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Developing a Child Cohort Research Strategy for Europe

Work Package 3

Deliverable 12 - Final Report

Research Priorities for Child Health Determinants

A project conducted within the

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Executive Summary

To develop a research strategy for mother-child cohorts with improved policy impactm it is essential to evaluate determinants of child health. Our general aim was to address the issues of research priorities for child health determinants. Specific aims were to: evaluate existing information on main child health determinants and on determinant-outcome relationships; to evaluate links to routine registries; to identify gaps in knowledge, and to develop recommendations for research action at European level for the next 15 years.

Five working groups were generated including 'Social and cultural conditions and inequalities', 'Nutrition and physical activity', 'Life-style and substance exposures (e.g. smoking, alcohol, illicit drugs)', 'Other environmental exposures (e.g. air pollution, radiations)', and 'Biological and genetic materials stored in Biobanks'. Each focussed on the fetal and postnatal period up to 18 years of age; the added value of a birth cohort approach; the European perspective; the added value of coordination between the birth cohorts; the research priorities that could benefit from collaboration; the study of inequalities, and the life-course approach.

Based on the work of the working groups, the overall recommendations for research priorities of child health are:

- All countries need information on childhood health determinants and their interactions to inform policies;
- Birth and pregnancy cohorts are extremely valuable to gain knowledge on childhood health determinants because of the prospective aspect and therefore high quality data collection;
- To improve methodologies to measure child health exposures to compare across all birth cohorts;
- To assess new and emerging child health determinants such as chemical toxics or social and cultural indicators, and mixture of exposures on child health outcomes;
- To encourage data sharing among cohort studies in Europe to enhance research at European level;
- To initiate the start of new birth cohorts to capture new exposures and new exposure scenarios;
- To initiate the start of new birth cohorts and to support birth cohorts in countries were infrastructure is currently lacking;
- To emphasize on the inclusion of minority groups in European birth cohorts;
- To strengthen collaboration of birth cohort studies for establishing biobanks for biological and genetic sample collections and storage in Western and Eastern Europe;

- To search for specific funding opportunities for collaborative studies on environmental, biological and genetic samples, especially in European consortia, to easily replicate findings, improve statistical power, and enabling research on rare determinants and interactions between genetic and environmental risk factors;

Eventually, our overall aim is that results of the implemented recommendations will be useful for developing strategies for identifying groups at risk and to improve and protect children's health.

1. Context

Introduction

For policy makers the traditional disease-oriented approach of research is often not the most useful. Policy makers generally attempt to intervene by eliminating risk factors or exposure leading to diseases. Also, it is increasingly recognised that there are shared risk factors (determinants) for many common diseases. Consequently, a determinant-oriented approach to research is recommended. To develop a research strategy for mother-child cohorts with improved policy impact it is essential to evaluate determinants of child health and their interactions. The main child health determinants include social and cultural factors, nutrition and physical activity, life-style exposures such as cigarette smoking, alcohol and illicit drug use, environmental factors such as chemical and physical exposures, and biological and genetic factors.

Birth cohort studies are, because of the prospective aspect of their data collection, in a very strong position to collect high quality data on multiple child health determinants and their interactions. Cohort research on many topics related to child health determinants has important potential policy implications, for example alcohol consumption during pregnancy, fish consumption during pregnancy, lead in petrol, folate intake, breastfeeding, environmental tobacco smoke, and air pollution and the possibility to reduce adverse child health outcomes. Research findings in these areas need to be consistent and conclusive in order to be useful for policy makers. It is important for birth cohorts to work closely together on developing the most precise, reliable, and comparable measurement tools. Evaluations of how the prevalence of child health determinants differs between European regions and how research can be targeted at the most relevant regions are long overdue. Collaboration between birth cohorts has not received much emphasis and is methodologically complex. However, any strategy for child cohort research across Europe should consider collaboration, particularly since they will necessitate large sample sizes and replication across different cohorts.

General aim

The aim of this document is to present the work that has been performed in work package 3 (WP3). The objectives of WP3 were:

- To evaluate existing information on major child health determinants and on determinant-outcome relationships from mother-child cohorts;
- To evaluate links to routine registries;
- To identify gaps in knowledge;
- To develop recommendations for research action at European level for the next 15 years;

Within WP3, 5 working groups (WG) were generated to address issues of research priorities for main child health determinants: 1. Social and cultural conditions and inequalities; 2. Nutrition and physical activity; 3. Life-style and substance exposures (e.g. smoking, alcohol, illicit drugs); 4. Other environmental exposures (e.g. air pollution, radiations); and 5. Biological and genetic materials stored in Biobanks. The originally planned WG 'Mixture of exposures' has assessed the various challenges involving more integrative methods to assess impact of multiple risk factors on child health. Insufficient evidence was found to base recommendations on. Extensive research is instead taken forward by a new FP7 funded 'exposome' project focussing on multiple exposures (HELIX).

Each WG had a leader that was responsible for its activities. The WG leaders and members were experts in their field and have made use of their expert knowledge to a large extent when writing the reports. In general, the focus of the WGs was broad, but with particular emphasis on the added value of a cohort approach, the European perspective, the added value of coordination between the cohorts, the research priorities that could benefit from collaboration, the study of inequalities, and the life-course approach. Birth cohorts to be evaluated were defined as follows: 1. birth and mother-child cohorts, population-based, recruitment at the latest during the first year of life (if data on outcome of pregnancy available, e.g. Millenium cohort), at least one follow-up point during first years of life, sample size or at least 300 subjects, start year from 1990 onwards, and located in one of the EU member states. Where relevant, WGs set out to evaluate the role of national registries with information on child health outcomes or determinants in their reviews. Child cohorts, historical cohorts, patient cohorts, and other study designs, should have been evaluated where relevant. An overview of the WGs, WG leaders and their reports are presented in part 2 of this report (page 13).

Highlights of results

WG '***Social and cultural conditions and inequalities***' firstly gained insight into the data collection of social and cultural indicators by different cohorts in Europe by using published literature and cohort websites. They identified seven cohorts and described the strengths and weaknesses of the commonest social and cultural indicators used in child health research. Also, this WG reviewed literature and observed ample evidence for the association between several indicators of social disadvantage and adverse pregnancy outcomes such as low birth weight and preterm birth. Similar patterns were found for the association between socioeconomic status and breastfeeding initiation and continuation, behaviors that have proven to be beneficial for infants both on the short and long term. That is, socioeconomic status is negatively associated with breastfeeding practices. On the other hand, ethnic minority status is positively related with breastfeeding initiation and continuation.

Across European birth cohorts, WG ***'Nutrition and physical activity'*** observed that most cohorts used well validated food frequency questionnaires to assess dietary intake in pregnancy and childhood in order to minimize the possibility of misclassification of exposure. Associations of both nutrition and physical activy with birth outcomes, postnatal growth, neurodevelopment and cardiovasculair diseases were assessed in many Eurpean birth cohorts. Depending on the outcome, results were not always consistent. The main gaps in research were: less participating cohorts of low income countries or with ethnic heterogeneity, few cohorts with physical activity data, no harmonization of methods to assess nutrition and physical activity data, and no linkage of cohorts with national registries.

WG ***'Life-style and substance exposures (e.g. smoking, alcohol, illicit drugs)'*** observed that questionnaire information on maternal and paternal use of tobacco and alcohol before, during and after pregnancy is included in most of the cohorts, while illicit drug use is more rarely assessed. A substantial number of publications from European birth cohorts have examined these variables as the main exposure of interest with many different outcomes. For preventive efforts, better understanding of the complex causal pattern behind initiation and continuation of substance is needed.

In Europe, there are a total of 43 birth cohorts that are collecting a wealth of information on environmental exposures and child health, according to the WG ***'Other environmental exposures (e.g. air pollution, radiations)'***. Overall, evidence exists suggesting strong associations between second hand smoke and occupational hazards and adverse birth outcomes; high levels of lead (Pb), mercury (Hg), polychlorinated biphenyls (PCBs), and dioxines and neuropsychological development and cognitive function; traffic-related air pollution exposure and domestic visible mould and asthma and related symptoms. The evidence is limited for the association of disinfection-by-products, low levels of Hg and Pb, PCBs & adverse pregnancy outcomes; and traffic-related air pollution & neuropsychological development and cognitive function. No evidence exists for an association between chronic noise exposure & pregnancy outcomes, because the number of studies is small.

According to WG ***'Biological and genetic materials stored in Biobanks'*** , information about exposures using biomarkers might overcome the potential for bias from studies using self reported data, increase power for association studies, and might give insight into the underlying causal mechanisms. This WG observed that many birth cohorts collect biological and genetic samples and had major investments for establishing biobanks, most cohorts are Western European; collaboration on logistics of biological and genetic sample collection, storage and use is scarce; many birth cohorts do have biological samples available but cannot make optimal use of them because of financial restrictions; and scientific collaboration using especially genetic samples has proven to be extremely successful. These collaborations are not funded yet.

Main conclusion and recommendations

Conclusions and recommendations **per WG** are given below.

Social and cultural conditions and inequalities:

- Large number of indicators are used by cohorts to capture social and cultural conditions in (early) childhood (most common: education, occupation and income);
- Need for development of potential relevant indicators (e.g. subjective indicators, peer status), standardization of assessment methods, development of new covariates (i.e. school and environmental factors), and increasing transparency among cohort studies in Europe to enhance research at the European level;
- Need for future research to examine the possible pathways that lead from social disadvantage to adverse child health outcomes. The unravelling of underlying mechanisms provides policymakers with specific information that is essential for accurate intervention mapping, since socioeconomic and ethnic factors are hard, if not impossible, to modify.

Nutrition and physical activity:

- Validated food frequency questionnaires to assess dietary intake are used in European birth cohorts and related to many different health outcomes;
- Not many cohorts include physical activity data;
- Those living on low incomes, or in lower income countries, or from diverse ethnic groups are underrepresented
- Main recommendations: low income cohorts or with ethnic heterogeneity need to be supported, and need for harmonization of methods and collaboration or cohorts;

Life-style and substance exposures (e.g. smoking, alcohol, illicit drugs):

- Many European birth cohorts assessed parental tobacco and alcohol use in different important time periods, but illicit drug use is more rarely assessed;
- Better understanding of the complex causal pattern behind initiation and continuation of substance is needed;
- Life-style and substance exposures are related with many different outcomes;
- Main recommendations are: to fund the infrastructure of birth cohorts in general, to set out calls for research questions that can be responded to by collaborating birth cohorts, and to encourage researchers to apply to the European Research Council for the resolution of new and innovative research questions through the use of data from existing birth cohorts.

Other environmental exposures (e.g. air pollution, radiations):

- Many cohorts have collected a wealth of information on environmental exposures and child health;
- There is fairly good cover of Europe, except Eastern Europe;
- The level of evidence differs between various environmental exposures and child health outcomes;
- Main recommendations are: standardization and improvement of existing environmental exposure assessments; Further combination of existing environment and health data; More work on the effects of new and emerging chemical exposures, indoor pollutants, and pesticides, and more research on the risks and benefits of environmental factors such as green space, solar UV, electromagnetic fields/mobile phones and soundscape/noise. Evaluate the role of mixtures of exposure on child health outcomes; Follow up of exisiting cohorts to determine health effects in later life, and initiate new birth cohorts to capture new exposures and new exposure scenarios.

Biological and genetic materials stored in Biobanks:

- European birth cohorts developed unique, large scale and expensive biobanks; These data cannot always be used because of financial restrictions.
- Biobanks are not equally distributed between Western and Eastern Europe;
- Main recommendations: to strengthen collaboration of birth cohort studies for establishing biobanks for biological and genetic sample collections and storage in Western and Eastern Europe; to search for specific funding opportunities for both collaborative studies on biological and genetic samples, especially in European consortia. These should be focused on promising research fields (epigenetics, expression and metabolomics)

Based on the work of the working groups, the **overall recommendations** for research priorities of child health WP3 are:

- All countries need information on childhood health determinants and their interactions to inform policies;
- Birth and pregnancy cohorts are extremely valuable to gain knowledge on childhood health determinants;
- To improve methodologies to measure child health exposures to compare across all birth cohorts;
- To assess new and emerging child health determinants such as chemical toxins or social and cultural indicators, and a mixture of exposures on child health outcomes;
- To encourage data sharing among cohort studies in Europe to enhance research at European level;

- To initiate the start of new birth cohorts to capture new exposures and new exposure scenarios;
- To initiate the start of new birth cohorts and to support birth cohorts in countries were infrastructure for such large scale research is currently lacking;
- To strengthen the inclusion of minority groups in European birth cohorts;
- To strengthen collaboration of birth cohort studies for establishing biobanks for biological and genetic sample collections and storage in Western and Eastern Europe;
- To search for specific funding opportunities for collaborative studies on environmental, biological and genetic samples, especially in European consortia, to easily replicate findings, improve statistical power, and enabling research on rare determinants and interactions between genetic and environmental risk factors.

Eventually, our overall aim is that results of the implemented recommendations will be useful for developing strategies for identifying groups at risk and to improve and protect children's health.

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 and preterm delivery
3. Selected maternal occupations and fetal health
4. Persistent Organic Pollutants and Birth Outcomes
5. Fish consumption in pregnancy and birth outcomes
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 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	Leader	Members (Institute, country)
Social and cultural conditions and inequalities	Hein Raat , Partner 5 Erasmus MC, the Netherlands, h.raat @erasmusmc.nl	- Laust Mortensen, University of Copenhagen, Denmark - Anne Wijtzes, Erasmus MC, the Netherlands - Ilse Flink, Erasmus MC, The Netherlands
Nutrition and physical activity	Leda Chatzi, Partner 3 University of Crete, Greece, lchatzi@med.uoc.gr	- Vasiliki Leventakou, University of Crete, Greece - Chariklia Chatzigeorgiou, University of Crete, Greece - Manolis Kogevinas, CREAL, Spain; National School of Public Health, Greece
Life-style and substance exposures (e.g. smoking, alcohol, illicit drugs)	Per Magnus, Partner 6 Norwegian Institute of Public Health, Norway, per.magnus@fhi.no	- Siri Håberg, University of Copenhagen, Norway - Katrine Strandberg-Larsen, University of Copenhagen, Norway - Vincent Jaddoe, Erasmus MC, the Netherlands
Other environmental exposures (e.g. air pollution, radiations)	Mark Nieuwenhuijsen, Partner 1 CREAL, Spain, mnieuwenhuijsen@creal.cat	- Maribel Casas, CREAL, Spain - Martine Vrijheid, CREAL, Spain - Ulrike Gehring, Institute for Risk Assessment Science (IRAS), the Netherlands
Biological and genetic materials stored in Biobanks	Vincent Jaddoe, Partner 5 Erasmus MC, the Netherlands, v.jaddoe@erasmusmc.nl	- Ann Marie Nybo Anderson, University of Copenhagen, Denmark - Leda Chatzi, University of Crete, Greece - Liesbeth Duijts, Erasmus MC, the Netherlands - Debbie Lawlor, University of Bristol, United Kingdom - Camilla Stoltenberg, Norwegian Institute of Public Health, Norway - Martine Vrijheid, CREAL, Spain

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Developing a Child Cohort Research Strategy for Europe

Working group

Social and cultural determinants of child health

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Summary

Work package 3 of the CHICOS project aims to 1) evaluate existing information on major child health determinants and on determinant-outcome relationships from mother-child cohorts, 2) evaluate links to routine registries, 3) identify gaps in knowledge (and thus research), and 4) to develop recommendations for research action at the European level for the next 15 years. Because a full review of all ongoing child health research in Europe is not feasible within the scope of this coordination action (and the limited time), some major child health determinants have been identified. This present report is the first product of the working group on social and cultural conditions and inequalities in child health.

