The Norwegian Institute of Public Health Twin Panel: A Description of the Sample and Program of Research

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The Norwegian Institute of Public Health in Oslo has an ongoing program of twin research using population-based cohorts of twins. The current database includes information on twins identified through the Medical Birth Registry of Norway and born from 1967–1979, altogether 15,370 twins. This is a longitudinal study with a cohort sequential design whereby new cohorts are recruited into the study at 5–6 year intervals. Sub-samples of these twins have participated in questionnaire studies and clinical assessment sub-projects. These projects include national and international collaborations. Our primary areas of interest include mental health and psychological well-being, obesity, asthma and allergies, health behaviors and health perceptions, comorbidity, and perinatal influences on health outcomes. This paper provides a brief overview of the data, sample, and the various research projects associated with this twin program of research.

Unlike the other Nordic countries with centralized twin registries, Norway has several twin registries that are associated with different research institutes. For an overview of the collective Norwegian twin data see Bergem (this issue). The purpose of this paper is to provide a description of the sample, data and program of twin research in genetic epidemiology at The Norwegian Institute of Public Health (NIPH) in Oslo (information accessible at http://www.fhi.no/). This program of research is based upon a population-based twin panel referred to as the NIPH Twin Panel. It includes like- and unlike-sexed twins and was initially established for the purpose of studying sex differences in health and development, and to investigate perinatal influences on adult health (Harris, Tambs & Magnus, 1995). This is an active program of research and new twin cohorts are added at 5–6 year intervals. The current panel includes information on 15,370 twins born from 1967 through 1979. The database includes information from the Medical Birth Registry (MBR), longitudinal questionnaire data, DNA, plus information collected in a number of clinical sub-studies that are briefly described below. This collection of research involves national and international collaborations. The main areas of interest include mental health and psychological wellbeing, obesity, asthma and allergies, health behaviors and health perceptions, comorbidity, and perinatal influences on health outcomes.

The NIPH Twin Panel Research Team

The twin data are administrated through the Division of Epidemiology at the Norwegian Institute of Public Health. Dr. J. Harris (human development and genetic epidemiology) has primary responsibilities associated with the scientific development, data coordination and regulation. The co-directors are Professor Per Magnus (genetic epidemiology), and Professor Kristian Tambs (psychology); both have joint appointments at the Norwegian Institute of Public Health and at the University in Oslo. Other NIPH researchers on the scientific team working with the NIPH twin panel include: Dr. W. Nystad, (respiratory epidemiology and exercise science), Dr. T. Reichborn-Kjennerud, (psychiatry), Dr. E. Røysamb (psychology), Dr. K. Skjold Rønningen, (molecular genetics and diabetes), Dr. C. Stoltenberg, (genetic and perinatal epidemiology) and Liv Stene-Larsen, (research technician).

Sample

Identification and Description of Twin Cohorts

The twins are identified through information about plural births contained in the national Medical Birth Registry (MBR). The MBR was begun January 1 1967, and requires mandatory notification of all live- and stillbirths of at least 16 weeks gestation. These notifications are filed within 1 week of delivery through standard reports completed by attending physicians and midwives. An item on the report form inquires whether the birth is singular or plural and the number of deliveries are recorded in each birth record. This reporting procedure ensures that the MBR contains information on virtually all twin births in Norway from 1967 onwards. More detailed description about the data collection and computerization for the MBR is provided elsewhere (Bjerkedal & Bakketeig, 1975; Medisinsk Fødselsregister, 1987).

A total of 15,370 twins were born in Norway during the 13 years spanning 1967 through 1979. During that time period the percentage of pairs for which both twins survived to age 3 ranged from 82 to 89%. The twins from

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these intact pairs are recruited into the NIPH program of research through mail-out questionnaires. Two questionnaire studies have been conducted thus far, in 1992 and in 1998. Table 1 lists the number of pairs and individuals in the study base by birth cohort and response status for the questionnaire studies.

No information regarding zygosity is available in the MBR. Our zygosity assignment is based upon questionnaire methodology, and future plans are to verify these with DNA analyzes. To classify the like-sexed pairs as identical (MZ) or fraternal (DZ) a weighted linear score was calculated using coefficients generated from a previous study of Norwegian twins (Magnus et al., 1983). In that study the validity of 20 questionnaire items about co-twin similarity during childhood were examined. Discriminant function analysis was conducted based upon a sample of 207 pairs using zygosity established by genetic markers as the criterion variable. The discriminant scores using pair responses to five items correctly classified 97.6% of the pairs. A somewhat different discriminant function, using individual responders rather than pairwise data, correctly classified 96.1% of the twins.

