

245 **Psychometric Assessment:**

246 Cross-sectional and longitudinal cognitive characteristics of all subjects are shown in Table 2.
247 We did not find any statistically significant differences between OSA indices and cognition across
248 healthy and OSA groups at baseline or longitudinally. To assess the relationship between
249 longitudinal changes in CSF A β ₄₂ and cognitive performance, we performed Pearson correlation
250 analyses comparing annual rate of change of CSF A β ₄₂ and annual change in cognitive z-scores.
251 No statistically significant correlations were found: Logic 2 (r=-.12, n.s.), AF (r=.15, n.s.), VF
252 (r=.09, n.s.), BNT (r=.006, n.s.), DSST (r=.16, n.s.), TMT-A (r=.001, n.s.) and TMT-B (r=-.08, n.s.).
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254 **CSF and PET Assessment:**

255 From the 208 participants, 179 subjects performed a lumbar puncture (LP) at baseline. A
256 second LP was obtained at follow-up in 104 subjects 2.42±0.88 years later. 86 subjects performed
257 PiB scans at baseline. A second PiB scan evaluation was obtained at follow-up in 34 subjects
258 2.50±0.39 years later. 57 participants performed both the LP and the PET scans at baseline. 25
259 participants performed the LP and PET scans at both baseline and follow-up (Figure 5). We will
260 refer to participants with both baseline and follow-up biomarker data available as “*completers*”,
261 whereas subjects with only baseline biomarkers data will be referred to as “*non-completers*”.
262 There were no differences between *completers* and *non-completers*, in terms of (age [t=-.27, n.s.],
263 sex [X^2 =.002, n.s.], BMI [t=.40, n.s.], MMSE [t=.00, n.s.], years of education [t=.17, n.s.], ApoE4
264 status [X^2 =.93, n.s.], TST [t=1.18, n.s.], AHIall [t=.82, n.s.] or AHI4% [t=.88, n.s.]). Summary
265 statistics of baseline, and annual changes of AD biomarkers are shown in Table 3. No significant
266 associations were observed between annual changes in CSF A β ₄₂ and age ($F_{1,93}$ =2.23, p=.13,
267 β =-1.68, 95% Confidence Interval [CI]= -.39 to .55, p=.13), sex ($F_{1,93}$ =.64, p=.42, β =13.64, 95%
268 CI = -20.17 to 47.47, p=.42), BMI ($F_{1,93}$ =.16, p=.69, β =-.61, 95% CI=-3.67 to 2.44, p=.69) or
269 ApoE4 ($F_{1,93}$ =.42, p=.51, β =-11.35, 95% CI= -46.03 to 23.32, p=.51). At cross-section and
270 longitudinally, we did not find any significant differences among the 3 OSA severity groups for
271 CSF P-Tau or T-Tau. Similarly, no cross-sectional or longitudinal effects were found for CSF A β ₄₂
272 across OSA severity groups using univariate analysis. No significant correlation between CSF
273 A β ₄₂ and AHI indices were observed at cross-section.

274 However, significant correlations were observed between longitudinal change in CSF A β ₄₂
275 levels and AHIall/AHI4 (rho=-0.24, p<.05, rho=-0.23, p<.05, respectively) and after controlling for
276 age, sex, BMI and ApoE4 (rho=-0.27, p<.05, rho=-0.24, p<.05, respectively). Significant
277 associations were also observed between annual rate of change of CSF A β ₄₂ and AHI indices at
278 baseline using hierarchical linear regression model (shown in table 4), including annual rate of
279 change of CSF A β ₄₂ as dependent and AHI indices (lnAHI4 and lnAHIall) as independent
280 variables, before ($F_{1,92}$ =5.41, p<.05, and $F_{1,93}$ =4.72, p<.05 respectively) and after accounting for
281 age, sex, BMI and ApoE4 ($F_{1,88}$ =4.26, p<.05 and $F_{1,87}$ =4.36, p<.05, respectively). The effect of the
282 type of sleep recording device and TST were not significant, thus we excluded them from the final
283 model. Figure 1 shows the relationship between delta change in CSF A β ₄₂ and the AHI indices at
284 baseline. Sensitivity analyses were performed excluding 5 subjects whose baseline sleep
285 evaluation was done after their first CSF measurements. Association between lnAHI4, lnAHIall,
286 and annual delta CSF A β ₄₂ remained unchanged.
287

288 Similarly, on univariate analysis no difference in AD_{PiB}-mask was observed between OSA
289 severity groups, and no significant correlation between AD_{PiB}-mask and AHI indices were
290 observed at cross-section. However, correlations were observed between longitudinal change in
291 AD_{PiB}-mask and AHIall or AHI4 (rho=0.374, p<.05, rho=0.302, p=0.09, respectively) after
292 controlling for age, sex, BMI and ApoE4. Using the same hierarchical linear regression model as
293 for CSF A β ₄₂, no statistically significant associations were observed between annual rate of
294 change of AD_{PiB}-mask and AHIs, including annual rate of change of AD_{PiB}-mask as dependent