In the first part of this report, we tried to gain insight into the data collection by different cohorts in Europe by using published literature and cohort websites. We started by selecting cohorts that were eligible for inclusion in our review, based on the selection criteria formulated in the protocol for WP3, and on the criterion that information on the collection of social and cultural determinants was available. This selection process resulted in a set of seven cohorts including the ABCD study, ALSPAC, Danish National Birth Cohort, Norwegian Mother and Child Cohort, Millennium Cohort Study, Generation R, and the Polish Mother and Child Cohort (explained in further detail in section 1.2). Furthermore, we describe the commonest social and cultural indicators used in child health research (i.e. socioeconomic status, poverty, 'other' social indicators, ethnicity and acculturation), and the strengths and weaknesses of each of these indicators. This section is concluded with a short overview of the indicators collected by the selected cohorts.

Next, we performed a literature review to examine the strength of evidence for exposure-response relationships from cohort research in Europe in the area of our interest (i.e. social and cultural determinants). To this end, we chose two themes: social disadvantage and pregnancy outcomes, and breastfeeding patterns in ethnic minority groups and low socioeconomic groups. The review showed that there is ample evidence for the association between several indicators of social disadvantage and adverse pregnancy outcomes such as low birth weight and preterm birth. Similar patterns were found for the association between socioeconomic status and breastfeeding initiation and continuation, behaviors that have proven to be beneficial for infants both on the short and long term. That is, socioeconomic status is negatively associated with breastfeeding practices. On the other hand, ethnic minority status is positively related with breastfeeding initiation and continuation.

Based on the reviews of literature and cohort website, we conclude that a vast amount of indicators is used by cohorts to capture social and cultural conditions in the (early) childhood years.

Of these indicators, education, occupation and income (i.e. traditional socioeconomic indicators) are collected most often. However, limitations of these indicators have been recognized and many studies collect additional information as well. We have recognized several gaps in current research that we translated into specific recommendations for research action at the European level, including development of potential relevant indicators (e.g. subjective indicators, peer status), standardization of assessment methods, development of new covariates (i.e. school and environmental factors), and increasing transparency among cohort studies in Europe. Our final recommendation, which constitutes the closing remark of this paper, concerns the need for future research to examine the possible pathways that lead from social disadvantage to adverse child health outcomes. The unraveling of underlying mechanisms provides policymakers with specific information that is essential for accurate intervention mapping, since socioeconomic and ethnic factors are hard, if not impossible, to modify.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

Socio-economic, ethnic and cultural factors are important determinants of child health. In Europe, child health risk factors are unequally distributed within and between countries [1]. Reducing socioeconomic inequalities in health is of prime concern to policy makers. Furthermore, the specific cultural and family situation in which a child grows up may influence its health. The context of the family varies by socio-economic and ethnic subgroup. The family unit has changed over the years and children now grow up under very different conditions. Child cohort research into the influence, for example, of parental work patterns on child health and development (breastfeeding, obesity) may have large policy implications [2-4]. Socio-economic, cultural and family contexts vary widely across Europe and European coordination in this area is of great importance.

This working group report currently consists of the following chapters:

1.2 Description of data currently available/being collected by the cohorts on social and cultural determinants of child health

1.3 Description of the contribution of (European) birth cohort research to scientific knowledge on social and cultural determinants and child health

1.4 Identification of gaps in knowledge, methods and tools regarding social and cultural factors

1.5 Recommendations

1.2 Description of data currently available/being collected by the cohorts on social and cultural determinants of child health

1.2.1 Methodology

In this section, we will provide an overview of the different social and cultural determinants generally used in child health research, and by the major birth cohorts in the EU in particular. The starting sample of cohorts included in this overview was based on an existing web-based birth cohort inventory [5] combined with a literature search. We then selected cohorts using the selection criteria (e.g. sample size, amount of follow-up points and start year) formulated in the protocol of WP3. Information on the social and cultural determinants measured in these cohorts was gathered using a literature search and by examination of the cohort websites. The final selection of cohorts used in this overview was as follows (see appendix a):

- ABCD (www.abcd-study.nl)
- ALSPAC (www.alspac.bristol.ac.uk)
- Danish National Birth Cohort (www.bsmd.dk)
- Norwegian Mother and Child Cohort (www.fhi.no/tema/morogbarn)
- Millennium Cohort Study (www.cls.ioe.ac.uk)
- Generation R Study (www.generationr.nl)
- Polish Mother and Child Cohort (www.repropl.com)

1.2.2 Cohort description

The ABCD study [6] and Generation R study [7] are two region-based cohort studies in the Netherlands, in Amsterdam and Rotterdam respectively. The populations of these two cities, the largest and second largest city in the country, comprise multiple ethnic groups including Dutch, Surinamese, Antillean, Turkish and Moroccan groups, among others. The Danish National Birth Cohort [8] and the Norwegian Mother and Child Cohort study [9] are two nation-based cohort studies from Denmark and Norway. ALSPAC [10], a region-based study from Bristol, and the Millennium Cohort Study [11] (nation-based) are cohort studies based in the UK. The final cohort, The Polish Mother and Child Cohort [12], is a nation-based study from Poland.

These cohort studies differ greatly in the amount and specificity of information gathered on social and cultural determinants, which can be explained by the (main) objectives of the studies. In the ABCD study, Generation R study, and the Millennium Cohort Study for example, one of the main aims is to investigate the effects of social and cultural conditions (e.g. social disadvantage) on the

development of children. In other studies, the main focus is on physical environmental factors such as heavy metals (e.g. Polish Mother and Child Cohort Study), and cultural and social indicators are mainly measured to control for possible confounding. In Table 1 (see appendix b), key information on these cohorts is summarized. In general, social and cultural conditions were measured by means of self-administered questionnaires or interviews.

1.2.3 Social and cultural determinants of child health

Inventory of determinants

Children's social position is usually classified according to parental socioeconomic position (SEP), also known as socioeconomic status (SES). Socioeconomic position refers to the social and economical recourses that influence what position individuals or groups hold within a society [13]. In health research, different indicators of SEP are used, depending on the particular research question and the hypothesized mechanisms underlying the (possible) association between SEP and the health outcome [14]. Additionally, use of particular indicators may be limited by the timing or setting of a study [14].

Main indicators of SEP are education, occupation, and income. Alternative measures include indicators of deprivation (or poverty), which are often combined with the traditional SEP indicators. Deprivation indicators are measures for the lack of material assets and possibilities (e.g. holidays and hobby's), and are more relative measures in the sense that they not only provide insight into people's resources, but also what they can do with those resources. Common examples of indicators for deprivation are shown in Table 2 (appendix c). We also distinguish a third category with indicators that are strongly correlated with SEP, and/or which are hypothesized to play a role in the explanation of socioeconomic disparities in child health [15] (e.g. neighborhood characteristics [16-17]).

Ethnicity and acculturation are the main indicators used to classify socio-cultural conditions. Ethnicity is either measured 'objectively' by using country of birth and/or proxy measures such as (native) language, or 'subjectively' by the concept of self-assigned ethnicity [18-19]. In the latter case, respondents state which ethnic group they consider themselves and/or their child to belong to (see Table 3, appendix c). Acculturation is an indicator for the extent to which foreign born people have adapted to the receiving country.

1.2.4 Strength and limitations of indicators

Although the overall approach to capture social and cultural conditions is very similar across cohorts, the amount and selection of indicators used to measure these conditions vary. This section will

elaborate a little on the advantages and disadvantages of the indicators commonly used in the mother-child cohorts (for extensive overviews of indicators of socioeconomic position, see [13-15]).

Education

Educational achievement is usually operationalized as level of education or vocational training (i.e. categorical). In some cases, additional information on whether someone actually attained a degree (vs. drop-out) is also collected. Education can also be measured as a continuous variable (i.e. years of education).

The first problem with using education as an indicator for socioeconomic position is the fact that young parents by definition have a shorter education compared to older parents. Furthermore, categorization of educational qualifications, which is often used in questionnaires, is largely dependent on the country, making it difficult to compare results among studies.

One of the main strengths of education is that it is a strong determinant of occupation and income, and therefore can be considered a rather generic measure of SEP. As educational attainment is strongly influenced by (socioeconomic) characteristics of the family of origin, education not only captures knowledge and resources of an individual, but also early life SEP of that individual. In addition, education has been shown to be one of the most consistent predictors of various child health outcomes and is frequently used as main socioeconomic determinant. Last, education is relatively easy to measure in self-administered questionnaires, and has a high response rate.

Occupation

Occupation is closely related to other measures of socioeconomic position, since it is largely dependent on educational attainment and is a direct predictor of income. Having a paid job is of especial importance in countries where access to health care or other social securities depends on employment.

Occupational status can be classified in terms of activity during 'working hours' such as paid job, being a student, being retired, being out of work and looking for a job, or receiving a welfare allowance. Other types of classification describe the number of working hours per week, or timing of the work during a week (e.g. shifts, working during weekends). Furthermore, the occupation can be fully described, e.g. through job title, type of appointment, a brief job description and type of institute or company. From this information, a certain level of prestige or status can be assigned to the occupation. Also, certain types of work-related exposures (e.g. chemical exposures and exposure to highly physical work) can be derived from the job description, which may be of special relevance during the preconception and prenatal period. When a single parent or two parents do not have a

(current) occupation (e.g. chronically disabled, unemployed or retired people, and parents staying home to take care of children), such an occupational status can not be assigned.

A large advantage of this indicator is its close relationship to other indicators of socioeconomic position such as income and education. Data on occupation is, similar to education, relatively easy to collect and categorize.

One of the most important limitations of occupation is that it cannot be used in case of unemployed people. Moreover, occupational classification is highly dependent on national context, therefore reducing comparability of results between studies.

Income

Income is often used as main measure of material resources. Typical indicators of income are household gross income or net income, often accompanied by information on household composition (e.g. number of people in household). Income can be assessed trough self-report or using municipal and national registries.

A high non-response rate for questions about income is one of the main issues with self-reported income. Also, people can experience difficulties estimating their (yearly) income. Furthermore, a household's net income is only a crude estimate of people's access to material resources and other activities beneficial to one's health (e.g. social activities or holiday). Other sources of income and regular expenses (e.g. rent and electricity) should be considered as well. The major strength of (relative) income as SEP indicator is that it is the most general estimate for children's access to resources.

Deprivation/poverty

Given the limitations to income as a direct estimate of (material) deprivation, new indicators have been used to more accurately estimate people's financial possibilities. It includes indicators like debts, material difficulties (car ownership, house ownership, difficulties buying food and clothing) and financial difficulties (e.g. difficulties paying rent and other monthly expenses). The advantage of these kinds of indicators is that they are more accurately estimated by respondents and that information is easily available. However, it has been argued that they should always be used in combination with the more traditional indicators of socioeconomic position.

Other

For the purpose of this inventory, remaining indicators of socioeconomic position (e.g. teenage pregnancy and single parenthood) have been placed in the category 'other'. Measures relating to

housing and neighborhood are associated with other socioeconomic indicators and can therefore be used as proxy for social and cultural conditions of the family. Furthermore, neighborhood characteristics have been related to child health outcomes, even after adjustment for individual level socioeconomic and demographic covariates [20-21].

Information on single parenthood, age when pregnant (teenage pregnancy yes/no) and intended pregnancy can be collected using self-administered questionnaires and interviews and by means of municipal or national registries. Characteristics of housing and neighborhood can be self-reported using objective questions (e.g. running water in household, computers and/or internet in the household) and/or subjective questions (e.g. *subjective perception* of quality of housing and neighborhood safety). Fieldwork exercises by researchers who visit the areas and assign scores according to predefined criteria constitute a more objective manner of measuring aspects of housing and neighborhood.

Arguments in favor of these indicators are that they are generally easy to collect and that they add more depth to the information provided by the other socioeconomic indicators.

Difficulties with these indicators concern sensibility issues (deliberate pregnancy) and practical issues, among others. For example, due to the increased divorce-rate many children may live with one of the parents, but increasing numbers may live with both parents alternately; the divorced parents may provide for the child together. It is not clear how to deal with such arrangements when describing social and cultural indicators of the parents in the context of studies on equity in childhood health. With regard to the environmental indicators (i.e. housing and neighborhood), one of the largest weaknesses is their limited cross-national comparability (and thus comparability among cohort studies), due to discrepancies in neighborhood and housing conditions across countries in Europe.

Peer status

One strictly social indicator, peer status, is highlighted here because it is one of the few true child-focused indicators. However, to our knowledge, this indicator has not been used in any of the cohort studies under review. Because we feel this indicator may contribute to the understanding of social inequalities in childhood health, we discuss this indicator briefly.

Similar to adults, children in a school class can be attributed a certain social status among his or her classmates (i.e. peer status) that indicates the extent to which a particular child is liked by others in the school class. Lower peer status during childhood has been associated with various adverse health outcomes during childhood [22] and adulthood (anxiety and depression [23]; limiting longstanding illness and self-rated health [24]; and overall morbidity and disease-specific morbidity [25]).

Peer status is usually measured by asking all children in a school class to name the names of three classmates they either like the best [22, 24], or prefer to work with [23 25]. Based on the amount of nominations, five status groups are created: marginalized (0 nominations), peripheral (1 nomination), accepted (2-3 nominations), popular (4-6 nominations) and favorite (7 or more nominations) children. As mentioned previously, one of the strengths of this indicator is that it is a true *child* indicator. Additionally it is assessed in a uniform manner, which makes it a suitable for comparison across studies. A disadvantage of peer status is that it is a limited indicator, assessing only social position (not socio*economic* position).

Ethnicity

Ethnicity has been measured in many different ways. There are more 'objective' measures, which include country of birth of the child (or parents and grandparents) and native language. A completely different way of measuring ethnicity is by the concept of self-assigned ethnicity, in which case respondents state which ethnicity they consider themselves and the child to belong to.

Limitations of the use of ethnicity as a cultural indicator are the disparities in assessment methods and definition, therefore limiting cross-national comparability. For example, children's ethnicity may be defined according to its own national origin (country of birth child), that of its parents, or that of its grandparents. The Scandinavian cohorts gather either a small amount or no amount of information on ethnicity, due to the homogenous composition of their population sample. Also, self-perceived ethnicity may be unstable over time; it should be used in combination with stable indicators such as country of birth.

Acculturation

In studies focusing primarily on social and cultural determinants of child health, measures of acculturation may be gathered as well. These measures (e.g. language proficiency, reason of migration, time in receiving country) provide extra information on cultural conditions in early childhood.

