Health registers as a ressource for research

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Epidemiology

- Distribution of diseases in
- Time
- Place
- Groups of people
- Main perspective is how this provides insights into etiology

Epidemiology in Denmark

- Resources
- Emerging new possibilities
- Barriers

Resources

- CPR
- Registers
- Socialized medicine
- Data protection

Data Protection in Denmark

- Complies with European Union rules
- Waives the need for informed consent when data are used for ”statistical and scientific purposes of significance to society”
- Stipulates rules for handeling of data
- Allows the use of individual information while minimizing the spread of these data
- No breaches after more than thirty years

More about registers……

- Family data

Schizophrenia

- Genes as well as environment are important
- No single major genes
- Many brain ”abnormalities” but none specific
- Some confirmed risk factors and early precursors but none that allow specific prevention

Is schizophrenia epidemiology difficult?

- Important public health problem but
- Low incidence and relatively low prevalence
- Difficult diagnosis
- Causes may act several decades prior to onset
- Multifactorial

What are schizophrenia epidemiologists doing?

- Look for large population-based samples
- Follow-up exposed and non-exposed individuals over long time periods
- Minimize bias due to non-participation
- Look for places with population-based registers!

Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk

Pedersen CB, Mortensen PB. Arch Gen Psychiatry 2001; 58: 1039-1046

Why study urban-rural differences in schizophrenia?

- Consistent finding
- Large relative risk
- Potentially large effect of preventive intervention

BUT

Intervention is not possible or relevant at present

Adjusted relative risk of schizophrenia in a population-based cohort according to family history, place of birth and season of birth

Variable	RR1*	95% CI	RR2	95% CI	RR3	95% CI
Family history						
Parental						
Father affected, Mother affected	65.49	(24.55-174.73)	59.74	(22.39-59.45)	46.90	(17.56-125.26)
Father affected, Mother not affected	8.34	(5.91-11.76)	7.97	(5.65-11.24)	7.20	(5.10-10.16)
Father not affected, Mother affected	11.33	(8.84-14.53)	10.19	(7.93-13.09)	9.31	(7.24-11.96)
Father not affected, Mother not affected (ref.)	1		1		1	
Father unknown, Mother affected	20.99	(12.59-35.00)	17.12	(10.24-28.64)	14.18	(8.48-23.70)
Father unknown, Mother not affected	2.48	(2.14-2.88)	2.45	(2.11-2.84)	2.00	(1.72-2.32)
Sibling						
One or more affected	9.04	(6.97-11.72)	7.33	(5.63-9.53)	6.99	(5.38-9.09)
No affected (ref.)	1		1		1	
Other factors						
Place of birth						
Capital	2.49	(2.21-2.80)	2.49	(2.20-2.80)	2.40	(2.13-2.70)
Capital suburb	1.64	(1.40-1.93)	1.64	(1.40-1.93)	1.62	(1.37-1.90)
Provincial cities	1.57	(1.36-1.81)	1.57	(1.36-1.81)	1.57	(1.36-1.81)
Provincial towns	1.24	(1.10-1.41)	1.24	(1.10-1.41)	1.24	(1.10-1.41)
Rural area (ref.)	1		1		1	
Greenland	3.71	(2.03-6.75)	3.71	(2.04-6.76)	3.71	(2.04-6.76)
Abroad	3.52	(2.74-4.52)	3.52	(2.73-4.52)	3.45	(2.69-4.44)
Unknown	1.28	(0.48-3.42)	1.26	(0.47-3.39)	1.22	(0.46-3.27)
Season of birth						
Amplitude|	1.12	(1.06-1.18)	1.11	(1.06-1.18)	1.11	(1.06-1.18)

* Relative Risk1: adjusted for age-gender interaction, calendar year, age of father and mother.
? Relative Risk2: as Relative Risk1 and adjusted for other variables in same category (family history/other factors).
? Relative Risk3: as Relative Risk1 and adjusted for all variables in the table.
| For all three adjustment scenarios (Relative Risk1, Relative Risk2, Relative Risk3) the estimated peak of the sine function was at 6 March (95 percent confidence interval from 6 February to 5 April).

