

# Register research in DK

## — opportunities and limitations

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1 / 30

Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities

## Outline

Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

Register research in DK  
— opportunities and limitations  
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Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities

2 / 30

## Possible questions to ask

- ▶ Does drug **X** influence the occurrence of complication **Y**?
- ▶ drug **X** (explanatory variable, covariate)
  - ▶ Starting on the drug
  - ▶ Using the drug
  - ▶ Amount used
  - ▶ Time used
  - ▶ Time since last use
  - ▶ ...
- ▶ complication **Y** (response variable, outcome)
  - ▶ 1<sup>st</sup> occurrence
  - ▶ no. occurrences

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— opportunities and limitations  
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Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities

3 / 30

## Concepts

- ▶ Observation of life history of persons (**data**):
  - ▶ Entry (date)
  - ▶ Exposures (periods)
  - ▶ Event (date)
  - ▶ Exit (date)
- ▶ Interpretation via a **model**:
  - ▶ Outcomes of interest:
    - ▶ Event rates (hazards) — modeling **target**
    - ▶ Ratios (hazard ratios)
    - ▶ Sojourn times (requires a full MS-model)
  - ▶ Determinants:
    - ▶ Demographics
    - ▶ Complication status
    - ▶ Medication history

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

4 / 30

## Available data sources in DK

- ▶ Central Person Register
- ▶ National Patient Register
- ▶ Register for Medicinal Product Statistics (Prescriptions)
- ▶ Health Services Register
- ▶ Diabetes Register
- ▶ Clinical quality databases
- ▶ Danish Adult Diabetes Database
- ▶ Cancer Register
- ▶ ...
- ▶ overview in [1]

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

5 / 30

## Central Person Register

- ▶ Start 1968-04-01
- ▶ Unique id of person
- ▶ Sex
- ▶ Link to parents / children (persons born before in 1968 not linked from parents)
- ▶ Marital status
- ▶ Residential history (partial)
- ▶ Migration history (partial)

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

6 / 30

## National Patient Register

- ▶ Start 1977
- ▶ Out-patient data from 1993
- ▶ Each contact by a person has a recording in the register:
  - ▶ Person id
  - ▶ Date
  - ▶ (a number of) diagnoses, procedures, operations
- ▶ Covers the entire resident population in DK
- ▶ **No** clinical data such as lab results or anthropometry
- ▶ ...only diagnoses / operations / procedures
  - possibly more per visit

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— opportunities and limitations  
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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

7 / 30

## Prescription Register

- ▶ Start 1995
- ▶ All **filled** prescriptions
  - ▶ Person-id
  - ▶ Date
  - ▶ Drug (brand-specific)
  - ▶ Amount purchased
  - ▶ Dosage prescribed (incomplete)
- ▶ **Note:** restricted access:
  - ▶ Public institutions (Uni, NHS, patient organizations):
    - access to individually linkable records
  - ▶ Private sector (companies, consultancies):
    - only aggregate data available
- ▶ Individually linkable records necessary for proper analysis

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— opportunities and limitations  
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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

8 / 30

## Health Services Register

- ▶ Start 1990
- ▶ All contacts with GPs
- ▶ Services for fee (blood samples etc.)
- ▶ Register of reimbursements from the NHS
- ▶ **No** clinical results of tests etc.

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— opportunities and limitations  
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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

9 / 30

## Diabetes Register(s!)

- ▶ National Diabetes Register: 1995–2012
- ▶ May include too many persons (women suspected of GDM)
- ▶ Discontinued 2012, replaced by:
- ▶ RUKS (Register of Select Chronic Diseases
  - among which are T1D and T2D, as separate diseases)
- ▶ RUKS criticized for not being sensitive enough
- ▶ Start 2000
- ▶ Individual records not available

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— opportunities and limitations

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

10/ 30

## Diabetes Register(s!)

- ▶ BxC has a “reconstructed” version of the NDR:
  - ▶ based on NPR, RMPS, HSR, DVDD, DiaBase.
  - ▶ includes a T1/T2 classification with emphasis on specificity for T1 classification
  - ▶ includes place of residence (at diagnosis)
  - ▶ usable for incidence from 1996-01-01
  - ▶ prevalent cases as of 1996-01-01 included
- ▶ Work in progress to use this to update / improve RUKS to a proper research register
- ▶ Time frame unknown

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— opportunities and limitations

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

11/ 30

## Danish Childhood Diabetes Register

- ▶ Start 1996
- ▶ Age at diagnosis 0–15 years
- ▶ Biobank data from cases and siblings
- ▶ Based on records for pediatric wards
- ▶ Patients will also be in the other diabetes registers