The main strength of these indicators is that they enable researchers to gain clearer insight into the cultural background of children. However, one should strive to use them in combination with ethnicity indicators. Reason of migration and time in receiving country are objective, easily available, indicators. Information on discrimination (social acceptance) and language use is harder to collect, since these are subjective measures that depend on respondents' perception.

1.2.5 Overview of determinants used by cohorts

Tables 4 and 5 (appendix d) give an overview of the social and cultural determinants that, to our best knowledge, have been measured in the different cohort studies. The traditional SEP variables are consistently collected in all studies. The specificity of the questions and the ways in which they are measured (open answer, categories etc.) do vary. In general, most studies add information on indicators of deprivation. Fewer studies also collect data on indicators in the 'other' category. Ethnic conditions are extensively studied in the ABCD, Generation R and the Millennium Cohort studies, due to their emphasis on (the explanation of) ethnic disparities in birth outcomes and child health.

1.2.6 Explanatory pathways

An extensive body of research shows that socioeconomic position and ethnic background are strong determinants of child health. It is assumed that these variables influence health primarily through the effects of mediating factors, rather than in a direct manner. The observed associations between SEP/ethnic background and child health can be explained by two types of factors; confounders and these mediating factors. Given that SEP and ethnic background are very distal ("upstream") to child health outcomes, the number of confounders that can be used to explain the associations is usually very small. Most, if not all, cohorts collect information on relevant confounders. In contrast, the number of potential mediating factors is usually very large. These factors may differ depending on the determinant and outcome of interest, as well as on the specific cohort (i.e. national context). For example, educational gradients in breastfeeding vary between cohort studies. Therefore, in different cohorts breastfeeding patterns may explain educational inequalities in child health outcomes in different ways. The birth cohorts in Europe contribute to our understanding of socioeconomic and ethnic inequalities in child health in several ways. First, cohort studies collect a rich selection of variables, enabling researchers to study the potential mediating role of a wide array of factors. Second, cross cohort comparisons make it possible to examine if the associations between determinants and health outcomes (as well as between determinants and mediating factors and between mediating factors and health outcomes) are robust across various contexts, which constitutes an important step in ruling out confounding and establishing causal effects. Additionally, examining the ways in which these associations differ across cohorts may provide important clues on how these associations depend on the larger social and material context.

1.3 Description of the contribution of (European) birth cohort research to scientific knowledge on social and cultural determinants and child health

The aim of the current chapter is to review the strength of evidence for exposure-response relationships from cohort research in Europe in the area of social and cultural determinants, and evaluate links between cohort research and routine registries.

1.3.1 Methodology

An online literature search was conducted in October and November 2010 and updated in April 2012 in Pub Med using Thomson endnote version X3. We identified literature on the previously defined cohort studies by searching for their study names in titles [ABCD Study AND/OR ALSPAC Study AND/OR Danish National Birth Cohort AND/OR The Norwegian Mother and Child Cohort AND/OR Millennium Cohort Study AND/OR Generation R Study AND/OR Polish Mother and Child Cohort]. Hereafter, we searched for the following terms in article abstracts: [income AND/OR ethnic AND/OR migrant AND/OR education AND/OR occupation AND/OR employment AND/OR deprivation AND/OR single parenthood]. We only included articles that studied the previous terms as main determinants. The search strategy generated 50 articles. In table 6 (appendix e) an overview is given of these articles. In table 7 (see appendix f) details are provided on the strength of the exposure-response relationships.

Of these 50 articles, two themes were chosen as case studies for further illustration of the strength of the exposure-response relationship. To make a valid selection of the themes the following criteria were used:

1. Differences/associations remain after adjusting for confounders
2. Replicated at least once within a different European cohort

1.3.2 Results

Two themes resulted from this selection: social disadvantage and pregnancy outcomes and breastfeeding patterns in ethnic minority and low socioeconomic groups. These two themes will be discussed as case studies in the following paragraphs. Additionally, a summary of all included studies can be found in table 7.

Social disadvantage and pregnancy outcomes

Various cohort studies in Europe have focused on the impact of social disadvantage on pregnancy outcomes. Social disadvantage to this end can include: neighborhood deprivation, ethnic minority status, low education, occupation and low income.

Agyemang and colleagues [20] studied the effect of neighborhood income and deprivation on Small for Gestational Age (SGA) births within the ABCD study [6]. They found that women living in a quartile of neighborhoods with the highest unemployment/social security benefit were more likely to have SGA birth. Morgen and colleagues [26] studied the association between income, occupation, maternal education and the risk of pre-term birth within the Danish Birth Cohort [8]. They found that mothers with <10 years of education had an elevated risk of preterm birth compared to mothers with >12 years of education. Paternal education, household income and occupation affected the risk to a lesser degree. Jansen and colleagues [27] also found an association between maternal education and preterm birth within the Generation R study. Additionally they looked at birth weight as an outcome and found similar patterns [28]. Farrow and colleagues [29] studied the association between maternal occupation and birth weight within the ALSPAC study [10]. After adjustment for sex of the infant, parity, maternal height, smoking, caffeine consumption and race, maternal job was no longer associated with birth weight.

Researchers focusing on ethnicity and birth weight within the Generation R study and the ABCD study have found that associations can be explained, to a great extent, by constitutional factors like maternal and paternal height [30-31].

Breastfeeding patterns in ethnic minority and low socio-economic groups

Within the birth cohorts in Europe various researchers have looked at breastfeeding patterns. Breastfeeding remains the best type of feeding for an infant and brings short- as well as long-term benefits. Researchers of the Generation R study Rotterdam and the Millennium Cohort study have found clear indications that ethnic minority groups are more likely to start and continue

breastfeeding than their white, native counterparts. Griffiths and colleagues [32] studied the contribution of parental and community ethnicity to breastfeeding practices within the Millennium Cohort [11]. Their study illustrated that white mothers were less likely to breastfeed than women from all other ethnic groups adjusted for ward type, socioeconomic position, maternal education, lone status reproductive history, including maternal age at first live birth, maternal age at cohort's child birth, and parity. They also found that having a partner from a different ethnic group was positively associated with breastfeeding initiation and continuation. In turn, white lone mothers were more likely to initiate breastfeeding if they lived in ethnic minority neighborhoods. Rossem and colleagues [33] looked at ethnic differences in breastfeeding initiation and continuation within the Generation R study [7]. They found that relative to native Dutch mothers, starting breastfeeding was significantly higher in all non-native groups. Adjustment for educational level strengthened the associations. In turn, mothers with a Mediterranean background (Turkish or Moroccan) were more likely to breastfeed at 2 and 6 months than Dutch mothers.

With regards to socio-economic factors, researchers have found that socio-economic position is negatively associated with breastfeeding initiation and continuation. Rossem and colleagues [33] assessed the effect of mother's educational level on starting and continuing breastfeeding and assessed the role of socio-demographic, lifestyle-related, psychosocial, and birth characteristics in this association. They found that mothers with a lower education were less likely to start breastfeeding and continue up to 2 months. Griffiths and colleagues [32] found that mothers who were younger, first time mothers, with semi routine or routine occupations or no academic qualifications were less likely to continue breastfeeding for at least one month. Beale and colleagues [34] looked at whether council tax valuation band predicts breastfeeding and socio-economic status within the ALSPAC study. The researchers found a strong relationship between CTVB and socioeconomic position. In turn, the CTVB-A (the lower income group) children were breastfed less at 4 weeks and a trend was found for the variable CTVB and breastfeeding.

1.3.3 Routine registries

Other study designs that may be of interest for studying social and cultural determinants of child health are routine registries like the birth registries or the centers for statistics registering population level data. Registries provide important insights into outcomes at the population level [35-36]. Routine registries may also provide important information about non-participation in birth cohorts [37].

1.4 Identification of gaps

1.4.1 Social and cultural determinants

There is a vast amount of different indicators used to determine children's social and cultural conditions in early life. The limitations of using only the traditional SES indicators have been recognized and newer, more sensitive, indicators are included in most studies. However, we noticed multiple gaps in the data collected by the cohorts.

First, although studies generally measure the amount or intensity of deprivation/poverty or other social conditions, information on the frequency, duration and timing of periods in which people experience poverty or deprivation is generally not asked for. It is plausible that poverty during certain important developmental periods affects child health more that poverty during other periods. If indicators are repeatedly measured during follow-ups these periods can be reconstructed, but the frequency of follow-up then poses a limitation to the specificity of information that can be collected.
Secondly, information on children's health outcomes and their determinants (exposure) is highly dependent on parental input. To get more precise measurements, particularly in young children, data collection from multiple informants (i.e. parents, children, teachers, grandparents) will be beneficial. Extra information on environmental factors outside the family, such as school and neighborhood factors, should also receive more attention since exposure to these factors will significantly increase as children grow older. The ALSPAC study for example [10], also sends out school questionnaires that are completed by staff from schools attended by ALSPAC participants. Neighborhood level data can either be collected by researchers (i.e. fieldwork), or be retrieved from municipal or country-level registries.

It is also very important to recognize that social and cultural position of children is almost always equated with social position of their parents. Although this is the most obvious solution for young children, it can be argued that in later stages of childhood (reaching adolescence) focus should shift from parents to the actual children.

Furthermore, the overall focus in the cohorts has been on the collection of objective measures and it can be questioned whether subjective measures are more appropriate indicators of social position. For example, perceived neighborhood safety has been associated with child health outcomes [21] and child health behavior [38].

1.4.2 Comparability

Considering the rationale behind coordination of European cohort research (comparing results and pooling data), it should be noted that there are still many disparities in the way certain social and cultural determinants are measured. Even a traditional social determinant such as socioeconomic status is not measured in one standardized manner among cohorts.

1.4.3 Explanatory factors

If social and cultural determinants affect health in a given context they do so through mediating factors. This report has examined breast feeding as one such factor. Collecting information on and quantification of the importance of mediating factors are important in birth cohort research because the mediators often are more easily targeted by interventions than the social and cultural determinants themselves.

1.4.4 Geographical distribution

A final remark regarding European birth cohort research is the distribution of the cohorts. Most of the birth cohorts are based in Central-Europe and Scandinavia; South-Europe and East-Europe in particular are relatively underrepresented. The birth cohorts from Denmark and Norway are especially impressive considering the number of participants and the amount of information collected. Scandinavian countries are well suited for cohort research because they have population-based registries on many outcomes (e.g. diseases and demography). The skewed geographical distribution of cohorts not only leads to a more homogenous research population, it also makes it difficult to evaluate (the effects of) child health determinants that are more frequently present or more expressed in countries without established cohort research.

1.5 Recommendations

1.5.1 Summary

European cohort research on (determinants of) inequalities in child health shows overlap in the use of indicators, but large discrepancies in the ways these indicators are measured or defined. The traditional indicators of socioeconomic status, including education, occupation and income, are still the most prevalent ones. In addition to social determinants, cultural determinants such as ethnicity and acculturation have been extensively studied as well. After correction for potential confounders, social disadvantage was a consistent risk factor for several adverse pregnancy outcomes [20, 26-28] and breastfeeding practices [32-34]. In contrast, studies on the association between ethnic background and breastfeeding practices have shown that women from ethnic minority groups are more likely to initiate and continue breastfeeding [32-33].

1.5.2 Recommendations

1.5.2.1 Gaps

In the previous section (1.4) we have indicated several gaps in current research. Summarizing these findings, we recommend the following actions:

- Development of new indicators
  - timing, duration and frequency of socially disadvantaged circumstances
  - subjective measures (e.g. self-perceived neighborhood safety)
  - socioeconomic position of children (not parents)
  - peer status
- Standardization of assessment methods
  - standardization of measurement of indicators
  - regular updates of indicators that can change rapidly (e.g. income, single parenthood)
- Development of new covariates/ extend body of existing covariates
  - school factors
  - neighborhood factors
- Manuscripts (published literature)
  - increase specificity of methodology in order to enhance transparency and - comparability among studies
  - replicate studies that have not yet been reproduced

1.5.2.2 Policy makers

To enable policy makers to tackle socioeconomic and cultural inequalities in child health, they need to be provided with extra information in addition to descriptive data on the prevalence of social and cultural risk factors and evidence on the relationships between these determinants and child health outcomes. Since socioeconomic and cultural factors are difficult to modify, clues on the causal pathways that lead from social disadvantage to adverse health outcomes are crucial in the development of effective interventions. Therefore, research in the area of child health should also focus on the examination of potential covariates (e.g. neighborhood and parenting style and practices) that may affect or mediate the associations between social and cultural conditions and child health [16, 39-40].

References

1. Mackenbach J. BM, Benach J. *Reducing Inequalities in Health: A European Perspective.* : London: Routledge; 2002.

2. Hawkins SS, Griffiths LJ, Dezateux C, Law C, Millennium Cohort Study Child Health G. Maternal employment and breast-feeding initiation: findings from the Millennium Cohort Study. *Paediatr Perinat Epidemiol.* May 2007;21(3):242-247.

3. Hawkins SS, Griffiths LJ, Dezateux C, Law C, Millennium Cohort Study Child Health G. The impact of maternal employment on breast-feeding duration in the UK Millennium Cohort Study. *Public Health Nutr.* Sep 2007;10(9):891-896.

4. Hawkins SS, Cole TJ, Law C. Maternal employment and early childhood overweight: findings from the UK Millennium Cohort Study. *Int J Obes (Lond).* Jan 2008;32(1):30-38.

5. Nybo Andersen A-M, Vrijheid M. www.birthcohorts.net.

6. van Eijsden M, Vrijkotte TG, Gemke RJ, van der Wal MF. Cohort Profile: The Amsterdam Born Children and their Development (ABCD) Study. *Int J Epidemiol.* Sep 2 2010.

7. Jaddoe VW, van Duijn CM, van der Heijden AJ, et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol.* Nov 2010;25(11):823-841.

8. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort--its background, structure and aim. *Scand J Public Health.* Dec 2001;29(4):300-307.

9. Magnus P, Irgens LM, Haug K, et al. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol.* Oct 2006;35(5):1146-1150.

10. Golding J, Team AS. The Avon Longitudinal Study of Parents and Children (ALSPAC)--study design and collaborative opportunities. *Eur J Endocrinol.* Nov 2004;151 Suppl 3:U119-123.

11. Smith K, Joshi H. The Millennium Cohort Study. *Popul Trends.* Spring 2002(107):30-34.

12. Polanska K, Hanke W, Gromadzinska J, et al. Polish mother and child cohort study--defining the problem, the aim of the study and methodological assumption. *Int J Occup Med Environ Health.* 2009;22(4):383-391. **13.** Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu Rev Public Health.* 1997;18:341-378.

14. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health.* Jan 2006;60(1):7-12.

15. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). *J Epidemiol Community Health.* Feb 2006;60(2):95-101.

16. Leventhal T, Brooks-Gunn J. The neighborhoods they live in: The effects of neighborhood residence on child and adolescent outcomes. *Psychological Bulletin.* Mar 2000;126(2):309-337.

17. Kohen DE, Leventhal T, Dahinten VS, McIntosh CN. Neighborhood disadvantage: pathways of effects for young children. *Child Dev.* Jan-Feb 2008;79(1):156-169.

