Keynotes:

# Advancing knowledge about childhood diseases through large birth cohort studies


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# Editorial on the Demise of the National Children's Study, *JAMA Pediatrics 2016 or 17*

VIEWPOINT

## In the Aftermath of the National Children's Study
## Is Large Birth Cohort Data Still a Priority?

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**The 2014 decision** to stop the US National Children's Study (NCS)[1] brings to the forefront questions about what has been lost and how studies such as this might still be important almost 20 years after initiation in 2000. The rationale then was clear.[2] Little progress had been made in the previous decades in understanding the causes of many major childhood disorders, and there was insufficient evidence available to confidently mount interventions to prevent many of them. A lack of evidence from cohort studies with prospective data had left a major evidence gap in childhood disease etiology, in stark contrast to efforts involving successful research on adult diseases where cohort studies were a central component.

Important pediatric conditions for which prospective data might be critical included birth defects, childhood cancer, type 1 diabetes, and autism.[2] The exposures of interest for these conditions embraced infections of the mother and infant, environmental

of interest.

Nonetheless, the proposition that this obstacle must be overcome if progress was to be made in understanding pediatric disease causation was clearly gaining strong support toward the end of the 20th century. As well as the decision to start the NCS, Danish and Norwegian birth cohort studies were launched in the period leading up to 2000. They benefited from the comprehensive sampling frames for health studies and health data linkage that those nations possess. Partly as a consequence of this, they were able to enroll and measure mothers in pregnancy and their infants and collect data on their 100 000 participants for what they perceived as acceptable costs, around US$20 million.

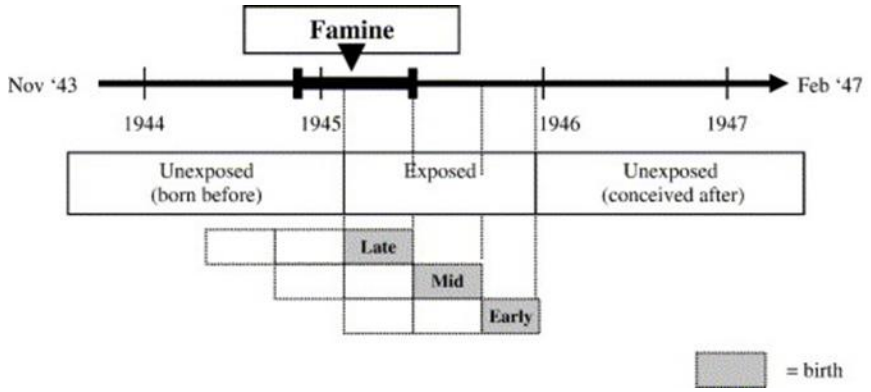
The NCS faced bigger cost hurdles because of the lack of such infrastructure. In addition, its planners argued that prenatal recruitment was necessary to avoid potential selection bias associated with failure to include mothers who miscarried or experienced a stillbirth and decided to sample from the only feasible sampling base in the United States that would include all potential new mothers: the household. Importantly, this would have enabled home-based collection of exposure data that the other more modestly funded international cohorts were unable to incorporate. Analyses conducted later by the NCS team revealed that this sampling approach would inflate the costs over an alternative scenario involving sampling of prenatal clinicians and

trum disorder.[6]

For some diseases, in particular cancer, type 1 diabetes, and cerebral palsy, it was apparent at the planning stage of these cohorts that even 100 000 participants would be marginal for providing the required power. Consequently, the Danish National Birth Cohort and Norwegian Mother and Child Cohort Study have participated in an initiative to pool data with some older studies that have relevant data to obtain the necessary power. These include the Jerusalem Perinatal Study, the

# Available evidence on early life exposures and childhood disease derived from:

1. Studies with biological endpoints




2. Studies with disease endpoints
   - Ecological studies
   - Retrospective epidemiological studies
   - A small number of prospective cohort studies, lacking depth of exposure measurement

# Comparison of maternal report to GP record data in relation to infant infection or proxy in the UK Childhood Cancer Case Control Study

## Regular social contact outside the home

Mother's report
OR = 0.6
(CI 0.5-0.9)

