Twin Research and Human Genetics
Volume 16 ▌ Number 1 ▌ pp. 285–295 ▌ © The Authors 2012 ▌ doi:10.1017/thg.2012.117

The Norwegian Twin Registry from a Public Health Perspective: A Research Update

Thomas S. Nilsen,[1] Gun Peggy Knudsen,[2] Kristina Gervin,[3] Ingunn Brandt,[1] Espen Røysamb,[2,4] Kristian Tambs,[2] Ragnhild Ørstavik,[2] Robert Lyle,[3] Ted Reichborn-Kjennerud,[2] Per Magnus,[1] and Jennifer R. Harris[1]

[1]Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway
[2]Division of Mental Health, Norwegian Institute of Public Health, Oslo, Norway
[3]Department of Medical Genetics, Oslo University Hospital and University of Oslo, Oslo, Norway
[4]Department of Psychology, University of Oslo, Oslo, Norway

We describe the importance of the Norwegian Twin Registry (NTR) for research in public health and provide examples from several programs of twin research at the Norwegian Institute of Public Health (NIPH), including the Nordic Twin Study of Cancer, our epigenetics platform, and our large program of research in mental health. The NTR has become an integral component of a national strategy for maximizing the research potential from Norwegian registries and biobank-based studies. The information provided herein builds upon and complements our recent report describing the establishment of the NTR and the cohorts comprising it. Although Norway has a long tradition in twin research, the centralization and administration of the twin data through a single register structure is fairly recent. The NTR was established in 2009 and currently includes 47,989 twins covering birth years 1895–1960 and 1967–1979; 31,440 of these twins have consented to participate in medical research (comprising 5,439 monozygotic pairs, 6,702 dizygotic same-sexed pairs, and 1,655 dizygotic opposite-sexed pairs). DNA from approximately 4,800 twins is banked at the NIPH biobank and new studies continuously add new data to the registry. The value of NTR data is greatly enhanced through record linkage possibilities offered by Norway's many nation-wide registries (medical, demographic, and socio-economic) and several studies are already taking advantage of these linkage opportunities for research.

■ **Keywords:** Norwegian Twin Registry, twins, NTR, registry linkage, MoBa

Recently, we reported on the establishment of a national Norwegian Twin Registry (NTR) founded on three major population-based twin panels (Nilsen et al., 2012). That report provides basic information describing the twin cohorts and data comprising the NTR, phenotypic areas of research concentration, opportunities to conduct linkages to other national registries, and access policies. The NTR is housed and administered through the Norwegian Institute of Public Health (NIPH), and this follow-up article provides several important updates. First, we describe the value of twin data from a public health perspective. Second, we introduce the NTR, as well as describe another valuable sample of twin data available for research from the Norwegian Mother and Child Cohort study. Third, we address representativeness of the Norwegian twin data. Fourth, we briefly describe a twin cancer consortia project that illustrates how the NTR can be used in conjunction with other national health registries to enhance public health research. Fifth, we describe our recently established twin-epigenetic platform and program of research. Finally, we summarize findings and from our large and active program of twin research in mental health and outline future plans.

The Value of Twin Registries From a Public Health Perspective

The vision of the NIPH is 'a healthier population', and the NTR is an integral part of that effort. To understand the value of the NTR from a public health perspective it is

RECEIVED 8 September 2012; ACCEPTED 13 October 2012. First published online 28 November 2012.

ADDRESS FOR CORRESPONDENCE: Dr. Jennifer R. Harris, Division of Epidemiology, Norwegian Institute of Public Health, PO Box 4404 Nydalen, 0403 Oslo, Norway. E-mail: jennifer.harris@fhi.no

important to understand the specific goals of the NIPH. These are to be prepared for acute health threats; advise and provide services that improve public health; conduct public health surveillance, including factors influencing public health; and obtain knowledge of the causes of common diseases and factors that improve health. One of the main targets in public health is prevention of disease. Toward this goal, the NIPH performs research, describes the burden of diseases, and advises the government and the public at large. In most other countries, twin registries are found in universities, particularly in departments of human genetics or epidemiology, and the agenda is not determined by the goal of disease prevention, although funding often comes from medical research councils. Meeting the goals of preventative work requires (1) research aimed at elucidating causes of diseases, (2) research that describes the occurrence and determinants of these etiological factors, and (3) intervention studies that test ways to reduce exposures. Although the major contributions of twin research have historically been in the first arena to identify causes of disease, it is important to recognize that twin research can contribute in all three of these areas.

In addition to research of relevance to disease prevention, twin designs are valuable for all kinds of basic and applied research, with results providing important insights into the causes of variability in human traits. For most chronic diseases, the main obstacle to prevention is more or less complete lack of causal insight. This is the case for most of the serious neurological diseases (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis), serious psychiatric disorders (autism, schizophrenia, bipolar illness), rheumatological diseases (rheumatoid arthritis, ankylosing spondylitis), endocrine diseases (type 1 diabetes, hyperthyreosis), and most cancers. Although some risk factors are known — including associations with specific genes for some disorders — these diseases are at present not possible to prevent, and collectively they account for a large disease burden. Many of these diseases can be treated in the sense that pain and suffering can to some extent be relieved, but it can be difficult to change the course of progression.

To enhance our ability to conduct etiological research it has been the NIPH's strategy to build a strong research infrastructure encompassing population-based cohorts, registries, and biobanks. The NTR is a critical part of this infrastructure; it supports multiple research endeavors that investigate a wide array of physical and psychiatric diseases and conditions that affect public health.

The NTR

The NTR is a merger of several population-based twin studies (Nilsen et al., 2012). It was established in 2009 at the NIPH in Oslo with initial funding from NIPH, the University of Oslo, and Oslo University Hospital. The NTR has no dedicated stream of funding from either the government or the Norwegian Research Council and is currently supported by the Division of Epidemiology at NIPH and by research projects utilizing NTR data. Currently, the NTR includes 47,989 twins covering birth years 1895–1960 and 1967–1979; 31,440 of these twins have consented to participate in medical research (comprising 5,439 monozygotic [MZ] pairs, 6,702 dizygotic [DZ] same-sexed pairs, and 1,655 DZ opposite-sexed pairs). DNA from approximately 4,800 twins is banked at the NIPH biobank. New studies continuously add new data to the registry, and the value of NTR data is greatly enhanced through the linkage possibilities offered by Norway's many nationwide registries (medical, demographic, and socio-economic).

