Twin Research and Human Genetics
Volume 16 ▌ Number 1 ▌ pp. 313–316 ▌ © The Authors 2012 ▌ doi:10.1017/thg.2012.68

Study of Dementia in Swedish Twins

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The Study of Dementia in Swedish Twins is a study of dementia in a defined population of twins. The goals included estimating heritability of Alzheimer's disease and identifying risk and protective factors in twin pairs discordant for the disease. The data, including not only diagnoses and age of onset but also extensive information about potential environmental risk factors, are now archived as Study ICPSR 25963 at National Archive for Computerized Data on Aging, Inter-university Consortium for Political and Social Research, at the University of Michigan, and available for researchers to use. Up to the time of archiving, 215 cases of dementia have been identified from a base sample of 2,394 individuals.

■ **Keywords:** twins, heritability, dementia, Alzheimer's disease, epidemiology

The Study of Dementia in Swedish Twins (sometimes referred to as 'SALZA') was launched in 1984 to identify all cases of dementia within the Swedish Adoption/Twin Study of Aging (SATSA). SATSA has been described in prior compilations of twin registers in this journal (Pedersen et al., 2002) and its predecessor (Pedersen et al., 1991). SATSA is itself a selected subset of the Swedish Twin Register (STR); specifically, SATSA is comprised of all STR twins who were separated and reared apart and a matched sample that were reared together. Because we superimposed a dementia study on an ongoing registry-based study of normal aging, the sample is population-based and is not limited to institutionalized cases or to those who have sought medical treatment.

In this article, we describe the SALZA study and available database archived at the National Archive for Computerized Data on Aging, Inter-university Consortium for Political and Social Research, at the University of Michigan, in order to encourage use by other researchers.

Sample

The SATSA population was comprehensively identified from the STR to include all reared apart pairs and a matched reared together sample. At baseline in 1984, 2,845 of these individuals were alive from a total of 1,919 pairs (3,838 individuals). However, not all twins responded to initial mailed SATSA questionnaires. For the dementia study, in addition to screening SATSA responders, we attempted to contact all of those non-responders who were born 1935 or earlier in order to have a comprehensive ascertainment of cases within this defined population. Individuals were included if they were alive in 1987 and if they were in the SATSA population as originally drawn, whether or not they had ever responded to any SATSA data collection effort, and whether or not their twin sibling was alive. The resulting base sample for SALZA consisted of 2,394 individuals.

Cognitive Screening Protocol

We employed telephone cognitive screening with non-responders. The interview protocol is referred to as TELE (Gatz et al., 1995). The TELE for twins includes a brief mental status test and questions about health and daily functioning. If twins did poorly on the cognitive screening or if we could not reach the twin, we sought to interview an informant. The informant version of TELE asks about the twin's memory and cognitive problems.

For twins participating in SATSA in-person testing, instead of telephone screening, we used their score on the Mini-Mental State Examination (MMSE; Folstein et al., 1975) that was administered as part of SATSA in-person testing. Any twin who met cutoffs on either the TELE or MMSE was invited to a complete clinical workup, as were their co-twins.

RECEIVED 24 July 2012; ACCEPTED 30 July 2012. First published online 9 October 2012.

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Screening began during the second wave of SATSA data collection and was repeated after each successive wave of SATSA in order to identify incident cases of dementia.

Clinical Assessment and Diagnosis

A physician and a psychologist visited each twin at home and completed a full clinical evaluation for dementia, including cognitive tests, physical exam, medical history, and an informant's description of the course of cognitive decline. Where possible, the twins were also referred for diagnostic neuroimaging, involving a CT at a local hospital. Individual images of the entire head were typically taken parallel to the orbitomeatal line, with CT performed without contrast unless contrast was necessary for clinical reasons. A consensus conference including members of the assessment teams and an independent clinician considered all of the information and arrived at a clinical diagnosis, including whether there was dementia present, age of onset, and type of dementia. Initially, diagnostic decisions were guided by DSM-III-R criteria for dementia (American Psychiatric Association, 1987), NINCDS-ADRDA criteria for probable and possible Alzheimer's disease (McKhann et al., 1984), and other criteria for other subtypes. As they became available, NINDS-AIREN criteria were used for vascular dementia (Roman et al., 1993), and DSM-IV (American Psychiatric Association, 2000) was used in addition to DSM-III-R.