Population attributable risk according to family history, place of birth, and season of birth

Variable	Population attributable risk %
Schizophrenia in one or both parents	3.8
Schizophrenia in one or more siblings	1.9
Schizophrenia in parent or sibling	5.5
Place of birth	34.6
Season of birth	10.5
Place and season of birth	41.4
All variables listed above	46.6

Some possible explanations for the urban-rural difference

- Methodological problems, e.g .detection bias
- Selective migration of schizophrenic patients or of persons genetically predisposed towards schizophrenia
- Urban-rural differences in exposure to risk factors or protective factors for schizophrenia

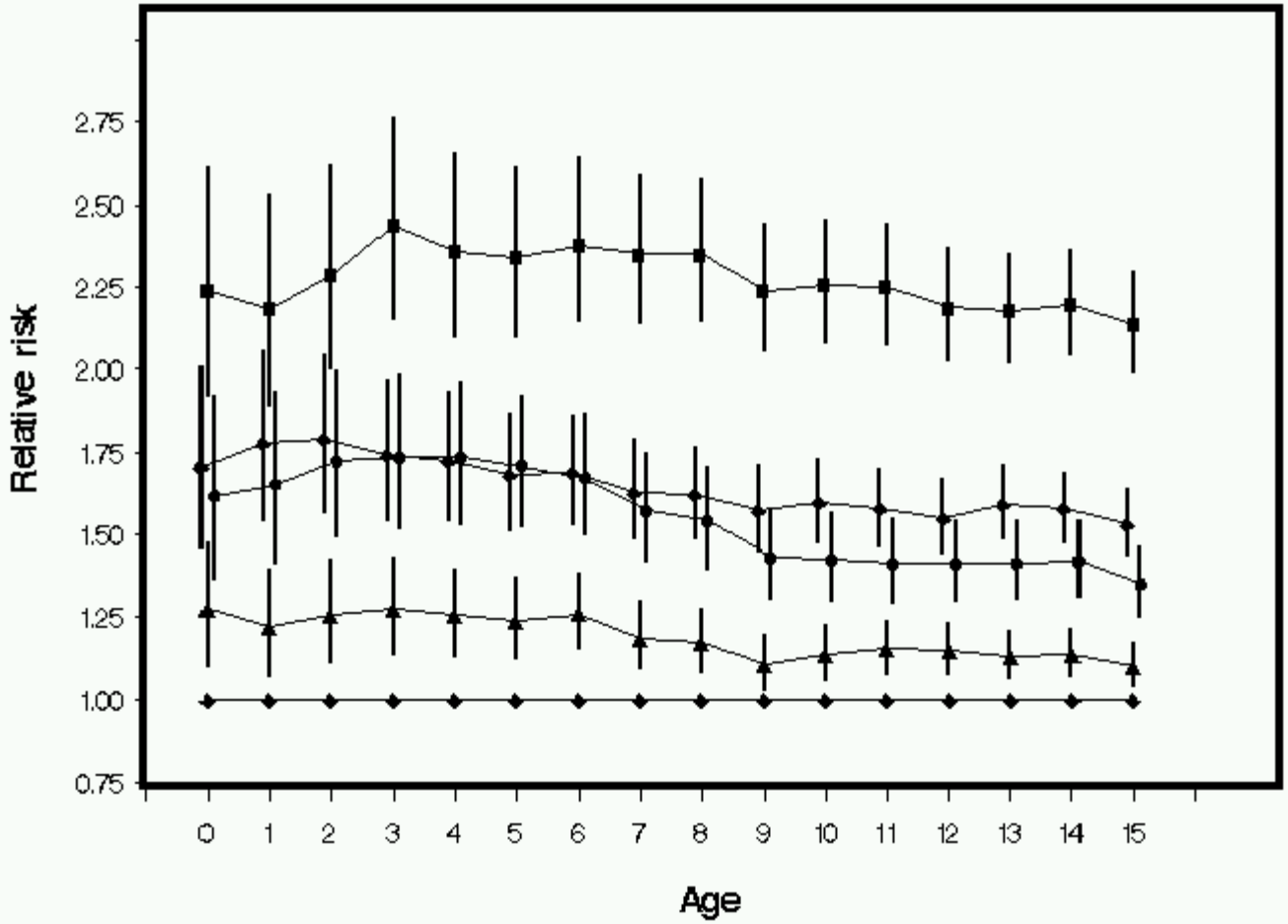
Distribution of 8,235 cases of schizophrenia and 27.1 million person-years at risk in a population based cohort of 1.89 million Danish people

