

The Norwegian Institute of Public Health Twin Program of Research: An Update

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The population-based twin program of research at the Norwegian Institute of Public Health (NIPH) was begun in 1992. It consists of a number of questionnaire and clinical interview projects exploring a broad array of mental and physical health outcomes. This article provides a brief update summarizing our research activities, some research highlights, new developments and potentials for further developing the program of twin research. In the most recent years a large effort has concentrated on completing a mental health interview study of Axis I psychiatric and substance use disorders and Axis II personality disorders. Although still in the early planning phases, one of the most significant developments is that an agreement is now in place to centralize the Norwegian twin data into a national Norwegian Twin Registry. This new registry will include twin cohorts born from 1905 onwards. Other resources for building twin projects are described. Nationally, there is great potential for linking the NIPH twin data with other health registries and with information in a number of Norway's large population-based biobank studies. Internationally, platforms such as those developed within GenomEUtwin, for data standards and data sharing and access are greatly facilitating international collaborations in twin research.

The population-based twin program of research at the Norwegian Institute of Public Health (NIPH) was begun in 1992 (Harris et al., 1995) and was originally established to study a broad range of health and developmental outcomes including research investigating sex differences in genetic and environmental influences. Since its inception, follow-up questionnaire and interview studies have been conducted on diverse aspects of mental and physical health (Harris et al., 2002). Many of these projects were just underway in 2002 when the special issue of *Twin Research* entitled 'Twin Registers as a Global Resource for Genetic Research' (vol. 5, no. 5, 2002) was published. The purpose of this article is to provide a brief update of the NIPH research activities and describe other available data resources and plans that will be valuable for developing twin studies in Norway.

Sample

The current program of research is population-based and identified all twins born in Norway between 1967

and 1979. A total of 15,374 twins were born during this period. Cohorts born from 1967 to 1974 were first contacted in 1992 via a mail-out questionnaire (Q1). These twins were recontacted in a longitudinal follow-up conducted in 1998 (Q2) at which time younger cohorts, born 1975 to 1979, were also recruited into the register. Altogether, 5864 twins including 2570 pairs responded to Q1 and 8045 twins including 3334 pairs responded to Q2. The longitudinal sample responding to both Q1 and Q2 included 4430 twins and 1725 pairs. DNA has been collected on more than 4700 twins. Further details about the study design, recruitment procedures, sample sizes by birth cohort and questionnaire items have been described previously (Harris et al., 1995, 2002). Plans to extend the questionnaire study are currently underway and will involve further longitudinal follow-up on twins already participating as well as recruitment of younger cohorts into the study.

Updated Zygosity Assignments: Comparing DNA to Questionnaire Results

Zygosity assignment was initially based on questionnaire methodology in conjunction with results obtained from a previous Norwegian twin study that assigned zygosity based on discriminant function analyses and used genetic markers as the criterion variable (Magnus et al., 1983). This procedure has been described in detail elsewhere (Harris et al., 1995). The questionnaire-based zygosity assignments conducted in the NIPH twin panel were updated in 2005 using new information derived from DNA analyses from 676 like-sexed pairs participating in the interview-based Mental Health Study (described below). The DNA-based zygosity was then used as the dependent variable in a new discriminant analyses which also contained items measuring various aspects of twin similarity in childhood plus the twins beliefs about their own zygosity. Results from the new discriminant analysis revealed that our questionnaire methodology correctly classified 97.5% of the pairs,

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while 17 pairs (2.5%) were misclassified. This value is just slightly greater than the misclassification rate of 2.4% from the earlier Norwegian twin study (Magnus et al., 1983). Eleven monozygotic (MZ) pairs were erroneously classified as dizygotic (DZ) pairs and six DZ pairs had been wrongly classified as MZ pairs. The disproportionately higher number of misclassified MZs might suggest a systematic bias; however, assuming a binomial distribution of the direction in which wrongly classified pairs may flip, the overweight of wrongly classified MZs is not statistically significant ($p = .26$). Further analysis based on data from only one twin reveals that the correct classification rate is somewhat lower than that derived from complete pairs, but the extent of this misclassification is uncertain because we don't have DNA from pairs where only one members of the twin pair responded to the questionnaire. The new zygosity assignments in the sample of complete pairs and single responders resulted in a total reclassification of 72 of 3529 liked-sex pairs (2.04%).

