The Role of AI

Algorithm to bedside symposia

DATA STORIES
From algorithm to bedside

Nermin Ghith, dual B.Sc. in bio/chem.; MPH, PhD

Senior Forsker

Gentofte or Herlev Hospital

03-14 Feb. 2025

Lunch symposia

Omics-Based Clinical and Population Studies (session 1: Mon. 3 Feb. 2025 - Specific Case Studies)

Contextual Epidemiology of Cardiometabolic Conditions, Polypharmacy and Multi-morbidity (session 2: Thurs. 6 Feb. 2025)

Scientific Methods in Biomedical Research (sessions 3 and 4: Mon and Thurs. 10 and 13 Feb. 2025)

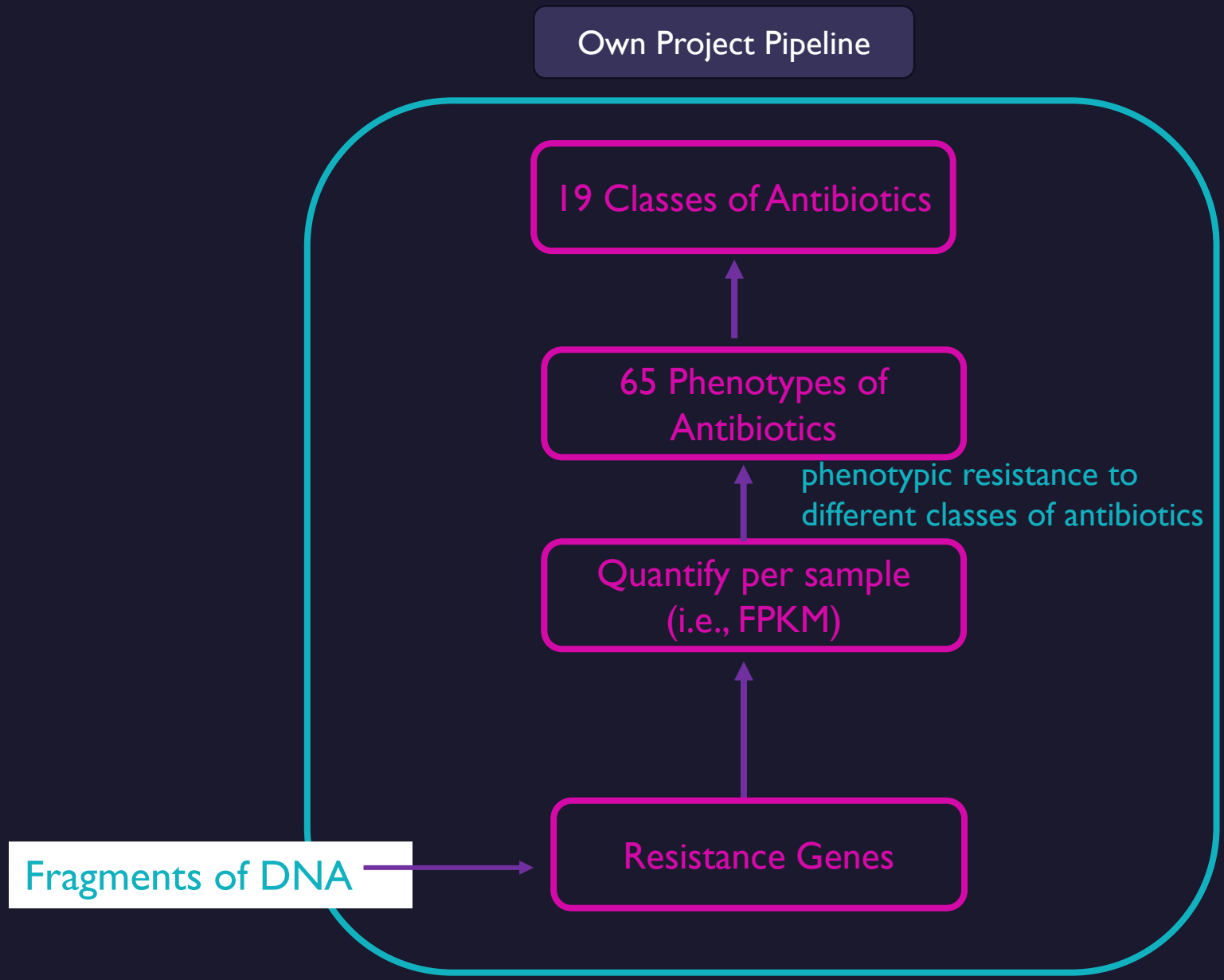
- Omics in biomedical research
- Evidence pyramid and analytics
- Global Burden of Disease, Health Analytics, and Access to Therapeutics
- Economic Evaluations

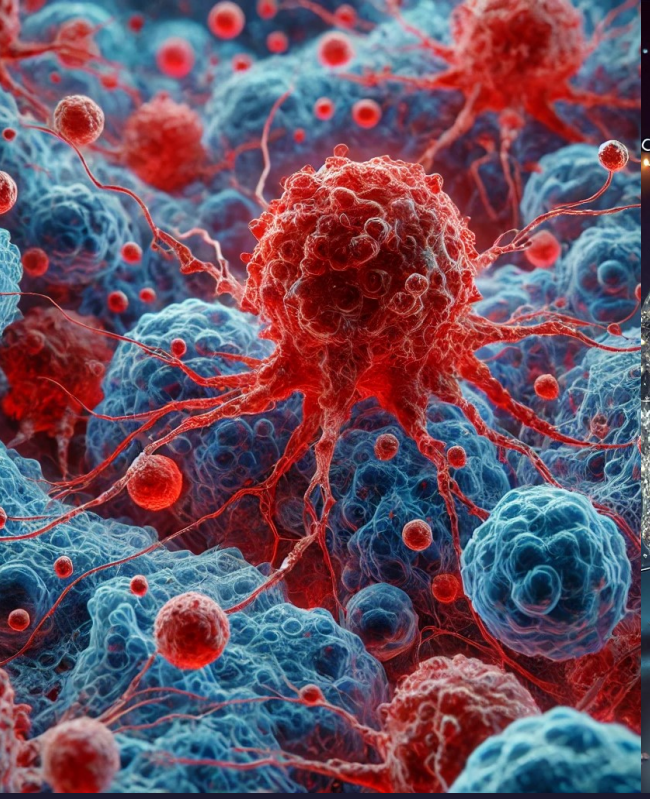
Catch up

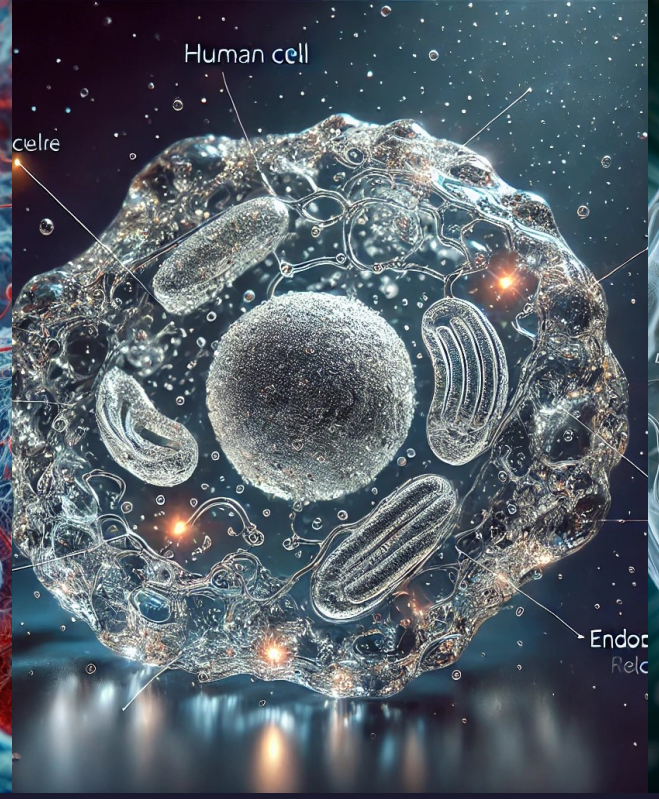
THERE ARE 3 KINDS OF LIES

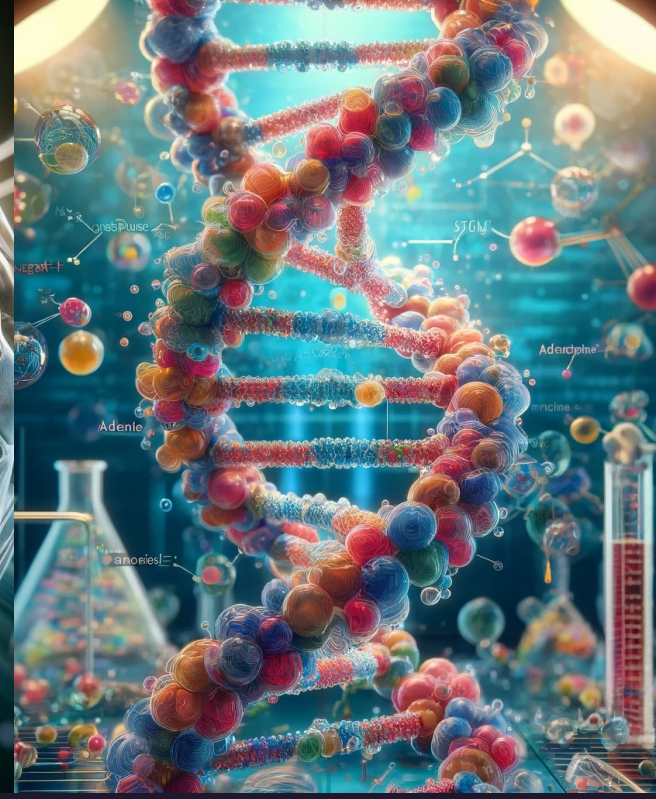
lies, damned lies, and statistics

Antimicrobial Resistance : Global burden of AMR – Microbiome and Metagenomics


Own Project Pipeline
19 Classes of Antibiotics
65 Phenotypes of Antibiotics
phenotypic resistance to different classes of antibiotics
Quantify per sample (i.e., FPKM)
Resistance Genes
Fragments of DNA



