

The Statistical Modeling of Aging and Risk of Transition Project: Data Collection and Harmonization Across 11 Longitudinal Cohort Studies of Aging, Cognition, and Dementia

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Abstract

Longitudinal cognitive trajectories and other factors associated with mixed neuropathologies (such as Alzheimer’s disease with co-occurring cerebrovascular disease) remain incompletely understood, despite being the rule and not the exception in older populations. The Statistical Modeling of Aging and Risk of Transition study (SMART) is a consortium of 11 different high-quality longitudinal studies of aging and cognition (N=11,541 participants) established for the purpose of characterizing risk and protective factors associated with subtypes of age-associated mixed neuropathologies (N=3,001 autopsies). While brain donation was not required for participation in all SMART cohorts, most achieved substantial autopsy rates (i.e., > 50%). Moreover, the studies comprising SMART have large numbers of participants who were followed from intact cognition and transitioned to cognitive impairment and dementia, as well as participants who remained cognitively intact until death. These data provide an exciting opportunity to apply sophisticated statistical methods, like Markov processes, that require large, well-characterized samples. Thus, SMART will serve as an important resource for the field of mixed dementia epidemiology and neuropathology.

Keywords: mixed dementia, longitudinal cohort, neuropathology, Alzheimer’s disease, epidemiology

1. Introduction

The prevalence of age-associated neurodegenerative disorders in the United States is increasing rapidly as the population ages (Nelson et al., 2011). Demographic trends suggest that with the predicted increase in age-associated dementias, health care costs and the social impact of neurodegenerative diseases will also rise significantly in the next few decades (Alzheimers Association, 2014). Importantly, identification of factors that promote or delay progression of neurodegenerative disease processes also provides the foundation for both basic science and clinical treatment and prevention research. The study of neurodegenerative diseases like Alzheimers disease (AD) requires consideration of multicausality, long latency periods, multiple brain pathologies, clinical diagnostic misclassification, and competing risks, such as mortality associated with other diseases. AD, for example, has a hypothesized latency period of at least 10 years (Sperling et al., 2011), and therefore identification of risk and protective factors related to the probability of AD, the timing of clinical symptom onset, and the rate of progression requires longitudinal studies with long follow-up of participants who were mostly cognitively intact at baseline.

The utility of clinical diagnosis for estimating risk factor associations, which is the outcome of interest in most epidemiological studies, is limited in the sense that clinical and gold-standard autopsy-based diagnoses are often discordant, even when the clinicians are experts (Beach et al., 2012). This discordance arises from many factors, not the least of which is that many research participants die with subclinical disease (Schmitt et al., 2000, SantaCruz et al., 2011), which in most cases we cannot reasonably expect to identify without autopsy. Further, the older the participant, the more likely it is that multiple brain pathologies are present (Nelson et al., 2011; Sinka et al., 2010); even when one underlying neuropathology is correctly identified by the clinician, additional pathologies may be incorrectly diagnosed or remain undetected. Analyses that focus on neuropathological findings as the diagnostic standard reduce the misclassification bias encountered when clinical endpoints alone are used. Yet, because of the expense and difficulty of following participants to death and obtaining a brain autopsy, most large dementia risk factor cohort studies

are based entirely or primarily on clinical diagnosis (Bienias et al., 2003; Fratiglioni et al., 2007; Montine et al., 2012a). While sensitivity and specificity of clinical diagnoses of AD are likely improved by evolving brain imaging techniques, such as positron emission tomography (PET) for amyloid beta and tau, and analysis of cerebrospinal fluid for these same AD biomarkers, such tools are not always available, even at academic research centers. Further, they do not address the problem of multiple brain pathologies.

Access to autopsy-based diagnoses solves some of the aforementioned methodological issues, but it also raises new problems. Identifying risk and protective factors for specific combinations of neurodegenerative pathologies requires a sufficient number of cases that share the same pathological phenotype. This is usually not possible for a single-center study, such as those conducted by the individual National Institute on Aging Alzheimer’s Disease Centers (ADCs), where the majority of patients will have AD neuropathology, with or without additional brain pathologies (Beach et al., 2012). While the National Alzheimer’s Coordinating Centers (NACC) Uniform Data Set (Morris et al., 2006) and Neuropathology Data Set (Beach et al., 2012) aggregate data from all ADCs and allow for examination of specific pathologies, collection of detailed longitudinal clinical data has been ongoing for less than 10 years as of this writing. Other large, multi-center longitudinal datasets, like the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (Mueller et al., 2005) and the Dominantly Inherited Alzheimer Network (DIAN) (Morris et al., 2012), which are biomarker rich, currently have shorter longitudinal records and limited neuropathological data.

