

The Vietnam Era Twin Registry

Jack Goldberg^{1,2}, Birute Curran¹, Mary Ellen Vitek³, William G. Henderson³, and Edward J. Boyko^{1,2,4}

¹VET Registry, Seattle Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA

²Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA, USA

³Hines VA Cooperative Studies Program Coordinating Center, Hines, IL, USA

⁴Department of Medicine, School of Medicine, University of Washington, Seattle, WA, USA

The Vietnam Era Twin (VET) Registry is composed of 7369 middle-aged male-male twin pairs both of whom served in the military during the time of the Vietnam conflict (1965–1975). The Registry is a United States Department of Veterans Affairs resource that was originally constructed from military records; the Registry has been in existence for more than 15 years. It is one of the largest national twin registries in the US and currently has subjects living in all 50 states. Initially formed to address questions about the long-term health effects of service in Vietnam the Registry has evolved into a resource for genetic epidemiologic studies of mental and physical health conditions. The management and administration of the VET Registry is described with particular attention given to the processes involved with database maintenance and study coordination. Several waves of mail and telephone surveys have collected a wealth of health-related information on Registry twins. More recent data collection efforts have focused on specific sets of twin pairs and conducted detailed clinical or laboratory testing. New Registry initiatives for the future include the construction of a web site and the development of a DNA repository.

Twins are a unique resource for research in helping to understand the genetic and non-genetic contribution to health and disease. In the Nordic countries, such as Sweden (Cederlof et al., 1970), Finland (Kaprio et al., 1987), Norway (Kringlen, 1978), and Denmark (Kyvik et al., 1996), registries of twins have existed for many generations. These registries have proven invaluable in teasing apart questions about the interplay of genes and environment in understanding complex diseases. In the United States there is a paucity of twin registries and this has been a serious impediment to research. Currently no formal national twin registry exists, though several states possess registries, such as Minnesota (Lykken et al., 1990), Missouri (Todd et al., 2001) and Virginia (Corey et al., 1991). The largest national twin registry in the US is the National Academy of Sciences Medical Follow-up Agency (MFUA) WW-II Twin Registry (Jablon et al., 1967). The MFUA Twin Registry was compiled in the 1960s and consists of approximately 16,000 white male-male twin pairs who both served in the military during the second World War. This Registry of elderly veterans has been used to study numerous diseases and conditions, including cardiovascular disorders (Feinleib et al., 1977) and more recently Parkinson's disease (Tanner et al., 1999) and Alzheimer's disease (Gallo & Breitner, 1995). The Vietnam Era Twin (VET) Registry is the only other national registry of twins in the US (Eisen et al., 1987; Henderson et al., 1990). Below

we provide a brief history of the VET Registry. This is followed by a presentation of the methods used to manage the VET Registry and the types of studies that have been conducted using this resource. We close with a description of plans for the future.

Method and Materials

Origins of the VET Registry

In the early 1980s the long-term health effects of military service during the Vietnam conflict was a cause of deep concern to many veterans. During the Vietnam era (1965–1975) a total of approximately 9 million individuals served on active duty in the U.S. military and approximately 3 million served in Vietnam. Numerous large federally supported studies by the Centers for Disease Control (Centers for Disease Control, 1987) and the Department of Defense (Wolfe et al., 1990) sought to investigate the long-term post-discharge effects of military service on the health of Vietnam veterans. A particular concern was the effects of Agent Orange, a defoliant used in Vietnam that was contaminated with the toxin dioxin (Wolfe et al., 1990). Sparked by a suggestion from Irving Gottesman and in response to a solicitation for studies on the health of Vietnam era veterans by the Department of Veterans Affairs (then the Veterans Administration), Seth Eisen, MD and William True, PhD submitted a proposal to study Agent Orange effects using veteran twin pairs. This project, as originally conceived, was to perform a comprehensive health examination of monozygotic twin pairs where one member of the pair served in Vietnam while the other member was in the military but did not serve in Vietnam. The VA authorized funding for planning the project in greater detail and decided that because of its size and scope, it should be managed by the VA Cooperative Studies Program under the direction of William Henderson, PhD.