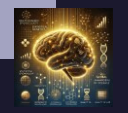




Cancer Epi-omics cohort

Epi-omics And Drug Use: Identification Of Late Effects Trajectories

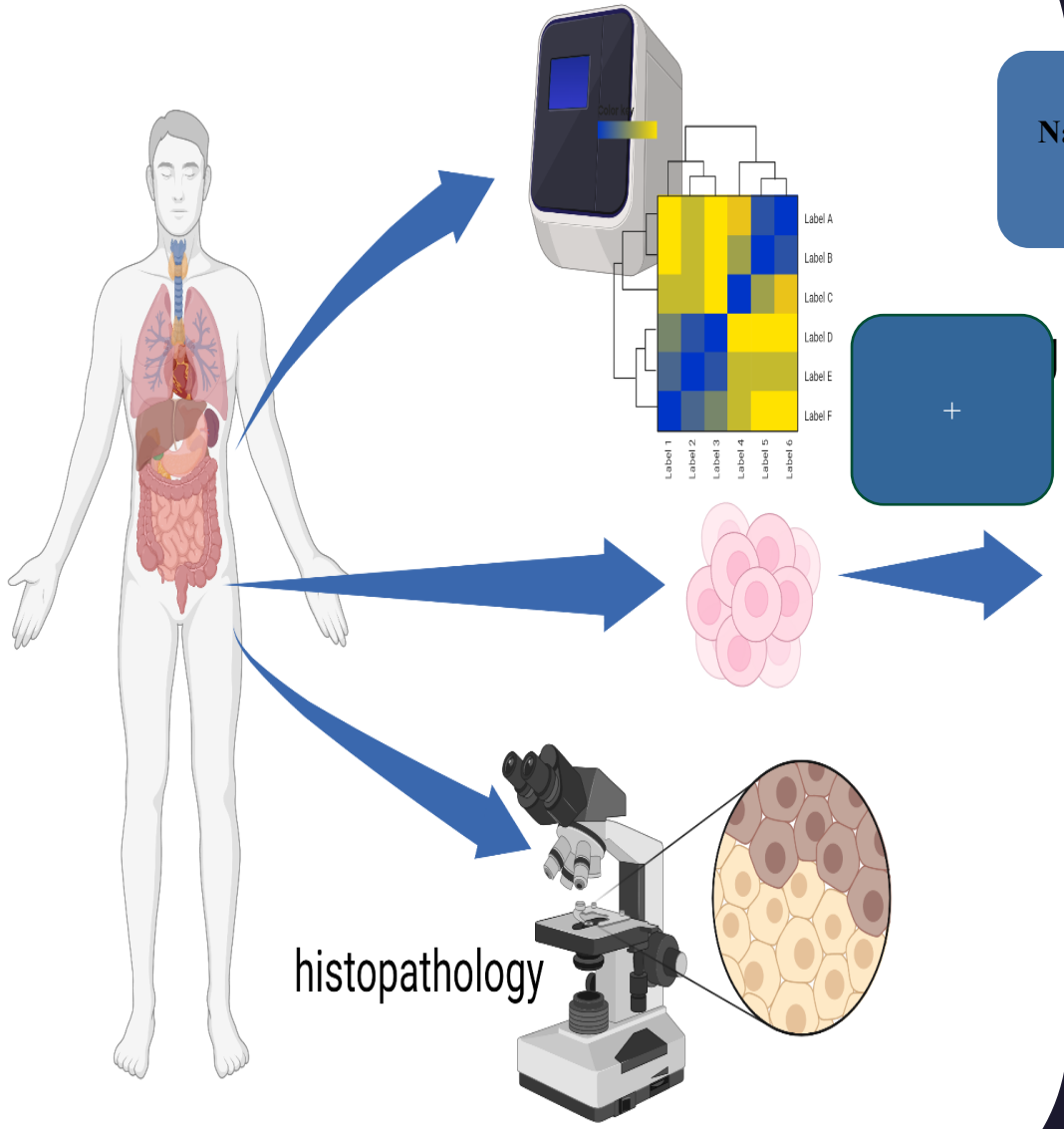
Variants of Uncertain Significance in Cancer and Patient Risk Profiles

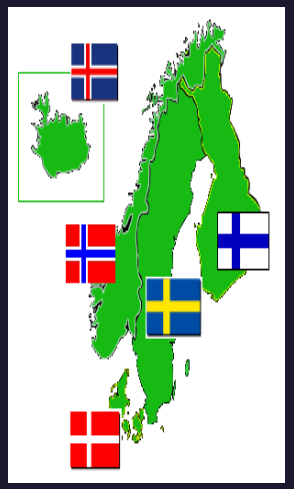


Nermin Ghith

Own data

NGS analysis





National cancer registries

Central population registries

Matched by sex, age and country

> 33,160 one-year survivors

> 212,892 comparisons

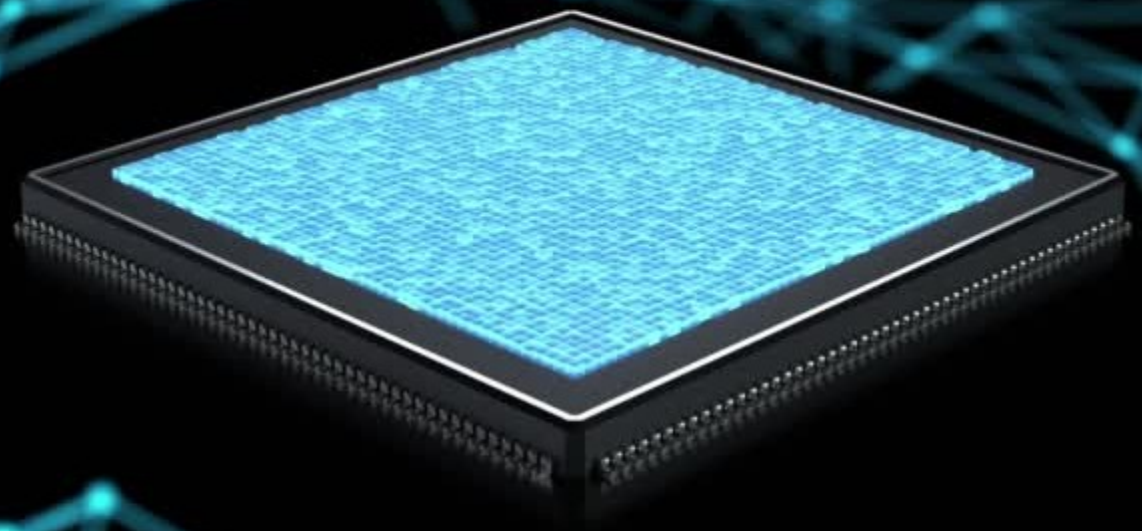
National hospital registries (discharge diagnoses according to ICD to evaluate late effects)

Algorithm to bedside

Contextual Epidemiology of Cardiometabolic Conditions, Polypharmacy and Multi-morbidity(session 2)

Data with no context is noise

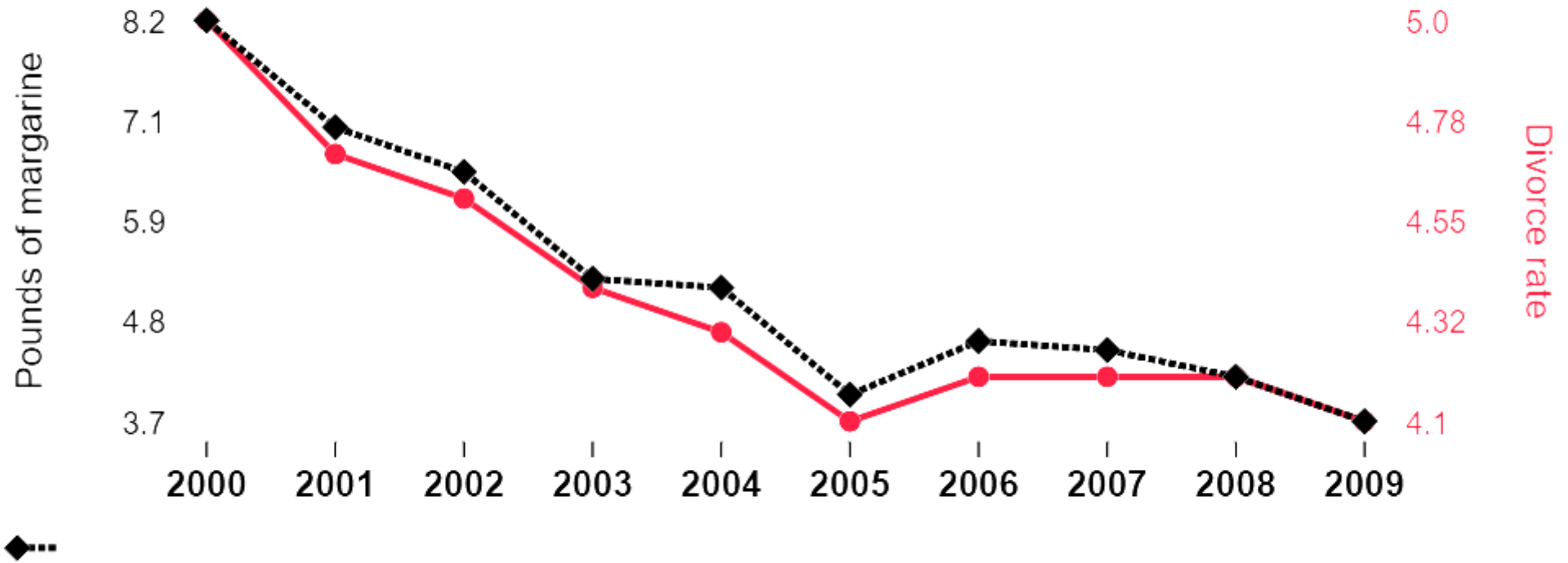
Algorithm to bedside



Per capita consumption of margarine

correlates with

The divorce rate in Maine



Patterns of Multimorbidity

2018-2019

KØBENHAVNS UNIVERSITET

2018-2019: Researcher, Research Unit of Chronic Conditions, CKFF

- Clusters of multimorbidity in the general population: a systematic review.
- Clusters of multimorbidity in the Danish population.
- Utilization of national healthcare services by individuals with multimorbidity in Denmark.

"k-means clustering (unsupervised learning)"

Table 1. Chronic conditions included in definition of multimorbidity (N = 16).

Allergies
Hypertension
High cholesterol
Diabetes (type 1 and type 2)
Heart disease
Stroke
Back pain
Joint disease
Osteoarthritis
Osteoporosis
Chronic obstructive pulmonary disease
Cancer
Dementia
Anxiety
Long-term use of antidepressants
Schizophrenia

https://doi.org/10.1371/journal.pone.0214183.t001

Cluster characteristics

- Cluster 1: **The Allergy cluster**. 100% patients has allergy, 42% hypercholesterolemia, 29% COPD 20%, depression, 20%, anxiety, cluster size 63.726, gender women 66%, mean age 57 years, mean number of conditions 2,6.
- Cluster 2: **The Hypercholesterolemia cluster.** 100% patients has hypercholesterolemia, 85% hypertension, none has diabetes and Chronic Heart Disease (CHD) 67.898 cluster size, 45% women, mean number of conditions 2,8.
- Cluster 3: **The Hypertension cluster.** 69% has hypertension, 28%osteoporosis, 26% depression, 24% COPD, 25% gout, 21% back symptoms, 20% cancer, cluster size 63.965, 67% women, mean number of conditions 2,4.
- Cluster 4: **The Diabetes Cluster.** 100% patients has diabetes, 82% hypertension, 72% hypercholesterolemia, none has CHC, cluster size 53.725, 48% women, mean number of conditions 3,3.
- Cluster 5: **The CHD cluster.** 100% patients has CHD, 75% hypertension, 75% hypercholesterolemia, 29 % diabetes, 52.443 cluster size, 44% women, mean number of conditions 3,9.

"Frequentist framework with MLE/EM"

PLOS ONE

Shared first coauthorship

RESEARCH ARTICLE

Multimorbidity, healthcare utilization and socioeconomic status: A register-based stud in Denmark

Anne Frølich[1,2]*, **Nermin Ghith**[3], **Michaela Schiøtz**[4], **Ramune Jacobsen**[5], **Anders Stockmarr**[6]

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Check for updates

OPEN ACCESS

Citation: Frølich A, Ghith N, Schiøtz M, Jacobsen R, Stockmarr A (2019) Multimorbidity, healthcare utilization and socioeconomic status: A register-based study in Denmark. PLoS ONE 14(8): e0214183. https://doi.org/10.1371/journal.pone.0214183

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Accepted: July 10, 2019

Published: August 1, 2019

Data Availability Statement: Due to restrictions related to Danish law and protecting patient privacy, the combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark. This state organisation holds the data used for this study. Danish scientific organisations can be authorized to work with data within Statistics Denmark and such organisations can provide access to individual scientists inside and outside of Denmark. Requests for data may be sent to Statistics Denmark: http://www.dst.dk/en/OmDS/organisation/

Abstract

Background

People with multimorbidity have reduced functional capacity, lower quality of life, higher mortality rates and use healthcare resources more intensively than healthy people or th with a single chronic condition. Multimorbidity was defined as the coexistence of two or more chronic conditions in the same person. The aim of this study was to explore assoc tions between multimorbidity and use of healthcare services and the impact of socioeco nomic status on utilization of hospitalizations and bed days.

Methods

The study population included all individuals aged 16 years and older who lived in the C tal Region of Denmark on January 1st, 2012. Data on chronic conditions, use of healthc services and demographics were obtained from Danish national administrative and hea registries. Zero-inflated models were used to calculate anticipated annual use of hospita tions and bed days.

