Duke Twins Study of Memory in Aging in the NAS-NRC Twin Registry

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The Duke Twins Study of Memory in Aging is an ongoing, longitudinal study of cognitive change and dementia in the population-based National Academy of Sciences-National Research Council (NAS-NRC) Twin Registry of World War II Male Veterans. The primary goal of this study has been to estimate the overall genetic and environmental contributions to dementia with a specific focus on Alzheimer's disease. An additional goal has been to examine specific genetic and environmental antecedents of cognitive decline and dementia. Since 1989, we have completed 4 waves of data collection. Each wave included a 2-phase telephone cognitive screening protocol, followed by an in-home standardized clinical assessment for those with suspected dementia. For many participants, we have obtained postmortem neuropathological confirmation of the diagnosis of dementia. In addition to data on cognition, we have also collected information on occupational history, medical history, medications and other lifetime experiences that may influence cognitive function in late life. We provide an overview of the study's methodology and describe the focus of recent research.

The Duke Twins Study of Memory in Aging began in 1989 to look into the epidemiology of dementia in the National Academy of Sciences-National Research Council (NAS-NRC) Twin Registry of World War II Veterans born between 1917 and 1927. Details of the development of the Twin Registry have been described elsewhere in this and a previous issue of this journal. (Page, 2002, 2006) Due to the recruitment strategy, the Registry is comprised of all males who are largely Caucasian. In this article we (1) describe the data collection methods for the Duke Twins Study during the past 17 years, (2) summarize the content of the database, and (3) describe recent research topics.

Sample and Data Collection

Sample for Duke Twins Study of Memory in Aging

Prior to the origination of the Duke Twins Study, many of the Registry members had completed one or both questionnaires mailed from the Medical Follow-up Agency of the Institute of Medicine to the twins in the late 1960s and early 1980s (Page, 2002). However, the majority of the individuals had not been contacted by telephone or in person for studies since the Registry had been compiled. As a result, investigators at Duke University spent considerable time locating twins and updating the contact information and vital statistics for the Registry members. The initial Duke Twins Study sample was created from this work, and comprised all NAS-NRC Registry twin pairs in which both members were thought to be alive and residing in the United States in 1989. Since that time, we have completed four waves of data collection using the procedures described below. All procedures were approved by the Duke University Medical Center Institutional Review Board and informed consent was obtained at the various phases of data collection.

Cognitive Screening Protocol

Each of the four waves of data collection began with a two-phase telephone screening assessment for cognitive impairment. For the first phase, the Telephone Interview for Cognitive Status, modified for epidemiological studies (TICS-m; Brandt et al., 1988; Plassman et al., 1994; Welsh et al., 1993) was administered to screen for cognitive impairment. When individuals could not complete the phone interview for any cognitive or physical reason, either the Informant Questionnaire on Cognitive Decline in the

Received 11 August, 2006; accepted 25 August, 2006.

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Elderly (IQCODE; Jorm & Jacomb, 1989) or another brief proxy interview was administered to a close family member or friend asking about the participant's cognitive status. At each of the assessment waves, individuals scoring below a set threshold on either the TICS-m or the proxy screening instrument progressed on to the second phase of telephone screening. This entailed the administration of the Dementia Questionnaire (DQ; Ellis et al., 1998; Kawas et al., 1994; Silverman et al., 1986) to a close family member or friend of the participant to collect a chronological history of his cognitive and functional symptoms, as well as relevant medical history. Individuals for whom the information collected on the DQ indicated suspected dementia were targeted for an in-person dementia evaluation.

Figure 1 summarizes the number of subjects who participated in each phase of the study. The initial screening phase for Wave 1 was done from March, 1990 to May, 1992. In addition to cognitive screening, information about the years of education completed, ethnicity, and parental age or age at death also was gathered for all participants. For Wave 2, the initial phase of cognitive screening was done from February 1993 to April 1995. This screening was conducted under the direction of the Parkinson's Institute (Tanner et al., 1999) as part of a joint screening of the Registry for Parkinson's disease, cerebrovascular disease, eye disease, cancer and dementia. Contact was attempted with all living twins, regardless of whether their co-twin was living or deceased. The only individuals excluded from Wave 2 were participants or their co-twins who had been identified as cognitively impaired or demented at Wave 1. For the most recent two waves of data collection, Waves 3 and 4, we again screened twin pairs in which both members were living and neither twin had been identified previously as demented or cognitively impaired. The initial phase of cognitive screening for Wave 3 was done from October 1996 to October 1998 and from January 2001 to August 2002 for Wave 4. During the Wave 3 and Wave 4 telephone screening interview, additional information about lifetime experiences and exposures was collected. The topics of inquiry included marital history, occupational history, height and weight, numerous medical conditions and environmental exposures. The items were chosen primarily for their potential association with cognitive decline or dementia. Table 1 summarizes the medical conditions and environmental exposures for which information was collected.

