

Twin Studies in Finland 2006

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In studies on the Finnish Twin Cohorts, genetic and environmental determinants of common, complex diseases, and their behavioral risk factors have been investigated in Finland. In 1974, the older twins were identified, with a total of 13,888 like-sexed pairs of known zygosity. They have participated since 1975 in mail surveys, clinical examinations for subsamples, have been used to recruit families, and have been followed up for morbidity using national medical registers. Opposite twin pairs were added later. Two longitudinal studies of adolescent twins and their families, known as the FinnTwin12 and FinnTwin16 studies, have focused on determinants of health-related behaviors and disease in adolescents and young adults. This article describes current, ongoing data collection and analyses.

In Finland, multiple births since the 1950s can be identified through the use of family member links added in the early 1970s for all persons in the database of the Population Register Centre, which cover all Finnish citizens and permanent residents. Thus, persons born on the same day to the same mother are considered multiples. From this database, we invited participation to two longitudinal studies in the 1990s: FinnTwin16 (twins born 1975–1979), and FinnTwin12 (twins born 1983–1987; Kaprio et al., 2002). Both studies have been a close collaboration with Professor Richard Rose and his colleagues at Indiana University over the past two decades. Prior to that, we had identified and studied older Finnish twins (born before 1958) starting in 1975 as described earlier (Kaprio & Koskenvuo, 2002). The present article provides updated information on the status of these three longitudinal study cohorts with a focus on phenotype collection and new analyses since 2002. We have not expanded our studies to include new birth cohorts. The update progresses from the youngest to the oldest twins.

FinnTwin12

A longitudinal study of five consecutive birth cohorts (1983–1987) of Finnish adolescent twins has enabled a rich database for the investigation of adolescent health. Some 2800 families have enrolled in this two-stage study. The twins born between 1983 and 1987 were ascertained from the Finnish population register.

In the first phase the twins, their parents and teachers filled out questionnaires when the twins were 11 to 12 years old, with a first follow-up of the twins at age 14. At baseline, both parents and twins completed questionnaire assessments of their use of alcohol, smoking, lifestyle and health status; parents and teachers assessed aspects of the twins' behavior. A second follow-up questionnaire, at age 17.5 years, was initiated in autumn of 2000 and completed in the spring of 2005. Each cohort was mailed questionnaires from either March to April, or from September to October, closest to the time when they were aged 17.5 years. Many items from the baseline and the questionnaire completed at age 14 are repeated, with additional age-specific items on health behaviors. We also asked for mobile phone and Internet use, as new means of social interaction common among today's youth. A total of 4236 questionnaires were returned out of 4594 mailed, a response rate of 92%.

From the five consecutive birth cohorts, a subset of 1035 families of twins was formed for the intensive study. All parents in the intensive subset were interviewed ($N = 1860$) with a semistructured psychiatric assessment interview; their twins had been interviewed at age 14 ($N = 1852$) with the adolescent version of the same instrument to assess substance use and psychiatric morbidity in adolescence.

In 2006 the fourth wave of data collection was initiated. The major goal of this research is to gather information on young adults' health at ages 20 to 24 years, in a large sample of Finnish twin pairs previously assessed on three different occasions. This wave will broadly inform, not only lifestyle (physical exercise, food habits, dieting), substance use and abuse, psychiatric conditions, chemosensory preferences, but also about psychological health (mood and regulation of emotions), general health (illnesses, body composition, metabolism, experienced health), personality, cognitive functions (like memory and attentiveness), and work life and occupation. Twins are invited for a 1-day assessment in Helsinki. Body composition is measured, blood samples taken for biochemistry and

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genetic analyses, and data is collected on taste and smell. A semistructured psychiatric assessment interview repeats the same key domains as at age 14. Furthermore, psychosocial factors are being assessed and neuropsychological tests conducted. The assessments will be completed by the end of 2008.

FinnTwin16

The FinnTwin16 study is a longitudinal study of twins born between 1975 and 1979 and their parents and siblings, with three adolescent questionnaires administered at ages 16, 17 and 18.5 years (Kaprio et al., 2002). Starting in the autumn of 2000, we semiannually contacted the annual birth cohorts, such that twins born in 1975 were contacted then, those born in 1976 and 1977 in spring and autumn of 2001 respectively, and during 2002, twins born in 1978 and 1979 were contacted in the spring and autumn to complete the fourth wave of data collection. The last questionnaires were returned in 2003. Of those who had participated at baseline, a total of 5594 subjects (2689 men, 2905 women) could be reached between 2000 and 2002, and questionnaires were returned by 4929 (2239 men, 2690 women), yielding a response rate of 88.1% (83% for men, 93% for women). These numbers included 173 questionnaires, out of 196 mailed, returned by twins born in the last 3 months of 1974, who had been pilot subjects for testing questionnaire functioning at all phases. In the last wave of data collection, twins who had not replied at baseline were contacted to give them

the opportunity of declining further participation. Of those that had not participated at baseline (either because they had chosen not to participate or we could not reach them), 307 out of 602 subjects responded (51%). The questionnaire administered to this group included items on zygosity not otherwise asked of those who had responded earlier, but the questionnaire was otherwise identical.

