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Developing a Child Cohort Research Strategy for Europe

Work Package 2

Deliverable 13 – Final Report

Research priorities for childhood diseases

A project conducted within the

European Union's 7th Framework Programme

Theme 1, Health

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SUMMARY

Policy and decision makers need a solid evidence base for the development and implementation of public health interventions and the incorporation of health goals in the definition and implementation of all policies, including those focused on child health. Mother-child cohorts are collecting a wealth of information on childhood diseases and their determinants across Europe, however, there has been little coordination of research and results between countries. All countries need information on childhood diseases to inform health policies. Birth cohorts are valuable sources of policy relevant research, but results are not always communicated and disseminated in a way that is useful and relevant for policy makers. Cohort studies have been particularly important when randomised controlled trials are not possible for practical or ethical reasons. The long follow up in birth cohorts makes them ideally suited to address new scientific or policy related questions. Cohorts contribute by identifying modifyable risk factors not only of child health, but also factors associated with social inequality, the quality of health services, and living conditions. The size and distribuiton of cohorts varies across Europe. Most of the large cohorts are situated in Northern Europe, whereas there is a lack of large cohorts in Southern and Eastern Europe. There are several minority groups in Europe that are underepresented in cohorts today.

Based on the results in workpackage 2 (WP2) the following main strategic recommendations are suggested:

- Birth cohorts should be developed in countries/regions where there is a lack of research infrastructures today
- Minority groups that are underrepresented in European cohorts should be included
- Support for greater and more efficient use of existing cohorts should be strengthened
- A strategy for cohort collaboration that can build a basis for speedy response to key research and policy questions should be developed
- In addition to cohorts complementary and alternative sources of data should be considered, in particular:
    - Routine registries
    - Case-control studies
    - Intervention trials

1. CONTEXT

1.1 Aims and objectives

The aim of this document is to present the work that has been performed in WP2. The objectives of WP2 are:

- To evaluate existing information on child health outcomes from cohorts
- To evaluate links to routine registries
- To identify gaps in knowledge
- To develop recommendations for research action at the European level for the next 15 years focusing on key areas of policy concern.

A full review of all on going child health research in Europe was not feasible within the scope of this project; therefore, seven major child health outcomes were identified to be the focus of WP2. The following outcomes were selected:

- Perinatal outcomes
- Asthma, respiratory health and allergies
- Obesity, and vascular and metabolic health
- Neuropsychological development
- Accidents and injuries
- Infectious diseases
- Childhood cancer

To address each outcome theme seven working groups (WGs) with expert members were appointed. Each working group had a leader that was responsible for the working group. An overview of the working groups and the working group leaders is presented in chapter 2.

1.2 Highlights of results

Perinatal outcomes

- Perinatal mortality and infant death have declined significantly in Europe over the last decades, but there is still significant variation between countries and over time
- Birth registries are essential for monitoring perinatal outcomes, while pregnancy cohorts are needed to address aetiological issues and validation.

- Several European birth cohorts have made a substantial contribution to research within modifiable risk factors for adverse birth outcomes, for example smoking, diet and other environmental exposures.
- To increase knowledge in this field, especially for rare conditions such as birth defects, collaboration between large cohorts is needed in order to study aetiological factors.
- A major benefit of several of the existing birth cohorts is the availability of biological samples, making studies of biological pathways possible.

Asthma, respiratory health and allergies

- Birth cohorts are suitable to study environmental and genetic risk factors, and their interactions, of asthma and allergy due to the longitudinal design, detailed data collection on multiple risk factors, outcomes and confounding factors.
- A large number of environmental and genetic risk factors seem to be associated with asthma and allergy, and detailed data collection and analyses are still ongoing.
- Gaps in current birth cohort research are the following:
    - Scarce publication of studies in Eastern European and low-income countries where prevalence of asthma is still increasing,
    - the partly non-comparable assessments tools for adequately measuring asthma and allergy,
    - the lack of combined analyses between cohorts, especially for risk factors with small effect estimates,
    - the paucity of research on environmental risk factors in very early life including fetal exposures in different trimesters of pregnancy where lung development is most susceptible,
    - the paucity of research on genetic risk factors with emphasis on gene-environment interaction studies, genome wide association studies and epigenetics,
    - the lack of tracking of observed results from childhood into adulthood.

Obesity, and vascular and metabolic health

- Most cohorts with relevant data on adiposity and cardiometabolic traits are situated in Northern Europe.
- Few studies include sufficient numbers of participants from minority ethnic groups.

- Measures of weight and height are available in the majority of existing European birth cohorts, but the availability of other measurements of adiposity or its distribution (e.g. waist, skinfold thicknesses, directly assessed fat mass, visceral fat) is more limited.
- Blood pressure is commonly measured, but relatively few cohorts have measurements of blood based measures or vascular function / structure measures.

Neuropsychological development

- Most of the identified studies come from the North of Europe. Limited research has been conducted in Central and East European countries.
- Cognitive development has been the most studied neuropsychological domain in the European birth cohorts, whereas social-emotional development and clinical phenotypes (such as ADHD, ASD and learning disabilities) have been less studied.
- There is a need for harmonization of the protocols of neuropsychological assessment among European birth cohorts to select: 1) the neuropsychological areas to study; 2) the ages of assessment; and 3) the most valid and reliable neuropsychological tests. A task force integrated by a panel of experts on this area is recommended.
- There is limited information on the effects of physical activity, maternal stress, medical treatment, maternal occupation during pregnancy, and sedentary life style on the neuropsychological development and child behaviour.
- The combination of data from questionnaires and biomarker analyses could advance in the assessment of several risk factors that required further research (i.e. smoking, metals, new pollutants such as bisphenol A or organophosphates).

Accidents and injuries

- Epidemiological injury research has typically used available routine data sources and registries and the role of birth cohorts in this field has been very limited up to now.
- Very few of the CHICOS birth and child cohorts have performed or are planning some assessments of injuries, most are situated in the North of Europe. No standardised questionnaires or protocols exist in this field.

- Birth and child cohorts have the potential to provide valuable information on environmental determinants (ie. social inequalities) and safety behaviours (ie. parental behaviour) associated with accident and injury prevention throughout childhood.

Infectious diseases

- All European countries have national surveillance and monitoring of severe infections, and some countries have national hospital registers including less severe infections.
- Several existing European birth cohorts have collected questionnaire data on infectious outcomes, as well as biological samples.
- Because some exposures and some outcomes are rare, results from individual cohorts may be inconclusive, however by pooling birth cohort data from several European sites will increase the sample size.
- Because birth cohorts rely on participants to actively participate, not all groups of children are included e.g. the most vulnerable children.
- Linking data from existing birth cohorts with surveillance data can provide a rapid and very flexible response to emerging infections and pandemics. Together, birth cohort data and routinely collected national registers provide both the detail needed to understand the underlying mechanisms of disease, and the magnitude needed to study all groups of European children.

Childhood cancer

- Most research on childhood cancer is based on a case-control approach. Only recently have efforts been made to coordinate large cohort studies evaluating childhood cancer or cancer-related biomarkers.
- Cancer is assessed through clinical records, histopathology and cancer registry records and, to this extent, outcome misclassification is minor.
- Information on cancer will be collected in the major European cohorts which are the main cohorts of the International Childhood Cancer Cohort Consortium (I4C).
- Power calculations indicate that a study would need to include several hundred thousand children to have adequate statistical power, which is higher than the number of children recruited in European birth cohorts with detailed exposure information.
- Very few studies are evaluating cancer-related effect biomarkers in children.
- Several cancer registries in Europe evaluate the frequency and time trends of childhood cancer, and can serve as a basis for case-controls studies on environmental factors.
- Development of new tools to evaluate genetic and environmental factors using minimal amounts of blood opens new possibilities for the use of blood spots in epidemiological cohort or nested case-control studies.

1.3 Main strategic recommendations

Below is a summary of the main strategic recommendations from the working groups. Specific recommendations for each outcome can be found in the working group reports in chapter 2.

- All countries need information on childhood diseases to inform policies
- Birth/pregnancy cohorts are valuable sources of such information
- Birth cohorts should be developed in countries/regions where there is a lack of research infrastructures today
- Minority groups that are underrepresented in European cohorts should be included
- Support for greater and more efficient use of existing cohorts should be strengthened
- Support for follow-up questionnaires of older children in existing cohorts is needed
- A strategy for cohort collaboration should be developed that can build a basis for speedy response to key research and policy, and collaborations. This will increase knowledge by:
    - Improving causal inference through cross-cohort comparisons and family designs

- Replication of findings
- Improving statistical power, enabling research on rare outcomes and interactions between genetic and environmental risk factors
- In addition to cohorts complementary and alternative sources of data should be considered, in particular:Routine registries
- Case-control studies
- Intervention trials

- Methodologies should be improved including protocols of biological and environmental sample collection and analysis.

1.4 Case studies and publications

In order to demonstrate the potential of cross-cohort collaboration between European birth cohorts, nine case studies were initiated within WP2 and WP3:

1. Alcohol consumption during pregnancy and birth weight
2. Socioeconomic inequalities in preterm delivery
3. Selected maternal occupations and fetal health
4. Persistent Organic Pollutants and Birth Outcomes
5. Fish consumption and fetal growth/neurodevelopment
6. Central fat mass, cardiovascular disease
7. Early growth and wheezing/asthma
8. Maternal complications in pregnancy, caesarean section and wheezing/asthma
9. Association between prenatal POPs exposure and respiratory infections and wheezing at early ages (0-2 years) within European birth-cohorts

One case study has been postponed due to lack of man power (Nutrition and childhood asthma and allergy) but will be conducted in near future. The aim of the case studies was to demonstrate how to combine data from different European cohorts and to discuss opportunities and challenges associated with these studies. We explored the usefulness of existing inventories for identification of relevant cohorts, the willingness of cohorts to participate in pooled studies, the ethical issues, the efforts needed to obtain data and the comparability of data. The following lessons have been learned from conducting the case studies:

- Many cohorts were interested and committed to participate in collaborative studies
- The inventory for European birth cohorts www.birthcohorts.net was useful as a first information source

- Case study guidelines prepared by CHICOS contained useful information to conduct uniform collaborations
- Differences between cohorts on data access policies, access fees and collaborative policies were observed
- Financial reimbursement for time and effort to provide previously collected datasets should be considered to increase the willingness of birth cohorts to participate in collaborative projects on combined data analyses
- Collecting, combining and harmonising data from different cohorts can be time and labour consuming
- Harmonisation of data can be challenging due to differences in methods of data collection
- Close contact, including frequent email, telephone conferences and face-to-face meetings between researchers and cohorts are necessary for commitment and feedback from experts in the field
- Pooling data from different cohorts is a unique resource for research objectives that require large datasets. Combined datasets from different cohorts provide an increase in power and hence more reliable results.

Currently, data collection has been finished and statistical analyses are ongoing. It is expected that results of the case studies will be published in peer-reviewed journals from 2013 onwards. At the time of submission of this WP2 report, the following scientific publications are being prepared:

"Adverse birth outcomes associated with selected maternal occupations in 12 European birth cohorts – a CHICOS initiative." Intended journal: under discussion Anticipated date of submission: April 2013

"Provisional title: Polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (p,p'-DDE) and birth outcomes in 11 European birth cohorts: dose-response relationship and effect modifiers."
Intended journal: Environmental Health Perspective Anticipated date of submission: March 2013

"Prenatal exposure to DDE and PCB153 and infant's respiratory health: A European meta-analysis."
Intended journal: Epidemiology Anticipated date of submission: June 2013

"Fish intake during pregnancy and birth outcomes: A Meta-analysis within 20 European Birth Cohorts Studies." Intended journals: Lancet, Am J Clin Nutrition Anticipated submission date: March 2013

"Adiposity, vascular and metabolic health."
Intended journal: under discussion Anticipated submission date: June 2013

" Preterm birth, birth weight and infant growth and the risk of childhood asthma: a meta-analysis of 147,000 European children."
Intended journal: under discussion Anticipated submission date: June 2013

"Maternal complications and conditions in pregnancy and wheezing in early childhood: a combined analysis of 14 European birth cohorts"
Intended journal: a respiratory journal Anticipated submission date: June 2013

2 WORKING GROUP REPORTS

In this chapter the reports from the working groups are presented. Below is an overview of the working groups and the working group leaders.

Working group (WG)	Leader	Participant id
Perinatal outcomes	Siri E. Håberg	Partner 6, Norwegian Institute of Public Health
Asthma and respiratory health and allergies	Liesbeth Duijts	Partner 5, Erasmus University
Obesity, and vascular and metabolic health	Debbie A. Lawlor	Partner 7, University of Bristol
Neuropsychological development	Jordi Sunyer	Partner 1, CREAL
Accidents and injuries	Maribel Casas	Partner 1, CREAL
Infectious diseases	Mads Kamper-Jørgensen	Partner 2, University of Copenhagen
Childhood cancer	Manolis Kogevinas	Partner 8, National School of Public Health

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Developing a Child Cohort Research Strategy for Europe

Perinatal outcomes

Leader: Siri Eldevik Håberg (Norwegian Institute of Public Health, Norway)

Researchers involved:

Anne-Marie Nybo Andersen (University of Copenhagen, Denmark), Leda Chatzi (University of Crete, Greece), Vincent Jaddoe (Erasmus MC, the Netherlands), Eric Steegers (Erasmus MC, the Netherlands), Martine Vrijheid (CREAL, Spain), Camilla Stoltenberg (Norwegian Institute of Public Health, Norway)

Summary

Perinatal mortality and infant death have declined significantly in Europe over the last decades. However, there is still significant variation between countries and over time, and low birth weight, stillbirth and perinatal and infant death remain important health challenges in all societies. Low birth weight, perinatal mortality, and infant death are sensitive and practical obtainable indicators not only of child health, but also of health conditions in the general society (Lopez et al 2006). Causes of low birth weight, stillbirth and perinatal/infant death are only partly known (Goldenberg et al 2008; Smith et al 2007), and the causes of birth defects are largely unknown (Dolk et al 2003). Several of the perinatal outcomes are associated with social inequality, the quality of health services, and living conditions. Also, they are closely related to future health outcomes, and serve as key exposures in life course studies (Kuh et al 2003; Saigalet al 2008). Birth registries are essential for monitoring of these outcomes, while pregnancy cohorts are needed to address aetiological issues and validation. Several European birth cohorts have studied pre- and perinatal factors related to birth outcomes, and have given a substantial contribution to research within modifiable risk factors for adverse birth outcomes, for example smoking, diet and other environmental exposures. To increase knowledge in this field, especially for rare conditions such as birth defects, collaboration between large cohorts is needed in order to study aetiological factors. Further work will focus on harmonizing the existing cohorts and collaborate across regions, while also working towards including cohorts from lower income countries. A major benefit of several birth cohorts is the availability of biological sample, making studies of biological pathways possible Thus, another aim is to work towards funding of projects which will investigate complex biological pathways and networks, involving genetics, epigentics, metabolomics, and so on.

1. Review of cohort contribution and existing cohort data

Several perinatal conditions are associated with later health and diseases in childhood and events in adult life. Depending on the research question, perinatal conditions can be regarded as either exposures or outcome. The present review of cohort contribution to the area of perinatal health focuses on the selected perinatal conditions as outcomes.

1.1. Description of current state of scientific knowledge

The objectives of this report are to:

1. Review the contribution of European birth cohort research to scientific knowledge on selected perinatal outcomes

2. Make recommendations for future research on perinatal outcomes in European birth cohort studies.

1.2. Description of the contribution of (European) birth cohort research to scientific knowledge

The term perinatal outcomes cover a wide range of conditions and diseases. To be able to handle perinatal outcomes in the context of CHICOS, we have limited the number of outcomes to the most serious in terms of number of lives lost and long-lasting consequesces for the individual and society. These are:

1. Fetal loss
2. Gestational duration, preterm birth
3. Fetal growth and size at birth
4. Congenital malformations
5. Preeclampsia
6. Infant death

The six selected perinatal outcomes are associated with each other, but also differ from each other in significant ways. Stillbirth/fetal loss, infant death, congenital malformations and preeclampsia are rare (≤a few per 1000) or relatively rare (a few per 100) events and conditions, while all children have a gestational age and birth weight. In order to investigate potential causes of the selected perinatal outcomes, access to data from pregnancy is an advantage, and in most cases a prerequisite. An added value is the availability of biological samples. We have summarized findings from cohorts in CHICOS with more than 1 000 children for which information and blood samples from pregnancy and birth are available. Two large cohorts in CHICOS did not fulfil the criteria to be included in this report, the MCS (The Millenium Cohort Study) for which inclusion started at 9 months of age, and NINFEA (Birth and Infancy: Effects of the Environment {Richiardi, 2007 240 /id}), which did not have biological samples from birth/pregnancy and also have no publications on the selected outcomes.

Birth cohort versus other study designs

Population-based prospective cohort studies that recruit mothers early in pregnancy or at birth are of great importance because they collect biological samples and information on many variables before the outcome occurs, limiting problems with recall bias and selection. Also, detailed information on lifestyle, maternal and paternal health conditions, and socioeconomic and psychological status in parents are possible to obtain in cohort studies. This information is often lacking in registry studies, making cohort studies a valuable contribution for studies of etiological associations between environmental and other exposures

and perinatal outcomes. However, cohort studies with inclusion during pregnancy or at birth will lack information on pregnancies ending before time of inclusion. Cohorts recruited at birth may lack information on miscarriages and stillbirths. Pregnancy cohorts may to some degree contain information on fetal loss after inclusion to the study, although women who continue to give information to a cohort study after experiencing fetal loss may be few, and differ in several ways from women with fetal loss in the general population, for example in age, educational level or smoking status, which can make it difficult to have enough women with information, and also make it difficult to study effects of several exposures related to fetal loss. Some registries include registrations of fetal loss, and may have more women with this outcome and therefore be a better source when studying fetal loss and stillbirths, however, registries will lack detailed information on exposures and lifestyle, limiting the possibilities to address associations with several exposures. There is a lack of cohort studies that have given priority to a design that would allow such studies, and a combination of studies including registry data and the details of cohort studies are desirable.

Contribution of European birth cohorts

Each of the selected CHICOS cohorts has contributed in this report with information and a summary of findings from published papers where the selected perinatal conditions were included as outcomes. Some of the cohorts have not yet published studies with these outcomes and are not listed in table 1. Table 1 shows a list of publications on the six perinatal outcomes from the selected European birth cohorts.

Description of the results

The Norwegian Mother and Child Cohort Study (MoBa)

MoBa is a pregnancy cohort with more than 105 000 pregnancies recruited from 1999-2008 (Magnus et al). Around 15000 mothers participated with more than one pregnacy, around 1800 twin pairs are inluded. Biological samples from mother and father (week 17 in pregnancy) and mother and cord blood (at birth) are stored in the MoBa Biobank (Rønningen et al). The families are followed longitudinally, and the oldest children in the cohort are soon reaching age 12. So far more than 100 publications have been published in MoBa, and more than 30 studies have been on the selected perinatal outcomes. A few studies have attempted to investigate fetal loss, infant survival, and birth defects, however there was limited power to study these outcomes. The risk of preterm birth and birth weight has been found to be associated to dietary factors, infections, maternal exercise, BMI and genes Preeclampsia was associated with infertility treatment, recurrent miscarriages, and dietary factors, whereas recreational physical activity was found to have little effect on the risk of preeclampsia.

The Danish National Birth Cohort (DNBC)

The Danish National Birth Cohort consists of more than 100 000 women and children. Data collection started in 1996 and the project covered all regions in Denmark in 1999. In October 2002, the goal of 100.000 recruitments was reached. Exposure information was collected by computer-assisted telephone interviews with the women twice during pregnancy and when their children were six and 18 months old. Participants were 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. The cohort has expanded its initial data collection with a 7-year follow-up, which was completed in August 2010. At the same time the 11-year follow up was launched. More than 200 publications have been published from the cohort, several on the selected perinatal outcomes in this report. Binge drinking in pregnancy was found to increase the risk of stillbirths, and alcohol consumption indicated a higher risk of preterm birth. Studies on nutrition and exercise in pregnancy have suggested that exercising and that intake of multivitamins is beneficial in pregnancy.

Avon Longitudinal Study of Parents and Children (ALSPAC)

Avon Longitudinal Study of Parents and Children (ALSPAC) (Golding J, 1990) includes more than 14,000 who were pregnant in 1991/1992. These women, the children and the women's partners have been followed up intensively over nearly two decades and comprehensive and detailed data have been collected throughout the lives of the children, who are now 17-18 years old. The cohort includes boys and girls from various ethnic groups and children growing up in poor socio-economic circumstances. Data have been collected using self-administered questionnaires, data extraction from medical notes, linkage to routine information systems and from research clinics that all the children have been invited to attend regularly from the age of seven years.

Generation R

The Generation R Study (Jaddoe VW) is a prospective cohort study from fetal life until young adulthood in a multi-ethnic urban population. The study is designed to identify early environmental and genetic causes of normal and abnormal growth, development and health from fetal life until young adulthood. This cohort includes around 10 000 mothers and children, and fathers enrolled between 2002 and 2006. Aims of the study are identification of early critical periods and causal pathways for growth, development and health.

Some of the results from Generation R suggests that air pollution is related to reduced fetal growth, and with preterm birth, and also with maternal blood pressure, and that maternal occupational exposure to chemicals, pthalates and pecticides may affects fetal growth and the pregnancy negatively. They have also found that preecamplsia and high blood pressure is associated with adverse birth outcomes, and that dietary factors during pregnancy may influence maternal blood pressure, however fish intake was not related to risk of adverse birth outcomes. Several genetic studies have revealed genetic associations with fetal growth.

INMA

INMA - Childhood and Environment (Guxens M) is a research network of several Spanish groups that created a project with the aim to study relevant environmental pollutants in air, water and diet during pregnancy and beginning of life, and their effects in the growth and development. The population of the study is around 3900 pregnant women of the general population who lived in several study areas in Spain and their children with recruitment from 1997 to July 2008. More than 130 articles have been published since 2001. Studies from INMA have shown that several environmental exposures are associated with the child's size at birth, for example exposure to air pollution, parental smoking, organochlorine compounds and dietary factors. They also found that high levels of exposure to endocrine-disrupting chemicals during pregnancy increases the risk of male urogenital malformations in the offspring.

RHEA

The Rhea mother-child cohort study in Crete, Greece is the only birth cohort study conducted in Greece, involving approximately 1,500 pregnant women and their children in the Heraklion prefecture of Crete. The study is designed to evaluate the impact of early life exposures on foetal and infants' growth, health and development. Among several published studies from RHEA, ten studies have focused on birth outcomes. Studies from RHEA have found that folic acid supplements may protect against preterm birth and low birth weight, while iron supplements may be harmful. Also, they have found that deprived sleeping and snoring during pregnancy increases the risk of preterm birth/growth restriction of the fetus. Smoking during pregnancy was found to increase risk of low birth weight and preterm birth. Metabolic syndrome in pregnancy was found to increase the risk of preterm birth. Maternal neuroticism, which predisposes to negative mood, may be a risk factor for fetal growth restriction. Women with thyroid autoimmunity were more likely to experience a spontaneous preterm delivery, while the combination of high TSH and positive thyroid antibodies was associated with increased risk of gestational diabetes, and low birth weight neonates.

Contribution of birth cohort collaboration

Collaboration between European countries on studies of some of these outcomes is well organised and uses registries as the main data source. Although a number of European population-based birth cohort studies include information on the six selected perinatal outcomes (www.birthcohortsenrieco.net) only a few of them are large enough to include a sufficient number of congenital malformations, and most cohort studies lack data on stillbirths/fetal losses, infant deaths, and if available for only a selected part of the population and after certain gestational lengths. Collaborations between cohorts with similar information and data collection will be valuable in studies of rare conditions and rare exposures.

1.3 Description of data currently available/being collected by the cohorts

Identification of cohorts

Birth and mother-child cohorts with data on one or more of the selected outcomes have been identified through different sources: 1) Birthcohorts.net webpage (www.birthcohorts.net) and the inventory carried out in connection with the CHICOS project; 2) the ENRIECO inventory (www.birthcohortsenrieco.net) that specifically collected data on cohorts with an environmental focus; 3) cohort websites; and 4) publications (PubMed). There are many pregnancy and birth cohorts in Europe that are collecting information on the six selected perinatal outcomes. Identification of cohorts to be included in this report has been done following these criteria:

- birth and mother-child cohorts
- population-based
- recruitment preferably in pregnancy, at latest at birth
- sample size: at least 300
- start year: 1990 onwards
- located in one of the EU member states
- Includes biological samples

See Table 2 for the identified Cohorts within CHICOS with more than 1000 participants, inclusion in pregnancy or at birth and biological samples from pregnancy and/or at birth.

Table 2. General description of CHICOS birth cohorts with data on six selected perinatal outcomes , more than 1000 participants and information from biological samples from birth/pregnancy

Cohort	*Country*	*Regions covered*	*Enrolment Period*	*N Children*
ALSPAC (The Avon Longitudinal Study of Parents and Children {Golding, 2001 220 /id})	UK	Bristol	1991-1992	14062
MoBa (The Norwegian Mother and Child Cohort Study {Magnus, 2006 239 /id})	Norway	Norway	1999-2008	107400
DNBC (Danish National Birth Cohort {Olsen, 2001 225 /id})	Denmark	Denmark	1992-2002	96986
Generation R {Jaddoe, 2008 229 /id}	Netherlands	Rotterdam	2001-2006	9778
RHEA (The Mother-Child cohort in Crete, Greece)	Greece	Heraklion	2007-2008	1500
INMA INfancia y Medio Ambiente (Environment and Childhood) (Guxens 2011)	Spain	Asturias, Gipuzkoa, Granada, Menorca, Sabadell, Ribera Ebre, València	1997-2008	3757
BiB (Born in Bradford {Raynor, 2008 29 /id})	UK	Bradford	2007-2010	13000
ELFE (French longitudinal study of children {Vandentorren, 2009 228 /id})	France	France	2011-2012	20000

Strengths and Limitations of current cohort studies

Strengths

- Information from pregnancy collected prospectively (no recall bias)
- Collection of a large number of variables
- Biological samples
- Possible to get information not obtainable through registries

Limitations

- Self-reported questionnaires/interviews (possible response bias)
- Selection bias (participants differ from general population)
- The number of participants may not be large enough to study important perinatal outcomes

- It may be difficult to include enough women with adverse birth outcomes, such as stillbirths, children with congenital malformations or other severe diseases

Opportunities

- Combine routine registries with cohorts
- Collaborative studies between countries with cohorts/registries

1.4 Identification of gaps

- Too few birth cohorts have recruitment early in pregnancy (or preconceptionally), making aetiologic studies of miscarriage and congenital anomalies sparse.
- Variation between countries in opportunities for linkage between registry data (preferably with full coverage) and cohort data
- Few Eastern and a limited number of Southern European countries with large cohorts
- Few low-income countries

2. Recommendations

- Establish and harmonize pregnancy cohorts and collect more in depth information (questionnaires, clinical, biological samples, validation of routine information, childhood outcomes)
- To be able to address fetal loss and preterm birth, and also early pregnancy exposures it is important to support establishment of birth cohorts with recruitment early in or before pregnancy
- For several perinatal outcomes, such as preeclampsia, preterm birth etc, there are still many unanswered questions about aetiology. We recommend funding of projects which will explore complex biological analyses and casual biological pathways/networks, including genetics, epigentics, metabolomics, etc.
- Facilitate collaborations between countries by working towards harmonizing and simplifying procedures related to practical, technical and juridical obstacles
- Develop national and routine national registration of
    - Perinatal outcomes from early pregnancy (including fetal loss, stillbirths)
    - Selected main exposures (smoking, maternal BMI, socio-economy etc) for example in Medical Birth Registries or other national registries with reporting of congenital abnormalities, also those not recognized at birth.

Table 1. European birth cohorts with published work on six perinatal outcomes (Fetal loss, Gestational age at birth, Birth weight/size, Congenital malformations, Preeclampsia, Infant death)

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
Fetal loss						
MoBa	Cupul-Uicab LA, et al	2011	In utero exposure to maternal smoking	Fetal loss	Limited power, no support of association	Hum Reprod
MoBa	Nezvalová-Henriksen K, et al	2011	Codeine in pregnancy	Infant survival	No effects	Eur J Clin Pharmacol
ALSPAC	Fergusson DM, et al	2002	Maternal use of cannabis	Late fetal and perinatal death	Not associatied	BJOG
DNBC	Andersen AM, et al	2002	Fever in pregnancy	Fetal death	No association	Lancet
DNBC	Zhu JL, et al	2004	Shift work, job stress	Late fetal loss	Fixed night increased the risk. Job stress was not associated	J Occup Environ Med
DNBC	Andersen AM, et al	2004	Advances paternal age	Fetal death	Increased risk from the age of 45 years	Am J Epidemiol
DNBC	Helgstrand S & Andersen AM	2005	Maternal underweight	Spontaneous abortion	Increased risk, especially losses occurring after 20 completed weeks	Acta Obstet Gynecol Scand
DNBC	Bech BH, et al	2005	Coffee	Fetal death	Increased risk	Am J Epidemiol
DNBC	Nohr EA, et al	2005	Prepregnancy obesity	Fetal death	Increased risk with advancing gestation	Obstet Gynecol
DNBC	Zhu JL, et al	2006	Work as hairdresser	Pregnancy outcomes, e.g. fetal loss	No association	Scand J Work Environ Health
DNBC	Zhu JL et al	2006	Occupational exposure to pesticides	Pregnancy outcomes, e.g. late fetal loss	Little effect on pregnancy outcomes	J Occup Environ Med
DNBC	Zhu JL, et al	2006	Laboratory work	Pregnancy outcomes, e.g. fetal loss	In general no high risk	Occup Environ Med
DNBC	Madsen M, et al	2007	Leisure time physical exercise during pregnancy	Miscarriage	Increased risk	BJOG
DNBC	Jellesen R, et al	2008	Maternal use of oral	Fetal death	No association	Paediatr Perinat

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
			contraceptives			Epidemiol
DNBC	Strandberg-Larsen K, et al	2008	Binge drinking in pregnancy	Fetal death	Increased risk of stillbirth, but not spontaneous abortion	Obstet Gynecol
DNBC	Strandberg-Larsen K, et al	2008	Use of nicotine replacement therapy during pregnancy	Stillbirth	Not associated with increased risk	BJOG
DNBC	Rebordosa C, et al	2009	Use of acetaminophen during pregnancy	Adverse pregnancy outcomes e.g. miscarriages, stillbirths	No association	Int J Epidemiol
DNBC	Morales-Suarez-Varela M, et al	2011	Unemployment	Fetal loss	No association	Scand J Public Health
DNBC	Nybo Andersen AM et al	2012	Moderate alcohol consumptiom	Fetal death	Increased risk of spontaneous abortion, but not stillbirth	Int J Epidemiol
DNBC	Norsker et al	2012	Socio-economic position	Spontaneous abortion	Increased risk with lower incime	BMJ Open
GENERATION R	Yap SC, et al	2009	women with repaired versus unrepaired atrial septal defect	Fetal loss	Association	BJOG
INMA	-	-	-	-	-	-
RHEA	-	-	-	-	-	-
Congenital malformations						
MoBa	van Gelder MM, et al	2011	Non-steroidal anti-inflammatory drugs during pregnancy	Birth defects	No association but limited power	PLoS One.
MoBa	Boyles AL, et al,	2011	Inhibited binding of folic acid to folate receptor alpha	Folate-related birth defects	Increased risk of NTDs but not oral facial clefts	Hum Reprod
MoBa	Nezvalová-Henriksen K, et al	2010	Triptan exposure during pregnancy	Birth defects	No association	Headache
MoBa	Nezvalová-Henriksen K, et al	2011	Codeine in pregnancy	Birth defects	No effects	Eur J Clin Pharmacol
ALSPAC	Hughes IA, et al	2002	birth weight, androgen dysfunction	Hypospadias	Association	Arch Dis Child Fetal Neonatal Ed.
ALSPAC	North K, et al	2000	Maternal vegetarian diet in pregnancy	Hypospadias	Association	J.BJU Int

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
DNBC	Zhu JL, et al	2006	Infertility, infertility treatment	Congential malformations	Increased risk	BMJ
DNBC	Morales-Suarez-Varela MM, et al	2006	Smoking habits, nicotine use	Congenital malformations	Increased risk in nonsmokers using nicotine substitutes	Obstet Gynecol
DNBC	Zhu JL, et al	2006	Work as hairdresser	Pregnancy outcomes, e.g. congenital malformations	No association	Scand J Work Environ Health
DNBC	Zhu JL et al	2006	Occupational exposure to pesticides	Pregnancy outcomes, e.g. congenital malformations	Little effect on pregnancy outcomes	J Occup Environ Med
DNBC	Zhu JL, et al	2006	Laboratory work	Pregnancy outcomes, e.g. congenital malformations	In general no high risk but exposure to radioisotopes may carry a high risk of congenital malformations	Occup Environ Med
DNBC	Rebordosa M, et al	2008	Acetaminophen use during pregnancy	Congenital abnormalities	No association	Am J Obstet Gynecol
DNBC	Varela MM, et al	2009	Socio-occupational status	Congenital anomalies	Low socio-occupational status associated with increased risk	Eur J Public Health
DNBC	Suarez-Varela MM, et al	2009	Hospital work	Pregnancy outcomes, e.g. congenital abnormalities	Increased prevalence in some subgroups of hospital workers	Int J Occup Environ Health
DNBC	Strandberg-Larsen K, et al	2011	Maternal alcohol drinking pattern during pregnancy	An isolated congenital heart defect	No statistically significant association	Birth Defects Res A Clin Mol Teratol
DNBC	Morales-Suarez-Varela M, et al	2011	Unemployment	Congenital abnormalities	No association	Scand J Public Health
GENERATION R	-	-	-	-	-	
INMA	Fernandez MF, et al	2007	exposure to endocrine-disrupting chemicals	cryptorchidism and hypospadias	Review	Gaceta Sanitaria (Spanish journal)
INMA	Fernandez MF, et al	2007	exposure to endocrine-disrupting chemicals	cryptorchidism and hypospadias	Increased risk	Environ Health Perspect
RHEA	-	-	-	-	-	-
Preeclampsia						

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
MoBa	Brantsæter AL, et al	2011	Intake of probiotic food	Preeclampsia		American Journal of Epidemiology
MoBa	Haugen M, et al	2009	Vitamin D supplementation	Preeclampsia	Protective effect, but may be confounding by fatty acids	Epidemiology
MoBa	Brantsæter A L	2009	A dietary pattern characterized by high Intake of vegetables, fruits and vegetable oils	Preeclampsia	Vegetable rich diet protects, processed meats, salt and sweet drinks increases risk	J Nutr
MoBa	Trogstad L, et al	2009	Recurrent miscarriage and infertility	Preeclampsia	Increases risk	BJOG
MoBa	Trogstad L, et al	2008	Previous abortions	Preeclampsia	Previous induced abortions protect	Int J Epidemiol
MoBa	Magnus P, et al	2008	Recreational physical activity	Preeclampsia	Limited protective effect	Am J Epidemiol
ALSPAC	Dudding T, et al V	2008	V Leiden	pre-eclampsia	Association	J Thromb Haemost
ALSPAC						
DNBC	Basso O, et al	2004	Height	Pre-eclampsia	Short stature was associated with increased risk	Int J Epidemiol
DNBC	Hylenius S, et al	2004	HLA-G genotype	Pre-eclampsia	Increased risk	Mol Hum Reprod
DNBC	Catov JM, et al	2007	Pre-existing conditions	Preeclampsia	Associated with a high proportion of cases. Obesity and overweight contributed to the risk	Int J Epidemiol
DNBC	Rebordosa C, et al	2009	Use of acetaminophen during pregnancy	Preeclampsia	Increased risk	J Matern Fetal Neonatal Med
DNBC	Catov JM, et al	2009	Periconceptional multivitamin use	Preeclampsia	Reduced risk. Folate-only supplement use was not associated	Am J Epidemiol
DNBC	Klemmensen A, et al	2009	Intake of vitamin C and E in pregnancy	Pre-eclampsia	Low dietary intake of vitamin C and high intake of vitamin E was associated with increased risk	BJOG
DNBC	Osterdal ML, et al	2009	Leisure time physical activity in early pregnancy	Pre-eclampsia	No protective effect but increased risk for the highest physical activity levels	BJOG
DNBC	Biggar RJ, et al	2010	HLA antigen sharing	Eclampsia, preeclampsia	No association	Hum Immunol

