

PHD
DISEASE **MENTAL**
EPIDEMIOLOGY HEALTH
CARDIOVASCULAR DIABETES
INFECTIONS **CLINICAL EPIDEMIOLOGY**
MORTALITY **COHORTS** REAL-LIFE DATA
REGISTRIES **KNOWLEDGE** DIAGNOSTICS
PROGNOSIS TREATMENT BIOMARKERS
EVIDENCE HEALTH CARE ECONOMIC
COMPETITIVENESS **PRESCRIPTION**
INTERNATIONAL **PHARMACOEPIDEMIOLOGY**
BIOSTATISTICS **CAUSE-SPECIFIC**
EDUCATION SAFETY **DATA SCIENCE**
BENEFIT-RISK-BALANCE
RESEARCH



AARHUS
UNIVERSITY

DEPARTMENT OF CLINICAL EPIDEMIOLOGY



Clinical epidemiology applies **epidemiologic principles** to questions relating to **disease prevention, diagnosis, prognosis and therapy**



HENRIK TOFT SØRENSEN, HEAD OF DEPARTMENT OF CLINICAL EPIDEMIOLOGY

Improving Diagnostics and Treatments

More clinical databases and registries. Better access to data. More advanced technological methods and solutions.

Much has happened within clinical epidemiology during the past 20 years. What previously took months to investigate now takes days. Clinical epidemiology has become indispensable to efforts to improve the effectiveness of health care systems.

Department of Clinical Epidemiology (DCE) at Aarhus University and Aarhus University Hospital has experienced rapid development since its establishment in 2000 with a staff of three. It has become a respected international research department providing a wide range of consultancy services to pharmaceutical and biotech industries as well as to Danish and international health agencies.

Today, DCE employs approximately 100 people from ten different countries. In addition, eleven leading international researchers are affiliated with the department as visiting professors, adjunct professors, or part-time professors.

DCE resources include highly specialized clinical, epidemiological, and biostatistical expertise combined with access to Denmark's many biobanks and clinical databases. Researchers can obtain decades of detailed documentation on use of health care services, disease incidence and prevalence, medication use, treatments, and course of diseases.

DCE publishes an average of 150 scientific papers in the field of clinical epidemiology each year – many in collaboration with international colleagues. As examples, recent research has shown that the number of heart attacks in Denmark has been halved in the past 25 years ⁽¹⁾. Another finding is that treatment with mechanical ventilators and associated stress increases risk of mental illness in patients discharged from intensive care units (ICUs) ⁽²⁾.

DCE researchers enjoy working with colleagues around the world. We welcome ideas for collaborative research projects.

Our mission is to improve clinical care by working in global partnership to conduct high-quality clinical epidemiological research, to further education, and to promote translation of new knowledge into clinical practice.

*Henrik Toft Sørensen,
Head of Department of Clinical Epidemiology*

(1) 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ*. 2012;344:e356.

(2) Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. *JAMA*. 2014;311:1133-42.



Henrik Toft Sørensen

Professor of Clinical Epidemiology

Head of Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital

Adjunct professor at Boston University, University of North Carolina, and Geisel School of Medicine at Dartmouth



Affiliated with Center for Advanced Study in the Behavioral Sciences at Stanford University



