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The Vietnam Era Twin Registry: A Quarter Century of Progress

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Now celebrating its 26th year of existence, the Vietnam Era Twin Registry continues to be one of the largest national samples of adult twins in the United States. The Registry twin member population is composed of 7,369 US male–male twin pair Veterans (14,738 total individuals) who served on active duty in the military during the Vietnam conflict (1964–1975). The Registry also maintains a register, data repository, and a biospecimen repository. Details on the operations of the Registry are described, as well as an overview of specific studies. Registry maintenance activities are also described, including the updating of contact information and vital status. Future plans include expanding the biospecimen repository and obtaining input from twins about study methods and diseases and conditions they would like to see investigated.

■ **Keywords:** twins, Veterans, Vietnam, aging, repository, epidemiology, genetics

The Vietnam Era Twin (VET) Registry is a national sample of US male–male twin pair Veterans who served on active duty in the military during the Vietnam conflict (1964–1975). The Registry, now celebrating its 26th year of existence, is one of the largest national samples of adult twins in the United States. During the past 3 decades the VET Registry has served as the platform for genetic epidemiological studies of the health of Veterans. Several waves of mail surveys, telephone interviews, in-person data collections, and secondary data analysis studies have investigated a wide range of both physical and mental health phenotypes.

The aims of this article are: (1) to describe the mission, goals, and operations of the VET Registry; (2) to present an overview of the data and biological resources maintained by the Registry; and (3) to discuss the future direction of the Registry.

Methods and Materials

Brief History of the VET Registry

During the early 1980s, the VET Registry was formed through a search of computerized records maintained by the Department of Defense and supplemented by the Department of Veterans Affairs (VA) database files. The initial purpose of creating the twin Registry was to establish a database of Veteran twin pairs, so that the long-term health effects of those that served in the military could be studied (Goldberg et al., 2002). A total of 7,369 male–male twin pairs (14,738 individuals) were identified, based on several criteria. The twins all had to have been born between 1939 and 1957 and both had to have served in the military during the time of the Vietnam conflict (1964–1975). A more detailed description of the construction of the VET Registry and identification of twins is available in a previous article (Goldberg et al., 2002).

The VET Registry also includes 2,251 presumed biological adult offspring of the twins (~50% male and ~50% female) and 1,336 biological, adoptive, and stepmothers of these offspring. The non-twin groups were added to the Registry in the late 1990s as part of a set of VET Registry family studies of substance use. The adult offspring were born between 1971 and 1992, and the mothers were born between 1951 and 1963. A more complete description of the

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adult offspring and mothers can be found in a previous article (Jacob et al., 2003) and the remainder of our discussion focuses on the twin members of the VET Registry.

Register, data, and biospecimen resources. Registry resources include individually identifying information (name and contact information), a data repository, and a biospecimen repository. The data repository is comprised of two primary types of information obtained about a twin member: non-genetic and genetic data. Non-genetic data come from several sources such as information collected directly from a twin or collected about a twin, such as study completion or refusal information. Other sources of non-genetic data include information extracted from public or private databases about a twin and data derived from biospecimen samples, such as blood chemistries. Genetic data are generated from biospecimen samples, which could include information resulting from the total genetic content in a cell, such as genome-wide markers or sequence data. The data repository also includes information derived from any of those resources. As a whole, the data repository contains a rich body of health and disease phenotypes, including longitudinal data on many of those phenotypes such as post-traumatic stress disorder (PTSD), body mass index, diabetes, cardiovascular disease, depression, and substance use. The biospecimen repository houses DNA, plasma, and serum obtained from twin members. Presently, there are 3,015 samples of both DNA and plasma from 1,798 individuals, or 890 complete twin pairs; 1,163 serum samples from 1,161 individuals, or 547 complete twin pairs, are also stored with the Registry.

Organization and Operations of the VET Registry

Mission and goals. The mission of the VET Registry is to advance scientific knowledge of Veteran health by promoting collaborative research between members of the Registry and its investigators. The goals of the VET Registry are: (1) to promote outstanding scientific research using the VET Registry; (2) to safeguard the VET Registry for current and future generations of scientists to investigate the genetic and non-genetic causes of disease in Veterans; (3) to maintain a secure and updated Registry database and biospecimen repository that includes health-related information collected from Registry members participating in research; and (4) to treat Registry members with dignity, respect, and deep appreciation for their participation.