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
			between mother and fetus			
DNBC	Larsen MH, et al	2010	The 3'-untranslated region of the HLA-G gene	Pre-eclampsia	Increased risk	Tissue Antigens
DNBC	Chavarro JE, et al	2011	Trans fat intake	Preeclampsia	No association	Eur J Clin.Nutr
GENERATION R	Gaillard R, et al	2011	Maternal age during pregnancy	third trimester blood pressure level	Associated	Am J Hypertens.
GENERATION R	Gaillard R, et al	2011	Maternal obesity	blood pressure and the risks of gestational hypertensive disorders	Obesity strongly associated with blood pressure and risks of gestational hypertensive disorders	J Hypertens
GENERATION R	van den Hooven EH, et al	2011	Air pollution, blood pressure	the risk of hypertensive complications during pregnancy	Associated	Hypertension
GENERATION R	Gaillard R, et al	2011	Blood pressure tracking during pregnancy	The risk of gestational hypertensive disorders	Blood pressure patterns associated with gestational hypertensive disorders	Eur Heart J.
GENERATION R	Bakker R, et al	2011	Maternal caffeine intake,blood pressure	risk of hypertensive complications during pregnancy	Not associated	Am J Hypertens
GENERATION R	Bakker R, et al	2010	Maternal smoking	blood pressure in different trimesters	Associated	J Hypertens
GENERATION R	van den Hooven EH, et al	2009	Residential traffic exposure	Preeclampsia	Not associated	Environ Health
GENERATION R	Silva LM, et al	2008	Low socioeconomic status	Preeclampsia	Associated	J Hypertens
GENERATION R	Timmermans S, et al	2011	Folic acid	uteroplacental vascular resistance	Associated	J Nutr Metab Cardiovasc Dis
GENERATION R	Timmermans S, et al	2011	Major dietary patterns	blood pressure patterns during pregnancy	Associated	Am J Obstet Gynecol
INMA	-	-	-	-	-	-
RHEA	-	-	-	-	-	-

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
Fetal growth, Birth weight, Gestational duration, Preterm birth						
MoBa	Adams SS, et al	2011	Maternal emotional distress	Small-for-gestational age	No association	Acta Obstet Gynecol Scand.
MoBa	Brantsæter AL, et al	2011	Maternal seafood intake	infant birth size	Positive association with birth weight, n-3 supplements negatively ass. with head circ.	Br J Nutr
MoBa	Nilsen RM, et al	2010	Maternal intake and status of folate	Infant birth size	No association	J Nutr
MoBa	Fleten C, et al	2010	Exercise during pregnancy, maternal prepregnancy body mass index	Birth weight	Minor impact from exercise, maternal BMI greater impact	Obstet Gynecol
MoBa	Owe KM	2009	Regular exercise	Excessive newborn birth weight	Reduces risk of heavy newborns	Obstet Gynecol
MoBa	Morken NH, et al	2011	Maternal febrile episodes, urinary tract infection, pneumonia and ear-nose-throat infections	Spontaneous preterm delivery	Upper respiratory Infections early in pregnancy increases risk	Eur J Obstet Gynecol Reprod Biol
MoBa	Myhre R, et al	2011	Intake of probiotic food	Spontaneous preterm delivery	Reduced risk	American Journal of Clinical Nutrition
MoBa	Ryckman KK, et al	2010	Maternal and fetal genetic associations of PTGER3 and PON1	Preterm birth	Increased risk associated with both maternal and fetal genotypes	PLoS One

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
MoBa	Morken N-H	2008	Description of subgroups	Preterm delivery	Subgroup composition of preterms in MoBa is similar to other populations	Acta Obstet Gynecol Scand
MoBa	Haugen M, et al	2008	Mediterranean-type diet	Preterm birth	No association, but fish intake protective	Acta Obstet Gynecol Scand
ALSPAC	Passaro KT, et al	1996	maternal drinking before conception and in early pregnancy	Birth weight		Epidemiology
ALSPAC	Dunger DB, et al	1998	INS VNTR	Size at birth		Nat Genet
ALSPAC	Passaro KT, et al	1998	paternal alcohol consumption before conception	Birth weight		Teratology
ALSPAC	Farrow A, et al	1998	maternal occupation	Birth weight		Occup Environ Med
ALSPAC	Shea KM, et al	1997	paternal occupation	Birth weight and gestational age		Am J Ind Med
ALSPAC	Wildschut HI, et al	1997	social class	preterm birth		Lancet
ALSPAC	Shea KM, et al	1997	preconception paternal x-ray exposure	Birth weight		Am J Epidemiol
ALSPAC	Matijasevich A,	2012	Socioeconomics	Preterm Birth	Association	J Epidemiol Community Health
ALSPAC	Rogers I, et al	1998	'Financial difficulties, smoking habits, composition of the diet	Birth weight		Eur J Clin Nutr

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
ALSPAC	Ong KK, et al	1999	The insulin gene VNTR, type 2 diabetes	Birth weight		Nat Genet
ALSPAC	Mason S, et al	2000	variant in insulin receptor	Birth weight	No association	Diabetologia
ALSPAC	Freathy RM, et al	2010	Gene variants	Birth weight		Nature Genetics
ALSPAC	Freathy RM, et al	2009	Gene variants	Birth weight		Diabetes
ALSPAC	Evans J, et al	2007	'Depressive symptoms during pregnancy	Birth weight		Br J Psychiatry
ALSPAC	Freathy RM, et al	2007	Type 2 diabetes Gene variants	Birth weight	Association	Am J Hum Genet
ALSPAC	Weedon MN, et al	2006	haplotype of the glucokinase gene	Birth weight		Am J Hum Genet
ALSPAC	Weedon MN, et al	2005	glucokinase gene	Birth weight		Diabetes
ALSPAC	McCarron P, et al	2004	Type 2 diabetes in grandparent	Birth weight		J Epidemiol Community Health
ALSPAC	Rogers I, et al	2004	Maternal fish intake in late pregnancy	low birth weight and intrauterine growth retardation		J Epidemiol Community Health
ALSPAC		2002	Swimming	Birth weight		Epidemiology

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
	Nieuwenhuijsen MJ, et al					
DNBC	Thorsen P, et al	2001	Identification of biological/biochemical marker(s)	Preterm delivery		Paediatr Perinat Epidemiol
DNBC	Basso O & Baird DD	2003	Infertility	Preterm delivery, birthweight	Increased risk	Hum Reprod
DNBC	Zhu JL, et al	2004	Shift work	Birth weight, gestational age at birth	Limited effects on indicators of fetal growth	Am J Obstet Gynecol
DNBC	Albertsen K, et al	2004	Alcohol consumption during pregnancy	Preterm delivery	Increased risk but not statistically significant	Am J Epidemiol
DNBC	Hviid TV, et al	2004	HLA-G genotype	Fetoplacental growth	Associated with increased birth weight , placental weight at birth placental ratio in the offspring	Hum Immunol
DNBC	Mikkelsen TB, et al	2006	Fruit and vegetable consumption	Birth weight	Positive association, especially among lean women	Scand J Public Health
DNBC	Zhu JL, et al	2006	Work as hairdresser	Pregnancy outcomes, e.g. preterm birth, small-for-gestational age	No association	Scand J Work Environ Health
DNBC	Zhu JL et al	2006	Occupational exposure to pesticides	Pregnancy outcomes, e.g. preterm birth and	Little effect on pregnancy outcomes	J Occup Environ Med

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
				small for gestational age		
DNBC	Zhu JL, et al	2006	Laboratory work	Pregnancy outcomes, e.g. preterm birth and small for gestational age	In general no high risk but exposure to radioisotopes may carry a high risk of preterm birth	Occup Environ Med
DNBC	Zhu JL, et al	2007	Infertility, infertility treatment	Fetal growth restriction	Infertility associated with increased risk, treatment may has a little effect	Obstet Gynecol
DNBC	Knudsen VK, et al	2007	Major dietary patterns in pregnancy	Fetal growth	Diet based on red and processed meat and high-fat diary was associated with increased risk of small for gestational age	Eur J Clin Nutr
DNBC	Halldorsson TI, et al	2007	High consumption of fatty fish during pregnancy	Fetal growth retardation	Possible association	Am J Epidemiol
DNBC	Fei C, et al	2007	Perfluorinated chemicals	Birth weight, length of gestation	Inverse association between Perfluorooctanoate and birth weight, no adverse effects on small for gestational age	Environ Health Perspect
DNBC	Bech BH, et al	2007	Reducing caffeine intake	Birth weight, length of gestation	No effect	BMJ
DNBC	Nohr EA, et al	2007	Obesity, gestational weight gain	Preterm birth	Increased risk	Paediatr Perinat Epidemiol

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
DNBC	Curry AE, et al	2007	Mid-pregnancy maternal plasma levels of interleukin 2, 6, and 12, tumor necrosis factor-alpha, interferon-gamma, and granulocyte-macrophage colony-stimulating factor	Spontaneous preterm delivery	IFN-gamma and IL-6 were associated with increased risk	Acta Obstet Gynecol Scand
DNBC	Orozova-Bekkevold I, et al	2007	Maternal vaccination	Preterm birth	Increased risk	Pharm World Sci
DNBC	Olsen SF, et al	2007	Milk consumption during pregnancy	Infant size at birth	Associated with higher birth weight for gestational age, lower risk of small-for-gestational age and higher risk for large-for-gestational age	Am J Clin Nutr
DNBC	Halldorsson TI, et al	2008	Polychlorinated Biphenyls (PCBs), fatty fish consumption	Reduced fetal growth	Inverse association between PCBs and birth weight and placental weight	Am J Epidemiol
DNBC	Fei C, et al	2008	Perfluorinated chemicals	Fetal growth	Perfluorooctanoate had an effect but not perfluorooctane-sulfonate	Am J Epidemiol
DNBC	Catov JM, et al	2008	Chronic hypertension	Preterm and term small for gestational age births	Increased risk	Obstet Gynecol
DNBC	Juhl M, et al	2008	Physical exercise during pregnancy	Preterm birth	Reduced risk	Am J Epidemiol

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
DNBC	Mikkelsen TB, et al	2008	Mediterranean-type diet	Preterm birth	Reduced risk	Acta Obstet Gynecol Scand
DNBC	Morgen CS, et al	2008	Socioeconomic position	Preterm birth	Low education level associated with increased risk	Int J Epidemiol
DNBC	Nohr EA, et al	2008	Combined associations of prepregnancy body mass index and gestational weight gain (GWG)	Outcome of pregnancy, e.g. growth restriction	GWG was associated with increased risk, especially for underweight women	Am J Clin Nutr
DNBC	Halldorsson TI, et al	2009	Dietary predictors of dioxin-like activity in plasma	Birth weight	No association	Environ Res
DNBC	Curry AE, et al	2009	First-trimester maternal plasma cytokine levels, prepregnancy body mass index	Spontaneous preterm delivery (sPTD)	Association between first-trimester plasma cytokine levels and sPTD may depend on pre-prepregnancy BMI	Acta Obstet Gynecol Scand
DNBC	Vogel I, et al	2009	Polymorphisms in the promoter region of relaxin-2	Preterm birth	Increased risk	In Vivo
DNBC	Rebordosa C, et al	2009	Use of acetaminophen during pregnancy	Adverse pregnancy outcomes, e.g. preterm birth, low birth weight, small for gestational age	Increased risk, but only in mothers with pre-eclampsia.	Int J Epidemiol
DNBC	Mortensen LM et al	2009	SEP, smoking, maternal BMI	LGA	Smoking and BMI mediated a large part ofthe social gradient in LGA	Human Reprod

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
DNBC	Sorensen M, et al	2010	Non-occupational exposure to paint fumes during pregnancy	Fetal growth	No causal relationship	Environ Res
DNBC	Juhl M, et al	2010	Physical exercise during pregnancy	Fetal growth measures	No effects apart from a modest decreased risk of small- and large-for-gestational-age infants	Am J Obstet Gynecol
DNBC	Halldorsson TI, et al	2010	Intake of artificially sweetened soft drinks	Preterm delivery	Increased risk	Am J Clin Nutr
DNBC	Lassen TH, et al	2010	Maternal use of nicotine replacement therapy (NRT) during pregnancy	Birthweight	No association, simultaneous use of more than one NRT product had negative but non-significant effect	Paediatr Perinat Epidemiol
DNBC	Tegethoff M, et al	2010	Maternal psychosocial adversity during pregnancy	Length of gestation, offspring size at birth	Life stress and emotional symptoms associated with reduced length of gestation, only life stress associated with increased offspring size at birth	Psychosom Med
DNBC	Catov JM, et al	2011	Periconceptional multivitamin use	Preterm or small-for-gestational-age births	Reduced risk	Am J Clin Nutr
DNBC	Morales-Suarez-Varela M, et al	2011	Unemployment	Preterm birth, small for gestational age status	No association but for women receiving unemployment and sickness or maternity benefits were at higher risk	Scand J Public Health

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
GENERATION R	El Marroun H, et al	2009	Intrauterine cannabis exposure	fetal growth trajectories:	Association	J Am Acad Child Adolesc Psychiatry
GENERATION R	Bakker R, et al	2011	Blood pressure in different gestational trimesters	Fetal growth, and the risk of adverse birth outcomes	Association	Am J Epidemiol
GENERATION R	Mook-Kanamori DO, et al .	2011	Genetic variants	Fetal growth characteristics in different trimesters	Associated ADCY5 and CCNL1	J Clin Endocrinol Metab
GENERATION R	Bakker R, et al	2011	Maternal age	Birth weight Preterm birth, SGA,LGA	Associated	BJOG
GENERATION R	Heppe DH, et al	2011	Maternal fish consumption	Birth weight Preterm birth	Not asssociated	Br J Nutr.
GENERATION R	Heppe DH, et al,	2011	Maternal milk consumption	fetal growth, and the risks of neonatal complications	Higher milk consumption leads to increased fetal growth	Am J Clin Nutr
GENERATION R	Ernst GD, et al	2011	C-reactive protein levels in early pregnancy	fetal growth patterns, and the risk for neonatal complications	Associated	Am J Obstet Gynecol

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
GENERATION R	Geelhoed MJ, et al	2010	Glucocorticoid receptor gene polymorphisms	Growth in fetal and early postnatal life	No association	BMC Med Genet
GENERATION R	Bakker R, et al	2010	Maternal caffeine intake from coffee and tea, fetal growth	Birth weight, SGA	Associated	Am J Clin Nutr
GENERATION R	Bakker R, et al	2010	Maternal alcohol consumption	Fetal growth characteristics in different periods of pregnancy	Not associated	Int J Epidemiol
GENERATION R	Mook-Kanamori DO, et al	2010	Risk factors and outcomes	first-trimester fetal growth restriction	Associated	JAMA
GENERATION R	Ay L, et al	2009	Maternal anthropometrics	fetal size in different periods of pregnancy and at birth	Strongly associated	BJOG
GENERATION R	Mook-Kanamori DO, et al	2007	Insulin gene variable number of tandem repeats	weight from fetal life until infancy	Not associated	Eur J Endocrinol
GENERATION R	Troe EJ,et al	2007	Ethinicity	Birth weight	Associated	BJOG

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
GENERATION R	Freathy RM, et al	2010	Gene variants	Fetal growth and birth weight	Associated ADCY5 and CCNL1	Nat Genet
GENERATION R	van den Hooven EH, et al	2009	Residential traffic exposure	Preterm birth, birth weight	Not associated	Environ Health
GENERATION R	Silva LM, et al	2010	Mother's educational level	Fetal growth	Associated	Int J Epidemiol
GENERATION R	Jansen PW, et al	2010	Employment status	Preterm birth , birth weight	Associated	Occup Environ Med
GENERATION R	Jansen PW, et al	2009	educational inequalities	preterm birth	Increased risk for low education AD	Arch Dis Child Fetal Neonatal Ed
GENERATION R	Jansen PW, et al	2009	educational inequalities	birth weight	Increased risk for low education	Paediatr Perinat Epidemiol
GENERATION R	Patra J, et al	2011	alcohol consumption	low birthweight, preterm birth and small for gestational age	Increased risk	BJOG
GENERATION R	Burdorf A, et al	2011	work-related maternal risk factors	time to pregnancy, preterm birth and birth weight	Increased risk	Occup Environ Med
GENERATION R	Timmermans S, et al	2009	Periconception folic acid	low birth weight and preterm birth	Increased risk for no folic acid use supplements	Br J Nutr

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
GENERATION R	Jaddoe VW, et al	2007	Moderate alcohol consumption during pregnancy	low birth weight and preterm birth	Not associated	Ann Epidemiol.
GENERATION R	Jaddoe VW,et al	2007	Maternal smoking	fetal growth characteristics in different periods of pregnancy	Increased risk of fetal growth restriction	Am J Epidemiol
GENERATION R	Geelhoed JJ, et al	2008	Gene variants	growth in foetal life and infancy	Not associated	Clin Endocrinol
GENERATION R	Rours GI, et al	2011	Chlamydia trachomatis infection during pregnancy	preterm delivery	Increased risk	Eur J Epidemiol
GENERATION R	Jaddoe VW, et al	2008	Active and passive maternal smoking during pregnancy	low birthweight and preterm birth	Increased risk, less effect of passive smoking	Paediatr Perinat Epidemiol
GENERATION R	Snijder CA, et al	2012	Occupational exposure to chemicals	fetal growth	Increased risk	Hum Reprod.
INMA	Mendez MA, et al	2010	Seafood consumption in pregnancy	Birth size	Only higher intakes of crustaceans and canned tuna increased the risk of SGA	J Epidemiol Community Health.
INMA	Llop S, et al	2010	Air pollutants during pregnanc	Preterm birth	Increased risk	Environ Res

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
INMA	Pastor-Valero M, et al	2011	Periconceptional folic acid supplement	Anthropometric measures at birth	Decreased birth height	Br J Nutr.
INMA	Lopez-Espinosa MJ, et al	2011	Prenatal exposure to organochlorine compounds	Birth size	Reduction of birth weight, length, and head circumference	Pediatrics
INMA	Estarlich M, et al	2011	Residential exposure to outdoor air pollution during pregnancy	Measures at birth	NO_2 exposure reduces birth length and weight	Environ Health Perspect
INMA	Sunyer J, et al	2012	Exposure to second hand smoke (depending on maternal asthma)	Birth weight	Asthma did not modify the effects of SHS on reproductive outcomes	Eur Respir J.
INMA	Aguilera I, et al	2010	Traffic-Related Air Pollution	Fetal Growth	BTEX exposure during mid-pregnancy reduces biparietal diameter	Environ Health Perspect
INMA	Iñiguez C, et al	2011	Active and passive smoking during pregnancy	Fetal Growth	Active smoking reduces of biparietal diameter (passive smoking also), abdominal circumference, femur length and estimated fetal weight	J Epidemiol Community Health.
INMA	Rodríguez-Bernal CL, et al	2010	Diet quality in early pregnancy	Fetal growth outcomes	Increase in birth size and reduction of the risk of fetal growth restriction	Am J Clin Nutr
INMA	Ballester F, et al	2010	Air pollution exposure	Birth size	Reduction in birth size	Environ Health

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
			during pregnancy			
INMA	Ramón R, et al	2009	Fish consumption during pregnancy, prenatal mercury exposure,	Anthropometric measures at birth	Large oily fish increase the risk of SGA for weight. Lean fish reduces the risk	Am J Clin Nutr
INMA	Ramón R, et al	2009	Vegetable and fruit intake during pregnancy	newborn anthropometric measures	Vegetable but not fruit intake during pregnancy is associated	J Nutr
INMA	Aguilera I, et al	2009	urban air pollution	birth weight	BTEX exposure reduces birth weight in women who spent <2hr/day in nonresidential outdoor environments	Environ Health Perspect
INMA	Ribas-Fitó N, et al	2002	hexachlorobenzene and other organochlorine compounds	anthropometric measures at birth	HCB reduces intrauterine physical linear growth	Pediatr Res
INMA	Alvarez-Pedrerol M, et al	2009	Iodine levels and thyroid hormones	birth weight	High TSH levels reduce birth weight and increase the risk of SGA	Eur J Endocrinol
INMA	Villanueva CM, et al	2011	Exposure to trihalomethanes through different water uses	birth weight, small for gestational age, and preterm delivery	Not associated	Environ Health Perspect
RHEA	L. Chatzi, et al.	2009	Metabolic syndrome	preterm birth, fetal growth	Associated with preterm birth	Am J Epidemiol

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
RHEA	L. Chatzi, et al.	2012	Maternal neuroticism	fetal growth	May be a risk factor	European Psychiatry
RHEA	L. Chatzi et al.	2012	Mediterranean diet	anthropometric measurements at birth, fetal growth	Protective effect only in smokers	Br J Nutr:
RHEA	E. Papadopoulou et al.	2012	Folic acid and iron supplementation	anthropometric measurements at birth, fetal growth, preterm birth	Associated	Eur J Nutr
RHEA	P. Karakosta et al.	2012	Thyroid function and thyroid antibodies in early pregnancy	anthropometric measurements at birth, SGA, preterm birth	Associated	J Clin Endocrinol Metab
RHEA	G. Kritsotakis et al.	2011	Maternal social capital	Preterm birth, fetal growth, anthropometric measurements at birth, SGA	May be associated with preterm birth	Soc Sci Med
RHEA	K. Micheli et al.	2011	Sleep patterns	Preterm birth, fetal growth	Associated	Epidemiology
RHEA	E. Patelarou et al	2011	DBPs	Birth weight, SGA, preterm birth	Not associated	Occupational and Environmental

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Conclusion*	*Journal*
						Medicine
RHEA	C. Vardavas et al.	2010	Smoking & smoking cessation	Fetal growth, birth weight, preterm birth	Associated	European Journal of Pediatrics
RHEA	Vande Loock et al.	2011	Micronucleus (MN) Frequencies in Umbilical Blood	Gestational age	MN frequency inversely associated with GA	Environ Health Perspect

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Asthma, respiratory health and allergies

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Summary

Asthma and allergies in childhood have a high prevalence across many countries world-wide. Mortality due to these diseases is uncommon but the morbidity and health care costs associated with it are considerable. The causes for high prevalences of asthma and allergies remain unclear but environmental and genetic factors are likely to be involved. The main aim was to identify European birth cohorts which assessed asthma and allergy as outcomes and their assessment tools, to evaluate environmental and genetic risk factors of asthma and allergies in these birth cohorts and, eventually, to develop recommendations for future research in Europe. Forty-two birth cohorts with data on asthma and allergy were identified of which 36 had been identified previously by the workgroup of Asthma and Allergy of the Environmental health Risks In European birth Cohorts consortium (ENRIECO). The CHICOS workgroup follows the recommendations of the ENRIECO workgroup that the ISAAC-based questionnaire assessment tool is the preferred assessment tool to study asthma and allergy in planned birth cohort studies. The use of pulmonary function tests, Skin Prick Tests (SPT) and measures of Immunglobulin E (IgE) should be carefully considered in epidemiology research due to their relatively poor predictive values, and large personal, technical and monetary input.

Birth cohorts are most suitable to study environmental and genetic risk factors of asthma and allergy, and their interactions, due to the longitudinal design, detailed data collection on multiple risk factors, outcomes and potential confounding factors. A large number of environmental and genetic risk factors have been shown to be associated with asthma and allergy, and detailed data collection and analyses are still ongoing. Limitations of current birth cohort research are the partly non-comparable assessments tools for adequately measuring asthma and allergy, the lack of combining analyses between cohorts, especially for risk factors with small effect estimates, the partly lack of studies with comprehensive and detailed measurements of a range of environmental exposures in pregnancy and early infancy, the paucity of research on environmental risk factors in very early life including fetal exposures in different trimesters of pregnancy where lung development is most susceptible, the paucity of research on genetic risk factors with emphasis on gene-environment interaction studies, genome wide association studies and epigenetics, are the shortcomings of current research on confounding and interaction of environmental and genetic risk factors, the lack of tracking observed results of childhood into adulthood, and scarce publication of studies in Eastern European and low-income countries where prevalence of asthma is still increasing. Birth cohorts should focus their research on these gaps. Also, collaboration of birth cohorts with the intention to combine their specific knowledge and harmonize data is necessary to increase the strength of causality regarding the associations of environmental and genetic risk factors with asthma and allergy. To date, several environmental (GA2LEN, ENRIECO, MEDALL) and genetic (EAGLE, Gabriel) consortia of birth cohorts

have already been established. In summary, birth cohorts are able to provide extensive and detailed knowledge to understand the environmental and genetic mechanisms, and their interactions, of asthma and allergy, and potentially may lead to novel preventive, diagnostic and therapeutic approaches to make a strong contribution to scientific knowledge in future years.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

Asthma and allergies in childhood have a high prevalence across many countries world-wide (1). The increase over the past decades seems to plateau in countries with highest prevalence, but is still rising in countries with low prevalence (2-5). The causes for the rise in asthma and allergies remain unclear but environmental and genetic exposures are likely to be involved (6-7). There is reason for concern regarding treatment effects. Despite the availability of effective, evidence-based treatments, morbidity remains considerable (8-9). Asthma affects family life and causes parental absence from work, contributing to the high economic impact in addition to drug and related healthcare costs. Also, asthma is a complex and heterogeneous disease, for which no universally agreed definition exists (10). The diagnosis is usually based on clinical assessment, which is not feasible for most large epidemiological prospective cohort-based surveys.

Environmental risks factors in early childhood associated with development of respiratory disease or poor airway function include exposure to parental smoking or ambient (traffic-related) air pollution, shorter duration of breastfeeding, obesity, larger family size, daycare attendance, infectious diseases in early childhood and acetaminophen use (6, 11-15). The available evidence for some common environmental risk factors is briefly discussed below. Recently, it was found in term born children that low birth weight is also associated with increased risks of respiratory symptoms in the first 7 years of life (16). Low birth weight per se is not likely to be the causal factor leading to asthma. The same birth weight might be the result of various growth patterns and different fetal exposures (17). Two relatively small sized studies have observed that fetal growth is associated with childhood asthma (18-19). However, the associations of detailed and prospective, longitudinally-measured fetal and early childhood growth patterns with wheezing or asthma, changes in lung function and lung structure in childhood adjusted for a large number of possible confounders remain to be studied.

Maternal smoking is the most important adverse fetal exposure in Western countries, and is strongly associated with fetal growth retardation and low birth weight (17). Recently, it was demonstrated that continued maternal smoking during pregnancy is associated with asthma symptoms, including wheezing, in

preschool children (11). These associations were independent of paternal smoking and imply a direct adverse effect of smoke exposure on fetal lung development. However, it is not known whether the associations between low birth weight and respiratory disease can be fully explained by fetal smoke exposure.

Higher exposure levels to air pollutants have been associated with increased risks of asthma exacerbations in adults and children aged ≥ 5 years (20-24). The influence of air pollution on asthma and wheezing or other respiratory symptoms in childhood is less clear (25-28), partly related to differences in study design, exposure assessment, confounder selection and data analysis. A recent collaboration of comparable cross-sectional studies in 12 countries revealed that long-term exposure to outdoor air pollution, characterized by the concentration of PM_{10}, is statistically (borderline) significant associated with increased respiratory symptoms such as phlegm, bronchitis, morning and nocturnal cough, but not with diagnosed asthma, asthma symptoms or lung function (29). However, the effect of individual generated exposure to air pollutants measured at the actual residential address, the exposure to other air pollutants such as SO_2 or NO_2, the differences between near-traffic exposures levels and urban background pollution exposure estimates, and possible modifying effects of fetal or child tobacco smoke exposure (22) on respiratory outcomes need to be explored preferably in collaborative studies.

Specific infant feeding patterns such as early introduction of bottle feeding or solid food instead of a long period of exclusive breastfeeding may lead to less optimal lung and airway growth or increased risk of childhood asthma (12, 30-33). Further studies are needed to explore more extensively micronutrients, atopic, infectious, suboptimal lung growth (34), and other possible underlying mechanisms for the associations between breastfeeding and asthma.

In the first years, childhood asthma or wheezing is predominantly associated with respiratory tract infections (14, 35-38). Respiratory infectious diseases in infancy also predict the risk of asthma and other respiratory diseases in childhood and adulthood (39-41). Whether these associations reflect causal mechanisms or reflect symptoms of the same underlying susceptible lung is not known.

Common or rare genetic variants might directly or indirectly through low birth weight lead to smaller lungs and airways and subsequently to asthma. Previous candidate gene studies and linkage studies identified more than 100 genes associated with asthma (42-43). However, most of these associations could not be robustly replicated. More recent genome wide association studies (GWAS) in large study populations successfully identified and replicated genetic variants related to asthma or asthma related phenotypes in

children (44-49). Variants in the *ORMDL3* gene and in neighbouring genes, such as gasdermin A and B (*GSDM*), has most consistently been associated with risk of the childhood-onset asthma. Therefore, further studies are needed that relate genetic variants to both early body and lung growth characteristics and respiratory diseases in later life. The effects of early life exposures such as maternal smoking and diet, breastfeeding and infant infectious diseases on the risk of asthma and COPD might be modified by a genetic susceptibility (50-56). The interaction of environmental exposures with common genetic variants could be explained by epigenetic modifications such as DNA methylation. Changes in DNA methylation of CpG dinucleotides of specific gene regions is influenced by several environmental exposures and affects gene expression, and is suggested to subsequently influence respiratory outcomes. Further gene-environment and epigenetic studies are needed, especially focused on the environmental exposures in the fetal and early childhood period, during which alveolar and airway development is largely completed.

The main aim of this WG is to identify European birth cohorts which assess asthma and allergies as outcomes, to identify their assessment tools, to evaluate environmental and genetic risk factors of asthma and allergies, and, eventually, develop recommendations for future research in Europe. The specific objectives are:

1. To identify birth cohorts with data on asthma and allergy and assess which assessment tools were used. CHICOS will build on the work carried out in ENRIECO
2. To review existing information on environmental risk factors in early life for asthma in European birth cohorts (groups at risk, effect estimates; public health perspective)
3. To review existing information on genetic risk factors for asthma in childhood (effect estimates; public health perspective)
4. To identify gaps in knowledge in priority topics of policy interest
5. To evaluate the role of cohorts as part of the development of a future research strategy
6. To conduct case studies in topics of policy interest to demonstrate the potential value of and challenges in combining environmental data across birth cohorts in Europe.

1.2. Description of the contribution of (European) birth cohort research to scientific knowledge

Prospective cohort studies that recruit mothers during pregnancy or around the time of birth are of great importance due to their longitudinal design and enabling collection of many potential determinants and confounders of disease prior to the outcomes. Therefore, the focus of this working group was on prospective mother and birth cohorts to study the natural history of asthma and allergies and its environmental and genetic determinants.

Routine registries

In several European countries the possibility to link individual prospectively collected register-based data on childhood asthma and allergy exists. However, studies relying on register-based data often include the most severe and hospitalized cases only. The majority of asthma and allergy symptoms are mild and do not lead to hospitalization. Also, many of the possible environmental or genetic determinants of asthma and allergy are not routinely registered. Therefore, it is not preferable to study the origins of asthma and allergy using register-based data.

Consortia

Several birth cohorts joined their forces in consortia to study environmental and genetic risk factors of asthma and allergy.

GA²LEN

The Global Allergy and Asthma European Network (GA²LEN) was created in 2004 to combat fragmentation in the European research area, ensuring excellence in European allergy and asthma research by bringing together institutions and researchers from across the EU (www.ga2len.net) (supported by European Union under the Health Cooperation Work Programme of the 6th Framework programme). The network notably constructed centralized structures overseeing the multiple assets in knowledge in the different GA²LEN partners, enabling them to optimally synchronize their research efforts. Also, GA²LEN aims to accelerate the application of research results into clinical practice development, to promote training and greater integration between public and academic sectors, and to contribute to developing better health care and improving the quality of life for allergy and asthma patients.

MEDALL

Since 2011, MeDALL (Mechanisms of the Development of ALLergy) is a collaborative project and encompasses 23 public and private institutions, including 3 European SMEs, who will combine their efforts to contribute to the elucidation of the mechanisms of allergy-associated diseases (supported by the European Union under the Health Cooperation Work Programme of the 7th Framework programme). The consortium is gathering leading experts in clinical allergy and aims to generate novel knowledge on the mechanisms of initiation of allergy from early childhood to young adulthood, in order to propose early diagnosis, prevention and targets for therapy. A novel definition of phenotypes of allergic diseases and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic phenotypes.

ENRIECO

Enrieco (Environmental Health Risks in European Birth Cohorts) is a project conducted within the European Union's 7th Framework Programme from 2009 until 2011 (www.enrieco.org). The overall aim was to advance knowledge on specific environment and health causal relationships in pregnancy and birth cohorts by providing support to exploitation of the wealth of data generated by past or ongoing studies funded by the EC and national programmes. The specific objectives were to make inventories of birth cohorts and their data collection, assure quality and interoperability and validate exposure, health and exposure-response data, obtain data access, build databases, and conduct analysis, make recommendations for data collection in the future to improve environment-health linkages and information, and to disseminate information. One of the working groups was focussed on asthma and allergy.

EAGLE

The EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium is a consortium of pregnancy and birth cohorts that aims to collaborate to investigate the genetic basis of phenotypes in antenatal and early life and childhood (started in 2009). EAGLE covers a broad range of pathways and phenotypes, and will integrate closely with the DOHaD (developmental origins of health and disease) community. One of the working groups is focussed on the phenotypes asthma, allergy and atopy.

GABRIEL

The European GABRIEL Consortium in conjunction with partners from many other countries has undertaken the largest study to date in the genetics of asthma (funded through an EC Framework 6 grant) (http://www.cng.fr/gabriel/index.html). The consortium involves over 150 scientists from 14 European countries, using the latest research across a variety of disciplines, including genetics, epidemiology and immunology, to identify key factors in the development of asthma.

1.3 Description of data currently available/being collected by the cohorts

We conducted a literature search in the computerized bibliographic database PubMed in order to describe the contribution of birth cohort research, particularly European cohorts, to the scientific knowledge on this field. Issues of primary interest were: the methods of data collection and definition of asthma and allergies, identification of early environmental factors (direct or proxies) and their interactions related to asthma and allergies and the contribution of identified genetic factors to explaining the variance in the development of asthma and allergies. The focus was on prospective birth and mother-child cohorts in Europe, with recruitment at the latest during the first year of life, with at least one year of follow-up, with a sample size

of least 1000 subjects, and started from 1990 onwards and located in one of the EU member states. Cohorts before 1990 were only included if relevant papers on the outcomes asthma and allergy had been published. Cohorts have been identified from: 1) Birthcohorts.net webpage (www.birthcohorts.net), this database functions as a tool for researchers and others with an interest in improving child health across Europe; 2) existing collaborations and consortia on environmental (ENRIECO (www.birthcohortsenrieco.net), GA2LEN) and genetic (EAGLE, GABRIEL) risk factors; 3) cohort's websites; and 5) published articles.

Cohorts studying asthma and allergy as outcomes

In addition to the previously 36 identified birth cohorts of the working group of Asthma and Allergy of ENRIECO, 19 birth or survey cohorts were identified. Of those, 12 did not have data on asthma or allergy (yet) (Copenhagen Child Cohort Study 2000, IVAAQ, Donald, Early childhood development cohort, Growing-up in Ireland, TI-MOUN, Trieste, Polish national mother and child cohort, Early childhood development cohort, ABIS, Newcastle Thousand Family Study and North Cumbria Community Genetics project) and 1 was a high-risk allergy cohort (Merthyr Allergy Study). The other 6 cohorts are presented in Table 1.