The first cohorts of twins, born 1967–1974, were recruited to the NIPH twin study in 1992 with a mail-out questionnaire. The questionnaire included six of the most efficient items identified by Magnus et al. (1983) for zygosity classification, the items and coefficients are reported elsewhere (Harris et al., 1995). Two scores were computed, first using the discriminant coefficients from the original analyses of pair-responders and then using the coefficients for the individual responders. These scores correlated 0.99, and differentially classified only eight of the 1774 like-sexed pairs with complete data. Therefore, the pairwise-derived coefficients were used to classify zygosity for all twins in our sample. The same procedure for zygosity assignment was used when new cohorts of twins were recruited in 1998.

NIPH Twin Database

Medical Birth Registry Data

The MBR includes computerized information about the delivery, the newborn, the mother and some information about the father. Information about delivery includes whether labor was induced, complications or special conditions of delivery and any pathology associated with the amniotic fluid, placenta, or umbilical cord. Information about the newborn includes status at birth, date of birth, gestational age, type of birth (single, twin, etc.), birth order, gender, signs of asphyxia, 1 and 5 minute Apgar scores, injuries, illnesses, familial history of serious illness congenital malformations, birth length and weight and head circumference. If the child died then length of life and reason for death were also recorded. Information about the mother includes age, parity, childbirth history, civil status, county of residence, biological relatedness between the mother and father, ICD diagnoses for maternal health before and during pregnancy and medical circumstances regarding delivery. Newborn and parental unique person numbers and demographic information about the parents are also available. Additionally, information recorded in the MBR about the father includes paternal person number, age and county of residence.

Questionnaire Studies

Q1: Questionnaire data from 1992. The first questionnaire (Q1) was sent in 1992 to all surviving pairs born between 1967 and 1974, where both twins were at least 18 years old and for whom we were able to obtain a current

Table 1

Distribution of Pairs by Birth Cohort and Sample Structure for 1992 and 1998 Questionnaire Data

Birth Cohort	Pairs Born (*N*)	Pairs Both Surviving (*N*)	Pairs Sent Q1 in 1992 (*N*)	Pairs Responded to Q1 (*N*)	Single Responders to Q1 (*N*)	Pairs Sent Q2 in 1998 (*N*)	Pairs Responded to Q2 (*N*)	Single Responders to Q2 (*N*)
1967	666	549	518	328	114	528	296	135
1968	667	552	526	354	107	537	308	130
1969	730	595	568	345	110	573	316	120
1970	650	544	518	330	109	529	272	142
1971	634	533	515	322	94	521	258	144
1972	574	484	472	305	73	475	257	109
1973	605	519	506	327	71	508	257	125
1974	552	455	373	259	46	442	240	103
1975	558	474	0	—	—	471	242	95
1976	533	447	0	—	—	444	234	81
1977	480	417	0	—	—	416	201	77
1978	556	490	0	—	—	481	244	64
1979	482	431	0	—	—	424	209	52
Total Pairs:	7687	6490	3996	2570	—	6349	3334	—
Individuals:	15,374	12,980	7992	5140	724	12,698	6668	1377

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address in Norway. Unique person numbers of the twins were used to match information from the National Census Registry to obtain vital status and current address. The questionnaire included items to assess zygosity, current height and weight, demographic information, physical health history with ages at onset and last episode, psychological wellbeing, self-perceived health, health behaviors, completed and planned education, occupation, handedness, degree of contact with co-twin, and years that the twins shared the same household and attended the same school class. Table 1 lists the distribution by birth cohort of pair and individual responses. Responses to Q1 were received from 5864 twins; the response rate was 75% and included 2570 pairs for which both members responded, and 724 responses from twins whose co-twin did not participate.

Q2: Questionnaire data from 1998. A second, greatly extended questionnaire was sent in 1998 to the cohorts who received Q1 (twins born 1967–1974), plus to five new birth cohorts (twins born 1975–1979). In addition to repeating all the questions from the 1992 study, the follow-up questionnaire was much more comprehensive regarding the measurement of physical health, mental health, health-related behaviors and exposures, and it included screening items for a number of sub-studies. The physical health section was elaborated upon to encompass health issues relevant to the wider age range of the sample, and to include more detailed symptom and exposure information for the illnesses studied in the sub-projects. The section on health-related behaviors included smoking status plus age of debut and quitting, alcohol habits, and exercise. These questionnaire items were taken primarily from a large, population-based Norwegian epidemiological study called the Health Study in Nord Trøndelag (HUNT). Perceived health is based on several standard questions (Short-form 36-health survey) to rate: current health, changes in health during the last 3 years, and the degree to which physical and mental health problems interfere with daily life.

