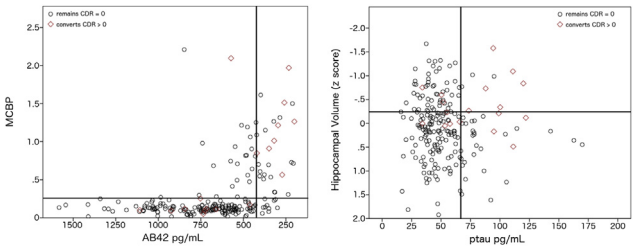
diagnostic categories (UCLA/Leuven-NC ΔSUVR=0.06, p=0.01; MCI ΔSUVR=0.13, p<0.0001; dementia ΔSUVR=0.04, p=0.0007). An effect was also seen for parietal SUVR in MCI (ΔSUVR=0.1, p=0.0004) and UCLA/Leuven-NC (ΔSUVR=0.05, p=0.04) as well as in frontal (ΔSUVR=0.09, p=0.0006) temporal (ΔSUVR=0.08, p=0.005), occipital (ΔSUVR=0.1, p=0.0004) and basal ganglia (ΔSUVR=0.08, p=0.0016) SUVR in MCI only. **Conclusions:** Higher SUVR is associated with worse cognitive performance in both the cognitively normal and impaired stages. Most significant SUVR increases per unit MMSE were seen in MCI, followed by NC and finally demented subjects in agreement with the sigmoid curve of increasing amyloid deposition.




## IC-P-020 COMPARISON OF NIA-AA PRECLINICAL ALZHEIMER'S DISEASE STAGING WITH CSF AND NEUROIMAGING BIOMARKERS

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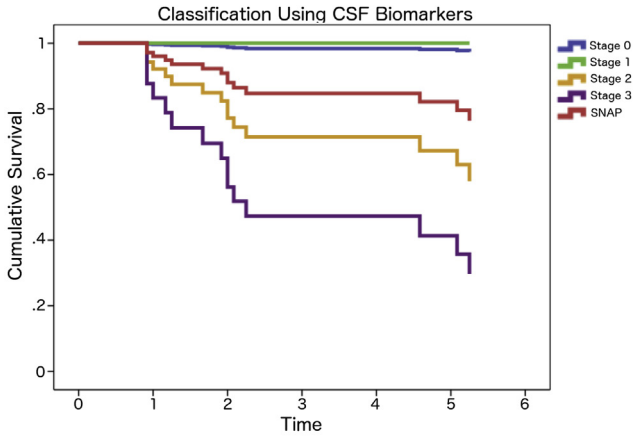
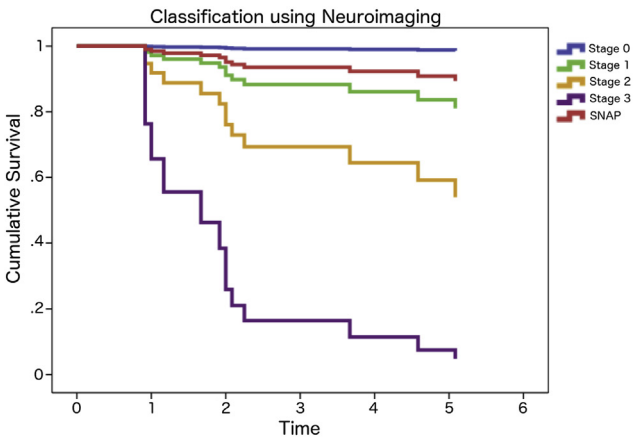
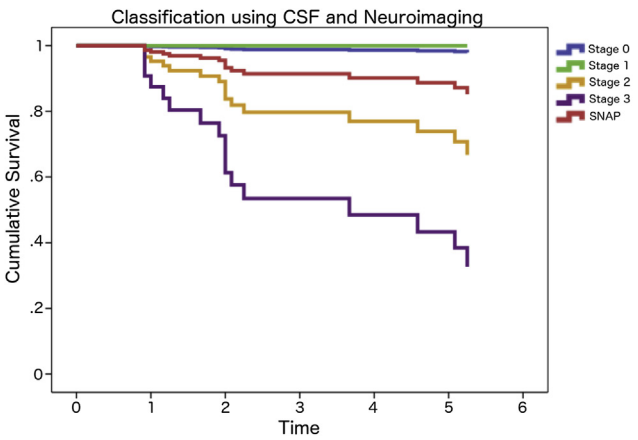
**Background:** Using the recently proposed National Institute of Aging and Alzheimer's Association (NIA-AA) criterion, cognitively normal individuals can be classified into preclinical stages using cerebrospinal fluid (CSF) and neuroimaging biomarkers: abnormal amyloid markers (stage 1), abnormal amyloid and neuronal injury markers (stage 2), and abnormal amyloid and neuronal injury markers and subtle cognitive changes (stage 3). Prior work has utilized either CSF or neuroimaging biomarkers for operationalization, but no analyses have taken an integrated approach. Here we directly compare CSF and imaging biomarkers, use both approaches to assign individuals to preclinical stages, and examine the longitudinal cognitive outcomes of individuals in each stage. **Methods:** We included 212 cognitively normal individuals (mean age 66. 8, females=132), with a clinical dementia rating (CDR) of 0. All participants had clinical data and a measurement of hippocampal volume on MRI, abeta1-42 and tau in CSF and amyloid binding on $^{11}$[C]Pittsburgh Compound B (PiB) PET, all within one year. Cutoffs to denote abnormality were determined using ROC analysis comparing cognitively normal individuals to those with very mild dementia (CDR=0.5) and a clinical AD diagnosis. Subtle cognitive impairment was defined using a composite of three neuropsychological tests. Using CSF biomarkers alone, neuroimaging markers alone, and using an integrated approach the cohort was classified into Stages 1-3, Suspected Non-Alzheimer

