Teaching Course 7

Comorbidity and multiple sclerosis: clinical and research issues

Chairs:  
H. Tremlett (Vancouver, CA)  
R.A. Marrie (Winnipeg, CA)

32 Comorbidity in multiple sclerosis: What do we know and what do we need to know?  
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33 Comorbidity: insights from administrative data  
H. Tremlett (Vancouver, CA)

34 Comorbidity: insights from registries and related databases  
M. Magyari (Copenhagen, DK)
Comorbidity in Multiple Sclerosis: What Do We Know & What Do We Need to Know?

Ruth Ann Marrie, MD, PhD
Professor
University of Manitoba
October 7, 2015

Learning Objectives

• To identify the most common physical and psychiatric comorbidities experienced by persons with MS

• To recognize the potential effect of comorbidity on outcomes

• To understand how comorbidity may influence treatment in MS
What is Comorbidity?

• Comorbidity: “The total burden of illness other than the specific disease of interest”
  – e.g. hypertension in a person with MS

• Complications and secondary conditions are physical and mental disorders that arise directly or indirectly from a primary disease
  – e.g. osteoporosis due to reduced mobility
  – e.g. urinary tract infections secondary to neurogenic bladder
Comorbidity

• Common in the general population
  – In 2005, Canadian Community Health Survey
    • Analysis of 7 high-impact chronic conditions suggested that 33% of Canadians had ≥ 1 chronic health conditions
• Increases with age
• Associated with a range of adverse health outcomes
  ↑ physical disability  ↓ functional status
  ↑ mortality  ↓ quality of life

JAMA 1996;276:1473-1479; Healthcare Quarterly 2008;11:70-76

What is the most common comorbidity in MS?

• Autoimmune thyroid disease
• Depression
• Psoriasis
• Arthritis
• Hypertension
Psychiatric Comorbidity is Common

- Depression
  - 50% lifetime prev. (3X higher than gen pop’n)
  - 12-month prev. 14% (vs. 5.9-7.3% in gen pop’n)
- Anxiety
  - up to 35% lifetime prevalence
  - Generalized anxiety disorder, social phobias
- Other disorders → less studied
  - Bipolar disorder: 0.30%-13% (5% in MB)
  - Psychosis: 0.09-0.8%
- Remains underdiagnosed & undertreated

Most Common Physical Comorbidities in MS

- Focus of early lit.: autoimmune & allergic disease
- Hypertension* 18.6% (13.9-23.2%)
- Hyperlipidemia 10.9% (5.6-16.1%)
- Chronic lung disease 10.0% (0-20.9%)
- Irritable bowel syndrome 12.2%
- Thyroid disease 6.4% (0.19-12.7%)
- Psoriasis 7.7%

*leading causes of disability in gen. pop’n are hypertension, arthritis, back/spine problems, lung disease, and heart disease
Comorbidity is common at diagnosis

- 4 Canadian provinces: 23,382 incident MS cases & 116,638 matched controls
What is the effect of comorbidity on disability at diagnosis?

- Define a virtual inception cohort (enrolled within 2 years of diagnosis)

- Polytomous logistic regression (mild, moderate, severe disability as defined by PDDS)

- Adjust for age of onset, year of onset, sex, SES

Virtual inception cohort

- Participants enrolled ≤2 yrs of dx. (n = 2375)
- Compared to entire study pop’n:
  - More women: 81.9% vs. 75.8%
  - Higher income ($>100,000): 14.2% vs. 11.9%
  - More private health ins.: 90.8% vs. 81.5%

- Disability at diagnosis
  - Mild: 55.5%
  - Moderate: 14.7%
  - Severe: 29.8%
Impact of Comorbidity at Diagnosis on Severity of Disability at Diagnosis


Comorbidity & Disability Progression

• Disability milestones (Cox proportional hazards model)
  – Unilateral assistance to walk (~ EDSS 6 [PDDS])

• Clinical questions:
  – Effect of comorbidity at diagnosis on future disability? → Comorbidity at diagnosis vs. never develop comorbidity (zero time = diagnosis of MS)
  – Effect of comorbidity at any point in disease course? Comorbidity as time-dependent covariate
Increased hazard (risk) of disability with comorbidity at any point in disease course