The questionnaires for the young adult cohort included a food frequency questionnaire, eating patterns, night eating, Eating Disorders Inventory, eating disorder history, self-reported height and weight, weight history and dieting attempts, a tape measure for waist circumference, physical activity, assessment of alcohol use and alcohol-related problems, tobacco use, cannabis use, religiosity, sexual history, health habits, mental health and various health indicators (asthma, hay fever, general health status, back problems, eating disorders, symptom frequency). This data set is being used for multivariate genetic modeling of the relationships between diet, eating patterns, disordered eating and anthropometrics as part of the EU-funded Diogenes-project (www.diogenes-eu.org), which is investigating the relationships of diet, genes and obesity.

Co-twin Control Studies

Within FinnTwin16, we have conducted a series of co-twin control studies to investigate the causes and consequences of obesity, alcohol use, eating disorders and physical fitness. We have used the FinnTwin16

Table 1

Phenotyping of Selected Twin Pairs Discordant and Concordant for Obesity in FinnTwin16

1. Fasting blood samples for DNA, routine hematology, biochemistry and lipids, cytokines, neuropeptides 1a clotting samples for EUROCLOT, a EU-funded project led by Tim Spector
2. Body composition and anthropometrics by DEXA, bioelectrical impedance, skinfolds, and circumferences
3. Body fat accumulation (subcutaneous and visceral fat content by MRI, intrahepatic and intramyocellular fat content by proton spectroscopy)
4. Adipocyte gene expression from subcutaneous fat biopsies, candidate genes and genome-wide microarray analyses, mitochondrial DNA sequencing & telomere length assays
5. Lipidomic analyses
6. Intra-arterial endothelial function
- 7a. Oral glucose tolerance test or
- 7b. Whole body insulin sensitivity under normoglycemic hyperinsulinemic conditions (the clamp technique)
8. Test meal with ghrelin and leptin assays
9. PROP- and fat-tasting procedures
10. Resting energy expenditure (indirect calorimetry) and a 14 day-total energy expenditure in free living conditions (the doubly labeled water technique)
11. Accelerometers and physical fitness by bicycle spirometry
12. Questionnaires and interviews on past and current food intake by food diary, food preferences, physical activity, use of alcohol and smoking, health-related attitudes, weight history, family history and quality of life. Includes retest of FinnTwin16 4th wave FFQ
13. Structural and functional brain MRI, SPECT
14. Autonomic nervous system assays
15. Structured psychiatric interview
16. Growth curves from birth, infancy and school records
17. Questionnaires and qualitative interviews of the parents

Note: The core assessments done on all pairs are underlined.

longitudinal database to identify informative pairs and carry out intensive phenotypic assessments on relatively small numbers of pairs. These are briefly described below.

One way to study the effects of obesity in the absence of confounding due to genetic effects is to study monozygotic (MZ) twin pairs discordant for obesity. With this co-twin control design, we have examined relationships between obesity, body fat distribution, liver fat, adipose tissue gene expression, vascular function and insulin sensitivity independent of genetic effects (Gertow et al., 2004; Kannisto et al., 2004; Pietiläinen et al., 2005; Pietiläinen et al., 2004). For comparison discordant dizygotic (DZ) and concordant MZ pairs have also been studied. The intensive examination of MZ ($N = 24$) and DZ twin pairs ($N = 60$) discordant and concordant for body mass index (BMI) was completed in 2005. Core assessments are done on all target twin pairs (underlined text in Table 1), while additional ones were done only on the most informative pairs and their controls (all MZ pairs and 11 most discordant DZ pairs). An additional 50 pairs chosen at random will be examined by the end of 2006.

From the FinnTwin16 database, we have invited twin pairs concordant and discordant for their alcohol use developmental trajectory for further study. The assessments included a structured psychiatric interview, blood tests, neuropsychological testing, and EEG/ERP measures. We have studied 302 pairs in this NIH-funded study lead by Professor Richard Rose. The clinical phase started in January 2002 and data collection is now complete.

Another clinical study has examined pairs with eating disorders, which included a psychiatric assessment, single photon emission computed tomography (SPECT) and functional MRI neuroimaging, exercise spiroergometry, anthropometric and Dual Energy X-ray Absorptiometry (DEXA) measures of body composition, a brief neuropsychological test, a tasting protocol, and blood tests. A total of 14 twin pairs discordant for bulimia nervosa were examined (six MZ, four same-sex DZ, four opposite-sex DZ) and three twin pairs (two MZ, one same-sex DZ) concordant for bulimia. We also assessed 14 control twin pairs where neither twin had an eating disorder.