The Statistical Models of Aging and Risk of Transition study (SMART) seeks to fill this gap. This project aggregates data from mature, extremely data-rich, and well-known longitudinal cohorts of older adults with high autopsy rates (in order of creation): the Memory and Aging Project (Washington University); the Oregon Brain Aging Study; Sanders-Brown Healthy Brain Aging Volunteers, also known as the Biologically Resilient Adults in Neurological Studies (BRAiNS) cohort; the Nun Study; the Honolulu Asia Aging Study; the Religious Orders Study; the Memory and Aging Project (Rush University); the African American Dementia and Aging Project; and the Klamath Exceptional Aging Project. An additional population-based cohort, the Einstein Aging Study, which is ethnically diverse but has less available autopsy data, will be used to validate clinical transition models. Participants included in SMART were primarily cognitively intact at baseline and were subsequently assessed for transition to mild cognitive impairment (MCI) and dementia over many years. This combined cohort presents a unique opportunity to study dementia in terms of the risk factors that lead to cognitive impairment, promote resistance to impairment, or allow progression to dementia due to the presence of different forms of neuropathology in the older brain.

2. Methods

2.1 Participants

Volunteers in the participating cohorts were recruited under Institutional Review Board protocols approved at each center. Descriptions of recruitment, clinical, and neuropathological procedures for each cohort have been described in detail elsewhere (please see below for references). Brief descriptions of each cohort follow. These and other details regarding cohort study designs are summarized in Table 1.

The Memory and Aging Project at the Washington University Knight Alzheimer’s Disease Research Center (MAPWU) enrolls healthy volunteers from the community; exclusion criteria include existing neurological disorders (e.g., Parkinson’s, Huntington’s, or Alzheimer’s disease) and psychiatric disorders (e.g., schizophrenia, substance abuse), as well as any active medical condition or treatment that impairs cognitive function (Berg et al., 1982). Participants are assessed annually, biomarkers are collected (blood, CSF, and neuroimaging [structural and functional]) and cognitive status is determined by the Clinical Dementia Rating (CDR) scale (Morris 1993); brain donation is encouraged but not required for enrollment (Berg et al., 1998).

The Oregon Brain Aging Study (OBAS) at the Oregon Health & Science University ADC has recruited participants in two waves (OBAS I & II). Volunteers are community-dwelling older adults with intact activities of daily living and free from chronic diseases (e.g., hypertension, diabetes, cardiovascular disease) and dementia at baseline (Green et al., 2000). Participants are assessed every six months for changes in cognition and health status and undergo MRI annually. Although brain donation is not required for participation, most volunteers agree to brain donation and autopsy (Green et al., 2000).

The BRAiNS cohort was established at the University of Kentucky ADC (Schmitt et al., 2001; Schmitt et al., 2012). Participants are community-dwelling residents of central Kentucky and free from major neurological and psychiatric disorders at entry. In 2005, a second wave of recruitment began that focused on healthy adults at least 70 years of age; only the first wave of participants is included in SMART. Cognition is assessed annually, and all participants agree to brain donation upon death (Markesbery et al., 2000; Schmitt et al., 2012).

The Nun Study was designed to assess the influence of early life exposures and cognitive ability on the development of Alzheimer-type dementia and pathology in late life (Mortimer, 2012; Tyas et al., 2007). Members of the School Sisters of Notre Dame religious congregation born between 1890 and 1916 and living in the midwestern, eastern, and southern United States were recruited to participate in annual cognitive and functional assessments, and all participants agreed to brain donation. Participants were clinically evaluated for dementia but MCI was not used as a diagnostic category. The Nun Study was established at the University of Kentucky in 1991 and moved to the University of Minnesota in 2008.

