**From the ADAMS data book:**

ADAMS data can be used for validation studies and to develop predicted probabilities of dementia and CIND in the HRS.

Identification of Risk Factors for CIND and Dementia

Linking ADAMS clinical assessment data to the wealth of available longitudinal HRS data will allow a wide range of studies on the natural history of cognitive change in older people. Additionally, the linked HRS-ADAMS data will facilitate studies of the demographic (e.g. age, gender, race), socioeconomic (e.g. education level, net worth), behavioral (e.g. tobacco and alcohol use, level of physical activity), medical (e.g. hypertension, heart disease, diabetes, head trauma), and genetic (APOE genotype) characteristics that are potential protective or risk factors for CIND and dementia. The combination of up to 10 years of prior HRS survey data (including risk factor information that may predate the onset of cognitive impairment) and the full clinical assessment from the ADAMS will provide a unique opportunity to study the onset of CIND and dementia in a nationally representative population based sample. Table 1 shows selected HRS and ADAMS variables that are available for studies of potential risk factors for CIND and dementia.

Estimation of the Likelihood of CIND and Dementia for All HRS Subjects

Data from the ADAMS clinical evaluation and consensus diagnosis will be combined with longitudinal HRS data for ADAMS subjects to estimate statistical models relating the ADAMS CIND and dementia diagnoses to the cognition, demographic, and health measures collected at each HRS interview. A **multinomial logistic model** estimated from the ADAMS sample will then be applied to the covariate measures for the full HRS data set to estimate for each case a vector of probabilities indexing the likelihood of being normal, CIND, or demented. These probability indices may be used directly as dependent variables to estimate dementia prevalence or to model risk factors for dementia and CIND [29]. The predicted probability indices may also be employed as independent variables in models and simulation studies of the effects of CIND and dementia on functional decline, institutionalization, health care costs, caregiver burden, and other outcomes.

**Identified Features in the Literature**

**Genetics**

**APOE gene:** There is likely no single memory gene, but the APOE gene, specifically the ε4 variant, has been widely identified as a very significant risk factor for cognitive decline. The APOE gene, located on chromosome 19, has three major alleles, ε2, ε3, and ε4, with six possible genotypes (ε2/ε 2, ε2/ε 3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ ε4). The ε2 allele shows a moderately protective effect against AD, and ε4 confers an increased risk. The ε4 allele frequency is approximately 15% in the general population but approximately 40% in patients with AD. APOE ε4 does not determine who will develop AD, but it is associated with earlier development of AD, and being homozygous for ε4 (ε4/ε4 genotype) confers the highest risk.

Interestingly, APOE ε4 predicts cognitive decline over time but not progression to AD (Brainerd et al. 2013).

Another study creates a genetic risk score for dementia using other dementia genes and finds that more genetic risk is associated with increased risk of cognitive decline (Hayden et al. 2015).

Marden et al. (2016) use HRS genetic data to create a polygenic risk score based on the top 22 AD-associated genes as an alternative to exclusively using APOE e4.

**Family history:** Offspring of parents with AD have six times greater risk for developing the disease compared to those without a family history of AD. Not surprisingly, APOE ε4 is overrepresented in individuals with family history; however, it appears that family history embodies a risk (either genetic, environmental, or both) that exerts an effect above and beyond ε4. The presence of family history together with APOE ε4 increases cumulative lifetime risk for AD. For first degree relatives of AD patients, possessing a 3/3 genotype is associated with a life time risk for AD of 29.2%. The life time risk increases to 46.1% for first degree relatives with a 3/4 genotype, and further increases to 61.4% for those with a 4/4 genotype.

**Demographics**

[Midlife predictors of Alzheimer's disease](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2895971/)

**Age:** Is a powerful predictor

**Gender:** The incidence of AD in women is 1.5–3 times higher than the incidence in men [40]. Women's increased risk for AD coincides with menopause [41, 42], implicating estrogen deficiency as the primary sex-related risk factor for AD. Estrogen reduces the formation of β-amyloid [43, 44] and protect against its toxic effects [45] in vitro. However, in contrast to other studies, female gender is not a predictor of Alzheimer’s risk in the ADAMS data.

**Race:** African Americans have an elevated risk, but this seems to be explained by the effect of education and APOE e4.

**Marital status:** Single people have a greater chance of dementia.

**Loneliness:** is emerging as a significant health risk. One study follows HRS participants aged 65 and

older from 1998 to 2010 and finds that loneliness and depressive symptoms both lead to cognitive decline over that period.