18. Stronks K, Kulu-Glasgow I, Agyemang C. The utility of 'country of birth' for the classification of ethnic groups in health research: the Dutch experience. *Ethn Health.* Jun 2009;14(3):255-269.

19. Winker MA. Measuring race and ethnicity: why and how? *JAMA.* Oct 6 2004;292(13):1612-1614.

20. Agyemang C, Vrijkotte TG, Droomers M, van der Wal MF, Bonsel GJ, Stronks K. The effect of neighbourhood income and deprivation on pregnancy outcomes in Amsterdam, The Netherlands. *J Epidemiol Community Health.* Sep 2009;63(9):755-760.

21. Lumeng JC, Appugliese D, Cabral HJ, Bradley RH, Zuckerman B. Neighborhood safety and overweight status in children. *Archives of Pediatrics & Adolescent Medicine.* Jan 2006;160(1):25-31.

22. Ostberg V. Children in classrooms: peer status, status distribution and mental well-being. *Soc Sci Med.* Jan 2003;56(1):17-29.

23. Modin B, Ostberg V, Almquist Y. Childhood Peer Status and Adult Susceptibility to Anxiety and Depression. A 30-Year Hospital Follow-up. *J Abnorm Child Psychol.* Oct 1 2010.

24. Ostberg V, Modin B. Status relations in school and their relevance for health in a life course perspective: findings from the Aberdeen children of the 1950's cohort study. *Soc Sci Med.* Feb 2008;66(4):835-848.

25. Almquist Y. Peer status in school and adult disease risk: a 30-year follow-up study of disease-specific morbidity in a Stockholm cohort. *J Epidemiol Community Health.* Dec 2009;63(12):1028-1034.

26. Morgen CS, Bjork C, Andersen PK, Mortensen LH, Nybo Andersen AM. Socioeconomic position and the risk of preterm birth--a study within the Danish National Birth Cohort. *Int J Epidemiol.* Oct 2008;37(5):1109-1120.

27. Jansen PW, Tiemeier H, Jaddoe VW, et al. Explaining educational inequalities in preterm birth: the generation r study. *Arch Dis Child Fetal Neonatal Ed.* Jan 2009;94(1):F28-34.

28. Jansen PW, Tiemeier H, Looman CW, et al. Explaining educational inequalities in birthweight: the Generation R Study. *Paediatr Perinat Epidemiol.* May 2009;23(3):216-228.

29. Farrow A, Shea KM, Little RE. Birthweight of term infants and maternal occupation in a prospective cohort of pregnant women. The ALSPAC Study Team. *Occup Environ Med.* Jan 1998;55(1):18-23.

30. Troe EJ, Raat H, Jaddoe VW, et al. Explaining differences in birthweight between ethnic populations. The Generation R Study. *BJOG.* Dec 2007;114(12):1557-1565.

31. Goedhart G, van Eijsden M, van der Wal MF, Bonsel GJ. Ethnic differences in term birthweight: the role of constitutional and environmental factors. *Paediatr Perinat Epidemiol.* Jul 2008;22(4):360-368.

32. Griffiths LJ, Tate AR, Dezateux C. The contribution of parental and community ethnicity to breastfeeding practices: evidence from the Millennium Cohort Study. *Int J Epidemiol.* Dec 2005;34(6):1378-1386.

33. van Rossem L, Vogel I, Steegers EA, et al. Breastfeeding patterns among ethnic minorities: the Generation R Study. *J Epidemiol Community Health.* Dec 2010;64(12):1080-1085.

34. Beale N, Kane G, Gwynne M, et al. Council tax valuation band predicts breast feeding and socio-economic status in the ALSPAC study population. *BMC Public Health.* 2006;6:5.

35. Troe EJ, Bos V, Deerenberg IM, Mackenbach JP, Joung IM. Ethnic differences in total and cause-specific infant mortality in The Netherlands. *Paediatr Perinat Epidemiol.* Mar 2006;20(2):140-147.

36. Troe EJ, Kunst AE, Bos V, Deerenberg IM, Joung IM, Mackenbach JP. The effect of age at immigration and generational status of the mother on infant mortality in ethnic minority populations in The Netherlands. *Eur J Public Health.* Apr 2007;17(2):134-138.

37. Jacobsen TN, Nohr EA, Frydenberg M. Selection by socioeconomic factors into the Danish National Birth Cohort. *Eur J Epidemiol.* May 2010;25(5):349-355.

38. Burdette HL, Whitaker RC. A national study of neighborhood safety, outdoor play, television viewing, and obesity in preschool children. *Pediatrics.* Sep 2005;116(3):657-662.

39. Rhee KE, Lumeng JC, Appugliese DP, Kaciroti N, Bradley RH. Parenting styles and overweight status in first grade. *Pediatrics.* Jun 2006;117(6):2047-2054.

40. Rhee K. Childhood overweight and the relationship between parent behaviors, parenting style ' and family functioning. *Annals of the American Academy of Political and Social Science.* Jan 2008;615:12-37.

41. Jansen PW, Raat H, Mackenbach JP, et al. Socioeconomic inequalities in infant temperament: the generation R study. *Soc Psychiatry Psychiatr Epidemiol.* Feb 2009;44(2):87-95.

42. Blair PS, Drewett RF, Emmett PM, Ness A, Emond AM. Family, socioeconomic and prenatal factors associated with failure to thrive in the Avon Longitudinal Study of Parents and Children (ALSPAC). *Int J Epidemiol.* Aug 2004;33(4):839-847.

43. Baker D, North K. Does employment improve the health of lone mothers? The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Soc Sci Med.* Jul 1999;49(1):121-131.

44. Majeed M, Williams C, Northstone K, Ben-Shlomo Y. Are there inequities in the utilisation of childhood eye-care services in relation to socio-economic status? Evidence from the ALSPAC cohort. *Br J Ophthalmol.* Jul 2008;92(7):965-969.

45. Chote AA, Koopmans GT, Redekop WK, et al. Explaining Ethnic Differences in Late Antenatal Care Entry by Predisposing, Enabling and Need Factors in the Netherlands. The Generation R Study. *Matern Child Health J.* Jun 9 2010.

46. Jayaweera H, Quigley MA. Health status, health behaviour and healthcare use among migrants in the UK: evidence from mothers in the Millennium Cohort Study. *Soc Sci Med.* Sep 2010;71(5):1002-1010.

47. Mortensen LH, Diderichsen F, Smith GD, Andersen AM. The social gradient in birthweight at term: quantification of the mediating role of maternal smoking and body mass index. *Hum Reprod.* Oct 2009;24(10):2629-2635.

48. Matijasevich A, Victora CG, Lawlor DA, et al. Association of socioeconomic position with maternal pregnancy and infant health outcomes in birth cohort studies from Brazil and the UK. *J Epidemiol Community Health.* Jul 13 2010.

49. Van Dijk AE, Van Eijsden M, Stronks K, Gemke RJ, Vrijkotte TG. The relation of maternal job strain and cortisol levels during early pregnancy with body composition later in the 5-year-old child: The ABCD study. *Early Hum Dev.* Oct 20 2011.

50. Kelly Y, Panico L, Bartley M, Marmot M, Nazroo J, Sacker A. Why does birthweight vary among ethnic groups in the UK? Findings from the Millennium Cohort Study. *J Public Health (Oxf).* Mar 2009;31(1):131-137.

51. Dunn J, Deater-Deckard K, Pickering K, O'Connor TG, Golding J. Children's adjustment and prosocial behaviour in step-, single-parent, and non-stepfamily settings: findings from a community study. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *J Child Psychol Psychiatry.* Nov 1998;39(8):1083-1095.

52. Shea KM, Farrow A, Little R. An investigation of the effect of paternal occupation group at conception on birth weight and gestational age. ALSPAC Study Team of Pregnancy and Childhood. *Am J Ind Med.* Jun 1997;31(6):738-743.

53. Griffiths LJ, Dezateux C, Cole TJ. Sex and ethnic differences in the waist circumference of 5-year-old children: Findings from the Millennium Cohort Study. *Int J Pediatr Obes.* Nov 15 2010.

54. Essex HN, Pickett KE. Mothers without companionship during childbirth: an analysis within the Millennium Cohort Study. *Birth.* Dec 2008;35(4):266-276.

55. Silva L, Coolman M, Steegers E, et al. Maternal educational level and risk of gestational hypertension: the Generation R Study. *J Hum Hypertens.* Jul 2008;22(7):483-492.

56. Kelly YJ, Watt RG. Breast-feeding initiation and exclusive duration at 6 months by social class--results from the Millennium Cohort Study. *Public Health Nutr.* Jun 2005;8(4):417-421.

57. Rogers I, Emmett P, Baker D, Golding J. Financial difficulties, smoking habits, composition of the diet and birthweight in a population of pregnant women in the South West of England. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Eur J Clin Nutr.* Apr 1998;52(4):251-260.

58. Silva LM, Coolman M, Steegers EA, et al. Low socioeconomic status is a risk factor for preeclampsia: the Generation R Study. *J Hypertens.* Jun 2008;26(6):1200-1208.

59. Morales-Suarez-Varela M, Kaerlev L, Zhu JL, et al. Risk of Infection and adverse outcomes among pregnant working women in selected occupational groups: A study in the Danish National Birth Cohort. *Environ Health.* Nov 15 2010;9(1):70.

60. Jansen PW, Tiemeier H, Verhulst FC, et al. Employment status and the risk of pregnancy complications: the Generation R Study. *Occup Environ Med.* Jun 2010;67(6):387-394.

61. Jansen PW, Raat H, Mackenbach JP, et al. National origin and behavioural problems of toddlers: the role of family risk factors and maternal immigration characteristics. *J Abnorm Child Psychol.* Nov 2010;38(8):1151-1164.

62. Silva LM, Steegers EA, Burdorf A, et al. No midpregnancy fall in diastolic blood pressure in women with a low educational level: the Generation R Study. *Hypertension.* Oct 2008;52(4):645-651.

63. Morales-Suarez-Varela MM, Toft GV, Jensen MS, et al. Parental occupational exposure to endocrine disrupting chemicals and male genital malformations: a study in the Danish National Birth Cohort study. *Environ Health.* 2011;10(1):3.

64. Morales-Suarez-Varela M, Kaerlev L, Zhu JL, et al. Unemployment and pregnancy outcomes: a study within the Danish National Birth Cohort. *Scand J Public Health.* Jul 2011;39(5):449-456.

65. Saridjan NS, Huizink AC, Koetsier JA, et al. Do social disadvantage and early family adversity affect the diurnal cortisol rhythm in infants? The Generation R Study. *Horm Behav.* Feb 2010;57(2):247-254.

66. Kelly Y, Sacker A, Schoon I, Nazroo J. Ethnic differences in achievement of developmental milestones by 9 months of age: The Millennium Cohort Study. *Dev Med Child Neurol.* Oct 2006;48(10):825-830.

67. O'Connor TG, Davies L, Dunn J, Golding J. Distribution of accidents, injuries, and illnesses by family type. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. *Pediatrics.* Nov 2000;106(5):E68.

68. van Rossem L, Oenema A, Steegers EA, et al. Are starting and continuing breastfeeding related to educational background? The generation R study. *Pediatrics.* Jun 2009;123(6):e1017-1027.

69. Snijder CA, Brouwers MM, Jaddoe VW, Hofman A, Roeleveld N, Burdorf A. Occupational exposure to endocrine disruptors and time to pregnancy among couples in a large birth cohort study: the Generation R Study. *Fertil Steril.* May 2011;95(6):2067-2072.

70. McMunn A, Kelly Y, Cable N, Bartley M. Maternal employment and child socio-emotional behaviour in the UK: longitudinal evidence from the UK Millennium Cohort Study. *J Epidemiol Community Health.* Jan 10 2011.

71. Panico L, Bartley M, Marmot M, Nazroo JY, Sacker A, Kelly YJ. Ethnic variation in childhood asthma and wheezing illnesses: findings from the Millennium Cohort Study. *Int J Epidemiol.* Oct 2007;36(5):1093-1102.

72. Gabriele C, Silva LM, Arends LR, et al. Early respiratory morbidity in a multicultural birth cohort: the Generation R Study. *Eur J Epidemiol.* Apr 4 2012.

73. Silva LM, Jansen PW, Steegers EA, et al. Mother's educational level and fetal growth: the genesis of health inequalities. *Int J Epidemiol.* Oct 2010;39(5):1250-1261.

74. Howe LD, Tilling K, Galobardes B, Smith GD, Gunnell D, Lawlor DA. Socioeconomic differences in childhood growth trajectories: at what age do height inequalities emerge? *J Epidemiol Community Health.* Aug 18 2010.

75. Snijder CA, Roeleveld N, Te Velde E, et al. Occupational exposure to chemicals and fetal growth: the Generation R Study. *Hum Reprod.* Mar 2012;27(3):910-920.

76. Pickett KE, Shaw RJ, Atkin K, Kiernan KE, Wilkinson RG. Ethnic density effects on maternal and infant health in the Millennium Cohort Study. *Soc Sci Med.* Nov 2009;69(10):1476-1483.

77. Clark EM, Ness A, Tobias JH, Team AS. Social position affects bone mass in childhood through opposing actions on height and weight. *J Bone Miner Res.* Dec 2005;20(12):2082-2089.

78. Hafkamp-de Groen E, van Rossem L, de Jongste JC, et al. The role of prenatal, perinatal and postnatal factors in the explanation of socioeconomic inequalities in preschool asthma symptoms: the Generation R Study. *J Epidemiol Community Health.* Jan 19 2012.

79. Timmermans S, Jaddoe VW, Mackenbach JP, Hofman A, Steegers-Theunissen RP, Steegers EA. Determinants of folic acid use in early pregnancy in a multi-ethnic urban population in The Netherlands: the Generation R study. *Prev Med.* Oct 2008;47(4):427-432.

80. Brophy S, Cooksey R, Lyons RA, Thomas NE, Rodgers SE, Gravenor MB. Parental factors associated with walking to school and participation in organised activities at age 5: analysis of the Millennium Cohort Study. *BMC Public Health.* 2011;11:14.

81. Troe EJ, Raat H, Jaddoe VW, et al. Smoking during pregnancy in ethnic populations: the Generation R study. *Nicotine Tob Res.* Aug 2008;10(8):1373-1384.

82. Kelly Y, Sacker A, Del Bono E, Francesconi M, Marmot M. What role for the home learning environment and parenting in reducing the socioeconomic gradient in child development? Findings from the Millennium Cohort Study. *Arch Dis Child.* Sep 2011;96(9):832-837.

83. van Eijsden M, Hornstra G, van der Wal MF, Bonsel GJ. Ethnic differences in early pregnancy maternal n-3 and n-6 fatty acid concentrations: an explorative analysis. *Br J Nutr.* Jun 2009;101(12):1761-1768.

84. Melotti R, Heron J, Hickman M, et al. Adolescent alcohol and tobacco use and early socioeconomic position: the ALSPAC birth cohort. *Pediatrics.* Apr 2011;127(4):e948-955.

