Genetic and Environmental Factors in Complex Diseases: The Older Finnish Twin Cohort

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In studies on the Finnish Twin Cohort, we investigate genetic and environmental determinants of common, complex diseases, and their behavioral risk factors in Finland, a genetically unique and culturally homogenous population. We have formed the following databases: 1) Like-sexed twin pairs (13,888 pairs of known zygosity) form the older Twin Cohort. They have participated since 1975 in mail surveys, in clinical examinations for subsamples, and have been followed-up for morbidity using national medical registers; 2) The older Twin Cohort was expanded in 1996 to include opposite-sex pairs born 1938–1957 (c. 8000 pairs); 3) Two, new longitudinal studies of adolescent twins and their families, form a complementary, ongoing study base described in more detail in an accompanying article. Genetic and environmental effects vary over the life-span, and only longitudinal studies in genetically informative data sets permits the evaluation of such effects. Finally, the inclusion of DNA-based genetic information in a phenotypically rich family data base will offer a unique resource for research in genetic epidemiology and behavioral medicine.

In Finland, there is a combination of unique resources that create an invaluable resource for population-based genomic epidemiological studies. These include its population history as a genetic isolate, genealogical records extending back many generations, a uniform and well-developed health care system with computerized records, and a well-educated population.

Genetic isolates are the result of some type of bottleneck in the history of a population, revealing the consequences of the founder effect and genetic drift on the population's gene pool. In human populations, isolation is suspected to be based on an exceptional geographic location or cultural history, or on the prevalence of relatively rare genetic diseases. The concept of "Finnish disease heritage" is well established in the literature, but solid data have only recently emerged regarding the uniformity of disease mutations at the molecular level in this population: for many Finnish diseases for which the molecular defect has been uncovered, over 90% of disease alleles carry the same causative mutation. This suggests dramatic isolation, especially in some subregions of the sparsely populated country. While extremely useful for monogenic disorders, it also appears to help in complex disorder studies (Peltonen et al., 2000).

In Finland, this molecular information can be combined with the exceptional genealogical data offered by a well established church record system which dates back to 1640, containing detailed information on births, deaths, marriages and movements of the majority of population. This provides excellent opportunities for special study designs for the identification not only of rare disease genes but also of major loci which contribute to complex diseases. Twin data sets collected from such an isolate such as Finland are of special value. Besides a higher degree of genetic homogeneity provided by isolation, maximized environmental homogeneity during foetal life and childhood minimize the problems often encountered in study populations collected for analyses of complex diseases. Concordant dizygotic twins offer ideal sibpair materials for diseases prevalent in the population, and concordant monozygotic pairs should expose the cases with exceptionally high degrees of genetic predisposition for association type studies. In addition, via twins, reliable information can be collected from other family members, and twins actually offer an easy access to collect representative families with multiple affected individuals. In the case of diseases that can be quantitatively dissected to subgroups, the possibility to collect phenotypically discordant dizygotic twins is a valuable asset not only for initial locus identification, but also for replication and confirmation studies.

A further feature of Finland is the existence of national registers of mortality and morbidity, which permit follow-up of cohort members for many diseases and disorders. Their high quality reflects the universal coverage of and access to the Finnish health care system. It is thus within this context that we have developed and expanded the Finnish Twin cohorts as resources for studies of the genetic and environmental contributions to risk in complex disorders and diseases.

Datasets

The Finnish Twin Cohorts (Kaprio et al., 1978; Kaprio, 1994) form a national resource for genetic epidemiological studies. Twins and their families have been ascertained in

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three stages from the Central Population Register for studies of the genetic and environmental determinants of common, chronic diseases. In this paper we will focus on recent and in-progress research based on the older twin cohort. A comprehensive list of publications and a review of studies completed by the early 1990s was published in 1994 (Kaprio, 1994).

Cohort of Older Like-sexed Twins (Born Before 1958)

The older part of the Finnish Twin Cohort consists of all Finnish twin pairs of the same gender born before 1958 with both co-twins alive in 1975. These twin pairs were selected from the Central Population Registry of Finland in 1974. Three surveys of the entire cohort have been carried out. The first questionnaire was mailed to all pairs in August–October 1975. Two follow-up questionnaire studies have been carried out in 1981 and 1990. Twin zygosity was determined by a validated questionnaire methods initially in the entire cohort (Sarna et al., 1978). In studies of selected twin pairs, genetic markers have been used for validation. The total number of MZ and DZ twin pairs was 13,888 in the beginning of prospective follow-up in August 1975.