Denmark as a Research Cohort of 9 Million People

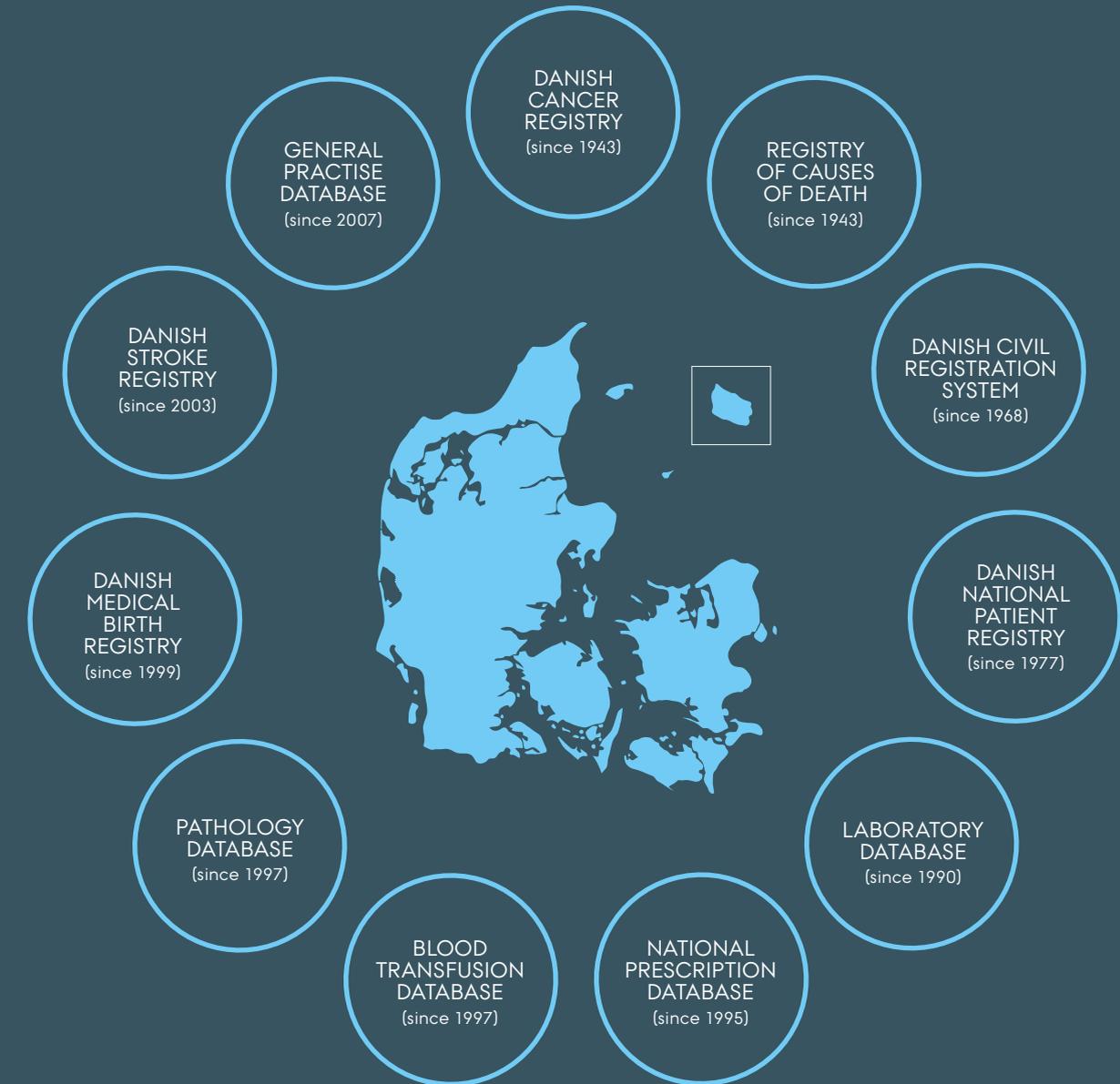
Because Danish residents have free access to health care and all primary and hospital-based care is documented, Danish physicians and researchers have unique opportunities to study disease patterns in a very large patient population. Data and biosamples have been collected for over half a century.

The public health service system in Denmark has numerous high-quality comprehensive administrative and medical registries. All are linkable using the personal identification numbers, part of the Danish Civil Registration System which was established in 1968.

Individual-level linkage of nationwide registries makes it possible to study the Danish population throughout the life span.

The Danish population thus represents a cumulative research cohort of more than nine million people. Denmark's national registries make it possible to study Danes throughout their life span. Persons can be easily tracked in studies, allowing nearly complete follow-up. The size of the study population increases the strength of research results, and has generated great international interest.

Danish medical databases provide researchers with a rich source of medical and genetic information. Universal access to public healthcare eliminates selection bias and ensures representation from all segments of the population. Once a research project has been approved, the majority of databases are available to researchers at little or no cost.