The Honolulu-Asia Aging Study (HAAS), established at the Kaukuni Medical Center, was designed to study prevalence, incidence, and risk factors for dementia among men of Japanese ancestry living in Oahu, HI (Gelber et al., 2012; White et al., 1996). HAAS comprises surviving participants from the Honolulu Heart Program, with about 80% of the surviving cohort participating in HAAS (Gelber et al., 2012). HAAS participants’ cognitive and motor function were evaluated every two to three years, with detailed clinical assessments for those participants who showed evidence of cognitive impairment on the primary cognitive outcome measure, the Cognitive Abilities Screening Instrument (CASI) (Gelber et al., 2012). In the absence of detailed clinical assessment, HAAS-derived CASI cutoffs were used to classify participants as cognitively intact, marginally cognitively impaired, or demented (Gelber et al., 2012). Brain donation was not required for participation, although many volunteers agreed to autopsy. Autopsy protocols for HAAS, the Nun Study (Mortimer, 2012), and the BRAiNS cohort (Markesbery et al., 2000) were designed by the late Dr. William R. Markesbery.

The Religious Orders Study (ROS) was designed to identify risk factors for incident dementia and cognitive decline and the neurobiology of cognitive decline. Established at Rush Alzheimer’s Disease Center at Rush University Medical Center in Chicago, ROS enrolls healthy Catholic nuns, sisters, priests, and brothers from over 40 groups across the United States (Bennett et al., 2012). Participants are primarily residents in religious communities and undergo detailed annual testing including cognitive, motor, and structured clinical evaluations (Bennett et al., 2004; Bennett et al., 2012). No other exclusions were applied, other than the requirement that volunteers were able to understand the implications of study participation and sign an Anatomical Gift Act for organ donation.

The Einstein Aging Study (EAS) at Albert Einstein College of Medicine, Yeshiva University, was designed to study cognitive aging and dementia in a non-institutionalized, urban, and multi-ethnic community. EAS systematically recruits older Bronx, NY residents who are English-speaking (Katz et al., 2012). Participants undergo annual in-person evaluations that include cognitive, neurological, functional, and physical assessments (Katz et al., 2012). EAS is not an autopsy study, and brain donation is not required for participation, but some volunteers do agree to autopsy (Strozyk et al., 2010).

The Rush Memory and Aging Project (MAPRU) conducted by the Rush Alzheimers Disease Center at Rush University Medical Center in Chicago was designed to identify neurobiologic mechanisms that promote or reduce the risk of AD and other common chronic conditions of aging (Bennett et al., 2005; Bennett et al., 2012). Participants are recruited primarily from retirement communities in the Chicago-metro area and are free from dementia at study entry. No other exclusions were applied, other than the requirement that volunteers were able to understand the implications of study participation and sign an Anatomical Gift Act for organ donation. In addition to detailed annual assessments of cognitive, neurological, and physiological function, participants also agree to donation of brain, spinal cord, nerve, and muscle (Bennett et al., 2005; Bennett et al., 2012).

The African American Dementia and Aging Project (AADAPt) at the Oregon Health & Science University ADC recruits older African Americans living in the metropolitan Portland, OR area. AADAPt seeks to identify risk factors for cognitive decline and dementia using twice yearly cognitive and clinical assessments, including MRI. Volunteers are asked to participate in the study through the end of life, but brain donation is not required.

The Klamath Exceptional Aging Project (KEAP) at the Oregon Health & Science University ADC studies the oldest-old residents of the Klamath Basin, which is a rural area of Oregon, including those residing in facilities (Kaye et al., 2009). Volunteers are visited in their homes by a geriatric research nurse every six months for neuropsychiatric testing and structured clinical interview. Brain donation is not required for participation, but some participants agree to autopsy (Kaye et al., 2009).

2.2 SMART Database

SMART investigators reviewed data collection protocols from each participating center and identified elements that were common to at least two centers. Common elements were then assessed for relevance to SMART aims, namely those that would help characterize participants cognitive and clinical trajectories prior to and through the development of cognitive impairment and dementia, as well as those that would characterize participants neuropathology.

logically. Data templates, based on the methods established by NACC Uniform Data Set (Beekly et al., 2004), were developed to request standardized data elements from the centers. Data templates for demographic information, genetics and family history of dementia, clinical diagnosis, motor function, medical history, medication use, physical examination, and neuropathology were the same for all centers. Since each center used multiple cognitive and neuropsychiatric tests, and in most cases those tests changed somewhat (either to a new version or different instrument that measured the same cognitive domain) during the course of participant follow-up, neurocognitive and neuropsychiatric measures were requested on a center-by-center basis with the intention of creating z-scores for cognitive domains that could then be compared across centers. Data were submitted as SAS, CSV, and Microsoft Excel files, based on the center data managers preference. SMART then converted all files to SAS 9.3®(SAS Institute, Inc., Cary, NC).