295 and AHI indices at baseline as independent variables after accounting for age, sex, BMI and
296 ApoE4. LnAHIall and LnAHI4 were not associated with increases in AD_{PiB}-mask most likely due to
297 the small sample size as there was a trend for LnAHIall ($F_{1,28}=2.96$, $p=.09$ and $F_{1,28}=2.32$, n.s.
298 respectively). Figure 2 shows the relationship between delta change in AD_{PiB}-mask and the AHIall
299 index at baseline, both variables were corrected for normal distribution by log transformation.

300 Further, we analyzed the association between longitudinal change in CSF A β_{42} and AD_{PiB}-
301 mask. Using a Pearson correlation, a significant negative correlation between longitudinal change
302 in CSF A β_{42} and AD_{PiB}-mask was observed ($r=-.44$, $p<.05$). Using an AD_{PiB}-mask SUVR ≥ 1.4 to
303 define presence of brain amyloid deposition (PiB+),³⁰⁻³² a secondary analysis performed only in
304 the initial cross-sectional cases, revealed a significant difference between the slopes of PiB+ and
305 PiB- cases (Figure 3). This was confirmed by the presence of an interaction between PiB status
306 and LnAHI4% ($F_{1,29}=5.54$, $p<.05$) as well as a positive trend between AHI4% and PiB uptake in
307 PiB+ subjects ($\rho=0.67$, $p=.07$). Similar findings were observed for AHIall (data not shown).
308 Figure 3 shows the relationships between the AHI4% and PiB SUVR uptake when comparing
309 PiB+ vs. PiB- groups.

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312 **DISCUSSION:**

313 The primary objective of this study was to determine if severity of OSA in cognitively normal
314 elderly is associated with CSF and PET AD-biomarkers at cross-section and their longitudinal
315 change across an approximate 2 year period. Our initial finding revealed that OSA was common
316 and affected 53% of our cognitively normal community-dwelling cohort. Second, we demonstrated
317 that baseline OSA severity was associated with two-year longitudinal decreases in CSF A β_{42} and
318 a trend towards increases in cortical PiB-PET uptake. Such changes are potentially consistent
319 with increased brain amyloid burden, which were also observed in our cohort (*i.e.*, a negative
320 correlation between longitudinal change in CSF A β_{42} and AD_{PiB}-mask), suggesting that OSA may
321 play a role in amyloid deposition in late-life. Moreover, the magnitude of these changes was higher
322 than the one predicted by the presence of the ApoE4 allele alone (Table 4), which to date is
323 considered the most important risk factor for sporadic AD. AHIall, which includes hypopneas
324 associated with oxygen desaturation or arousals, was a better predictor of longitudinal increases
325 in amyloid burden than AHI4%, which includes only hypopneas associated with 4% oxygen
326 desaturation. This raises the possibility that sleep fragmentation is a more critical
327 pathophysiological mechanism by which OSA contributes to AD risk. However, AHIall and AHI4%
328 were highly correlated in our cohort ($r=0.91$, $p<.01$) and this study was unable to differentiate the
329 individual effects of sleep fragmentation versus intermittent hypoxia.

330

331 Although OSA severity was associated with increases in brain amyloid burden, it was not
332 predictive of cognitive deterioration based on neuropsychological performance, which is in
333 agreement with prior studies.^{33;34} This is not completely surprising given that the relationship
334 between amyloid burden and cognition is probably nonlinear and dependent on additional factors
335 such as tau pathology and microvascular changes. Low sensitivity of the neuropsychological tests
336 used may have been another factor. Sensitivity could be increased in the future by employing
337 cognitive tasks that are known to be sleep-dependent.

338 Current evidence suggests that cognitive decline in AD is associated with decreases in CSF
339 A β_{42} and increases in amyloid PET uptake.³⁵ However, little is known about the temporal course
340 of CSF A β_{42} in the preclinical or early stages of the disease, with some recent animal and human
341 studies showing A β_{42} elevations prior to A β_{42} reductions,^{36;37} suggesting an intermediate stage of
342 increased soluble A β levels prior to amyloid deposition. Interestingly, we and others have shown
343 that reduced slow wave activity (SWA) at cross-section as well as one night of SWS disruption,