Both members of twin pairs were followed longitudinally. Pairs where both were non-demented continued to be followed by SATSA. The same diagnostic procedures were used when incident cases were found from longitudinal evaluations of twins who had been diagnosed as not demented at first assessment or in later waves of SATSA.

Because SATSA has continued to collect data at approximately three-year intervals, we have added new cases of dementia identified at subsequent waves of SATSA. The archived database currently continues through the sixth wave of in-person testing, with dementia diagnoses through 2004. In all, 215 twins were considered demented and given a differential diagnosis for dementia.

DNA Collection

Blood collected during the clinical evaluation has been used for clinical chemistries, DNA extraction, and confirmation of zygosity using microsatellite markers (Lichtenstein et al., 2002) whenever not available from the STR or SATSA.

Questionnaires

At the time of the clinical workup, the twin and an informant were extensively interviewed with respect to family history, medical risk factors, and environmental risk or protective factors. Twins were asked to provide a comparative rating whether oneself or ones twin had greater exposure to a variety of putative risks (Reynolds et al., 2005). Questionnaire forms as well as the resulting data are included with the archived database. Additionally, all SATSA twins were asked similar questions about risk and protective factors in the third wave of in-person testing and in the fourth wave of mailed questionnaires, comprising prospective information for incident cases, and also included with the archived database.

The public-use data cover background information; ages at each data collection point; cognitive screening; clinical dementia diagnoses; cognitive test results; medical history and medical risk factors; residential, occupational, and leisure activities history; family history of dementia; and APOE genotype (see Table 1 for N of participants with each data element).

Previously Collected Data

Because SALZA twins were from the STR, data collected from STR surveys in the 1960s or 1970s provide prospective information about midlife risk or protective factors, e.g., participation in leisure activities. For those SALZA twins who participated in SATSA prior to being identified for SALZA, there are cognitive test results from the time prior to dementia onset and prospective risk or protective factors from both questionnaires, e.g., personality, and biomarkers, e.g., cholesterol levels. Further, because the STR is regularly linked with the Swedish Patient Registry, information is available about hospitalization for diseases such as heart disease or diabetes prior to dementia onset.

Research Approach

Analyses using SALZA data include estimating heritability of Alzheimer's disease (Gatz et al., 1997; Pedersen et al., 2001; Ripatti et al., 2003) and applying a discordant twin pair design to identify risk and protective factors where results from matched pairs are compared to case-control results (e.g., Gatz et al., 2001; Wetherell et al., 1999). Combined SATSA and SALZA data are analyzed with longitudinal growth and survival methods. Genetic analyses use combined data from multiple Swedish twin studies of aging.

Archiving the data makes it possible for other investigators not only to use the data for new analyses but also to pool with other dementia studies.

Subsequent Work

As described in prior special issues of this journal on twin registers (Lichtenstein et al., 2006; Pedersen et al., 2002), beginning in 1998, all twins in the Swedish Twin Registry born before 1958 were screened by telephone for the most common complex diseases in the effort known as Screening Across the Lifespan Twin (SALT) study. Several

https://doi.org/10.1017/thg.2012.68 Published online by Cambridge University Press

