

Current Status of the Chinese National Twin Registry

Liming Li, Wenjing Gao, Jun Lv, Weihua Cao, Siyan Zhan, Huiying Yang, and Yonghua Hu

Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China

The Chinese National Twin Registry is the first and largest population-based twin registry in China. It was established in 2001. The primary goal of this program is the establishment of a population-based twin registry of 45,000 twin pairs from several regions representing north, south, urban, and rural areas in China. A secondary goal is to study genetic contributions to complex diseases, and to test associations of candidate genes with related phenotypes. Seven thousand, four hundred and twenty-three twin pairs have been enrolled in the registry, in which 1613 pairs have undergone detailed questionnaire assessments and physical examination. Based on the baseline registry, a twin cohort was established. Continued research includes studies on intermediate phenotypes of cardiovascular and cerebrovascular diseases and psychological studies in adult twins, studies on growth and development in adolescent twins, and so forth. The current state and future plans for the Chinese National Twin Registry will be discussed in this article.

The Chinese National Twin Registry (CNTR), established with the financial support of the China Medical Board, New York (CMB01-746) in 2001, is the first population-based twin registry in China. Chinese twins are invited to join this voluntary registry regardless of zygosity type, age, health or medical history. In the early days of its establishment, this program focused on genetic epidemiological studies of cardiovascular and cerebrovascular diseases. Since its expansion, the CNTR provides in addition an important resource for researchers across a broad range of disciplines.

The primary goal of the CNTR is the establishment of a population-based twin registry of 45,000 twin pairs from several regions representing north, south, urban, and rural areas in China. Beijing, Qingdao, Shanghai and Lishui were selected as representative regions. A secondary goal is the study of genetic contributions to complex diseases, and the testing of associations of candidate genes for these disease phenotypes. The establishment of the CNTR and all genetic epidemiological study protocols were reviewed and approved by the Ethics Committee for Human Subject Studies of the Peking University Health Science Center.

Recruitment of Twins in the CNTR

The CNTR is a voluntary registry. Twins were recruited through the following: residence registry in the public security bureaus, public media, local health care networks and neighborhood/village committees (Yang et al., 2002). The registration of twins was achieved mainly through the three-tiered prevention and health system (village, township and county level) in China. However, for twins who underwent detailed assessment, certain recruitment methods played a more predominant role than others in particular locations. For example, in Qingdao, twins were recruited mainly through the newspaper, TV and neighborhood/village committees, while in Lishui twins were recruited mainly through local general practitioners in the health care system. Only twins where both twins were alive and living in the twin registry coverage area were included in the registry.

The CNTR is administered through the Department of Epidemiology and Biostatistics, School of Public Health, Peking University. The data and samples of twins were collected and reported by local Centers for Disease Control and Prevention (CDCs). The database of the CNTR uses Epidata as the interface.

Various Registries in the CNTR

By the end of 2005, the field work of the CNTR had been carried out in Beijing, Qingdao and Lishui, which resulted in the enrollment of 7423 twin pairs in total. These 7423 twin pairs included 5895 pairs who were registered in the Qingdao registry between 2001 and 2004, 787 pairs who underwent simple assessments in the Beijing registry in 2004, and 741 pairs who underwent detailed assessments in the Lishui registry between 2002 and 2005. The age and sex distributions of the registered twins in Qingdao, Beijing and Lishui are listed in Tables 1, 2, and 3, respectively. In addition to these three, twin registration is in progress in Shanghai. According to the local

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Address for correspondence: Liming Li, Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, 38 Xueyuan Road, Haidian District, Beijing 100083, China. E-mail: lmlee@vip.163.com

household register, currently about 1500 twin pairs reside in Huangpu district in Shanghai.

Scientific Research

Detailed Assessment

In the CNTR, a total of 1613 twin pairs in Qingdao and Lishui were administered an interview questionnaire

(zygosity determination, medical history, smoking and drinking, medical history of their linear relatives, etc.) and physical examination (height, weight, blood pressure, waist, hip and pulse). To determine concentrations of some biochemical indices (Table 4 for detail) and to keep DNA, a fasting blood sample was collected from each participant after written informed consent was obtained. For adolescents, their sitting height, circumference of chest, shoulder width, pelvis width, and skin fold were also measured to reflect their growth status.