As the planning process for the twin study moved forward the project was divided into two components: 1) the development of a twin registry, and 2) the clinical examination of Vietnam discordant twins. The purpose of the twin registry was to establish a list of veteran twin pairs that could

Address for correspondence: Birute Curran, VET Registry Coordinator, Seattle ERIC/VET Registry (MS 152E), VAPSHCS, 1660 South Columbian Way, Seattle, WA 98108-1597, USA. Email: birute.curran@med.va.gov

be used for the clinical examination component of the study. It quickly became apparent that identifying twins who served in the military was a daunting task and not easily accomplished (Eisen et al., 1987). The military did not collect information about whether a particular serviceperson is a member of a twin pair. Further, even once a twin was identified from the military records they would have to be contacted to determine zygosity. It should be noted that after careful consideration by the VA the second component of the original twin project involving the clinical examination of Vietnam discordant twins was never undertaken.

Identification of Vietnam Era Veteran Twins

Numerous possible twin finding strategies were analyzed (Eisen et al., 1987) and it was ultimately decided that the best approach was to use computerized records maintained by the Department of Defense (DoD), supplemented with VA computer files. It was during the Vietnam era that the DoD began to computerize their record keeping and not all discharged veterans were contained within the files; each branch of service (Army, Navy and Marines, Air Force, Coast Guard) transitioned from the old pencil and paper systems to computerization at different times during the era. The DoD estimated that roughly 5.5 out of the 9 million Vietnam era veterans were included in their systems. With help from the DoD, a computerized record linkage methodology was developed that identified pairs of records that had a reasonable probability of being twins. The algorithm that was used involved the following criteria: males, born between 1939–1957, served on active duty during the Vietnam era (the interval 1965–1975), same last name, different first name, same date of birth, and same first 5 digits of the Social Security Number (Goldberg et al., 1993). In total 15,711 potential Vietnam era veteran twin pairs were identified using the matching algorithm.

All military records of discharged veterans are maintained at the National Personnel Records Center (NPRC) in St. Louis. The records of veterans from the Vietnam era are all stored in hard-copy format and take up approximately seven shelf-miles of space. There is no central computer file at NPRC aside from a crude index that serves as a pointer to the hard-copy storage location for the record of a particular veteran. The hard-copy military record for each of the potential twin pairs was retrieved. Within the hard-copy record for each veteran is his place of birth and the full names of both parents. Twinship was confirmed when there was an exact match on place of birth and parental names. In total, 7369 twins were confirmed from the initial pool of potential twins identified from the record matching. These twins form the core of the VET Registry.

Management of the VET Registry

From the initiation of the VET Registry it was recognized that it would be a national resource with broad interest for VA and non-VA scientists. Because of this it was felt essential that systems be put into place that would safeguard the Registry and ensure that the resource be maintained for the future. Below we describe some of these systems.

Maintaining registry files. The Registry records are maintained in two formats: hard-copy and electronic medium.

A limited set of hard-copy records are kept and include access agreements and consent forms signed by the twin pairs. All identifiable hard-copy records are maintained in locked filing cabinets. Three different electronic databases are maintained by the VET Registry. The first database contains name and address information useful for locating and contacting individual twins. This database also contains both the permanent Registry identification number and unique identification numbers that are assigned for specific studies. This database permits the Registry to link information across different studies so that critical data elements (i.e., age, zygosity, etc.) can be appended for data analysis. The database is maintained off-line in a secure locked filing cabinet and only used when necessary to contact twins and merge Registry data.

A second database contains the information on participation of each twin in specific projects; this allows for a simple and easy way to respond to inquiries about the availability of twins with a particular set of data elements. The third database represents the study specific information on individual research projects that have collected data from the twins. This study database has grown to include thousands of individual data elements that have been ascertained from the twins during the history of the Registry.

Confidentiality of the VET Registry databases has been maintained for more than 15 years. The systems for assuring confidentiality have continued to evolve and are being refined over time. Current policy has all investigators and staff at the Registry and each participating institution sign an access agreement with the Registry. This document explicitly states that access to VET Registry data and twins is a privilege granted by the Registry director. The access agreement informs investigators that they are obligated to treat Registry twins in a professional and ethical manner and that they must maintain the highest standards of scientific integrity during data collection. It further stipulates that all publications derived from VET Registry data must acknowledge the Registry and that a complete copy of all newly collected data must be provided to the Registry at the completion of the study.