Twins in the Norwegian Mother and Child Cohort Study

Currently, the NTR only includes twins who are older than 18 years of age and have consented to be included in the Registry. However, another important set of twin data maintained by the NIPH and available for research is not currently integrated into the NTR. These data are from pairs who are younger than 18 years old and are part of the Norwegian Mother and Child Cohort Study, abbreviated MoBa (www.fhi.no/moba˙en; Magnus et al., 2006). MoBa is a large population-based pregnancy cohort for which the pregnancy is the unit of the study. Women were recruited around the time (usually week 17 of pregnancy) of the first routine ultrasound scan in 50 out of 52 eligible hospitals during the period 1999–2008. The participation rate was about 38%. More than 108,000 pregnancies have been included in the cohort from approximately 91,000 different women, thus a sub-sample of the mothers participate more than once. In addition, about 82,000 fathers are participating. There are 1,862 twin births and both children were live-born in 1,813 of these pairs. This sample of twins includes 581 like-sexed male pairs, 553 like-sexed female pairs, and 679 unlike-sexed pairs, suggesting that the proportion of MZ pairs is about 34%.

Blood and urine samples from the mother and a blood sample from the father were taken at recruitment, and a second blood sample from the mother and a fetal blood sample from the umbilical vein were drawn after birth. DNA was extracted and aliquoted from fresh samples. The mother and father each responded to a general questionnaire at the time of recruitment; and the mother also responded to a food frequency questionnaire at about 22 weeks of pregnancy and a new general questionnaire at about 30 weeks. After birth, questionnaires have been sent out when the child was 6 months, 18 months, and after 3, 5, 7, and 8 years. Some data from the ultrasound scan at 17 weeks is available, and the record from the Medical Birth Registry of Norway (MBR) is part of the data set. In addition, linkages can be made to the Norwegian Prescription Database, the Vaccination Registry, the Cancer Registry, the Patient

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

Registry (International Classification of Diseases (ICD)-codes from hospitals), and several other disease-specific registries. Linkages are also possible to additional registries in Statistics Norway, which include information on education, income, and ethnic background. There are now plans to send out a short zygosity questionnaire to the mothers of the like-sexed twins. In addition, a linkage between the NTR and MoBa will be performed to analyze the pattern of diseases in pregnancy in female twins and spouses of male twins, as well as to analyze patterns of disease in offspring of twins.

Representativeness of NTR for Studies of Physical and Mental Health

Twin studies are generally confronted with two aspects of representativeness. First, concerns whether the causes of disease are qualitatively different among twins than among singletons due to factors inherent or unique to twinning. If so, this could have implications regarding whether the sources of variance (genetic and environmental) underlying disease development are qualitatively the same in twins and singletons. Second, relates to how well any particular twin sample represents its population of inference; this is important to ensure that the full range of relevant genetic and environmental sources of variation is captured by the twin sample. A main argument against generalizability from twins to the background population focuses on special intrauterine experiences leading to low birth weight and low gestational age among twins (Pharoah, 2002; Phillips et al., 2001). Our investigations of the association between birth weight and a series of health outcomes (Grjibovski et al., 2005; Harris et al., 1997b) revealed little evidence of significant effects for most of the health outcomes studied, yet it is important to recognize that the potential of such effects should be studied on a disease-by-disease basis. Several other studies have also established that twins generally are representative of singletons with regards to the prevalence of specific diseases and mortality patterns (Andrew et al., 2001; Christensen et al., 1995, 2001, 2006) and these results are confirmed in our NTR-based studies of specific diseases including asthma (Harris et al., 1997a), epilepsy (Kjeldsen et al., 2005), and psoriasis (Olsen et al., 2005).

However, twin cohorts are not primarily used for incidence and prevalence studies and a more relevant issue is whether twins in NTR are representative of the Norwegian population. The twin cohorts born 1967–1979 and recruited to questionnaire studies in 1992 (cohorts born 1967–1974) and 1998 (cohorts born 1967–1979; Harris et al., 2002) were identified through the MBR. Thus, variables from the MBR could be used to predict first-time participation in a questionnaire study of all twins who had been invited. Extensive analyses of the MBR predictors of participation after first invitation (Q1 or Q2) revealed that just a few factors (female sex, positive placenta previa, no asphyxia, and normal birth weight) predicted participation in an initial questionnaire study, while having an unmarried mother and having older siblings predicted non-participation. For the cohorts invited to both Q1 and Q2 (twins born 1967–1974), demographic and health factors measured in Q1 that predicted participation in Q2 included monozygosity, female sex, being unmarried, having no children, and higher education, whereas unhealthy lifestyle (smoking, alcohol consumption, and low exercise), positive symptoms of anxiety and depression, low subjective well-being (SWB), history of autoimmune and stomach/intestinal diseases, and reading/writing problems were associated with non-participation. However, not all of these factors retained significance in further analyses adjusting for the other predictors in the model. Those results indicated that participation was predicted by older age, female sex, higher education, monozygosity, higher well-being, and history of stomach/intestine illness (Tambs et al., 2009b).

With regards to mental health outcomes, analyses of the representativeness of the participating twins in the 1998 questionnaire study and the subsequent Mental Health interview study (described below) revealed that none of the psychiatric variables in the 1992 questionnaire predicted cooperation in 1998 (Tambs et al., 2009b). Moreover, none of 22 psychiatric variables in the 1998 questionnaire predicted participation in the interview-based Mental Health Study.

Of approximately 128,000 twins born in the period covered by the registry (cohorts born 1895–1979 — with the exception of cohorts 1961–1967), the NTR contains 47,989 twins (37%). Only complete pairs who were at least 18 years old were invited (for birth cohorts 1915–1960 only same-sexed pairs). For cohorts 1895–1960, the twins had to be alive for the 1960 census, which is the basis for establishment of National Identity Numbers in Norway. If this imposes a significant selection bias, then a 'healthy twin effect' will be observed because pairs with both twins surviving to the age of 18 years are in better health than those who did not. Consequently, the high-risk pairs may be excluded from recruitment due to the greater risk of disease for co-twins of probands, especially in MZ pairs. This might account for lower total cancer incidence rates in Norwegian twins (Standardized Incidence Ratio (SIR): 0.92, 95% CI : 0.89–0.96) rather than a true effect of being a twin as previously reported in Iversen et al (2001). Thus, a more immediate concern is whether there is bias from non-response that causes divergence between the co-twin correlations in the NTR and the co-twin correlations in the study population. Selection bearing on co-twin similarity could influence variance components estimates and would need to be investigated on a study-by-study basis. This was undertaken in the Mental Health Study. Analyses of 25 measures from the 1998 data (including proxies for all 10 personality disorders [PDs], five axis-I psychiatric

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

disorders and alcohol abuse) showed no differences in the genetic and environmental variance component results between the data from participants and non-participants in the first wave interview (Tambs et al., 2009b). Overall, our analyses of representativeness for the various outcomes that have been studied in the NTR indicate no serious bias with regard to the general population.