2.3 Data Harmonization

Although data were submitted in a standardized format, harmonizing the data across centers has proved challenging in three major areas: clinical diagnosis, cognitive testing, and neuropathology. Although all centers used roughly the same criteria for diagnoses of all-cause dementia (DSM-III-R or DSM-IV) (APA, 1987; APA, 1994) and clinical AD (McKhann et al., 1984), clinical diagnoses of milder cognitive impairments were less consistent. This stems in large part from the fact that the participating studies predate the first consensus-based criteria for MCI diagnosis by many years (Petersen, 2004; Winblad, 2004). Thus, for the majority of follow-up, centers did not and were not able to use MCI as a diagnostic category. In the tables and text below, an MCI designation indicates a clinical diagnosis of MCI or, absent a diagnosis, CDR = 0.5 or other study-specific designations, as in HAAS (see Gelber et al., 2012). Future research will assess how multiple modern definitions of clinical states such as MCI and intact cognition behave when applied to each cohort retrospectively based on the available demographic, neuropsychological, and clinical data.

In addition, since some centers perform each year’s clinical assessment and diagnosis blinded to the participant’s prior clinical history, “back transitions” (i.e., recovery from more impaired to less impaired cognitive states between visits) were more frequent at some centers than others. In cases of back transitions from MCI to intact cognition, no data were recoded. However, in some cases an apparent recovery from dementia was made. To address this, SMART has employed two approaches for classifying the diagnostic record of each participant: (1) the original data were preserved; and (2) data were recoded based on future clinical assessment. Specifically, in cases where participants made an apparent recovery from dementia to MCI or intact cognition and were later re-diagnosed with dementia, the record was recoded so that all assessments after the first diagnosis of dementia were coded as dementia. In cases where participants made an apparent recovery from dementia to MCI or intact cognition and were never re-diagnosed with dementia, the diagnosis of dementia was recoded as MCI.

Due to the aforementioned variety of neuropsychological test instruments employed across centers, z-scores for each individual test were derived within each cohort. Linear modeling, based on the methods used by Kryscio and colleagues (2006), was used to predict baseline scores for participants who were not demented at baseline based on age, educa-

tional attainment, sex, and, where applicable, race. Each participants predicted score was subtracted from the observed score, and the difference was divided by the model root mean square error (RMSE). The resulting z-scores were used to classify participants as impaired or not impaired on each instrument based on a cut point of 1.5 standard deviations below the mean. Individual test z-scores were also averaged within cognitive domains to produce domain scores.

With the exceptions of Animal Naming and Boston Naming Test (versions vary), no single neurocognitive or neurobehavioral measure was used in every cohort. The Mini Mental State Examination (MMSE) was used by all cohorts except HAAS, but MMSE scores can be derived from the CASI. The Wechsler Memory Scale Logical Memory test (versions vary) was used by all but HAAS; Trail Making Test A was used by all but MAPRU, ROS, and the Nun Study; and the CERAD Word List was used by all but MAPWU and EAS. Thus, use of raw scores will be limited.

While many neuropathological outcomes, such as Braak stage (Braak and Braak, 1991) and Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) plaque rating (Mirra et al., 1994), are measured consistently across centers, other neuropathological ratings may be somewhat less standardized. For example, neuropathological definitions of AD may vary between centers, or even within the same center over time. Moreover, most pathological diagnoses of AD have until recently relied on the presence or absence of clinical manifestations of the disease, which the field has to come recognize as suboptimal. Thus, the recent National Institute on Aging-Alzheimer’s Association criteria for the neuropathological assessment of AD (Montine et al., 2012b) was used to define AD neuropathologically. Amyloid beta ($A\beta$) plaque score (i.e., Thal phase) is not available in the SMART database, and global ratings of diffuse plaque density (coded as ‘none’, ‘sparse’, ‘moderate’, and ‘frequent’) were used instead. Braak stages and CERAD neuritic plaque ratings were used as described in the Montine et al. guidelines. Additional neuropathological data harmonization challenges include defining the presence or absence, as well as severity, of cerebrovascular disease (CVD). Here, the presence of any vascular lesion or ischemic or hemorrhagic pathology denotes “cerebrovascular pathology,” which means that very mild cases are included. Thus, presence of CVD pathology should not be interpreted as a diagnosis of vascular cognitive impairment.

