# Challenges in epidemiological research of childhood cancer

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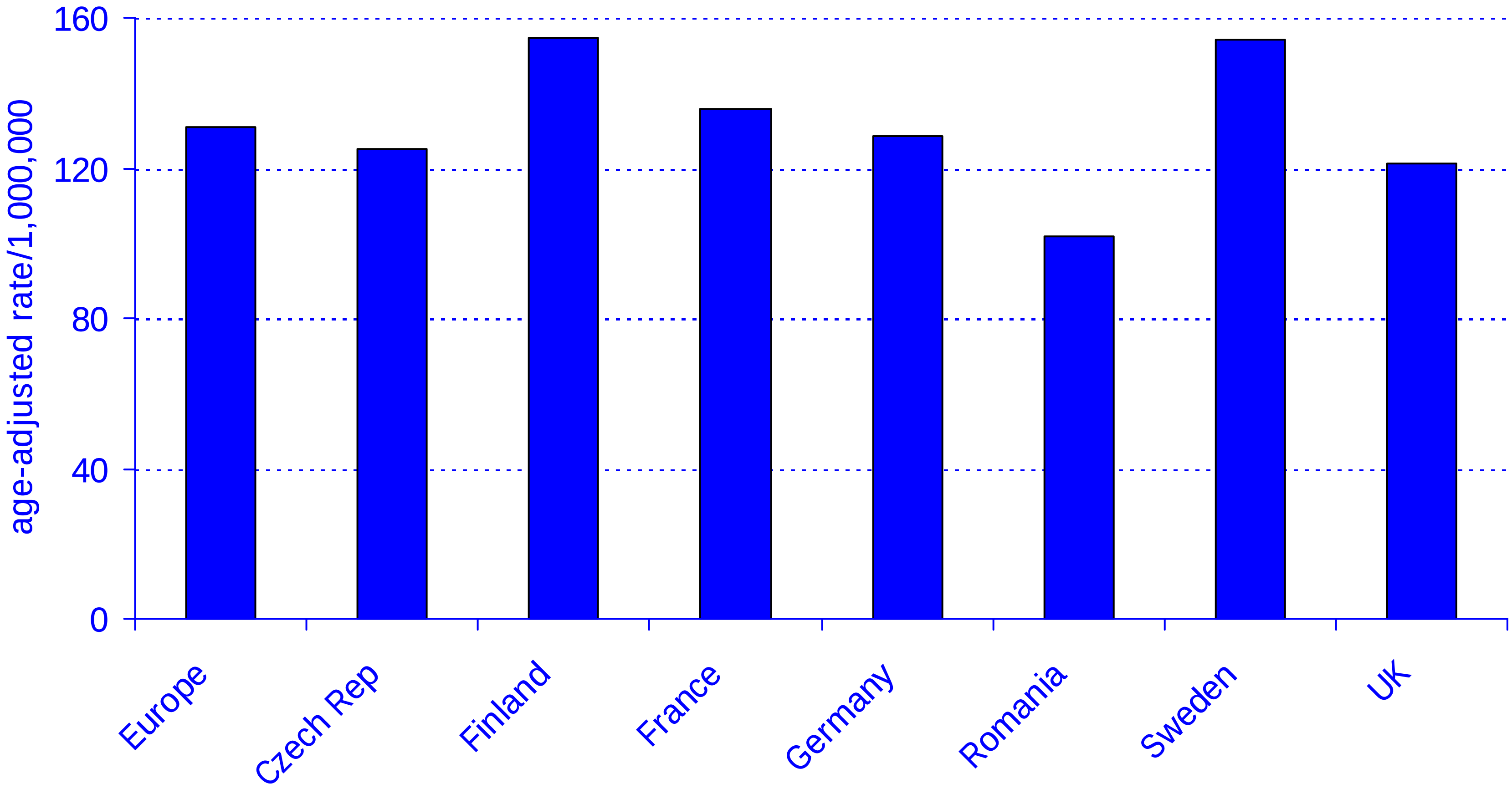
# Automated Childhood Cancer Information System (ACCIS)

- Collection, presentation, and interpretation of data for cancer incidence and survival in children (aged 0–14) and adolescents (aged 15–19) in 35 European countries
- Data from 80 population-based cancer registries covering about half the population aged 0–14 years
- It includes 160 000 cases of childhood and adolescent cancer diagnosed from 1970 to 2001 (1.3 billion person-years)
- Funded by DG-SANCO, IARC, Scotland MoH

