Acta Genet Med Gemellol 43: 89-94 (1994)

International Congress
40th Anniversary of The Mendel Institute

The National Academy of Sciences – National Research Council Veteran Twin Registry

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INTRODUCTION

With recent advances in molecular biology and genetics, cohorts such as the National Academy of Sciences-National Research Council (NAS-NRC) Twin Registry may become of increasing importance. This paper outlines the creation and history of the NAS-NRC Twin Registry, methodologies utilized for analysis of twin data, studies that have been completed or are underway, and possible future types of studies.

Key words: Twins, Epidemiologic, Registries, Cohort Studies, Veterans Administration

DESCRIPTION OF THE TWIN REGISTRY

Two reports have described the construction, zygosity determination and many of the operational details of the NAS-NRC Twin Registry [6,8]. Briefly, during the mid-1950's, a search of birth certificates was undertaken and this identified 54,000 white male multiple births that had occurred in the United States during the years 1917 through 1927. It has been estimated that this represents 93% of such births that occurred during this period. Then in 1958-1959, records of the identified multiple births were sought in the files of the U.S. Veterans Administration. Matches were found for the 15,924 twin pairs that compose the NAS-NRC Twin Registry. In 1965, a questionnaire was mailed to the twins of the NAS-NRC Twin Registry with the primary purpose of determining zygosity and obtaining a medical history. In 1967, a second questionnaire was mailed to the twins. It obtained information about tobacco and alcohol consumption, diet, social and enviromental factors, as well as other factors related to respiratory and coronary heart disease. About 4,700 twin pairs, or 84% of those contacted, responded to the second

questionnaire. In 1983, a modified version of the prior questionnaire was distributed to update its information; about 3,600 twin pairs responded.

Zygosity has been determined for 13,486 pairs of twins in the NAS-NRC Twin Registry. Answers to simple questions on their similarity as children provided the basis for zygosity determination in approximately 11,000 pairs. Zygosity was also determined for approximately 1,950 pairs on the basis of blood typing, and for approximately 800 pairs based on physical characteristics, primarily fingerprints. These results have been cross-validated within the NAS Twin Registry [6,8] and also other groups of twins [3,5,9]. These validity studies suggest that questionnaire data alone provide correct assignment of zygosity in approximately 95% of twin pairs. As the Veterans Administration requires the submission of death certificates for the payment of death benefits to surviving family, this also provided a relatively complete ascertainment of mortality and cause of death [2,10,11]. Through 1990, 9,364 (29.4%) of the 31,848 twins were reported deceased.

METHODOLOGICAL APPROACHES TO ANALYSIS

Central to the study of twins is the fact that monozygotic (MZ) twins share virtually 100% of their genes whereas dizygotic (DZ) twins share, on average, half their genes. A brief outline follows of some of the more common approaches to the study of twins.

The Classic Twin Study

If MZ twins share environment to no greater an extent than DZ twins, then a greater similarity or concordance between MZ than between DZ twins for a particular trait would be supporting evidence of a genetic influence on that trait. However, the assumption that environmental covariance does not vary by zygosity is often violated in practice. Often investigators lack specific knowledge of the degree to which sharing of pertinent environmental factors differs between MZ and DZ twins. When such knowledge is lacking, a greater concordance in MZ than in DZ twins for a trait should, therefore, be interpreted as indicating the *possibility* of genetic effects. Conversely, a concordance between MZ twins equal to or less than that between DZ twins may indicate the absence of genetic effects.

The Study of Twins Separated at Birth

The potential problems of greater environmental covariance among MZ than DZ twins can, to a large degree, be obviated by restricting study to twins separated at birth. It has been suggested that this study approach provides "the simplest and most powerful method for disentangling the influence of environment and genetic factors on human characteristics". However, application of this approach is limited by the rarity of twins reared apart [1].

Cotwin Control Study

Epidemiologic case-control studies are usually interested in determining whether a particular factor is related to disease. Cases and controls are sometimes matched (or chosen to be similar) for variables that may distort or confound the assessment of a possible association between the factor in question and disease e.g. age, sex and race. In the cotwin control design, twins affected with the specific disease (or condition) under study are the cases and their disease-free cotwins are the controls. The frequency among cases of having the particular exposure is then compared to that among controls. Again, in this same design, twins discordant on an exposure, say smoking, could be compared on the frequency of an outcome, such as lung cancer or heart disease. The cotwin control design can usually provide considerably closer matching than the usual case-control studies on variables such as age, race, socioeconomic factors, and environment. When MZ twins are studied, full matching on genetic factors is also achieved.

Perinatal and In-Utero Effects

The in-utero and perinatal experience of twins is unique. For example, the mean weight of twins at birth is substantially lower than for singletons [14]; approximately two thirds of MZ twins are monochorionic and therefore share, though sometimes unequally, placental circulation [12]; and maternal estrogen levels are higher during twin pregnancies than during singleton pregnancies, with levels more elevated in DZ than in MZ gestations [7,15]. This latter observation has been hypothesized to explain why DZ twins may possibly have a somewhat higher risk for breast cancer than MZ twins, as has been reported [7]. Studies of the incidence of disease or other conditions among MZ and DZ twins may, therefore, provide insight into potential perinatal and in-utero effects.

