

Impact of Growth Hormone Deficiency (and Replacement) on Mortality in Adults

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Mortality in hypopituitary patients:

- Patients:
 - "patients with pituitary tumour or pituitary insufficiency" 1956-1987
 - "laboratory evidence of thyroid, adrenocortical, or gonadal insufficiency"
 - 333 (204 men, 129 women)
- GH deficiency:
 - 51/53,
 - percentage treated: not mentioned
- Mortality increased in:
 - total
 - *women compared to men (ns)*

Ref: Rosen T, Bengtsson BA. Lancet 1990.

Mortality in hypopituitary patients:

- Patients:
 - "all patients investigated for hypopituitarism" 1967-1993
 - "at least one biochemically confirmed hypofunctioning pituitary axis"
 - 172 (102 men, 70 women)
 - age: 1-78 yrs
- GH deficiency:
 - 94/98,
 - percentage treated: not mentioned
- Mortality increased in:
 - total
 - *women compared to men (ns)*
 - younger patients
 - radiotherapy

Ref: Bates AS et al. J Clin Endocrinol Metab 1996

Mortality in hypopituitary patients:

- Patients:
 - patients operated for pituitary tumour 1946-1988
 - 344 (214 men, 130 women)
 - age 7-67 yrs – 10th and 90th percentile
- GH deficiency:
 - 56/62,
 - percentage treated: not mentioned
- Mortality increased in:
 - total
 - women compared to men
 - *younger patients (ns)*



Queen Margrethe II and mortality in Danish women

Hugo Kesteloot

All-cause mortality in women is declining in all western European countries, apart from in Danish women. All-cause mortality in Danish women, age-adjusted to 45–74 years was compared with all-cause mortality in women in Scotland and with the mean of the other countries of the European Union for 1970–96. The decline of all-cause mortality in Danish women stopped in 1978 whereas the decline continued in Scotland. In 1996, all-cause mortality was 48% higher in Denmark than that of the mean for the European Union countries. Many Danish women are smokers. Halting of the decline in mortality occurred about 5 years after the ascension to the throne of Denmark by Queen Margrethe II. The queen is very popular in Denmark and a known cigarette smoker. As a role model for women, the Queen's example could offer an explanation for the unusual mortality in Danish women.

In the western world, there was a decline in all-cause and total cardiovascular mortality rates in women between 1955 and 1995, but at different rates in each country.^{1,2} This decline occurred even during those periods when all-cause mortality in men increased. Between 1955 and 1975, Scandinavian countries including Denmark had low-mortality rates compared with most other European countries, except for some Mediterranean countries, such as Greece. In Denmark, all-cause mortality in women (age-adjusted to 45–74 years) declined³ between 1970 and 1978. This decline, however, stopped at around 1978 and was followed by a slight increase. This pattern was not seen in Scotland, a country with a high mortality rate in women, nor in any other western European country.

Mortality rates among women in Denmark

The ratio of male to female mortality at age 55–64 years during 1988–91 was 1.52 in Denmark and 1.64 in Scotland, compared with a mean of 2.05 (range 1.37–2.66) in 36 other industrialised countries. The ratio was 1.96 in Sweden, 2.03 in Norway, and 2.69 in Finland.⁴ Until 1974, women in Denmark had a lower mortality than the mean of western European countries but in 1996 it was about 48% higher (figure 1). This difference is unexpected, considering that the Danish population has the highest income in the European Union, excellent education facilities, comprehensive social security with medical coverage for all, and a high standard of medical care. The social status of women in Denmark, including in education, is among the highest in the world.⁵ Of 50 industrialised countries, including most of the former Soviet Russian Republics, Japanese women have the lowest all-cause mortality, Danish women ranked 39th and 35th in the age classes 55–64 years and 65–74 years, respectively. By contrast, Danish men ranked 32nd in both age classes.¹

Smoking in Danish women

There is a high prevalence of cigarette smoking among women in Denmark. Among 31 European countries,

Danish women older than age 15 years had the highest smoking prevalence of all countries—33% versus a median of 23%. In the Monica study,⁶ comparing 30 different regions in Europe, Danish women aged 35–64 years also had the highest prevalence of smoking (45% vs a median of 24%). Smoking prevalence is a better indicator of cigarette smoking habits in women than in men, because few women smoke pipe or cigars. Cigarette smoking is associated with lung cancer, all cancers, cardiovascular mortality, and therefore with all-cause mortality. All-cause mortality is the only measure of mortality that does not need standardisation.

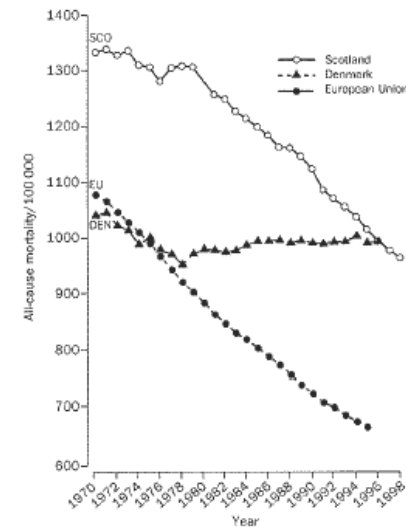


Figure 1: All-cause mortality in women. Age-adjusted 45–74 years per 100 000 population, 3-yearly smoothed data.

Lancet 2001; 357: 871–72

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Why Danes are smug: comparative study of life satisfaction in the European Union

Kaare Christensen, Anne Maria Herskind, James W Vaupel

Introduction

Danes are unrivalled in satisfaction with life. The University of Leicester recently published the World Map of Happiness (http://news.bbc.co.uk/2/shared/bsp/hi/pdfs/28_07_06_happiness_map.pdf) with Denmark as number one. For more than 50 years this country with five million inhabitants has ranked first in Eurobarometer surveys (europaeu.int/comm/public_opinion/index_en.htm). More than two thirds of Danes are "very satisfied" with their lives according to these surveys. In no other Eurobarometer country has this proportion exceeded a half, and for most of the countries the proportion is less than a third (figure). To explain Danish contentment we sifted through literature, statistics, and common knowledge.

Hypotheses, methods, and results

We focused on accounting for why life satisfaction in Denmark substantially exceeds that in Sweden and Finland, the two Eurobarometer countries most similar to Denmark. We have ordered our hypotheses roughly from most to least implausible.

Hair colour—It may indeed be the case that "blondes have more fun." This hypothesis was launched in the 1950s by a commercial slogan for a hair dye and was cemented in popular culture in 1978 by rock musician Rod Stewart's album of the same title. Sweden, however, has a higher prevalence of blondes than Denmark.¹

Genes—Genetic factors might influence differences in life satisfaction within a country,² and Danes might have a special genetic constitution. Genotypes in Sweden, however, are similar to those in Denmark because most Swedes were Danes until the 17th century.