Expansion of Older Cohort in 1996 to Include Opposite-sex Pairs

In 1996, opposite-sex (OS) twins born 1938–1949 have been identified from the Central Population Registry. So far, questionnaire data and DNA samples from over 1500 pairs have been collected in 1997. These are pairs in which one or both of the twins reported that they have been diagnosed with one of selected chronic diseases. This new material represents a substantial new population of sibpairs, while permitting the expansion of the twin design to assess sex by gene, sex by environment as well as sex by gene by environment interactions. Questionnaire data have been used to study sex-limitation models such as for height (Silventoinen et al., 2001), but also as phenotypic information to identify affected sibpairs for molecular genetic studies as described in Table 1.

Younger Twins

In 1986, a new twin panel was established from all twin pairs (including parents of twins) born in Finland during 1958–1986. It consists of 21,958 twin pairs (6114 monozygotic, 7922 same-sexed dizygotic and 7922 pairs of opposite sex). From 1974 onwards it corresponds closely to the number of twin births recorded by the Central Statistical Office. Higher-order multiple births are also included. Two main studies, the longitudinal FinnTwin12 and FinnTwin16 studies are based on the younger cohort and these are described in more detail in an accompanying article. Current numbers of twins from all cohorts are shown in Table 2.

Resources and Follow-up Of Twins

The Department of Public Health, University of Helsinki provides core facilities of office and storage space, and computer network access for the cohort studies, but funding has nearly all been through competitive grant money. We have our own dedicated server, with an Oracle database to ensure data integrity and data protection.

Morbidity follow-up of the twins has also been through nationwide computerized medical registries: incident malignancies through the Cancer registry (Lichtenstein et al., 2000), hospitalizations through the Hospital Discharge Register (Keskimäki & Aro, 1991), and information on selected diseases based on the Register for fully-reimbursable medications. Mortality follow-up is currently complete up to June 2001. Extensive analyses of this data have been carried out and reported.

Community Relations, Ethics and Data Protection

We have also actively informed the media (TV, radio, and press) of major results, publications and other milestones through interviews and press releases. Thus, we disseminate project results to the public primarily through the media, but also using personal feedback to the participants.

No selection criteria except age on twins' ascertainment were initially used to establish the cohorts; these are population samples. Initial contact with the twins has been made in a letter, which explains the study purpose. Any individual

Table 1

The Components of the Finnish Twin Cohort

Birth years	Like-sexed pairs	Opposite-sex (OS) pairs	Notes
Before 1938	13,888 pairs of known zygosity (compiled 1974)	Not identified	—
1938–1949		5017 candidate pairs, estimated c. 85% twins	New cohort compiled in 1996 from CPR
1950–1957		3047 twin pairs	
1958–87	21,958 pairs of which 7922 OS-pairs (compiled 1987) born 1958–1986		FinnTwin16: twins born 1975–79 FinnTwin12: twins born 1983–1986 & 1987 (added later)

Table 2

The Age, Sex and Zygosity Distribution and Sex of Twins from Pairs with Both Members Alive in 2001 in the Finnish Twin Cohorts

Age	MZ twins (*n*)	DZ twins (*n*)	Total
15–24	3856	8158	12,014
25–34	3278	8298	11,576
35–44	3530	12,370	15,900
45–54	2598	11,268	13,866
55–64	1468	7226	8694
Over 64	1106	2486	3592
Total	15,836	49,806	65,642

Note: In some age-groups, the distribution is partly estimated from the male/male, female/female and male/female distribution of pairs.

No OSDZ pairs born before 1938 are included, and therefore the proportion of DZ twins in the oldest age group is smaller than elsewhere.

in new proposed research may decline to complete a questionnaire or may decline subsequent participation without penalty of any kind; likewise requests not to participate are honored, in accordance with data protection legislation. Data are collected for research purposes only. All questionnaire and registry data are obtained in coded format, based on assignment of research codes to each twin and for each individual member within each family, and outsiders cannot identify individuals or families in the subject samples. With this procedure, risks to confidentiality are minimized.

Twin subjects receive no direct health benefit from their participation in questionnaire studies, but they are given informational feedback on various aspects of the questionnaire content. Twins participating in clinical studies get feedback on results, and if for any reason further investigations are necessary, they receive the necessary guidance and information to contact their physician/hospital. Families/twins also receive newsletters from the research group. The overall cohort study was set up with permission from the Ministry of Social Affairs and Health, and has since been approved by the data protection ombudsman. Individual studies are approved by the participating institutions' ethical committees.

The study also is a resource for training and education of researchers, and has been used in the doctoral theses of both Finnish and foreign students (Table 3).

