

**HelmholtzZentrum münchen**

German Research Center for Environmental Health

# Radiation-induced genetic effects and ecological dose-response analyses

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Hagen Scherb and Kristina Voigt

Institute of Biomathematics and Biometry



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- **Ecological dose-response**
- **New data: Sex odds in USA, Europe, and parts of Asia: 1970 – 2007**
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# Genetic effects – *discovery and definition*

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## Discovery of X–ray mutagenesis by HJ Muller 1926\*

- Muller carried out experiments with varied doses of X-rays to *Drosophila*. A connection between radiation and lethal mutations emerged
- By 1928, others had replicated his results, expanding them to other model organisms such as wasps and maize

\*Muller HJ (1927). *Artificial transmutation of the gene*. *Science* 66: 84-87

## Genetic effect – definition

- A genetic effect may be the result of radioactivity or substances that cause damage to (the genes of) a reproductive cell (sperm or egg), or a somatic cell, which can then be passed from one generation to another, or may induce disease (e.g. cancer) in an individual.
- Examples: leukemia, thyroid cancer, sex ratio, birth defects, stillbirths, neonatal death

<http://www.doh.wa.gov/Hanford/publications/overview/genetic.html>

<http://www.nrc.gov/reading-rm/basic-ref/teachers/09.pdf>

# Genetic effects – basic concepts

Radiation Causes Ionizations of:

ATOMS

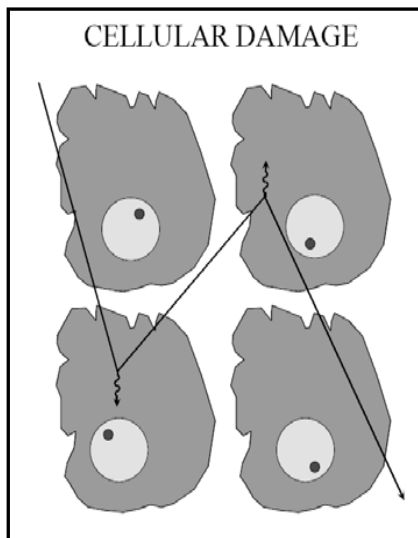
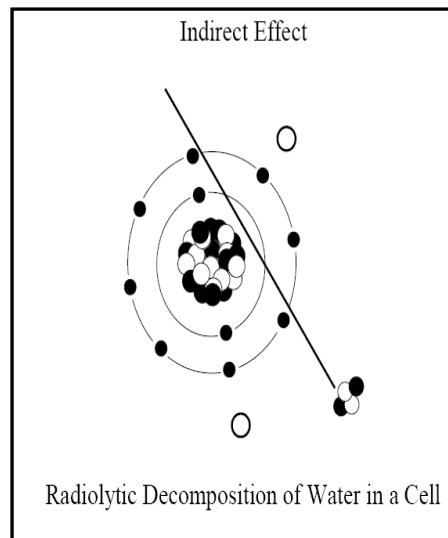
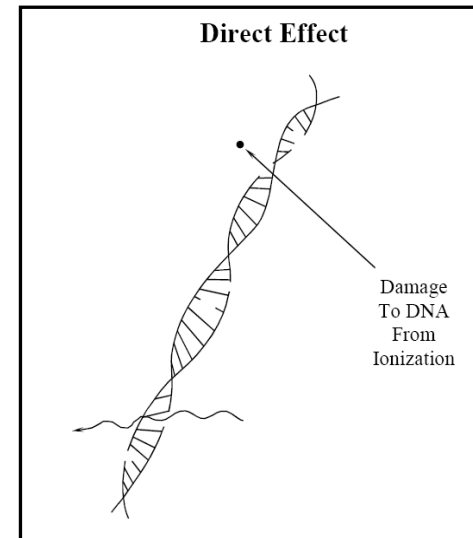
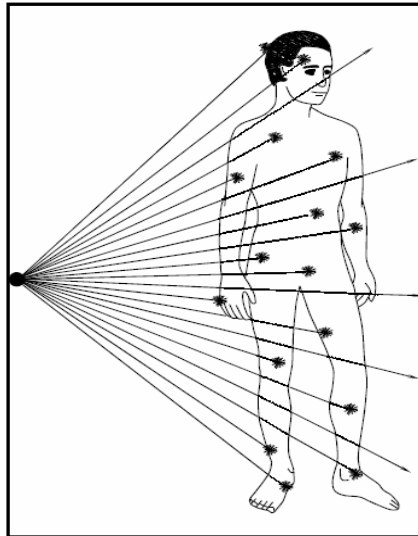
which may affect  
MOLECULES

which may affect  
CELLS

which may affect  
TISSUES

which may affect  
ORGANS

which may affect  
THE WHOLE BODY



- DNA mutation
- genomic instability
- bystander effect

# Genetic effects – sex odds (or less systematically: sex ratio)

## Genetic theory for the human sex odds at birth

### Irradiated parents and offspring gender

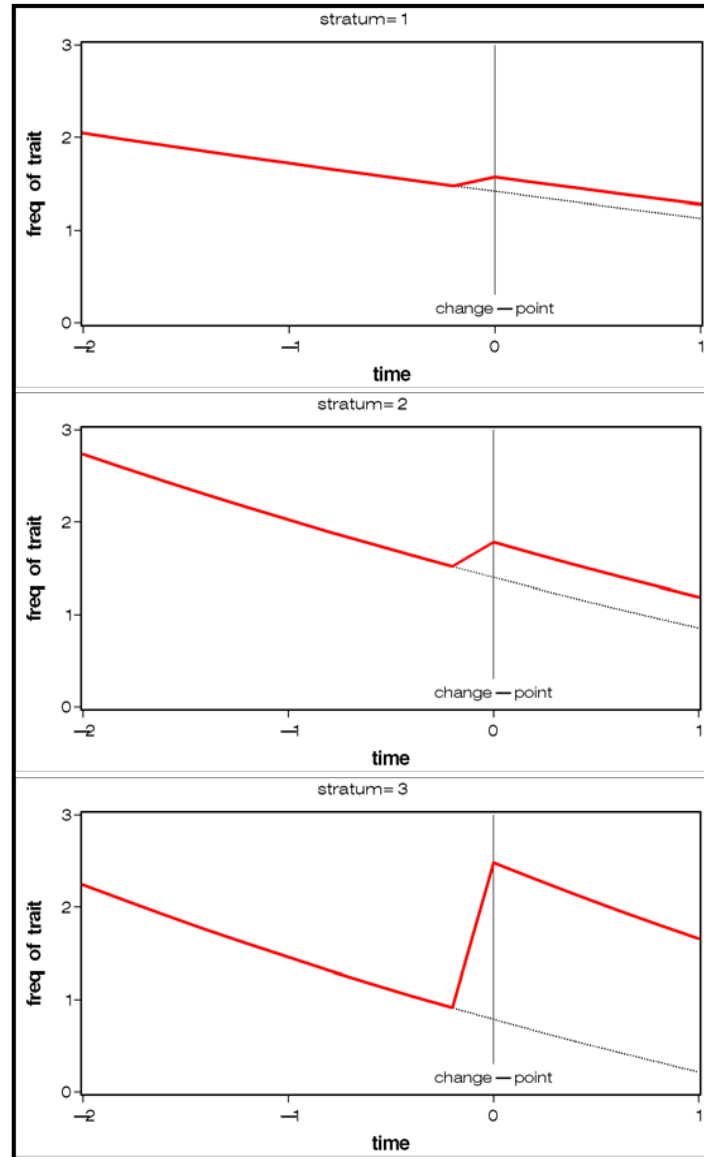
Fathers only	=>	sex odds ↑
Mothers only	=>	sex odds ↓
Both parents	=>	???