Food—Meals in Denmark can be politely described as unmemorable. "Danish cuisine" is an oxymoron, except perhaps the open faced "butter breads" that accompany the beer and aquavit Danes consume for lunch. Older Danes satisfy their hunger with potatoes, gravy, and a bit of pork, and younger ones devour hotdogs, hamburgers, and Baltic-style pizzas. Danish cuisine has some similarities with food from Switzerland and Austria, the second and third happiest nations according to the World Map of Happiness; this suggests that the consumption of comfort foods may be important for life satisfaction.

Climate—Danes bask in a somewhat colder and cloudier version of the balmy English weather. In 2004 there were 1539 sunshine hours in Copenhagen compared with 1573 in London and 1821 in Stockholm, not to mention 2538 in Rome (Danish Meteorological Institute, www.dmi.dk). A remarkable feature is the oscillation in life satisfaction during the year in Denmark. The proportion given in the figure is the average of spring and autumn assessments; satisfaction

with life is, for good reason, as much as 38% higher in spring than autumn.

Native tongue—The Danish word "tilfreds" may have a subtly different meaning than the English "satisfied" or the Swedish "nöjd." A millennium ago the three languages were close relatives, but today they differ considerably with English evolving from the rich merger of Germanic and Latin sources, Swedish developing into an effeminate sing song, and Danish faithfully preserving the guttural grunts of the Vikings. The root meaning of the Danish "tilfreds" is "at peace" and it can be translated as the English "contented" as well as "satisfied." Having considered the issue at length, the bilingual authors of this article conclude that it is difficult to be "tilfreds" if you are not satisfied and that very satisfied people are almost always very "tilfreds." Studies of the multilingual Swiss population show a consistent reporting level in Switzerland that is different from that in France, Italy, and Germany and show no cross border similarity dependent on language group in Switzerland.³

Alcohol and smoking—High levels of smoking and drinking are associated with low wellbeing, but Danes are among those with the highest consumption in Europe. This is reflected in causes of death and low life expectancy.⁴ A reviewer of our paper suggested that one reason that Danes seem smug may be that they were drunk when they participated in the Eurobarometer surveys.

Marriage and children—It is well documented that marriage and having children are both associated with life satisfaction. Denmark is the number one country in Europe with regard to marriages, but the divorce rate is correspondingly high, giving Denmark a leading position in the EU second only to Belgium (Statistics Denmark, www.dst.dk/HomeUK.aspx). When it comes to children, Denmark is among the EU countries with the highest fertility. Recent Danish research, however, suggests that children beyond the first child decrease life satisfaction, especially for women.⁵

General health—Good health is associated with life satisfaction. If self reported health is considered, Danes do well. When measured objectively, however, by diagnosed physical conditions and performance, the health of Danes is mediocre.⁶ The life expectancy of Denmark falls 13th among the 15 old EU countries (news.cia.gov/cia/publications/factbook/index.html).

Welfare state—Cross national studies show that a prosperous economy and a well functioning democracy are associated with a high level of wellbeing,⁷ although longitudinal studies of life satisfaction do not indicate any stable

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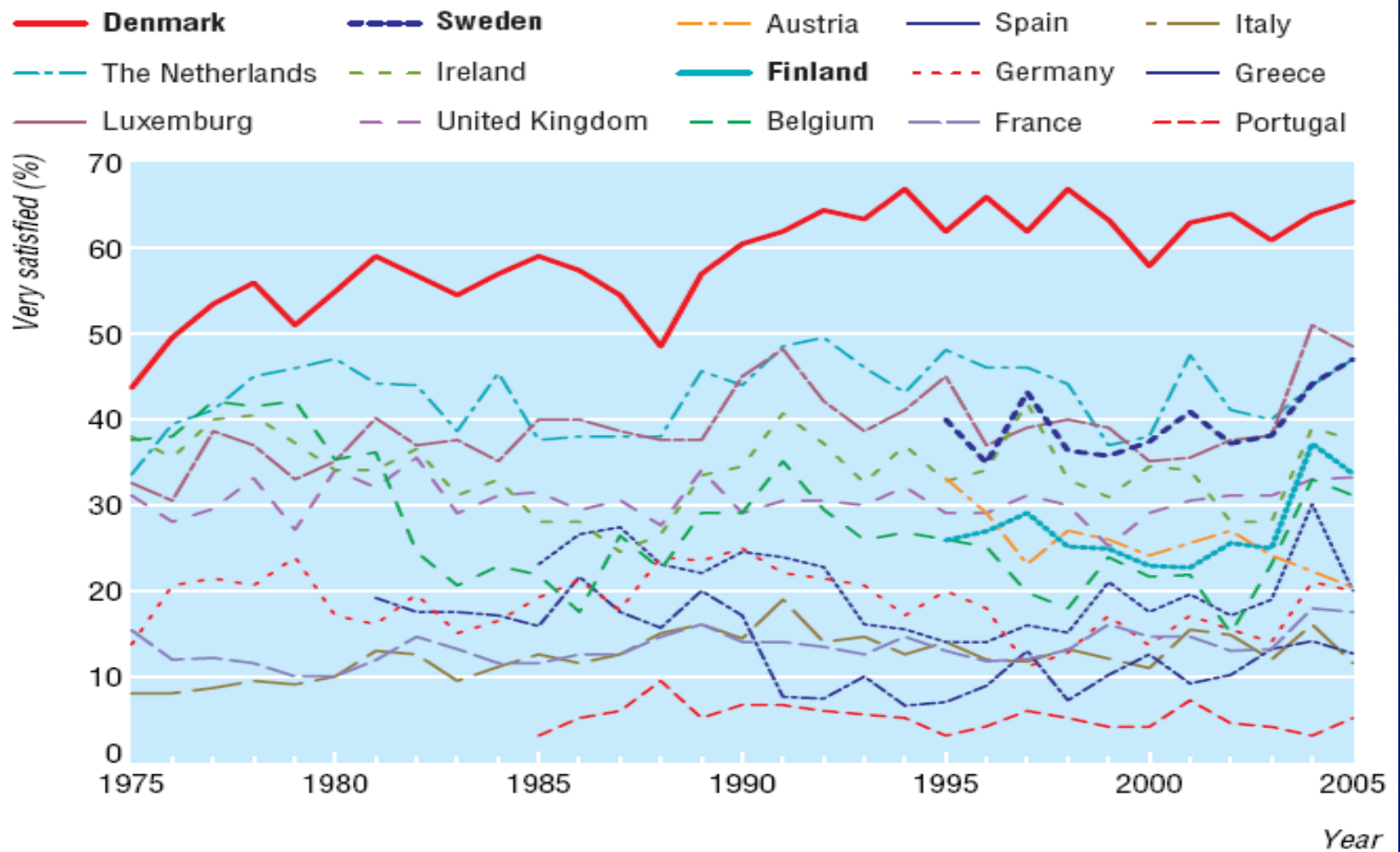
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Dane, at peace



Proportion who report to be very satisfied in 15 EU countries according to Eurobarometers (europa.eu.int/comm/public_opinion/index_en.htm)