GP records
OR = 1.7
1.1-12

## History of infection

Mother's report
OR = 0.94

GP records
OR = 1.12

Prospective questionnaire data or biospecimen analysis needed

# Framingham Cohort Study

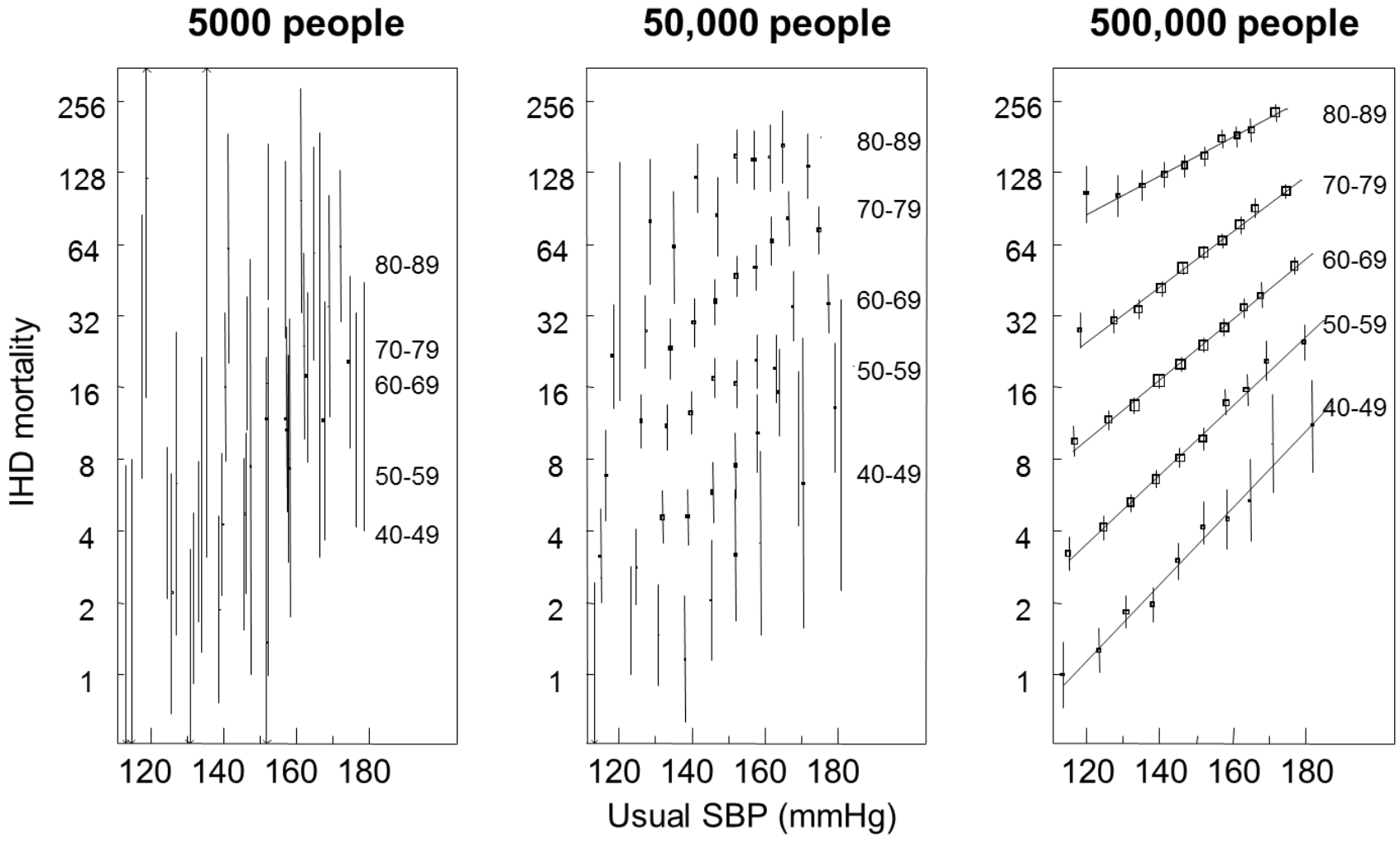


**Table 10—Serum Total Cholesterol in Relation to Incidence of ASHD in Four-Year Follow-Up, Males 45–62**

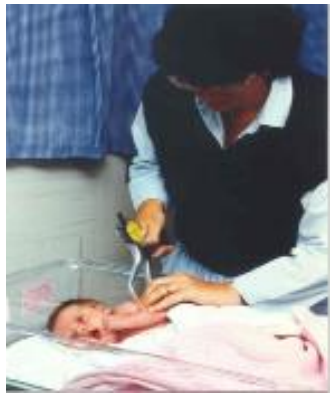
| | Population at Risk | New Disease | Rate/1,000 |
|---|---|---|---|
| All persons | 898 | 52 | 58 |
| Cholesterol measured at Examinations I or II: | | | |
| 260 mg per cent and over | 172 | 21 | 122 |
| 225–259 mg per cent | 265 | 12 | 45 |
| Less than 225 mg per cent | 445 | 18 | 40 |
| Unknown | 16 | 1 | * |
| Cholesterol measured at Examination I: † | | | |
| 260 mg per cent and over | 131 | 16 | 122 |
| 225–259 mg per cent | 188 | 8 | 42 |
| Less than 225 mg per cent | 334 | 13 | 39 |
| Unknown | 228 | 14 | 61 |

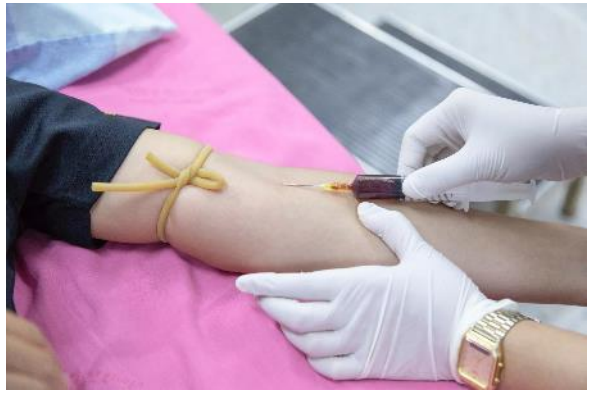
* Rate not computed for base less than 50.
† Included above.

# Minimising Uncertainty



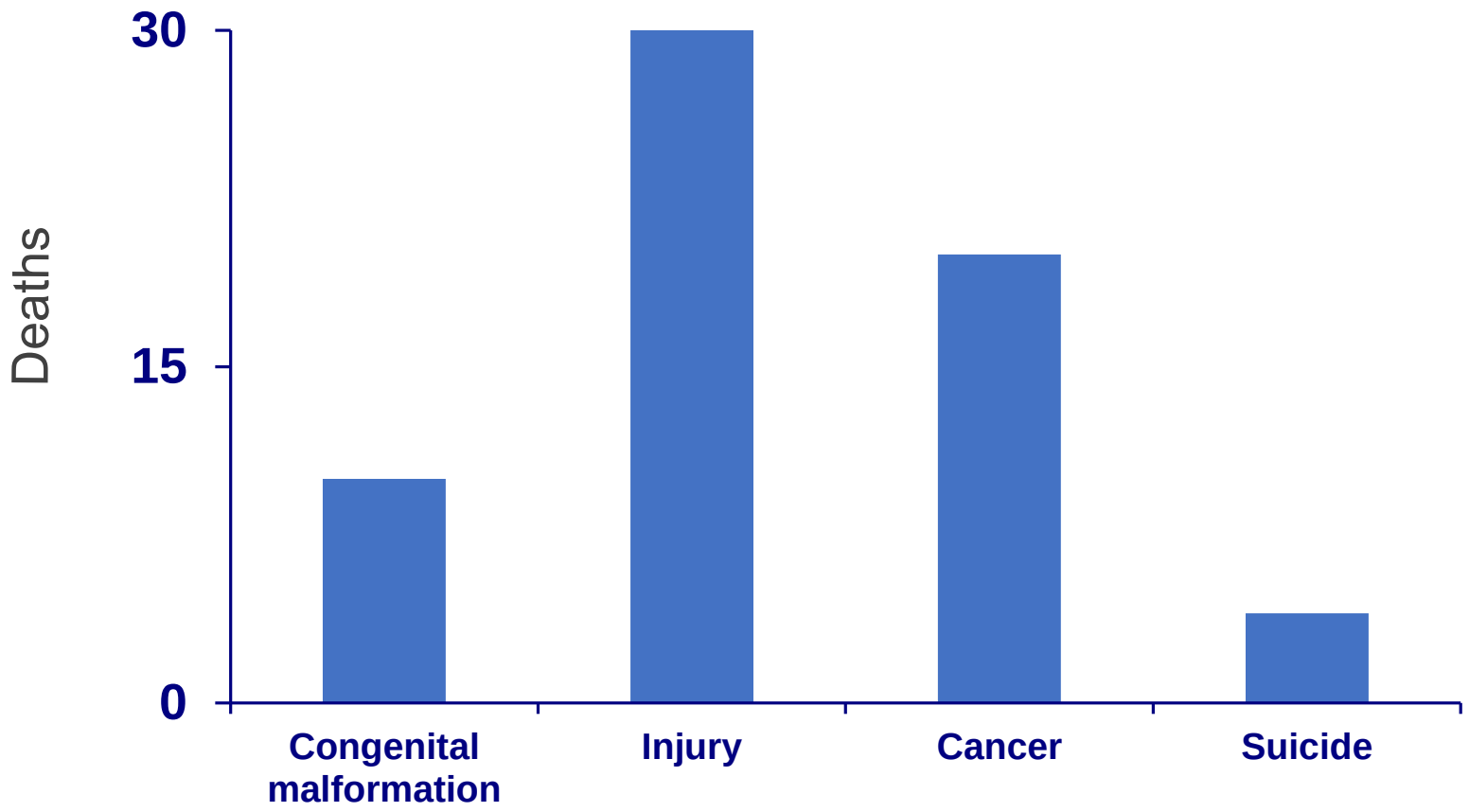
# Birth cohort studies and childhood diseases