3. Results

Data on 11,541 participants enrolled in 11 longitudinal studies were submitted to SMART (Table 2). The majority of participants were female and white, with the exception of HAAS, where all participants were male and Asian American, and AADAPt, where all participants were African American. Average age at enrollment ranged from 73.4 (BRAiNS) to 88.5 (KEAP) years, and average educational attainment ranged from 10.5 (HAAS) to 18.2 (ROS) years, all of which indicate important differences in the cohort reference populations. The proportion of APOE-4 carriers in most cohorts are in line with population estimates, which range from 18-29% (see Farrer et al., 1997).

Follow-up assessments were performed under annual protocols in some cohorts, while in other cohorts participants were assessed more (every six months) or less (every two to three years) frequently (see study descriptions under Methods). For the purposes of

this presentation, six-month assessments (i.e., those occurring between annual assessments) were ignored. The average number of assessments in each cohort ranged from 3.2 (EAS) to 10.7 (BRAiNS). Given the lengthy follow-up in most cohorts, SMART is well-positioned to examine factors that may promote or reduce the risk of transition to clinically impaired states including MCI and dementia, as well as factors that may promote or reduce the risk of dying with no cognitive impairment or dementia.

A substantial portion of the cohorts have died and many participants have also come to autopsy (Table 4). Based on the average age at death across the cohorts, it is clear that the oldest old (age 85+) are well represented in SMART. The proportion of deceased participants in each cohort ranged from 31.6 (AADAPt) to 98.8% (Nun Study). In cohorts that required brain donation in order to participate, autopsy rates are expectedly high (BRAiNS, Nun Study, ROS, MAPRU), but it is worth noting that autopsy rates were at least 50% in all but four cohorts.

The distribution of observed levels of AD pathological changes varied by cohort (Table 4). The three cohorts with the largest proportion of cases with a high level of AD changes (BRAiNS, ROS, and MAPWU) also had among the highest proportions of APOE-4 carriers (cf. Table 2). Conversely, cohorts with the highest average ages at death (OBAS I, OBAS II, KEAP) were least likely to show high levels of AD pathological changes. These same cohorts also had among the highest rates of CVD pathology. However, CVD pathology was most frequently reported in BRAiNS, which had among the lowest average ages at death. This inverse association between CVD pathology and age at death in BRAiNS may be due to either (1) an ascertainment bias, which is less likely to be the case since the same neuropathologists performed autopsy assessments not only for BRAiNS but also for the Nun Study and HAAS, or (2) a higher burden of CVD in this cohort. There is some supporting evidence for the latter hypothesis. BRAiNS volunteers are largely born in and lifetime residents of the southern United States, where CVD is an established public health problem (Glymour et al., 2008). In addition, the prevalence of smoking is high in this cohort, with over 50% of BRAiNS participants reporting current or former use of cigarettes at baseline (Kryscio et al., 2013). Again, these results suggest important cohort-specific differences that must be accounted for analytically.

4. Discussion

SMART combined longitudinal data from 11 cohort studies of aging and cognition with lengthy follow-up and substantial autopsy rates. It was designed to study the clinical phenotypes of and risk factors for mixed neuropathologies (e.g., AD + CVD, AD + Lewy body disease, AD + hippocampal sclerosis of aging (HS-Aging)), which are the rule and not the exception, especially among the oldest-old (Nelson et al., 2007; Schneider et al., 2004). Results presented here are preliminary and represent a fraction of the overall SMART database, which includes longitudinal neuropsychological, physical, and neurological assessments, along with medical history and medication use. These data elements can be queried as potential risk factors, comorbidities, protective environmental influences, or indicators of important genotype/phenotype relationships in human populations. Thus, SMART will be able to make important, unique, and timely contributions to the field of mixed dementia epidemiology.