TABLE 1

Selected Content in the SALZA Data Archive

Variable	*N*
Background information	
Demographics: zygosity, sex, year born, rearing status	2,394
Education	2,131
Age at death (if deceased)	1,758
Cognitive screening outcomes	
Baseline (1987–1992): TELE for twin, TELE for informant, MMSE	1,469
Post-mortem interview with informant	40
Longitudinal (1990–1997)	846
Clinical diagnosis	
DSM-III-R or DSM-IV diagnosis, NINCDS-ADRDA Alzheimer's disease criteria, NINDS-AIREN vascular dementia criteria dementia $N = 158$ questionable dementia $N = 75$ not demented $N = 90$	323
Clinical Dementia Rating (CDR)	154
Autopsy diagnosis	25
Additional dementia cases identified through 2004	57
Age of onset of dementia	215
Familial risk	
Family history of dementia (for pairs where one or both were demented)	231
APOE genotype	607
Cognitive tests and psychological assessment	
Baseline: Block design (Koh's), Clock test, Coin test, Comprehension (WAIS), Depression (CES-D), Digit Span, Figure copying (CERAD), Figure identification, Figure logic, Information (WAIS), Logical memory, Swedish apartment test, Swedish naming, Symbol-digit, Synonyms, Thurstone Picture memory, Verbal fluency (CERAD), Word list recall/recognition (CERAD)	188
Informant reported: Blessed Dementia Rating Scale, Depression (CIDI-SF)	147
18 months follow-up	58
36 months follow-up	53
54 months follow-up	14
72 months follow-up	17
Medical history and medical risks: Cases and controls	
Blood pressure	134
Labs (thyroid, folate, hemoglobin)	128
Smell survey (National Geographic)	99
Informant reported: neurologic, coronary, psychiatric diseases; head injury; loss of consciousness; fevers; allergies; exposure to radiation (X-rays, CTs), anesthesia; aspirin, antacids, medications for arthritis, blood pressure, depression; alcohol use; smoking	217
Self-reported	131
Medical risks: Prospective	
Self-reported: head injury; loss of consciousness; anesthesia; psychiatric medication	1,450
Environmental risks: Cases and controls	
Informant reported: residential history; presence of well water at residences and vacation homes; travel; exposure to organic solvents, painting, welding, hairdressing, agriculture, pesticides, aluminum, crystal, carbon monoxide, radiation, raw meat and game; participation in contact sports; dietary history with respect to fish, baked goods, acidic foods prepared in aluminum pans	229
Self-reported	126
Comparative risk (which twin had the greater exposure)	58
Informant reported occupational history (jobs coded according to NYK 78 (Nordic Occupational Classification)	231
Self-reported occupational history	75
Environmental risks: Prospective	
Self-reported: exposure to organic solvents, painting, welding, hairdressing, pesticides, crystal, carbon monoxide, radiation; participation in contact sports; dietary history with respect to acidic foods prepared in aluminum pans; presence of well water	1,450
Comparative risk	536
Residential and occupational history	512

Note: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CES-D = Center for Epidemiologic Studies-Depression; CIDI-SF = Composite International Diagnostic Interview Short Form; DSM-III-R and DSM-IV = Diagnostic and Statistical Manual for Mental disorders, 3rd edition revised and 4th edition; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherché et l'Enseignement en Neurosciences; WAIS = Wechsler Adult Intelligence Scale.

studies with additional data collection from twins with a specific disease were launched, including an expanded Study of Dementia in Swedish Twins (Gatz et al., 2005), known as HARMONY. Data from HARMONY for SALZA twins are included in the SALZA archive. Other HARMONY data are presently being prepared for data archiving at the National Archive for Computerized Data on Aging, but meanwhile are being used in multiple international collaborations.

Acknowledgments

The Study of Dementia in Swedish Twins and its archiving have been supported by the National Institutes of Health (Grants No. R03-AG031262, R01-AG08724, R01-AG04563, and R01-AG10175) and the Alzheimer's Association (ZEN-02-3895). For assistance with archiving, we thank James McNally at the National Archive for Computerized Data on Aging and Ellen Waters at USC. We thank our many

https://doi.org/10.1017/thg.2012.68 Published online by Cambridge University Press

co-investigators and collaborators who have been part of the Study of Dementia in Swedish Twins, including: Gerd Agerberg, Anders Ahlbom, Stig Berg, Amy Fiske, Boo Johansson, Kurt Johansson, James A. Mortimer, Samuel F. Posner, Chandra A. Reynolds, Matti Viitanen, and Bengt Winblad. We gratefully acknowledge the nurses, psychologists, and physicians who conducted the clinical assessments and especially the twins for their generosity in volunteering to participate in this work.

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