Findings

The study population comprised 1,397,173 individuals; the prevalence of multimorbidity 22%. Prevalence was inversely related to educational attainment. For people with multi bidity, utilization of hospitalizations and bed days increased approximately linearly with number of chronic conditions. However, a steep increase in utilization of bed days was observed between five and six or more chronic conditions. An educational gradient in ho talization rates and use of bed days was observed regardless of the number of chronic c ditions. Educational attainment was strongly associated with health

Zero-inflated models:

- Use of hospitalizations and bed days.

- Hospitalizations and bed days were adjusted for emergency visits, out-patient visits, GP visits, out-of-hours GP visits, yearly controls in general practice, private specialist visits, number of conditions, age, gender, cohabitation status, education attainment, and employment status.

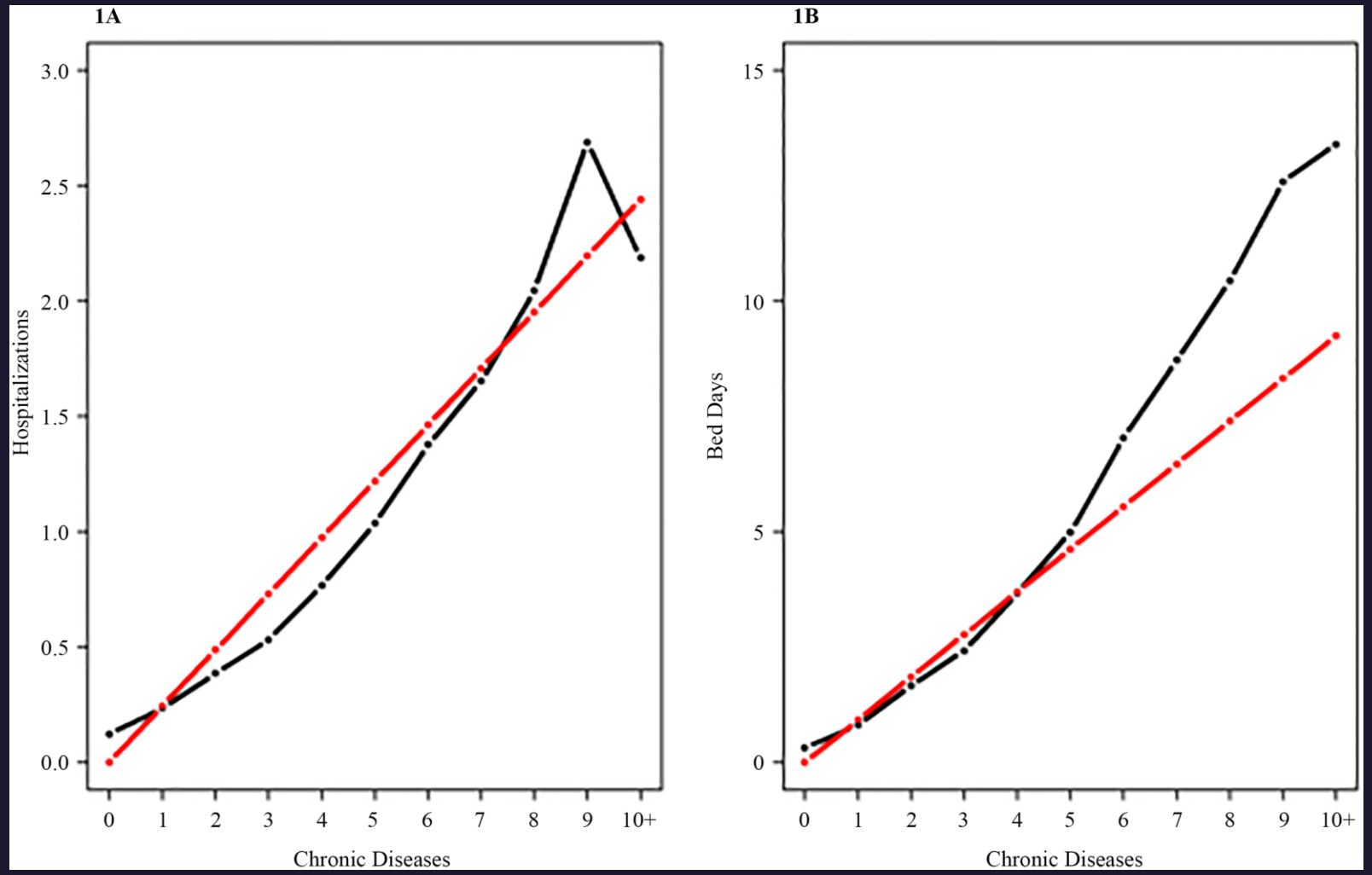


Fig 1. Multimorbidity, healthcare utilization and socioeconomic status: A register-based study in Denmark
Relationship between numbers of chronic conditions and hospitalizations **(1A)** and between numbers of chronic conditions and bed days **(1B).**

(1A) The black line indicates the observed number of hospitalizations by the number of chronic conditions. The red line indicates the reference regression line that shows the mean number of hospitalizations multiplied by the number of chronic conditions. **(1B)** The black line indicates the observed number of bed days by number of chronic conditions. The red line indicates the reference regression line that shows the mean number of bed days multiplied by the numbers of chronic conditions.

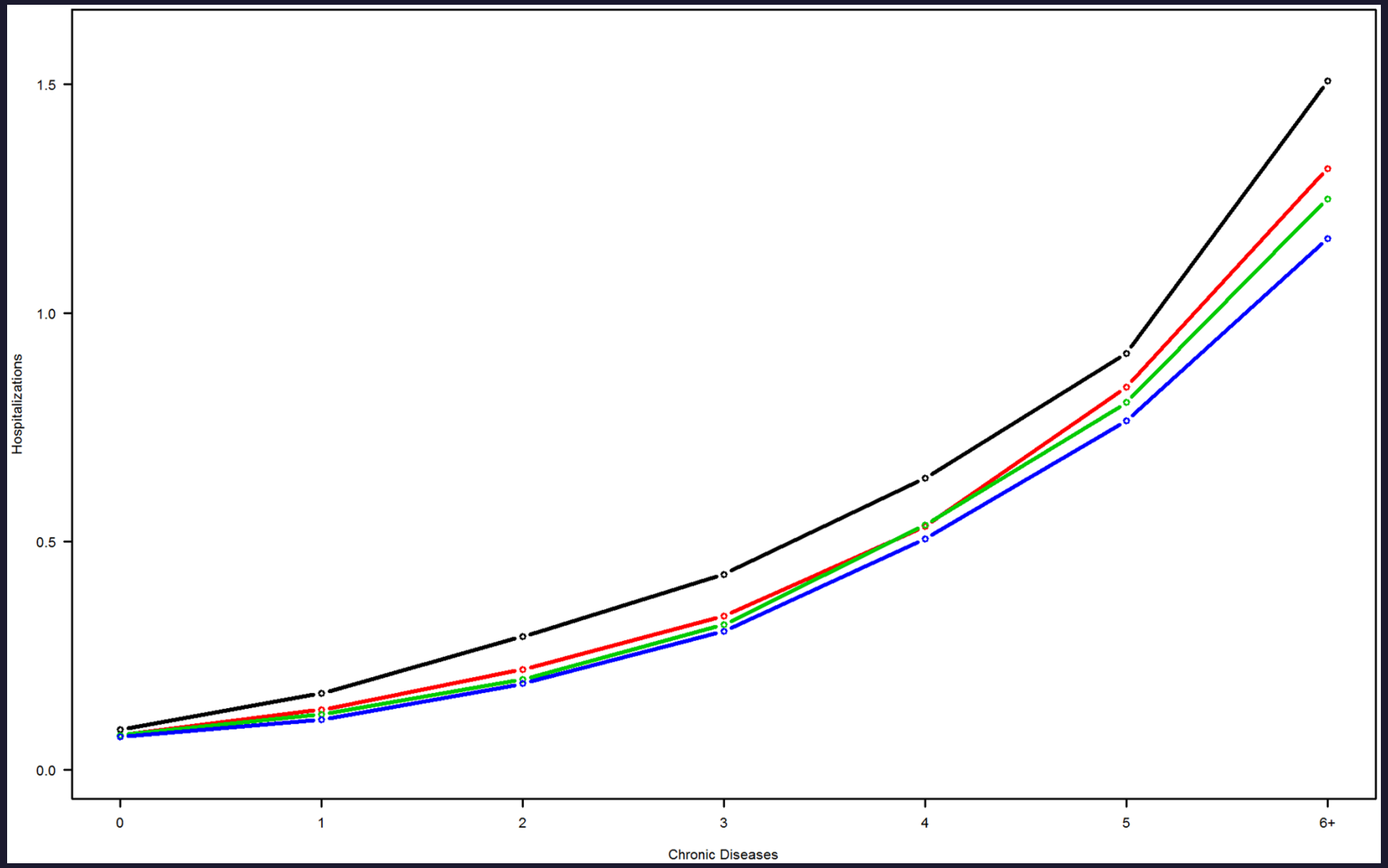


Fig 2. Number of chronic conditions associated with the modeled rate of hospitalizations by educational attainment levels. Black line, no education; red line, short education; green line, medium education; blue line, long education.

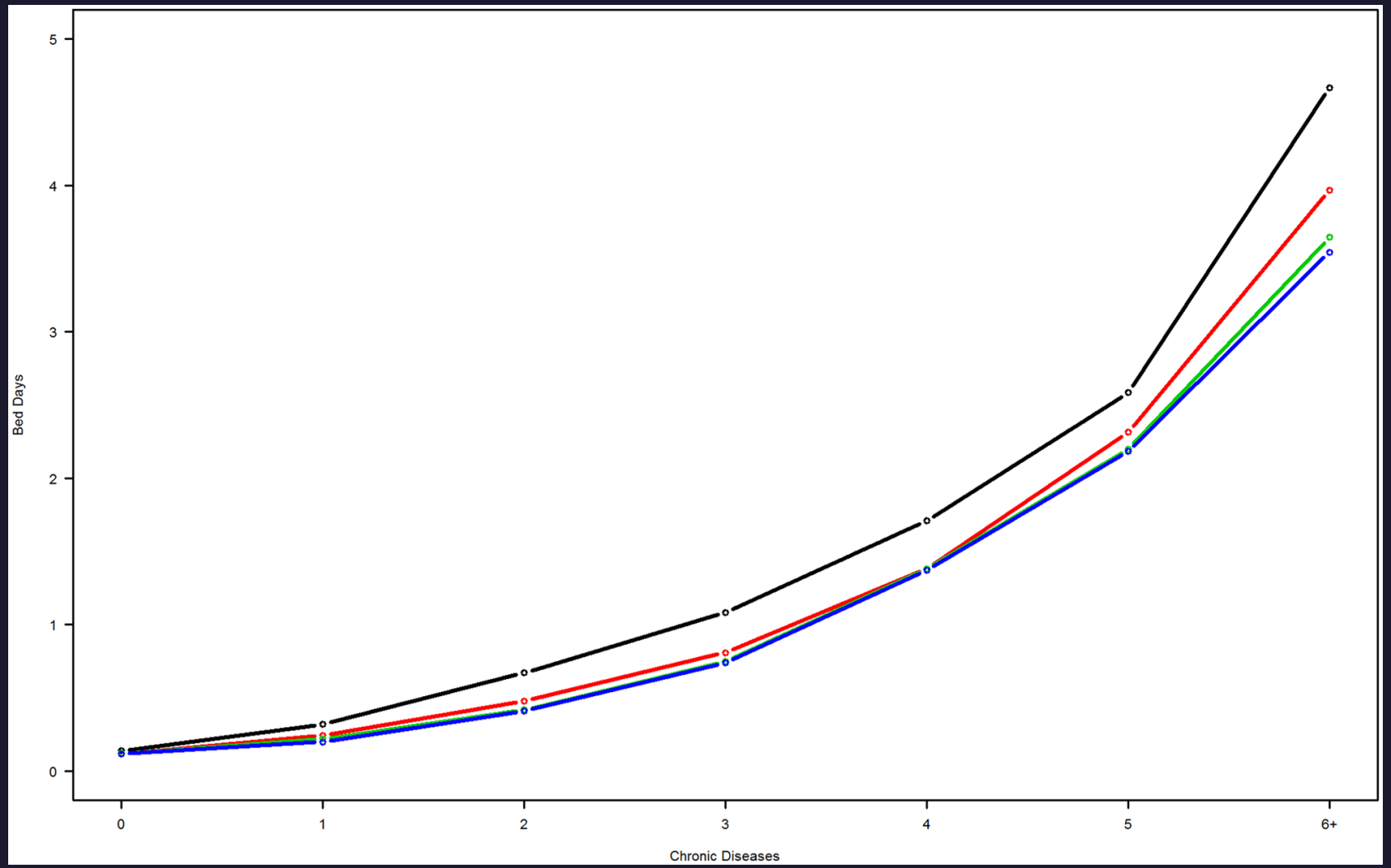


Fig 3. Number of chronic conditions associated with the modeled rate of bed days by educational attainment. Black line, no education; red line, short education; green line, medium education; blue line, long education.

