estimates. Iteration continues until convergence. We extend this algorithm to include nonlinear effects on each outcome for age, gender, education, APOE4 genotype, A β, tau, and their interactions. Covariates are selected for each outcome at each stage of the iteration based on the Akaike Information Criterion using a generalized additive model approach. Outcome measures considered include assessments (ADAS13, MMSE, FAQ, and RAVLT), MRI brain volumetrics (hippocampus, ventricles, and entorhinal cortex), CSF (A β, tau, p-tau), and PET (PiB, Florbetapir, and FDG). **Results:** Similar attempts at this estimation have stratified by covariates or ignored them altogether. Our current approach will allow closed form, as opposed to bootstrap, estimation of important covariate effects for each outcome. Covariate adjustment for age is particular important since our progression curve estimates span 20 years. **Conclusions:** The proposed method provides improved estimates of long-term progression curves, interrogation of covariate effects, and inspection of different patterns of progression.

F3-02-03 OPTIMALLY WEIGHTED ENDPOINTS FOR CLINICAL TRIALS IN MILD COGNITIVE IMPAIRMENT AND PRE-CLINICAL ALZHEIMER'S DISEASE

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Background: Composite endpoints formed by combining scales or subscales from existing clinical, functional, and neuro-psychometric assessment batteries have been proposed as primary endpoints for clinical trials of mild cognitive impaired (MCI) as well as pre-clinical Alzheimer's disease. However, composites constructed by a simple summing or averaging of the component scale scores may fail to properly utilize information contained in the subscale data compared to optimally weighted composite scales determined through reference to formal statistical models. **Methods:** We present an approach for determining optimal composite weights that maximize the signal-to-noise ratio of change score outcome measures. The algorithm assigns weights to the different components by taking into account trial design, the correlation structure among the component scales, and the longitudinal progression rates of the individual components. We illustrate by way of example the potential improvement in efficiency of optimally weighted composite endpoints versus other proposed or implemented composites using placebo arm data from the Alzheimer's Disease Cooperative Study (ADCS) clinical trial of donepezil and vitamin E in MCI subjects [N Engl J Med 2005;352]. Efficiency is characterized as the relative statistical power or sample size required to detect treatment effects assuming a mixed model repeated measures analysis of a two arm clinical trial with equal allocation to both arms. **Results:** Optimally weighted composites consistently outperformed composites constructed using alternative weights. For example an optimally weighted composite of the Clinical Dementia Rating scale sum of boxes (CDR-sb) pooled with items 1, 4, 7, and 8 of the Alzheimer's Disease Assessment Scale (ADAS) reduced sample size required to power a 36 month trial by 14.4 percent compared to the unweighted composite score. **Conclusions:** Formal statistical metrics that characterize the relative performance of outcomes measures can be used to derive optimally weighted clinical trial endpoints. Such optimally weighted composites can substantively improve the efficiency of clinical trials, reducing the sample size or trial duration required to establish a treatment effect and increasing the probability that effective treatments will be identified.

F3-02-04 USE OF INTRA-INDIVIDUAL DISTRIBUTIONS OF DAILY ACQUIRED HOME-BASED MEASURES INCREASES RCT SENSITIVITY

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Background: Trials in Alzheimer's disease are increasingly focusing on prevention in asymptomatic individuals. This poses a challenge in examining treatment effects since currently available outcome measures are not optimally sensitive to detect cognitive decline or trial-induced improvements. Consequently large sample sizes are required for randomized controlled trials (RCTs). More sensitive outcomes and better statistical approaches are needed. We aimed to develop a new metric sensitive to improvement/decline in functional outcomes by using individual-specific distributions (as opposed to group-norms). We used unobtrusively monitored in-home data, which allows us to collect enough data points to generate individual-specific distributions of functional outcomes such as computer usage and walking speed/variability within a short duration of time (e.g., 3 months). Our objective was to compare sample sizes required to achieve sufficient power to detect prevention trial effects in two scenarios: (A) annually assessed neuropsychological test scores modelled as a function of time using mixed effects models (a conventional approach), and (B) the likelihood of hitting subject-specific low performance thresholds modeled as a function of time using generalized mixed effects models. **Methods:** 114 subjects enrolled and followed over 3 years in the Intelligent Systems for Assessing Aging Study at Oregon Health & Science University. Using the difference in empirically identified time slopes between those remaining normal during the follow-up (normal control, NC) and those who transited to mild cognitive impairment (MCI), we estimated sample sizes required for achieving 80% statistical power for detecting 20% (i.e., the difference in time slopes between NC and MCI will be reduced by 20%), 30% and 40% treatment effects. **Results:** Sample size estimates indicated approximately 2000 subjects with a follow-up duration of 3 years would be needed to achieve 30% effect size if the outcome is memory test scores (Logical memory scores). If the outcome is hitting low threshold of walking speed (10 th %tile of individual-specific walking speed), 262 subjects are required. For computer use (40 th %tile low use) 26 subjects are required. **Conclusions:** Individual-specific thresholds of low functional performance based on high-frequency in-home monitoring data distinguish trajectories of MCI from NC and could reduce sample sizes in prevention RCTs.

