Distinctive Databases for CP Etiologic Investigations:
MOBAND, OWL, NCPP, ELGAN, UM registry, and others

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1/30/13

Objectives

- **Briefly note opportunities for collaboration by introducing planned analyses aiming to examine the relation between methodological factors and the *consistency* of estimated treatment effects and/or estimated magnitudes of association**

- **Review *selected* distinctive databases for cerebral palsy etiologic investigations including**
  - **National Collaborative Perinatal Project (NCPP);**
  - **Neonatal Brain Hemorrhage Study (NBH);**
  - **Extremely Low Gestational Age Newborn (ELGAN) study;**
  - **University of Michigan Cerebral Palsy Registry;**
  - **Origins, Wellness and Life-History (OWL) case-control study;**
  - **the combined Norwegian and Danish national birth cohort studies (collectively referred to as MOBAND), and others.**

The Problem (Opportunity)

- **Observational research in general is plagued by heterogeneous findings, many are imprecise, grossly exaggerated, biased and/or invalid**

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

PLoS Medicine | www.plosmedicine.org

August 2005 | Volume 2 | Issue 8 | e124

Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 – β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

--Lies, Damned Lies, and Medical Science
By David H Freedman / The Atlantic / November 2010
"Simply put, if you're attracted to ideas that have a good chance of being wrong, and if you're motivated to prove them right, and if you have a little wiggle room in how you assemble the evidence, you'll probably succeed in proving wrong theories right."

The Problem (Opportunity)

- **Identification of legitimate biomarkers has proven to be a challenging task, these same challenges apply to the identification of etiologic factors (perhaps more so)**

Clinical Chemistry 59:1
202–204 (2013)

Opinions

Biomarker Failures

John P.A. Ioannidis[1,2,3*]

Table 1. Four indicative examples of biomarker failures.[a]

Biomarker process	PSA	Proteomic pattern for ovarian cancer	Gene expression cancer signatures	Personal genetics
Analytical validity				
Accurate technology	+	–	+	++
Standardization	+	–	+ for some	++
Predictive discrimination				
Strong predictive effects	–	+	+	–
Reclassification				
Actionable reclassification	–	+	–/+	– mostly
Discovery process				
Accounted multiplicity	–	+	+	+
Accounted bias	–	–	+	+
Validation practices				
External validation	+	–/+	+ for some	+
Large-scale evidence				
Large-scale evidence obtained	+	–	–	+
Clinical utility				
Demonstrated efficacy	–	–	–/+	– mostly
Excluded harms	–	–	–	–
Implementation				
Ease of implementation	+	–/+	–/+	–/+

[a] Indicated are the translational steps where the biomarker did poorly (–) or did well (+).

Biomarker failures are unfortunate, but we can learn from them and apply them in future efforts. A main take-home message is that skipping any of the steps listed in Table 1 and cutting corners to expedite translation may not be a good idea. Development of biomarkers that work will take concerted efforts, and the necessary steps in the translation process need to be respected. Given that a few hundred thousand studies on biomarkers have already been performed and tens of thousands more are conducted every year, yet only a handful of biomarkers are used reliably in practice, there is no impetus to just publish more papers on biomarkers. We need to improve on our systematic evaluation of the evidence and on promoting—from each translational step to the next—the biomarkers that have the best evidence and can be the eventual winners. That will require a coordination of the wider biomarker research agenda. Such coordination may also benefit more from the fostering of international multiteam collaborations rather than from the fragmented efforts of small, opportunistic studies.

The Problem (Opportunity)

- **Like every other line of investigation, CP etiologic research is plagued by the same concerns, perhaps more so due largely to the complexity of the subject matter**

Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review

Michael K Mwaniki, Maurine Atieno, Joy E Lawn, Charles R J C Newton

www.thelancet.com Vol 379 February 4, 2012

Despite the fact that we initially identified many studies, few had data that were suitable for analysis, which is common in reviews of global estimates. For example, in a series of reviews of child mortality data,[14] only 308 studies were included from more than 17 000 abstracts. Data for morbidity and impairment are even worse, which is indicative of the low value placed on the collection of disability data.