Variable	No. of cases	Person-Years
Gender		
Male	5,462	14,150,781
Female	2,773	12,964,444
Maternal history		
Schizophrenia	234	86,524
Schizophrenia like psychoses	257	196,298
Other mental disorders	1,323	2,067,383
Mother not affected	6,421	24,765,019
Paternal history		
Schizophrenia	98	45,980
Schizophrenia like psychoses	106	96,483
Other mental disorders	888	1,573,112
Unknown father	640	990,119
Father not affected	6,503	24,409,531
History in siblings		
Schizophrenia	284	05,515
Schizophrenia like psychoses	115	80,535
Other mental disorders	546	705,134
No affected siblings	7,290	26,224,040
Urbanicity at birth		
Capital	2,594	5,008,126
Capital suburb	793	2,328,013
Provincial cities	1,073	3,451,055
Provincial towns	2,375	9,405,666
Rural area	1,400	6,922,365

Distribution of 8,235 cases of schizophrenia and 27.1 million person-years at risk in a population based cohort of 1.89 million Danish people

Variable	No. of cases	Person-Years
Urbanicity at age 5 years		
Capital	559	940,862
Capital suburb	635	1,720,492
Provincial cities	449	1,239,834
Provincial towns	836	3,220,339
Rural area	822	4,114,556
Other countries	29	80,010
Unknown	6	7,909
Unaccessible information	4,893	15,775,738
Urbanicity at age 10 years		
Capital	913	1,427,445
Capital suburb	1,139	2,915,199
Provincial cities	660	1,988,951
Provincial towns	1,416	5,369,404
Rural area	1,602	7,224,640
Other countries	47	131,801
Unknown	10	18,555
Unaccessible information	2,448	8,039,228
Urbanicity at age 15 years		
Capital	1,240	2,011,689
Capital suburb	1,559	4,017,883
Provincial cities	896	2,760,442
Provincial towns	2,020	7,629,875
Rural area	2,453	10,547,958
Other countries	57	126,824
Unknown	10	20,553
Total	8,235	27,115,224

Risk of schizophrenia according to urbanicity and age at residence



Adjusted relative risk of schizophrenia according to urbanicity in a population-based cohort of 1.89 million Danish people

