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.

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).

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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