The Problem (Opportunity)

- **Absent an ability to clearly differentiate biased, exaggerated and/or false findings from true and therefore meaningful variation, the pace of science is slowed since**
  - **The credibility of science is hampered**
  - **'Hard sciences' are less able to identify which observational findings to examine in greater detail**
  - **The problem, heterogeneous methods and spurious findings, is perpetuated rather than alleviated**
  - **Systematic reviews and meta-analyses aggregate these findings and they are viewed as somehow valid (by some)**

- ***Accordingly, in addition to classical methods, 'pure science as demonstrated by our speakers later today', it is time to examine ourselves, our studies, our methods, and our interpretations with a presiding criterion of evaluation being replication***

The Problem (Opportunity)

- **Specifically, a series of analyses involving multiple patient level data-sources, *simulated datasets* and meta-analytic methods to examine the implications of methodological factors with regard to our ability to identify replicable findings of treatment effects and/or estimated magnitudes of association**

- **Factors including,**
  - **Study design (i.e., cross-sectional versus longitudinal)**
  - **Inclusion/Exclusion criteria (i.e., truncation by birth weight versus gestational age at birth)**
  - **Choices made during the course of statistical analyses (i.e., use of stepwise multivariable regression model selection methods, residual confounding, adjustment for intermediaries, inclusion of too many covariables with not enough cases, etc.)**
  - **Unmeasured confounders (learning from and perhaps extending the work of VanderWeele & colleagues)**
  - **And others (collaborators are welcome to discuss and participate in this afternoon's breakout session, 'Using the CP databases: Collaborative opportunities',** Led by N. Paneth**)**

The Problem (Opportunity)

- These are not ‘new’ concepts, but applying them specifically to CP etiologic research is perhaps novel
- The aim is to better quantify the variation in estimates accounted for by study design and analytic choices with the intent of extending an evidence base in support of optimal considerations
  - The task is to operationalize ‘good epidemiologic practices’, however we define these as a team, and to perform a range of analyses examining whether they are indeed associated with consistent, replicable estimates as determined by the best of our understanding
- The following selected distinct databases for CP etiologic investigations are reviewed with the purpose of informing a later conversation.

Recent Efforts to Coordinate Across Cohort Studies & to Make Pertinent Data Available for New Investigations

Birthcohorts.net

- A prerequisite for collaboration across cohort studies is that they are well documented and information about design and data on the existing cohorts is collected in a comparable form and are easily accessible. This website aims to serve this purpose.

- **Which cohorts are included?**
  - Cohorts started in pregnancy or at least at birth
  - Cohorts with at least one year of follow-up
  - Cohorts with at least 300 mother-child pairs

- **The inventory is not complete.**
  - PI must register their cohort

Birthcohorts.net

Inventory of Birth Cohorts

Register/edit cohort

Inventory of ENRIECO

European birth cohorts with data on environmental contaminant exposures

Which cohorts are included?

- Cohorts started in pregnancy or at least at birth
- Cohorts with at least one year of follow-up
- Cohorts with at least 300 mother-child pairs

Inventory of Birth Cohorts

Cohort information can be retrieved in the following ways:

A. View the complete inventory of Birth Cohorts

Click here

B. Search by selecting criterias below

(This performs a search for cohorts with information on selected exposures, outcomes, biological samples or health and development)
Please, be aware that this search may take up to a few minutes.

1. Choose group

Search

C. Search by region

Africa

Search

D. Enter keyword(s) to search the inventory:

(This performs a search in user names, countries, institution names, contact persons, key references and cohort descriptions)

Search

Children's Health and the Environment in the Faroes - Cohort 1

CHEF 1

Philippe Grandjean ; Pål Weihe
Institute of Public Health ; The Faroese Hospital System, Faroe Islands

Enrollment: 1986-03-01 - 1987-12-01
Expected number of children in cohort: 1022

Children's Health and the Environment in the Faroes - Cohort 3

CHEF 3

Philippe Grandjean ; Pål Weihe
Institute of Public Health ; The Faroes Hospital System, Faroe Islands

Enrollment: 1998-04-24 - 2000-02-29
Expected number of children in cohort: 656

Duisburg

Michael Wilhelm
Department of Hygiene, Social and Environmental Medicine, Ruhr-University Bochum, Universitätsstr. 150, 44801 Bochum, Germany, Germany (Deutschland)

Enrollment: 2000-00-00 - 2003-00-00
Expected number of children in cohort: 234

Endocrine disruptors: Longitudinal study on pregnancy abnormalities, infertility, and childhood

