The Norwegian Twin Registry

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ABSTRACT

The Norwegian Twin Registry (NTR) is a large population based twin cohort for research purposes. At present, the registry has 14 692 complete twin pairs with information on zygosity and to varying degree information on somatic and mental health, lifestyle and demographics. The registry covers birth years 1895-1960 and 1967-1991. NTR was established in 2009, at the Norwegian Institute of Public Health, as a merger of three major twin panels, the oldest originating in the 1960s. Since then Norwegian twin research has been a notable contributor to twin research internationally. Norwegian twin researchers have published over 250 papers based on Norwegian twin data, spanning a broad range of somatic and mental health phenotypes. In twin studies of heritability a data structure with both variance within and between pairs is required. Therefore a large sample is necessary, especially when studying rare diseases and conditions, and it is of vital importance to expand the registry. NTR is actively recruiting new twins, both young and older, but declining response rates are a challenge. The value of NTR is greatly enhanced through the linkage possibilities offered by Norway's many nationwide registries (medical, demographic, and socio-economic). Access to data is permitted by the NTR steering group and will in most instances need permission from the Regional Ethics Committee.

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INTRODUCTION

The purpose of this paper is to present the Norwegian Twin Registry (NTR), which is a recent merger of three older Norwegian twin panels. In that context we will give an overview of scientific output based on Norwegian twin data. We will also discuss present and future challenges concerning the twin registry.

NTR is part of the Norwegian Institute of Public Health (NIPH) research infrastructure and integral to the efforts towards the realization of the NIPH vision: 'Better health for all'. From this vision follows specific goals and tasks for NIPH: to be prepared for acute health threats, to give scientifically based advice, to provide services that improve public health, to conduct public health surveillance and to obtain knowledge of the causes of common diseases and factors that improve health. Conducting high quality research is one of several foundations to achieve these goals, and NIPH maintains a large research portfolio with special focus on (1) elucidating causes of diseases, (2) describing the occurrence and determinants of these etiological factors and (3) testing the effect of public health interventions and policies. NIPH is responsible for several public health registries and large research cohorts. The Norwegian Twin Registry is particularly suited to address research questions in the first of the above mentioned categories.

Twin research is a fundamental resource for investigating the genetic basis of complex human traits (1). Furthermore, due to the possibility to control for confounding due to genetic and shared environmental effects, the twin method is also ideally suited to explore causal associations between exposure and disease. For some diseases, e.g. malignant melanoma and ischemic cardiac disease, environmental risk factors with major impacts on disease risk have been identified, and for other diseases, e.g. certain breast cancers, specific genes conferring strong effects have been found. Twin studies have been important in elucidating the importance of these genetic and environmental effects, but they have also revealed that genetic influences may affect the putative environmental exposures, such as smoking. The potential confounding that arises if genetic effects simultaneously influence exposure and outcome can be addressed using the discordant co-twin control design. However, most common complex disorders and traits are influenced by numerous genetic and environmental factors, many of which have relatively low effects. For many disorders with a huge impact on public health we still lack sufficient causal insight to be able to prevent and/or change the course of progression.

Addressing these challenges was part of the motive for establishing a Norwegian Twin Registry (NTR) in 2009 as an integral part of the NIPH health registry and biobank research infrastructure. NIPH, the University of Oslo and Oslo University Hospital, which all had population-based twin cohorts, decided to merge their respective cohorts and establish a national twin registry in order to fully capitalize on the potential in Norwegian twin data and make the data more accessible to researchers. They also provided the initial funding (2,3).

Table 1. Twins in the Norwegian Twin Registry by birth cohort and zygosity.