Most ENRIECO and CHICOS birth cohorts used questionnaires, tests for pulmonary function and allergic sensitizations to evaluate the history, frequency and severity of symptoms. The main conclusions of the ENRIECO report are still applicable: ISAAC-based questionnaire assessments for asthma, allergic rhinitis and eczema are well established and highly comparable in ongoing epidemiological research and should be applied in planned cohort studies as well. Pulmonary function tests, bronchial hyperreactivity tests, Skin Prick Tests (SPT) and measures of Immunglobulin E (IgE) have relatively poor predictive values and their usefulness in clinical practice and prospective cohort research is therefore limited. Also, these tests require large personal, technical and monetary input. The cost-benefits of conducting these tests in epidemiology research should be carefully considered and might be useful for cohorts studying specific research questions with respiratory function or diseases as the main outcomes. Some disadvantages of current birth cohort research are the different time-points of follow-up, the use of own or modified questions and the use of other approaches than ISAAC guidelines which make between-study comparisons still difficult. International clinical guidelines for pulmonary function tests, which partly measure the underlying pathology of asthma, are published by the European Respiratory Society and the American Thoracic Society (http://www.thoracic.org/statements/). These clinical guidelines might be extrapolated on epidemiological research to obtain comparable results. Both Skin Prick Tests (SPT) and measures of Immunglobulin E (IgE) lack an internationally acknowledged standard definition.

Cohorts studying early environmental and genetic risk factors of asthma and allergy

Birth cohorts have played a major role in defining the natural history of asthma and related wheezing symptoms and detecting cause-effect relationships in this area. The working group has focussed on the CHICOS core cohorts (ALSPAC, DNBC, GENERATION R, MOBA, and INMA) to be able to handle extensive and detailed results of European birth cohorts on asthma and allergy. Relevant publications of the results on the associations of environmental and genetic risk factors on asthma, wheezing, lung function, allergy and eczema as outcomes of these cohorts are presented in Table 2. Also, environmental risk factors of asthma and allergy will be described in detail by the other working groups focussed on determinants of diseases, including 'Social and cultural conditions and inequalities', 'Nutrition and physical activity', 'Life-style and substance exposures (e.g. smoking, alcohol, illicit drugs)' and 'Other environmental exposures (e.g. air pollution, radiations)'. Genetic risk factors of asthma and allergy will be described in detail by the working group 'Biological and genetic materials stored in Biobanks'. In summary, many longer existing and recently established birth cohorts are currently ongoing. A large number of data on environmental and genetic risk factors that might be associated with asthma and allergy have been or are being collected. Childhood asthma and allergy are strong predictors for adult asthma, and increasing evidence suggests that the factors that determine the expression of later disease operate very early in life (57). Important findings have resulted from careful follow-up of airway symptoms and partially from lung function, and have identified contributing or protective factors such as low birth weight, prenatal and passive tobacco smoke exposure, exposure to air pollution, feeding habits, farming environment and family size (58-60). Complex interactions of genetic factors, including gene-gene and gene-environment interactions are likely to be involved (51, 59, 61-66). It is only by careful, long-term follow-up that the impact of early respiratory morbidity for respiratory health in adult life can be estimated. Each environmental or genetic risk factor has an estimated effect size. However, the majority of the effect sizes are of modest magnitude suggesting either multiple common exposures or rarer exposures interacting with genetic risk factors for asthma and allergy. Collaboration of birth cohorts with the intention to combine their specific knowledge and data will increase the strength of causality regarding the associations of environmental and genetic risk factors with asthma and allergy taking different methods into account to prevent ascertainment or information bias. Furthermore, risk factors might be analysed further in depth including their interactions and may potentially be followed by novel preventive, diagnostic and therapeutic approaches to make a strong contribution to scientific knowledge in future years.

1.4 Identification of gaps

Based on the scientific knowledge contributed by (European) birth cohort research and ongoing data collection the gaps in research on method, definition, early environmental and genetic risk factors of

asthma and allergy are:

- Lack of fully harmonized assessment tools for adequately measuring asthma and allergy
- The lack of combining analyses between cohorts, if comparability of measures is feasible, especially for risk factors with high prevalence i.e. prospectively measured restricted fetal growth, maternal stress during pregnancy, childhood obesity.
- The partly lack of studies with comprehensive and detailed measurements of a range of environmental exposures in pregnancy and early infancy.
- The paucity of research on environmental risk factors in very early life including fetal exposures in different trimesters of pregnancy where lung development is most susceptible.
- The paucity of research on genetic risk factors with emphasis on gene-environment interaction studies, genome wide association studies and epigenetics, i.e. tobacco smoke exposure or maternal and infant feeding, and DNA-methylation
- The partly lack of research on confounding and interaction of environmental and genetic risk factors, i.e. tobacco smoke exposure or maternal and infant feeding, maternal stress during pregnancy,, and DNA-methylation explaining associations between birth weight and respiratory outcomes.
- The lack of tracking observed results of childhood into adulthood in pregnancy recruited birth cohorts
- Publication of results of studies in Eastern European and low-income countries where prevalence of asthma is still increasing

2. Short report on case studies – lessons learned from the data pooling exercises on this topic

Four case studies have been proposed to study the associations of early environmental risk factors with asthma or wheezing:

- Social inequalities and asthma (postponed)
- Early growth (birth weight, catch up growth) and wheezing/asthma
- Maternal and infant's nutrition, use of vitamins/medication and wheezing/asthma/allergy - *postponed*
- Maternal complications in pregnancy, procedures at birth and association with wheezing and asthma

Possible cohorts for these case studies have been selected, approached to participate, exchanged their data, and currently statistical analyses are ongoing. Results from these case studies will be published in peer-reviewed journal from the end of 2013 onwards.

3. Recommendations

We follow the recommendations made by the ENRIECO consortium regarding the assessment tools and definition of the outcomes of asthma and allergy, and additionally made recommendations for epidemiological research on early environmental and genetic risk factors for asthma and allergy:

- To harmonise assessments tools for measuring asthma and allergy to improve comparison of results between cohorts
    - ISAAC-based questionnaire assessments for asthma, allergic rhinitis and eczema are well established and highly comparable. They are implemented in ongoing epidemiological research and should be applied in planned cohort studies as well.
    - Considering the large personal, technical and monetary input only cohorts with a clear focus on the assessments of asthma and allergy should use PFTs, SPTs and IgE-tests as there is limited usefulness in clinical practice as well as in population based research for the rather poor predictive values.
- To combine analyses especially for risk factors with small effect estimates to improve statistical power and strengthen the effect estimates of the observed associations taking studies in different environments with different detailed information into account
- To extend research on environmental risk factors with emphasis on early life including fetal exposures in different trimesters of pregnancy
- To extend research on genetic risk factors with emphasis on genome wide association studies and epigenetics
- To extend research on confounding and interaction of risk factors
- To extend research with follow-up in adults (tracking, for at least respiratory diseases)

- To stimulate initiation of more prospective cohort studies in Eastern European and low-income countries where prevalence of asthma is still increasing and to stimulate publication of results of ongoing studies in these countries

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Table 1. Asthma/wheezing, lung function, allergic rhinitis, eczema and allergic sensitization assessed by birth cohorts.

Cohorts presented are *additional* to the 36 cohorts included in the inventory by ENRIECO (all CHICOS cohorts included), Report ENV-FP7-2008-226285, Deliverable 17, Tables 29-33, Evaluation of Health Information and Recommendations in European Birth Cohorts, www.enrieco.org.

Cohort	Country, enrolment period	N children initially enrolled	N children with outcome	Age outcome measured	Method	Description of method	Reference
Historical							
HHf2 (Healthy Habits for two)	Denmark 1984-87	11,300	Asthma: 888 Wheezing: 1,232 Hayfever:1,083 Eczema: 1,248	'Ever'	Questionnaire (mother reported); Danish Questionnaire developed from the UK Party's questionnaire for atopic dermatitis (asthma, hay fever, atopic eczema), ISAAC (wheezing)	'Have you ever been informed by a doctor that your child has asthma/ hay fever/ eczema' 'Have your child before 3 years of age ever had wheezing or whistling in the chest'?(67-68)	www.birthcohorts.net
Isle of Wight birth cohort study	United Kingdom 1989-90	969	Asthma: Wheezing ever: 46.7% Wheezing current: 19.9% IgE: 945 SKP: 1,036 (prevalence aeroallergens 1.3%, 6.4%, and 10.7% at 1, 2, and 3 years of age. Prevalence food allergens were 2.8%, 3.9%, and 3.7%) Spirometry: 981 Bronchial provocation tests: 784	Birth, 1, 2, 4, 10 years	Questionnaires, ISAAC (age 10 years) Blood samples, IgE (birth, 10 years) Skin prick test (4, 10 years) Lung function (10 years)	'Has your child ever had wheezing or whistling in the chest at any time in the past?' 'Has your child had wheezing or whistling in the chest in the last 12 months?(69) Total IgE SKP: 14 common food and aero-allergens(70) Spirometry: FVC, FEV1, FEV1/FVC(71) Bronchial provocation tests(69)	http://www.cls.ioe.ac.uk

Recent							
Life-Cross Generation Cohort Study	United Kingdom (Ireland) 2001-03	1,074	~66	3 years	?	?(72)	www.birthcohorts.net
GUS (Growing Up in Scotland)	United Kingdom (Scotland) Open cohort since 2005	5,217	?	<1, 2, 3, 4, 6 years	Interview	'Does ^*childname* have any *[^other]* longstanding illness or disability, i.e. asthma, hayfever?' 'Did ^*childname* has had any health problems or illnesses since we last saw you last year, i.e. wheezing/asthma/eczema?' 'Is *childname* suffering from asthma in the last three months (a big problem, a bit of a problem, not a problem)?'	http://www.crfr.ac.uk/gus
Millennium cohort study	United Kingdom 2000-01	188,118	Ever asthma: 1,902 Ever wheeze: 3,030	3 years	Parental reported questionnaires ISAAC	'Has your child ever had wheezing or whistling in the chest at any time in the past?' 'Has your child had wheezing or whistling in the chest in the last 12 months?'(73)	http://www.cls.ioe.ac.uk
SEATON	United Kingdom	1,924	Asthma: Wheezing: ~15-19% Atopic dermatitis: ~16-32% Lung function: 638	6, 12, 24 months, 5 years	Questionnaires, ISAAC Spirometry	'Has your child ever had wheezing or whistling in the chest at any time in the past?' 'Has your child had wheezing or whistling in the chest in the last 12 months?(74) Spirometry: FEV0.5, FEV0.75, FEV1, FEF25–75, and FEF50(75)	http://www.abdn.ac.uk/seatonstudy

Table 2. Relevant publications on the associations of environmental and genetic determinants of wheezing, asthma, lung function, allergy, eczema, hay fever and allergic rhinitis. The working group has focussed on the CHICOS core cohorts (ALSPAC, DNBC, GENERATION R, MOBA, and INMA) to be able to handle extensive and detailed results of European birth cohorts on asthma and allergy.

Cohort	Reference
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Developing a Child Cohort Research Strategy for Europe

Obesity, vascular and metabolic health

Researchers involved:

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Summary

Having detailed measurements on adiposity and cardiometabolic traits from infancy through childhood and into adulthood is likely to be important for fully understanding the determinants of obesity and diabetes and cardiovascular disease risk in future decades. The added value of combining information from birth cohorts across Europe are that this would allow key aetiological factors to be more robustly established than in any one single cohort, because of the larger sample sizes available and potential for cross-cohort comparisons. Furthermore, there is value in this approach with respect to EU policy. EU policy in this area might include, for e.g., regulation of food labelling and regulation of advertising certain foods to children. Having data on cohorts from across the EU will allow a better understanding of how any such policy is likely to impact childhood obesity and vascular and metaboic health in each country and across the Union.

The aim of this working was to identify all European birth cohort studies that had at least one measure of adiposity (e.g. body mass index (BMI), waist circumference or fat mass) OR at least one measure of a cardiometabolic risk factor (e.g. blood pressure, blood lipids, blood glucose). In total we identified 71 cohorts, including four that had begun recruiting participants but were still enrolling (and hence could not contribute to information on numbers of participants). These cohorts included over 570,000 participants at enrolment. Most cohorts with relevant data are in Northern Europe (representing 44% of the cohorts and 74% of participants), followed by Western Europe (24% of cohorts and 17% of participants). Southern Europe had the smallest proportion of participants (21% of cohorts and 3% of participants) and Eastern Europe the smallest number of studies (8% of cohorts and 6% of participants). Birth cohorts in Southern Europe were notable for being of small sample size, often fewer than 500 and rarely more than 1000. In all other areas there were several cohorts that included more than 4,000 participants and in Northern Europe there were 3 cohorts with ~ 100,000 participants and several with greater than 10,000. Few studies include sufficient numbers of participants from minority ethnic groups for precise analyses in these groups to be undertaken. In general the cohorts were relatively young, which means that few currently have information on participants up to adolescence and few have many repeat measurements. Weight and height are commonly measured, whatever the original focus of the study. Thus, BMI (kg/m^2), ponderal index (PI; kg/m^3) or any other measure of adiposity derived from weight and height, tend to be available in the majority of existing European birth cohorts. The availability of other measurements of adiposity or its distribution (e.g. waist, skinfold thicknesses, directly assessed fat mass, visceral fat) is more limited. Blood pressure is commonly measured, but relatively few cohorts have measurements of blood based assays or vascular function/structure measures.

Based on these findings, if having a representative set of birth cohorts from across Europe that together have adequate measurements of adiposity and cardiometabolic risk factors to contribute to aetiological epidemiological studies in the era of rising childhood obesity (and also genetic and omics developments) is seen as a priority, we would recommend that investment is made to continue further follow-up and repeat assessments of adiposity and cardiometabolic traits in existing European birth cohorts and that new birth cohorts in Southern and Eastern Europe are established. In Southern Europe investment in large birth cohorts should be a priority. Consideration should also be given to funding cohorts that include larger numbers of key minority ethnic groups, defined as those groups who form a substantial proportion of the EU population (in terms of numbers) and/or have specific health needs. With respect to obesity and cardiometabolic health this would include those of South Asian and Middle Eastern origin who are at greater risk of obesity, type II diabetes and cardiovascular disease and those of Afro-Caribbean origin who are at greater risk of hypertension, renal and cardiovascular disease. We would recommend that European birth cohorts are funded to obtain repeat measurements of weight, height and blood pressure across infancy, childhood and adolescence (ideally at least annually to age 7 and then every 2 years to 11 and then 2 yearly to age 18/19, so that the periods of rapid growth and development in infancy, adiposity rebound and pubertal growth spurt, can be adequately characterised). In addition we would recommend that cohorts are funded to collect fasting blood glucose, insulin, lipids and liver enzymes at least once in childhood (e.g. between age 5-10) and at least once in adolescence (e.g. 13-19 years). We also recommend that sub-groups of studies or of participants within cohorts have more detailed assessments of adiposity and its distribution and of vascular and heart function and structure.

It is important to note that studies other than birth cohorts (for example cohorts that recruit children after birth/12 months of age, and population register studies) might fill some of the gaps that we have identified. However, assessing the extent to which this is the case is beyond the scope of CHICOS.

1. Background review of the contribution of (European) birth cohorts to adiposity and cardiometabolic health research

1.1. Description of current state of scientific knowledge

Background

Measurement of adiposity and its distribution

An important issue with respect to collecting information on adiposity in European birth cohorts is which measurement(s) to use. Recent evidence in European origin children,(1,2) and adults(3) suggests that commonly used measurements of central adiposity (waist circumference, waist:hip ratio) are no more strongly associated with cardiovascular risk factors and disease events than is BMI. These findings suggest that either central adiposity is no more cardiometabolic toxic than is general adiposity, or that measurements, such as waist circumference or waist to hip ratio, are not able to fully detect the toxic centrally distributed adiposity (for example, fat in the liver may be the key exposure).

In children, in particular, it has been suggested that BMI is a poor marker of total fat mass, but again the limited available evidence (one UK cohort study) suggests similar magnitudes of association of BMI with cardiometabolic risk factors as that seen with DXA determined total body fat.(2) Further research is required to establish whether across a number of childhood populations in Europe associations of BMI, waist and directly assessed fat mass with cardiometabolic risk traits are similar. If they are then this would suggest that for routine surveillance of adiposity in European children measuring weight and height (to calculate BMI/PI), which are relatively easy to measure reliably, is adequate for monitoring adiposity related future cardiometabolic risk. If there are differences between these different measurements in different European populations this needs further exploration to understand what this means for aetiology and surveillance. For example, it is possible that the findings of similar associations of BMI, directly assessed fat mass and waist circumference with cardiometabolic outcomes in European origin children/adolescents,(1,2) may not extend to other ethnic groups resident in European countries. It has been found, for example, that BMI underestimates total body fat of South Asian origin UK children and overestimates that of Black African origin UK children.(4) Whilst detailed assessment of fat distribution (e.g. deposits of fat in the liver) would be perhaps too expensive to undertake in all participants in all European birth cohorts, having these measurements in some cohorts is needed to really understand the aetiology of how adiposity increases adverse cardiometabolic outcomes.

Measurement of cardiometabolic outcomes in children

Greater adiposity is associated with adverse cardiometabolic risk factors, such as higher blood pressure, total cholesterol, low density lipoprotein cholesterol (LDHc), triglycerides, glucose and insulin and lower high density lipoprotein cholesterol (HDLc), in children, as it is in adults.(1, 2) But relatively few birth cohorts appear to have repeat assessments of such measurements, particularly those that require blood sampling from early age. Very few studies have measurements of vascular function and structure, such as arterial stiffness, endothelial function, cardiac mass or left ventricular function, though there is some evidence that changes in these precursors of cardiovascular disease emerge in late childhood/adolescence.(5) Where these data have been collected in European birth cohorts it has been

possible to examine perinatal and early life determinants of different patterns of change with increasing age.(see for example (6), (7), (8),(9))

Using thresholds to define obesity/hypertension etc. in children

Most associations (either of a given risk factor, such as physical activity, with adiposity, or of adiposity with an outcome such as diabetes) are linear (or J-shaped), with graded associations across the whole BMI distribution, rather than a threshold effect, in both adults and children.(1,2,3) However, for assessing public health burden and in clinical practice there is a need to define those at highest risk by categorising individuals as overweight or obese. Overweight and obesity are usually defined on the basis of being above a given threshold of BMI (kg/m^2). Where we are interested in the prevalence of overweight or obesity in children there is an issue of what threshold to use to define overweight/obesity, because at different ages between birth and adulthood (e.g. 18 years) children will have very different weights and heights and a single threshold (as in adulthood) for all ages is clearly not appropriate. Commonly, for children either country specific reference charts are used, with various percentiles used to define overweight (e.g. 80^{th} or 85^{th}) and obesity (e.g. 85^{th}, 90^{th}, 95^{th}) or the international obesity task force (IOTF) thresholds(10) are used. These were developed to reflect the equivalent adult thresholds of $25kg/m^2$ and $30kg/m^2$ that a child would have at a given age and gender if they followed on the same trajectory (growth trend) into adulthood, and provide a means of being able to apply a standard definition to all children in all countries. There is evidence that the definition used affects the prevalence of childhood overweight/obesity in a given population and also associations with risk factors, including with age and gender.(11)

This issue of how to define overweight/obesity extends to other cardiometabolic outcomes. There are a number of cardiovascular and metabolic risk factors/outcomes that can and are increasingly measured in children and adolescence. Most of these are continuously measured traits – blood pressure, glucose, lipids etc. – that in adults are dichotomised for clinical purposes. This dichotomising does not reflect a true threshold effect in any association of these traits with other characteristics, and for many of these there are no clear thresholds for children / adolescents.

Having information on adiposity and cardiometabolic traits across all European birth cohorts (including collections at different ages) could contribute to debates about which thresholds to use for these traits or how best to describe their distributions for comparisons between different geographical areas and over time in the European region in a way that is valid and reproducible.

Repeat measurements

A key value of prospective cohort studies is the ability to repeatedly measure characteristics, such as markers of adiposity and cardiometabolic health. This is important for being able to understand key periods of the lifecourse when interventions to promote best health are likely to be most effective and also for predicting future trend of adverse health outcomes. Recent developments of methods for producing valid trajectories using repeat measurements(12,13) have resulted in greater exploitation of such repeat measurements in research using birth cohorts.(14-20) This work has been used to describe socioeconomic differentials in adiposity from birth to age 10(14), how more rapid increase in BMI between age 8-10 years

is a stronger predictor of adverse cardiometabolic risk factors in adolescence than is change in BMI in any other age period between birth and age 8,(15) and that different cohorts (e.g. from UK, Brazil, Belarus) and populations from different ethnic backgrounds (South Asian versus European) have broadly speaking similar patterns of weight and height growth during infancy and early childhood.(15) They have also been used across several cohorts to show patterns of blood pressure change from early childhood through to old age.(20) This work has largely been completed on individual studies, but it highlights the value of having such measures for policy relevant research in this area.

Outcomes and exposures

Whilst WP2 is concerned with outcomes, it is clear that adiposity/obesity and associated cardiovascular and metabolic traits in children/adolescents are both outcomes and exposures and research in birth cohorts with these characteristics will contribute to policy both when they are considered as outcomes and as exposures and therefore we have not restricted our search only to studies where they are used as outcomes.

1.2. Description of the contribution of (European) birth cohort research to scientific knowledge

Contribution of European birth cohorts

European birth cohorts have contributed to several aspects of scientific knowledge related to childhood adiposity and cardiometabolic risk. **Table 1** shows a list of (selected) publications from European birth cohorts that have used data on adiposity and/or cardiometabolic traits. Mostly these studies have examined perinatal or early infancy/childhood risk factors for later adiposity in childhood or the association of childhood adiposity with cardiometabolic traits.

1.3 Other study designs

Important research relevant to European policy on adiposity and cardiometabolic outcomes in children/adolescents is likely to come from other study types:

1. **National surveys** – for example the Health Survey for England (and equivalents in Scotland and Wales) measure BMI (and increasingly other related characteristics and risk factors e.g. blood pressure and accelerometer assessed physical activity) in children (as well as adults) on an annual basis in a nationally representative sample. These are likely to make important contributions to understanding the national burden and changes with time of overweight/obesity in children (see for example (11)(22)).

2. **Population linkage registers** – the Scandinavian population registers where there is conscription examination data (assessed at mean age 18 in men only) have made important contributions to understanding perinatal and early childhood risk factors for variation in BMI and blood pressure (see for example (23)(24)).

3. **Non-birth/pregnancy cohorts or cross-sectional studies** – There are a number of childhood cross-sectional and cohort studies available in Europe that fall outside our definition of a birth cohort because children were recruited after birth/ 12 months of age. Three of the most detailed of these with respect to contributing to adiposity and cardiometabolic policy relevant research that we are aware of are the European Youth Heart Study (EYHS), Cardiovascular Risk in Young Finns Study and Child Heart and Health Study in England (CHASE). EYHS is a cross-sectional study that recruited children aged 9 and 15 years (to have a group who were prepubertal and a group of adolescents) from four countries – Denmark, Estonia, Norway and Portugal. Weight, height, waist, blood pressure, fasting blood assays and accelerometer assessed physical activity were measured and it has contributed to research exploring risk factors associated with adiposity and cardiometabolic outcomes (for example (25-27)). The Cardiovascular Risk in Young Finns Study is a prospective cohort study that recruited children aged 2-18 years and has followed them up into adulthood and has made major contributions to understanding the contributions of childhood and adult risk factors to, for example, carotid intima media thickness,(28) amongst other research relevant to this area. CHASE is an English a multi-ethnic prospective cohort study that recruited children aged 9-10 years and has a specific research focus on comparing cardiometabolic health between different ethnic groups.(4) There are likely to be several other examples of European childhood/adolescent cross-sectional/cohort studies that do not fit the criteria of 'birth cohort', but that are likely to be important for research relevant to EU policy in this area. However, a detailed review of the existence of such studies and of the data that they have collected is beyond the scope of the CHICOS project.

4. **Randomised controlled trials in children / adolescents to reduce obesity and associated risk factors** – Most trials, to date, of children/adolescents that are concerned with adiposity/cardiometabolic health have been of school based interventions, with reviews suggesting higher quality and some effect in the more recent trials (29). Most studies are in the US, but there are studies beginning in Europe (see for e.g. (30)) that will yield results on the effectiveness of interventions to reduce the prevalence of childhood overweight/obesity. There are also trials of treatment for children with obesity and economic evaluations of these (31). Again a detailed review of all such trials in Europe are beyond the scope of CHICOS but should be borne in mind by EU policy makers when considering research in this area.

It is likely that these other study designs make as much, if not more, contribution to policy relevant research in the area of obesity, cardiovascular and metabolic outcomes in Europe and this should not be forgotten. However, CHICOS has to limit itself to the remit of birth cohorts. Two key advantages of birth cohorts that these other studies are less able to contribute to are (a) exploring early life (developmental origins) of variation in adiposity and cardiometabolic outcomes and (b) determining lifecourse trajectories of adiposity and cardiometabolic traits (i.e. using repeat measurements) from birth to adulthood.

1.4 Contribution of birth cohort collaborations

With the exception of genetic collaborations, there are few birth cohort collaborations for addressing research questions concerned with childhood adiposity or cardiometabolic health. In part this reflects that fact that the outcomes are relatively common and/or measured on a continuous scale and therefore

individual studies tend to have adequate statistical power to address many research questions. However, it is becoming clear that for example, the benefits of cross-cohort comparisons and importance of replication of findings mean that even outside of genetic association studies, greater collaboration in this area would have important benefits. Furthermore, evaluating the current published literature it is evident that not all outcomes that are measured are used widely. This may reflect current work in progress that is due to be published, reflect the paucity of measurements or the possibility that resources and funding is not available to undertake the analysis. Collaborative work could be a method of ensuring greater use of data such as adiposity and cardiometabolic outcomes. Moreover, collaborative programmes may ensure outcomes, such as BMI and blood pressure, measured in cohorts that have been established for specific research priorities that do not focus on these outcomes (e.g. environmental exposures, asthma and allergies) are utilised efficiently to address additional research questions, such as those related to adiposity and cardiometabolic health.

2 Identification and description of contemporary European birth cohorts with adiposity or cardiometabolic data

2.1 Aim

The aim of this project was to identify all European birth cohort studies that had some information on either adiposity or cardiometabolic risk factors.

2.2 Identification of cohorts

There are many pregnancy/birth cohorts in Europe that are collecting information on some measure of adiposity and associated cardiometabolic traits. Identification of cohorts included in this report has been done following these criteria:

- Birth/pregnancy mother-child cohorts, defined as recruitment in pregnancy, at birth or in the first year of life if there was access to birth data, and either with established follow-up or funds to complete follow-up (at least one assessment of the child after birth)
- Population-based
- Start year: 1990 onwards
- Located in Europe

Relevant cohorts have been identified through different sources:

1) the ENRIECO inventory (www.birthcohortsenrieco.net);

2) Birthcohorts.net webpage (www.birthcohorts.net);

3) cohort websites;

4) literature searches.

The ENRIECO project (www.enrieco.org) performed an inventory of all European birth cohort studies that have collected information on environmental exposures (www.birthcohortsenrieco.net). However, that registry also provide information on some relevant outcomes for this working group (e.g. information on BMI) as well as providing a relevant initial contact list of European birth cohorts that we could use to obtain additional information from study Principal Investigators (PIs). Birthcohorts.net webpage (www.birthcohorts.net) has also been used as a source of relevant birth cohorts; this is described in detail in work package 1. Other studies were identified through our literature search:

We performed a series of literature searches in Medline. Relevant publications from (1966) to (December 2011) were identified by using the following search:

1. [Birth OR Pregnan*] AND [BMI OR waist OR fat mass OR percentage fat OR skinfold OR adiposity OR fat OR obesity].

2. [Birth OR Pregnan*] AND [blood pressure OR systolic OR diastolic].

3. [Birth OR Pregnan*] AND [glucose OR glycaemia OR HbA1C OR glycated haemoglobin OR diabetes].

4. [Birth OR Pregnan*] AND insulin.

5. [Birth OR Pregnan*] AND [cholesterol OR lipid or HDLc OR LDLc or high density lipoprotein cholesterol OR low density lipoprotein cholesterol OR triglycerides].

6. [Birth OR Pregnan*] AND [pulse wave velocity OR PWV OR arterial distension OR arterial stiffness OR carotid intima media thickness].

7. ['NAME of COHORT' (i.e. where we knew a study name that we thought was a birth cohort)] AND [BMI OR waist OR fat mass OR percentage fat OR skinfold OR adiposity OR fat OR obesity].

8. ['NAME of COHORT' (i.e. where we knew a study name that we thought was a birth cohort)] AND [blood pressure OR systolic OR diastolic].

9. ['NAME of COHORT' (i.e. where we knew a study name that we thought was a birth cohort)] AND [glucose OR glycaemia OR HbA1C OR glycated haemoglobin OR diabetes].

10. ['NAME of COHORT' (i.e. where we knew a study name that we thought was a birth cohort)] AND insulin.

11. ['NAME of COHORT' (i.e. where we knew a study name that we thought was a birth cohort)] AND [cholesterol OR lipid or HDLc OR LDLc or high density lipoprotein cholesterol OR low density lipoprotein cholesterol OR triglycerides].

12. ['NAME of COHORT' (i.e. where we knew a study name that we thought was a birth cohort)] AND [pulse wave velocity OR PWV OR arterial distension OR arterial stiffness OR carotid intima media thickness].

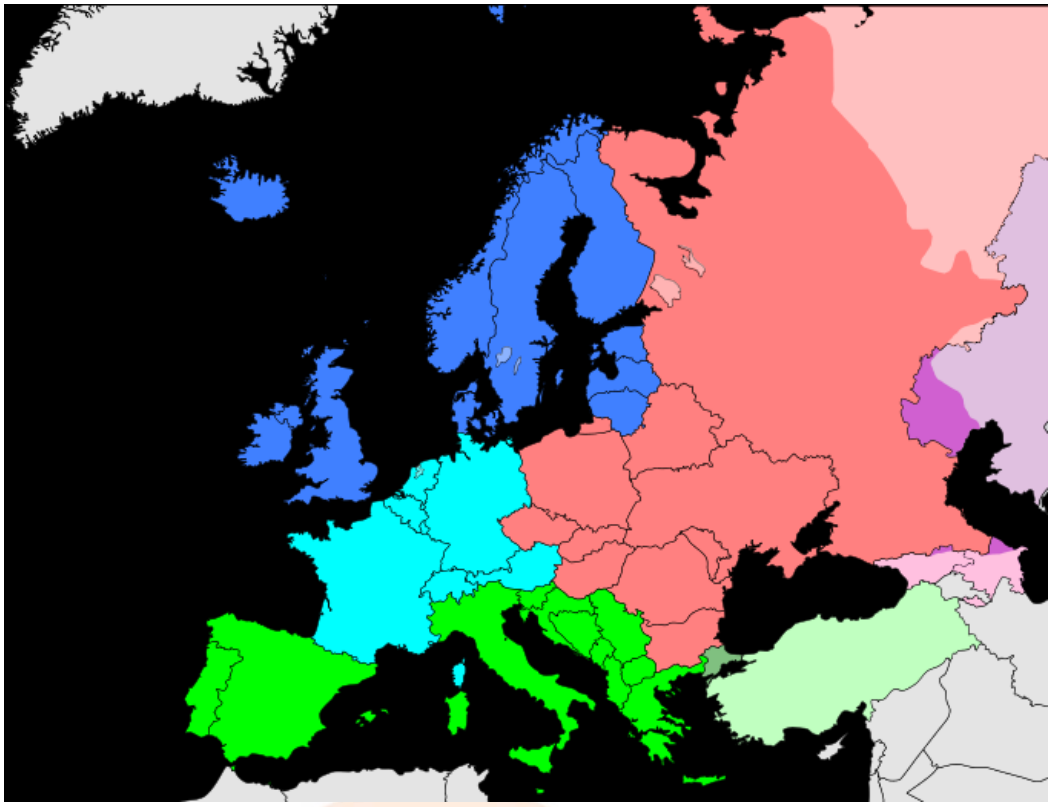
We also tried to contact every cohort PI or manager to ascertain whether or not the study was relevant to the aims of this project.

The last time that the above databases were reviewed and the literature search completed was December 2011.

We defined cohorts as having relevance to adiposity / cardiometabolic research if they **had at least one measure of adiposity or at least one cardiometabolic trait** (assessed at any age).

For the purposes of describing which region of Europe the birth cohorts that we have identified come from we have used the WHO definitions as show in **Figure 1**.

Figure 1: Definition of geographical areas of Northern (coloured royal blue), Western (coloured turquoise), Southern (coloured lime green) and Eastern (coloured dark pink).



Northern Europe includes: Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden and the UK.

Western Europe includes: Andorra, Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Netherlands and Switzerland.

Southern Europe includes: Albania, Bosnia-Herzegovina, Croatia, Greece, Italy, Kosova, Macedonia, Malta, Montenegro, Portugal, San Marino, Serbia, Slovenia and Spain.

Eastern Europe includes: Belarus, Bulgaria, Czech Republic, Hungary, Moldova, Poland, Romania, Russia, Slovakia and Ukraine.

2.3 Results

Based on these criteria together with those listed above we have identified **72 European birth cohorts that are potentially of relevance to adiposity/cardiometabolic research**.

Characteristics of each individual cohort are summarised in **Table 2** and summary characteristics across all of these 71 cohorts are presented in **Table 3**.

These cohorts included 570,387 participants at enrolment (4 studies are still enrolling participants and have therefore not contributed to these numbers). Most cohorts with relevant data are in Northern Europe (representing 44% of the cohorts and 74% of participants), followed by Western Europe (24% of cohorts and 17% of participants). Southern Europe had the smallest proportion of participants (21% of cohorts and 3% of participants) and Eastern Europe the smallest number of studies (8% of cohorts and 6% of participants). Two European birth cohorts are multicenter, with participants from two or more European countries (3% of cohorts; 1% of participants). Birth cohorts in Southern Europe were notable for being of small sample size, often fewer than 500 and rarely more than 1,000. In all other areas there were several cohorts that included more than 4,000 participants and in Northern Europe there were 3 cohorts with ~

100,000 participants and several with greater than 10,000. Few studies include sufficient numbers of participants from minority ethnic groups for precise analyses in these groups to be undertaken. In general the cohorts were relatively young, which means that few currently have information on participants up to adolescence and few have many repeat measurements. Weight and height are commonly measured, whatever the original focus of the study. Thus, BMI, PI or any other measure of adiposity derived from weight and height, tend to be available in the majority of existing European birth cohorts. The availability of other measurements of adiposity or its distribution (e.g. waist, skinfold thicknesses, directly assessed fat mass, visceral fat) is more limited. Blood pressure is commonly measured, but relatively few cohorts have measurements of blood based assays or vascular function/structure measures.

2.4 Strengths and limitations of European birth cohorts in relation to their contribution to policy relevant research concerned with adiposity and cardiometabolic outcomes

Strengths

- We have identified 71 birth cohorts that have at least one measure of adiposity or a cardiometabolic risk factor. This means that there exist a reasonable number of the birth cohorts in Europe currently that can make some contribution to research in this area.
- Approximately half of the cohorts that we have identified have weight and height (hence PI/BMI) and also at least one cardiometabolic measurements (most commonly blood pressure, but with ~ one-third also having total cholesterol/other lipids) and so can make some contribution to examining the relationship between childhood adiposity and adverse cardiometabolic risk profiles.
- A minority have increasingly sophisticated measurements of cardiac and arterial development (including in utero from ultrasound scans) and e.g. assessment of liver fat, which are likely to make important contributions to aetiological / mechanistic insights in the future, and which demonstrate the potential for adding such measurements to other birth cohorts.
- Through we limited the search to cohorts that began recruitment in 1990 or more recently (i.e. in the last ~ 20 years at the start of this project), it is notable that most of the European birth cohorts with adiposity or some cardiometabolic traits are young, commonly only being initiated in the last 5-10 years. This has the strength that there is potential for funders to determine what measurements are collected in these cohorts whilst participants are still in childhood and could standardise some data collection across cohorts of a similar age. It also results in some limitations (see below)

Limitations

- The relatively young age of many cohorts means that few have assessments of adiposity in mid/late childhood, which is the age at which greater adiposity begins to be robustly related to future cardiovascular risk.(21) The young age of most cohorts also means that few have repeat measurements of adiposity and cardiometabolic traits and few could currently explore prospective associations. Thus, currently there are limits to what these relatively young European birth cohorts can contribute to policy relevant research around adiposity and cardiometabolic health. If future

funding is not secured for these cohorts their potential to contribute to these research questions in the future will clearly be compromised.

