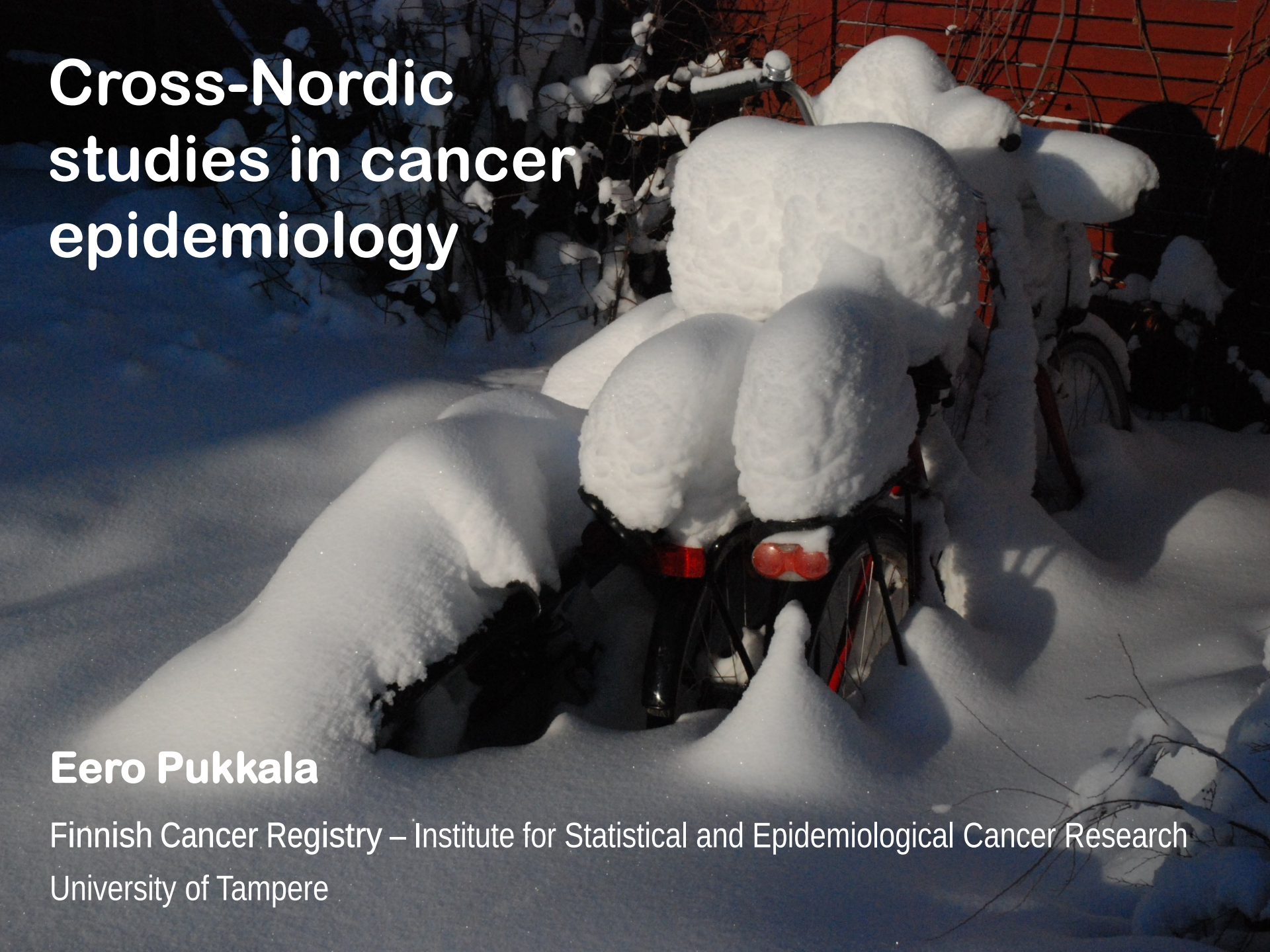
Cross-Nordic studies in cancer epidemiology

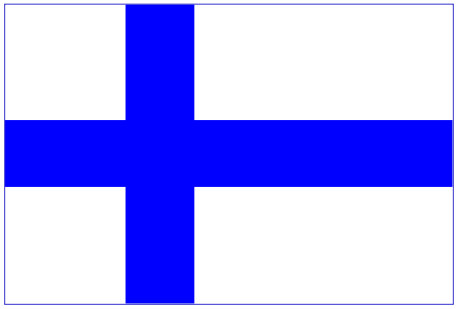


Eero Pukkala

Finnish Cancer Registry – Institute for Statistical and Epidemiological Cancer Research

University of Tampere

Finland



- Northernmost population of the world (5.6 million)
- 0.6 million lakes
  - 0.3 lakes per family
- 1.3 saunas per family
- Best schools
- Least corrupted
- Happiest people
- Cleanest air (WHO)
- Makes most good to other nations
- Paradise of epidemiology

Cross-Nordic studies in cancer epidemiology

- Examples of Nordic research types
- What should be checked and understood?
- Brain storming exercises

- Tomorrow: **Utilization of multigenerational data**

Outline

- How to **perform** the analyses

Outline

- What should be done **before starting** the analysis
  - Relevant a priori research question => study desing
  - Understand the data you are going to use
  - Are you really ustilising all relevant data sources?

- How to **perform** the analyses

Outline

- What should be done **before starting** the analysis
  - Relevant a priori research question => study desing
  - Understand the data you are going to use
  - Are you really ustilising all relevant data sources?

- How to **perform** the analyses

- Correct **interpretation** of the results?


Nordic Summer School in Cancer Epidemiology
(–30°C)
NEXT COURSE 2019-20: APPLY SOON
4 2 2006


TALLINN • TARTU
Le Coq
PREMIUM
ÕLUT · BIER
4,5% vol

Eero Pukkala:

Top cited research 12 Sep 2018

1. Environmental and Heritable Factors in the Causation of Cancer — Analyses of Cohorts of Twins from Sweden, Denmark, and Finland. Aug 2000 · New England Journal of Medicine. Paul Lichtenstein & al (2883 citations)
3. Human Papillomavirus Infection as a Risk Factor for Squamous-Cell Carcinoma of the Head and Neck. May 2001 · New England Journal of Medicine. Jon Mork & al (723 citations)

716. Nordic Cancer Registries – an overview of their procedures and data comparability. Feb 2018 · Acta Oncologica. Eero Pukkala & al (55 citations)

FIMM
Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

Genetic susceptibility to cancer and lifestyle risk factors in the elderly

Danish Cancer Society
November 6, 2016

Jaakko Kaprio, MD, PhD

Director, FIMM

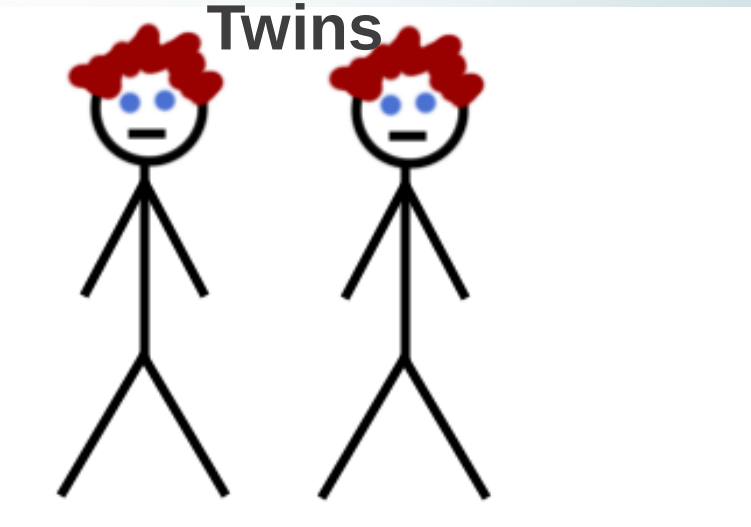
Consulted for Pfizer on nicotine dependence in 2012-2014

Familial aggregation of cancer

- Many cancers are known to run in families and family history is a risk factor for such cancers
- Family history may reflect inheritance of ‘cancer genes’ or familial aggregation of risk factors/exposures (or both).
  - For example exposure to radon at home
  - Dietary, alcohol use or smoking patterns learnt in childhood
- Twin studies can be used to distinguish between genetic factors and environmental exposures and experiences shared by family members.
- So far, twin studies of cancer risk have rarely examined differences in familial and genetic risk by age (mostly due to lack of power)

Why study twins?

Monozygotic (MZ) Twins



Share 100% of genes

Dizygotic (DZ) Twins

Share ~50% of segregating genes

Familial aggregation

- If concordance MZ >> DZ: Genetic effects
- If concordance MZ = DZ: Shared environment
- If aggregation in MZ and DZ twins is low: Nonshared environment

The NorTwinCan Team

Finnish Twin Cohort


Jaakko Kaprio


Eero Pukkala


Tellervo Korhonen


Kauko Heikkilä

Danish Twin Registry


Axel Skytthe


Jacob Hjelmborg

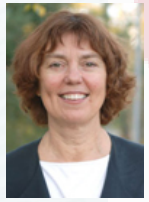

Thomas Scheike


Niels Holms

Swedish Twin Registry


Kamila Czene


Mikael Hartman


Juni Palmgren


Nancy Pedersen

Norwegian Twin Registry


Jennifer Harris


Ingunn Brandt


Thomas Nilsen

Harvard School of Public Health


Lorelei Mucci


Hans-Olov Adami


Kathryn Penney


David Havelick


Peter Kraft

Funding from Ellison Foundation, US and Nordic Cancer Union

Estimation of twin concordance and heritability in same-sex pairs

Table 1. Characteristics of the NorTwinCan Cohort of 203 691 Individual Twins With Follow-up for Cancer Incidence

	Denmark	Finland	Norway	Sweden	Total
Birth cohort date range	1870-2004	1875-1957	1915-1979	1886-2000	
No. of individual twins	68 320	24 661	23 683	87 027	203 691
Individual twins, No. (%)					
Same-sex dizygotic	43 534 (64)	16 949 (69)	12 993 (55)	49 906 (57)	123 382 (61)
Monozygotic	24 786 (36)	7712 (31)	10 690 (45)	37 121 (43)	80 309 (39)
Female	33 330 (49)	12 410 (50)	12 749 (54)	45 762 (53)	104 251 (51)
Follow-up					
First date	January 1943	Febuary 1974	January 1964	April 1961	
End date	December 2009	December 2010	December 2008	December 2009	
Median (IQR), y	41.6 (26.8-41.8)	34.7 (29.4-34.7)	27.9 (16.1-28.5)	25 (5.0-37.0)	32.2 (15.5-37.0)
Age at start, median (IQR), y	12.3 (0-25.7)	32.1 (24.4-45.8)	29.8 (23.4-41.2)	32.1 (21.4-42.4)	26.4 (14.9-38.9)
No. of incident cancers	8904	4049	2805	11 398	27 156

Abbreviations: IQR, interquartile range; NorTwinCan, Nordic Twin Study of Cancer.

Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, Graff RE, Holst K, Möller S, Unger RH, McIntosh C, Nuttall E, Brandt I, Penney KL, Hartman M, Kraft P, Parmigiani G, Christensen K, Koskenvuo M, Holm NV, Heikkilä K, Pukkala E, Skytthe A, Adami HO, Kaprio J**.** JAMA 2016

Nordic Twin Registers as a basis for studies on cancer causes and control

-

400,000 twins, 13 million person-years and 40,000 prospective cancers

Eero Pukkala
Finnish Cancer Registry

NorTwinCan Project

Starting point

- **Numerous published papers based on Twin Register cohorts**
- **Standard description of data in the manuscript**
  - *”Twin Registers covered all twins during years X-Y from population in country Z”*
- **Standard questions by the reviewers:**
  - *How population represenative are these subjects?*
  - *Selection?*
- **Needed: reference article that describes the cohorts and gives answers to above questions**

Acta Oncologica, 2007; 46: 286–307

informa
healthcare

ORIGINAL ARTICLE

Nordic biological specimen banks as basis for studies of cancer causes and control – more than 2 million sample donors, 25 million person years and 100 000 prospective cancers

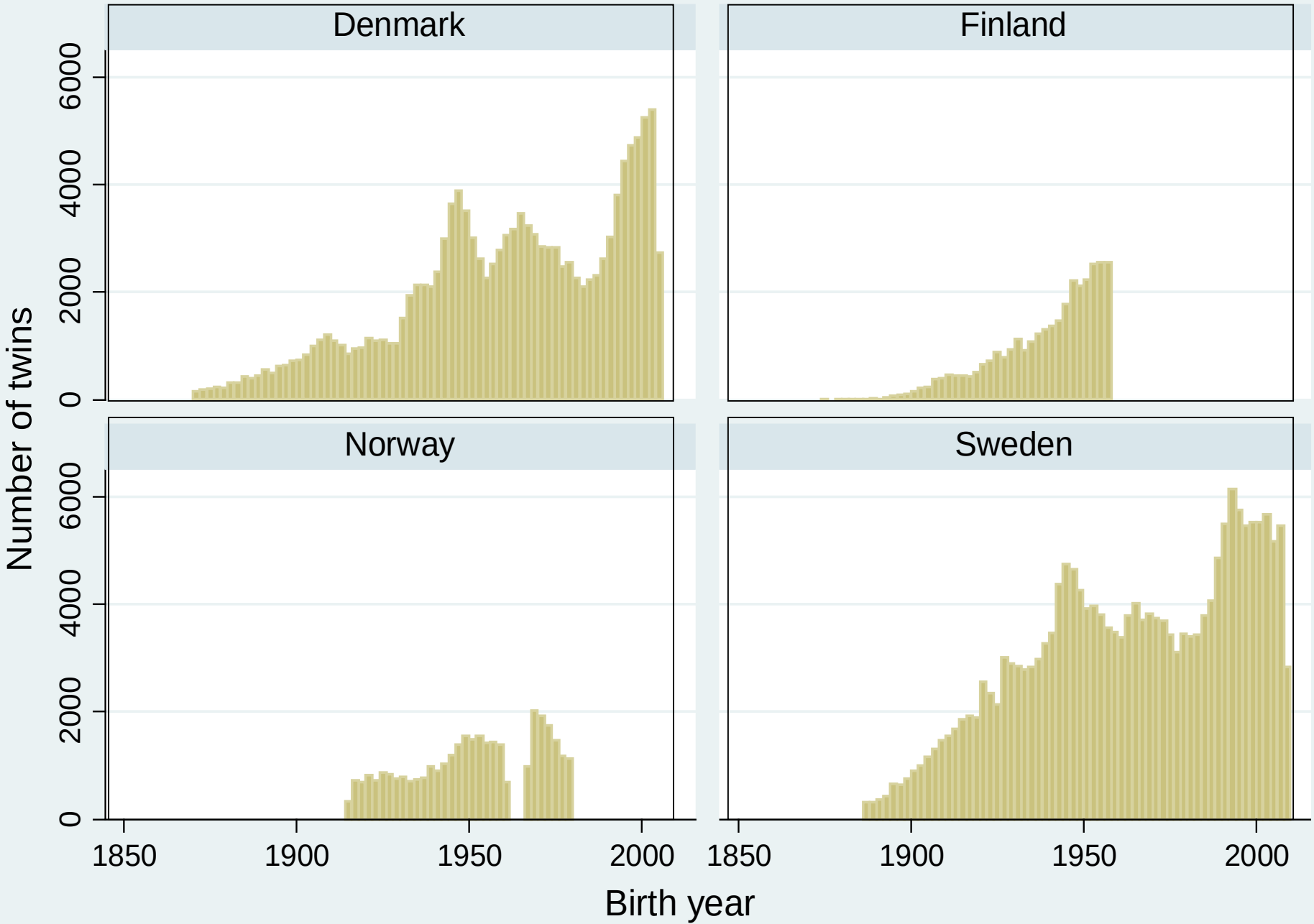
EERO PUKKALA[1,2], AAGE ANDERSEN[3], GÖRAN BERGLUND[4], OSS[3],
VILMUNDUR GUDNASON[5], GÖRAN
PEKKA JOUSILA NEN[1],
PER LENNER[10],
HELGA ÖGMUN
LAUFEY TRYGG
ANDERS WIDELI

[1]*Finnish Cancer Registry,* Public *Health, University of Tam* *Oslo, Norway,* [4]*Malmö Di* *Sweden,* [5]*Icelandic Heart Association, Kópavogur, Iceland,* [6]*Department of P* *Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden,* [7]*Institute of Clinical Biochemistry, Rikshospitalet University Hospital, Oslo, Norway,* [8]*National Public Health Institute, Helsinki and Oulu, Finland,* [9]*Social Insurance Institution, Helsinki and Turku, Finland,* [10]*Cancer Registry of Northern Sweden and Department of Radiation Sciences, Umeå University Hospital, Umeå, Sweden,* [11]*Department of Medical*

Skytthe, A., Harris, J.R., Czene, C., Mucci, L.A., Adami, Christensen, K., Hjelmborg, J., Holm, N.V., Nilsen, T., Kaprio, J., Pukkala, E.: **Cancer incidence and mortality in 260,000 Nordic twins with 30,000 prospective cancers.** Submitted to Twin Res. Hum. Genet. (November 2018).

