

NEWS

Scandinavian registries boost autism research

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Every baby born in Denmark, within the first few days of life, receives a unique, 10-digit identification number. The baby's name and number become a part of the Danish Medical Birth Registry, a comprehensive electronic record of the birth details — from birth weight and length to parents' smoking habits — established in 1968.

"[The identification number] is nearly tattooed on your forehead, you cannot get rid of it," says Poul Thorsen, associate professor of epidemiology at the University of Aarhus. "It's fixed to you and anything you do for the rest of your life."

As babies grow older, more than 200 linked electronic registries keep track of their every encounter with the nationalized medical establishment, recording every condition diagnosed and every drug prescribed. In recent years, these massive data collections have played a pivotal role in epidemiological medical research, particularly in identifying risk factors for complex psychiatric diseases such as autism and schizophrenia.

One collection, the Danish Psychiatric Central Register (DPCR), has tracked every person admitted to a psychiatric hospital since 1938, and nearly every person diagnosed with autism since 1995. Since 1982, the **Statens Serum Institut** in Copenhagen has stored dried blood spot samples pricked from the heel of every newborn. This biobank, called the Danish Newborn Screening Biobank (NBS-Biobank), holds more than 2 million samples, with roughly 70,000 more added each year.

Danish citizens, through their physicians, have the right to access these collections for health reasons whenever they need. For instance, doctors initially draw the blood for the NBS-Biobank so that babies can be tested for phenylketonuria (PKU), a deadly metabolic disease that can be

prevented by diet.

Together, these Danish registries and biobanks hold medical information about all 5.5 million living Danish citizens, as well as many millions of others who have died since the registries' conception. For autism, with its relatively low prevalence of about 1 in 150, the huge numbers may prove to be a godsend.

Most of the data from the registries is managed by Denmark's National Board of Health, based in Copenhagen. For interested researchers, access to the anonymized data requires approval from the Danish Data Protection Agency, the National Board of Health and various ethical committees, depending on the type of research proposed.

For instance, researchers from Aarhus University Hospital analyzed registry samples from 444 children with autism and 444 controls and reported on 13 January that, contrary to indications from previous studies, the glutamate decarboxylase gene 1 on chromosome 2 is not associated with autism¹.

In December, drawing from more than 400,000 Danish registry samples, an international group of epidemiologists found that the apparent increase in autism prevalence from 1994 to 1999 is partly due to a drop in the age at which the children were diagnosed².

These registries are "a great resource for the world," says Thorsen, an author on both reports and on dozens of other autism studies that used registry data.

Multiple uses:

The registries may also prove useful for researchers studying schizophrenia. For instance, in the last decade, studies using the Danish Psychiatric Central Register have identified several environmental risk factors for schizophrenia, including prenatal viral infections³, a family history of autoimmune disease⁴, and advanced age of the father at birth⁵.

"I think [Denmark] is the best place to study the epidemiology of schizophrenia in the world, by far. That's why I'm doing it," says **William Eaton**, chair of the department of mental health at the Johns Hopkins Bloomberg School of Public Health, who has authored many of the schizophrenia risk factor studies using European registry data.

The samples are useful not only because of their number and ethnic uniformity, but also because of the health care system under which they're managed, according to Eaton. "Their medical profession is homogenous, too. They use a single textbook of psychopathology, going through licensing exams and so forth," he says. "For schizophrenia, they are almost famous for being conservative about diagnosis."

Precious resource: The Danish Newborn Screening Biobank holds more than 2 million samples of dried blood.

For complex psychiatric disorders, the registries have a couple of significant drawbacks, however. First, because the diagnostic information does not enter the system until the patient contacts a doctor or hospital, there may be a selection bias that wouldn't exist in rigorous general-population epidemiological studies.

For instance, a study published in May analyzing 32,000 records from Swedish registries found that parents of children with autism are more likely to have been hospitalized for a mental disorder than parents of typically developing children⁶. The study's researchers suggested that this indicates a biological link between the two disorders, but others say the link may be circumstantial.

"If I just look at who shows up at my hospital, I'm going to find certain combinations of diseases that I wouldn't find if I looked in the general population, because people with more diseases are going to end up more often in the doctor's office," says **David Mandell**, assistant professor of psychiatry and pediatrics at University of Pennsylvania School of Medicine. In this case, people with schizophrenia may be more likely to take their child into the doctor for psychiatric review, Mandell says.

Limited data:

Another problem is that the type of data recorded, particularly that related to environmental factors, is relatively limited.

For instance, psychologist Simon Baron-Cohen of the University of Cambridge is measuring testosterone levels of 90,000 samples of amniotic fluid from the Danish Historical Birth Cohort Biobank — another collection managed by the Statens Serum Institut — testing his hypothesis that the **hormone is linked to autism**. But the existing biobanks don't have data on other environmental factors, such as **maternal folate intake** or other **aspects of diet**.

"Once you start talking about the potential impact for risk-factor studies, then registries may have some limitations because there is not a wide range of exposures or risk factors that you can look at," says **Craig Newschaffer**, professor and chairman of the department of epidemiology and biostatistics at the Drexel University School of Public Health.

"There's basically a trade-off between large numbers and great representation [of the population] against some limitations on quality and availability of the information you have on hand," he adds.

Scandinavian countries, particularly Denmark, have a long history of maintaining population records. The Church of Denmark began keeping track of all births and deaths in the country in 1645. Sweden and Israel also have national health registries, but they are not nearly as extensive. Privacy issues have prevented similar systems from cropping up elsewhere.

The thorough record-keeping system "is something that the Scandinavians are very comfortable with in a way that Americans and some other European countries are not," says Mandell.

That may be slowly changing, however. In 2004, Northern California insurance giant Kaiser Permanente launched the Early Markers for Autism study, in which researchers analyze blood samples from California pregnant women and their babies drawn from July 2000 to September 2001. Using that data, researchers reported in April 2008 that high levels of a protein that circulates in blood, called brain derived neurotrophic factor, is an early biomarker for autism⁷. Kaiser Permanente is also developing plans to request DNA samples from its 2 million adult members.

In June 2006, Children's Hospital of Philadelphia began collecting DNA from children patients in hopes of amassing a \$40 million, 100,000-person database of genetic profiles that will help researchers find risk factors for common diseases.

American registries will be particularly important to local and state governments trying to manage the growing number of autism diagnoses, Mandell predicts. "We've given communities so few resources to meet the growing demand," he says, particularly for hospitals and special education programs. "Communities are sort of left on their own to plan, and registries are one planning tool."

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