**Social activity:** These results point to a possible causal relationship between social activities and cognitive function, especially in strengthening short-term memory.

**Income:** Lower household income is associated with greater dementia risk.

**Self-observed cognitive decline:** HRS asks participants to give their own subjective assessments of their memory. Hülür et al. (2015) find that those who report steeper declines of subjective memory indeed show steeper declines of memory performance over time.

**Education level:** Higher educational levels are associated with higher cognitive functioning, but these studies show that the effect of education does not affect the rate of decline in cognitive functioning.



**Mothers education:** Compared to participants whose mothers had at least eight years of education, those with mothers having fewer than eight years of education have a significantly elevated risk of CIND or dementia, 31% versus 45%, respectively. This strong risk remains even after taking into account other known dementia risk factors, such as the APOE e4 allele and the individual’s own educational level.

**Education quality:** Below- average self-assessed school performance is associated with a four-fold risk of AD independent of educational level, literacy score, and other relevant risk factors. Educational level attained is an important asset, but educational quality may do even more to build cognitive capacity. Those who say they did well in school, regardless of the level completed, have a much lower risk of being diagnosed with AD later in life.

**Vision:** Those diagnosed with dementia, especially AD, have poorer vision at baseline and have received fewer eye services prior to their diagnosis than those who do not experience serious cognitive decline. Uncorrected poor vision is a very significant risk factor for dementia.

**Acute health events:** Information on hospitalization for severe sepsis was obtained from linked Medicare data (Iwashyna et al. 2010) and used to identify HRS participants who had an episode of severe sepsis. Severe sepsis is associated with substantial and persistent new cognitive impairment and functional disability among survivors.

**Head traumas:** Alzheimer’s patients who suffered significant head injuries before age 65 showed symptoms at an earlier age than those who hadn’t had head injuries.

**Heart history:** Trouble with the vascular system is linked to Alzheimer’s. High blood pressure, especially in midlife, increases your risk. So can your heart history. People who have previously had a heart attack are more than twice as likely to develop dementia, whether it's Alzheimer’s or another type. Weiner emphasizes the importance of controlling your blood pressure. Decreasing stress also helps lower your risk of developing Alzheimer’s.

**High blood pressure:** Treated hypertension decreases dementia risk.

**Depression:** Interestingly, although depression is a risk factor for cognitive decline, Saczynski et al. (2015) follow HRS participants for six years and show that the use of antidepressants does not make any difference in cognitive changes.

**Stroke history:** Is associated with increased risk of dementia

**Alcohol:** Mild drinking (one to three drinks per week) provides protection against dementia, while excessive consumption increases the risk of cognitive decline and dementia.

**Smoking:** There are inclusive results relating smoking to dementia, research tends to indicate that there is complicated gene environment interplay between smoking and dementia risk.

**Body weight:** Maintaining optimal body weight may be especially important to reduce risk of cognitive decline. Xiang and An (2015a) show that being underweight, having a body mass index less than 18.5, is a robust risk factor for onset of cognitive impairment in later life. While obesity increases your odds, especially for women, who may be three times as likely to develop Alzheimer’s as their thinner peers, according to the Fortanasce-Barton Neurology Center. Obese men increase their risk by about 30 percent.

**Exercise:** Vigorous physical activity for at least 12 months over the study period reduces dementia risk by 21%.

**Neuropsychiatric symptoms:** such as anxiety, agitation, elation and delusions are prevalent among those with cognitive impairment. e percentage of those with three or more symptoms increases sharply going from mild to moderate dementia (from 15.2% to 44.3%) but then decreases slightly with severe dementia (38.2%). Some research suggests that neuropsychiatric symptoms may actually precede dementia.

[**Retirement**](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1518440)**:** The human capital framework suggests that retirement may cause an increase in cognitive decline, since after retirement individuals lose the market incentive to invest in cognitive repair activities.

**Amyloid protein:** Michael Weiner, principal investigator for the Alzheimer’s Disease Neuroimaging Initiative and director of San Francisco’s Center for Imaging of Neurodegenerative Disease, works with PET scans of study participants’ brains. While definitive Alzheimer’s diagnoses have formerly been made postmortem, Weiner said he was surprised to discover he could detect the Alzheimer’s-correlated amyloid protein in living people. Brain changes can begin 25 years before the onset of the disease.

**Serum ceramide:** A 2012 study led by Dr. Michelle Mielke of the Mayo Clinic found that women with the highest level of a fatty compound called serum ceramide in their blood were 10 times more likely to develop Alzheimer’s than women with lower levels of the compound.