ALGORITHM TO BEDSIDE

All models are wrong. Some are Useful!

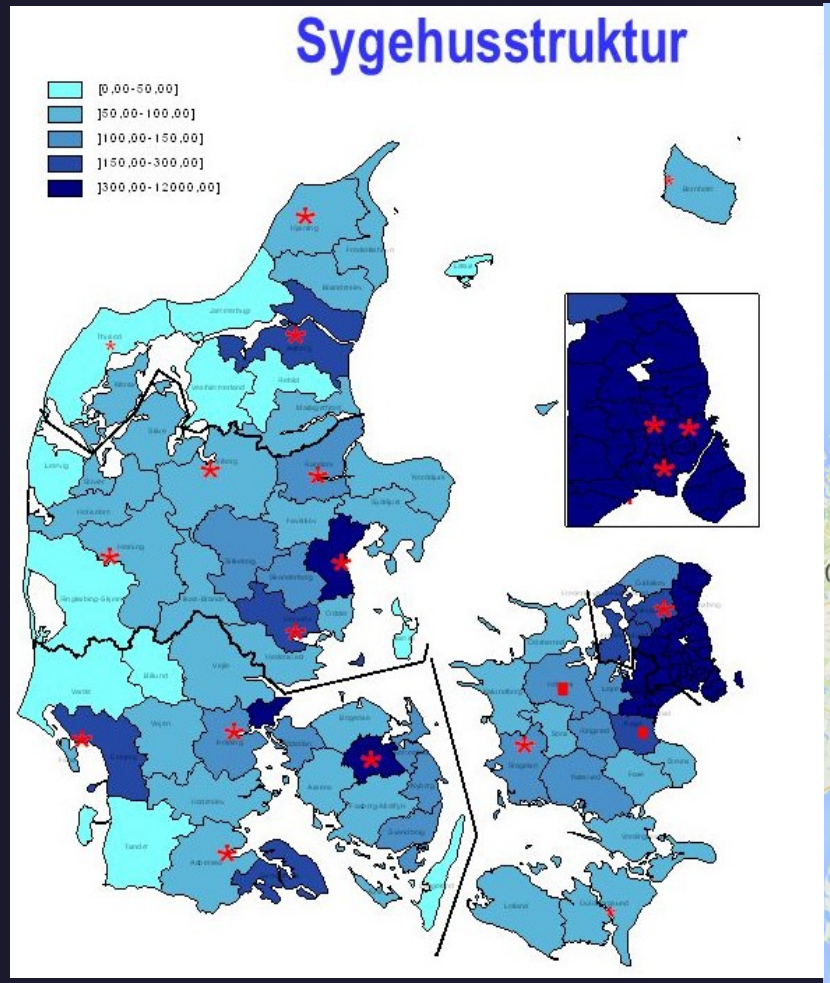
Ph.D. Thesis research work

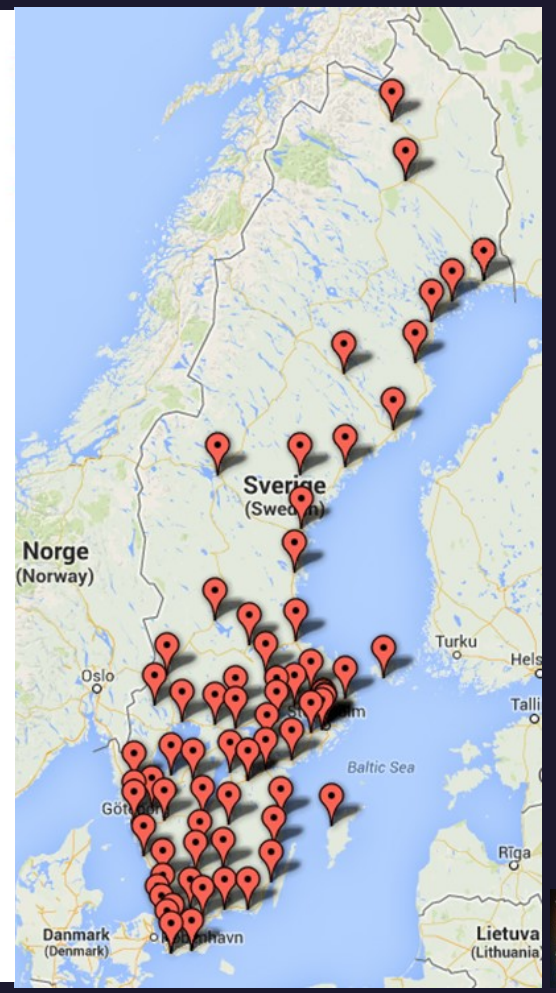
Ph.D. Thesis

Statistical multilevel analysis of individual patient heterogeneity (MAIH) to investigate hospital quality of care focusing on clinical patient indicators - The case of patients with heart failure and diabetes.

National patient data were collected from all hospitals/clinical sites by healthcare professionals :

- 42-57 clinical sites/departments within 32 Hospitals in Denmark
- 565 clinical sites/departments within 71 hospitals in Sweden
- Clinical effectiveness, prognosis, morbidity/risk, and survival

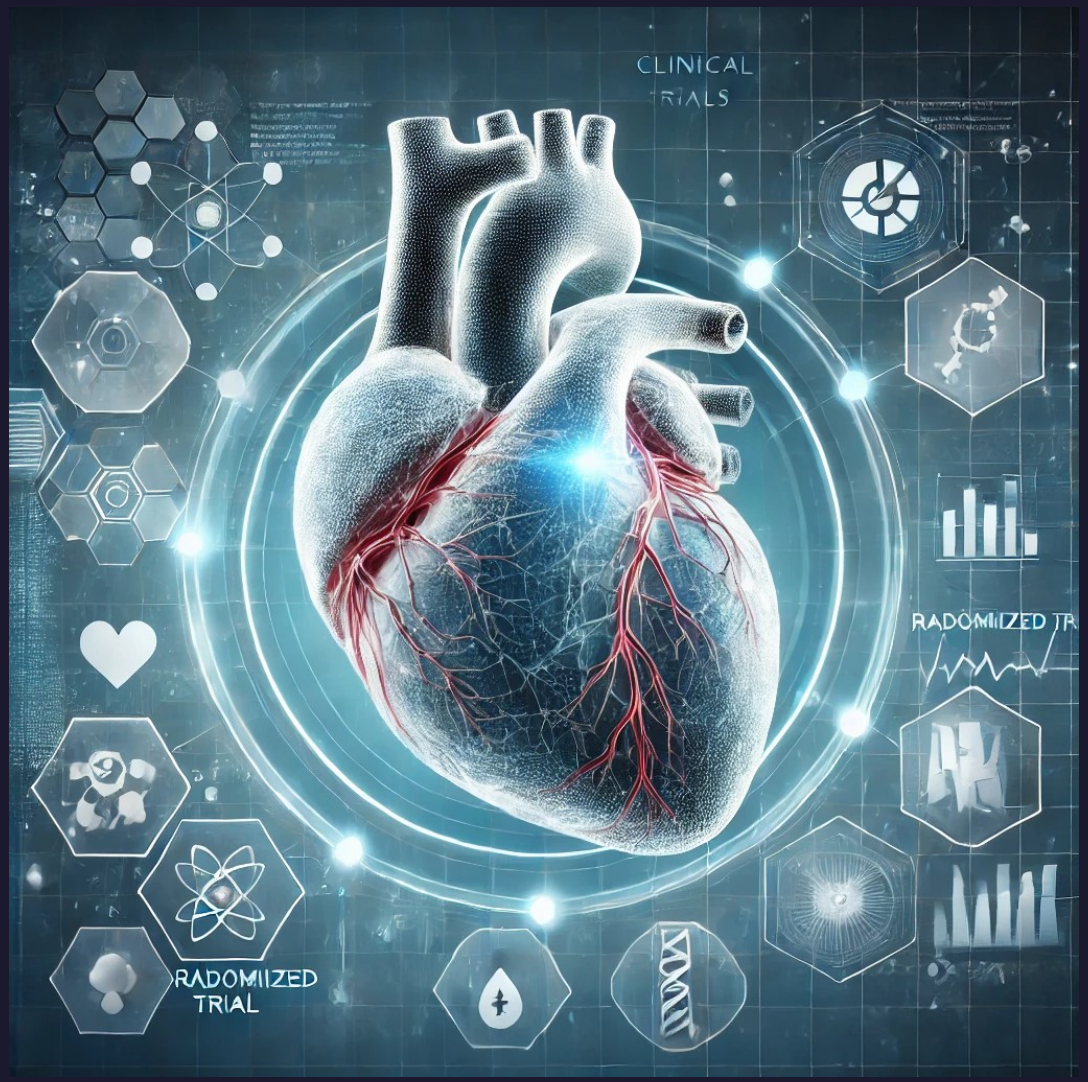




Quantitative evaluations of hospital quality of care
Data and Methods

1. Data sources
    - Population and patient registers
    - Clinical quality registers
    - Social and administrative databases

2. Traditional methods focus on assessing <u>differences between hospital averages</u> by using, for instance
    - Aggregated data
    - Single-level regression analyses



Quantitative evaluations of hospital quality of care

Patient variation (*differences*) in outcomes of care

- According to **MAIH**, what matters most is not the differences between hospital averages but rather the proportion of the total patient differences at the hospital level.
- MAIH proposes the concept of general contextual effect (GCE) instead of averages.
- This is expressed by, for instance,
    - the Intraclass Correlation (ICC); that is, the share of the total patient **variation** that is at the hospital level
    - The area under the Receiver Operating Characteristic (ROC) curve