Relative degree of urbanization at place of residence 5 years later

	No. of cases			Relative Risk (95% Confidence Interval)					
				First adjustment			Second adjustment		
Urbanicity	Higher	Same	Lower	Higher	Same	Lower	Higher	Same	Lower
Birth (Age 0 years)									
Capital	-	503	430	-	2.75 (2.39- 3.17)	2.08 (1.80-2.41)	-	2.53 (2.19-2.92)	1.94 (1.68-2.25)
Capital suburb	22	268	56	2.01 (1.30-3.10)	1.82 (1.55-2.15)	1.55 (1.16-2.06)	1.82 (1.18-2.81)	1.74 (1.48-2.05)	1.44 (1.08-1.92)
Provincial city	9	367	124	1.63 (0.84-3.16)	1.94 (1.67-2.25)	1.46 (1.19-1.80)	1.44 (0.74-2.79)	1.92 (1.65-2.24)	1.41 (1.14-1.73)
Provincial town	117	658	332	2.21 (1.79-2.74)	1.37 (1.20-1.57)	1.20 (1.03-1.40)	2.02 (1.63-2.51)	1.35 (1.18-1.55)	1.17 (1.00-1.37)
Rural area	100	315	-	1.95 (1.56-2.45)	1.00 (ref)	-	1.83 (1.46-2.30)	1.00 (ref)	-
Age 5 years									
Capital	-	434	117	-	2.70 (2.39-3.04)	2.04 (1.67-2.48)	-	2.63 (2.33-2.96)	1.53 (1.22-1.90)
Capital suburb	32	514	84	2.74 (1.92-3.90)	1.72 (1.54-1.93)	2.17 (1.73-2.72)	2.04 (1.41-2.95)	1.67 (1.49-1.87)	1.62 (1.26-2.07)
Provincial city	9	375	62	3.01 (1.56-5.82)	1.79 (1.58-2.03)	2.01 (1.55-2.61)	2.16 (1.11-4.21)	1.84 (1.63-2.09)	1.5 (1.16-2.02)
Provincial town	43	707	85	2.41 (1.77-3.27)	1.28 (1.16-1.42)	1.54 (1.23-1.92)	1.78 (1.29-2.46)	1.30 (1.17-1.45)	1.16 (0.90-1.48)
Rural area	116	704	-	1.92 (1.58-2.34)	1.00 (ref)	-	1.45 (1.16-1.81)	1.00 (ref)	-
Age 10 years									
Capital	-	725	179	-	2.38 (2.17-2.60)	2.61 (2.23-3.05)	-	2.41 (2.20-2.64)	1.93 (1.63-2.28)
Capital suburb	58	955	114	3.14 (2.42-4.09)	1.61 (1.49-1.75)	1.99 (1.64-2.41)	2.26 (1.73-2.96)	1.60 (1.47-1.73)	1.41 (1.16-1.73)
Provincial city	7	582	70	2.40 (1.14-5.04)	1.47 (1.34-1.62)	1.96 (1.54-2.50)	1.70 (0.81-3.59)	1.53 (1.39-1.69)	1.45 (1.13-1.86)
Provincial town	53	1,242	115	2.14 (1.63-2.82)	1.16 (1.07-1.25)	1.59 (1.31-1.92)	1.52 (1.14-2.01)	1.18 (1.10-1.28)	1.15 (0.94-1.40)
Rural area	180	1,417	-	1.94 (1.66-2.27)	1.00 (ref)	-	1.37 (1.16-1.62)	1.00 (ref)	-

*1: Estimates of relative risk were adjusted for gender and its interaction with age, calendar year, and mental illness in a parent or sibling.
*2 Estimates of relative risk were adjusted for all variables in *1 and for change of the municipality (Table 2).

Adjusted relative risks according to number of changes of municipality in a population based cohort of 1.89 million Danish people

Number of changes of municipality	No. of cases	Person-Years	Relative Risk (95% CI) $
From 0 to 4 years (p=0.34)			
None	1,004	3,890,119	1.00 (ref)
1	328	1,123,412	0.92 (0.82-1.05)
2	131	376,364	0.97 (0.80-1.16)
3+	90	217,165	0.91 (0.73-1.13)
From 5 to 9 years (p<0.0001)			
None	2,390	9,119,282	1.00 (ref)
1	601	1,570,244	1.18 (1.07-1.29)
2	216	433,266	1.29 (1.12-1.49)
3+	135	216,693	1.28 (1.07-1.54)
From 10 to 12 years (p<0.0001)			
None	4,845	17,244,968	1.00 (ref)
1	665	1,455,258	1.16 (1.07-1.26)
2	199	283,956	1.40 (1.21-1.62)
3+	78	91,815	1.36 (1.08-1.70)
From 13 to 14 years (p<0.0001)			
None	6,324	22,485,003	1.00 (ref)
1	696	1,240,162	1.45 (1.34-1.57)
2	184	217,825	1.79 (1.54-2.08)
3+	76	55,656	2.49 (1.97-3.13)

$: Estimates of relative risk were adjusted for age and its interaction with gender, calendar year, urbanicity at birth, mental illness in a parent or sibling, and change of the municipality.
Categories with unaccessible information are not shown.