PÉLAGIE

Sylvaine Cordier
INSERM, France

Enrollment: 2002-01-01 - 2005-01-01
Expected number of children in cohort: 4000

Etude Longitudinale Francaise depuis l'Enfance

ELFE

Marie-Aline Charles
Unit INED-INSERM-EFS, France

Enrollment: 2011-04-01 - 2011-12-05
Expected number of children in cohort: 20000

Genetic and Environment: Prospective Study on Infancy in Italy

GASPII

Daniela Porta
Department of Epidemiology Regional Health Service lazio Region, Italy (Italia)

Enrollment: 2003-06-01 - 2004-10-31
Expected number of children in cohort: 708

Hamamatsu Birth Cohort for Mothers and Children

HBC Study

Kenji J. Tsuchiya
Hamamatsu University School of Medicine, Japan (日本)

Enrollment: 2007-11-19 - 2011-03-31
Expected number of children in cohort: 1260

Kaunas cohort

NICHD/DESPR Biospecimen Repository Access and Data Sharing (BRADS)

- The Division of Epidemiology, Statistics and Prevention Research of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) maintains an extensive repository of datasets from completed studies, biospecimens, and ancillary data.

- The Division intends to make datasets and biospecimens more widely available to the research community for use by qualified researchers and to establish procedures for access consistent with the National Institutes of Health (NIH) Data Sharing Policy.

- The Division has established an internal committee, the Biospecimen Repository Access and Data Sharing Committee (BRADSC), to oversee the repository access and data sharing program.

brads.nichd.nih.gov/

EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

DIVISION *of* EPIDEMIOLOGY STATISTICS *and* PREVENTION RESEARCH

NICHD/DESPR Biospecimen Repository Access and Data Sharing (BRADS)

- BRADS Program Synopsis 2011
- General Information About Requesting Biospecimens
- Biospecimens And Currently Available Data
- Currently Funded Projects
- Register for Access and Approved Users

  You MUST have registered and received your Username and Password BEFORE you will be granted access to NICHD/DESPR study data and/or biospecimens available on this website.

- File Transfer Facility
- DESPR Resources Master List 2012

For additional information or questions, contact the BRADS Committee at bradsc@mail.nih.gov

brads.nichd.nih.gov/

Distinctive Databases for CP Etiologic Research

Collaborative Perinatal Project (CPP)

- Pregnant women were enrolled between 1959-1966 at the time of perinatal care at any of 12 university hospital clinics throughout the US,
- The mothers' blood (serum) was collected approximately every 8 weeks, at delivery, and six weeks postpartum
- The children were systematically assessed for the presence of birth defects and other outcomes through age 7 years
  - Examiners were residents or staff members in pediatrics or neurology, age 1 and age 7 examiners were blinded,
  - At age 7 exam, extensive quality control program implemented,
    - In 1,045 test-retest comparisons of children considered to be abnormal, the diagnoses in four patients (0.38%) were found to exhibit a difference in judgment as to the presence of significant neurologic abnormalities.

http://www.archives.gov/
www.niehs.nih.gov/research/atniehs/labs/epi/studies/dde/index.cfm