NIPH Twin Research Projects

Table 1 contains an overview of the main NIPH Twin Research Projects currently analyzing or collecting data. These projects include national and international collaborations. All of the subprojects are based on samples of twins who participated in the Q1 and/or Q2. Most of these projects have been introduced elsewhere (Harris et al., 2002) or detailed in publications and will not be described again here. As evidenced by the project titles, much of the research concerns mental health and we foresee that this will continue to be a strong area of research development within the program.

The Mental Health Study

Since collecting the 1998 questionnaire data our largest research efforts have been devoted to the interview-based Mental Health Study (principal investigator, K. Tambs) that assessed lifetime history of personality disorders (PDs; Axis II) and major psychiatric disorders and substance use (Axis I) disorders in a

Table 1

Overview of Major Studies in the NIPH-Twin Program of Research

Study (Years conducted)	Sample	Description/Purpose
Questionnaire 1 (1992–Q1)	Birth cohorts 1967–1974: responses from 5864 twins includes 2570 complete pairs	To study sex differences in health and development.
Questionnaire 2 (1998–Q2)	Birth cohorts: 1967–1979: responses from 8045 twins includes 3334 complete pairs	Continuation of above and extension to longitudinal design. DNA collected on subsample.
Mental Health Interview Study (1999–2003)	Includes twins born 1967–1979 and sampled from Q2. Interview sample includes 1391 pairs plus 19 twins.	Population-based interview (CIDI* & SID-P**) study of major Axis I psychiatric and substance use disorders and Axis II personality disorders. DNA collected.
Genetics and personality (ongoing)	Includes twins born 1967–1979 and sampled from Mental Health Interview Study	To find genes that affect personality disorders, especially borderline personality.
Reactivity to CO ₂ and Anxiety Disorders (2002–2005)	Includes twins born 1967–1979 and sampled from the Mental Health Interview Study. A total of 712 twins were tested including 346 complete pairs.	To explore genetic and nongenetic influences on reactivity to carbon dioxide, and to analyze genetic and environmental mediation of the relationships between CO ₂ reactivity with clinical symptoms of anxiety disorders. DNA collected.
GenomEUtwin (ongoing)	Selected twin pairs born 1967–1979	Identify genes that modify risk for disease and obesity.
Pain sensitivity and pain regulation (2002–2004)	188 twins selected from cohorts born 1967–1979.	Analysis of genetic and environmental influences explaining individual differences in sensitivity to different pain modalities.
Twin-Family Study on the Genetics of Epilepsy (ongoing)	Twins born 1967–1979 whose questionnaire responses indicate a history of epilepsy and seizures in self or family.	Multinational study that collects information from twin kindreds to study how genetic factors modify risk for specific epilepsies and epileptic syndrome types.
A Twin Study of Inflammatory Bowel Disease (2002–2005)	Based on sample of twins in Q2 who indicated that they had inflammatory bowel disease or diagnosed Crohn's disease. Supplemental data collection includes telephone interviews, medical chart reviews and blood samples.	This is part of an international twin study on inflammatory bowel disease (IBD). The purpose is to estimate genetic and environmental risk or protective factors. Blood samples collected for DNA.
Danish and Norwegian Study of Bechterew's Disease (2003–2005)	Twins with positive self reports of Bechterew's disease contacted for diagnostic follow up	To estimate the degree to which genetic factors affect onset and development of Bechterew's disease. Blood samples for tissue type and DNA.
Asthma-related phenotypes (1999–2001)	Sample selected from questionnaire study, 170 pairs living within greater Oslo area.	To study genetic and environmental covariance structures between atopic phenotypes and biomarkers. DNA collected on subsample.

Note: Descriptions of the tabled studies, lists of principal and co-investigators, and respective funding agencies described previously (Harris et al., 2002).