Adjusted relative risk according to a log-linear model for urbanicity during upbringing

Urbanicity from 0 to 15 years	Relative Risk (95% CI) per year	Relative Risk (95% CI) per 15 year	P-value
Capital	1.07 (1.06-1.08)	2.75 (2.31-3.28)	
Capital suburb	1.04 (1.02-1.05)	1.69 (1.43-1.99)	
Provincial cities	1.04 (1.02-1.05)	1.71 (1.41-2.06)	
Provincial towns	1.02 (1.01-1.03)	1.32 (1.13-1.54)	
Rural area (ref)	1.00	1.00	<0.00001

The relative risk per 15 years is calculated by raising the relative risk per year to the 15th power, e.g. $1.07^{15}=2.75$.

$: Estimates of relative risk was adjusted for age and its interaction with gender, calendar year, mental illness in a parent or sibling, and change of the municipality.

Some possible explanations for the urban-rural difference

- Methodological problems, e.g .detection bias
- Selective migration of schizophrenic patients or of persons genetically predisposed towards schizophrenia
- Urban-rural differences in exposure to risk factors or protective factors for schizophrenia

Candidate risk factors

- Complications of pregnancy or birth
- Infections
- Household crowding
- Exposure to pets
- Birth order and sibship size
- Social class variables
- Toxic effects of pollution
- Psychological factors
- Dietary factors
- Different effects during fetal life, at birth, or at different ages during childhood and adolescence?

Next steps

- Combine population-based epidemiology with biological data, e.g.,
- Molecular genetic studies
- Biological measures of early infections, perinatal stress, etc.
- Better measurement of psychological stress?
- Preventive intervention?

More about registers……

- Family data
- Geographical data

Distance to road as a proxy measure of pollution from traffic and the risk of schizophrenia

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Objective

- To investigate the hypothesis that pollutants from traffic increase schizophrenia risk
- And whether this potential effect can explain the urban rural differences in schizophrenia risk

Data

- Danish Psychiatric Central Register
- Danish Civil Registration system, including:
  - Current and historical information on address in Denmark (municipality, street, house number)
  - Information on address is complete from 1971

Data (cont)

- Danish address and road database (DAV)
  - Geographic location on all roads in Denmark
  - Information on size of road
    - Motorways
    - Motor roads
    - Main roads between cities
    - Main roads within cities
    - Roads 3-6 metres wide
    - Other roads

Study population

- All persons born in Denmark
- From 1956 to 1983
- Alive at the 15th birthday

- 1.89 million people

Study Design

- Main exposures
  - The degree of urbanization (CPR)
  - The distance from the nearest major road (DAV)
  - Evaluated at the 15th birthday
- Follow-up study for development of schizophrenia

