Research on drug safety and effectiveness using Nordic pharmaco-epidemiological databases

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Department of Drug Design and Pharmacology
Conflicts of interest

• Participate(d) in research projects funded by AstraZeneca, H. Lundbeck & Mertz, Novartis, Nycomed, Merck Sharp & Dohme and Pfizer, with grants paid to the institutions where I have been employed

• Personally receive(d) fees from Medicademy, the Danish Pharmaceutical Industry Association for teaching at pharmacoepidemiology courses

• Professorship in pharmacovigilance funded by the Novo Nordisk Foundation
Combining observational data from multiple countries is attractive

<table>
<thead>
<tr>
<th>Possibilities/advantages</th>
<th>Challenges</th>
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<tbody>
<tr>
<td>• Increased power</td>
<td>• Permissions</td>
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<tr>
<td>• Rare exposures</td>
<td>• Logistics</td>
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<tr>
<td>• Rare outcomes</td>
<td>• Analysis</td>
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<tr>
<td>• Subgroups</td>
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<tr>
<td>• Validate results across countries</td>
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<tr>
<td>• Learn from between-country differences</td>
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Cancer Risk and Insulin analogues

General introduction

The CARING (Cancer Risk and Insulin analogues) project will obtain precise data on the incidence of cancer in diabetic patients and determine any link with use of various insulin and insulin analogues.

The study will utilise high quality prescription databases and other national data sources, integrated at European level with advanced methods of harmonising data.
Research questions in CARING WP3

• To **develop a common data model** allowing the integration of information from differently structured databases

• To **evaluate meta-analysis of aggregate patient data (APD) as compared with individual patient data (IPD)** for the analysis of the association between exposure to different types of insulin and risk of cancer
Data sources

- National registers from Denmark, Norway and Sweden and the UK CPRD

STUDY PERIOD

1989

CARING

CPRD (UK)

Finland

Denmark

Norway

Sweden

2013
Swedish health registers

- **Patient Register**
  - Inpatient admission and discharge dates
  - Outpatient contact date
  - Hospital, clinic, county
  - Diagnoses, procedure codes

- **Prescribed Drug Register**
  - Drug, dispensing form, strength
  - Package, amount, dose text
  - ATC code, DDDs
  - Patient and prescriber information

- **Hospital Electronic Records**
  - Clinical information
  - Measurements and lab data
  - Inpatient medical treatment
  - Discharge summary

- **Laboratory data**
  - Date, measurement, value, unit

- **Primary Care Electronic Records**
  - Date of contact, diagnoses
  - Clinical and lab data
  - Weight, blood pressure
  - BMI, smoking, alcohol
  - Prescribed medicine

- **Medical Birth Register**
  - Identity of mother and child
  - Social factors, smoking, snuff
  - Maternal, pregnancy, delivery and infant clinical information

- **Quality registers**
  - Specific diagnoses, treatment
  - Age at onset of disease
  - Clinical and lab data
  - Disease severity
  - Risk/prognosis assessment
  - BMI, smoking

- **Cancer Register**
  - Date of cancer diagnosis
  - Type of malignancy, histology
  - TNM staging

- **LISA**
  - Education, income, employment
  - Country of birth
  - Place of residence

- **Multi-Generation Register**
  - Identity of relatives

- **Cause of Death Register**
  - Date of death
  - Causes of death
  - Injury, poisoning, intent

- **Total Population Register**
  - Dates of Immigration, emigration, death
Swedish health registers

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Data management in an epidemiological study

RAW DATA → CLEANED DATA → ANALYSIS DATASET → RESULTS

DATA IMPORT AND CLEANING

DATABASE SOFTWARE <— STATISTICAL SOFTWARE

SIMPLIFIED:

RAW DATA → CLEANED DATA → ANALYSIS DATASET → RESULTS
CARING study data challenge

Five complex databases with different medical classification systems – like five different studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Databases</th>
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<tbody>
<tr>
<td>DK</td>
<td>ICD7, ICD8, ICD9, ICD10, ICDO3</td>
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<tr>
<td>FI</td>
<td>ICD8, ICD9, ICD10, ICDO3, NCSP</td>
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<td>ICD9, ICD10, ICDO3, NCSP, ATC</td>
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<tr>
<td>SE</td>
<td>ICD10, ICDO3, NCSP, ATC</td>
</tr>
<tr>
<td>UK</td>
<td>READ, CPRD PC</td>
</tr>
</tbody>
</table>
CARING study data solution

Alternative: decide on a common data model

DK
- ICD7
- ICD8
- ICD9
- ICD10
- ICDO3
- NCSP
- ATC

FI
- ICD7
- ICD8
- ICD9
- ICD10
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- ATC

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- ICD7
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DK: ICD7, ICD8, ICD9, ICD10, ICDO3, NCSP, ATC
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NO: ICD7, ICD8, ICD9, ICD10, ICDO3, NCSP, ATC
SE: ICD7, ICD8, ICD9, ICD10, ICDO3, NCSP, ATC
UK: READ, CPRD PC
Overview of CDM data flow in the CARING project

DK -> NO -> SE -> FI -> UK

Nordic Data Model

CARING Common Data Model

Concept Dictionary

Analysis datasets

Statistics Denmark
Multi-database analytic approaches

• Individual patient data meta-analysis
  • Pooled data in one place necessary

• Aggregate data meta-analysis
  • Distributed analysis in separate databases possible
Other insulin versus human insulin – different adjustment models

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<tr>
<th>AGGREGATION LEVEL</th>
<th>OUTCOME</th>
<th>ADJUSTMENT MODEL</th>
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<tbody>
<tr>
<td>META-ANALYSIS</td>
<td>Colorectal cancer</td>
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<td></td>
<td></td>
<td>Common</td>
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<tr>
<td></td>
<td></td>
<td>Optimized</td>
</tr>
<tr>
<td></td>
<td>Breast cancer</td>
<td>Unadjusted</td>
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<td>Age, sex, calendar</td>
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<td>Prostate cancer</td>
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<tr>
<td>POOLED (INDIVIDUAL LEVEL)</td>
<td>Colorectal cancer</td>
<td>Country adjusted</td>
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0.71  1.25
Pooled individual patient analysis or meta-analysis on aggregate data?

- Favors aggregate level Meta-analysis
- Favors individual patient analysis

- Power in each dataset (+)
- Common confounder covariates (+)

(-)
Multi-database networks in pharmacoepidemiology
Nordic studies of SSRIs in pregnancy

Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries

Helle Kieler ass
Anders Engeland
Helga Zoega, pc researcher

Selective Serotonin Reuptake Inhibitors During Pregnancy and Risk of Stillbirth and Infant Mortality

Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy

Randi Selmer1*, Bengt Haglund2, Kari Furu1, Morten Andersen2,3, Mette Nørgaard4, Helga Zoëga5 and Helle Kieler2

1Department of Pharmacoepidemiology
2Centre for Pharmacoepidemiology
3Research Unit for General Practice
4Department of Clinical Epidemiology
5Centre of Public Health Sciences

NorPEN
Nordic PharmacoEpidemiological Network
A common Nordic pharmacoepidemiology database for the future?

Approaches

• Distributed database network + analysis programs

• Distributed network + secure servers and common analysis platforms for individual-based data

• Common Nordic database, all in one place
A common Nordic pharmacoepidemiology database for the future?

Approaches

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• Distributed network + secure servers and common analysis platforms for individual-based data

• Common Nordic database, all in one place
A common Nordic pharmacoepidemiology database for the future?

All approaches involve

• Collaboration on a common data model

• A common platform for data management and analysis

• A coordinated process for data access (legal, ethical, mutual agreements)
Opportunities in safety and effectiveness research using Nordic healthcare databases

• Pharmacovigilance: Systematic proactive monitoring, signal detection and risk evaluation using healthcare databases

• Comparative safety and effectiveness: Pragmatic clinical trials linked to healthcare databases (including electronic health records and quality registers)

• Developments in personalised/precision medicine linking healthcare data to biobanks