Organizational structure overview. The VET Registry is located at the Seattle Epidemiologic Research and Information Center (ERIC), located at the Seattle Division of the VA Puget Sound Health Care System. The Seattle ERIC is a research center within the Cooperative Studies Program, which is part of the Clinical Sciences Research & Development service within the Office of Research & Development, based in the VA Central Office in Washington, DC. All of these programs reside within the Veterans Health Administration, a subdivision of the VA.

Access to the Registry. The VET Registry and its data and biospecimen repositories are open for access to qualified VA, VA-affiliated, and non-VA investigators working for not-for-profit, academic, and research centers. Researchers representing for-profit entities are considered on a case-by-case basis. Student researchers are required to have appropriate sponsorship and mentorship.

Scientific Ethics and Oversight Committee. The Registry maintains an external Scientific and Ethics Oversight Committee (SEOC) to assist the Registry Director in ensuring the goals of the VET Registry are met. The SEOC consists of senior scientists in the fields of genetics, genomics, twin research, medicine, psychiatry, epidemiology, and biostatistics. Any study that is seeking access to the Registry must submit an application package that is reviewed by the SEOC. The SEOC considers the scientific merit of the study and the study's contribution to a balanced research portfolio for the Registry. The SEOC also examines the availability of Registry resources, including members, data or biospecimens, level of subject burden, ethical treatment, and privacy implications to members. The SEOC has no role in the funding of Registry studies.

Privacy, Confidentiality, and Data Security

It is a top priority of the VET Registry to keep the Registry members' information confidential, secure, and protected. In 2008, the Registry obtained a Certificate of Confidentiality from the National Institute of Health (NIH). The NIH Certificate of Confidentiality protects the members' privacy by allowing the Registry to refuse disclosure of names or other identifying information of members to anyone outside of the research project and institution, even by a court subpoena.

VET Registry Consent Process

When the VET Registry was created in the 1980s, it underwent human subjects review by a VA Cooperative Studies Program Human Rights Committee. The Committee determined that formal written consent was not required and that consent was implied by virtue of members' willingness to respond to a mail or telephone survey. In June 2007, following a review of VET Registry operations by the VA's Office of Research Oversight, it was decided to update the VET Registry consent process. The updated consent process involved mailing information sheets to all VET Registry members. The information sheets provided a detailed description of what it means to be a member of the VET Registry. Through this process, 96% of all twin members completed the updated consent process and only 4% of twin members withdrew their participation from the VET Registry.

Types of Studies and Recruitment

The VET Registry supports a wide variety of research, including primary data collection and secondary data analyses. Below we provide an overview of the Registry processes used for conducting mailed survey, telephone interview, in-person assessment, and secondary data analysis projects.

Mailed survey. For a mail survey study, an introductory letter is mailed to Registry twin members describing a new study on VET Registry letterhead. This letter bears signatures of the Registry Director, and if appropriate or requested, the study investigator and the third party contractor project lead. Twin members are provided with complete and accurate information about any new study before they are asked for their consent to participate. If the project is solely based on a mailed survey, the survey may be included with the letter sent to the participant along with a postage-paid business-reply envelope.

Telephone interview. In a telephone interview study, the twin members are first sent a packet of information by mail that includes an introductory letter describing the new study. The letter informs the twin members that if they are interested in participating, they should return the opt-in form with best times to call them, and that they will then receive a follow-up telephone call to schedule the interview.

In-person assessment. Initial contact about a new in-person study is by mail with an introductory letter informing twin members of an upcoming study. The mail-out packet also contains a permission-for-study contact form for twin member signature and may also contain a prototype of the consent form for the in-person assessment protocol. The member is asked to sign and return the permission form that then allows the Registry to forward their name to the investigator. The in-person assessments in the past have typically involved twin members traveling, usually by airplane, to the home institution of the investigator. In general, twin pairs have been examined at the same time, but this is not always a requirement.

Secondary data analysis. Some study investigators request specific phenotypic and/or genotypic variables from the VET Registry data repository. The VET Registry extracts the requested variables for the study investigator. Then the study investigator is sent a coded data set, without individually identifiable information on twin members, for the secondary data analysis study.

