201 (4.7)	1554 (4.3)	REF	REF	REF	REF
TN+ Participants by OSA status							
OSA+ (N=20)	9 (45)	1194 ± 107 (3.3)	1019 (2.8)	2.36 (1.15, 3.58)	<.001	2.04 (1.11, 2.97)	<.001
OSA- (N=180)	55 (31)	1382 ± 121 (3.8)	1084 (3.0)	REF	REF	REF	REF
TN- Participants by OSA status							
OSA+ (N=11)	2 (18)	1652 ± 152 (4.5)	1460 (4.0)	2.61 (1.00, 4.71)	0.05	2.33 (0.57, 4.09)	0.06
OSA- (N=47)	5 (11)	1917 ± 208 (5.3)	1625 (4.5)	REF	REF	REF	REF
OSA Positive (OSA+) Participants by TN status							
TN+ (N=20)	9 (45)	1194 ± 107 (3.3)	1019 (2.8)	3.55 (1.71, 5.39)	0.02	3.31 (1.36, 5.27)	0.03
TN- (N=11)	2 (18)	1652 ± 152 (4.5)	1460 (4.0)	REF	REF	REF	REF
OSA Negative (OSA-) Participants by TN status							
TN+ (N=180)	55 (31)	1382 ± 121 (3.8)	1084 (3.0)	3.54 (1.98, 5.15)	0.02	3.46 (1.78, 5.14)	0.02
TN- (N=47)	5 (11)	1917 ± 208 (5.3)	1625 (4.5)	REF	REF	REF	REF
All TN+ Participants OSA & Aβ load							
OSA+/Aβ+ (N=10)	5 (50)	1019 ± 151 (2.8)	904 (2.5)	3.22 (1.36, 5.08)		3.17 (1.19, 5.15)	
OSA+/Aβ- (N=10)	4 (40)	1312 ± 102 (3.6)	1051 (2.9)				
OSA-/Aβ+ (N=84)	32 (38)	1367 ± 142 (3.7)	1013 (2.8)	REF	<.001	REF	<.001
OSA-/Aβ- (N=96)	23 (24)	1597 ± 147 (4.4)	1455 (4.0)			REF	
All TN- Participants OSA & Aβ load							
OSA+/Aβ+ (N=6)	2 (33)	1496 ± 152(4.1)	1471 (4.0)	1.58 (1.04, 3.12)	<.001	1.49 (1.06, 2.84)	<.001

Characteristics N	Mild Cognitive Impairment n (%)	Mean time-to-MCI	Median time-to-MCI	Model 1		Model 2	
				Days (Years)	HR 95% CI	P-value	HR 95% CI
Cox proportional relative hazard of progression from Cognitive Normal to Mild Cognitive Impairment.							
OSA+/Aβ- (N=5)	0 (0)						
OSA-/Aβ+ (N=11)	2 (18)	1752 ± 172 (4.8)	1675 (4.6)		REF		
OSA-/Aβ- (N=36)	3 (8)	1847 ± 167 (5.1)	1725 (4.7)				REF
Cox proportional relative hazard of progression from Mild Cognitive Impairment to Alzheimer's Disease.							
Characteristics N	Alzheimer's disease n (%)	Mean time-to-MCI	Median time-to-MCI	Model 1		Model 2	
				Days (Years)	HR 95% CI	P-value	HR 95% CI
TN+ vs. TN- Participants							
TN+ (N=612)	269 (44)	1478 ± 127 (4.0)	1376 (3.8)		3.57 (2.03, 5.11)		3.34 (1.79, 4.89)
TN- (N=173)	29 (17)	1795 ± 129 (4.9)	1697 (4.6)		REF		REF
TN+ Participants by OSA status							
OSA+ (N=60)	32 (53)	1377 ± 211 (3.8)	1356 (3.7)		2.93 (1.11, 4.76)		2.72 (1.17, 4.27)
OSA- (N=552)	237 (43)	1776 ± 109 (4.9)	1652 (4.5)		REF		REF
TN- Participants by OSA status							
OSA+ (N=31)	7 (23)	1753 ± 181 (4.8)	1648 (4.5)		1.78 (1.14, 3.42)		1.48 (1.09, 2.87)
OSA- (N=142)	22 (15)	1879 ± 206 (5.1)	1789 (4.9)		REF		REF
OSA Positive (OSA+) Participants by OSA status							
TN+ (N=60)	32 (53)	1377 ± 211 (3.8)	1356 (3.7)		3.55 (1.67, 5.43)		3.37 (1.86, 4.88)
TN- (N=31)	7 (23)	1753 ± 181 (4.8)	1648 (4.5)		REF		REF
OSA Negative (OSA-) Participants by Aβ load							
TN+ (N=552)	237 (43)	1776 ± 109 (4.9)	1652 (4.5)		2.81 (1.05, 4.57)		2.76 (1.11, 4.41)
TN- (N=142)	22 (15)	1879 ± 206 (5.1)	1789 (4.9)		REF		REF

Characteristics N	Mild Cognitive Impairment n (%)	Mean time-to-MCI Days ± SD (Years)	Median time-to-MCI Days (Years)	Model I		Model 2	
				HR	95% CI	HR	95% CI
Cox proportional relative hazard of progression from Cognitive Normal to Mild Cognitive Impairment.							
All TN+ Participants by OSA & Aβ load							
OSA+/Aβ+ (N=35)	26 (74)	1262 ± 122 (3.5)	1197 (3.3)	3.98 (2.26, 5.70)		3.47 (1.96, 4.98)	
OSA+/Aβ- (N=25)	6 (24)	1656 ± 167 (4.5)	1596 (4.4)		<.001		<.001
OSA-/Aβ+ (N=388)	174 (45)	1581 ± 206 (4.3)	1524 (4.2)	REF			
OSA-/Aβ- (N=164)	63 (38)	1697 ± 154 (4.7)	1583 (4.3)				REF
All TN- Participants by OSA & Aβ load							
OSA+/Aβ+ (N=15)	7 (47)	1596 ± 155 (4.4)	1483 (4.1)	1.56 (1.07, 3.05)		1.23 (1.03, 2.43)	
OSA+/Aβ- (N=16)	0 (0)						
OSA-/Aβ+ (N=28)	13 (46)	1801 ± 156 (4.9)	1717 (4.7)	REF	<.001		<.001
OSA-/Aβ- (N=114)	9(8)	2190 ± 115 (6.0)	1979 (5.4)				REF

Model I: Adjusted for age, sex, education, body mass index and ApoE4 status

Model II: Adjusted for age, sex, BMI, education, CPAP-use, ApoE4 status, alcohol use, baseline biomarker data, hypertension, diabetes, history of cardiovascular disease (e.g. including ischemic heart disease, heart failure, and stroke/TIA), and history of traumatic brain injury