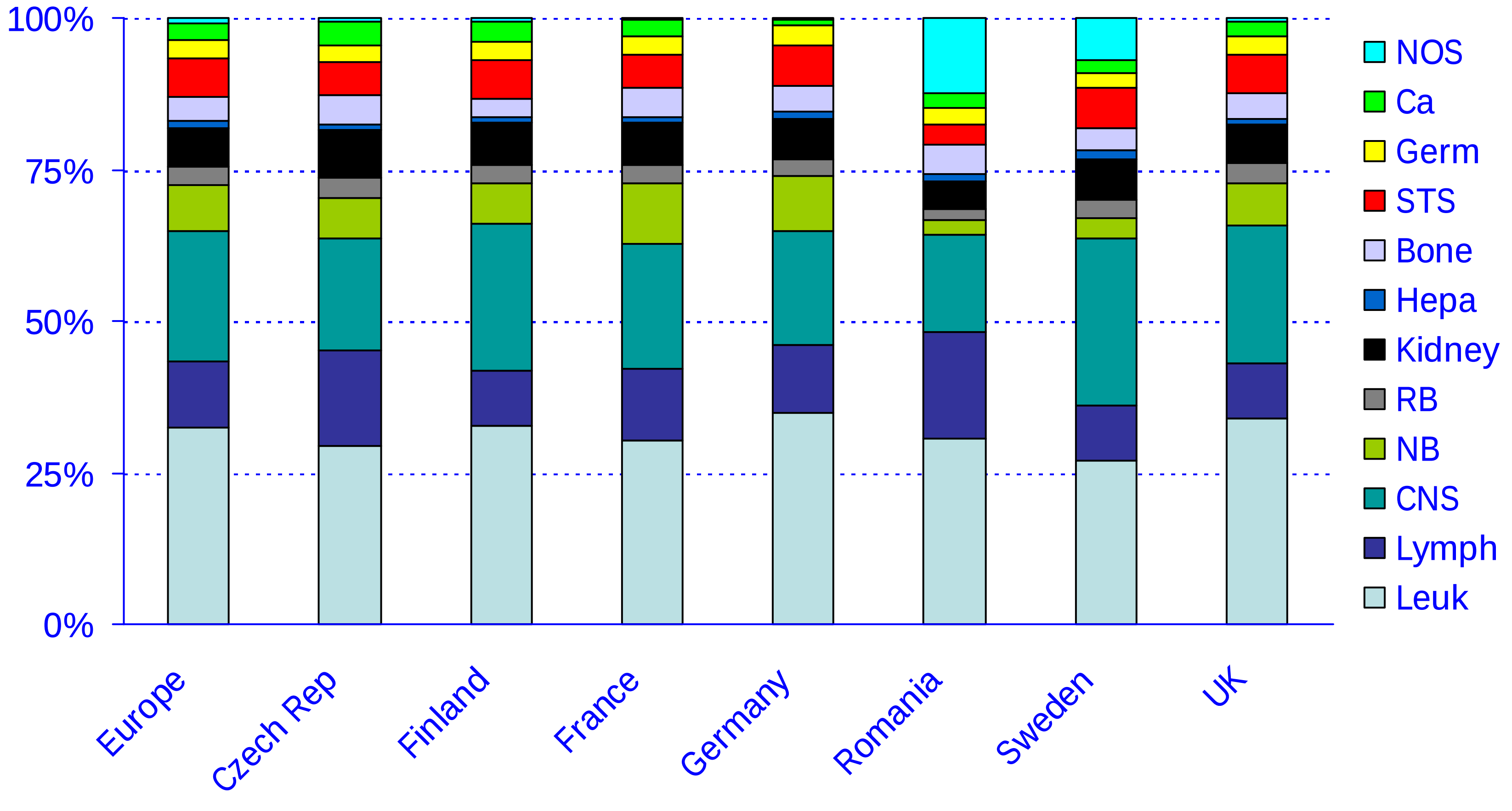
# ACCIS coverage

# Incidence rate of childhood cancer (0-14) in selected European countries - 1990s



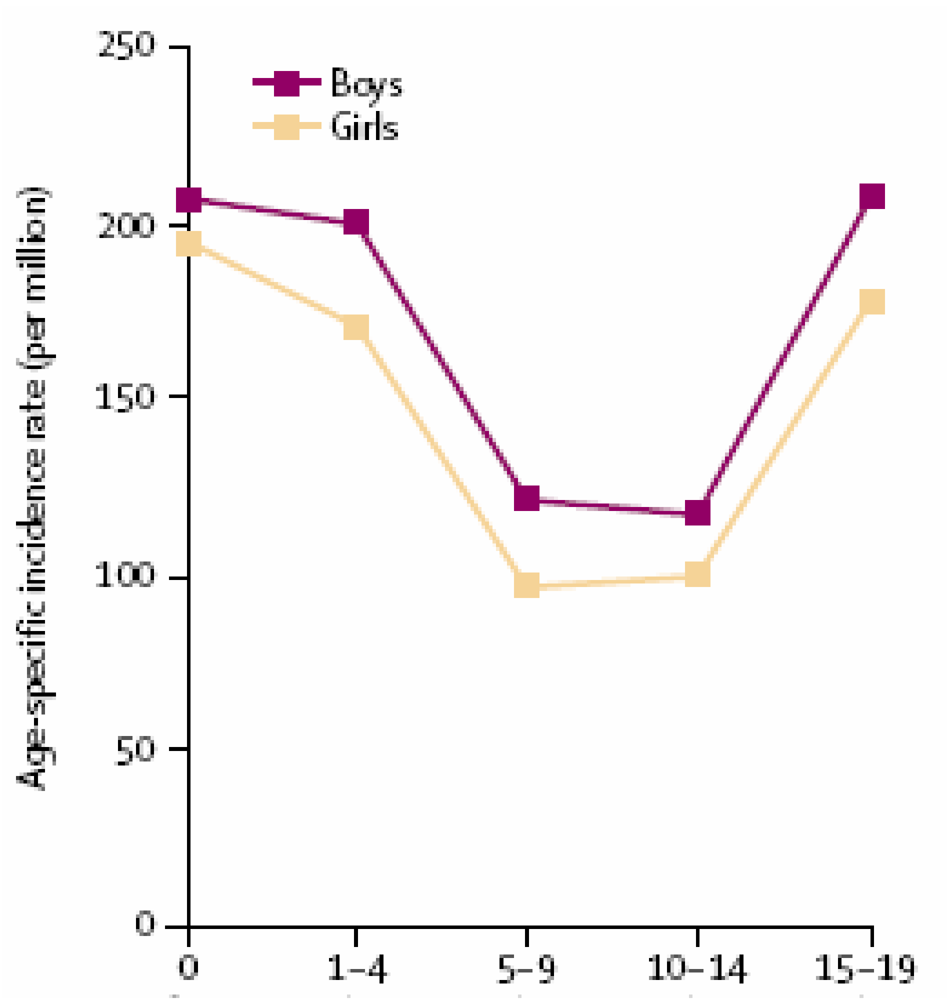

ACCIS Project

# Percentage of groups of childhood cancer (0-14) in selected European countries - 1990s



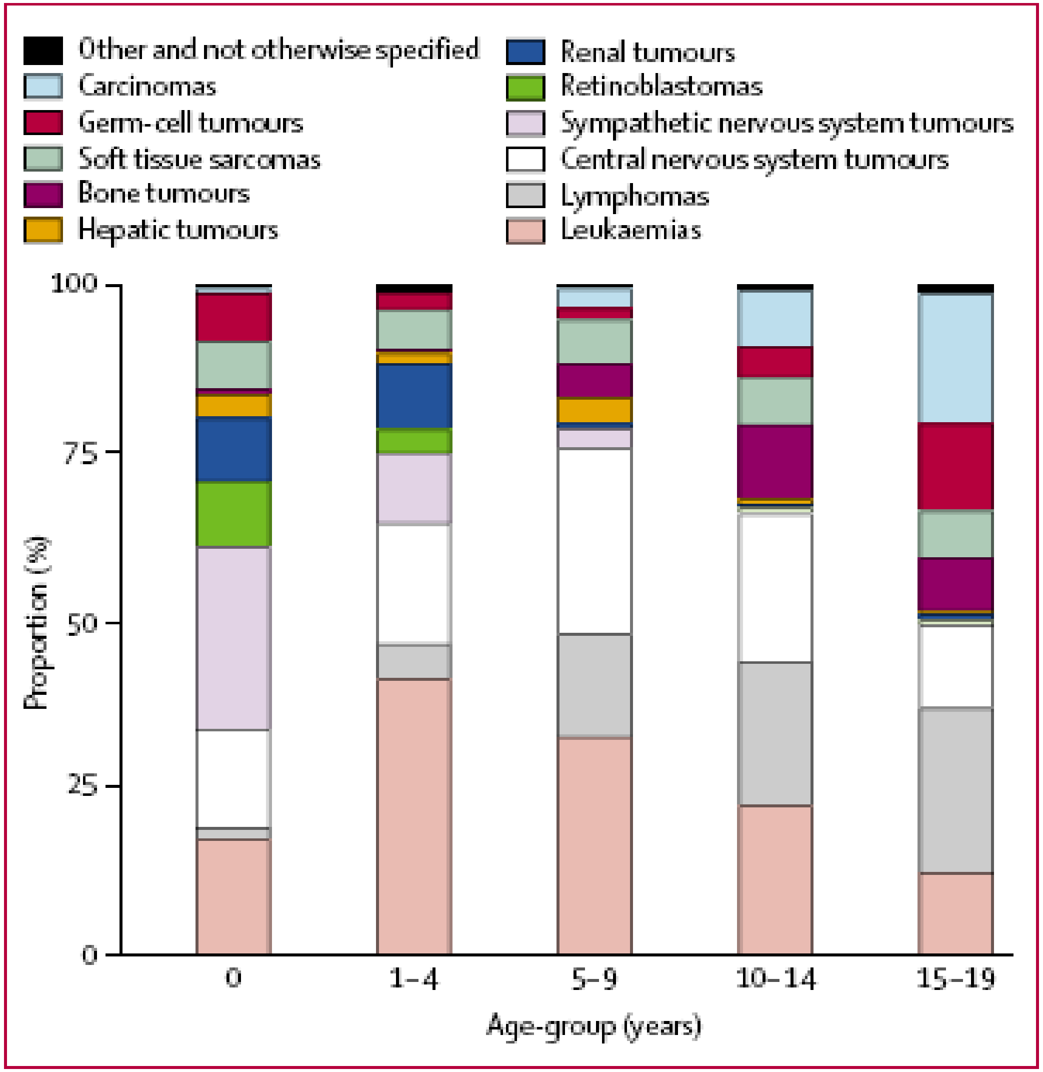

ACCIS Project

# Age- and sex-specific incidence rates of groups of childhood cancer in Europe - 1990s



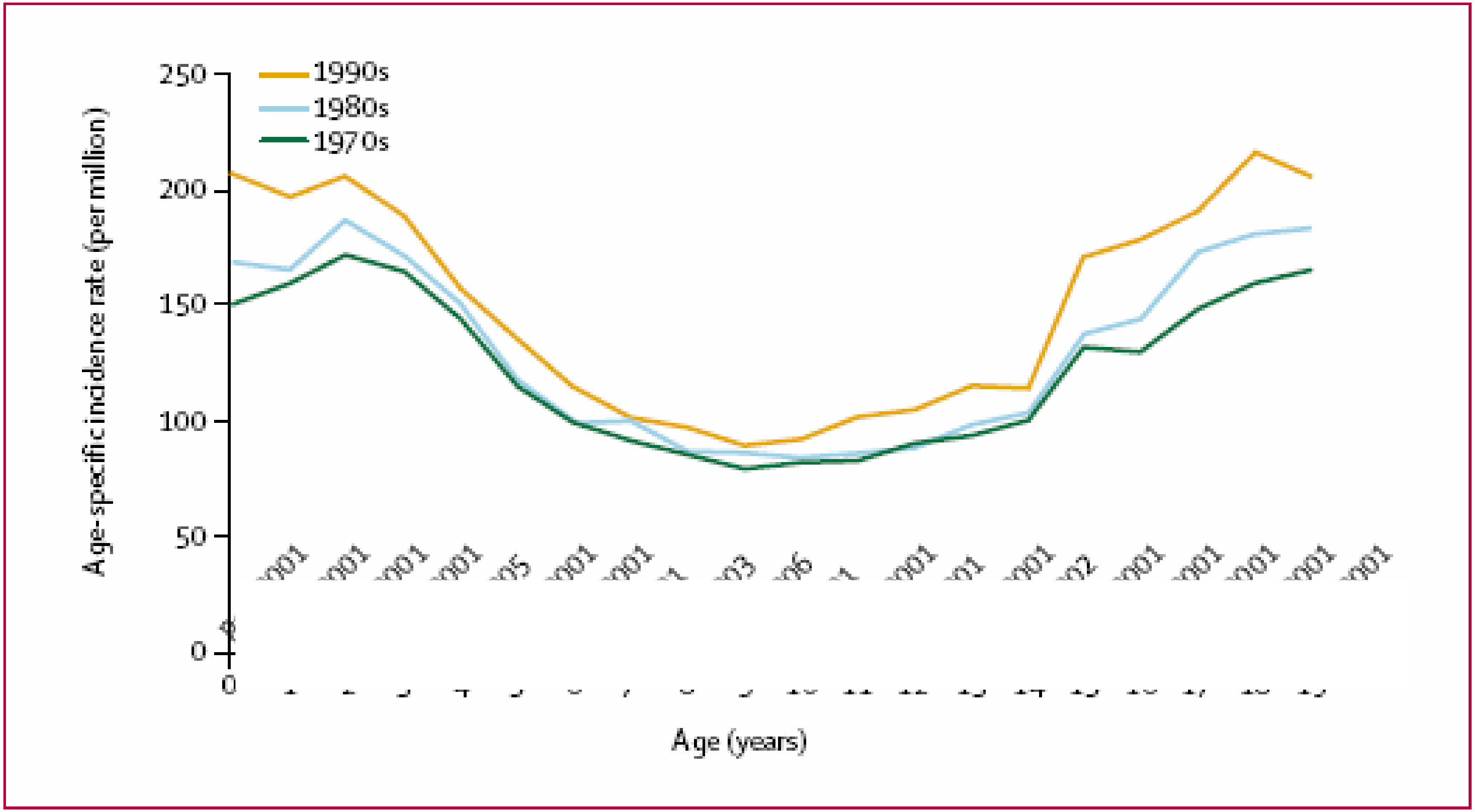

ACCIS Project

# Age-specific percentage of groups of childhood cancer in Europe - 1990s



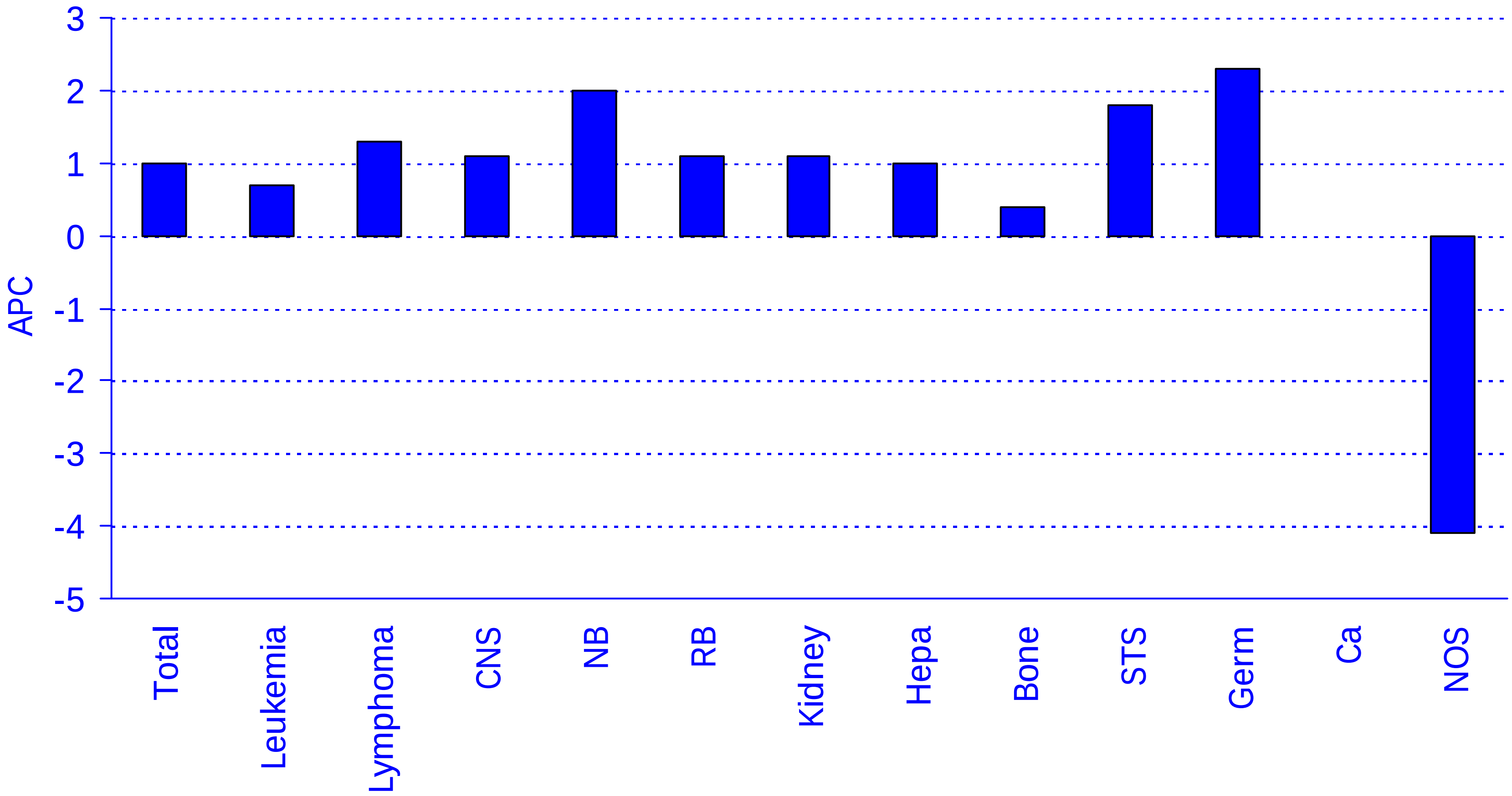

ACCIS Project

# Decade- and age-specific incidence rate of childhood cancer in Europe



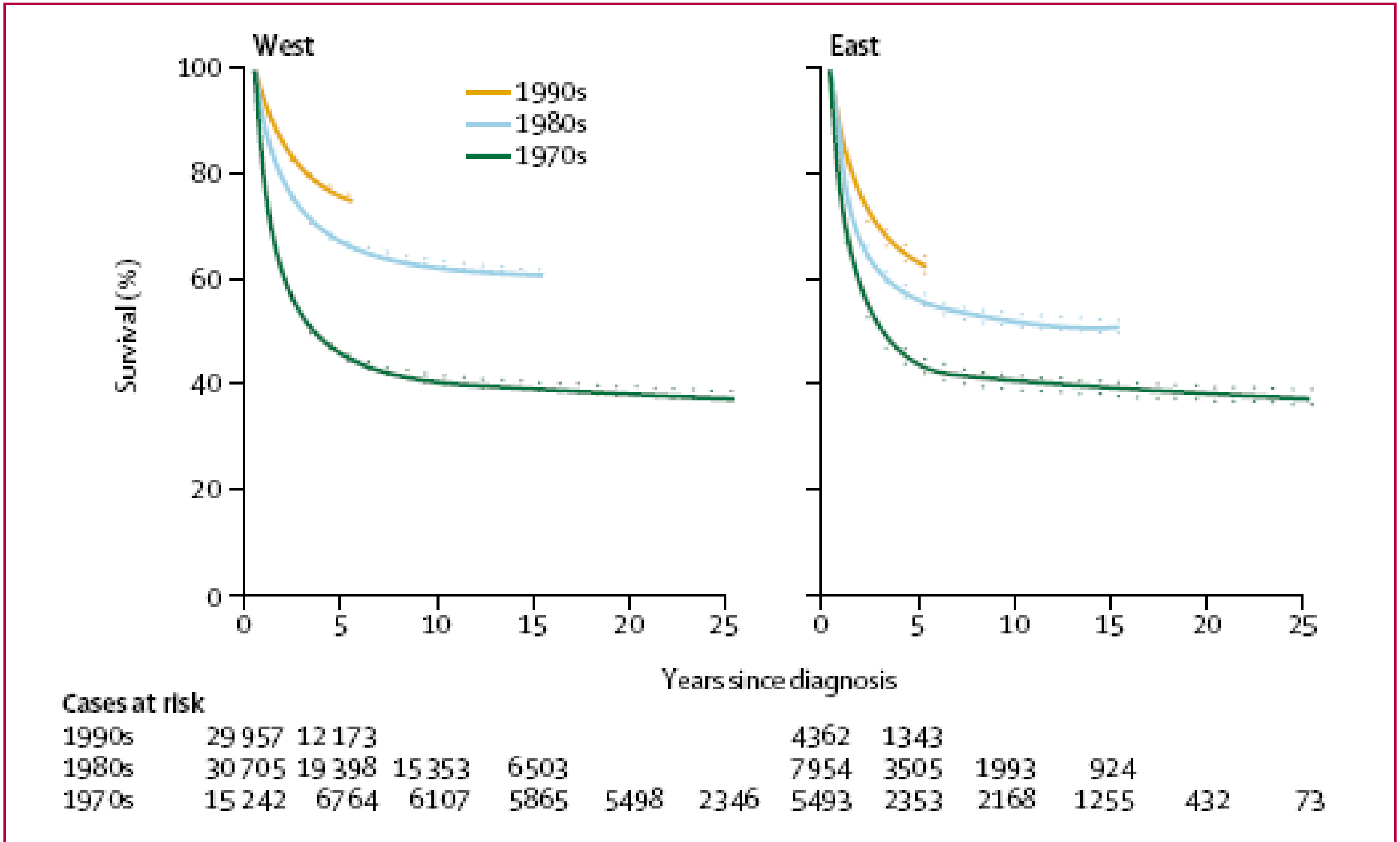

ACCIS Project