Birth cohorts	MZ pairs	DZ-SS pairs	DZ-OS pairs	Total number of complete pairs with zygosity information	Total number of twins (individuals)
1895-1945	–	–	1714	1714	7676
1915-1960	3847	5344	3	9194	21930
1967-1991	1738	1114	932	3784	11033
Total	5585	6458	2649	14692	40639

MZ: monozygotic, DZ-SS: dizygotic same sex, DZ-OS:dizygotic opposite sex

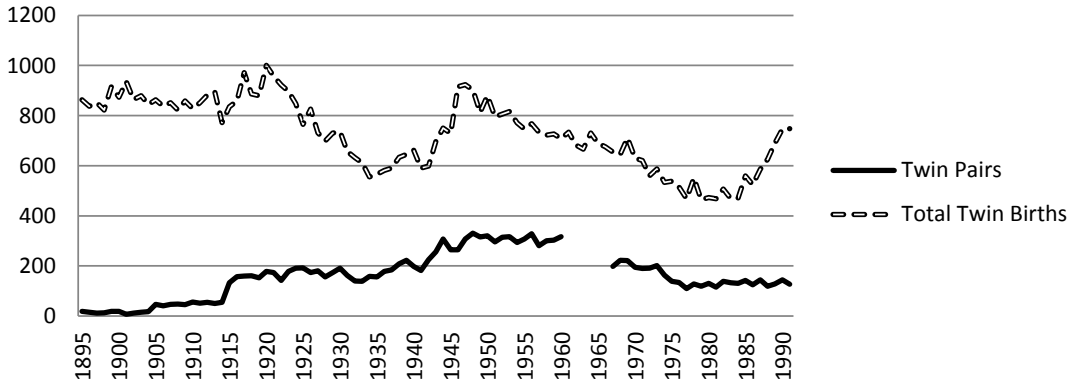

Figure 1. Complete twin pairs with zygosity in NTR and total number of twin births 1895-1991.

TWIN COHORT

The number of single twins in the registry is 40 639, of which 33 740 constitute 16 870 complete twin pairs. For 2 178 twin pairs zygosity has not been determined, resulting in 14 692 complete pairs eligible for twin studies (Figure 1). Zygosity has been determined by questionnaire. The method has been verified for a subsample of twins by concordance of genetic markers in blood, serum and red cell enzyme systems, and later by DNA-based analysis. These tests revealed high validity of the questionnaire-based method – the margin of error being 2-3% (4,5). Table 1 provides an overview of the number of twin individuals and complete pairs across cohorts and zygosity. All twins in NTR were at least 18 years old at time of recruitment.

The partition into different birth cohorts/twin panels reflects the three constituent parts of NTR and differences in ascertainment (6-8). We will in the following just briefly outline the establishment of these twin panels in order to illustrate the structure of NTR twin cohorts. A fuller account is presented in the papers by respectively E. Kringlen and P. Magnus et al in this special issue.

Motivated by the need for a large and representative sample appropriate for studies on schizophrenia, the first twin cohort was compiled in 1963. Covering birth years 1901-1930, and later extended to 1895-1945, the founders identified a total of 37 000 twin pairs through Statistics Norway. Of these, 18 972 could be identified in the national population registry (by their national identity number (NI)) which also provides address information. Numerous studies were based on subsamples derived from this cohort (9-13). Zygosity was only determined for the subsamples and not for the general cohort. Therefore, of complete pairs from this cohort, only opposite sexed twin pairs have zygosity information as they are dizygotic. This cohort and substudies are described in detail elsewhere (14).

A second cohort, covering birth years 1915-1960 and derived from a combination of the first cohort and updated information from Statistics Norway, was compiled at the institute of Medical Genetics, University of Oslo, in the late 1970s (8). For this cohort there was the more explicit aim of creating a registry containing zygosity information, followed by extensive data collection on somatic health, lifestyle and reproductive history. Three waves of questionnaires where sent the twins in the period 1978-1992. Only same sexed twins were invited.

The third cohort, originally covering birth years 1967-1979, recruited in two waves, was established at NIPH in 1992. Twins were identified in the medical birth registry, which started mandatory registration of all births in Norway in 1967. The first wave in 1992 invited twins born 1967-1974, who later were followed up in a second wave in 1998 in a longitudinal design. This second wave also expanded the cohort to include birth years 1974-1979 (7,15). All surviving twin pairs 18+ years were invited. In contrast to the second cohort (birth years 1915-1960) all opposite sexed twin pairs were also invited, allowing testing of statistical models were genetic factors differ between the sexes. This cohort has been the most extensively used. Subsamples have participated in several questionnaire studies, interviews and clinical examinations. Blood