Age 0 5

# Major causes of death 5 - 14 years Per 60,000 births in 2001



# Incidence of major adult & children's diseases

| Disease | Number of events per year | |
|---|---|---|
| Adult Cohort 100,000 | | |
| CHD | 200 – 700 | |
| Infant/child cohort 100,000 | | |
| SIDS | 400* | |
| Congenital malformations | 500 | 200 for NTD |
| Type 1 diabetes | 10-40 | |
| Cancer | 10-20 | |

* High Risk Areas

# International Childhood Cancer Cohort Consortium (I4C)

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*JECS*
*IARC*
*National Cancer Institute, NIH USA*
*MCRI*
*NINFEA*

# Risk Factors for Childhood Leukemia

**Known Risk Factors**

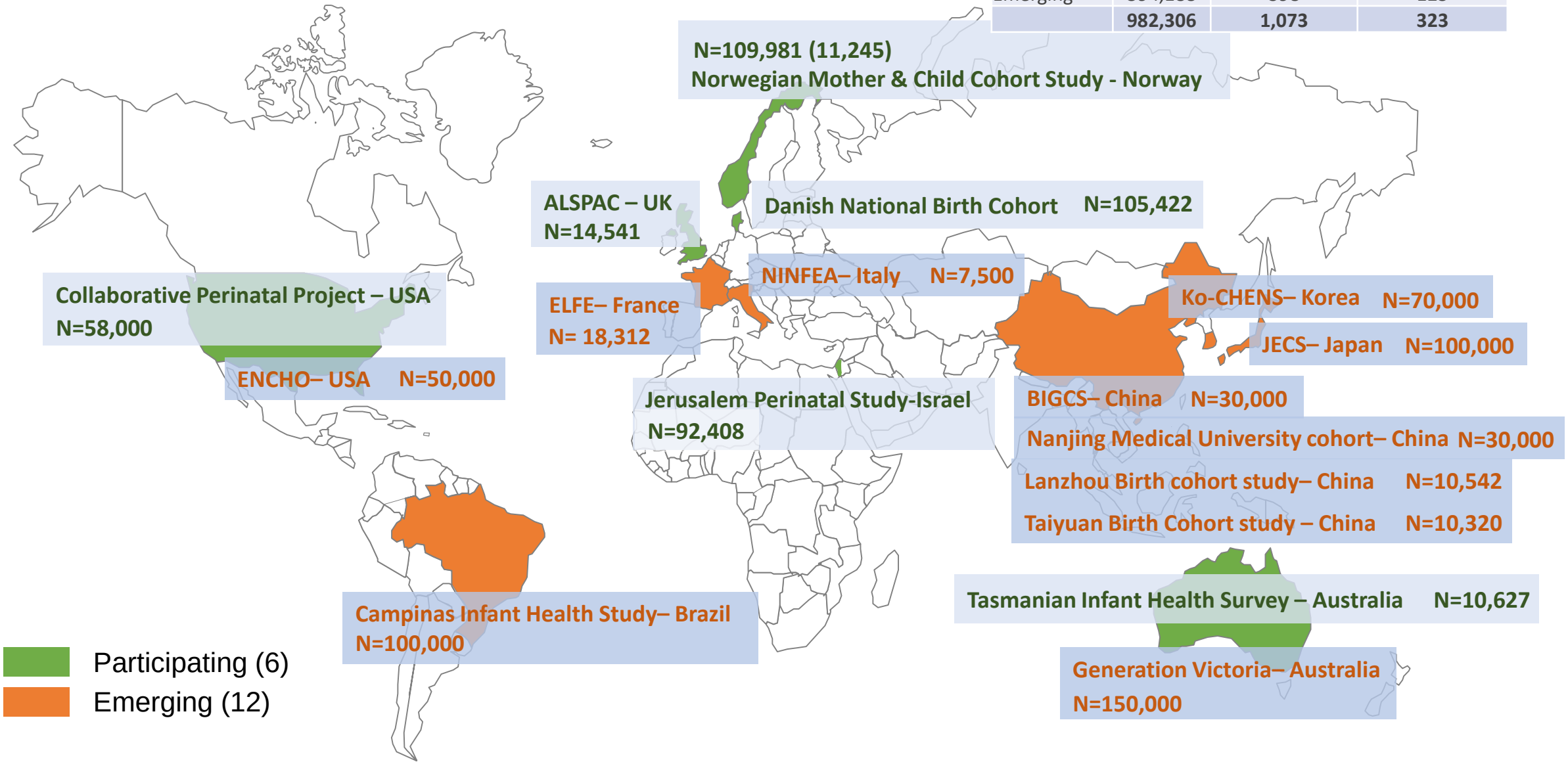
- High-dose single exposure to ionizing radiation
- Pre-natal diagnostic x-ray exposures
- Chemotherapy
- Genetic & constitutional disorders  (e.g., Down syndrome, neurofibromatosis type I)
- Pediatric leukemia in sibling of proband
- Established risk factors explain <10% of childhood leukemia