The SMART database is well positioned to capitalize on an evolving awareness that prior assumptions about AD, dementia, and brain aging, are incomplete and at times misleading. Cognitive status (e.g., dementia) and brain diseases are not readily classifiable at the population level as simply present or absent as both cognition and pathology exist on a continuum. Statistical methods, like Markov chain and semi-Markov multistate models (see, e.g., Abner et al., 2014; Kryscio et al., 2013), that allow simultaneous consideration of multiple cognitive or neuropathological states and competing risks for the outcomes of interest require large samples and many events (i.e., many subjects transitioning between states); the SMART database meets both of these needs.

Furthermore, it is important to consider the various biases, particularly those related to dementia clinic-based studies that limit our understanding of dementia in the general older adult population. Dementia clinic-based studies have greatly expanded our understanding of neurodegenerative diseases including rarer entities such as frontotemporal lobar degeneration (FTLD), but those same studies skew the perceptions of the impact of those diseases on the general population. For example, dementia clinics are enriched for AD and may over or underrepresent FTLD, but tend to undersample CVD and HS-Aging pathologies. Data from study samples that arise from population-based designs, like ROS, HAAS, the Nun Study, and EAS, tend to have more diversity in their study populations.

There are limitations to SMART’s study design. As stated above, current clinical definitions of MCI did not exist during most or all of the follow-up periods of the included cohorts. Thus, studies of MCI in these data will necessarily be complicated by the definitions applied and how well those definitions can be implemented in each cohort. While most cohorts followed roughly the same kind of procedures, neurocognitive and neuropsychological tests administered to each cohort may have different interpretations given the age and other demographic characteristics of the enrolled population. The use of z-scores and domain scores rather than raw neurocognitive test scores is also an important limitation, particularly for instrument scores that may violate the normal distribution assumption. Research questions involving performance on specific tests may not be well suited for this database. However, we are confident that participants within each cohort are well characterized cognitively, and the data can be used to generate well defined cognitive states at each assessment. Additionally, alternatives to z-score harmonization, including latent variables and multiple imputation (see Griffith et al., 2014), will be considered. Missing data, arising from elements that were not collected at all centers, or not for the entire follow-up period, will also be an important statistical challenge. Likewise, center effects, arising from differences in population characteristics and examiner effects, will be important sources of variability.

While combining data from multiple independent cohorts is a strength, it also requires a consideration of selection bias. Recruitment strategies vary, and cohorts that require autopsy consent will necessarily have characteristics that make them different from the general population of older adults. Educational attainment tends to be very high, for example. Moreover, selection bias may also arise from cohort-specific differences in attrition and mortality rates, as well as differences in autopsy rates. Because this study is focused on autopsy-verified diagnoses, and not all participants have died and come to autopsy, we will weight observations by inverse probability sampling according to the methods proposed by Haneuse et al. (2009). Confounding due to age and sex, which are strongly associated

with cognitive decline as well as many of its risk factors, will need to be addressed in all analyses.

SMART also has several significant strengths. One aspect worth highlighting is the ready access to data collected longitudinally over many years: over 80% of participants in this database began follow-up while cognitively intact, with 7.3 ± 5.3 average years of follow-up. Moreover, a significant proportion of each cohort's participants died while still cognitively intact, despite the advanced ages at death observed in the cohorts. Thus, it will be possible to examine how death as a competing risk influences effect estimates for established risk factors for dementia as well as to identify factors associated with successful cognitive aging.

Additionally, the neuropathological assessments in three of the 11 cohorts (BRAiNS, Nun Study, and HAAS) were developed by a single neuropathologist, the late Dr. William Markesbery, who also performed many of the autopsies. The cohorts contributing data are large, well-established, and well-designed studies with lengthy follow-up, rigorous cognitive assessments, high autopsy rates, and state-of-the-art neuropathologic evaluations (including newly described diseases such as HS-Aging). In addition to – and in combination with – the neuropathology data, extensive additional data can be analyzed using the SMART database. Since state-of-the-art neuropsychiatric and cognitive evaluations were administered to most of the participants, these data provide an important resource for understanding the neurocognitive domains and disease-related trajectories that can be associated with various subtypes of neuropathological observations. We anticipate the application of novel statistical approaches that can capitalize on these harmonized data.