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— opportunities and limitations

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

12/ 30

## Clinical quality data bases

- ▶ DVDD (Danish adult diabetes database)
  - ▶ Initiated 2005
  - ▶ Clinical data on diabetes patients
  - ▶ Update approx. once / year
  - ▶ Currently little coverage of T2 patients only seen in GP
  - ▶ Likely to be complete w.r.t. T1 patients (all T1 patients are allocated to hospital clinics)
- ▶ diaBase
  - ▶ Start 2012
  - ▶ Date of eye examination
  - ▶ Result of eye examination
  - ▶ Update approx. once / year
  - ▶ Complete for T1,  $\approx 30\%$  of T2 included

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— opportunities and limitations

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

13 / 30

## Cancer Register

- ▶ Start 1943 (!)
- ▶ World's oldest cancer register
- ▶ Tumours recorded:
  - ▶ date
  - ▶ topology / morphology
  - ▶ stage
  - ▶ **no** clinical information available
- ▶  $\Rightarrow$  Information on previous cancer diagnoses are reliable

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— opportunities and limitations

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

14 / 30

## Pharmacoepidemiology — descriptives

- ▶ Descriptives of drug use:
  - ▶ Population prevalence of users of drug **X** at a given time
  - ▶ Survival as a user of drug **X**
  - ▶ Succession drugs to **X**
  - ▶ Survival as a non-user of drug **X**
  - ▶ Events defined as:
    - ▶ Switch to another drug
    - ▶ Switch to **Z**
    - ▶ Add another drug
    - ▶ Add **Z**
    - ▶ Death
- ▶ — these all require a definition of:
  - ▶ “being a user”
  - ▶ “not being a user anymore”
- ▶ But we only have dates and amounts of drug purchases. . .

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— opportunities and limitations

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

15 / 30

## Pharmacoepidemiology — event rates

- ▶ Analysis of (adverse) event (complications) rates:
  - ▶ Outcome: events (only 1<sup>st</sup>?)
  - ▶ Determinants:
    - ▶ Drug history
    - ▶ Disease history
    - ▶ Demographics
  - ▶ Models: log-linear models for rates (HR as primary target)
    - ▶ Poisson-models
    - ▶ Cox-type models (baseline rates not seen)

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

16/ 30

## Actual pharmacological treatment in DK ptt.

- ▶ Define from prescription register records when a person is in a particular treatment group:
  - ▶ mono therapy (met, SU, ...)
  - ▶ combination therapy (met+SU, met+ins, ...)
  - ▶ not treated
- ▶ for each day since 1995-01-01:
  - ▶ who is DM patient
  - ▶ what proportion of these are in each treatment group

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Concepts

Available data sources

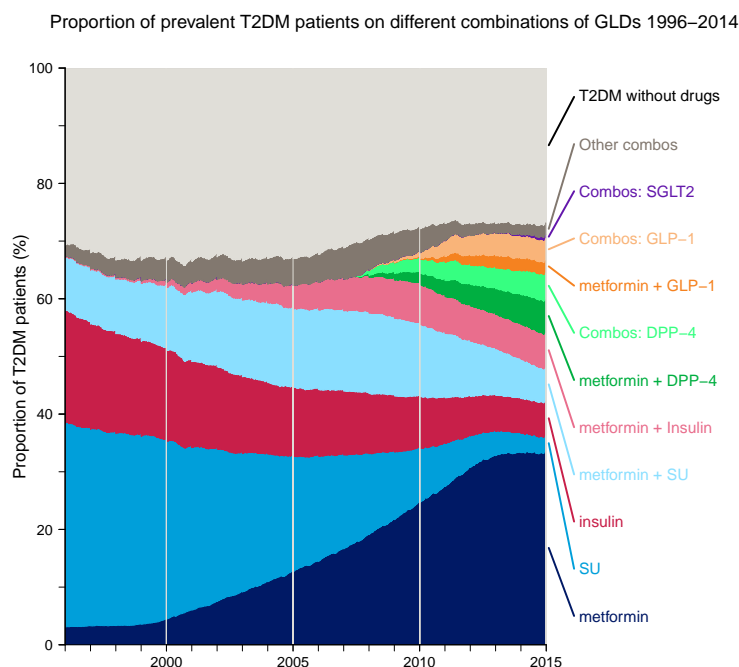
Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