TUESDAY, JULY 15, 2014
FEATURED RESEARCH SESSIONS
F3-03
TRAUMATIC BRAIN INJURY AND NEURODEGENERATIVE DISEASE: FROM EPIDEMIOLOGY TO BIOMARKERS

F3-03-01 TRAUMATIC BRAIN INJURY AND DEMENTIA RISK: AGE AND SEVERITY MATTER

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Background: There is conflicting epidemiological evidence regarding the importance of traumatic brain injury (TBI) as a risk factor for dementia. Few prior studies have used non-TBI trauma (NTT) patients as controls and age/severity stratification. **Methods:** In this retrospective cohort study, we assessed dementia-free survival in adults diagnosed with TBI versus NTT. Using a California state-wide emergency department (ED) and inpatient database, we identified all patients aged $\geq$55 diagnosed with TBI (based on ICD-9 code Center for Disease Control (CDC) definitions) or NTT in 2005-2006 who survived the hospitalization. Subjects with baseline dementia (based on validated inpatient ICD-9 code definitions) were excluded. The primary outcome was a new ED or inpatient ICD-9 code diagnosis of dementia $\geq$1 year after the initial trauma during the follow-up period ending in 2011. The association between TBI and dementia was estimated using Cox proportional hazard models before and after adjusting for known dementia predictors and pre-specified interactions and also stratified by TBI severity (mild vs. moderate/severe based on ICD-9 code CDC definitions) and age category (age 55-64, 65-74, 75-84, and 85+). **Results:** The cohort included 165,655 trauma subjects, of whom 51,792 (31%) had TBI. Over the study period, 9.2% of TBI patients developed dementia versus 6.2% of

NTT patients (p<.001). TBI was significantly associated with increased dementia risk (hazard ratio/95% confidence-interval (HR/CI): 1.46/1.41-1.52) even after adjusting for multiple dementia predictors and trauma severity score (HR/CI: 1.26/1.21-1.31). Stratification by TBI severity suggested a dose-response that was further elucidated by age-stratification. An interaction between age category and TBI severity was found (p<.0001) such that moderate/severe TBI was associated with increased dementia risk across all ages, with highest risk in adults age 55-64 (HR/CI: 1.69/1.38-2.07), while mild TBI became a relatively more important dementia predictor with increasing age (age 55-64 HR/CI: 1.10/.79-1.52 vs. age 65-74 HR/CI: 1.26/1.05-1.52). **Conclusions:** Moderate/severe TBI sustained at age ≥55 or any TBI sustained at age ≥65 may represent significant risk factors for dementia over the subsequent 5-6 years. Adults under age 65 may be more resilient to, or take longer to manifest, the effects of mild TBI than adults over age 65.