VISUAL STATISTICS…from my PhD Thesis

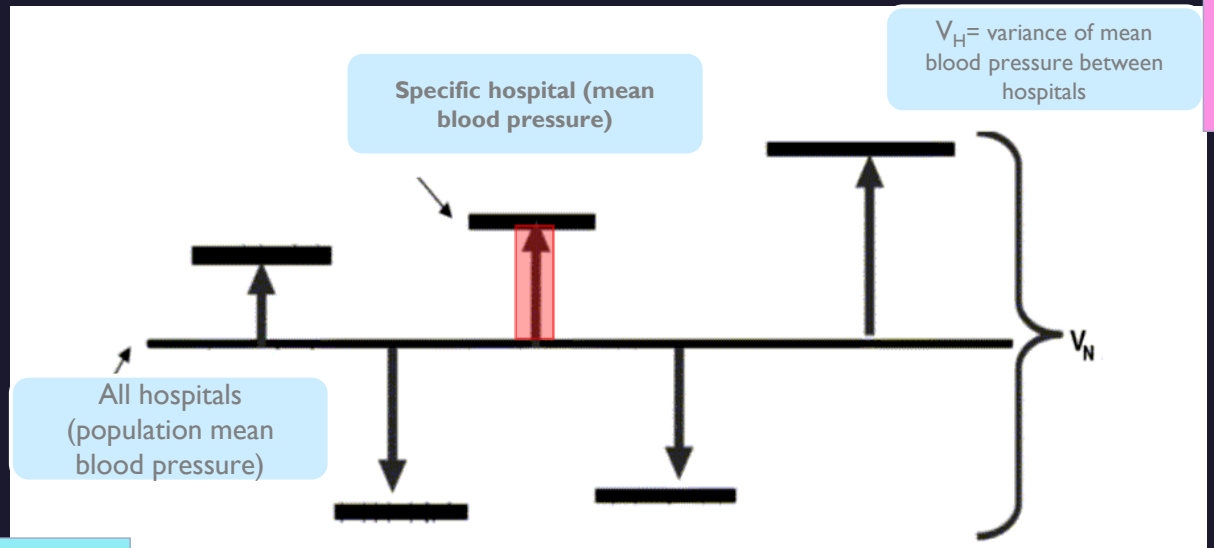
"VARIANCE"

Example…. patients, hospitals, and systolic blood pressure/death/…

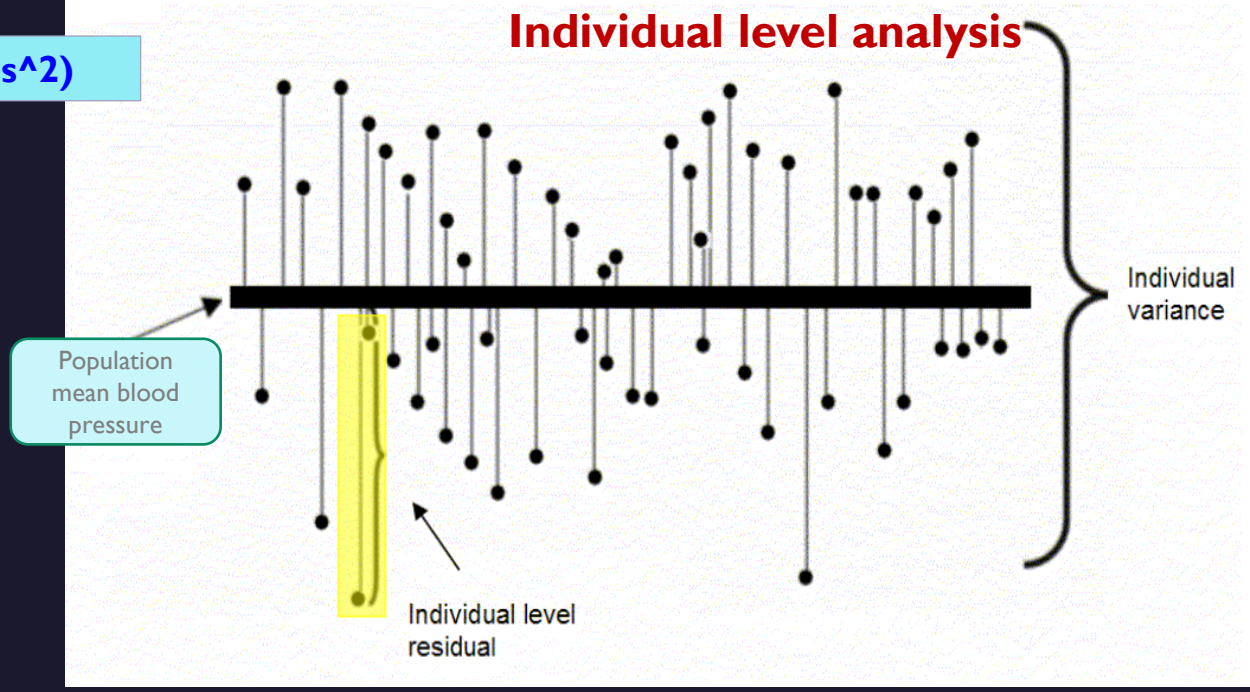
Residual = mean – unit value

Variance = average (residuals^2)

Aggregated level analysis



Individual level analysis

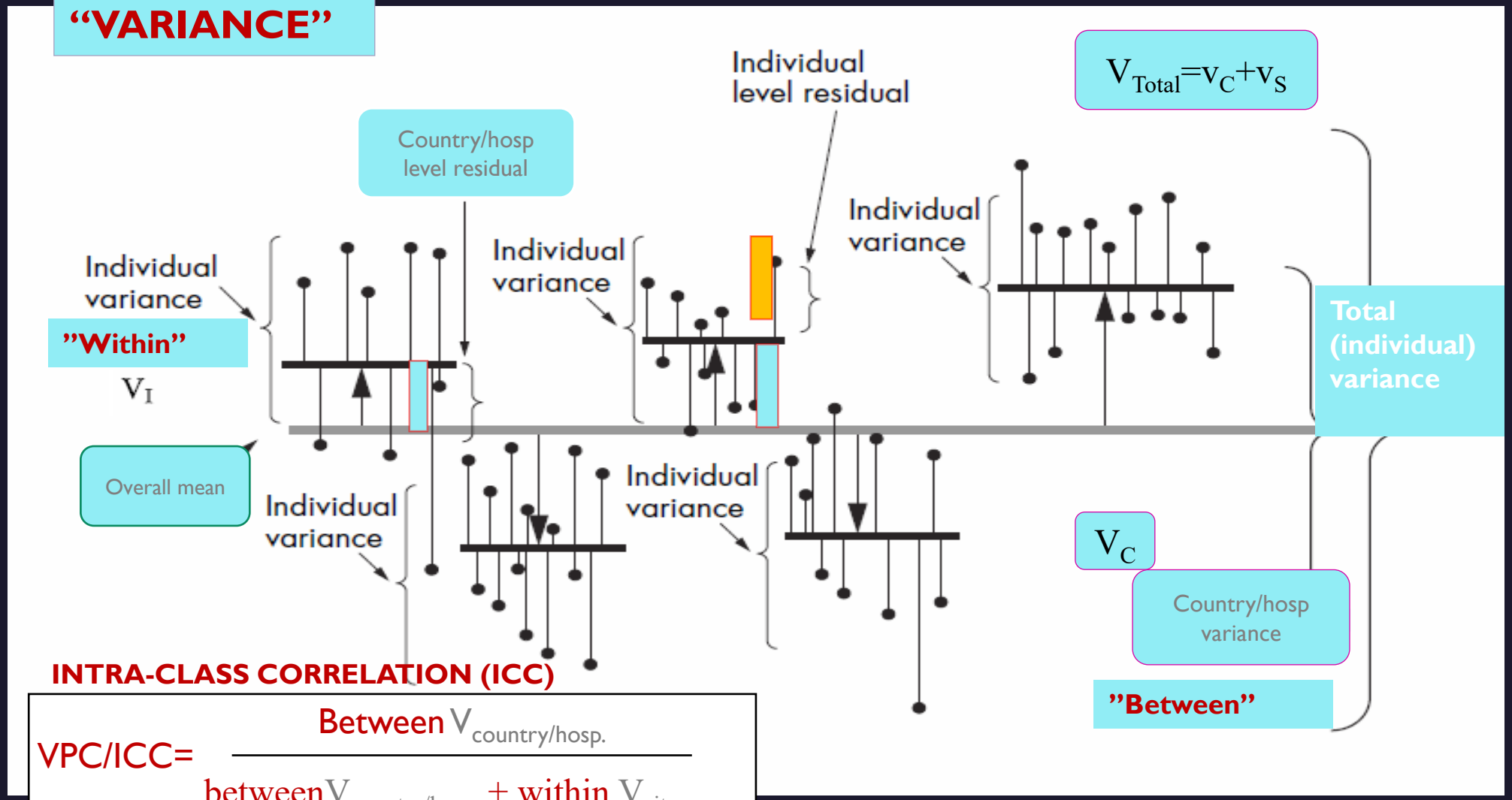


"Bayesian framework with MCMC"

VISUAL STATISTICS…from my PhD Thesis

Multilevel analysis

"VARIANCE"



INTRA-CLASS CORRELATION (ICC)

$$VPC/ICC = \frac{\text{Between } V_{country/hosp.}}{\text{between } V_{country/hosp} + \text{within } V_{site}}$$

Total individual (site) variance= within (site) + between

PLOS | ONE

RESEARCH ARTICLE

Short Term Survival after Admission for Heart Failure in Sweden: Applying Multilevel Analyses of Discriminatory Accuracy to Evaluate Institutional Performance

Nermin Ghith[1,2]*, Philippe Wagner[1,3], Anne Frølich[2], Juan Merlo[1]

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OPEN ACCESS

Citation: Ghith N, Wagner P, Frølich A, Merlo J (2016) Short Term Survival after Admission for Heart Failure in Sweden: Applying Multilevel Analyses of Discriminatory Accuracy to Evaluate Institutional Performance. PLoS ONE 11(2): e0148187. doi:10.1371/journal.pone.0148187

Editor: Pablo Garcia de Frutos, IIBB-CSIC-IDIBAPS, SPAIN

Received: September 10, 2015

Accepted: January 14, 2016

Published: February 3, 2016

Data Availability Statement: The database we analyzed is not publicly available for ethical and data safety reasons according to the Swedish National Board of Health and Welfare. However, the same dataset can be constructed by request to the Swedish National Board of Health and Welfare after approval of the research project by an Ethical Committee and by the data safety committee at the Swedish National Board of Health and Welfare.

Funding: This work was supported by the Swedish Research Council (VR) [#2013-2484, Juan Merlo] and by grants from the University of Copenhagen and

Abstract

Background

Hospital performance is frequently evaluated by analyzing differences between hospital averages in some quality indicators. The results are often expressed as quality charts of hospital variance (e.g., league tables, funnel plots). However, those analyses seldom consider patients heterogeneity around averages, which is of fundamental relevance for a correct evaluation. Therefore, we apply an innovative methodology based on measures of components of variance and discriminatory accuracy to analyze 30-day mortality after hospital discharge with a diagnosis of Heart Failure (HF) in Sweden.

Methods

We analyzed 36,943 patients aged 45–80 treated in 565 wards at 71 hospitals during 2007–2009. We applied single and multilevel logistic regression analyses to calculate the odds ratios and the area under the receiver-operating characteristic (AUC). We evaluated general hospital and ward effects by quantifying the intra-class correlation coefficient (ICC) and the increment in the AUC obtained by adding random effects in a multilevel regression analysis (MLRA). Finally, the Odds Ratios (ORs) for specific ward and hospital characteristics were interpreted jointly with the proportional change in variance (PCV) and the proportion of ORs in the opposite direction (POOR).

Findings

Overall, the average 30-day mortality was 9%. Using only patient information on age and previous hospitalizations for different diseases we obtained an AUC = 0.727. This value was almost unchanged when adding sex, country of birth as well as hospitals and wards levels. Average mortality was higher in small wards and municipal hospitals but the POOR values were 15% and 16% respectively.