Identification of Patients



A historical view

1645 Church files

1769 The First Census

1856 The First Disease Registry -*The Leprosy Registry in Norway*

1924 National Population Registry

1925 The Registry of Cerebral Paresis

1937 The Registry of Tuberculosis

1943 The Cancer Registry

1943 The Registry of Causes of Death

1953 The Central Psychiatric Registry

1968 The Civil Registration System

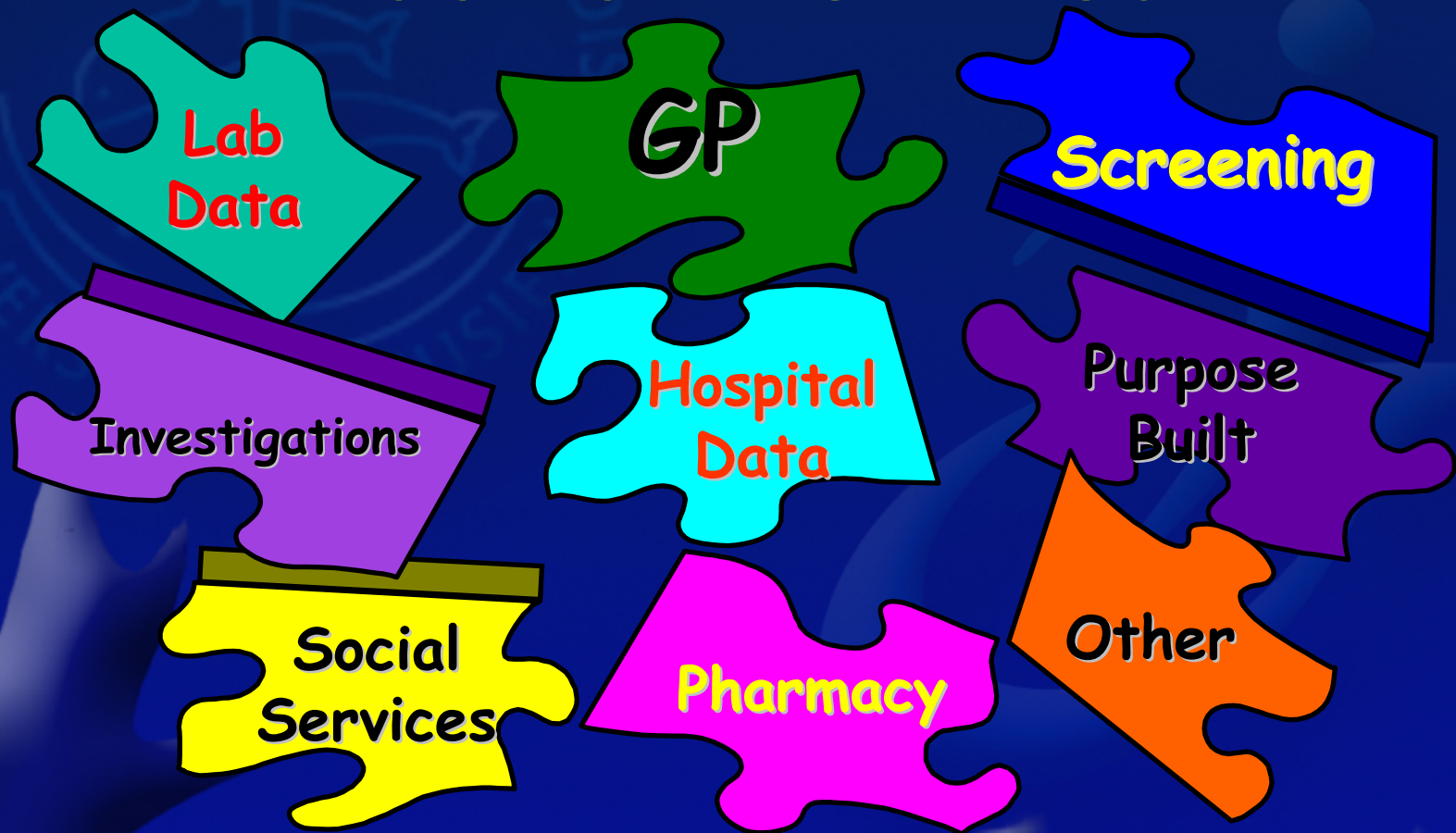
1973 The Medical Birth Registry

1977 The National Registry of Patients