*Schull WJ, Neel JV (1958). Radiation and the sex ratio in man. Science 128: 343-348*

*Dickinson HO et al. (1996). The sex ratio of children in relation to paternal preconceptional radiation dose. J Epidemiol Community Health 50(6): 645–652*

*Padmanabhan et al. (2004) Heritable anomalies among the inhabitants of regions of normal and high background radiation in Kerala. Int J Health Serv 34 (3), 483-515*

# Ecological dose-response – *principle*



- **Global time trend model**
- **Stratum specific partial trends**  
partial intercepts (interactions)  
partial slopes (interactions)
- **Stratum specific jumps at time=0**  
stratum specific exposure

# Ecological dose-response – *methodology*

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Example in **SAS** notation for n=5 strata

➤ **Unconditional logistic regression**

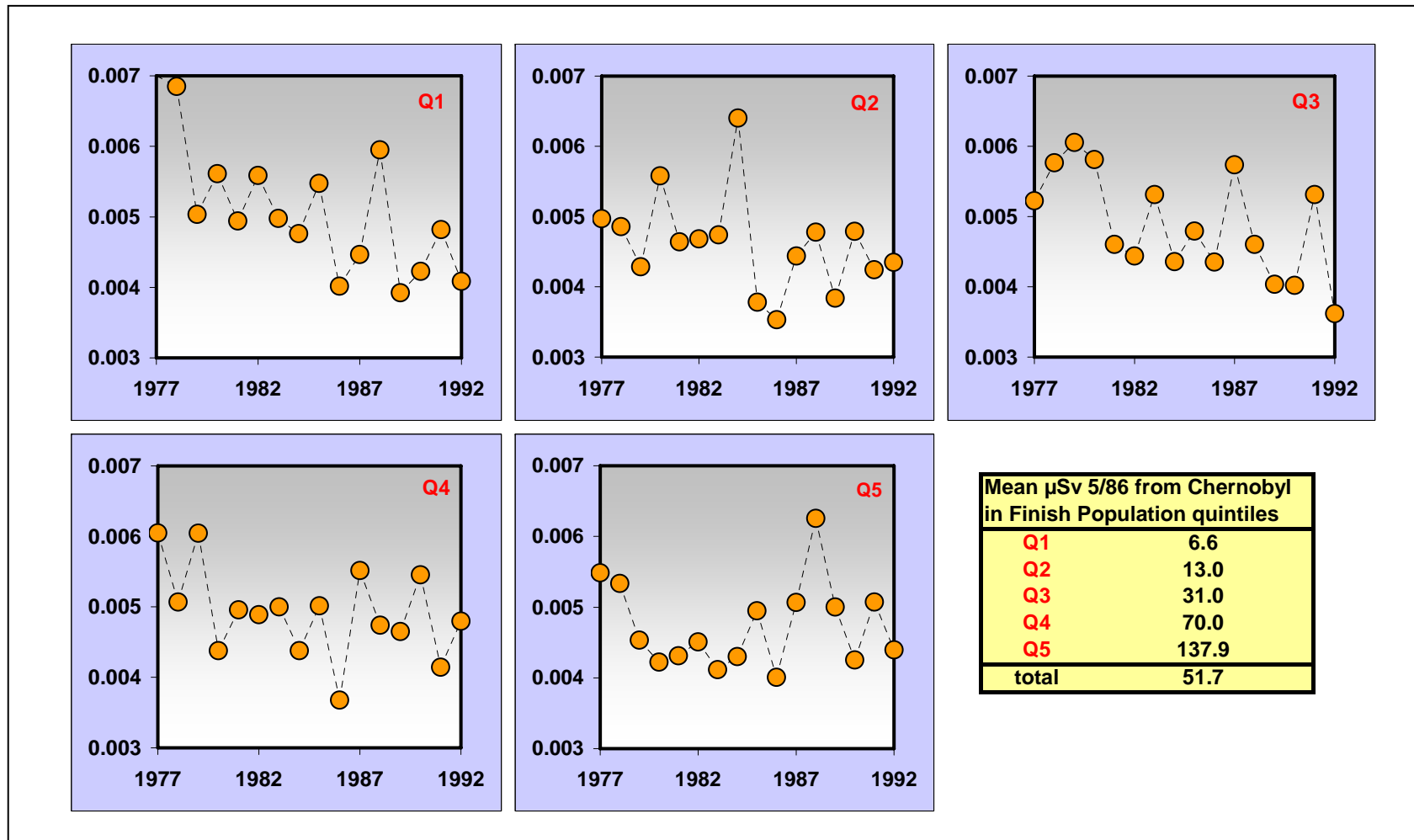
```
proc logistic;  
model response = q2 q3 q4 q5 q1*t q2*t q3*t q4*t q5*t exposure;  
run;
```

➤ **Conditional logistic regression**

```
proc phreg;  
model time*response(0) = time exposure ;  
strata q1 - - q5 ;  
run;
```

# Ecological dose-response – example

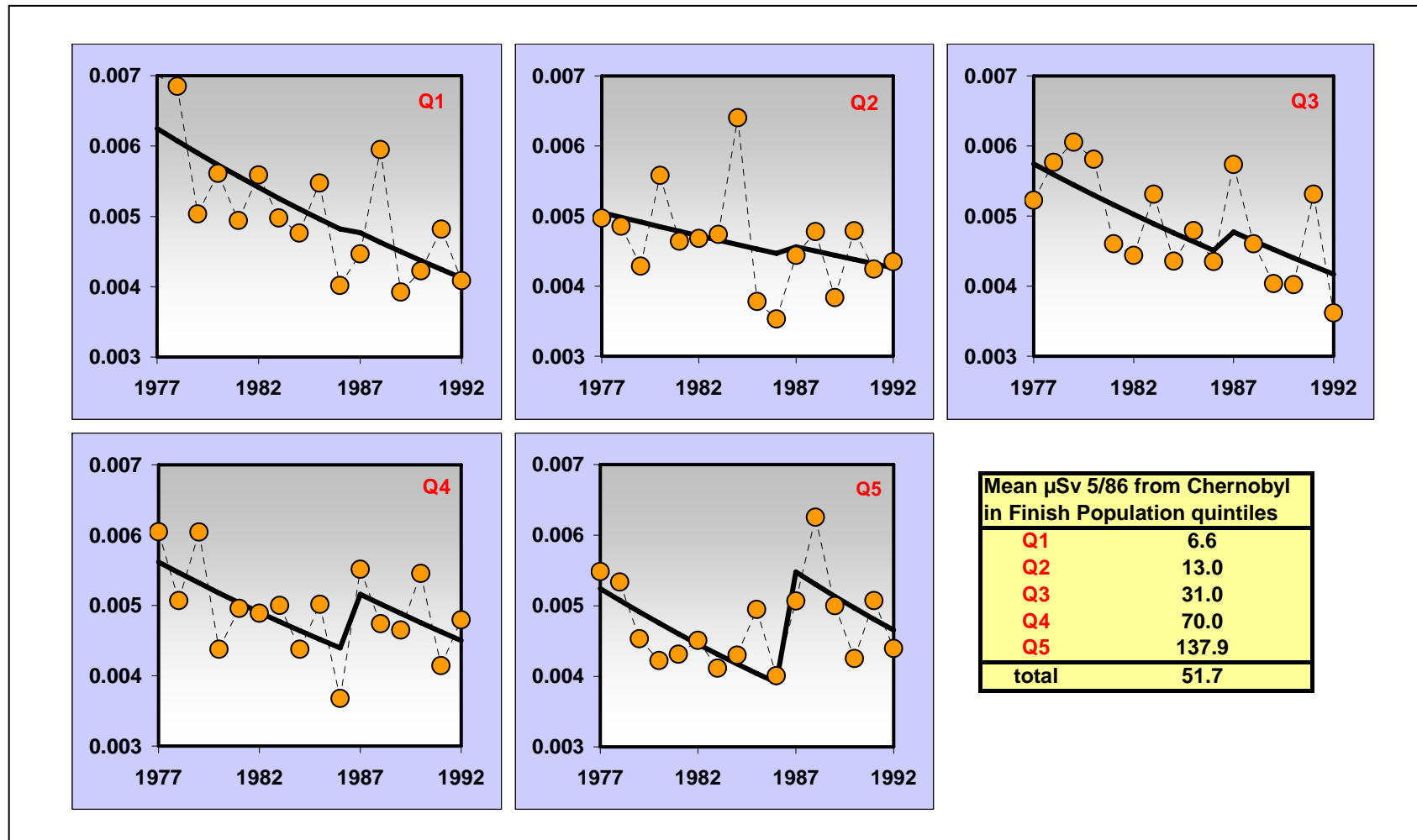
Stillbirth in Finland, 1977 – 1992 prevalence data by exposure quintiles