Distance to nearest major road

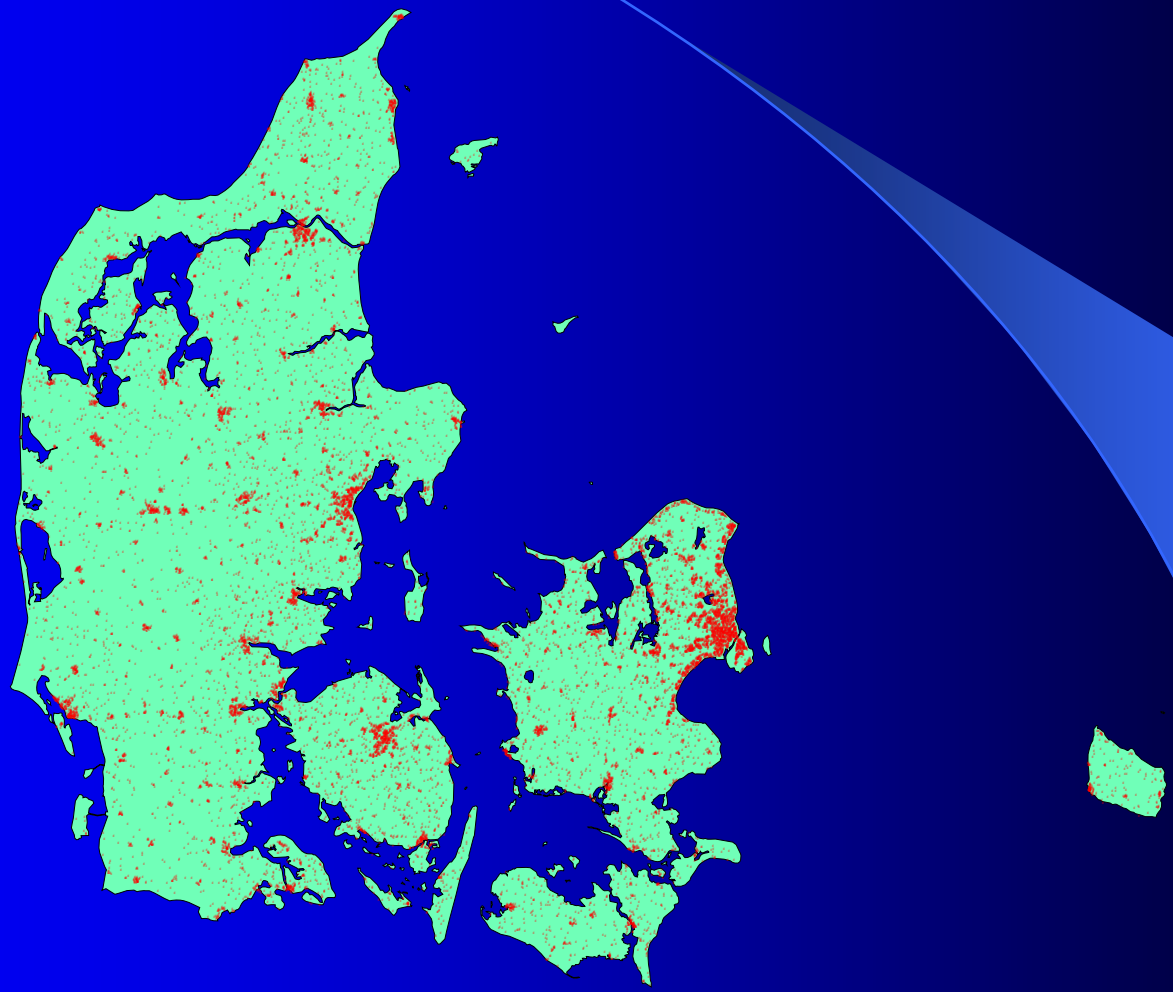
Distance	Relative Risk	Relative Risk
0-50m	1.15 (1.01-1.31)	1.03 (0.91-1.17)
50-100m	1.25 (1.09-1.42)	1.06 (0.93-1.22)
100-250m	1.26 (1.12-1.41)	1.06 (0.94-1.19)
250-500m	1.27 (1.13-1.43)	1.03 (0.92-1.17)
500-1000m	1.33 (1.18-1.49)	1.07 (0.95-1.20)
1000-2000m	1.15 (1.01-1.31)	1.03 (0.90-1.17)
>2000m	1.00 (ref)	1.00 (ref)