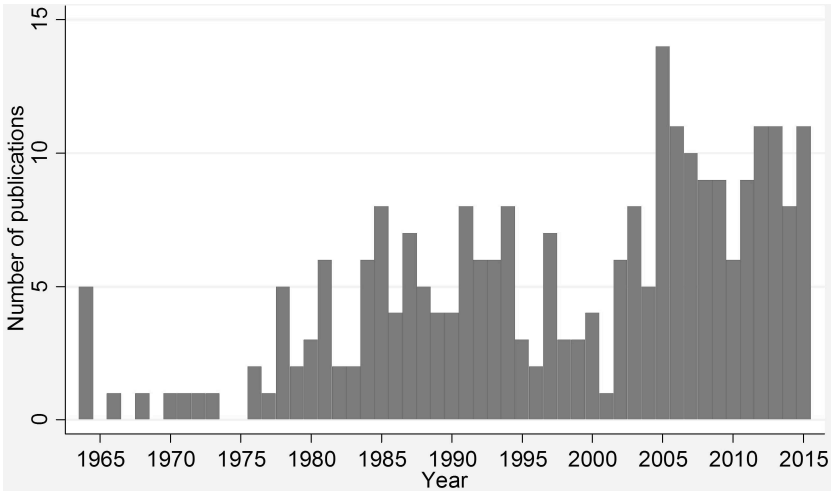

Figure 2. Number of publications based on Norwegian twin data (Total: 251).

and DNA have been collected from around 4000 twins (born 1967-79) and are stored at the NIPH biobank (2, 3,16). Cohorts 1980-1991 were recruited in 2013 with a short questionnaire to primarily assess personality and zygosity and in addition some demographic and lifestyle variables.

NTR is a consent based health registry with a concession from the Norwegian Data Inspectorate. This means that all twins in NTR must provide consent, which regulates the use of their personal data and biological material and linkage with other registries. The oldest birth cohorts who never were contacted and subsequently have no consents are now mostly deceased. Thus, data about them are usually allowed to be used for research since laws regulating personal information and consents mostly concerns living persons. New studies will in most cases require permission from the Regional Ethics committee, which will also assess whether the study in question is within the scope of existing consents or if new consents are required.

SCIENTIFIC OUTPUT

With a few exceptions (e.g. (17,18)) most twin research in Norway is based on data from twin cohorts now comprised in NTR. To measure the scientific output from Norwegian twin data, based on cohorts now in NTR, we conducted a search in the three most commonly used bibliographical databases in epidemiology: Scopus (Elsevier), PubMed (National Institutes of Health) and ISI Web of Science (Thomson Reuters). The search was conducted on combinations of Norway/Norwegian/twin* plus names of key authors and principal investigators. Reviews, editorials and publications that did not relate to data on twins in NTR were excluded. Abstracts belonging to older publications were often not available and may have been misclassified. During the period from 1964-2015 a total of 251 publications were found. Figure 2 shows the development in number of published papers based on NTR twins over time.

A further index of productivity was garnered from a recent meta-analysis of 2748 twin studies, of these 91 Norwegian studies on 333 traits which places Norway 8th on a country list of 30 countries conducting twin research (http://match.ctglab.nl/#/home). The discrepancy between this number of studies and the total number of published papers based on NTR twins described above is due to different bibliographical search strategies, the former being narrower for the purpose of the meta-analysis. In the same study twin researchers with ≥ 25 papers were set up in an authorship co-occurrence matrix which shows which authors were publishing together in twin research. This matrix showed that Norwegian twin research is a noticeable contributor to twin research and Norwegian twin researchers constitute one of the main authorship communities internationally and also publish extensively with international partners (1).

Thematically, research is at present predominantly focused on mental health, but there are also studies on somatic disease: e.g. various cancer forms, IBS/IBD and arthrosis. Table 2 presents a selection of findings based on twins now included in NTR. As illustrated by the examples listed in this table Norwegian twin research spans a broad range of interests, including outcomes that one normally associates with the social sciences, as criminality and sick leave.

INTERNATIONALIZATION AND ACCESS

The present trend in epidemiological research is to amass large cohorts across time and countries. Funding agencies are increasingly geared towards the building of international consortia, as exemplified by the EU framework programs. This was originally partly driven by genetics, which necessitates huge samples in order to gain power and ability to detect effects of single genes, but is now standard practice in the so called "omics" sciences and towards the realization of personalized medicine. Moreover, twin research has inherent features which require large samples. The pair

Table 2. Selected results from twin studies on heritability based on NTR twins.