Some of Denmark's many nationwide registries

LARS PEDERSEN, PROFESSOR OF CLINICAL DATA SCIENCE

Large Data, Big Opportunities

Why do pregnant women taking medication for mild depression seem to be at higher risk of giving birth to a child with malformations? And why do cancer patients who suffer from other serious conditions receive limited benefit from new cancer treatments, compared to cancer patients with no comorbidity?

To answer such questions, DCE has developed a unique system encompassing linkable high-quality healthcare data from multiple sources. Medical registry data and routinely collected administrative data are loaded continuously into this system using standard file formats and uniform data file structures. Data are fully anonymized and pose no security risks for individual patients.

The system offers unique, internationally recognized opportunities:

- record linkage at the individual level
- ability to create large disease cohorts with long and complete follow-up data
- ability to validate data through medical chart review or other external data sources
- ability to link to biobanks

Large data are central to modern epidemiology. In 2012, an EU-funded project demonstrated that by combining data from several countries, serious adverse events associated with pharmaceutical products could be identified much earlier than in traditionally conducted epidemiological studies. The project was based on data from 25 million subjects in four countries, including data from DCE.

Large data also open up an array of new possibilities. For instance, current technologies permit rapid, inexpensive, and comprehensive molecular profiling of large numbers of individuals, who can be linked to existing data sources. Recently, DCE has linked tissue-derived molecular information with individual patients' medical history, laboratory tests, and hospital diagnoses. This technique provides unparalleled opportunities for future research on personalized medicine, e.g., breast cancer treatment.

The advantage of large sample sizes is reduction of random errors and the opportunity to study rare exposures. However, it remains crucial to understand the context in which the data are generated, including coding practices and clinicians' decision-making behavior. The current appetite for big data and data-driven epidemiology can produce misleading results if fundamental issues related to data validity are not well understood. DCE addresses these issues in its daily work.

Incidence of adenocarcinoma among patients with Barrett's esophagus.
N Engl J Med 2011; 365: 1375-83.

CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark.
J Natl Cancer Inst 2011; 103: 489-500.



Lars Pedersen

Professor of Clinical Data Science

Chief Statistician of the Centre for Biostatistics and Clinical Informatics at
Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital

Co-initiator of European networks aiming to exploit healthcare
databases for drug safety signal detection in >45 million patients

Examples of Studies Using Denmark's Comprehensive Data System to Improve Clinical Care

PHD
DISEASE MENTAL
EPIDEMIOLOGY HEALTH
CARDIOVASCULAR DIABETES
INFECTIONS CLINICAL EPIDEMIOLOGY
MORTALITY COHORTS REAL-LIFE DATA
REGISTRIES KNOWLEDGE DIAGNOSTICS
PROGNOSIS TREATMENT BIOMARKERS
EVIDENCE HEALTH CARE ECONOMIC
COMPETITIVENESS PRESCRIPTION
INTERNATIONAL PHARMACOEPIDEMIOLOGY
BIOSTATISTICS CAUSE-SPECIFIC
EDUCATION SAFETY DATA SCIENCE
BENEFIT-RISK-BALANCE
RESEARCH

RAISE DRUG SAFETY

- **AIM:** In 2010, the European Medicines Agency suspended sales of the oral antidiabetic agent rosiglitazone after a meta-analysis showed an increased risk of myocardial infarction in patients taking this drug. The study examined cardiovascular risks associated with prescribing rosiglitazone, and the effect of rosiglitazone suspension on diabetes control.
- **RESULTS:** Publication of evidence concerning the cardiovascular risks of rosiglitazone use was associated with a precipitous decline in rosiglitazone use in Europe. Absence of rosiglitazone from the spectrum of therapeutic options did not translate into worsening of diabetes control among patients, based on measurements of glycated haemoglobin and fasting plasma glucose.
- **SOURCES OF DATA:** Clinical Laboratory Information System, Aarhus University Prescription Database, Danish National Patient Registry, and Danish Civil Registration System.
- **PERSPECTIVES:** Study results indicated that physicians change their prescribing behavior in light of new evidence about established medications.

