ALLEN INSTITUTE for BRAIN SCIENCE

Aging, Dementia and TBI Study

TECHNICAL WHITEPAPER:
ACT COHORT

ADULT CHANGES IN THOUGHT STUDY

History of ACT

The Adult Changes in Thought (ACT) study began with enrollment of the Original Cohort in 1994-1996, which included 2,581 people age ≥65 without dementia. The ACT study was originated by PI Eric B. Larson, MD MPH, and is now headed by Dr. Larson together with Paul K. Crane, MD MPH, who serve as Multiple PIs. Kaiser Permanente Washington participants who were not in nursing homes and without established diagnoses of dementia were invited to an initial visit. Cognitive functioning was measured with the Cognitive Abilities Screening Instrument (CASI)[1]. People with CASI scores >85 were invited to join the prospective cohort. Those with CASI scores ≤85 were further evaluated with a clinical evaluation and a battery of neuropsychological tests. Those data and clinical data including laboratory test results and neuroimaging studies were reviewed at a consensus conference. People without DSM-IV diagnoses of dementia[2] and without NINCDS-ADRDA criteria for Alzheimer's disease[3] were invited to join the prospective cohort.

Follow-up visits occur on a 2-year cycle. The CASI is repeated and the same criteria used to identify people who receive secondary follow-up with a clinical evaluation, neuropsychological battery, and consensus diagnoses of incident dementia and Alzheimer's disease.

An Expansion Cohort of 811 people in 2000-2003 was enrolled using the same methods. A Continuous Enrollment period was started in 2005 to enroll 10-15 people per month to maintain a cohort of n=2,000 people who are actively enrolled in the cohort and at risk for dementia and Alzheimer's disease. Total enrollment as of December 2015 was approximately 5,100 people. To date, over 1,000 people have been diagnosed with dementia, and more than 800 with probable or possible Alzheimer's disease from the ACT study.

Inclusion of Individuals into ACT

Inclusion criteria include age ≥65, free of dementia, and willing to volunteer for a longitudinal study. Participants were selected based on a random draw of Kaiser Permanente Washington members from the greater Seattle catchment area.

Inclusion/Exclusion Criteria for ACT as a Whole

Exclusion criteria include established diagnoses of dementia and residence in a nursing home. At enrollment and every subsequent visit, participants may be seen at the study research clinic or in their own home at the participant's preference[4]. Study visits after baseline may occur in nursing homes.

Assessments

The dementia psychometric battery includes clock drawing[5], verbal fluency[6], Mattis Dementia Rating Scale[7], Boston naming[6], verbal paired associations and recall, logical memory and recall[8], Word List Memory[6], Constructional Praxis and recall[6], Trails A and B[9], and Information and Comprehension subtest items[8]. All

clinical data are reviewed at a consensus conference. If dementia is diagnosed, clinical laboratories and imaging results are considered in assigning dementia subtype (*e.g.* Alzheimer's disease, thyroid disease, normal pressure hydrocephalus, vascular dementia, etc.). When these results are not available from medical records, they are requested to be ordered by the delivery system, results are obtained, and then reviewed again at a subsequent consensus conference.
Dementia onset is assigned half way between the prior biennial and the exam that diagnosed dementia. These procedures have been used since 1986. ACT incidence rates are consistent with those found worldwide[10], supporting the validity of our case definitions. Furthermore, forest plots of associations between alleles of single nucleotide polymorphisms and dementia from Alzheimer's disease suggest similar strength of association for cases and controls ascertained by the ACT study as those from more than a dozen other research studies of dementia from Alzheimer's disease[11].

The ACT neuropsychological battery is characterized by good assessment of executive functioning (Mattis initiation and concept scales, comprehension, Trails, fluency, and clock drawing) which would aid in identification of vascular cognitive impairment/vascular dementia and fronto-temporal dementia. There is good assessment of spatial ability (clock and Mattis construction) that would help with the diagnosis of Lewy body dementia and Parkinson's disease with dementia. It should be emphasized that the diagnostic process is based not only on psychometric test results but especially historical and clinical elements considered by an expert consensus of clinicians and neuropsychologists using all available data including results from the psychometric tests.