The Nordic Twin Study of Cancer (NorTwinCan)

The NorTwinCan illustrates how the registry infrastructure facilitates NTR-based etiological research that otherwise would not be possible. NorTwinCan is an international collaboration of the Nordic population-based twin cohorts from the Norwegian, Danish, Finnish, and Swedish twin registries with researchers at Harvard University. The aims of NorTwinCan are to study the genetic and environmental underpinnings of a broad spectrum of cancers. Analytically, this project enhances traditional twin statistical methodologies that have explored the influence of genetic and environmental factors on cancer susceptibility by accounting for delayed entry to the study due to variable initiation of cancer registration in the participating countries, right censoring (i.e., those alive at the end of follow-up with no diagnosis of cancer) plus the competing risk of death. Ignoring these issues can bias estimates of prevalence, concordance, and heritability. Population-based data are needed to address the goals of NorTwinCan and each country has linked their twin cohort data to their respective national cancer and mortality registries with essentially complete follow-up of cancer incidence and mortality covering four decades.

The resulting cohort includes 267,000 twins. It is the largest twin study of cancer to date and will enable investigations of 23 unique types of cancers. The large study size, coupled with the long follow-up period, will also enable estimations of rarer malignancies. The novel statistical methodologies being implemented, which take into account issues of censoring (both at the start and the end of follow-up) and potential competing risk of death from other causes, will provide new insights into our understanding of the heritable basis of cancers. These analyses are made possible by the availability of national data obtained through linkages with information in the Cancer and the Cause of Death registries. NorTwinCan researchers have already harmonized a substantial amount of the linkage-based information and several manuscripts are nearly complete. Establishment and analyses of the NorTwinCan data have been funded through the Ellison Foundation in the United States. We are now applying for further research funds that will allow us to expand our studies of cancer incidence, mortality, and heritability by incorporating exposure data into the models, and by assembling a tumor repository for specific cancers from existing archived tissue to enable investigations of the molecular alterations and pathological markers in tumors.

Epigenetic Program of Research

The creation of our twin-epigenetics platform is a new development since our 2006 update (Harris et al., 2006). It was established under the national Functional Genomics Programme of the Research Council of Norway (NFR ES427401, PIs: Undlien & Lyle). The opportunity to interrogate aspects of genetic and epigenetic variation has already revolutionized our ability to reveal the function of the genome, and twin studies offer special niches for these applications. There is an increasing belief that epigenetic factors could provide an explanation for some of the missing heritability in complex diseases. Although our understanding of epigenetic variation and heritability is still limited and it is unclear to what extent the heritable phenotypic variability can be explained by epigenetic factors, twin studies offer great potential to address these specific issues. However, one major challenge in epigenetic research into complex diseases is that the relevant tissue must be studied. This is more feasible for some diseases (e.g., cancer, autoimmunity) than for others, and there is still little knowledge regarding how specific disease effects become manifested in tissue-specific epigenomes.

Our twin epigenetic program of research recruited healthy MZ and DZ pairs to study sources of variation in epigenetic profiles (Gervin et al., 2011) and also recruited MZ pairs discordant for immune-mediated disorders, including psoriasis (Gervin et al., 2012), asthma, and inflammatory bowel disease (IBD). A main advantage of using the discordant MZ design is the power to detect differential methylation in relatively few twin pairs (15–25 pairs). We briefly describe the protocol for recruitment of sub-groups of twins, procedures for cell isolation, strategies used for the epigenetic analyses, and plans for future expansion of the study.

Recruitment and Blood/Skin Biopsy Collection Protocols

Healthy MZ and DZ pairs were recruited pair-wise from the population-based study of Norwegian twins born 1967–1979 (Harris et al., 1995, 1997a). Initial screening was conducted for the absence of health problems and diseases using self-reported health history data collected in 1998 (Harris et al., 2002). Consenting pairs were then invited to a clinical interview conducted by a nurse to determine if they had remained illness-free. Additional information was also collected, related to medication use, family health history, and lifestyle factors. Among the 354 pairs invited from the screening phase, 121 pairs consented and 108 pairs participated; 60 mL EDTA-blood was collected. MZ twin pairs discordant for psoriasis, asthma, and IBD were also recruited pair-wise. Initial screening was conducted for self-reported disease based on health history data from two earlier sets of questionnaires (Harris et al., 2002; Nilsen et al., 2013). For the psoriasis sub-study, 105 pairs were invited to

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

participate: 60 pairs from the cohorts born 1967–1979 and 45 pairs from the cohorts born 1924–1960. The selection of discordant MZ pairs was based on a two-step procedure. Initial screening was conducted using self-reported data collected via questionnaires in earlier studies (Bergem, 2002; Harris et al., 2002, 2006). Pairs for which both twins consented to participate were called in to a clinical dermatology interview and skin examination at Oslo University Hospital, where additional information was also collected. Among the 105 pairs invited through the initial screening phase, 35 pairs consented and 27 pairs (22 female and 5 male pairs) clinically evaluated to be discordant for psoriasis participated. From all individuals, 60 mL of blood was taken, and we also collected skin biopsies (3 mm) from psoriatic skin and non-lesional skin. In addition, skin samples from the upper epidermis at the surface of psoriatic plaque and non-lesional skin were harvested using tape (four samples from each spot; Benson et al., 2006).

Isolation of Lymphocyte Sub-Populations and Biobanking of Samples

Our focus is on autoimmune diseases which are characterized by immune-mediated destruction of an individual's own cells or tissues. Lymphocytes, in particular T-cells, are key players in autoimmune and immune-mediated disorders. These cells can be easily obtained by drawing blood samples. To overcome the problem of epigenetic heterogeneity in whole blood we sequentially separated different lymphocyte populations in a semi-automated way using positive and negative isolation kits from Miltenyi (Bergisch Gladbach, Germany) on an autoMACS Pro Separator.

As part of this project, we have established a biobank consisting of DNA, RNA, serum, and isolated sub-populations of cells: $CD19^+$, $CD8^+$, $CD4^+$, $CD4^+CD25^+$, and $CD294^+$ (CRTH2, only from twins discordant from asthma) isolated from MZ twins discordant for psoriasis, asthma, IBD, and healthy MZ and DZ twins. Currently, the twin epigenetic biobank includes samples from 56 twins from asthma-discordant pairs, 58 twins from psoriasis-discordant pairs, and 13 twins from IBD discordant pairs. In addition, there are samples from 98 MZ twins and 80 DZ twins from the healthy concordant pairs.