344 are associated with increases in CSF A β levels, potentially as a consequence of increases in
345 neuronal firing and/or decreases in amyloid clearance.³⁸⁻⁴¹ It remains to be determined how
346 universal a period of elevated CSF A β_{42} in humans is observed prior to a decline, but the above
347 mentioned studies suggest that sleep disruption might be associated with elevations of CSF A β_{42}
348 which in chronic sleep disorders such as OSA could foster its aggregation and manifest as
349 longitudinal decreases in CSF A β_{42} over time such as the one observed in our study. This
350 hypothesis would also explain the absence of significant associations at cross-section. Whether
351 OSA-related sleep fragmentation increases AD-risk through disruption of SWS or other sleep
352 stages is unknown. The ends of apneas are associated with arousals or awakenings that prevent
353 sleep⁴² and these are more commonly observed in NREM1-2 and REM sleep. Apneic episodes
354 are less common in SWS, which has been associated with a higher respiratory arousal
355 threshold^{43;44} as well as more stable breathing.⁴⁵ However, the temporal course of SWA has been
356 shown to be slower in mild OSA,⁴⁶ while severe OSA patients show up to a 40% rebound in SWS
357 duration during OSA treatment with CPAP,⁴⁷ which suggest that changes in SWS quality may also
358 be involved. However, a recent prospective study reported the association between decreased
359 percentage of REM sleep and increased risk of dementia, implicating also REM sleep as a
360 possible mediator for AD risk.⁴⁸ In addition, actigraphy-assessed arousals and circadian rhythm
361 disruption have also been shown to increase the risk of MCI/dementia in the elderly,⁴⁹ indicating
362 that the relationship between OSA-related sleep fragmentation and amyloid deposition might not
363 be stage-specific.

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365 Another possible mechanism by which OSA might increase amyloid deposition is through
366 impairment in the CSF-ISF exchange promoted by the glymphatic system⁴⁰ resulting in decreased
367 clearance of ISF A β_{42} . This mechanism was suggested in a recent study of 31 controls and 10
368 severe OSA middle-age subjects where neuronally derived proteins were decreased in the OSA
369 group when compared to controls.⁴⁰ The authors propose that elevations in the intrathoracic and
370 intracranial pressure as well as a sudden pressure reversal at the end of the apnea would impede
371 the glymphatic flow of metabolites from ISF into CSF.⁴⁰ Another potential pathway of impairment
372 of CSF-ISF exchange could be cerebral edema secondary to intermittent hypoxia, as proposed
373 recently in a study in which severity of OSA correlated with increased volume and thickness of
374 the left lateral prefrontal cortex as well as increased thickness of the right frontal pole, the right
375 lateral parietal lobules, and the left posterior cingulate cortex.⁵⁰ Similar findings were observed as
376 brain volume reductions after six months of treatment with CPAP which also suggests the
377 existence of brain edema in OSA.⁵¹

378
379 Finally, the effects of OSA directly increasing ISF A β_{42} burden as suggested by some
380 intermittent hypoxia animals models,^{52;53} or indirectly through other intermediate mechanisms
381 such as oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial
382 dysfunction or metabolic dysregulation cannot be discarded although it is feasible that these and
383 other consequences of OSA may decline with age^{10;54} and might not be as relevant in the elderly
384 as in middle age.

385
386 Among participants with initial PiB+ scans at cross-section, Figure 3 suggest that a higher
387 severity of OSA is associated with greater brain A β deposition, while no such association is found
388 in participants with PiB- scans, implying that presence or absence of amyloid burden might act as
389 a moderator in these relationships. This would be in agreement with previous studies showing
390 increased amyloid deposition associated with higher AHI indices in MCI patients but not in
391 cognitively normal controls at cross-section.¹³ We did not observe this effect in the CSF sample
392 when we compared *amyloid* positive vs. negative cases based on the NYU CBH CSF bank A β_{42}
393 cut-offs (*i.e.* CSF A β_{42} ng/ml <500), so this finding should be interpreted with caution. It may be
394 that the effects of OSA/hypoxia on A β aggregation are most pronounced after significant A β

395 accumulation has already occurred, leading to an acceleration of further A β deposition in a feed-
396 forward cycle¹³ (Figure 4) with OSA-related arousals worsening sleep quality and increasing
397 amyloid deposition. In addition, 33/34 of the subjects that had PiB PET follow-up scans were PiB-
398 at baseline, indicating that the observed longitudinal increases in PiB uptake were not dependent
399 on amyloid status.

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401 Our observations are consistent with our hypothesis that there is an association between
402 severity of OSA-related sleep fragmentation and longitudinal increase in amyloid burden in
403 cognitively normal elderly. This implies that existing therapies for OSA such as CPAP could delay
404 the progression to MCI or dementia in elderly with OSA, as was suggested by our previous
405 epidemiological studies using the ADNI database¹¹ and a recent cross-sectional study in which
406 OSA patients showed lower CSF A β_{42} concentrations, as well as higher T-tau/A β_{42} ratio when
407 compared to OSA-CPAP patients.¹⁵