Database Quality

Bring Quality Assurance methods of other types of best cohort studies to NorTwinCan network

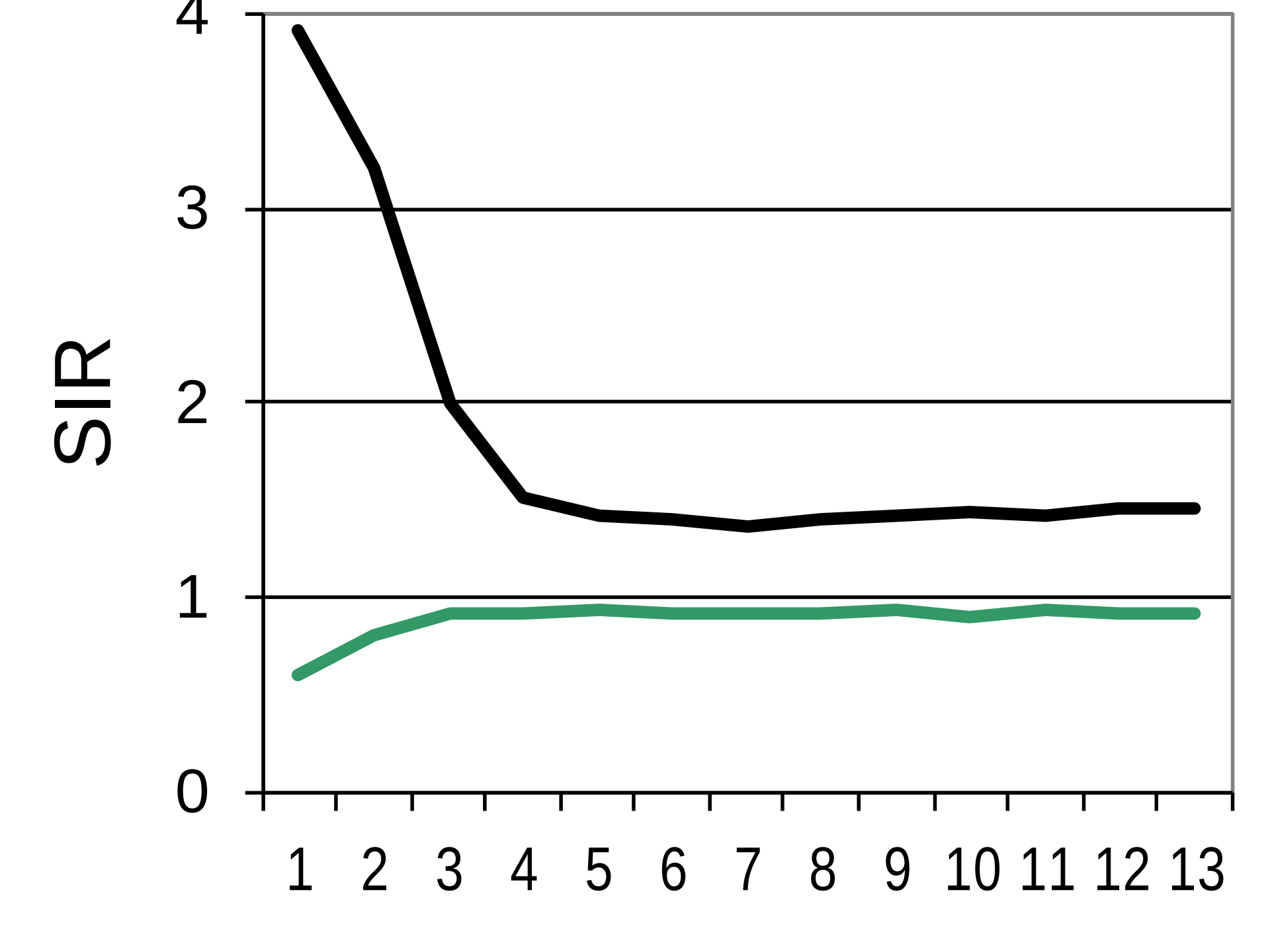

Denmark
Finland
Norway
Sweden
Number of twins
0
2000
4000
6000
1850
1900
1950
2000
Birth year

Estimated SIRs and 95% confidence intervals: all sites, males TABULATION BEFORE QA

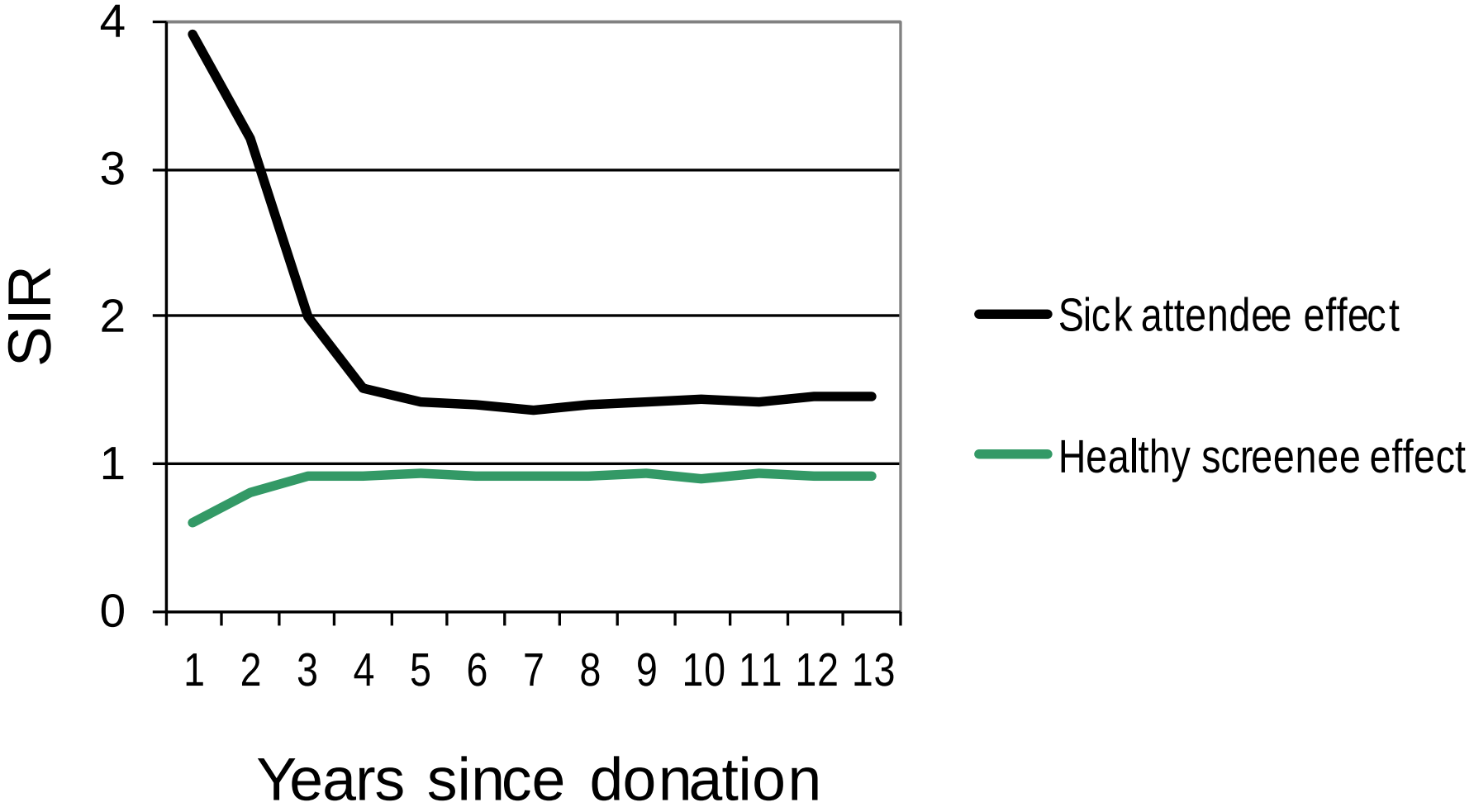
Country	zyg	O	E	SIR	Lower	Upper
Denmark	MZ	1273	1425.64	**0.8929**	**0.8452**	**0.9434**
Denmark	DZ	2576	2722.5	0.9462	0.9103	0.9834
Denmark	UZ	382	420.6	0.9082	0.8216	1.004
Denmark	OS	1327	1425.76	0.9307	0.882	0.9822
Finland	MZ	630	594.59	1.0596	0.98	1.1456
Finland	DZ	1351	1376.96	0.9811	0.9302	1.0349
Finland	UZ	350	400.41	**0.8741**	**0.7872**	**0.9707**
Norway	MZ	673	747.18	0.9007	0.8352	0.9714
Norway	DZ	1005	1212.15	**0.8291**	**0.7794**	**0.882**
Norway	OS	19	18.51	1.0266	0.6548	1.6095
Sweden	MZ	1964	2009.38	0.9774	0.9351	1.0216
Sweden	DZ	3199	3414.99	0.9368	0.9048	0.9698
Sweden	UZ	564	577.54	0.9765	0.8992	1.0606
Sweden	OS	17487	18835.42	**0.8734**	**0.8374**	**0.9109**

Reasons for low SIRs

- The cohort members **really** have lower cancer incidence than the reference population
  - Reason for this should be understood
- Selection bias related to the cohort collection
  - Temporal or constant?


SIR
4
3
2
1
0
1 2 3 4 5 6 7 8 9 10 11 12 13

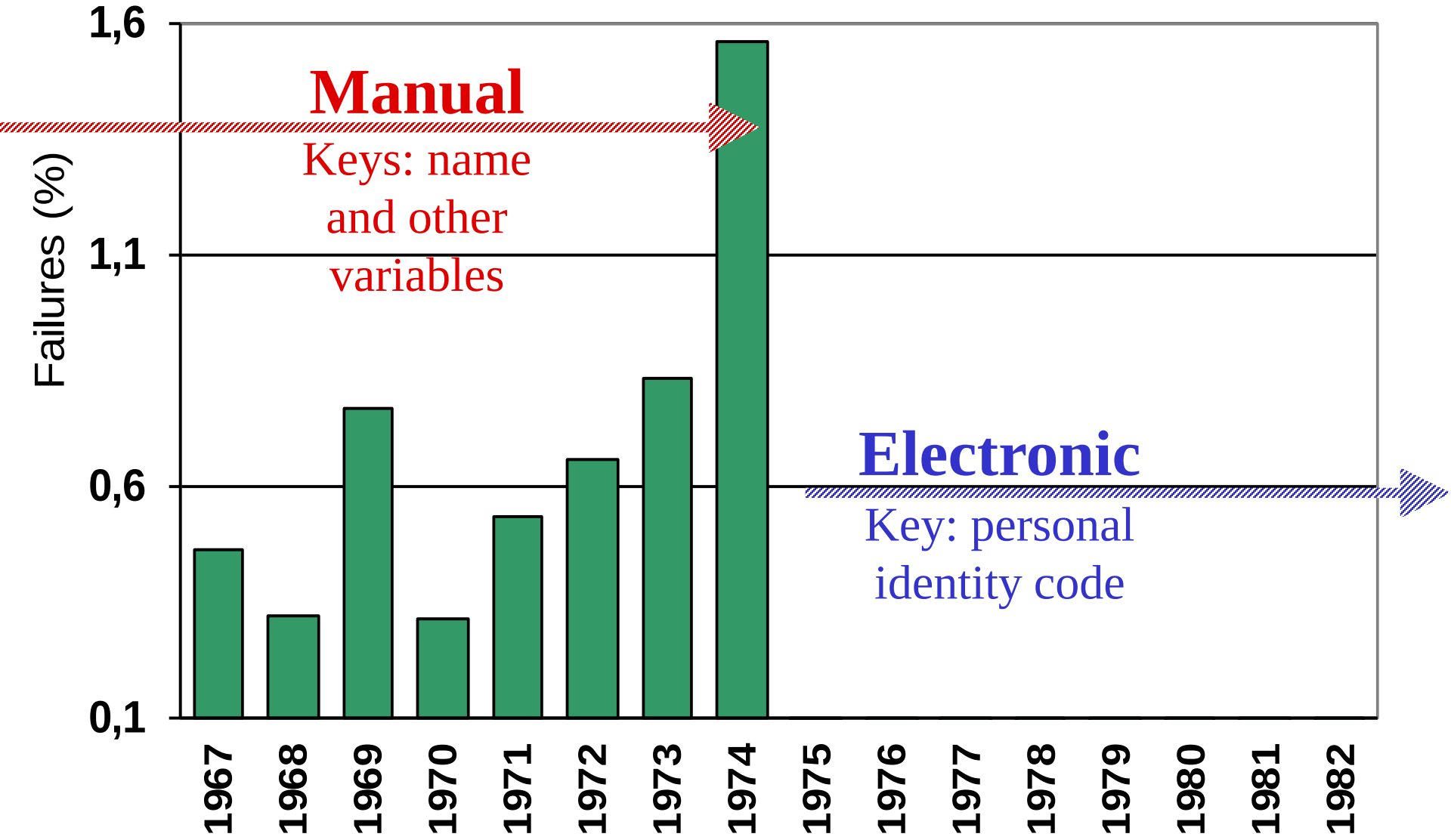
Biases related to the indication of serum donation

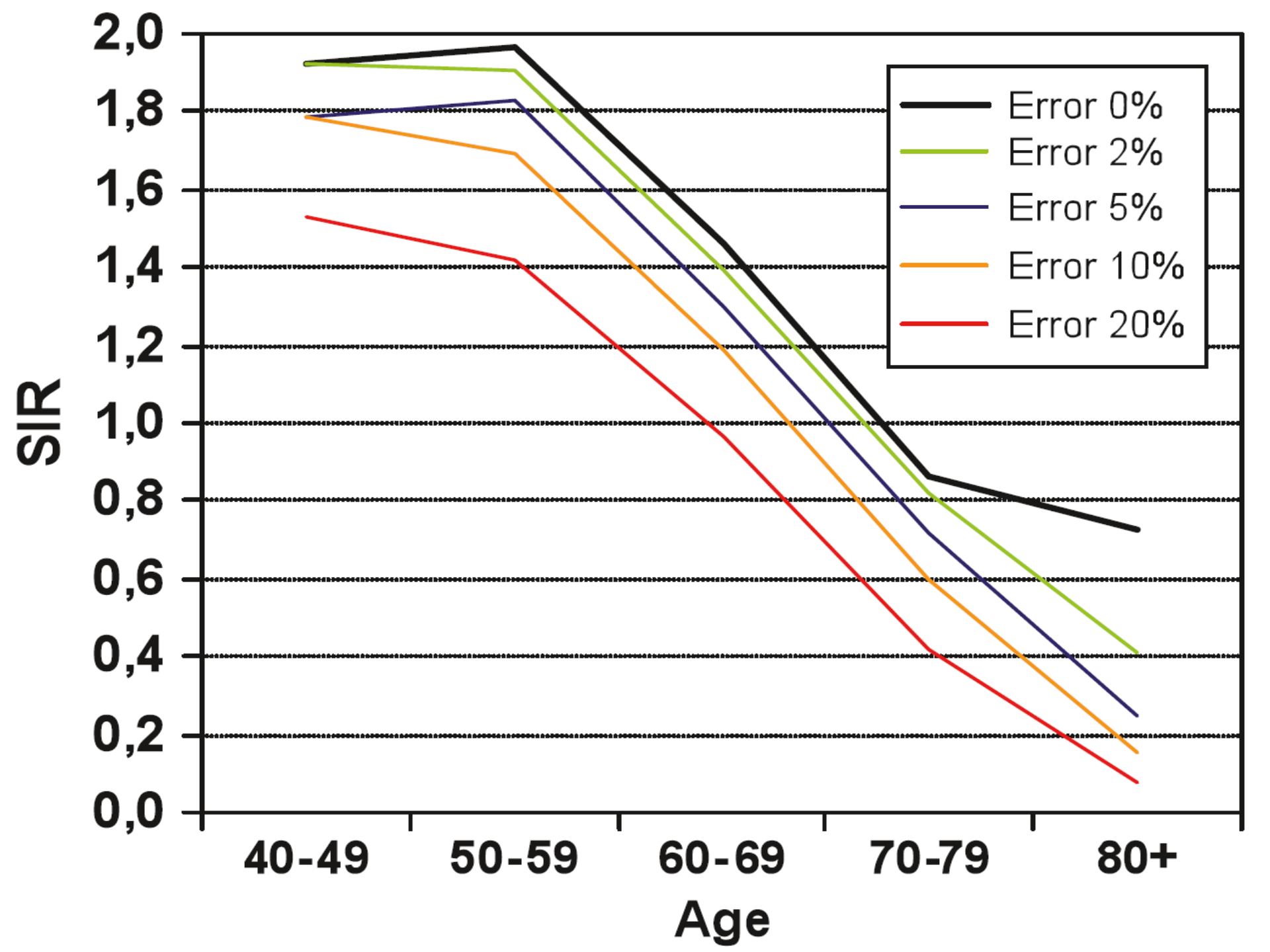


Reasons for low SIRs

- Technical: study cohorts (especially collected long time ago) include cumulated problems that lead to too low cancer risk estimates
  - Need for systematic updates; e.g. those who are not known to have died/emigrated should be identified alive in Population Register
  - Linkage key incomplete (pre-PID period?)

Failures in record linkage between Finnish Cancer Registry and death certificate data




2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
SIR
Error 0%
Error 2%
Error 5%
Error 10%
Error 20%
40-49
50-59
60-69
70-79
80+
Age

Effect of errors in linkage key:

Cancer risk among **asbestos mine workers,**

age category 80+ (old cohort, long follow-up)

Error %	Obs	Exp	SIR	95% CI
0	100	80	1.25	1.02-1.51

Effect of errors in linkage key:

Cancer risk among **asbestos mine workers,**

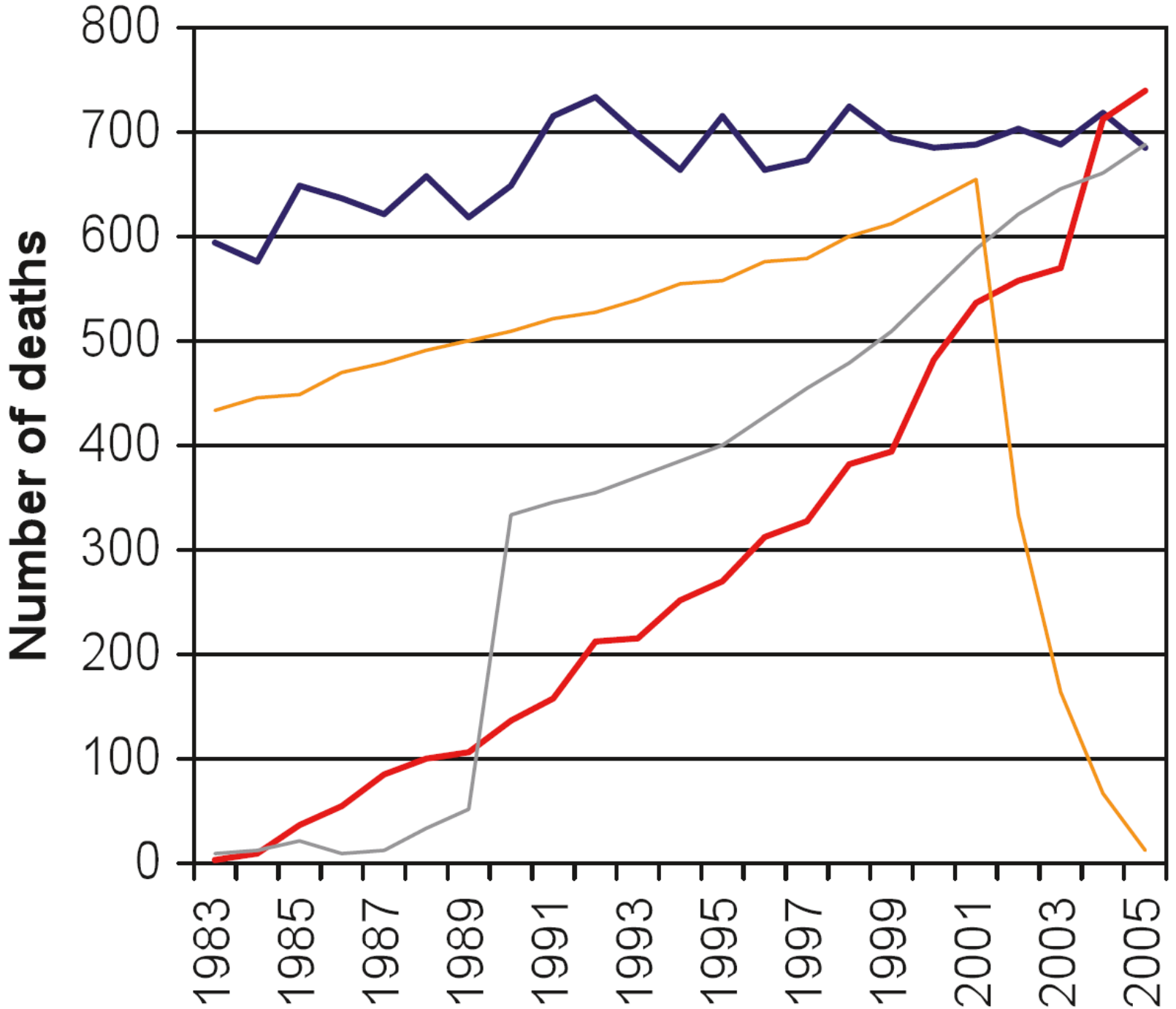
age category 80+ (old cohort, long follow-up)