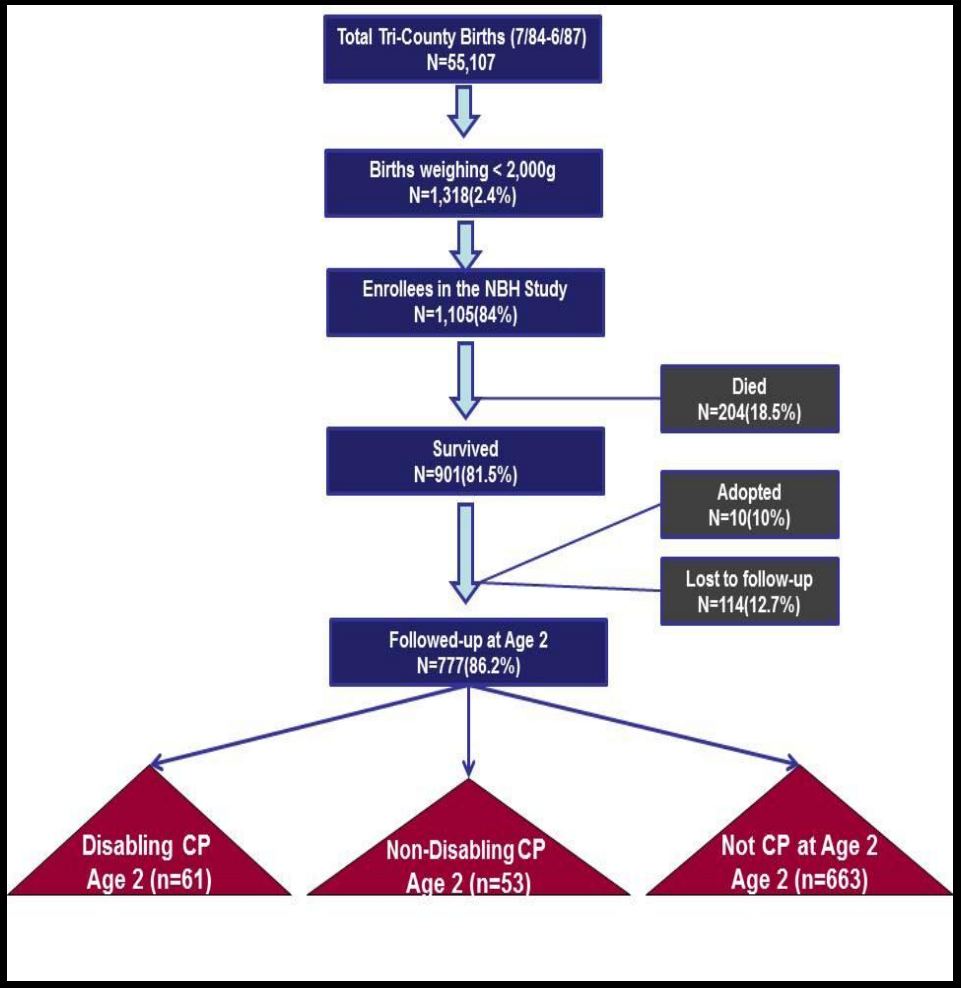
CPP

- 51,285 live-born singleton pregnancies
- 45,559 children with known outcomes at age 7
  - 189 had CP
    - 41% IQ < 70
    - 23% had at least one non-febrile seizure by age 7

Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. I. Univariate analysis of risks. *American Journal of Diseases of Children*. 1985; 139:1031-1038.

Neonatal Brain Hemorrhage (NBH) study

- The NBH included all 1,105 children born 9/1984-6/1987 weighing between 500 and 2000g at birth born-in or transferred to three neonatal intensive care units.
- These three centers provided care to 85% (386/454) of babies weighing between 501-2000g at birth, and 90% of infants weighing less than 1,500g at birth in the three counties of Ocean, Middlesex and Monmouth, NJ.



Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics*. 1995; 95:249-254.