At each wave of data collection, the co-twins of individuals assigned a diagnosis of dementia or 'cognitively impaired, but not demented' (CIND) following the clinical assessment (described below) were assessed using the DQ, regardless of their score on the TICS-m or proxy screener. Subsequently, they were followed using the TICS-m or DQ at set intervals to detect any changes in cognition.

Clinical Assessment

Individuals who were suspected of having significant cognitive impairment based on the two-stage telephone screening protocol were then assessed in-person. This evaluation was a 3 to 4 hour structured assessment conducted in the participant's residence by a nurse and psychometrician. The assessment has been described previously (Breitner et al., 1995; Plassman et al., 2000). In summary, we collected the following information about the participant from a proxy informant: (1) a chronological history of cognitive and functional changes, (2) medical history, (3) current medications, (4) current neuropsychiatric symptoms, (5) measures of severity of cognitive and functional impairment, and (6) family history of memory problems. At the same assessment, the participant completed: (1) a battery of neuropsychological measures, (2) a standardized neurological examination, (3) a blood pressure measure, (4) collection of buccal or blood DNA samples, and (5) a 7-minute videotaped segment covering portions of the cognitive status and neurological examinations.

We sought medical records from the participant's personal physician regarding evaluations for memory disorders, neuroimaging results, or records of other diagnoses that might affect cognition. We also sought to obtain relevant medical records for subjects who were either deceased prior to completion of a clinical assessment or who refused the clinical assessment. For participants who completed the clinical assessment prior to the Wave 3 screening interview, we collected the additional information about lifetime experiences and exposures in telephone interviews with the participant or his proxy informant following the in-person assessment.

Assigning a Diagnosis. All information collected at the clinical assessment and from medical records was reviewed and final diagnoses were assigned by a consensus expert panel of geropsychiatrists, neurologists, and neuropsychologists. Diagnoses fell within the three general categories of: (1) demented, (2) cognitively impaired, but not demented (CIND), and (3) cognitively normal. Table 2 summarizes the number in each diagnostic group to date. Standard criteria for dementia (American Psychiatric Association, 1987) and Alzheimer's disease (AD; McKhann et al., 1984) were used throughout the study. Current published criteria for vascular (Roman et al., 1993; Tatemichi et al., 1994) and other types of dementia were used from the time of their publication forward (Lund & Manchester Groups, 1994; McKeith et al., 1996; McKeith et al., 1999). For the diagnosis of CIND and its subtypes, we used standardized criteria that we have developed for all of our studies. (Breitner et al., 1994b; Breitner et al., 1999; Langa et al., 2005) Age of onset of dementia was assigned based on the age at which the person unambiguously met criteria for dementia. For the participants with

https://doi.org/10.1375/twin.9.6.950 Published online by Cambridge University Press