Genetic Epidemiological Studies of the Entire Cohort

The older twin cohort has been analyzed for many traits to estimate the contribution of genetic factors using the classical twin model. Examples of high, moderate and low heritability traits are shown in Table 4. The tables and following examples are not exhaustive of all studies that have been done, but illustrate recent work.

We have used the dataset to investigate the interrelationships of physical activity, familial factors and disease outcomes. A physically active lifestyle has been reported to prevent from many chronic diseases, but genetic selection has been claimed as an explanation. By investigating the Finnish Twin Cohort we have shown that genetic selection accounts for some of the beneficial effects of physical activity, but after controlling for genetic and other familial factors physical activity itself also has a protective effect. This has been examined in relation to a variety of outcomes: premature mortality (Kujala et al., 1998) coronary heart disease, diabetes and hip fractures(Kaprio et al., 2000; Kujala et al., 2000; Kujala et al., 2000) and for the use of hospital care ((Kujala et al., 1999)). Most of these analyses have been based on the co-twin-control method (Duffy, 2000), which is an application of a matched case-control design to twin data.

After demonstrating a genetic component to asthma in one of the first population studies (Nieminen et al., 1991),

Table 3

The Following Doctoral Theses Have Been Completed Since 1993 Based Completed or Partly on the Finnish Twin Cohort

1. Erkki Vesterinen. *Natural killer cells, asthma and cancer risk.* Helsinki 1993.
2. Christer Hublin: *Narcolepsy — Epidemiology, clinical picture and treatment.* Helsinki 1994.
3. Pentti Järvinen: *Twin studies of rheumatic disease.* in Finnish. Tampere 1994.
4. Elise Kosunen: *Adolescent reproductive health in Finland: Oral contraception, pregnancies and abortions from the 1980s to the 1990s.* Tampere 1996.
5. Leena v Hertzen. "*Chlamydia pneumoniae infection in chronic obstructive pulmonary disease — Diagnostic, epidemiological and immunological aspects.* Helsinki 1996.
6. Kirsi Appelberg. *Interpersonal conflicts at work: Impact on health behavior, psychiatric morbidity and work disability.* Helsinki 1996.
7. Helena Kemppainen. *Peptic ulcer disease — Effect of age, risk factors, gastric function and heritability.* Turku, 1997.
8. Riitta Simonen. *Determinants of adult psychomotor speed — A study of monozygotic twins.* Jyväskylä 1997.
9. Heli-Tuulie Koivumaa-Honkanen. *Life satisfaction as a health predictor.* Kuopio 1998.
10. Laura Gibbons. *Back function testing and paraspinal muscle magnetic resonance image parameters: Their associations and determinants. A study of male, monozygotic twins.* Jyväskylä 1998.
11. Maarit Korkeila. *Genetic and environmental determinants of body mass index and weight gain.* University of Helsinki, Helsinki 1999
12. Laura Oksanen. *Common variants of the leptin, leptin receptor and β_3-adrenergic receptor genes in human morbid obesity.* Helsinki 1999
13. Markus Perola. *Molecular genetics of hypertension and related traits.* Helsinki 1999
14. Sirpa Sarlio-Lähteenkorva. *Losing weight for life? — Social, behavioral and health-related factors in obesity and weight loss maintenance.* Helsinki 1999.
15. Maija Räsänen: *Familial aggregation and risk factors for asthma and hay fever among finnish adolescent twins — A twin family study.* Helsinki 2000.
16. Karri Silventoinen: *Body height: determinants and associations with social position and adult health.* Helsinki 2000.
17. Mikko Kallela. *Clinical characteristics and pathophysiological mechanisms of familial migraine with and without aura.* Helsinki 2000.
18. Miina Öhman. *The search for genes predisposing to obesity.* Helsinki 2001.
19. Mika Palvanen. *Upper body fractures in older adults.* Tampere 2001.
20. Danielle M Dick. *Genes, environments and interactions: Specifying influences on alcohol use and related phenotypes.* Indiana University 2001

Table 4

Estimates of Heritability for Selected Traits Studied in the Finnish Twin Cohort, Together with Some Comparative Data from other Studies