**Risk Factors currently under investigation in I4C**

- Birth weight
- Birth order
- Pesticides and herbicides
- Maternal infection

# Participating and emerging cohorts

| Cohorts | Sample size | Current no. of cancers | Current no. of leukemias |
|---|---|---|---|
| Participating | 388,118 | 675 | 198 |
| Emerging | 594,188 | 398 | 125 |
| | **982,306** | **1,073** | **323** |



# Sample size in I4C's participating and emerging cohorts

| Country | Study title | Acronym | Recruiting years | Sample size | Current no. of cancers | Current no. of leukemia | By 2020 no. of cancers | By 2020 no. of leukemia |
|---|---|---|---|---|---|---|---|---|
| **Participating cohorts** | | | **Sub total** | **388,118** | **675** | **198** | **746** | **222** |
| Australia | Tasmanian Infant Health Study | TIHS | 1988-1995 | 10,625 | 27 | 4 | 27 | 4 |
| Denmark | Danish National Birth Cohort | DNBC | 1996-2002 | 101,042 | 202 | 64 | 238 | 75 |
| Israel | Jerusalem Perinatal Study | JPS | 1964-1976 | 92,408 | 172 | 39 | 172 | 39 |
| Norway | Norwegian Mother and Child Cohort Study | MoBa | 1999-2007 | 109,981 | 200 | 70 | 235 | 82 |
| UK | Avon Longitudinal Study of Parents and Children | ALSPAC | 1990-1992 | 14,062 | 24 | 5 | 24 | 5 |
| USA | Collaborative Perinatal Project | CPP | 1959-1965 | 60,000 | 50 | 16 | 50 | 16 |
| **Emerging cohorts*** | | | **Sub total** | **594,188** | **398** | **125** | **539** | **172** |
| Australia | Generation Victoria | Gen V | 2018+ | 80,000 | 0 | 0 | 20 | 7 |
| Brazil | Campinas Infant Health Study | | 2014+ | 100,000 | ? | ? | ? | ? |
| China | Born in Guangzhou Cohort Study | BIGCS | 2012-2017 | 30,000 | 10 | 3 | 26 | 9 |
| China | Lanzhou Birth Cohort Study | | 2010-2012 | 10,542 | 11 | 4 | 13 | 4 |
| China | Taiyuan Birth Cohort study | | 2012-2016 | 10,320 | 4 | 1 | 11 | 4 |
| Denmark | Aarhus Birth Cohort | ABC | 1989-1996 | 106,370 | 200[#] | 60[#] | 200[#] | 60[#] |
| Denmark | Healthy habits for two | HHf2 | 1984-1987 | 11,144 | 26 | 8 | 26 | 8 |
| France | Etude Longitudinale Française depuis l'enfance | ELFE | 2011 | 18,312 | 19 | 6 | 25 | 8 |
| Italy | Nascita ed Infancia. Gli Effetti dell'Ambiente | NINFEA | 2005+ | 7,500 | 11 | 4 | 14 | 5 |
| Japan | Japan Environment and Children's Study | JECS | 2011-2014 | 100,000 | 60 | 20 | 105 | 35 |
| Korea | Korean Children's Environmental Health Study | Ko-CHENS | 2015 -2019 | 70,000 | 3 | 1 | 24 | 8 |
| USA | Environmental influences on Child Health Outcomes | ENCHO | >35 cohorts | 50,000 | 53 | 18 | 75 | 25 |
| | | | **Grand total** | **982,306** | **1073** | **323** | **1285** | **394** |

*, number of cases for emerging cohorts were estimated
[#], excluding 20% of cases that were duplicated in DNBC

# Data availability of key exposure domains for mothers in I4C

| Variables | ALSPAC | CPP | DNBC | JPS | MoBa | TIHS | BIGCS | ABC | HHf2 | ELFE | NINFEA | JECS | Others |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Education | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Marital status during pregnancy | √ | √ | √ | √ | √ | √ | √ | ? | ? | ? | ? | √ | ? |
| Income (gross per household) | √ | √ | √ | ? | √ | √ | √ | √ | | √ | | √ | ? |
| Anthropometric measures | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Smoking | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Passive smoking during pregnancy | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Illicit drug use | ? | | √ | | √ | | | √ | | | √ | ? | ? |
| Alcohol consumption at pregnancy | √ | | √ | | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Diet during pregnancy | √ | | √ | | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Vitamin supplement use during pregnancy (folic acid) | √ | | √ | | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Other medical conditions during pregnancy (DM, hypertension) | √ | √ | √ | √ | √ | | √ | √ | √ | √ | √ | √ | ? |
| Atopy/Asthma in mother | √ | √ | √ | √ | √ | | √ | | √ | √ | √ | √ | ? |
| Prescription medications | √ | √ | √ | | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Reproductive history | √ | √ | √ | √ | √ | | √ | √ | √ | √ | √ | √ | ? |
| Occupation | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | ? |
| Infections during pregnancy | √ | √ | √ | | √ | √ | √ | √ | | √ | √ | √ | ? |
| Pesticide/chemical exposures | √ | | √ | | √ | | √ | ? | ? | ? | ? | √ | ? |
| Antenatal radiation exposure | √ | √ | | √ | √ | √ | | | | | | √ | ? |