Respite periods. In the interest of ensuring members are not burdened by excessive invitations to take part in Registry studies, and to minimize potential confusion about multiple study participation, the VET Registry monitors the timing and frequency of study recruitment. Generally, the respite period between studies that require member contact is 6 months. In other words, there are several months between the end of the twin member's involvement in one study and the enrollment in another study. Subject burden and the rights and welfare of members are the first priority when determining the length of a respite period.

An Overview of Specific Registry Studies

Over the past 3 decades, there have been 66 studies that have investigated the physical and mental health of Registry twin members. We summarize some of these studies and also provide details about study participation.

Registry-Wide VET Registry Studies

Five VET Registry studies have attempted to collect data from all Registry twin members in the VET Registry: 1987 Survey of Health (SOH), 1991 National Heart Lung and Blood Institute (NHLBI) Survey, 1993 Harvard Twin Study of Substance Abuse, 1999 Male Health Survey, and 2012 Veterans Health Study (VHS). We briefly discuss the first four studies (more details on these studies can be found in a previous report [Goldberg et al., 2002]) and give a more complete description of the recently completed 2012 Veteran Health Study.

1987 SOH. In 1987, the first major survey was conducted by the VET Registry. The SOH involved completion of a 24-page mail survey that contained self-report questions about zygosity, general health, and several specific physical and mental health phenotypes. Three mailings and a telephone follow-up of non-responders were conducted to increase participation. Overall, a total of 10,979 individual twins responded (74% individual response rate) that included 4,774 complete pairs (pair-wise response rate of 64%; Goldberg et al., 1990).

1990 NHLBI Survey. The NHLBI Survey was a 25-page mail and telephone survey, which focused on risk factors and disorders related to heart, lung, and blood disorders. The study achieved an individual response rate of 75% (Lauderdale et al., 1997). In total, there were 8,870 individual twins who responded to this survey, 3,698 of which were complete pairs.

1992 Harvard Twin Study of Substance Abuse. The third major study of twin members was the Harvard Twin Study of Substance Abuse, more commonly referred to as the Harvard Drug Study (HDS). The HDS collected information on a variety of psychiatric disorders including depression, PTSD, and substance use disorders using a telephone survey. A total of 8,169 individual twins, of which 3,372 were complete pairs (pair-wise response rate of 66%), completed the telephone interview (Tsuang et al., 1996).

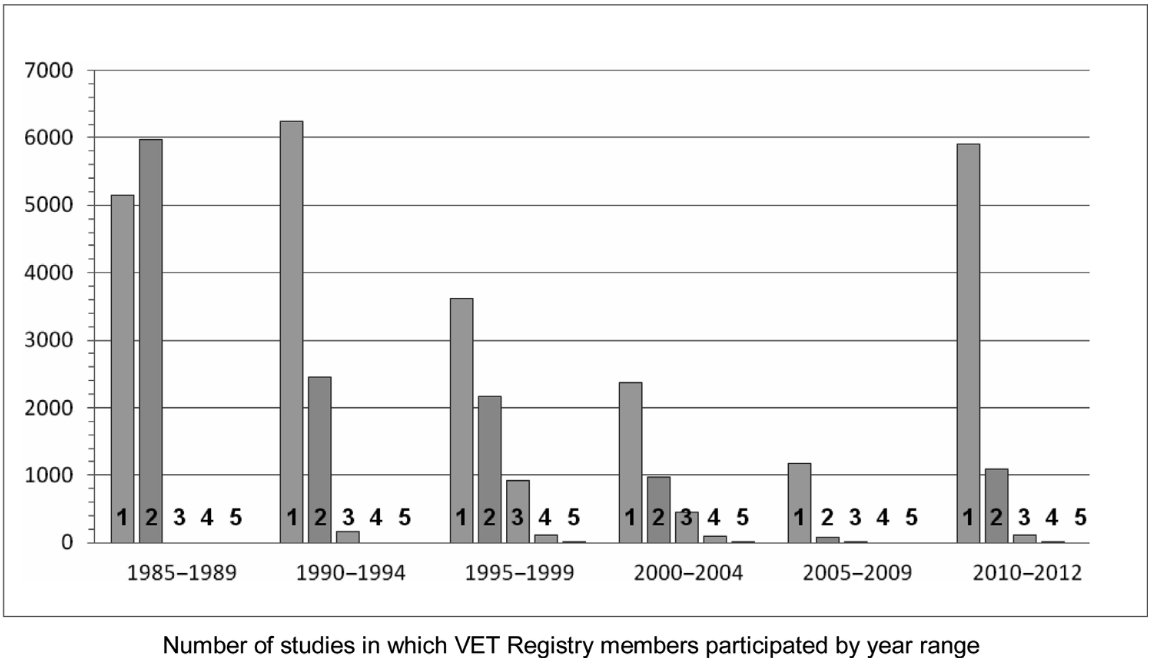

FIGURE 1
VET Registry twin member study participation over time.