**Diabetes:** Insulin-resistant diabetes could double or even quadruple your chances of getting Alzheimer’s. An enzyme in your brain is responsible for decreasing both insulin and amyloid, so too much insulin may interfere with the enzyme’s ability to remove the amyloid.

**Mental Stimulation:** A general lack of mental stimulation correlate with increased risk of Alzheimer’s.

**Dancing:** Verghese led a study that identified dancing as the most helpful physical activity for avoiding Alzheimer’s, partly due to the social aspect. “You don’t usually dance alone,” he says. “Social interaction has been said to reduce stress levels, which are bad for the brain.”

**Diet - Lack of fruits, vegetables and spices in diet:** Diets low in vegetables may speed cognitive decline. One reason for this involves homocysteine, an amino acid in blood plasma. Higher levels seem to increase your risk of Alzheimer’s, among other deadly diseases. You need folate and other B vitamins to properly break down homocysteine. While all types of vegetables will help, Sabbagh recommends kale, squash, eggplant, collard greens and blueberries as cognitive superstars. Certain spices, notably cinnamon and turmeric, may also have a dramatic effect. “There’s clear evidence that people in India, at least from epidemiological data, have less Alzheimer’s,” says Sabbagh. “One of the environmental things people attribute it to is the presence of turmeric.”

**Gait changes:** A deteriorating gait and the inability to simultaneously walk and talk may indicate the onset of Alzheimer’s. “Walking while talking is a divided attention task,” says Verghese, who has long studied gait changes in patients with non-Alzheimer’s dementia. “Now, if you are in the early stages of dementia or actually have dementia, then this becomes more challenging because you have limited attention resources.” Five different studies presented at the 2012 Alzheimer’s Association International Conference tied gait change to the disease. Alzheimer’s correlated with slower and/or erratic walking and difficulty in performing such tasks as walking while counting backward.

**Poor navigation:** Since Alzheimer’s starts in the hippocampus, often called the brain’s seat of memory, disorientation is a hallmark of the disease. “Navigational problems might arise very early in the course of cognitive decline,” says Verghese. Need to study people’s ability to navigate and whether those who are navigationally challenged will face faster cognitive decline.

**Sleep problems:** A study released in 2012 correlated sleep disruption and Alzheimer’s in humans. The Washington University study, led by David Holtzman of the college's Department of Neurology, studied 145 cognitively normal people. Those with biomarkers for Alzheimer’s, as measured in their spinal fluid, were the worst sleepers. They spent more of their time in bed awake and napped more frequently during the day than those without the Alzheimer’s biomarkers.

**Recommendations:** Sabbagh recommends making lifestyle changes as a preventative strategy right away. Eat your greens. Exercise. Value your social connections, and use your brain power. “You should not wait,” Sabbagh says, “because by the time you become symptomatic, the pathology in your brain is significant.”

[**Future directions in Alzheimer's disease from risk factors to prevention.**](https://s3.amazonaws.com/academia.edu.documents/45213814/Future_Directions_in_Alzheimers_Disease20160429-8152-1ynazw2.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=1528001763&Signature=CLDiE6ryY8qje12R6YY%2FWvO4uKg%3D&response-content-dispositio)**:**

Great paper on what models have been produced (paper is dated 2014, so could be more since then – will keep looking for newer stuff), their features and summary of their results:

From the abstract:

Several vascular, lifestyle, psychological and genetic risk factors influencing this latent period have been recognized and ***they may act both independently and by potentiating each other***.

**This tends to indicate that the relationships may be linear or non-linear, which might be something that decision tree or neural net might be able to pick up.**

**Some of the models used:**

[**Prediction of Dementia in Primary Care Patients:**](http://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0016852&type=printable) Multivariate Cox proportional hazard regression

[**Midlife risk score for the prediction of dementia four decades later:**](https://www.alzheimersanddementia.com/article/S1552-5260(13)02465-5/fulltext) Logistic regression analysis was first used for reasons of direct comparison with the originally published CAIDE logistic regression models. Next, we applied Cox proportional hazard models for prediction modeling, because it accounts for time during the 12+-year period of follow-up for dementia, with appropriate right censoring for (i) termination of health plan membership (defined as a lag of 3 months or more), (ii) death, or (iii) the end of the study period on June 1, 2006.

Models have tended to be logistic regressions

**Overall:** Suggests there are a lot of possible linked variables as explained above, so a machine learning approach across a large number of features could be more successful than existing models.