408 The high prevalence of mild and moderate to severe OSA in cognitively normal elderly in
409 asymptomatic adults undergoing screening for OSA as part of a protocol on memory and normal
410 aging adds to the importance of these findings. Strengths of our study include that our community
411 residing subjects were not recruited for the study based on sleep complaints, and thus should
412 have been free of selection biases potentially affecting sleep-clinic based cohorts which typically
413 include younger, more frequently male, obese and symptomatic (e.g. excessive daytime
414 sleepiness, treatment resistant hypertension, etc.). We also utilized a state-of-the-art method for
415 home-monitoring of OSA, as well as longitudinal standardized CSF and PET biomarkers.
416 Potential weaknesses of the study were the relative short duration and the lack of longitudinal
417 sleep data which did not allow us to test whether preclinical-AD brain lesions increase the risk for
418 OSA, or the lack of a longer clinical assessment to test whether amyloid deposition is followed by
419 cognitive decline to MCI or AD. Another limitation of the study was that not all subjects had a
420 longitudinal follow up, although both *completers* and *non-completers* were not different in terms
421 of sociodemographics, BMI, MMSE, AHIall or AHI4%.

422 In summary, to our knowledge this study is the first to document that OSA is associated with
423 longitudinal changes in amyloid burden in a sample of cognitively normal elderly. The implication
424 of these findings is that we have identified a contribution of OSA in increasing the amyloid beta
425 burden prior to significant cognitive decline. Our data support testing whether clinical interventions
426 aimed at OSA, such as treatment with CPAP or dental appliances, could be implemented during
427 the early phase in which tissue damage precedes clinical symptoms and neuronal dysfunction, to
428 mitigate the progression of cognitive impairment.

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434 **ACKNOWLEDGMENTS:**

435 The authors are indebted to the study subjects for their patience, and for their participation in and
436 contribution to the research. The authors acknowledge contributions to patient recruitment and
437 data collection by Ms. Kimberly Clay, Mr. Michael Yablon, Ms. Christine Grosso, and Ms. Gabriella
438 Petrongolo. They also thank Dr. Pauline McHugh for their assessment of research subjects. This

439 work was supported by grants from: NIH/NIA/NHLBI R01HL118624, R01HL111724,
440 R21AG049348, R01AG035137, R01AG022374, R01AG13616, R01AG12101 and
441 P30AG008051; Foundation for Research in Sleep Disorders, the American Sleep Medicine
442 Foundation Junior Faculty Award, and the Friedman Brain Institute. Dr. Rosenzweig is supported
443 by the Wellcome Trust [103952/Z/14/Z]. Dr. Zetterberg is supported by the Swedish Research
444 Council (grant no: 2013-2546) and the European Research Council (grant no: 681712). Dr. Nadia
445 Gosselin is supported by a salary award from the *Fonds pour la recherche du Québec – Santé*.

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461 **Tables**

Characteristics	All	Normal	Mild OSA	Moderate-Severe OSA
No. of Participants (%)	208 (100)	97 (46.63)	76 (36.53)	35 (16.82)
Female sex, number (%)	129 (62)	67 (69.1)	44 (57.9)	18 (51.4)

BMI (Kg/m2), median (IQR)	25.79 (22.7,29.87)	24.61 (22.32,28.17)*	26.89 (23.32,29.9)	29.76 (23.49,33.51)*
Age, years, mean \pm SD	68.46 \pm 7.38	67.56 \pm 7.32	68.60 \pm 7.19	70.68 \pm 7.69
Education, years, median (IQR)	17 (16, 18)	16.5 (16,18)	17 (16,18)	16 (14,19)
Hypertension, number (%)	86 (41.3)	34 (35.1)	32 (42.1)	20 (57.1)
Diabetes, number (%)	12 (5.8)	4 (4.1)	4 (5.3)	4 (11.4)
Cardiovascular disease, number (%)	9 (4.3)	1 (1)	7 (9.2)	1 (2.9)
Thyroid disease, number (%)	34 (16.3)	16 (16.5)	11 (14.5)	7 (20)
APOE4 positive, number (%)	71 (34.1)	34 (35.1)	25 (32.9)	12 (34.3)
AHI4% ,median (IQR)	5 (1.55, 11.40)	1.45 (0.725,3.00)*	7.75 (5.81,10.52)*	25.00 (19.3,37.00)*
AHIall, median (IQR)	17 (10.85, 24.00)	10.40 (6.75,13.65)*	20.05 (17.05, 24.00)*	39.00 (31,57)*
Mean O2 Saturation, median (IQR)	94.19 (93.15, 95.6)	94.57 (93.78,95.6)*	94.9 (92.77,95.71)a	93.47 (92.1,94.5)* a
ESS, median (IQR)	5 (3,8)	4 (3,7)	6 (3.5,8.5)	6 (4,9)
TST, hours, median (IQR)	7 (6.5, 8)	7.48 (6.75,8)	7.00 (6.5,8)	7.50 (6.5,8)

*, a Statistical significant difference between the groups.