**Gait**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular: any time</td>
<td>1.54</td>
<td>1.44 - 1.65</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.28</td>
<td>1.11 - 1.49</td>
</tr>
<tr>
<td>Heart disease</td>
<td>0.99</td>
<td>0.85 - 1.15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.25</td>
<td>1.15 - 1.36</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.33</td>
<td>1.23 - 1.44</td>
</tr>
<tr>
<td>Peripheral vasc. disease</td>
<td>1.25</td>
<td>0.99 - 1.59</td>
</tr>
</tbody>
</table>

*Adjusted for sex, year of symptom onset, age of symptom onset, income, health insurance, race, region of residence
Risk persisted when disability at diagnosis considered (virtual inception cohort)
Comorbidity & Disability Progression II

- Kirby et al. → Reviewed >1700 patient records
  - 625 (36.4%) clinically sign. psychiatric symptoms
    - Shorter times to EDSS 3, 4, and 6 (p<0.003).
  - Asthma also assoc with decr. time to EDSS 3
- Dallmeijer et al. → 3 year study of 146 patients with recently diagnosed MS
  - MS + MSK comorbidities: 5 point ↓ in the motor scale of the Functional Independence Measure vs.
  - MS - MSK comorbidities: 2 point ↓


Comorbidity & Disease Progression III

- 422 RRMS patients
  - EDSS, BMI, lipid profile (HDL, LDL, tot. chol, TAGs), MRI (atrophy, lesion number, lesion volume)
  - Worsening EDSS over 2 years assoc with ↑ LDL, TAGs, total cholesterol
  - ↑ HDL assoc. with ↓ likelihood Gd+ lesions
  - ↑ TAGs assoc. with ↑ likelihood Gd+ lesions
- In CIS cohort treated with Avonex (n = 135)
  - Higher LDL and total chol assoc with incr. T2 lesions over 2 years.
Comorbidity increases risk of non-MS related hospitalizations but not MS-related hospitalizations

<table>
<thead>
<tr>
<th>Comorbidity Count</th>
<th>MS popn Non-MS hosp.</th>
<th>MS popn MS hosp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>1.34 (0.94, 1.91)</td>
<td>1.23 (0.72, 2.10)</td>
</tr>
<tr>
<td>2</td>
<td>1.95 (1.42, 2.69)</td>
<td>1.06 (0.59, 1.90)</td>
</tr>
<tr>
<td>3</td>
<td>2.35 (1.71, 3.24)</td>
<td>1.08 (0.51, 2.26)</td>
</tr>
<tr>
<td>≥4</td>
<td>4.29 (3.18, 5.79)</td>
<td>1.08 (0.64, 1.81)</td>
</tr>
</tbody>
</table>

Comorbidity Gen pop’n MS pop’n

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Gen pop’n</th>
<th>MS pop’n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>1.83 (1.68, 1.98)</td>
<td>1.58 (1.36, 1.86)</td>
</tr>
<tr>
<td>Lipid</td>
<td>1.16 (1.08, 1.25)</td>
<td>0.99 (0.86, 1.15)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.65 (1.52, 1.25)</td>
<td>1.49 (1.25, 1.77)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2.30 (2.11, 2.51)</td>
<td>2.01 (1.67, 2.41)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1.23 (1.09, 1.30)</td>
<td>1.27 (1.05, 1.53)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.19 (1.09, 1.30)</td>
<td>0.95 (0.80, 1.14)</td>
</tr>
<tr>
<td>Migraine</td>
<td>1.16 (1.06, 1.27)</td>
<td>0.94 (0.80, 1.11)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.32 (1.21, 1.44)</td>
<td>1.46 (1.24, 1.71)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.19 (1.10, 1.29)</td>
<td>1.17 (0.99, 1.36)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1.42 (1.24, 1.63)</td>
<td>1.37 (1.09, 1.71)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>1.41 (1.31, 1.53)</td>
<td>1.29 (1.11, 1.50)</td>
</tr>
</tbody>
</table>
### Comorbidity & Mortality