DNA Methylation Analyses

During the course of our epigenetics project we have continuously updated our methodologies to keep pace with the widening spectrum of methods recently developed to map DNA methylation at a genome-wide level. In a short period of time, analysis has moved from being restricted to specific loci to now being performed at a genome-wide level with the characterization of the whole methylome at single-base-pair resolution. In a recently published study, we used the array-based 27K Infinium assays which covers ~27,000 CpGs (Gervin et al., 2012). At the time this was considered to be a good choice because it covers most gene promoters and CpG islands (genomic regions that contain a high frequency of sites where cytosine [C] is next to guanine [G] and bonded through a phosphodiester bond) in the human genome for a low price. Although it is a relatively sparse array with each gene represented by ~2 CpGs, it is suitable for screening a high number of samples. The 450K BeadChip can assay over 480K CpGs and include coverage of 99% of RefSeq genes, 96% of CpG islands (University of California, Santa Cruz (UCSC)), as well as CpG island shores (regions of less dense CpG dinucleotides up to 2 kb distant from CpG islands) and other relevant regions. More recently, we have expanded our previous analyses using high-throughput, sequence-based technology, reduced representation bisulfite sequencing, and increased the coverage from 0.01% to 7% of the total CpGs in the genome.

Future Directions

We are expanding our epigenetic studies and analyses in several important ways as outlined below.

Increasing the study size. We have established a biobank of samples collected from MZ and DZ twins over the past 5 years. We are continuously trying to expand our study through recruitment of twins discordant for diseases, also from outside Norway. Specifically, we have established a collaboration with the Swedish Twin Registry with the aim of collecting more MZ twins discordant for psoriasis.

Follow-up studies including correlation with histone modifications. We are expanding our analyses to study other epigenetic mechanisms such as histone modifications. This approach enables an integrated analysis of the interplay between DNA methylation, histone modifications, and gene expression in order to identify disease-associated epigenetic patterns and dysregulated genes.

Whole-genome bisulfite sequencing. We will continue to expand and explore the potential of the huge fraction of CpGs overlooked in our previous studies by performing whole genome bisulfite sequencing (WGBS). In a pilot project we plan to pool MZ twins discordant for psoriasis and search for disease-associated differences in DNA methylation. WGBS is still very expensive and the strategy behind the pooling of samples is to achieve the needed sequencing depth to an acceptable cost. However, it is possible to separate the samples within the pools by tagging them with a sample-specific index.

Micro RNA (miRNA) expression in MZ twin discordant for psoriasis. miRNAs are a class of post-transcriptional regulators of gene expression and exert their effects by targeting specific mRNAs for degradation. Several studies have linked specific miRNA profiles to psoriasis by investigating affected and normal skin. We are currently conducting a comprehensive analysis miRNAs in $CD4^+$ cells using

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

high-throughput sequencing in our psoriasis twin cohort. Whereas other studies have explored this in skin by comparing affected and normal skin, we are doing this in blood cells isolated from discordant MZ twins. This study will produce a large data set of small RNA from $CD4^+$ cells at sufficient depth aiming to identify novel mRNAs associated with psoriasis with high sensitivity.

Allele-specific methylation and gene expression in healthy MZ twins. The analysis of allele-specific gene expression has turned out to be a powerful approach in the search for functional variants. Heterozygous genetic variants are useful markers of the allelic origin of a transcript and allele-specific expression. The discovery of allelic-specific methylation (ASM) and the observed correlations between genotype and epigenotypes have encouraged us to do an integrated analysis of the genotype (exome) and transcriptome (RNA sequencing) using high-throughput sequencing and epigenotypes interrogating the DNA methylation status of ~450,000 CpGs using Illumina 450K arrays. We have an ongoing project exploring this in isolated $CD4^+$ cells from healthy MZ twin pairs.

Norwegian Twin Research of Mental Health in a Public Health Perspective

Brain disorders account for one-third of the burden of all diseases in Europe, with a total economic cost of €798 billion in 2010, which is substantially higher than for cardiovascular disorders (€192 billion) and cancer (€150–250 billion; Olesen et al., 2012; Olesen & Leonardi, 2003). Mood disorders are the leading cause of burden of disease in middle- and high-income countries, and account for the highest economic health costs in Europe (WHO, 2004, 2009). Major depression affected 30.3 million in Europe in 2010 (Olesen et al., 2012). Harmful alcohol use is considered the third leading cause of ill health and premature death in the world, and for middle- and high-income countries, alcohol use disorders are prevalent and have a high burden of disease and a high economic cost. Compared to mental disorders like major depression, psychoses, and anxiety disorders (called axis I disorders), social and economic consequences of PDs (called axis II disorders) have been studied to a limited degree only. The consequences of PDs, however, seem to be equal to or even exceed those of major depressive disorder (MDD; Gunderson et al., 2011; Skodol et al., 2002, 2007; Soeteman et al., 2008). Mental disorders, both axis I and axis II disorders, are thus highly relevant in the public health perspective, and research in order to increase knowledge of risk factors, causes, prevention, and treatment is one of the main priorities by the NIPH.

The twin research of mental health at NIPH primarily focuses on elucidating the etiology of mental health symptoms or disorders. Because twin samples are often population based, the research projects also generate prevalence estimates.

Mental Health Measures in NTR

The NTR contains data on mental health from the questionnaire surveys in 1992, $n = 5{,}864$ and 1998, $n = 8{,}045$, and the interview-based Mental Health Study (1999–2004), $n = 2{,}801$. The 1992 questionnaire included mostly demographic and somatic health questions, but also a five-item, short version, SCL-5 of the symptoms checklist (SCL-25; Tambs & Moum, 1993), four items on SWB (Roysamb et al., 2002), and some mood questions and questions on nicotine and alcohol use. The 1998 questionnaire included 91 items related mainly to personality pathology and axis II disorders (Kendler et al., 2007), SCL-5, the same SWB items as in the 1992 questionnaire, and questions related to major depression, dysthymia, psychotic disorders, alcohol consumption, anxiety disorders, and eating disorders. In the Mental Health study, the lifetime history of all major axis I disorders, were assessed using the computerized Norwegian version of the Composite International Diagnostic Interview (CIDI; Wittchen & Pfister, 1997) developed by the World Health Organization and used in most major psychiatric surveys all over the world in recent years. A Norwegian version of the Structured Interview for DSM-IV Personality (SIDP-IV; Pfohl et al., 1997) was used to assess axis II disorders, including questions relating to criteria for all DSM-IV 10 PDs. Results indicated that the prevalence of one or more categorical PD diagnoses was 6.3% ($n = 175$); 65.8% of participants met at least one criterion for any PD, and the mean number of criteria met in the whole group was 3.1%. The lifetime prevalence was 14.0% for MDD, 26.7% for any anxiety disorder, and 9.4% for alcohol abuse/dependence. The 12-month prevalence for MDD and alcohol abuse/dependence was 4.8% and 4.3%, respectively.