Disorder or trait	Heritability (%)	First author & (year)
Bipolar I disorder	93	Kieseppä (2001)
Schizophrenia	83	Cannon (1998)
Height	66–82, age, sex dependent	Silventoinen (2000)
Hay fever	74–82	Räsänen (1998)
BMI, age 16 & 17	> 80	Pietiläinen (1999)
BMI, adults	male 72, female 68	Korkeila (1991)
Asthma, adolescents	65–79	Laitinen (1998)
Asthma, adults	< 50	Nieminen (1991)
Type 1 diabetes	76	Kaprio (1992)
Migraine	40–50	Honkasalo (1995)
Migraine with aura	68	Ulrich (1999), Danish study
Migraine without aura	61	Gervil (1999), Danish study
Rheumatoid arthritis	Finland 65 ,UK 53	McGregor (2000)
Osteoarthritis	40–49	Kujala (1999)
Sleepwalking	57 F, 66M	Hublin (1998)
Prostate cancer	42	Lichtenstein (2000)
Breast cancer	27	Lichtenstein (2000)
Colorectal cancer	35	Lichtenstein (2000)
Age at menarche	74	Kaprio (1995)
Leptin levels	F 34, M 45	Kaprio (2001)
Peptic ulcer	39	Räihä (1998)
Alcohol consumption, adult users	36	Kaprio (1987)
Neuroticism	27–31	Loehlin (1992), pooled analysis
Extraversion	32–36	Loehlin (1992), pooled analysis
Educational level	Female 43, Male 47	Silventoinen (2000)
Religious fundamentalism	Female 11, Male 22	Winter (1999)
Alcohol passout frequency	6	Kaprio (1987)
Basal cell carcinoma of the skin	8	Milan (1998)

we have continued by dissecting the genetic component by age and family history based on our FinnTwin16 study. (Laitinen et al., 1998). Dr. Elisa Huovinen is doing epidemiologic analyses based on the old cohort, examining changes in the prevalence and incidence of asthma (Huovinen et al., 1999), but also predictors on adult-onset asthma (Huovinen et al., 2001; Huovinen et al., 2001).

Sleep disorders have been included in the older cohort study program for nearly 20 years. These have included analyses of sleep length and quality on health outcomes in close collaboration with Markku Partinen and Christer Hublin (Hublin et al., 2001a; Hublin et al., 1996). We have continued by studying the genetic epidemiology of narcolepsy and common parasomnias based on data from the 1990 older twin cohort questionnaire (Hublin et al., 1994; Kaprio et al., 1996; Hublin et al., 1997; Hublin et al., 1999b; Hublin et al., 1999a; Hublin et al., 2001b; Hublin et al., 1998c; Hublin et al., 1998a; Hublin et al., 1998b). Sleep disorders show some comorbidity with psychiatric disorders; more so for adult parasomnias than in childhood. However, studies of depression have been based mainly on the Beck depression inventory given as part of the 1990 questionnaire (Verkasalo et al., 1997).

Cancer studies have shown that the incidence of cancer in the older cohort is no different from that of the general population (Verkasalo et al., 1999), apart from breast cancer (Verkasalo et al., 1999) where the incidence is higher in DZ twin sisters than MZ twin sisters. A joint Nordic analysis of cancer incidence in twins indicated sites (breast, prostate and colorectal) with genetic effects that were in excess of those accounted for by known cancer genes (Table 3), while confirming epidemiological evidence for a primary role of environmental factors in the etiology of most common cancers (Lichtenstein et al., 2000). The concordance for skin cancers appears to be quite small (Milan et al., 1998). Risk factor data in the early questionnaires has been used to examine psychological risk for breast cancer in a prospective design (Lillberg et al., 2001).

Current and Planned Projects

Studies on Samples of Twins

The TwinSpine study started as a study of male monozygotic twin pairs discordant for putative risk factors for low back pain as well as a sample chosen at random (Battié et al., 1991; Battié et al., 1995; Videman et al., 2001). This has now been expanded to include DZ twins, and specific gene markers in relation to environmental risk factors for low back pain and disc degeneration, assessed by magnetic resonance imaging, are being examined. The examinations on MZ and DZ pairs will be repeated to track changes over time, and their determinants.

The twin migration study examines chronic disease, risk factors and disability in *twin pairs discordant or concordant for migration to Sweden.* The higher rates of CAD in Finland than Sweden can arise from genetic or environmental differences. Extensive migration from Finland to Sweden has permitted identification of 1542 Finnish twin pairs, in which at least one twin has resided in Sweden for at least one year. This natural experiment permits the comparison of migrants with their age-matched sibs and controls partly or fully for genetic background and childhood experiences. Compared to their co-twins who remained in Finland, the mortality of the migrants first increased among males after migration, but after 15 to 20 years in Sweden, their risk of death became smaller (Hammar et al., 2002). In collaboration with Niklas Hammar at the Karolinska Institute, in 1998–99 we surveyed these pairs with an extensive mailed questionnaire, which had sections on migration history, integration in Swedish society (for the migrants only), health and lifestyle, work-related factors and an extensive dietary history. The migrant study includes a detailed clinical, state-of-the-art examination of cardiovascular status in 76 male twin pairs discordant for long term (at least 20 years) residence in

Sweden carried out in collaboration with professor Tapani Rönnemaa at the Turku University Central Hospital.