* = Composite International Diagnostic Interview

** = Structured Interview for DSM-IV Personality

population sample of twins. PDs have received increasing attention within psychiatry; they are common, can have strong functional consequences, and often co-occur with other psychiatric disorders or with alcohol use/dependence. Although clinical samples and self-report data implicate familial and genetic factors in the etiology of PDs, characterization from a basic genetic epidemiological perspective requires interview assessments in population-based samples. To the best of our knowledge, the NIPH Mental Health Study is the first population-based twin to use structured interview-based assessment of personality disorders in twins.

The epidemiological interview-based mental health study was designed as a follow up to the Q2 data that included a short version of the symptom checklist-25 (SCL-25), tapping symptoms of anxiety and depression, 90 items to assess personality and personality disorders, 10 items about eating disorders, 5 items about alcohol consumption and 30 items to assess phobias, panic reactions, obsessive-compulsive symptoms and conduct problems.

Data were collected using face-to-face interviews with two structured instruments. The computerized version of the Composite International Diagnostic Interview (CIDI; Wittchen & Pfister, 1997) is a comprehensive structured diagnostic interview for the assessment of all the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) Axis I and International Classification of Diseases (10th rev.; ICD-10) diagnoses. The CIDI was originally developed by the World Health Organization (WHO, 1997). The Structured Interview for DSM-IV Personality (SIDP-IV; Pfohl et al., 1995) was used to measure personality disorders.

The interview study started in 1999 and was completed in 2003. Twins who were eligible to participate were recruited from a sample of 3221 pairs participating in the NIPH twin program of research. Altogether 2801 twins, 1391 complete pairs and 19 single twins (44% of those eligible) were interviewed. Blood samples were collected from 70% of the twins and DNA from mouth swabs was collected from the remaining twins except for 2%. In addition, the data are linked to information from the Medical Birth Registry of Norway (MBRN; Irgens et al., 2000) to permit studies investigating how pre- and perinatal factors increase or decrease risks for personality and psychiatric disorders.

Upon completion of the data collection researchers at the NIPH entered into a collaboration with researchers at the Virginia Institute of Psychiatric and Behavioral Genetics through an analysis grant (principal investigator, K. Kendler; co-principal investigator, T. Reichborn-Kjennerud). This project is currently underway with an extensive series of analyses that may help to elucidate etiology and provide insight into factors contributing to comorbidity. These findings could have important implications for the diagnosis

and classification of PDs. For example, results investigating the variance and covariance structure analyses of the Cluster A personality disorders: paranoid, schizoid, and schizotypal, revealed modest heritabilities (21% to 28%), and provided support for the validity of the Cluster A construct (Kendler et al., 2006).

Highlights of Recent Findings

A wide range of studies in physical and mental health has been conducted since our 2002 report. These are based upon data from the various twin projects listed in Table 1. While it is not the purpose of this update to detail these findings, we briefly highlight some findings that illustrate current research interests. To understand factors affecting subjective well-being (SWB) we have investigated the genetic and environmental covariance structure between SWB and other measures of health. One study addressed whether healthier people are happier by analyzing the relationship between SWB, perceived health and somatic illness. The genetic correlation between SWB and perceived health was substantial for males (.72) and females (.82), whereas the relationships between SWB and measures of somatic health were more modest. Furthermore, environmental factors affecting well-being were, largely, independent of those affecting health (Røysamb et al., 2003). Another study found a large and negative genetic correlation (-.85) between SWB and sleep problems, suggesting that genetic influences that positively affect well-being are protective against sleep problems (Nes et al., 2005). Longitudinal analyses of SWB (over a 6-year period) revealed that additive genetic influences are important for explaining stability, whereas change is mostly attributed to individual environmental factors (Nes et al., 2006). Collectively, these findings reveal that differential genetic and environmental pathways are involved linking various health and well-being related factors to SWB.