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Data Sharing

Researchers interested in the accessing the SMART database may contact one of the PIs: Drs. Richard J. Kryscio (kryscio@email.uky.edu) or Frederick Schmitt (fascom@uky.edu). Additionally, at the conclusion of the study, a copy of the database will be archived with the National Alzheimer's Coordinating Center and made available for use.

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Table 1. Cohort study design characteristics

Cohort ^a	Year established	Study sample	Study focus	Brain donation required	Minimum age for enrollment	Exclusion criteria
MAPWU	1979	Convenience	Effects of aging on intellectual functioning	No	63	Major psychiatric or neurological disorders; medical conditions that impair cognition; dementia
OBAS I & II	1989 2004	Convenience	Effects of aging on the nervous system	No	55 (OBAS I) 85 (OBAS II)	Chronic diseases; dementia
BRAiNS	1989	Convenience	Normal and pathological brain aging	Yes	60	Major psychiatric or neurological disorders; medical conditions that impair cognition; dementia
Nun Study	1991	Birth cohort	Influence of early life exposures on late life cognition and risk of dementia	Yes	75	None
HAAS	1991	Population-based	Prevalence, incidence, and risks for dementia	No	71	None
ROS	1993	Convenience	Risks for cognitive decline and dementia	Yes	55	Known dementia
EAS	1993	Population-based	Cognitive aging and dementia	No	70	Institutional living at enrollment
MAPRU	1997	Convenience	Neurologic mechanisms that affect risk for Alzheimer's disease	Yes	55	Known dementia
AADAPt	1999	Convenience	Risks for cognitive decline and dementia	No	65	None
KEAP	1999	Population-based	Cognitive function of the oldest old	No	80	None

a. MAPWU = Memory and Aging Project (Washington University), OBAS = Oregon Brain Aging Study, BRAiNS = Biologically Resilient Adults in Neurological Studies, HAAS = Honolulu Asia Aging Study, ROS = Religious Orders Study, EAS = Einstein Aging Study, MAPRU = Memory and Aging Project (Rush University), AADAPt = African American Dementia and Aging Project, KEAP = Klamath Exceptional Aging Project.

Table 2. Baseline participant characteristics by cohort.

Characteristic ^a	MAPWU	OBAS I	OBAS II	BRAiNS	Nun Study	HAAS	ROS	EAS	MAPRU	AADAPt	KEAP
N	788	216	89	649	678	3734	1137	2097	1617	117	419
Age, y	76.0±8.6	80.0±9.2	87.0±2.0	73.4±7.4	83.3±5.5	78.3±4.7	75.6±7.5	79.0±5.4	79.9±7.6	73.8±7.1	88.5±4.0
Sex (%F)	60.8	57.9	65.2	63.9	100	0	68.6	61.2	73.5	70.9	66.1
Education, y	14.6±3.3	14.7±2.7	14.1±2.5	15.9±2.5	17.7±3.6	10.5±3.2	18.2±3.3	12.9±3.7	14.4±3.3	13.4±3.4	12.1±3.3
Race (n)											
African American	90	0	0	5	0	0	84	581	98	117	2
American Indian/ Alaska Native	1	1	1	0	0	0	6	0	4	0	1
Asian American	1	1	2	1	0	3734	0	9	0	0	0
Native Hawaiian/ Pacific Islander	1	0	0	0	0	0	0	0	0	0	0
White	695	213	86	643	678	0	1038	1487	1506	0	415
Other/Unknown	0	1	0	0	0	0	9	20	9	0	1
APOE-ε4 carriers (n)	156	41	10	194	141	672	259	440	321	35	67
APOE-ε4 unknown (n)	101	12	3	0	59	115	153	1095 ^f	264	16	80
Clinical diagnosis (n)											
No dementia ^b		--	--	--	540	--	--	--	--	--	--
Intact cognition ^b	788	216	89	649	--	3216	774	1503	1094	93	194
MCI ^c	0	0	0	0	--	187	278	419	413	20	157
Dementia	0	0	0	0	138	320	83	258	89	4	68
Other impairment ^d	0	0	0	0	--	11	0	0	0	0	0
Unknown ^e	0	0	0	0	--	0	0	65	21	0	0