# Ecological dose-response – example

Stillbirth in Finland, 1977 – 1992 spatial temporal model



# Ecological dose-response – *example*

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Stillbirth in Finland, 1977 – 1992    dose specific risk

OR per mSv/a	1.25
95% CL	[1.10, 1.42]
p-value	0.0006

# Ecological dose-response – further examples

## ➤ Perinatal mortality and stillbirths

[Scherb H, Weigelt E, Bruske-Hohlfeld I](#) European stillbirth proportions before and after the Chernobyl accident. *Int J Epidemiol.* 1999 Oct; 28(5)

[Scherb H, Weigelt E, Bruske-Hohlfeld I](#) Regression analysis of time trends in perinatal mortality in Germany 1980-1993. *Environ Health Perspect.* 2000 Feb; 108(2)

## ➤ Birth defects

[Scherb H, Weigelt E](#) Congenital Malformation and Stillbirth in Germany and Europe Before and After the Chernobyl Nuclear Power Plant Accident. *ESPR - Environ Sci & Pollut Res*, 10 Special (1) 2003 Dec, 117-125

[Scherb H, Weigelt E](#) Cleft lip and cleft palate birth rate in Bavaria before and after the Chernobyl nuclear power plant accident [Article in German, Abstract in English]. *Mund Kiefer Gesichtschir.* 2004 Mar; 8(2): 106-10

[Sperling K, Neitzel H, Scherb H \(2008\)](#) Low dose irradiation and nondisjunction: Lessons from Chernobyl, 19th Annual Meeting of the German Society of Human Genetics, April 8-10, 2008, Hanover, Germany, Abstractbook, p. 174-175

## ➤ Thyroid Cancer

[Mürbeth S, Rousarová M, Scherb H, Lengfelder E.](#) Thyroid cancer has increased in the adult populations of countries moderately affected by Chernobyl fallout. *Medical Science Monitor*, 2004; 10(7): CR300-306.

## ➤ Sex odds in Europe

[Scherb H, Voigt K](#) Trends in the human sex odds at birth in Europe and the Chernobyl Nuclear Power Plant accident. *Reproductive Toxicology*, Volume 23, Issue 4, June 2007, Pages 593-599

[Scherb H, Voigt K](#) Analytical ecological epidemiology: Exposure-reponse relations in spatially stratified time series. *Environmetrics*, published Online: 12 Sep 2008

# New data: Sex odds in USA, Europe, and parts of Asia: 1970 – 2007

## Pertinent demographic INTERNET data bases

<http://data.euro.who.int/hfad/>

<http://data.un.org/Data.aspx?d=POP&f=tableCode%3a4>

<http://data.un.org/Data.aspx?d=POP&f=tableCode%3A54>

<http://unstats.un.org/unsd/demographic/products/dyb/dyb2.htm>

[http://www.coe.int/t/e/social\\_cohesion/population/BELTAB2.xls](http://www.coe.int/t/e/social_cohesion/population/BELTAB2.xls)

[http://epp.eurostat.ec.europa.eu/portal/page?\\_pageid=0,1136184,0\\_45572595&\\_dad=portal&\\_schema=PORTAL](http://epp.eurostat.ec.europa.eu/portal/page?_pageid=0,1136184,0_45572595&_dad=portal&_schema=PORTAL)

<http://www.johnstonsarchive.net/policy/abortion/ab-poland.html>

# New data: Sex odds in USA, Europe, and parts of Asia: 1970 – 2007

## Europe and parts of Asia

Europe IIIa, 1970-2007, complete data			Births and sex odds	
Belgium	Luxembourg	Portugal	total	80,373,314
France	Malta	Switzerland	male	41,249,601
Ireland	Netherlands	UK	sex odds	1.0543

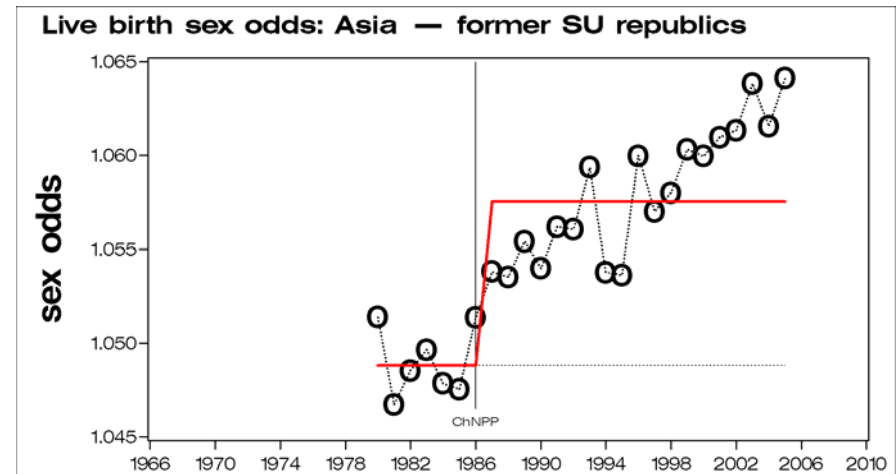
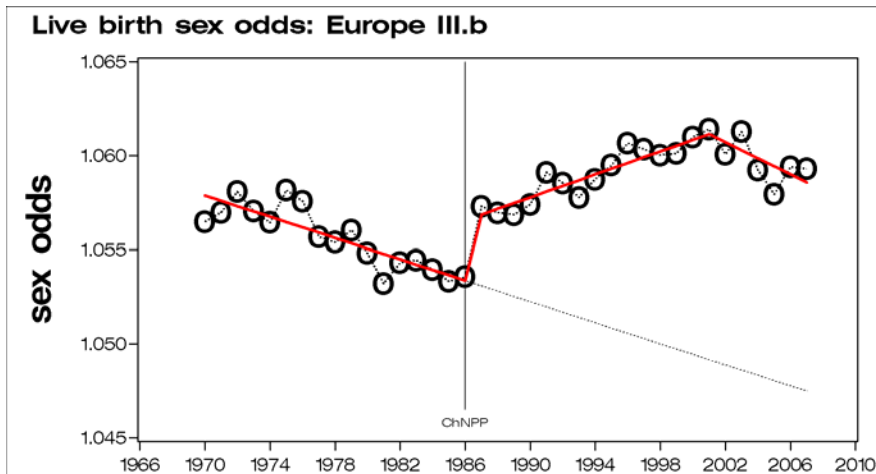
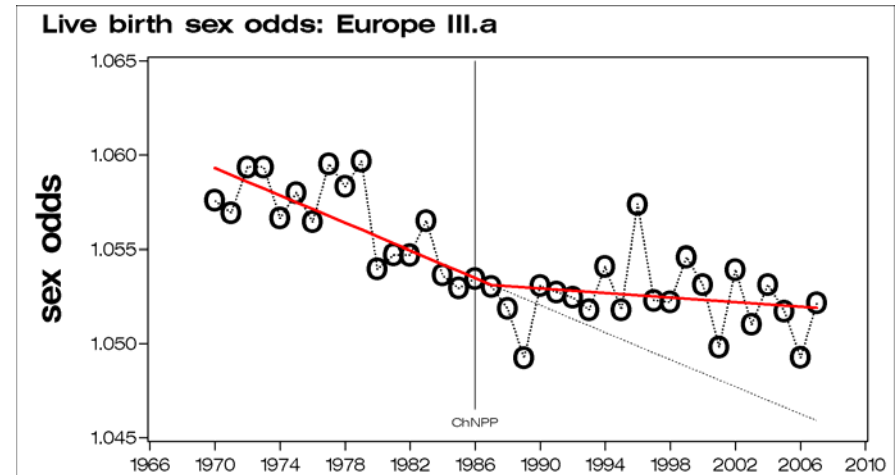
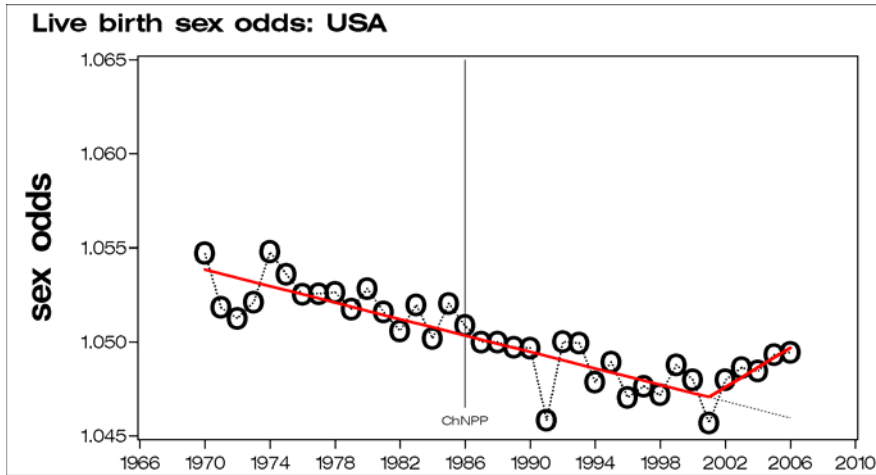
Europe IIIb, 1970-2007, complete data			Births and sex odds			
Albania	Germany	Poland				
Austria	Greece	Romania				
Belarus	Hungary	Russ. Fed.				
Bulgaria	Iceland	San Marino				
Czechoslovakia (f.)	Italy	Sweden				
Denmark	Latvia	Yugoslavia (f.)				
Estonia	Lithuania					
Finland	Norway					
					total	216,491,268
					male	111,258,587
			sex odds	1.0573		