Binge-eating disorders (BED) have been explored in another series of articles that have analyzed symptom and syndrome level measures of binge eating. Findings based on the symptom measure revealed no sex differences in heritability and that genetic differences account for approximately half the variation in liability to binge eating disorders (Reichborn-Kjennerud et al., 2003). Syndrome-level analyses focused on binge eating without compensatory behavior and in the absence of anorexia or bulimia nervosa. Heritability estimates were significant but somewhat lower than those found at the symptom level. These findings lend support to the validity of the core features of BED as a diagnostic category (Reichborn-Kjennerud, Bulik, Tambs, et al., 2004). Further research reported significant comorbidity between binge eating in the absence of compensatory behaviours with psychiatric symptoms and less pronounced comorbidity between binge eating with medical symptoms (Reichborn-Kjennerud, Bulik, Sullivan, et al., 2004). A study that investigated the sources of variation associated with placing undue importance

on weight in self-evaluation reported that shared and nonenvironmental variation explained most of the variation for men and women. These findings may indicate distinct sources of familial resemblance for different symptoms of bulimia nervosa (Reichborn-Kjennerud, Bulik, Kendler, et al., 2004).

Among the physical health phenotypes studied there are several new findings regarding otitis media and recurrent tonsillitis. Reliability analyses indicated that retrospective self-reports of childhood otitis media by adults were relatively reliable and that reporting inconsistency is likely to be associated with less severe disease (Kvestad et al., 2006a). Investigations of sex effects reported greater heritability among the males (.72) than the females (.61) but there was no evidence for sex differences in the genes affecting liability (Kvestad et al., 2004). These results are similar to those found for recurrent tonsillitis which showed significant genetic effects (.62) but no evidence of sex-specific genetic effects (Kvestad et al., 2005). Epidemiological studies have demonstrated that genetic factors are prominent in explaining this comorbidity (Kvestad et al., 2006b).

Analyses comparing genetic and environmental variance structures for asthma, hay fever and eczema with symptoms of the same diseases concluded that genetic effects account for greater variation in reported diseases than symptoms. The relationships between the diseases and symptoms are mainly explained by genetic effects common to both phenotypes, but non-shared environment is also important. These findings have implications for epidemiological studies that rely on symptom reports to study disease because reported disease and symptoms of the same disease may not reflect the same underlying disorder with the same etiological factors (Nystad et al., 2005).

Examples of other areas of ongoing research include studies on the etiology of individual differences in pain sensitivity (Nielsen, et al., 2005), birthweight effects on adult health (Grjibovski et al., 2005), psoriasis (Olsen et al., 2005), astigmatism (Grjibovski et al., 2006), seizures (Kjeldsen et al., 2005), inflammatory bowel syndrome (Bengtson et al., in press), and body mass index (Schousboe et al., 2003).

Developing the Norwegian Twin Data: A National and International Research Resource

The data collected through the NIPH twin program of research have been generated through a series of studies that were funded through specific research grants. Although funds have never existed to finance the infrastructure required for establishing a large-scale data delivery platform, we have provided data to qualified, outside researchers on several occasions. Those studies are not described or referenced further in the present article.

National Norwegian Twin Registry

Historically, the Norwegian population-based twin registries were not centralized into one resource but

existed as three major twin panels. These included the NIPH twin panel plus two other panels that, jointly, covered cohorts born 1895 to 1960 and which are currently under the administration of the University of Oslo. Primary research areas based upon the data in the two later panels include psychiatric, cardio-vascular, epilepsy and birthweight studies. The samples and research associated with the twin cohorts born 1895 to 1960 have been described previously (Bergem, 2002).

Researchers associated with the twin studies have long recognized the importance and potential to develop a national scientific resource that brings together and builds upon the data in the various registries. To this end an agreement has recently been signed to establish a national Norwegian Twin Registry. This agreement, between the NIPH, the University in Oslo and Ullevål University Hospital, is the foundation for unifying the twin panels into a central register that will include data and biological samples from the twin studies. We plan to include twins born from 1905 and onwards, including the recruitment of younger twins who have not yet been recruited into the NIPH twin studies. Main goals of the centralization are to harmonize data collection and data access procedures and promote a diverse range of research using the twin data. To help realize this agreement a steering group will be put in place with representatives from the contributing registries and institutes. The NIPH in Oslo will have responsibility for this register in accordance with Norwegian laws regulating health registers and biobanks. Now that the agreement has been reached, we are working to secure the funds needed to move forward with this effort.