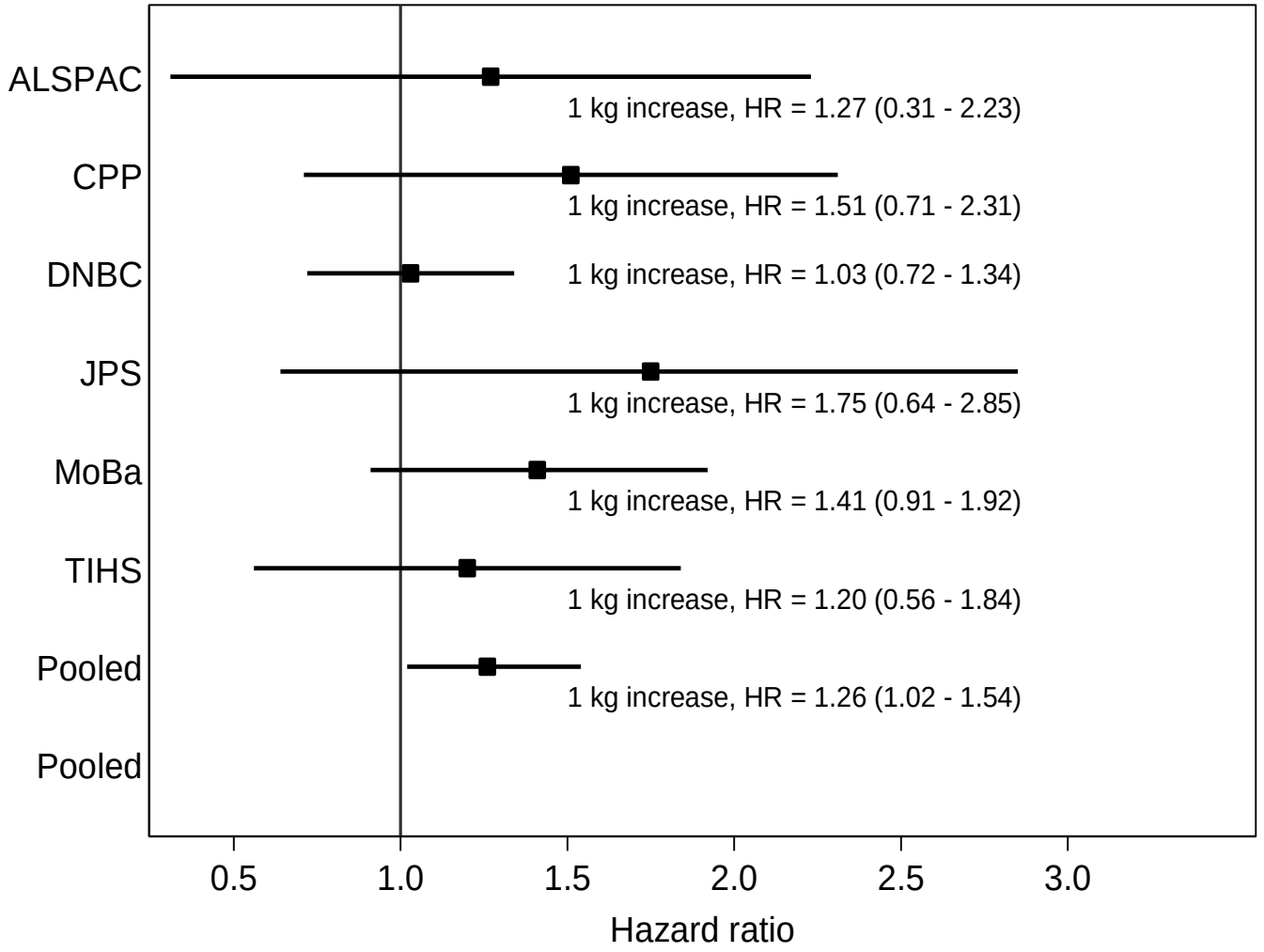
√, data collected

# Odds ratios for childhood leukemia and prenatal exposure to pesticides by time period from birth to interview (Schuz et al Am J Epidemiol 2003)

| | < 4 years | 4 – 6 years | > 6 years |
|---|---|---|---|
| Father | 2.11 | 1.77 | 1.05 |
| Mother | 4.04 | 1.91 | 1.54 |

# Proxies of Nutrition Status - Birth weight and Childhood Cancer

# Hazard ratio for any cancer by sub-cohort and birth weight continuous (kg increase), adjusted for gestational age and sex of child.



# Focus on later born and Leukemia - Is there an association?

| Model | HR | 95% CI | P |
|---|---|---|---|
| Crude | 0.78 | 0.58 – 1.05 | 0.097 |
| Adjusted for birth weight | 0.74 | 0.55 – 1.0 | 0.051 |
| **BUT** | | | |
| Interaction BW* later born | | | 0.036 |

**The plot thickens**

| Birth weight, kg | Observations, N | Leukemia, N | HR | 95% CI | | *p*-value |
|---|---|---|---|---|---|---|
| < 3.0 | 49,539 | 26 | 0.31 | 0.14 | 0.72 | 0.006 |
| (3.0 – 4.0) | 115,545 | 119 | 0.83 | 0.57 | 1.20 | 0.316 |
| ≥ 4.0 | 14,733 | 40 | 0.97 | 0.48 | 1.94 | 0.922 |

Yes, but modified by birth weight

# Birth weight, paternal age, birth order interaction

| Paternal age, years | Birth weight, kg | Later born HR | 95% CI | | *p*-value |
|---|---|---|---|---|---|
| 40 | 1 | 0.09 | 0.02 | 0.38 | 0.001 |
| 40 | 2 | 0.17 | 0.06 | 0.46 | 0.000 |
| 40 | 3 | 0.32 | 0.17 | 0.61 | 0.000 |
| 40 | 4 | 0.61 | 0.33 | 1.10 | 0.102 |
| 40 | 5 | 1.15 | 0.46 | 2.88 | 0.759 |
| 25 | 1 | 0.21 | 0.05 | 0.81 | 0.023 |
| 25 | 2 | 0.40 | 0.17 | 0.96 | 0.040 |
| 25 | 3 | 0.76 | 0.46 | 1.25 | 0.281 |
| 25 | 4 | 1.44 | 0.86 | 2.42 | 0.166 |
| 25 | 5 | 2.74 | 1.11 | 6.78 | 0.029 |