In collaboration with Professor Leena Peltonen at the National Public Health Institute, Helsinki and clinical investigators, we have used the twin cohort to search for *specific liability loci* for using candidate gene and genome scan approaches with respect to osteoarthritis (Leppävuori et al., 1999), hypertension (Kainulainen et al., 1999), migraine (Kallela et al., 1999) & obesity (Oksanen et al., 1997; Perola et al., 2001). Informative sibpairs and families selected through the older twin cohort have been the basis for these studies, and in some cases combined with family data from clinical and epidemiological studies.

A study of *twin pairs discordant for schizophrenia* identified through the family data set of psychotic disorders at the Department of Mental Health and Alcohol Research, National Public Health Institute (Professor Jouko Lönnqvist) in collaboration with professor Tyrone Cannon, UCLA examines neuropsychological and neuroimaging characteristics of phenotypically discordant MZ and DZ pairs (Cannon et al., 1998). At present 80 affected (30 MZ and 50 DZ pairs including 9 concordant) pairs and 76 (30 MZ and 36 DZ) non-psychotic control pairs selected from the Finnish Twin Cohort have also been studied by interview, neuropsychological tests and structural MRI (Cannon et al., 2000; Thompson et al., 2001). In smaller subsamples, functional MRIs and PET-scans of selected pairs are ongoing. A parallel study of *bipolar disease* was initiated in 1998. The protocol is nearly identical to that used in the schizophrenia study, with the same neuropsychological and neuroanatomical tests and imaging, with additional assessment of risk factors specific to bipolar disorder (Kieseppä et al., 2001). Thirty-eight pairs born 1940–1957 have been identified and studied, with a very high heritability estimate (Kieseppä et al., submitted).

In an ongoing study of dementia in twins, we have screened nearly 400 pairs of elderly MZ twins to identify Alzheimer's disease discordant pairs, using a sensitive and specific telephone screen — TELE, (Gatz et al., 1995, Järvenpää et al., in press). Confirmation of discordance was done using neuropsychological tests and MRI scans at the University of Turku. analyses of regional cerebral glucose metabolic rates (rCMRgluc) with fluorodeoxyglucose (FDG) PET-scans in eleven pairs of monozygotic twins discordant for dementia indicated differences between demented twins, healthy co-twins and age-sex-education matched controls.

The Finnish Twin Study on Ageing (FITSA) examines the process of frailty and disability in older women. A sample of 217 pairs of female MZ and DZ twins aged 65–75 years was recruited from among participants in the 1975 and 1981 questionnaires. A brief questionnaire concerning functional capacity and willingness to participate the study was mailed to 414 twin pairs in early autumn 2000, together with an invitation to a laboratory examination in the next six months at the University of Jyväskylä under the leadership of docent Taina Rantanen and professor Eino Heikkinen. Finally, 102 MZ pairs and 115 DZ pairs were investigated with a focus on physical capacity and functional abilities. Two re-examinations are planned.

Finally, we are participating in a multicenter family study funded by the United States (US) National Institutes of Health and headed by Professor Pamela Madden (Washington University, St. Louis) to search for genes involved in nicotine dependence and smoking cessation.

Why Study Twins?

We are using the Finnish Twin Cohort to identify the most genetically informative families for specific disease studies, which ultimately leads to discovery of novel disease mechanisms. Secondly, the long-standing longitudinal studies permit examination of the determinants of the dynamics of disease risk and risk factor levels over the lifespan. This research will increase our understanding both of the *genetic* factors contributing to the susceptibility to complex disease and health-related behaviors, as well as of the *environmental* factors causally involved in these conditions.

Earlier research has indicated that heredity often plays a significant causal role based on the results of family, twin, and adoption studies. The mode of inheritance, by definition, is not a simple Mendelian one and the exact patterns of inheritance of complex disorders have not been determined. Thus, it is not surprising that the relevant genes have generally not been found, and that the associations reported by some investigators have not been replicated in many cases, or are weak and clinically of little importance (Goldstein & Brown, 1997). Because of the clear environmental contribution in health-related behaviors, these are multifactorial disorders with complex genetics. The resolution of even some genes contributing to increased risk for alcohol abuse, sedentariness, smoking as well those for obesity and other complex somatic and psychiatric disorders would yield important insights into the pathophysiological mechanisms. This might again lead to better treatment modalities, targeted interventions and more rational prevention.

