BIOCARD Study – Key Features of Datafiles

The BIOCARD study is a longitudinal study with several key features that should be understood in order to utilize the datafiles and their accompanying data dictionaries. This document is designed to explicate the nature of the study so that maximum use can be made of the data.

Overall Study Design

The BIOCARD study was designed to recruit and follow a cohort of cognitively normal individuals who were primarily in middle age when they were enrolled. By design, approximately 75% of the cohort had a family history of dementia at enrollment. The study was conducted by intramural investigators at NIMH from 1995 to 2005 (when the study was stopped for administrative reasons). In 2009, the NIH funded investigators at Johns Hopkins University (JHU) to re-establish the cohort and continue to follow the participants. The study therefore includes a four-year gap during which no subject visits occurred.

Visit Numbers

In order to make it easy to determine which visits occurred at the NIH and which visits occurred at JHU, a different visit number sequence has been used to signify where the visit occurred (both represented by the same variable - 'VisitNo'). The visits that took place at the NIH are represented by one or two digits (e.g., 1, 2, 3…10), whereas the visits that have taken place at JHU are represented by three digits (i.e., 101, 102, 103, etc.).

Number of Visits Per Subject

The dataset includes data from approximately 91% of the cohort; this includes subjects who have completed JHU visits, subjects who died prior to enrollment at JHU, and subjects who have provided written agreement for JHU investigators to use their NIH data but have not agreed to further follow-up. The subjects from the original cohort whose data are not included in the datafiles (~9%) represent those who have not yet provided written permission for JHU investigators to use their data or to be re-enrolled, and those who have refused to be re-enrolled at JHU. The nature of the subject enrollment process at the NIH has an impact on the number of visits per subject. Subjects were enrolled over time at the NIH, between 1995 and 2005. For example, subjects enrolled in 1995 could have had up to 10 visits at the NIH, whereas subjects enrolled in 2005 could only have one NIH visit. Thus, many subjects have fewer NIH visits than JHU visits, because they were enrolled toward the end of the enrollment period at the NIH (i.e., 2005) but have been followed regularly at JHU. It is also the case, however, that some subjects have only NIH visits; this may be because they were seen at the NIH and died prior to the initiation of the study at JHU, or because they were seen at the NIH and provided written permission for JHU investigators to use their data, but did not agree to participate in JHU visits.

Diagnostic Procedures

The investigators at JHU have conducted a uniform diagnostic evaluation for each subject whose data are in the datafiles. Consensus diagnoses have been completed prospectively for all visits completed by the JHU research team and retrospectively for all visits conducted at the NIH. The diagnostic approach employed in the BIOCARD study is identical to that employed in the Alzheimer's Disease (AD) Centers program throughout the U.S.

Syndromic Diagnoses:

Each subject is coded with one of four syndromic diagnostic categories: (1) Normal, (2) Mild Cognitive Impairment (MCI), (3) Dementia, and (4) Impaired not MCI. The syndromic diagnosis is based on two types of information: the Clinical Dementia Rating (CDR) interview and neuropsychological testing. The CDR is given as a semi-structured interview, with probe questions specifically designed for individuals with very mild impairments, as described elsewhere. The performance of the subjects on the cognitive test battery is evaluated in relation to age-adjusted norms (and, where available, education and education adjusted norms). The diagnostic criteria for MCI and dementia due to Alzheimer's disease

(AD) are consistent with those recommended by the National Institute on Aging/Alzheimer's Association workgroups.

It should be noted that the category of 'Impaired not MCI' is used by investigators at JHU to primarily represent two groups of individuals: (1) those with no evidence of declines on cognitive testing but reports by the subject or the study partner/collateral source of problems in daily activities that may reflect cognitive change, or (2) subjects with evidence of declines on cognitive testing but no reports by the subject or study partner of problems in daily activities suggestive of cognitive decline. These subjects therefore do not meet the diagnostic criteria for MCI. In all analyses published to date, JHU investigators have conducted sensitivity analyses to determine whether the outcomes differ if the subjects with a diagnosis 'Impaired not MCI' are included in the group of normals. To date, the results of these analyses indicate that it is most appropriate to include the subjects with a diagnosis of 'Impaired Not MCI' in the group of normals.