Phenotype	Outcome	Results	Authors
Schizophrenia	Pairwise concordance	MZ 0.25-0.38, DZ 0.04-0.10	Kringlen 1968 (19)
Common crime	Probandwise concordance	MZ 0.22-0.26 DZ 0.15-0.18, Hereditary factors not important for etiology of crime	Dalgard & Kringlen 1976 (20)
Variation in birth weight	Variance explained	> 50% fetal genes, < 20% maternal genes, 20-30% random environmental effects	Magnus 1984 (21)
CHD and risk factors	Heritability	Cholesterol 0.43, Triglycerides (fasting) 0.4 (male 0), ApoB level 0.66, ApoA-I and II level, 0.53 and 0.69	Berg 1984 (22)
Genetic and environmental contribution to covariance between occupation status, educational attainment and IQ	Heritability	Birth cohort dependent rates Occupational status 0.16-0.43 Educational attainment 0.10-0.51 IQ 0.37-0.66	Tambs et al 1989 (23)
DSM III R Schizophrenia	Probandwise concordance	MZ 0.48 DZ 0.04	Onstad et al 1991 (24)
Systolic and diastolic blood pressure	Correlation	SBP MZ 0.52 DZ 0.19 DBP MZ 0.43 DZ 0.23	Tambs et al 1992 (25)
Body Mass Index	Heritability	AE model: Men 0.71 Women 0.79 Male female genetic correlation 0.62 Sex specific genetic influence	Harris et al 1995 (26)
Alzheimer and vascular dementia	Probandwise concordance	Alzheimer 0.83 MZ 0.46 DZ Vascular dementia 0.29 MZ 0.29 DZ	Bergem et al 1997 (27)
Body height	Heritability	Men 0.87 Women 0.89 AE model	Silventoinen 2003 (28)
Subjective well-being	Heritability	A 0.45 C 0.13 ACE model	Røysamb et al 2003 (29)
Otitis media	Heritability	AE model: Men 0.72 Women 0.61	Kvestad et al 2004 (30)
Asthma, hay fever	Heritability	Asthma 0.71, Hay Fever 0.69 DE model	Nystad et al 2005 (31)
Cluster A personality disorders	Heritability	0.21-0.28 AE model	Kendler et al 2006 (32)
Stability and change in subjective well-being	Heritability	≈ 80% AE model	Bang Nes et al 2006 (33)
Depressive personality disorder and major depressive disorder	Heritability	Depr. Pers. Disorder 0.40 AE model Major depr. Disorder 0.32 AE model	Ørstavik et al 2007 (34)
Psoriasis	Heritability	AE model: 0.66	Grjibovski et al 2007 (35)
Cluster C personality disorders	Heritability	0.27-0.35 AE model	Reichborn-Kjennerud et al 2007 (36)
Pain sensitivity	Heritability	ADE model Cold-pressor pain: 0.60 Contact heat pain: 0.26	Nielsen et al 2008 (37)
Cluster B personality disorders	Heritability	0.24-0.38 AE model	Torgersen et al 2008 (38)
Inflammatory bowel disease (IBD)	Relative risk for concordant disease	Crohns diseases MZ 95.4, DZ 42.4 Ulcerative colitis MZ 49.5, DZ 0.0	Bengtson et al 2010 (39)
Phobias in women	Heritability	0.43-0.63 AE model	Czajkowski et al 2011 (40)
Long term sick leave and disability pension	Heritability	0.49 and 0.66 AE model	Gjerde et al 2013 (41)
Epilepsy and febrile seizures	Probandwise concordance	Epilepsy: MZ 0.39 DZ 0.07 Febrile seizures: MZ 0.41 DZ 0.14	Corey et al 2011 (42)
Early age alcohol initiation and alcohol use disorder	Heritability	Alcohol initiation 0.37 ACE model Alcohol use disorder 0.62 AE model	Ystrøm et al 2014 (43)
Prostate cancer	Heritability	0.58 ACE model	Hjelmborg et al 2014 (44)