<table>
<thead>
<tr>
<th>Comorbidity &amp; Mortality</th>
<th>Matched pop’n</th>
<th>MS pop’n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.66</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>(1.53, 1.80)</td>
<td>(1.25, 1.73)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.11</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>(1.03, 1.20)</td>
<td>(0.80, 1.05)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.87</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>(1.73, 2.03)</td>
<td>(1.28, 1.75)</td>
</tr>
<tr>
<td>Depression</td>
<td>1.52</td>
<td>1.62</td>
</tr>
<tr>
<td></td>
<td>(1.37, 1.67)</td>
<td>(1.39, 1.88)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.79</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>(0.72, 0.87)</td>
<td>(0.61, 0.84)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1.56</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>(1.31, 1.86)</td>
<td>(0.83, 1.47)</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>0.83</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>(0.71, 0.97)</td>
<td>(0.77, 1.33)</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.71</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>(0.61, 0.82)</td>
<td>(0.48, 0.76)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1.25</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>(0.40, 3.90)</td>
<td>(0.27, 4.31)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>1.73</td>
<td>1.21</td>
</tr>
<tr>
<td></td>
<td>(1.60, 1.87)</td>
<td>(1.03, 1.42)</td>
</tr>
</tbody>
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**Comorbidity negatively impacts HRQOL**

- 949 adults: definite MS, from 4 provincial clinics
- High frequency comorbidity
  - One (43.4%), two (29.8%), three (14.8%), ≥four (4.0%)
- HRQOL ↓ with ↑ no. comorbidities
How might comorbidity affect treatment?

• Knowledge is limited

• Adherence to treatment
  – Reduced in depressed persons with MS but improves with treatment of depression
  – Multiple conditions & medications may also act as barrier to adherence

• Polypharmacy
  – Interactions – incr. risk adverse effects, ?affect effectiveness of treatment

Comorbidity & Disease-modifying Therapy

• Many trials exclude patients with comorbidities
  – Lack knowledge of efficacy, safety, tolerability of treatment in these patients
  – How does this affect decision-making? (to be discussed by Dr. Tremlett)

• Newer therapies may incr. risk comorbidity
  – e.g. alemtuzumab – autoimmune disease
  – e.g. fingolimod – lung disease, macular edema
  – What is the net impact on HRQOL?
Comorbidity & Fatigue Management

• Secondary analysis of longitudinal data from clinical trial of telephone intervention for fatigue
• 181 community dwelling adults with MS
• Self-reported diabetes, arthritis, heart disease, hypertension, respiratory disease, stroke, thyroid disease
• 112/181 (61.9%) had ≥1 condition
  – Hypertension 27%, arthritis 26%
• Comorbid heart or respiratory disease = more fatigue at baseline and over time

Comorbid diabetes slows improvement

Conclusion

• Comorbidity is common

• Associated with ↑ disability at diagnosis, ↑ risk of disability progression, ↓ quality of life, ↑ hospitalizations & mortality

• Should be considered when selecting treatment regimens and may affect outcomes
  – Many gaps in knowledge regarding comorbidity and management of MS which require further research

• Requires a more holistic approach to care

Acknowledgements

• Lindsay Berrigan
• Virender Bhan
• Anne-Marie Beuno
• Leanne Bresma
• Denise Campagnolo
• Gary Cutter
• John Fisk
• Elaine Kingwell
• Stella Leung
• Yue Liu
• Scott Patten
• Joanne Profetto-McGrath

• Karen Stadnyk
• Tuula Tyry
• Helen Tremlett
• Stacy Trochuk
• Karen Turpin
• Tim Vollmer
• Yan Wang
• Sharon Warren
• Tina Wolfson
• Nancy Yu
• Bin Zhu
• Feng Zhu
Acknowledgements

- NIH
- CIHR
- Research Manitoba
- MS Society of Canada
- Public Health Agency of Canada
- Rx & D Health Research Foundation
Comorbidity and MS: insights from health administrative data

Helen Tremlett, PhD
Canada Research Chair in Neuroepidemiology and MS
Professor, Faculty of Medicine (Neurology)
University of British Columbia, Vancouver, Canada
ECTRIMS 2015