Why is it of importance to distinguish between genetic and environmental influences affecting the incidence of disease or variability of a trait? First, research resources are limited, and thus research areas and topics must be ranked in importance. For example, the use and abuse of alcohol is of greater importance than all other neurological and mental disorders, because of its vast public health and economic impact. It has been estimated that the cost of medical care and lost productivity in the United States due to abuse of alcohol was over 100,000 million USD — the figure for Finland is probably of the same magnitude relative to population size. Alcohol drinking is common and alcohol abuse and dependence is highly prevalent; so too are the consequences of smoking and obesity. As specific disorders, back problems, hypertension and schizophrenia all differ in the type of public health impact, yet all are major public health problems. In the study of the etiology of these complex disorders and traits, it might be reasonable to allocate research resources roughly in proportion to the probable impact of postulated causes. That is, if genetics accounted for a small portion of the variance, then it would be reasonable to allocate only a minor fraction of resources to their study. Alternately, if genetics accounted

for a large portion of the variance, then it might be reasonable to devote a larger portion of research resources.

Second, genetic effects imply predisposition, though not predetermination in complex disorders. The larger heritability, the smaller the impact we can expect environmental manipulations to have, in the range of environmental variation observed typically in our population. Thus, if traits are moderately heritable, attempting to modify them will affect them less, than if they are only slightly or not at all heritable; the age and time period of greatest probability for environmental intervention can also be identified. For example, results to date suggest that intervention on drinking in adolescents is likely to be more productive than expending the same effort on older adults. On the other hand, heritability tells us little about the likely effects of new environmental agents such as the introduction of a new drug, law, or incentive plan into a population. This obviously has great implications for primary or secondary prevention proposals.

Twin and twin-family studies can permit the resolution of environmental factors from genetic influence. At its most simplest mode, the existence of monozygotic twin pairs discordant for a disease or trait are prima facie evidence for environmental effects. Sophisticated statistical analysis can permit the quantification of the role of environmental factors, and the significance of specific factors can be tested, while taking into consideration other environmental factors, and simultaneously genetic susceptibility. This permits distinguishing between causal and non-causal environmental factors.

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References

Battié, M. C., Videman, T., Gibbons, L. E., Fisher, L. D., Manninen, H., & Gill, K. (1995). 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. *Spine, 20,* 2601–2612.

Battié, M. C., Videman, T., Gill, K., Moneta, G. B., Nyman, R., Kaprio, J., & Koskenvuo, M. (1991). 1991 Volvo Award in clinical sciences. Smoking and lumbar intervertebral disc degeneration: An MRI study of identical twins. *Spine, 16,* 1015–1021.

Cannon, T. D., Huttunen, M. O., Lönnqvist, J., Tuulio-Henriksson, A., Pirkola, T., Glahn, D., et al. (2000). The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *American Journal of Human Genetics, 67,* 369–382.

Cannon, T. D., Kaprio, J., Lönnqvist, J., Huttunen, M., & Koskenvuo, M. (1998). The genetic epidemiology of schizophrenia in a Finnish twin cohort. A population-based modeling study. *Archives of General Psychiatry, 55,* 67–74.

Duffy, D. L. (2000). The co-twin control study. In T. D.Spector, H. Snieder, & A. J. Macgregor (Eds.), *Advances in twin and sib-pair analysis* (pp. 54–66). London: Greenwich Medical Media.

Gatz, M., Reynolds, C., Nikolic, J., Lowe, B., Karel, M., & Pedersen, N. (1995). An empirical test of telephone screening to identify potential dementia cases. *International Psychogeriatrics, 7,* 429–438.

Goldstein, J. L., & Brown, M. S. (1997). The clinical investigator: Bewitched, bothered, and bewildered — But still beloved [editorial]. *Journal of Clinical Investigation, 99,* 2803–2812.

Hammar, N., Kaprio, J., Hagström, U., Alfredsson, L., Koskenvuo, M., & Hammar, T. (2002). Migration and mortality — A 20 year follow-up of Finnish twin pairs with migrant co-twins in Sweden. *Journal of Epidemiology and Community Health*, *56*, 362–366.

Hublin, C., Kaprio, J., Partinen, M., Heikkilä, K., & Koskenvuo, M. (1996). Daytime sleepiness in an adult, Finnish population. *Journal of Internal Medicine, 239,* 417–423.

Hublin, C., Kaprio, J., Partinen, M., Heikkilä, K., & Koskenvuo, M. (1997). Prevalence and genetics of sleepwalking: A population-based twin study. *Neurology, 48,* 177–181.

Hublin, C., Kaprio, J., Partinen, M., & Koskenvuo, M. (1998a). Nocturnal enuresis in a nationwide twin cohort. *Sleep, 21,* 579–585.