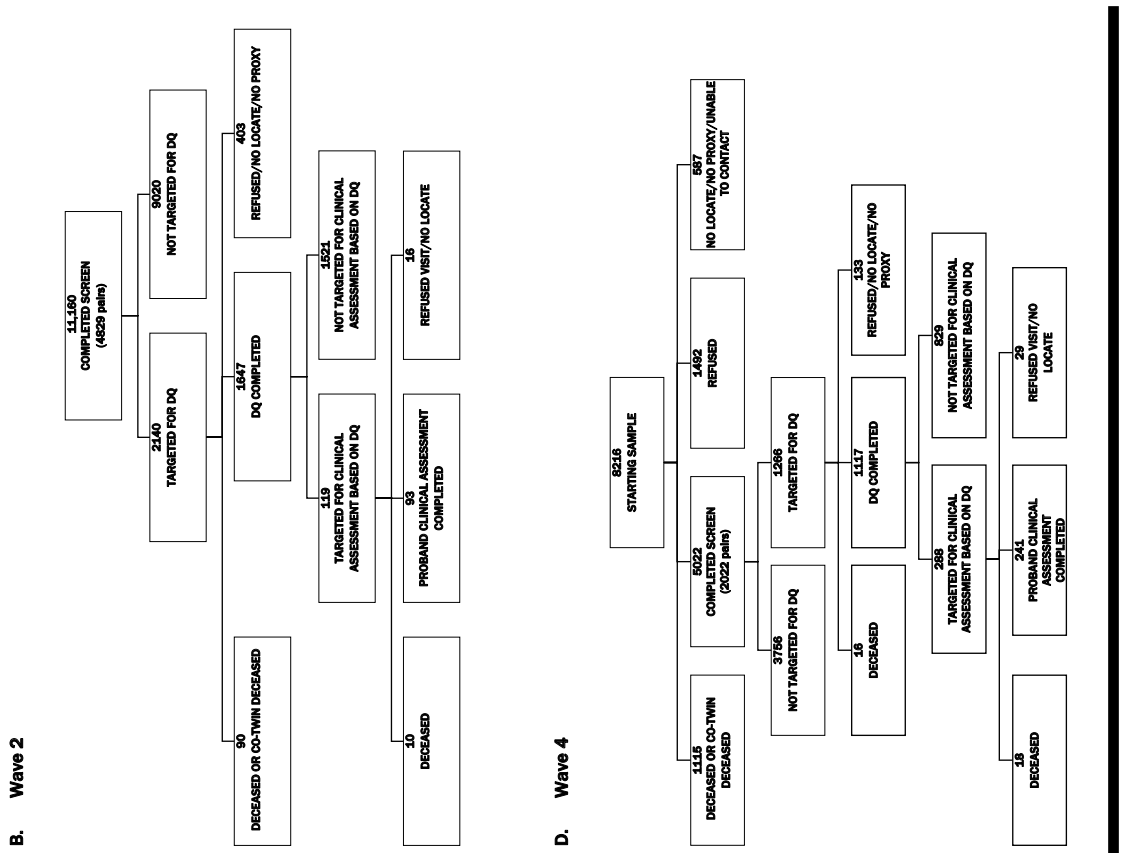

Figure 1

Flowchart of individuals participating at each wave of data collection. The number of individuals for each outcome for each phase of Waves 1–4 are reported. First level of cognitive screening was comprised of the modified Telephone Interview for Cognitive Status or a proxy screener. Wave 2 flowchart begins with the number of individuals who completed the first level of cognitive screening, as this phase of the protocol was completed by collaborators and reasons for nonparticipation at this phase are not available. Further details of the study protocol are described elsewhere in this article.

Note: DQ – Dementia Questionnaire.

https://doi.org/10.1375/twin.9.6.950 Published online by Cambridge University Press

Table 1

Selected Information Collected during Wave 3 and/or Wave 4 Telephone Interview

Topics of Inquiry	# Yes	Total *N*	%
Regular exposure to the following for at least one year:			
Metal working	953	7373	12.9
Machining	949	7373	12.9
Welding	748	7373	10.2
Foundry work	253	7373	3.4
Smelter work	77	7373	1.0
Any metals	1868	7373	25.3
Pesticides in home gardening	4184	7373	56.8
Organic solvents	4904	7386	66.6
Gasoline, kerosene, jet fuel	1458	7368	19.8
Coal tar, soot, pitch, creosote, asphalt	323	7368	4.4
Plastic, epoxy, fiberglass resins	399	7368	5.4
History of the following medical conditions or lifestyle issues:			
Parkinson's disease	149	7340	2.0
Alzheimer's disease	56	5097	1.1
Head injury	1557	7371	21.1
Seizures	115	7371	1.6
Stroke	1190	7371	16.1
Diabetes	1446	7371	19.6
Hypertension	3597	7371	48.8
High cholesterol or high triglycerides	3225	7370	43.8
Heart attack	1397	7369	19.0
Coronary bypass surgery	1097	7369	14.9
Coronary angioplasty	676	5080	13.3
Congestive heart failure	519	7369	7.0
Angina	301	5080	5.9
Thyroid disease	270	5080	5.3
Endorsed symptoms of depression	1426	7280	19.6
Tobacco use	4903	7280	67.4
Current alcohol use	2631	7280	36.1
Medical symptoms resulting from using chemicals at work	781	7368	10.6
Health problems affecting ability to perform activities of daily living and instrumental activities of daily living	4656	7363	63.2
Boxing	537	7365	7.3
Health problems limiting daily activities	4656	7367	63.2
History of Alzheimer's disease in a 1st degree relative	643	7390	8.8
History of the use of the following medications:			
Anti-inflammatory and pain medications	1923	7078	27.2
Medications for treatment of hyperlipidemia or triglycerides	1887	5062	37.3
General anesthesia	6342	7371	86.0