EXAMINE MENTAL HEALTH ISSUES

- **AIM:** To examine the risk of psychiatric inpatient admissions and outpatient visits among Danish patients with congenital heart defects (CHD).
- **RESULTS:** We identified 6,927 CHD patients. We found that patients both with and without invasive therapeutic interventions for their CHD were at increased risk of developing mental and other psychiatric disorders. These sequelae seemed to develop earlier in CHD patients than in patients with diabetes mellitus or asthma.
- **SOURCES OF DATA:** Danish National Patient Registry, Danish Civil Registration System, Danish Psychiatric Central Research Registry, Danish Medical Birth Registry, and Integrated Database for Labour Market Research.
- **PERSPECTIVES:** The data indicate the importance of addressing mental health issues to optimize CHD follow-up and care.

IMPROVE QUALITY OF TREATMENT

- **AIM:** To examine the effectiveness of different glucose-lowering add-on drugs for early glycaemic control among type-2 diabetics who had been using only metformin.
- **RESULTS:** We identified 3,089 metformin users who received an add-on therapy within the first year after diagnosis. The HbA1c target of <7% was attained by 61% of study participants within 3-6 months after initiation of the add-on therapy.
- **SOURCES OF DATA:** Danish Civil Registration System, Danish National Patient Registry, Clinical Laboratory Information System, Aarhus University Prescription Database.
- **PERSPECTIVES:** The results will be used to examine the association between quality of early glycaemic control and clinical outcomes.

MAP RISK FACTORS

- **AIM:** To examine the long-term prognosis of patients with chronic immune thrombocytopenia (ITP). This study estimates risk of infections, hemorrhage resulting in hospitalization, hematologic malignancies, and total and cause-specific mortality among patients with chronic ITP compared to the general population.
- **RESULTS:** A national cohort of 407 patients with chronic ITP has been identified with a median follow-up of 4.6 years (range, 0-11.5 years). At diagnosis, 225 patients (55.3%) were ≤ 60 years old and 254 (62.4%) were women. Overall 5-year mortality was 24% (95% CI, 20%-29%) -more than 2 times higher than mortality in the general population. A nearly 5-fold increased risk of hematologic malignancies and a 12-fold increased risk of hemorrhage-related deaths within 5 years after diagnosis of chronic ITP were observed, compared to the general population.
- **SOURCES OF DATA:** Danish Civil Registration System, Danish National Patient Registry, Danish Cancer Registry, and Danish Registry of Causes of Death.
- **PERSPECTIVES:** The study indicates the need for improved disease management for these patients.

Focus Area 1: Mapping Clinical Pathways to Diseases

DCE research seeks to clarify the clinical pathways leading to diseases, with a special interest in cardiovascular diseases, diabetes, psychiatric disorders, cancer, and venous thrombosis.

Venous thrombosis is a common condition often associated with a poor prognosis and contributing both to morbidity and mortality within the Western world.

For venous thrombosis we have focused on:

- further understanding the clinical pathways leading to a thrombotic event
- preventing initial and recurrent episodes
- avoiding or diminishing the clinical consequences of a thrombotic event

Using the Danish registries, DCE has designed and conducted cohort studies, nested case-control studies, and population-based case-control studies to further understand these three topics.

PUBLICATIONS OF INTEREST

30-year mortality following venous thromboembolism: A population-based cohort study.
Circulation. 2014; 130: 829-36.

Arterial cardiovascular events, statins, low dose aspirin and subsequent risk of venous thromboembolism: a population-based case-control study.
J Thromb Haemost 2009; 7: 521-8.

Venous thromboembolism and subsequent hospitalization due to acute arterial cardiovascular events: a 20-year cohort study.
Lancet 2007; 370: 1773-79.