Former SU Republics, 1980-2005, incomplete data			Births and sex odds	
Kazakhstan (E)	Tajikistan	Uzbekistan	total	47,655,378
Kyrgyzstan	Turkmenistan		male	24,463,930
Moldova (E)	Ukraine (E)		sex odds	1.0549

*40 countries with territory in Europe + 4 Asian countries; Spain omitted because of unusual trend; also omitted: Andorra, Liechtenstein, Monaco, Turkey, and Vatican due to no data at all, or essentially incomplete data.*

# New data: Sex odds in USA, Europe, and parts of Asia: 1970 – 2007

## Summary: USA, Europe, and parts of Asia



# Sex odds and ecological dose-response

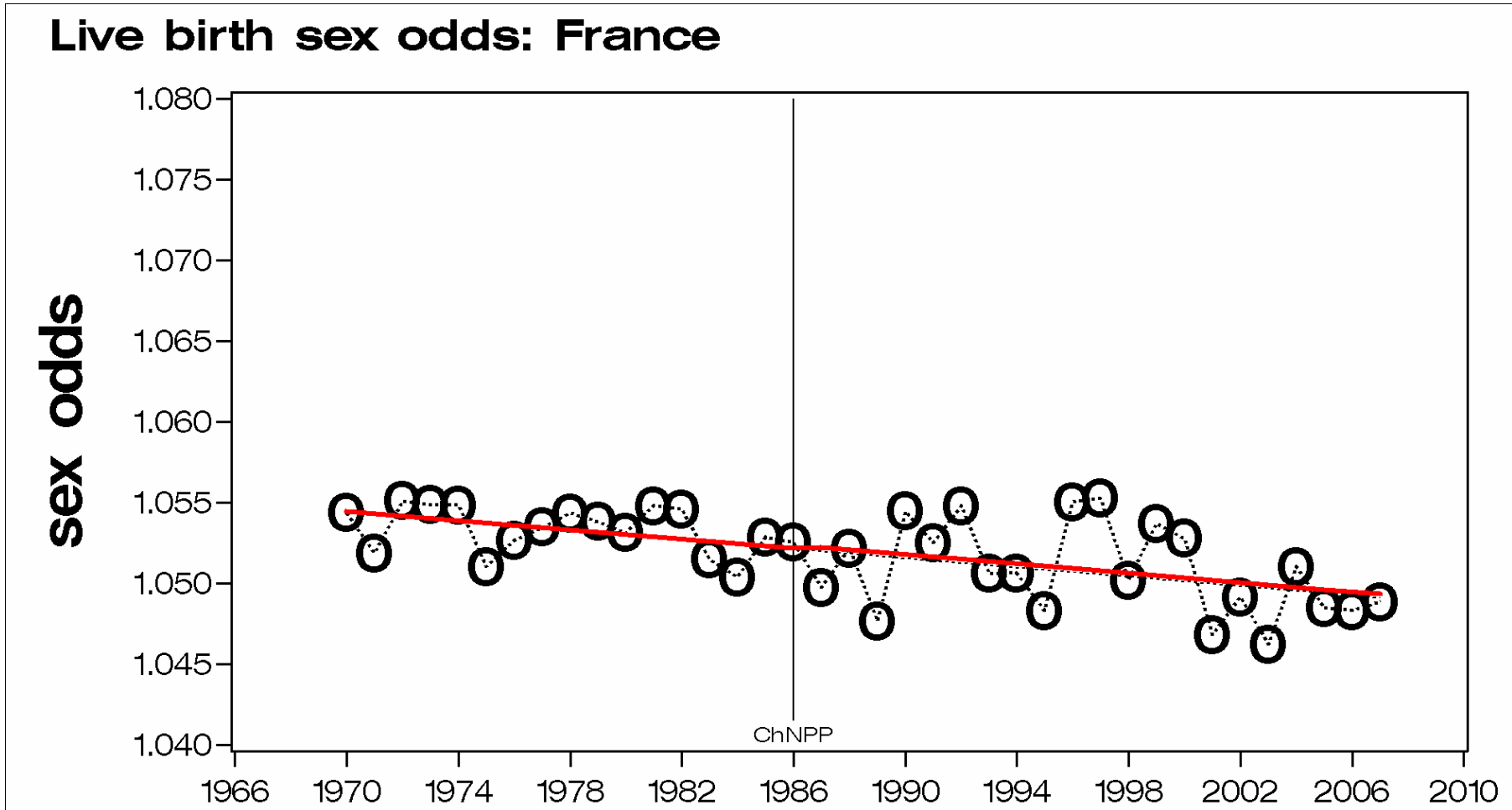
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➤ **Hypothesis**      Jump heights in sex odds after Chernobyl are depending on the amount of fallout (=> national excess average effective doses)

➤ **Test**              Consider sex odds ratios in countries with differing levels of fallout after Chernobyl