Key Results From Mental Health Studies Based on NTR Data

The mental health data in NTR have been used in a wide range of twin studies covering the common axis I disorders (MDD, anxiety disorders, alcohol use disorders, eating disorders), all the 10 DSM-IV defined PDs, and SWB. Studies range from heritability estimation using a univariate approach to complex multivariate analysis of common etiological factors for two or more traits or disorders. Multivariate analyses of the structure of genetic and environmental risk factors for DSM-IV cluster A (Odd/excentric; Kendler et al., 2006), B (Dramatic/Emotional; Torgersen et al., 2008), and C (Anxious/Fearful; Reichborn-Kjennerud et al., 2007a) PD traits have been conducted. As assessed at personal interview, the criterion counts (number of endorsed criteria) for all of the 10 PDs were modestly heritable. Genetic influences included both factors shared across

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

personality clusters and disorder-specific influences. To determine if the modest heritability observed for PD traits resulted in part from measurement error, a longitudinal model using questionnaire-based items and our SID-P interview were examined. After correcting for unreliability, substantial increases in heritabilities were found for both cluster A (Kendler et al., 2007), B (unpublished), and C (Gjerde et al., 2012) PD traits. The criterion counts for all 10 PDs in DSM-IV in a single multivariate twin model were subsequently performed, and showed three underlying genetic factors: a broad vulnerability to negative emotionality, high impulsivity/low agreeableness, and introversion (Kendler et al., 2008). The results did not confirm overarching roles of the DSM-IV cluster A, B, and C in etiologic models for PDs.

The comorbidity for key axis I–II combinations has also been examined. Both for depressive PD traits and MDD (Orstavik et al., 2007), and for avoidant PD traits and social phobia (Reichborn-Kjennerud et al., 2007b) all the genetic risk was shared between the axis I and II disorders. In analyses of all PD traits together with MDD, the strongest genetic relationship was found between MDD and borderline PD traits (Reichborn-Kjennerud et al., 2010). Furthermore, the structure of genetic and environmental risk factors for several groupings of Axis I disorder have been studied: phobias (Czajkowski et al., 2011), drug use and abuse (Kendler & Prescott, 2006), anorexia (Mazzeo et al., 2009), binge eating (Reichborn-Kjennerud et al., 2003), and all anxiety disorders (Tambs et al., 2009a).

Of the more extensive analysis is a detailed phenotypic exploratory and confirmatory factor analysis of 14 Axis I disorders as well as criterion counts for 11 PDs (Roysamb et al., 2011). Four correlated factors were identified, labeled internalizing, externalizing, cognitive-relational disturbance, and anhedonic introversion. Finally, expanding the complexity in multivariate genetic analyses, joint twin analyses of 12 common Axis I disorders and criterion counts for all 10 DSM-IV PDs (Kendler et al., 2011) were completed. Four genetic factors that resembled the phenotypic factors were identified: (1) Axis I internalizing, (2) Axis II internalizing, (3) Axis I externalizing, and (4) Axis II externalizing. Three environmental factors were identified: Axis II disorders, Axis I internalizing disorders, and externalizing versus anxiety disorders.

In addition to the focus on mental disorders, several studies have addressed issues related to SWB. Three studies have investigated genetic and environmental contributions to well-being, with a focus on sex-specific effects (Roysamb et al., 2002), family factors (Nes et al., 2010a), and marital status (Nes et al., 2010b). We have also examined associations between well-being and perceived health, musculoskeletal pain (Roysamb et al., 2003), sleep problems (Nes et al., 2005), and anxiety/depression (Nes et al., 2008). Finally, one study has examined the etiology of stability and change in well-being (Nes et al., 2006).

Large Ongoing and Future Mental Health Projects

Axis I and Axis II Psychiatric Disorders in Norwegian Twins: A Follow-Up Study

In 2010, a follow-up study of the participants from the interview-based Mental Health Study (1999–2004) was initiated. This study included one short (four pages) questionnaire and psychiatric diagnostic interviews. The data collection was funded by the Research Council of Norway and the NIPH. The questionnaire included items on basic demographic variables, life satisfaction, normal personality, and stressful life events. Personality traits were measured by the Big Five Inventory (BFI; John & Srivastava, 1999). The BFI is a 44-item, self-report inventory, measuring the five basic Five Factor Model (FFM) traits. The advantages of the BFI include established reliability and validity, widespread international use, a relatively brief format, and previous applications in Norwegian samples (DeYoung, 2006; Engvik & Føllesdal, 2005; John & Srivastava, 1999). Stressful life events were measured by items that have been validated in the ongoing adult twin studies of psychiatric and substance use disorders in the Virginia Twin Registry (Kendler & Prescott, 2006). These life events include sexual abuse, combat experience, witness or involvement in a serious accident, violence or natural disasters, long-term or life-threatening disease, or death of a loved one. Finally, parental alcoholism, depression, or generalized anxiety disorder (GAD) was briefly assessed, along with parental and own divorce, financial problems, unemployment, and long-lasting personal conflict with someone.

To maximize participation rate, interviews were conducted by telephone and only included a selection of axis I and axis II disorders to reduce the duration to less than 1 hour. The most prevalent axis I disorders — MDD, GAD, panic, social phobia, specific phobia, agoraphobia, and alcohol use disorders — were assessed using the relevant CIDI modules. From SIDP-IV, two PDs from each cluster were included: schizotypal-, paranoid-, anti-social, borderline-, avoidant-, and obsessive-compulsive PD. Interviewers were clinical psychology students in the final part of their training or psychiatric nurses. They received standardized training programs and supervision during the data collection period (Reichborn-Kjennerud et al., 2007b).

Of the 2,801 twins interviewed in the first wave (1999–2004), 2,758 were eligible and invited to participate in the follow-up study. After three reminders, completed interviews from 2,294 (response rate 83.1%) and interviews or questionnaires on 2,393 subjects (86.8%) were obtained. Interviews were completed on both members of 512 MZ and 475 DZ pairs and 310 single twins.