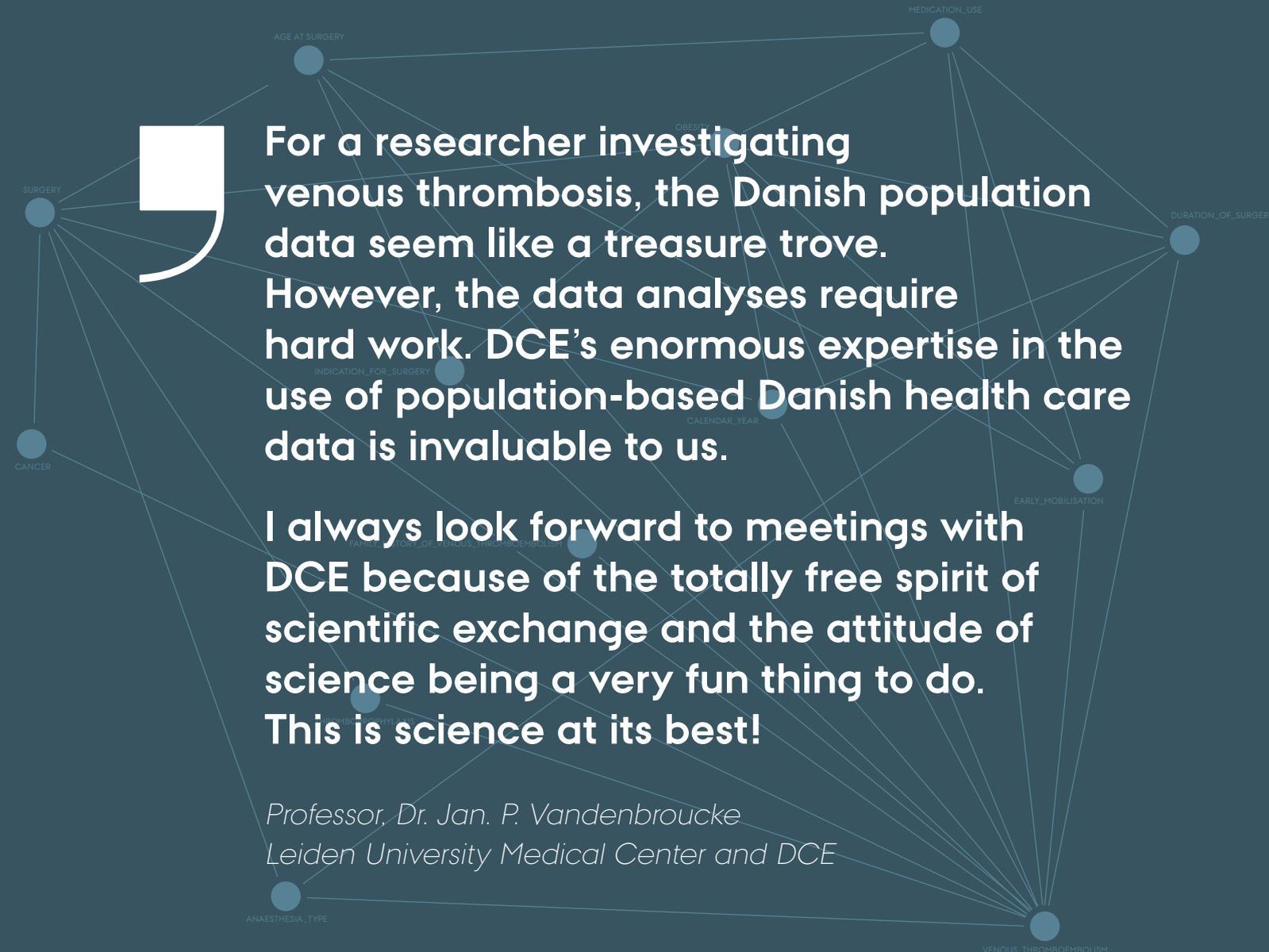
Acute infections and venous thromboembolism.
J Intern Med 2012; 271: 608-18.

Prognosis of cancers associated with venous thromboembolism.
N Engl J Med 2000; 343:1846-50.

For a researcher investigating venous thrombosis, the Danish population data seem like a treasure trove. However, the data analyses require hard work. DCE's enormous expertise in the use of population-based Danish health care data is invaluable to us.