Table 2: Cognitive characteristics of NYU cohort at baseline and follow-up evaluations

	All (n=108)	Normal (n=50)	Mild OSA(n=43)	Moderate-Severe OSA (n=15)
MMSE baseline(mean \pm SD)	29.31 \pm 0.99	29.40 \pm 0.93	29.18 \pm 0.98	29.33 \pm 1.30
MMSE follow-up	29.36 \pm 0.85	29.51 \pm 0.718	29.29 \pm 0.867	29.00 \pm 1.206
CDR baseline	0 \pm 0	0 \pm 0	0 \pm 0	0 \pm 0
CDR follow-up	0.010 \pm 0.071	0 \pm 0	0 \pm 0	0.083 \pm 0.19
Animal fluency (z-scores)	0.207 \pm 0.99	0.24 \pm 1.14	0.05 \pm 0.81	0.50 \pm 0.95
Animal fluency (delta change z-scores)	-0.23 \pm 0.87	-0.30 \pm 0.98	-0.20 \pm 0.85	-0.11 \pm 0.54
Vegetable Fluency (z-scores)	-0.042 \pm 1.1	-0.023 \pm 0.98	-0.14 \pm 1.28	0.15 \pm 0.96
Vegetable Fluency (delta change z-scores)	-0.14 \pm 0.99	-0.39 \pm 0.87	0.087 \pm 1.08	-0.02 \pm 0.98
Boston Naming Test (z-scores)	-0.20 \pm 1.03	-0.10 \pm 1.06	-0.38 \pm 0.98	-0.017 \pm 1.07
Boston Naming Test (delta change z-scores)	0.11 \pm 0.71	0.24 \pm 0.69	0.12 \pm 0.71	-0.28 \pm 0.69
Logic 1 (z-scores)	0.19 \pm 0.96	0.11 \pm 1.0	0.24 \pm 0.90	0.29 \pm 1.05
Logic 1 (delta change z-scores)	-0.007 \pm 0.86	-0.03 \pm 0.87	-0.07 \pm 0.82	0.23 \pm 0.96
Logic 2 (z-scores)	0.10 \pm 1.0	0.11 \pm 1.07	0.008 \pm 0.97	0.33 \pm 0.88
Logic 2 (delta change z-scores)	-0.012 \pm 0.75	0.042 \pm 0.8	-0.06 \pm 0.75	-0.04 \pm 0.67
Trails Making Test-A time (z-scores)	0.062 \pm 1.06	-0.14 \pm 0.88	-0.33 \pm 1.04	0.12 \pm 0.89
Trails Making Test-A time (delta change z-scores)	0.048 \pm 0.88	0.025 \pm 0.14	0.127 \pm 0.7	-0.093 \pm 1.03
Trails Making Test-B time (z-scores)	-0.17 \pm 0.96	-0.14 \pm 0.89	-0.33 \pm 1.04	0.12 \pm 0.9
Trails Making Test-B time (delta change z-scores)	-0.034 \pm 0.72	-0.007 \pm 0.65	-0.002 \pm 0.63	-0.19 \pm 0.64
DSST (z-scores)	0.2 \pm 0.95	0.2 \pm 0.83	0.14 \pm 1.03	0.36 \pm 1.11

DSST(delta change z-scores)	0.07±0.44	0.1±0.44	-0.003±.45	0.18±0.37
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462 *Statistical significant difference between the groups. Lower scores represent worse cognitive function.

	ALL (n=208)	Normal (n=97)	Mild OSA (n=76)	Moderate-Severe OSA (n=35)
CSF Aβ42 baseline (n=179) Mean ± SD	681.31 ±236.43	681.88 ± 243.18	690.61 ± 233.99	657.48 ± 224.79
CSF Aβ42 annual change (n=104) Median (Interquartile range)	29.40 (-9.53,71.06)	40.59 (4.23,80.80)	26.97 (-29.99,66.71)	-4.088 (-18.97,27.92)
CSF P-tau baseline (n=179) Median (Interquartile range)	41 (31,52)	42.50 (31.5,52.05)	43.55 (30,55)	40.97 (31.71,49)
CSF P-tau annual change (n=104) Mean ± SD	1.42 ± 3.93	1.35 ± 3.18	0.73 ± 4.27	3.43 ± 4.90
CSF T-tau baseline (n=179) Median (Interquartile range)	257.96 (202,360.91)	268.04 (217.65,362)	244.85 (198,382)	248.14 (174,343)
CSF T-tau annual change (n=104) Mean ± SD	8.24 ± 21.42	7.52 ± 18.86	5.85 ± 21.83	17.04 ± 27.53
AD _{PIB} PET baseline (n=86) Median (Interquartile range)	1.05 (1.02,1.11)	1.047 (1.02,1.09)	1.061 (1.00,1.11)	1.06 (1.01,1.14)
AD _{PIB} PET annual change (n=34) Median (Interquartile range)	0.0005 (-0.009,0.014)	-0.0020 (- 0.0095,0.0078)	-0.0022 (-0.0126,0.0224)	0.014 (0.006,0.028)

463 *Statistical significant difference between the groups.

