

Review Article

Review of selected databases of longitudinal aging studies

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Abstract

One of the recommendations of the 2010 Leon Thal Symposium, organized to develop strategies to prevent Alzheimer's disease, was to build a global database of longitudinal aging studies. Although several databases of longitudinal aging studies exist, none of these are comprehensive or complete. In this article, we review selected databases of longitudinal aging studies. We also make recommendations on future steps to create a comprehensive database. Additionally, we discuss issues related to data harmonization.

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1. Background

One of the four major recommendations from the 2010 Leon Thal Symposium, which brought together experts in brain aging and dementia to examine national strategies to prevent Alzheimer's disease (AD), was "... initiation of a Global Database that extends the concept of the National Database for Longitudinal Studies for longitudinal studies beyond the United States;" [1].

As implied in the aforementioned recommendations, creation of a global database of longitudinal aging studies is crucial to facilitating large collaborative studies and providing the research community with the greatest opportunity to conduct efficient, optimally informed research. Multiple longitudinal aging studies exist around the world that could contribute valuable data to such a database [2,3]. Currently, a few databases have systematically collected and stored data/information from two or more longitudinal aging studies. These databases were created for different purposes, and the amount and type of data they provide vary. Additionally, how useful these databases are to the research community in general is unclear. This review

aims to answer several questions related to these databases: Which are the main databases that include data on or information about longitudinal aging studies? Are these databases used in their current format? What future steps should be taken to improve the utilization of such databases? To try to answer these questions, this article reviews selected databases and makes recommendations for future attempts in creating a database of longitudinal aging studies.

2. Identification of databases

We aimed to identify all Web-based databases that provide either individual-level data from longitudinal aging studies or information on which longitudinal aging study includes what types of variables. To find Web-based databases, the majority of which do not have a related publication, we used Internet searches and relied on discussions with experts in the field to obtain a comprehensive list.

Existing databases were identified through Web searches, using the Internet search engines "Google" and "Google scholar," conducted on December 15, 2010 and June 27, 2011. The following search terms were used: "aging database," "Alzheimer disease," "Alzheimer's disease," "longitudinal aging study," "aging study network," or "longitudinal study on aging." Sites not related to human aging research

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were excluded. We also repeated our search using MEDLINE for years 1946 through the last 3 weeks of June 2011, using the same search phrases. Our search did not identify any additional Web sites. In fact, most of the databases or other aging-relevant Web sites were not captured using this method. The list was further compiled from discussions with experts in the field.

From this extensive list, we only selected for review databases that (1) focused on brain aging, (2) included studies with biomarker measures, and (3) are publicly available as a Web-based database.

3. Databases

Our search yielded more than 100,000 sites. From this list, we first compiled a table including all Web sites/networks that were related to human aging research, available in English, and had a searchable Web-based database (Table 1). The sites/networks/databases without a Web-based searchable database, but relevant to human aging research, are presented separately (Supplementary Table 1). The focus and collection methods of these databases/networks vary widely. While some gather aging-related survey data with a focus on qualitative measures and policy issues, some focus on publications and resources relevant to aging. Others include information on cognitive or biomarker variables from longitudinal aging studies. Several of the databases focus on genetics of aging. Some of these databases provide information about what measures are available from different longitudinal aging studies, whereas others provide data at the individual subject level. A few of these databases are private, where data are not available to nonaffiliated investigators (Supplementary Table 1). In the end, from the list of sites in Table 1, the following databases were selected for further review based on their focus on the aging brain, biomarker annotation, and public availability as a searchable Web site of the database: the National Institute on Aging (NIA) Database of Longitudinal Studies (DLS) [4], Cognitive and Emotional Health Project (CEHP) [5], the Integrative Analysis of Longitudinal Studies on Aging (IALSA) [6,7], the National Alzheimer Disease Coordinating Center (NACC) database [8], and the Alzheimer Disease Neuroimaging Initiative (ADNI) database [9]. NACC and ADNI differ from the other databases because they provide data sets at the individual subject level and focus on AD. Additionally, ADNI is not a “database” in the true sense. However, because both include cognitive and biomarker data obtained from multiple longitudinal aging studies, we believed they were relevant to this review.