Note: Selected topics of inquiry in the Waves 3 and 4 telephone interviews. The number of individuals who endorsed (# Yes), the total number who answered the question (Total *N*), and the resulting percentage (# Yes/Total *N*). The values include those who responded at either Wave 3 or 4. Total *N*s vary because of missing item data at either wave or because the item was only asked at Wave 4.

suspected dementia who did not complete a clinical assessment, we reviewed all available information including medical records, DQ information, and autopsy results to assign a diagnosis.

Follow-up protocol. In the early years of the study (1990–1994) targeted probands and their co-twins were assessed in person on an annual basis. In the subsequent years, due to limited funding, individuals were visited only once if they were given a diagnosis of dementia. Those with CIND or mild to moderate dementia were followed using structured telephone interviews with a knowledgeable informant for the participant. If previously nondemented individuals were thought to have crossed the threshold for dementia

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Table 2

Cumulative Number of Individuals Assigned to Each Diagnostic Category

Clinical categories	*N*
Demented	
Alzheimer's disease (AD)	
Probable AD	114
Possible AD	164
Vascular dementia (VaD)	
Probable VaD	14
Possible VaD	49
Subcortical dementias	
Parkinson's disease	10
Normal pressure hydrocephalus	2
Other dementias	
Dementia of undetermined etiology (Breitner et al., 1994b)	62
Frontal lobe dementia	2
Dementia due to other etiologies	11
Cognitive impairment, not demented (CIND)	
Mild-ambiguous (Breitner et al., 1994b)	33
Cognitive impairment secondary to vascular disease	28
Stroke	16
Other neurological conditions	17
Other medical conditions	31
Depression	9
Psychiatric disorder	10
Low baseline intellect/suspected learning disorder	3
Alcohol abuse (past)	6
Alcohol abuse (current)	9
Cognitively normal	119
Neuropathological categories	
Definite AD	54
Possible AD	2
Vascular changes consistent with vascular dementia	3
Lewy body dementia	4
Idiopathic Parkinson's disease	4
Dementia lacking distinctive histology	1
Neuropathological changes not consistent with AD	1
Frontal–temporal lobe dementia	6
Neuropathological changes consistent with other types of dementia	2

Note: References are provided for diagnostic categories unique to the present study.

based on a telephone interview, they were then visited and received a complete clinical assessment.

DNA Collection

At the time of the in-person assessment, we attempted to collect blood or buccal samples for determination of zygosity and APOE genotype. Beginning in 1996, we collected buccal samples almost exclusively. In 1998, using a mail DNA collection protocol, we also began collecting buccal samples from the unaffected co-twins of probands. To date, we have collected DNA samples on 771 individuals. Collaborators using the Twin Registry have shared zygosity and APOE results on an additional 709 subjects in our database (Reed et al., 2005).

For the majority of twin pairs, zygosity had been determined by questionnaire, from military records (physical characteristics such as height, weight, eye and hair color), fingerprint records, and (for a small sample) blood group testing (Hrubec & Neel, 1978; Jablon et al., 1967). This method of establishing zygosity has been estimated by cross-validation with DNA to be 97 percent accurate (Reed et al., 2005). Considering zygosity from all sources, there are a total of 2798 complete monozygotic pairs, 3126 complete dizygotic pairs, and 442 pairs with unknown zygosity that have participated in the Duke Twins Study.