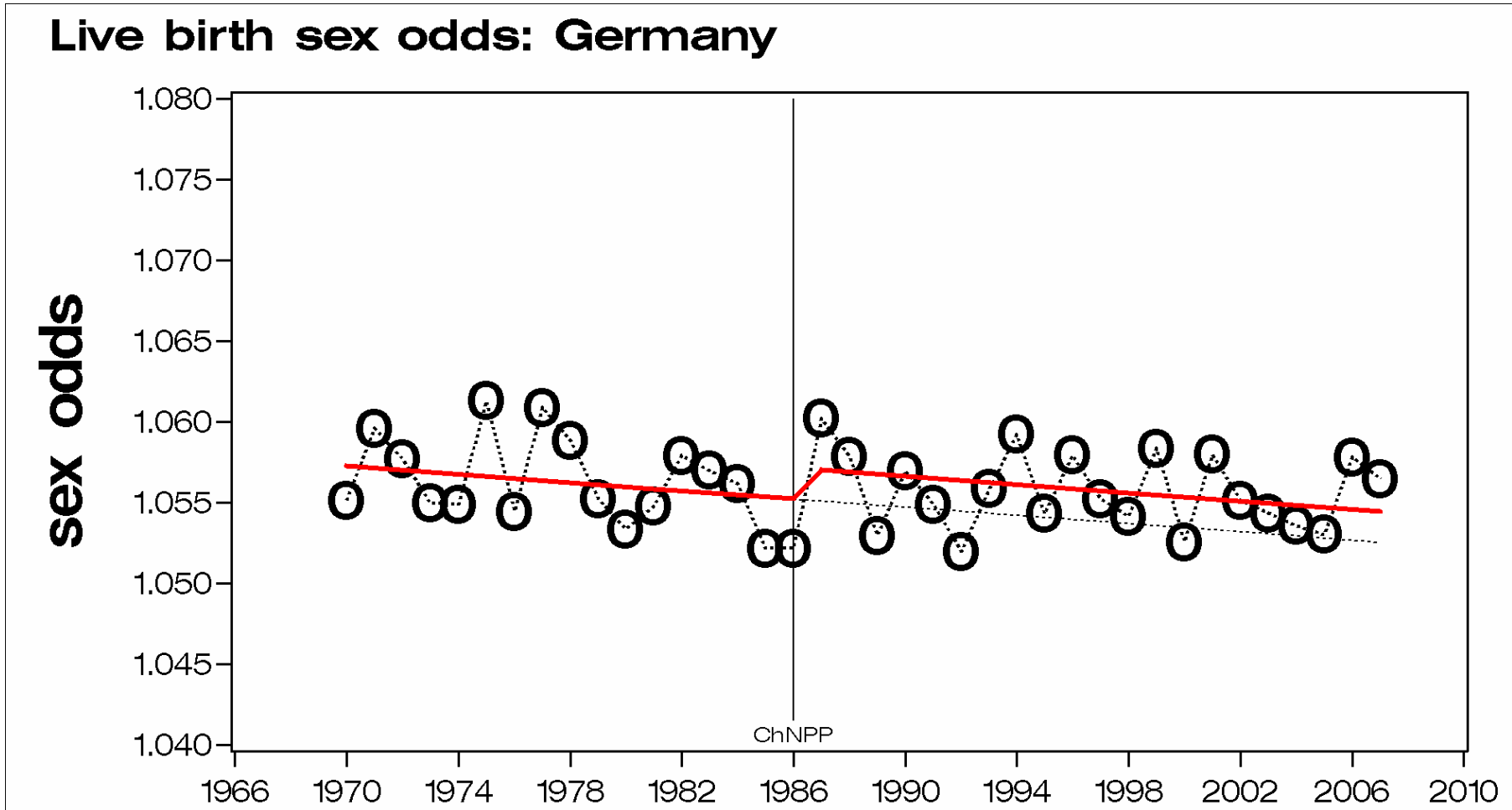
➤ <b>Fallout level</b>	<b>low</b>	<b>France</b>
	<b>intermediate</b>	<b>Denmark, Germany, Italy, Yugoslavia (f.)</b>
	<b>high</b>	<b>Belarus, Russian Federation</b>