1999 Male Health Survey. In 1999, a short mail survey that focused on major male health conditions was conducted. This survey was done in conjunction with a mailing of the VET Registry newsletter. The total response rate was 48% where 5,361 individual twins and 1,621 complete pairs responded (Fischer et al., 2004).

2012 VHS. A two-phase data collection effort was undertaken between 2010 and 2012 on all twin members of the VET Registry. The first phase included a 21-page mail survey that included measures of socio-demographics, healthcare utilization, functional status, disability, resilience, social support, general health, selected physical health conditions, and scales of depression and PTSD. The second phase involved a semi-structured psychiatric telephone interview and collected information on the diagnosis of PTSD, depression, anxiety, and substance use. The 2012 VHS included many identical question items used in the 1987 SOH, the 1990 NHLBI Survey, and the 1992 HDS.

Studies Using Selected Twin Pairs

Many studies involving the VET Registry are based on subsamples of Registry twin members. Typically, the sampling is based on the phenotypes already collected in the Registry database; studies range in size from less than 100 pairs to over 1,000 pairs. In total, 37 separate studies have been completed or are ongoing using subsets of twin members. There are 17 mail survey and telephone interview studies and 20 in-person assessment studies. During in-person assessments, a study may also collect biospecimen samples from a member. Biospecimens are collected at the study site and then sent to the VET Registry for processing at the VA Puget Sound Core Research and Development Laboratory. The biospecimens are stored temporarily there until the end of the specific study's aims. Upon the completion of a study's aims, if the consent form options indicate storage for future use, the Registry ships all biospecimens to the VA Massachusetts Veteran ERIC in Boston, Massachusetts, for long-term storage.

Secondary Data Analysis Studies

In more recent years, there have been many successful secondary data analysis studies. In total, 24 studies have been completed or are ongoing. Secondary data analysis projects may use information derived from several different mail survey, telephone interview, or in-person assessment studies.

Twin Participation

The number of twins participating in VET Registry research has varied with the number and the type of research being conducted over the past 26 years. Figure 1 depicts participation study counts from 1985 to 2012.

Among Registry twin members who have participated in studies, the modal number of studies is four, as displayed in Figure 2. However, participation has ranged from a single study to more than 12 studies.

In general, participation rates have varied over the types of studies. For example, studies conduct different types of procedures or may require cross-country travel to a study