Registry staffing. The VET Registry maintains a core staff of four individuals: a director, a staff epidemiologist, a Registry coordinator and a computer programmer. The director and epidemiologist provide general scientific direction for the Registry. The Registry has maintained a policy that all manuscripts written using VET Registry data are reviewed by the director prior to submission to a scientific journal. Similarly, all conference presentations or abstract submissions are required to be submitted to the Registry. The Registry coordinator is chiefly responsible for all day to day administrative activities. This includes interactions with investigators currently using the Registry and the twins themselves via a toll free number. The programmer maintains the Registry databases and provides updates and analyses as needed.

Registry access fees. In the early years of Registry creation and development the VET Registry was fully subsidized by the VA. During the first 5 years of the Registry's existence investigators using the Registry were not assessed an access

fee or the fee was nominal. However, the Registry is now primarily supported by access fees from individual research projects. These access fees are used to provide the administrative support necessary for the management and smooth functioning of the Registry. The standard Registry access fee for National Institutes of Health supported grants is currently \$35,000 (US) per year plus indirect costs of approximately 5%; grants from the VA are charged \$20,000 per year and indirect costs of approximately 5%.

Advisory committee. The VET Registry maintains an Advisory Committee to assist the Registry director. The Advisory Committee is made up of 5–6 senior scientists in the fields of genetics, twin research, medicine, psychiatry, epidemiology and biostatistics. The role of the Committee is to provide external review of all registry studies and broad direction to the Registry on matters of policy. Each new study that is applying for external support must undergo formal review by the Advisory Committee; this applies to studies that will be collecting new data and to secondary data analysis projects using already existing Registry data. The Committee's charge is to determine the scientific merit of a particular study and the need to involve Registry twins. The Advisory Committee has no role in determining funding since the Registry does not provide external funding for research. The Advisory Committee also examines issues of overlap amongst studies and suggests ways of reducing respondent burden by combining similar projects. The Committee meets once a year in-person and conducts periodic conference calls on an as-needed basis.

Registry newsletter. At the recommendation of the Advisory Committee the VET Registry established a newsletter that is mailed to all twins. The newsletter serves multiple purposes: 1) it provides direct feedback to the twins about the results of studies in which they have participated, 2) it helps to maintain the interest of the twins in the Registry and likely increases the probability that they will continue to participate in new studies, and 3) it is a way for the Registry to maintain contact with the twins and to obtain address updates. A newsletter is mailed to twins approximately every two years. The twins have provided positive feedback regarding the newsletter and many of them request copies of scientific manuscripts that are abstracted in the newsletter.

Types of Studies

The VET Registry receives numerous inquiries from investigators for potential studies involving the twins. These inquiries are initially handled by the Registry coordinator and are then passed on to the Registry director and epidemiologist. Investigators are told that direct contact between an investigator and the twins is not permitted without prior written agreement from the twins. If the investigator is interested in developing a new study using the twins the Registry coordinator then describes the process. After a new study obtains funding and is approved by the Advisory Committee, the Registry staff, and the investigator develop a data collection plan. Twins are typically allocated to data collection in batches that represent a third or quarter of the total needed. This allows the

Registry to monitor data collection activities and balance the competing needs of multiple studies for access to twins.

The Registry strictly prohibits investigators from having direct access to twins. All contact with Registry twin pairs is either by Registry staff or through an approved third party contractor. The third party contractor serves as an intermediary between the investigator and the twins and works in close coordination with the Registry. The third party contractor must sign a letter of agreement regarding the privacy and confidentiality of information collected from the twins. The Registry provides twin names, addresses and telephone numbers to the third party contractor in order to contact twins. This personal information can never be released to investigators and all data collected, after being transmitted to the Registry, must be destroyed by the third party contractor.