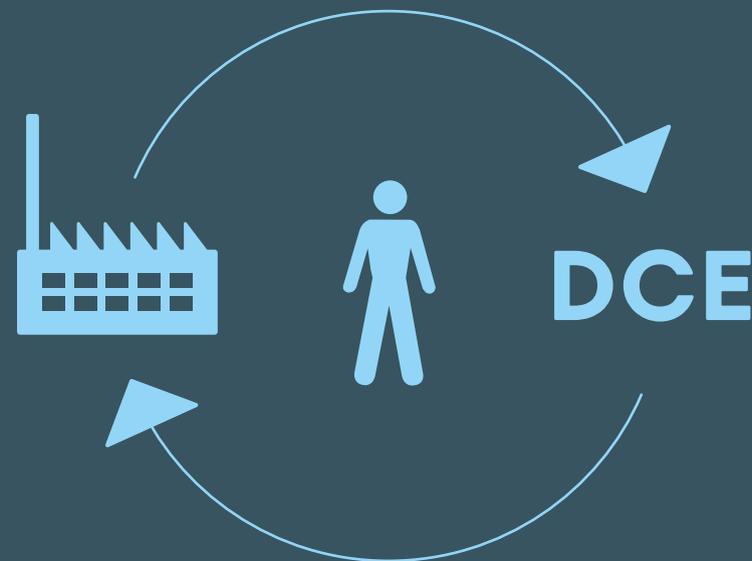
I always look forward to meetings with DCE because of the totally free spirit of scientific exchange and the attitude of science being a very fun thing to do. This is science at its best!

Professor, Dr. Jan. P. Vandenbroucke
Leiden University Medical Center and DCE



Do all types of patients benefit equally from the treatment?

Is there a safety signal?



How does the drug perform compared to other treatments?

Does the drug address an unmet need?

Focus Area 2: Pharmacoepidemiology Reveals Drug Benefits and Risks

In addition to their benefits, treatments and diagnostic procedures pose potential risks to patients. The field of pharmacoepidemiology, another DCE focus area, is concerned with effectiveness and safety of drug treatments.

Rare or long-term side effects of drug treatments often do not come to light until the treatments are used routinely in diverse groups of patients. Pharmacoepidemiologists use real-life data from everyday clinical practice to monitor rare or long-term benefits and side effects of drug treatments. Pharmacoepidemiology aids clinical decision-making by supplying evidence on the benefit-risk balance of treatments and its variation among specific groups of patients.

DCE routinely conducts both investigator-initiated pharmacoepidemiology studies and regulator-mandated post-authorization studies of novel or established therapies, including studies of effectiveness, safety, and risk minimization.

Proactive assessment of safety from the moment a drug enters the market is a component of pharmacovigilance. The Danish Nationwide Prescription Database allows identification of all users of specific drug treatments and subsequent monitoring of potential adverse events via linkage to registries and databases that track hospital visits, diagnoses, procedures, surgeries, laboratory tests, and deaths.

In some cases, it is necessary to supplement registry data with primary data collection, by accessing medical records. An example is collecting information on drug treatments administered in the hospital. In feasibility and pilot studies, information from medical records is also routinely used to assess quality of registry data.

DCE has conducted multiple studies examining the safety of drugs used to treat diabetes, cancer, cardiovascular diseases, osteoporosis, and depression, as well as safety of drug use in pregnancy.

PUBLICATIONS OF INTEREST

Use of β -blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and risk of breast cancer recurrence: a Danish nationwide prospective cohort study.
J Clin Oncol. 2013;31:2265-72.

Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study.
J Natl Cancer Inst. 2011;103:1461-8.

Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study.
BMJ. 2011;343:d3450

PROFESSOR KENNETH J. ROTHMAN, DEPARTMENT OF EPIDEMIOLOGY, BOSTON UNIVERSITY

Attractive Collaborator

What makes DCE attractive as a collaborator? Excellent data resources. First rate researchers. Successful funding and publication history. DCE also has been remarkably successful in training researchers in clinical epidemiology. All these factors contribute to making it an attractive place for any researcher, and any collaborator. It certainly has been for me for the past 15 years.

I originally got to know DCE through my personal relationship with Henrik Toft Sørensen, the founding head of DCE. I hope, and do believe, that it has been a mutually beneficial collaboration.

My greatest involvement has been with the "Soon Pregnant" and "Soon Parents" projects, both of which are formal collaborations between DCE and Boston University. The impetus for these projects is that roughly 20 percent of couples experience periods of reduced fertility, and for one out of four couples the reasons are unknown. The aim of these two projects is to determine how lifestyle choices and other personal characteristics influence both male and female fertility. Although the projects are being conducted solely in Denmark, we hope that the results will be applicable to women everywhere. There already has been a growing list of scientific publications from the projects, and much work is currently underway.