Disclosures
Received research support from:
UK MS Trust
National Multiple Sclerosis Society
Canadian Institutes of Health Research
Multiple Sclerosis Society of Canada (Don Paty Career Development)
Michael Smith Foundation for Health Research Scholar award
Canada Research Chair Program

Speaker honoraria and/or travel expenses to attend conferences:
Consortium of MS Centres (2011, 2013)
Bayer Pharmaceutical (speaker, 2010, honoraria declined)
Teva Pharmaceuticals (speaker 2011), Novartis Canada (2012), Biogen
(speaker, 2014, honoraria declined)
Chesapeake Education Program, US Veterans Affairs (2012, honorarium declined)

All speaker honoraria are donated to an MS charity or as an unrestricted grant for use by research group.
Outline

Gain insight into health administrative data and its application to MS and study of comorbidity

• How does MS impact life expectancy?
• What’s the cancer risk in MS?
• Does drug exposure (beta-interferon) alter cancer risk in MS?
• Do comorbidities alter access to drug treatments for MS?

Example: health administrative data linkage in Canada e.g. British Columbia

Prescription data → Hospital Separations Data → Physician claims → Vital statistics → Registration file → Census Geo Data

Drug exposure → MS, comorbidity, morbidity, health service utilization → Birth & death information → Residency & demographic → Income Data [SES]

Study Cohort: individuals with MS and general population controls
Challenges of health administrative data

Universal: *know your data*
- how was it collected?
- for what purpose?
- is your (research) Q appropriate for the available data?
- what was not collected (e.g. salaried physicians vs. fee-for-service)
- one ICD code ≠ disease
- validation, validation, validation

Oh.. I think that data arrived

Major benefits of health administrative data*

Population-based
No / minimal selection bias
No / minimal recall bias
General population controls available
‘Diseased’ controls available
Already coded information
Highly cost-effective
Valid data source
Control for confounders

*in the universal healthcare system!
Median absolute survival for men and women with MS in British Columbia

From Birth

From MS onset

**RESEARCH PAPER**

**Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada**

Elaine Kingwell,1 Chris Bajdik,2 Norm Phillips,2 Feng Zhu,1 Joel Oger,1 Stanley Hashimoto3 and Helen Tremlett1

**ABSTRACT**

To examine mortality and factors associated with survival in a prospective database (ICMS) of 115 patients newly diagnosed with multiple sclerosis (MS) in British Columbia (BC) in the period 1980–2000. Median survival from birth was 74.3 years (95% CI: 73.1–75.4) and from MS onset was 41.3 years (95% CI: 38.6–44.1) for men. Among women, median survival from birth was 78.5 years (95% CI: 77.5–79.7) and from MS onset was 49.8 years (95% CI: 47.9–51.8). The median survival was significantly shorter for men than for women (p < 0.001). The survival rates increased over time, and similar improvements were observed in the general population. The improved survival over time has important implications for understanding the natural history of MS and for patient care and public health planning.

**METHODS**

The cohort and data sources: The BC MS database was established in 1980 and includes 115 patients newly diagnosed with MS in the province of BC (British Columbia). Vital statistics and drug exposure data were collected until the end of 2000. Clinical information including data on demographics, illness and disease course was prospectively collected by trained neurologists during visits and compiled into the database. The cohort included 115 patients with a definite diagnosis of MS based on the revised diagnostic criteria. The database contained information on drug exposure, age at onset, and time period of data collection.

**RESULTS**

The median survival was significantly shorter for men (74.3 years, 95% CI: 73.1–75.4) than for women (78.5 years, 95% CI: 77.5–79.7). The survival rates increased over time, and similar improvements were observed in the general population. The improved survival over time has important implications for understanding the natural history of MS and for patient care and public health planning.

**DISCUSSION**

The improved survival over time has important implications for understanding the natural history of MS and for patient care and public health planning. The results of this study provide evidence of improved survival rates in patients with MS over time, which may be attributed to improvements in medical care and increased awareness of the disease. The results also highlight the need for continued research into the mechanisms underlying the improved survival rates, as well as the development of targeted interventions to optimize patient care and improve outcomes.