For the twin pairs who underwent detailed assessments, a stepwise procedure was taken to determine their zygosity (Lv et al., 2003). Firstly, dizygotic (DZ) twins with different sex and/or different ABO blood type, which were tested by a forward typing, were excluded. Then the zygosity of remaining twins was determined by simultaneous detection of multiple short tandem repeat (STR) loci. This method is widely used in the forensic field for individual identification. The probability of monozygosity determined by identity of all markers in the CNTR is estimated to be at least .996. Of the 1613 twin pairs who received zygosity determination, 1039 were monozygotic (MZ) and 574 DZ twins. The ratio of MZ to DZ was approximately 1.8:1.

Table 1
The Age and Sex Distribution of Registered Twins in Qingdao

| Birth year | Twins (pairs) | | | Triplet+ | Total |
|------------|---------------|--------|-------|----------|-------|
| | Male | Female | Mixed | | |
| < 1929 | 11 | 5 | 2 | 0 | 18 |
| 1930–1939 | 13 | 7 | 6 | 0 | 26 |
| 1940–1949 | 33 | 12 | 10 | 0 | 55 |
| 1950–1959 | 119 | 40 | 40 | 0 | 199 |
| 1960–1969 | 253 | 136 | 112 | 3 | 504 |
| 1970–1979 | 339 | 279 | 157 | 4 | 779 |
| 1980–1989 | 440 | 436 | 246 | 11 | 1133 |
| 1990–1999 | 921 | 805 | 472 | 17 | 2215 |
| 2000– | 436 | 339 | 181 | 10 | 966 |
| Total | 2565 | 2059 | 1226 | 45 | 5895 |

Table 2
The Age and Sex Distribution of Registered Twins in Beijing

| Birth year | Twins (pairs) | | | Triplet+ | Total |
|------------|---------------|--------|-------|----------|-------|
| | Male | Female | Mixed | | |
| 1930–1939 | 1 | 0 | 0 | 0 | 1 |
| 1940–1949 | 2 | 1 | 0 | 0 | 3 |
| 1950–1959 | 10 | 4 | 1 | 0 | 15 |
| 1960–1969 | 22 | 19 | 11 | 0 | 52 |
| 1970–1979 | 32 | 21 | 16 | 0 | 69 |
| 1980–1989 | 77 | 74 | 50 | 0 | 201 |
| 1990–1999 | 106 | 109 | 74 | 2 | 291 |
| 2000– | 55 | 68 | 31 | 1 | 155 |
| Total | 305 | 296 | 183 | 3 | 787 |

Table 3
The Age and Sex Distribution of Registered Twins in Lishui

| Birth year | Twins (pairs) | | | Triplet+ | Total |
|------------|---------------|--------|-------|----------|-------|
| | Male | Female | Mixed | | |
| 1920–1929 | 4 | 0 | 0 | 0 | 4 |
| 1930–1939 | 13 | 2 | 3 | 0 | 18 |
| 1940–1949 | 16 | 3 | 7 | 0 | 26 |
| 1950–1959 | 50 | 37 | 16 | 0 | 103 |
| 1960–1969 | 137 | 94 | 43 | 1 | 275 |
| 1970–1979 | 114 | 97 | 34 | 1 | 246 |
| 1980–1989 | 36 | 26 | 7 | 0 | 69 |
| Total | 370 | 259 | 110 | 2 | 741 |

Follow-Up Investigation

After a period of 2.5 years, a follow-up investigation for the adult twins (older than 25 years) was undertaken. They were assessed by the same means (questionnaire

Table 4
Biochemical Items Measured in Lishui and Qingdao

| | Lishui | Qingdao |
|--------------------------|--------|---------|
| ABO blood type | √ | √ |
| Rh blood type | | √ |
| HBsAg | √ | √ |
| Fasting blood glucose | √ | √ |
| CHOL | √ | √ |
| TG | √ | √ |
| HDL-C | √ | √ |
| LDL-C | √ | √ |
| Apo A1 | √ | |
| Apo B | √ | |
| LPL (a) | √ | |
| ALT | √ | √ |
| CR | √ | √ |
| UA | √ | √ |
| BUN | √ | √ |
| K | √ | √ |
| Na | √ | √ |
| Regular blood test | | √ |
| Regular uric test* | | √ |
| Other biochemical items† | | √ |

Note: *NIT, PH, GLU, PRO, BLD, KET, BIL, URO.