Several mental health phenotypes are measured in Q2. The questionnaire included 91 questions related mainly to Axis II disorders that had been validated against interview data (Structured Interview for DSM-III-R personality; SIDP-R) in an epidemiological study (representative sample of 4000 individuals from the general population (Kringlen et al., 2001; Torgersen, personal communication; Torgersen et al., 2001). It also included a short version of SCL-25 and questions related to major depression, dysthymia, anxiety disorders, psychotic disorders, eating disorders, alcohol consumption and several somatic disorders. Demographic information includes education, occupation, measures to construct familial constellations and degree of personal contact with their co-twin.

Altogether, 12,700 twins were sent Q2, responses were received from 8045 twins, the sample included 3334 pairs and 1377 single responders, which represents a 63% response rate. The distribution of responses to Q2 is also listed by cohort in Table 1. The combined Q1 and Q2 questionnaire samples include 9478 twins who responded to at least one of the questionnaires. The longitudinal sample includes 4430 twins who participated in both the Q1 and Q2 questionnaire studies and includes 1725 intact pairs and 980 single responders. The zygosity distribution by pair or single response for participation in both questionnaires is listed in Table 2.

Principal Investigator (PI): J. Harris, (NIPH), Co-investigators listed alphabetically: P. Magnus (NIPH), W. Nystad (NIPH), E. Røysamb, (NIPH), T. Reichborn-Kjennerud (NIPH) and K. Tambs (NIPH). Funded by the Research Council of Norway and The Norwegian Foundation for Health and Rehabilitation through the Association for Psychological Health and through the Norwegian Asthma and Allergy Association.

DNA by mail-out buccal smear kits. DNA is currently being collected from all of the questionnaire participants using mail-out collection kits and mouth swabs. The samples are returned by mail to the molecular laboratory at Norwegian Institute of Public Health for DNA extraction and sample freezing. Approximately 3500 samples have been processed thus far.

PI: J. Harris, (NIPH), Co-investigators listed alphabetically P. Magnus (NIPH), K. Skjøld Rønningen (NIPH) and K. Tambs (NIPH). Funded by the Research Council of Norway.

Brief Description of NIPH Twin Sub-Studies

A number of other projects and clinical sub-projects based upon the twin sample participating in the questionnaire studies are either completed, collecting data, or funded to

Table 2

Distribution of Twins by Zygosity and Pair-response in Questionnaire 1 (Q1) and 2 (Q2) Databases

	Q1				Q2			
	Both Twins Responded		One Twin Responded[1]		Both Twins Responded		One Twin Responded	
Group	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ
Male-male:	832	774	101	147	1052	794	188	274
Female-female:	1056	886	71	113	1554	1310	159	207
Male-female:	—	1592		291	—	1958	—	549
Total:	1888	3252	172	551	2606	4062	347	1030

Note: [1] There was one twin among the single responders for whom zygosity could not be established from the questionnaire response.

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begin within this year. These projects and the scientists associated with them are briefly described below.

Using Genes and Environments to Define Asthma Related Phenotypes

This study assessed lung function, bronchial responsiveness, skin prick sensitivity and biomarkers of inflammation in a sample of 170 twin pairs living in the greater Oslo area between 1999 and 2000. The sample of twins was unselected with respect to asthma or allergy status. The purpose is to analyze the covariance between the atopic phenotypes and biomarkers using quantitative biometric models. A broad range of clinical measures were collected including spirometry, a methacholine challenge, exhaled nitric oxide, induced sputum, acoustic rhinometry, nasal lavage, skin prick tests and biomarkers from blood. These include IgE, eosinophilic cationic protein (ECP), tryptase, and calprotectin. Supplemental questionnaire information about environmental exposures, symptoms and medical history, quality of life, and perceived dyspnea were collected. DNA was also collected using buccal smears and candidate genes will be included in combined molecular and quantitative approaches. Analyses of these data are currently underway.