Studies of Monozygotic Twins to Estimate Environmental Effects

Monozygotic twins are virtually genetically identical. Consequently, differences in phenotype among MZ twins can be attributed to environment. Stochastic processes or random variation may also contribute to observed differences within twin pairs.

AREAS OF STUDY

Investigations carried out on the twins in the NAS-NRC Twin Registry have contributed to scientific understanding in many subject areas. Some past and current study areas are listed in the Table. Many of these studies employed the classic twin study design. They estimated the heritability or genetic component of the characteristic of interest based on the simple assumption that environmental covariance between MZ twins is equal to that between DZ twins.

Table - Overview of research in the NAS-NRC Twin Registry

Area of Study	Exposures and outcomes studied
Cardiovascular disease	
Clinical tests	Blood pressure, serum lipids, ECG
Behavioral	Type A & B personality
Outcomes	Death, cardiovascular disease, stroke
Predisposing conditions	Obesity, diabetes
Substance use	Smoking, alcohol, caffeine
Cancer	Lung, colon, testicular cancer mortality
Psychiatric disorders	Suicide, schizophrenia, anti-social behavior
Neurological diseases	Alzheimer's disease, Parkinson's disease, cognitive dysfunction

SOURCES OF DATA

Data for analysis in these studies comes from a variety of sources: information obtained at induction into the armed forces; the 1965 questionnaire which requested information on zygosity determination; the 1967 and 1983 questionnaires that primarily requested information on cardiovascular and respiratory disease risk factors, and mortality reports through the Veterans Administration. Recently, in 1990 and 1992-94, telephone contact has been made with surviving twins. The focus of this most recent effort was to assess function and risk factors related to Alzheimer's disease and Parkinson's disease. The telephone questionnaire also gathered information about cancer and stroke. In addition, a subset of 1,024 twins ("The National Heart, Lung, and Blood Institute cohort") in the NAS-NRC Twin Registry has been more extensively interviewed and clinically examined since 1970. Multiple studies primarily relating to cardiovascular disease have been undertaken in this group.

EXAMPLES OF FUTURE STUDIES

The recent technological breakthroughs in molecular biology and genetics are resulting in the identification of genes associated with numerous disorders, including diseases of old age. Study of elderly twins may help to understand how these genes are expressed. For instance, a gene, apolipoprotein E4, related to an increased risk for Alzheimer's disease has recently been identified [4]. Study of concordance for the disease among MZ twins can provide unique confirmation of this finding and further investigations, including the determination of the apolipoprotein E4 genotype, may help in understanding the gene's penetrance, cofactors, and relation to age at onset of Alzheimer's disease.

Cancer susceptibility genes may alter the likelihood of occurrence of common tumors. These genes control the metabolism (activation or elimination) of carcinogens. Study of a cancer susceptibility gene, by comparing the metabolism of a given drug in

twin pairs, could further the mechanistic understanding of cancer susceptibility genes. If metabolism varies less between MZ than between DZ twins, this would constitute some support for a genetic influence. As a simple example, pairs of twins can be asked to consume a given amount of caffeine in coffee. The levels of caffeine metabolites in their urine can then be related to the activity of the cytochrome p450 enzyme 1A2, an enzyme involved in activation of aromatic and heterocyclic amines that have been associated with bladder cancer. Another study approach could be to compare drug metabolism in MZ twins concordant for exposure, but discordant for disease: e.g. smokers discordant for lung cancer. Disease discordant pairs may have different levels of metabolism, perhaps due to other exposure factors.

SUMMARY AND CONCLUSION

The entire NAS-NRC Twin Registry is composed of 31,848 twin individuals in 15,924 complete pairs. Compiled in the 1950s, the registry is limited to white males; in the creation of new registries it would be desirable to include women and ethnic minorities. In 1994, about 20,000 aged 67 through 77 years are alive. Zygosity is known for 85% of the twins, with about 95% accuracy.

Twin studies may be useful for the investigation of familial, genetic and environmental effects. The study design and analytic methodology employed will depend on the scientific question asked. Some general areas that have been studied in the NAS-NRC twin registry include cardiovascular disease, substance use, cancer, psychiatric disorders and neurological diseases. Recent advances in the technology of genetic analysis, such as the polymerase chain-reaction technique of DNA amplification, coupled with the potential of obtaining DNA samples by mail (without phlebotomy) through self-administered buccal brushes [13] may create new opportunities to further expand knowledge through twin studies.

Acknowledgement: The National Academy of Sciences-National Research Council Twin Registry is administered within the Medical Follow-up Agency of the National Academy of Sciences, 2101 Constitution Avenue, Washington DC 20418, USA. The director of the Twin Registry is Dr. William Page, and the director of the Medical Follow-up Agency is Dr. Richard Miller.

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