# What other reliable proxies for fetal nutrition might be available in cohort data?

# Association of pre-pregnancy BMI and weight gain during pregnancy with childhood cancers

| Exposure | Cancer | | Leukaemia | | ALL | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| **Pre-pregnancy BMI (per unit increase)** | | | | | | |
| Crude | 1.01 (0.98, 1.03) | 0.619 | 1.02 (0.98, 1.05) | 0.391 | 1.00 (0.96, 1.05) | 0.958 |
| Adjusted* | 1.01 (0.99, 1.03) | 0.562 | 1.02 (0.98, 1.06) | 0.358 | 1.00 (0.96, 1.05) | 0.908 |
| **Weight gain during pregnancy (per kg increase)** | | | | | | |
| Crude | 1.01 (0.99, 1.02) | 0.435 | 1.03 (1.00, 1.06) | 0.050 | 1.04 (1.00, 1.08) | 0.027 |
| Adjusted* | 1.01 (0.99, 1.03) | 0.373 | 1.03 (1.00, 1.07) | 0.044 | 1.04 (1.00, 1.08) | 0.028 |

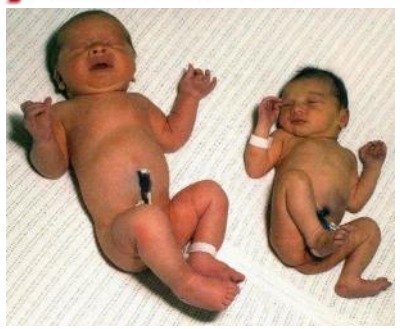
HR, hazard ratio
ALL, acute lymphoblastic leukaemia

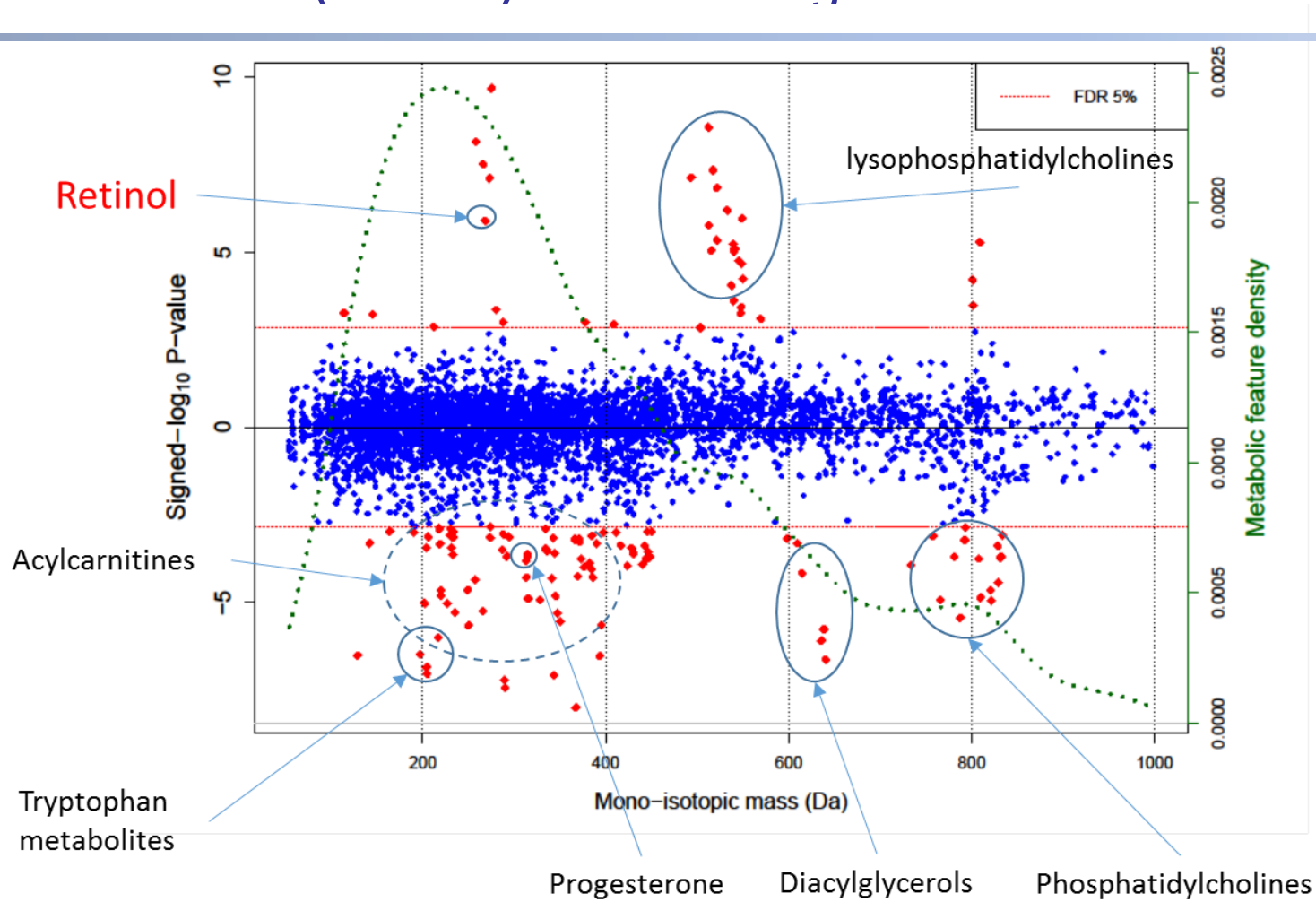
All HRs were adjusted for cohorts
* Adjusted for gestational age