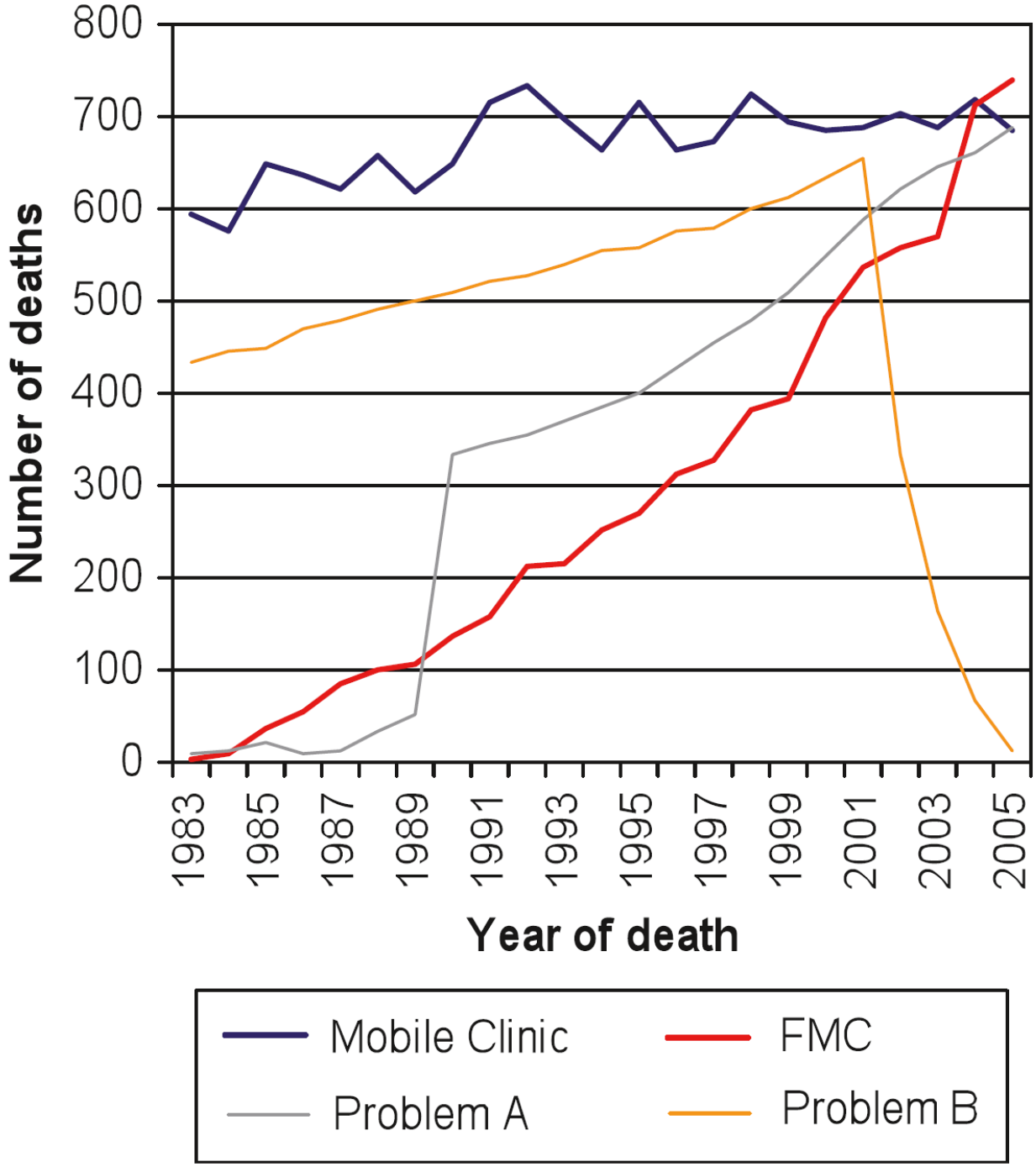
Error %	Obs	Exp	SIR	95% CI
0	100	80	1.25	1.02-1.51
2	98	128	0.77	0.62-0.93

Effect of errors in linkage key:

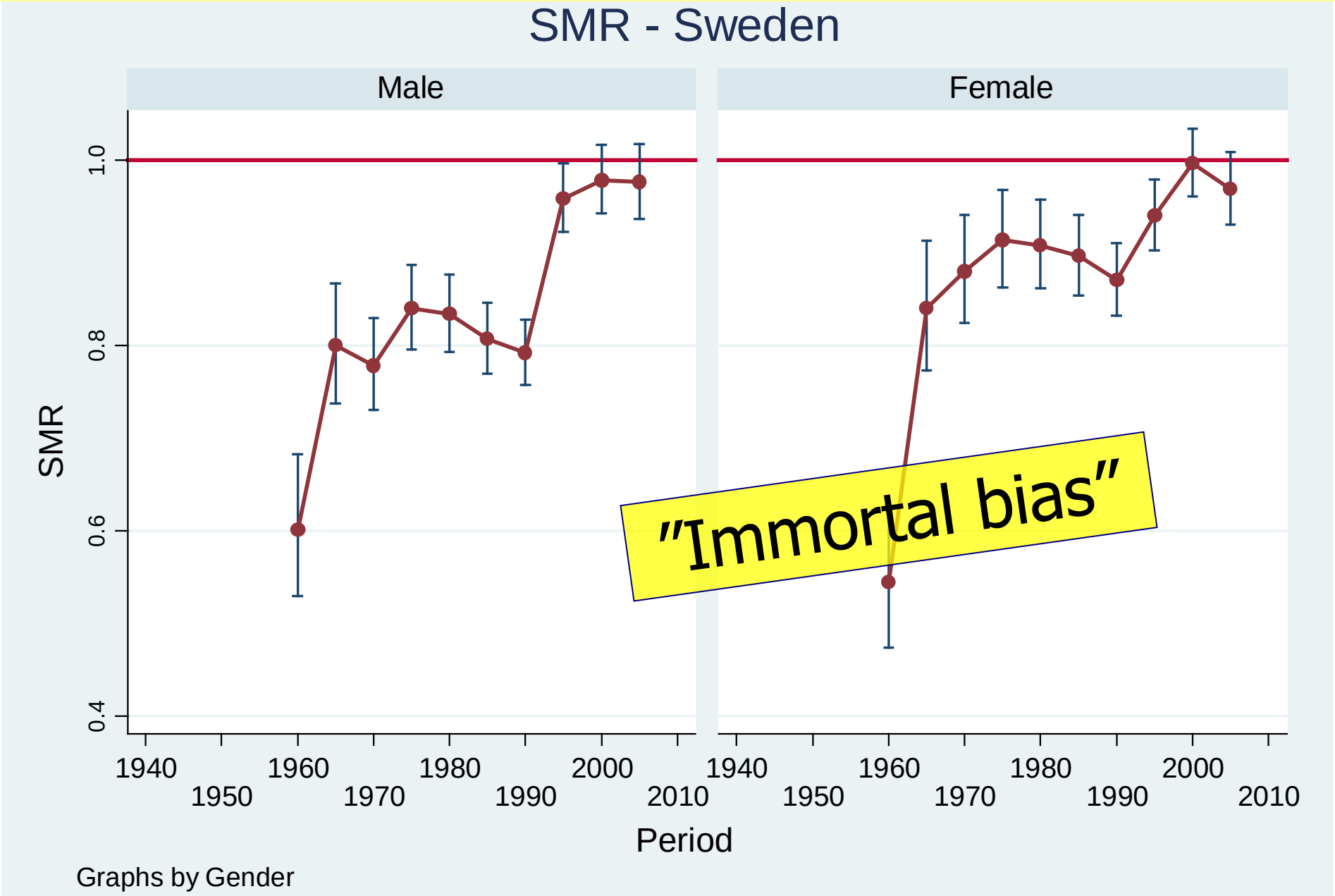
Cancer risk in an old cohort with long follow-up, age category 80+

Error %	Obs	Exp	SIR	95% CI
0	100	80	1.25	1.02-1.51
2	98	128	0.77	0.62-0.93
10	90	245	0.37	0.30-0.45

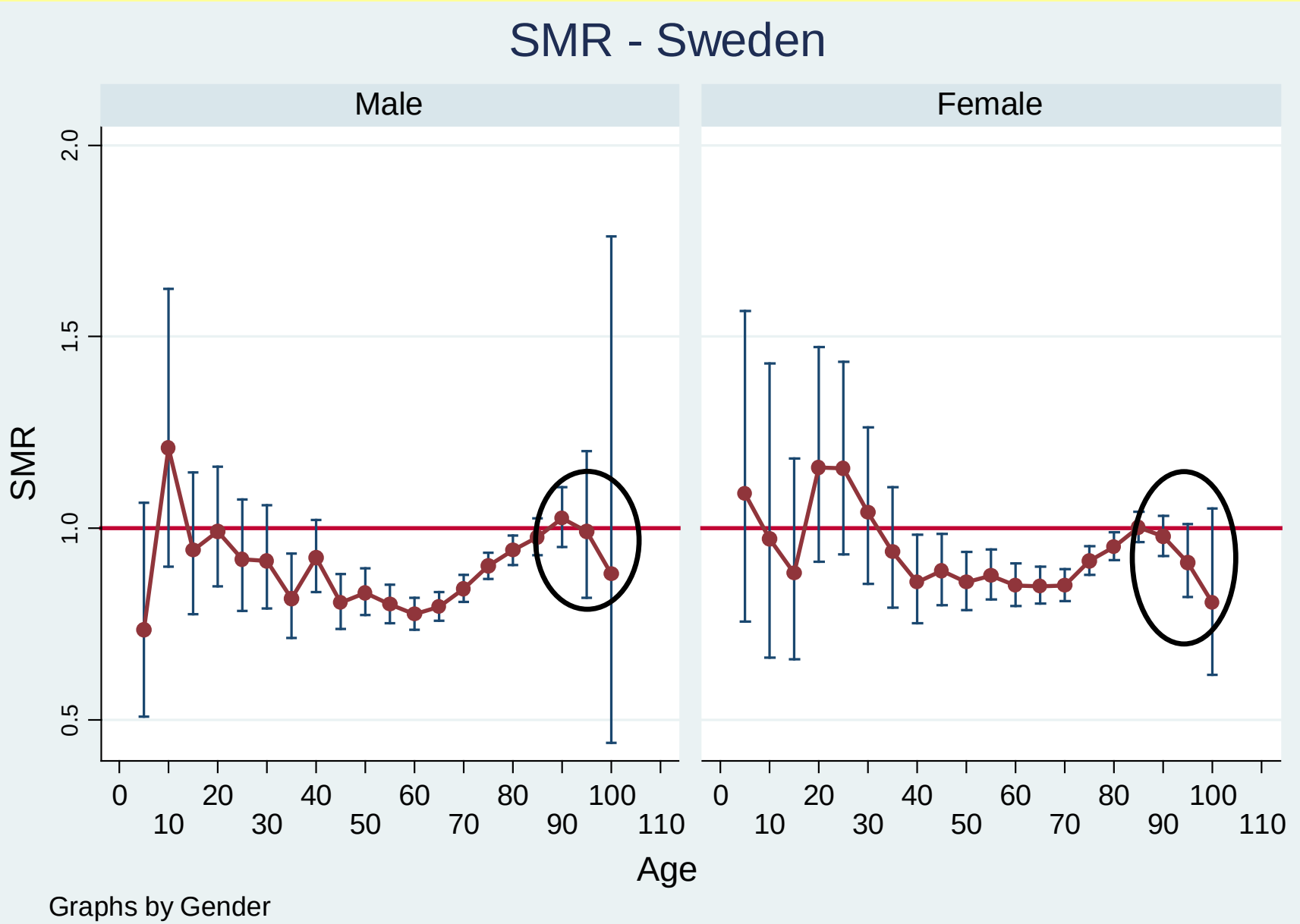

Number of deaths
800
700
600
500
400
300
200
100
0
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005


800
700
600
500
400
300
200
100
0
Number of deaths
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
Year of death
Mobile Clinic
FMC
Problem A
Problem B