The NIA-DLS resulted from the recommendations of the 2003 NIA Longitudinal Data on Aging working group [4]. This group was assembled to facilitate research initiatives to identify risks and protective factors for diseases associated with brain aging. As a first step, the working group recommended establishing a database of existing sources of longitudinal aging-related data. The primary purpose of

the database was to establish a resource for investigators applying for NIA grants. The NIA-DLS includes a total of 55 longitudinal studies. Data from the Canadian Institutes of Health Research (CIHR) review of Longitudinal Studies on Aging were used in the development of the NIA database [10]. The CIHR review resulted from a review of longitudinal studies on aging undertaken by the Division of Aging and Seniors, Health Canada. The CIHR review does not have a Web-based database, but it resulted in a document that includes information on the design and current status of the studies and study variable domains. In contrast, the NIA database is a Web-based searchable database and provides information on which studies have collected which variables. How studies were selected to be included in the NIA-DLS is not described. Although most studies included focus on brain aging, some of the studies enrolled younger subjects and did not include brain aging as the main focus (such as the Canadian Multicentre Osteoporosis Study or the Bogalusa Heart Study; Supplementary Table 2). Two reviews of longitudinal studies on aging have concluded that some studies with valuable findings were not included in the NIA-DLS [3,11]. One such study, for example, is the well-known Framingham study.

The CEHP, initiated in 2001, is another Web-based searchable database supported by the NIA, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke. Its aim is to “...assess the state of longitudinal and epidemiological research on demographic, social and biologic determinants of cognitive and emotional health in aging adults” [5]. Unlike other databases, CEHP has well-defined selection criteria: studies were included if they had a sample size of >500 subjects, and studied a broad range of demographic, biological, and psychosocial risk factors. However, the CEHP database is not limited to studies focusing on middle-aged or elderly individuals. Longitudinal studies with a focus on brain health and enrolling young adults, for example, have also been included. Examples of such studies are the San Antonio Lupus Study of Neuropsychiatric Disease, the Work and Iron Status Evaluation, and the neurobiological studies of Huntington disease (Supplementary Table 2). A Web-based searchable questionnaire database was created based on the responses to a questionnaire sent to 80 studies, not all of which had a focus on age-related cognitive changes. Additionally, not all of the studies had a sample size of >500 subjects, as initially mentioned in the inclusion criteria. The CEHP database also provides information on constituent variables of the participating studies.

The IALSA network, whose meta-data tool development started in 2005, aims to create “...a collaborative research infrastructure for coordinated interdisciplinary, cross-national research aimed at the integrative understanding of within-person aging-related changes in health and cognition” [6,7]. It is an open and growing network, and more than 25 longitudinal aging studies from around the world have joined this network [12]. The IALSA database provides

Table 1

Summary of aging-relevant sites with a Web-based searchable database identified through Web searches using the following search terms: “aging database,” “Alzheimer disease,” “Alzheimer’s disease,” “longitudinal aging study,” “aging study network,” or “longitudinal study on aging”