- Few studies have assessed cardiometabolic traits beyond blood pressure. In general few have blood based measurements and those that do have tended to assess total cholesterol only. There are increasing concerns that the obesity epidemic is leading to increased risk of type 2 diabetes in children and adolescents, but without systematic measurements of fasting glucose and insulin in European birth cohorts it is impossible to determine the extent of this problem in European children. There are also increasing concerns about non-alcoholic fatty liver disease (NAFLD) emerging in children and adolescents as a result of the obesity epidemic,(32) but since only one of the European cohorts that we know of has measurements of liver enzymes and ultrasound scan assessment of liver fat, it is impossible to assess the extent of this problem across children in European.
- Some cohorts have used self/parent-reported weight and height and it is possible that selective response bias will affect these studies – i.e. the likelihood of more overweight/obese children to have their weight underreported and shorter children to have their height exaggerated in self report.
- Key risk factors such as physical activity are also largely based on self/parent report in questionnaires (see work package 3 report). Evidence from the UK ALSPAC cohort suggests that this can result in associations e.g. of physical activity with adiposity that are weaker than the true associations when physical activity is assessed by movement sensors.(33)
- Baseline response varies with some (commonly regional rather than national cohorts – e.g. ALSPAC, Generation-R and Born in Bradford) having high responses (>70%) and little evidence of key problems with generalisablity to the source population at baseline.(34-36) However, these regional cohorts may not be generalisable to the whole country from which they originate. Large national birth cohorts, such as the Danish and Norwegian National birth cohorts have poorer baseline response but cover the whole of the source country.(37,38) Thus, either through their regional design or relatively poor response few of the cohorts will necessarily represent the country population from which they originate. No single cohort is likely to represent the whole of Europe. Where the aim is to use the cohorts to provide prevalence estimates (for example of the proportion of children who are overweight or obese) and geographical or time differences in these, this lack of generalisability could result in bias. Such prevalence estimates may be better obtained from National one off surveys (though even these may have systematic response bias). However, associations, for example of adiposity with cardiometabolic risk, or of perinatal risk factors with cardiometabolic outcomes, are usually generalisable across very broad populations even if these are not represented in the cohort(s) examining the association. This is because in general epidemiological associations are consistent across different populations (e.g. high cholesterol and smoking have been shown to increase cardiovascular risk in many and diverse populations). Nonetheless the mixture of birth cohorts in Europe from different countries and with different designs (modest regional cohorts with good baseline response to very large national cohorts with poorer response) is a further reason for cross-cohort comparisons to confirm that associations in children are similar in these different studies, and if not to explore why this might be the case.

- The relative lack of birth cohorts in Eastern Europe and of participants in birth cohorts in Southern Europe means that comparing distributions of adiposity and cardiometabolic traits across the whole of Europe and understanding whether the epidemiology varies across the whole of Europe is limited. Evidence from one Eastern European cohort suggests that there are key regional (rural versus urban) and socioeconomic differences in childhood overweight/obesity,(39) highlighting the importance of further studies in geographical areas that are currently underrepresented.
- Few studies have repeat measurements of adiposity and cariometabolic traits which means they currently have limited ability to examine how changes in adiposity relates to changes in cardiometabolic health or which risk factors are associated with health benefiting changes in adiposity or cardiometabolic traits and which are related adverse changes in these outcomes.

2.5 Identification of gaps

A number of gaps have been highlighted from the completion of this work.

1. There are relatively **few studies or participants from Southern and Easter European countries**.
2. **Few studies have sufficiently large numbers of participants from key minority ethnic groups** in Europe to examine differences in distributions of adiposity and cardiometabolic traits between ethnic groups or explore whether important associations differ by ethnicity.
3. The majority of studies that have been identified are **relatively young** (less than 10 years) with a very small number of birth cohorts in adolescence.
4. Generally studies have measurements of BMI and blood pressure, but **few have more detailed assessments of adiposity or its distribution, of blood based cardiometabolic assays or of vascular function** beyond blood pressure.
5. **Few studies have repeat measurements** of adiposity or cardiometabolic traits across infancy and childhood.

Points 4 and 5 above may reflect the relatively young age of many European birth cohorts, but unless these cohorts continue to receive funding for further data collection these gaps will remain.

3. Case Study

In order to demonstrate the potential of cross-cohort collaboration between European birth cohorts, we have undertaken a case study to estimate the associations of childhood adiposity with cardiometabolic outcomes and to determine whether magnitudes of association differ between BMI, waist (an indicator of centrally distributed adiposity) and directly assessed fat mass. This topic has important policy implications – e.g. to address questions about whether national surveillance of childhood adiposity/obesity should continue to use BMI (as used currently in the UK) or add or replace BMI with a measure of central adiposity (e.g. waist) that would be feasible to do in surveillance of all school children. This case study has been conducted alongside our search for relevant studies for this work package as a whole (as reported above) and has also been central to our effort of identify which European cohorts have which measures of adiposity and cardiometabolic outcomes.

Status report

Inclusion criteria and identification of studies

Our initial inclusion criteria for this case-study were quite restrictive (assessment of adiposity at age 7 – years or older as associations with adult risk only emerge from mid-childhood (21)); having at least two comparative measurements of adiposity; having a cardiometabolic trait (any) assessed at a later age – so that associations would be prospective). Of the 41 cohorts initially examined (from ENRIECO only) we found that just two had relevant data.

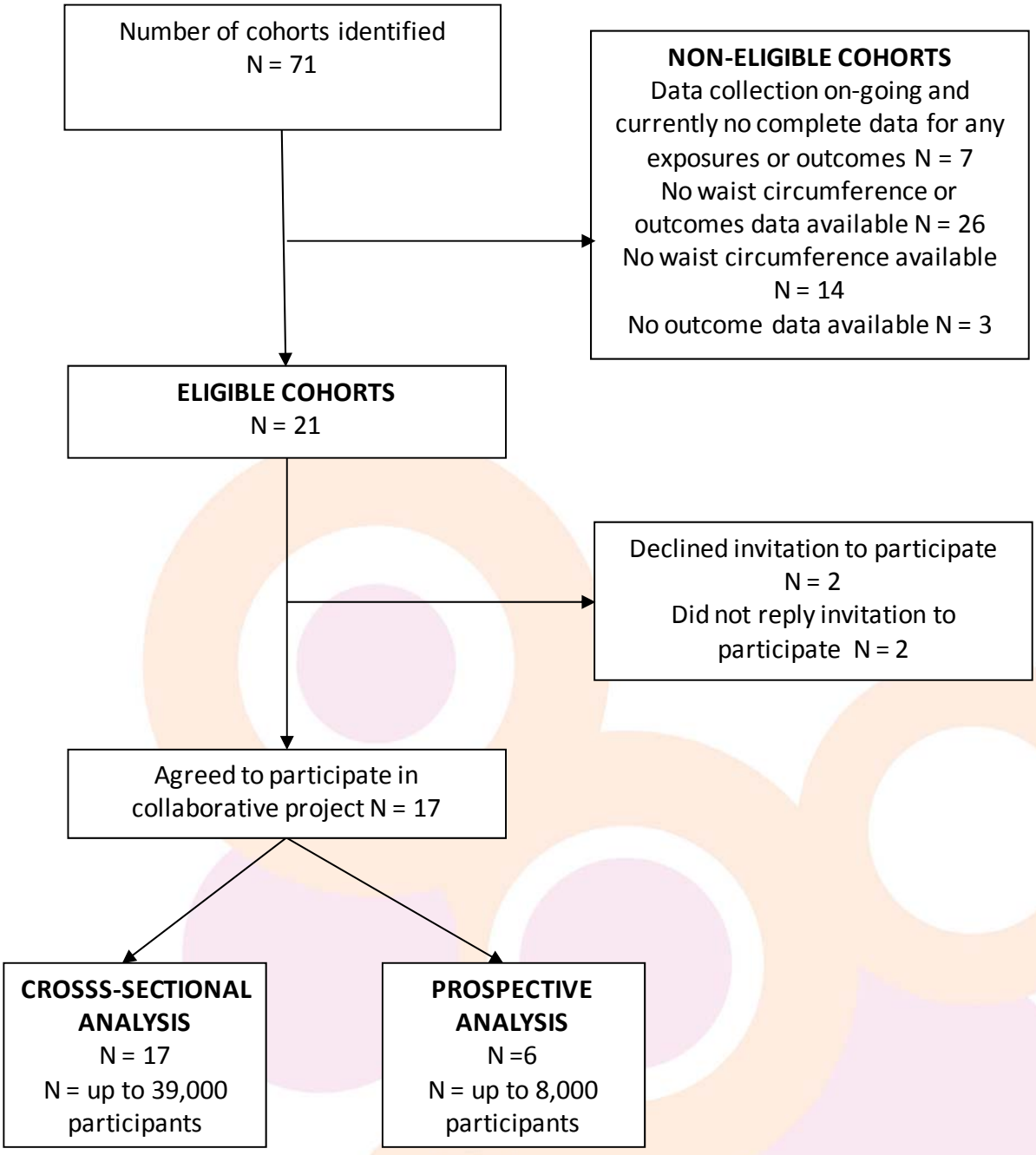
This initial work made us realise that we need to widen our inclusion criteria in order to be able to examine this question within European birth cohorts. Our inclusion criteria were therefore changed and are

- European birth cohort (defined as above)
- At least one measure of **all** three of weight, height and waist circumference assessed at any age in childhood (between 12 months to 18 years) **and** a measure of at least one cardiometabolic risk factor (systolic blood pressure [SBP], diastolic blood pressure [DBP], total cholesterol, high density lipoprotein cholesterol [HDLc], low density lipoprotein cholesterol [LDLc], triglycerides, glucose or insulin), measured either at the same time and/or after the assessment of weight, height and waist circumference.

These criteria mean that we include prospective and cross-sectional studies, but we *a priori* decided these would be analysed separately and results compared between the two study designs. It also meant that we examined associations at any age in childhood/adolescence. A priori we planned to examine whether age contributed to any observed heterogeneity (differences) between individual cohorts in any associations.

Figure 2 illustrates the eligible cohorts and those that have participated in the case study from the 71 discussed above and summarised in Table 2.

Figure 2: Participation flow diagram for the case study for obesity, vascular and metabolic health



Data harmonisation and analysis

To aid in the process of data harmonisation and analysis a standardised analysis protocol was developed which collects methodological data in a standard way from all cohorts and applies an identical analytical approach to all cohorts. Cohorts who wished to participate are able to either send anatomised datasets or complete the analysis in-house and send results in standardised tables to the Bristol team. To further facilitate this standardised approach, a Stata do-file has been made available to cohorts completing data analysis in-house; this is written so that the code could also be easily modified for use in other statistical packages.

Analyses have now been completed on all of the 17 eligible cohorts that have agreed to participate and we are currently pooling results from these studies and exploring sources of heterogeneity .

Paper writing

A draft of the paper has started to be written and we anticipate circulating to all co-authors by end of May 2013 and submitting the paper in June 2013.

4. Recommendations:

Main strategic recommendations for adiposity / cardiometabolic research:

- If the EU wishes to be able to assess differences in distributions of adiposity and cardiometabolic traits in children across Europe and have birth cohorts across the whole region that can examine aetiology and prediction there is a need to continue to support existing cohorts so that relevant repeat assessments of adiposity and cardiometabolic risk factors can be obtained.
- In terms of study and participant numbers, East and South Europe are under represented and support for new studies in these areas should be considered. Studies that oversample different minority ethnic groups are also necessary to further understand differences between ethnic groups in Europe with respect to the distribution of adiposity, how it is best measured and whether different ethnic groups already have different cardiometabolic risk profiles in childhood as they do in adulthood (e.g. with more risk of insulin resistance and type 2 diabetes in those of south Asian origin and more risk of hypertension and renal disease in those of Afro-Caribbean origin).
- Few studies have detailed measurements of adiposity beyond BMI or waist and even where studies do have these measurements they rarely have them assessed repeatedly across infancy and childhood. To answer questions about how best to assess adiposity and its distribution and how these might impact future health the collection of more detailed measurements of adiposity is required. At a minimum it would be valuable for all cohorts to have BMI and waist measured in all participants on repeat occasions between birth and adolescence (if possible every 6-12 months to age 4-5 and then every 2 years). It would be useful to have subgroups within cohorts that have much more detailed assessments including MRI scan assessments of subcutaneous
- With increasing concerns about the adverse effects of the childhood obesity epidemic it would be valuable to have cardiometabolic traits beyond blood pressure collected in more cohorts. In particular, it would be useful for all cohorts to have at least one assessment of fasting glucose, insulin, lipids and

liver enzymes in childhood and one assessment of these in adolescence. More detailed and costly measurements of cardiovascular structure and function should be considered for sub-groups of participants.

Recommendations for collaborative research across European birth cohorts in general:

- Collaborative research projects need adequate funding over and above the funding available for each individual study. Exploring whether relevant data exist, where it does whether it is sufficiently similar for collaboration, agreeing standardised analysis protocols, pulling out datasets from each study, analysing these and then combining results appropriately is not trivial and requires adequate funds.
- To ensure collaborative projects run smoothly an early telephone conference or face to face meeting that brings together all relevant researchers may be necessary to ensure commitment to the project. At this initial contact identification of a named researcher within each cohort that the co-ordinating team can primarily deal with is essential.
- Not all studies have clear information about their collaborative policy on their website. Having this information makes establishing a collaboration much more efficient.

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Table 1. Examples of published work on obesity, cardiovascular or metabolic outcomes from European birth cohorts

Cohort	*Author, Year*	*N children*	*Age exposure*	*Main exposure(s) measured*	*Age outcome*	*Main outcome(s) measured*	*Research objective(s)*
ABCD study	de Hong et al 2011	3156	Birth to 2	Pre-natal, birth outcomes and post-natal factors	4	BMI	Ethinis disparites of overwieght at early age
ABIS (All Babies in SouthEast Sweden)	Huus et al 2007	16058	Childbirth to 5	BMI (repeated) and parental reposted qquestionnaires		BMI	Is high BMI at early age predictive of high BMI in later childhood and the risk factors associated with this
ALSPAC	Lawlor, et al 2010		9-10	BMI, DXA fat mass, Waist	15-16	BP, lipids, glucose, insulin	Is childhood adiposity prospectively associated with CVD risk factors? Does change in adiposity with age relate to these outcomes? Is BMI as strongly associated with outcomes as WC or fat mass?
DNBC	Ajslev, et al 2011	28,354	Pregnancy/ birth/infancy	Maternal BMI, mode delivery, use antibiotics in infancy	7	BMI	To investigate whether delivery mode, maternal pre-pregnancy BMI and early exposure to antibiotics (<6 months of age) influence child's risk of overweight at age 7 years
Generation R	de Jonge et al 2011	974	1, 5, 6 and 24 months	BMI, subcutaneous fat mass (skinfold measures) and blod pressure	2	Left ventricular structure	The relationship between growth and obesity with cardiac structutures
Generation R	de Jonge, et al 2011	974	1.5, 6 and 24 months	BMI, weight, height and subcutaneious fat (and change in these)	1.5, 6 and 24 months	Left atrial diameter, left ventricular diastolic diameter, left ventricular mass, aortic root diameter, fractional shortening and BP	What is the association of obesity and infancy growth with cardiac structure in infancy and at age 2?

Cohort	*Author, Year*	*N children*	*Age exposure*	*Main exposure(s) measured*	*Age outcome*	*Main outcome(s) measured*	*Research objective(s)*
GIUNIPlus and LISAPlus	Thiering et al 2011	470	Prenatal and postnatal	Environmental tobacco smoke exposure from inutero to 10	10	Fasting insulin and glucose	The association between environmental smoke exposure and insuin resistance
INMA	Mendez et al 2011	518	Prenatal	Organochloride compund	6 and 14 months	BMI	Prenatl exposure to organochloride xompunds and rapid weight gain in early life and overweight in later infancy
KOALA	Gubbels et al 2010	2396	7 months, 1 and 3	Child-care use	1 and 2	BMI	Child care use with obesity and overweight
KOALA	Gubbels et al 2011	1819-2026	5	Parental practices, dietary intake and physical activity	5 and 7	BMI	Are parenal behavious, energy intake and physical activity prospectively association with BMI
MoBa	Garthus-Niegel, et al. 2010	10,860	18 and 36 months	Behavioural problems assessed by parent completed shortened version of child behaviour checklist	18 and 36 months	BMI	To examine whether child behavior problems and body mass index are associated in toddlers and whether overweight is a risk for behavior problems or vice versa
PIAMA	Wijga et al 2010	3693	5-7	Physical activity, dietary intake, breastfeeding	8	BMI	To examine the prospective associations between physical activity dietary habits and BMI in childhood
Southampton Womans Survey	Cole et al 2011	530	6	Fat mass (DEXA)	6	Bone mass	To examine the relationship between fat mass and bone density and bone mass in childhood.

Table 2. General description of European birth cohorts with data on adiposity and/or cardiometabolic traits

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
Aarhus Birth cohort	Denmark	Largely white European	Pregnancy 1990-ongoing	100,000 infants	0 19	PI BMI	19	BP, HDLc, LDLc	SI Cohort inventories
ABCD	Netherlands	Mixed ethnicity	Pregnancy 2003-2004	8, 266 pregnant women 7,982 infants	0,several repeats up to 4, 5	PI/BMI, waist, bioelectrical impedance	5	BP, cholesterol, HDLc, LDLc, triglycerides, glucose, C-peptides	SI Pu
ABIS	Sweden	Largely white European	Birth 1997-1999	17,000 mother-infant pairs	0, 1, 3, 5, 8, 11	PI/BMI, waist	7-8, 10-11	Glucose C-peptide	SI Cohort inventories
ALSPAC	United Kingdom	Largely white European	Pregnancy 1991-1992	14,541 pregnant women 14,062 infants	0, several repeats to age 5, 7, 9, 10, 11, 15, 17	PI/BMI, waist, bioelectrical impedance, DEXA assessed fat mass	7, 9, 11, 15, 17	BP, cholesterol, HDLc, LDLc, triglycerides, ApoA1, ApoB, glucose, insulin, CRP, IL6, adiponectin, leptin, apolipoproteins, liver enzymes, endothelial function, arterial stiffness, CIMT, PWV, dynamic BP, 24-hour BP, heart USS, liver USS	SI

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
BAMSE	Sweden	Largely white European	Birth 1994-1996	4,089 infants	0, 1, 2, 4, 6, 7, 8, 12, 16	PI/BMI	16	BP only	Cohort inventories
BASELINE	Ireland	Largely white European	Pregnancy 2008-2011	? pregnant women 2,185 infants	0, 3 and 6 months, 1, 2	PI/BMI Percentage fat mass	2	BP only	Cohort inventories Pu
Babycare	Germany 1999-ongoing	Largely white European	Pregnancy 1999-ongoing	25, 000 mothers and infants	0	Birthweight, weight	None	None	SI
BILD	Switzerland	Largely white European	Pregnancy 1999-2017	400 pregnant women and 400 infants	0, 6, 12	PI/BMI	6	BP only	Pu Cohort inventories
Born in Bradford	United Kingdom	Largely biethnic-white European and Pakistani	Pregnancy 2007-2010	13,776 pregnant women 13,818 infant	0, 1, 2, 3	PI/BMI, skinfold thickness	None	None	SI Pu Cohort inventories
C. Faroes 3	Denmark	Largely white European	Birth 1998-2000	656 mother-infant pairs	0, 5, 7	PI/BMI, waist	5, 7	BP only	SI Cohort inventories
C. Faroes 5	Denmark	Largely white European	Birth 2007-2009	491 mother-infant pairs	0, 1	PI/ BMI	None	None	SI Cohort inventories
CO.N.ER	Italy	Largely white European	Pregnancy 2004-2005	651 pregnant women 654 infants	0, 1, 2, 3	PI/ BMI	None	None	Cohort inventories
Copenhagen Child Cohort	Denmark	Largely white European	Birth 2000	6,090 infants	0, 1, 11	PI/BMI	11 (data still being collected)	BP (data still being collected)	SI Pu Cohort inventories

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
Children in Care – Danish study	Denmark	Largely white European	Birth 1995	576 infants	7-8	BMI	None	None	SI
CHOP Study	Belgium, Germany, Italy, Poland and Spain	Largely white European	Birth 2002-2004	1,678 infants	0, 3 and 6 months, 1, 2, 3, 4, 5, 6, 7, 8, 11	PI/BMI Other anthropometric measures	3, 4, 5, 6, 7, 8, 11	BP, cholesterol, HDLc, LDLc, tryglicerides, insulin, glucose	Cohort inventories Pu
Czech Early Childhood Health	Czech Republic	Largely white European	Pregnancy 1994-1998	7,522 pregnant women 7,577 infants	0	Birth weight	None	None	Cohort inventories
DARC	Denmark	Largely white European	Birth 1998-1999	556 mothers 562 infants	0	Birth weight	Unknown	Unknown	Pu
DNBC	Denmark	Largely white European	Pregnancy 1996-2002	100,418 pregnant women 95,000 infants	0, 7, 11	PI/ BMI, waist	None	None	SI Cohort inventories
Duisburg	Germany	Largely white European	Pregnancy 1999-2002	234 mother-infant pairs	0, , several repeats to age 2, 4, 8, 6, 7, 9	BMI, skinfold thickness	None	None	SI Cohort inventories
EDEN	France	Largely white European	Pregnancy 2003-2006	2,002 pregnant women 1,900 infants	0, 1,2,4,5,8	PI/BMI, waist, skinfold thickness, bioelectrical impedance	3, 5	BP Triglycerides Insulin Glucose	Pu SI Cohort inventories
ELFE	France	Largely white European	Birth 2011	20,000 infants	0, 1	PI/BMI	None	None	Cohort inventories

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
Environment for Healthy Living	United Kingdom	Largely white European	Pregnancy 2010-2013	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Still enrolling	SI Cohort inventories
Families and Children of Ukraine	Ukraine	Largely white European	Pregnancy 1992-1996	4,510 pregnant women 4,510 infants	0 and annually until 16	PI/BMI	3,7	BP only	Cohort inventories
FLEHS	Belgium	Largely white European	Pregnancy 2002-2006	1,186 mothers and 1,196 infant	0, 3	PI/BMI	Unknown	Unknown	Pu
GASPII	Italy	Largely white European	Birth 2003-2004	708 mothers; 693 offspring	0, 15 months, 4, 7 (currently in progress)	PI/BMI, waist, hip (currently in progress)	7 (currently in progress)	BP only (currently in progress)	Cohort inventories SI
Gateshead Millennium Study	United Kingdom	Largely white European	Birth 1999-2000	1,011 mothers 1,029 infants	0, several repeats to age 1, 7, 9, 12	Birthweight BMI, waist, bioelectrical impedance, skinfold thickness	None	None	Cohort inventories
GECKO Drenthe cohort	Netherlands	Largely white European	Pregnancy 2006-2007	2,997 infants	0, several repeats up to 2,	PI/BMI, waist, bioelectrical impedance	9 months, 2 years	HbA1c, BP	PI Cohort inventories Pu

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
Generation R	Netherlands	Mixed ethnicity	Pregnancy 2002-2006	9,778 pregnant women 9,745 infants	0, 2, 5	PI/ BMI, DEXA assessed fat mass	2, 5	Left atrial diameter, left ventricular diastolic diameter, left ventricular mass, aortic root diameter, fractional shortening, BP	SI Pu Cohort inventories
Generation XXI	Portugal	Largely white European	Pregnancy 2005-2006	8,495 pregnant women 8,647 infants	Several repeat measures of weight and height 0-4, 5	BMI, waist, bioelectrical impedance	5	BP, cholesterol, HDLc, LDLc, triglycerides, glucose, insulin	SI Cohort inventories
GINIplus	Germany	Largely white European	Birth 1995-1998	5,991 infants	0, several repeat measures of weight and height upto 2, 3, 6,10,15	PI/BMI	6,10,15	BP, cholesterol	SI Pu Cohort inventories
Growing Up in Ireland	Ireland	Largely white European	9 months 2001	11,000 infants	0, 9 months, 3	Birthweight, BMI	None	None	Website
Growing Up in Scotland	Scotland	Mixed ethnicity	10 months 2005	5,000 infants	0, 1, 2, 3, 4, 5	PI/BMI	None	None	Website
HUMIS	Norway	Largely white European	Birth 2003-2009	2,500 mother-infant pairs	0,1,2, 8	PI/BMI	None	None	Cohort inventories

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
INMA Asturias	Spain	Largely white European	Pregnancy 2004-2007	494 pregnant women 485 infants	0, 14 months, 4	PI/BMI, waist	4	BP, cholesterol, HDLc, LDLc, triglycerides, glucose	SI Cohort inventories Website
INMA Gipuzkoa	Spain	Largely white European	Pregnancy 2006-2008	638 pregnant women 612 infants	0, 14 months, 4	PI/BMI	None	None	SI
INMA Granada	Spain	Largely white European	Birth 2000-2002	668 pregnant women 668 infants	0, 4, 9-10	PI/BMI, waist, skinfolds, bioelectrical impedance	None	None	SI
INMA Menorca	Spain	Largely white European	Pregnancy 1997-1998	530 pregnant women 492 infants	0, 4-5, 6-7, 11-12	PI/BMI, waist, bioelectrical impedance	11-12	BP only	SI Cohort inventories Website
INMA Ribera Ebre	Spain	Largely white European	Pregnancy 1997-1999	102 pregnant women 102 infants	0, 4	BMI, bioelectrical impedance	None	None	SI Website
INMA Sabadell	Spain	Largely white European	Pregnancy 2004-2006	657 pregnant women 622 infants	0, 14 months, 4	PI/BMI, waist	4	BP, cholesterol (cholesterol assays ongoing)	SI Cohort inventories Website
INMA Valencia	Spain	Largely white European	Pregnancy 2003-2005	827 pregnant women 787 infants	0, 14 months, 4-5	PI/BMI, waist bioelectrical impedance	4-5	BP, cholesterol, HDLc, LDLc, triglycerides, glucose	SI Cohort inventories Website
INUENDO	Sweden, Greenland, Poland, Ukraine	Largely white European	Pregnancy 2002-2004	2,269 pregnant women 1322 infants	0, 6-7	PI/BMI	None	None	SI Cohort inventories

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
IVAAQ	Greenland	Greenland Inuit	Pregnancy 1999-2005	220 infants	0	PI/BMI	Unknown	Unknown	Pu
KANC	Lithuania	Largely white European	Pregnancy 2007-2009	4,329 pregnant women 4,405 infants	0	PI	None	None	Cohort inventories Website
KOALA	Netherlands	Largely white European	Pregnancy 2000-2002	2,834 pregnant women 2,834 infants	0, 5, 6,7	PI/BMI, waist and skinfold thickness	2, 7	BP, cholesterol, HDLc, LDLc, triglycerides	SI Pu
Krakow cohort	Poland	Largely white European	Pregnancy 2000-2003	528 pregnant women 505 infants	0, 3, 4,,5, ,6,7, 8, 9	PI/BMI	8, 9	BP only	SI Cohort inventories
Leicester Respiratory Cohort Study	United Kingdom	Largely biethnic White European or South Asian	Birth or infancy (up to age 4); N=6060 (58.6%) recruited in first year of life 1998	10,350 infants	0, 1 ,8, 18, 38 months 9-13	BMI, waist	9-13	BP only	SI Pu Cohort inventories
LIFE child cohort	Germany	Still enrolling; likely largely white European	Pregnancy 2011-2014	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Cohort inventories

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
Lifeways Cross Generation Cohort Study	Ireland	Largely white European	Pregnancy 2001-2003	1,061 pregnant women 1,074 offspring	0, 5, 8	Birthweight, BMI, waist circumference	8 (data still being collected)	BP, cholesterol, HDLc, LDLc, triglycerides, glucose, insulin (data still being collected)	SI Cohort inventories
LISAPlus	Germany	Largely white European	Birth 1997-1998	3,097 infants	0, Several repeats up to age 2, 6, 10, 15	PI/BMI	6, 10, 15	BP, cholesterol, HDLc, glucose, insulin	SI Cohort inventories Pu
LUKAS	Finland	Largely white European	Pregnancy 2002-2005	442 mother-infant pairs	0, 1, 4, 5, 6	PI/BMI	4	Cholesterol and HDLc	SI Cohort inventories
MAAS	United Kingdom	Largely white European	Pregnancy 1995-1997	1,211 pregnant women 1,184 offspring	0, 3, 5, 8, 11	BMI, bioelectrical impedance	None	None	SI
MAS	Germany	Largely white European	Birth 1990	1, 314 infants	0, several repeat measures up to 2, annually up to age 18	PI/BMI, Skinfold thickness, bioelectrical fat mass	10	BP only	SI Pu Cohort inventories
Millennium Cohort Study	United Kingdom	Mixed ethnicity	9-months 2000-2001	18,818 infants	0, 3, 5, 7	PI/BMI	None	None	Website

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
MoBa	Norway	Largely white European	Pregnancy 1998-2000	90,700 mothers 108,500 infants	0, 6, 8, 12, 15-18 months, 2, 3, 4, 5, 6, 7 years	PI/BMI	None	None	SI Cohort inventories
MUBICOS	Italy	Largely white European	Birth 2009	500 mother-twin pairs 1,000 infants	0, 1, 2, 3	PI/BMI	None	None	SI Cohort inventories
Newcastle Preterm Birth Growth Study	United Kingdom	Largely white European	Birth 1993-1999	246 mother-infant pairs	0, 1, 2, 9-12	PI/BMI, waist, DEXA assessed fat mass, bioelectrical impedance	9-12	BP, cholesterol, triglycerides, glucose and insulin	SI Pu
Odense Child Cohort	Denmark	Largely white European	Pregnancy 2010 (ongoing0	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Still enrolling	SI Cohort inventories
NINFEA	Italy	Largely white European	Pregnancy 2005- (on-going)	7,500 mothers; 7,500 infants	0, 2, 4	PI/BMI	None	None	SI Cohort inventories
PARIS	France	Largely white European	Birth 2003-2006	3,840 infants	0, 1, 2, 3, 4, 5, 6, 7, 8	PI/BMI	2	BP only	Cohort inventories Pu
PCB cohort	Slovakia	Largely white European	Birth 2001-2004	1,134 mother-infant pairs	0, 1, 2, 3, 4, 6,7	PI/BMI, waist, skinfold thickness, bioelectrical impedance	7	BP, cholesterol, glucose and insulin	SI Cohort inventories
PÉLAGIE	France	Largely white European	Pregnancy 2002-2006	3,421 pregnant women ? infants	0, 2, 6	PI/BMI	0	Cholesterol, triglycerides (assayed on cord blood)	Pu Cohort inventories

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
PIAMA	Netherlands	Largely white European	Pregnancy 1996-1997	4,146 pregnant women 3,963 infants	0, 8, 12	BMI, waist	8, 12	BP, cholesterol, HDLc	SI Cohort inventories
Picolli Plus	Italy	Largely white European	Birth 2011-2012	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Cohort inventories
Pride	Netherlands	Largely white European	Pregnancy 2011-(still on-going)	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Still enrolling	Cohort inventories
PROBIT	Belarus	Largely white European	Birth 1996-1997	17,056 mother-infant pairs	0, 1, 2, 3, 6, 9, 12 m 2, 3, 4, 5, 6.5, 11.5	PI/BMI, waist, skinfolds	6.5, 11.5	BP, glucose, insulin, adiponectin, ApoA1, ApoB	SI
REPRO_PL	Poland	Still enrolling; likely largely white European	Pregnancy 2007-2011	1,800 pregnant women 1,800 infants	0, 1, 2	PI/BMI	None	None	SI Cohort inventories
Rhea	Greece	Largely white European	Pregnancy 2007-2008	1,610 pregnant women 1,590 infants	0, 1, 2, 3, 4	PI/BMI, waist	4	BP, cholesterol, LDLc, HDLc, triglycerides, glucose, insulin	SI Cohort inventories
SEATON	United Kingdom	Largely white European	Pregnancy 1997-1998	2,000 pregnant women 1,400 infants	0, 5, 11	PI/BMI	None	None	SI Cohort inventories

Cohort	Country	Ethnicity	Age and time of recruitment	Number recruited	Age at adiposity measures (years)*	Adiposity measures*	Age at cardiometabolic measures (years)*	Cardiometabolic measures	Information verified using
Southampton Woman's Survey	United Kingdom	Largely white European	Women recruited pre-conceptual 1998-2002	12,579 women aged 20-34 2,567 infants	0, 6 months, 1, 2, 3, 4, 6, 8 (currently in progress)	PI/BMI, waist, DEXA fat mass, bioelectrical impedance	3, 8 (currently in progress)	BP only	SI Cohort inventories
Trieste child development cohort	Italy	Largely white European	Pregnancy 2007-2009	900 mother-infant pairs	0	PI	None	None	Cohort inventories
WHISTLER	Netherlands	Largely white European	Birth 2003-2011	2,000 infants	0, 6	PI/BMI, waist, Ultrasonography intra-abdomial fat and subcutaneous fat	6	BP, CIMT, arterial wall distentibility.	SI Cohort inventories

PI- ponderal index; BMI – body mass index; BP- blood pressure; DEXA - Dual X-Ray Absorptiometry; HDLc-high density lipoprotein cholesterol; LDLc-low density lipoprotein cholesterol; Apo: apolipoproteins; PWV-pulse wave velocity; USS-ultrasound scan
SI-study investigators, Pu- publications
Cohort inventories- www.birthcohorts.net and/or http://www.enrieco.dk. Last accessed 28/10/12-05/11/12
*Not all measures are necessarily completed at all of these ages but at least one of those in the list for either adiposity or cardiometabolic measures are assessed at each of the ages listed. Ages are all in years unless otherwise indicated.

Table 3: Summary of key characteristics of the 71 cohorts described in table 2 above

Characteristic	Categories	Number (%) of cohorts N = 71
Geographical area	Northern Europe	31 (44)
	Western Europe	17 (24)
	Southern Europe	15 (21)
	Eastern Europe	6 (8)
	Multiple countries	2 (3)
Ethnicity	Largely white European	64 (90)
	Mixed	6 (8)
	Non-white Europeans	1 (1)
Years of birth	1990-94	4 (5)
	1995-99	18 (25)
	2000-04	25 (35)
	≥ 2005	24 (35)
Number of infants recruited	< 1000	21 (29)
	1,000-1,999	12 (17)
	2,000-4,999	12 (17)
	5,000-9,999	8 (11)
	10,000-14,999	4 (6)
	15,000-19,999	4 (6)
	≥20,000	5 (7)
	Still enrolling	5 (7)
Age at recruitment	Pregnancy	44 (62)
	Birth	22 (31)
	Within first year of life	5 (7)
Repeat measurements of adiposity	1 measure	6 (7)
	2-5 measures	37 (52)
	≥ 5 measures	22 (31)
Type of adiposity measured	Weight and height (PI/BMI) only	30 (42)
	Weight and height (PI/BMI) and waist	11 (15)
	Weight and height (PI/BMI) and other measure	9 (13)
	Weight and height (PI/BMI), waist and other	13 (18)
	Birthweight/weight only	1 (1)
Type of cardiometabolic trait measured	BP only	11 (15)
	Lipids only	2 (3)
	Insulin or glucose only	2 (3)
	BP and lipids	4 (6)
	BP, and glucose or insulin or HbA1C	2 (3)
	BP, lipids, and glucose or insulin or HbA1c	8 (11)
	BP, lipids, glucose or insulin or HbA1c and some measure of vascular function / structure	2 (3)

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Developing a Child Cohort Research Strategy for Europe

Neuropsychological development

Leader: Jordi Sunyer

Researchers involved: Joan Forns, Leda Chatzi, Mònica Guxens, Katerina Koutra, Janny Niclasen, Martine Vrijheid, Dania Valvi, Mireia Gascon, Marina Vafeiadi, Maribel Casas

Summary

The brain's vulnerability is particularly important during early development period, but it extends until adolescence. Our environment can promote (i.e., social supports) or disrupt (i.e., psychosocial stress, chemical toxicants) brain development which is strongly influenced by heritable genetic. A potential silent pandemic of brain underdevelopment due to the current environment may exist.