NBH study

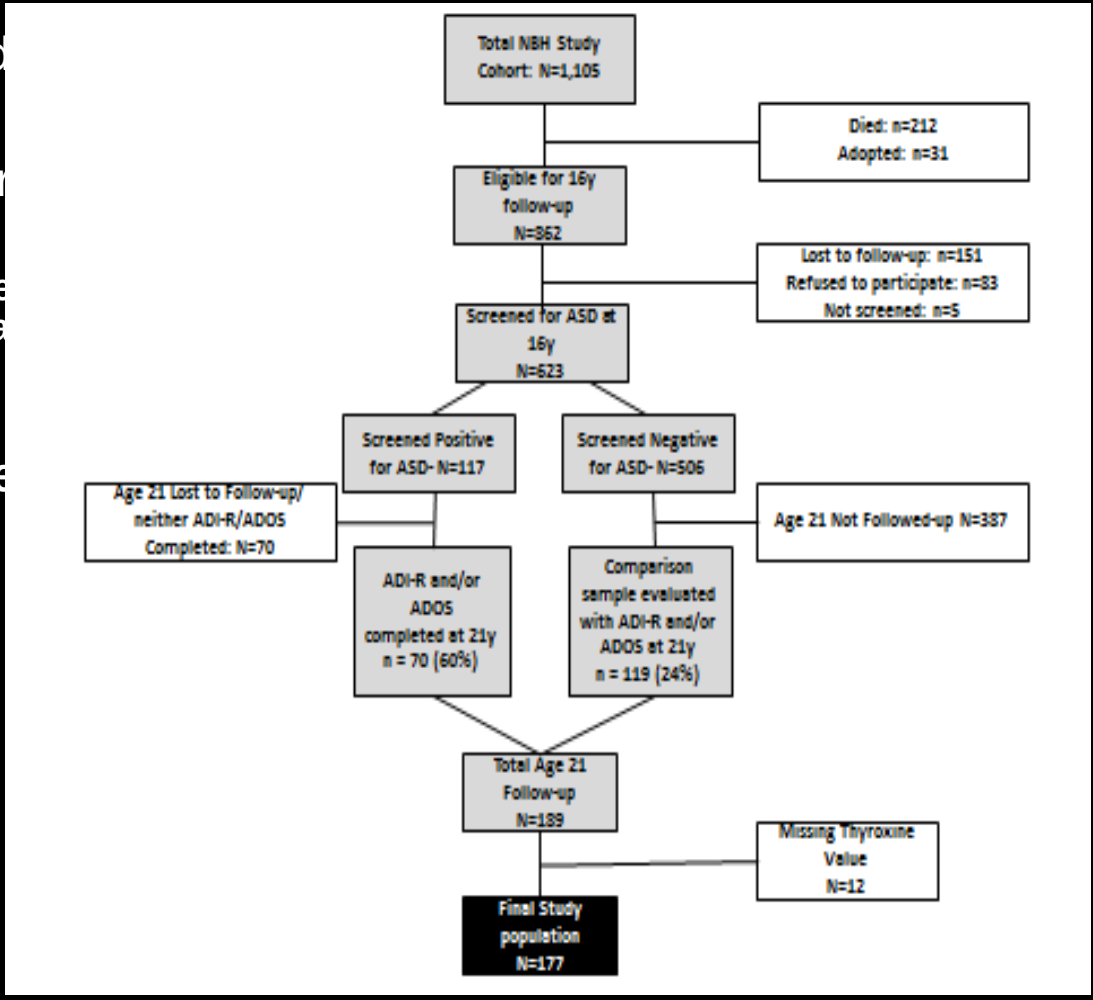
- **Relevant information extracted:**
  - **maternal data – including demographic information and history of smoking, alcohol and drug use;**
  - **pregnancy complications – infections, hypertensive disorders of pregnancy, vaginal bleeding;**
  - **labor and delivery data – mode of delivery, labor duration, duration of membrane rupture, clinical chorioamnionitis, placental and cord abnormalities;**
  - **infant data – birth weight, head circumference, cranial ultrasound results, mortality during the first 28 days and separately during the first 12 months of life;**

- **Cranial ultrasound scan was performed prospectively on 1,088 of the 1,105 (98.5%) infants in the cohort.**
  - **They were timed as closely as possible to ages 4 hours, 24 hours and 7 days.**
  - **A pre-discharge and or monthly CUS for longer stay infants was added to the protocol several months after the study had begun,**
    - **517 of the 1105 infants (46.8%) had four or more scans**

Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics*. 1995; 95:249-254.

NBH study

- Selected pertinent data collected
  - Age two years (corrected for gestational age)
    - disabling and non-disabling cere palsy diagnoses, Bailey Mental a Motor scores.
  - Ages six and again at nine ye
    - Riley Motor Problems Inventory
  - Age 16,
    - activity limitation, health status
  - Age 21, strategic follow-up, examining Autism Spectrum Disorder (ASD)



Korzeniewski et al. Association between Transient Hypothyroxinemia of Prematurity and Adult Autism Spectrum Disorder in a Low Birthweight Cohort: An Exploratory Study. *Paediatric and Perinatal Epidemiology* (accepted for publication)

The Developmental Epidemiology Network (DEN)

- **Sample.**

  1095 of the 1605 infants born between 1/1/91 and 12/31/93 with birth weights of 500-1500 g at one of four participating hospitals were included (461 were excluded because their placentas were was not available for examination, 49 were excluded due to missing data).

- **Placenta Examination**

  Pathologists at each of the participating institutions collaboratively developed a manual of standard definitions for all of the features studied. Gross and histologic examination of the placentas was performed, findings were recorded on a standardized collection form. Placentas were examined grossly in the fresh state. Formalin fixed, paraffin embedded, and hematoxylin- and eosin-stained sections of the umbilical cord, placental membranes, and placental parenchyma were histologically assessed for multiple items

Hansen A, Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, et al. The correlation between placental pathology and intraventricular hemorrhage in the preterm infant. *Pediatric Research*. 1998; 43:15-19.

The Developmental Epidemiology Network (DEN)

- Ultrasound examination.
  - Standard neonatal cranial ultrasound examinations were performed by experienced technicians using a 7.5-Hz transducer.
  - Readings were recorded on a standardized collection form and read by consensus.

- Maternal/neonatal data.
  - pregnancy, labor, and delivery information were collected by a combination of maternal interview and maternal and infant chart review.
  - These data included, but were not limited to, maternal receipt of magnesium sulfate, and antenatal glucocorticosteroids.