Table 1

| N=212 | CSF Biomarkers | Imaging Markers | CSF or Imaging |
|---|---|---|---|
| Stage 0 | 118 (56%] | 107 (51%) | 74 (35%) |
| Stage 1 | 23 (11%) | 32 (15%) | 29 (14%) |
| Stage 2 | 12 (6%) | 9 (4%) | 30 (14%) |
| Stage 3 | 7 (3%) | 2 (1%) | 11 (5%) |
| SNAP | 40 (19%) | 45 (21%) | 62 (29%) |
| Unclassified | 12 (6%) | 17 (8%) | 6 (3%) |



Pathophysiology (SNAP), a normal or an unclassified group (Table 1). Longitudinal progression to CDR>0 was modeled using survival analyses. **Results:** Controlling for appropriate covariates, correlations between CSF A$\beta$ $_{42}$ and the mean cortical PIB binding potential (MCBP) were significant (r=-.39, p<.0001), while the relationships between adjusted hippocampal volume and CSF (r=.04, p=.52) and ptau (r=.03, p=.62) were not (Figures 1 & 2). Individuals classified as Stage 2 and 3 were at an elevated risk of later dementia relative to those in Stage 0. (Figures 3-5). **Conclusions:** The NIA-AA preclinical stages successfully stratify dementia risk using both CSF and neuroimaging biomarkers. Measures of amyloid were highly congruent, while measures of neurodegeneration were often incongruent. This suggests that such markers cannot be used interchangeably to represent the same pathology.