Brain function is a life-course event that only could be tracked in longitudinal studies. Having detailed measurements on functional traits and disorders such as ADHD, autism or school performance from infancy through childhood is important for providing the evidence base for interventions. The assessment of child neuropsychological development has received much attention in recent years, and consequently the number of studies has increased exponentially. However the full causes of cognitive impairment and behaviour disorders remain mainly unknown. This is in part due to limitations in study design, given that few studies followed a prospective direction such as the birth cohorts.

We have identified a total of 42 European birth cohorts that have data on child neuropsychological development mostly in Northern and Western Europe (n=28). We identified 9 cohorts in Southern Europe and 5 cohorts in Eastern Europe. Cognitive development has been the most studied domain, whereas school performance, attachment and mental health have been assessed less.

We have found that there is a constellation of socio-environmental factors during pregnancy that have been analysed in relation to the neuropsychological development and child behaviour. However, the level of consistency is still rather poor for most of the risks taken one by one. For example, the case of smoking is still under debate and it is not clear to what extent observed effects are a marker of differences in family education and social class. To this extent the inclusion of biomarkers of active and passive smoking during pregnancy and infancy using samples from the biobanks of the birth cohorts is advised. Similarly, the role of mild alcohol intake during pregnancy or new chemicals needs to be better understood and the use of biomarkers using biobanks could facilitate this endeavour. Two areas with very limited information refer to the medical treatment and maternal occupation during pregnancy. Exploitation of the data already collected in the birth cohorts and joint analyses is a priority. Another area of current interest with rather poor information refers to the role of maternal stress, mental health and physical activity. Among the new exposures occurring in infancy and early childhood the combination of time in front of the TV screen, sedentary life style, consumption of sweet beverages and junk food, stress, sleep duration and sleep disturbances, and mobile phone use require urgent research.

A major limitation however is that European birth cohorts are very heterogeneous in the neuropsychological assessment which precluded combined analyses. There is a need for a task force design to harmonize the neuropsychological assessment. It is recommended that a panel of experts on child neuropsychological development from all European regions works together on a document to establish some guidelines and recommendations for selecting: the neuropsychological areas to study, the target ages of assessment and the most valid and reliable neuropsychological tests.

The group concludes that investments have to be made to continue further follow-up and repeat assessments of brain function and behaviour disorders from ongoing European birth cohorts at least until adolescence. It also recommends combining information from birth cohorts across Europe since this would allow key aetiological factors to be robustly established providing the evidence base for interventions. We also recommend performing biomarker analyses of the ongoing collected biological samples which could

advance in the assessment of several risk factors that required further research. New birth cohorts in low income areas and in Eastern Europe need to be established.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

The developing human brain is particularly susceptible to environmental hazards such as industrial and chemical agents (mercury, lead, polychlorinated biphenyls (PCBs), solvents, etc.) and factors related to lifestyle such as tobacco smoke, alcohol, certain drugs, maternal stress, and maternal Intelligence Quotient (IQ) (*1*). These environmental factors can promote or disrupt the development of the central nervous system depending on whether they are positive (social supports, cognitively-stimulating environment, etc.) or negative (psychosocial stress, chemical toxicants, malnutrition, etc.) (*1*). This process is also strongly influenced by heritable genetic. Some authors indicate that genetic endowment accounts for 50% in the variance of the cognitive abilities of an individual (*2*). Brain's vulnerability is particulalry important during early development period, but it extends through infancy and childhood (*3*).

Forns et al (*4*) recently defined two levels of outcomes or phenotypes for child neuropsychological development: functional and clinical (figure 1). The functional level refers to the skills, abilities, capacities, and/or knowledge acquisition acquired during maturation of the brain and its interaction with the social and educational environment. The clinical level refers to some neuropsychological disorders or the presence of symptoms of these disorders in the population scrutinized in environmental epidemiology studies (subclinical symptomatology). This model will allow epidemiologists to design future studies and to homogenize terminology for developing combined analysis of data from different cohorts.

During the past two decades, a growing body of studies has investigated the effects of early exposure to neurotoxic agents on neuropsychological development in infancy and childhood. However the full influence of environmental factors on cognitive impairment (ie. critical windows of exposure, effect of low doses), and the underlying mechanisms are still unknown. Furthermore, environmental factors have been related to attention deficit and hyperactivty disorder (ADHD) and autism spectrum disorders (ASD), including food additives/diet, lead contamination, cigarette and alcohol exposure, maternal smoking during pregnancy, and low birth weight (*5;6*). Grandjean et al (*7*) suggested that a potential silent pandemic due to the current environment may exist.

Therefore, the objectives of this report are: i) to review the contribution of European birth cohort research to scientific knowledge on child neuropsychological development; ii) to review the main neuropsychological and psychological tests used for CHICOS birth cohorts; iii) to review the primary preventive interventions in the specific case of ADHD by country; and iv) to make recommendations for future research in neuropsychological development in European birth cohort studies.

1.2. Description of the contribution of (European) birth cohort research to scientific knowledge

Birth cohort versus other study design

The assessment of child neuropsychological development has received much attention in recent years, and consequently the number of studies has increased exponentially; however, many of these studies are

weakened in methodology (*8*). Cross-sectional studies for instance cannot enhance our understanding of the developmental process. On the other hand, retrospective studies are limited by recall bias and although they can collect some information retrospectively (smoking during pregnancy, breastfeeding, etc) they cannot provide biological samples from this period – which are crucial to study the effects of some environmental chemicals such as Persistent Organic Pollutants (POPs) or metals. Prospective cohort studies of "high-risk" selected population, such as children with ASD, cannot explain the effects of some factors on the general population.

Therefore, population-based prospective cohort studies (unselected sample) that started early in pregnancy or at birth can avoid the above-mentioned bias. This study design has important strengths such as that it collects data on many co-variates and follows children up several years after birth, thereby providing insights into developmental problems at birth as well as in the first years of life. Relationships between exposures, outcomes, and other influential factors can be considered in a temporal context avoiding a recall bias. Moreover, if birth cohort is followed prenatally, exposures present at the time of conception (genetics), during pregnancy (chemical hazards, smoking, alcohol, maternal stress, etc.), at birth (asphyxia, trauma, etc.) and during the postnatal period (infection, environmental exposures, diet and breastfeeding, social environment, etc) can be considered. This is extremely important for answering questions regarding the genetic and environmental origins of cognitive and behavioural developmental delays and disorders. Grandjean et al emphasized the need to conduct prospective epidemiological studies to explain toxic exposures of metals on neurodevelopmental disorders (*7*). The major problems of this methodology are the risk of loss to follow-up over time and the costs, in terms of time, budget or personal. Several existing reviews have summarized the role of cohorts in evaluating mental health of children (*8-10*).

Contribution of European birth cohorts

In order to describe the contribution of birth cohort research, particularly the European ones, to the scientific knowledge in this field, we performed a literature search in the computerized bibliographic database PubMed. Relevant publications until 31th July 2011 and related to social, diet, lifestyle, and environmental exposures (mainly metals and persistent organic pollutants) were identified. Inclusion criteria were as follow: (i) reports of longitudinal, cross-sectional, and nested case-control analysis within cohort studies; (ii) start enrolment during pregnancy or at birth; (iii) social, diet, lifestyle, or environmental exposures were the primary exposure; (iv) child neuropsychological development was the primary outcome; (v) and report original data. The following search terms were used: *Europe AND birth cohort AND social/diet-physical activity/lifestyle/environmental exposures AND (cognitive OR behaviour OR neurodevelopment OR autism OR psychomotor OR auditory OR visual OR hyperactivity OR attention OR mental health OR personality OR school achievements OR intelligence OR memory OR language OR executive function)*. Specific search terms used for social, diet, lifestyle and environmental exposures were:

- social: education, social class, family income, occupation
- diet/physical activity: diet, physical activity
- lifestyle: smoking, alcohol*, drugs* (*indicates that PubMed will search all words related with alcohol or drugs; ie. alcoholism, alcoholic)

- environmental exposures: metal, mercury, methylmercury, lead, cadmium, chromium, arsenic, nickel, manganese, selenium, boron, aldrin, chlordane, DDT, DDE, dieldrin, endrin, heptachlor, HCB, mirex, toxaphene, chlordecone, α-HCH, β-HCH, lindane, γ-HCH, PeCB, PCBs, PBBs, PFOS, perfluorooctane sulfonyl fluoride, polybrominated diphenyl ether, PBDEs, PCDD, PCDF, dioxins, POPs, bisphenol A, phthalates

Manual searches of references of articles identified by the electronic search were also performed. Overall, a total of 1587 publications were initially identified. Studies that did not fulfil the inclusion criteria were excluded. In the case of metals publications that had already been described in other reviews (i.e. (*11*)) were also not included. Finally, a total of 85 papers remained for the present report. Table 1 shows a list of all the publications identified that have been published by the European birth cohorts regarding neuropsychological development.

Description of the results

Social

Eleven papers were included regarding social class, education, occupation, or family income. Because these terms are usually overlapped all manuscripts have been included together in table 1. The 7 cohorts that studied social class started the recruitment before the '70s; we could not be able to identify any recent cohort that has assessed the association between social class and child neuropsychological development. All of them were situated in Northern Europe and were relatively big cohorts (1000-22000 participants). Furthermore, all these studies explored the relationship between parental social position at birth and offspring's neuropsychological development later in infancy and in adulthood (7-50 yrs); none of them studied its influence at early ages. Personality disorders, psychological distress, and mental health were the outcomes mostly studied.

Diet

Concerning diet and physical activity, a total of 18 publications belonging to 9 European birth cohorts were identified. The majority of them (N=7) are located in the North of Europe. Half of the studies assessed the effects of maternal diet intake during pregnancy on child neuropsychological development whereas the others studied breastfeeding duration or dietary patterns during childhood and its effect on the child neuropsychological development at later ages. Diet during pregnancy was mainly assessed using food frequency questionnaires (FFQ), whereas other methods such as telephone interviews, postal, self-reported or internet-based questionnaires, 24h recall, and food diaries were used to assess diet intake during childhood (data not shown in table 1). Psychological based tests were mostly used. The NFBC cohort in Finland was the only cohort that studied the effects of physical activity on behavioural problems and school achievement, conducting a cross-sectional study when children were 15-16 yrs old. They used a questionnaire concerning their moderate- to vigorous-intensity physical activity or a clinical examination by a submaximal cycle ergometer test.

Lifestyle

A total of 23 publications related with smoking (N=11), alcohol (N=8), or drugs (N=4) were identified. They came from 17 different European birth cohorts, most of them located in the Northern and Central part of Europe (N=14) (Denmark, Finland, Sweden, The Netherlands, and UK), whereas only 3 from the Southern

and Eastern part (France, Greece, Poland, and Spain). The number of children in each cohort ranged from <100 until 80000. Smoking information (ie. yes/no, number of cigarettes) was basically collected through self-reported questionnaires; only one cohort (REPRO_PL) had information on an exposure biomarker (cotinine). Alcohol and drug information was also collected using self-administered questionnaires. The majority of cohorts (N=12) started the recruitment after 1970 and therefore, they evaluated the effect of maternal/paternal smoking, alcohol consumption or drugs during pregnancy on neuropsychological development in infancy and early adolescence (1-15 yrs). Cohorts which started the enrolment before 1970 (N=5), mostly assessed the effect of offspring smoking, alcohol or drugs consumption on neuropsychological development in adolescence and adult life (16-53 yrs). Cognitive development and clinical symptomatology (particularly for ADHD) were the main outcomes evaluated; although psychologist based tests were mostly used, some studies, particularly the biggest ones, used parent or teacher-based tests or national standardized school attainment tests.

Environmental exposures

In Europe, a total of 8 studies were published regarding metals exposure during pregnancy and their effects on early life. All of them used human biomonitoring, except one that also investigated exposure to inorganic mercury through amalgam fillings (ALSPAC). Mercury (Hg) and lead (Pb) were the most studied metals, because their presence on fish (Hg) and on traffic/industrial related activities (Pb). These studied were mainly focused in disentangle the possible neurotoxic effects at low levels of exposure (data not shown). Larger consumer of fish regions (Faroe Islands and Spain) studied the effects of Hg exposure on child cognitive development, whereas Poland, an industrialized city with high levels of lead in air pollution attributed to traffic density, explored the effects of lead on behaviour and cognitive development in children.

Twenty-five publications belonging to 8 different cohorts and exploring the association between POPs and child neuropsychological development were identified. PCBs were the most studied, followed by brominated flame retardants (BFRs, mostly polybrominated diphenyl ethers (PBDEs)), dichlorodiphenyltrichloroethane (DDT), mirex, hexachlorobenzene (HCB), and perfluorinated compounds (PFCs, mostly perfluorooctanesulfonic (PFOS) and perfluorooctanoic acid (PFOA)). All these studies used human biomonitoring to assess their exposure during pregnancy life; consequently cohorts were not larger than 1000 subjects. Neuropsychological development was assessed in children during their first years of life (from first months to 9 years) being neurological optimality, cognitive development, and behaviour, the most explored domains.

Three European birth cohort studies explored the possible neuropsychological development impairments caused by air pollution exposure (*12-14*) (not included in table 1). Two came from Spain (INMA) and they explored the adverse effects of residential nitrogen dioxide (NO_2) and benzene exposure - based on land use regression modeling - on cognitive development (*13;14*). The other study, conducted in Poland (Krákow cohort), used an air pollution biomarker with low specificity, the polycyclic aromatic hydrocarbons (PAH) – based on personal monitoring -, to assess the relationship with child IQ (*12*).

None publications on bisphenol A, phthalates (endocrine disruptor chemicals) were identified related with child neuropsychological development in Europe.

Contribution of birth cohort collaboration

Even though there is a number of European population-based birth cohort studies that measure neuropsychological development outcomes in children (www.birthcohortsenrieco.net), few of them have enough statistical power to elucidate the dose-response relationships. Therefore pooling of data across European cohorts may be particularly valuable. In the context of the ESCAPE project (European Study of Cohorts for Air Pollution Effects – www.escapeproject.eu) a case study on the impact of ambient air pollution on adverse child neuropsychological development outcomes is being conducted. A total of 10 European birth cohorts are taking part on it: ABCD, CATTS, DNBC, Duisburg, EDEN, Generation R, GASPII, INMA, GINIplus/LISAplus and RHEA. These cohorts have used different neuropsychological tests and at different time points; consequently one of the challenges of this case study will be to try to combine these data together. Tables 2 and 3 show the tests used in ESCAPE-cohorts to assess cognitive and motor development, as an example of using different neuropsychological tests for conducting a combined analysis.

The EArly Genetics and Lifecourse Epidemiology (EAGLE-http://www.copsac.com/content/eagle-consortium) Consortium is a consortium of pregnancy and birth cohorts that aims to collaborate to investigate the genetic basis of phenotypes in antenatal and early life and childhood. There is a working group on behavior and cognition where they will conduct 3 different GWAS (Genome-Wide Association Studies) on aggressive behavior, motor and language development. The participating cohorts are: ALSPAC, Essen Study, Generation R, INMA, GINIplus/LISAplus, NFBC, NTR, RAINE, TEDS, and 1958BC.

1.3 Description of data currently available/being collected by the cohorts

Identification of cohorts

There are many pregnancy and birth cohorts in Europe that are collecting a wealth of information on neuropsychological development assessment and environmental and social determinants. Identification of cohorts to be included in this report has been done following these criteria:

- birth and mother-child cohorts
- population-based
- start enrolment during pregnancy or at birth (or during first year of life if data on birth outcomes is collected from medical records)
- at least one follow-up point during first years of life
- sample size: at least 300
- start year: 1990 onwards
- located in one of the EU member states

We have also included other cohorts that do not strictly fulfil these criteria because they provide valuable information of neuropsychological development assessment – cohorts that have less than 1000 participants.

Birth and mother-child cohorts with data on neuropsychological development assessment have been identified through different sources: 1) Birthcohorts.net webpage (www.birthcohorts.net); 2) the ENRIECO inventory (www.birthcohortsenrieco.net); 3) cohort's websites; and 4) publications. We have identified a

total of 42 European birth cohorts that have data on child neuropsychological development (table 4). The geographical distribution of these cohorts is shown in figure 2. They are situated in 17 European countries mostly in Northern and Western Europe (n=28). We identified 9 cohorts in Southern Europe and 5 cohorts in Eastern Europe.

In Europe, there are also many child cohorts that have collected information on child neuropsychological development. These cohorts start the enrolment during childhood and if they have data during pregnancy, it has been collected retrospectively. However, there are some of them that are following a huge number of participants (ie. Growing up in Ireland N= 11000 (9 mo) and 8570 (9 yrs); Growing up in Scotland N= 5000 (10 mo) and 3000 (24 mo); or The Millenium Cohort Study), and consequently the information is also of great interest. However, we have not described them in the present report.

Current work in the European birth cohorts

The 45 European birth cohorts identified have assessed or are planning to assess any of the following neuropsychological development domains: cognitive measures, school performance, language, attachment, neurodevelopment, or mental health. Tables from 5 to 10 show which cohorts and when (years during childhood) they have assessed any of the abovementioned domains. Cognitive measures have been the most studied domain, whereas school performance, attachment, and mental health have been assessed less. The ENRIECO inventory provides a detailed list of the neuropsychological tests used by cohorts that have data on environmental exposures. All these tests are summarized in the ENRIECO report on "Neurobehavior assessment" (available in www.enrieco.org).

Strengths and Limitations

Strengths

- Information from pregnancy collected prospectively (no recall bias)
- In general, great number of covariates collected (ej. social-economic status, smoking, anthropometry).
- In general well standardized neuropsychological tests have been used during the first years of life (particularly Bayley Scales of Infant Development).
- Most of the tests have been assessed by a psychologist (data not shown)

Limitations

- Different outcomes, tests, and time points used → difficult to harmonize data
- Heterogeneity in the neuropsychological protocol used at older ages.
- Some cohorts have used non published or non standardized tests
- Little information collected about social-emotional development
- Many tests used to evaluate one outcome (ie. cognition) but they are methodologically different
- Some cohorts have used self-reported questionnaires (response bias)

1.4 Identification of gaps

- Few studies in Eastern and Southern European cohorts
- Few cohorts set up in low-income populations
- Need for harmonization of ages and protocols of assessment
- Little information collected about social-emotional development
- Need for harmonization of confounders considered
- Follow-up until older ages
- Poor research on:
    - biomarkers for smoking exposure assessment
    - alcohol consumption in Southern and Eastern cohorts
    - physical activity
    - social determinants in recent birth cohorts
    - effects of social determinants at early ages (< 7 yrs)
    - low doses of other metals a part from Pb and Hg (ie. arsenic, aluminium)
    - the possibility to combine data from different cohorts to explore POPs and metals at low doses of exposure (explore difficulties: different matrices, different follow-ups, different tests, etc)
    - the effects of emerging neurotoxins such as bisphenol A or phthalates
    - air pollution - use biomarkers with high specificity

ADHD in Europe: policy, diagnosis and treatment. Example of a common childhood behavioural disorder

The ADHD-Europe (http://www.adhdeurope.eu/), published a survey in 2009 to find out more about the work, the existence of policy, provision of diagnosis, treatment, educational support, and employment measures for people with ADHD in the member countries in Europe (19 European countries) (*15*). In order to have an overview of the ADHD policies in Europe, we have selected 4 European countries as representative of the 4 European regions: North (Norway), South (Spain), East (Poland), and Central (The Netherlands). Table 4 summarizes the policy, diagnosis, and treatment of ADHD in these countries. Overall, there is lack of national policy, data and research concerning ADHD in Europe.

3. Recommendations:

Main strategic recommendations for neuropsychological neurodevelopment research in European birth cohorts:

- In order to be able to assess differences in neuropsychological development distributions in children across Europe, there is a need to support the existing birth cohorts in **Eastern and Central Europe** and establish new ones. This support has to be addressed particularly to low-income cohorts from these regions. Furthermore, there is a need to support **new follow-ups of existing cohorts** for evaluating neuropsychological development in later childhood and adolescence.
- There is a need for a **task force design** to harmonize the neuropsychological assessment in environmental epidemiological studies. It is recommended that a panel of experts on child neuropsychological development from all the European regions work together on a document to establish some guidelines and recommendations for selecting: (i) the neuropsychological areas to study; (ii) the target ages of assessment; and (iii) the most valid and reliable neuropsychological tests. This task force would help to perform future combined analyses with data from different birth cohorts (meta- or pooled-analysis) and therefore, to harmonize the research conclusions in environmental epidemiological studies. The publication of the paper "A conceptual framework in the study of neuropsychological development in epidemiological studies" by Forns et al in Neuroepidemiology (*4*) can be viewed as a starting point of this task force.
- **Future research**: there is a constellation of socio-environmental factors during pregnancy that have been analysed in relation to the neuropsychological development and child behaviour; however, the level of consistency is still rather poor for most of the risks taken one by one. For example the case of smoking is still under debate and it is not clear to what extend is just a marker of differences in family education and social class. To this extend the inclusion of biomarkers of active and passive smoking during pregnancy and infancy using samples from the biobanks of the birth cohort studies is advised. Similarly, the role of mild alcohol intake during pregnancy needs to be better understood; the use of biomarkers of alcohol intake will improve the quality of the research. Experimental data suggest the need to investigate in human populations the role of several environmental chemicals such as metals beyond Pb and Hg and new pollutants like PFOS, bisphenol A or organophosphates. The availability of biological samples from biobanks in the birth cohorts could facilitate this endeavour. Another group of exposures refers to particulate material and gases in the urban air. The use of the new geographical methods to assess cumulative exposure and personal devices and individual sensors would facilitate a big improvement in the cumulative exposure. Two areas with very limited information refer to the medical treatment and the maternal occupation during pregnancy. Exploitation of the data already collected in the birth cohorts and join analyses is a priority. Another area of current interest with rather poor information refers to the role of maternal stress, mental health and physical activity. Overall, the group concludes that combination of data from ongoing birth cohorts and biomarker analyses of the ongoing collected biological samples could advance in the assessment of several risk factors that required further research. Among the exposures occurring in infancy and early childhood there is urgency to understand the exposures related with new technologies and the new ways of living in the brain development. In particular the combination of time in front of the screen, sedentary, sweet beverages and junk food and stress, sleep duration and sleep disturbances, and mobile phone use requires urgent research. Similarly the built environment combining access to green spaces and place for exercise and social life in combination to levels of air pollution as a contextual concept is a new area of research in the field of brain development.

Tables & Figures

Table 1. European birth cohorts with published work on Neurodevelopment

Cohort, country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied test*	*Main outcome measured*	*Test used*
LIFESTYLE							
Smoking							
British 1946 Birth Cohort, UK	Richards 2003 (*16*)	3035	36, 43 & 53 yrs	offspring smoking	43 & 53 yrs	cognitive development	Word learning and visual search tasks
Greek Birth Cohort, Greece	Palili 2011 (*17*)	2695	pregnancy	maternal smoking	7 & 18 yrs	ADHD-like symptoms	NA
Groningen Perinatal Project, The Netherlands	Batstra 2003 (*18*)	1186	pregnancy, 5.5-11 yrs	parental smoking	5.5-11 yrs	school achievement & emotional-behavioural problems	standardised Dutch tests (for academic achievement) & parents-teacher questionnaires on child's behaviour
INMA, Spain	Sunyer 2010 (*19*)	418	pregnancy	maternal smoking	4 yrs	cognitive development	MSCA
	Julvez 2007 (*20*)	420	pregnancy to 4 yrs	parental smoking	4 yrs	cognitive and motor abilities	MSCA
NFBC 1985/86, Finland	Kotimaa 2003 (*21*)	9357	pregnancy	maternal smoking	8 yrs	hyperactivity	Children's Behavior Questionnaire (Rutter B2)
NFBC 1966, Finland	Isohanni 2001 (*22*)	10542	14 & 31 yrs	offspring smoking	up to age 31 yrs	school achievement	NA – from national registries
Pelotas, Brasil ALSPAC, UK	Brion 2010 (*23*)	509 (Pelotas) 6735 (ALSPAC)	pregnancy	parental smoking	4 yrs	cognitive development and behavioural problems	CBCL (Pelotas) SDQ (ALSPAC)
REPRO_PL, Poland	Polanska 2009 (*24*)	63	pregnancy	maternal smoking, cotinine	1 year	phychomotor development	BSID-III
NCDS, UK	Collins 2007 (*25*)	6380	pregnancy & 16 yrs	parental & offspring smoking	16 & 18 yrs	school achievement	British standardised achievement tests
	Fogelman 1988 (*26*)	8200	pregnancy	maternal smoking	23 yrs	school achievement	-----
Alcohol							
British 1946 Birth Cohort, UK	Richards 2005 (*27*)	1764	43 years	offspring alcohol consumption	43 & 53 yrs	cognitive development	Word learning and visual search tasks
Children in a New Stockholm suburb, Sweden	Nordberg 1991 (*28*)	452	pregnancy	parental alcohol consumption	1 & 4 yrs	cognitive development, psychiatric health	Griffiths, DSM-III
	Nordberg 1993 (*29*)	532	pregnancy	parental alcohol consumption	1 & 4 yrs	behaviour	Griffiths, DSM-III
	Nordberg 1994 (*30*)	532	pregnancy	parental alcohol consumption	1 & 4 yrs	cognitive development, psychiatric health	Griffiths, DSM-III
DNBC, Denmark	Eliasen 2010 (*31*)	80552	pregnancy	maternal alcohol consumption	Infancy (~4-5 yrs)	autistic spectrum disorders	NA – from national registries
MCS, UK	Kelly 2009 (*32*)	9640	pregnancy	maternal alcohol consumption	3 yrs	cognition & behavioural problems	SDQ, BAS, BSRA
NCDS, UK	Staff 2008 (*33*)	9107	16 yrs	offspring alcohol consumption	up to 42 yrs	school achievement/ qualifications	NVQ

Cohort, country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied test*	*Main outcome measured*	*Test used*
NFBC 1986, Finland ABC, Denmark HHT, Denmark	Rodriguez 2009 (*34*)	28595	pregnancy	maternal alcohol consumption	7-15 yrs	ADHD-like symptoms	SDQ (ABC, HHT), Rutter Scale (NFBC)
				Drugs			
Copenhagen, Denmark	Reinisch 1995 (*35*)	296	pregnancy	phenobarbital	adult life	cognition (IQ)	Wechsler adult intelligence scale Danism military draft board intelligence test (Børge Priens Prøve)
EPIPAGE, France	Marret 2010 (*36*)	452	pregnancy	aspirin – low dose	5 yrs	cognition (IQ)	MPC scale of Kaufman Assessment Battery for children
NSHD, UK	Colman 2006 (*37*)	~3000	31, 36, 43 & 53 yrs	antidepressants, anxiolytics, hypnotics	36, 43 & 53 yrs	mental disorders	PSE (36y), PSF (43y), GHQ (53y)
Stockholm, Sweden	Eriksson 2000 (*38*)	65	pregnancy	amphetamine	14-15 yrs	school performance and behavioural problems	Interview with social worker - no specific test
				DIET			
				Diet			
ALSPAC, UK	Daniels 2004 (*39*)	7421	pregnancy, 6 & 15 mo	fish intake	15 mo	cognitive development	MCDI, Denver
	Hibbelin 2007 (*40*)	11875	pregnancy	fish intake	6, 18, 30, 42 yrs	behaviour & cognition	Denver
	Feinstein 2008 (*41*)	7703	3, 4 & 7 yrs	dietary patterns childhood	4-5 yrs 6-7 yrs 10-11 yrs	school achievement	Entry assessments to school (4-5 yrs) KS1 (6-7 yrs) KS2 (10-11 yrs)
	Wiles 2009 (*42*)	4000	4.5 yrs	childhood diet (''junk food'' diet)	7 yrs	behavioural problems	SDQ - maternal completion
	Northstone 2011 (*43*)	3966	3, 4, 7 & 8.5 yrs	dietary patterns childhood	8.5 yrs	cognitive development	WISC-III
DNBC, Denmark	Lauritzen 2004 (*44*)	97	0-4 mo	fish oil supplementation lactation	2 & 4 mo	visual acuity	swept visual evoked potential
	Lauritzen 2005 (*45*)	175	0-4 mo	fish oil supplementation lactation	9 mo, 1 & 2 yrs	cognitive development	The Infant Planning Test (9 mo), MCDI (1 & 2 yrs)
	Oken 2008 (*46*)	25466	pregnancy, 6 mo	fish intake, breastfeeding	6 & 18 mo	developmental milestones	-----
Generation R, The Netherlands	Rosa 2010 (*47*)	4214	pregnancy	folic acid intake	18 mo	behavioural problems	CBCL
INMA, Spain	Mendez 2009 (*48*)	392	pregnancy	fish intake	4 yrs	cognitive development	MCSA - Spanish version
MCS, UK	Sacker 2006 (*49*)	14660	0-4 mo	breastfeeding	9 mo	developmental milestones	Denver

Cohort, country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied test*	*Main outcome measured*	*Test used*
MoBa, Norway	Bekkhus 2010 (*50*)	25343	pregnancy	caffeine intake	18 mo	inattention/over activity	NA
NSHD, UK	Richards 1998 (*51*)	511	after birth	breastfeeding	8 yrs	sentence completion, reading, vocabulary	NA
	Mishra 2009 (*52*)	636	36, 43 & 53 yrs	dietary intakes of vitamins B	53 yrs	psychological distress, symptoms of anxiety, depression and somatic problems	GHQ-28
				Physical health/activity			
NFBC 1986, Finland	Kantomaa 2008 (*53*)	7002	15-16 yrs	MVPA	15-16 yrs	emotional and behavioural problems	Youth Self-Report questionnaire
	Koivukangas 2010 (*54*)	6987	15-16 yrs	physical activity, cardiorespiratory fitness	15-16 yrs	psychosis	PROD-screen questionnaire
	Kantomaa 2010 (*55*)	7002	15-16 yrs	MVPA + maternal education	15-16 yrs	school achievement, emotional & behavioural problems	self reported academic performance summary score, YSR (Finish version)
Swedish	Nordberg 1989 (*56*)	532	0-1 yr	children's physical health and development	10-18 mo	cognitive development, behaviour	Griffiths
				SOCIAL			
				Social class/Occupation/Family income/Education			
NFBC 1966, Finland	Rantakallio 1987 (*57*)	12000	birth	social class	14 yrs	mental retardation	NA
	Elovainio 2007 (*58*)	4257	during childhood	social class	31 yrs	psychological distress	SCL-25
	Kantojärvi 2008 (*59*)	1588	birth	social class	31 yrs	personality disorders	DSM-III-R
NCDS, UK	Buchanan 2000 (*60*)	8441	birth	social class	16 & 33 yrs	psychological problems & distress	Rutter A health and Behaviour Checklist Malaise Inventory
	Power 2006 (*61*)	13980	birth	social class	7, 11, 16, 33 yrs	cognitive development	mathematics tests
NCDS and BCS, UK	Mensah 2008 (*62*)	22504	birth-16 yrs	social class	33 yrs	cognitive development, behaviour	Malaise Inventory
Newcastle cohort, UK	Tiffin 2005 (*63*)	5030	birth	social class	50 yrs	mental health	GHQ-28
Scottish cohort, UK	Lawlor 2005 (*64*)	10424	birth	social class	7, 9, 11 yrs	cognition (IQ)	Morey House test and Schonell and Adams essential test A & B
Stockholm Cohort, Sweden	Timms 1996 (*65*)	6928	birth & 27 yrs	occupational class	19 & 27 yrs	mental health	NA
1958 British birth cohort, UK	Jefferis 2002 (*66*)	10845	birth	social class	7, 11, 16, 33 yrs	cognitive development	School test created, Goodenough draw a man test
	Power 2002 (*67*)	5340	birth, 7, 11, 17, 23, 33 yrs	parental education and social class	23 & 33 yrs	psychological distress	Malaise Inventory
				ENVIRONMENTAL EXPOSURES			
				Metals			

Cohort, country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied test*	*Main outcome measured*	*Test used*
ALSPAC, UK	Daniels 2007 (*68*)	7375	prenatal	maternal dental history, mercury levels	15 mo	language development	MCDI
	Chandramouli 2009 (*69*)	488	30 mo	lead levels	7-8 yrs	development, behaviour, education	SDQ, DAWBA, TEACh, SATs
Faroes, Faroe Islands	Julvez 2010 (*70*)	878	birth, 7, 14 yrs	mercury levels	14 yrs	attention function, time speed processing	NES2 CPT-HRT
	Choi 2008 (*71*)	1204	birth	mercury levels	7 yrs	different neuropsychological domains	NES, FTT, HECT, WISC-R, WISC-R Block Design, BVMGT, BNT, CVLT, NOS
INMA, Spain	Freire 2010 (*72*)	72	4 yrs	mercury levels, fish intake	4 yrs	cognitive development	MSCA
Krákow cohort, Poland	Jedrychowski 2008 (*73*)	452	birth	lead levels	6 mo	visual recognition memory	FTII
	Jedrychowski 2009 (*74*)	444	birth	lead levels	12, 24, 36 mo	cognitive development	BSID-II
	Jedrychowski 2009 (*75*)	457	birth	lead levels	12, 24, 36 mo	cognitive development	BSID-II
				Persistent organic pollutants			
DNBC, Denmark	Fei 2008 (*76*)	1400	pregnancy	PFOS, PFOA levels	birth, 6-18 mo	development milestones	Apgar, motor and mental developmental milestones
Dutch PCB/Dioxin study, The Netherlands	Huisman 1995 (*77*)	418	pregnancy, birth	PCBs, PDCC/Fs levels	10-24 d	neurological optimality	Prechtl, NOS
	Huisman 1995 (*78*)	418	pregnancy, birth	PCBs levels	18 mo	neurological optimality	NOS, FCS
	Koopman-Essenboom 1996 (*79*)	207	pregnancy, birth	PCBs levels	3, 7, 18 mo	cognitive development	BSID
	Lanting 1998 (*80*)	394	pregnancy, birth	PCBs levels	42 mo	motor development, neurological optimality	Touwen/Hempel, NOS
	Patandin 1999 (*81*)	395	pregnancy, birth	PCBs levels	42 mo	cognitive development	KABC, RLDS
	Vreugdenhil 2002 (*82*)	372	pregnancy, birth	PCBs levels	6.5 yrs	cognitive development	MCSA
	Vreugdenhil 2002 (*83*)	207	pregnancy, birth	PCBs levels	6.8 yrs	play behaviour	PSAI
	Vreugdenhil 2004 (*84*)	83	pregnancy, birth	PCBs levels	9 yrs	different neuropsychological domains	RCFT, SRT, AVLT, TOL
	Walkowiak 2001 (*85*)	171	pregnancy, birth	PCBs levels	7, 18, 30, 42 mo	cognitive development, home environment	BSID-II, KABC, HOME-scale
Duisburg, Germany	Wilhelm 2007 (*86*)	189	pregnancy, birth	PCBs, PDCC/Fs levels	2 w & 18 mo	neurological optimality, cognitive development	NOS, BSID
Faroes , Faroe Islands	Steuerwald 2000 (*87*)	182	birth	PCBs levels	2 w	neurological optimality	NOS

Cohort, country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied test*	*Main outcome measured*	*Test used*
	Grandjean 2001 (*88*)	435	birth	PCBs levels	7 yrs	different neuropsychological domains	NES2, WISC-R, BVMGT, CVLT, BNT
Germany	Winneke 2005 (*89*)	70	pregnancy, birth	PCBs levels	72 mo	home environment, cognitive development	KABC, HOME-scale
Groningen infant COMPARE, The Netherlands	Roze 2009 (*90*)	62	pregnancy	organohalogens including BFRs levels	5-6 yrs	cognition, motor performance, behaviour	WPPSI-R, NEPSY-II, AVLT, Test of Everyday Attention for Children
INMA, Spain	Ribas-Fitó 2003 (*88;91*)	92	birth	DDE, PCBs, HCB levels	13 mo	cognitive development	BSID, GMDS
	Ribas-Fitó 2006 (*92*)	475	birth	DDT/DDE levels	4 yrs	cognitive development	MCSA
	Ribas-Fitó 2007 (*93*)	475	birth	HCB levels	4 yrs	behaviour, ADHD-like symptoms	CPSCS, ADHD-DSM-IV
	Puertas 2009 (*94*)	104	birth	mirex levels	4 yrs	cognitive development	MCSA
	Gascon 2011 (*95*)	482	birth	PBDEs levels	4 yrs	cognition, ADHD-like symptoms, social competence	MSCA, ADHD-DSM-IV, California Preschool Social Competence Scale
PCB cohort, Slovakia	Park 2009 (*96*)	147	birth	6 congeners of OH-PCBs levels	16 mo	cognitive development	BSID–II
	Park 2010 (*97*)	760	birth	dioxin-like PCB, non-dioxin-like PCB, antiestrogenic PCBs levels	16 mo	cognitive development	BSID

ABC: Aarhus Birth Cohort; ALSPAC: Avon Longitudinal Study of Parents and Children; BCS: British Cohort Study; COMPARE: Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens; DNBC: Danish National Birth Cohort; EPIPAGE: Etude Epidemiologique des Petites Ages Gestationnels; HHT: Healthy Habits for Two; INMA: Infancia y Medio Ambiente (Environmental and Childhood); MCS: The Millenium Cohort Study; MoBa: Norwegian Mother and Child Cohort; MVPA: moderate-to-vigorous intensity physical activity; NA: non available; NCDS: National Child Development Study; NFBC: Northern Finland Birth Cohort; NSHD: National Survey of Health and Development.