Hansen A, Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, et al. The correlation between placental pathology and intraventricular hemorrhage in the preterm infant. *Pediatric Research*. 1998; 43:15-19.

Extremely Low Gestational Age Newborn (ELGAN) study

- **Considerations leading to the study**
  - **Processes that lead to preterm delivery can contribute to brain damage**
    - **Likely inflammatory**
    - **Involve fetus**
    - **Are complex**
    - **Probably persist for days if not weeks**
    - **Need not be initiated by microorganisms**
      - **Original focus on was inflammatory exposures, expanded to processes that impair fetal growth.**

O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development.* Nov 2009;85(11):719-725.

the ELGAN study

- Developmental processes during 23-27 weeks GA may be most vulnerable
  - Transformation of oligodendrocyte precursor
  - Migration of neuron precursors from germ germinal plate
  - Excitatory neurotransmitter pathways are up-regulated in immature brain,
    - apparently to facilitate neuronal migration, division, organization and development of synapses and synaptic networks
- ELGANs are born before they can synthesize adequate amounts of proteins normally provided by the placenta/mother
  - Many of these proteins promote the differentiation/maturation of neurons and oligodendroglia (neurotrophins) and have the capacity to protect these cells against adversity.

O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development.* Nov 2009;85(11):719-725.

ELGAN Biomarkers

- **Specimens Include:**
  - **Organisms recovered from the placenta parenchyma**
    - **67% of vaginal deliveries following labor,**
    - **45% of C-section following labor,**
    - **24% of C-section for preeclampsia**
  - **Placenta histologic characteristics**
  - **Blood proteins in maternal blood,**
  - **Umbilical cord blood**
  - **Postnatal blood (obtained 1,3,5,7,14,21 and 28 days after birth)**

- **Created a tissue bank for future studies**

O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development.* Nov 2009;85(11):719-725.

ELGAN Ultrasound Data

- Scans obtained (clinically) were read by 2 independent readers blinded to clinical information
  - 1 at institution of birth, 2nd at other study site
    - 3rd reader used as a tie-breaker
  - Computed kappa (agreement),
  - Assessed data based on concordant relative to discordant scans
  - Considered those collected at three stages: 1-5 days, 5-14 days, 15-40 days

O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development.* Nov 2009;85(11):719-725.

ELGAN Neurodevelopmental

- **Early assessment included:**
  - **Score for Acute Neonatal Physiology (SNAP, I & II)**
  - **Bayley Scales of Infant Development & Mental Development Index**

- **2 year corrected age follow-up:**
  - **cerebral palsy (consider diplegia, quadriplegia & hemiplegia separately) ,**
  - **developmental delay**
  - **Autism spectrum disorder screening**
    - **Evaluation of the M-CHAT tool**

- **Funded for age 9 follow-up**
  - **Evaluation of school performance, psycho-social outcomes**

O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development.* Nov 2009;85(11):719-725.

ELGAN Strengths & Weaknesses

- **Strengths**
  - Large sample size,
  - Selection by GA rather than birth weight
    - Minimizes confounding by differential inclusion of growth restricted infants
  - Prospective data collection
  - Minimized observer variability
  - Employed blinding
  - Minimized attrition (80%-93% follow-up depending on outcome)

- **Weaknesses**
  - Those of all observational studies
    - Unable to distinguish between association & causation
    - Potential confounding by indication
    - Sickest infants more likely to be treated aggressively

O'Shea TM, Allred EN, Dammann O, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development.* Nov 2009;85(11):719-725.

University of Michigan/ CPrcOM Registry

- This registry is designed both as a repository of names of folks willing/interested in serving as research participants.
- It is also envisioned as a mechanism for dissemination of information and a “sandbox” for researchers to connect.
- While housed in U of M’s PM&R Department, the registry is also part of the CP collaborative sponsoring this conference.
- This effort is envisioned as a centralized online spot for families to ‘see what’s going on’ and participate, and further for the many Michigan University Research Corridor investigators to initiate collaborations

http://www.med.umich.edu/pmr/research/cprcom.htm
https://www.umms.med.umich.edu/umclinicalstudies/detail_pub_study.do?show=YES&id=35366&TYPE=

Origins, Wellness and Life-History (OWL) case-control study

- This study takes a comprehensive etiologic approach to CP, recruits cases across our state, and makes use of multiple sources of exposure information:
  - maternal interviews,
  - birth certificates,
  - maternal and newborn hospital discharge abstracts and,
  - most importantly, newborn blood spots archived after newborn genetic screening.