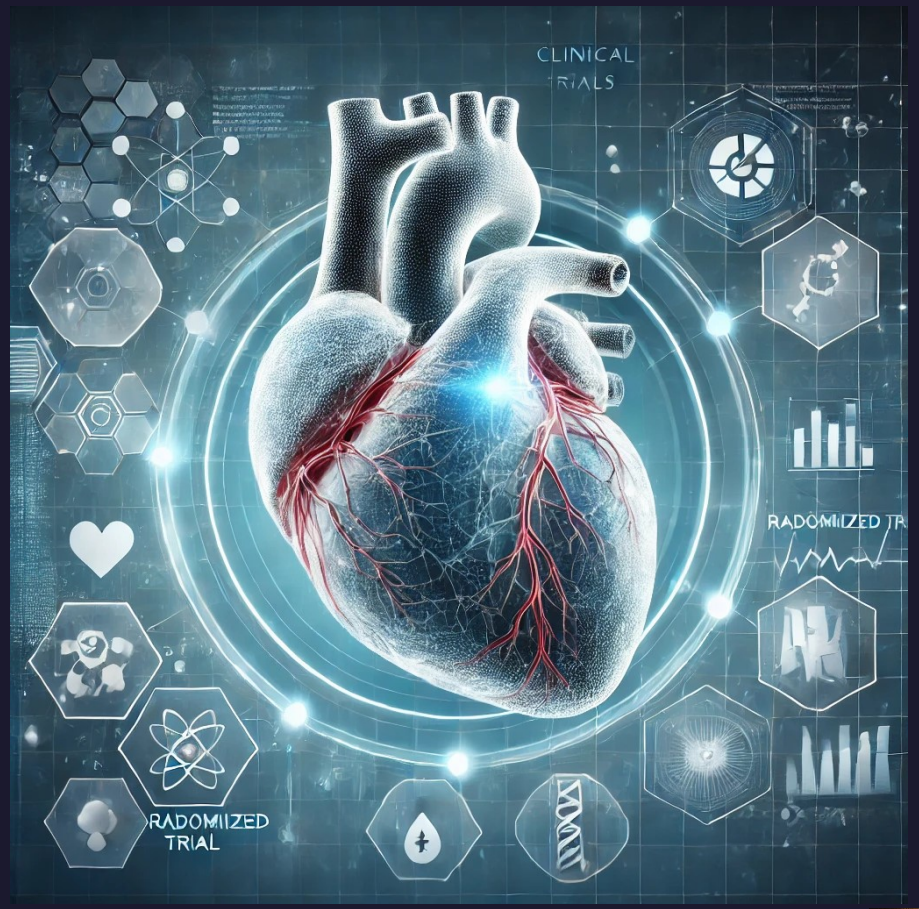
•https://doi.org/10.1371/journal.pone.0148187

Study I – Methods and findings

Data: using a unique personal identification number, the research database included linked data from

- the Swedish patient register with
- the Cause of Death Register and
- the Longitudinal Integrated Database for Health Insurance and Labour Studies (LISA).

- **Population:** covered 36,943 patients aged 45-80 who were treated in 565 departments at 71 hospitals.
  - with a discharge diagnosis of heart failure (International Classification of Diseases code I50) ; (2007-2009)



Two step analytical approach

From my PhD Thesis: Variance measures are expressed as median values and 95% credible intervals (CIs)

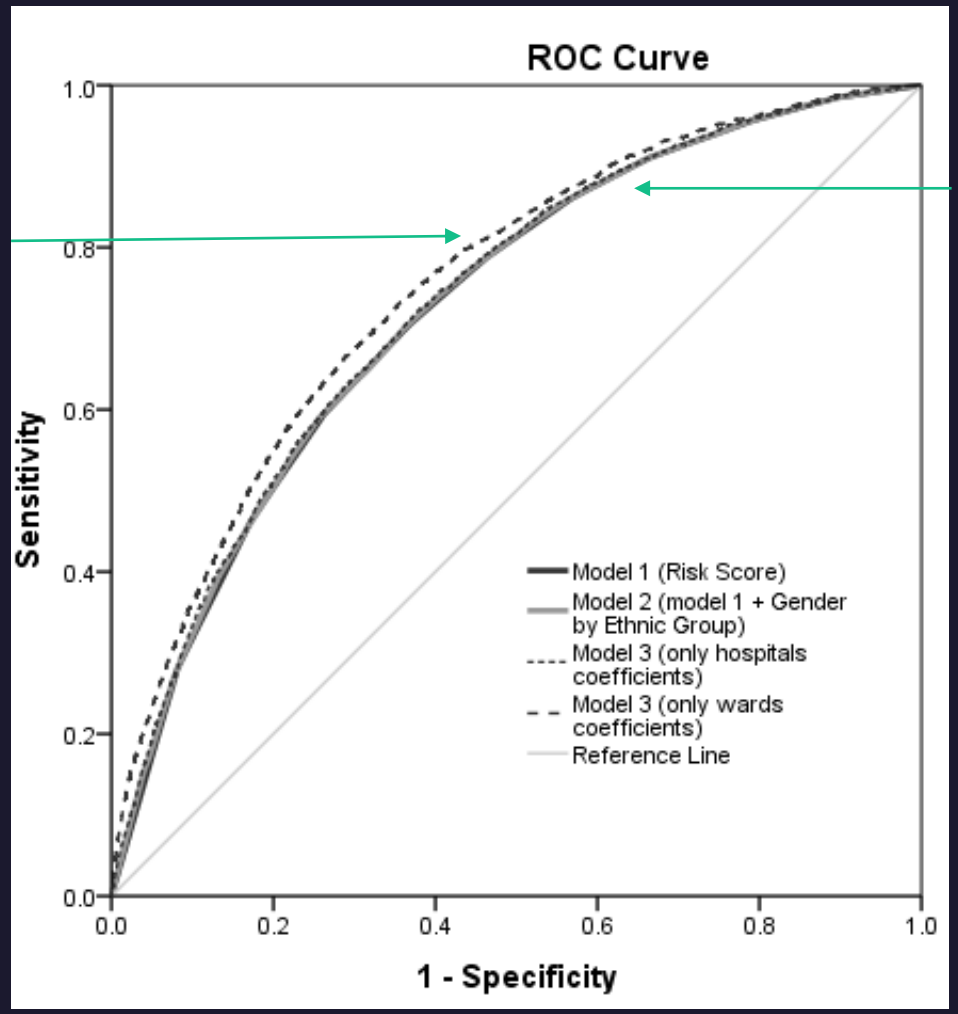
Patients within departments within hospitals

	Single level Logistic Regression models		Three Level Multilevel Logistic Regression Models	
Measures of the GCE	Model 1 (RS) 36 variables on patient case-mix	Model 2 (RS+gender/age)	Model 3 (RS+gender/age)	Model 4 (RS+ gender/age+ patient volume, hospital classification)
AUC	0.727 (0.719-0.736)	0.729 (0.721-0.738)	0.753 (0.745-0.762)	0.752 (0.743-0.760)
ICC_H			**0.04%** 0.004 (0.000-0.014)	0.002 (0.000-0.015)
ICC_D			**5.3%** 0.053 (0.035-0.081)	0.036 (0.020-0.064)

Average 30-day mortality was 9 %

From my PhD Thesis: Variance measures are expressed as median values and 95% credible intervals (CIs)

Multilevel model 3
AUC ≈ 0.753

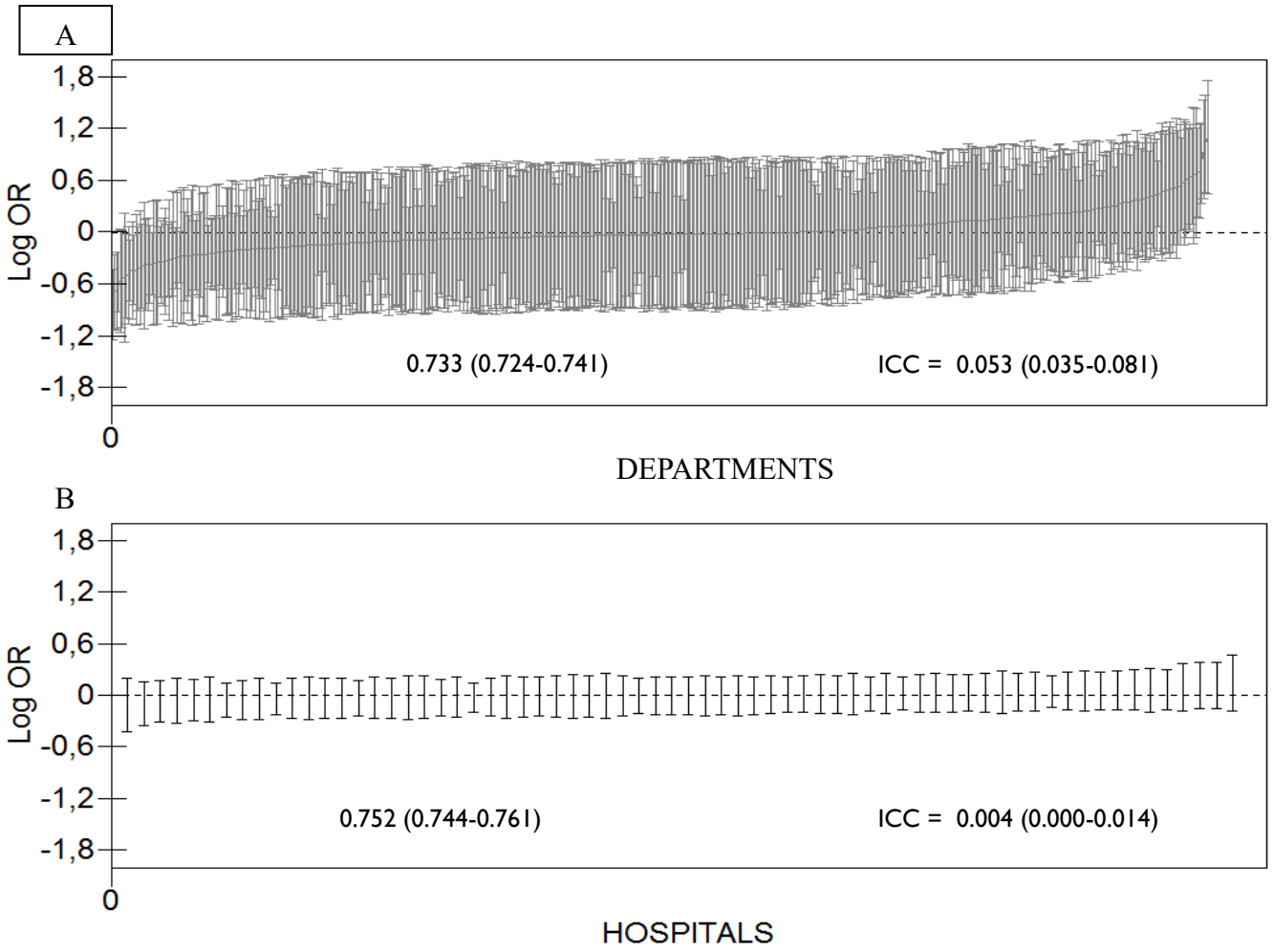


Single level model 2
AUC = 0.729

the increase in the AUC in model 3 compared to model 2 represents the *ceiling* of the hospital's general contextual effects.

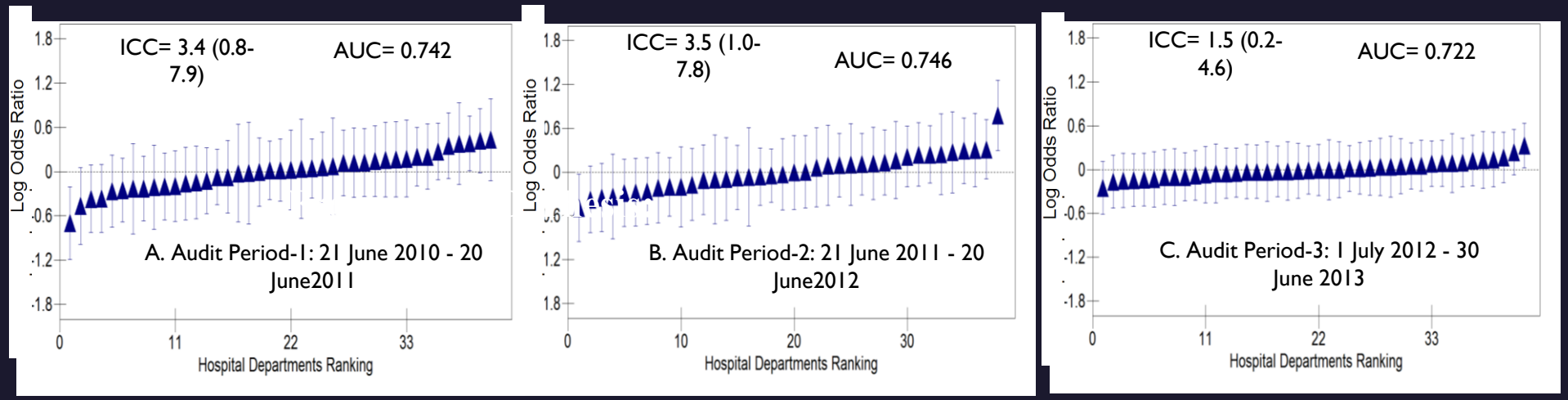
Since measures on the GCE were so small, information on the specific contextual effects (patient volume and hospital classification) are not relevant.