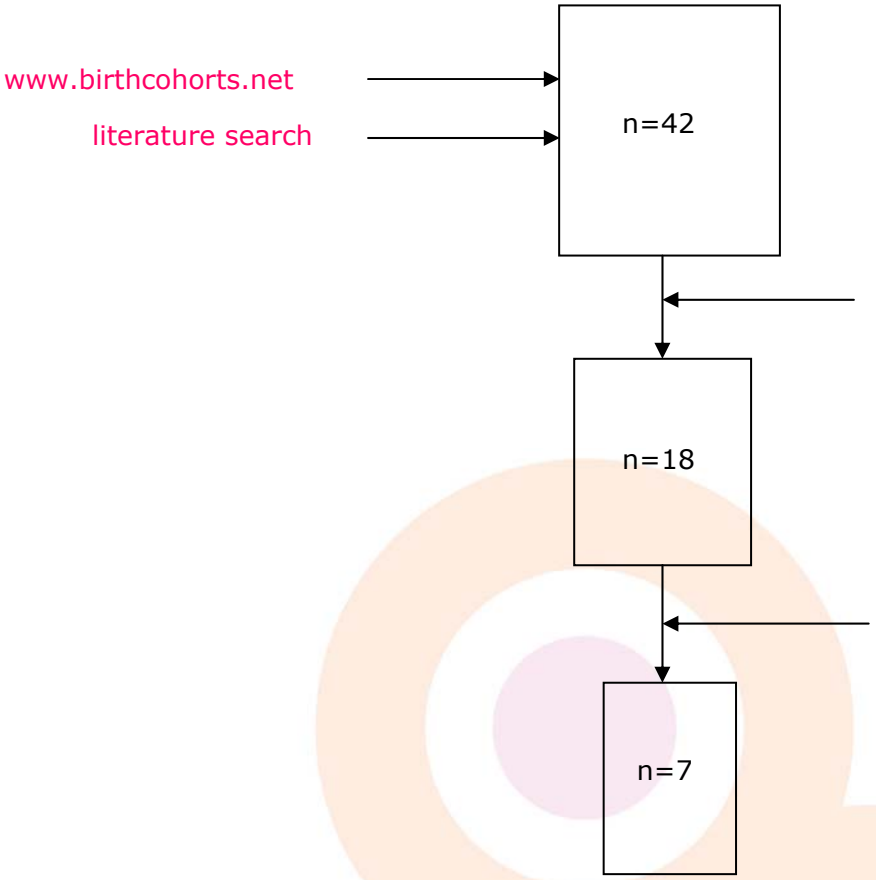
85. de Hoog ML, van Eijsden M, Stronks K, Gemke RJ, Vrijkotte TG. Overweight at age two years in a multi-ethnic cohort (ABCD study): the role of prenatal factors, birth outcomes and postnatal factors. *BMC Public Health.* 2011;11:611.

86. de Hoog ML, Stronks K, van Eijsden M, Gemke RJ, Vrijkotte TG. Ethnic differences in maternal underestimation of offspring's weight: the ABCD study. *Int J Obes (Lond).* Jan 2012;36(1):53-60.

87. Hof MH, van Dijk AE, van Eijsden M, Vrijkotte TG, Zwinderman AH. Comparison of growth between native and immigrant infants between 0-3 years from the Dutch ABCD cohort. *Ann Hum Biol.* Sep 2011;38(5):544-555.

88. Matijasevich A, Golding J, Smith GD, Santos IS, Barros AJ, Victora CG. Differentials and income-related inequalities in maternal depression during the first two years after childbirth: birth cohort studies from Brazil and the UK. *Clin Pract Epidemiol Ment Health.* 2009;5:12.

Appendix A Flowchart of selection process that led to the final selection of cohorts used in this WG report



Selection criteria (WP3):

- Birth and mother-child cohorts
- Population-based
- Recruitment at the latest during 1st yr of life
- At least 1 follow-up point during 1st yrs of life
- Sample size at least 300

Selection criterion:

- Availability of information on social and cultural determinants (cohort websites & literature search)

Appendix B Objectives and methodologies (Table 1: Main objectives and methodology of selected European cohort studies (n=7))

	Main objective of study	Methodology
ABCD	Investigation of the association between lifestyle and environmental factors during pregnancy and early childhood and children's health at birth and in later life. Special focus is on explaining ethnic differences in pregnancy outcomes and children's health.	Postal questionnaires Hands-on clinic assessments Biological samples Linkage to routine information (municipal health service)
ALSPAC	Identification of factors within the environment, genotypes and the interaction between these two, that affect the health, development and well-being of children throughout life.	Postal questionnaires Hands-on clinic assessments Biological samples Linkage to routine information Abstraction from medical records Environmental monitoring
Danish National Birth Cohort	Investigation of the influence of exposures in early life (conception to early childhood) on health outcomes in early childhood and later life.	Computer assisted telephone interviews Postal questionnaires Biological samples Linkage to routine information
Millennium Cohort Study	Understanding of the social conditions surrounding birth and early childhood, and their effects in later life. The study has a strong emphasis on socio-economic conditions.	Computer assisted personal interview Computer aided self-completion interview Hands-on clinic assessments Linkage to routine information Environmental monitoring Teacher's survey
The Norwegian Mother and Child Cohort	Findings of causes of diseases to prevent damage to the mother or child.	Postal questionnaires Biological samples
Generation R	Identification of early environmental and genetic causes of normal and abnormal growth, development and health from fetal life until young adulthood. Special emphasis is on ethnic differences in growth, health and development.	Postal questionnaires Hands-on clinic assessments Biological samples Linkage to routine information
Polish Mother and Child Cohort	The examination of early exposure to different environmental factors during pregnancy and after birth on pregnancy outcome and children's health. Specific focus is on the effects of heavy metals, polycyclic aromatic hydrocarbons and environmental tobacco smoke.	Questionnaires Hands-on clinic assessments Biological samples Environmental monitoring

Appendix C Social determinants in child health research

Table 2: Social determinants in child health research

Category	**Indicators**
Socioeconomic Position (SEP)	Occupation/ Occupational status Income Education
Deprivation/Poverty	Income Debts Financial difficulties (difficulties paying bills) Material difficulties (lack of car, food, shoes etc) Non-material deprivation (lack of hobby's, vacation) Social security
Other	Single parenthood Age when pregnant (teenage pregnancies) Intended pregnancy Peer status Housing characteristics Neighborhood characteristics

Table 3: Cultural determinants in child health research

Category	**Indicators**
Ethnicity	Country of birth (child/ parents/ grandparents) (Native) language Self-assigned ethnicity
Acculturation	Language proficiency (new language) Social acceptance/discrimination Generational status Reason of migration Time since migration

Appendix D Social determinants in cohorts

Table 4: Overview of social determinants collected in cohort studies

Social Determinants	SEP	Deprivation	Other
ABCD	x	x	x
AlSPAC	x	x	x
Danish National Birth Cohort	x	x	x
The Norwegian Mother and Child Cohort	x	x	?
Millennium Cohort	x	x	x
Generation R	x	x	x
Polish Mother and Child Cohort	x	?	?

Table 5: Overview of cultural determinants collected in cohort studies

Cultural Determinants	Ethnicity		Acculturation
	'Objective' ethnicity	Self-perceived ethnicity	
ABCD	x	x	?
AlSPAC	-	x	?
Danish National Birth Cohort	x	?	?
The Norwegian Mother and Child Cohort	x	-	?
Millennium Cohort	x	x	?
Generation R Study	x	x	x
Polish Mother and Child Cohort	?	?	?

Notes

X Determinant is collected
- Determinant is not collected
? Unclear whether determinant is collected

Appendix E Studies on social and cultural determinants

Table 6: Overview of studies on social and cultural determinants of child health within European cohort research

Socio-economic position				Cultural determinants		
Education	***Occupation***	***Employment status***	***Income***	***Neighborhood deprivation***	***Ethnic minority status***	***Family situation***
Infant temperament [41]	Infant growth [42]	Maternal health [43]	Health care utilization [44]	Pregnancy outcomes [20]	Health care utilization [45-46]	Maternal health [43]
Birth weight [27 47 48]	Pre-term birth [26]	Childhood overweight [4 49]	Breastfeeding [34 48]		Birth weight [30-31, 50]	Adjustment and pro-social behaviour [51]
Pre-term birth [26-27 48]	Birth weight [29, 52]	Breastfeeding initiation [2]	Pre-term birth [26 48]		Waist circumference [53]	Pregnancy complications [54]
Gestational hypertension [55]	Breastfeeding patterns [56]	Breastfeeding duration [3]	Diet during pregnancy [57]		Breastfeeding patterns [32-33]	Maternal health [54]
Preeclampsia [58]	Gestational age [52 59]	Pregnancy complications [60]	Birth weight [57 48]		Behavioral problems [61]	Pre-term birth [54]
Diastolic blood pressure [62]	Congenital anomalies [59 63]	Pregnancy outcomes [64]	Dysregulation of diurnal cortisol secretion [65]		Child development [66]	Accidents, injuries and illnesses in children [67]
Breastfeeding patterns [32, 68 48]	Time to pregnancy [69]	Socio-emotional behavior [70]	Maternal depression [48]		Asthma/respiratory morbidity [71 72]	
Infant/child growth [42 73 74]	Intrauterine growth patterns [75]		Intrauterine growth [48]		Ethnic density and child and maternal health [76]	
Bone mass [77]	Placental weight [75]		Asthma symptoms [78]		Folic acid use [79]	
Intrauterine growth [48]			Physical activity [80]		Smoking during pregnancy [81]	
Asthma symptoms [78]			Child development [82]		Maternal n-3 and n-6 fatty acid concentrations [83]	
Adolescent alcohol and tobacco use [84]					Overweight [85 86]	
					Infant growth [87]	

Appendix F

Table 7: Strength of exposure-response relationships in studies on social and cultural determinants of child health within European cohort research

Education	Number of studies	Strength of relationship per study	Conclusions
Infant temperament	1	+	"SES inequalities in temperament were already present in six months old infants and could partially be explained by family stress and maternal psychological well-being." [41]
Birth weight	2	+/++	"Study confirmed remarkable educational inequalities in birth weight, a large part of which was explained by pregnancy characteristics, anthropometrics, the psychosocial and material situation, and lifestyle-related factors." [28] "BMI and smoking affected the association between maternal education and birth weight, albeit in different directions." [47]
Pre-term birth	3	++/++/+	"Pregnant women with a low educational level have nearly a twofold risk of preterm birth than women with a high educational level." [27] "Mothers with <10 years of education had an elevated risk of preterm birth compared with mothers with >12 years of education." [26] "An inverse association (higher prevalence among the poorest and less educated) was observed for almost all outcomes, with the exception of caesarean sections where a positive association was found." [48]
Gestational hypertension	1	+	"Adjusted for age and gravity, women with mid-low and low education had a higher risk of gestational hypertension than women with high education." [55]
Preeclampsia	1	++	"Low maternal socioeconomic status is a strong risk factor for preeclampsia." [58]
Diastolic blood pressure	1	0	"Although women with high, midhigh, and midlow education had a significant midpregnancy fall in diastolic blood pressure, those with low education did not." [62]
Asthma symptoms	1	+	"The direction of the association between SES and asthma symptoms changed from a positive association at age 1 year into a negative association at age 3 and 4 years." [78]
Breastfeeding patterns	3	++/+/++	"After adjustment for factors found to be significant in univariate analyses, those educated to a degree level or above were more likely to start breastfeeding." [32] "Educationally related differences were present in starting breastfeeding and the continuation of breastfeeding until two months but not breastfeeding continuation between 2 and 6 months." [68] "Less-educated women from the ALSPAC and the 2004 Pelotas cohort studies showed higher risk of breast feeding their infants for less than 3 months compared to those with the highest levels of educational attainment."[48]

Education	Number of studies	Strength of relationship per study	Conclusions
Infant/childhood growth	3	0/+/+	"Traditional markers of socio-economic status such as poor parental education and low occupational status were not associated with failure to thrive in multivariate analyses." [42] "Low maternal education is associated with a slower fetal growth and this effect appears stronger for growth of the head than for other body parts." [73] "There was a clear gradient in birth length across categories of maternal education. Socioeconomic differences in childhood growth were small, and only resulted in minimal widening of the height inequality with increasing age." [74]
Bone mass	1	++	"After adjusting for height, which was positively related to social position, a strong negative association was observed between BMC and housing tenure, maternal education, paternal education, and social class. Similar results were obtained for bone area." [77]
Intrauterine growth	1	+	"An inverse association (higher prevalence among the poorest and less educated) was observed for almost all outcomes, with the exception of caesarean sections where a positive association was found." [48]
Asthma symptoms	1	+	"The direction of the association between SES and asthma symptoms changed from a positive association at age 1 year into a negative association at age 3 and 4 years." [78]
Adolescent alcohol and tobacco use	1	++	"Alcohol drinking was more common in young people from higher-income households but less common with higher levels of maternal education. A consistent inverse socioeconomic gradient with tobacco smoking was apparent." [84]
Infant growth	1	0	"Traditional markers of socio-economic status such as poor parental education and low occupational status was not associated with failure to thrive in multivariate analyses." [42]

Occupation	Number of studies	Strength of relationship per study	Conclusions
Pre-term birth	1	0	"No difference was found in the mean birth weight of preterm babies, or in the rate of preterm delivery, when analyzed by paternal occupation at conception." [52]
Birth weight	1	0	"There was no significant association between job and birth weight after adjustment." [29]
Breastfeeding patterns	1	N.A.	"After adjustment for factors found to be significant in univariable analyses, mothers with managerial and professional occupations were more likely to start breastfeeding." [32]
Gestational age	1	0	"No difference was found in the mean birth weight of preterm babies, or in the rate of preterm delivery, when analyzed by paternal occupation at conception." [52]
Congenital anomalies	2	+/+0	"Pregnant women who worked with patients or children or food products had an excess risk of sick leave during pregnancy for more than three days. Most of negative reproductive outcomes were not increased in these occupations but the prevalence of congenital anomalies (CAs) was slightly higher in children of women who worked with patients. The prevalence of small for gestational age infants was higher among women who worked with food products." [59] "We observed a modestly increased risk for hypospadias in relation to maternal occupational EDC exposure and paternal exposure to heavy metals while the risk of cryptorchidism was not increased." [63]
Time to pregnancy	1	+	"Paternal occupational exposure to heavy metals and overall exposure to Eds was statistically significantly associated with an increased TTP." [69]
Intrauterine growth patterns	1	+	"Maternal occupational exposure to several chemicals is associated with impaired fetal growth during pregnancy and a decreased placental weight."[75]
Placental weight	1	+	"Maternal occupational exposure to several chemicals is associated with impaired fetal growth during pregnancy and a decreased placental weight." [75]