BFRs: brominated flame retardants; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; HCB: hexachlorobenzene; HHT: Healthy Habits for Two; PBDEs: polybrominated diphenyl ethers; PCBs: polychlorinated biphenyls; PDCC/Fs: Polychlorinated dibenzo-p-dioxins/dibenzofurans; PFCs: perfluorinated compounds; PFOS: perfluorooctanesulfonic; PFOA: perfluorooctanoic acid.

ADHD-DSM: Attention Deficit Hyperactivity Disorder Criteria of Diagnostic and Statistical Manual of Mental Disorders (edition: IV); AVLT: Rey's auditory verbal learning test; BAS: British Ability Scale; BNT: Boston Naming Test; BSID: Bayley Mental Development Index (edition: II, III); BSRA: Bracken School Readiness Assessment; BVMGT: Bender Visual Motor Gestalt Test; BVMGT: Bender Visual Motor Gestalt Test; CBCL: Child Behaviour Checklist; CPSCS: The California Preschool Social Competence Scale; CPT-HRT: Continuous Performance Test Hit Reaction Time; CVLT: California Verbal Learning Test; DAWBA: Development And Well-being Assessment; Denver: Denver development screening; DSM: Diagnostic and Statistical Manual of Mental Disorders (edition: III; R: revised); FCS: fluency cluster score; FTII: Fagan Test of Infant Intelligence; FTT: Finger-Tapping Test; GHQ: General Health Questionnaire; GMDS: Griffiths Mental Development Scales; HECT: Hand-Eye Coordination Test; HOME: Home Observation for Measurement of the Environment; KABC: Kaufman assessment battery for children; KS1: Key Stage 1 national tests; KS2: Key Stage 2 national tests; MCDI: MacArthur-Bates Communicative Development Inventory; MPC: Mental Processing Composite; MSCA: McCarthy Scales of Children's Abilities; NEPSY: Neuropsychological assessment (edition: II); NES: Neurobehavioral Evaluation System; NOS: Neurologic Optimality Score; NVQ: National Vocational Qualification; PROD-screen: questionnaire screening prodromal symptoms; PSAI: Pre-School Activity Inventory; PSE: Present State Examination; PSF: Phychiatric Symptom Frecuency; Rey Complex Figure Test; RLDS: Reynell Language Developmental Scale; SATs: Standard Assessment Test; SCL-25: Hopkins Symptom Checklist-25; SDQ: Strengths and Difficulties Questionnaire; SRT: speech reception threshold; TEACh: Test of Everyday Attention for Children; TOL: Tower of London; WISC: Wechsler Intelligence Scale for Children (R: revised); WPPSI: Wechsler Preschool and Primary Scale of Intelligence (R: revised); YSR: Youth self-reported.

Table 2. Tests used in ESCAPE-Cohorts to assess cognitive development

Child's age	*Test used*	*Function*	*Cohort*	*N children*
6 months	Developmental milestones	Congitive/language score	DNBC	12214
1.5 years				11383
1-2 years	Bayley Scales for Infant Development (BSID)	Mental score (Cognitive, Expressive Language, Receptive Language)	INMA, RHEA, Duisburg	2213 585 186
1.5 years	Denver Developmental Screening Test (DDST)	Language subscale	GASPII	573
3 years	MacArthur-Bates Communicative Development Inventory (MCDI)	Language score	Generation R	4998
2 year	MacArthur-Bates Communicative Development Inventory (MCDI)	Language score	EDEN	1344
2.5 years	MacArthur-Bates Communicative Development Inventory (MCDI + LSD)	Language score	Generation R	4674
2.5 years	Parent Report of Children's Abilities (PARCA)	Non-verbal score	Generation R	4635
4 years	Behavior Rating Inventory of Executive Function (BRIEF)	Executive funtion	Generation R	4889
4 years	McCarthy Scales of Children Abilities (MCSA)	General cognitive score / Verbal score / Perceptive-performance / Executive Function	INMA	649
4 years	Conners' Kiddie Continuous Performance Test (K-CPT)	Inattention / Hyperactivity-impulsivity / Visual speed processing	INMA	404
5 years	Amsterdam Neuropsychological Tasks (ANT)	Attention / Visuomotor coordination / Response inhibition and flexibility	ABCD	3087

Table 3. Tests used in ESCAPE-Cohorts to assess motor development

Child's age	*Test used*	*Function*	*Cohort*	*N children*
6 months	Developmental milestones	Motor score	DNBC	13138
1.5 years				11644
1-2 years	Bayley Scales for Infant Development (BSID)	Psychomotor score (Fine motor, Gross motor)	INMA, RHEA, Duisburg	2213 585 186
1.5 years	Denver Developmental Screening Test-II (Denver-II)	Fine motor score / Gross motor score / Global motor score	GASPII	573
4 years				512
3 years	Ages and Stages questionnaires (ASQ)	Fine motor score / Gross motor score / Global motor score	EDEN	1261
3 years	Minnesota Infant Development Invertory (MIDI)	Fine motor score / Gross motor score / Global motor score	Generation R	4932
4 years	McCarthy Scales of Children Abilities (MCSA)	Fine motor score / Gross motor score / Global motor score	INMA	649

Table 4. General description of European birth cohorts with data on Neuropsychological development

Cohort	*Country*	*Enrolment Period*	*N Children*
1.ABCD (Amsterdam Born Children and their Development study)	Netherlands	2003-2004	7863
2.ABIS (All Babies in Southeast Sweden)	Sweden	1997-1999	17000
3.ALSPAC (The Avon Longitudinal Study of Parents and Children)	UK	1991-1992	14062
4.BASELINE (Babies After SCOPE: Evaluating the Longitudinal Impact using Neurological and Nutritional Endpoints)	Ireland	2008-2011	2185
5.BiB (Born in Bradford)	UK	2007-2010	13000
6.CCC2000 (Copenhagen Child Cohort 2000)	Denmark	2000	6090
7.CHOP Study (Childhood Obesity - Early Programming by Infant Nutrition)	Germany	2002-2004	1678
8.Co.N.ER (Bologna Birth Cohort)	Italy	2004-2005	654
9.DNBC (Danish National Birth Cohort)	Denmark	1992-2002	96986
10.Duisburg (Duisburg cohort)	Germany	2000-2003	234
11.EDEN (Study of determinants of pre and postnatal developmental, psychomotor development and child health)	France	2003-2006	1873
12.ELFE (French longitudinal study of children)	France	2011-2012	20000
13.EHL (Growing up in Wales)	UK	2009-2012	420
14.EPIPAGE (The Etude Epidémiologique sur les Petits Ages Gestationnels)	France	1997	2833
15.Faroes (Children's Health and the Environment in the Faroes)	Faroe Islands	1986-2009	2351
16.FCOU (Family and Children of Ukraine)	Ukraine	1992-1996	4510
17.FLEHS I (Flemish Environment and Health Survey)	Belgium	2002-2004	1196
18.GASPII (Gene and Environment: Prospective Study on Infancy in Italy)	Italy	2003-2004	708
19.Generation R (*98*)	Netherlands	2001-2006	9778
20.GMS (Gateshead Millennium Study)	UK	1999-2000	1029
21.GINIplus (German Infant Nutritional Intervention study - plus influence of pollution and genetics on allergy development)	Germany	1995-1998	5991
22.HHf2 (Healthy Habits for two)	Denmark	1984-1987	11144
23.HUMIS (Norwegian Human Milk Study)	Norway	2002-2009	2500
24.INMA (Environment and Childhood)	Spain	1997-2008	3768
25.INUENDO (Biopersistent organochlorines in diet and human fertility)	Greenland, Sweden, Poland, Ukraine	2002-2004	1322
26.KANC (Kaunas cohort)	Lithuania	2007-2009	4405
27.KOALA (Child, parents and health: lifestyle and genetic constitution)	Netherlands	2000-2003	2834
28.Kraków cohort	Poland	2001-2004	505
29.LIFE Child	Germany	2011-2014	2000
30.Lifeways Cross-Generation Cohort Study	Ireland	2001-2003	1074
31.LISAplus (Influences of life-style related factors on the immune system and the development of allergies in childhood – plus)	Germany	1997-1998	3097
32.MAS (Multicentre Allergy Study)	Germany	1990	1314
33.MoBa (The Norwegian Mother and Child Cohort Study)	Norway	1999-2008	107400
34.MUBICOS (Multiple Births Cohort Study)	Italy	2009	1000

35.NINFEA (Birth and Infancy: Effects of the Environment)	Italy	2005+	7500
36.Odense Child Cohort	Denmark	2010+	1650
37.PCB cohort (Early Childhood Development and PCB exposures in Slovakia)	Slovakia	2001-2003	1134
38.PÉLAGIE (Endocrine disruptors: Longitudinal study on pregnancy abnormalities, infertility, and childhood)	France	2002-2006	3460
39.PIAMA (Prevention and Incidence of Asthma and Mite Allergy)	Netherlands	1996-1997	3963
40.Piccolipiù	Italy	2011-2012	2000
41.PRIDE Study (PRegnancy and Infant DEvelopment Study)	The Netherlands	2011-2015	385
42.REPRO_PL (Polish Mother and Child Cohort)	Poland	2007-2011	1800
43.RHEA (Mother Child Cohort in Crete)	Greece	2007-2008	1500
44.SWS (Southampton Women's Survey)	UK	1998-2007	3159
45.TRIESTE cohort (Trieste child development cohort)	Italy	2007-2009	900

Table 5. European birth cohorts that have assessed or are planning to assess COGNITIVE MEASURES (from www.birthcohorts.net and www.birthcohortsenrieco.net)

Cohort	*Child age (years) at assessment*																		
	<1	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
ABCD						X													
ALSPAC					X				X							X			
BASELINE			X																
CCC2000		X										X							
CHOP Study							X		X										
Duisburg	X	X				X	X	X	X	X	X								
EDEN				X	X	X													
Faroes 1								X							X				
Faroes 3								X											
FCOU				X															
FLEHS I			X	X	X	X													
GASPII									X										
Generation R	X	X	X			X				X									
GINIplus																X			
HHf2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INMA		X			X							X							
Kraków cohort				X		X	X	X	X	X									
LIFE child	X																		
LISAplus											X					X			
MAS			X	X	X	X													
MUBICOS						X													
NINFEA					X														
PÉLAGIE							X												
PCB cohort		X	X	X	X	X	X	X	X	X	X								
REPRO_PL		X	X																
RHEA			X		X														
SWS					X		X												
TRIESTE		X		X				X											

Table 6 European birth cohorts that have assessed or are planning to assess SCHOOL PERFORMANCE (from www.birthcohorts.net and www.birthcohortsenrieco.net)

Cohort	*Child age (years) at assessment*																		
	<1	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
ABCD						X													
ABIS									X			X							
ALSPAC								X											
DNBC												X							
EDEN									X										
EHL					X	X													
Faroes 1															X				
FCOU								X											
GASPII									X										
GINIplus											X					X			
HHf2					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LIFE Child									X	X	X	X	X	X	X	X	X	X	X
LISAplus											X					X			
MoBa						X			X										
MUBICOS						X													
NINFEA								X											
PIAMA												X							

Table 7. European birth cohorts that have assessed or are planning to assess LANGUAGE (www.birthcohorts.net and www.birthcohortsenrieco.net)

Cohort	*Child age (years) at assessment*																		
	<1	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
ABCD						X													
CCC2000		X	X	X			X					X							
CHOP Study								X											
DNBC		X						X											
EDEN			X	X		X													
ELFE		X	X	X															
Faroes 1								X							X				
Faroes 3								X											
FCOU				X															
GASPII		X		X															
Generation R		X																	
HHf2		X	X	X	X	X	X	X											
HUMIS		X	X																
INMA		X			X							X							
Lifeways Cross-Generation		X	X	X															
LIFE Child		X	X	X	X														
MoBa		X		X		X			X										
MUBICOS			X			X													
Odense Child Cohort			X																
REPRO_PL		X	X																
RHEA			X		X														
TRIESTE		X		X				X											

Table 8. European birth cohorts that have assessed or are planning to assess ATTACHMENT (from www.birthcohorts.net and www.birthcohortsenrieco.net)

Cohort	*Child age (years) at assessment*																		
	<1	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
ABCD	X					X													
ABIS		X		X															
CCC2000	X	X					X					X							
CHOP Study								X											
Co.N.ER		X	X																
DNBC	X	X																	
EDEN		X	X																
ELFE		X	X																
FCOU				X				X											
GASPII	X	X		X															
Generation R		X	X																
GMS						X							X						
HHf2								X	X	X	X	X	X	X	X	X	X	X	X
LIFE Child	X																		
MoBa	X	X		X		X			X										
RHEA			X																
SWS				X															

Table 9. European birth cohorts that have assessed or are planning to assess NEUPSYCHOLOGICAL DEVELOPMENT (from www.birthcohorts.net and www.birthcohortsenrieco.net)

	Child age (years) at assessment																		
Cohort	*<1*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
BASELINE			X																
CCC2000	X	X					X					X							
CHOP Study								X											
Co.N.ER		X	X																
DNBC		X						X											
EDEN		X	X	X	X	X													
ELFE	X	X	X	X															
Faroes 1	X							X							X				
Faroes 3								X											
Faroes 5	X	X																	
FCOU				X				X											
GASPII	X	X		X					X										
Generation R	X	X	X	X	X	X				X									
HHf2								X	X	X	X	X	X	X	X	X	X	X	X
HUMIS	X	X	X						X										
INMA		X			X							X							
KANC						X													
LIFE Child	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MoBa	X	X		X		X		X	X										
MUBICOS	X	X	X	X	X	X													
NINFEA					X														
PÉLAGIE							X												
PIAMA												X			X				
Piccolipiù	X	X	X																
PCB cohort			X																
PRIDE Study	X																		
REPRO_PL		X	X																
RHEA			X		X														
TRIESTE		X		X				X											

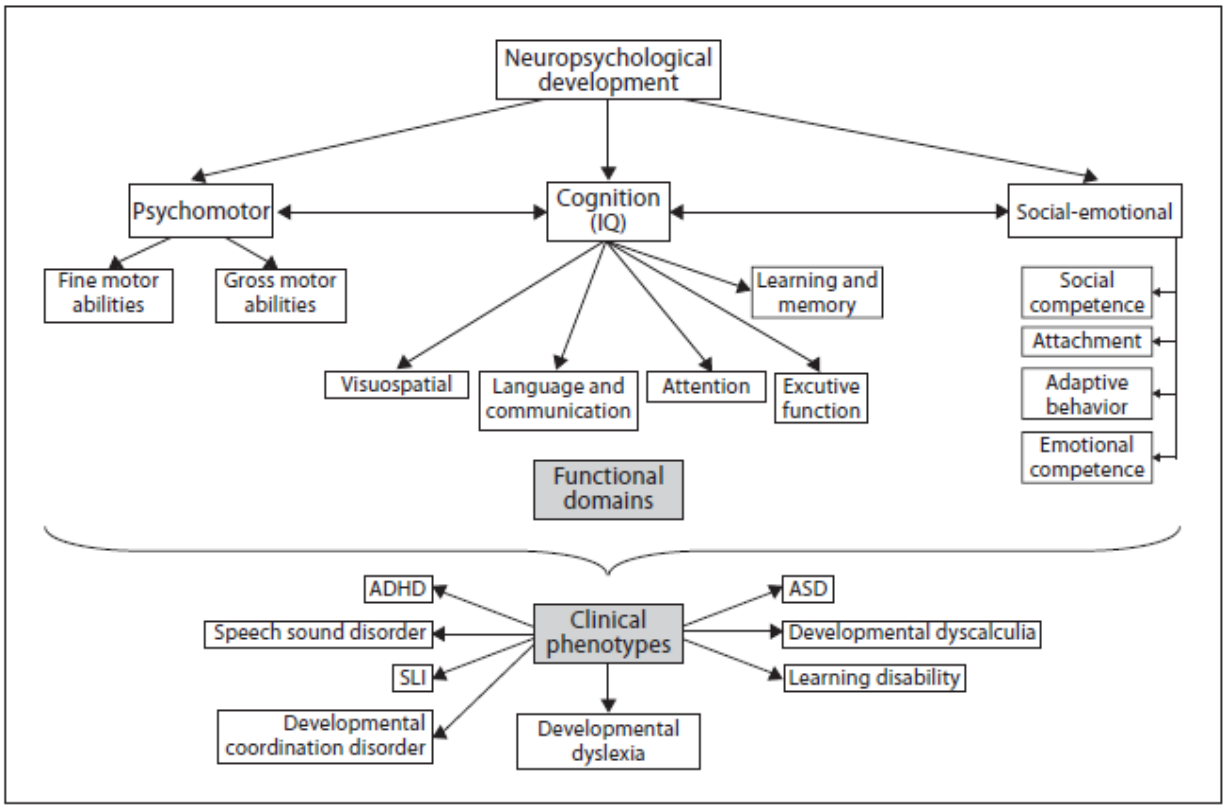
Table 10. European birth cohorts that have assessed or are planning to assess MENTAL HEALTH (from www.birthcohorts.net and www.birthcohortsenrieco.net)

Cohort	*Child age (years) at assessment*																		
	<1	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
ABCD	X					X													
ABIS	X		X	X		X			X			X							
CCC2000	X	X					X					X							
CHOP Study								X											
DNBC	X	X	X	X	X	X	X	X	X	X	X	X							
EDEN		X	X	X		X			X										
ELFE	X	X	X	X															
Faroes 1								X							X				
Faroes 3						X		X											
Faroes 5		X																	
FCOU				X				X											
HHf2																			X
HUMIS	X	X	X						X										
KANC						X													
KOALA		X	X																
LIFE Child	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MoBa						X			X										
REPRO_PL	X	X	X																
TRIESTE		X	X					X											

Table 11. Policy, diagnosis and treatment of ADHD in 4 European countries (from (*15*))

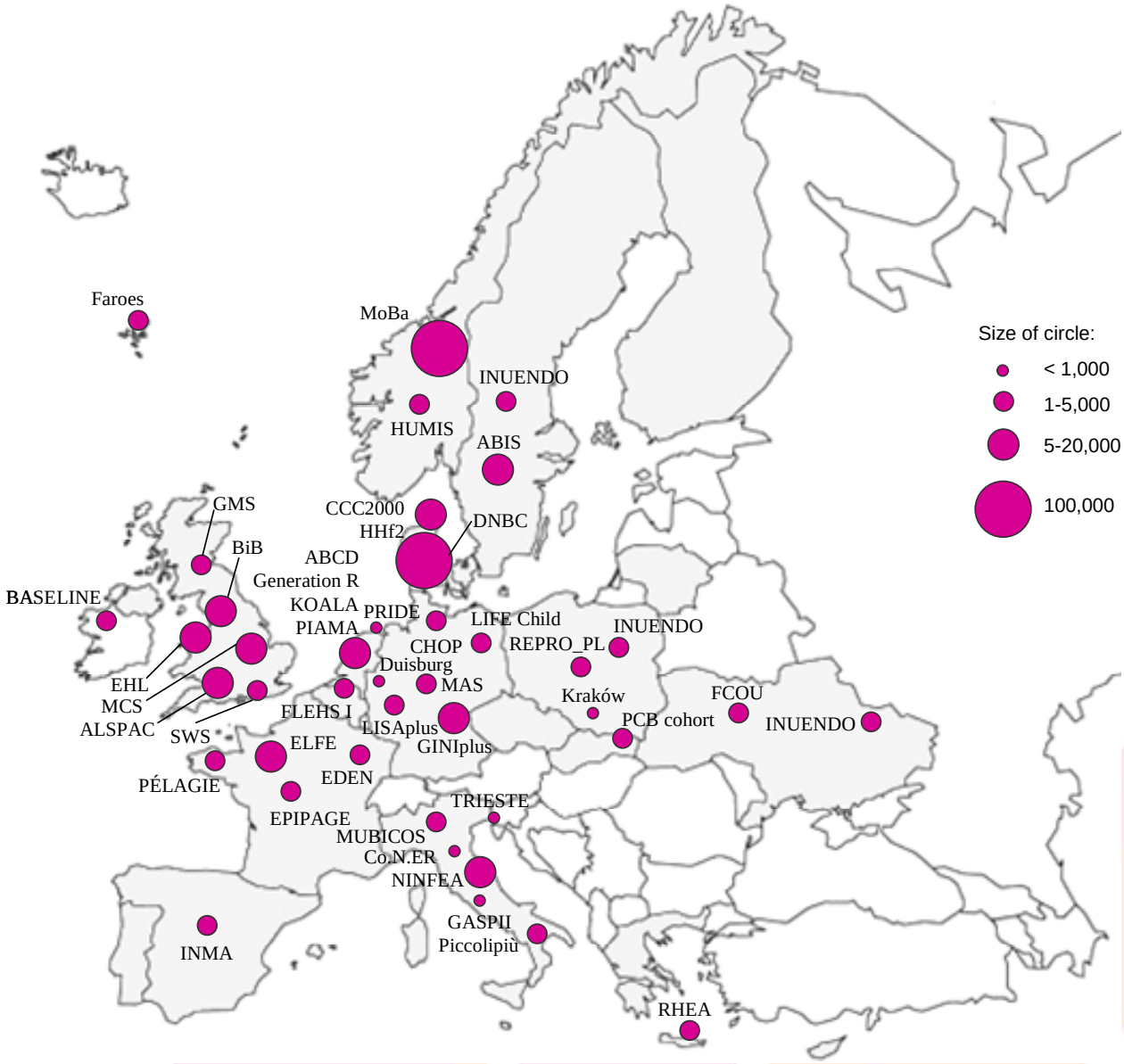
Country	*National Policy*	*Who diagnoses?*	*Treatment*	*Innovative treatment programmes*	*Teacher's knowledge (0=poor;5=excellent)*	*Associations*
Norway	non existing, only National guidelines for diagnostic and treatment	paediatrician, neurologist, psychologist (who works with paediatrician), child psychologist, neuro psychologist, child psychiatrist or neurologist	behavioural therapy, coaching (small scale/private), parent training (provided by public health service) *most therapies by public health system	non existing	2	ADHD Norge (www.adhdnorge.no/)
Poland	non existing	paediatrician, neurologist, family physician, psychologist, child psychologist, psychiatrist	behavioural therapy, parent training, group therapy, as a supplementary treatment: kinesiology, aggression replacement therapy biofeedback, sensory therapy provided by some local authorities but sometimes provided by NGOs; funded public/private sources	non existing	2	Polish ADHD Association (http://www.ptadhd.pl/)
Spain	Regional policies – autonomic communities	paediatrician, neuro paediatrician, neurologist, physician (less common), psychologist, child psychologist, educational psychologist, psychiatrist *diagnosis free	free (but not medication) behavioural therapy (mostly private), coaching (rare), parent training and support (provided by public & some private, but mostly by parent associations), psycho pedagogical help (private or parent associations)	non existing – some initiatives from parent associations with professionals from the Public Health Care at the local level (Adana Foundation & Vall d'Hebron Hospital, Barcelona)	2	Adana Foundation (http://www.f-adana.org/) Spanish Federation of ADHD Supporting Associations (www.feaadah.org)
The Netherlands	Diagnosis and Treatment of ADHD, was published in 2000 (*99*)	paediatrician, child neurologist, physician, psychologist, child psychologist, child psychiatrist, (ortho)pedagogue	behavioural therapy, coaching, parent training and support (peer contact). *treatment provided by state institutions for mental health, psychiatrists, psychologists, etc.; payment for treatment depends on insurance and medication type	neurofeedback, elimination diets, working memory training, computer games (not scientifically investigated or proven)	3	Balans (http://www.balansdigitaal.nl/) Impuls (http://www.impulsdigitaal.nl/)

Figure 1. Conceptual framework of the Neuropsychological Developmental Process



ADHD: Attention Deficit Hyperactivity Disorder; SLI: Specific Language Impairment; ASD: Autism Spectrum Disorder

Figure 2. Geographical distribution of European birth cohorts with data on neuropsychological development



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Developing a Child Cohort Research Strategy for Europe

Accidents and Injuries

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Summary

Child injuries are a global public health problem which start under the age of 1 year and progressively contribute more to the overall rates of death until children reach adulthood. The burden of injuries in children of the European region is primarily due to unintentional injuries and most are preventable. In Europe, low- and middle-income countries and deprived communities from high-income countries bear a disproportionately higher share of this burden. Epidemiological injury research has typically used available routine data sources and registries and the role of birth cohorts in this field has been very limited up to now; some work has used historical birth cohorts and child cohorts. These cohorts have frequently reported the incidence of injuries and the associated risk factors; only one cohort has studied the utility of safety behaviours in predicting childhood injury. Most of these studies come from the North of Europe (n=25); limited research have been conducted in Central and East European countries, where the prevalence of injuries is higher and the health inequalities are stronger. Very few of the CHICOS birth and child cohorts (n=12) have performed or are planning some assessment of injuries. Ten of these cohorts are situated in the North & West of Europe. All of them have collected this information through self-reported questionnaires; however, no standardised questionnaires or protocols exist in this field. Because cohorts collect data at individual level prospectively from the early life years onwards, birth and child cohorts have the potential to provide valuable information on environmental determinants (ie. social inequalities) and safety behaviours (ie. parental behaviour) associated with accident and injury prevention throughout childhood. Recommendations can be summarized as follows: (i) use of a standardized set of questions to assess determinants of injuries and safety behaviours; (ii) more focus on children from low-income and ethnic minority communities; particularly in cohorts from the Eastern part of Europe; (iii) links of cohort data with hospital registers; (iv) comparison studies between European cohorts to explore determinants and heterogeneity between studies; (v) collaboration with other European projects, such as the TACTICS project (European Child Safety Alliance initiative); (vi) effective communication between cohorts and policy makers and other stakeholders.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

Mortality rates from childhood injuries (including road traffic accidents, poisoning, falls, drowning, and burns) have declined in many European countries over the past decade, but injury remains the leading cause of childhood death and disability in the EU (European Report on Child Injury Prevention 2008; Sethi et al. 2008; Valent et al. 2004). In 2004, 42,000 children and adolescents aged 0–19 years died from unintentional injuries in the WHO European Region - but the impact of injuries is much greater, with many children suffering form long-term disability (Polinder et al. 2005), and millions of hospitalizations and emergency care visits (Sethi et al. 2008). Differences in childhood injury rates have been reported within Europe and rates are particularly high in low- and middle-income countries, with rates of injury mortality among children more than three times greater than in high-income countries (particularly Central and Eastern Europe) (Ellsasser and Berfenstam 2000; Petridou 2000; Sibert and Stone 1998; Valent et al. 2004). Furthermore, in high-income countries, deprived communities bear a disproportionately higher share of the burden (Sethi et al. 2008). The Child Safety Report Cards, developed as part of the Child Safety Action

Plan initiative (European Child Safety Alliance), are overviews that summarise countries' levels of safety provided to their children through national policy in order to provide countries with an informed starting place for child safety action (http://www.childsafetyeurope.org/reportcards/index.html) (the cards were recently awarded the Gastein 2011 European Health Award (http://www.ehfg.org/fileadmin/ehfg/Website/Preis/FR-E-European_Health_Award-FINAL.pdf).

The burden of injuries in children of the European region is primarily due to unintentional injuries, and most are preventable. Home-related unintentional injuries remain an important health threat among children. In Western countries for instance, unintentional injuries are the main cause of death among preschool children and the primary reason for them to visit the emergency in the hospital (Sethi et al. 2008). Among preschool children, toddlers aged 1-2 years, have the highest risk to get injured. Policies and services aimed at prevention could therefore reduce the health burden significantly. For this purpose, injury databases are being developed in different European countries to provide surveillance data to identify emerging threats, describe the nature and circumstances of the injury events to allow increased understanding and prioritisation, to inform the development of programmes and policies, and provide a source of data for evaluation. A large injury database was also developed to address a number of the limitations of the existing routinely collected data (Petridou 2000) (The European Injury Database (IDB): https://webgate.ec.europa.eu/idb).

Epidemiological injury research has mostly used routine data sources and registries (for example (D'Souza et al. 2008)) and the role of birth cohorts in this field has been very limited up to now; some work has used historical birth cohorts and child cohorts (Laflamme et al. 2004; Lawlor et al. 2007; Osler et al. 2007; Rowe et al. 2004). However, as part of the development of a future research strategy, the potential role of birth cohorts (potentially by linking data national health registers, including national injury registers, national disability registers, and treatment registers, such as Hospital Discharge Registers) in establishing incidence, examining causes, exploring relationships with other health outcomes, exploring inequalities, and evaluating effects of interventions, needs to be evaluated. Therefore, the main aim of this working group is to evaluate potential for future birth and child cohort contribution in the area of injury prevention and evaluation of interventions.

1.2. Description of the contribution of (European) birth cohort research to scientific knowledge

1.2.1 Birth and Child cohort studies – contribution to scientific knowledge

In order to evaluate the contribution of European birth and child cohort studies to the scientific knowledge in this field, we have performed an internet literature search in PubMed. Relevant publications until 6th July 2011 were identified by using the following search terms: *(birth cohort OR child cohort) AND (accidents OR injuries) AND Europe*. In this search a total of 308 publications were initially identified. Cohorts that studied the health consequences of unintentional injuries, that follow a specific group of patients, and retrospective studies, were excluded. Finally, a total of 20 papers remained for the present report. An additional search was performed to identify publications from European cohorts that collect information on injuries (see section 1.3 and table 2); following these search terms: *name of the cohort AND (accidents OR injuries)*. This search identified 7 publications more. Manual searches of references of articles identified by the electronic search were also performed. Overall, a total of 29 publications were included (table 1). They

were classified as: a) recent birth cohorts - if they started the recruitment after 1990; b) historical birth cohorts - if they start the recruitment before 1990; and c) child cohorts (<18 years).

1.2.1.1 Recent birth cohorts

Six out of the 29 publications were identified as recent birth cohorts. Five of them originated from the Avon Longitudinal Study of Parents and Children (ALSPAC) with more than 10000 participants. In ALSPAC information regarding injuries was collected through self-reported questionnaires at different child ages. The incidence of injuries was reported, showing that falls without injuries are the most frequent accident. Children from single-parent families, younger mothers, and of children from families of low socio-economic status have more risk of having an accident. The Coventry Cohort Study recruited more than 2000 children and followed them for 8 weeks. Parents reported the frequency of injuries requiring medical attention during this period.

1.2.1.2 Historical birth cohorts

Twelve publications were identified from historical birth cohorts, particularly from the 1958 and 1970 British birth cohorts and from the Northern Finland 1966 Birth Cohort. The two British cohorts, including more than 10,000 children each, reported the incidence of unintentional injuries per cohort in children aged 0-17 years old. Self-reported questionnaires were used to collect the data. Home accidents were the most frequent injuries, particularly burns. They also reported some factors that may increase the risk of being injured, such as abnormal child behaviour, having family problems, teenage mothers, or having a low social position. The NFBC 1966 birth cohort evaluated the incidence of injuries and possible factors associated linking the cohort data with national registers of injuries. They found that criminal behaviour, single-parent families and alcohol drinking during adolescence, all increased the risk of injuries in adulthood.

Two cohorts of Northern Europe studied the association between cognitive function measured in children (7-18y) and risk of injuries during later childhood and adulthood. Registers were used to collect data on injuries. An inverse association was found in both studies, and this relationship was partly explained by educational attainment. Finally, the Copenhagen Birth Cohort 1959-61 (N= 9,006 mothers) showed that injuries occurring during the first years of life did not have any effect on the quality of life in adulthood.

1.2.1.3 Child cohorts

A total of 11 cohorts were identified as child cohorts, independently of the start of the recruitment. In France, a cohort of middle and high school children was followed over one year to study the risk factors for single and multiple injuries. An injury questionnaire was completed by the school nurse. Younger age and frequent use of psychotropic drugs were more strongly related to frequent injuries than single injury. The Millennium Cohort Study in the UK studied the influence that childcare and household moves during pregnancy had on child injuries during the first years of life. Overall, moving homes during pregnancy and infancy increased the risk of injuries particularly in less affluent groups. Another cohort in UK (Nottingham), which studied children between 0 and 7 years old, concluded that focussing prevention of injuries at family and ward levels rather than at neighbourhood level would be more efficient in reducing inequalities in injury rates. The same cohort examined the utility of home safety behaviours (smoke alarms, storing sharp objects safely, stair gates, etc) in predicting childhood injury, showing that hospital admissions rates were lower in families having smoke alarms, stair gates and storing sharp objects safely. Other cohorts in UK,

Scotland and Greece, also identified that low socioeconomic status, younger mothers, and family problems (such as alcohol and depression) increase the risk of childhood injuries. Finally, Reinberg et al studied the rhythmicity of paediatric injury occurrence seeing that there is a peak at 4 pm independently of sex, age and traffic load.

1.2.2 Other study designs – contribution to scientific knowledge

Most of the research in injuries has used other epidemiological design such as patient cohorts which follow a specific group of children, intervention studies, or registries.

1.2.2.1 Patient cohorts

Patient cohorts are used to study the risk of having an accident/injury in a specific group of patients, or to study the health consequence of having an accident/injury. The first question has mostly been mostly studied in patients with a specific pathology or disability such as diabetes, Down's syndrome, epilepsy, cerebral palsy, or vision defects (Cumberland et al. 2004; Miao et al. 2005; Morton et al. 2006; Turner et al. 1990; van den Broek M. and Beghi 2004). Data is collected from hospitals or health care centres registers.

The second set of studies, evaluate the consequence of road traffic accidents, specific injuries such as traumatic brain injury or nervous system trauma, fractures or unintentional ingestions (Brockstedt et al. 2004; Kopjar and Wickizer 1998; Rantakallio and von Wendt 1985; Timonen et al. 2002). These studies also collect patient information from hospital records. Health effects studied most frequently are psychological stress in children involve in road traffic accidents, disabilities, chronic diseases, activity restriction after a fracture, or long-term "health-related quality of life" (Stallard et al. 1998; Sturms et al. 2003; Sturms et al. 2005).