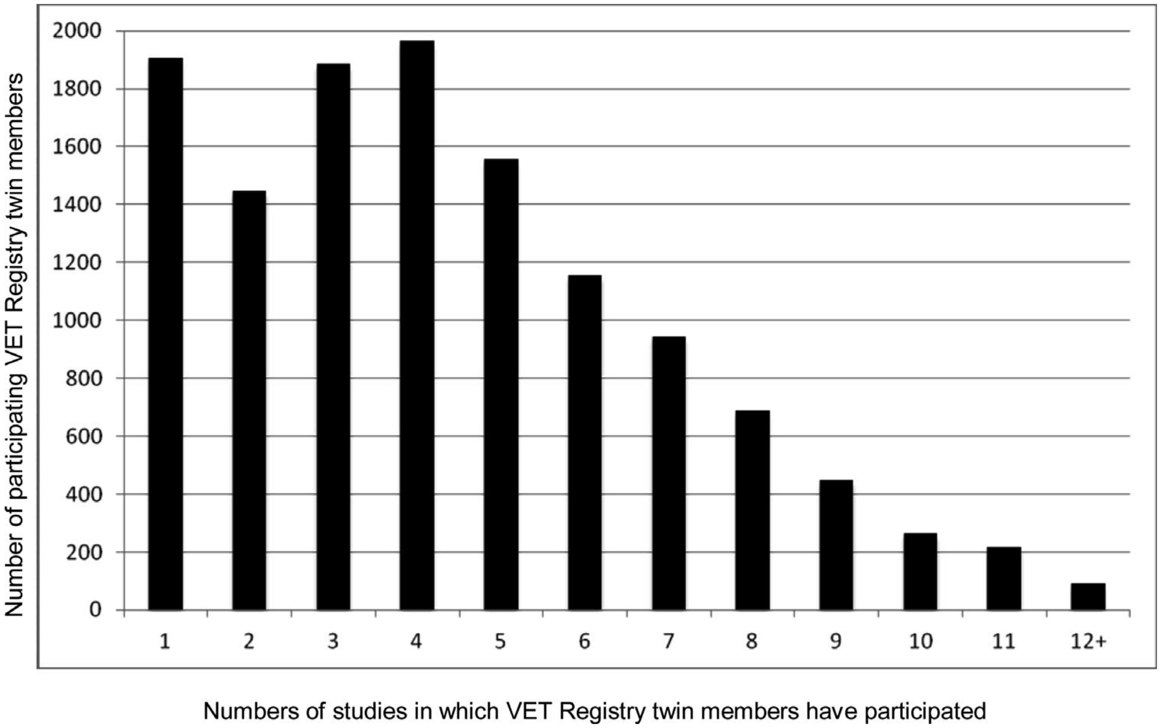

FIGURE 2

VET Registry twin member study participation total.
Note: This figure excludes the 2,261 VET Registry Twin Members who have not participated in any studies.

site. These variations have led to a wide range of participation rates. For mail surveys, the average participation rate has been 62.9% and for telephone interviews, it has been 62.3%. Additionally, the average participation rate for in-person studies has been 32.0%.

Genetic Testing

Genetic testing may be conducted in conjunction with some of the previously mentioned types of studies. Genetic testing is performed on biospecimen samples collected from Registry twin members. When providing a biospecimen sample for a specific study, twin members complete an informed consent form and indicate the extent to which their samples can be tested. Among those who provided a biospecimen sample, 87% indicated their samples could be used for the specific study and any future research studies (Figure 3). The remaining twin members chose other options that limit the use of their biospecimen.

Genetic testing takes place in a testing laboratory of the study investigator's choice. Samples are sent to the testing laboratory with a coded DNA identification number. Upon completion of the testing, the results are sent to the Registry where the DNA identification number is replaced by a Study identification number. The purpose for this is so that the testing laboratory cannot link the sample to any individually identifiable information.

Updating and Maintaining the VET Registry

In order to maximize the scientific value of the VET Registry, it is essential to maintain updated contact information, vital status, and zygosity of Registry twin members. We use a variety of methods to ensure we have the most up-to-date information.

Updating contact information via newsletters and a toll-free number. As part of the consenting process the VET Registry mails members a newsletter, titled *Twin Times* (http://www.seattle.eric.research.va.gov/VETR/Newsletters.asp), approximately every 2 years. The newsletter provides members with information about past, ongoing, and upcoming Registry studies and other Registry-related activities. It is also a way for the Registry to obtain updated contact information on members so that the Registry and other studies can reach them in the future. Members can also call the VET Registry at any time to provide updates to their contact information.

Vital status update. To maintain accurate morality status on Registry twin members, the Registry updates its vital status data yearly. The purpose is twofold: an up-to-date status ensures that the Registry does not send Registry materials to deceased members or their families, and it provides an accurate count of living Registry members. The VET Registry searches both the VA Vital