†TBIL, DBIL, IBIL, D/I, AST, S/L, AKP, GGT, TP, ALB, GLB, A/G, PA, TBA, CHE, LDH, Cl, Ca, Mg, P, C02CP, AG, CP, TRF.

interview, physical examination, and biochemical testing) as the baseline. The link between the baseline and the follow-up was made by means of a unique ID assigned to each of the twins. New twins were also recruited at the same time. The baseline and follow-up assessments in the Qingdao and Lishui registries are listed in Table 5. By the end of 2005, a total of 579 twin pairs had been assessed in both rounds. A new round of follow-up assessments in Qingdao is being considered to improve the rate of follow-up. Further data analyses are in progress.

Zygoty Determination

Zygoty determination through STR genotyping is taken as gold standard. However, due to its costs, it is not affordable here within a large-scale twin register system. To develop a cost-effective method, MZ and same-sex DZ twin pairs determined by genotyping were chosen to evaluate the accuracy of simple questionnaire and physical features comparison in zygoty determination. The results showed that the questionnaire-based zygoty assessment in our Chinese adult twin sample could still be regarded as a valid and valuable classification method. The comparison of physical features, however, could only provide limited information (Gao et al., 2006). Further data analysis is ongoing.

The Secular Trend of Twin Birth Ratios and Factors Associated With Twin Birth in Qingdao

The immunization register records of Qingdao Center for Disease Control and Prevention were analyzed to investigate the secular trend of multiple births in Qingdao. The major index was twin birth ratio which came from the ratio of the number of live twin births to total live-births. The results indicated that the twin birth ratio of Qingdao increased from 1987 to 2002. The twins born in autumn and winter were more than those born in spring and summer. The twin birth ratios in urban and coastal areas were higher than that in rural and inland areas (Zhou et al., 2005). A case-control study including 185 twin pairs and 185 singletons who were born in Qingdao in 2003 showed that a maternal and/or paternal family history of twins, mother's previous history of abortion and noncontraception drugs, the age of the father at conception, contraception use of mother, and the reproductive desire of mother were all associated with the twin birth.

Studies on the Intermediate Phenotypes of Cardiovascular and Cerebrovascular Diseases in Adult Twins

Genetic and environmental contributions to cardiovascular and cerebrovascular diseases and related intermediate traits were studied (Gao et al., 2005; Li et al., 2003; Ren et al., 2003; Wu et al., 2005). Four gene polymorphisms were genotyped, including $\beta 2$ adrenoreceptor Gln27Glu, $\beta 3$ adrenoreceptor Trp64Arg, glucose transporter 1 Xba1 G→T, and lipoprotein lipase Ser447-stop. The associations between those polymorphisms and related intermediate phenotypes (obesity, insulin sensitivity, and lipids level) were analyzed (Huang et al., 2005a, 2005b; Li et al., 2004).

Psychological Studies in Adult Twins

Two psychological studies were conducted with Qingdao twins. One study involved 55 pairs of MZ and 34 pairs of DZ twins. These participants were administered Type A Personality Questionnaire, Eysenck Personality Questionnaire and 16PF (Pang, Zhai, et al., 2003; Peng et al., 2003; Wang et al., 2003). The other study involved 453 pairs of twins. The Personality Diagnostic Questionnaire-4 (PDQ-4), Symptom Checklist 90 (SCL-90), Social Network Questionnaire (SNQ), and Life Experience Scale (LES) were administered to these twins. The results showed that genetic effects maybe exist in somatization, interpersonal sensitivity, anxiety and phobic anxiety. Further data analysis is ongoing.

Studies on Growth and Development in Adolescent Twins

Studies to determine the effects of genes and environments on traits associated with adolescent growth and development were carried out. In these studies, we examined anemia (Chen et al., 2004a), serum lipids and lipoproteins (Chen et al., 2004b, 2005), insulin-like growth factor-1 (IGF-1; Li et al., 2005a, 2005b), leptin (Li et al., 2005c, 2005d), luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), estradiol (E2; Wang et al., 2004a), androgens (Wang et al., 2004b), dental caries in deciduous and permanent tooth (Qi et al., 2004; Zhang et al., 2004), skeletal age (Wang et al., 2004), intelligence and behavior (Zhen et al., 2002a, 2002b).

Publications

By the end of 2005, 34 original papers and reviews on the basis of the CNTR had been published. There are an additional two papers in press.