Etiologic Diagnoses:
Each subject is coded with one or more etiologic diagnosis. The etiology incorporates all of the clinical data available on the subject, including medical, neurologic and psychiatric history, medication use, neurologic and psychiatric assessments, neuropsychological testing and findings from the CDR interview. The etiologic diagnoses utilize the standard diagnostic criteria in the field, as described elsewhere. Consistent with the AD Centers program, multiple etiologies can be endorsed for each subject (e.g., AD and vascular disease, Parkinson's disease and depression, etc.).

Estimated Age of Onset of Clinical Symptoms
Each subject with a diagnosis of MCI or dementia or Impaired not MCI also has an estimated age of onset of clinical symptoms. This estimation is based primarily on the information from the CDR interview with the subject and the study partner. It is represented by the variable ('DECAGE') in the diagnosis datafile. The estimated 'age of onset of clinical symptoms' has been used as the primary outcome in many of the analyses conducted by BIOCARD investigators (e.g., survival analyses), since the four year gap in time when subjects did not have study visits precludes using 'date of diagnosis' for many analyses.

Neuropsychological Test Battery
The neuropsychological battery currently used at JHU includes tests that were also administered at the NIH, with one exception (the grooved pegboard). Participants in the study have received neuropsychological testing approximately annually throughout the course of the study, except during the four-year gap, when no visits occurred. However, the cognitive battery utilized at the NIH differed from that used at JHU in two ways: (1) the battery given at the NIH was generally longer than the one currently given at JHU; this is largely because subjects were admitted for a three day stay at the NIH Clinical Center and more testing was therefore feasible, and (2) some tests were introduced at varying points in time while the study was at the NIH; thus some tests currently given at JHU were part of the test battery initiated in 1995, but others were added later. Additionally, some tests were given annually at the NIH, while others were given on alternate years. A timeline accompanies this document showing the details of when each test was administered at the NIH. It should be noted that the tests provided in these datafiles are those that JHU investigators have used in analyses and therefore the appropriate edit and range checks have been implemented.

Auxiliary Clinical Assessments:
Several auxiliary clinical assessments were added to the study protocol, beginning in 2015. This includes: (1) an assessment of physical function, (2) an assessment of leisure activities, (3) an assessment of hearing, and (4) actigraphy to evaluate sleep and rest-activity patterns. The physical function measures are available for data sharing but the other measures are not yet available for sharing.

Magnetic Resonance Imaging Measures

All of the magnetic resonance imaging (MRI) measures in the datafiles are based on MRI scans collected at the NIH. These were 1.5T scans acquired on a GE scanner. Two different analytic methods have been used by JHU investigators to analyze the volumetric (SPGR) images: (1) LDDMM (large deformation diffeomorphic metric mapping) and (2) Freesurfer. FLAIR images were also collected at the NIH; these have recently been analyzed, but the data are not yet available for sharing. Additional longitudinal MRI scans from participants have been collected since 2015, using a 3T Philips scanner. These scans include MPRAGE, T2, FLAIR, DTI and rs-fMRI sequences; measurements from these scans are not yet available for data sharing.

Positron Emission Tomography - Pittsburgh Compound B

Positron Emission Tomography (PET) scans using Pittsburgh Compound B (PiB) have been collected once in the participants; measures from these scans are not yet available for data sharing.

Cerebrospinal Fluid Measures

All of the cerebrospinal fluid (CSF) measures in the current datafiles are based on CSF collected at the NIH. All the specimens were analyzed at the same point in time by JHU investigators, using the Alzbio3 assay from Innogenetics, using the same protocol employed in ADNI-1 and ADNI-2. Additional CSF from the participants has been collected since 2015, but these values are not yet available for data sharing, as newer, fully automated assays are in the process of being implemented.

Blood Collection

Blood specimens were collected and stored approximately every other year at the NIH. Blood has been collected at each in-person visit at JHU. Analyses of these blood specimens are currently underway; the data are yet available for sharing.

Neuropathology

JHU investigators have made every effort to obtain ante-mortem autopsy approval and to follow the participants to autopsy. The neuropathological data based on these autopsies are available for data sharing.

Publications

The BIOCARD research team at JHU maintains a website, which includes links to publications from the study, as well as additional details about the data sharing policy – www.biocard-se.org