# Epigenome-wide association studies (EWAS) on birthweight

4 European birth cohorts
- ENVIRONAGE (Belgium)
- INMA (Spain)
- Piccolipiu (Italy)
- Rhea (Greece)

481 cord blood samples
UPLC-QTof-MS

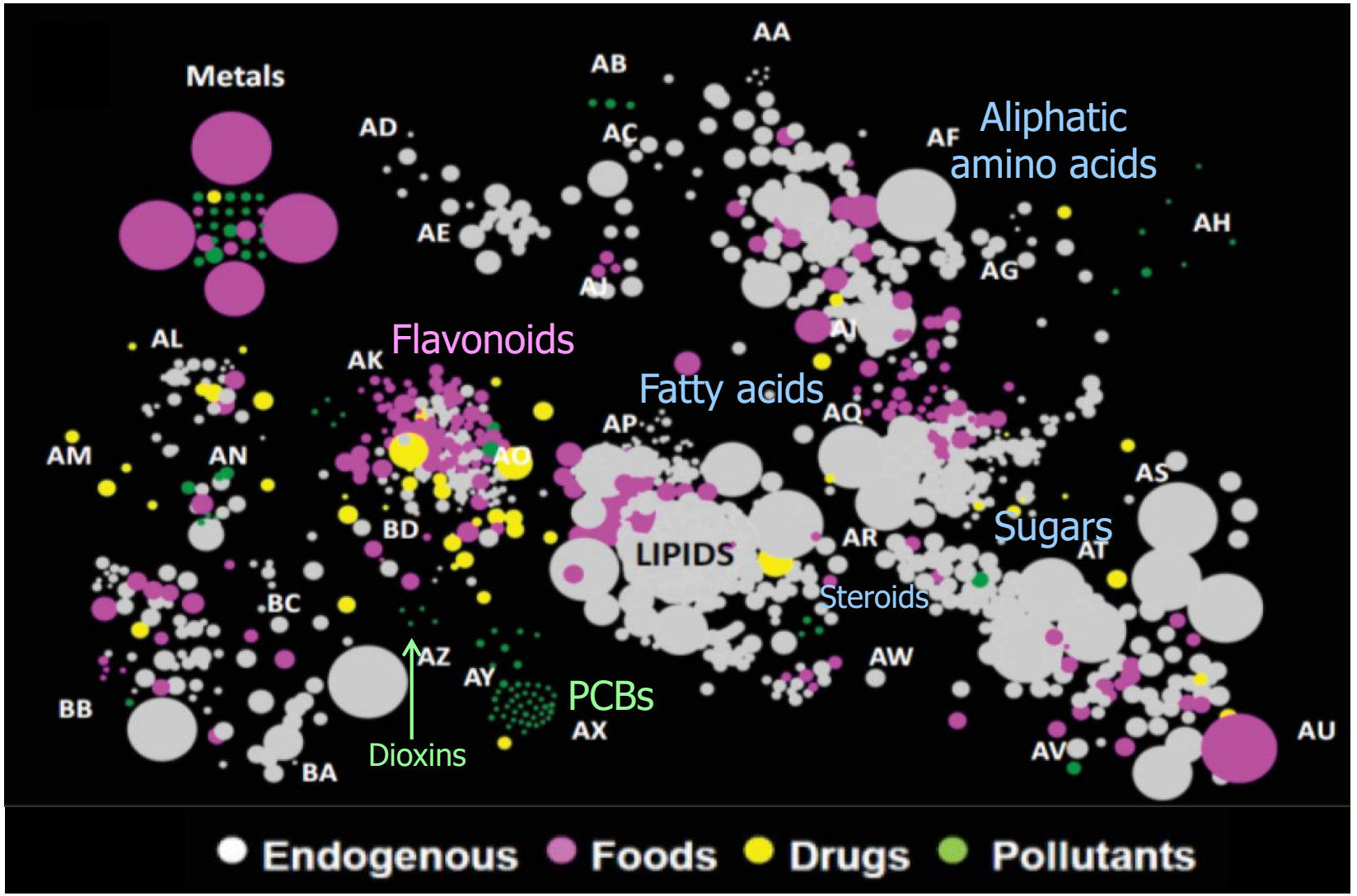





- 68 metabolites associated with birthweight
- Retinol associated with both birthweight and smoking

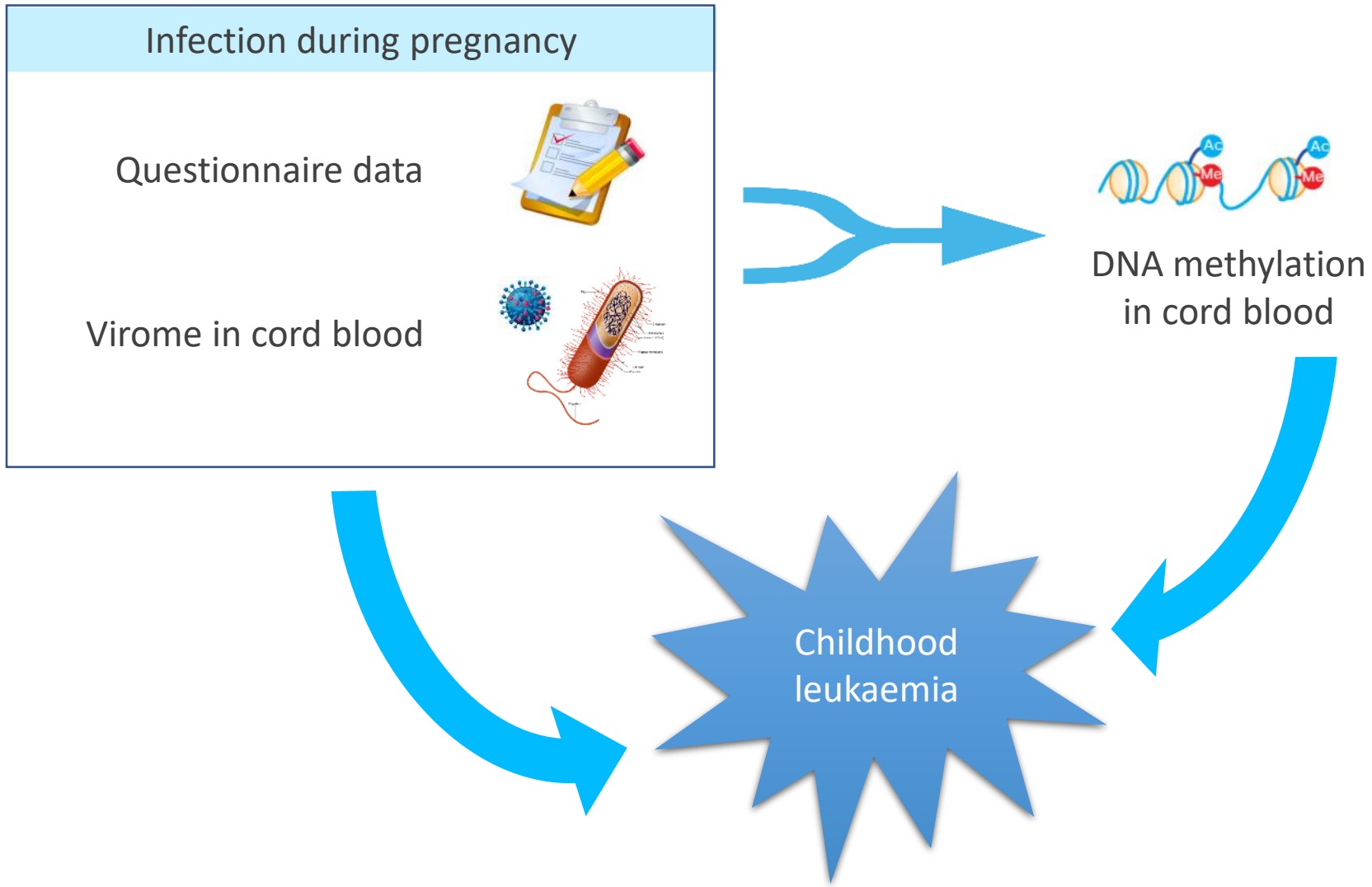
*Robinson et al., 2018, J. Proteome Res*