Adjusted for urbanicity

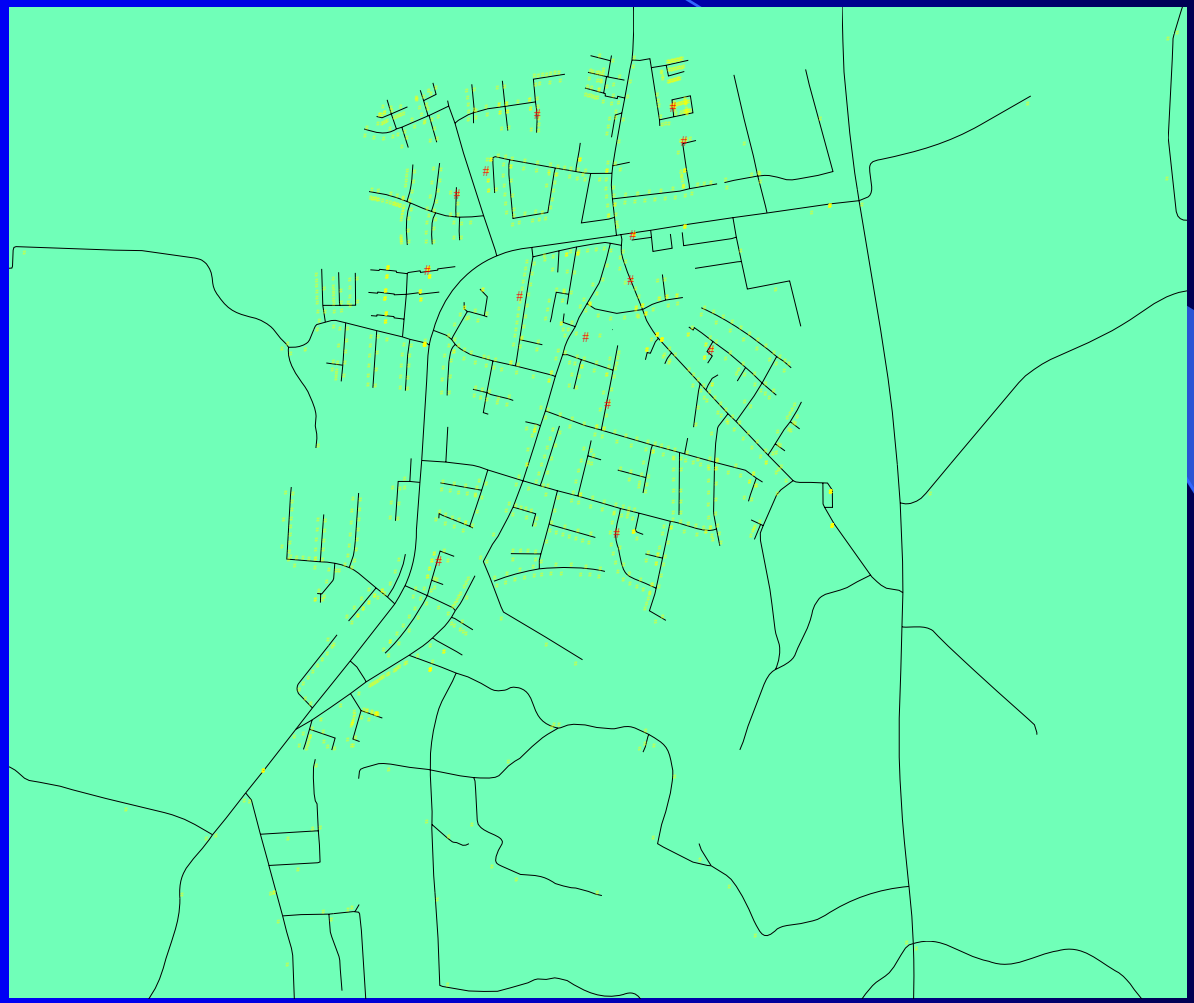
Conclusion

- Distance to nearest major road as a proxy measure of pollution from traffic
- cannot
- explain the urban-rural differences in schizophrenia risk