PI: W. Nystad (NIPH). Co-investigators listed alphabetically: J. Boe (National Hospital in Oslo: NH) J. Harris (NIPH) P. Magnus (NIPH). J. Kongerud (NH) and. M.B. Lund (NH). Funded by The Norwegian Foundation for Health and Rehabilitation through the Norwegian Asthma and Allergy Association, and Pharmacia & Upjohn. Project dates: 1999–2001.

The Norwegian Twin Study on the Genetics of Personality and Mental Health

This study started in 1999 with the goal of conducting clinical assessments of personality disorders and psychiatric problems in a normal population sample. At completion the study should include approximately 1500 pairs. All pairs who responded to the questionnaire study will be invited to participate. Personality disorders are diagnosed based on the Structured Interview for DSM-IV personality (SIDP-IV). Axis I disorders are diagnosed with the Composite International Diagnostic Interview (CIDI) developed by the World Health Organization and used in several epidemiological studies all over the world. A team of trained interviewers is associated with the project. Depending on the geographic area of residence for the twin, the face-to-face interviews are either conducted in Oslo at the Norwegian Institute of Public Health or the interviewer travels to the twin. In addition, DNA is collected using mouth swabs. Project dates: 1999– 2003.

PI: K. Tambs, (NIPH), Co-investigators listed alphabetically: J. Harris, (NIPH), E. Kringlen, (UiO), P. Magnus (NIPH), T. Reichborn-Kjennerud, (NIPH) and S. Torgersen (UiO). Funded by The Norwegian Foundation for Health and Rehabilitation, through the Association for Psychological Health.

Genetics and Personality

The study on personality and mental health described above was extended in 2001 with the addition of a molecular genetics study. The main goal of this component is to find QTLs or genes that affect the development of personality disorders, particularly borderline personality disorder. All participants in the clinical interview diagnostic assessments will be recontacted for the purpose of collecting blood samples for genome scans. Quantitative analyses will be conducted to estimate the degree to which borderline personality is genetically influenced. Another goal is to analyze the sources of comorbidity between borderline personality and other personality disorders. The genome scans are being conducted at Rockefeller University. Project dates: 2001–2003.

PI: S. Torgersen (UiO). Co-investigators listed alphabetically: J. Harris, (NIPH), M. Karayiorgou (Rockefeller University), P. Magnus (NIPH), T. Reichborn-Kjennerud (NIPH) and K. Tambs (NIPH). Funded by the Norwegian Foundation for Health and Rehabilitation, through the Association for Psychological Health and by the Foundation for Borderline Research.

A Twin Study of Reactivity to CO_2 and Anxiety Disorders.

This study builds upon The Norwegian Twin Study on the Genetics of Personality and Mental Health. The purpose is to explore the genetic and non-genetic determinants of reactivity to carbon dioxide, and to analyze genetic and environmental mediation of the relationships between CO_2 reactivity with clinical symptoms of anxiety disorders. Inhalation of air enriched with CO_2 provokes a sudden increase in anxiety among individuals with panic disorder (PD), sporadic panic attacks (SPA), and social phobia (SP). This trial is well tolerated (as it lasts from a few seconds to less than one minute), and is employed as a valid psychobiological probe for some anxiety disorders. Although the causes of abnormal sensitivity to inhaled CO_2 are unclear, there may be some overlap between the regulatory mechanisms of CO_2 hypersensitivity with brain processes that direct the normal reaction to suffocative stimuli. Project start: 2002.

PI: M. Battaglia, Inst. Scient. H.S. Raffaele, Milano, Co-investigators listed alphabetically: J. Harris, (NIPH), A. Ogliari (Inst. Scient, H.S. Raffaele, Milano) K. Tambs (NIPH). T. Reichborn-Kjennerud, (NIPH), and S. Torgersen (UiO). Funded in part by The National Alliance for Research in Schizophrenia and Affective Disorders (NARSAD).

Genome-wide Analyses of European Twin and Population Cohorts to Identify Genes Predisposing to Common Diseases (GENOMEUTWIN).

This is a multi-national project due to start in September 2002, and funded under the fifth framework program of the European Community. It is based on collaboration between the investigators of the twin registers in 5 countries (Denmark, Finland, Italy, The Netherlands, Norway and Sweden) other European researchers and the MORGAM (Monica, Risk, Genetics, Archiving and Monograph) population cohorts. This is an integrated project with components in research, networking, and training and mobility. The main purpose is to identify genes that modify the risk for common diseases such as migraine, overweight, coronary heart disease and stroke. There is considerable emphasis on the development and integration of novel

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approaches, at molecular and statistical levels of genetic analysis, and to develop new strategies to utilize unique features of the data in the twin studies, including the availability of longitudinal data.

