

The Hungarian Twin Registry

Levente Littvay,¹ Julia Métneki,² Ádám D. Tárnoki,³ and Dávid L. Tárnoki³

¹Central European University, Budapest, Hungary

²National Institute for Health Development, Budapest, Hungary

³Department of Radiology and Oncotherapy, Semmelweis University, Budapest, Hungary

(The authors contributed equally to this article and appear in alphabetical order.)

The first Hungarian Twin Registry was established in Budapest in 1970 through the mandatory reporting of multiple-births. In the 1980s a second, volunteer adult registry was also founded. Unfortunately, both registries ceased to exist in the 1990s. Efforts started in 2006 to revive a Hungarian twin registry. The team spearheading this effort reports here on this progress. Currently, the voluntary Hungarian Twin Registry consists of 310 adult twin pairs and multiplets. Current research focuses on cardiovascular and respiratory health and yielded multiple awards and publications. Efforts are on the way to expand into social, psychological, and obesity studies.

■ **Keywords:** Central and Eastern Europe, post-communist era, international twin study, arterial stiffness, hypertension, lung function

In 2006, two medical students — Adam and David Tarnoki (identical twins themselves) — and Levente Littvay began an effort to revive the Hungarian Twin Registry. This effort benefited greatly from the help of Julia Métneki (a twin herself), the person responsible for most of Hungarian twin studies and the management of two twin registries from the 1970s to the 1990s. Levente Littvay is especially grateful to Nicholas Martin for his encouragement to get in touch with Julia Métneki and continue the work she started in the 1970s. This team now reports the progress of this project, the rebirth of a volunteer twin registry in Hungary and future plans.

History

Twin studies in Hungary date back to 1970s, on the basis of three different databases, all of them through the efforts of Andrew Czeizel. The Budapest Twin Registry (BTR) was launched in 1970 by the Department of Human Genetics and Teratology, National Institute of Hygiene. The notification of all multiple births (including stillbirths) was carried out by physicians of obstetrical institutions in the capital. The registry's purpose revolved first around ensuring twins' developmental health in the perinatal and postnatal periods. Placentas were collected and analyzed in the Heim Pál Children's Hospital. In addition, twin zygosity was determined in all dichorionic like-sex twins by determining their blood and serum protein groups. Twins' health was assessed by pediatricians at 6 months and at 1, 3, 6, and 10 years of

age (Czeizel et al., 1979). As a byproduct, the BTR offered a unique opportunity for scientific research. For example, a connection between contraceptive pills containing high dose hormones used in the periconceptional period and frequency of dizygotic twin births was demonstrated (Métneki & Czeizel, 1980). Other research associated with the BTR focused not only on genetic questions but risk factors in twin births. One such study assessed retinopathy prematorem, which is associated with premature births and is a risk factor of multiple births (Métneki et al., 1991). Also, the duration of gestation and the intrauterine growth of multiple fetuses was compared to singletons (Török et al., 1985, 1988). Additional research evaluated the demographic and epidemiological characteristics of multiple births (Métneki, 1996; Métneki & Czeizel, 1983, 1986).

Unfortunately, due to a lack of funding, the twins' health program was dissolved in the 1980s, and in the 1990s institutional and administrative changes led to the complete discontinuation of the registry. In the early 1980s, after a successful study of lactose intolerance on the population and the need for an adult twin sample in order to

RECEIVED 1 September 2012; ACCEPTED 7 September 2012. First published online 19 October 2012.

ADDRESS FOR CORRESPONDENCE: Levente Littvay, Central European University, Nádor u. 9., Budapest 1051, Hungary. E-mail: littvayl@ceu-budapest.edu

estimate the hereditary model of this phenomenon, Julia Métneki and Andrew Czeizel initiated a second, volunteer adult twin registry, recruiting with newspaper ads and other media presence (Flatz et al., 1985; Métneki, 1996; Métneki et al., 1984).

These two twin registries allowed for multiple national research projects assessing child age math aptitude, intelligence, creativity, and musical talent, augmented with neurophysiological assessments (Métneki, 1996). Other studies focused on psychological and sociological characteristics; one study assessed premenstrual syndrome symptoms as a mood disorder and suicide risk factors (Métneki, 1996), another the impact of metal load on heart rate variability (Láng et al., 1992).

In a collaboration with dentists, a comparative study was performed on the consumption of cariogenic food in MZ and same-sex DZ twins (Pados et al., 1989).

After investigating the effect of periconceptional multivitamin supplementation containing folic acid on fertility in the pregnant women taking part in the Hungarian Optimal Family Service, Andrew Czeizel and Julia Métneki first reported their 'side-effect', namely, the higher frequency of twin pregnancies (Czeizel et al., 1994).

Recently, a never before published psychosexual assessment was made available to the international research community (Métneki et al., 2011). Much of the results were reconstructed from notes, summary statistics, and presentation slides from the 1980s and 1990s. Attempts to revive the original data involved going through bulk paper storage without appropriate filing, often matching handwriting, for surveys where the paper clips had fallen off and the pages had become shuffled. Despite our efforts, we could not reconstruct all of the original data (due to one missing container with almost all DZ male respondents). The female sample was almost entirely reconstructed and is being processed now in the hope of future studies.

The availability of the registries also led to multiple international collaborations, including a study with the Hamburg Genetic Institute on alcohol consumption, sensitivity, and metabolism (Agarwal et al., 1997), a melanoma prevention study in collaboration of the Hamburg Dermatology Clinic looking at naevi (Roser et al., 1993; Breitbart et al., 1996; Weichenthal et al., 1994), and the already cited study on adult lactose intolerance in collaboration with the World Health Organization and the Hannover Human Genetics Institute (Flatz et al., 1985; Métneki et al., 1984).