## IC-P-021 LOWER BODY MASS INDEX IS ASSOCIATED WITH GREATER ALZHEIMER PATHOLOGY IN ASYMPTOMATIC INDIVIDUALS

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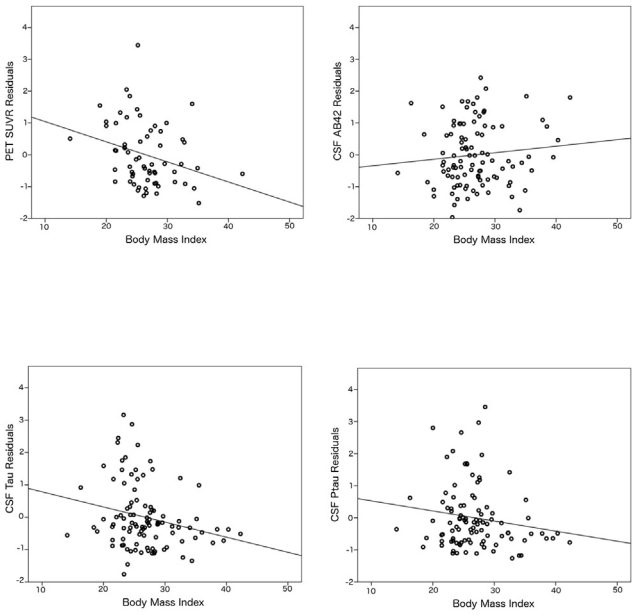
**Background:** Large-scale cross-sectional and longitudinal epidemiological studies indicate that chronic metabolic dysfunction such as diabetes, insulin resistance, and obesity increases the risk of developing Alzheimer disease (AD) (Akomolafe et al., 2007; Crane et al, 2013). This relationship has led some researchers to characterize AD as a metabolic syndrome. Conversely, a subset of work has demonstrated an almost protective relationship between AD pathology and weight or insulin resistance (Burns et al., 2007; 2012). **Methods:** Participants were 100 cognitively normal individuals (mean age of 72.1, stdev 5.1, 50 females) with a Clinical Dementia Rating (CDR) of 0. All participants had measures of body mass index (BMI), *APOE* genotyping, and a lumbar puncture to measure cerebrospinal fluid (CSF) levels of A$\beta_{42}$, tau, and ptau$_{181}$. 64 individuals also had positron emission tomography (PET) amyloid imaging using $^{11}$[C]Pittsburgh Compound B (PiB). Regression modeling examined the main effects of age, gender, *APOE* genotype(ε4+/-) and BMI. **Results:** In all models advancing age and the presence of the ε4 allele were associated with greater AD pathology, while increasing BMI was associated with less pathology (Figure 1). In the model examining amyloid PET there was a significant effect of age (B=0.06, $F_{1,59}$=11.0, p<0.01), *APOE* genotype (B=0.7, $F_{1,59}$=16.6, p<0.01), and BMI (B=-0.05, $F_{1,59}$=6.4 p<0.01). For ptau$_{181}$ there was a significant effect of age (B=1.3, $F_{1,95}$=4.4, p<0.05) and trends for both *APOE* (B=13.9, $F_{1,95}$=3.6, p=0.06), and BMI (B=-1.2, $F_{1,94}$=3.7, p=0.06). For tau there were significant effects for age (B=10.9, $F_{1,95}$=13.1 p<0.001), *APOE* genotype (B=74.3, $F_{1,95}$=4.1, p<0.05), and BMI (B=-9.4, $F_{1,95}$=6.8, p<0.05). For CSF A$\beta_{42}$ there was a significant effect of age (B=-17.9, $F_{1,95}$=10.7, p<0.01) and *APOE* genotype (B=-211.7, $F_{1,95}$=13.3, p<0.001). **Conclusions:** Lower values of BMI were associated with elevated levels of AD pathology in cognitively normal older adults. The mean BMI for the sample was 26.8 and only three individuals were underweight (BMI<18.5), suggesting individuals with very low weight did not drive this effect. Instead the effects may represent a subtle loss in appetite or behavioral alterations in meal preparation as AD pathology accumulates.




## IC-P-022 CEREBRAL GLUCOSE METABOLISM IN A 5XFAD BUTYRYLCHOLINESTERASE-KNOCKOUT MOUSE MODEL OF ALZHEIMER'S DISEASE

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**Background:** Alzheimer's disease (AD) is a neurodegenerative disorder that causes dementia. Characteristic hallmarks of AD include the deposition of pathological $\beta$-amyloid plaques (A$\beta$) and neurofibrillary tangles (NFT) in the brain. The AD brain also exhibits cholinergic dysfunction; loss of cholinergic neurons contributes to the cognitive and behavioural symptoms of AD. Furthermore, cholinesterases such as butyrylcholinesterase (BuChE) associate with A$\beta$ and NFT pathology. Recent work in our lab involving a novel BuChE knock-out mouse model of AD (5XFAD/BuChE-KO) has revealed that the absence of BuChE expression leads to diminished fibrillar forms of A$\beta$ pathology in the brain. However, the exact role of BuChE on brain function in AD has not been determined. To further elucidate the effects of BuChE on metabolic regulation (thus brain function) in AD, we assessed cerebral glucose metabolism in this 5XFAD/BuChE-KO model using 18FDG-PET. **Methods:** Male 5XFAD/BuChE-KO mice (n=5) and age-matched BuChE-KO wild type controls (n=2) at 5 months underwent PET scanning 30 min after 18FDG administration and subsequently imaged using CT and MRI. Whole brain ROIs were generated from co-registered PET/CT/MRI data. 18FDG standardized uptake values (SUVs) were then compared between 5XFAD/BuChE-KO and BuChE-KO groups. **Results:** At 5 months, significant A$\beta$ deposition was present in the 5XFAD/BuChE-KO mouse brain. 5XFAD/BuChE-KO animals demonstrated a 23% decrease