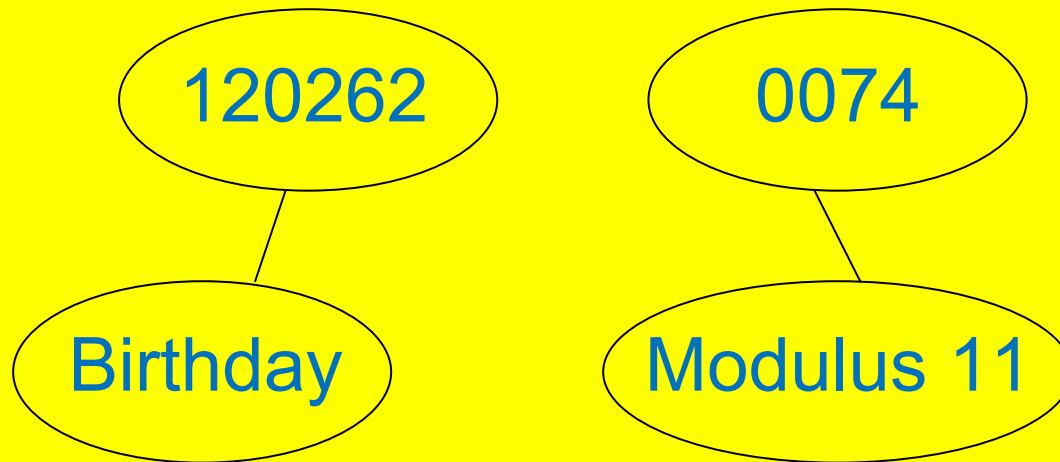
1989/90 Regional Prescription Database

1995 The National Prescription Registry

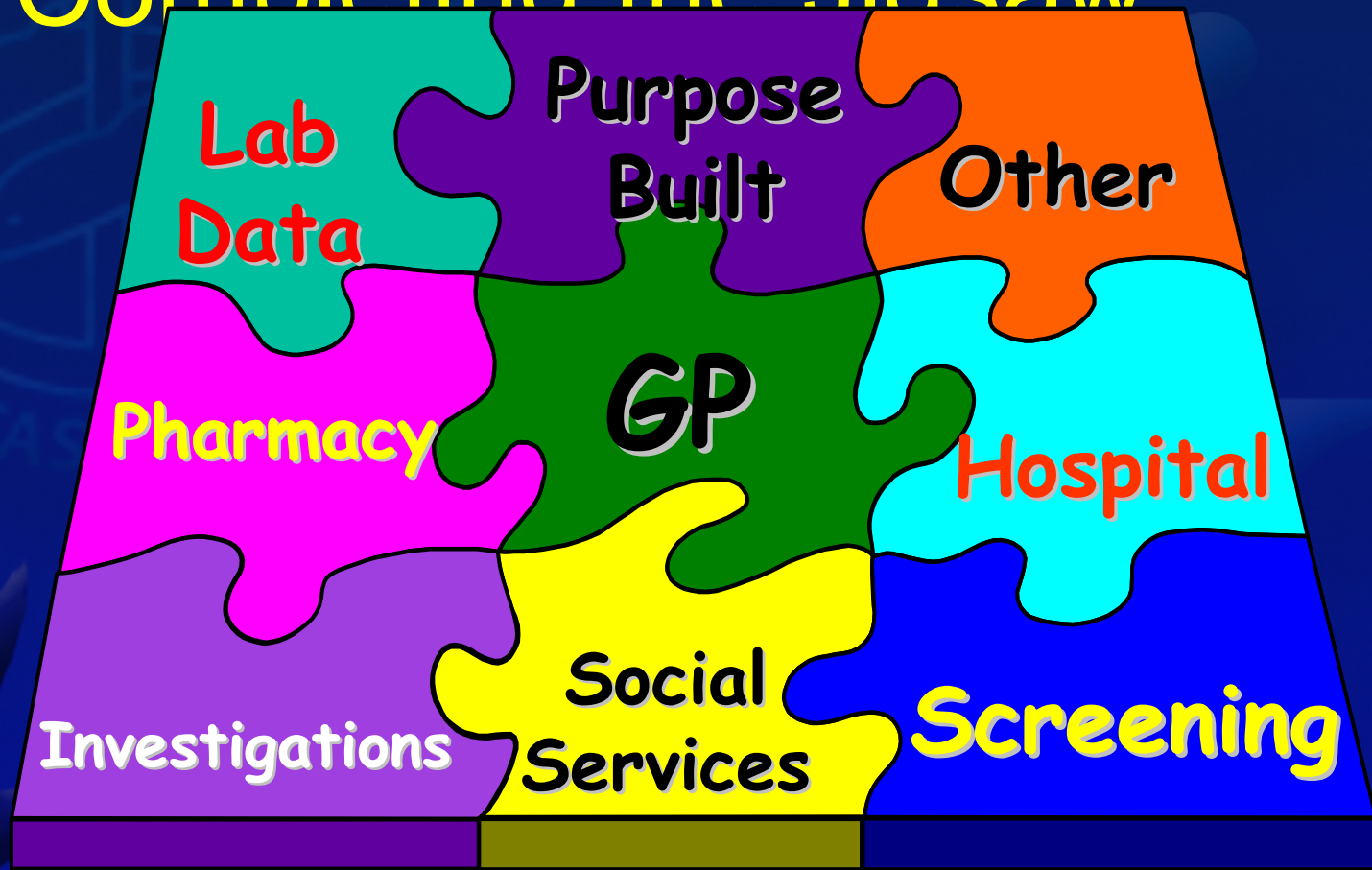
Data, data everywhere. But not much of it is linked



Personal Identification Number



Record-Linked Data – Completing the Jigsaw



Identification of Patients



Identification of Patients

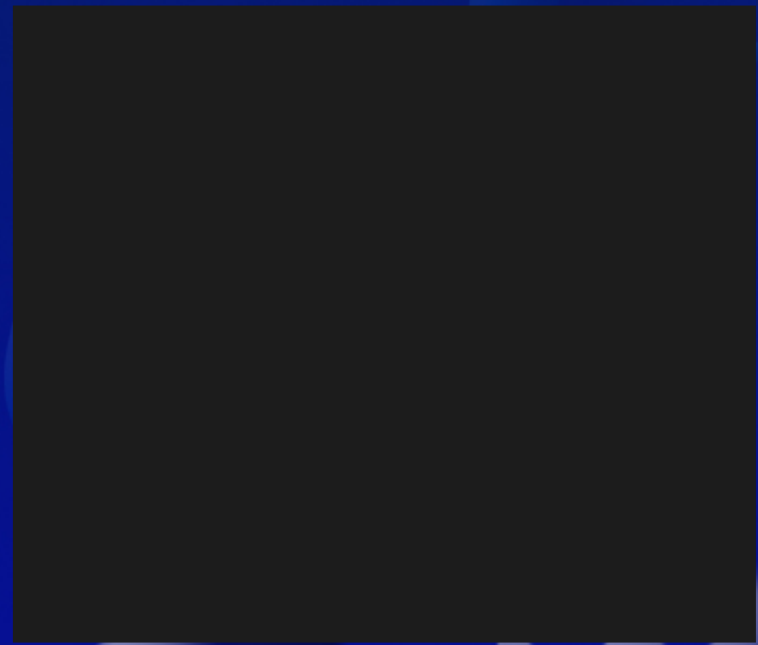


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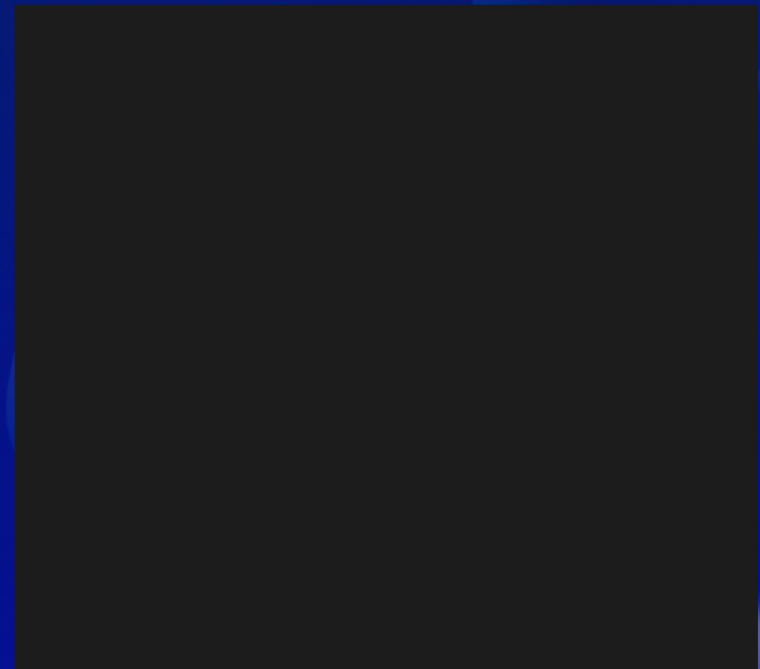
Citizens