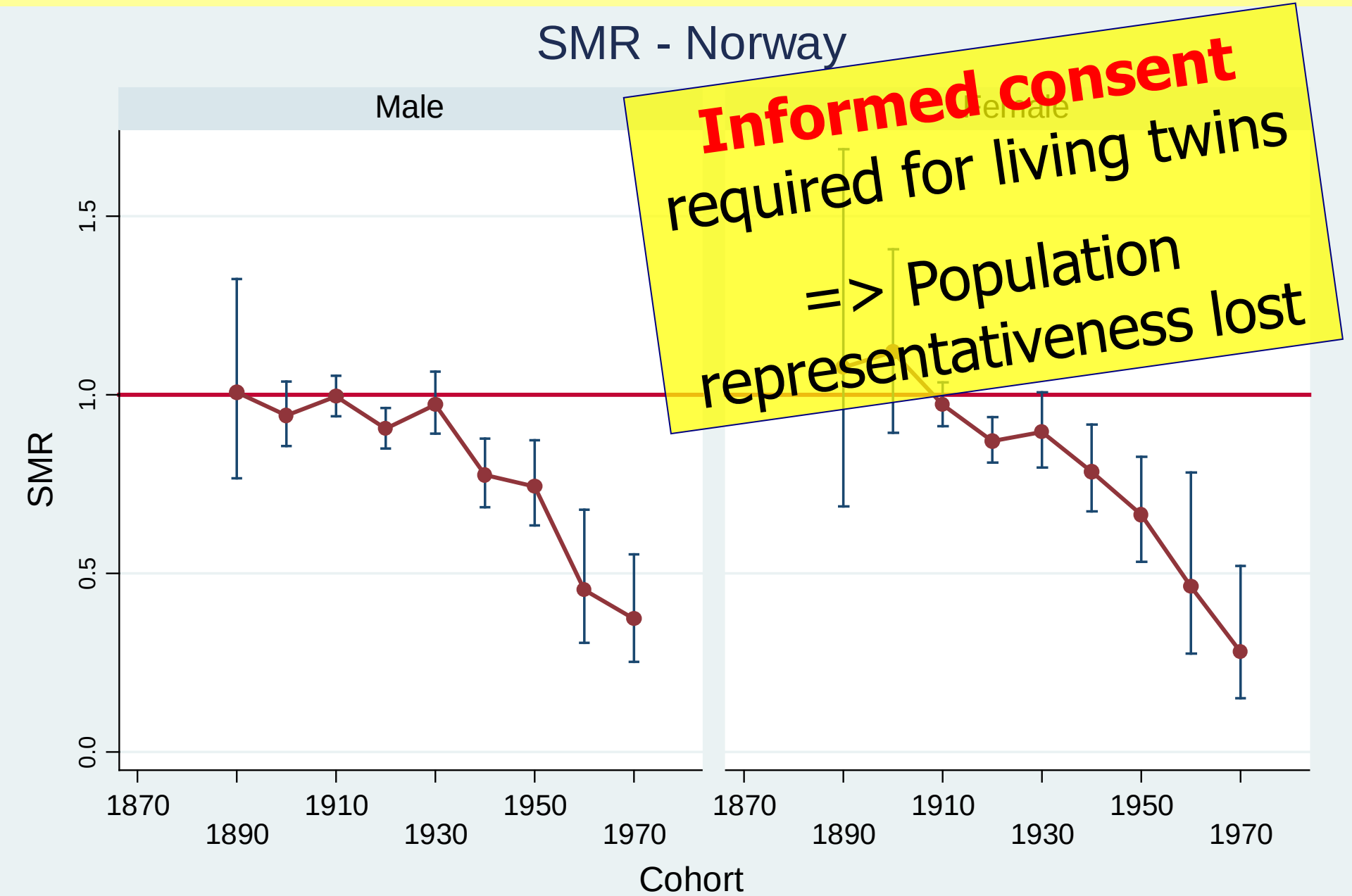
All-cause mortality



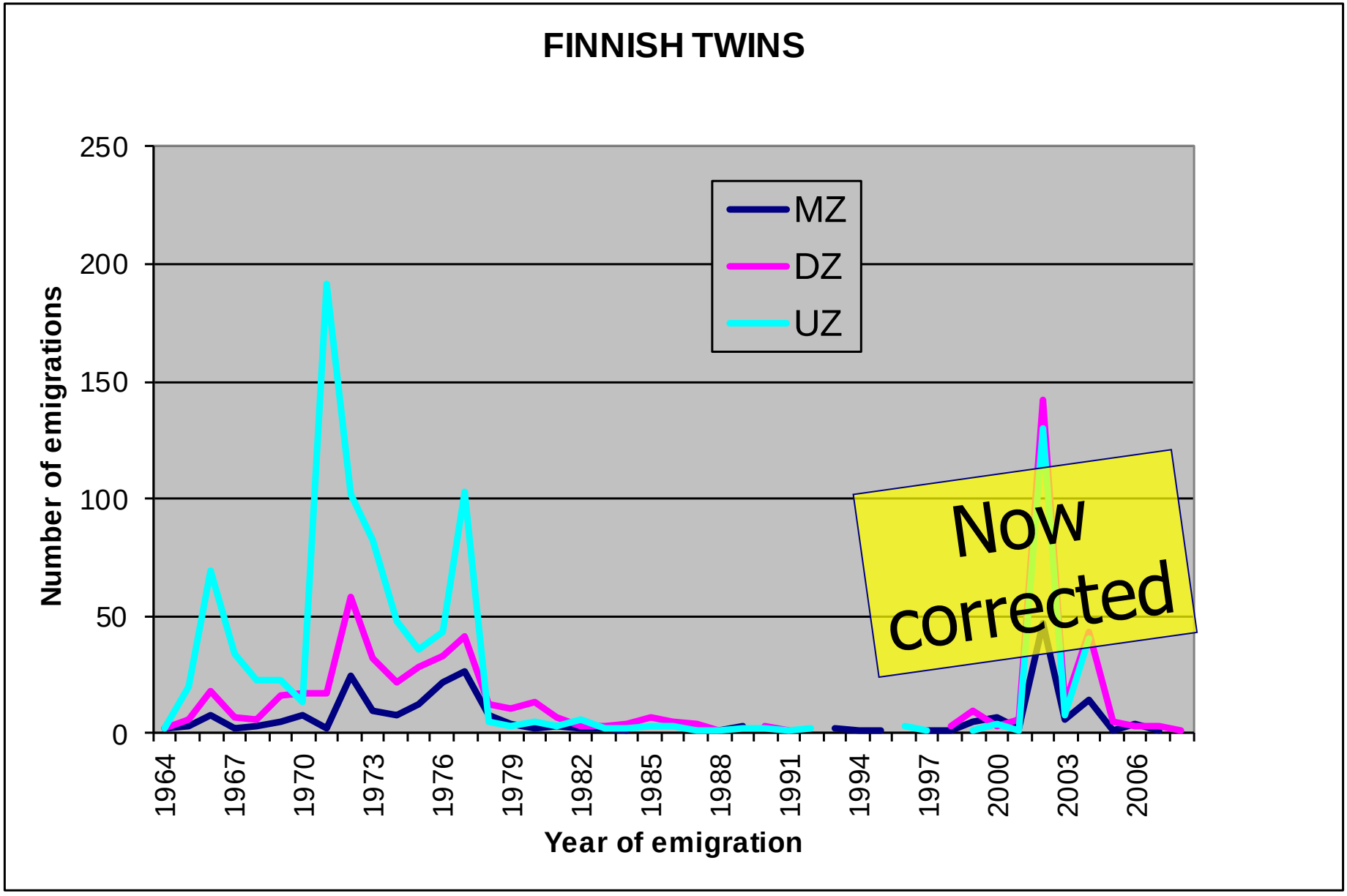
All-cause mortality



All-cause mortality

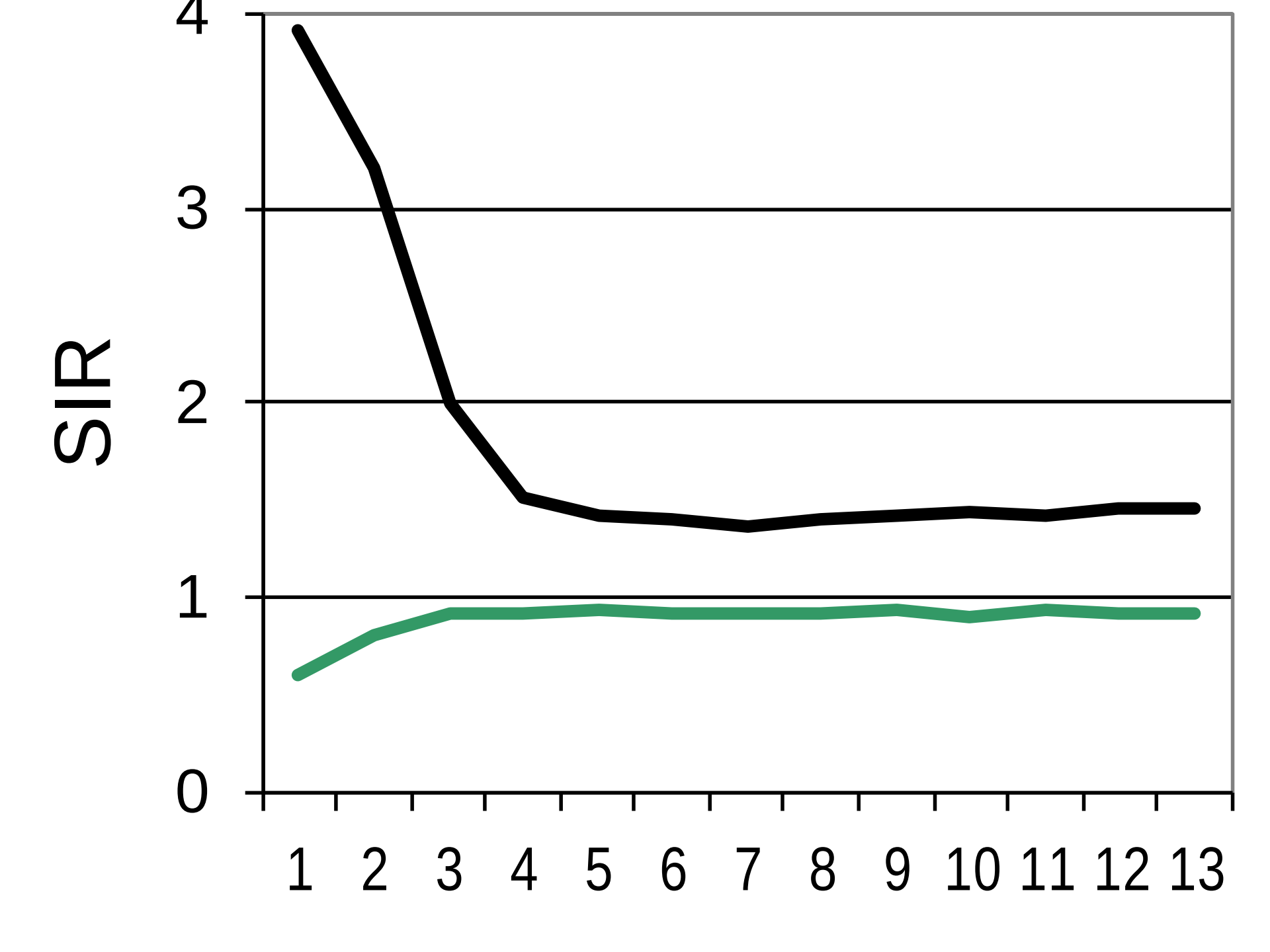


EMIGRATIONS



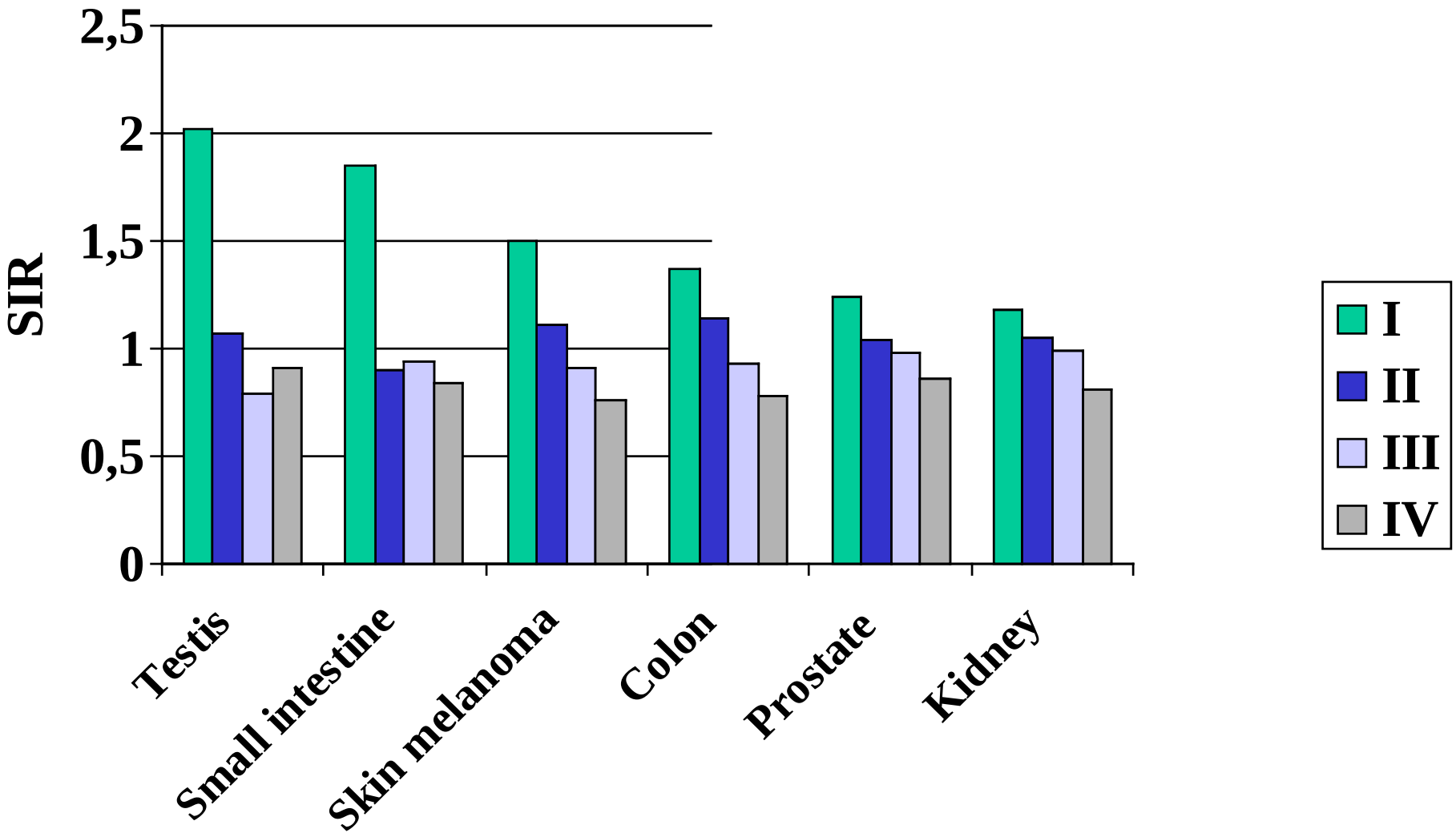
Correct date of beginning of unbiased follow-up (BOF) in Twin Registers?

- Twins selected from a register
  - If the register only includes persons alive on day X, BOF cannot be before X
  - If linkage to cancer registry or vital statistics is based on person IDs, BOF cannot be before the date when that key has been used in all registers (before that manual linkage possible => errors)
- Zygosity status
  - If based on questionnaires => BOF for MZ/DZ categories cannot be before date of response (follow-up before that belongs to UZ category)
  - ”Healthy responder effect”
    - Temporal selection bias during the first years of follow-up in MZ/DZ category **ALWAYS**
    - Possible permanent selection bias


SIR
4
3
2
1
0
1 2 3 4 5 6 7 8 9 10 11 12 13

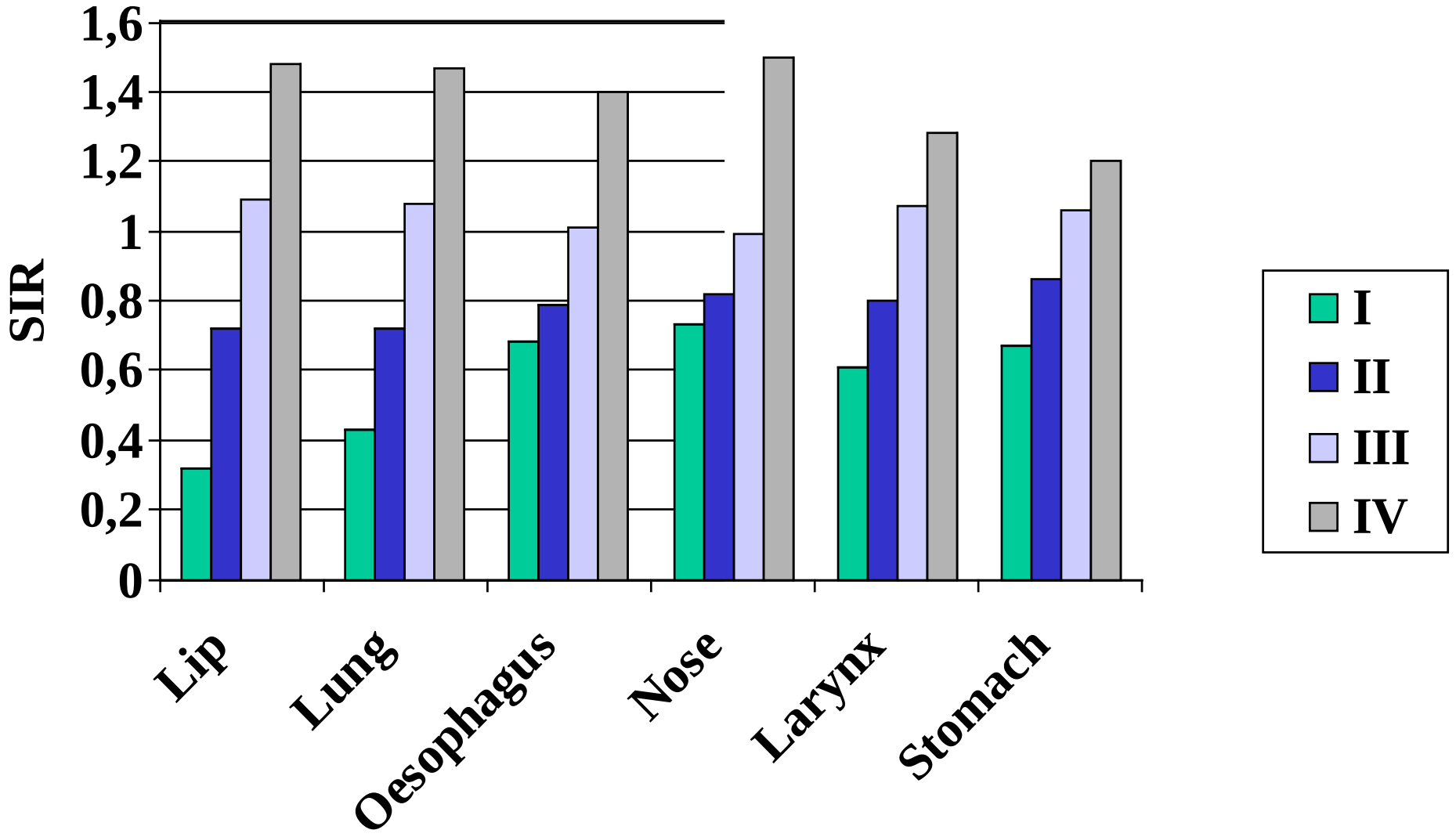
Cancers of HIGH social class, men

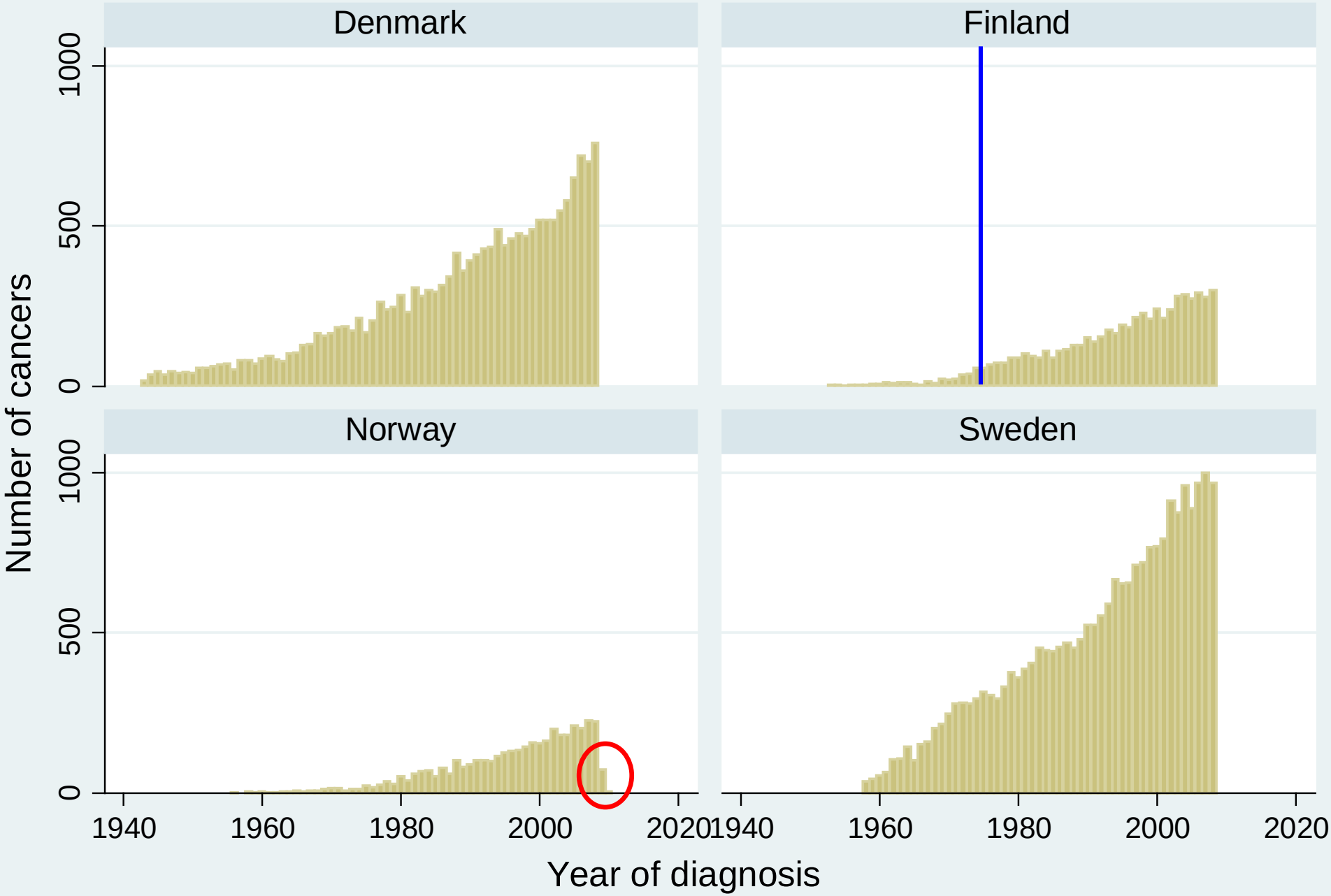
Finland 1991-1995



Cancers of LOW social class, men

Finland 1991-1995




Denmark
Finland
Norway
Sweden
Number of cancers
0
500
1000
1940
1960
1980
2000
2020
Year of diagnosis
Graphs by Country