Autopsy

We have also obtained brain autopsy on a number of the participants. To date, we have a neuropathological postmortem diagnosis of 77 participants. We have stored fixed and frozen tissue on the majority of these individuals. We have recently reported that our assessment and diagnostic methods show an overall sensitivity of a clinical diagnosis of Probable or Possible AD of 93% and a rate of overall diagnostic agreement of 81% (Plassman et al., 2006). This rate of agreement is comparable to reports of large samples from major referral centers and university-based clinics specializing in dementia (Lim et al., 1999; Massoud et al., 1999).

Other Sources of Data

The Duke Twins Study of Memory in Aging in the NAS-NRC Twin Registry of Aging Veterans is unique in the United States as a resource for the study of aging-related changes in health and cognition. In addition to 'exposure' data from interviews conducted from 1996 to 2002, there is additional information available on the twins from two other sources. First, there is limited information, primarily on physical characteristics, from the participant's record of military service during the 1940s. For a minority of the sample, the military entrance exam scores are also available. Second, there is information about medical conditions, leisure activities, occupational stress, smoking and alcohol use, and other topics collected on mailed questionnaires in 1967, 1982, and 1998.

Current Major Research Focus

The combined information collected by the Duke Twins Study and other investigators working with the NAS-NRC Twin Registry covers a period of over 60 years and spans the majority of the life of these twins. The current perspective on the time course of AD suggests that the predisposing factors for the disease and the neuropathological changes of the disease are present years, if not decades, prior to the onset of clinical symptoms. This being the case, the collective data

https://doi.org/10.1375/twin.9.6.950 Published online by Cambridge University Press

on the NAS-NRC Twin Registry is uniquely suited to investigate antecedents for AD and other late life medical conditions.

Although a variety of topics have been investigated in the Duke Twins Study, the focus of the research has been primarily in three areas: (1) estimating the influence of genes and environmental factors in general on risk of dementia, and more specifically AD, (2) identifying specific exposures that affect onset of AD and other dementias, and (3) identifying specific exposures associated with cognitive performance in late life.

In the past, we have reported interim estimates of the heritability of AD (Meyer & Breitner, 1998; Plassman et al., 2004) in the Registry. With the advancing age of the twins and longitudinal follow-up, the number of cases of AD has increased, thus improving the precision with which we can estimate the role of genetic and environmental factors in the development of AD. We are currently preparing an update to our previous estimates on the heritability of AD.

To address the second research focus, identifying specific exposures that affect onset of AD and other dementias, we reported one of the early findings suggesting the protective role of nonsteroidal anti-inflammatory medications on risk of AD (Breitner et al., 1994a) We have also investigated the association between cognitive and physical activity during adult midlife and risk of dementia in late life (Carlson et al., 2004). Current analyses are focused on the role of various medical conditions and occupational exposures on dementia risk.

The third main area of focus for our research has been investigating specific exposures throughout the life course that influence performance on the cognitive screening measure, the TICS-m. Addressing this topic, we have reported that scores on an intelligence test in early adulthood predict performance on the TICS-m 50 years later (Plassman et al., 1995). We have also reported on the effect of a number of cardiovascular conditions and risk factors, such as coronary artery bypass graft (Potter et al., 2004), diabetes, hypertension, and hyperlipidemia (Xiong et al., 2006), on change in the TICS-m score over a several year period. Another study examined the association between the characteristics of individuals' primary occupation during their working career and longitudinal change in the TICS-m (Potter et al., 2006). This analysis capitalized on the extensive work done, as part of the study, to classify the occupational data using both the Census Occupation Codes (Minnesota Population Center University of Minnesota) and the Dictionary of Occupational Titles (DOT) codes (United States Employment Service, 1991).

The Duke Twins Study investigative team collaborates with many other researchers to extend the use of the data and to meet scientific aims. Sharing of the data is typically conducted via a collaborative process and a limited data use agreement is generally required.

Acknowledgments

We acknowledge with appreciation the staff of the Program in Epidemiology of Dementia at Duke University Medical Center for their many efforts on the project. We are grateful for the ongoing participation in the projects of the members of the NAS-NRC Twin Registry. Supported by grant from NIH-AG-08549 (Plassman), NIH R03 AG22683-01 (Potter), Alzheimer's Association NIRG-03-6072 (Potter).

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https://doi.org/10.1375/twin.9.6.950 Published online by Cambridge University Press