Concordance rate: The risk of a twin of an affected co-twin of developing the disease. The difference in concordance rate between MZ and DZ twins indicate the magnitude of genetic influence on phenotypic variance. Pairwise and Probandwise reflects the difference between complete and incomplete ascertainment of cases.
Heritability: Phenotypic variance is decomposed into additive genetic influence (A), non-additive genetic influence (D), Shared environmental influence (C) and non-shared environmental influence (E). Heritability is reported as portion of total phenotypic variance explained by A – narrow sense heritability. Through model fitting the most parsimonious model is selected. Where model is not specified heritability is the ratio of genetic variance to total variance,

structure of twin data means that one needs complete MZ and DZ twin pairs that are discordant/ concordant for disease and exposure, depending on the study design. This has a multiplying effect on the needed sample size, especially for rare diseases. Considering that twins comprise 2-3% of the population (based on a Norwegian mean historical twinning rate of 1.25% (45)), collaboration with other countries is fundamental. Norwegian twin research has always been international in character with extensive collaboration with Northern Europe, especially Scandinavia, and the USA. Indeed, given Norway's natural advantages for epidemiological research, substantial parts of NTR data and numerous research projects have had foreign funding. What is new is the pooling of NTR data with those from other twin registries in order to increase sample size and statistical power. Currently NTR has contributed to several large international cohorts, NorTwinCan (cancer cohort including more than 300 000 twins) CODATwins (height and weight, about 430 000 twins) and EuroDiscoTwin (metabolic disorders, 34 000 twin pairs) (44,46,47). Research across such cohorts poses the challenge of data harmonization and sharing. In order to fully realize the potential in NTR regarding international projects it is vital to 1) harmonize and standardize variables according to international standards or seek to agree on such standards with other twin cohorts, and 2) to implement new technologies that let researchers access data remotely. Several initiatives exists to that end, national and international, e.g. DataShield (48).

Also in a national context, there are issues concerning the accessibility of data. Linkage with other registries is a long and complicated and, often, expensive process. There are efforts, technical and administrative, to ease this process. For example, the RAIRD project, by the Norwegian Social Science Data Service and Statistics Norway is developing and infrastructure which let researchers access data and do linkages themselves remotely and which at the same time protects privacy rights (raird.no).

However, before NTR can be part of such solutions a solid IT infrastructure must be in place. Data in NTR are currently being stored in flat files and are insufficiently documented. There is need for a flexible database solution which can integrate well with data sharing platforms, secure coherent management of participant's rights and tracking of participants and data. A new database will underpin web-based metadata systems which are crucial for promoting NTR data and remote access solutions. Further development of NTR along these lines will take place within the NIPH general strategy for 2014-2018 (www.fhi.no). A major component of this strategy is to develop a modern knowledge infrastructure which entails a strengthening and modernization of digital solutions at the NIPH and contribute to national trends for such systems, through e-health work and the national health registry project (www.helseregistre.no).

EXPANSION OF THE REGISTRY

Building a robust twin registry is a challenge. The general decline in participation rates in epidemiologic studies is especially felt in twin studies (49). Twin births comprise 1-2% of all births in Norway, hence for a start only a small subgroup of the population is eligible for inclusion. Moreover, twin models are based on complete twin pairs. This makes recruitment more demanding as the probability that both twins in a pair will participate is less than the probability of one twin participating. Both points are reflected in our latest recruitment drive (birth cohorts 1980-91) where the overall response rate was 37% and the pairwise response rate only 25%. It follows that NTR is particularly vulnerable to attrition as one withdrawal of consent for many purposes means the loss of the entire twin pair. In twin studies of heritability a data structure with both variance within and between pairs is required. Therefore a large sample is necessary when studying rare diseases and conditions, and it is of vital importance to expand the NTR registry. We will in the next years invite birth cohorts covering years 1961-1966, which have formerly not been included (Figure 1). These cohorts are important as they have attained an age where there will be variance in disease outcomes obtainable by national health registries. It is also important that NTR covers unbroken series of birth cohorts in order to elucidate temporal changes in heritability and gene environment interaction.