# Annual percentage change in the incidence of groups of childhood cancer in Europe – 1970-2000




ACCIS Project

# Survival from childhood cancer by European region – 1970-2000



# Issues in descriptive epidemiology of childhood cancer

- Completeness of diagnosis, registration and histologic characterization

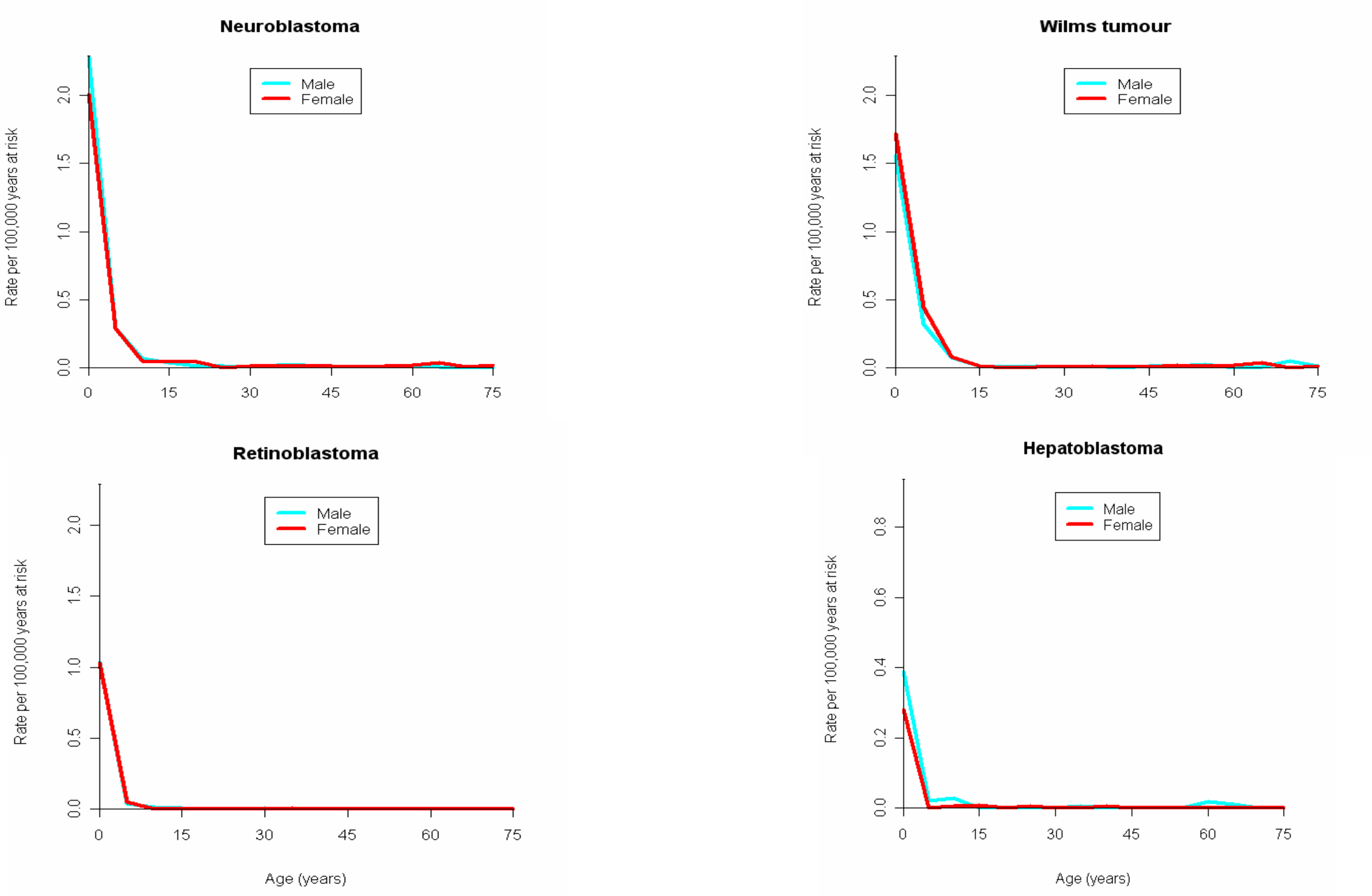
- Geographic and temporal patterns in incidence may reflect differences and trends in exposure to environmental agents, diagnostic procedures, survival of high-risk individuals

# Embryonal tumours

- Embryonal tumours are a group of specialised neoplasms characteristically seen in very young children

- The microscopic appearance of these neoplasms  resembles the structures seen in developing tissues and organs in the embryo and fetus

# Age-specific incidence of selected embryonal tumours



# Etiological implication of these patterns

- The very young ages of diagnosis and the embryonal histology of these tumours implies a pre-natal origin
- Most if not all events leading to tumour development are likely to have occurred before birth
- Any post-natal exposures / influences of aetiological importance probably act soon after birth or in infancy

# Etiological implication of these patterns

- Probably fewer steps involved in pathway from normal to malignant cell than adult cancers
- Consistent with undifferentiated nature of cells of origin and genetic factors may be important
- Effect is to reduce the number of steps in the carcinogenic pathway and/or speed up the process