Finally we have initiated a study of MZ pairs discordant for physical fitness based on the FinnTwin16 sample. While studies in athletes and untrained subjects suggest that exercise training induces adaptations in cardiac structure and function, the role of genetic variation on the results has largely been ignored in these studies (Hannukainen et al., 2005). In order to investigate the effects of long-term volitionally increased physical activity on electrocardiographical, echocardiographical parameters and muscle metabolism during exercise, 12 male MZ twin pairs discordant for physical activity and fitness were recruited. All subjects completed a maximum oxygen

uptake (VO₂ max) test, electrocardiography and echocardiography studies. Positron Emission Tomography (PET) imaging studies of liver and muscle metabolism were conducted during an exercise protocol (Hannukainen et al., 2006).

The Older Finnish Twin Cohort

The older Finnish Twin Cohort study started in 1975, with follow-up questionnaires in 1981 and 1990. There has been registry-based follow-up, and numerous clinical and intensive studies on smaller numbers of twin pairs as described earlier (Kaprio & Koskenvuo, 2002). For the past 5 years, our focus has been on registry-based follow-up, reporting on studies in which data collection has been completed, and participation in multicentre studies.

The Family Study of Nicotine Dependence is part of an international consortium led by Dr Pam Madden, and primarily funded from 2001 to 2005 by NIH to address the genetics of nicotine dependence. The study sample consists of families ascertained for heavy smoking in at least two siblings, who have been sampled from amongst the older twin cohort (born before 1958) first assessed by questionnaire in 1975. Data on lifetime tobacco use, nicotine dependence, and associated factors were obtained by a detailed diagnostic telephone interview (average duration 120 minutes) and subsequent questionnaire. The interview yields diagnoses of nicotine dependence defined using *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) and the Fagerström Test for Nicotine Dependence, and the questionnaire yields a quantitative measure of nicotine dependence from the Nicotine Dependence Syndrome Scale (Shiffman et al., 2004). In addition, multiple other measures of smoking history including details on initiation, cessation and withdrawal symptoms are assessed as well as alcohol use, psychiatric comorbidity and demographics. DNA samples are collected by blood sampling at local health centers. A total of 2265 individuals from 762 families participated; 59% of invited families participated. Participants were somewhat older than nonparticipants, more often women than men, but participants and nonparticipants did not differ in amount smoked based on earlier questionnaire information.

GenomEUtwin (www.genomeutwin.org; PI Leena Peltonen) is a European Union-funded project running from 2002 to 2007 that combines twin cohorts/registers from seven European countries (Denmark, Finland, Italy, the Netherlands, Norway, Sweden and United Kingdom) and Australia. The GenomEUtwin sample consists of almost 700 000 twin pairs. We have participated in studies of height, BMI, migraine, cardiovascular risk factors, coronary heart disease and stroke, and longevity as part of the project. In the project, standard operating procedures and standardized data reporting procedures have been developed. To permit multicentre analyses

Table 2

Doctorate Theses Based Partly or Entirely on the Twin Cohort Data Sets and Substudies in 2002–2006