Employment status	Number of studies	Strength of relationship per study	Conclusions
General health mother	1	+	"Overall, the movement from 'welfare to work' is unlikely to improve the health of lone mothers." [43]
Childhood overweight	2	+/0+	"Children were more likely to be overweight for every 10 h a mother worked per week." [4] "Job strain was not associated with higher BMI, WHtR or FMI. Higher maternal cortisol was independently associated with marginally higher FMI in girls, but marginally lower FMI in boys." [49]
Breastfeeding initiation	1	+	"Women employed full-time were less likely to initiate breast feeding than mothers who were not employed/students, after adjustment for confounding factors." [2]
Breastfeeding duration	1	+	"Current policies may encourage mothers to enter or return to employment postpartum, but this may result in widening inequalities in breast-feeding and persistence of low rates." [3]
Pregnancy complications	1	0	"No indications found that paid employment during pregnancy affects the health of the mother and child." [60]
Pregnancy outcomes	1	+	"We found no indication that being unemployed during pregnancy benefits or endangers the health of the child. Within the subgroups of unemployed women, we observed that women receiving unemployment and sickness or maternity benefits were at higher risk for some adverse pregnancy outcomes." [64]
Socio-emotional behavior	1	0+	"There was no evidence of detrimental effects of maternal employment in the early years on subsequent child socio-emotional behavior. There were significant gender differences in the effects of parental employment on behavioral outcomes." [70]

Income	Number of studies	Strength of relationship per study	Conclusions
Health care utilization	1	+	"Children from lower socio-economic status groups were less likely to see an eye-care specialist or to use screening services." [44]
Breastfeeding	2	N.A./+	"CTVB (Council Tax Validation Band) predicts breast-feeding rates and links them with social circumstances." [34] "Education had a much more marked effect on breast feeding than income in ASPAC study." [48]
Pre-term birth	2	0/+	"After correction for confounders no association was found between household income and pre-term birth." [26] "An inverse association (higher prevalence among the poorest and less educated) was observed for almost all outcomes, with the exception of caesarean sections where a positive association was found." [48]
Diet in pregnancy	1	N.A.	"Women with greater difficulty in affording food had lower intakes of protein, fibre, vitamin C, niacin, pyridoxine, iron, zinc, magnesium and potassium than did women with little or no difficulty. They were more likely to use cooking and spreading fats with a high saturates content, and less likely to eat fish, fruit, vegetables and salad." [57]

Birth weight	2	0/+	"Financial difficulty was found to have no significant relationship with birth weight." [57] "An inverse association (higher prevalence among the poorest and less educated) was observed for almost all outcomes, with the exception of caesarean sections where a positive association was found." [48]
Dysregulation of diurnal cortisol secretion	1	+	"Infants of low income families, in comparison to high income families, showed higher AUC levels and a positive CAR."[65]
Intrauterine growth	1	+	"An inverse association (higher prevalence among the poorest and less educated) was observed for almost all outcomes, with the exception of caesarean sections where a positive association was found."[48]
Maternal depression	1	++	"Income-related inequalities in maternal depression after childbirth were high and of similar magnitude in both cohort studies at the three time assessments." [88]
Physical activity	1	+	"In general, walking to school is associated with lower income, while taking part in organized sports is associated with higher income." [80]
Child development	1	++	"Children in the highest income group were less likely to have socioemotional difficulties compared with those in the lowest income group at 3 and 5 years and had higher mean scores: age 3 'school readiness."[82]

Neighborhood deprivation	**Number of studies**	**Strength of relationship per study**	**Conclusions**
SGA births	1	+	"After adjustment for individual-level factors, women living in low-income neighbourhoods (third, second and first quartiles) were more likely than women living in high-income neighbourhoods (fourth quartile) to have SGA births." [20]

Ethnic minority status	**Number of studies**	**Strength of relationship per study**	**Conclusions**
Health care utilization	2	++/0/+	"Non-Dutch mothers were more likely to enter antenatal care later than Dutch mothers." [45] "After adjustment for socio-demographic factors, neither country of birth nor ethnic group is significantly associated with antenatal care." [46] "In adjusted analysis however, country of birth is no longer significantly associated with receiving immunizations for their cohort infant., but ethnicity remains significant for Black Caribbean mothers." [46]
Birth weight	3	+/+/+	"Term birth weight differences between non-Dutch and Dutch newborns were largely explained by constitutional

			rather than environmental determinants." [83] "These results confirm significant differences in birth weight. The study points to the importance of determinants that cannot easily be modified, such as parental height." [30] "The results suggest that socioeconomic factors are important in explaining birth weight differences in Black Caribbean, Black African, Bangladeshi and Pakistani infants. Maternal and infant characteristics are important in explaining birth weight differences in Indian and Bangladeshi groups." [50]
Waist circumference	1	+/-	"Black children had larger waists, and children from other minority ethnic groups had smaller waists than White children." [53]
Breastfeeding patterns	2	+/++	"White mothers are less likely to breastfeed and, for these women, partner and community ethnicity have an important relation to starting and continuing breastfeeding." [32] "More non-native mothers started breastfeeding than native mothers, but relative fewer continued." [33]
Behavioral problems	1	+	"Children from various non-Dutch backgrounds all had a significantly higher mean behavioral problem score. After adjustment for family risk factors, like family income and maternal psychopathology, the differences attenuated, but remained statistically significant." [61]
Child development	1	+	"Black Caribbean, Black African and Indian infants were less likely to show delay in the attainment of gross motor milestones compared with White infants after adjustment for a range of explanatory variables." [66]
Asthma	2	+/+	"After adjustments, the disadvantage in asthma and recent wheeze for Black Caribbeans was mostly explained by socio-economic factors for asthma. The Bangladeshi advantage lost statistical significance, mostly due to adjustment for markers of cultural tradition." [71] "Compared to Dutch infants, Antillean infants had an increased risk of lower respiratory symptoms at 24 months. Infants of Turkish ethnicity more often reported infections, upper respiratory symptoms and eczema than Dutch in the first 2 years of life."[72]
Ethnic density and child and maternal health	1	+	"For some measures of maternal health, in some ethnic groups, the psychosocial advantages of shared culture, social networks and social capital may override the adverse effects of material deprivation". [76]
Folic acid use	1	++	"All non-Dutch groups had increased risks for inadequate folic acid use." [79]
Smoking during pregnancy	1	N.A.	"Compared with Dutch women, Turkish and Moroccan women were less likely to quit smoking before pregnancy." [81]
maternal n-3 and n-6 fatty acid concentrations	1	++	"Compared with Dutch women, Surinamese, Antillean, Turkish and Moroccan women had generally lower proportions of n-3 fatty acids but higher proportions of n-6 fatty acids. Ghanaian women had higher proportions of EPA and DHA, but generally lower proportions of n-6 fatty acids." [83]
Overweight	1	++	"Turkish and Moroccan children in the Netherlands have 2- to 3-fold higher odds for being overweight at age 2 years, which is largely attributed to maternal pre-pregnancy BMI and weight gain during the first 6 months of life." [85]
Maternal perceptions of overweight	1	++	"Mothers frequently underestimate the actual weight status of their child, especially mothers from Turkish or Moroccan origin." [86]
Infant growth	1	++	"All models including the covariate country of origin of the mother fitted the data better ($p < 0.0005$), but the observed differences were small." [87]

Family situation	Number of studies	Strength of relationship per study	Conclusions
Adjustment and pro-social behavior	1	N.A.	"The contribution of family type to differences in adjustment and prosocial behavior largely disappeared when account was also taken of negativity in family relationships, maternal age, education level, depressive symptomatology, and history of previous live-in relationships, mothers' support networks, and the family's current financial and housing circumstances." [51]
Pregnancy complications	1	N.A.	"Mothers unaccompanied at birth were more likely to have an emergency cesarean section (vs. spontaneous vaginal delivery) and spinal pain relief or a general anesthetic (vs. no pain relief), a shorter labor." [54]
Maternal health	1	N.A./N.A.	"Mothers unaccompanied at birth were more likely to have lower satisfaction with life (vs. high satisfaction) at 9 months postpartum." [54] "Lone mothers were significantly more likely than women with partners to report poorer well being, to have a major depressive disorder and to report wheeze, but significantly less likely to report cough/cold or hemorrhoids." [43]
Pre-term birth	1	N.A.	"Mothers unaccompanied at birth were more likely to have a preterm birth (vs. term)." [54]
Accidents, injuries and illnesses in children	1	+	"At 2 years of age, children in single-parent and stepfamilies were disproportionately likely to experience accidents and receive medical treatment for physical illnesses." [67]

Notes

\+ Social/cultural risk factor is associated with ill health/health behavior and the association remains after adjusting for confounders

++ Social/cultural risk factor is associated with ill health/health behavior and the association remains after adjusting for confounders and OR>2 and/or p-value <0.001

N.A. No data available on confounding/difficult to interpret

chicos

Developing a Child Cohort Research Strategy for Europe

Working Group

Nutrition and physical activity

Leader: Leda Chatzi (University of Crete, Greece)

Researchers involved: Vasiliki Leventakou, Chariklia Chatzigeorgiou (University of Crete, Greece), Manolis Kogevinas (CREAL, Spain; National School of Public Health, Athens, Greece)

Review of cohort contribution and existing cohort data

1.1 Description of current state of scientific knowledge

1.1.1 Nutrition

In the first stages of life, nutrition has a significant impact on the maintenance of lifelong health [1]. Over recent decades, much progress has been made toward understanding the way in which metabolic tissues and physiological systems develop, and the impact of early life nutrition on these processes [2]. Different epigenetic mechanisms are elicited by dietary factors in early critical developmental ages that are able to affect the susceptibility to several diseases in adulthood [3-4]. A substantial body of epidemiological evidence now suggests that an adverse intrauterine environment, elicited by maternal dietary or placental insufficiency, may "program" susceptibility in the fetus to later development of chronic diseases such as cardiovascular or metabolic diseases [5-6], asthma and allergies [7], and neurocognitive disorders[8]. This concept is known as early nutrition programming or metabolic programming, which has gained broad recognition among researchers [9]. An example of early nutrition programming is the effect of early life diet on the development of asthma and allergies. The prevalence of asthma and allergic diseases has increased dramatically over the past few decades with the highest incidence occurring in children [10]. Epidemiological and immunological studies suggest that airway and immune development during fetal life and early childhood are critical time periods of susceptibility during which environmental exposures, such as diet, could exert disproportionately potent irreversible long-term influences on the development of asthma and atopic disease during childhood and possibly adulthood [11]. The current dietary hypotheses relate to antioxidants, lipids, electrolytes and probiotics [10]. A recent systematic review and meta-analysis has shown that birth cohorts research is suggestive of potentially beneficial associations of early life intake of vitamins A, D, and E; zinc; fruits and vegetables; and Mediterranean diet, particularly in relation to childhood asthma [7]. These observational data have led to calls for randomized controlled trials (RCTs) of early-life dietary interventions, particularly in pregnant women [12-13].

There is increasing major public health interest about the concept of early nutrition programming and statements reflecting this concept are appearing in policy documents, leaflets, research publications and other documents. Several European cohort studies have extensively evaluated dietary habits during pregnancy, lactation and early childhood and their association with different health outcomes. The aim of this review was to describe key contributions to knowledge from EU

birth cohorts regarding early life diet and a range of child health outcomes, to identify opportunities for and challenges to collaborative research using existing EU cohorts, to identify gaps in knowledge that may not be met only by existing birth cohorts, and to provide a set of recommendations that address needs for birth cohort research on diet.

1.1.2 Physical Activity

Physical activity has been established as an important intervention for obesity prevention and health promotion among youth, and there is evidence that physical activity habits track from childhood into adulthood [14]. In many Western settings, a large proportion of children and adolescents do not meet recommended physical activity guidelines and, typically, those who are more physically active have lower levels of body fat than those who are less active. Active behaviors have been displaced by more sedentary pursuits which have contributed to reductions in physical activity energy expenditure [15]. Safety and access are among some of the environmental barriers to children's participation in extracurricular physical activity that have not be fully addressed up to now in epidemiological studies [16]. Analyses of the relationship between physical activity and sedentary screen time also continue to show inconsistent results, although evidence in support of active video games is increasing. Physical activity has been inversely related to percentage body fat, although the associations between physical activity and body mass index as a measure of adiposity in preschool children remain elusive [17]. The availability of green spaces close to the residence has been proposed as a wider factor affecting through multiple pathways physical activity and health [18].

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

1.2.1 Birth Cohorts and other study design

The last decade a large number of studies has evaluated the effect of nutrition and physical activity on various health outcomes. Our publication research was focused on birth cohort studies, while we included also information on other study designs like historical and intervention cohorts. For the historical cohorts the abstracted data from these studies is responsible to some extent for the development of the younger birth cohort studies. The *Dutch Hunger Winter Cohort* (1943- 1947) in the Netherlands, known as 'Dutch famine', and the *Oxford Nutrition Survey study* (1942-1944) in United Kingdom measured as main exposure the malnutrition during pregnancy due to World War II circumstances and examined the consequences of starvation on adult diseases [19] [20]. In this framework well known cohorts is the *Metropolit Birth Cohort* including Danish boys born in 1953

with prospectively collected information on nutrition starting in 1965, and the *Stockholm Birth Cohort Study* established in 2004-2005 with participants born in 1953 and lived in Stockholm Metropolitan in 1963 with dietary data starting in early life [21-22]. The *Hertfordshire Cohort study* (1931-1939) starting in 1998, collected prospectively information on the effect of physical activity on mineral bone density [23]. Despite the information bias due to difficulties to trace the population for the planned follow ups and the relatively small sample sizes, the historical cohorts have established the basis for future research on early nutrition programming and health outcomes in later life. The *Prevention of Allergy among Children in Trondheim (PACT) study* is an example of a different study design in Norway including a control cohort starting in 2000 and an intervention cohort in 2002 [24-25].

1.2.2 Nutrition in European birth cohorts

Many birth cohorts have been established in Europe and more are being planned. In total, the established birth cohorts encompass over 300,000 children and their parents. There are many large scale prospective birth/pregnancy cohorts assessing diet in different time points, (pregnancy, early infancy and later childhood) in Europe. The inclusion of so many cohorts provides a geographical diversity within Europe. The majority of the participating countries are represented from more than one cohort and are located in Central and Northern Europe (N=26) (Norway, Denmark, Sweden, Netherlands, Germany and UK), whereas only eight are in the Southern and Eastern part of Europe (France, Greece, Italy, Poland, and Spain). Most of cohorts with information on diet (N=27) started the recruitment after 1990 (Table 1). UK is the country where 12 birth cohorts have collected information on nutrition in pregnancy and childhood.

Table 1 summarizes information on birth cohort studies with information on dietary exposures during pregnancy/ childhood. Information on number of subjects enrolled in the cohort and period of enrolment was obtained from published data and the internet site on European birth cohorts (www.birthcohort.net).

Maternal diet during pregnancy: Maternal diet during pregnancy in European birth cohorts was mainly assessed using questionnaires completed in different ways (personal/telephone interview, postal/self-completed or internet-based questionnaires).

Breastfeeding practices: Diet in infancy (including breastfeeding practices and introduction of solid foods) was assessed by 36 cohorts using questionnaires (postal, self-reported or internet-based questionnaires), 24h recalls (MAS 5 cities Birth Cohort and Southampton Women's Survey), and food diaries (LISA/GINI, ALSPAC, ABIS, and Gateshead Millenium Study).

Diet in childhood: Diet in childhood was assessed by 34 cohorts using questionnaires (postal, self-reported, interviewer-administered or internet-based questionnaires) 24h recalls (MAS 5 cities birth cohort), and food diaries (ALSPAC, Southampton Women's Survey, British Birth Cohort (1946) and (1970)).