# Sex odds and ecological dose-response

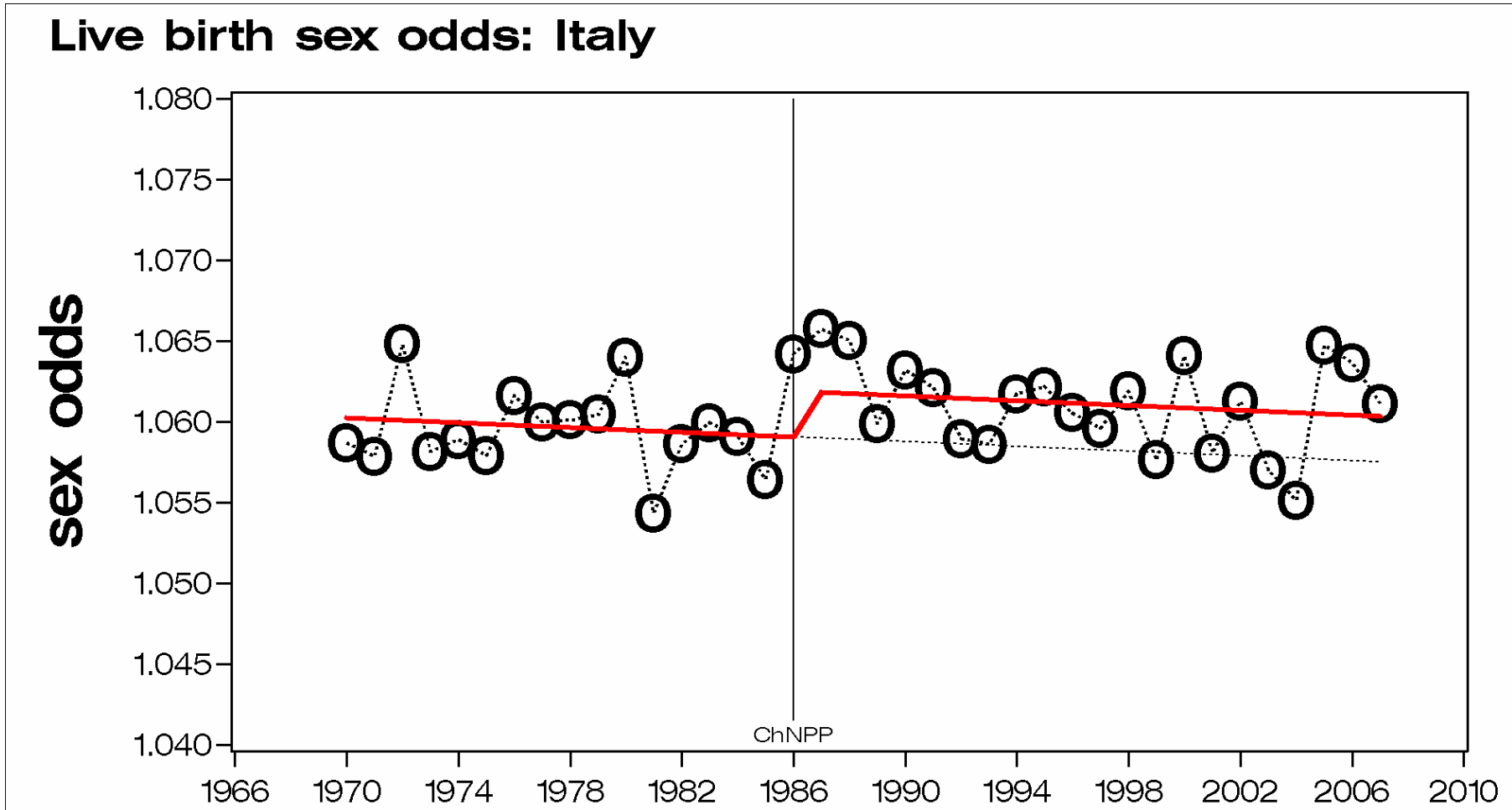




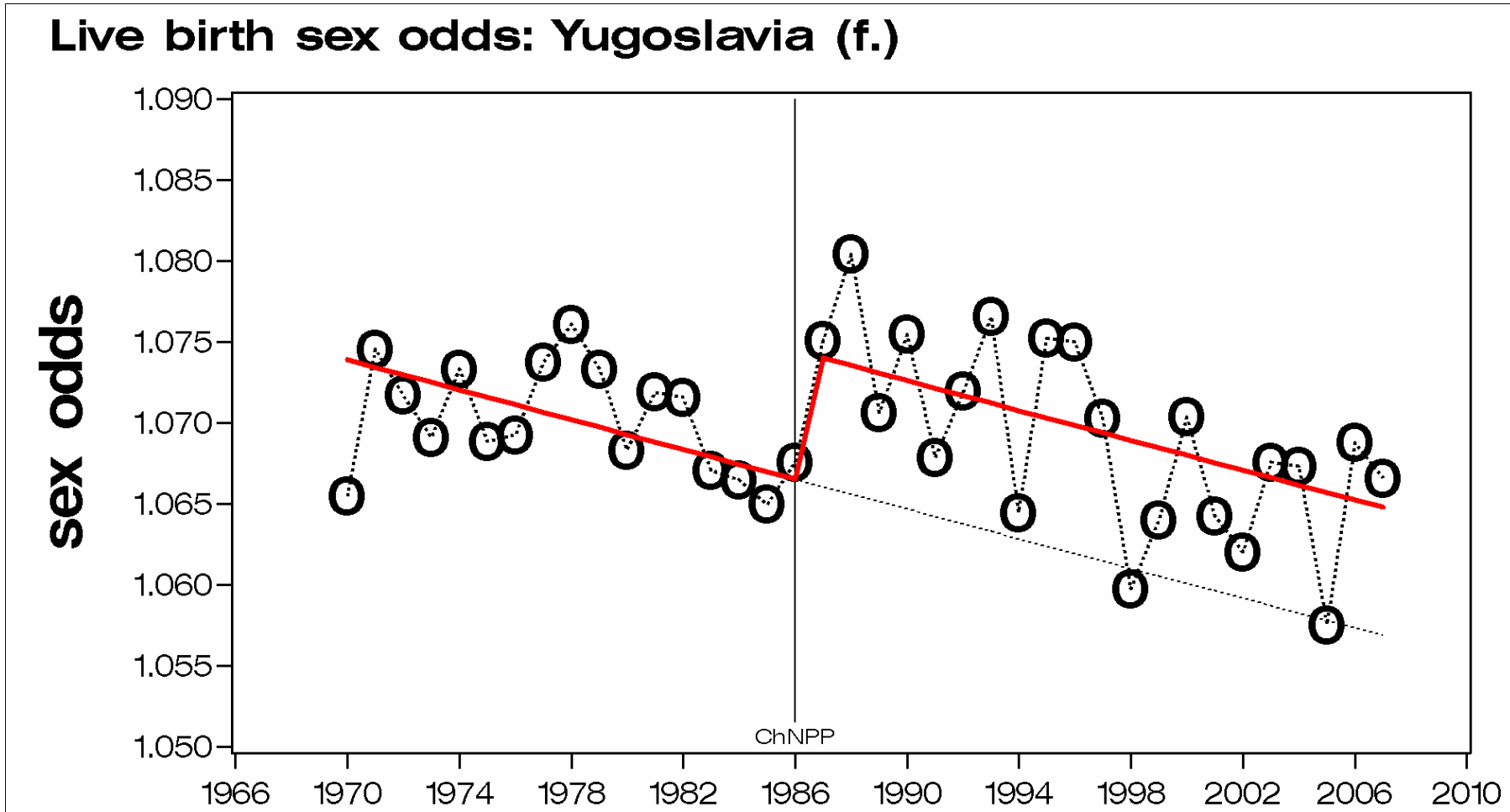
# Sex odds and ecological dose-response



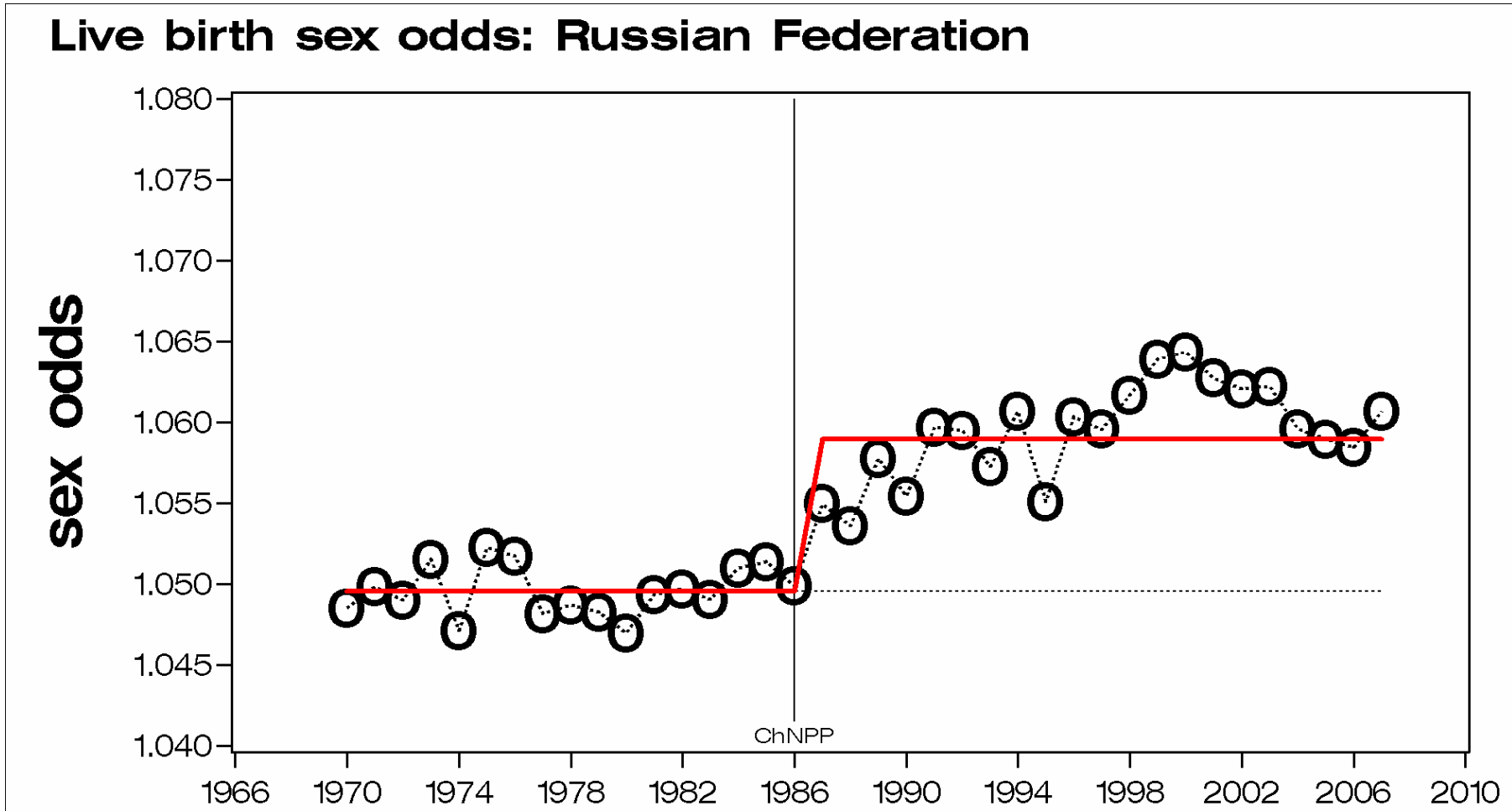
# Sex odds and ecological dose-response



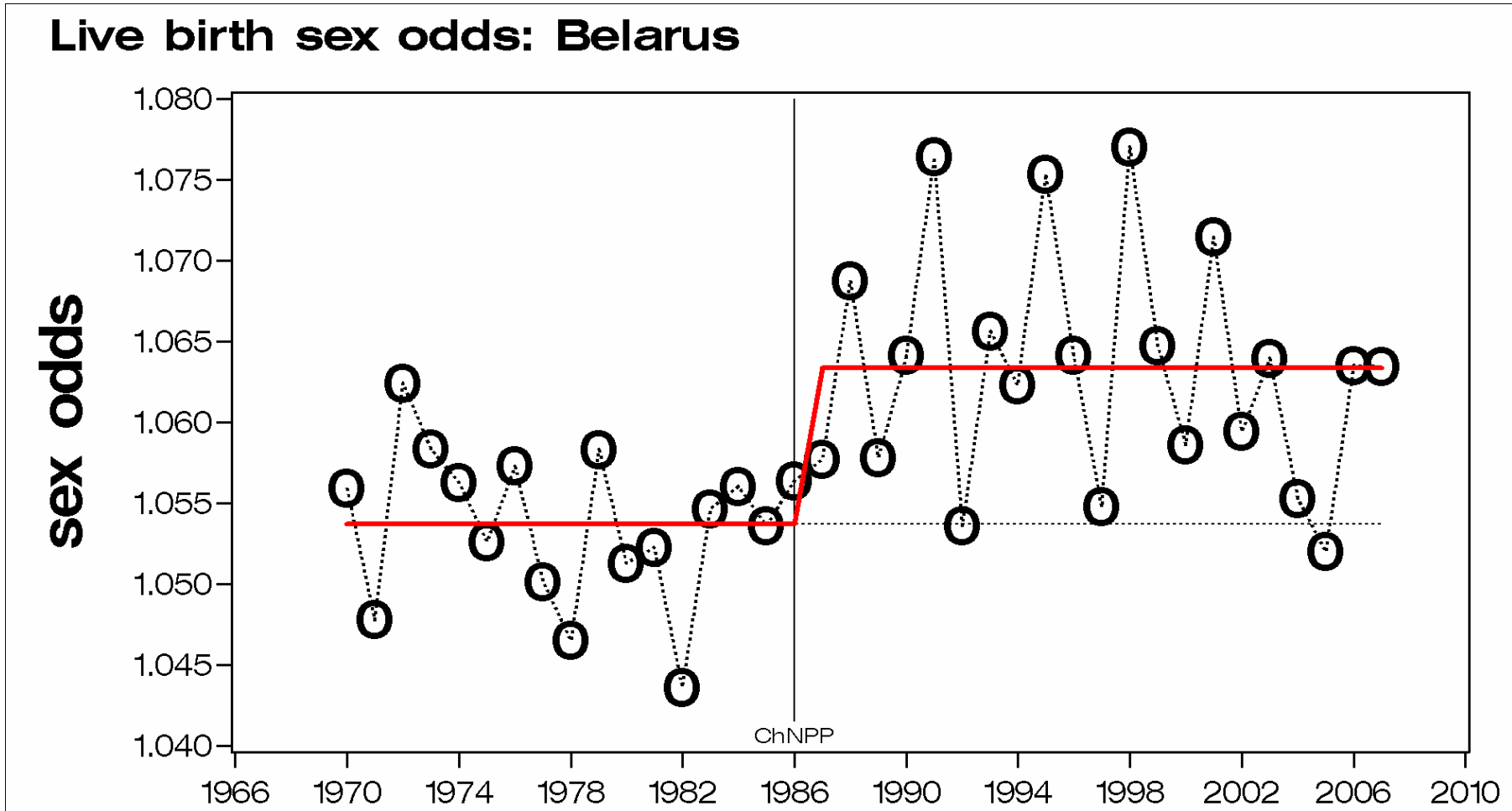
# Sex odds and ecological dose-response



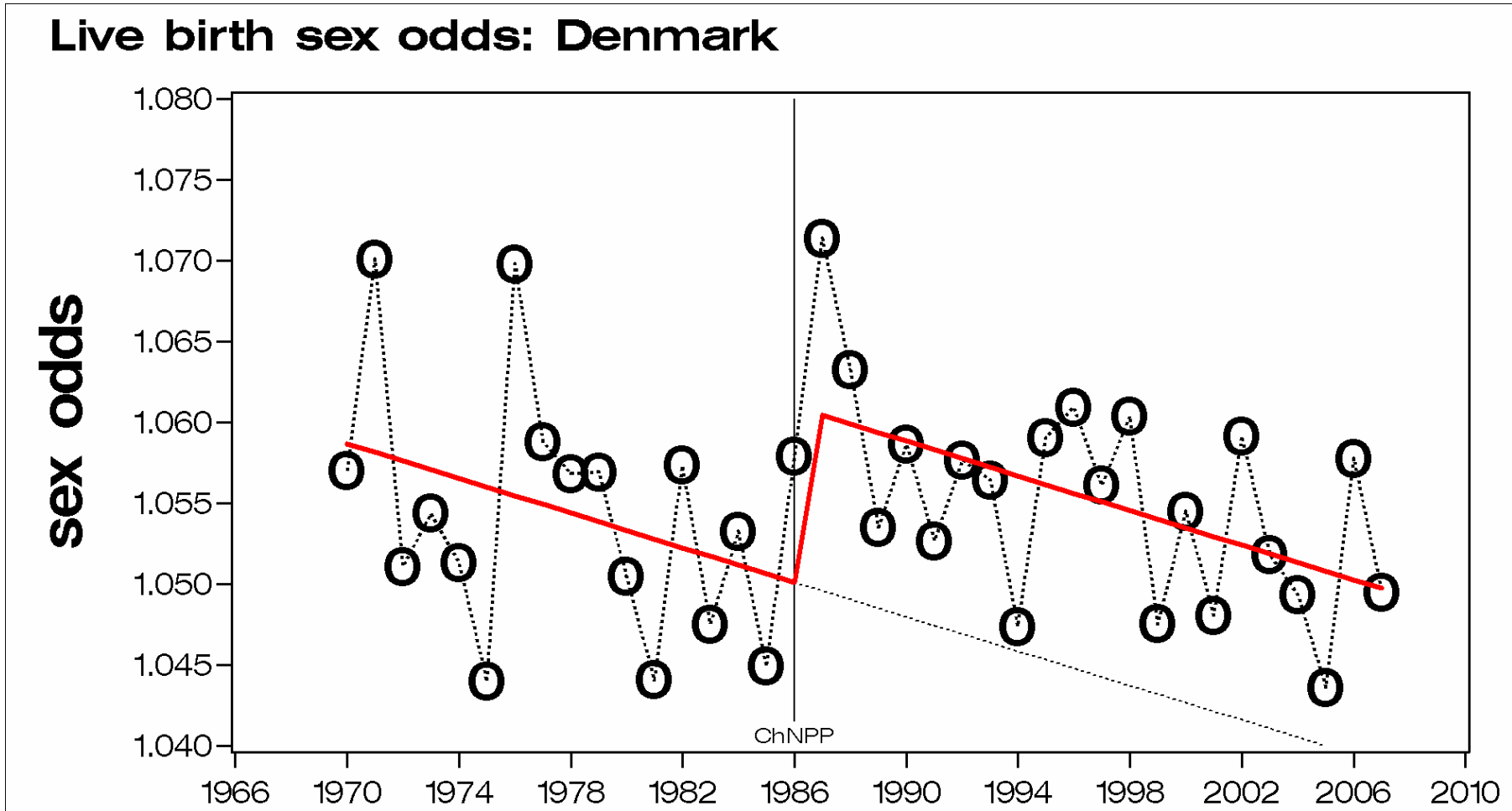
# Sex odds and ecological dose-response



# Sex odds and ecological dose-response



# Sex odds and ecological dose-response

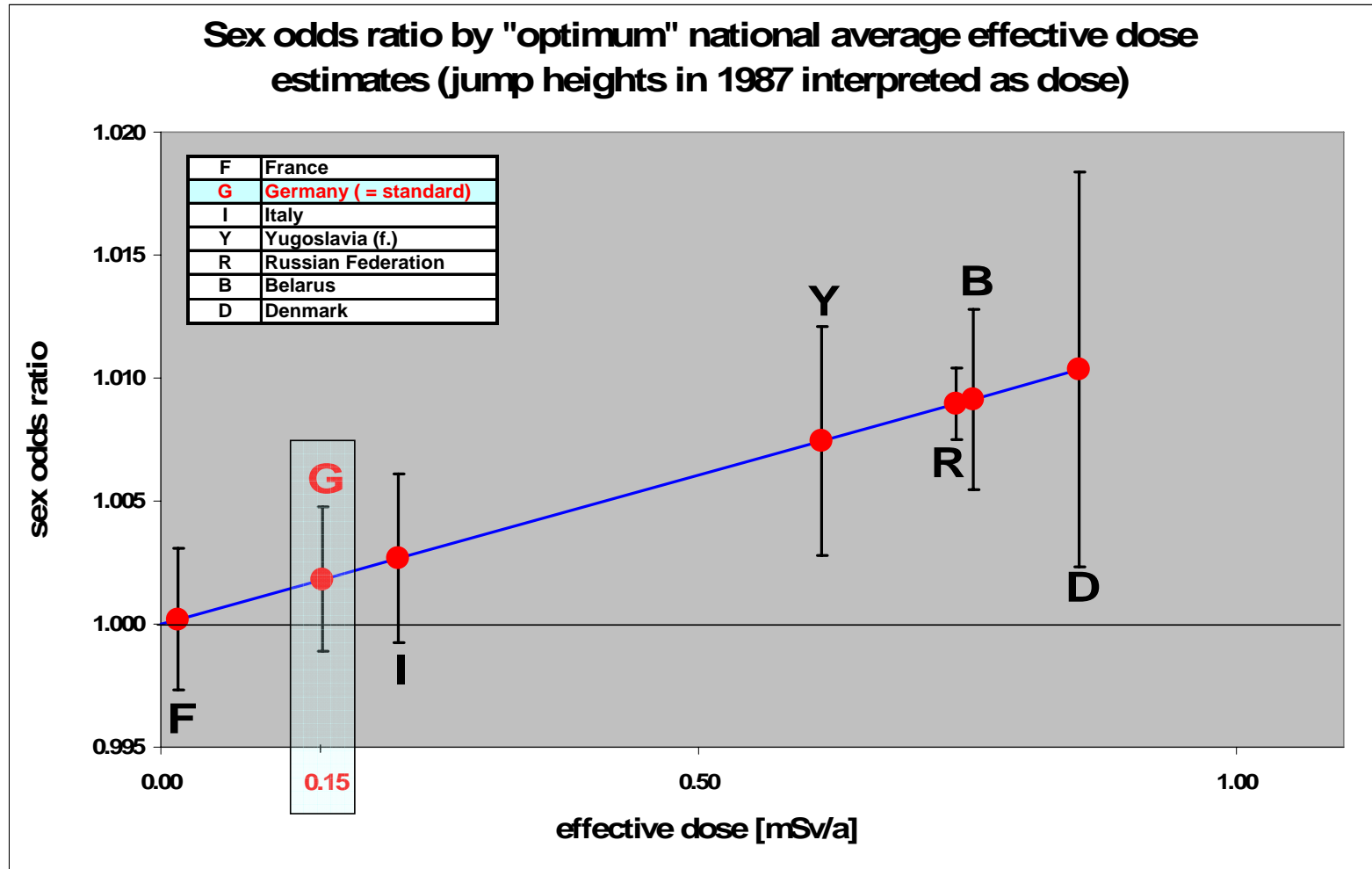


## Sex odds and ecological dose-response – *collective dose data*

Vergleich der in den Jahren 1986, 1987, 1996 und 2006 berechneten effektiven Dosen für Erwachsene durch die SSK

Gebiet	Effektive Dosis im 1. Jahr (mSv)				Gesamte effektive Dosis für die nach dem Unfall folgenden 50 Jahre (mSv)			
	1986	1987	1996	2006	1986	1987	1996	2006
Voralpengebiet		1,2	0,65	0,5		3,8	2,2	2,1
Südlich Donau	0,5-1,1	0,6	0,35	0,3	1,5-4,0	1,9	1,3	1,1
Nördlich Donau		0,2	0,17	0,1		0,6	0,55	0,4