The steering group includes Coordinator: L. Peltonen (PI), National Public Health Institute, Helsinki) M. Perola, National Public Health Institute, Helsinki, U. Pettersson, Uppsala University (Genotyping Core), K. Christensen, University of Southern Denmark (Epidemiological Core), K. Ohm Kyvik, University of Southern Denmark (Danish Twin Registry), A. Evans, University of Belfast (Epidemiological Core and MORGAM), K. Kuulasmaa, National Public Health Institute, Finland (Database Core), N. Pedersen, Karolinska Institutet, Sweden (Database Core and Swedish Twin Registry), J. Harris, The Norwegian Institute of Public Health, Norway (Ethical Issues Core and Norwegian Twin Registry), A. Palotie, Finnish Genome Center (Genotyping Core), L. Sandkuijl, Erasmus University, Netherlands (Statistical Core), D. Boomsma, Vrije Universiteit, Netherlands (Dutch Twin Registry), J. Kaprio, University of Helsinki (Finnish Twin Cohort Study), and A. Stazi, Istituto Superiore di Sanità (Italian Twin Registry). Funded by the European Commission. Project dates: 2002–2006.

Genes and Environments in Disease Development: Nordic Twin and Adoption Studies

This project is scheduled to begin in November, 2002, and is awaiting specific level of funding information. It is based upon the work of the Nordic Twin-Epidemiology Network (J. Harris, PI, J. Kaprio co-PI) which was established in 2001 through funds from the Nordic Academy for Advanced Sciences (NorFa). The purpose of this network was to identify Nordic projects with longitudinal data and formulate research projects in which these data could be analyzed to understand health and disease development. Six longitudinal, population-based and genetically informative databases comprise the basis for this research into disease development. The participating registers include the NIPH twin panel, the Danish, Finnish, Swedish and Netherlands twin registers plus the Danish adoption register. The participating registries span several generations with information on certain phenotypes such as BMI, asthma and allergies in more than 65,000 twin pairs. For certain phenotypes the high degree of similarity in the genetic and environmental variance structure, coupled with comparable measures in the different registries permits data pooling of certain data configurations. Such a large pooled data base would increase the statistical power to detect putative shared environmental effects, allow for dissection of genetic and environmental effects over different generations, ages and sexes which is not possible within single registries due to lack of statistical power and/or limited age spans. With the existing data on socioeconomic status, occupation, smoking and living setting (urban/rural) the effect of different environmental factors and geographic differences can be explored.

Three research themes were identified for which common measures are already available through the databases at the participating centers and for which collaboration would provide analytic opportunities into developmental health questions beyond those based on any single data source. The specific areas of focus will be: 1) developmental effects of genes and environment on metabolic disorders, obesity and diabetes 2) genetic epidemiology and pre-and perinatal influences on health outcomes, and 3) developmental effects of genes and environment on asthma and allergies.

The participating studies and steering group members include: The Danish Adoption Registry, T. Sørensen, Copenhagen University Hospital The Danish Twin Registry, K. Ohm Kyvik, University of Southern Denmark, The Finnish Twin Cohort Study, J. Kaprio (Co-PI), University of Helsinki, and M. Koskenvuo, Univ. of Turku. The Netherlands Twin Registry, D. Boomsma and C. van Baal, Vrije Universiteit. The Norwegian Twin Panel, J. Harris, (Coordinator, PI) and K. Tambs, The Norwegian Institute of Public Health. The Swedish Twin Registry, N. Pedersen & P. Lichtenstein, Karolinska Institutet, Stockholm. Funding to be awarded by The Nordic Academy of Advanced Sciences (NorFa). Project dates 2002–2004.

A Twin–Family Study on the Genetics of Epilepsy

This study collects information from twin kindreds on epilepsy from several twin databases in different countries. These data are valuable for exploring a number of seizure-related questions. The purposes of this study are to assess the role of genetic factors in determining risk for specific epilepsies and epileptic syndrome types, evaluate heterogeneity within epilepsy types, test for specific environmental and maternal effects that influence the occurrence of seizures, and evaluate sex differences in risk of seizures.

PI: L. Corey (Medical College of Virginia, Richmond, USA), Co-investigators listed alphabetically: M. Friis (University of Southern Denmark), J. Harris (NIPH), P. Magnus (NIPH), M. Kjeldsen (Danish Twin Registry and University of Southern Denmark), K. Nakken (Special Hospital for Epilepsy), J. Pellock (Virginia Commonwealth University), M. H. Solaas (UiO). Funded by The National Institute of Neurological Disease and Stroke, NIH. Project dates: 2002-2005.