- The overall aim of the project is to integrate a broad range of exposure information with analyses of relevant biomarkers to assess several potential etiologic pathways to CP and its sub-types, with a particular emphasis on uncovering opportunities for early prevention.

Norwegian and Danish national birth cohort study data (collectively referred to as MOBAND)

- On behalf of the MOBAND study group, Dr. Allen Wilcox of NIEHS recently approached Dr. Nigel Paneth for assistance leveraging these data to realize new understandings of CP
- Dr. Paneth recently initiated a monthly work group to discuss analytic opportunities
- The analyses must, however, first leverage clinical data prior to accessing biological sample

Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2006;35:1146–1150
doi:10.1093/ije/dyl170

COHORT PROFILE

Cohort profile: The Norwegian Mother and Child Cohort Study (MoBa)

Per Magnus,[1]* Lorentz M Irgens,[1,2] Kjell Haug,[2] Wenche Nystad,[1] Rolv Skjærven,[1,2] Camilla Stoltenberg[1] and The Moba Study Group[†]

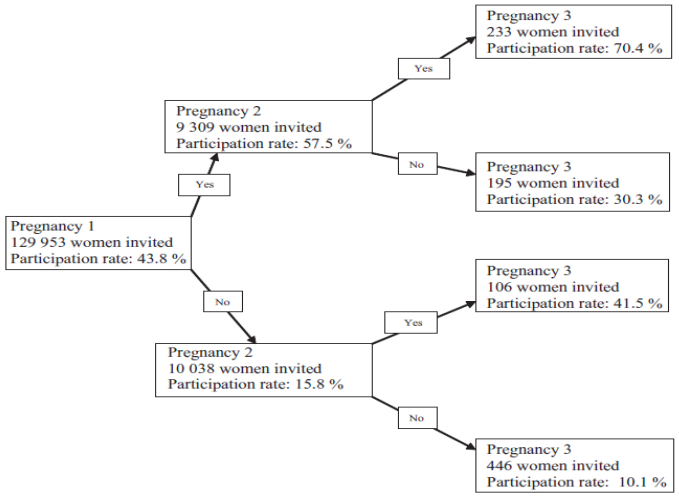


Figure 1 Participation rates by participation in previous pregnancies. Pregnancy 1 means the first pregnancy in which the woman was invited to participate in MoBa, and it does not correspond to birth order

What has been measured?

In addition to the questionnaire variables (http://www.fhi.no/morogbarn), variables are added as a result of laboratory analyses or record linkage. Norway has several mandatory national health registries. For every birth that takes place in Norway after gestational week 16 (from 2002 week 12), a medical record is sent to the MBRN.[1] All records from this registry for MoBa participants are included in the study database. In addition to the MBRN, a cancer registry, a prescription database, a cause of death registry, and a vaccination registry exist. The Ministry of Health has also recently proposed that a Norwegian patient registry (hospital and outpatient clinic discharge registry) shall be established. Thus, even if no questionnaires or biological samples are returned from the participating woman, her partner, or the child, her pregnancy will provide information.

Can I get hold of the data? Where can I find out more?

A set of guidelines for researchers applying for data has been set up (http://www.fhi.no/morogbarn). The main criterion for access to data is scientific quality. A short protocol with specific research question, choice of variables, and plan for analysis and publication must be provided. A contract is signed for each data delivery.

Table 1 Participation percentages and numbers of included pregnancies by year of recruitment and pregnancy number in the MoBa study, 1999–2005

Year of recruitment	Pregnancy 1[a]		Pregnancy 2		Pregnancy 3		Pregnancy 4		Total	
	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
1999	47.0	862							47.0	862
2000	50.6	2643	37.5	9					50.6	2652
2001	47.8	5603	30.4	102					47.3	5705
2002	44.0	10 521	34.7	457					43.5	10 978
2003	42.8	11 617	34.1	1105	23.8	20			41.8	12 742
2004	44.2	11 819	36.0	2107	35.6	90	11.1	1	42.6	14 017
2005	41.5	13 820	36.8	3154	32.2	202	20.0	4	40.4	17 180
Total	43.8	56 885	35.8	6934	31.8	312	17.2	5	42.7	64 136

[a] Pregnancy number 1 is the first pregnancy in which the woman was invited (not the same as birth order 1).