# Some features common to embryonal tumours

- Abnormal birthweight patterns

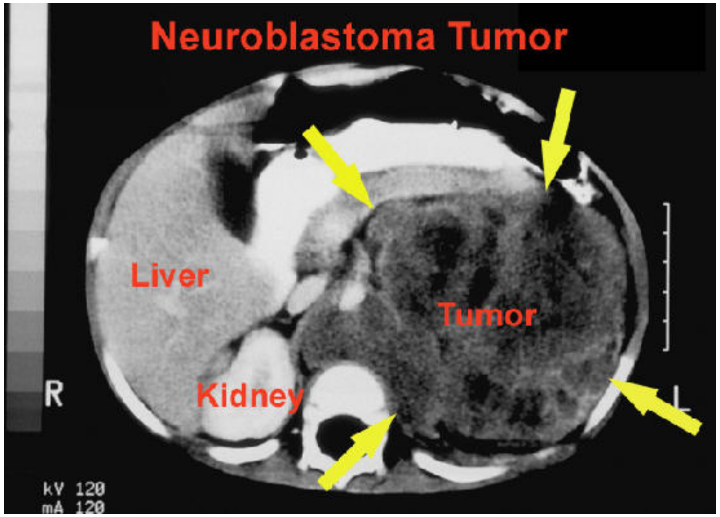
- Associations with congenital anomalies and syndromes

- Associations with germline mutations that also predispose to adult-onset cancers

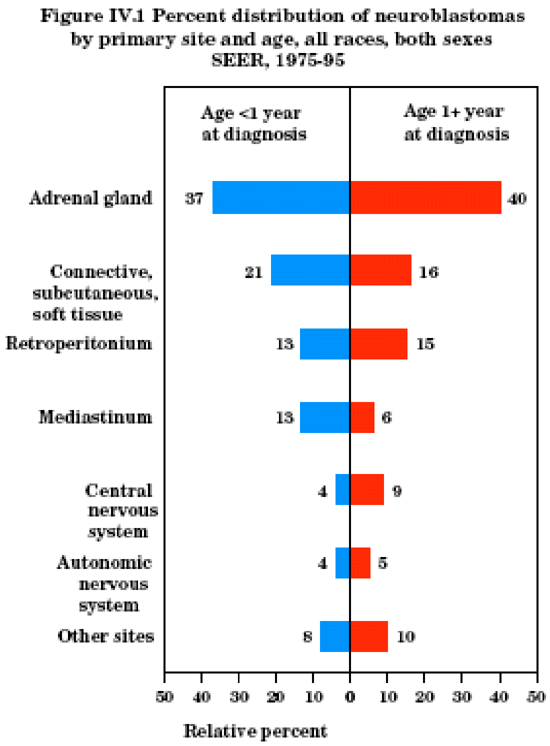
- Heterogeneity within tumour types

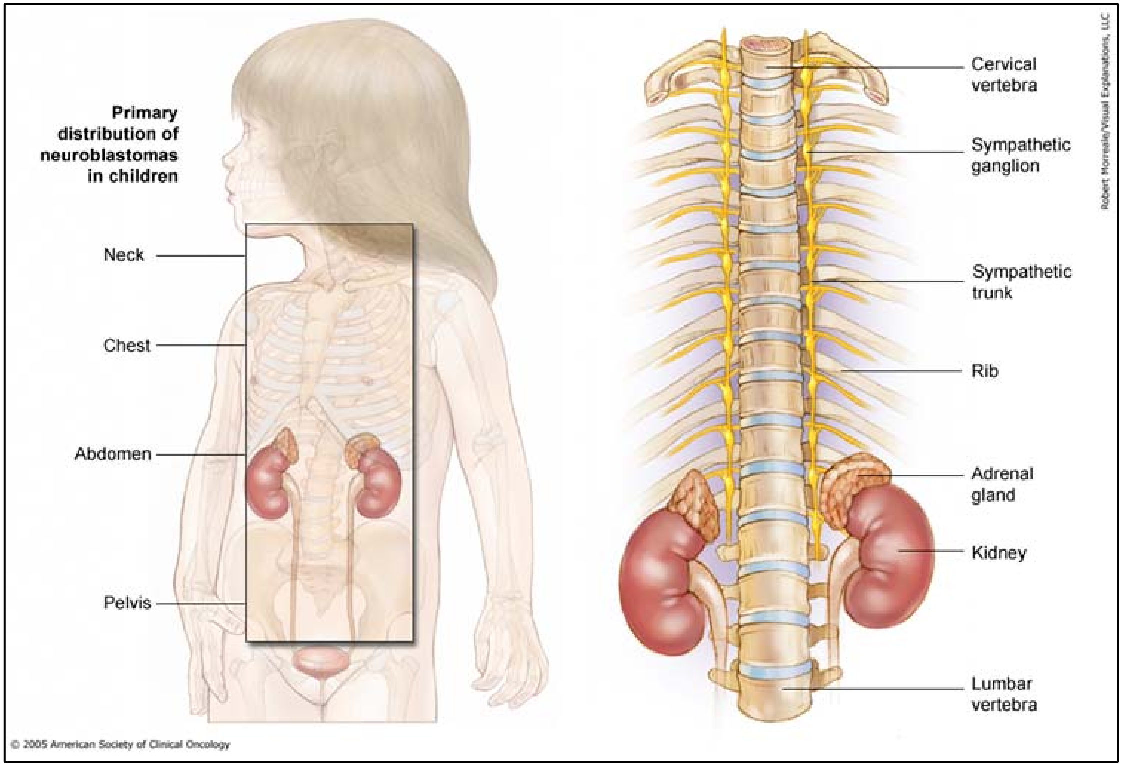
# Origin of neuroblastoma

- Malignant tumor of the cells of the neural crest
- Neural crest cells migrate to create the sympathetic nervous system, tissue of heart, jaw, head



# Sites of Neuroblastoma



# Genetic syndromes associated with NB

- Beckwith-Wiedemann syndrome
- Rubenstein-Taybi syndrome
- von Recklinghausen syndrome
- Hirschsprung's disease

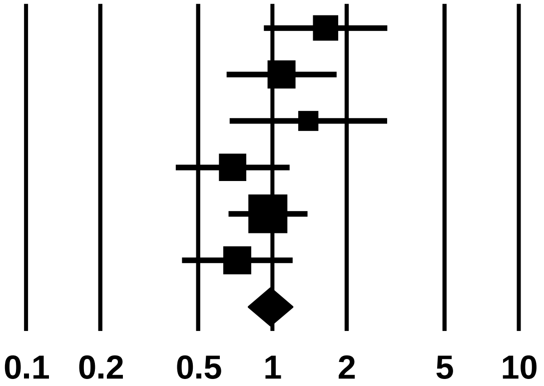
- They explain a minority of cases
- Family history of disease occurs in <5% of cases

# Maternal factors - 1

## Younger Maternal Age

| Study name | Statistics for each study | | | | |
|---|---|---|---|---|---|
| | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
| N Carolina (<20 years) | 1.645 | 0.932 | 2.903 | 1.715 | 0.086 |
| Minnesota (21 years) | 1.090 | 0.657 | 1.809 | 0.333 | 0.739 |
| US/Canada (<20 years) | 1.400 | 0.676 | 2.898 | 0.906 | 0.365 |
| New York (<18 years) | 0.690 | 0.408 | 1.166 | -1.387 | 0.165 |
| California (<20 years) | 0.959 | 0.669 | 1.375 | -0.227 | 0.820 |
| Washington (<20 years) | 0.720 | 0.433 | 1.198 | -1.265 | 0.206 |
| | 0.982 | 0.801 | 1.204 | -0.171 | 0.864 |

**Odds ratio and 95% CI**



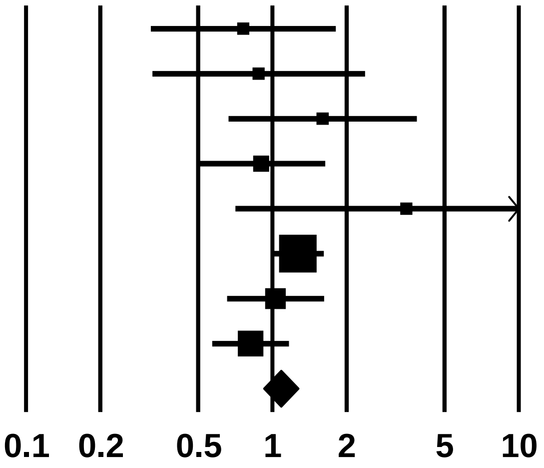
# Maternal factors - 2

## Older Maternal Age

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| N Carolina (> 30 years) | 0.762 | 0.324 | 1.794 | -0.622 | 0.534 |
| Minnesota (>35 years) | 0.880 | 0.329 | 2.357 | -0.254 | 0.799 |
| New York (>35 years) | 1.600 | 0.669 | 3.825 | 1.057 | 0.290 |
| Germany (>35 years) | 0.900 | 0.498 | 1.625 | -0.349 | 0.727 |
| US/Canada (>40 years) | 3.500 | 0.714 | 17.146 | 1.545 | 0.122 |
| New York (31-40 yrs) | 1.270 | 1.005 | 1.604 | 2.003 | 0.045 |
| Washington (>35 years) | 1.030 | 0.659 | 1.609 | 0.130 | 0.897 |
| California (>35 years) | 0.816 | 0.574 | 1.159 | -1.137 | 0.256 |
| | 1.086 | 0.924 | 1.276 | 1.006 | 0.314 |