Dependent variable		R ²	ΔR ²	Independent variables	B	95% CI	p
Annual ΔCSF Aβ42	Model 1	-.008	.035	Age	-1.36	-3.67, .95	.24
				Sex	6.63	-27.72, 40.99	.70
				BMI	.88	-2.36, 4.12	.59
				ApoE4	-15.54	-50.69, 8.81	.36
	Model 1 +AHI4	.028	.046	AHI4	-13.35	-26.06, -.64	.04
	Model 1	-.008	.035	Age	-1.57	-3.86, .70	.17
				Sex	4.07	-30.36, 38.51	.81
				BMI	1.0	-2.27, 4.27	.54
				ApoE4	-17.89	-52.58, 16.79	.30
	Model 1 +AHIall	.027	.044	AHIall	-29.08	-57.08, -1.08	.04

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Dependent variable		R ²	ΔR ²	Independent variables	B	95% CI	p
Annual Ln ΔPiB	Model 1	-.068	.062	Age	.001	-.001, .004	.28
				Sex	.001	-.036, .038	.96

			BMI	-.001	-.004, .002	.37	
			ApoE4	.01	-.026, .046	.36	
	Model 1 +AHI4	.134	.072	AHI4	.013	-.004, .03	.13
	Model 1	-.068	.062	Age	.001	-.001, .004	.25
				Sex	.001	-.036, .038	.96
				BMI	-.001	-.004, .002	.37
				ApoE4	.01	-.026, .046	.56
	Model 1 +AHIall	.151	.09	AHIall	.026	-.005, .057	.09

465 Table 4: Final model showing relationship of annual Δ CSF A β 42 and annual ln Δ PiB with AHIall and AHI4%.

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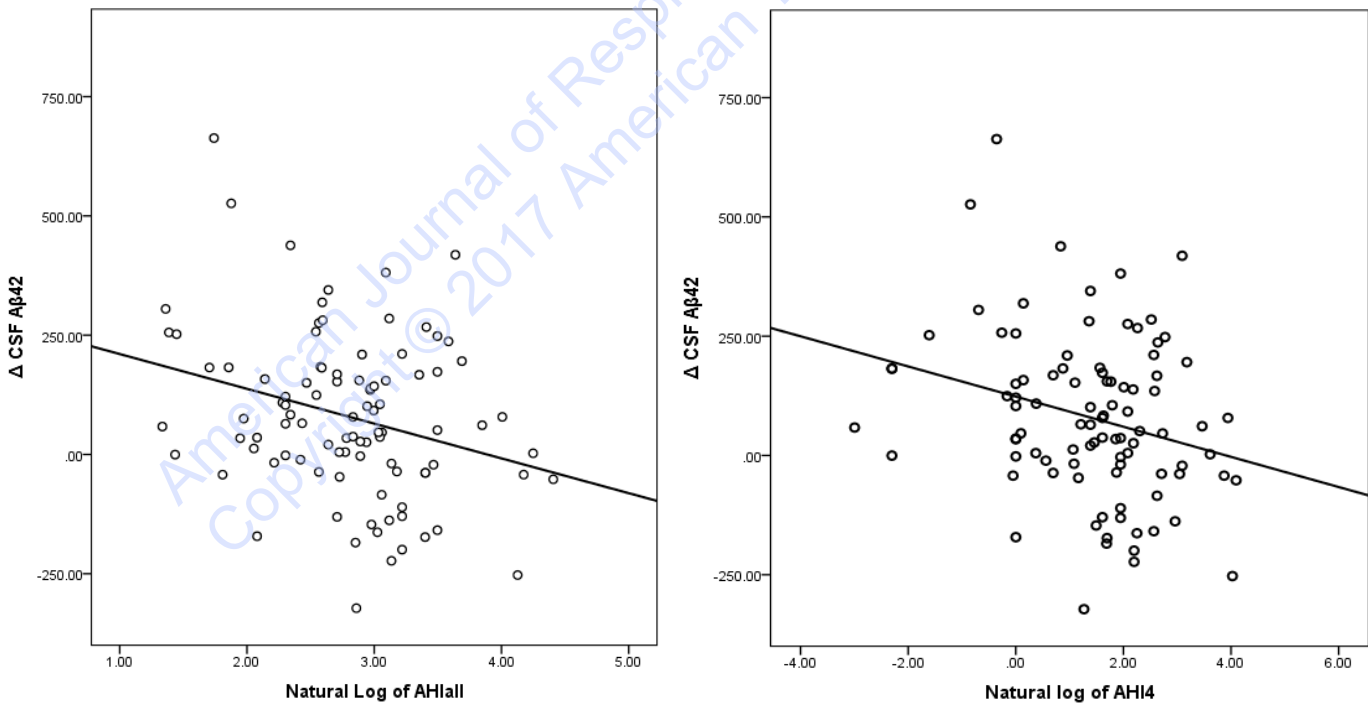
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470 **Figures**