League tables



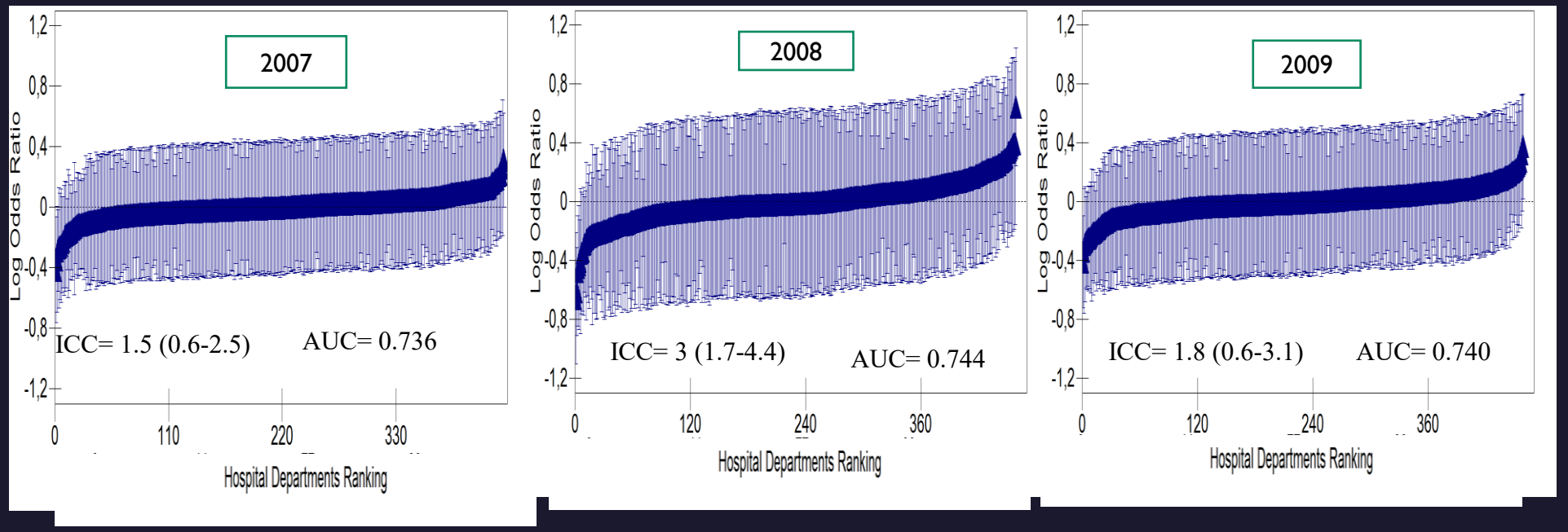
From my PhD Thesis: https://doi.org/10.1371/journal.pone.0148187

League tables
Danish departements



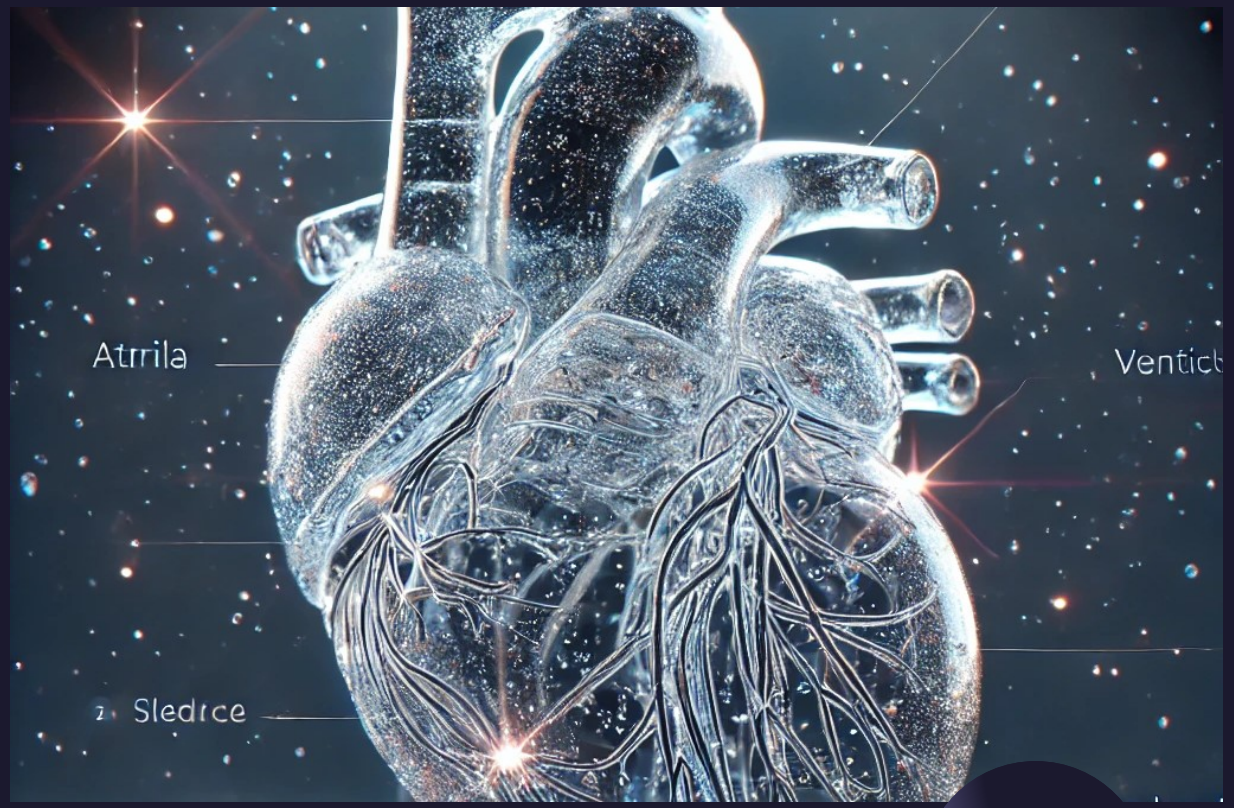
From my PhD Thesis: https://doi.org/10.1371/journal.pone.0189050

League tables
Swedish Departments



From my PhD Thesis: https://doi.org/10.1371/journal.pone.0189050

Study I – Brief statement on findings



- The average 30-day mortality was 9%. Using only patient information on the RS, we obtained an AUC = 0.727
- This value was almost unchanged when adding gender/ethnicity as well as hospital and department levels.
- Department ICC was 5.3 % and hospital ICC was 0.04%
- Knowledge of a patient's RS was the best predictor of the 30-day mortality rate, and this information did not improve by knowing the gender and ethnicity or where the patient was treated.

Open access Original article

BMJ Open Quality

Albuminuria measurement in diabetic care: a multilevel analysis measuring the influence of accreditation on institutional performance

Nermin Ghith,[1,2] Juan Merlo,[2] Anne Frølich[1]

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjoq-2018-000449).

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ABSTRACT

Background Studies assessing institutional performance regarding quality of care are frequently performed using single-level statistical analyses investigating differences between provider averages of various quality indicators. However, such analyses are insufficient as they do not consider patients' heterogeneity around those averages. Hence, we apply a multilevel analysis of individual-patient heterogeneity that distinguishes between 'general' ('latent quality' or measures of variance) and 'specific' (measures of association) contextual effects. We assess general contextual effects of the hospital departments and the specific contextual effect of a national accreditation programme on adherence to the standard benchmark for albuminuria measurement in Danish patients with diabetes.

Methods From the Danish Adult Diabetes Database, we extracted data on 137 893 patient cases admitted to hospitals between 2010 and 2013. Applying multilevel logistic and probit regression models for every year, we quantified general contextual effects of hospital department by the intraclass correlation coefficient (ICC) and the area under the receiver operating characteristic curve (AUC) values. We evaluated the specific effect of hospital accreditation using the ORs and the change in the department variance.

Results In 2010, the department context had considerable influence on adherence with albuminuria measurement (ICC=21.8%, AUC=0.770), but the general effect attenuated along with the implementation of the national accreditation programme. The ICC value was 16.5% in 2013 and the rate of compliance with albuminuria measurement increased from 91.6% in 2010 to 96% in 2013.

Conclusions Parallel to implementation of the national accreditation programme, departments' compliance with the standard benchmark for albuminuria measurement increased and the ICC values decreased, but remained high. While those results indicate an overall quality improvement, further intervention focusing on departments with the lowest compliance could be considered.

INTRODUCTION

In 2000, the Danish state developed the National Indicator Project for monitoring and improving quality of care for a number of chronic conditions.[1] By 2010, the National Indicator Project was expanded to include all clinical quality databases under one Secretariat, the Regions' Clinical Quality Improvement Program (RKKP).[1] Parallel to that, hospitals implemented three types of accreditation in different areas of the country between 2002 and 2015.[2] All hospitals were accredited by the Danish quality model (DDKM) in 2010–2013 and reaccredited in 2013–2015.[2]

Literature indicates that diabetes is responsible for, or associated with, a wide range of chronic conditions including cardiovascular diseases.[3] According to the Danish Diabetes Association, around 320 545 Danes (5.7% of the population in 2011) were diagnosed with diabetes, which is almost double the rate reported 10 years earlier. In 2004, Danish health authorities established the Adult Diabetes Database or *Dansk Voksen Diabetes Database* (DVDD) to register, monitor and support the quality of care in patients with diabetes.[4] All hospital departments are audited annually against a set of standard benchmarks.[4] Data on quality indicators are collected periodically for each hospital and aggregated for further analysis and release every year to the public and healthcare professionals. Hospital performance is compared with the national overall average for each indicator.

One of the mandatory high-volume processes is the albuminuria measurement that accounted for 12.8% of the total amount of diabetes care delivered in Denmark in 2010–2013. Albuminuria is a strong predictor of kidney impairment and cardiovascular disease in patients with both type 1 and type 2 diabetes.[5 6] Thus, periodic monitoring of albuminuria is crucial in those patients.[7] The DVDD audit commission recommended that hospital departments should measure albuminuria in at least 95% of patients with diabetes. Danish hospitals were audited against that benchmark.[4]

RESEARCH ARTICLE

The role of the clinical departments for understanding patient heterogeneity in one-year mortality after a diagnosis of heart failure: A multilevel analysis of individual heterogeneity for profiling provider outcomes

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Data Availability Statement: The databases we analyzed are not publicly available for ethical and data safety reasons according to the Swedish National Board of Health and Welfare and the Danish Clinical Registries Program (RKKP). These are third party data (i.e., register based data not collected by the authors). However, data are available from both national bodies access / ethics Committee for researchers who meet the criteria for access to confidential data. In Sweden, the dataset can be obtained from the National Board of

Abstract

Purpose

To evaluate the general contextual effect (GCE) of the hospital department on one-year mortality in Swedish and Danish patients with heart failure (HF) by applying a multilevel analysis of individual heterogeneity.