Table 5

The Baseline and Follow-Up Investigations in Qingdao and Lishui

| | | Qingdao | Lishui |
|-----|--|----------------|----------------|
| 1st | Date | Nov.–Dec. 2001 | Sep.–Oct. 2002 |
| | No. of adult twin pairs studied | 505 | 503 |
| 2nd | Date | Aug.–Sep. 2004 | Jan.–Mar. 2005 |
| | No. of adult twin pairs who participated in the follow-up assessment | 244 (48.3%) | 335 (66.7%) |
| | No. of adult twin pairs newly recruited | 183 | 69 |

Discussion

The CNTR has achieved many social benefits (Pang et al., 2002, Pang, Bo, et al., 2003). 'A happy party for Qingdao twins' was organized in Zhongshan Park, Qingdao on August 18, 2002, hosted jointly by the Department of Epidemiology and Biostatistics, Peking University, Qingdao CDC, and the press office of Qingdao Morning News. Hundreds of twin pairs and their family members attended the party. The 'Qingdao Twins' Health Promotion Association' was established in December 2002. A 'twin day' is held in Zhongshan Park annually on the second Sunday of August, by the Department of Epidemiology and Biostatistics, Peking University, Qingdao Twins' Health Promotion Association, Qingdao CDC, Zhongshan Park, the press office of Qingdao Morning News, and Qingdao Opera and Dance Drama Theater. To date, four twin days in the park have been successfully hosted. The Twins' Arts Troupe was established in July 2003, and the activities have greatly promoted the CNTR and attracted more twins to the registries.

Using the three-tiered prevention and health system (village, township and county level) in Qingdao to access twins has provided methods and expertise for other regions' registries, with high efficiency, high coverage and accuracy of information registered. However, there was some overlap in the twins of the noncommunicable disease control and prevention system and the immunization program of CDC. Researchers should be especially careful when they use both systems. The CNTR avoided overlapping by limiting the birth year of twins, which may be useful for other regions.

The goal of the CNTR is to establish one of the largest twin registries in the world. With the experience gained over the past 5 years, the CNTR has gradually developed appropriate methodology for the Chinese twins' registry. However, affected by the 2003 SARS outbreak, the twin registry progress for those operated by CDCs slowed down. Over the past 3 years, the CNTR has focused on the detailed assessment and follow-up assessment of twins, which has resulted in a gradual increase in registrations. Future plans include the expansion of the registry to include 45,000 twin pairs using a computer retrieval system of the local bureau of statistics and the bureau of public security, established local networks of women and child health, an immunization program in CDC and family planning commission, school recruitment and media support. The registry plans to achieve the following three objectives.

Intensive Research on Cardiovascular and Cerebrovascular Diseases

We plan to conduct detailed phenotyping on a subset of twins aged 30 years or older for clinical and sub-clinical (or intermediate) traits related to cardiovascular and cerebrovascular diseases. For example, (1) clinical diseases, such as coronary artery

disease, stroke (separately for ischemic and hemorrhagic stroke), and hypertension; (2) quantitative measures of related traits, such as carotid artery intimal medial wall thickness (IMT), blood pressure, body mass index, waist/hip ratio; and (3) biochemical measures, such as fasting lipid profile, apoA, apoB, fasting glucose, insulin, homocysteine, and so forth. We plan to estimate the heritability of these traits in this population to determine phenotypes useful for further gene identification studies. The logic here is that if a trait is mainly influenced by environmental factors, the effort to identify susceptibility genes may be too great to be successful. Therefore, we will initially focus on those traits with significant genetic contribution (e.g., heritability greater than .5) for family studies.

Expand Twins to Twin Families

We will expand twin pairs to twin families including twins' parents, siblings and offspring, acquiring questionnaire information on demographics, medical history, and lifestyle on smoking and drinking, and so forth. Height, weight, waist circumference, hip circumference, blood pressure and pulse will also be measured. In addition, after obtaining informed consent, a fasting venous blood sample will be collected in to obtain data on laboratory measures and extract DNA. These efforts will allow further laboratory research on the susceptibility genes for cardiovascular and cerebrovascular diseases.

Longitudinal Follow-Up Assessments of Twins in the Registry

We are planning to develop a follow-up scheme based on age and initial physical exams. For example, older twins and/or twins with high blood pressure will be followed up most frequently, for example, annually. However, younger twins will be followed up less frequently, every other year or at 5-year intervals depending on resources.

The purposes of follow-up study are (1) to provide health education and promote healthy behavior, (2) to identify early cases and provide timely medical attention, and (3) to evaluate long-term effects of identified risk factors for cardiovascular and cerebrovascular diseases.

The CNTR has become an important national and international resource for a broad range of research. With its coverage expanding, the registry will play a more and more important role in Chinese genetic epidemiology. Any national or international potential collaboration proposals are invited to make full use of the resources available and to use the model for other registries in China.

Author Note

The CNTR e-mail is lmlee@vip.163.com

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