I should add that one of the most gratifying aspects of my collaboration over the years has been the personal contacts that I have made and maintained. The people at DCE are a pleasure to work with.

What makes DCE attractive as a collaborator? Excellent data resources. First rate researchers. Successful funding and publication history.

*Professor Kenneth J. Rothman, DMD, MPH, DrPH
Boston University, School of Public Health,
Department of Epidemiology*

*Adjunct Professor,
Department of Clinical Epidemiology,
Aarhus University*

PROJECT "SOON PREGNANT" (SNARTGRAVID.DK)

- Prospective cohort study of pregnancy planners (2007-2011)
- Enrolled 6,000 women trying to become pregnant
- Recruitment and data collection via the Internet
- Bimonthly follow-up on pregnancy status and lifestyle exposures for up to 12 months
- Collaboration between DCE and Boston University
- Fourteen scientific publications, two PhDs completed, and two in progress

PROJECT "SOON PARENTS" (SNARTFORÆLDRE.DK)

- Prospective cohort study of pregnancy planners (2011-ongoing)
- Includes both males and females
- Data on health and lifestyle including diet, exercise, and medications
- Bimonthly follow-up until pregnancy or for up to 12 months
- Collaboration between DCE and Boston University

Both studies are supported by the U.S. National Institute of Child Health and Human Development

Young Talent is Important

The DCE mission to improve clinical care also is implemented by encouraging talented scientists - often in collaboration with international partners. By attracting and educating talented researchers and training health care personnel, we aim to bridge research and clinical practice.

Meet a few of our young researchers:



My most important contribution is based on an international collaboration utilizing Danish biospecimens. We have demonstrated that a specific subtype of colorectal polyps, previously thought to be benign, carries a high risk of evolving into cancer. DCE has taught me the essentials of clinical research, opened doors to some of the world's leading gastroenterologists, and prepared me for a future as an independent researcher.

*Rune Erichsen, MD,
PhD, External researcher*

I believe that very few other work places are capable of offering a similarly high level of motivation and healthy competition along with the supportive and friendly social atmosphere found at DCE.

*Dennis Simonsen, medical student,
research year student*

I came to DCE to be part of a highly motivating environment that strives to deliver research meeting high international standards.

Using the LABKA database, we identified the largest cohort of hyponatremic patients ever - a unique data resource that has fostered collaboration across specialties and borders. As hyponatremia is present in one out of seven acute internal medicine patients and is associated with increased mortality, our research has a major potential public health impact.

*Louise Holland-Bill, MD,
PhD student*

International collaboration is a great strength at DCE. Having visited Boston University, Ohio State University, and California Pacific Medical Center Research Institute, I consider the opportunity to work with and learn from leading experts from all over the world a great strength of DCE.

*Morten Schmidt, MD,
PhD student*

150

THE NUMBER OF PUBLICATIONS PER YEAR

PHD

DISEASE MENTAL

EPIDEMIOLOGY HEALTH

CARDIOVASCULAR DIABETES

INFECTIONS CLINICAL EPIDEMIOLOGY

MORTALITY COHORTS REAL-LIFE DATA

100+

THE NUMBER OF COLLABORATIVE AGREEMENTS

45

THE NUMBER OF CURRENT PHD PROJECTS

7

THE NUMBER OF AWARDS IN A ROW FOR AARHUS UNIVERSITY HOSPITAL AS "BEST HOSPITAL IN DENMARK" (2006-2013)

DIAGNOSTICS

PROGNOSIS TREATMENT BIOMARKERS

EVIDENCE HEALTH CARE ECONOMICS

COMPETITIVENESS PRESCRIPTION

INTERNATIONAL PHARMACOEPIDEMIOLOGY

65

THE NUMBER OF FULL-TIME STAFF

BIOSTATISTICS CAUSE-SPECIFIC

EDUCATION SAFETY DATA SCIENCE

BENEFIT-RISK-BALANCE

RESEARCH

5-10

THE NUMBER OF COMPLETED PHD PROJECTS PER YEAR