Database	Web site	Focus	Available to public Y/N	Number of studies/subjects
AgeInfo	http://www.cpa.org.uk/ageinfo/ageinfo.html	Database on aging-related articles, organizations, and events	N	4000 organizations, more than 50,000 book articles or reports
AgeLib	http://www.uncioa.org/ageilib/	Database of aging resources: articles, books, data sets, reports, Web sites	Y	5089 aging-related resources
AgeLine	http://www.ebscohost.com/academic/ageline	Database of literature on gerontology	N	200 journals on aging
AgeSource/AgeStat Worldwide	http://www.aarpinternational.org/database/	A database of clearinghouses, databases, training modules, major reports, and Web meta-sites in aging; focus on policy information exchange	Y	95 data-bases
Aging Gene DB	http://www.uwaging.org/genesdb/	A database of genes related to aging	Y	379 genes
Alzheimer Research Forum (AlzGene database)	http://www.alzgene.org/	A database of genetic-association studies on AD phenotypes	Y	1395 studies
ADNI	http://adni.loni.ucla.edu/	Individual-level data on imaging, plasma, DNA biomarkers and clinical measures	Apply for access	~ 800 subjects
ARC Research Network in Ageing Well	http://www.ageingwell.edu.au/index.htm	A network with involvement and links to databases relevant to aging research	Y	N/A
Aging Research Online	http://www.aro.gov.au/	Database under the ARC Research network of policy and research initiatives in aging	Y	
CEHP	http://trans.nih.gov/CEHP/	Information about study size, duration of study, and available measures from longitudinal studies focusing on brain health in adults	Y	70 studies
dbGAP	http://www.ncbi.nlm.nih.gov/gap	Collects data from studies examining the relationship between genotypes and phenotypes	Y	122 studies
ERA-Age	http://era-age.group.shef.ac.uk/content/60/resources-overview	Database of European research on aging, funding agencies, research programs, and centers	Y	89 research centers
EDAC	http://www.searchedac.org/	Articles on aging studies that inform and advance policy discussions regarding aging care and the role of social workers	Y	1344 articles
GAN	http://gan.usc.edu/public/index.jsp	Data mining platform to query, analyze, and visualize age-related genomic data	Y	243 microarray experiments on <i>Homo sapiens</i>
IALSA	http://www.ialsa.org/	Information on available measures from participating longitudinal aging studies	Apply for access	25 studies
IDL	http://www.supercentenarians.org/default.htm	Collects data on individuals with very long lifespans internationally	Apply for access	672 subjects
JenAge	http://www.jenage.de/about.html	A database of databases, centers, and libraries in aging and systems biology research	Y	36 aging-related databases
CFAS	http://www.cfas.ac.uk/	Collection of large U.K.-based longitudinal multicenter studies looking at health and cognitive function in older people	Y	47,000 people
NACC	http://www.alz.washington.edu/	Individual-level data on imaging, biomarkers, and clinical measures	Y	~86,743 subjects
NDAR	http://www.cpa.org.uk/research/ndar_about.html	Database of U.K. research projects in progress and forthcoming on all nonmedical aspects of older age	Y	N/A
NIA-DLS	http://www.nia.nih.gov/ResearchInformation/ScientificResources/LongitudinalStudies.htm	Information on available measures from longitudinal studies focusing on aging	Y	55 studies
NetAge Database	http://netage-project.org/	Collection of protein interaction networks for longevity, age-related diseases, and associated processes	Y	8118 <i>Homo sapiens</i> ’ genes
P3G	http://www.p3gobservatory.org/	Facilitation, harmonization, and summary of biobank data	Y	155 studies
RQRV	http://www.rqrv.com/en/index.php	A network with involvement and links to databases on animal and human aging	Y	4 databases

(Continued)

Table 1

Summary of aging-relevant sites with a Web-based searchable database identified through Web searches using the following search terms: “aging database,” “Alzheimer disease,” “Alzheimer’s disease,” “longitudinal aging study,” “aging study network,” or “longitudinal study on aging” (*Continued*)

Database	Web site	Focus	Available to public Y/N	Number of studies/subjects
WHO-SAGE	http://www.who.int/healthinfo/systems/sage/en/index.html	Individual-level data on multinational survey questionnaire responses, not limited to aging studies	Y	~ 107,826 subjects
The 10/66 Dementia Research Group	http://www.alz.co.uk/1066/	Population-based research into dementia, noncommunicable diseases, and ageing in low- and middle-income countries	Apply for access	Multiple studies of varying scope.
DYNOPTA	http://dynopta.anu.edu.au/Publicsite/Contributingstudies/index.php	Individual-level data of questionnaire responses, risk factor, and health behavior variables	Apply for access	9 studies
HAGR-GenAge	http://genomics.senescence.info/	Collection of databases on genetics of aging	Y	261 human genes, 4000 species
NACDA	http://www.icpsr.umich.edu/icpsrweb/NACDA/	A database of survey, incidence/prevalence, and some cohort study data sets	Y	65 data sets
AD&FTDMDB	http://www.molgen.ua.ac.be/admutations/	Database of known mutations and nonpathogenic coding variations in the genes related to AD and frontotemporal dementia	Y	415 mutations