1.2.2.2 Intervention studies

Intervention studies are necessary to evaluate strategies for reducing the incidence of unintentional injuries that will be implemented at different population levels. Randomized controlled trial is the study design mostly used. In Europe, intervention studies have focused on prevention of road traffic injuries (Forjuoh and Li 1996), home injuries (Ingram et al. 2011; Phelan et al. 2009), thermal injuries including fireworks (D'Argenio et al. 1996; Turner et al. 2004), use of cycle helmets (Royal et al. 2005), and poisoning prevention including alcohol, among others. The European Report on Child Injury Prevention, published in 2008 by the European Child Safety Alliance, describes in detail all the interventions conducted in Europe on road traffic injuries, poisoning, drowning, falls and burns (Sethi et al. 2008). A systematic review of controlled trials gives a good example of an effective intervention to promote smoke alarms – programs that provided and installed smoke alarms appeared to be more efficient than interventions that only promoted smoke alarms (DiGuiseppi and Higgins 2000). In Krakow (Poland), a community-based multi-method programme was implemented to prevent mushroom poisoning for young schoolchildren. Evaluation showed significant improvements in knowledge and decreased intention to eat wild mushrooms. Kendrick et al. (Kendrick et al. 2011) recently tested the effectiveness of thermostatic mixing valves in reducing bath hot tap water temperature in families in young children. A systematic review about the effectiveness of programmes in decreasing unintentional injury rates to children in the home has recently been published (Pearson et al. 2011). The Collaboration for Accident Prevention and Injury Control

(CAPIC-http://www.capic.org.uk.html) maintains an ongoing list of all systematic reviews on injury prevention.

A recent intervention study implemented in Europe is the BeSAFE project (www.besafe-onderzoek.nl) developed by the Erasmus MC – Rotterdam (Netherlands). This project is a randomized controlled trial with a baseline measure point prior to the intervention (5-8 months age of child) and a follow-up measure point 6 months after the intervention. The objective is to evaluate the effect of on-line, internet-based, tailored safety information combined with personal counselling on parents child safety behaviours (intervention group). Also, a process evaluation will be conducted to provide insight in the feasibility of the intervention. This study hypothesizes that after follow-up the parents of the intervention group show more safety behaviour compared to the control group (van Beelen et al. 2010).

1.2.2.3 Registries

Patient registries and databases are important instruments to develop research in the field of childhood injuries, and to improve patient care and healthcare planning. The registration of treatment has traditionally covered inpatient care only, but increasingly outpatient care in hospitals, primary care and GPs is registered. They provide sufficient sample size for epidemiological research. Studies using registers have focused on the study of the incidence and determinants of injuries such as socioeconomic variables (maternal characteristics, family income, etc.), household characteristics (built form, neighbourhood, etc), and the evaluation of interventions.

In Europe, the European Injury Database (IDB) (https://webgate.ec.europa.eu/idb) provides central access to the data collected in the emergency departments of the member states hospitals regarding injuries; at present, a total of 15 Member States are providing sample of the data, which is not representative of the whole country. All count Furthermore, the EU funded JAMIE (Joint Action on Monitoring Injuries in Europe - http://www.eurosafe.eu.com/csi/eurosafe2006.nsf/wwwVwContent/l3projects-333.htm) project is developing a system in which all countries should be able to provide minimum datasets on injuries as well as the full dataset used in IDB. To date, 24 European countries join the project. There are also some national accident and injury admissions registers and some mixed injury surveillance/treatment registers in different European countries such us Denmark (Danish National Patient Registry: http://www.si-folkesundhed.dk/), Norway (The Norwegian Patient Register: http://www.nsd.uib.no/polsys/data/en/forvaltning/enhet/37606), The Netherlands (Dutch Injury Surveillance System:http://www.swov.nl/index_uk.htm), Greece (Katsaragakis et al. 2009), Germany (Neugebauer et al. 1990), and UK (TARN database: www.tarn.ac.uk).

Many studies have been conducted in Europe collecting information on injuries from registers. Some of these are large prospective cohort studies which include essentially all the children in a country, and follow them for some years. In a study conducted in Sweden for example, all children and adolescents aged 5–19 in 1990 (more than 1 million) were grouped into three age cohorts, and each cohort was then followed up for 5 years (1990–1994) with regard to injuries (as registered in the national Hospital Discharge and Causes of Death registers) (Engstrom et al. 2003). In Denmark, a similar study was conducted where all Danish children were grouped in three independent cohorts of children (more than 500 000 children) and followed at 0–2, 6–8, and 12–14 years (Laursen 2006).

1.3 Description of data currently available/being collected by the European birth cohorts

There are some birth and child cohorts in Europe that are collecting information on injuries. Cohorts have been identified from different sources: 1) the website of individual cohort studies; and 2) publications.

As of late 2011, we have identified a total of 9 birth cohorts and 3 child cohorts that have recorded or are planning to record data on injuries (table 2). All of them are situated in the Northern and Western part of Europe, except the INMA and the GASPII cohorts situated in the Southern part. One study, the Norwegian Mother and Child Study (MoBa) has recruited around 100,000 mother-child pairs. The new UK Birth Cohort is also planning to recruit nearly 100,000 children. Four cohorts have recruited between 8,000-15,000 children (ALSPAC, Generation R, Growing up in Ireland, and MCS) whereas the rest have recruited less than 5,000 mother-child pairs (table 2). The EHL Study (Environments for Healthy Living), embedded within the Wales Electronic cohort for Children (N=800,000), is planning to recruit 1,000 children. It is noteworthy that all of these cohorts have collected this information through self-reported questionnaires (table 3).

The ALSPAC birth cohort asks about burns, falls, choking injuries or those occurring while playing a sport or games when children are 6 and, 12months, and 6-7, 8-9 and 11-12 years old. They also ask if because of the incident the child has a scar, a physical disability or a psychological problem. The DNBC cohort has included questions on injuries at 11 years old follow-up but the questionnaire is not available in English yet (Danish version). In Italy, the Co.N.ER Cohort asks at 6 and 15 months and 4 years if the child has burned him/herself, has fallen and/or if a visit to the emergency ward was needed. At 4 years they also ask if the child has swallowed something or ingested a toxic substance after 12 months of life. The Generation R Birth Cohort asks at 4 different time points during childhood: at 6 and 18 months, and at 2 and 5-6 years. They ask which type of accident he/she had, the type of wounds it caused, the type of treatment and the consequence. Questions concerning house environment and parent behaviour at home were also included. The Growing up in Ireland Child Cohort asks how many accidents or injuries the child has had that required hospital admission. The 4 INMA new cohorts (Asturias, Gipuzkoa, Sabadell and Valencia) ask at 12m and 24m if the child has required some medical assistance from a doctor who is not the habitual doctor and the cause of this (open question). The Lifeways Cross-generational Cohort study they asked how many injuries or accidents the child has had that needed the attention of a doctor and if he had to stay in a hospital for at least one night. The Millennium child cohort study on the other hand, asks at 4 different time points (1-2, 4-5, 6 and 8 years) the type of accident or injury the child had (specific responses) and if it required hospital admission. Finally, the Norwegian Birth Cohort (MoBa) asks at 18 and 36 months if the child has had an accident or an injury, without specifying the type.

Although we were not able to find the questionnaires used in the Growing up in Scotland Child Cohort, they collected information on injuries because they reported the prevalence of injuries that required the National Health Service, the most common type of accident, and the general characteristics of those children (Anderson et al. 2007; Bradshaw et al. 2008).

1.4 Identification of gaps

- Low-income and ethnic minority communities have major risk of injuries; however, very low-income populations are frequently under-represented in epidemiological studies, including the European birth cohorts because of educational and access restraints.

- Poor research in Central and East European countries where the prevalences of injury are higher. Child Safety Alliance: "For the period 2010 to 2015, the focus will be on unintentional injuries and deaths for children with an emphasis on actions to begin to reduce inequities between Member States including initiating and enhancing capacity especially in Central and Eastern Europe. We will concentrate on promoting the wider application of safety practices that are proven to be effective. The scope of work will include the area of accident and risk factors analysis".
- Good data on mortality, morbidity, exposure, outcomes and costs are needed to provide a foundation on which to develop and monitor policies that promote child safety. Most countries need better information on the circumstances and activities surrounding an injury and the socioeconomic determinants, which are essential to understanding exposure and risk and to developing comprehensive responses (from European Report on Child Injury Prevention).
- There is currently not much information collected about environmental safety in cohort studies through whole Europe. Further research could be done here – including a comparison between countries.
- Countries from the Commonwealth of Independent States (CIS) (Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, and Uzbekistan), Eastern part of the WHO European region (Albania, Bosnia and Herzegovina, Georgia, Liechtenstein, Montenegro, Serbia, Turkmenistan, and Ukraine) and Lichtenstein are not included in the European Child Safety Alliance (http://www.childsafetyeurope.org/) and consequently they have not had the opportunity to be part of a common strategy for child injury prevention.

Potential contribution of birth cohorts in future

In order to identify the future contribution of birth and child cohort research in this field we have followed the different steps of the "model for planned health education and health promotion" suggested by (Brug et al. 2005) (figure 1). This model was initially developed for behavioural nutrition and physical activity interventions but in our case it will be useful to identify the different steps that should be followed to promote child health in the area of injuries and which will be the possible role of birth and child cohort studies. We have chosen this model as an example, even though other ecological models exist, such as the Ken McLeroy et al. (McLeroy et al. 1988) model for health promotion which focuses attention on both individual and social environment.

- Analysis of population health: identification of health problem. European injury registers and databases may be the best sources to obtain this information. The European Child Safety Alliance for example (http://www.childsafetyeurope.org/actionplans/index.html), which is part of the European Association for Injury Protection and Safety Promotion (EuroSafe http://www.eurosafe.eu.com/), provides the injury incidences 30 European countries. However, child cohorts and birth cohort studies can be linked with national registries and obtain such information.
- Analysis of behaviour: identification of possible behavioural causes of the health problem. One example could be the parental behavioural attributes aiming to adapt the home environment to make it safer. Cohort studies (child and birth cohorts) can be very useful to explore the parental behaviour role and the compliance with injury prevention measures (i.e. use of booster seats; use of

stair gates, etc). Some cohorts have used the "Home Safety Questionnaire" to evaluate the family ecology at home (birth cohorts: Faroes, FLEHS, PCB cohort - www.birthcohortsenrieco.net); others are planning to collect home safety information using web based assessments (www.SafeHome.co.uk).

- Analysis of determinants of behaviour: analysis of the determinants of health-related behaviours. These determinants can be divided in: 1) personal or internal determinants such as self-efficacy, attitudes and risk perception, 2) environmental or external determinants, such as physical and social environmental factors. Research identifying personal and environmental factors associated with injury preventive behaviour is limited (Trifiletti et al. 2005). In this case, cohort studies (child and birth) are crucial in exploring these relationships (explore inequalities - individual vs society level) and also with other health outcomes (cognition, behaviour, etc.), because they collect information on many co-variates and follow children up for several years (Haynes et al. 2008; Sun et al. 2010).
- Intervention development: to establish changes in the determinants and the actual behaviour. Intervention studies have been the most used study design in this case comparing a group subject to an intervention and another group not subject.
- Intervention implementation and dissemination: evaluation of the developed interventions is crucial to determine whether they have had the expected outcomes (effect evaluation). Cohort studies can be useful in evaluating effects of interventions. Such evaluation should take place during the whole process of planned health education.

2. Recommendations:

Conclusions

Contribution of European historical and recent birth and child cohorts in injuries research is not insignificant. Most studies have come from the North of Europe (n=25) – limited research in Central and East European countries, where the prevalence of injuries are higher and the health inequalities stronger. They have frequently reported the incidence of injuries and the associated risk factors; only one cohort has studied the utility of safety behaviours in predicting childhood injury. The risk factors most frequently studied have been socioeconomic status, family/ward/neighbourhood characteristics, child behaviour and cognition, and alcohol/drugs consumption.

Patient cohorts have mostly used register data to explore the risk of injury of a specific group of children or to study their health consequence. Intervention studies, on the other hand, use randomized controlled trials to evaluate the feasibility of the intervention. Overall, epidemiological injury research has typically used available routine data sources and registries.

Very few of the CHICOS birth and child cohorts (n=12) have performed or are planning some assessment of injuries. All cohorts have included questions on type of injury and the treatment if needed. Most cohorts include an open question ("type of incident") and 2 cohorts a close question (burn, fall, choking, etc). Two cohorts (ALSPAC and Generation R) ask about the consequence of the injury (scar, physical disability, etc). Only one cohort (Generation R) includes questions regarding the house environment and parental behaviour at home. There are no standardised questionnaires or protocols in this field.

Recommendations

- It is recommended that European cohorts use a set of standardised questions to assess determinants of injuries and safety behaviours. A short proposal of these questions is included in Appendix I. It is recommended that questions related to house environment and parent attitude towards home injury prevention are included as part of that set.
- Children from socioeconomically deprived backgrounds have an increased risk of injury; therefore, it is recommended that existing cohorts, particularly those situated in Southern and Eastern Europe (particularly those from the CIS Eastern part of the WHO Euro region), include injury related questions in the next follow-ups. It is recommended that new cohort studies in Europe include children in low-income and ethnic minority communities in the initial recruitment. Increase in capacity and resources should be recommended for Central and Eastern Europe to adequately address the issue.
- Cohorts collect data at individual level and thus they provide an opportunity to explore exposure data including hazards and uptake of preventive measures. They can also calculate population estimates. It is recommended that birth and child cohorts use a hospital register, if possible, to obtain information that is not available through questionnaires (i.e. medical register of injuries on treatments). Unique identifiers facilitate the linkages between different data sources, even though matching of different data can be also done without them. Data protection regulations and rules may, however, complicate or even ban such linkages in some European countries. Cohorts should explore linkages with other data sources and examples of where this has been successfully achieved can be written up and shared.
- Data on exposures is generally poorly collected in cohort studies. Web based assessments are being developed which will allow respondents to provide data on exposures at different time points such as the www.SafeHome.co.uk (in construction) for the EHL cohort in Wales and hopefully for use in the new UK Birth Cohort Study. Also, the development of methods for anonymised data linkage at individual, household and area levels will allow to incorporate environmental exposure and safety data into cohorts (existing and new) without needing to add to respondent burden (Rodgers et al. 2011).
- Although data from CHICOS cohorts are limited and questions are not standardized, some comparison studies on determinants and heterogeneity between studies (inventorising the variables and collection methods) should be carried out as a first step towards a potential future European analyses of risk factors of specific injuries (ie. burn, falls); European combination may be particularly useful for injuries with a low prevalence in one cohort. Guidance can be found in the systematic review of child injury and socioeconomic status for the Goverment of Canada in 1999 (http://www.phac-aspc.gc.ca/hp-ps/dca-dea/stages-etapes/childhood-enfance/injury-blessure/pdf/injury_e.pdf) which highlights also the challenges in comparing results from differently collected injury questionnaires.
- New European cohort studies should be developed to provide evaluations of multiple interventions which might have a direct or indirect effect on safety. The key issue is to accurately tag the people, households or areas receiving the intervention.
- It is recommended that cohorts in CHICOS collaborate with other European projects that focus on childhood injuries, such as the TACTICS project. TACTICS is a large scale, multi-year initiative of the European Child Safety Alliance that is working to provide better information, practical tools and resources to support adoption and implementation of evidence-based good practices for in Europe. One specific objective is to explore the effect of health and social inequalities as they relate to

childhood injury and more specifically target capacity building efforts at the regional and local levels. TACTICS has the participation of partners from more than 30 European countries, including national and international experts (www.childsafetyeurope.org).

- Effective communication between cohorts and policy makers and other stakeholders is needed. It is recommended that cohorts work together with health sectors, local and national institutions on making environments safer for children.

Tables and figures

Table 1. Birth cohorts (recent and historical) and Child cohorts in Europe with published work on Injuries

Cohort (country)	*Author, Year*	*N children*	*Age studied*	*Objective*	*Information source of injuries*	*Main results*
Recent birth cohorts						
ALSPAC, UK	O'Connor, 2000 (O'Connor et al. 2000)	10000	2y	Distribution of accidents, injuries and illnesses by family type	Questionnaires	Children in single-parent and stepfamilies were more likely to have accidents.
ALSPAC, UK	Warrington, 2001 (Warrington and Wright 2001)	11466	0-6m	Incidence of accidents and injuries	Questionnaires	Falls are common (22%) while burns are rare (1.5%).
ALSPAC, UK	Reading, 2008 (Reading et al. 2008)	14062	0-5y	Neighbourhood-level influences on the risk of injuries	Questionnaires	Factors related with a higher risk of accidents: children with more displayed greater conduct and behavioural problems, younger mothers, without work, unemployed and alcohol drinking fathers, and financial stress. Parental and household social circumstances influenced more than the level of neighbourhoods (physical).
ALSPAC, UK	Haynes, 2008 (Haynes et al. 2008)	9391	Pre-school	Accidents and neighbourhoods	Questionnaires	The risk of accidents and factors associated varied significantly between neighbourhoods.
ALSPAC, UK	Beale, 2010 (Beale et al. 2010)	10000	6-8m	Reported accidental injuries and socioeconomic status	Questionnaires	The lower the socioeconomic status, the higher the clinical burden.
Coventry cohort study, UK	Spencer and Coe, 2000 (Spencer and Coe 2000)	2572	0-8w	Parent-reported infant health and illness (birth to 8w)	Questionnaires	Incidence rate of accidents: 16 (95%CIs 9-21)/1000
Historical birth cohorts						
1958 British birth cohort, UK	Peckham 1973 (Peckham 1973)	17000	7-11y	Incidence of accidents	Questionnaires	Accidents: 52% (29% boys, 23% of girls and more common in manual workers): home accidents: 17%-particularly burns; school accidents: 3%; road accidents: 2%. Drowning: 3%. Poisoning: 2%.
1958 British birth cohort, UK	Pless, 1989 (Pless et al. 1989)	16000	7-11y	Factors that may affect the risk of having a traffic injury	Questionnaires	Fidgety, abnormal behaviour, crowding, family problems and living in the care of the local authority were associated with injuries.
1970 British birth cohort, UK	Taylor, 1983 (Taylor et al. 1983)	11981	0-5y	Health outcomes in children born to teenage mothers compared to those born to older mothers	Questionnaires	Frequent accidents, poisoning, burns, and superficial injuries were more often reported by teenage mothers, even after adjusting for socioeconomic circumstances.
1970 British birth cohort, UK	Bijur, 1988 (Bijur et al. 1988)	10394	0-10y	Injuries between 0-5y and injuries between 5-10y	Questionnaires	The number of injuries before 5y of age was the best predictor of injuries reported between 5-10y.
1970 British birth cohort, UK	Beattie, 1999 (Beattie et al. 1999)	1416	10-17y	Incidence, site and severity of injuries requiring medical attention	Questionnaires	Incidence of injuries: 43% (males higher than girls).
Copenhagen Birth Cohort 1959-61, Denmark	Vendegodt, 2006 (Ventegodt et al. 2006)	7222	31-33y	Factors occurring during the first years of life and the quality of life later as an adult	Questionnaires	Accidents did not have an effect.
NFBC 1966, Finland	Sauvola, 2000 (Sauvola et al. 2000)	Non reported	16-28y	Single-parent family background and physical illness	Not specified	Hospital-treated injuries were more common in women of single-parent family background than among two-parent family background.
NFBC 1966, Finland	Timonen 2003 (Timonen et al. 2003)	10934	0-33y	Adverse physical disorders and criminal behaviour	Registers	Criminal behaviour increased the risk of injuries.

Cohort (country)	*Author, Year*	*N children*	*Age studied*	*Objective*	*Information source of injuries*	*Main results*
NFBC 1966, Finland	Winqvist, 2006 (Winqvist et al. 2006)	10424	14-35y	Adolescents' drinking habits and risk of traumatic brain injury	Registers	The habit of frequent drinking increased the risk for TBI in adolescence and young adulthood.
NFBC 1966, Finland	Winqvist, 2007 (Winqvist et al. 2007)	12058	0-34y	Incidence of TBI	Registers	Incidence: 118/100,000; Prevalence at 34y: 269/100,000. Pick incidence at 6-7y in both genders and 18-23y in men (these ones were associated with alcohol drinking).
Metropolit 1953 male birth cohort, Denmark	Osler, 2007 (Osler et al. 2007)	11532	12y	Cognitive function in childhood is a modifiable risk factor for adult injury	Questionnaires and registers	Cognitive function (12, 18y) was inversely associated with any form of unintentional injury, and this relationship was partly explained by educational attainment.
The Aberdeen Children of the 1950s Cohort Study, UK	Lawlor, 2007 (Lawlor et al. 2007)	11103	7-11y	Childhood intelligence and hospital admissions for injuries in childhood	Questionnaires and registers	Childhood intelligence (7, 8, 11y) was inversely related to hospital admissions for injuries, and this relationship is partly explained by educational attainment.
Child cohorts						
France	Chau, 2007 (Chau et al. 2007)	2398	Middle and high school	Individual characteristics in school injury	Questionnaires	Prevalence: 13% (boys and girls). Sports/physical training injury was more frequent among girls. Potential risk factors are: age <15y, being not calm, obesity, not living with both parents, etc.
France	Chau, 2008 (Chau et al. 2008)	2396	Middle and high school	Individual characteristics in school injury	Questionnaires	Risk factors for single injury and multiple injuries occurred during one school year were different.
MCS, UK	Pearce, 2010 (Pearce et al. 2010)	18114	9m, 3y	Impact of childcare on childhood unintentional injury	Questionnaires	At 9m, infants from low socioeconomic group were more likely to be injured. At age 3y informal childcare was associated with an increased risk of injury overall.
MCS, UK	Tunstall, 2010 (Tunstall et al. 2010)	18197	9m	Health status of pregnant mothers that move home within developed countries	Questionnaires	Families that moved during pregnancy and infancy had higher risk of accidents among infants than non-movers.
Nottingham, UK	Kendrick and Marsh, 2001 (Kendrick and Marsh 2001)	771	3-25m	Medically attended unintentional injury, sociodemographic characteristics and previous injury	Questionnaires	Live in a deprived ward is associated with any medically attended injury, with hospital admission and with number of injuries received.
Nottingham, UK	Kendrick, 2005 (Kendrick et al. 2005b)	2357	0-7y	Safety behaviours at home and child injuries	Questionnaires	Hospital admissions rates were lower in families having smoke alarms, stair gates and storing sharp objects safely.
Nottingham, UK	Kendrick, 2005 (Kendrick et al. 2005a)	2357	0-7y	Role of neighbourhood effects in childhood injury	Questionnaires	No association found – family and ward characteristics play a major role.
Scotland, UK	West and Sweeting, 2004 (West and Sweeting 2004)	2586	11-15y	Socioeconomic influence on accidents and injuries	Questionnaires	A social gradient is shown in males at 15y, accident rates increasing from group I to V.
Switzerland	Reinberg, 2005 (Reinberg et al. 2005)	20703	0-16y	Rhythmicity of paediatric injury occurrence	Hospital register	Circadian rhythms (peak around 4pm) were not influenced by age, sex, or motor vehicle traffic load.
Sweden	Larsson, 1996 (Larsson and Aurelius 1996)	366	0-10y	Children experienced psychological stress had higher risk of having accidents.	Not specified	Having a parent with alcohol problems and having symptoms of depression, anxiety and problems in social relationships increase the risk of accidents among boys and girls, respectively.
Velestino study,	Petridou, 2005	748	0-14y	Incidence of unintentional injuries	Questionnaires	Incidence: 28 per 100 person-years

Cohort (country)	*Author, Year*	*N children*	*Age studied*	*Objective*	*Information source of injuries*	*Main results*
Greece	(Petridou et al. 2005)					Family related variables are more important than somatometric characteristics of the child. Children of younger and less educated parents had higher risk for injury

MCS: Millennium Cohort Study; NFBC: North Finland Birth Cohort; TBI: Traumatic brain injury
Questionnaires: self-reported, medical, parental or teachers'

Table 2. General description of CHICOS birth and child cohorts with data on Injuries

Cohort	*Country*	*Regions covered*	*Enrolment Period*	*N Children*
Birth cohorts				
46.ALSPAC (The Avon Longitudinal Study of Parents and Children (Golding et al. 2001))	UK	Bristol	1991-1992	14,062
47.DNBC (Danish National Birth Cohort (Olsen et al. 2001))	Denmark	Denmark	1996-2002	96,986
48.GASPII (Gene and Environment: Prospective Study on Infancy in Italy (Porta et al. 2007))	Italy	Rome	2003-2004	708
49.Generation R (Jaddoe et al. 2008)	Netherlands	Rotterdam	2001-2006	9,778
50.EHL (Growing up in Wales: Environments for Healthy Living (Hill et al. 2010))	UK	Wales	2012	1,000
51.INMA new (Environment and Childhood (Ribas-Fito et al. 2006))	Spain	Asturias, Gipuzkoa, Sabadell, Valencia	2003-2008	2,505
52.Lifeways Cross-Generational Cohort Study (O'Mahony et al. 2007)	Ireland	Galway	2001-2003	1,055
53.MoBa (The Norwegian Mother and Child Cohort Study (Magnus et al. 2006))	Norway	Norway	1999-2008	107,400
54.New UK Birth Cohort	UK		2012-2013	100,000
Child cohorts				
55.Growing up in Ireland	Ireland	Ireland	2006	
Nine-month old cohort				11,000
Nine-year old cohort				8,570
56.Growing up in Scotland	Scotland		2005-2006	5,000 (10m) 3,000 (34m)
57.MCS (The Millennium Cohort Study) (ref: Book: Dex, S. & Joshi, H. (2005) Children of the 21st Century: From Birth to Nine Months. The Policy Press, Bristol, UK)	UK		2000-2001	19,000

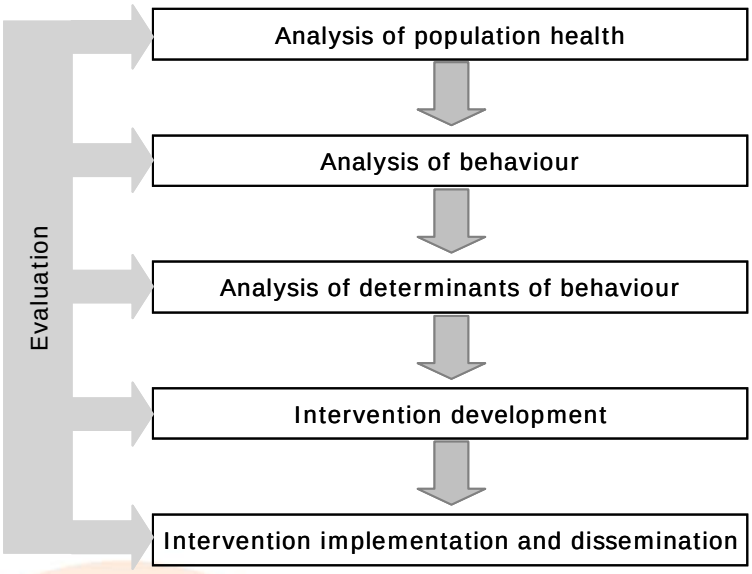
Table 3. Questions on injuries currently used in CHICOS birth and child cohort questionnaires

ALSPAC	MOTHER
6m	(*) Has your child ever been burnt or scalded? (yes/no) If yes, how many times? For each burn or scald please describe below what happened: Place accident happened, What was she burnt with?, Date of accident, Injuries caused, Who was with the baby?, What did the person with the baby do? (nothing/treated her themselves/took to doctor/took to hospital/other) What treatment did the person with the baby give? What other treatment did she have? Please describe how each accident happened: burn 1, burn 2, burn 3 Same questions (A) for: dropped or had a fall/other accident or injuries
12m	Same questions as (*) for: "been burnt or scalded since he was 15 months old", "dropped or had a fall", "swallowed anything he shouldn't have (pills, buttons, disinfectant) since he was 15 months old" and "other accident or injuries". Has your son ever had an accident that has left him with a scar, a physical disability or a behaviour or psychological problem? (yes/no) If yes, is there a scar? (yes/no) If yes, please describe where it is, and how he got it. Is there a physical disability? (yes/no) If yes, please describe where it is, and how he got it. Did he develop a behaviour or psychological problem after an accident? (yes/no) If yes, please describe this, and whether he still has this problem.
77m	MOTHER
103m 140m	Same questions as (*) for: "burnt or scalded in the past 12m", "had an accident while playing sports or games in the past 12m", "swallowed anything he shouldn't have (pills, buttons, disinfectant) in the past 12m", "had any injuries involving traffic in the past 12m", "has ever been injured by the action of another person (whether intentionally or not)", "has any other accidents or injuries in the past 12m". Has he had any of the following happen since he was born? Broken arm/hand, broken leg/foot, broken/cracked skull, other broken bone, unconscious because of a head injury, cut(s) requiring stitches, burn or scald having a skin graft, a road traffic accident, an accident in a playground, an accident at school, nursery or traffic, stung by wasp or bee, bitten by animal or human, badly sunburnt, nearly drowned, front tooth (teeth) knocked out, front tooth/teeth chipped or injured, other tooth/teeth knocked out or chipped (yes, aged 0-2y/yes, aged 3-4y/yes, since 5th birthday/yes, since 7th birthday/yes, since her 9th birthday – depends on the questionnaire) Has the study child ever had an accident that has had effects that are still present? (yes, a scar/yes, a behaviour difference/yes, other)
GASPII	MOTHER
6m	In the first 6 months of life did your child burn himself? (y/n) If yes, how many times? For each accident, please describe: age; injury; the child was with; what the person who was with him/her did (nothing, he/she treated him/her by him/herself, he/she took him/her to the physician, he/she took him/her to the hospital, other); treatment In the first 6 months of life has your child fallen? (y/n) If yes, how many times? For each accident, please describe: age; from where he/she fell; injury; the child was with; what the person who was with her/him did (nothing, he/she treated him/her by him/herself, he/she took him/her to the physician, he/she took him/her to the hospital, other); treatment In the first 6 months of life did you take your child to the emergency ward? (y/n) If yes, how many times? For each time, please describe: age; reason; diagnosis; hospital admission (y/n); discharge diagnosis

15m	Same questions as 6m follow up for: "between 6 and 15 months of life"
4y	Same questions as 6m follow up for: "after 12 months of life" Did your child swallow something or ingest a toxic substance after 12 months of life? (y/n) If yes, how many times? For each accident, please describe: age; from where he/she fell; injury; the child was with; what the person who was with her/him did (nothing, he/she treated him/her by him/herself, he/she took him/her to the physician, he/she took him/her to the hospital, other); treatment
Generation R	MOTHER
6m	Has your child ever had an accident at or near home or with traffic? (no/yes) What type of accident was it? (a fall, at or near home/injury from fire or scalding fluid/Ingestion of certain products/Traffic accident/other) What types of wounds did it cause? (Bruising, bleeding/Cut or graze/Burn/Fracture/break of bone/Brain damage/Internal injury/other) Who treated it? (No treatment was required/Family, other friends, passers-by/GP/Doctor at Emergency Help/other) Was your child hospitalised? (no/yes) Does your child still have symptoms or scars as a result of the accident? (no/yes)
18m	MOTHER Do you use any one of the following products in your home? Wall socket guard, door hinge guard, protective corner pieces for tables or furniture, non-slip mat in the bath or shower, window guards, safety hooks for cupboards, cooker rack, stair guard at the top of your stairs, stair guard at the bottom of your stairs (yes/no) If you have a stair guard, how often do you close it after use? (never/hardly ever/almost always/always) Is your child ever to be found in any one of the following rooms or in the garden without an adult present? Kitchen, bathroom, shed or garage, stairwell, garden (never/hardly ever/almost always/always) How high is the probability that your child in your home: Falls down the stairs, Falls against a piece of furniture, Falls out of the Windows, Eats or drinks household detergents, Eats or drinks medicines, Burns himself/herself with hot water from the tap, Swallows small objects (never at all serious/a bit serious/serious/very serious) Do you think you can stop your child having an accident at home by paying close attention to it? (certainly not/mostly doesn't apply/mostly does apply/yes certainly) Do you think you can prevent your child having an accident at home by using safety products? (certainly not/mostly doesn't apply/mostly does apply/yes certainly) How important were the following in encouraging you to use safety products? Advice given by friends, advice given by the health worker, poster and brochures at the doctors or at the child welfare centre, other reason (certainly not/slightly important/important/very important)
24m	MOTHER Has your child been injured as the result of an accident during the last 6 months, at home or in traffic for example? (no/yes, once/yes, twice/yes, more than twice) If yes, what sort of accident was it? If there has been more than one accident, answer this question with reference to the most serious accident. Fell down in or around the house, injury caused by fire or hot liquids, injury caused by ingesting certain products or implements, a different accident in or around the house, traffic accident, swallowing foreign objects, other. What sort of injuries was caused, and was a doctor consulted about them? Bruising, contusions, Cuts or grazes, burns, Broken bone, Brain damage, Internal damage, poisoning (no/didn't go to the doctor/yes, went to the doctor/yes, went to the hospital)

5-6y	Does your child still have complaints or scars resulting from the accident now? (no/yes) How often in the past year have you taken your child to the doctor (family doctor or emergency room) for the following accidents? A fall in or around the house, Injury from fire or hot liquids, Poisoning by ingesting non-edible products (for example, cleaning materials) or medicines, Swallowing of foreign (non-edible) objects, Other accidents in or around the house, Car accident (in the car), Bicycle accident (on the bicycle), Pedestrian accident (walking), Accident at school or in after-school care, Other (never/once/2 or 3 times/4 or more times)
Growing up in Ireland Unknown	PARENTS Has the Study Child ever had an accident or injury that required hospital treatment or admission? (yes/no) How many separate accidents have the Study Child ever had that required hospital treatment or admission? (N accidents) How many of these accidents involved bone fractures or breaks?
INMA new 12m 24m	MOTHER Has your child required medical assistance out of your habitual doctor? (yes/no) If yes: admission, emergency, GP. Why? Cause?
Lifeways Cross-Generational Cohort Study 5y	MOTHER During the last 12 months, was your Lifeways child hurt, injured or had an accident that needed attention from a doctor or hospital? (yes/no/don't know) Number of accidents during the last 12 months that needed attention from a doctor or hospital? Type of injury or accident that needed attention from a doctor or hospital? (bone broken or fractured bones/burn or scald/dislocation/cut or scrape/concussion or internal head injury/internal injury (not head)/dental injury/accidental poisoning/other accident/don't know During the last 12 months has your Lifeways child stayed in hospital for at least one night because of any of these injuries or accidents? (yes/no/don't know)
Millennium 1-2y 4-5y 6y 8y	PARENTS Has *^Jack* ever had an accident or injury for which *^he* has been taken to the doctor, health centre, or hospital? If yes, how many accidents? Thinking about the most severe (or only) accident or injury, what sort of accident or injury was it? loss of consciousness, bang on the head, broken bone, swallowed object, swallowed household cleaner/other poison/pills, cut needing stitches, cut or graze, burn or scald, something stuck in eye-throat- nose-ear or other part of body, animal or insect bite or sting, other sort of accident or injury. How many months old was *^Jack* when this accident happened? Did *^Jack* go to hospital? If yes: Was this just to casualty or was *^he* admitted to a hospital ward? (no, didn't go to hospital/yes, went to Causality/Accident and Emergency/yes, was admitted to a Hospital Ward)
MoBa 18m 36m	MOTHERHas your child had any of the following illnesses/health problems between 6 and 11 months and/or 12 and 18 months? Specify how many times and whether your child has been admitted to hospital for this health problem. Lots of options and one is "Injury or accident": at 6-11m, at 12-18m, (yes/no) Was admitted to hospital for this? (yes/no)

Figure 1. A model for planned health education and health promotion (from (Brug et al. 2005))



Appendix I

A. Accidents and injuries

1. Has your child ever had an accident?

☐ no
☐ yes

2. If yes, what type of accident was it? (several answers possible)

☐ Road traffic injury: collisions or incidents occurring on public roads and involving at least one moving vehicle
☐ Drowning
☐ Poisoning: exposure to a substance that causes cellular injury or death (ingested, inhaled, injected or absorbed)
☐ Thermal injuries: scalds, burns (flame, radiation, electricity, chemicals…)
☐ Falls

For each of the accident, please describe:

Accident 1

2.1. How many accidents of this type your child has had in the last year?

☐ one
☐ two
☐ three
☐ four or more

2.2. Who treated it?

☐ no treatment was required
☐ family or friends
☐ general practicioner
☐ outmatient clinic/emergence room
☐ hospital admittance

2.3. What types of wounds did it cause? (several answers possible)

☐ bruising, bleeding
☐ cut or graze
☐ burn
☐ fracture
☐ head injuries/traumatic brain injuries
☐ internal injury
☐ other

2.4. Who treated it? (several answers possible)

☐ no treatment was required
☐ family, other friends, passers-by
☐ general practitioner

☐ doctor at Emergency Help
☐ other

2.5. Was your child hospitalised (meaning admitted to hospital for at least one night)?

☐ no
☐ yes

B. Parents' child safety behaviour

3. Do you have and use any one of the following products in your home?

☐ wall socket guard
☐ door hinge guard
☐ protective corner pieces for tables or furniture
☐ non-slip mat in the bath or shower
☐ window guards
☐ safety hooks for cupboards
☐ safety storage of medication
☐ safety storage of cleaning products
☐ cooker rack
☐ stair guard at the bottom/top of your stairs
☐ smoke detector

4. Do you think you can prevent your child having an accident at home by using safety products?

☐ certainly not
☐ mostly doesn't apply
☐ mostly does apply
☐ yes certainly

5. Is your child ever to be found in any one of the following rooms or in the garden without an adult present?

	never	hardly ever	almost always	always
Kitchen	☐	☐	☐	☐
Bathroom	☐	☐	☐	☐
Shed or garage	☐	☐	☐	☐
Stairwell	☐	☐	☐	☐
Garden	☐	☐	☐	☐

Appendix II

Examples of injury databases in the European Union and National trauma registries:

- European injuries database: https://webgate.ec.europa.eu/idb
- National trauma registries:
    - UK: TARN (Trauma Audit & Research Network): www.tarn.ac.uk
    - Denmark: Danish National Patient Registry; The Injury Registry (National Institute of Public Health: http://www.si-folkesundhed.dk/ - Research – Accidents – Statistics)
    - The Norwegian Patient Register

      (http://www.nsd.uib.no/polsys/data/en/forvaltning/enhet/37606)
    - Swedish Health and Welfare Statistical Databases (The National Board of Health and Welfare Statistics: http://www.socialstyrelsen.se/statistics. Open our statistical database/diagnosis in in-patient care/select or change/diagnosis/Injury, poisoning and certain other consequences of external causes)
    - Netherlands: Consument en Veiligheid (http://www.veiligheid.nl/); Dutch Injury Surveillance System (http://www.swov.nl/index_uk.htm)
    - "Guidelines in Multiple Injured Patients. The Approach of the German Trauma Registry" (Neugebauer et al. 1990)
    - "The Implementation of a National Trauma Registry in Greece. Methodology and Preliminary Results" (Katsaragakis et al., 2009)
- Other European websites of interest:
    - Injury Epidemiology and Prevention Research (http://www.nottingham.ac.uk/Injuryresearch/index.aspx)
    - National Home Safety Equipment Scheme (http://www.safeathome.rospa.com/)
    - EuroSafe: European Association for Injury Prevention and Safety Promotion (http://www.eurosafe.eu.com/)
    - European Child Safety Alliance – linked to EuroSafe (http://www.childsafetyeurope.org/); the Child Safety Good Practice Guide (http://www.childsafetyeurope.org/publications/goodpracticeguide/info/good-practice-guide.pdf); the Child Safety Report Cards (http://www.childsafetyeurope.org/reportcards/index.html)
    - RoSPA – The Royal Society for the Prevention of Accidents (http://www.rospa.com/)
    - Best practices. Poisoning interventions. Seattle, Harborview Injury Prevention Research Centre, 2008 (http://depts.washington.edu/hiprc/practices/topic/.poisoning/packaging.html)

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Developing a Child Cohort Research Strategy for Europe

Infectious diseases

Researchers involved

Leader: Mads Kamper-Jørgensen (University of Copenhagen, Denmark)

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Summary

Many of the most severe infectious diseases among European children are well controlled. However, poor vaccine coverage, doubts about vaccine safety, and lack of knowledge about prevention maintain childhood infectious disease as one of the major health related problems among children in Europe. Several existing European birth cohorts have collected questionnaire data on infectious outcomes, as well as biological samples. Such data offers a unique possibility to investigate the aetiology of childhood infections. Because some exposures and some outcomes are rare, results from individual cohorts may be inconclusive. One feasible way to achieve conclusive results by increasing the sample size is by pooling birth cohort data from several European sites. Another advantage of pooling data is the possibility to compare the association under study between sites, and thereby evaluate the plausibility. Because birth cohorts rely on participants to actively participate, not all groups of children are included e.g. the most vulnerable children. All European countries have national surveillance and monitoring of severe infections, and some countries have national hospital registers including less severe infections. Linking data from existing birth cohorts with surveillance data provides a rapid and very flexible response to emerging infections and pandemics. Together, birth cohort data and routinely collected national registers provide both the detail needed to understand the underlying mechanisms of disease, and the magnitude needed to study all groups of European children.