Hublin, C., Kaprio, J., Partinen, M., & Koskenvuo, M. (1998b). Sleep bruxism based on self-report in a nationwide twin cohort. *Journal of Sleep Research, 7,* 61–67.

Hublin, C., Kaprio, J., Partinen, M., & Koskenvuo, M. (1998c). Sleeptalking in twins: Epidemiology and psychiatric comorbidity. *Behavior Genetics, 28,* 289–298.

Hublin, C., Kaprio, J., Partinen, M., & Koskenvuo, M. (1999a). Limits of self-report in assessing sleep terrors in a population survey. *Sleep, 22,* 89–93.

Hublin, C., Kaprio, J., Partinen, M., & Koskenvuo, M. (1999b). Nightmares: Familial aggregation and association with psychiatric disorders in a nationwide twin cohort. *American Journal of Medical Genetics, 88,* 329–336.

Hublin, C., Kaprio, J., Partinen, M., & Koskenvuo, M. (2001a). Insufficient sleep — A population-based study in adults. *Sleep, 24,* 392–400.

Hublin, C., Kaprio, J., Partinen, M., & Koskenvuo, M. (2001b). Parasomnias: Co-occurrence and genetics. *Psychiatric Genetics, 11,* 65–70.

Hublin, C., Kaprio, J., Partinen, M., Koskenvuo, M., & Heikkilä, K. (1994). The Ullanlinna Narcolepsy Scale — Validation of a measure of symptoms in the narcoleptic syndrome. *Journal of Sleep Research, 3,* 52–59.

Hublin, C., Kaprio, J., Partinen, M., Koskenvuo, M., Heikkilä, K., Koskimies, S., & Guilleminault, C. (1994). The prevalence of narcolepsy: An epidemiologic study in the Finnish Twin Cohort. *Annals of Neurology, 35,* 709–716.

Huovinen, E., Kaprio, J., & Koskenvuo, M. (2001). Asthma in relation to personality traits, life satisfaction, and stress: A prospective study among 11,000 adults. *Allergy, 56,* 971–977.

Huovinen, E., Kaprio, J., Laitinen, L. A., & Koskenvuo, M. (1999). Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest, 115,* 928–936.

Huovinen, E., Kaprio, J., Laitinen, L. A., & Koskenvuo, M. (2001). Social predictors of adult asthma: A co-twin case-control study. *Thorax, 56,* 234–236.

Järvenpää, T., Rinne, J. O., Räihä, I., Koskenvuo, M., Löppönen, M., Hinkka, S., & Kaprio, J. (2002). Characteristics of two telephone screens for cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 13,* 149–155.

Kainulainen, K., Perola, M., Terwilliger, J., Kaprio, J., Koskenvuo, M., Syvänen, A.-C., et al. (1999). Evidence for involvement of the type 1 angiotensin II receptor locus in essential hypertension. *Hypertension, 33,* 844–849.

Kallela, M., Wessman, M., Färkkilä, M., Palotie, A., Koskenvuo, M., Honkasalo, M. L., et al. (1999). Clinical characteristics of migraine in a population-based twin sample: Similarities and differences between migraine with and without aura. *Cephalalgia, 19,* 151–158.

Kaprio, J. (1994). Lessons from twin studies in Finland. *Annals of Medicine, 26,* 135–139.

Kaprio, J., Hublin, C., Partinen, M., Heikkilä, K., & Koskenvuo, M. (1996). Narcolepsy-like symptoms among adult twins. *Journal of Sleep Research, 5,* 55–60.

Kaprio, J., Kujala, U. M., Koskenvuo, M., & Sarna, S. (2000). Physical activity and other risk factors in male twin-pairs discordant for coronary heart disease. *Atherosclerosis, 150,* 193–200.

Kaprio, J., Sarna, S., Koskenvuo, M., & Rantasalo, I. (1978). The Finnish Twin Registry: Formation and compilation, questionnaire study, zygosity determination procedures, and research program. *Progress in Clinical and Biological Research, 24 Pt B,* 179–184.

Keskimäki, I. & Aro, S. (1991). Accuracy of data on diagnosis, procedures and accidents in the Finnish hospital discharge register. *International Journal of the Health Sciences, 2,* 15–21.

Kieseppä, T., Lönnqvist, J., & Kaprio, J. (2001). Accuracy of register- and record-based bipolar I disorder diagnoses in Finland — A study of twins. *Acta Neuropsychiatrica, 12,* 106–109.

Kujala, U. M., Kaprio, J., Kannus, P., Sarna, S., & Koskenvuo, M. (2000). Physical activity and osteoporotic hip fracture risk in men. *Archives of Internal Medicine, 160,* 705–708.