Nationwide health and demographic/socioeconomic registries are a competitive advantage for Norwegian epidemiology. The value of NTR is largely constituted by the linking opportunities offered by the health registries, which can provide information on most disease endpoints and the socioeconomic registries which have information on both socioeconomic exposures and endpoints. What is lacking in these registries are more specific exposure information and life events, and, of course, all "softer" endpoints, such as measurements of quality of life, symptom levels of mental and somatic disorders, and pain. A recent meta-analysis showed a weighted average heritability of 0.49 across results from all human traits and diseases studied in twin studies through a 50 year period (1). The results clearly demonstrate the importance of environmental factors in disease development and the necessity of a broad approach as to what kind of environmental and exposure information should be collected and examined (1). E.g. Kendler and Halberstadt (50) showed that a biographical approach to the life of twins can add to the understanding of the causal interrelationship between environmental experiences and outcome. Through detailed interviews of the twins' life experiences insight was gained in the ways that environmental experiences could contribute to major depression. Such biographical information is not available through registry linkage and not well suited for questionnaires. This poses the question as to what

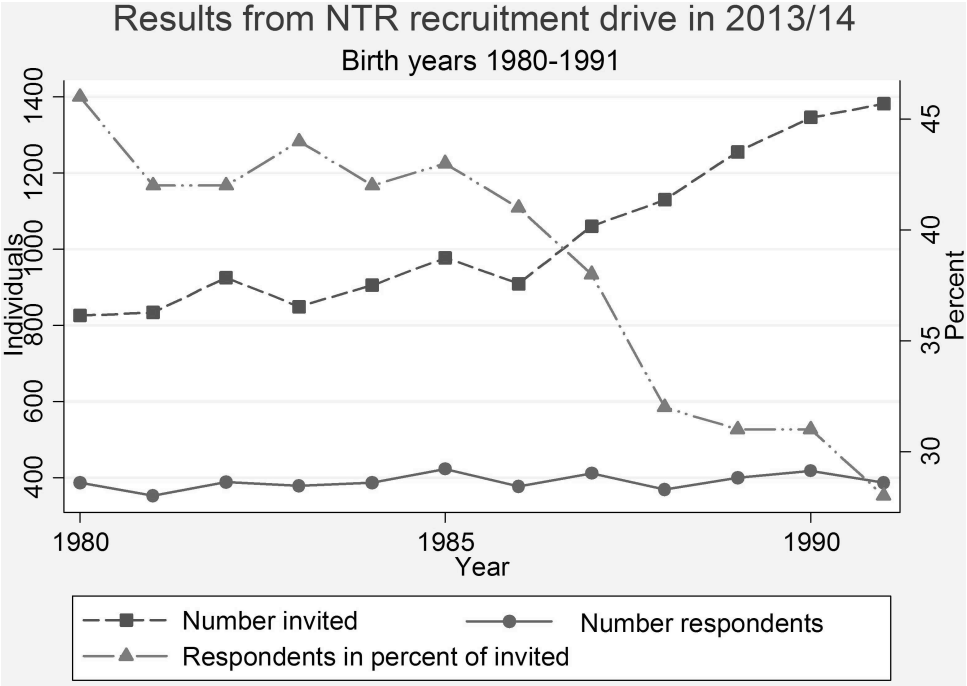

Figure 3. Response rates for birth cohorts 1980-1991. The x-axis is birth years. The left hand y-axis is number of twin individuals. The dashed line describes the number of invited twin individuals for each year. Only twins from pairs were both were alive and ≥ 18 years old were invited. The increase in number of invited twins reflects the rising twin rate over the same period – mostly due to the introduction of assisted reproductive technologies in the mid 1980s. The solid line is overall response in number of individuals, left hand y-axis. The right hand y-axis is response in percent of invited twins for each birth year (dashed line with two dots).

information NTR should focus on collecting and by which methodology. As of now most data in NTR is the result of research projects collecting data for their specific purposes, and NTR initiated data collection is limited. Collecting fine-grained information through questionnaires or interviews is expensive and detrimental to participation rates. However, new approaches to data collection and new data sources have potential which hitherto have been unexploited. NTR should consider exploring the possibilities in obtaining data from e.g. wearables (e.g. activity trackers), smartphones, social media (e.g. Facebook, Twitter), and purchase history from large retail chains.