TBI Exposure
Participants are asked at study entry, "Have you ever had an injury so severe that you lost consciousness?" If an injury is reported, participants are further queried to determine whether the injury was a head injury or other type of injury (*e.g.*, near drowning, electric shock), and the age at which this injury was sustained. At study entry, all lifetime injuries leading to loss of consciousness are recorded. Duration of loss of consciousness had response options including:

- a few seconds
- a few seconds – 1 minute
- 1-9 minutes
- 10 minutes – 1 hour
- >1 hour

A person who reported a history of multiple head injuries leading to loss of consciousness would have all of those head injuries reported. Only head injuries that involved loss of consciousness are recorded. From these data, age at injury and duration of loss of consciousness can be derived for every head injury with loss of consciousness reported by ACT participants.

Questions at every follow-up visit focused on injuries leading to loss of consciousness in the intervening period since the baseline evaluation. Follow-up questionnaires had the same format and response options as at baseline.

Dementia Diagnosis
As described above, dementia is diagnosed at consensus conferences using DSM-IV criteria[12], and Alzheimer's disease using probable or possible Alzheimer's disease as defined by NINCDS-ADRDA criteria[3].

Additional Data in ACT and How to Access It
The ACT study incorporates many other data elements from ACT study sources, Kaiser Permanente Washington clinical data, and other sources such as linkage to the SEER registry. In **Table 1**, some examples of data sources and papers that have used data from those sources are shown.

Table 1. Sources of data for the ACT cohort.

Source Data	Data Elements
ACT study data	TBI with loss of consciousness[13], over the counter non-steroidal anti-inflammatory drugs (NSAIDs)[14,15], vitamin supplements[16], physical performance as an exposure[17] and as an outcome[18-20], frailty (from depression data, weight, and physical performance assessment)[21], blood pressure[22,23], depression[24], neuropathology findings as an exposure[25-30] and as an outcome[15,23,31-39], self-rated health[19], living situation (alone vs. with others) and social support[40], imaging of postmortem brain tissues[41], smoking[37,38], central auditory dysfunction[42] or presbycusis[43], mild cognitive impairment[44,45], exercise[46], education[47,48], cognition[47-54], subjective memory impairment[55], falls[56,57], alcohol use[51,53], successful aging[58], dementia and Alzheimer's disease incidence[10], ADLs and IADLs[20], functional decline[59], attitudes toward long term care[60]
KP administrative data	ICD codes for atrial fibrillation[61,62], depression[24], critical illness[18,50], ICD "phenome-wide" studies[63-67], thrombosis and cancer phenotypes[68], ICD codes for dementia[69,70], billing codes for hospitalizations[71]
KP pharmacy data	Anticholinergic medications[72], prescription NSAIDs[14,15], histamine H_2 blockers[73], HMG-CoA-reductase inhibitors ("statins")[74-76], antidepressants[24], prescription opioids[77], diabetes identified by anti-diabetic medication prescriptions[35,78]
KP clinical laboratory data	Cholesterol levels[79], glucose and HbA1c[78], thyroid stimulating hormone (TSH)[80], platelet counts[65], monocyte counts[81], renal function from creatinine levels[82], white blood cell count[83]
DNA	Long runs of homozygosity[84], local and global African ancestry[85], SNP-derived genetic risk scores[86,87], variants in *MAPT*[88], rare variants from the exome chip[89], genome-wide SNPs (GWAS)[31-33,65,66,80,90-95], gene-wide analyses[96], heritability[97], chromosomal mosaicism[98], *APOE* ε4 alleles[27,47], *TOMM40* intron 6 poly-T length[99,100], variants in *GBA*[34], Alzheimer's disease-associated SNPs[2], *FOXE1*-related SNPs[67]
Death index data	Mortality[13,101]
KP address data	Neighborhood walkability[102,103]

Abbreviations: KP, Kaiser Permanente Washington

These data are available, but need to be cleared through ACT procedures. To request access to other data from the ACT cohort, please send an email to KPWA.actproposals@kp.org with your request.

IRB and Kaiser Permanente Washington

ACT is a Repository at Kaiser Permanente Washington Health Research Institute, which means that it has established policies and procedures for sharing data with external investigators. Participants sign an informed consent form at enrollment and review that consent at every study visit, and consent includes permission for sharing de-identified data with external investigators. Data available from the project web site do not require any additional Institutional Review Board (IRB) approval or permissions. Linking those data with other ACT study or Kaiser Permanente Washington data would require additional paperwork. All those steps are initiated after contacting KPWA.actproposals@kp.org

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