Potential Matching of NIPH Twin Data to Other Registries

Norway has been leading efforts to establish and coordinate research using population biobanks as a tool for understanding the causes of disease. Nationally, there are several population-based health and research registries that with appropriate permissions may be interlinked and also matched to other data, including the NIPH Twin Data, for research purposes. These registries, briefly described in Table 2, contain a wealth of exposure, health and other data, including biological samples. We are currently planning several projects that will take advantage of the rich data sources provided through data linkage. For the NIPH twin cohorts, the potential research benefits garnered from such linkages will become more and more valuable as the twins age and health problems unfold. Once established, linkage of the national Norwegian Twin Registry to data from these registries will be vital to a myriad of research projects.

Ethics

As evidenced by the GenomeUtwinn project, twin studies are increasingly involved in large-scale genetic

Table 2

Overview of Major Norwegian Population-Based Registries and Research Biobank Studies for Potential Linkage with the NIPH Twin Data

National Norwegian Registers

Cause of Death Registry (1951–)	Person number, international ICD coding (since 1996) for cause of death. Includes cause and place of death. All deaths that occur for residents of Norway are registered. Approximately 45,000 new cases per year, updated yearly, recent years not immediately available.
Cancer Registry (1953–)	Person number, mandatory, standardized registration of all cancers in Norway, includes information on the patient, the cancer and treatment, participation in cancer studies, and registration of death. Approximately 23,000 new cases per year. Updated yearly, recent years not immediately available.
Medical Birth Registry (1967–)	Person number, standardized registration of perinatal measures plus information on mother's health and pregnancy. NIPH twin data are already matched to this register. 60,000 new births per year.
Prescription Medicine Registry (2004–)	Person number, registration of all prescriptions and information on the patient, the medication and dosage, price and pharmacy. Updated monthly.
Patient Discharge Registry	Person number, this register is currently under development.
Norwegian Diabetes Register (1989–)	Continual updates. Person number, diabetes mellitus between birth and age 18, age at onset, clinical information & blood samples.

Norwegian Population-Based Health Studies

Cohort of Norway (CONOR)	Started in 1994: A network of Norwegian health studies with standardized health, exposure and blood collections. Will include 200,000 adults.
Norwegian Mother and Child Cohort Study (Magnus et al., 2006)	Cohort includes standardized health and exposure data plus biological samples from mothers, children and fathers. Ongoing project at NIPH (currently more than 60,000 recruited), started in 2000. Target sample is 100,000 pregnant women, 100,000 children and 70,000 fathers.
40-year-old examination	Health information and blood lipids from 450,000 males and females who participated in cardiovascular study from 1985–1999.
The Nord-Trøndelag Health Study (HUNT)	Integrated family and person database of 103,000 persons. HUNT 1 (1984–1986): 74,599 persons aged 20 and older with a main focus on hypertension, diabetes, lung diseases and quality of life, HUNT 2 (1995–1997) includes about 70,000 participants and blood sample collections from 65,000 persons aged 20 and older. Longitudinal assessments and biological samples are available for more than 45,000. HUNT 3 is scheduled to start in 2006.

and genomic research. In combination with advances in genetic analyses, the twin design brings unique advantages for addressing questions of complex etiology. For example, the identical twin design holds great promise for exploring environmental epigenetics. These transitions have occurred in the age when twin studies have become biobanking studies and there are initiatives to develop data sharing platforms and publicly available sequence data. Some of the ethical issues faced by twin researchers are the same as in any human genetic research study, including consenting for unknown, future use of samples, confidentiality and data security procedures that protect privacy and reduce risks of deductive disclosure and genomic identifiability. Twin studies also raise particular ethical issues (Harris et al., 2003) related to the genetic identicalness of MZ twins, the twins' own beliefs about their zygosity, and feedback to twin pairs versus twin individuals. The Ethics Core of the GenomeEUTwin project is based at the NIPH in Oslo and has been working internationally on ethical issues and data sharing across twin studies. In conjunction with the GenomeEUTwin database core we have established routines for data sharing and access to help promote international twin research. In addition, the Database Core of GenomeEUTwin has developed data standards that facilitate the analysis and use of data across studies. These efforts are currently being networked

into several international collaborations that hold great potential to use twin data in conjunction with other large-scale epidemiological and clinical studies.

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