The aims of the follow-up study are to: (1) estimate the contribution of genetic and environmental factors to the longitudinal stability and change PDs in early adulthood; (2) estimate the contribution of genetic and environmental factors to the longitudinal associations between selected

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

PDs and axis I disorders; (3) estimate the degree to which normal personality traits and PDs reflect the same versus distinct genetic and/or environmental factors; (4) investigate how much of the comorbidity between selected PDs and axis I disorders can be accounted for by etiological factors influencing normal personality; and (5) explore the association between stressful life events and selected PDs and axis I disorders, to understand how much these events contribute to comorbidity. The follow-up study has now completed the data collection, and is in the analytic phase.

Consequences of PDs and Common Axis I Disorders

In this project, our aim is to study the impact of PDs on socially important psychosocial outcomes such as workforce participation, sick leave and disability, and to examine how genetic and environmental factors contribute to these outcomes. Compared to Axis I disorders, social and economic consequences of PDs have been studied to a limited degree only. Socio-economic status aggregate strongly in families and is influenced by genetic factors (Baker et al., 1996; Bemmels et al., 2008; Kendler & Baker, 2007; Tambs et al., 1989). Although studied to a limited degree, this is probably also true for workforce participation and disability: by linking large, population-based twin cohorts to public registries, recent investigations have examined how genetic factors might influence workforce participation. Using this approach in Finland (Harkonmaki et al., 2008), genetic factors were shown to contribute significantly to granted disability pensions. A similar study from Sweden (Narusyte et al., 2011) presented evidence for qualitative genetic sex effects on disability pensioning. We plan to examine whether these findings replicate in the Norwegian sample, and then to use bi- and multivariate analyses to explore how genetic and environmental factors that influence mental disorders are related to sick leave, disability. and other psychosocial outcomes. By linking previously obtained data from questionnaires (1998) and interviews (Mental Health Study, 1999–2004) to registries, we can conduct a longitudinal investigation of how PDs and Axis I disorders influence important life outcomes, including education, income, employment, paid sick leave and disability, and marital and family status.

The matching of own data with national registry data is based on unique national identification numbers granted to Norwegian citizens at birth. FD-Trygd is a historical event database including demography, social conditions, social security (including disability pension, sick leave, and diagnoses for receiving such benefits), and employment. The individual specific information in the database consists of registrations of events during lifespan. The national income registry and The National Education Database contain data on income, wealth, and education. The registries contain complete and validated information on health, demographic data on the entire population.

Future Plans for Studies of Mental Health

Since 2008, Norway has a Patient Registry (NPR) of all hospital admissions and outpatient clinical treatment in the psychiatric health service. Data from the NPR are person identifiable and can be linked to the NTR and other health registries, including the Norwegian Medical Birth Registry, the Prescription Registry, the Cause of Death Registry, and FD-Trygd. Norway also has excellent registries covering demographic variables, education, and so forth. We plan to apply for permission to link data from the NTR to a large number of registries, and if possible, also including a relationship database where familial relationships can be identified and used in analyses of a number of mental health phenotypes, including schizophrenia and bipolar disorders, which we have not previously been able to study.

Concluding Comments

The NTR is a valuable research resource for national and international studies covering a broad spectrum of health-related issues. It is becoming increasingly integrated into the Norwegian registry infrastructure to optimize its role in public health research. Having merged the three largest twin cohorts in Norway into a single source, the next step is to make data more accessible through online solutions: for example, 'variable shopping' and electronic application for data as well as through integration with the Norwegian biobanking infrastructure-building activities that aim for updated cataloguing of the data and biological specimens available for research. The various projects supported by data from the NTR have ambitious plans for extending and expanding their work; and the new data generated and technologies developed will continue to enhance the scope and quality of NTR data.

Acknowledgments

Development and use of the NTR has been supported from research funds granted through the European Union's Seventh Framework Programme (FP7/2007–2013), ENGAGE Consortium, grant agreement HEALTH-F4–2007-201413; BioSHaRE-EU, grant agreement HEALTH-F4–2010-261433, the Ellison Foundation in the United States, and The Norwegian Research Council through funds for Biobank Norway (NFR 197443/F50), grants to establish the NIPH twin panel (NFR 363.92/004, NFR 363.93/010) and grants for Axis I and Axis II Psychiatric Disorders in Norwegian Twins: A Follow-Up Study (NFR 196148) and Consequences of Common Mental Disorders and Personality Disorders (NFR 193615). We thank the Norwegian twins for their participation.

References

Andrew, T., Hart, D. J., Snieder, H., de, L. M., Spector, T. D., & MacGregor, A. J. (2001). Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. *Twin Research, 4*, 464–477.

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

Baker, L. A., Treloar, S. A., Reynolds, C. A., Heath, A. C., & Martin, N. G. (1996). Genetics of educational attainment in Australian twins: Sex differences and secular changes. *Behavior Genetics*, *26*, 89–102.

Bemmels, H. R., Burt, S. A., Legrand, L. N., Iacono, W. G., & McGue, M. (2008). The heritability of life events: An adolescent twin and adoption study. *Twin Research and Human Genetics*, *11*, 257–265.

Benson, N. R., Papenfuss, J., Wong, R., Motaal, A., Tran, V., Panko, J., & Kreuger, G. G. (2006). An analysis of select pathogenic messages in lesional and non-lesional psoriatic skin using non-invasive tape harvesting. *Journal of Investigative Dermatology*, *126*, 2234–2241.

Bergem, A. L. (2002). Norwegian Twin Registers and Norwegian twin studies — An overview. *Twin Research*, *5*, 407–414.

Christensen, K., Petersen, I., Skytthe, A., Herskind, A. M., McGue, M., & Bingley, P. (2006). Comparison of academic performance of twins and singletons in adolescence: Follow-up study. *BMJ*, *333*, 1095–1097.

Christensen, K., Vaupel, J. W., Holm, N. V., & Yashin, A. I. (1995). Mortality among twins after age 6: Fetal origins hypothesis versus twin method. *BMJ*, *310*, 432–436.

Christensen, K., Wienke, A., Skytthe, A., Holm, N. V., Vaupel, J. W., & Yashin, A. I. (2001). Cardiovascular mortality in twins and the fetal origins hypothesis. *Twin Research*, *4*, 344–349.

Czajkowski, N., Kendler, K. S., Tambs, K., Roysamb, E., & Reichborn-Kjennerud, T. (2011). The structure of genetic and environmental risk factors for phobias in women. *Psychological Medicine*, *41*, 1987–1995.

DeYoung, C. G. (2006). Higher-order factors of the Big Five in a multi-informant sample. *Journal of Personality and Social Psychology*, *91*, 1138–1151.