**ACKNOWLEDGEMENTS**

The authors acknowledge the contributions of all individuals involved in the data collection and management. The study was supported by grant number GM109938 from the National Institutes of Health (NIH), and the Canadian Institute of Health Research (CIHR). The authors thank the patients and their families who participated in the study, as well as the healthcare professionals who provided care.

**REFERENCES**


The overall cancer risk was lower than expected in the British Columbia MS cohort (compared to the age, sex & calendar year matched general population)

Adjusted SIRs (95%CI)

- Increased risk
- Reduced risk

Adapted from: Dr Elaine Kingwell, Brain 2012

Multiple sclerosis and risk of cancer: a meta-analysis

Adam E Handel and Sreeram V Ramagopalan

J Neurol Neurosurg Psychiatry 2010 81: 1413-1414 originally published online August 19, 2010

doi: 10.1136/jnnp.2009.195776

Figure 1  Forest plot of the risk of cancer in multiple sclerosis. This forest plot shows the ORs and 95% CIs for the multiple sclerosis cohort relative to the control cohort in each individual study and the pooled results for all cancers. The model used was generic inverse variance (IV) and random effects.
Goal:
Examine effects of comorbidity on initiation of injectable disease-modifying therapies (DMTs)

IFNB exposure not significantly associated with cancer risk: OR: 1.28 (95%CI: 0.87-1.88)
Trend for breast cancer risk: OR: 1.77 (95%CI: 0.92 - 3.42)
But no evidence of a dose-response effect
Comorbidity was associated with a lower likelihood of DMT initiation

**General effect:**
total number of comorbidities ➔ reduced likelihood

- Diabetes
- Chronic lung diseases
- Bipolar disorder
- Depression
- Anxiety
- Epilepsy
- Hyper-tension
- Hyper-lipidemia
- Ischemic heart disease
- Multiple Sclerosis N= 10,698

28% lower hazard (likelihood) (adj.HR 0.72; 95%CI 0.59 – 0.87)

22% lower hazard (likelihood) (adj.HR 0.78; 95%CI 0.69-0.87)

**Specific effect:**
Comorbidity was associated with a lower likelihood of DMT initiation

**Summary**

Health administrative data can be a powerful tool to investigate comorbidities in population-based MS studies

- **How does MS impact life expectancy?**
  
  *More individuals with MS reaching ‘older’ age than ever before
  Underscores need to understand comorbidities in MS*

- **What’s the cancer risk in MS?**
  
  *Cancer comorbidity lower than expected*

- **Does drug exposure (beta-interferon) alter cancer risk in MS?**
  
  *No strong evidence that IFNB exposure alters risk of cancer comorbidity*

- **Do comorbidities alter access to drug treatments for MS?**

  *Yes. More comorbidities ➔ lower likelihood of DMT initiation
  Anxiety and ischemic heart disease ➔ 22% to 28% reduced likelihood of DMT initiation*
Comorbidity

Insights from Registries and related databases

Melinda Magyari
Danish Multiple Sclerosis Center
Danish Multiple Sclerosis Registry
Rigshospitalet, Copenhagen, Denmark

Disclosures

Melinda Magyari has served on scientific advisory board for Biogen Idec and Teva; has received honoraria for lecturing from Biogen Idec, Merck Serono, Novartis, Teva; has received support for congress participation from Biogen Idec, Teva, Genzyme and Novartis.
Comorbidity studies, why?