NORDCAN

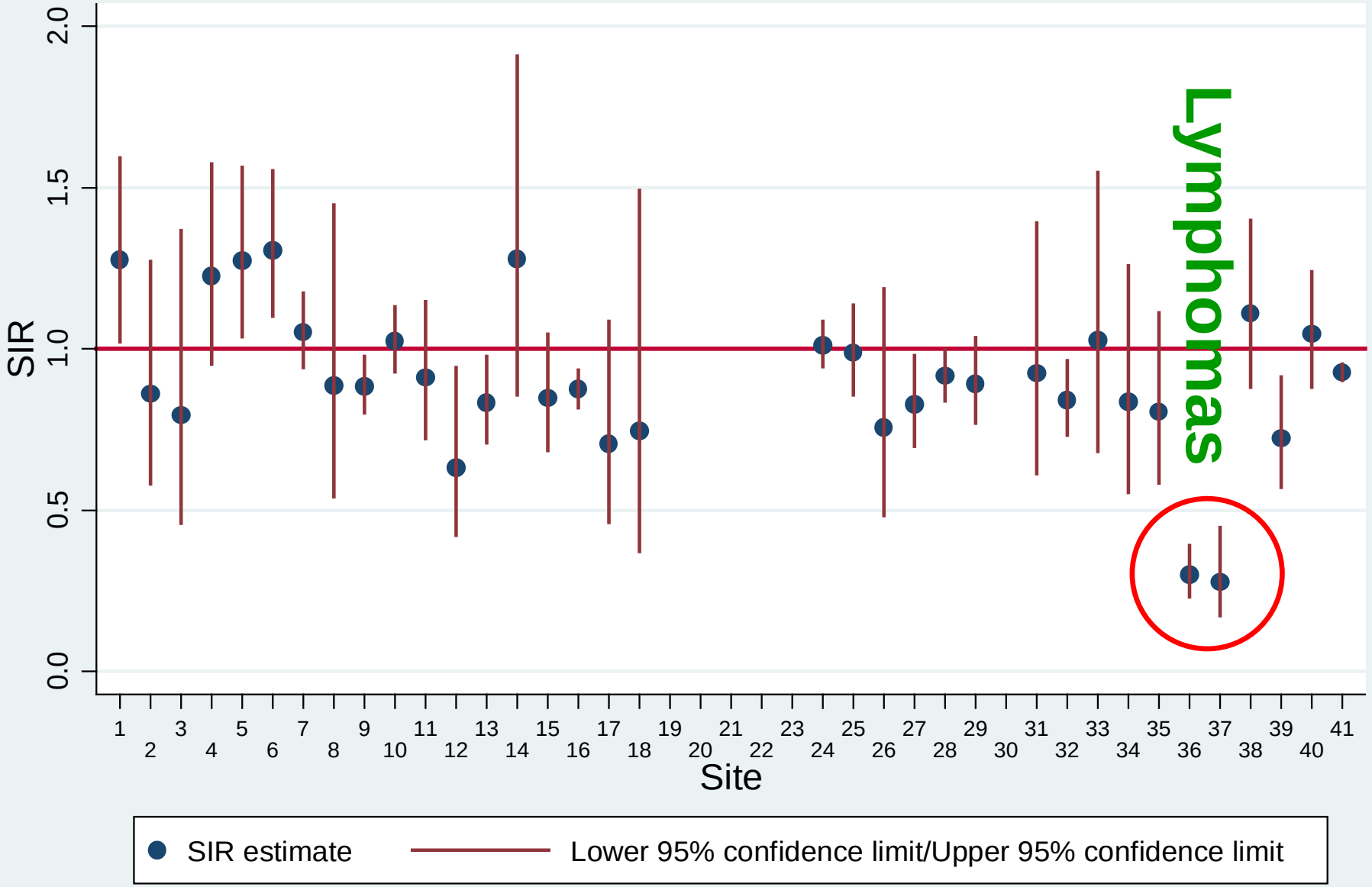
Association of the Nordic Cancer Registries

www.ancr.nu

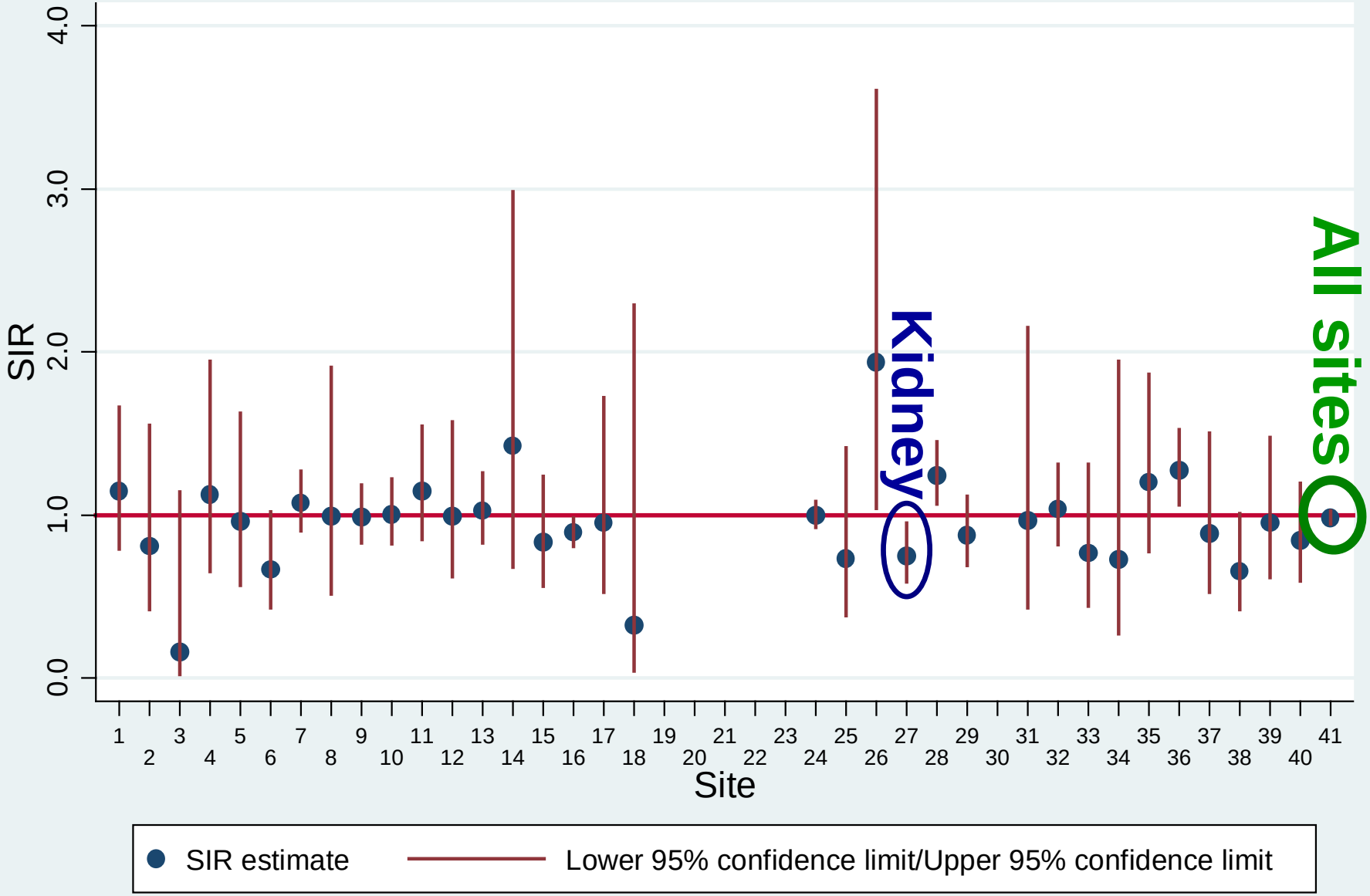
The NORDCAN Cancer Groups

1 Lip
2 Tongue
3 Salivary glands
4 Mouth
5 Pharynx
6 Oesophagus
7 Stomach
8 Small intestine
9 Colon
10 Rectum and anus
11 Liver
12 Gallbladder and extrahepatic bile ducts
13 Pancreas
14 Nose, sinuses
15 Larynx
16 Lung (incl. trachea and bronchus)
17 Pleura
18 Breast
19 Cervix uteri
20 Corpus uteri
21 Uterus, other
22 Ovary and uterine adnexa
23 Other female genital organs
24 Prostate
25 Testis
26 Penis and other male genital organs
27 Kidney
28 Bladder and other and unspecified urinary organs
29 Melanoma of skin
30 Skin, non-melanoma
31 Eye
32 Brain, central nervous system
33 Thyroid
34 Bone
35 Soft tissues
36 Non-Hodgkin lymphoma
37 Hodgkin's disease
38 Multiple myeloma
39 Acute leukaemia
40 Other leukaemia

Denmark - Men


Lymphomas
SIR
0.0
0.5
1.0
1.5
2.0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41
Site
SIR estimate
Lower 95% confidence limit/Upper 95% confidence limit

Finland - Men


SIR
4.0
3.0
2.0
1.0
0.0
Kidney
All sites
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41
Site
SIR estimate
Lower 95% confidence limit/Upper 95% confidence limit

Kidney cancer among Nordic twins

	Gender	N cases	SIR	95% CI
Finland	M	69	0.74	0.59-0.94

Kidney cancer among Nordic twins

	Gender	N cases	SIR	95% CI
Finland	M	69	0.74	0.59-0.94
	F	45	0.70	0.52-0.93
Denmark	M	135	0.81	0.68-0.96
	F	88	0.77	0.62-0.95
Sweden	M	177	0.65	0.56-0.75
	F	156	0.76	0.65-0.89
Norway	M	57		
	F	33		

After this excercise & baseline article

- **Quality assurance** tools
  - Continue the **improved way of thinking** that data-related QA is important
  - Continue utilisation of the **instruments developed to identify errors**
  - Remember what we have learned about the **population representativeness** (short-term and long-term selection)

Extremely precise estimates on cancer risk among twins.

Nordic Cancer Registries – similarities and differences

Eero Pukkala
on behalf of the ANCR Board

ACTA ONCOLOGICA, 2018
VOL. 57, NO. 4, 440–455
https://doi.org/10.1080/0284186X.2017.1407039

Taylor & Francis
Taylor & Francis Group

SPECIAL ARTICLE

Nordic Cancer Registries – an overview of their procedures and data comparability

Eero Pukkala[a,b], Gerda Engholm[c], Lise Kristine Højsgaard Schmidt[d], Hans Storm[c], Staffan Khan[e], Mats Lambe[f,g], David Pettersson[e], Elínborg Ólafsdóttir[h], Laufey Tryggvadóttir[h,i], Tiina Hakanen[a], Nea Malila[a,b], Anni Virtanen[a,j], Tom Børge Johannesen[k], Siri Larønningen[k] and Giske Ursin[k]

[a]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland; [b]Faculty of Social Sciences, University of Tampere, Tampere, Finland; [c]Danish Cancer Society, Copenhagen, Denmark; [d]Danish Cancer Registry, The Danish Health Data Authority, Copenhagen, Denmark; [e]Swedish Cancer Registry, the Swedish National Board of Health and Welfare, Stockholm, Sweden; [f]Regional Cancer Centre Uppsala-Örebro, Uppsala, Sweden; [g]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [h]Icelandic Cancer Registry, Icelandic Cancer Society, Reykjavik, Iceland; [i]Faculty of Medicine, University of Iceland, Reykjavik, Iceland; [j]Department of Pathology, University of Helsinki and HUSLAB, Helsinki University Hospital, Helsinki, Finland; [k]Cancer Registry of Norway, Oslo, Norway

Why?

- Repeated need for documentation on the similarities and dissimilarities of the Nordic Cancer Registries, e.g.,
  - for joint study planning purposes
    - Are variables needed for a study similarly accessible from each Nordic country?
  - as a reference when writing manuscripts based on Nordic Cancer Registry data
    - ”All Nordic countries have similar population-based high accuracy cancer registries .”
- How comparable are the cancer statistics in NORDCAN in the national publications?
  - Why the differences?

Data sources (baseline data collection)

	Denmark	Finland	Iceland	Norway	Sweden
public hospitals	yes	yes	no	yes	yes
private clinicians	yes	yes	no	yes	yes
dentists	yes	yes	no	no	no
laboratories, pathological samples	2004+ *	yes	yes	yes	yes
laboratories, haematological samples	no	yes	yes	no	yes
laboratories, cytological samples	no	yes	yes	yes	yes
death certificates	yes	yes	yes	yes	no
inpatient registry	2004+	2016+ ?	1999+	2000+	no
radiotherapy data (from all machines)				1997+	

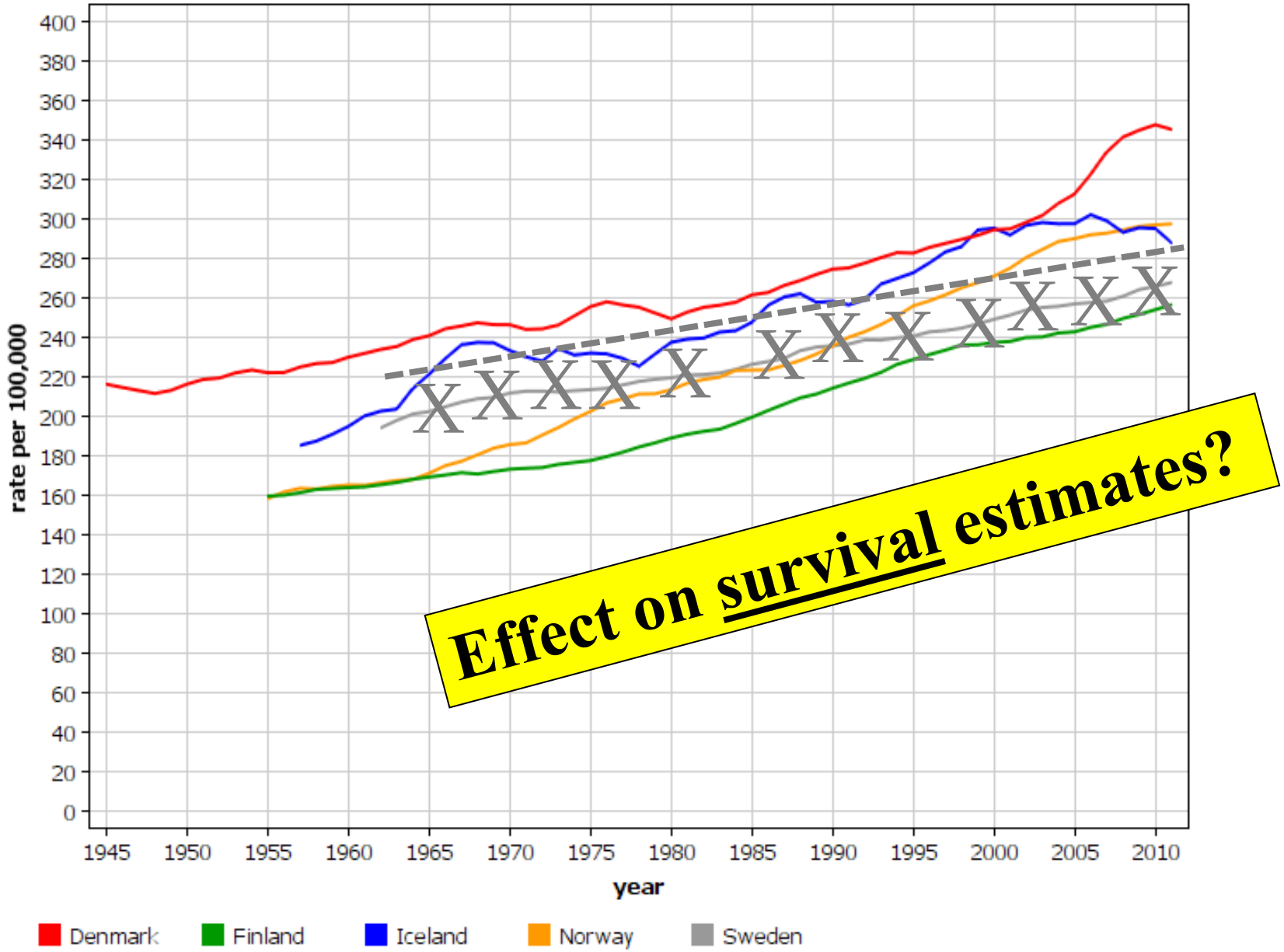
** Used for cases that have been coded since 2004.*

Death certificate initiated cases

- In Sweden **4% underregistration of incident cases** because the Swedish system does not use death certificates as a source of information.
- In addition to the cases which would be based on death certificate only (DCO), those cases which actually are diagnosed before death but which could only be traced starting from the death certificate information are also missed in Sweden.
- In other Nordic countries there is a follow-back system (inquiries sent to the treating hospitals) which finds additional information for most of the cases first known through death certificates.

Mattsson B (1984). Cancer registration in Sweden. Studies on completeness and validity of incidence and mortality registers.