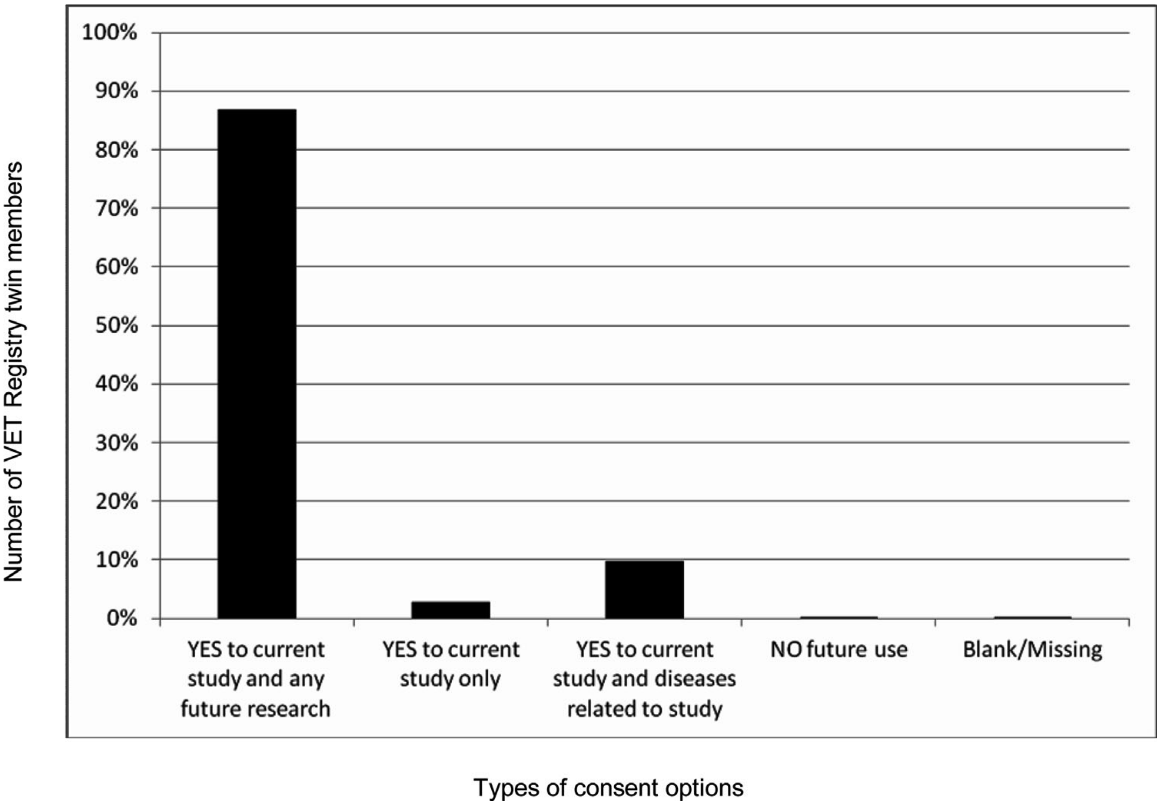

FIGURE 3
VET Registry twin member sample consent options.

Status files (Sohn et al., 2006) and National Death Index (NDI) Plus system. Specifically, the VA Vital Status files provide information about mortality and demographics, as maintained by the Veterans Health Administration (http://www.virec.research.va.gov/VSF/Overview.htm). The VA Vital Status files are highly accurate for identifying Veteran deaths but do not include the cause of death (Cowper et al., 2002). Cause of death information is obtained from the NDI Plus system (Cowper et al., 2002).

We also maintain information obtained from the VA Vital Status files about the proportion of Registry twin members that utilize the Veterans Health Administration. The Veterans Health Administration is the United States' largest integrated healthcare system, which provides healthcare services to the nation's Veterans (http://www.va.gov/health/aboutVHA.asp). In total, 38.5% of all Registry twin members have used Veterans Health Administration services at some point in their lifetime. In recent years (2010–2011), 29.9% of Registry twin members utilized the healthcare services of the Veterans Health Administration.

Zygosity assignment. A 20-item zygosity questionnaire was included as part of the 1987 SOH. Originally, these question items were used to assign zygosity without DNA. Over the years, however, DNA has been collected from many Registry twin members. In 2010, an updated predictive algorithm for zygosity assignment was created using the zygosity question items and DNA (Forsberg et al., 2010). For those twin members who did not complete the 1997 SOH but have since completed another VET Registry study, a two-page supplemental questionnaire is mailed to obtain the missing zygosity items. In-person assessment studies continue to collect DNA that can be tested for zygosity, given the twin members' consent. These data, as well as newly collected DNA, are used to continuously update twin members' zygosity assignment.

Conclusion and Future Plan

The Registry continues to be an important resource for many genetic epidemiological studies of mental and physical health conditions. Maintained by the VA, the VET Registry is open to all researchers as a broad resource, which includes data from individual studies using the twin pairs. Contact information, vital status, and zygosity status are consistently updated to keep the Registry current.