Survey or Interview Projects

After full human subjects approval an informational letter is mailed to Registry members describing the new survey project on VET Registry letterhead. This letter bears signatures of the Registry Director, the investigator and the project leader at the third party contractor. The twins are provided with complete and accurate information about any new study before they are asked if they are willing to participate. The Registry maintains strict control on how twins can be solicited for individual research projects. Twins who have agreed to participate in any study are permitted to withdraw at any time. If the project is solely based on a mailed questionnaire then the survey questionnaire is included with the letter sent to the twins along with a business reply envelope. If it is a telephone survey the twins are told that within 2–3 weeks they will receive a telephone call to conduct the interview. Sometimes twins are provided with an appointment letter that they can return indicating the dates and times that are best to call them.

In-person assessments

Following human subjects approval an informational letter is mailed to Registry members describing the new in-person assessment protocol. This letter bears the signature of the Registry director, the investigator and the project leader at the third party contractor. This letter is on VET Registry letterhead stationery and describes the study to the twins. The mail-out packet also contains a release form for twin signature and an actual consent form for the in-person assessment protocol. The consent form is for informational purposes only. The twin is asked to sign and return the release form which authorizes the Registry to release their name to the investigator to provide more information about the in-person assessment to the twin and, if he is agreeable, schedule the assessment. The signed release form is then forwarded to the Registry by the third party contractor. It is only when the signed release forms are obtained from *both* members of a pair that the identifying information is released by the Registry to the investigator. The in-person assessments in the past have typically involved the twins traveling, usually by airplane, to the home institution of the investigator. The process of scheduling the twins for the in-person assessments is very complex and tends to take several months after the signed

release forms are obtained. In general the twins have been examined at the same time but this is not a requirement.

Results

Full VET Registry Data Collection Initiatives

The twin identification process from military records took approximately 3 years from 1983–1986. Since that time there have been four research initiatives that have attempted to collect information from all twins on the VET Registry. We present a snapshot of data available from the: a) 1983–1986 Registry military record, b) 1987 Survey of Health, c) 1991 National Heart Lung and Blood Institute Survey, d) 1993 Harvard Twin Study of Substance Abuse, and e) 1999 Male Health Survey.

Military Record Information

Data were abstracted from the veteran military records as part of the construction of the VET Registry (Eisen et al., 1987). The limited set of variables included: date of birth, date of enlistment into the military, rank at enlistment, education at enlistment, height, and weight at enlistment, blood pressure, medals received, and date of discharge.

1987 Survey of Health

The 1987 Survey of Health represented the first direct contact with the twin pairs. A 24-page survey was developed that assessed a broad range of health outcomes. The survey was designed to serve several purposes, the first being most critical: 1) define the zygosity so that monozygotic and dizygotic twins could be reliably distinguished (Eisen et al., 1989) and 2) assess the most likely health-related long-term consequences of service in Vietnam (Eisen et al., 1991; Goldberg et al., 1990). Data collection was by mail with telephone follow-up for non-responders. Data items include: zygosity, combat exposure, symptoms of posttraumatic stress disorder, physical health problems, cigarette smoking and alcohol consumption, marriage and divorce history, and number of children. In total 10,979 individuals responded to the mail and telephone survey for a 74% response rate; the pairwise response rate for twins was 64% representing approximately 4774 pairs where both responded.

1990 National Heart Lung and Blood Institute Survey

In 1990 the National Heart Lung and Blood Institute contracted with the VA under an inter-agency agreement to

Table 1

Summary of VET Registry Data Collection Projects

Study Name	Type of Study	Recruitment Period	Number Participated	Complete Pairs
Registry Construction				
Military Records	Record Abstracts	1983–1986	14,750	7375
Surveys of the Full Registry				
Survey of Health	Mail/ Telephone Follow-up	1987	10,979	4774
NHLBI VET Study of Cardiovascular Disease	Mail/Telephone Follow-up	1990	8870	3698
Harvard Twin Study of Drug Abuse and Dependence	Telephone	1991–1993	8169	3372
Male Health Survey	Mail	1999	5349	1615
Studies of Selected Twins				
Impulsivity and Aggression	Mail/Telephone Follow-up	1992	796	314
Consequences of Drug Abuse	In-person	1995–1996	254	127
Alcohol and Health Services Utilization	Telephone	1995	2936	—
Biologic Markers for PTSD	In-person	1995–98	322	161
	Telephone	1995–96	2003	322
Alcohol Vulnerability	In-person	1997–99	760	380
PTSD Sleep Study	In-person	Ongoing	11/22	9
	Telephone	Ongoing	207/248	248
Family Alcohol Study	Telephone and Mail	Ongoing	533	214
PTSD MRI Study 1	In-person	Ongoing	48	45
PTSD MRI Study 2	In-person	Ongoing	52	—
New Studies of Selected Twins				
Pathological Gambling	Telephone	Newly Funded	2510*	1255*
Spirituality and PTSD	Mail	Newly Funded	510*	255*
Cardiovascular Disease and Depression	In-person	Newly Funded	320*	160*
Teenage & Young Adult Offspring of Drug-Dependent Twins	Telephone and Mail	Newly Funded	1060*	530*