All sites
Incidence: ASR (World), Female age 0-85+

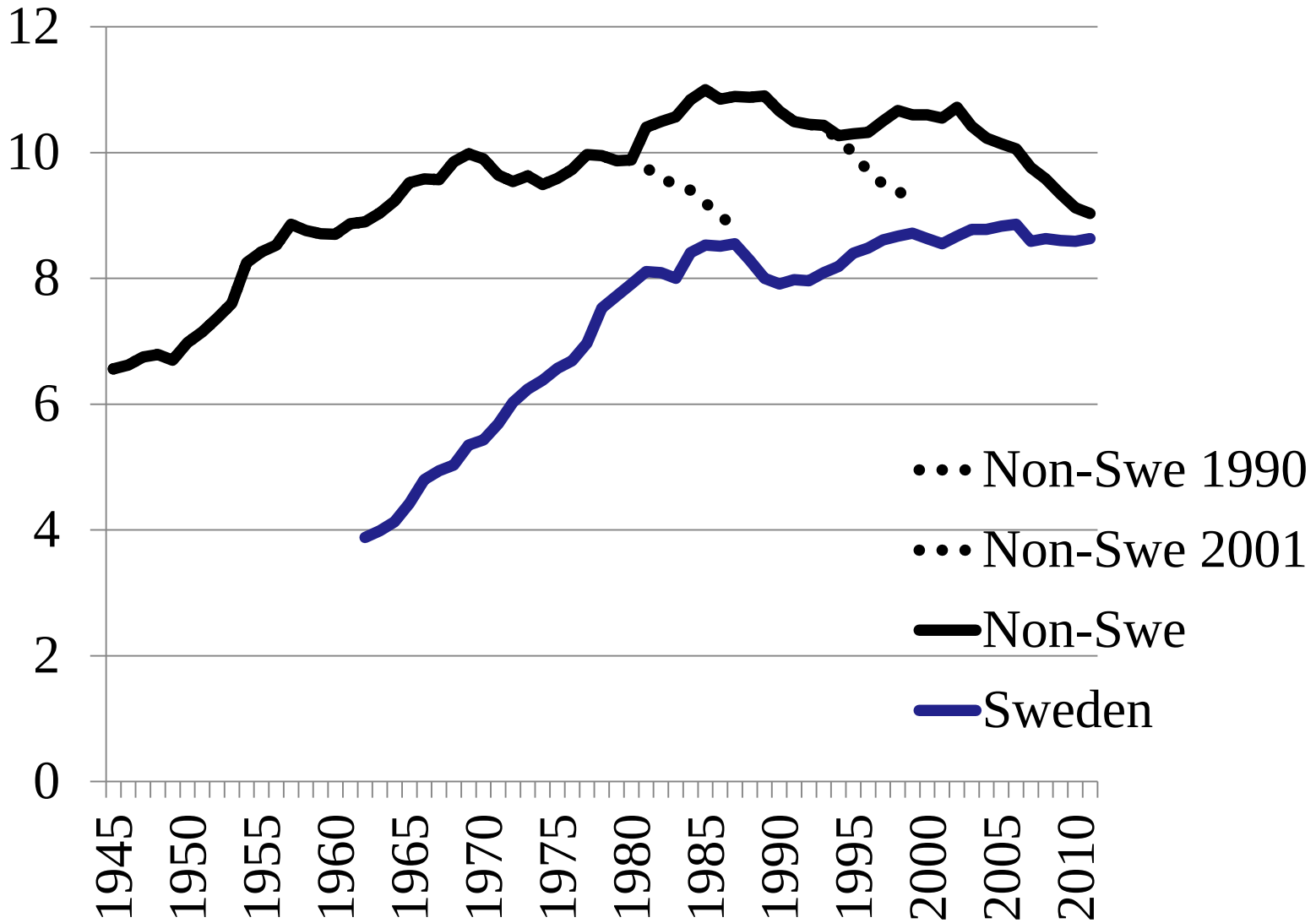


Death certificate initiated cases

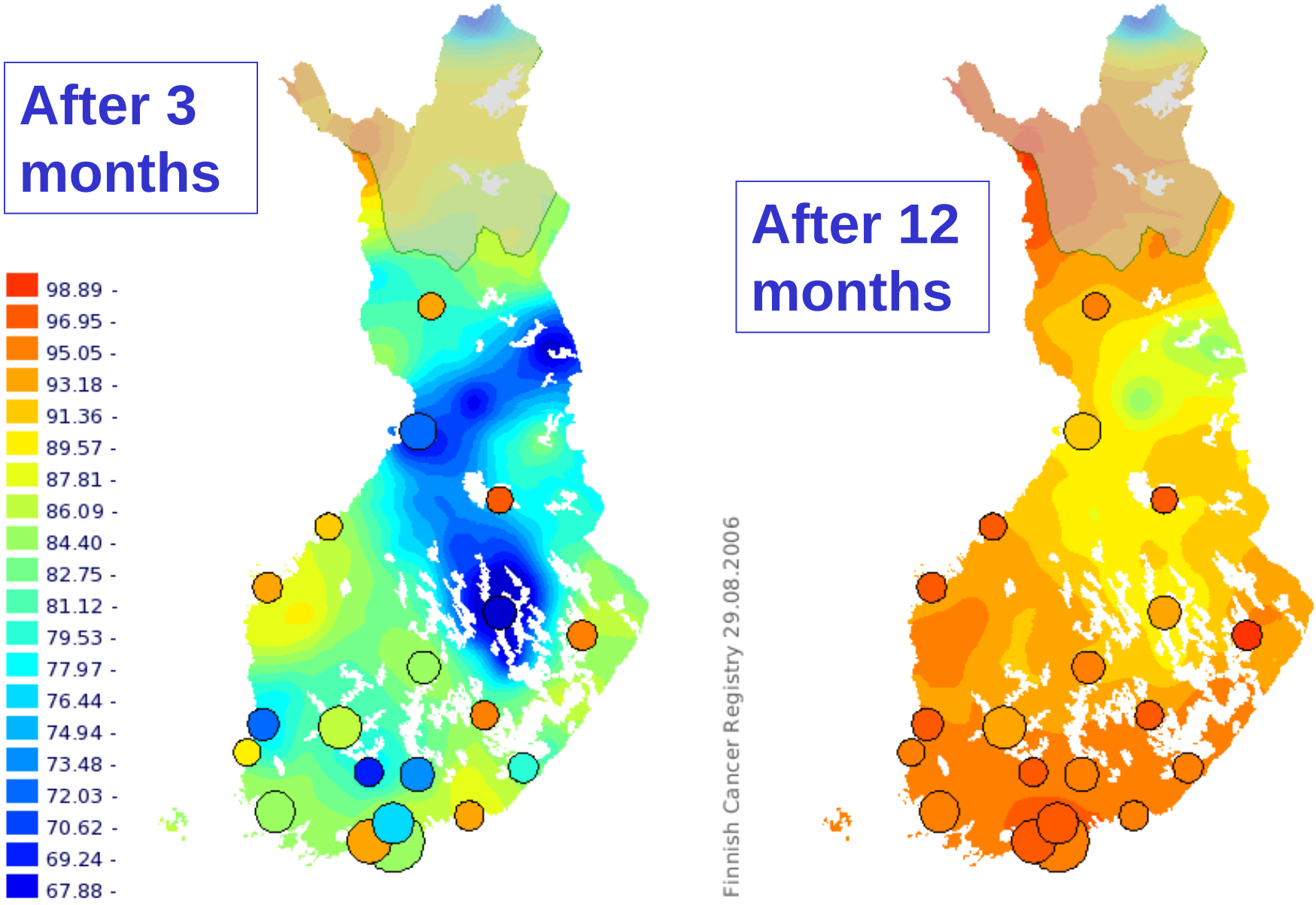
- **The underregistration in Sweden is highest in leukaemia (18%).**

Mattsson B (1984). Cancer registration in Sweden. Studies on completeness and validity of incidence and mortality registers.

Leukaemia (incidence / 100,000)



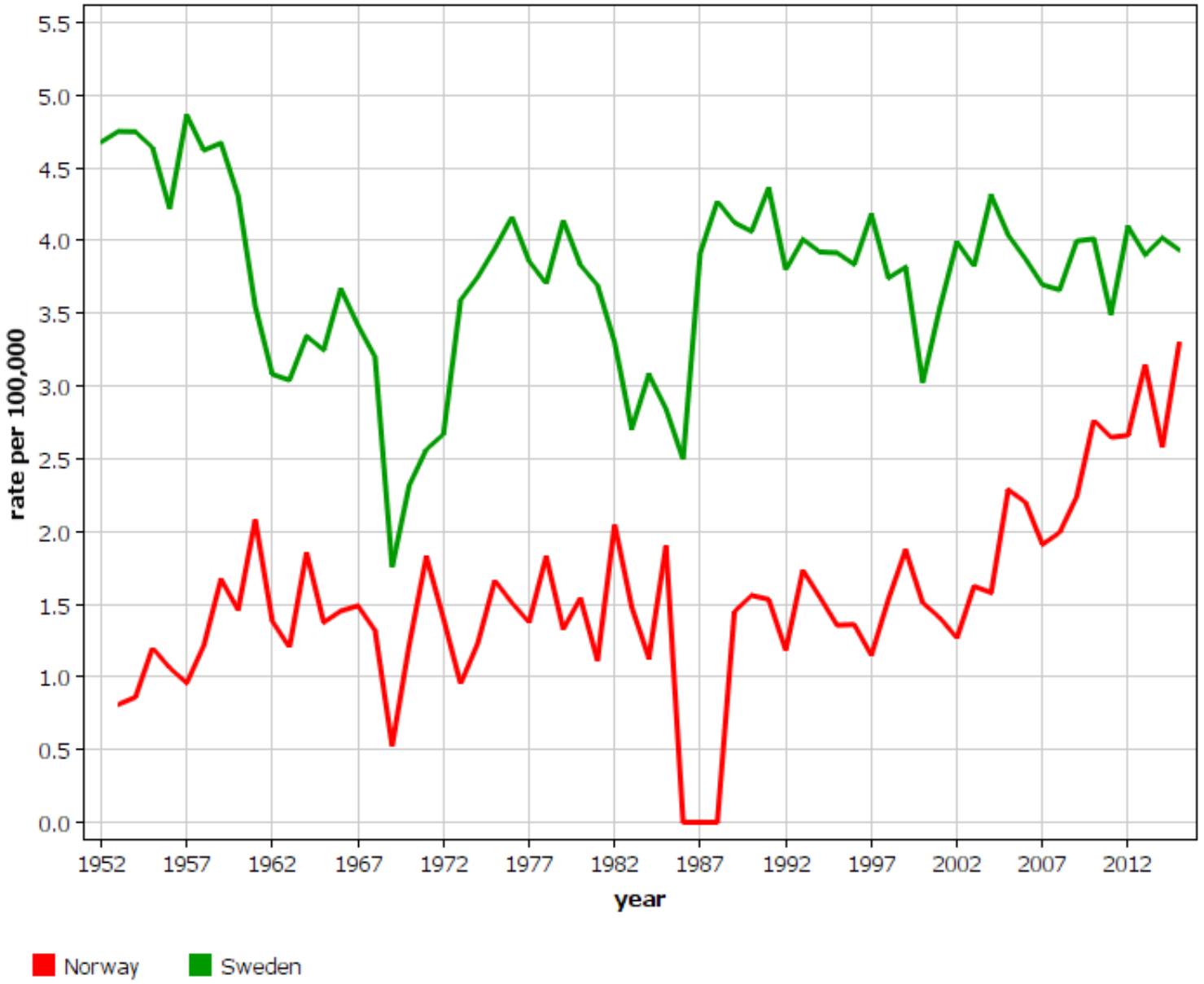
Percentage of cancers registered to Finnish Cancer Registry (2001)



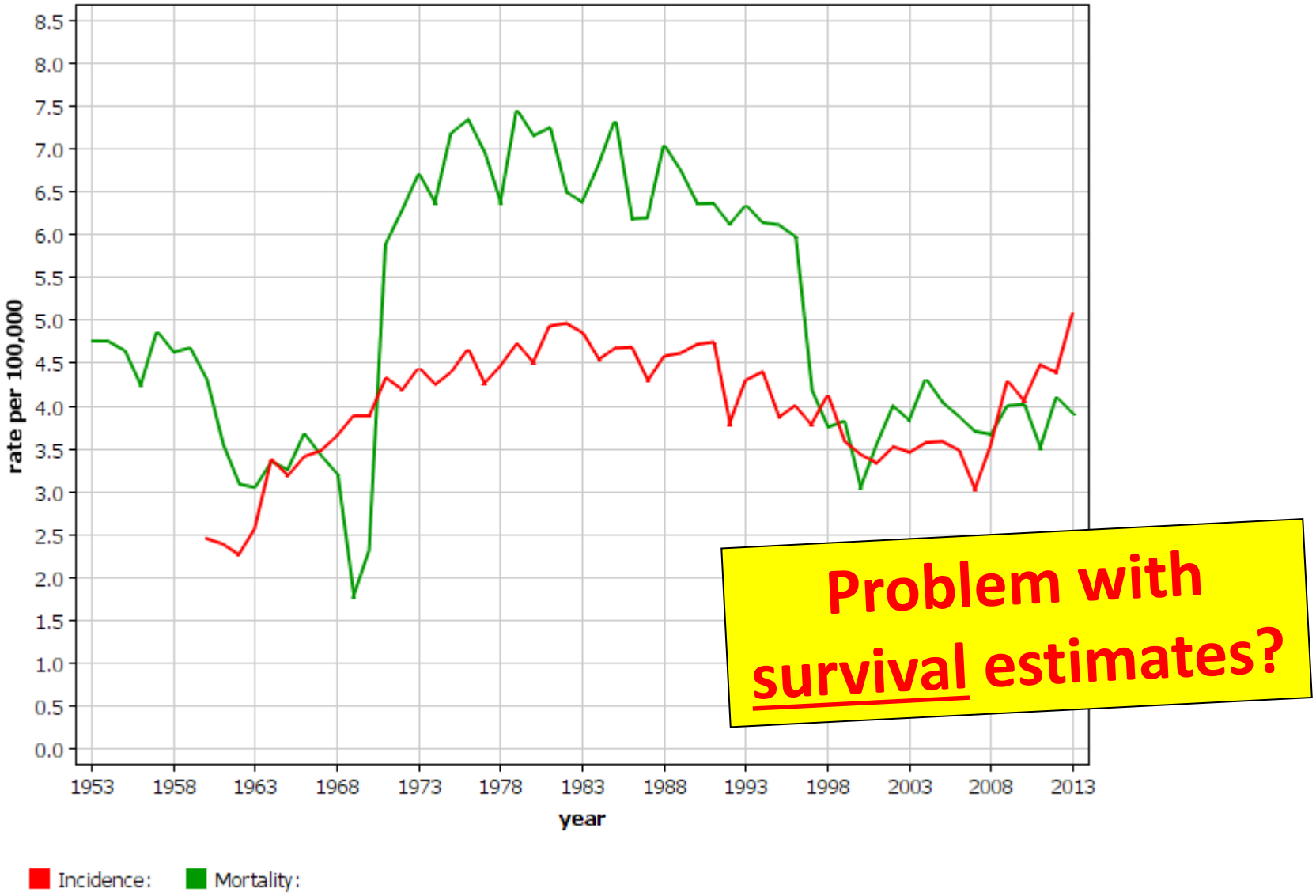
Could we get same results with cancer mortality statistics?

- Wrong topography in cause of death (liver, lung, brain, …)

Liver
Mortality: ASR (World), Male age 0-85+

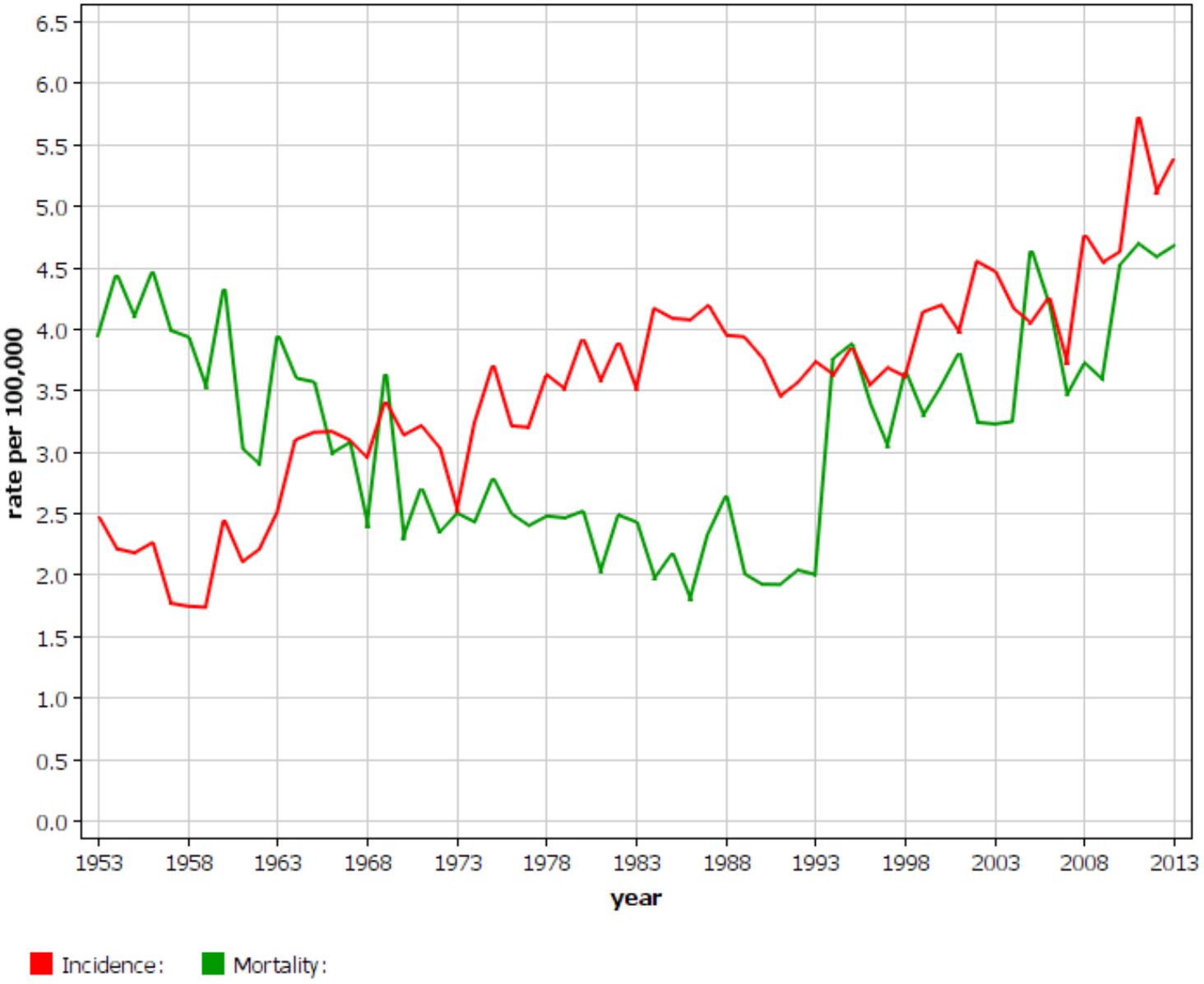


Sweden
Liver
ASR (World), Male age 0-85+



Problem with survival estimates?

Denmark
Liver
ASR (World), Male age 0-85+



Could we get same results with cancer mortality statistics?

- Wrong topography in cause of death (liver, lung, brain, …)
- No morphology information
- Different survival between categories?

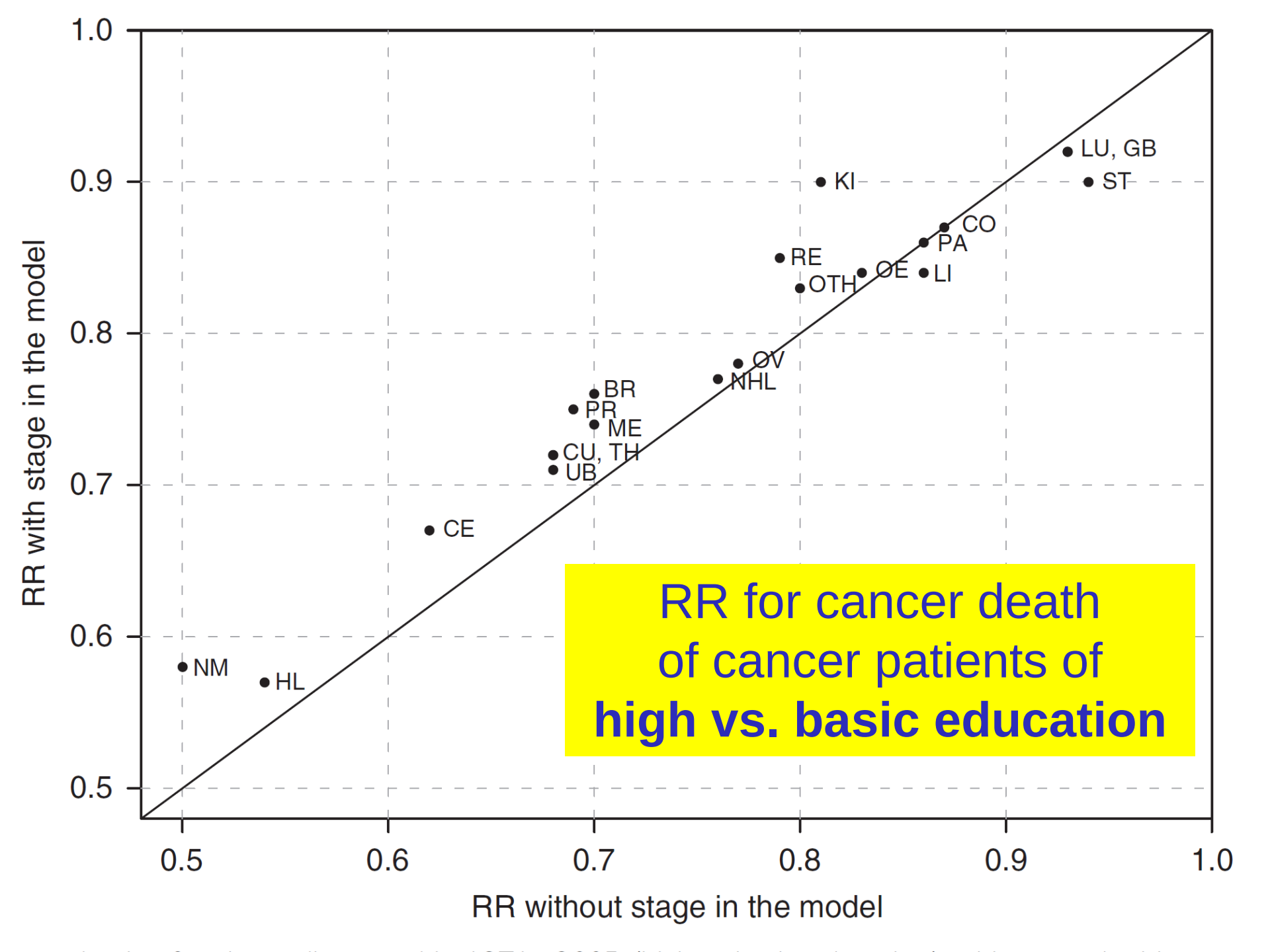
British Journal of Cancer (2010) 103, 1109 – 1114