Recently, the VET Registry surveyed members who have had limited participation in previous studies. This update has identified ~950 individuals, a number of them paired,

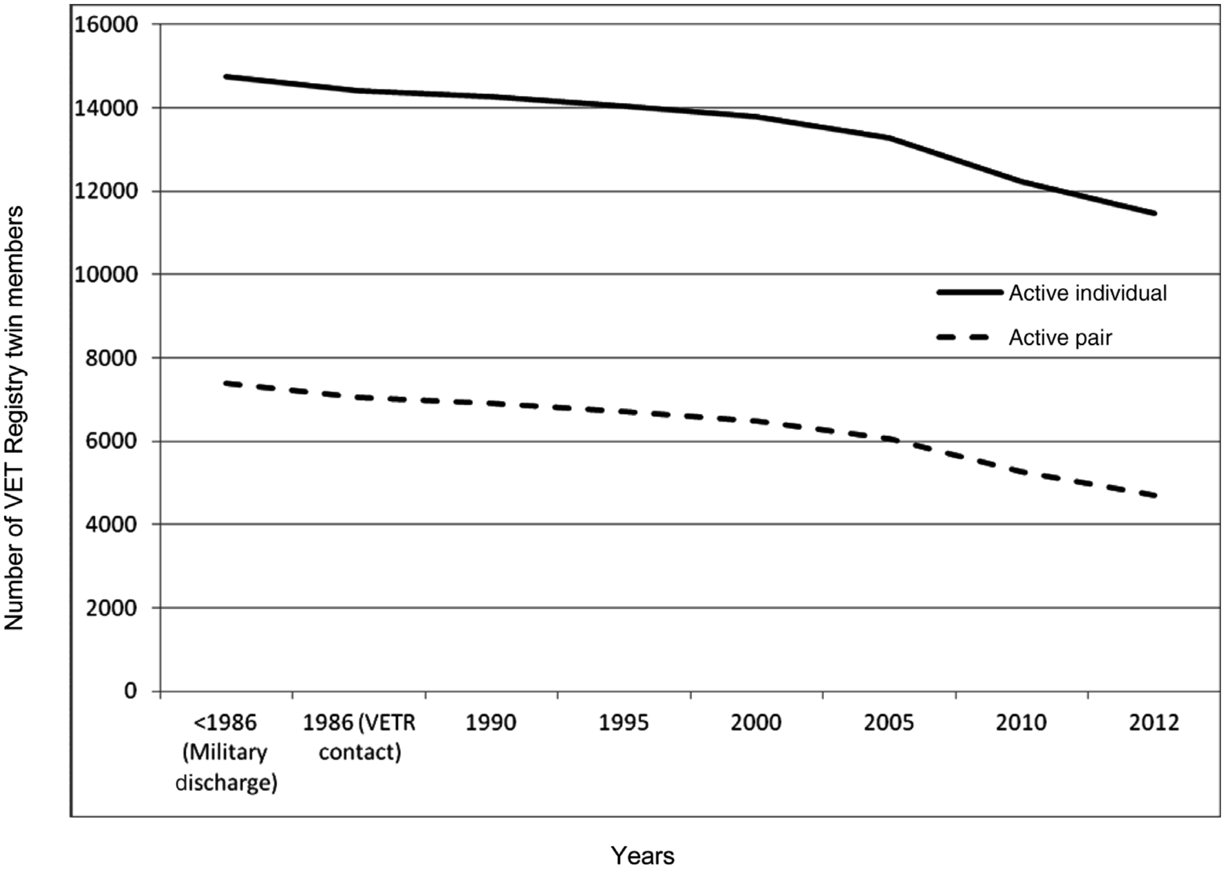

FIGURE 4
Active VET Registry twin members over time.

that will be available for recruitment for future studies. Additionally, the potential to conduct longitudinal analysis has increased as VET Registry studies have collected data from members over time. For example, a large number of twins have repeated measures on body mass index over a very long time period: these include measured height and weight from the enlistment examination into the military as well as self-reported weight in 1987, 1990, and 2010–2012.

It is of continued importance to the Registry that we serve the needs and interests of our Veteran twin sample. We recently developed a 10-page mail survey titled *Your Opinion Matters!* to collect information about twin members' experiences with the Registry and past and current Registry studies and VA research in general. The survey asks about their opinions on what physical and mental health topics they would like to see in future VET Registry research. Additionally, we ask questions about obtaining biospecimen samples from twin members. Data collection is currently under way and we expect the results will assist us in developing new studies that are of interest to our twin members.

Displayed in Figure 4 are the counts of active twin individuals and pairs over time. Heading into the future, the Registry will continue to expand its research platform and broaden the scope of studies. Data generated and biospecimen samples obtained from new studies would expand the data and biospecimen repositories' usefulness to the broader scientific community.

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