We will continue to recruit new cohorts from younger twins, i.e. those born after 1991. These twins will so far not have reached the age of incidence of most common chronic and non-communicable diseases. On the other hand, in a life course epidemiology context, it is important to map risk factors and relevant exposures from an early age. Ideally, a future NTR could be imagined to be set up as a birth cohort similar to that of the Norwegian Mother and Child Cohort (MoBa) (51). Such a design could also elucidate fundamental assumptions in twin research concerning the proposition of equal environment and the role of in utero environment which is believed to have an effect of life course trajectories of twin pairs. However, MoBa has 1800 twin births in its cohort which constitute a rich resource in this context and can, when attaining legal age, be recruited into NTR.

Data collection and recruitment to NTR is through questionnaires and interviews. Due to legal reasons NTR has no data from other nationwide registries, apart from basic information from the Medical Birth Registry from which we identify twins for recruitment. However, separate research projects using NTR data will in many cases obtain endpoint data through registry linkage. As mentioned above, the participation rate in epidemiological studies is declining (49). Figure 3 shows the results of our latest recruitment drive (2013), where 12 000 twins from the birth years 1980-1991 were invited to complete a short questionnaire for zygosity classification and examination of personality (Big Five) and some basic lifestyle and demographic variables. The overall response rate was 37%, which is markedly lower than for the previous recruitment drive for birth cohorts 1967-1979, which was 73% in 1992 and 63% in 1998 (7). There is also a clear relationship between age and response rate, with higher response in older than younger twins. Reasons for this overall decline are not clear, but new technologies and methods for recruitment and data collection must be explored. NTR has recently explored secure internet based questionnaire solutions, available on mobile phones and tablets as well as computers. The birth cohorts 1980-1991, which we invited in our latest recruitment drive, where followed up in 2015/16 where we invited 7415 of the non-responding twins to fill in the questionnaire online. We got response from 540 twins, which is a 7% response rate. Although this

was from a group of non-responders to the mailed questionnaire, i.e. we did not expect a high participation rate; it clearly shows that we have a challenge getting through to people the importance of our research and reasons for participating. This means that new ways of communicating with the twins must be considered. Social media, SMS, E-mail and other forms of electronic communication will be increasingly important as paper based communication is declining in society as a whole.

LEGAL ISSUES

In order to be a high quality and renowned national and international research infrastructure, NTR must at all times comply with the legal foundation of the registry and make sure that the approved research projects and registry linkages are within the legal and ethical framework. Limitations in types of scientific aims covered by the informed consent and the NTR concession from the Norwegian Data Inspectorate are at times challenging. E.g. it is well known that twin research is highly relevant for social scientists who seek to investigate the role of genetic endowments on social, demographic and economic outcomes is (52). However, NTR was originally set up as a medical research registry, limited to health research, and projects with non-medical exposures and outcomes might from a NTR legal status point of view be considered problematic. Also data sharing with researchers in other countries and registry linkage is not always straightforward. Hence NTR is continuously working towards updating older consents, e.g. when new data on older cohorts are collected. Also when new cohorts are recruited the new consent statement covers a broad set of phenotypes and explicitly includes general registry linkage and data sharing. Legal developments and new technologies might change the way consents are given. For example, in the near future twins might be alerted by SMS and asked for consent to a new study, or each twin has a personalized web page where they can update their consent status, fill in questionnaires and review their personal data.

ORGANISATION AND FUNDING

NTR is housed in the newly established department for Population based Health Surveys. This department is embedded in the equally new division for Health Data and Digitalization at NIPH. In order to meet the aims of NIPH strategy NIPH has recently reorganized and one of the goals of the reorganization was to emphasize research infrastructure. Hitherto, the lack of a unified structure for health registries, health surveys and biobanks led to inefficiencies and fragmented resources and solutions. A more comprehensive approach to NIPH research infrastructure assets should be able to provide better services and technical solutions.

NTR has no dedicated funding from either the government or the Norwegian Research Council and is currently supported by NIPH and by research projects utilizing NTR data. Research projects pay an access fee for data and administrative costs. Access to data is permitted by the NTR steering group and will in most instances need permission from the Regional Ethics Committee. An updated website, www.fhi.no/tvilling has information about the registry, current research projects and access policy, as well as information of special interest to the participants.

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