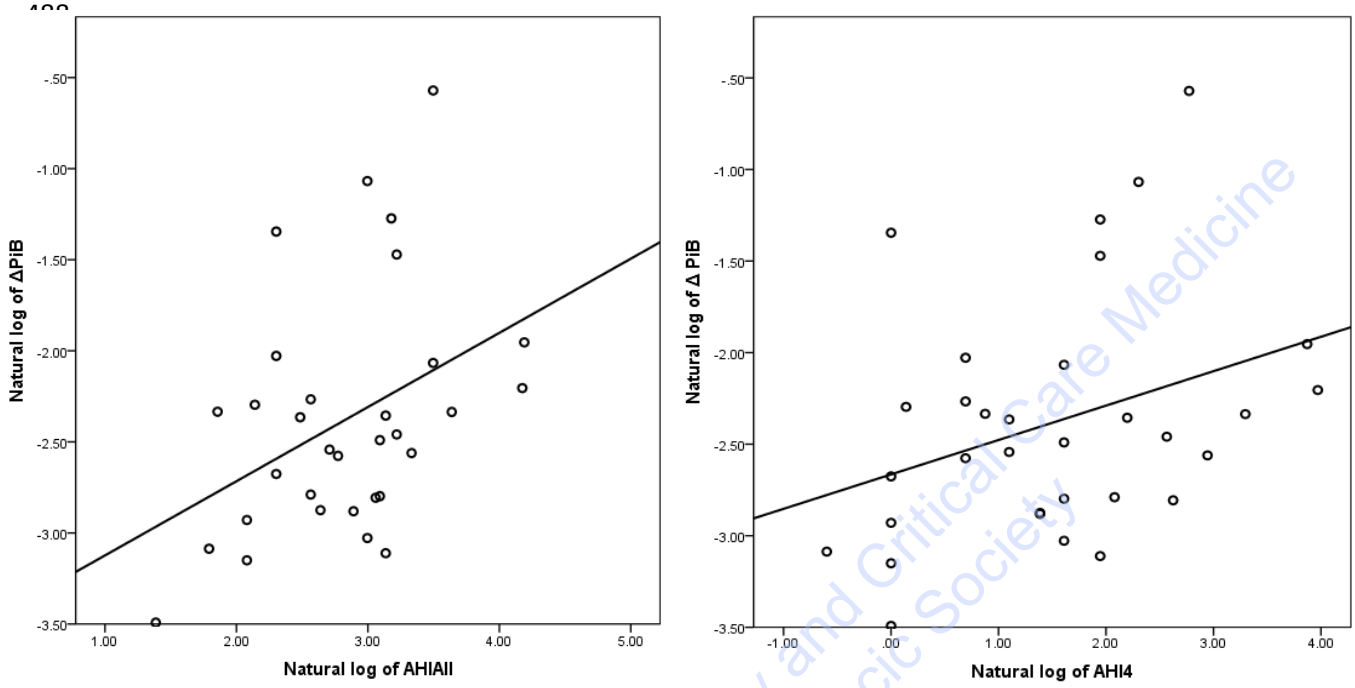
471 **Figure 1**



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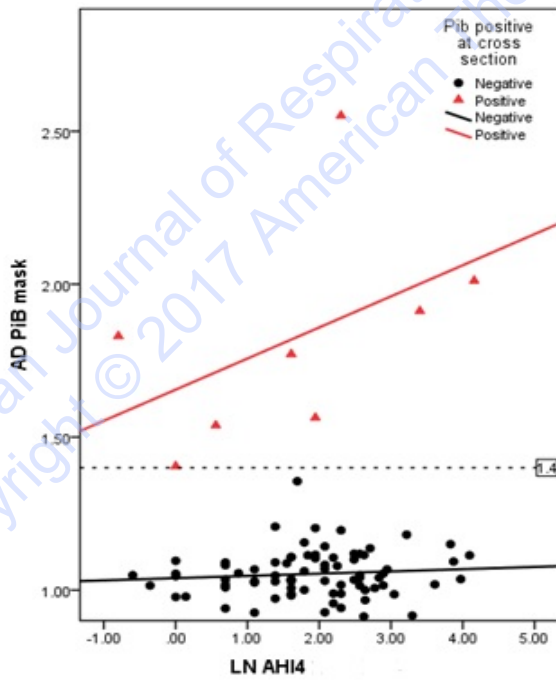
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514 Figure 4