Table 3 Distribution of parity, maternal age, preeclampsia, gestational age, preterm birth (below 37 weeks), birth weight, and low birth weight (<2500 g) for 26 777 participants in MoBa and for the total 226 057 births in Norway 2000–2003

	MoBa participants	Total population
Parity (%)		
0	40.3	40.7
1	36.9	35.7
2+	22.8	23.6
Maternal age (%)		
<20	1.2	2.4
20–24	11.1	14.9
25–29	34.7	34.2
30–34	37.5	33.2
35+	15.5	15.3
Preeclampsia (%)		
Yes	3.8	3.9
Gestational age (days)		
Mean (SD)	277.3 (14.7)	276.8 (15.0)
Median	280	279
Preterm birth (%)		
Yes	7.2	7.7
Birth weight (g)		
Mean (SD)	3587 (626)	3538 (632)
Median	3630	3575
Low birth weight (%)		
Yes	4.6	5.1

The births have gestational age >22 weeks and birth weights >400 g.

The Danish National Birth Cohort – its background, structure and aim

Jørn Olsen, Mads Melbye, Sjurdur F Olsen, Thorkild IA Sørensen, Peter Aaby, Anne-Marie Nybo Andersen, Dorthe Taxbøl, Kit Dynnes Hansen, Mette Juhl, Tina Broby Schow, Henrik Toft Sørensen, Jente Andresen, Erik Lykke Mortensen, Annette Wind Olesen and Charlotte Søndergaard

Danish Epidemiology Science Centre, Copenhagen and Aarhus, Denmark

Scand J Public Health 2001; 29: 300–307

Background: It is well known that the time from conception to early childhood has importance for health conditions that reach into later stages of life. Recent research supports this view, and diseases such as cardiovascular morbidity, cancer, mental illnesses, asthma, and allergy may all have component causes that act early in life. Exposures in this period, which influence fetal growth, cell divisions, and organ functioning may have long-lasting impact on health and disease susceptibility. *Methods*: To investigate these issues the Danish National Birth Cohort (*Better health for mother and child*) was established. A large cohort of pregnant women with long-term follow-up of the offspring was the obvious choice because many of the exposures of interest cannot be reconstructed with sufficient validity back in time. The study needs to be large, and it is aimed to recruit 100,000 women early in pregnancy, and to continue follow-up for decades. The Nordic countries are better suited for this kind of research than most other countries because of their population-based registers on diseases, demography and social conditions, linkable at the individual level by means of the unique ID-number given to all citizens. Exposure information is mainly collected by computer-assisted telephone interviews with the women twice during pregnancy and when their children are six and 18 months old. Participants are also asked to fill in a self-administered food frequency questionnaire in mid-pregnancy. Furthermore, a biological bank has been set up with blood taken from the mother twice during pregnancy and blood from the umbilical cord taken shortly after birth. Data collection started in 1996 and the project covered all regions in Denmark in 1999. By August 2000, a total of 60,000 pregnant women had been recruited to the study. It is expected that a large number of gene-environmental hypotheses need to be based on case-control analyses within a cohort like this.

Table I. *Smallest detectable relative risk (RR) in a case-control analysis nested within the cohort, using four controls per case*[a]

Expected cases	Outcome	Exposure prevalence among controls: 10% RR	5% RR	1% RR
3,400	All congenital malformations	1.14	1.25	1.60
560	Genital malformations	1.5	1.7	2.7
150	Facial clefts	2.1	2.5	5.0
220	All child cancers	1.8	2.2	4.1
55	Leukaemia	3.1	3.9	9.4

The estimates are based on 80% power to detect the indicated relative risk (or higher) at a testing level of 0.05 in a cohort of 100,000 newborns.
[a]*Sources*: Sundhedsstyrelsen. Sundhedsstatistik 1999: 3 and Basso et al. Am J Epidemiol 1999; 150: 598–604.

Table III. *Compliance with the data collection scheme*

	Time	Percentage
1st blood sample	Gestational weeks 6–12	97
1st interview	Gestational week 12	87
2nd blood sample	Gestational week 24	77
Food frequency questionnaire	Gestational week 25	77
2nd interview	Gestational week 30	88
Umbilical cord blood sample	At delivery	65
3rd interview	6 months after delivery	87
4th interview	18 months after delivery	75

Those interested in collaborating are welcome to explore these ideas and more during this afternoon's breakout session, 'Using the CP databases: Collaborative opportunities', Led by N. Paneth

THANK YOU

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