Engvik, H., & Føllesdal, H. (2005). The Big Five Inventory på norsk. *Tidsskrift for Norsk psykologforening*, *42*, 128–129.

Gervin, K., Hammero, M., Akselsen, H. E., Moe, R., Nygard, H., Brandt, I., . . . Lyle, R. (2011). Extensive variation and low heritability of DNA methylation identified in a twin study. *Genome Research*, *21*(11), 1813–1821.

Gervin, K., Vigeland, M. D., Mattingsdal, M., Hammero, M., Nygard, H., Olsen, A. O., . . . Lyle, R. (2012). DNA methylation and gene expression changes in monozygotic twins discordant for psoriasis: Identification of epigenetically dysregulated genes. *PLoS Genetics*, *8*, e1002454.

Gjerde, L. C., Czajkowski, N., Roysamb, E., Orstavik, R. E., Knudsen, G. P., Ostby, K., . . . Reichborn-Kjennerud, T. (2012). The heritability of avoidant and dependent personality disorder assessed by personal interview and questionnaire. *Acta Psychiatrica Scandinavica*, *126*, 448–457.

Grjibovski, A. M., Harris, J. R., & Magnus, P. (2005). Birthweight and adult health in a population-based sample of Norwegian twins. *Twin Research and Human Genetics*, *8*, 148–155.

Gunderson, J. G., Stout, R. L., McGlashan, T. H., Shea, M. T., Morey, L. C., Grilo, C. M., . . . Skodol, A. E. (2011). Ten-year course of borderline personality disorder: Psychopathology and function from the Collaborative Longitudinal Personality Disorders study. *Archives of General Psychiatry*, *68*, 827–837.

Harkonmaki, K., Silventoinen, K., Levalahti, E., Pitkaniemi, J., Huunan-Seppala, A., Klaukka, T., . . . Kaprio, J. (2008). The genetic liability to disability retirement: A 30-year follow-up study of 24,000 Finnish twins. *PLoS One*, *3*, e3402.

Harris, J. R., Magnus, P., Samuelsen, S. O., & Tambs, K. (1997a). No evidence for effects of family environment on asthma. A retrospective study of Norwegian twins. *American Journal of Respiratory and Critical Care Medicine*, *156*(1), 43–49.

Harris, J. R., Magnus, P., & Tambs, K. (1997b). Does normal variation in birthweight confer susceptibility to health problems? A co-twin control study. *The Norwegian Journal of Epidemiology*, *7*, 41–47.

Harris, J. R., Magnus, P., & Tambs, K. (2002). The Norwegian Institute of Public Health Twin Panel: A description of the sample and program of research. *Twin Research*, *5*, 415–423.

Harris, J. R., Magnus, P., & Tambs, K. (2006). The Norwegian Institute of Public Health twin program of research: An update. *Twin Research and Human Genetics*, *9*, 858–864.

Harris, J. R., Tambs, K., & Magnus, P. (1995). Sex-specific effects for body mass index in the new Norwegian twin panel. *Genetic Epidemiology*, *12*, 251–265.

Iversen, T., Tretli, S., & Kringlen, E. (2001). An epidemiological study of cancer in adult twins born in Norway 1905–1945. *British Journal of Cancer*, *84*, 1463–1465.

John, O., & Srivastava, S. (1999). The Big-Five Trait Taxinomy: history, measurement, and theoretical perspectives. In L. Pervin & O. John (Eds.), *Handbook of personality: Theory and research* (2nd ed., pp. 102–139). New York: Guilford Press.

Kendler, K. S., Aggen, S. H., Czajkowski, N., Roysamb, E., Tambs, K., Torgersen, S., . . . Reichborn-Kjennerud, T. (2008). The structure of genetic and environmental risk factors for DSM-IV personality disorders: A multivariate twin study. *Archives of General Psychiatry*, *65*, 1438–1446.

Kendler, K. S., Aggen, S. H., Knudsen, G. P., Roysamb, E., Neale, M. C., & Reichborn-Kjennerud, T. (2011). The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *American Journal of Psychiatry*, *168*, 29–39.

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: A systematic review. *Psychological Medicine*, *37*, 615–626.

Kendler, K. S., Czajkowski, N., Tambs, K., Torgersen, S., Aggen, S. H., Neale, M. C. & Reichborn-Kjennerud, T. (2006). Dimensional representations of DSM-IV cluster A personality disorders in a population-based sample of Norwegian twins: A multivariate study. *Psychological Medicine*, *36*, 1583–1591.

Kendler, K. S., Myers, J., Torgersen, S., Neale, M. C., & Reichborn-Kjennerud, T. (2007). The heritability of cluster A personality disorders assessed by both personal interview and questionnaire. *Psychological Medicine*, *37*, 655–665.

Kendler, K. S., & Prescott, C. A. (2006). *Genes, environment and psychopathology: Understanding the causes of psychiatric and substance use disorders*. New York: Guilford Press.

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

Kjeldsen, M. J., Corey, L. A., Solaas, M. H., Friis, M. L., Harris, J. R., Kyvik, K. O., . . . Pellock, J. M. (2005). Genetic factors in seizures: A population-based study of 47,626 US, Norwegian and Danish twin pairs. *Twin Research and Human Genetics*, *8*, 138–147.

Magnus, P., Irgens, L. M., Haug, K., Nystad, W., Skjaerven, R., & Stoltenberg, C. (2006). Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology*, *35*, 1146–1150.

Mazzeo, S. E., Mitchell, K. S., Bulik, C. M., Reichborn-Kjennerud, T., Kendler, K. S., & Neale, M. C. (2009). Assessing the heritability of anorexia nervosa symptoms using a marginal maximal likelihood approach. *Psychological Medicine*, *39*, 463–473.

Narusyte, J., Ropponen, A., Silventoinen, K., Alexanderson, K., Kaprio, J., Samuelsson, A., & Svedberg, P. (2011). Genetic liability to disability pension in women and men: A prospective population-based twin study. *PLoS One*, *6*, e23143.

Nes, R. B., Czajkowski, N., Roysamb, E., & Reichborn-Kjennerud, T. (2008). Well-being and ill-being: Shared environments, shared genes? *The Journal of Positive Psychology*, *3*, 253–265.

Nes, R. B., Czajkowski, N., & Tambs, K. (2010a). Family matters: Happiness in nuclear families and twins. *Behavior Genetics*, *40*, 577–590.

Nes, R. B., Roysamb, E., Harris, J. R., Czajkowski, N., & Tambs, K. (2010b). Mates and marriage matter: Genetic and environmental influences on subjective wellbeing across marital status. *Twin Research and Human Genetics*, *13*, 312–321.