Statistics for each study

Odds ratio and 95% CI

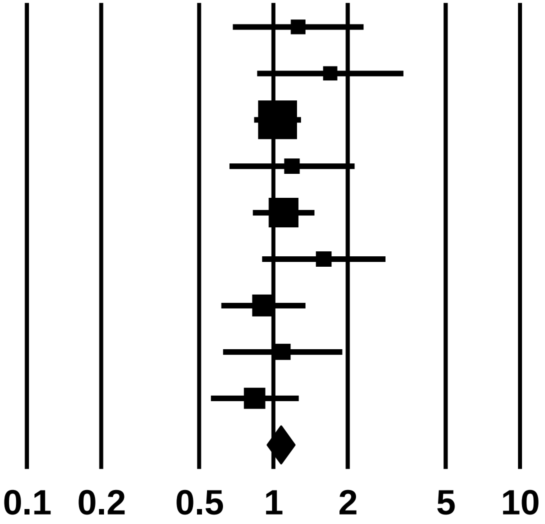


# Exposures in pregnancy - 1

## Tobacco Use in Pregnancy

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Pennsylvania 1987 | 1.260 | 0.690 | 2.302 | 0.752 | 0.452 |
| Tennessee 1992 | 1.700 | 0.866 | 3.339 | 1.541 | 0.123 |
| UK 1995 | 1.040 | 0.842 | 1.284 | 0.365 | 0.715 |
| New York 1996 | 1.190 | 0.669 | 2.117 | 0.592 | 0.554 |
| US/Canada 2001 | 1.100 | 0.832 | 1.455 | 0.668 | 0.504 |
| New York 2001 | 1.600 | 0.907 | 2.822 | 1.623 | 0.105 |
| UK 2003 | 0.910 | 0.619 | 1.338 | -0.480 | 0.631 |
| New York 2005 | 1.090 | 0.629 | 1.888 | 0.307 | 0.758 |
| Washington 2006 | 0.840 | 0.562 | 1.255 | -0.851 | 0.395 |
| | 1.074 | 0.946 | 1.218 | 1.103 | 0.270 |

Odds ratio and 95% CI



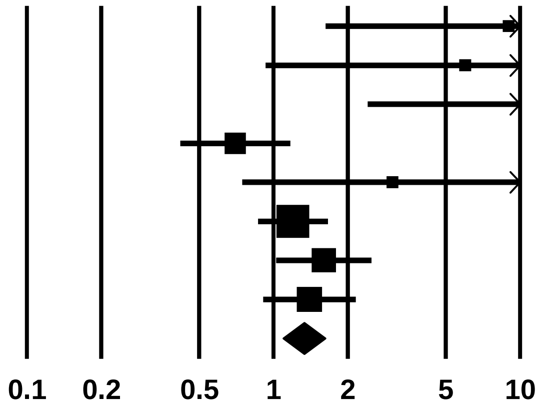
# Exposures in pregnancy - 2

## Alcohol Use in Pregnancy

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Pennsylvania (>= 1 drink/day) | 9.000 | 1.642 | 49.338 | 2.531 | 0.011 |
| Pennsylvania (>= 3 drink/occasion) | 6.000 | 0.935 | 38.503 | 1.889 | 0.059 |
| Pennsylvania (either daily or binge) | 12.000 | 2.430 | 59.259 | 3.050 | 0.002 |
| Tennessee (Daily) | 0.700 | 0.422 | 1.161 | -1.382 | 0.167 |
| Germany (Daily) | 3.040 | 0.754 | 12.261 | 1.563 | 0.118 |
| US/Canada - 1st trimester (any/none) | 1.200 | 0.873 | 1.649 | 1.124 | 0.261 |
| US/Canada - 2nd trimester (any/none) | 1.600 | 1.033 | 2.479 | 2.104 | 0.035 |
| US/Canada - 3rd trimester (any/none) | 1.400 | 0.917 | 2.139 | 1.557 | 0.120 |
| | 1.336 | 1.098 | 1.624 | 2.899 | 0.004 |

Statistics for each study

Odds ratio and 95% CI

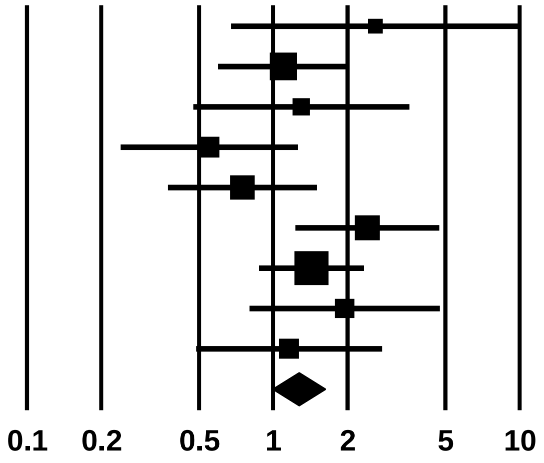


# Pregnancy-related factors - 1

## Low Birthweight

**Study name** | **Statistics for each study** | **Odds ratio and 95% CI**

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| US/Canada - Very low | 2.600 | 0.679 | 9.956 | 1.395 | 0.163 |
| US/Canada - Low | 1.100 | 0.601 | 2.013 | 0.309 | 0.757 |
| N Carolina - Hospital controls | 1.300 | 0.477 | 3.540 | 0.513 | 0.608 |
| N Carolina - BC controls | 0.550 | 0.242 | 1.250 | -1.427 | 0.154 |
| Washington | 0.750 | 0.376 | 1.495 | -0.817 | 0.414 |
| Germany | 2.410 | 1.239 | 4.687 | 2.592 | 0.010 |
| New York State | 1.430 | 0.883 | 2.317 | 1.453 | 0.146 |
| Texas | 1.950 | 0.808 | 4.707 | 1.485 | 0.137 |
| California | 1.160 | 0.491 | 2.743 | 0.338 | 0.735 |
| | 1.275 | 1.001 | 1.624 | 1.967 | 0.049 |

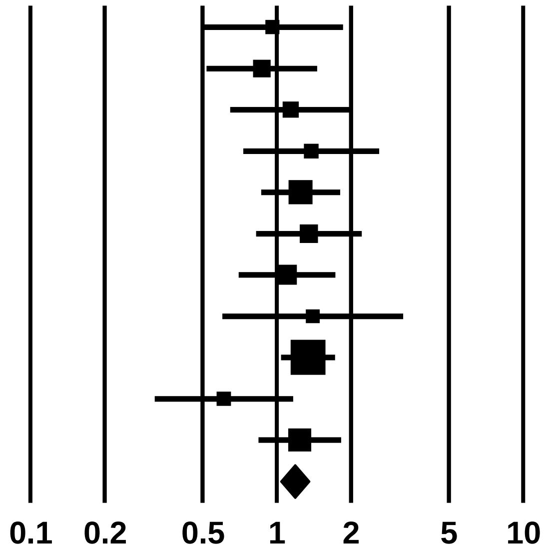


# Pregnancy-related factors - 2

## High Birthweight

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| | **Statistics for each study** | | | | |
| Minnesota | 0.960 | 0.500 | 1.842 | -0.123 | 0.902 |
| Tennessee | 0.870 | 0.523 | 1.448 | -0.536 | 0.592 |
| N Carolina, Hosp controls | 1.140 | 0.653 | 1.990 | 0.461 | 0.645 |
| N Carolina, BC controls | 1.380 | 0.738 | 2.582 | 1.008 | 0.314 |
| Washington State | 1.250 | 0.871 | 1.793 | 1.212 | 0.225 |
| Germany | 1.350 | 0.831 | 2.193 | 1.212 | 0.225 |
| US/Canada, High | 1.100 | 0.706 | 1.714 | 0.421 | 0.674 |
| US/Canada, Very High | 1.400 | 0.606 | 3.233 | 0.788 | 0.431 |
| NY State | 1.340 | 1.050 | 1.710 | 2.352 | 0.019 |
| Texas | 0.610 | 0.322 | 1.156 | -1.515 | 0.130 |
| California | 1.240 | 0.850 | 1.809 | 1.116 | 0.265 |
| | 1.188 | 1.041 | 1.357 | 2.547 | 0.011 |