# Human metabolome *in collaboration with IARC, Scalbert*



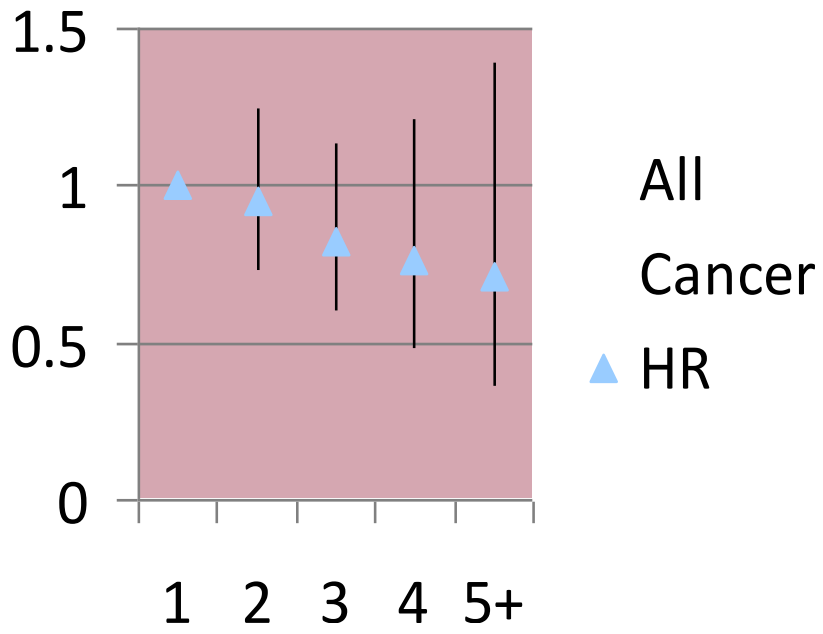

*Rappaport et al., 2014, Environ. Health Perspect.*

# Maternal infection, cord blood DNA methylation and childhood leukaemia

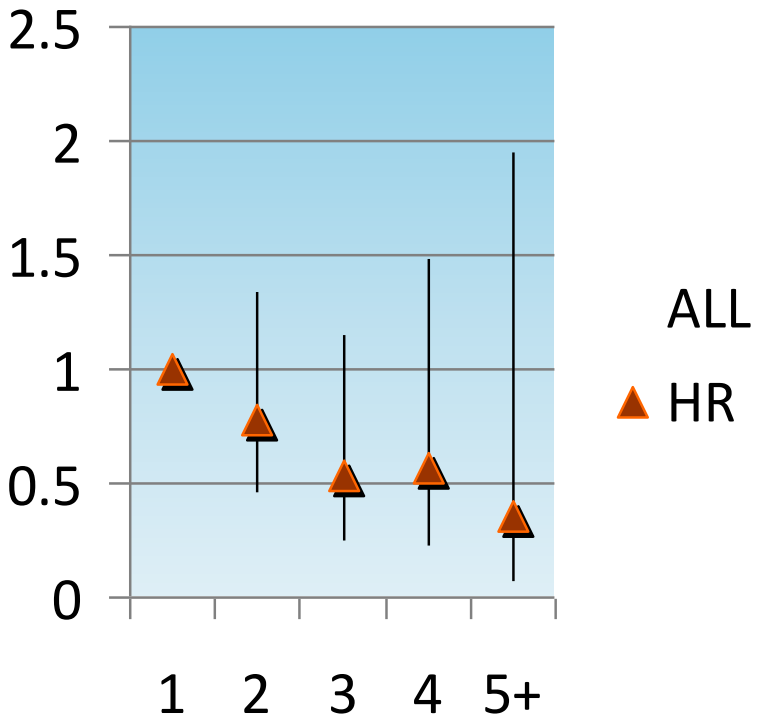


# Hazard ratios for successive birth order

Adjusted for Sex of child, gestational age and birth weight (N=112,943)




Birth order



# Fathers' occupational exposure: Pesticides

| | Exposure Prob. | Cases | Hazard Ratio[a] | 95% CI |
|---|---|---|---|---|
| **All Cancers** | **Low** | 7 | 0.9 | 0.4-1.8 |
| | **High** | 14 | 1.0 | 0.6-1.7 |
| **Leukemia** | **Low** | 3 | 1.2 | 0.4-3.8 |
| | **High** | 5 | 1.4 | 0.6-3.4 |
| ***ALL*** | **Low** | 1 | - | - |
| | **High** | 2 | 0.7 | 0.2-2.8 |
| ***AML*** | **Low** | **2** | **5.0** | **1.1-2.2** |
| | **High** | **3** | **4.8** | **1.4-1.6** |
| **Non-leukemias** | **Low** | 4 | 0.7 | 0.2-1.8 |
| | **High** | 9 | 1.0 | 0.5-1.8 |
| ***CNS*** | **Low** | 2 | 0.8 | 0.2-3.4 |
| | **High** | 2 | 0.6 | 0.1-2.3 |
| ***Non-CNS*** | **Low** | 2 | 0.6 | 0.2-2.6 |
| | **High** | 7 | 1.1 | 0.5-2.3 |

[a]Adjusted for cohort, child's sex, and paternal age