The third database, the Hungarian Congenital Abnormality Registry (HCAR), was established in the same year as the BTR (1970) and included personal and medical data of multiple births (Czeizel, 1996). This population-based registry offered also a unique opportunity to study the relation of twinning and birth defects in national (Métneki, 1978; Métneki & Czeizel, 1987; Métneki et al., 1992, 1996) and international studies (Mastroiacovo et al., 1999). In a Hungarian study of conjoined twins, the role of genetic factors was

found to be negligible as compared to the environmental (teratogenic and maternal) effect in the etiology (Métneki & Czeizel, 1989). Recently, HCAR took part in a multicenter worldwide collaborative epidemiological study of the International Clearinghouse for Birth Defects Surveillance and Research, including 21 Clearinghouse Surveillance Programs related to conjoined twins (Mutchinick et al., 2011). The recent international registry-based study in collaboration with 14 European countries 1984–2007 organized by EUROCAT outlined the long-term consequences of the increasing prevalence of multiple births observed in the last two decades (Boyle et al., in press).

Current Research

A Hungarian Twin Club was founded in the early 1980s, and since then twin meetings are common around the country. Annual meetings are held at Szigethalom (13th annual national meeting in 2012), Ágfalva (6th annual international meeting in 2012), and Kunhegyes (9th biannual meeting in 2012). The old volunteer registry and these meetings are at the foundation of the new volunteer twin registry. Additionally, we are augmenting this list with social media presence, a continuous push in the more traditional media, and via the website (<http://www.ikerkutatas.club.hu>). Adam and David Tarnoki (winners of the 'Most alike male twins between 20–25 years' award at Twinsburg in 2006) regularly appear in the media discussing twin meetings and new findings of twin studies, and regularly make public appeals for both MZ and DZ twins to join the registry.

Since the revived efforts in 2007, multiple studies have been published. A study led by Gyorgy Jermendy and János Osztovits involved 101 twin pairs and investigated the genetic effects on the risk factors of metabolic syndrome and cardiovascular autonomic function (Jermendy et al., 2011a, 2011b, 2011c; Osztovits et al., 2011). The article published in the Hungarian Medical Journal (*Orvosi Hetilap*) received the journal's prestigious Markusovszky award of excellence in 2011. Additional twin studies focused on sensitivity to weather changes (Tárnoki et al., 2007) and venous biomechanics (Tárnoki et al., 2012a).

In addition to the national studies, the registry already engaged in multiple international collaborations mainly with the Italian Twin Registry (Fagnani et al., 2006). An international twin study was organized by Adam and David Tarnoki in Hungary, Italy (Rome, Padua, Perugia), and in the United States (Twinsburg) in 2009 and 2010 involving 160 Hungarian, 180 Italian, and 50 American twin pairs. Italian twins were recruited by the Italian Twin Registry. The study involved over 20 comprehensive, mainly anthropometric, cardiovascular, respiratory, and ophthalmologic measurements. The results were presented at various international meetings and one study received the European Respiratory Society's Annual Inflammatory Airway Diseases and Clinical Allergy Grant award for the third best paper

in 2010. The publication of the results is still in progress (Medda et al., 2012; Rácz et al., 2011; Tarnoki et al., 2010a, 2010b, 2010c, 2011a, 2011b, 2012a, 2012b, 2012c, 2012d, 2012e).

In 2012, data was collected on ideology and political participation to supplement a multi-country meta-analysis of political attitudes. We are planning additional studies on obesity-discordant MZ twins with the collaboration of Kirsi Pietiläinen (Finnish Twin Registry) (Kaprio, 2006). In addition, a social, psychological, further cardiovascular, and respiratory twin studies are in progress.

Characteristics of the Registry

Currently, the registry consists of 310 adult twin pairs (or multiplets — 65% MZ, 15% DZ, 20% DZO — 6 triplets, 1 quadruplet, 70% female, mean age 44 ± 16 years). As it is common with volunteer registries, we also have a higher proportion of MZ and female twins (Lykken et al., 1978). In the current database, we have data on risk factors, diseases, and surgeries in addition to contact information (including address, telephone, and email). We archived various data on past studies (e.g., blood pressure, arterial stiffness; carotid, cervical, and abdominal ultrasound; lung function; airway responsiveness; grip strength; body composition; echocardiography; venous distensibility and elasticity; several laboratory parameters; smoking, nutrition, physical, and social activity data).

Zygoty is assessed with multiple questions and latent class analysis in line with the recommendations of Heath et al. (2003). Due to lack of funding, twins rarely receive any incentives for participation in studies. In the study led by György Jermendy they were offered travel reimbursements.

Future Directions

At this point in time, the management of the increased interest in twin studies is challenging. It is especially important that twins are not bothered too often with study requests. In the short run, we are increasing the size of the volunteer registry and continuing the work that started in 2007 with international collaborations. In the long run, we are hoping for the establishment of a population-based twin registry either through the utilization of the 1970–1980s Budapest multiple birth records cited above or using population databases available to the government which contain birth name, birthplace, birthday, and mother's maiden name. Matching on all these records could yield a list of highly probable twin individuals. Unfortunately (or fortunately), Hungary's strict privacy laws and the quickly changing legal structures (e.g., recently changed constitution, uncertainty concerning existing case law, rewriting of many laws, all done in the past few years) make both of these efforts difficult. Health records and family relation information have, in the past, been classified as especially sensitive by law and case law. Hopefully, the uncertainty associated

with the legal changes will be alleviated as time passes or, if needed, new regulations will make the expansion of a population-based twin registry possible.

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