**Odds ratio and 95% CI**



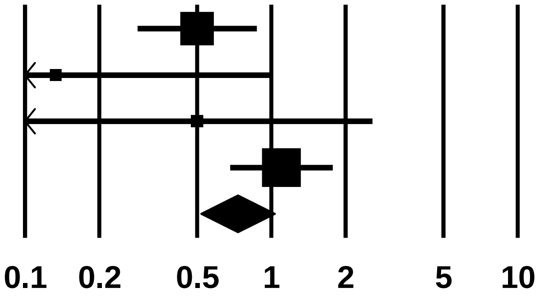
# Exposures in childhood - 1

## Breastfeeding

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| US/Canada - > 13 months | 0.500 | 0.289 | 0.866 | -2.473 | 0.013 |
| Russia - >12 months | 0.133 | 0.018 | 1.009 | -1.951 | 0.051 |
| Sweden - > 6 months | 0.500 | 0.098 | 2.550 | -0.834 | 0.404 |
| Germany - > 6 months | 1.100 | 0.686 | 1.764 | 0.396 | 0.692 |
| | 0.732 | 0.519 | 1.034 | -1.772 | 0.076 |

Statistics for each study

Odds ratio and 95% CI



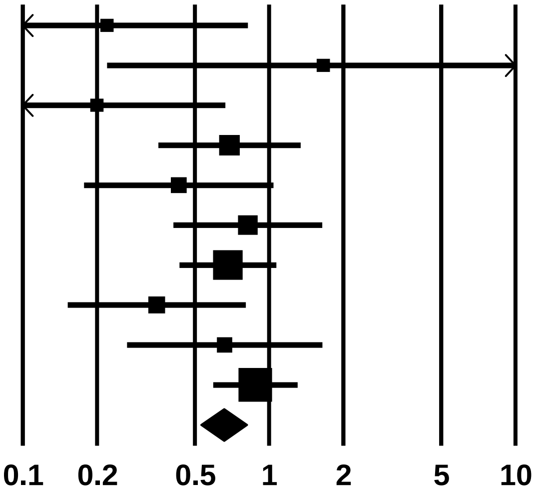
# Exposures in childhood - 2

## Child or Familial History of Allergic Diseases

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| N Carolina - Allergies | 0.220 | 0.060 | 0.813 | -2.270 | 0.023 |
| N Carolina - Asthma | 1.660 | 0.222 | 12.432 | 0.493 | 0.622 |
| Germany - Allergies | 0.200 | 0.061 | 0.658 | -2.648 | 0.008 |
| US/Canada - Asthma | 0.690 | 0.358 | 1.331 | -1.107 | 0.268 |
| US/Canada - Hay Fever | 0.430 | 0.179 | 1.034 | -1.886 | 0.059 |
| US/Canada - Eczema | 0.820 | 0.413 | 1.630 | -0.566 | 0.571 |
| US/Canada - Any allergic disease | 0.680 | 0.436 | 1.060 | -1.701 | 0.089 |
| N Carolina - Maternal asthma | 0.350 | 0.153 | 0.798 | -2.496 | 0.013 |
| N Carolina - Maternal allergies | 0.660 | 0.267 | 1.632 | -0.900 | 0.368 |
| Germany - Maternal allergies | 0.880 | 0.598 | 1.295 | -0.648 | 0.517 |
| | 0.657 | 0.530 | 0.814 | -3.841 | 0.000 |

Statistics for each study

Odds ratio and 95% CI



# Challenges in epidemiological research of childhood cancer

- Need to think about what the birthweights and anomalies are pointing to regarding critical stages of gestation at which risk factors may act
- Need to relate knowledge of biology and evolution of tumours to pre-natal and post-natal growth and development and descriptive epidemiology
- Need to think about what sorts of aetiological agents might produce these biological and epidemiological patterns
- Need to consider the role of genetic variability in susceptibility (of the child and the mother)

# Timing of exposures

- Pre-conception
  - – parental germ cells, de novo/inherited mutations and polymorphisms
  - – parental exposures
- Pre-natal
  - – tissue and organ development in embryo and fetus: what are the targets and critical periods?
  - – growth factors and imprinting
  - – transplacental factors, maternal exposures (including via father/partner etc)

Post-natal

–neonatal care, nutrition, infections etc.: what are the vulnerable organs/tissues and critical periods of growth and development?

# Conclusions

- Incidence rates of childhood cancer have been increasing in the last decades in most countries
- It is unclear whether this reflects a real phenomenon or an artifact due to better diagnosis and reporting
- Current knowledge on etiological factors of childhood cancer remains limited
- Future studies should integrate epidemiology, clinical research, genetics and molecular biology