17/ 30



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Concepts

Available data sources

Analysis opportunities

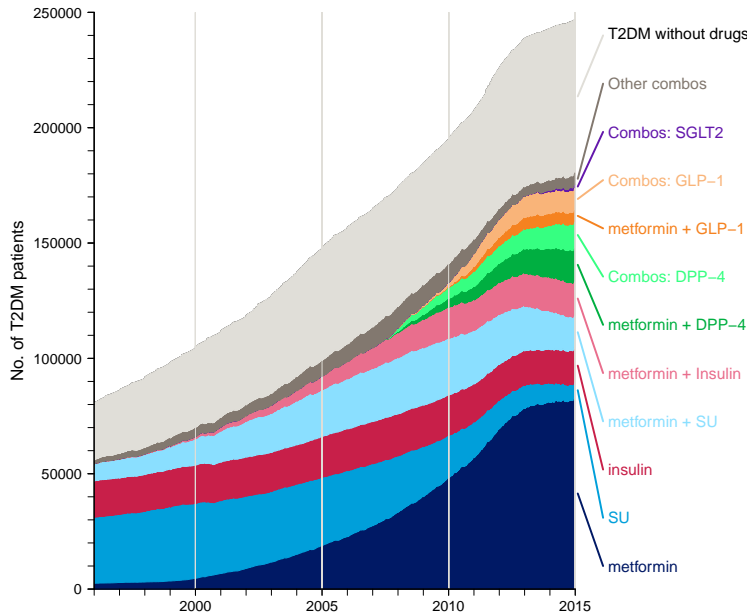
Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

18/ 30

Number of T2DM patients on different combinations of GLDs 1996–2014



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Bendix Carstensen  
Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities  
18/ 30



## Incidence of Ketoacidosis in the Danish Type 2 Diabetes Population Before and After Introduction of Sodium–Glucose Cotransporter 2 Inhibitors—A Nationwide, Retrospective Cohort Study, 1995–2014

DOI: 10.2337/dc16-2793

Majken Linnemann Jensen,<sup>1</sup>  
Frederik Persson,<sup>1</sup>  
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Martin Ridderstråle,<sup>1</sup> John J. Nolan,<sup>1</sup>  
Bendix Carstensen,<sup>1</sup> and  
Marit E. Jørgensen<sup>1,2</sup>

The U.S. Food and Drug Administration warns that sodium–glucose cotransporter 2 (SGLT2) inhibitors may lead to diabetic ketoacidosis (DKA). To establish a baseline occurrence of DKA in type 2 diabetes, we used national registries in Denmark to estimate incidence rates of DKA and linked the data to information

diabetes diagnosis identified through national registers (1995–2014) (1,2) were included. Patients were followed from the date of diagnosis until an event or censoring due to death or emigration, or by end of study 31 December 2014, whichever occurred first. Events of DKA were defined as a primary or secondary

of 30 years were excluded. Rates of incidence were analyzed with Poisson regression, adjusted for sex, current age, calendar time, and duration of diabetes, with natural splines (5 knots) describing the time effects. The inclusion of calendar time was essential in order to avoid confounding, as SGLT2 inhibitors were

Register research in DK — opportunities and limitations  
Bendix Carstensen  
Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities  
19/ 30

Denmark to estimate incidence rates of DKA and linked the data to information on filled prescriptions to determine treatment exposure, with special attention to SGLT2 inhibitor use.

Patients with filled prescription(s) for antidiabetes medication or a type 2

whichever occurred first. Events of DKA were defined as a primary or secondary diagnosis in the National Patient Register between 1 January 1995 and 31 December 2014. Patients diagnosed with type 1 diabetes or who had a filled prescription for any antidiabetes drug before the age

dar time was essential in order to avoid confounding, as SGLT2 inhibitors were first introduced in Denmark in December 2012.

During follow-up, 415,670 patients had 4,045 first events of DKA in 3 million person-years, corresponding to a crude