Abbreviations: AD, Alzheimer’s disease; Aging Gene DB, Aging Gene Database; ADNI, Alzheimer’s Disease Neuroimaging Initiative; ARC, Australian Research Council; CEHP, Cognitive and Emotional Health Project; dbGAP, Database of Genotypes and Phenotypes; ERA-Age, European Research Area in Aging; EDAC, Evidence Database of Aging Care; GAN, Gene Aging Nexus; IALSA, Integrative Analysis of Longitudinal Studies on Aging; IDL, International Database on Longevity; JenAge, Jena Centre for Systems Biology of Aging; CFAS, Medical Research Council for Cognitive Function and Ageing Study; NACC, National Alzheimer Disease Coordinating Center Database; NDAR, National Database of Ageing Research; NIA-DLS, National Institute on Aging Database of Longitudinal Studies; P3G, Public Population Project in Genomics; RQRV, Quebec Network for Research on Aging; WHO-SAGE, Study of Global Aging and Adult Health; DYNOPTA, the Dynamic Analyses to Optimize Ageing; HAGR-GenAge, the Human Aging Genomic Resource; NACDA, the National Archive of Computerized Data on Aging; AD&FTDMDB, Alzheimer Disease & Frontotemporal Dementia Mutation Database.

summary information regarding constituent variables of the participating studies. The IALSA network also does not have strictly defined criteria on study inclusion in the network, as it began as a grassroots effort among an initially smaller group of collaborating programs with strong interests in starting the network. Together, the NIA-DLS, CEHP, and IALSA databases cover 132 unique studies, with some overlap.

One large-scale database with a specific focus on AD and whose data collection spans from the year 1984 to present is the NACC database [8]. NACC states one of its aims as “... to promote collaborative research among the Alzheimer’s Disease Centers through research funding and technical support.” It provides a Web-based query site for data from 29 NIA-funded Alzheimer Disease Centers around the United States. Data include standardized cognitive, clinical, and biomarker measures collected since 1999. Both summary data and data at the individual subject level are available from the NACC site [13].

Another network with a focus on AD is ADNI [9]. Started in 2005, it is a multisite longitudinal cohort study of biomarkers in brain aging and cognitive impairment. Although ADNI is not an aggregating database in the true sense, it was designed from inception to readily provide relevant clinical and biomarker (including imaging) data to the research community worldwide. It currently includes data for >600 participants who come from 59 clinical centers across the United States and Canada. Data are

available to nonparticipating investigators through the ADNI Web site. Similar initiatives are underway in Japan [14], Europe [15], and Australia [16].

In contrast to the NIA, CEHP, and IALSA study information databases, NACC and ADNI provide data at the individual subject level. Both of these databases were initiated as part of a large collaborative effort by multiple institutions with standardized data collection methods. These types of databases, because of the availability of standardized variables across large numbers of subjects, are able to facilitate a large number of research projects and publications.

The NACC alone has provided data to 180 funded projects, resulting in more than 125 publications [13]. Similarly, use of the ADNI database has generated 213 publications since 2005 [17]. Identifying studies and publications resulting from the other databases is more difficult, as there is no formal mechanism that tracks use of Web sites linking to these databases. The IALSA network, funded by the National Institutes of Health (NIH), with further funding from CIHR, has generated a number of ongoing projects involving cross-cohort and cross-national comparisons (S. Hofer, personal communication, June 2011). We were not able to determine the number of studies or publications resulting from the NIA or CEHP databases.