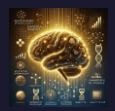
Methods

Using the Swedish patient register, we obtained data on 36,943 patients who were 45–80 years old and admitted for HF to the hospital between 2007 and 2009. From the Danish Heart Failure Database (DHFD), we obtained data on 12,001 patients with *incident* HF who were 18 years or older and treated at hospitals between June 2010 and June2013. For each year, we applied two-step single and multilevel logistic regression models. We evaluated the general effects of the department by quantifying the intra-class correlation coefficient (ICC) and the increment in the area under the receiver operating characteristic curve (AUC) obtained by adding the random effects of the department in a multilevel logistic regression analysis.

Results

One-year mortality for Danish *incident* HF patients was low in the three audit years (around 11.1% -13.1%) and departments performed homogeneously (ICC ≈1.5% - 3.5%). The discriminatory accuracy of a model including age and gender was rather high (AUC≈ 0.71–0.73) but the increment in AUC after adding the department random effects into these models was only about 0.011–0.022 units in the three years.

One-year mortality in Swedish patients with first hospitalization for heart failure, was relatively higher for 2007–2009 (≈21.3% - 22%) and departments performed homogeneously



AI and Personalization of Medicine

ALGORITHM TO BEDSIDE

Use of prescription drugs in Danish and Swedish childhood cancer survivors

A population-based cohort study from the SALiCCs research program

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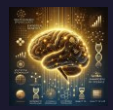
Head of Research Group Childhood Cancer

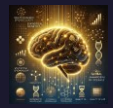
Methods

- All children with cancer before the age of 20 years
- Nationwide cancer registries
- Denmark (1945-2008) and Sweden (1958-2011)
- 16,742 (5,955, dk; 10,787, se) childhood cancer survivors
- International Classification of Childhood Cancer
- 77,701 population comparisons randomly selected from the population registers in a 5 to 1 selection
- 23,105 sibling comparisons



Methods

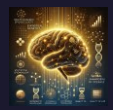
- Linking the three cohorts to the nationwide prescription registries
  - all drugs dispensed at pharmacies – ATC classification system
- Each dispensing: using the hierarchical Anatomical Therapeutic Chemical (ATC) classification system
  - ATC-code at 5th level (chemical substance) and date.
- All codes : All prescriptions were grouped into 11 ATC 1st main level and 65 ATC 2nd level therapeutic groups of prescription drugs.
- Relative rates (RRs) of prescriptions were calculated for
  - the 11 ATC 1st level groups of prescription drugs
  - each of the 65 ATC 2nd level
  - Rates ratios (RRs) and 95% confidence intervals (CIs) for filled drug prescriptions were calculated in marginal rates models allowing each individual to have several prescriptions during follow-up. Relative rates of prescriptions were calculated for the 11 ATC 1st main level and each of the 65 ATC 2nd level therapeutic groups of prescription drugs.



Methods

- Calculated rate ratios (RRs) and 95% CIs for filled drug prescriptions
  - Used marginal rates models
  - Allowing each individual to have several prescriptions during follow-up

“marginal rates models Frequentist framework with MLE/EM ”



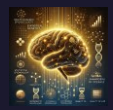
Results

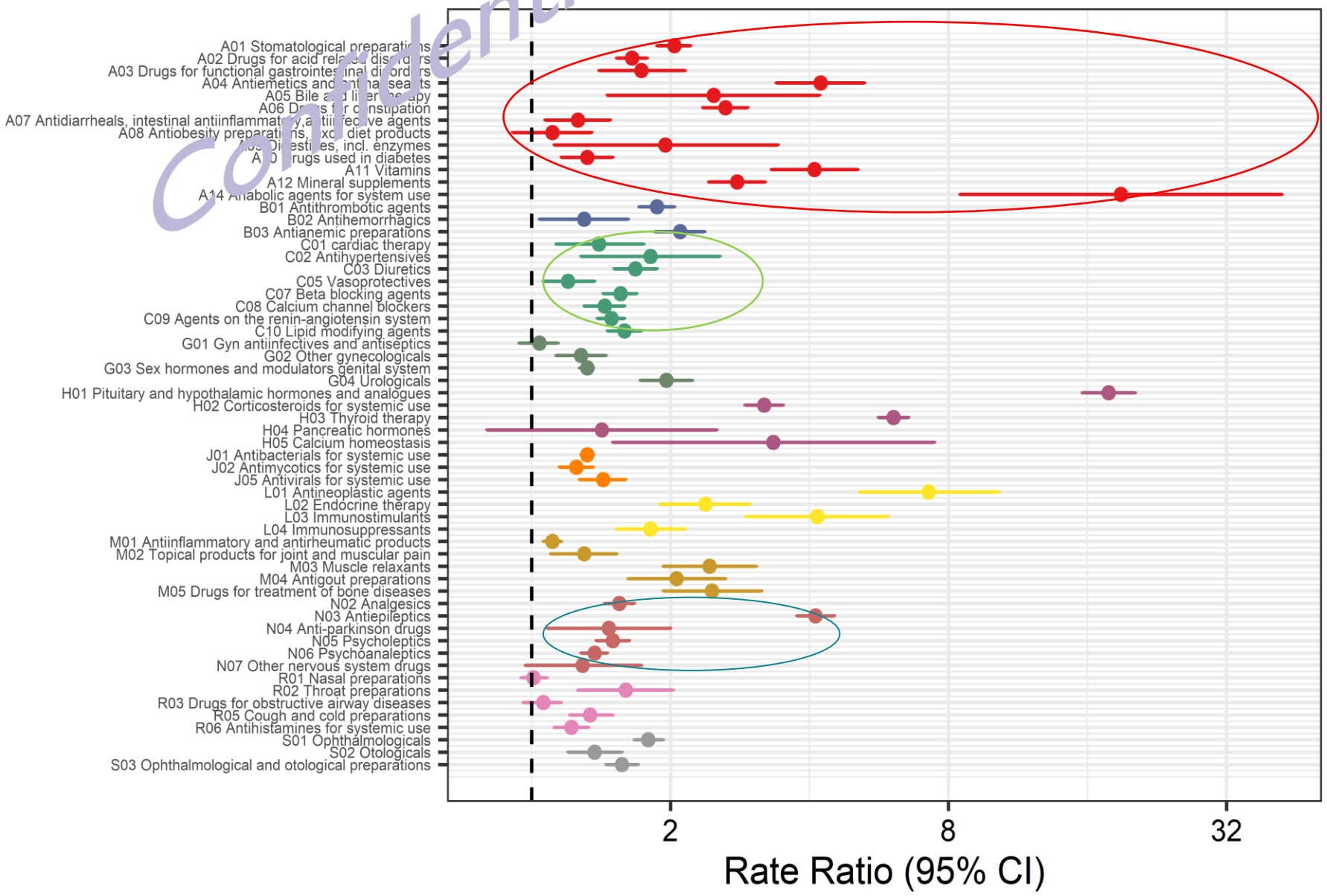
- **Survivors** had higher rates (table 1) of filling prescriptions compared with
  - **population** comparisons (RR 1.55; 95% CI 1.52-1.59)
  - **siblings** (RR 1.63; 95% CI 1.58-1.67)
- The highest rate of prescriptions (table 1) was seen for survivors of **CNS** tumors (RR 1.98; 95% CI 1.90-2.07)

Results

Use of prescription drugs

- The **relative rates** of prescriptions for survivors compared with **population** comparisons were higher in all **11 1st ATC** level of drugs
    - the highest rates seen for systematic hormonal preparations and antineoplastic and immunomodulating agents.





A A Alimentary tract and metabolism

B B Blood and blood forming organs

C C Cardiovascular system

G G Genito urinary system and sex hormones

H H Systemic hormonal preparations, excl. sex hormones and insulins

J J Antiinfectives for systemic use

L L Antineoplastic and immunomodulating agents

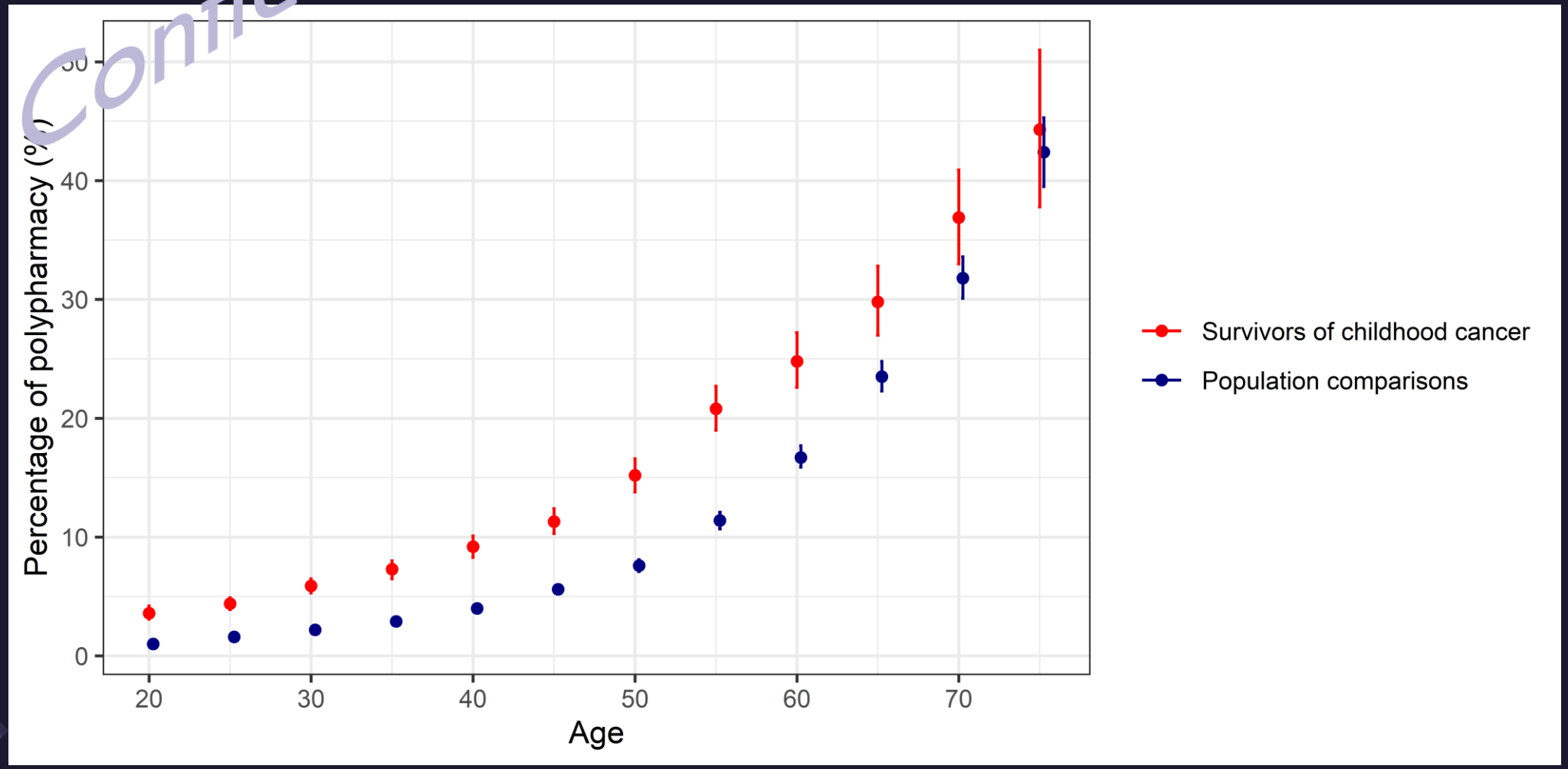
M M Musculo-skeletal system

N N Nervous system

R R Respiratory system

S S Sensory organs

Figure 3. Prevalence and 95% confidence intervals in childhood cancer survivors and population comparisons with polypharmacy



Conclusions:

Our findings indicate the need for increased awareness for this vulnerable group of patients having a high risk for drug-drug interactions and adverse health outcomes that might result from multiple chronic medications.

Thank You

Comments/questions/brainstorm

Linkedin connect!