1.2.3 Physical Activity in European Birth cohorts

Up to February 2011, 17 studies have published data on physical activity in childhood and six of them include also data on physical activity during pregnancy. All of them are located in Central and Northern Europe. Some countries are represented by more than one cohort. The majority of cohorts with physical activity data (N=9) started the recruitment after 1990.

The physical activity assessment methods in different time points across European birth cohort studies are summarized in Table 3.

Maternal physical activity: Seven cohorts have used questionnaire to evaluate physical activity during pregnancy.

Physical activity in childhood & adulthood: 17 cohorts assessed physical activity in childhood using questionnaires, 24h recalls and 4 of them (DNBC, KOALA, and SWEDES) have used motion sensor (accelerometer) to validate children's physical activity.

1.2.4 The role of registries or other databases

The utility of routine registries is essential for the successful development of birth/pregnancy cohorts in some countries. Their role is identified especially for the historical cohorts where participants need to be traced in order to attend the follow up in adolescence or adulthood. In the Nordic countries the introduction of a personal identification number by the Danish Civil Registration System facilitated the connection of the cohorts, like DNBC, with national registers. In DNBC and other cohorts in Denmark, the National Hospital Discharge Registry provided data on pregnancy diseases, the National Population Registry on mortality and immigration, the National Patient Register on hospitalizations. Based on the information collected in the Danish Psychiatric Central Register, the Aarhus birth cohort study has been able to address the association of maternal diet during pregnancy with hyperkinetic disorder in childhood [26-27]. A challenge for MoBa cohort is the linkage of the cohort with population registries like the Central population Registry, and the Medical Birth Registry of Norway (MBRN) that enables the investigation of various health outcomes [28]. However, the links of birth cohorts with health outcome registries may warrant further discussion, as their utility may

depend on the quality of data for making successful linkages, and on the comprehensiveness of coverage of these registries

1.2.5 Collaboration between birth cohorts

Cohort studies with information on diet and physical activity are essential to prospectively evaluate possible exposure response relationships. However sample sizes are often too small to lead to conclusive results on their own, or have led to inconsistent and sometimes opposite results. Whilst it is clear that individual cohorts can, and have, made important contributions to understanding nutritional causes of childhood disease and ill-health, it is also becoming increasingly clear that their full potential can only be realized with collaboration across large regions in Europe.

Up to now, five European funded projects included information on early life nutrition and physical activity from birth cohorts in Europe:

1. **EARNEST:** EaRly Nutrition programming- long term Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research. The project was a large collaborative investigation into the long-term consequences of early nutrition by metabolic programming. It brought together a multi-disciplinary team of scientists from 38 institutions in 16 European countries.[www.metabolic-programming.org] 2005-2010.
2. **OBELIX:** (OBesogenic Endocrine disrupting chemicals: LInking prenatal eXposure to the development of obesity later in life): is a research project with the main goal of investigating if early life exposure to endocrine disrupting chemicals in food plays a role the development of obesity and related disorders later in life. [www.theobelixproject.org] 2009-2013.
3. **NewGeneris:** was a collaborative project of the Sixth Framework of the European Union aiming to develop and apply biomarkers of dietary exposure to genotoxic and immunotoxic chemicals and of biomarkers of early effects, using mother-child birth cohorts and biobanks. [www.newgeneris.org] 2006-2011.
4. **GA^{2}LEN**: (Global, Allergy and Asthma European Network) is also a common database where 18 European birth cohorts on asthma and allergic diseases are included, starting at different times between 1985 and 2004. Dietary intake and breastfeeding data are part of the various exposure variables studied within GA^{2}LEN [29].
5. **EarlyNutrition" ("Long-term effects of early nutrition on later health"):** It is a collaborative project of the Seventh Framework Programme of the European Union. The project aims at providing the scientific foundations for evidence based recommendations for optimal early nutrition that incorporate long-term health outcomes. [http://www.early-nutrition.org] 2011-15

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

1.3.1 Identification of cohorts

The participation of European birth cohorts in this project provides a diverse geographical coverage within the European Union. There are many pregnancy and birth cohorts from different countries with various sample sizes, from 700 to 100.000 children that are collecting a wealth of information on diet and physical activity and their association with different health outcomes. Identification of cohorts to be included in this report has been done following these criteria:

- ✓ birth and mother-child cohorts
- ✓ population-based
- ✓ recruitment at the latest during the first year of life (if data on outcome of pregnancy available)
- ✓ at least one follow-up point during first years of life
- ✓ sample size: at least 1000
- ✓ start year: 1990 onwards
- ✓ located in one of the EU member states

We have also included other cohorts that do not strictly fulfill these criteria, i.e. cohorts with smaller sample size and start year preceding 1990. Information for these cohorts is presented in Table 1 and 3.

1.3.2 Current work in European Birth cohorts

The aim of this work is to gather all available information on dietary and physical activity exposures during pregnancy and childhood in birth cohorts in Europe. For that reason we performed a literature research in the computerised bibliographic databases *Pubmed*, and *Scopus*, as well as in the official websites of the cohorts, the www.birthcohort.net, and the www.chicosproject.eu. Only publications in English were included along with those **published up to February 2011**. Table 2 and 4 show a list of all publications identified from European birth cohorts on diet and physical activity up to February 2011.

1.3.3 Description of results

1.3.3.1 Diet in association with different health outcomes (Table 2)

a. Birth outcomes: Ten European birth cohorts (ALSPAC, DNBC, Generation R, MoBa, INMA, EDEN, Pelagie, HUMIS, ABCD, and Aarhus Birth cohort) have published data on the association of maternal diet during pregnancy (including fish, fruits and vegetables, caffeine intake, adherence to Mediterranean Diet, and supplement use) with birth outcomes. There are no consistent results on the effect of fish intake on fetal growth and gestational age, probably due to the large variation of the type and amount of fish consumed in different countries [30-32]. Similarly, there are no consistent results on the effect of fruits and vegetables intake during pregnancy on birth weight [33-34]. Increased caffeine intake was associated with higher risk for preterm birth and low birth weight [35-36]. The women who did not use folic acid supplements during pregnancy were at higher risk of fetal growth retardation and small for gestational age neonates (SGA) [37-38].

b. Postnatal growth: The ALSPAC, DNBC, LISA/GINI, ABCD, Generation R, PIAMA, Mas 5, Millenium Cohort Study (MCS), KOALA, SWS, Dundee Infant Feeding Study and the Gateshead Millenium Study investigated the relation of dietary intake in early infancy and childhood with postnatal growth. Duration and type of breastfeeding were the major dietary exposures examined in all cohorts. Breastfed infants showed lower weight gain rate in the first year of life [39-42]. Prolonged breastfeeding (≥ 12 months) was also related to lower fat mass at the age of 4 years compared to children never breastfed [43]. High energy intake in early infancy or childhood was associated with higher weight gain and BMI in later childhood [44-45]. Introduction of solid foods before 3 months of age was associated with increased weight gain rate and obesity risk [46-48]. The association of diet in childhood and age at menarche was also investigated. British girls aged 3 and 7 years with high protein intake diet were more likely to reach menarche by 12 years 8 months [49].

c. Allergic diseases: The ALSPAC, DNBC, LISA/GINI, INMA, PIAMA, BAMSE, KOALA, PACT, PIPO, Isle of Wight Birth Cohort Study, the British Birth Cohort in 1958, and a Birth Cohort in Aberdeen, have published data on early dietary exposures in association with allergic diseases in childhood. The protective effect of breastfeeding on wheeze in early but not later childhood has been reported by ALSPAC cohort [50], while in DNBC cohort breastfeeding had no significant effect on the risk of atopic dermatitis [51]. In INMA cohort fish intake during pregnancy was associated with lower risk of eczema at 1 year of age [52], while a high adherence to Mediterranean diet during pregnancy has shown a protective effect against asthma-like symptoms and atopy in childhood [53]. In GINI and BAMSE cohorts there was no evidence to support the beneficial effect of breastfeeding against the development of atopic dermatitis [54] and asthma respectively [55], while in KOALA cohort organic

dairy products intake by infants was associated with lower eczema risk for the first two years of life [56].

e. Neurodevelopment: The ALSPAC, DNBC, INMA, Generation R, MoBa, MCS, SWS, Aarhus Birth Cohort, Copenhagen Perinatal Birth cohort and the British Birth Cohorts (’46, ’58 & ’70) have highlighted the role of nutrition on neurodevelopmental outcomes. Fish intake during pregnancy has been positively associated with higher cognitive and other developmental scores [57-59]. Dietary patterns like ‘‘junk food diet’’ during early childhood (3, 4 and 7 yrs) were related to poor cognitive scores and behavioural problems in later childhood (8 years) [60-61]. Caffeine intake during pregnancy had a small effect on the risk of inattention/overactivity disorders in early childhood [26, 62].

d. Cardiovascular diseases: The ALSPAC, DNBC and Generation R cohorts have investigated the effect of diet on cardiovascular outcomes in childhood. The ALSPAC cohort showed negative associations of breastfeeding on blood pressure levels[63], and no association between breastfeeding and cardiorespiratory fitness in late childhood [64]. In Generation R cohort, there was no effect of breastfeeding on blood pressure levels in the first two years of life [65]. DNBC cohort also demonstrated no association between maternal fish oil supplementation during breastfeeding with blood pressure levels at 2.5 years old children [66].

1.3.3.2 Physical activity in association with different health outcomes (Table 4)

a. Birth outcomes: ALSPAC, DNBC, MoBa and SWS cohorts have investigated the effect of physical activity during pregnancy on birth outcomes. In ALSPAC cohort, a sedentary lifestyle during pregnancy was positively associated with higher risk for lower birth weight [67]. In DNBC cohort, exercise during pregnancy showed a modest decreased risk of small and large for gestational age infants [68]. In MoBa cohort, maternal regular exercising pre-pregnancy was positively related to physical exercise in 17th week of gestation. Regular exercise in the 30th week of gestation was positively associated with low gestational weight gain [69]. In SWS women who worked >40 h were more likely to give birth to babies with small head circumference [70].

b. Postnatal growth: The ALSPAC, British Birth Cohort (1958), KOALA, Millenium Cohort, NFBC, NFBC 1966, PIAMA, STRIP and SWEDES have published data on the association between physical activity during childhood and postnatal growth. In ALSPAC cohort higher levels of physical activity, in particular activity of moderate to higher intensity were associated with lower levels of fat mass in early adolescence [71]. In NFBC cohort the intensity and the absence of physical activity was positively associated with the appearance of musculoskeletal pains [72-73]. In Millenium cohort

families that reported good health behaviours (non-smoking, low TV viewing) and played with their children were more physically activated [74].

e. Neurodevelopment: In NFBC cohort, physical inactivity was related to several emotional and behavioural problems in children aged 15-16 years old [75], and those individuals who developed psychosis were more likely to be physically inactive [76]. In Millennium cohort, there was observed a positive association between participation in sports and better mental health in childhood [77].

c. Cardiovascular diseases: ALSPAC cohort has shown a positive association between higher levels of physical activity and lower blood pressure in children aged 11-12 years[78]. In Copenhagen cohort study on infant Nutrition and Growth, arterial stiffness was inversely associated with physical activity [79].

1.3.4 Strengths and limitations

Strengths

There are several unique features of the birth cohort study design, that make it particularly important for evaluating the causality of relationships between dietary exposures and child health: Population-based prospective cohort studies (unselected sample) that started early in pregnancy or at birth can avoid the recall bias that has been seen in retrospective approaches trying to reconstruct the past dietary histories of individuals. Cross-sectional study designs cannot separate exposure and outcome assessment in time and are thus not able to. Moreover, if a birth cohort is followed prenatally, exposures present at the time of conception (genetics, alcohol intake, folate status, maternal body fat), during pregnancy (diet, chemical hazards, smoking, alcohol, maternal stress, etc.), at birth (asphyxia, trauma, etc.) and during the postnatal period (breastfeeding, diet, infection, environmental exposures, social environment, etc) can be considered. This is extremely important for answering questions regarding the effect of early nutritional programming. Most of birth cohorts in Europe have used well validated food frequency questionnaires to assess dietary intake in pregnancy and childhood therefore they minimize the possibility of misclassification of exposure.

Limitations

There are several limitations in the direct comparability of levels of intake indicating the need of harmonization of dietary assessment methods across European birth cohorts. Few birth cohorts include assessments of dietary intakes prenatally and there are few cohorts that have not used standardised questionnaires or protocols in this field. A further consequence of the long-time gap between diet exposure and outcome is that even when associations are observed from well-conducted prospective studies, and therefore likely to be robust, their relevance to contemporary

pregnant women, infants and children is unclear. Another challenge of birth cohort studies to causal inference is the potential for substantial degrees of confounding. For example, a number of studies have investigated the effect of breastfeeding on later health outcomes, such as obesity, blood pressure, cancer risk, and cognitive function. However, in many societies breastfeeding is strongly related to higher socioeconomic circumstances and associated phenomena, such as maternal non-smoking, healthy diet, lower toxic occupational exposures, and a generally better quality of physical and social environment. The links between breastfeeding and these other factors would generate relationships between breastfeeding and the many health outcomes that they influence.

1.4 Identification of gaps

- ✓ Few cohorts with ethnic heterogeneity
- ✓ Few low income cohorts
- ✓ Few cohorts with physical activity data
- ✓ Need for harmonization of methods
- ✓ Misclassification of dietary intake
- ✓ Validation of methods to assess diet intake
- ✓ Validation of methods to assess physical activity
- ✓ Linkage of cohorts with national registries

2. Recommendations

2.1 Recommendations for existing cohorts

- Harmonization of dietary assessment methods – examples:

  Infant feeding practices: There is a huge diversity of questionnaires assessing breastfeeding practices. In order to conduct pooled analyses of different cohorts about breastfeeding, only questionnaires including similar types of questions could be considered. It is also recommended to use WHO definitions for exclusive, predominant, and complimentary breastfeeding.

- Validation of methods to assess dietary intake and physical activity in birth cohorts:

  Diet: It is strongly recommended to validate food frequency questionnaires by using biomarkers as gold standards.

  Physical Activity: It is strongly recommended to validate questionnaires for physical activity in pregnant women or children by using objective measures of physical activity (*i.e.* accelerometers).

- Confounders: In order to reduce residual confounding, some confounders have to be taken into consideration: Parental socioeconomic variables (*i.e.*: social class, education, country of birth, employment status, age), maternal smoking during pregnancy, paternal smoking habits, exposure to environmental pollutants during pregnancy/ childhood, maternal BMI-pre pregnancy, paternal BMI, eating behaviours.
- Evaluation of non-response bias: Reasons for non-participating in dietary assessment should be investigated to define possible sources of bias.

2.2 Recommendations for future cohort studies

- Methodology:
  - ✓ Take at least one assessment of diet during pregnancy using validated measures.
  - ✓ Have at least one measure of dietary habits before 2 years of age (including breastfeeding practices, introduction of solid foods).
  - ✓ Use standard questions for breastfeeding practices.
  - ✓ Collect biological samples during pregnancy/childhood for nutrition-related biomarkers measurements.
  - ✓ Apply several quality controls during fieldwork to study the reliability and validity in the study of each test used.