Maija Harrela	<i>Twin and epidemiological studies on insulin-like growth factor binding protein I, relationships to insulin sensitivity and cardiovascular risk.</i> University of Helsinki, 2002.
Elisa Huovinen	<i>An epidemiological study of occurrence, prognosis and predisposing factors of adult asthma.</i> University of Helsinki, 2002.
Marja Aarnio	<i>Leisure-time physical activity in late adolescence — A cohort study of stability, correlates and familial aggregation in twin boys and girls.</i> University of Kuopio, 2002.
Sofia Carlsson	<i>Weight history, low birth weight, alcohol consumption and type 2 diabetes.</i> Karolinska Institute, 2003.
Tarja Järvenpää	<i>Monozygotic twins and cognitive decline with emphasis on Alzheimer's disease.</i> University of Turku, 2003.
Tiina Milan	<i>Genetic and lifestyle determinants in skin cancer: Study of the nationwide twin and cancer registry cohorts.</i> University of Turku, 2003.
Laura Jartti	<i>Markers of subclinical atherosclerosis. A study of middle-aged male twins discordant for migration from Finland to Sweden.</i> University of Turku, 2003.
Kirsi Lillberg	<i>Psychological stress, personality and risk of breast cancer: Follow-up studies in the Finnish Twin Cohort.</i> University of Helsinki, 2003.
Torsten Winter	<i>Abstinence and its determinants among youths (in Finnish).</i> University of Helsinki, 2004.
Karl Gertow	<i>Fatty acid transport proteins.</i> Karolinska Institute, 2004.
Elina Vierikko	<i>Genetic and environmental effects on aggression.</i> University of Jyväskylä, 2004.
Katja Kannisto	<i>The metabolic syndrome — Studies on thrifty genes.</i> Karolinska Institute, 2004.
Miika Hernelahti	<i>Physical activity, inherited characteristics, and hypertension.</i> University of Helsinki, 2004.
Anna Keski-Rahkonen	<i>Genetic and environmental influences on body image, disordered eating, and weight control.</i> University of Helsinki, 2004.
Kirsi Pietiläinen	<i>Born to be heavy? Determinants of body size from birth to early adulthood.</i> University of Helsinki, 2004.
Hanna Harno	<i>Migraine and episodic ataxia type 2: A clinical, genetic, neurologic, and magnetic resonance spectroscopy study.</i> University of Helsinki, 2005.
Tuula Kiesepää	<i>A twin study on genetic and environmental factors in bipolar disorder.</i> University of Helsinki 2005.
Jussi Hirvonen	<i>Brain dopamine receptors and genetic risk for schizophrenia — A twin study using positron emission tomography.</i> University of Turku, 2005.
Mari Kaunisto	<i>Assignment of genetic loci and variants predisposing to migraine with aura and episodic ataxia type 2.</i> University of Helsinki, 2005.
Elina Suviolahti	<i>Search for genetic variants conferring susceptibility to obesity and related metabolic traits.</i> University of Helsinki, 2005.
Jarna Hannukainen	<i>Effects of increased physical activity and aerobic fitness on healthy monozygotic twins — With special reference to heart and skeletal muscle.</i> University of Turku, 2006.
Varpu Penninkilampi-Kerola	<i>Implications of co-twin dependence for twins' social interactions, mental health and alcohol use. A follow-up study of Finnish twins from adolescence to early adulthood.</i> University of Helsinki, 2006.
Kristina Tiainen	<i>Heritability of skeletal muscle characteristics and functional limitation among older female twins.</i> University of Jyväskylä, 2006.
Satu Pajala	<i>Postural Balance and Susceptibility to Falls in Older Women — Genetic and environmental influences in single and dual task situations.</i> University of Jyväskylä, 2006.

without jeopardizing data security, a federated database has been created. A 2003 special issue of *Twin Research* was devoted to the project, to which the reader is referred (Peltonen, 2003)

The Finnish Twin Study on Aging (FITSA) lead by Professor Taina Rantanen is a study of genetic and environmental effects on the disablement process in older female twins. Four hundred and fourteen female pairs aged 63 to 76 years old and alive in 2000 were initially contacted. Further description of the participation in FITSA was reported earlier (Pajala et al., 2004; Tiainen et al., 2004; Tiainen et al., 2005). The final study sample at baseline included 103 MZ and 114 DZ complete pairs, who participated in a 1-day laboratory assessment of functional abilities (such as

muscle strength, walking speed, balance), and health status (such as hearing ability and risk of falls during a 1-year follow-up) at the University of Jyväskylä. Three years later an invitation to participate in the follow-up examinations was sent to all baseline participants. As 106 individuals consented to participate solely in an interview, the follow-up sample consisted of 145 MZ and 168 DZ individuals after excluding deceased subjects and refusals. These 313 twins participated in the laboratory measurements in addition to the interview.

In collaboration with the University of Turku and the Turku PET Centre, elderly (born before 1938) MZ and DZ twins are being screened to identify twin pairs discordant with respect to Alzheimer's disease. Screening will be completed in 2006. Out of a large

number of twin pairs, we first identified a small sample of MZ pairs discordant for dementia. These pairs were then invited for clinical assessment and underwent extensive neuroimaging using MRI and PET imaging (Järvenpää et al., 2004; Järvenpää et al., 2003a; Järvenpää et al., 2003b). We have shown that binge-drinking in middle age predicts dementia 25 years later (Järvenpää et al., 2005)

Concluding Remarks

This article is not an exhaustive description of all the studies or publications on the Finnish twin cohorts based at the Department of Public Health, University of Helsinki. Over the years we have collaborated with many scientists in Finland and abroad; such collaboration is possible when it is compatible with the aims of the ongoing studies. Such collaborations have resulted in single papers but also Doctorate thesis work (Table 2). Secondary analyses of existing data could also be carried out. Please contact the author for more details.

In addition there are other twin studies conducted in Finland, such as the highly respected long-term studies on the development of twins lead by Professor Irma Moilanen at the University of Oulu. Recently, studies on normal and abnormal sexual behavior were conducted in 2005 and 2006 at Åbo Academy, Turku. These are independent of our studies; despite agreeing to avoid overlap in target birth cohorts, twins in FinnTwin12 and FinnTwin16 were also targeted. When considering approaching twins researchers know to have participated in earlier studies, careful coordination with the researchers of the prior study should be undertaken in order not to jeopardize the participation of twins and their families in planned and future research.

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