F3-03-02 COGNITIVE EFFECTS OF TBI IN OLDER VETERANS

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Background: Older veterans have a high prevalence of traumatic brain injury (TBI). Despite an association between TBI and increased risk of dementia, the etiology and clinical profile of TBI-associated dementia are unclear. The purpose of our study was to characterize cognitive function in older veterans with TBI history. **Methods:** In this cross-sectional study we collected data from 66 residents at the Armed Forces Retirement Home, Washington, DC, and Veterans Home of California-Yountville. TBI diagnosis was determined by the Ohio State University TBI Questionnaire and defined as head injury resulting in medical care or hospitalization. Participants (28 controls, 38 TBI) self-reported medical and psychiatric history and completed a comprehensive neuropsychological battery. **Results:** Veterans were, on average, 77.2 years old, had completed 14.4 years of education, and were mostly male (83%). Within the TBI group, 81.6% had loss of consciousness (LOC), and of those, 45.2% had LOC > 30 minutes. Mean interval from TBI to initial study visit was 49.7 years. The TBI group was more likely male (p=0.01), younger (p=0.10), and less educated (p=0.06). History of post-traumatic stress disorder did not differ between the groups (p=0.28); veterans with TBI had more depressive symptoms (p=0.05). In a model controlling for age, education, and gender, global cognitive function (Mini-Mental State Examination) did not differ between the groups (p=0.27). Participants with TBI history performed worse than controls on several tests of executive function: 0.25 standard deviations (SD) lower on Trails B (p=0.04), 0.76 SD lower on the Flanker task (p=0.04), and 3.6% of controls were unable to perform the N-back task compared to 18.9 % of TBI (p=0.03). However, the TBI group performed 0.58 SD better than controls on verbal memory (Auditory Verbal Learning Test-long delay; p=0.01). The results remained similar after controlling for depressive symptoms. **Conclusions:** The results of our study suggest that cognitive performance may differ in older veterans with and without a history of TBI. Future studies using neuroimaging or biomarkers may help determine the etiology underlying late life cognitive performance in individuals with a history of TBI.

F3-03-03 CSF AND PLASMA BIOMARKERS FOR MILD TRAUMATIC BRAIN INJURY

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Background: Mild traumatic brain injury, defined as a head trauma resulting in brief loss of consciousness and/or alteration of mental state, is most often benign but may cause persisting and sometimes progressive symptoms. It is unknown if there is a certain threshold for the amount of brain injury and/or individual vulnerability that may lead to such long-term consequences. Further, there is a lack of established diagnostic methods that can tell whether a blow to the head indeed affected the brain and in what way. **Methods:** CSF and plasma samples have been collected on boxers and concussed versus non-concussed elite ice hockey players and examined using established and novel techniques for neuronal and astroglial injury markers, such as tau, neurofilament light, VILIP1, S-100B, and neuron-specific enolase. **Results:** CSF and plasma biomarkers change in a dynamic manner following concussion. The magnitude of biomarker changes correlate with symptom duration. Some individuals have prolonged biomarker elevations. Biomarkers for axonal injury (tau and neurofilament light) appear to be more sensitive than biomarkers for astroglial injury. These data will be discussed in relation to the existing literature on more severe brain injuries and in relation to the biomarker literature on neurodegenerative diseases. **Conclusions:** There is a need to develop these biomarkers further and to implement them in clinical practice in cases of head trauma where the brain might have been impacted. Specifically, there is a need to implement them in the management of sports-related concussion, the most common cause of mild traumatic brain injury in the young, with the goal to prevent long-term neurological sequelae due to concussive or subconcussive blows to the head.

F3-03-04 EFFECTS OF TRAUMATIC BRAIN INJURY AND POST-TRAUMATIC STRESS DISORDER ON ALZHEIMER'S DISEASE (AD) IN VETERANS USING ADNI

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Background: Both traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) may increase risk for cognitive decline, AD, and other neurodegenerative disorders. We test the hypothesis that TBI and/or PTSD increase the risk for AD, and decrease cognitive reserve, determined with imaging/biomarkers, in Vietnam Veterans, using ADNI sites and methods. **Methods:** Vietnam War Veterans with a documented history of moderate/severe TBI or evidence of ongoing PTSD, and controls are screened by telephone. We plan to enroll over 400 subjects in ADNI sites for baseline measurements of cognition, function, blood and cerebrospinal fluid analyses (CSF), MRI (structural, diffusion tensor, and resting state BOLD fMRI) and amyloid PET imaging with Florbetapir and one year follow-up. The 3 groups will include half who are cognitively normal and half with MCI. A diagnosis of dementia is exclusionary. **Results:** To date 8,953 letters were sent to veterans with documented history of TBI or PTSD, 5,282 telephone calls made, 1,841 subjects were prescreened, 269 subjects provided written informed consent, 197 subjects completed telephone evaluations, 122 subjects were referred to DOD ADNI sites, and 31 subjects completed baseline evaluations (19 with PTSD, 3 with TBI, 4 subjects with both a TBI and PTSD, and 5 controls). Enrollment is proceeding rapidly. **Conclusions:** Enrolling Vietnam veterans in a multisite study of TBI and PTSD using multiple biomarkers is feasible. This study is an important step towards larger, more comprehensive studies of dementia risk factors in Veterans which will inform the design and statistical powering of a prevention trial to reduce the burden of AD in Veterans and in the general population.