A Twin Study of Pain Sensitivity and Pain Regulation

Clinical and experimental evidence demonstrate considerable individual differences in sensitivity to pain, and findings from animal studies indicate that genetic factors play an important role in the mediation of these differences. Some data suggest that the primary locus of this genetic influence lies in pain inhibitory mechanisms in the spinal cord and brain.

Human genetic studies of pain are scarce, and none to our knowledge have assessed pain inhibitory mechanisms. In this study we will be assessing pain sensitivity and several types of pain inhibition in a sample of twins. Twins participating in the study will be subjected to two commonly used types of experimental pain: heat stimulation 43–50 C and cold-pressor pain. The subjects rate each pain stimulus using Visual-Analogue Scales for pain intensity and discomfort. In the first session, pain will be assessed during baseline and cognitive distraction conditions. In the second session pain

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will be assessed in baseline, opioid (remifentanil) and placebo (saline) conditions. This study began in 2002.

PI: C. S. Nielsen (UiO), collaborators listed in alphabetical order include J. Harris (NIPH), D. D. Price (University of Florida, USA). A. Stubhaug (The National Hospital, Oslo) and O. Vassend (UiO). The project is funded by the Research Council of Norway and by The Norwegian Foundation for Health and Rehabilitation through The Norwegian Rheumatism Association.

A Danish and Norwegian Twin Study of Bechterews Disease

The spondyloarthropathies (SpAs) refer to a family of related disorders including ankylosing spondylitis (AS), also known as Bechterew's Disease. The SpAs are chronic inflammatory diseases involving mainly the sacroiliac joints and axial skeleton, but other joints and organs can be affected. Bechterew's Disease involves inflammation and fusing of the spine. Although etiology is unknown, familial clustering occurs. Genetic and environmental factors are implicated in the pathogenesis of the SpAs and they also share common genetic configurations associated with the HLA class-I gene, HLA-B27. The purpose of this twin study is to estimate the degree to which genetic influences affect the onset and development of Bechterew's Disease. In addition, possible factors that trigger disease will be explored by investigating lifestyle factors, events and stressors. This study is based upon twins participating in the NIPH and the Danish twin studies. The Norwegian part of this study is scheduled to begin: in 2003. The NIPH pairs were screened for Bechterew's Disease in the Q2 questionnaire and pairs for which at least one had indicated a positive history of Bechterew's Disease will be invited to participate. The diagnosis will be confirmed using a questionnaire and through clinical examination. Blood samples will also be taken to analyze tissue type and DNA.

PI: O. B. Perdersen (Odense University Hospital, Denmark). Co-investigators listed alphabetically: J. Tore Gran (Tromsø University, Norway), J. Harris (NIPH), P. Junker (Odense University Hospital, Denmark) and P. Magnus (NIPH). This project is funded by The Danish Rheumatism Association and the Danish Psoriasis Research Foundation.

A Twin Study of Inflammatory Bowel Disease

Although identified genetic factors are important in the pathogenesis of inflammatory bowel disease (IBD), the complete picture of etiology is unclear. This study is part of an international twin study on IBD and is based on parallel protocols conducted in Sweden and Denmark. The purpose is to estimate the degree to which genetic and environmental factors influence the liability to develop IBD, to study genes that predispose to IBD, and to explore environmental influences that may increase risk or protect against disease development. The prevalence of IBD among the relatives of the twins will also be assessed. The Norwegian part of this study began in 2002. It is based on the sample of twins who indicated in Q2 that they had had bowel disease or diagnosed Crohn's disease. Supplemental questionnaire data are collected, medical charts are reviewed, plus a telephone interview is completed with the twins. Where necessary, a clinical examination is also completed. Blood samples are also collected for the purpose of identifying genes predisposing to IBD.

PI: M. Vatn (The National Hospital, Oslo). Co-investigators listed alphabetically: M.B. Bengston (Vestfold Central Hospital, Norway) and J. Harris (NIPH).

A Few Research Highlights

The results published to date are based upon information in the Medical Birth Registry or questionnaire studies. The data from the clinical studies are under collection, or only recently ready for analysis. A brief overview of a few findings representing our principal areas of research is briefly summarized.