Note: *Projected

conduct a mailed and telephone survey of the VET Registry twins to obtain data on disorders of interest to the Institute. A 24-page survey was developed in collaboration with staff at NHLBI. The data items include: cardiovascular risk factors, self-reported heart, lung and blood disorders, sleep problems, diet and exercise (Fabsitz et al., 1997). In total 8870 individuals responded to the mail and telephone survey; and this resulted in 3698 pairs where both responded.

1993 Harvard Twin Study of Substance Abuse

This study was initiated in 1993 to study the genetics of substance abuse. All data were collected by telephone interview using the Diagnostic Interview Schedule (Robins et al., 1981) to assess a wide variety of psychiatric disorders according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM III-R*; American Psychiatric Association, 1987). This interview included 15 psychiatric diagnoses, such as: alcohol and drug abuse (Tsuang et al., 1996), posttraumatic stress disorder, depression, and antisocial personality. In total 8169 individuals responded to the telephone interview resulting in responses from 3372 complete twin pairs.

1999 Male Health Survey

This study was initiated in 1999 with internal support from the VA. All data were collected by a two page mail survey as part of the VET Registry newsletter. The brief survey focused on issues related to male health, such as symptoms of urinary tract problems and erectile dysfunction. In total 5349 individuals responded to the survey which resulted in 1615 complete pairs.

Data Collection Using Selected Twin Pairs

Nine separate studies have been completed using selected subsets of VET Registry twins. The type and size of these studies has varied markedly. Three of the studies have collected data using mail and/or telephone surveys; the remaining have involved in-person assessments where the twins travel for a clinical assessment. The size of the studies ranges widely from 9 pairs to several hundred. All of the studies using selected samples have focused on mental health with several involving post traumatic stress disorder (PTSD), alcohol and substance abuse. The participation of twins in these studies has generally been very good with a greater than 70% response rate in telephone surveys. For studies that involve travel a 50% pairwise participation rate is typically observed, though this varies with the complexity and length of the clinical protocol.

Several new studies have recently obtained funding and data collection has just been initiated. These new studies continue to focus on mental health issues and involve a mix of data collection methodologies including mail, telephone and in-person assessments. Coordination and planning for data collection amongst these new studies is now underway at the Registry.

Discussion

The VET Registry has been a highly productive resource for genetic epidemiologic studies. As custodian of the Registry, the VA is responsible for managing the resource

and maintaining its viability for the future. The Registry has evolved over time and the number and type of studies has increased in size and complexity. While the first studies that used the Registry collected data by mail and telephone interview it is now common for projects to involve clinical and laboratory assessments.

A number of systems have been implemented to manage the VET Registry. These systems include a set of databases that are secure and allow ready identification of twin participation in current and previous research projects. A newsletter is used to stay in regular contact with twin pairs and provide feedback to the twins. An Advisory Committee of senior scientists provides oversight to the Registry and conducts an external review of all new projects. Human subject protections are in place that strictly limit access to twins and require projects to use approved third party contractors to serve as intermediaries between the investigators and twin pairs.

The VET Registry is actively pursuing several new directions for the future. As the twins age it is likely that new projects will be initiated that focus on the common physical health problems of older age. The Registry is seeking projects studying chronic diseases such as hypertension, diabetes, heart disease, and arthritis. Within the next year the Registry will be establishing a web site that provides information to researchers and VET Registry twin pairs. The Registry will also be conducting a mortality follow-up of all twin pairs originally identified using the US National Death Index and obtaining cause of death information. Plans are currently under development to collect DNA from all twins and establish a permanent resource for new studies.

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