Many different diseases and many different hypotheses
Increased or decreased occurrence of certain other diseases in MS patients due to
  • Common risk factors
  • Independent risk factors
  • Secondary or symptomatic association, e.g.
    • increased risk of cardiovascular diseases or infections in immobile MS patients
    • less exposure to certain disease-causing factors

Comorbidities may influence the course of MS and survival

Medical and social consequences of comorbidity in MS patients

Observational studies

• Cohort studies
Identification of a group of individuals about whom certain exposure information is collected. The group is then followed forward in time to ascertain the occurrence of the diseases of interest

• Case-control studies
Compare cases of the disease of interest with individuals without disease of interest (controls) with respect to their exposure
Potential data sources

**Disease registry** is a collection of standardized information about a group of patients who share a condition

**Clinical database** is a list of well defined systematically collected variables related to clinical observations, diagnostic procedures, treatments, outcomes, covering a reasonably well-defined population

**Clinical dataset** is a collection of data for a special project and only includes patients who meet specific inclusion criteria

**Administrative data** are collected for health system management and reimbursement

**Combined data** by linkage

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Characteristics of registers and databases

**Registers**
- Population based
- Onset-defined cohort
- Multiple sources of notification
- Well defined inclusion and exclusion criteria
- High completeness
- High diagnostic validity
- Long-time follow-up
- Continuous maintenance
- Permanent

**Databases**
- Clinic/multicentre based
- Clinical and paraclinical data must be *detailed* *standardized*
- Rating scales
- Follow-up
- Treatment
- Quality of life measures
- Limited in time
Key considerations for ensuring quality data

- Appropriate data source addressing the study questions
- Comprehensive knowledge about the purpose and method of data collection /secondary data
- Quality of a disease registry "Garbage In, Garbage Out"
- Time period covered by the data source
- Linkage with other registries and databases

Example 1

Autoimmune diseases in patients with multiple sclerosis and their first-degree relatives: a nationwide cohort study in Denmark

NM Nielsen¹, M Frisch¹, K Rostgaard¹, T Wohlfahrt¹, H Højgrimm¹, N Koch-Henriksen²,³, N Melbye¹ and T Westergaard¹

Multiple Sclerosis 2008; 14: 823–829

Population based cohort study

- Linkage of MS registry, Danish National Patient Registry by ID number
  10 596 persons with MS
- RRs for 42 autoimmune diseases calculated from age, gender, and period specific national incidence rates from 1977 to 2004
- MS patients were not at any unusual risk of autoimmune diseases overall, but increased risk of IBD, pemphigoid, lower risk of rheumatoid arthritis, temporal arteritis
Issues Example 1

Data sources
• Limited outpatient contacts
• No data from GPs and private specialists
• Findings biased toward more severe disease

Validity of diagnoses
• Primary or secondary diagnosis, reported at least twice in the same patient
• Coding bias?
• Shift from ICD 8 to ICD 10; not always interchangeable

Comorbidity studies requires a combination of hospital, outpatient and GP claims to optimize sensitivity and specificity

Example 2

Gender and autoimmune comorbidity in multiple sclerosis

Melinda Magyari1,2,3, Nils Koch-Henriksen2,4, Claudia C Pfieger5, and Per Soelberg Sorensen1,3

Case-control study
• Population based onset defined cohort, 1403 MS cases 35 045 matched controls
• Linkage of MS registry, Danish National Patient Registry, and prescription claims for some diagnoses
• Autoimmune comorbidity is rare in MS, but more common in male MS patients, especially for DM, IBD
### Issues Example 2

**Data sources**
- Underpowered sample size
- Limited outpatient contacts and no data from GPs
- Findings biased toward more severe disease
- Follow up time max. 10 years after onset

**Validity of diagnoses**
- Insufficient validation for some diagnoses (single hospital admission - diagnoses for most of the disorders), sensitivity vs. specificity
- Coding bias?

**Immortal time bias?**

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**Example 3**

*Neuroepidemiology*

**Original Paper**

*Neuroepidemiology* 2010;35:267–274

**Risk of Arterial Cardiovascular Diseases in Patients with Multiple Sclerosis: A Population-Based Cohort Study**

Christian Fynbo Christansen, Steffen Christensen, Dóra Körömdiné Farkas, Montserrat Miret, Henrik Toft Sørensen, Lars Pedersen

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**Population based cohort study**

- Danish National Patient Registry, independently collected data on MS and CVD 1977-2006, 13,963 MS cases, 66,407 matched controls

- MS was associated with increased risk of myocardial infarction, stroke and heart failure within the first year after the MS diagnosis

- During long-term follow-up, only the increased risk of stroke and heart failure persisted
**Issues Example 3**

**Data sources**
- Low completeness (86.9%) of MS diagnosis in DNPR compared with the Danish MS registry
- Lack of information of lifestyle factors and use of cardiovascular drugs
- Follow-up time starts from MS diagnosis, not from MS onset

**Validity of diagnoses**
- First time hospital MS and CVD diagnosis. The validity of MS diagnosis in DNPR reported to be 96%.  CVD ?