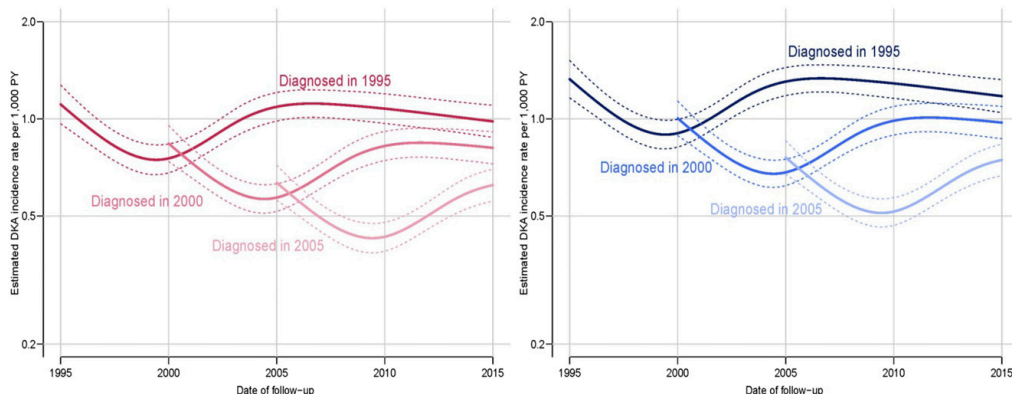
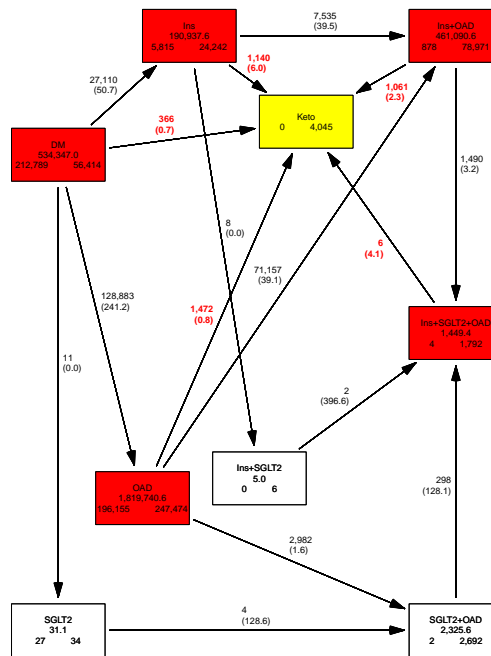


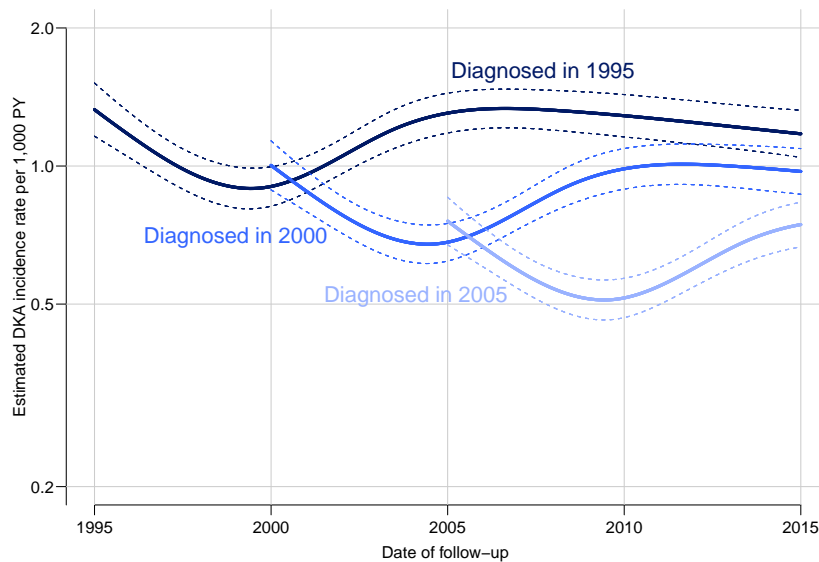
Figure 1—Estimated incidence rates of a first DKA event per 1,000 person-years (PY) among women (left panel) and men (right panel) diagnosed with type 2 diabetes at age 65 years in 1995, 2000, and 2005 and exposed to noninsulin glucose-lowering drugs.

Register research in DK — opportunities and limitations  
Bendix Carstensen  
Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities  
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20/ 30

- ▶ Multistate model
- ▶ Keep track of who is exposed to what when
- ▶ Rates of:
  - ▶ treatment change
  - ▶ DKA occurrence
- ▶ Compare DKA rates between treatments:
- ▶ Is there an elevated risk of DKA with SGLT-2i?