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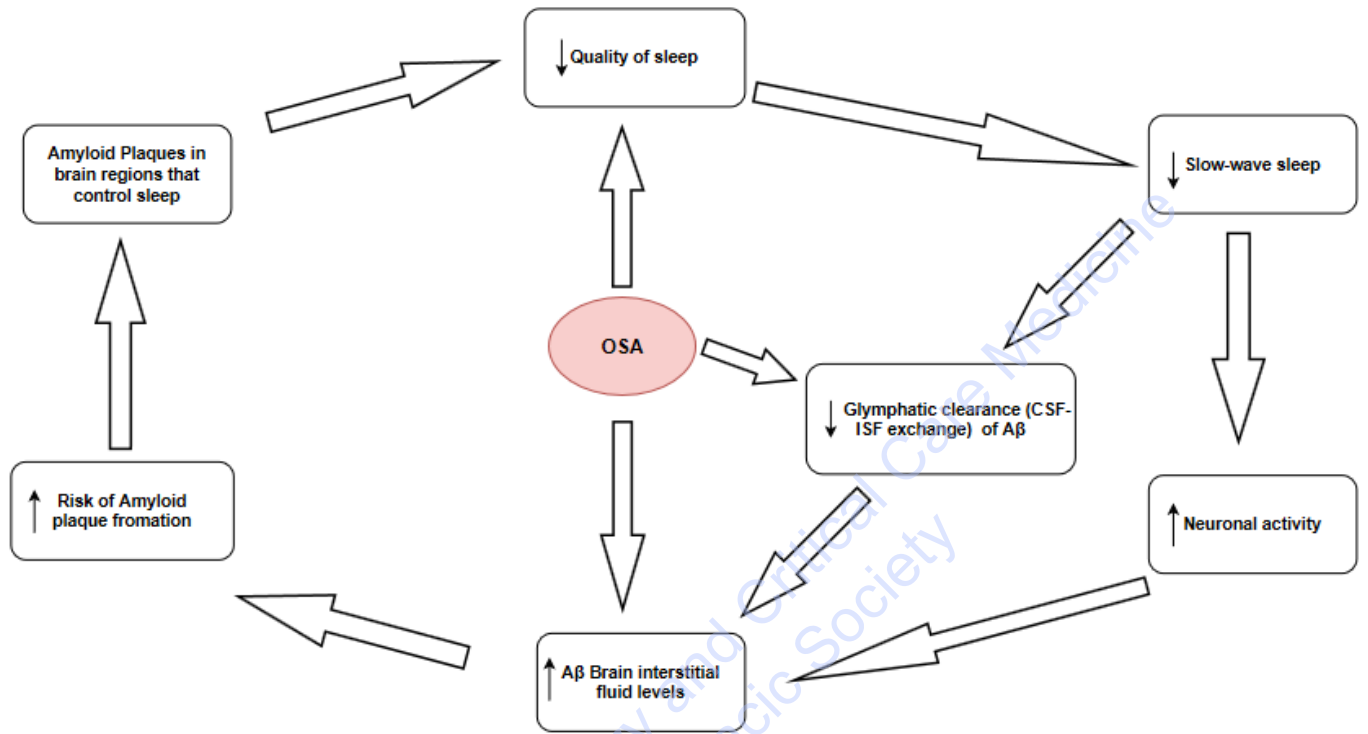
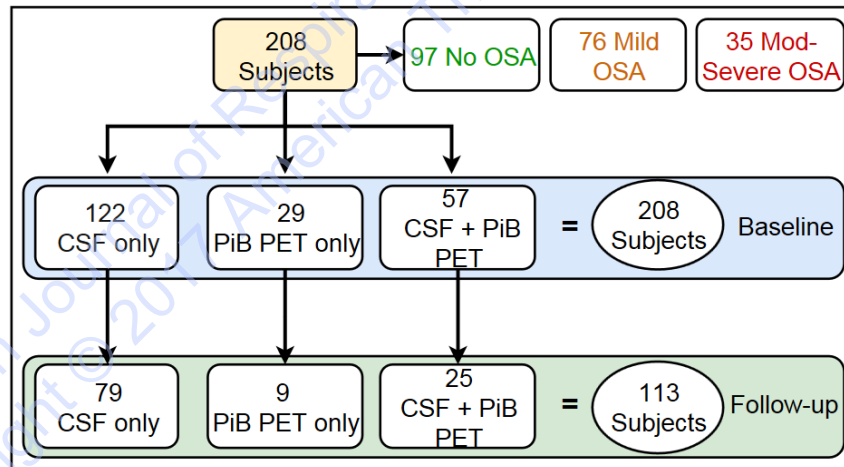


Figure 5



Study flow chart showing a detailed breakdown of subjects based on AD biomarker evaluations at the baseline and follow up visits.

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