Kujala, U. M., Kaprio, J., & Koskenvuo, M. (2000). Diabetes in a population-based series of twin pairs discordant for leisure sedentariness. *Diabetologia, 43,* 259.

Kujala, U. M., Kaprio, J., Sarna, S., & Koskenvuo, M. (1998). Relationship of leisure-time physical activity and mortality: The Finnish twin cohort. *Journal of the American Medical Association, 279,* 440–444.

Kujala, U. M., Kaprio, J., Sarna, S., & Koskenvuo, M. (1999). Future hospital care in a population-based series of twin pairs discordant for physical activity behavior. *American Journal of Public Health, 89,* 1869–1872.

Laitinen, T., Räsänen, M., Kaprio, J., Koskenvuo, M., & Laitinen, L. A. (1998). Importance of genetic factors in adolescent asthma: A population-based twin-family study. *American Journal of Respiratory & Critical Care Medicine, 157,* 1073–1078.

Leppävuori, J., Kujala, U., Kinnunen, J., Kaprio, J., Nissilä, M., Heliövaara, M., et al. (1999). Genome scan for predisposinglLoci for distal interphalangeal joint osteoarthritis: Evidence for a locus on 2q. *American Journal of Human Genetics, 65,* 1060–1067.

Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., et al. (2000). Environmental and heritable factors in the causation of cancer — Analyses of cohorts of twins from Sweden, Denmark, and Finland. *New England Journal of Medicine, 343,* 78–85.

Lillberg, K., Verkasalo, P. K., Kaprio, J., Teppo, L., Helenius, H., & Koskenvuo, M. (2001). Stress of daily activities and risk of breast cancer: A prospective cohort study in Finland. *International Journal of Cancer, 91,* 888–893.

Milan, T., Kaprio, J., Verkasalo, P. K., Jansen, C. T., Teppo, L., & Koskenvuo, M. (1998). Hereditary factors in basal cell carcinoma of the skin: A population-based cohort study in twins. *British Journal of Cancer, 78,* 1516–1520.

Nieminen, M. M., Kaprio, J., & Koskenvuo, M. (1991). A population-based study of bronchial asthma in adult twin pairs. *Chest, 100,* 70–75.

Oksanen, L., Öhman, M., Heiman, M., Kainulainen, K., Kaprio, J., Mustajoki, et al. (1997). Markers for the gene ob and serum leptin levels in human morbid obesity. *Human Genetics, 99,* 559–564.

Peltonen, L., Palotie, A., & Lange, K. (2000). Use of population isolates for mapping complex traits. *Nature Reviews, Genetics, 1,* 182–190.

Perola, M., Öhman, M., Hiekkalinna, T., Leppävuori, J., Pajukanta, P., Wessman, M., et al. (2001). Quantitative-trait-locus analysis of body-mass index and of stature, by combined analysis of genome scans of five Finnish study groups. *American Journal of Human Genetics, 69,* 117–123.

Sarna, S., Kaprio, J., Sistonen, P., & Koskenvuo, M. (1978). Diagnosis of twin zygosity by mailed questionnaire. *Human Heredity, 28,* 241–254.

Silventoinen, K., Kaprio, J., Lahelma, E., Viken, R. J., & Rose, R. J. (2001). Sex differences in genetic and environmental factors contributing to body-height. *Twin Research, 4,* 25–29.

Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V. P., Huttunen, M., C. et al. (2001). Genetic influences on brain structure. *Nature Neuroscience, 4,* 1253–1258.

Verkasalo, P. K., Kaprio, J., Koskenvuo, M., & Pukkala, E. (1999). Genetic predisposition, environment and cancer incidence: A nationwide twin study in Finland, 1976–1995. *International Journal of Cancer, 83,* 743–749.

Verkasalo, P. K., Kaprio, J., Pukkala, E., & Koskenvuo, M. (1999). Breast cancer risk in monozygotic and dizygotic female twins: A 20-year population-based cohort study in Finland from 1976 to 1995. *Cancer Epidemiology, Biomarkers & Prevention, 8,* 271–274.

Verkasalo, P. K., Kaprio, J., Varjonen, J., Romanov, K., Heikkilä, K., & Koskenvuo, M. (1997). Magnetic fields of transmission lines and depression. *American Journal of Epidemiology, 146,* 1037–1045.

Videman, T., Gibbons, L. E., Battié, M. C., Maravilla, K., Vanninen, E., Leppävuori, J., et al. (2001). The relative roles of intragenic polymorphisms of the vitamin D receptor gene in lumbar spine degeneration and bone density. *Spine, 26,* E7–E12.