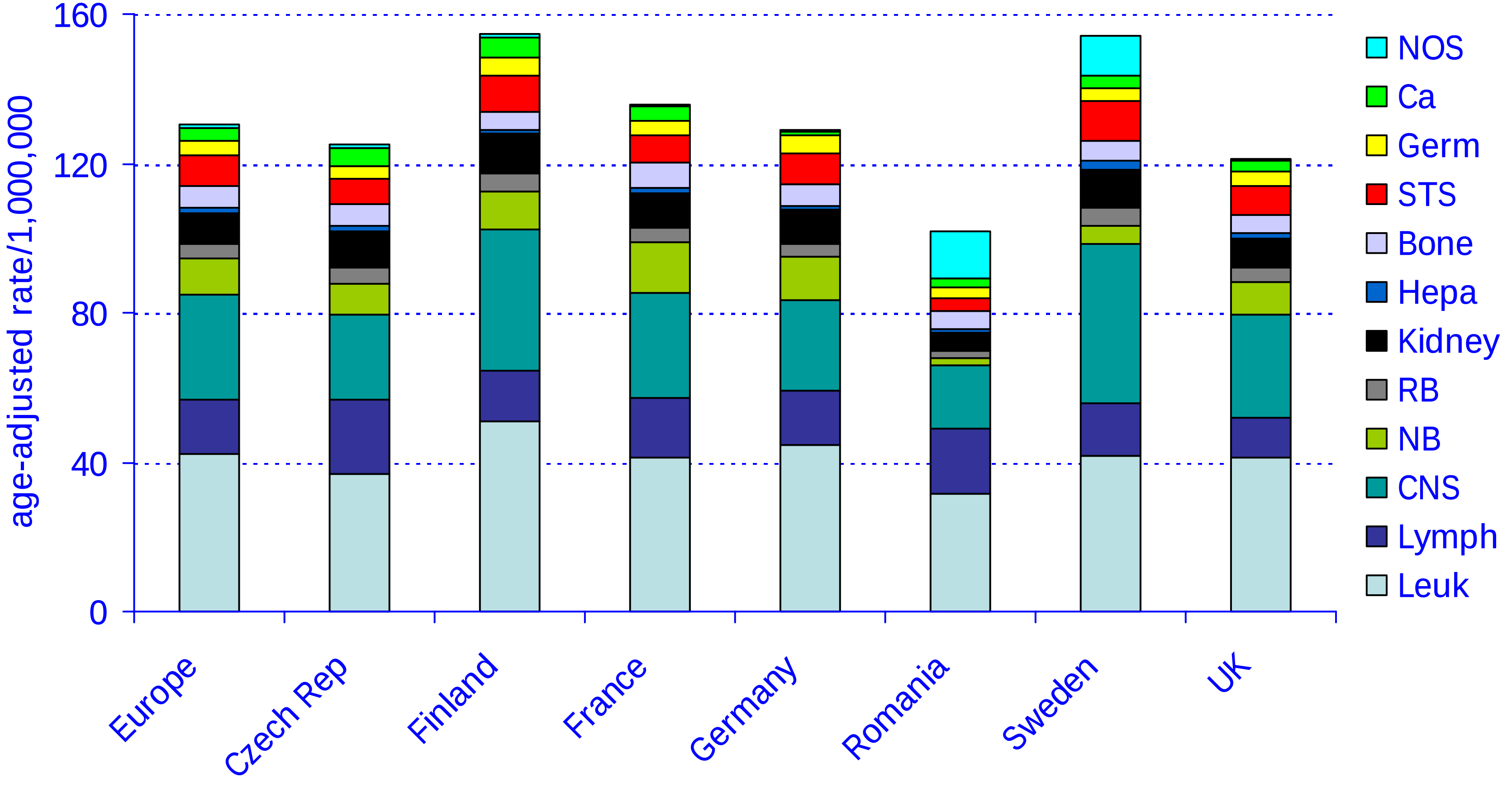
# The ISET study

- Case-control study of non-CNS solid tumours in childhood
- Large-scale collaboration
  - epidemiologists; clinicians (SIOP); geneticists
- Emphasis on gene-environment interactions
- NB, RMS as pilot projects

# ISET participants

- **France**
  - INSERM: Florence Menegaux, Jacqueline Clavel
- **Italy**
  - Ospedale Pediatrico Bambino Gesù: Marina Cuttini
  - U. Turin: Corrado Magnani, Franco Merletti
- **Germany**
  - U. Mainz: Maria Blettner
- **The Netherlands**
  - Radboud U. Nijmegen Medical Centre: Nel Roeleveld
- **UK**
  - University of Manchester: Jillian Birch
  - ICR: Kathy Pritchard-Jones
  - U. Leeds: Patricia McKinney
  - U. Oxford: Michael Murphy
- **Czech Republic**
  - Vladimir Bencko
- **Serbia and Slovenia**
  - Simona Ognjanovic
- Switzerland
  - U. Bern: Claudia Kuehni
- **USA**
  - U. Berkeley: Patria Buffler
- **Canada**
  - SLRI / U. Toronto : Rayjean Hung
- **Brazil**
  - A C Camargo Cancer Hospital: Beatriz de Camargo, Karina Braga Ribeiro
  - NIC, Rio de Janeiro: Maria S. Pombo de Oliveira
- **India**
  - Tata Memorial Centre : PA Kurkure
- **Japan**
  - National Research Institute for Child Health and Development : Tomohiro Saito
- **Australia**
  - Institute for Child Health Research: Liz Milne

# Incidence rate of groups of childhood cancer (0-14) in selected European countries - 1990s



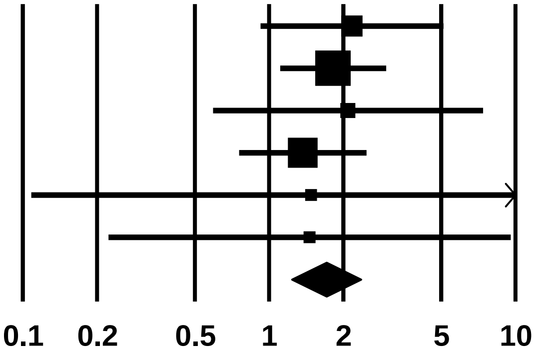

ACCIS Project (DG-SANCO, IARC, Scotland MoH)

# Exposures in pregnancy - 3

## Recreational Drug Use in Pregnancy

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| New York (Any drug use) | 2.170 | 0.930 | 5.062 | 1.793 | 0.073 |
| US/Canada (Any recreational) | 1.820 | 1.117 | 2.965 | 2.404 | 0.016 |
| US/Canada - Cocaine | 2.090 | 0.596 | 7.328 | 1.152 | 0.249 |
| US/Canada - Marijuana | 1.370 | 0.762 | 2.464 | 1.051 | 0.293 |
| US/Canada - Hallucinogens | 1.480 | 0.109 | 20.063 | 0.295 | 0.768 |
| US/Canada - Stimulants | 1.460 | 0.224 | 9.501 | 0.396 | 0.692 |
| | 1.712 | 1.239 | 2.366 | 3.258 | 0.001 |

Odds ratio and 95% CI

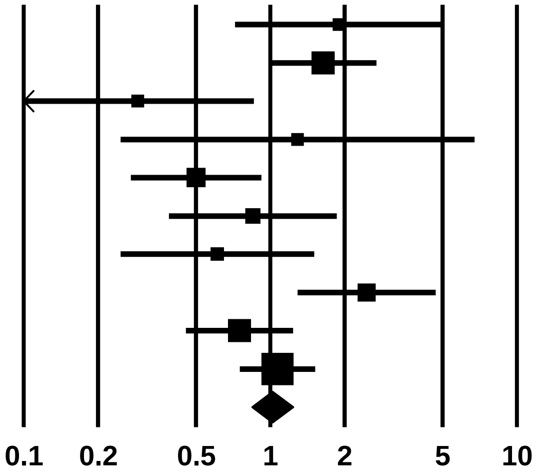


# Pregnancy-related factors - 3

## Preterm Birth

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| US/Canada (<32 weeks) | 1.900 | 0.726 | 4.975 | 1.307 | 0.191 |
| New York (<35 weeks) | 1.640 | 1.007 | 2.671 | 1.987 | 0.047 |
| Texas (< 36 weeks) | 0.290 | 0.099 | 0.850 | -2.255 | 0.024 |
| Minnesota (< 37 weeks) | 1.290 | 0.249 | 6.677 | 0.304 | 0.761 |
| US/Canada (33-36 weeks) | 0.500 | 0.274 | 0.913 | -2.257 | 0.024 |
| N Carolina (<36 weeks) - HC | 0.850 | 0.391 | 1.846 | -0.411 | 0.681 |
| N Carolina (<36 weeks)- BC controls | 0.610 | 0.249 | 1.494 | -1.081 | 0.280 |
| Germany (< 36 weeks) | 2.460 | 1.302 | 4.648 | 2.773 | 0.006 |
| California (<36 weeks) | 0.750 | 0.459 | 1.226 | -1.147 | 0.252 |
| New York (<37 weeks) | 1.070 | 0.759 | 1.508 | 0.386 | 0.699 |
| | 1.022 | 0.844 | 1.238 | 0.227 | 0.820 |

**Odds ratio and 95% CI**



# Exposures in childhood - 1

## Birth Order or Family Size

| Group | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| Firstborn | Minnesota | 1.190 | 0.713 | 1.985 | 0.666 | 0.505 |
| Firstborn | N Carolina - Hosp Controls | 1.310 | 0.657 | 2.610 | 0.768 | 0.443 |
| Firstborn | N Carolina - BC controls | 2.260 | 1.000 | 5.109 | 1.959 | 0.050 |
| Firstborn | Germany | 1.140 | 0.819 | 1.587 | 0.776 | 0.438 |
| Firstborn | New York | 1.150 | 0.931 | 1.421 | 1.294 | 0.196 |
| Later born | Pennsylvania | 1.520 | 0.803 | 2.879 | 1.285 | 0.199 |
| Later born | Tennessee | 0.990 | 0.633 | 1.548 | -0.044 | 0.965 |
| Later born | Sweden | 1.440 | 0.857 | 2.421 | 1.376 | 0.169 |
| Family size | New York - 2 or more | 0.670 | 0.442 | 1.015 | -1.889 | 0.059 |
| Family size | New York - 3 or more children | 0.780 | 0.429 | 1.417 | -0.815 | 0.415 |
| Family size | California - 3+ prior pregnancies | 0.630 | 0.438 | 0.906 | -2.492 | 0.013 |
| Family size | Washington - 2+ prior births | 1.120 | 0.797 | 1.574 | 0.653 | 0.514 |

Odds ratio and 95% CI