Cases



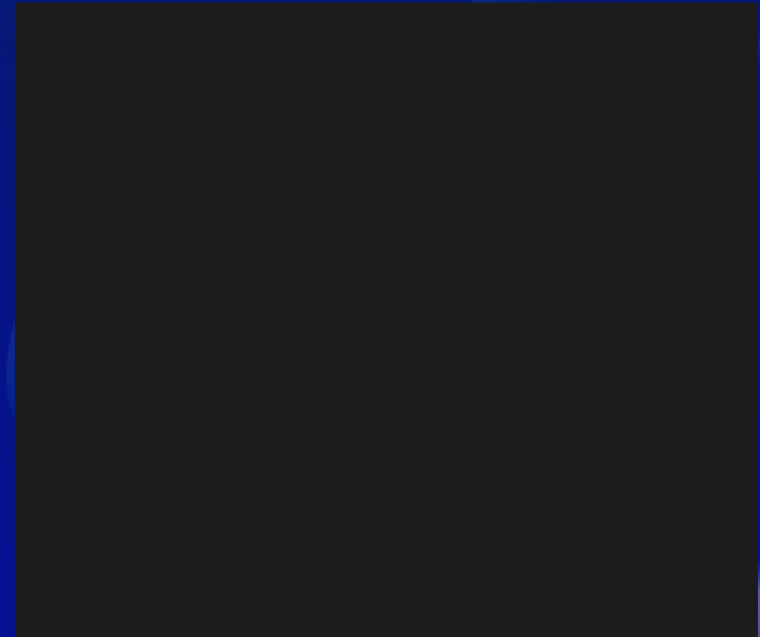
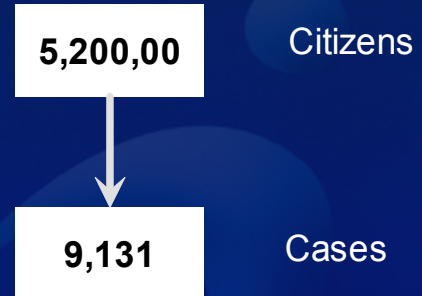
Identification of Patients



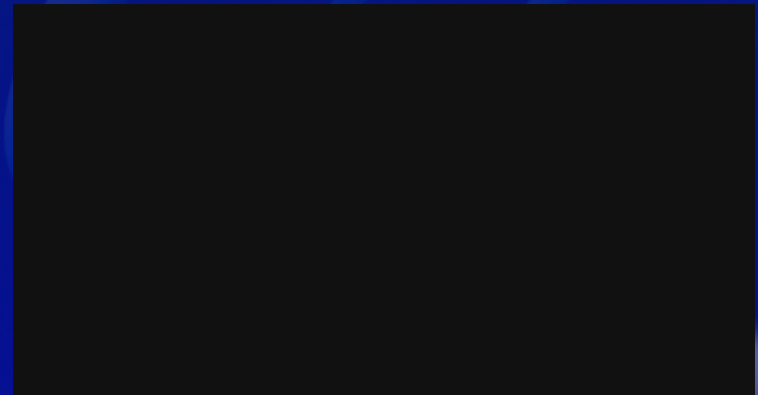
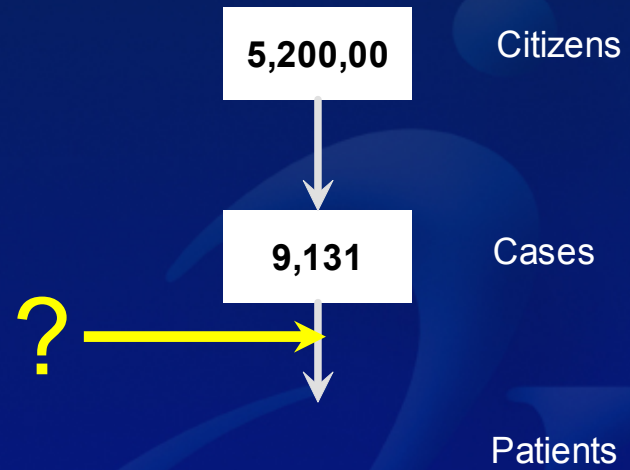
Identification of Patients

- The National Patients Registry
- The Cancer Registry
- The Causes of Deaths Registry

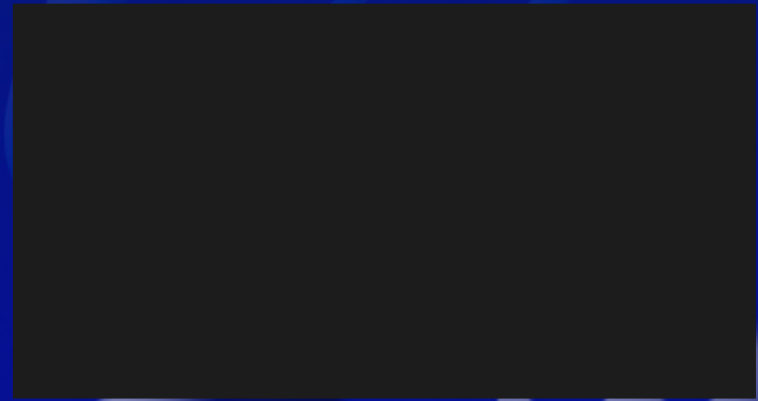
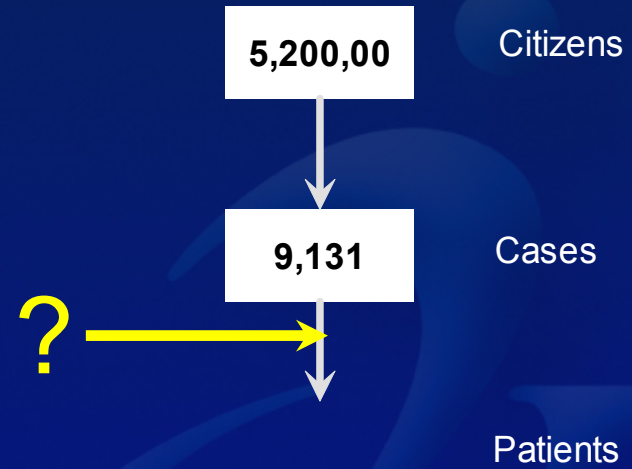
Identification of Patients