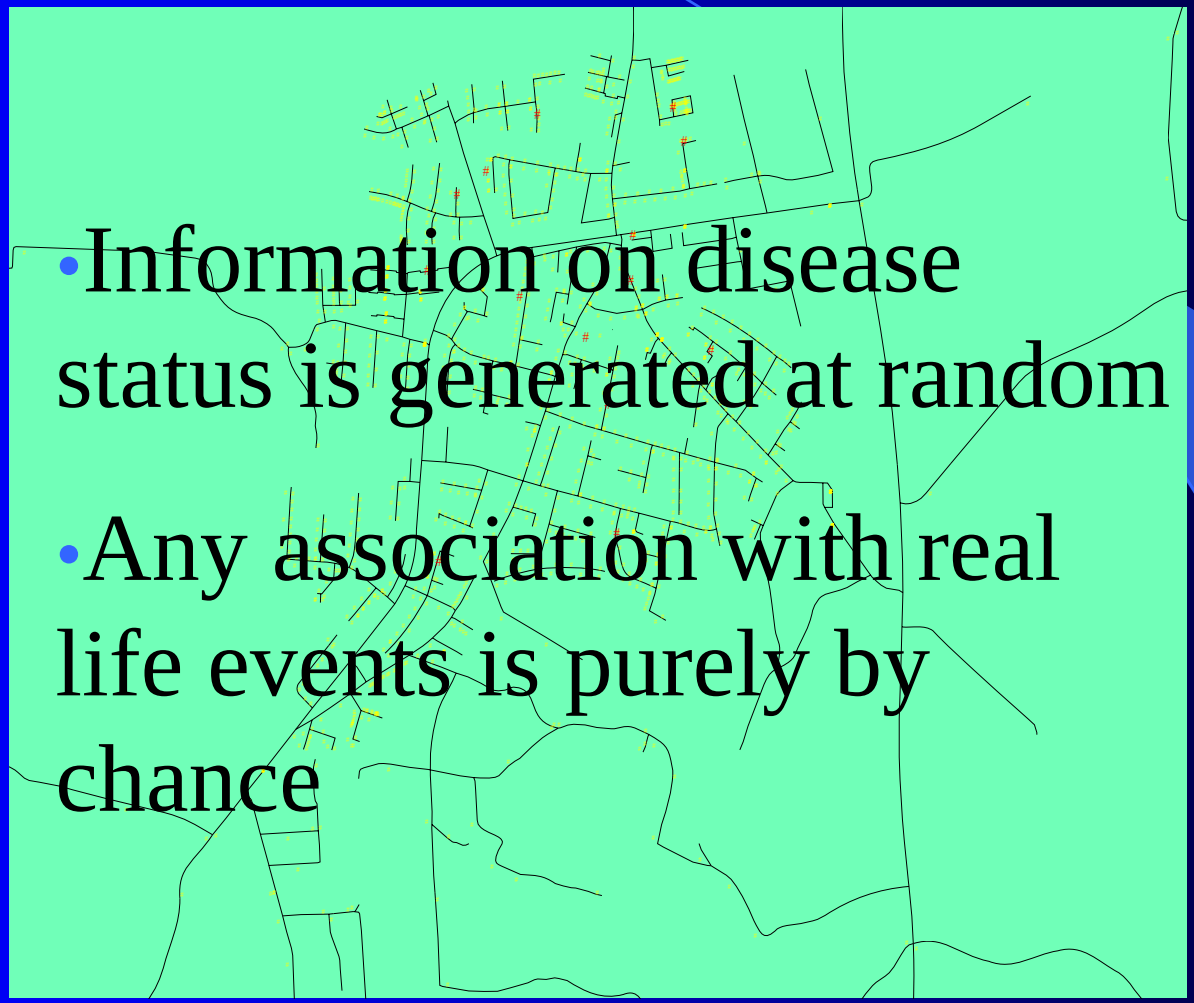
Schizophrenic Births



Schizophrenic Births



Schizophrenic Births



- Information on disease status is generated at random
- Any association with real life events is purely by chance

More about registers……

- Family data
- Geographical data
- Prescription data

Emerging new possibilities

- Better (access to) clinical data
- Combination with bio-banks

Future types of studies

- Population-based genetic epidemiology
- Comorbidity and familial clustering of diseases
- Studies outside of Scandinavia!

Barriers

- Money
- People
- Ideas
- Data access

How to progress?

- Uniform rules and simle permission procedure
- Resources allowing resonable waiting times and prices for data
- Available documentation
- Interaction between researchers and register authorities
- Time!