Sex-specific Effects

Sex-specific effects have been investigated for a number of phenotypes including body mass index (BMI), symptoms of anxiety and depression, subjective wellbeing, (all in the Q1 data) and Binge-Eating (in the Q2 data). Heritability for BMI was similar to the estimates derived from other twin studies: 0.71 for men and 0.79 for women. However, we found evidence for sex-specific effects; the male-female genetic correlation was 0.62 suggesting some overlap but some differences in the genetic influences on BMI among during young adulthood. Modeling results also indicated that shared environmental factors may be important for males but not for females (Harris et al., 1995). Our modeling results suggested that some of the discrepancy in the BMI literature regarding the magnitude of the genetic components and the role of shared environment for BMI may partially arise because sex-specific effects are often not tested directly. Depending on the power of the study and the methods used, sex differences in the variance architecture for BMI may be reflected in less robust sex-differences such as the relative contribution of additive and dominant effects, and shared environment.

Resolving sex-specific effects for symptoms of anxiety and depression was not straightforward. At least one sex-specific causal factor was needed to explain the structure of the data, but several alternatives were possible (Tambs et al., 1995). Selection of the model with the lowest AIC values suggested that the nature of the sex-specific effects was related to differences in common environments. This study also reported a greater level of co-twin contact within the MZ than the DZ pairs and this social closeness was significantly related to the co-twin correlation for anxiety and depression. Interestingly, adjustment for this apparent violation of the equal environments assumption did not substantially alter genetic and environmental parameter estimates for symptoms of anxiety and depression. A second study exploring the relationship between symptoms of anxiety and depression with alcohol in males and females revealed sex-differences in the factors mediating this relationship. The bivariate phenotypic correlations were modest (0.23 in men and 0.18 in women), and was explained primarily by genetic influences among men, but by non-shared environment plus a familial effect in women (Tambs et al., 1997).

Analyses of subjective wellbeing suggested sex differences in the variance structure with somewhat lower heritability

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for men (0.46) than for women (0.54), and partly different genes influencing variability across the sexes (male-female genetic correlation = 0.64) (Røysamb et al., 2002). In contrast, the results for binge-eating showed yet another pattern of sex-specific effects (Reichborn-Kjennerud et al., 2002). The magnitude of genetic and non-shared environmental effects was the same (0.51) for males and females, but there is evidence that the genetic risk factors are not identical.

Collectively, these results highlight the phenotype-specific nature of sex differences, and when interpreted within the context of the larger literature, these sex-specific effects may also vary by age.

Asthma and Atopic Phenotypes

Asthma and atopic phenotypes have been studied in many of the large-scale twin studies (for a review see Los et al., 2001). Despite age differences in the samples and the types of assessments used, the quantitative results for asthma are strikingly similar. Analyses of our Q1 data indicated that the lifetime prevalence of self-reported asthma in our twins was approximately 6%. Although the prevalence did not differ significantly between males and females, the incidence density varied across age for both sexes. The rates for males peak within the first 2 years of life, and a smaller elevation occurs between ages 8 and 11. Among the females the rates are greatest between 8 and 11 years of age, and second peak is observed during the teenage years between 14 and 17. The concordance and heritability estimates revealed significant genetic influences (heritability = 0.75) yet no evidence for effects of common environment (Harris et al., 1997a). This was somewhat perplexing because many exposures typically cited in the epidemiological literature as important factors in the development of asthma would have fallen into the realm of shared environment (parental smoking, air quality, number of siblings, attendance at day care, mites, domestic pets) in our Q1 sample. Unlike the previous twin asthma studies that were characterized by a very broad age range (18 to 88 in Australia: Duffy et al., 1990; and 42–81 in Sweden: Edfors-Lubs, 1971) the NIPH study was the first large-scale twin study with a relatively young sample. More than 80% of the cases occurred by age 15 when both twins (93% of respondents) were still living at home. Given the ages in the previous studies, it was reasonable to assume that early life effects were not as strongly expressed, or that later life environmental influences would be more likely to be non-shared. As reviewed in a previous volume of Twin Research (Los et al., 2001), remarkably similar results followed from several other twin studies, including those based on younger samples than ours (Lichtenstein et al., 1997). In general, the AE models fit best, heritability accounts for 70 to 75 percent of the variation, and there is no evidence for shared environment. To the best of our knowledge no twin study has yet included and estimated the effect of measures cited in the epidemiological literature as known risk factors for asthma. However, the collective results from the twin literature highlight the complexities in the pathogenesis of asthma, in particular that gene-environment interactions may be important in disease etiology and therefore shared environmental effects are not detected.