Nes, R. B., Roysamb, E., Reichborn-Kjennerud, T., Tambs, K., & Harris, J. R. (2005). Subjective wellbeing and sleep problems: A bivariate twin study. *Twin Research and Human Genetics*, *8*(5), 440–449.

Nes, R. B., Roysamb, E., Tambs, K., Harris, J. R., & Reichborn-Kjennerud, T. (2006). Subjective well-being: Genetic and environmental contributions to stability and change. *Psychological Medicine*, *36*, 1033–1042.

Nilsen, T. S., Brandt, I., Magnus, P., & Harris, J. R. (2013). The Norwegian Twin Registry. *Twin Research and Human Genetics*. 2012 Sep 5:1-6, [Epub ahead of print]

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H. U., & Jonsson, B. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology*, *19*, 155–162.

Olesen, J., & Leonardi, M. (2003). The burden of brain diseases in Europe. *European Journal of Neurology*, *10*, 471–477.

Olsen, A. O., Grjibovski, A., Magnus, P., Tambs, K., & Harris, J. R. (2005). Psoriasis in Norway as observed in a population-based Norwegian twin panel. *British Journal of Dermatology*, *153*, 346–351.

Orstavik, R. E., Kendler, K. S., Czajkowski, N., Tambs, K., & Reichborn-Kjennerud, T. (2007). The relationship between depressive personality disorder and major depressive disorder: A population-based twin study. *American Journal of Psychiatry*, *164*, 1866–1872.

Pfohl, B., Blum, N., & Zimmerman, M. (1997). *Structured Interview for DSM-IV Personality: SIDP-IV*. Washington, DC: American Psychiatric Press.

Pharoah, P. O. (2002). Neurological outcome in twins. *Seminars in Neonatology*, *7*, 223–230.

Phillips, D. I., Davies, M. J., & Robinson, J. S. (2001). Fetal growth and the fetal origins hypothesis in twins — Problems and perspectives. *Twin Research*, *4*, 327–31.

Reichborn-Kjennerud, T., Bulik, C. M., Kendler, K. S., Roysamb, E., Maes, H., Tambs, K., & Harris, J. R. (2003). Gender differences in binge-eating: A population-based twin study. *Acta Psychiatrica Scandinavica*, *108*, 196–202.

Reichborn-Kjennerud, T., Czajkowski, N., Neale, M. C., Orstavik, R. E., Torgersen, S., Tambs, K., . . . Kendler, K. S. (2007a). Genetic and environmental influences on dimensional representations of DSM-IV cluster C personality disorders: A population-based multivariate twin study. *Psychological Medicine*, *37*, 645–653.

Reichborn-Kjennerud, T., Czajkowski, N., Roysamb, E., Orstavik, R. E., Neale, M. C., Torgersen, S., & Kendler, K. S. (2010). Major depression and dimensional representations of DSM-IV personality disorders: A population-based twin study. *Psychological Medicine*, *40*(9), 1475–1484.

Reichborn-Kjennerud, T., Czajkowski, N., Torgersen, S., Neale, M. C., Orstavik, R. E., Tambs, K., & Kendler, K. S. (2007b). The relationship between avoidant personality disorder and social phobia: A population-based twin study. *American Journal of Psychiatry*, *164*, 1722–1728.

Roysamb, E., Harris, J. R., Magnus, P., Vitterso, J., & Tambs, K. (2002). Subjective well-being. Sex-specific effects of genetic and environmental factors. *Personality and Individual Differences*, *32*, 211–223.

Roysamb, E., Kendler, K. S., Tambs, K., Orstavik, R. E., Neale, M. C., Aggen, S. H., . . . Reichborn-Kjennerud, T. (2011). The joint structure of DSM-IV Axis I and Axis II disorders. *Journal of Abnormal Psychology*, *120*, 198–209.

Roysamb, E., Tambs, K., Reichborn-Kjennerud, T., Neale, M. C., & Harris, J. R. (2003). Happiness and health: Environmental and genetic contributions to the relationship between subjective well-being, perceived health, and somatic illness. *Journal of Personality and Social Psychology*, *85*, 1136–1146.

Skodol, A. E., Gunderson, J. G., McGlashan, T. H., Dyck, I. R., Stout, R. L., Bender, D. S., . . . Oldham, J. M. (2002). Functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. *American Journal of Psychiatry*, *159*, 276–283.

Skodol, A. W., Johnson, J. G., Cohen, P., Sneed, J. R., & Crawford, T. N. (2007). Personality disorder and impaired functioning from adolescence to adulthood. *British Journal of Psychiatry*, *190*, 415–420.

Soeteman, D. I., Hakkaart-van, R. L., Verheul, R., & Busschbach, J. J. (2008). The economic burden of personality disorders in mental health care. *Journal of Clinical Psychiatry*, *69*, 259–265.

Tambs, K., Czajkowsky, N., Roysamb, E., Neale, M. C., Reichborn-Kjennerud, T., Aggen, S. H., . . . Kendler, K. S. (2009a). Structure of genetic and environmental risk factors for dimensional representations of

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press

DSM-IV anxiety disorders. *British Journal of Psychiatry*, *195*, 301–307.

Tambs, K., & Moum, T. (1993). How well can a few questionnaire items indicate anxiety and depression? *Acta Psychiatrica Scandinavica*, *87*, 364–367.

Tambs, K., Ronning, T., Prescott, C. A., Kendler, K. S., Reichborn-Kjennerud, T., Torgersen, S., & Harris, J. R. (2009b). The Norwegian Institute of Public Health twin study of mental health: Examining recruitment and attrition bias. *Twin Research and Human Genetics*, *12*, 158–168.

Tambs, K., Sundet, J. M., Magnus, P., & Berg, K. (1989). No recruitment bias for questionnaire data related to IQ in classical twin studies. *Personality and Individual Differences*, *10*, 269–271.

Torgersen, S., Czajkowski, N., Jacobson, K., Reichborn-Kjennerud, T., Roysamb, E., Neale, M. C., & Kendler, K. S. (2008). Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: A multivariate study. *Psychological Medicine*, *38*, 1617–1625.

WHO. (2004). *World Health Report 2004*. Geneva: Author.

WHO. (2009). *World Health Report 2009*. Geneva: Author.

Wittchen, H. U., & Pfister, H. (1997). *DIA-X Interviews (M-CIDI)*. Frankfurt: Swets & Zeitlinger.

https://doi.org/10.1017/thg.2012.117 Published online by Cambridge University Press