predictors of preclinical AD defined by CSF $ptau_{181}/A\beta_{42}$ ratio. Self-reported spatial navigation (AUC=.592, p=.022) was a significant predictor of preclinical AD defined by hippocampal volume. Additionally, self-reported attention was a significant predictor of the CSF $ptau_{181}/A\beta_{42}$ ratio (p<.001) and self-reported memory was a significant predictor of hippocampal volume (p=.024) when controlling for depressive symptoms. Informant-reports were not significant predictors of preclinical AD (all ps>.074).
There was a nonsignificant trend for the objectively measured executive function AUC to be higher than for self-reported attention in detecting preclinical AD defined by CSF $ptau_{181}/A\beta_{42}$ ratio and was significantly higher than self-reported attention in detecting preclinical AD defined by hippocampal volume (p=.084 and p<.001, respectively). For memory and spatial navigation/visuospatial domains, the AUCs for self-reported and objective measures did not differ in detecting preclinical AD defined by either CSF $ptau_{181}/A\beta_{42}$ ratio or hippocampal volume (ps>.129).
Conclusions: Although the self-reported subsections produced significant AUCs, these were not high enough to indicate clinical utility based on existing recommendations (all AUCs<.60; Mandrekar, 2010). Nonetheless, there was evidence that self-reported cognitive change has promise as a screening tool for preclinical AD but there is a need to develop questionnaires with greater sensitivity to subtle cognitive change associated with preclinical AD.

Categories: Dementia (Alzheimer's Disease)
Keyword 1: dementia - Alzheimer's disease
Keyword 2: cognitive screening
Keyword 3: self-report
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51 Pupillary Responses During Verbal Fluency Tasks as a Biomarker of Risk for Alzheimer's Disease

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Objective: We examined the use of pupillometry as an early risk marker of Alzheimer's disease (AD). Pupil dilation during a cognitive task has been shown to be an index of cognitive effort and may provide a marker of early change in cognition even before performance begins to decline. Individuals who require more effort to successfully perform a task may be closer to decline. We previously found greater compensatory effort to perform the digit span task in individuals with amnestic mild cognitive impairment (aMCI) who may be at greater risk for AD than individuals with non-amnestic MCI (naMCI). Task evoked pupil dilation is linked to increased norepinephrine output from the locus coeruleus (LC), a structure affected early in the AD pathological process. In this study, we measured pupil dilation during verbal fluency tasks in participants with aMCI or naMCI, and cognitively normal (CN) individuals. Based on our findings using the digit span task, we hypothesized that participants with aMCI would show greater compensatory cognitive effort than the other two groups.
Participants and Methods: This study included 101 older adults without dementia recruited from the UC San Diego Shiley-Marcos Alzheimer's Disease Research Center and San Diego community (mean [SD] age = 74.7 [5.8]; education = 16.6 [2.5]; N=58 female; N=92 White); 62 CN, 20 aMCI and 19 naMCI participants. Pupillary responses (change relative to baseline at the start of each trial) were recorded at 30 Hz using a Tobii X2-30 (Tobii, Stockholm, Sweden) during semantic (animals, fruits, vegetables) and phonemic (letters F, A, S) fluency tasks. Participants generated as many words as possible in a category (semantic) or starting with a given letter (phonemic) in 60 seconds.
Results: Repeated measures ANOVA (3 groups X 2 fluency conditions) with age, education and sex as covariates showed a significant main effect of group ($F(2,95)=3.64$, p=.03), but no group X condition interaction (F<1). Pairwise comparisons showed significantly greater fluency task-evoked dilation for aMCI relative to CN (p=.015) and naMCI (p=.019) participants. When controlling for performance (total letter or category words produced), pupil dilation (cognitive effort) remained significantly greater in

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aMCI relative to the other two groups in both fluency conditions, suggesting pupil dilation informs risk beyond information provided by task performance.
Conclusions: In a previous sample of community-dwelling men who were an average of 13 years younger than the present sample, we found significantly greater pupil dilation during a digit span task in aMCI relative to naMCI and CN groups. In the present study, we replicated those findings in an older sample using a different cognitive task. Significantly greater pupil dilation was found in individuals with aMCI on verbal fluency tasks, indicating greater compensatory cognitive effort to maintain performance. Pupillometry provides a promising biomarker that might be used as an inexpensive and noninvasive additional screening tool for risk of AD.

Categories: Dementia (Alzheimer's Disease)
Keyword 1: dementia - Alzheimer's disease
Keyword 2: effort testing
Keyword 3: verbal abilities
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52 Bayesian Logistic Regression Bias Adjustment for Data Observed without a Gold Standard: A Simulation Study of Clinical Alzheimer's Disease

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Objective: Definitive diagnosis of Alzheimer's disease (AD) is often unavailable, so clinical diagnoses with some degree of inaccuracy are often used in research instead. When researchers test methods that may improve clinical accuracy, the error in initial diagnosis can penalize predictions that are more accurate to true diagnoses but differ from clinical diagnoses. To address this challenge, the current study investigated the use of a simple bias adjustment for use in logistic regression that accounts for known inaccuracy in initial diagnoses.
Participants and Methods: A Bayesian logistic regression model was developed to predict unobserved/true diagnostic status given the sensitivity and specificity of an imperfect reference. This model considers cases as a mixture of true (with rate = sensitivity) and false positives (rate = 1 – specificity) while controls are mixtures of true (rate = specificity) and false negatives (rate = 1 – sensitivity). This bias adjustment was tested using Monte Carlo simulations over four conditions that varied the accuracy of clinical diagnoses. Conditions utilized 1000 iterations each generating a random dataset of n = 1000 based on a true logistic model with an intercept and three arbitrary predictors. Coefficients for parameters were randomly selected in each iteration and used to produce a set of two diagnoses: true diagnoses and observed diagnoses with imperfect accuracy. Sensitivity and specificity of the simulated clinical diagnosis varied with each of the four conditions (C): C1 = (0.77, 0.60), C2 = (0.87, 0.44), C3 = (0.71, 0.71), and C4 = (0.83, 0.55), which are derived from published values for clinical AD diagnoses against autopsy-confirmed pathology. Unadjusted and bias-adjusted logistic regressions were then fit to the simulated data to determine the models' accuracy in estimating regression parameters and prediction of true diagnosis.
Results: Under all conditions, the bias-adjusted logistic regression model outperformed its unadjusted counterpart. Root mean square error (the variability of estimated coefficients around their true parameter values) ranged from 0.23 to 0.79 for the unadjusted model versus 0.24 to 0.29 for the bias-adjusted model. The empirical coverage rate (the proportion of 95% credible intervals that include their true parameter) ranged from 0.00 to 0.47 for the unadjusted model versus 0.95 to 0.96 for the bias-adjusted model. Finally, the bias-adjusted model produced the best overall diagnostic accuracy with correct classification of true diagnostic values about 78% of the time versus 62-72% without adjustment.
Conclusions: Results of this simulation study, which used published AD sensitivity and specificity statistics, provide evidence that bias-adjustments to logistic regression models are needed when research involves diagnoses from an imperfect standard. Results showed that unadjusted methods rarely identified true effects with credible intervals for coefficients including the true value anywhere from never to less than half of the time. Additional simulations are

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