Part of our goal in conducting multiple clinical assessments and collecting questionnaire data on atopic phenotypes is to apply quantitative models to explore questions of differential diagnosis and etiological heterogeneity of these related measures. Differences in twin resemblance were analyzed for two types of asthma (with versus without eczema or hay fever). Genetic effects account for variability in developing asthma. However, there does not appear to be differential resemblance for type of asthma between identical (MZ) and fraternal (DZ) twins. The intraclass correlations for asthma with eczema or hay fever were 0.63 in MZ and 0.17 in DZ twins, and for asthma alone were 0.71 in MZ and 0.20 in DZ twins. There was a 32% chance of developing asthma with eczema or hay fever and 45% chance for developing asthma alone among MZ twins whose co twin had a history of the same type of asthma. Among DZ twins these chances were 5% and 9%, respectively. These results suggest no difference in the magnitude of genetic effects for liability to both types of asthma. However, the extent to which types are etiologically distinct is unknown.

Q2 included measures of atopic disease (asthma, hay fever and eczema) and symptomatology (wheeze, sneeze and itch). Work in progress (Nystad et al., 2002) suggests differences in etiology between disease and symptoms. For the disease categories (asthma, hay fever and eczema), modeling results reveal sizable genetic effects (from 0.69 to 0.72) for atopic diseases (asthma, hay fever and eczema) and much more moderate genetic effects (0.38 to 0.55) for variation in liability to symptoms. Rather, environmental influences were more important for symptomatology.

Twin Data May Be Used to Investigate Hypotheses About Development and Disease

A creative approach to studying the hypothesis that pre-eclampsia is caused by maternal reactions to paternally derived fetal genes was presented by Magnus and colleagues (2001). They predicted an increased risk of pre-eclampsia among mothers of DZ twins compared to mothers of MZ twins or singletons because maternal exposure to paternal genes is greater among the DZ pregnancies. The hypothesis was tested by comparing the risk of pre-eclampsia in 5,232 mothers carrying twins with known zygosity. Further analysis based on data about 17,517 mothers of twins in the birth registry explored the effect of the sex of the twin pair on the risk of pre-eclampsia. The relative risks were adjusted for parity, maternal age, and twins' year of birth. No association was found between zygosity of the twins and risk of pre-eclampsia in the mother. However, the number of females in the twin pair tended to increase the risk of pre-eclampsia. They concluded that the increased number of different paternally derived fetal genes in DZ twins does not increase the risk of pre-eclampsia in the mother. A slightly increased risk in female twin pregnancies suggests that hormonal levels or other effects of sex chromosomes play a role in the etiology of pre-eclampsia.

The consequences for fetal growth of having an unlike-sexed twin in utero was studied based on the sample of

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twins born between 1967 and 1979. A number of previous findings suggested that male hormones may have a masculinizing effect development of the female co-twin, but there was no evidence to suggest a similar "feminizing" effect in males from unlike-sexed pairs. To investigate the magnitude and nature of masculinizing or feminizing effects on twin growth mean birthweights were compared between twins from like and unlike-sexed DZ pairs. Findings revealed a tendency for greater birth weight among females with a male co-twin compared to females from like-sexed pairs. The average difference was 37.6 grams (Glinianaia et al., 1998). There was no evidence that having a female co-twin affected growth in the males.

Another study explored whether normal variation in birthweight confers disadvantage for a variety of illnesses and health problems that were included in the questionnaires (Harris et al., 1997b). The birthweights for more than 25% of our sample are lower than 2500 grams, a commonly used cut-off defining low birthweight. MZ pairs were classified as birthweight discordant if the discrepancies in the co-twins weights differed by more than 25% of the heavier twin's birthweight. Analyses of differential prevalence in health outcomes for members of these pairs provided no evidence that lower birthweight is a predisposing factor for later health outcomes. A second approach analyzed birthweight differences in health discordant pairs.

Future Plans

We plan to continue building this program of research by extending the longitudinal measurements and linking data to build a twin-family structure (sibs, parents, and offspring). It is clear that, in order to study complex phenotypes with enough statistical power to address questions of development, continued efforts at harmonizing projects and data for cross-country collaborations are needed. We are also working towards centralizing the twin data in Norway so that data from all of the Norwegian twin cohorts (described by Bergem, this issue) will be available as a research resource in Norway and for collaborations.

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