**Berkson bias ?**
- If hospital based cases/controls have different exposures than population based cases/controls, OR could be over or underestimated

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**Example 4**

*Autoimmune disease in families with multiple sclerosis: a population-based study*

- Canadian Collaborative Study Group, CCPGMS cohort
- 5031 MS patients, 30 259 of their first-degree relatives, and 2707 spousal controls
- No increased risk of any of the 10 investigated autoimmune diseases
Issues Example 4

Data sources
• Self reported diseases
• Spousal controls, overmatching?

Validity of diagnoses
• Gender differences in reporting

Surveys as data source?

Studies based on questionnaires should be interpreted with caution because
• only surviving patients can participate, that may result in underestimation of comorbidity
• willingness to participate may be different in cases and controls and may be associated with the presence of (co)morbidities
• depends on the memory of the subjects

Register linkage studies are free of these weaknesses, but depend on completeness and validity of the registered diagnoses.
NARCOMS registry

- 8,875 participants
- Self-reported smoking status, diagnoses of autoimmune diseases (AD) in 2006
- A range of socioeconomic variables
- Smoking was associated with an increased risk of reporting AD after MS onset

Issues

Data sources
- Response rate 56% (54.5% smokers; 45.5% non-smokers)
- Self-reported diagnoses

Advantage
- Information about life style factors
Observational studies — Selection bias?

Concern is that subjects have different probability of being selected according to exposures or outcomes of interest, creating a biased measure of association (i.e. odds ratio, relative risk).

Selection bias

Case ascertainment (surveillance) bias occurs if the presence of one chronic condition may increase health care utilisation, leading to enhanced opportunities for diagnosis of second conditions:

- More complete diagnosis of other diseases in MS patients because of more frequent contact with doctors or hospitals
- Conversely, MS "shadows" other diseases, either because symptoms mistakenly perceived as being caused by MS or the enthusiasm to diagnose other diseases at the elderly patient is limited

Referral bias (admission rate/Berkson) refers to a situation where admission with a disease changes the likelihood of being registered with another previously undiagnosed disease.
**Selection bias**

**Diagnostic bias** occurs when the diagnostic approach is related to knowledge of prior exposure to a putative cause.

**Immortal time bias** leads to selective misclassification of unexposed "person time" as exposed person time (early death due to MS or comorbidity).

**Non-response bias** occurs due to the differences in response rates of participants.

**Loss to follow-up** is the differences in completeness of follow-up between comparison groups.

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**Comorbidity studies based on registries/databases**

- For most registries applies that their value increases with the time they have existed.
- Affordable and quickly tests new hypotheses without necessarily having to make new data collections.
- No response rate problem, partly because registries can "preserve the memory" - no recall bias.
- It enables highly reliable data and makes it possible to establish data sets "retrospectively".
- Have the power to answer complex questions.
- Allows study of rare disorders.
Generalisability

• Any inferences or extrapolations of the findings to other populations should consider differences in ethnic composition, national differences in the prevalence of the diseases and socioeconomic status

• Differences in diagnostic methods and treatment patterns

• Differences between the health care systems

• Differences in availability, cost, prescribing guidelines

• The patterns of medical services utilization change over time; therefore data may not be comparable over such long periods

Challenges

• To optimise the use of data available from established registers/databases

• How data from the electronic patient record systems may be used as source for a clinical database

• Inclusion of patient reported information

• Establishing a research network to increase the size of a study, but only if the populations are comparable

• Ethics, Data Ownership, and Privacy questions

• Registers must face new and strong regulations to ensure data security and protection. This requires in addition to scientific and technical insight, that researchers also have insight into public legal governance
Thank you for listening
Reference List for Teaching Course