www.bjcancer.com

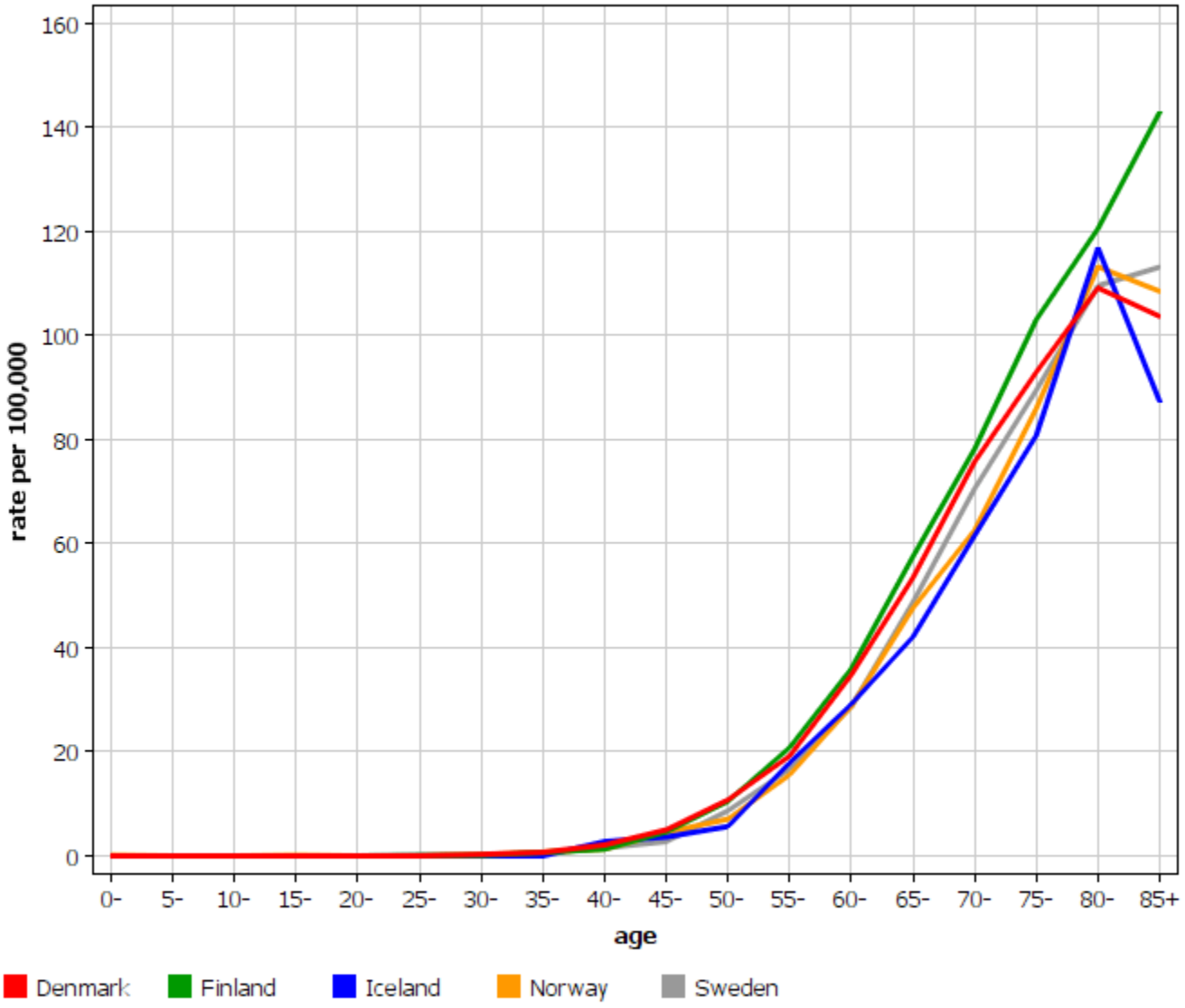
Education, survival and avoidable deaths in cancer patients in Finland

A Pokhrel*[,1], P Martikainen[2], E Pukkala[1], M Rautalahti[3], K Seppä[1] and T Hakulinen[1]

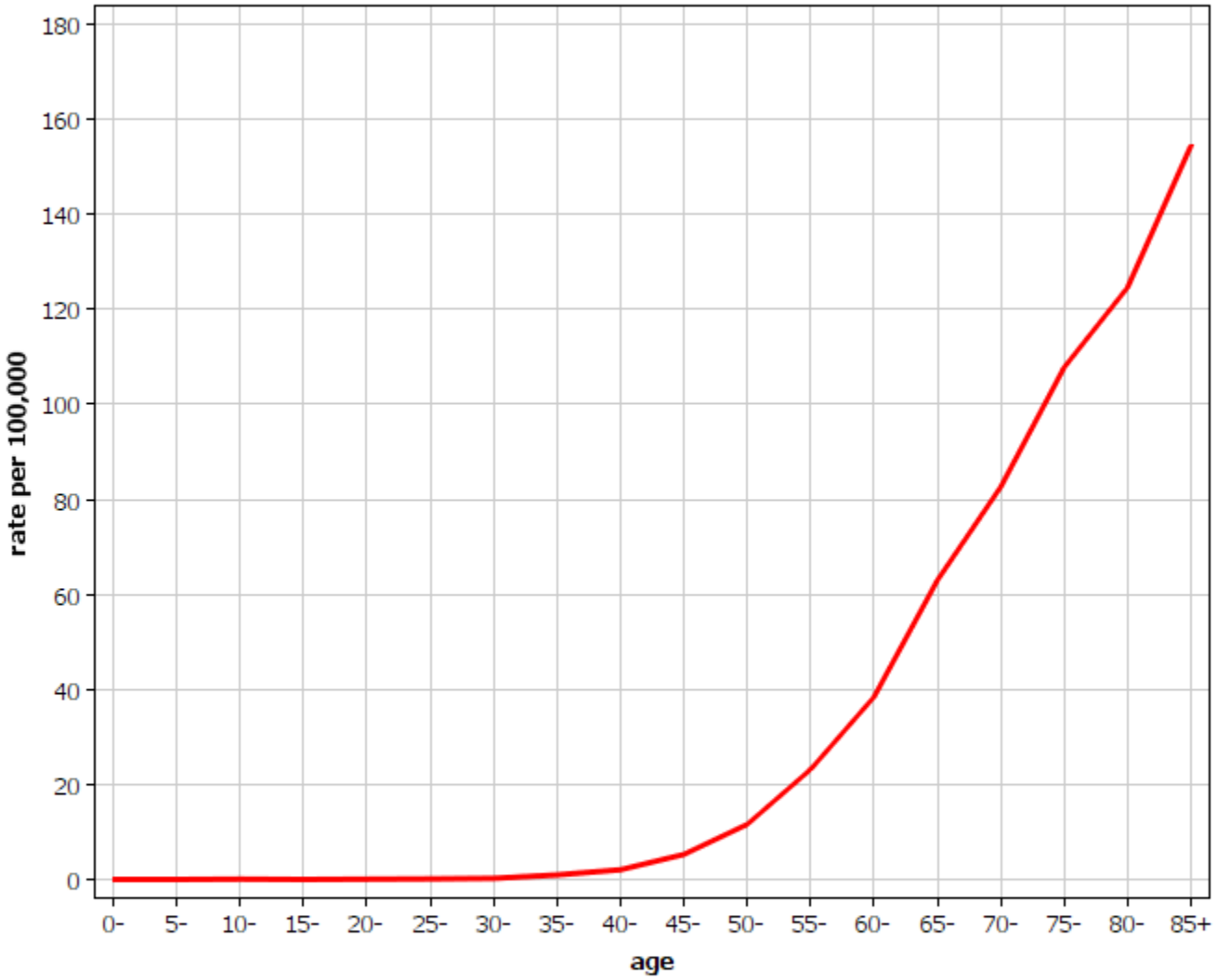
[1]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Pieni Roobertinkatu 9, FI-00130, Helsinki, Finland; [2]Department of Sociology, FI-00014 University of Helsinki, Helsinki, Finland; [3]Cancer Society of Finland, Pieni Roobertinkatu 9, FI-00130, Helsinki, Finland


1.0
0.9
0.8
0.7
0.6
0.5
RR with stage in the model
0.5
0.6
0.7
0.8
0.9
1.0
RR without stage in the model
LU, GB
ST
KI
CO
PA
RE
OE
LI
OTH
OV
NHL
BR
PR
ME
CU, TH
UB
CE
NM
HL
RR for cancer death
of cancer patients of
high vs. basic education

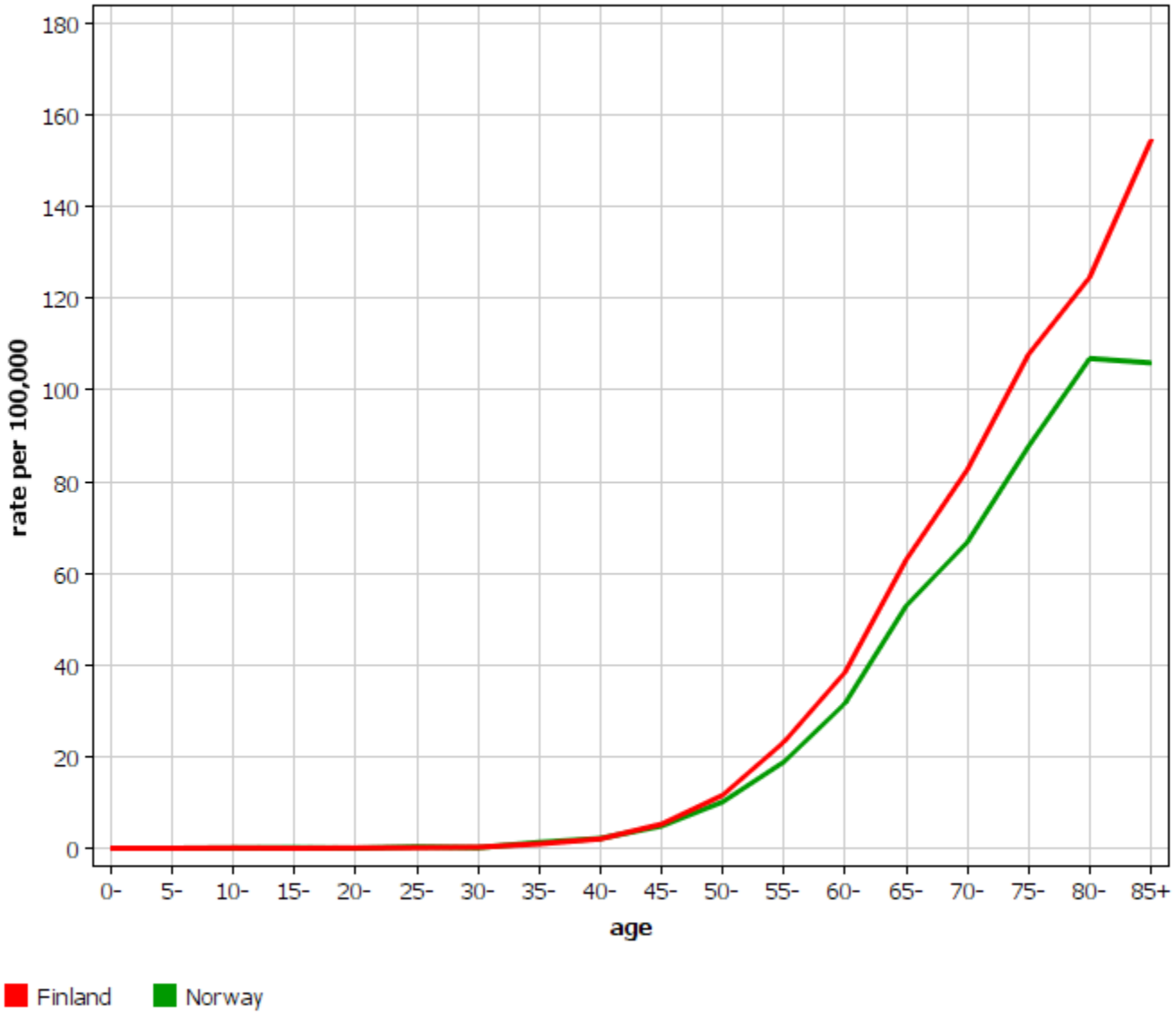
Mortality (2006-2015)
Pancreas: Male



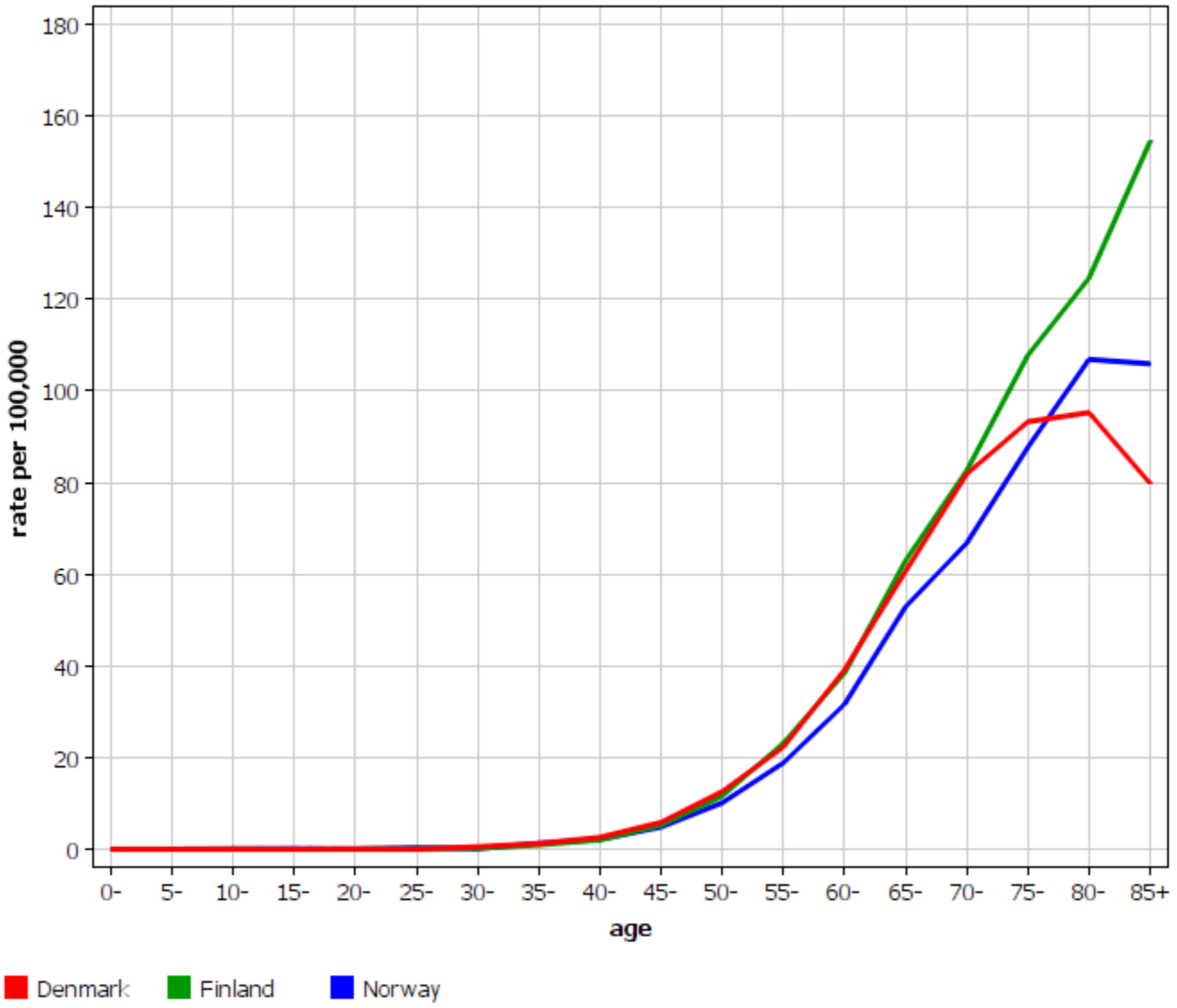
Finland-Incidence (2006-2015)
Pancreas: Male