Relevant clinical and biomarker data from aging studies are also available through other databases that do not specifically focus on brain aging. Although these are out of the scope of this review, examples worth mentioning are the

Public Population Project in Genomics [18] and the Database of Genotypes and Phenotypes [19]. We anticipate that there likely are many more aging-related databases/resources inadvertently left out of this review. We hope this review will serve as a starting point to build an inclusive inventory of aging-relevant databases/resources.

4. Conclusion

Our review of databases providing longitudinal data relevant to brain aging found several existing useful and evolving resources. For a number of reasons, these databases overlap. They are variable in the data aggregated, as well as the level of detail contained within the database itself. Determining how widely used some of these databases are, is challenging. However, we believe that many researchers around the world do access these sites for a number of reasons, not the least of which is to simply obtain a sense of where the field is and whom they might consult or collaborate with on planned or subsequent projects. Although databases of longitudinal aging studies can be important resources in the development of large-scale collaborative studies or the identification of confirmation samples, we suspect that in their current form, there exist several limitations to their use and further development.

One such limitation is related to the completeness of these databases. We found more than a dozen longitudinal aging studies, some NIA-funded, that were not included in some of the databases. Examples of studies that have not been included in the NIA database are the Framingham study and the Nurses' Health Study. Moreover, the CEHP database, in contrast, includes some studies that do not necessarily focus on the aging brain. Documenting all the studies worldwide not belonging to any known database is an arduous endeavor because of the lack of a priori knowledge of study name, location, or some study-specific search terms, and it may be a near-impossible goal to achieve. However, moving forward, a well-described process on study selection methods and how many studies did not agree to participate should be provided as part of the database description. Equally important is the regular update of such a database. The ability to achieve the aforementioned criteria will depend on the individual study's participation, which in most cases has been voluntary. It is possible in the future that, similar to clinical trials' registries, consideration might be made to requiring longitudinal studies to register as part of their funding process. Even if this were the case, there would need to be a site maintained that aggregates and curates the studies for public access.

A second limitation to the use of such a database is the fact that cognitive and biomarker variables have been measured using different methodologies across different studies. Data harmonization and the implementation of methods to control for these variations enable comparability and are crucial for data use across sites and subjects [5]. Data harmonization may be retrospective or prospective.

There are many challenges associated with retrospective data harmonization, and for a global comprehensive database with hundreds of variables, this may simply not be feasible. We suggest that retrospective data harmonization should be considered for hypothesis-driven efforts on selected variables. Conversely, funding agencies and investigators of aging cohort studies should increasingly consider using agreed-upon guidelines for collection and measurement of at least a core set of important biomarker variables to ensure prospective data harmonization. An example of such an effort in AD-related research is to standardize measurement of cerebrospinal fluid markers and neuroimaging measurements across studies as part of the U.S. ADNI and the European ADNI [15].

We identified 132 longitudinal studies, mostly related to aging, belonging to the NIA-DLS, IALSA, or CEHP databases (Supplementary Table 2). The challenging task of creating an inclusive database will require collaboration of experts from multiple disciplines within the aging field, bioinformatics, and funding agencies. Data harmonization, both retrospective, so as to optimize the continued use of what is likely to be terabytes of existing data, and prospective, with a keen eye toward what outcome measures serve the greatest use to the research community, should be considered as being key to these valued efforts.

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The screenshot shows the journal's homepage with a navigation menu on the left and a main content area. The 'Current Issue' section for November 2008 (Vol. 5, No. 8) is highlighted. A red arrow points to the text 'Full-text articles are available from July 2008 to the present. Access to abstracts is complimentary. Access to full text is limited to print subscribers. Non-subscribers may purchase individual articles or bundles or login to:'. A red circle highlights the 'Full-text articles' link in the 'Full-text articles' section. Other sections include 'Featured Article', 'JOURNAL ACCESS', 'RESOURCES', and 'ABOUT THE ALZHEIMER'S ASSOCIATION'.

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