Register research in DK — opportunities and limitations  
Bendix Carstensen  
Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities



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Bendix Carstensen  
Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities

## Clinical trials (CT) and register studies (RS)

- ▶ Clinical measurements (baseline, several FU): **CT, RS**
- ▶ Allocation **recorded**: **CT, RS**
- ▶ Allocation **randomized**: **CT**
- ▶ Population:
  - ▶ **CT**: Selected (entry criteria)
  - ▶ **RS**: Unselected — “real world”

Register research in DK — opportunities and limitations  
Bendix Carstensen  
Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities



## Clinical trials (CT) and register studies (RS)

- ▶ **CT** directly addresses the causal effect:
  - ▶ an infinitely large study will yield the causal effect of the intervention
  - ▶ in the long run the average bias across **CTs** will be 0
  - ▶ — but no guarantee that the single study is unbiased
- ▶ **RS** describes the un-manipulated “reality”:
  - ▶ Occurrence rates
  - ▶ their variation by medication
  - ▶ **very** strong confounding by indication in relation to disease events
  - ▶ we estimate combined effect of (unknown) base status on prescription of drug and effect of drug on outcome
  - ▶ popular to use propensity scoring to control (some of) the confounding by indication.

Register research in DK  
— opportunities and limitations  
Bendix Carstensen

Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities

24/ 30

## Mimicking a clinical trials: Propensity scoring

- ▶ Select groups that are comparable w.r.t. determinants of drug exposure (*i.e.* prescription)
- ▶ Control for all possible covariates that influence drug exposure
- ▶ Model the probability of being put on drug **X**, versus being put on drug(s) **Z**.  
This is the **propensity score**, PS.
- ▶ Match persons exposed to **X** to persons exposed to **Z** with similar PS values.
- ▶ ... or include PS as a covariate  
(another way of comparing like PS with like PS)
- ▶ Both assume some sort of continuous effect of PS

Register research in DK  
— opportunities and limitations  
Bendix Carstensen

Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities

25/ 30

## Propensity scoring pitfalls

- ▶ Basic assumption:
- ▶ The variables at hand are the **only** confounders of drug effect
- ▶ ... essentially assumes that prescribing physicians act like programmed robots, ignoring personal / tacit knowledge about the patients
- ▶ In **RS** there are rarely clinical measurements
- ▶ — and if there are, their presence is determined by their values
- ▶ No way to assess in which direction residual confounding goes.

Register research in DK  
— opportunities and limitations  
Bendix Carstensen

Concepts  
Available data sources  
Analysis opportunities  
Projects at SDCC  
Relation to clinical trials  
Nordic collaboration and opportunities

26/ 30

## Matching in general

- ▶ Loses the “real world” w.r.t. descriptives
- ▶ Only HRs will be generalizable
- ▶ ...subject to the validity of the basic assumption

Register research in DK — opportunities and limitations

Bendix Carstensen

Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

27 / 30

## Nordic collaboration?

- ▶ Data from different Nordic countries are largely similar in content
- ▶ ...but not in (time) extent
- ▶ Medical practice differ between countries
- ▶ DK has the longest drug record series
- ▶ — and patient register
- ▶ No formal procedures exist for pooling data — legal obstacles
- ▶ Work in progress between Nordic statistical bureaus.
- ▶ ⇒ separate analyses from different countries
- ▶ Pooling of analysis results to obtain joint results across countries

Register research in DK — opportunities and limitations

Bendix Carstensen

Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

28 / 30

## Danish (SDCC) opportunities

- ▶ Old drugs can be used (register back to 1995)
- ▶ Population wide:
  - ▶ no opting in and out of the recording of drugs (only by em/immigration)
  - ▶ complete match to the patient register
- ▶ Access to individual level drug data
- ▶ Trends in disease / drug use can be described and controlled in models
- ▶ Experience in data processing and reporting
- ▶ High academic level of statistical analysis
- ▶ Independent

Register research in DK — opportunities and limitations

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Concepts

Available data sources

Analysis opportunities

Projects at SDCC

Relation to clinical trials

Nordic collaboration and opportunities

29 / 30

## References



L. C. Thygesen and Ersbøll A. K. (eds.).

Danish population-based registers for public health and health-related welfare research — A description of Danish registers and results from their application in research.

*Scandinavian Journal of Public Health*, 39(7 suppl), 2011.



M. L. Jensen, M. E. Jørgensen, E. H. Hansen, L. Aagaard, and B. Carstensen.

Long-term patterns of adherence to medication therapy among patients with type 2 diabetes mellitus in Denmark: The importance of initiation.

*PLoS ONE*, 12(6):e0179546, 2017.



M. L. Jensen, F. Persson, G. S. Andersen, M. Ridderstrale, J. J. Nolan, B. Carstensen, and M. E. Jørgensen.

Incidence of Ketoacidosis in the Danish Type 2 Diabetes Population Before and After Introduction of Sodium-Glucose Cotransporter 2 Inhibitors-A Nationwide, Retrospective Cohort Study, 1995-2014.

*Diabetes Care*, 40(5):e57–e58, May 2017.