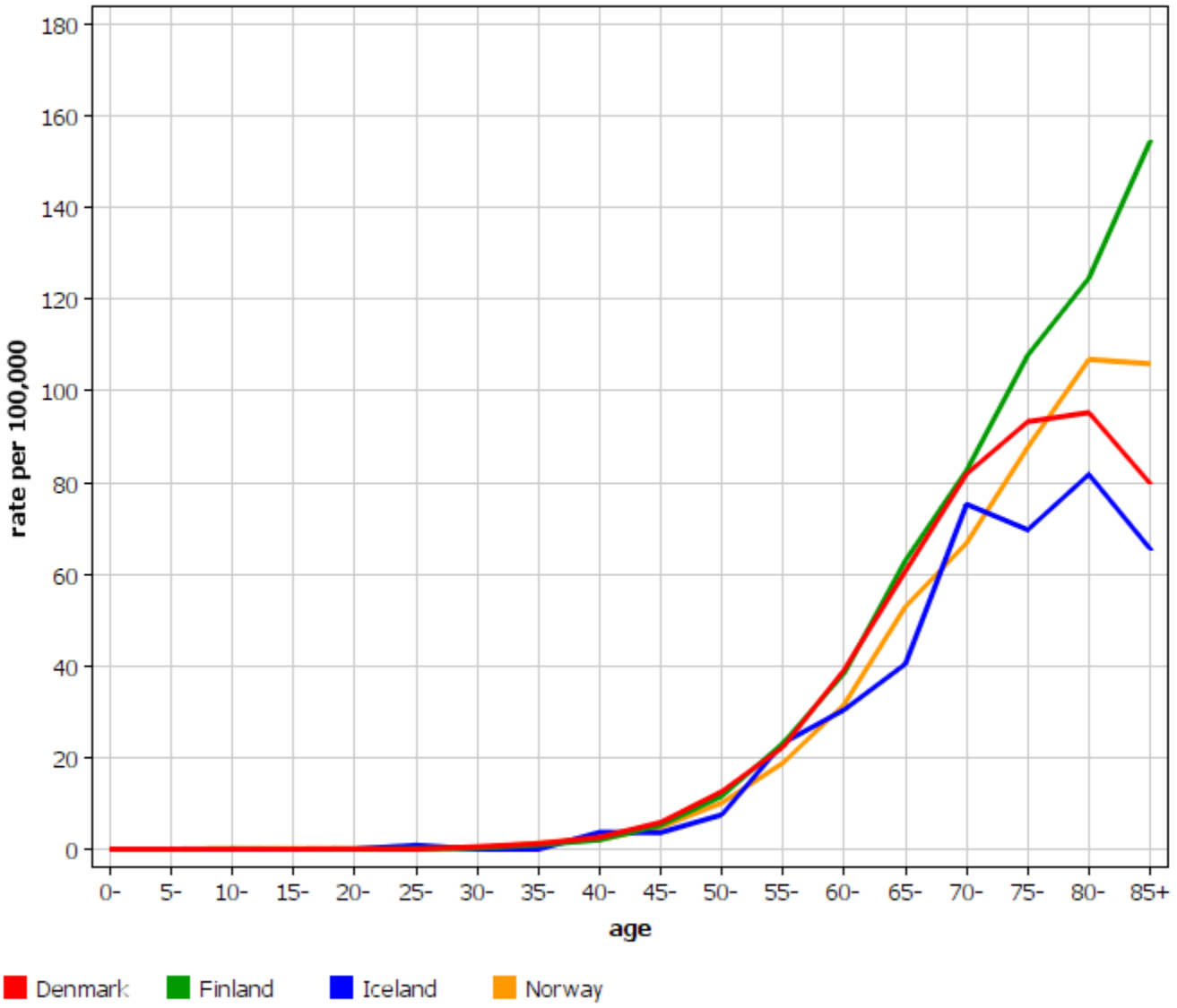
Incidence (2006-2015)
Pancreas: Male



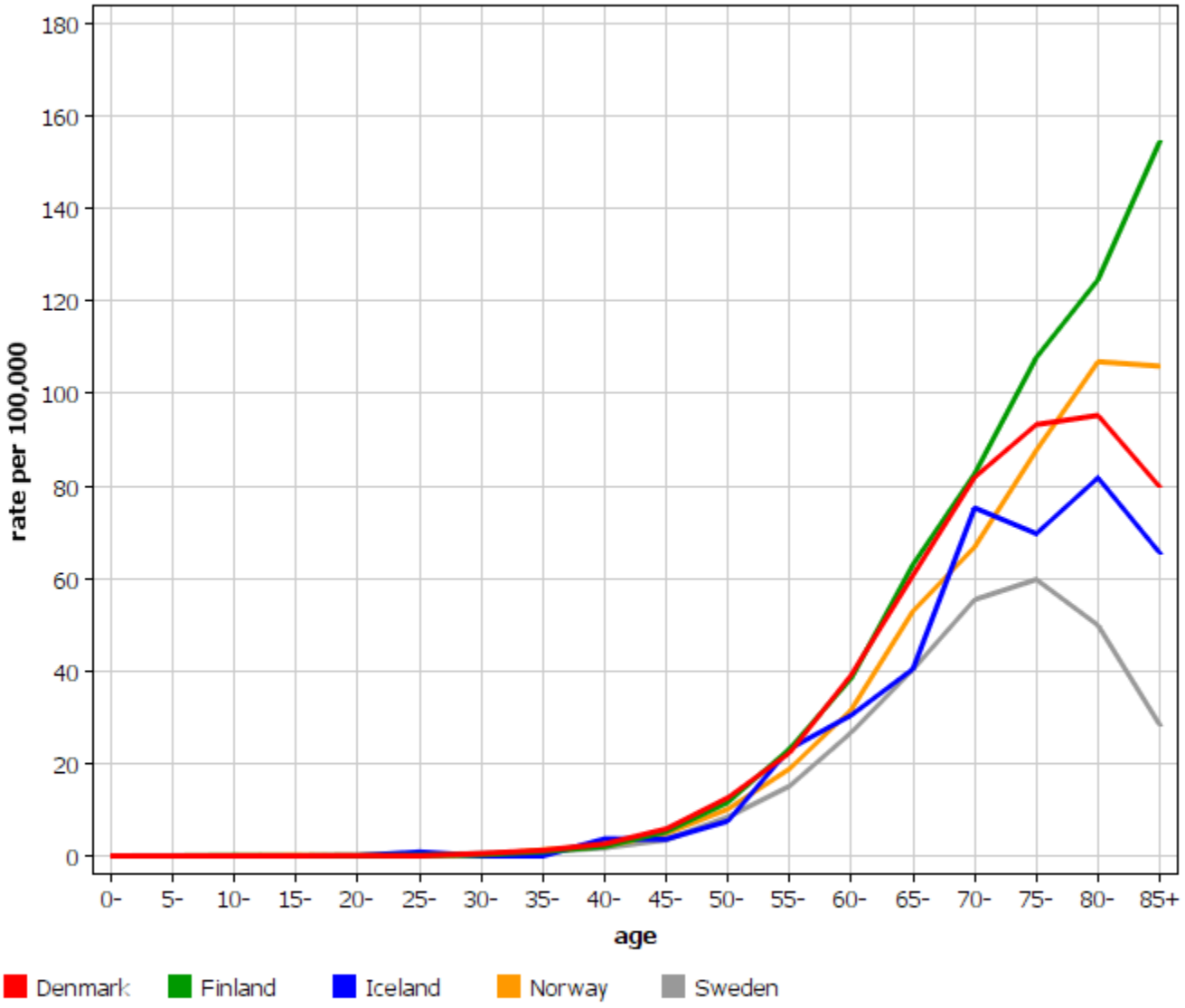
Incidence (2006-2015)
Pancreas: Male



Incidence (2006-2015)
Pancreas: Male



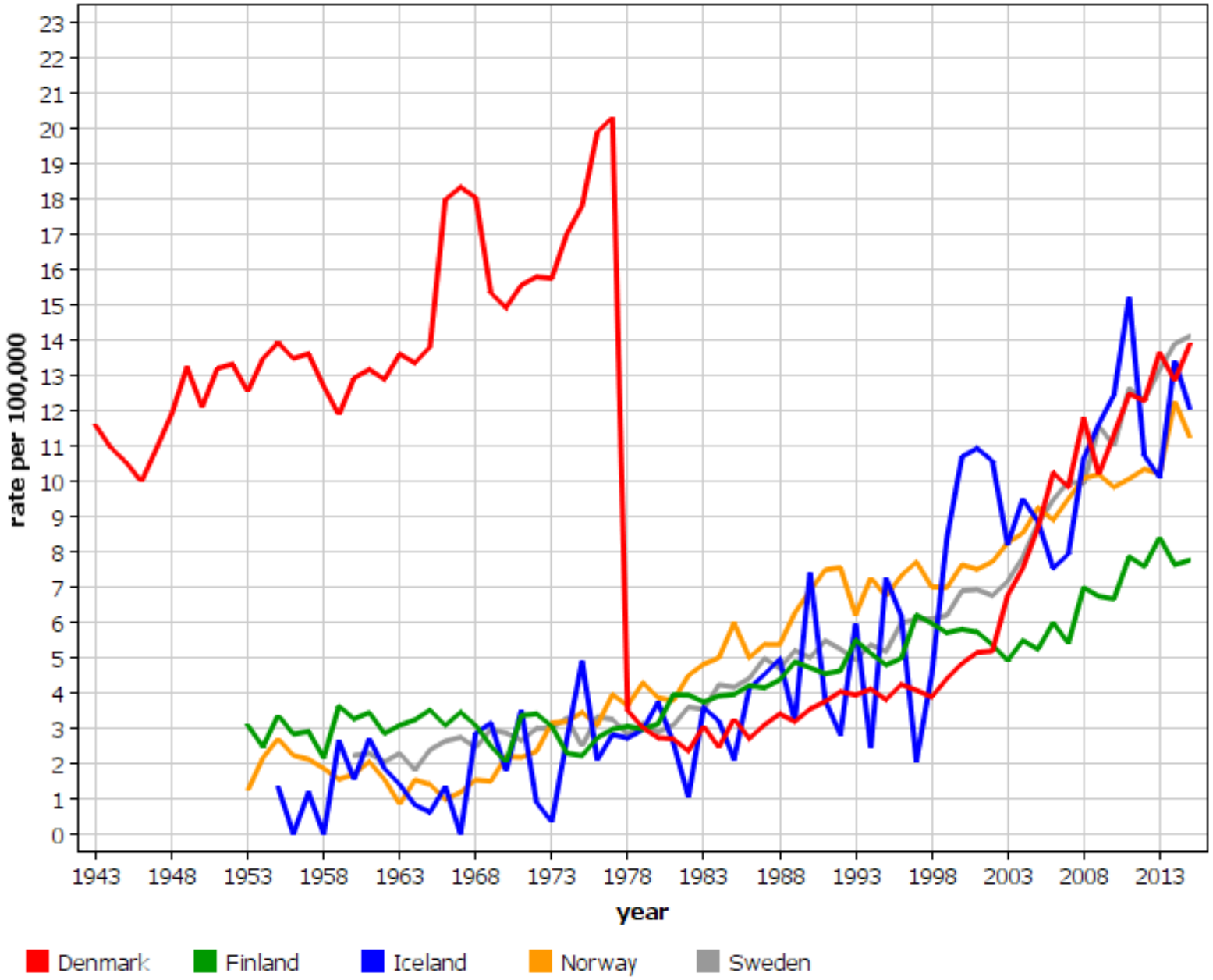
Incidence (2006-2015)
Pancreas: Male



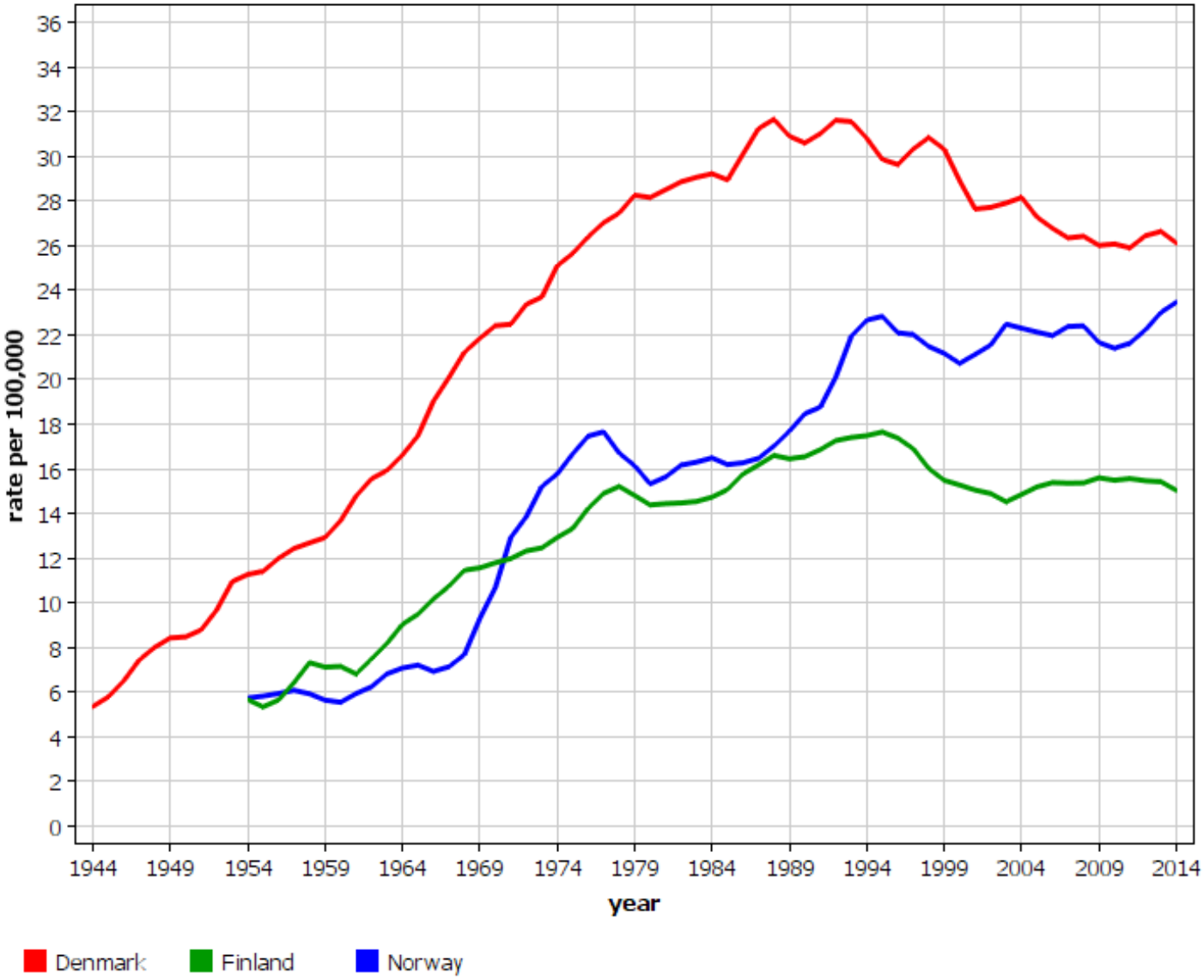
Does it matter

(in SIR estimates)?

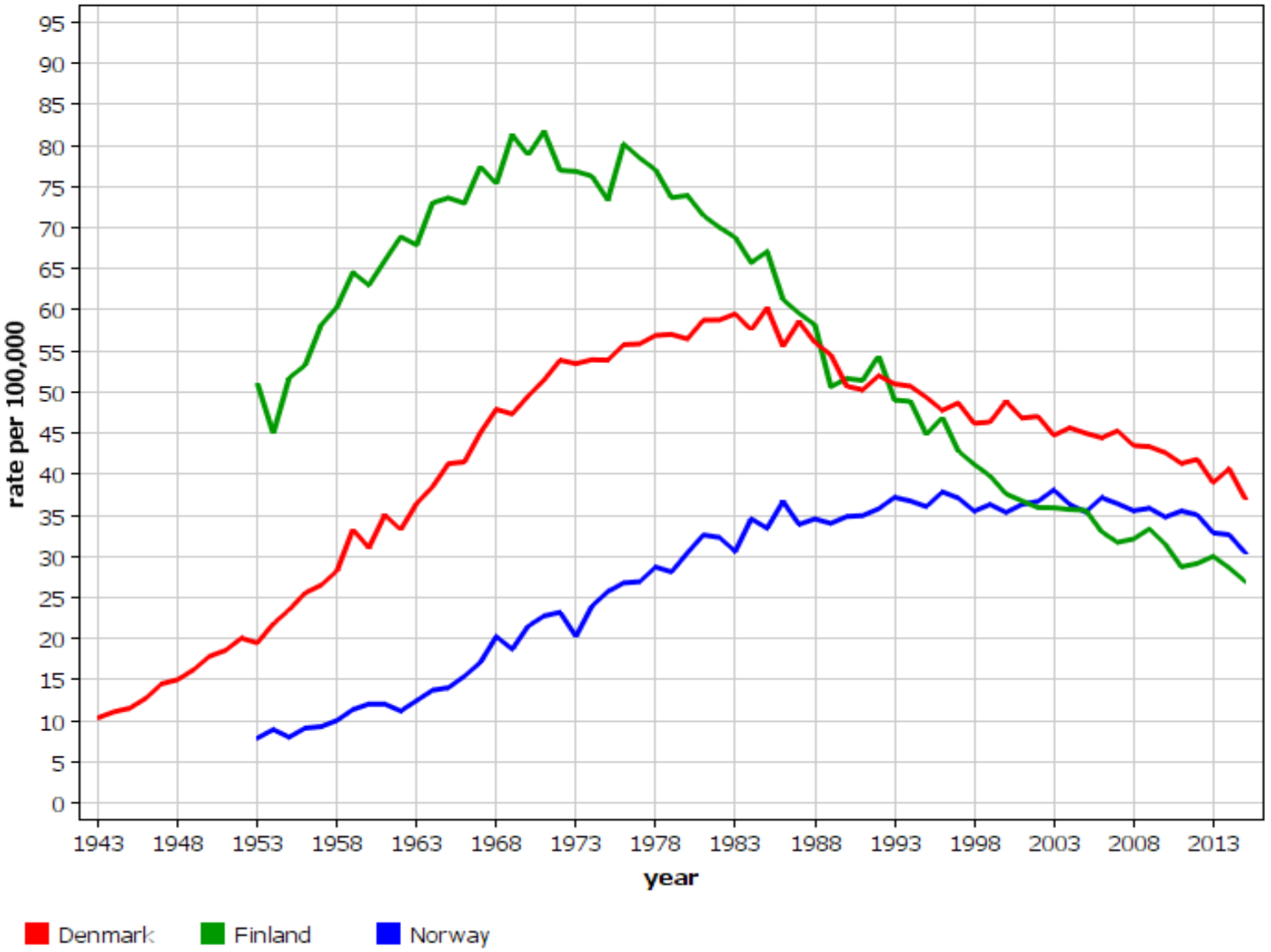
Skin, non-melanoma
Incidence: ASR (World), Female age 0-85+



Bladder etc.
Incidence: ASR (World), Male age 0-85+



Lung
Incidence: ASR (World), Male age 0-85+



Effect of primary prevention:

Anti-Smoking Policy

(1990s +)

Lung cancer, Nordic **men**

Effect of primary prevention:

Anti-Smoking Policy

(1990s +)

Lung cancer, Nordic **women**

Conclusion

Are the Nordic cancer registries similar?

YES

NO

EXCERCISES

Practicals:

desing your own register-based study on a given topic

Purpose

- thinking
  - Is a design that ”all others have used” the best one?
- realities
  - What can and what can not be done?
- creativity in design
  - Epidemiology is ***arts***.

Requirements for a register-based record linkage **study**

- **Idea => hypothesis**
- **Register/file of exposed persons & exposures**
- **Data indicating when the persons were at risk**
- **Register of outcome events**
- **Data on confounders (from another register?)**
- **Linkage key**
- **Permissions**
- **Money**
- **Epidemiological skills**
- **Imagination, creativeness, fearlessness**

Main data sources
(computerised and linkable)

Whole population

Population sample

Usually not true:
"This cannot be done."

Statistics Finland
* Longitudinal
1950
–198
occup
SES, p
* cause

Social Insurance Insti
* reimbursable di
* reimbu

Registry
* **cancer incidence 1953+**
* cancer screenings 1963+

stitute tional H)
of persons exposed to carcinogens (ASA)
* numerous cohorts of exposed persons

Population Register Center (VRK) 1967+
* complete ID
* place of birth
* residencial history
* living coordinates
* living conditions
* parent-child links
* PIDs of children
* immigration/emigration date
* date of death

National Research and Development Centre for Welfare and Health (Stakes)
* hospital discharges
* birth parameters
* malformations
* Finnish Information Centre for Register Research (RETKI)

2009: THL

Public Health Institute (KTL)
* Survey data (Mini Finland 1967, FinRisk 1972+, Adult Population Health Survey 1978+): life habits (smoking, alcohol, diet, BMI, physical exercise etc)
* Blood sera (maternity cohort etc.)

Cohort study or case-control study?

- ✓ Text books: cohort studies are expensive
- ✓ This is not quite true in Nordic countries: register-based cohort studies are
  - ✓ cheap
  - ✓ rapid
  - ✓ powerful
- ✓ They are also qualitatively good, if
  - ✓ registers are non-selective
  - ✓ accuracy of the data is good
  - ✓ there are people who understand the pitfalls
- ✓ Case-control approach is justified
  - ✓ if routine registers offer low-quality data
  - ✓ if additional data need to be collected
  - ✓ if laboratory tests etc. are required

Exercise: plan a register-based study

1. Does asbestos at work cause peritoneal mesothelioma (very rare cancer, cannot be studied in normal work place cohorts)?
2. Does living close to dump areas cause cancer?
3. Does baldness medication (prescribtion drug with some hormonal effects) increase risk of male breast cancer?
4. Do jetlags increase your cancer risk?