a. Results presented are mean±standard deviation or proportions. b. 'No dementia' vs. 'Intact cognition' reflects uncertainty about less severe cognitive impairments at baseline for Nun Study participants. c. MCI refers to a clinical diagnosis of mild cognitive impairment (OBAS I & II, BRAiNS, ROS, EAS, MAPRU, AADAPt, KEAP), CDR = 0.5 (MAPWU), or study specific designations (HAAS; see Methods for references) d. Other impairment includes participants who did not meet formal criteria for dementia but had a CDR greater than 0.5. e. Unknown diagnosis reflects participants who did not receive a clinical diagnosis within the cohort study. f. Genotype results are pending and unavailable at this time.

Table 3. Clinical assessments and cognitive transitions by cohort

Characteristic	MAPWU	OBASI	OBAS II	BRAiNS	Nun Study	HAAS	ROS	EAS	MAPRU	AADAPt	KEAP
N (participants)	788	216	89	649	678	3734	1137	2097	1617	117	419
Assessments ^a per participant	6.1±4.9	10.5±5.2	8.6±3.5	10.7±4.7	5.4±3.8	4.5±3.2	9.4±5.1	3.4±3.1	5.3±3.4	5.8±3.2	3.8±2.5
Transitions ^b											
Intact → MCI	232	143	64	173	--	477	532	321	473	24	101
Intact → Dementia	29	3	2	41	198	353	71	43	54	0	8
Intact → Death ^c	194	45	16	215	342	1895	185	476	205	20	68
MCI → Intact	82	70	9	19	--	112	437	237	374	21	50
MCI → Dementia	58	63	19	79	--	65	217	96	211	4	86
MCI → Death ^c	91	34	28	34	--	404	140	164	164	11	90

a. Assessments conducted annually, or, for HAAS, every 2-3 years; b. Number of participants making this transition at least once; c. Death without prior history of dementia.

Table 4. Deaths, Alzheimer’s disease associated pathological changes, and cerebrovascular pathology, by cohort

Characteristic	MAPWU	OBAS I	OBAS II	BRAiNS	Nun Study	HAAS	ROS	EAS	MAPRU	AADAPt	KEAP
N (participants)	788	216	89	649	678	3734	1134	2097	1595	117	419
Deaths	326	142	60	324	670	3266	609	830	608	37	295
(n [% of cohort])	(41.3)	(65.7)	(67.4)	(49.9)	(98.8)	(87.5)	(53.7)	(39.6)	(38.1)	(31.6)	(70.4)
Age at death, y	89.5±8.0	94.0±6.2	95.4±2.9	87.1±7.5	90.3±5.4	87.7±5.6	87.2±6.9	87.0±6.2	88.7±6.2	84.1±8.5	93.1±4.3
Autopsies	172	90	32	271	533	774	555	37 ^d	456	1	80
(n [% of deaths])	(52.8)	(63.4)	(53.3)	(83.6)	(78.6)	(23.7)	(91.1)	(4.5)	(75.0)	(2.7)	(27.1)
Level of Alzheimer’s disease pathological changes ^a (n)											
High	28	7	0	52	67	28	71	4 ^c	98	0	5
Intermediate	34	25	9	67	68	214	225	23 ^c	263	1	14
Low	49	20	10	87	127	192	68	8 ^c	79	0	21
No AD changes	20	30	13	65	30	279	92	2 ^c	115	0	30
Unknown	41	8	0	0	241	61	0	0 ^c	0	0	10
Any cerebrovascular pathology ^b (n)	120	68	28	263	396	533	296	28	332	1	71

a. Categories were adapted from National Institute on Aging-Alzheimer’s Association criteria for the neuropathologic assessment of Alzheimer’s disease (AD) (Montine et al., 2012b). Please see Methods for additional details. b. ‘Any cerebrovascular pathology’ includes all infarcts, hemorrhages, and other vascular lesions noted in the neuropathological assessment. Very mild to severe cases are included under this definition. c. Ratings based on Braak stage only: 0 = No AD Changes, I/II = Low, III/IV = Intermediate, V/VI = High. d. EAS is not an autopsy study, and brain donation is not required for participation.