1. Review of cohort contribution and existing cohort data

Depending on the research question, childhood infectious diseases can be regarded as either an exposure or an outcome. The present review of cohort contribution to the area of childhood infectious diseases focuses on childhood infectious disease as an outcome. Other CHICOS working groups discuss childhood infectious diseases as an exposure.

1.1. Description of current state of scientific knowledge

Whereas many of the most severe infections such as polio, diphtheria, and tetanus are close to being eradicated in Europe thanks to vaccination, other infectious diseases including measles, influenza, and common cold continue to cause health problems among European children. Despite being vaccine-preventable, measles are not always well controlled due to poor vaccine coverage[1] and unwarranted doubts about vaccine safety[2]. Every winter hundreds of thousands of European children fall seriously ill as a result of the seasonal influenza[3]. Since the influenza viruses change from one season to the next, most influenza cases are not preventable by vaccination, and having had influenza does not necessarily impose future immunity against influenza. Also, most children fall ill several times during childhood with less

serious but very common childhood infections not routinely vaccinated for or not preventable by vaccine, such as common cold, otitis media, gastrointestinal infection, or urinary infection. According to a recent Danish survey 14% of all 0-15-year old children had been sick with an infection within the last two weeks[4]. Many childhood infections can be prevented by simple measures such as prolonged breast feeding[5] or improved hygienic measures[6], why efforts to reduce childhood infections often prove to be easy to implement. Moreover, such efforts not only improve child wellbeing, they also markedly reduce parental sick leave which in turn has proven to be very cost-efficient. Thus, childhood infectious diseases constitute a substantial health problem among European children. A large part of this problem is preventable, leading to both improved child health and financial gains due to reduced parental sick leave.

1.2. Description of the contribution of European birth cohort research to scientific knowledge

Although European birth cohorts are very heterogeneous in terms of design, sample size, and collected information, one common feature of these as opposed to other non-cohort sources used for research on childhood infectious diseases, is an in-depth knowledge about each individual in the cohort. European cohort data include a variety of possible exposures and outcomes, none of which are registered elsewhere. Further, a hallmark of European birth cohorts is that data is collected in a prospective manner i.e. information about the exposure is collected before the onset of the outcome, which makes it possible to draw inference regarding causality of infectious diseases with a high degree of certainty. In several European countries the possibility to link individual prospectively collected register-based data on childhood infectious disease exists. However, studies relying on register-based data often include only the most severe and hospitalized cases. As the majority of common childhood infections are mild and thus not leading to hospitalization, these are not possible to study using register-based data. Also, many of the exposures thought to be the cause of childhood infectious diseases are not routinely registered. Although not suitable for drawing inference about causes of childhood infectious disease, grouped surveillance data on e.g. the number of reported measles cases in a country over a period is regularly used to attract attention towards specific problems.

Below, as well as in appendix Table 1, research studies of childhood infectious diseases based on European birth cohorts are summarized, according to the cohort used. These studies have mainly sought to identify modifiable factors causing or preventing disease. Among these are common exposures during pregnancy such as parental smoking, maternal overweight and maternal infection, and common early life exposures such as pacifier sucking, childhood nutrition, and crowding. As reflected, childhood infectious disease is currently shown to have a multi-factorial etiology. Being the most common subtype of childhood infectious

disease, the majority of studies have focused on respiratory tract infections. Finally, some individually linked register-based studies, and studies based on grouped surveillance data are mentioned briefly.

The Danish National Birth Cohort (DNBC)

Using the DNBC, risk factors for the main reason for lower respiratory tract disease, namely Respiratory Syncytial Virus (RSV) among children younger than 18 months were studied by Stensballe and colleagues. They reported asthmatic disposition and wheezing to significantly protect against RSV hospitalization[7], that maternally derived RSV neutralizing antibodies in cord blood protected infants against RSV hospitalization[8], and that a clear temporal association exists between maternally derived RSV neutralizing antibodies in cord blood and RSV seasonality[9]. Also, Fei et al. used DNBC data to refute the hypothesis that prenatal exposure to organic pollutants increases the risk of hospitalization due to infectious diseases in early childhood[10].

Avon Longitudinal Study of Parents and Children (ALSPAC)

Hepworth et al. used the British ALSPAC cohort to study the relationship between variables commonly used as proxies for early life infections and infectious symptom profiles. They identified five classes of symptoms, to which children could be assigned with differently reported combinations of symptoms at age six months[11]. North and colleagues used ALSPAC to show that infectious diseases were more frequent among pacifier sucking infants compared with digit suckers, but also concluded that determining the direction of causality was almost impossible[12].

The Norwegian Mother and Child Cohort Study (MoBa)

With seven studies published, MoBa is the most extensively used European birth cohort in the area of childhood infectious diseases. Recently, Hancock et al. reported no excess risk of respiratory symptoms among children born to mothers who used oral contraceptive pills soon before pregnancy[13]. Bentdal et al. found a moderate excess risk of acute otitis media among children born prematurely[14]. In four studies, Håberg et al. reported maternal smoking during pregnancy to be associated with an increased risk of acute otitis media in early childhood[15], an unadjusted excess risk of respiratory infections among infants of obese mothers[16], that maternal folic acid intake during pregnancy slightly increases the risk of lower respiratory tract infections up to 18 months of age in the offspring[17], and pre- and postnatal exposure to parental smoking to be associated with lower respiratory tract infection in the offspring[18] Finally, Nystad and colleagues found that baby swimming did not increase the risk of lower respiratory tract infections[19].

Generation R

Using the Dutch Generation R data, Duijts and colleagues reported no effect of maternal smoking during pregnancy on respiratory tract infections in the offspring[20], a significant reduction of respiratory and gastrointestinal morbidity in infants exclusively breast fed until the age of four months[5], and that nasopharyngeal bacterial carriage in the first year of life was not a an independent risk factor for otitis media in the second year of life[21].

BAMSE

The Swedish BAMSE cohort was used to study selective IgA deficiency and the risk of childhood infectious diseases until 8 years of age. Janzi et al. report that IgA deficient children were at significantly increased risk of parentally reported pseudocrop[22].

Collaboration between European birth cohorts

The majority of presently established risk factors for childhood infectious diseases have been identified using data from birth cohorts, primarily European and North American. As previously mentioned, cohorts offer the possibility to establish the temporality between the studied exposure and outcome, and they often include data on exposures and infectious disease outcomes not registered elsewhere. We have not identified published collaborative studies of European birth cohort data with a focus on childhood infectious disease. However, as will be discussed later, European birth cohorts have each collected data on several exposures and outcomes, which makes pooling of questionnaire data and biological specimens feasible. Pooling information increases the study sample size, which in turn reduces the statistical uncertainty of the studied association. Moreover, pooling information offers the possibility to study associations in settings with different setups of factors that may influence the studied association. Thus, finding associations between an exposure and an outcome to be consistent across different settings increases the likelihood of the association to be causal rather than an artefact caused by confounding factors.

Within the area of childhood infectious diseases, we anticipate that establishing collaboration between European birth cohorts will make considerable contributions to the following areas over the next decade

- scientific questions which require large sample sizes because the exposure is rare, for example the association between immune deficiency and lower respiratory infections
- scientific questions where the temporality between exposure and outcome is not clear or may change over age, for example the association between pacifier sucking and common childhood infections
- scientific questions where the reported association between exposure and outcome may be differently confounded by factors in the study setting, for example the association between maternal smoking during pregnancy and respiratory tract infections

Individually linked register-based studies

The need for large sample sizes in order to study subgroups of children, made Kamper-Jørgensen and colleagues perform individually linked register-based studies of the effect of childcare attendance on infectious disease hospitalization[23]. Reportedly, childcare attendance was associated with an increased transient risk of hospitalization for acute respiratory infections, but only among the youngest children[24;25]. Further, no excess risk of gastrointestinal infection hospitalization was observed among children in childcare[26]. Using register-based data from the Norwegian Surveillance System for Communicable System and the Norwegian National Vaccination Register, Vestrheim and colleagues found that vaccine coverage quickly reached high levels after introduction of the pneumococcal conjugate vaccination in the childhood vaccination programme in Norway. Also, they describe a substantial decrease in the incidence of invasive pneumococcal disease among children younger than 2 years after introduction of the vaccine[27].

European Centre for Disease Control (ECDC)

The ECDC was established in 2005 with the aim to strengthen Europe's defences against infectious diseases. In line with the idea of CHICOS, ECDC director Marc Sprenger states in the ECDC annual epidemiological report on communicable diseases from 2010[3] that 'There is clear added value in having Europe-wide data'. Data presented in the report is grouped surveillance data, and thus not suited for evaluating causal relationships. However, the reporting of trends in incidence of infectious diseases in different European regions is undoubtedly valuable in the fight against infectious diseases in European children.

1.3 Description of data currently available/being collected by the cohorts

Inventory of birth cohorts

An inventory located at www.birthcohorts.net which contains information about birth cohorts in the CHICOS cooperation, was developed in CHICOS work package 1. The inventory functions as a tool for researchers and others with an interest in improving child health across Europe. As of ultimo April 2012 a total of 39 birth cohorts in the inventory indicate having collected information on childhood infections. Birth cohorts from most of Europe are represented, with a predominance of North-European cohorts. Reportedly, these cohorts contain much data on infections in early life. This may prove to be fruitful not only in collaborative projects focusing on risk factors for childhood infections, but also in future collaborations taking the life-course approach to identifying possible intra-uterine and early life determinants of adult disease. Presently, the degree to which data on exposures, confounders, and childhood infections between cohorts is possible to pool, is not known. Although none is yet planned, we believe this report will initiate collaborative case-studies enjoying the advantages of the CHICOS collaboration. The CHICOS inventory is continuously being updated with new cohorts.

1.4 Identification of gaps

Considering the wealth of information regarding childhood infections collected by European birth cohorts, surprisingly few studies have been carried out with childhood infections as the outcome. Some factors such as exposure to siblings, childcare attendance, and breast feeding are unquestionably linked with childhood infections, and only few further studies are needed. However, a considerable proportion of childhood infections are not readily explained by current knowledge. As discussed earlier, the advantages of having a huge sample size, a well-known sequence of the exposure and the outcome, and having data from settings with different confounder structure, will help close existing gaps. In our view, pooling cohort data and cooperating across European settings have two main advantages. First, we believe the CHICOS cooperation will render it possible to study infectious diseases which are rare on a population level, but are very serious to the few children who contract them. Thus, we believe that the focus brought about by this report will encourage researchers to focus also on e.g. infections of the skin, the urinary system and the gastrointestinal tract. Secondly, we believe that areas with conflicting findings may benefit greatly from working together to disentangle the influence of the factors in that particular setting i.e. the influence of the confounder structure. No specific collaborative projects focusing on infectious disease outcomes among European children have been set up within the CHICOS cooperation yet. Thus, we do not know to which degree it is possible to pool existing cohort data, e.g. if exposures and outcomes are comparable, or whether the ethnicity pattern is too different between birth cohorts. Although similar validated

questionnaires regarding childhood infectious diseases do not exist and were thus not used by the cohorts, they all collected data on major infectious groups, e.g. respiratory tract infections, gastrointestinal tract infections, urinary infections, and skin infections. Also common exposures such as breast feeding and siblings are similarly collected. Most data on exposures and outcomes are based on questionnaire data, but several cohorts have biological specimens as well. Despite challenges regarding the alignment of data, ECDC each year publishes a report on routinely registered European infectious surveillance data. The ECDC experience is that much is to be gained from pooling such data. Because not all groups of European children are well represented in the existing cohorts, we believe that linkage between cohort data and routinely registered hospitalisation and surveillance data registered by public national institutions will increase knowledge about vulnerable groups. Also, recent experience from Norway shows that linking cohort data to surveillance data is invaluable in prevention and preparedness against emerging infections and pandemics, such as *H1N1*.

2. Recommendations

We believe that the way forward in studying and preventing infectious diseases among European children is through linking already existing European data sources. A wealth of very detailed individual data has already been collected by European birth cohorts. Joining forces by linking data across European birth cohorts may render it possible to study rare exposures and outcomes, to study sub-groups of children, to evaluate the association under study in different settings, and to study biological material. Already collected birth cohort data may also be utilized as a rapid and very flexible response to disease outbreaks and emerging infections through conducting pragmatic nested case-control studies at time of outbreak. Further, the area of childhood infectious diseases is enriched by the possibility of individual linkage to national routinely registered surveillance data. Such linkage also offers the possibility to longitudinally study the most severe infections, which is not possible through surveillance data alone. Some European countries further offer the possibility to link existing cohort data to routinely collected hospitalisation registers. Together, birth cohort data and routinely collected national registers provide both the detail needed to understand the underlying mechanisms of disease, and the magnitude needed to study all groups of European children.

Appendix table 1.

Cohort	Author	Exposure	Outcome	Conclusion	Category	Journal	Year
DNBC	Stensballe LG et al.[7]	Atopic dermatitis, wheezing, maternal and paternal asthma	RSV associated hospitalization	Asthmatic disposition and wheezing are strong determinants for RSV hospitalization	LRT	Pediatrics	2006
DNBC	Stensballe LG et al.[8]	Maternally derived RSV neutralizing antibodies in cord blood	RSV associated hospitalization	Neutralizing antibodies protect against RSV hospitalization	LRT	J Allergy Clin Immunol.	2009
DNBC	Stensballe LG et al.[9]	Maternally derived RSV neutralizing antibodies in cord blood	RSV associated hospitalization	Temporal pattern suggests that RSV neutralizing antibodies play a role in RSV seasonal pattern	LRT	J Pediatrics.	2009
DNBC	Fei C et al.[10]	Prenatal exposure to PFOA and PFOS	Hospitalization for infection	Prenatal exposure to PFOA and PFOS is not associated with hospitalization for infection	All	Environ Res.	2010
ALSPAC	Hepworth SJ et al.[11]	Commonly used proxies for infection	General infection, gastrointestinal, mild respiratory, colds/earache	Latent class analyses is a flexible method of investigating the relationship	URT, LRT, GIT	Eur J Epidemiol.	2010

ALSPAC	North SK et al.[12]	Pacifier and digit sucking	Cold, earache, vomiting, measles, chicken pox, other infection	More infection with pacifier use. Direction hard to establish	All	Early Hum Dev.	2000
MOBA	Hancock DB et al.[13]	Oral contraceptive pills	Lower respiratory infection	Oral contraceptive pills do not increase the risk of lower respiratory infection	LRT	Pediatr Allergy Immunol.	2011
MOBA	Bentdal YE et al.[14]	Preterm birth and low birth weight	Otitis media	Preterm birth gives modest increased risk of having otitis media	URT	Int J Pediatr Otorhinolaryngol.	2010
MOBA	Håberg SE et al.[15]	Parental tobacco smoking	Otitis media	Maternal smoking associated with increased risk of otitis media	URT	Acta Pediatr.	2010
MOBA	Håberg SE et al.[16]	Maternal BMI in pregnancy	Lower respiratory infections	Unadjusted association between high maternal BMI and LRI. None when adjusted	LRT	Paediatr Perinat Epidemiol.	2009
MOBA	Håberg SE et al.[17]	Maternal folate supplements during pregnancy	Lower respiratory infections	Folate supplements were associated with a slightly increased risk of LRI	LRT	Arch Dis Child.	2009
MOBA	Nystad W et al.[19]	Baby swimming	Recurrent respiratory infections and otitis media	Baby swimming and respiratory infections may be linked	URT, LRT	Acta Pediatr.	2008
MOBA	Håberg SE et al.[18]	Parental smoking	Lower respiratory infections	Maternal smoking during pregnancy is an independent risk factor for LRI	LRT	Am J Epidemiol.	2007

Generation R	Duijts L et al.[20]	Maternal smoking	Respiratory tract infection	No effect of maternal smoking during pregnancy on respiratory tract infection	URT, LRT	Eur J Epidemiol	2008
Generation R	Duijts L et al.	Breast feeding	Infectious disease	Exclusive breastfeeding reduces the risk of infectious disease	URT, LRT, GIT	Pediatrics	2010
Generation R	Labout JA et al.[21]	Risk factors	Bacterial airway pathogens	Previous otitis media and siblings increased the risk of otitis media	URT	Eur J Epidemiol	2010
BAMSE	Janzi M et al.[22]	IgA deficiency	Pseudocrop	IgA deficiency increases the risk of pseudocrop	URT	Clin Immunol	2009

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Developing a Child Cohort Research Strategy for Europe

Childhood cancer

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Summary

Childhood cancer is rare in Europe (typically, 100 cases for 1 million children yearly) but increases in the incidence of childhood cancer in Europe and specifically leukaemia have been recently reported. Only few risk factors have been established for childhood cancers including infective agents, medical history and specific syndromes, ionising radiation and birth weight. We evaluated existing information on cancer research in birth cohorts and make recommendations for further research.

Most research on childhood cancer is based on a case-control approach. Only recently have efforts been made to coordinate large cohort studies evaluating childhood cancer or cancer-related biomarkers. Cancer is assessed through clinical records, histopathology and cancer registry records and, to this extent, outcome misclassification is minor. Information on cancer will be collected in the major European cohorts that, at present, constitute the main cohorts of the International Childhood Cancer Cohort Consortium (I4C). Power calculations indicate that for an exposure with a prevalence of 15% and a 50% increase in risk associated with this exposure (RR= 1.5), a study would need to include 447,000 children to have adequate statistical power. This figure is higher than the number of children recruited in European birth cohorts with detailed exposure information. The corresponding figure for a similar exposure and a relative risk of two would be around 130.000 children. Although most cohorts collect biological samples from the mother and the children, very few studies are evaluating cancer-related effect biomarkers in children. Cancer biomarkers studied in adults such as micronuclei have been used as an outcome in some birth cohorts. Several cancer registries in Europe evaluate the frequency and time trends of childhood cancer, and can serve as a basis for case-controls studies on environmental factors. Finally, the development of new tools to evaluate genetic and environmental factors using minimal amounts of blood opens new possibilities for the use in epidemiological cohort or nested case-control studies, of blood spots that are routinely collected and stored in many European countries.

Recommendations: Existing European birth and mother-child cohorts provide a potential for combined analyses on cancer and cancer-related biomarkers. Statistical analyses of existing cohorts should take into account environmental exposures during the relevant time windows (prenatal and postnatal) and make efficient use of the longitudinal nature of information. The main problem relative to the evaluation of childhood cancer is, by far, that of statistical power. Childhood cancer is a main cause of death in children but remains a rare event. Existing European cohorts lack power to evaluate many potentially relevant exposures. For future studies, we encourage the participation and further development of the international consortium (I4C), in which European researchers should play a central role. The development of biomarker-based studies is crucial, as is the evaluation of the potential use of existing large biobanks such as blood

spots in newborns. The combination of epidemiological with more mechanistic approaches (e.g., epigenetics), in nested case-control studies within the cohorts may provide clues for causation. Finally, registry-based approaches are complementary to cohort studies and are crucial to evaluate trends in childhood cancer and childhood leukaemia in Europe.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

Childhood cancer is rare in Europe with incidence rates ranging between 80 and 150 cases per million annually. Increases in the incidence of childhood cancer in Europe and specifically leukaemia have been recently reported (Figure 1).

Cancer in children is diagnosed through clinical protocols and is defined as a cancer below the age of 15 (although some studies have used older age as the cut-off). The cancers in decreasing order of the incidence rates are leukaemia (acute lymphoblastic (ALL) and acute myeloid leukaemia), brain/central nervous system tumours (astrocytoma, primitive neuroectodermal tumours, glioma, ependymomas), lymphomas (non-Hodgkin, Hodgkin), sympathetic nervous system (neuroblastoma), soft tissue sarcomas (rhabdomyosarcomas), renal tumour (Wilms tumour, renal carcinoma), bone tumours (osteosarcoma and Ewing's sarcoma) and other tumours.

Well established risk factors for childhood cancers such as Down syndrome or inherited predisposing conditions account for only a small number of cases. Only few exogenous risk factors have been established for childhood cancers including diagnostic in utero radiation and infective agents such as Epstein-Barr virus (Ross and Spector 2006). Evidence from several studies including two meta-analyses (Caughey and Michels, 2009), Caughey, IJC 2009), shows that high birth weight is associated with all leukaemia and with ALL. Several hypotheses are being investigated concerning non-genetic factors. These include: pre-natal and post-natal exposure to pesticides, maternal and early infancy dietary factors, maternal folate acid intake and polymorphisms in genes controlling the enzyme methylenetetrahydrofolatereductase (MTHFR), paternal pre-conception occupational exposures, paternal pre-conceptional smoking, chromosomal translocations present at birth, the interplay of maternal or early postnatal immune system handling of common infections, parental age and specifically paternal age, exposure to electromagnetic fields (Linet et al 1997), early child exposure to diagnostic radiation or radiation from other sources, and other factors. The evidence on gene–environment interactions in childhood cancer is still very limited (see for example Infante-Rivard et al, 2002).

1.2. Description of the contribution of (European) birth cohort research to scientific knowledge

Existing studies have been remarkably unsuccessful to identify major risk factors for childhood cancers. Evidence is mostly based on case-control studies and findings have frequently not been replicated particularly environmental exposures. The difficulties encountered in existing studies to identify causal factors may reflect the fact that relevant exposures may refer to both the parents and the child and that very large cohort studies are needed to evaluate environmental or other risk factors.

The main problem encountered in studies on childhood cancer is that of lack of statistical power, resulting in the conduct of uninformative studies. Since pooling all cancer types together is unlikely to be etiologically relevant, power calculations have been conducted for specific cancer types separately. In the case of acute leukaemia (ALL and AML), the most frequent type of childhood cancer, these calculations (Table 1) indicate that for an exposure with a prevalence of 15% and a 50% increase in risk associated with this exposure (RR= 1.5), a study would need to include 446,633 children followed-up from birth until the age of 15 to have adequate statistical power. Although the power calculations were done for a follow-up to the age of 15, a shorter follow-up would not require a much larger sample because the majority of cancer cases among children occur at an earlier age with a considerable proportion occurring before age 6. The corresponding figure for a similar exposure and a relative risk of two would be 125,813 children. Even assuming such a large RR, rare exposures such as exposure to Extremely Low Frequency Electromagnetic Fields (ELF EMF) to levels higher than 0.4microTesla with a prevalence of less than 1% in the European populations (Ahlbom et al 2000) would need far above one million children.

1.3 Description of data currently available/being collected by the cohorts

Information on cancer will be collected in the major European cohorts that constitute the backbone of the International Childhood Cancer Cohort Consortium (I4C). The two largest cohorts (MOBA and DNBC) that include around 200.000 mother-child pairs are done in countries with complete cancer registries. There are additional cohorts in Europe (see WP1, CHICOS) that have collected information on numerous exposures and that could add from an additional 50.000 to 100.000 thousand children depending on the type and detail of exposure information examined.

The main current research initiative at the global level in epidemiological research in childhood cancers is the I4C (International Childhood Cancer Cohort Consortium). The I4C is expected to eventually include all major birth cohorts adding to around 500.000 or more children. At present, the main contributors are the European cohorts included in ENRIECO such as MOBA and DNBC. The total number of mother–child pairs

included will depend on the future of the large US National Children's Study and the development of several large cohorts in Asia including cohorts in China, Korea, Taiwan and Japan.

The I4C is currently organised in two large working groups, one on environmental (non-genetic) exposures and one on genetics. The environmental exposure working group is currently developing protocols for the evaluation of pesticides exposures and of birth weight. Pesticides will be evaluated using information on occupation of the parents and satellite mapping. The genetics group is currently evaluating the feasibility of a study on epigenetics in relation to exposure to smoking and passive smoking. This study is designed as a nested case-control study within the larger I4C cohort.

Cancer Registries. Although not cohort studies, there exist several cancer registries in Europe that evaluate the frequency and time trends of childhood cancer (see Figure 1).

Biomarker-based studies. Only a few studies are evaluating cancer related biomarkers in children. They have used biomarkers that have been studied in adults such as micronuclei (Bonassi et al 2007), and that have been shown to predict future cancer risk. However, there are yet no existing studies evaluating whether they predict cancer in children. There are no specific definitions applying to the biomarkers that should be shown to be related with later occurrence of cancer. Micronuclei (Figure 2) are the most informative generic cancer biomarker used in the largest existing biomarker-based project in Europe, such as New-Generis (see www.newgeneris.org). Micronuclei are small extranuclear bodies containing genetic material such as acentric chromosome/chromatid fragments or whole chromosomes/chromatids that lag behind during anaphase. They are not included in the daughter nuclei but encapsulated into a separate, smaller nucleus, a micronucleus. Micronucleus formation occurs as a result of both direct and indirect DNA damage and can be used to classify chemicals into clastogens (inducing chromosome breakage) or aneugens (inducing chromosome loss) (Kirsch-Volders et al. 1997). .Other biomarkers of interest for studies focused on environmental exposures are epigenetic biomarkers. Epigenetics study inherited changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence (for example SNPs). The interest for studies evaluating environmental factors is that these changes in the expression of the genes are caused by non-genetic (environmental) factors.

The largest initiative in Europe and internationally is the Newborns and Genotoxic exposure risks project - NewGeneris (Merlo et al 2009). NewGeneris is examining associations between foetal exposure to dietary contaminants, including polycyclic aromatic hydrocarbons, heterocyclic amines, nitrosamines, acrylamide, the mycotoxin deoxynivalenol, dioxin and polychlorinated biphenyls, alcohol and DNA-reactive aldehydes, and the occurrence of cancer and immune related biomarkers (Table 2). The hypothesis tested is that maternal exposure to these dietary compounds results in in utero exposure and in molecular events in the unborn child, leading to increased risks of cancer and immune disorders in childhood. The study focuses on

assessing the relationship between (a) dietary questionnaire data and biomarkers of exposure and (b) exposure and biomarkers of effect, relevant to both carcinogenicity and immune status. Questionnaires and a wide range of biomarkers are used to measure exposure, individual susceptibility to toxic agents, and early effects. The biomarkers are measured in blood samples collected from mother-child pairs recruited in six European mother and child cohorts. Different categories of biomarkers of exposure are being applied, including chemical metabolites and both DNA and protein adducts. Validated biomarkers of genotoxic (micronuclei frequencies) and immunotoxic (cytokines) effects are being measured simultaneously with novel effect biomarkers based on transcriptomics and proteomics to study how dietary exposure can affect patterns of gene expression and protein production. In addition, interindividual differences in genotoxic responses will be evaluated genotypically and phenotypically, in relation to the level of DNA repair. Moreover, polymorphisms encoding for susceptibility are examined.

Many mother child cohorts within CHICOS have extensive collections of biological samples. Some biomarkers can be analysed retrospectively in adequately preserved samples (e.g. DNA, serum) while other require elaborate processing (e.g. micronuclei), and therefore cannot be analysed in cohorts in which specific protocols have not be applied.

Use of blood spots. Other possibilities include the use of routinely collected samples in biobanks such as blood spots collected from all newborns. The development of new tools to evaluate genetic and environmental factors using minimal amounts of blood opens new possibilities for the use in epidemiological cohort or nested case-control studies, of blood spots that are routinely collected and stored in many European countries. For example, blood spots have been used for the evaluation of albumin adducts to benzene oxide (Func et al 2008). The use of such biobanks entails serious ethical issues that will have to be discussed before embarking in projects using existing biobanks.

1.4 Identification of gaps

Existing European birth and mother-child cohorts provide a potential for combined analyses on cancer and cancer-related biomarkers. Statistical analyses of existing cohorts should take into account environmental exposures during the relevant time windows (prenatal and postnatal) and make efficient use of the longitudinal nature of information. The main problem relative to the evaluation of childhood cancer is, by far, that of statistical power. Childhood cancer is a main cause of death in children but remains a rare event. Existing European cohorts lack power to evaluate many potentially relevant exposures. For future studies, we encourage the participation and further development of the international consortium (I4C), in which European researchers should play a central role. The development of biomarker-based studies is crucial, as is the evaluation of the potential use of existing large biobanks such as blood spots in newborns.

The combination of epidemiological with more mechanistic approaches (e.g., epigenetics), in nested case-control studies within the cohorts may provide clues for causation. Finally, registry-based approaches are complementary to cohort studies and are crucial to evaluate trends in childhood cancer and childhood leukaemia in Europe.

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Tables & Figures

Table 1. Sample sizes needed for a statistical power of 80% to detect associations for an OR of 1.5 and 2.0 with varying exposure rates with acute leukaemia (ALL and AML) and with an expected follow-up time of 15 years. From Brown et al 2007.

Exposure (%)	Minimum OR detectable	Sample size required
5	1.5	1 180 059
15	1.5	446 633
30	1.5	277 781
5	2	328 992
15	2	125 813
30	2	79 594

Table 2. Exposure to specific agents investigated in mother-child pairs, their source of exposure, and class of toxicity. NewGeneris project (from Merlo et al 2009)

Model compound	Chemical class	Source of exposure	Class of toxicity
Benzo(*a*)pyrene	Polycyclic aromatic hydrocarbons	Environmental contamination of the food chain; formation during baking and frying; smoking and exposure to environmental tobacco smoke	Genotoxic carcinogenesis, immunotoxicity
2 Amino 3 methylimidazo[4,5] quinoline 2 amino 1 methyl 6 phenylimidazo[4,5 *b*]pyridine	Heterocyclic amines	Formation during baking and broiling	Genotoxic carcinogenesis
Monoacrylamide	Acrylamides	Formation during baking and frying	Genotoxic carcinogenesis
Dimethylnitrosamine	Nitrosamines	Environmental nitrate contamination of the food chain and subsequent endogenous formation	Genotoxic carcinogenesis
Deoxynivalenol	Mycotoxins	Environmental contamination of the food chain	Immunotoxicity
Dioxin (TCDD) PCB	Organochlorines	Environmental contamination of the food chain	Cocarcinogenesis, immunotoxicity, endocrine disruption
4 Hydroxynonenal malondialdehyde	Aldehydes (DNA reactive)	Macronutrients	Genotoxicity via lipid peroxidation immunotoxicity
Ethanol	Alcohols	Lifestyle factor	Cocarcinogenesis immunotoxicity

Figure 1: Age-specific incidence rates of cancer in children and adolescents in Europe (p values test difference between first and last decade; from Steliarova-Foucher, Lancet 2004).

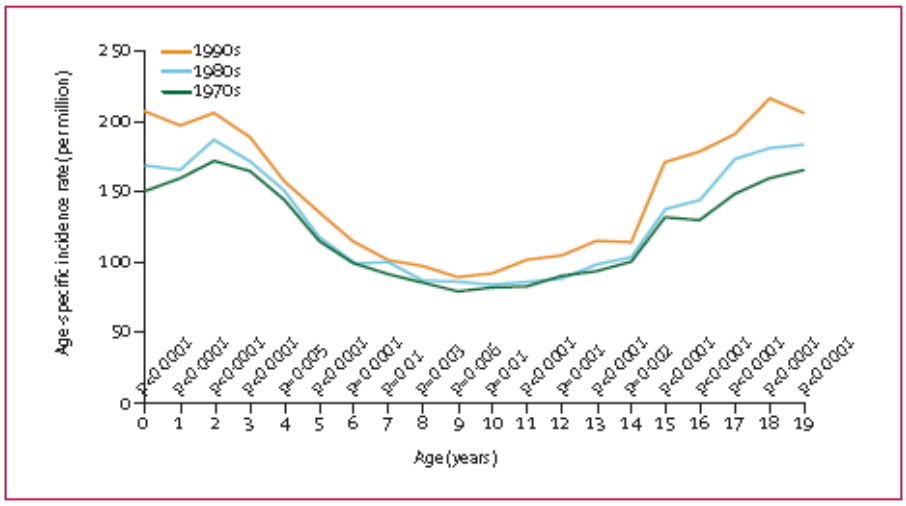

Figure 2. Micronuclei, a biomarker predictive of future cancer risk in adults