# Sex odds and ecological dose-response – “national dosimetry”





## Sex odds and ecological dose-response – “national dosimetry”

Optimum **excess collective doses per year** in France, Italy, former Yugoslavia, Russian Federation, Belarus, and Denmark based on the linearity assumption, the jump heights in 1987 and the overall excess collective dose in Germany of 0.15 mSv/year from 1987 to 2007 (Germany serves as a standard)

Country	jump OR	mSv/a
France	1.0002	0.02
<b>Germany</b>	<b>1.0018</b>	<b>0.15</b>
Italy	1.0027	0.22
Yugoslavia (f.)	1.0074	0.61
Russian Federation	1.0090	0.74
Belarus	1.0092	0.75
Denmark	1.0104	0.85
<b>jump OR per mSv</b>	<b>1.0121</b>	

# Consequences

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- Consider 1,000,000 parents/births preconceptionally/prenatally exposed to 1 mSv
- Assume a “normal” sex odds of 1.0500 and a sex odds ratio/mSv of 1.0145 (see: [Scherb&Voigt 2007](#))

- **A.** If only female births were susceptible

⇒ **7,000 missing girls**

- **B.** If the sex odds of lost children were 3:10

⇒ **12,800 missing children**

- **C.** In Europe and parts of Asia ca. 200,000,000 million births 1987-2009 at ca. 0.5 mSv/a

⇒ **ca. 1,000,000 missing children after Chernobyl**

# Conclusion

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**By straightforward spatial-temporal analyses, we have shown that after Chernobyl, and in significant association with fallout density, there have been increasing frequencies of detrimental genetic effects like birth defects, stillbirths, and disturbed human sex ratios at birth**

**Therefore, our results contribute to disproving the prevailing believe that**

**Radiation-induced hereditary effects have yet to be detected in human populations \***

\*United Nations Scientific Committee on the Effects of Atomic Radiation - UNSCEAR. Sources and effects of ionizing radiation. I, 3, 2000

**[see also: The Lesvos Declaration, 2009](#)**

# Thank you

Dr. Hagen Scherb and Dr. Kristina Voigt  
Institute of Biomathematics and Biometry, Helmholtz Zentrum München –  
[German Research Center for Environmental Health](#)  
Ingolstaedter Landstr. 1, D-85764 Neuherberg, Germany  
[scherb@helmholtz-muenchen.de](mailto:scherb@helmholtz-muenchen.de)