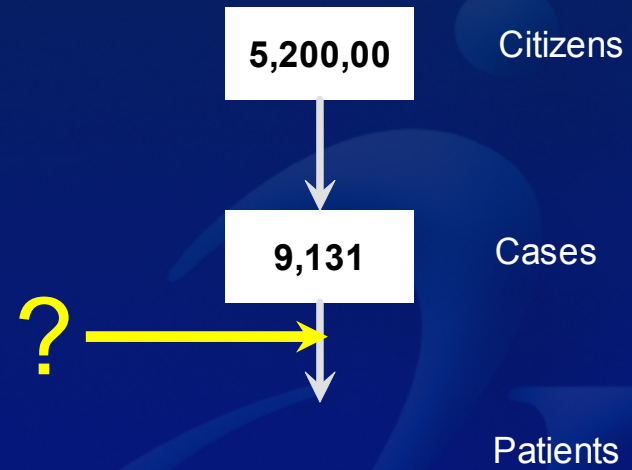
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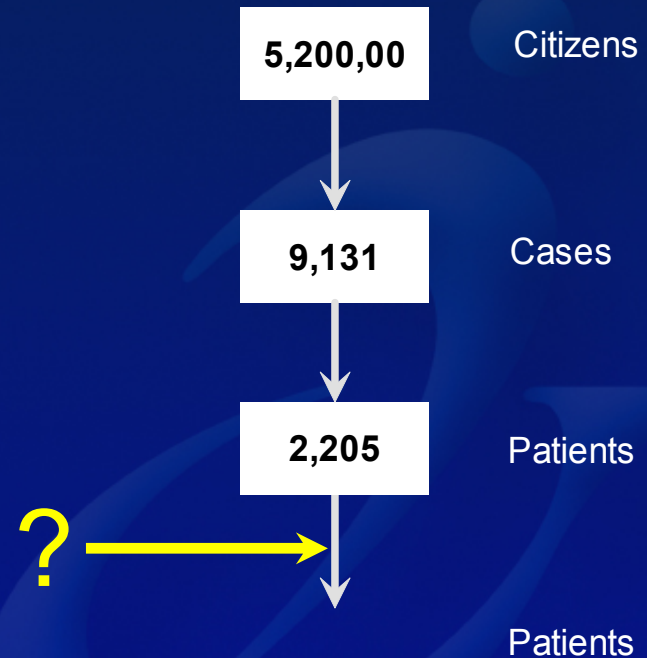
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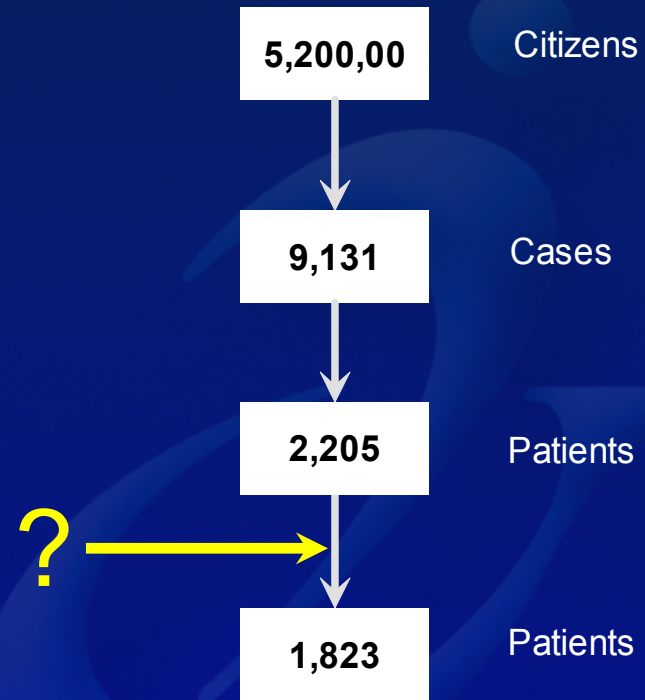


Identification of Patients



Identification of Patients

- Study period
– 1980-1999

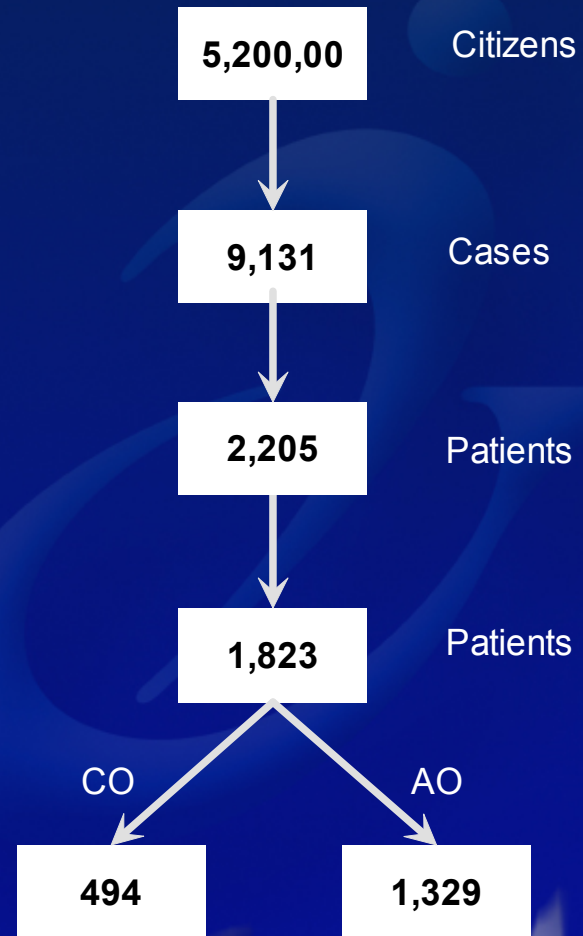





PREVALENCE OF GHD:

350/mio

Identification of Patients





MORBIDITY AND MORTALITY

Materials and Methods

Controls

- The Office of Civil Registrations
 - 1:5 matched on gender and age

and diseases

- The National Patients Registry
 - Cause specific morbidity

using waiting time until first registration

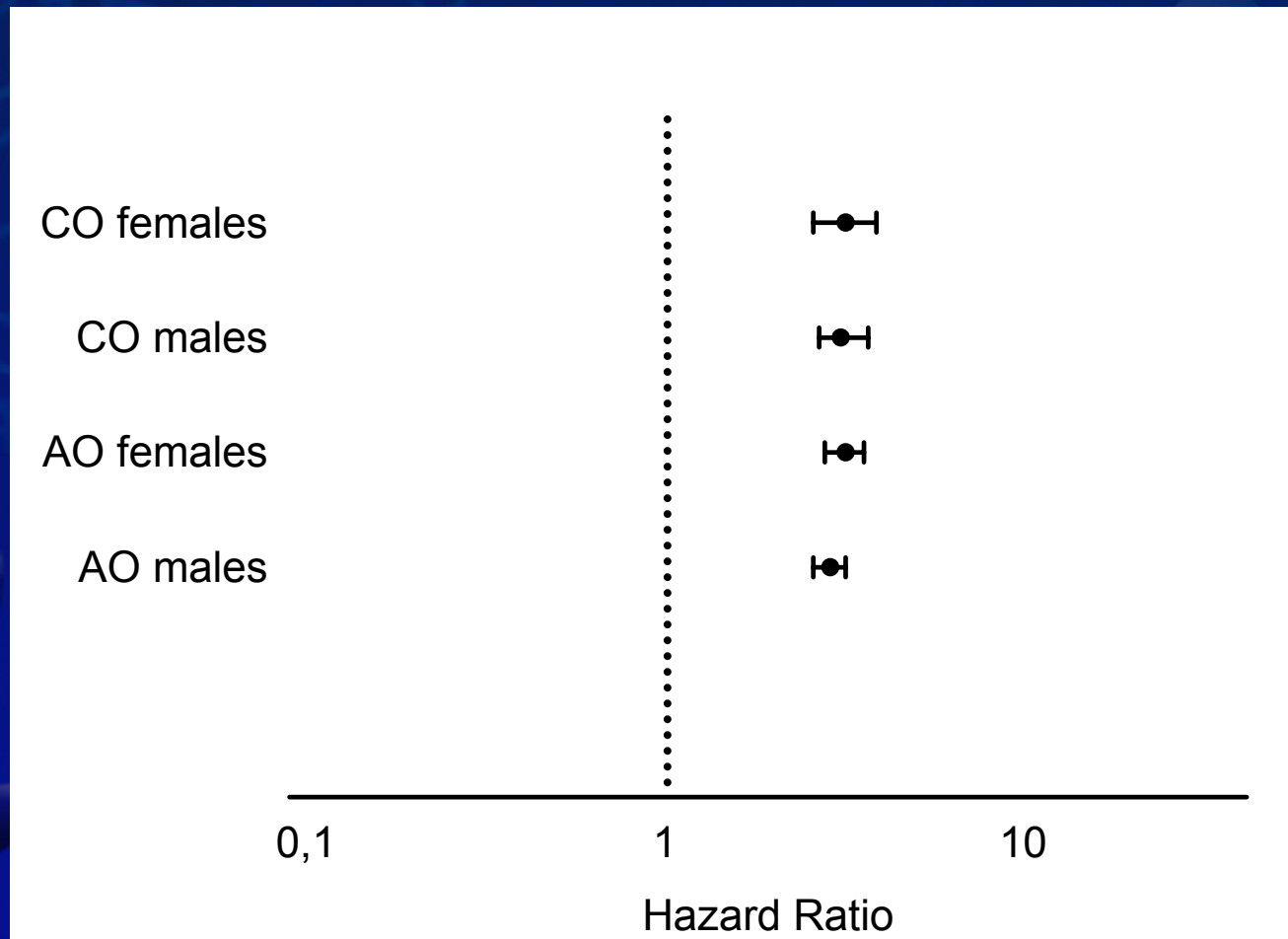
Childhood onset GHD

| | CO | |
|------------------------------|-------|---------|
| | Males | Females |
| Number of patients | 299 | 187 |
| Irradiation (%) | 30 | |
| Surgery (%) | 35 | |
| Growth hormone treatment (%) | 74 | |
| No other deficits (%) | 35 | |
| 1-2 additional deficits (%) | 35 | |
| 3-4 additional deficits (%) | 30 | |

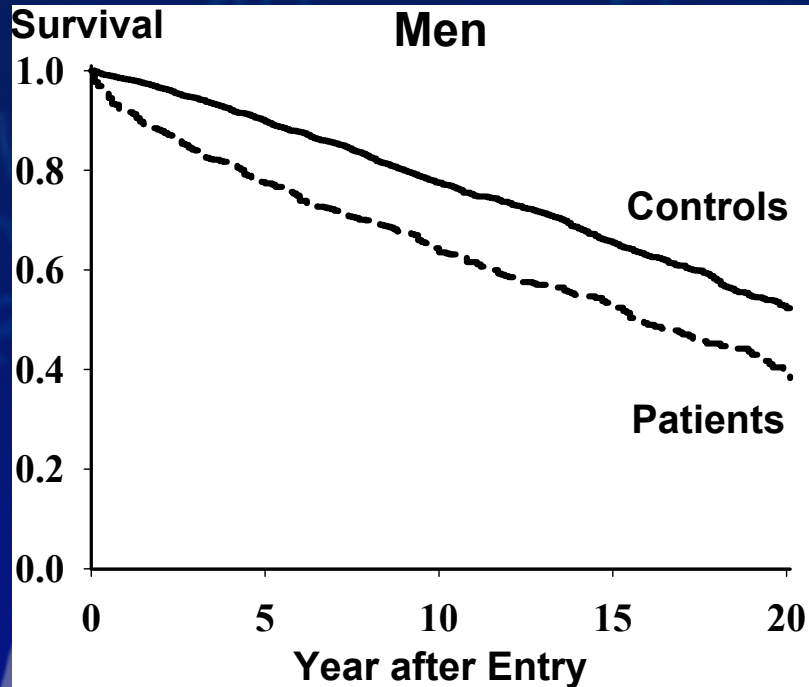
Adult onset GHD

| | AO | |
|--|-----------|-----------|
| | Males | Females |
| Number of patients | 732 | 576 |
| Irradiation (%) | 20 | |
| Surgery (%) | 70 | |
| Growth hormone treatment (%) | 30 | |
| No other deficits (%) | 6 | 9 |
| 1-2 additional deficits (%) | 33 | 47 |
| 3-4 additional deficits (%) | 61 | 44 |
| <i>Treated hypogonadism (%)</i> | 90 | 75 |

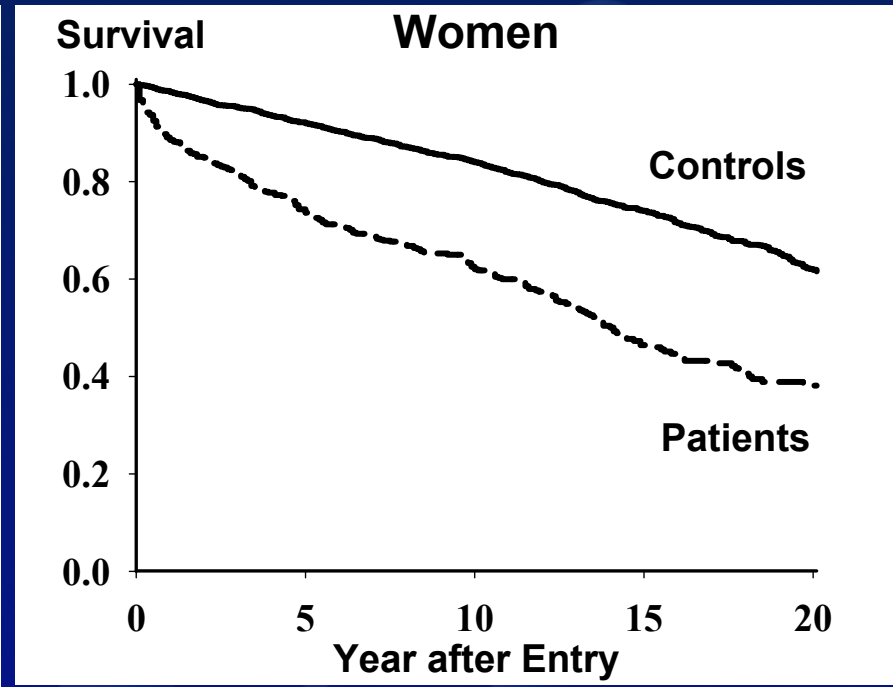
Total morbidity



Mortality in the Danish Cohort:

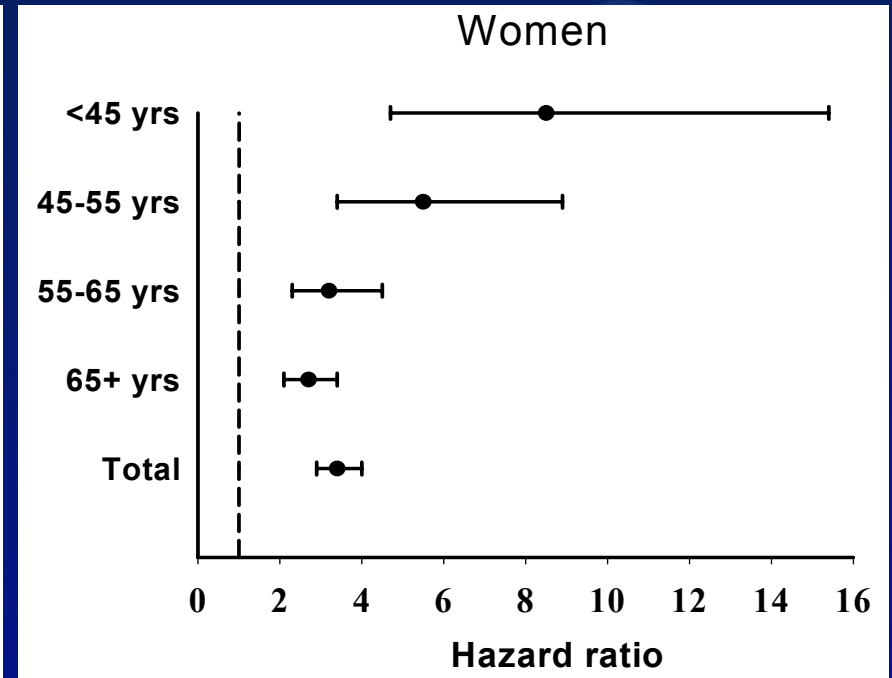
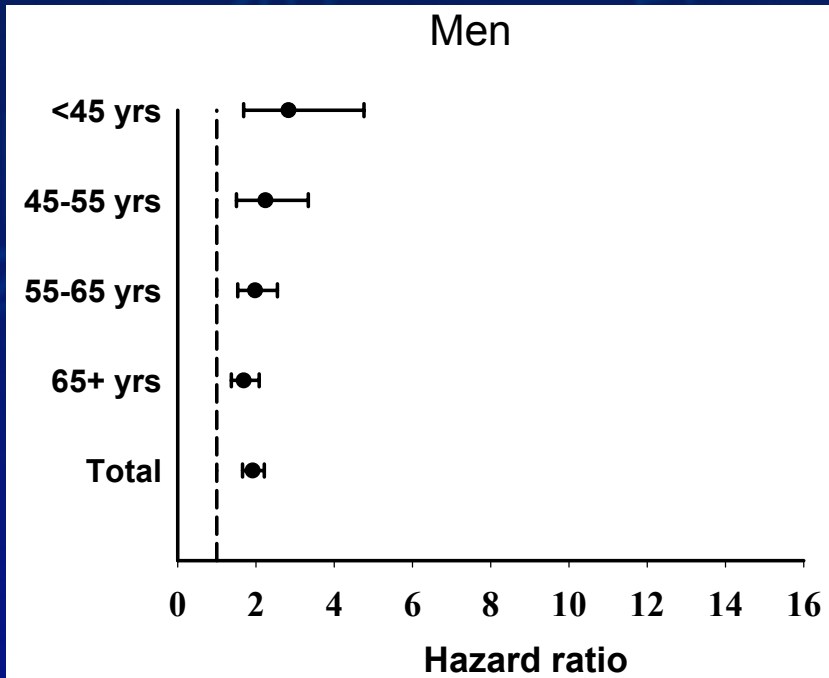


Log rank $p < 0.0001$
Deaths: 329 observed
208.0 expected



Log rank $p < 0.0001$
Deaths: 275 observed
117.7 expected

Mortality in the Danish Cohort:



- Decreasing hazard ratio with increasing age
- Increased hazard ratio women compared to men

CONCLUSION

- Prevalence of GHD in Denmark is 350/mio – of which 100 is of childhood onset
- Morbidity is significantly increased – from multiple causes
- Allcause mortality is increased – in particular among younger female

Epidemiology of adult GHD

- mortality in relation to GH replacement therapy

| | men – not treated | women – not treated | men – treated | women – treated |
|------------------------------------|----------------------|------------------------|------------------|--------------------|
| Number of patients | 560 | 456 | 184 | 129 |
| Percentage tested for GHD # | 13.9 | 14.9 | 78.8 | 82.2 |

p<0.05, not treated vs. treated

Epidemiology of adult GHD

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|--|----------------------|------------------------|------------------|--------------------|
| Number of patients | 560 | 456 | 184 | 129 |
| Percentage tested for GHD # | 13.9 | 14.9 | 78.8 | 82.2 |
| Median age and range at onset (yrs) # | 56.1 (18.1-91.3) | 53.4 (18.4-94.6) | 43.4 (18.3-77.0) | 35.5 (18.0-71.0) |
| Median year and range of entry # | 1989 (1980-1999) | 1989 (1980-1999) | 1993 (1980-1999) | 1992 (1980-1999) |

p<0.05, not treated vs. treated

Epidemiology of adult GHD

- mortality in relation to GH replacement therapy

| | men – not treated | women – not treated | men – treated | women – treated |
|--------------------------------|----------------------|------------------------|------------------|--------------------|
| Irradiation (%) | 18.4 | 20.6 | 22.8 | 21.7 |
| Diagnosis of cancer (%) | 6.4 | 5.9 | 3.8 | 3.1 |
| Surgery (%) # | 68.0 | 64.0 | 78.8 | 79.1 |

p<0.05, not treated vs. treated

Epidemiology of adult GHD

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| Irradiation (%) | 18.4 | 20.6 | 22.8 | 21.7 |
| Diagnosis of cancer (%) | 6.4 | 5.9 | 3.8 | 3.1 |
| Surgery (%) # | 68.0 | 64.0 | 78.8 | 79.1 |
| No other deficits (%) # | 7.3 | 10.3 | 2.7 | 4.7 |
| 1-2 additional deficits (%) | 36.3 | 50.9 | 25.6 | 31.8 |
| 3-4 additional deficits (%) | 56.4 | 38.8 | 71.7 | 63.6 |

p<0.05, not treated vs. treated

Epidemiology of adult GHD

- mortality in relation to GH replacement therapy

| | men – not treated | women – not treated | men – treated | women – treated |
|--|----------------------|------------------------|------------------|--------------------|
| Number of patients | 560 | 456 | 184 | 129 |
| Number of deceased patients | 314 | 266 | 15 | 9 |

Conclusion:

- **The typical treated patient:**
 - younger at onset
 - entry more recently
 - tend to have
 - more operations
 - more additional deficits
 - whereas there are no differences in
 - percentage of irradiation
 - cancer as primary disease

Conclusion:

- **The questions remain:**
 - Can the younger age explain the difference in mortality?
 - Can the recent entry explain the difference in mortality?

Conclusion:

- **The questions remain:**
 - Can the younger age explain the difference in mortality?
 - Can the recent entry explain the difference in mortality?
 - Or can growth hormone treatment?

Thanks to:

- Kirstine Stochholm
- Claus Gravholt
- Torben Laursen
- Anders Green



- Det er vanskeligt at stille en diagnose i Deres tilfælde – jeg tror, det er spiritus.
- Na, ja ja, så kommer jeg igen, når doktoren er ædru!