- ✓ Use validated questionnaires for physical activity in childhood.
- ✓ Include questions on sedentary activities and access to green spaces.

- Support research in Eastern European countries and in low-income cohorts: Children and women from socioeconomically deprived background have increased risk to adapt unhealthy dietary habits. It is important that new cohorts include these subgroups in their future follow ups.
- A better communication between the cohorts is recommended. There are limited published data resulting from the collaboration between 2 or more cohorts within the same country or different countries. Comparable analyses across countries can facilitate the development of regional policies and programs related to diet during pregnancy/childhood, analogous to the ongoing development of regional guidelines for the general population[80]. Given the cost and complexity of establishing multicountry studies, pooled or meta-analyses that take advantage of existing studies conducted in different countries provide a practical approach for the study of the health effects of dietary exposures in early life.

Tables and Annexes

Table 1. General description of European birth cohorts with dietary assessment during pregnancy or childhood

Country	Cohort	Source Population	Enrolment Period	N Children	Maternal (Prenatal) Diet	Type of Assessment	Breastfeeding	Type of Assessment	Postnatal (Child's) Diet	Type of Assessment
Belgium	FLEHS I	Region-Based	2002-2004	1.196	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire
	PIPO cohort	Region-Based	1997-2001	1.128	No	–	Yes	Questionnaire	Yes	Questionnaire
Denmark	Aarhus Birth cohort	Region-Based	1990-1992	8.729	Yes	Questionnaire (FFQ)	NA		NA	
	Copenhagen Perinatal cohort	Region-Based	1959-1961	9.125	No	–	Yes	Questionnaire	No	–
	Danish National Birth Cohort	Nation-Based	1996-2002	95.000	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire
France	EDEN, Poitiers, Nancy	Hospital - Based	2003-2005	1.900	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire
	EFESE/ELFE	Nation-Based	2011-2012	20.000	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire
	PELAGIE	Region-Based	2002-2006	4.000	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire
Germany	LISA/GINI, Munich	Region-Based	1995-1997	7.500	Yes (LISAPlus)	Questionnaire (FFQ)	Yes	Questionnaire & Food Diaries	Yes	Questionnaire

Country	Cohort	Source Population	Enrolment Period	N Children	Maternal (Prenatal) Diet	Type of Assessment	Breastfeeding	Type of Assessment	Postnatal (Child's) Diet	Type of Assessment
	MAS 5 cities birth cohort	Region-Based	1990	1.314	No	–	Yes	Questionnaire & 24-h recall	Yes	Questionnaire & 24-h recall
Greece	RHEA, Heraklion	Region-Based	2007-2008	1.590	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire (FFQ)
Ireland	Growing up in Ireland	Nation-Based	2008-2009	10.000	No	–	Yes	Questionnaire	Yes	Questionnaire
Italy	GASP II, Rome	Hospital-Based	2003-2004	700	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire (FFQ)
	NINFEA, Turin	Nation-Based	2005-	7.500	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire
Lithuania	KANC, Kaunas	Region-Based	2007-2009	4.405	Yes	Questionnaire	No	–	No	–
Netherlands	ABCD, Amsterdam	Region-Based	2003-2004	6.161	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire
	Generation R	Region-Based	2002-2006	10.000	Yes	Questionnaire (FFQ)	Yes	Questionnaire (FFQ)	Yes	Questionnaire (FFQ)
	KOALA	Region-Based	2000-2003	2.834	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire
	PIAMA,	Region-Based	1996-1997	4.000	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire
Norway	HUMIS	Region-Based	2003-2009	2.500	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire
	MoBa	Nation-Based	1999-2008	108.500	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire
	PACT	Region-	2000-2005	7.845	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire

Country	Cohort	Source Population	Enrolment Period	N Children	Maternal (Prenatal) Diet	Type of Assessment	Breastfeeding	Type of Assessment	Postnatal (Child's) Diet	Type of Assessment
		Based	*control* 2002-2006 *interventional*							
Poland	REPRO_PL	Nation-Based	2007-2011	1.800	Yes	Questionnaire (FFQ)	Yes	Questionnaire	No	–
Portugal	Generation XXI	Region-Based	2005-2006	8.647	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire
Slovakia	Early Childhood Development Cohort	Region-Based	2001-2003	1.134	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire (FFQ)
Spain	INMA	Region-Based	1997-2008	3.768	Yes	Questionnaire (FFQ)	Yes	Questionnaire	Yes	Questionnaire (FFQ)
Sweden	ABIS study	Region-Based	1997-1999	17.000	Yes	Questionnaire (FFQ)	Yes	Questionnaire (FFQ) & Food Diaries	Yes	Questionnaire
	BAMSE, Stockholm	Region-Based	1994-1996	4.000	No	–	Yes	Questionnaire	Yes	Questionnaire
United Kingdom	ALSPAC	Region-Based	1990-1992	14.000	Yes	Questionnaire (FFQ)	Yes	Questionnaire (FFQ) & Food Diaries	Yes	Questionnaire (FFQ) & Food Diaries
	Birth cohort (Aberdeen)	Region-Based	1997-1999	2.000	Yes	Questionnaire (FFQ)	No	–	Yes	Questionnaire (FFQ)
	British Birth cohort	Nation-Based	1946	5.362	No	–	Yes	Questionnaire	Yes	Questionnaire & Food Diaries
	British Birth	Nation-	1958	17.416	No	–	Yes	Questionnaire	Yes	Questionnaire

Country	Cohort	Source Population	Enrolment Period	N Children	Maternal (Prenatal) Diet	Type of Assessment	Breastfeeding	Type of Assessment	Postnatal (Child's) Diet	Type of Assessment
	cohort	Based								(FFQ)
	British Birth cohort	Nation-Based	1970	16.570	No	–	No	–	Yes	Questionnaire & Food Diaries
	Born in Bradford	Region-Based	2007-2010	14.000	Yes	Questionnaire	Yes	Questionnaire	Yes	Questionnaire
	Dundee Infant Feeding Study	Region-Based	1983-1986	674	No	□	Yes	Questionnaire	No	□
	Gateshead Millenium Study	Region-Based	1999-2000	1.029	No	–	Yes	Questionnaire & Food Diaries	Yes	Questionnaire
	Growing up in Scotland	Region-Based	2005-2006	8.000	No	–	Yes	Questionnaire	Yes	Questionnaire
	Isle of Wight Birth cohort	Region-Based	1989-1990	1.456	No	–	Yes	Questionnaire	No	–
	Millennium Cohort Study	Nation-Based	2001	18.000	No	–	Yes	Questionnaire	Yes	Questionnaire
	Southampton Women's Survey	Region Based	1998-2002	12.583	Yes	Questionnaire (FFQ)	Yes	Questionnaire (FFQ) & 24-h recall	Yes	Questionnaire (FFQ) & Food Diaries

Abbreviations: FFQ, Food Frequency Questionnaire; NA, Non Available.

Table 2 Overview of studies on dietary exposures during pregnancy/childhood within European cohort research

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
				Birth Outcomes				
Aarhus Birth Cohort, Denmark	Olsen et al., BMJ, '02	8.729	Fish intake pregnancy	16 & 30 wk of gestation	No	No	Preterm delivery & Birth weight	Birth
	Wisborg et al., BMJ, '03	18.478	Coffee intake Pregnancy	16 wk of gestation	No	No	Stillbirth & Infant death	Birth
	Olsen et al., Eur J Epidemiol,'06	8.729	Fish intake pregnancy	16 & 30 wk of gestation	No	No	Pregnancy duration	Birth
ABCD, Netherlands	van Dijk et al., Am J Obstet Gynecol, '10	4.044	Folate status (serum) in pregnancy	16 wk of gestation	No	No	Birth weight, Gestational age	Birth
	van Eijsten, Hornstra et al., Am J Clin Nutr, '08	4.366	Maternal fatty acid intake in pregnancy	12 wk of gestation	No	No	Birth weight	Birth
	van Eijsten, Smits et al., Am J Clin Nutr, '08	3.153	Folate Depletion pregnancy	12 wk of gestation	No	No	Birth weight & Gestational age	Birth
	Leffelaar et al., Brit J Nutr, '10	3.730	Vitamin D status pregnancy	12 wk of gestation	No	No	Birth weight & Gestational age	Birth
ALSPAC, UK	Rogers et al., J Epidemiol Community Health, '04	10.040	Fish intake pregnancy	32 wk of gestation	No	No	Birth weight & Intrauterine growth	Birth
DNBC, Denmark	Mikkelsen et al., Scand J Public	43.585	Fruit & Vegetable intake pregnancy	25 wk of gestation	No	No	Birth weight	Birth

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Health, '06							
	Mathews et al., BMJ, '99	693	Maternal Diet pregnancy	28 wk of gestation	No	No	Birth & Placental weight	Birth
	Bech et al., BMJ, '07	1.207	Birth	Caffeine intake pregnancy	Birth weight & length of gestation	20, 25, 34 wk of gestation & 4 wk after birth	No	No
	Halldorson et al., Am J Clin Nutr, '10	59.334	Sugar-sweetened soft drinks pregnancy	~ 25 wk of gestation	No	No	Preterm birth	Birth
	Halldorson et al., Am J Epidemiol, '07	44.824	Fish intake pregnancy	25 wk of gestation	No	No	Birth weight, length & HC	Birth
	Halldorson et al., Am J Epidemiol, '08	9.815	Fish intake pregnancy	25 wk of gestation	No	No	Birth weight, length & HC	Birth
	Knudsen et al., Eur J Clin Nutr, '08	44.612	Dietary patterns pregnancy	25 wk of gestation	No	No	Gestational age	Birth
	Mikkelsen et al., Acta Obstet et Gynecol, '08	1.677	Mediterranean type diet pregnancy	25 wk of gestation	No	No	Preterm birth	Birth
	Olsen et al., Am J Clin Nutr, '07	50.117	Milk intake pregnancy	25 & 35 wk of gestation	No	No	Birth weight, Gestational age	Birth
EDEN, France	Drouillet et al., Paediatr Per Epidemiol, '09	1.805	Seafood intake Pre-pregnancy	First & last trimester	No	No	Fetal growth	Pregnancy & Birth

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Drouillet et al., BJN, '09	1.446	Fatty acid intake	First & last trimester	No	No	Fetal growth	Birth
	Drouillet et al., BJN, '10	645	Mercury, Selenium	First & last trimester	No	No	Fetal growth	Pregnancy
GENERATION R, Netherlands	Timmermans et al., British J Nutr, '09	6.353	Folic acid intake (before & during) pregnancy	~ 15 wk of gestation	No	No	Birth weight & Preterm birth	Pregnancy & Birth
	Bakker et al., Am J Clin Nutr, '10	7.346	Pregnancy & Birth	Caffeine intake pregnancy	Fetal growth & Birth outcomes	<18, 18-24 & ≥25 wk of gestation	No	No
	Heppe et al., British J Nutr, '10	3.380	Fish intake pregnancy	~ 13 wk of gestation	No	No	Fetal growth & Birth outcomes	Pregnancy & Birth
HUMIS, Norway	Eggesbo et al., Environ Res, '09	300	HCB in breast milk	Yes	No	No	Birth weight, Length, preterm birth, SGA	Birth
INMA, Spain	Ramon et al., Am J Clin Nutr, '09	554	Fish intake pregnancy	10- 13 & 28-32 wk of gestation	No	No	Birth weight, Preterm birth & Gestational age	Birth
	Ramon et al., J Nutr, '09	787	Fruit & Vegetable intake in pregnancy	10- 13 & 28-32 wk of gestation	No	No	Birth weight, length & Gestational age	Birth
	Rodrıguez-Bernal et al., Am J Clin Nutr, '10	787	Dietary patterns in pregnancy	During 1st trimester	No	No	Birth weight, length , HC & Gestational age	Birth
MoBa, Norway	Haugen et al., Acta Obstet	26.125	Mediterranean type diet pregnancy	17-24 wk of gestation	No	No	Preterm birth	Birth

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Gynecol, '08							
	Nilsen et al., J Nutr, '10	2.934	Maternal folic acid use in pregnancy	~ 18 wk of gestation	No	No	Birth outcomes	Birth
	Bulik et al., Int J Eat Disord, '09	35.929	Eating disorders	~ 18 wk of gestation	No	No	Birth outcomes	Birth
PELAGIE, France	Guldner et al., Environ Health '07	2.353	Fish intake Pre-pregnancy	First trimester	No	No	Birth weight, preterm birth, SGA	Birth
			Postnatal Growth					
ALSPAC, UK	Jago et al., Public Health Nutr, '09	5.134	Childhood Diet	No	No	10 yrs	Childhood Obesity	10 yrs
	Ong et al., Pediatr Res, '02	1.355	Breastfeeding	No	3 mo	No	Childhood Growth	Birth to 5 yrs
	Rogers et al., Public Health Nutr, '10	3.298	Childhood Diet	No	No	3, 7 & 10 yrs	Age at Menarche	3, 7 & 10yrs
	Ong et al., Pediatrics, '06	881	Diet intake Infancy	No	4 mo	No	BMI & Postnatal body weight	Birth to 1 yr & 2, 3, 5yrs
	Rogers et al., Public Health Nutr, '06	1.382	Milk intake childhood	No	No	7-8 yrs	Growth: Height, leg-length, sitting height	7-8 yrs
	Johnson et al., Nutrition, '07	521 & 682	Beverage intake Childhood	No	No	5 & 7 yrs	Fat mass	5 & 7 yrs
	Johnson et al., Int J Obesity, '08	682	Dietary energy intake Childhood	No	No	5 & 7 yrs	Fat mass	9 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Johnson et al., Am J Clin Nutr, '08	521 (at 5 & 9yrs), 682 (at 7 & 9yrs)	Dietary patterns childhood	No	No	5 & 7 yrs	Fat mass	9 yrs
	Laura et al., PloS ONE, '09	2.275	Dietary energy intake childhood	No	No	10 yrs	Obesity (BMI)	13 yrs
	Leary et al., J Epidemiol Community Health, '05	6.663	Maternal diet pregnancy	32 wk of gestation	No	No	Growth: Height, leg-length, sitting height	7.5 yrs
	Timpson et al., Am J Clin Nutr, '08	3.641	Childhood Diet	No	No	10-11 yrs	Fat Mass & Obesity (BMI)	10-11 yrs
DNBC, Denmark	Baker et al., Am J Clin Nutr, '04	3.768	Infant feeding infancy	No	6 & 18 mo	No	Weight gain	1 yr
	Lauritzen et al., Pediatr Res, '05	72	Maternal fish oil supplementation Lactation	No	Lactating mothers diet	No	Growth: HC, weight, length	2, 4, 9 mo & 2.5 yrs
Dundee Infant Feeding Study, UK	Wilson et al. BMJ, '98	545	Breastfeeding	Weight, height, BMI, Body fat	During the first 2 yrs	No	No	Mean: 7.3 yrs
Gateshead Millennium Study, UK	Wright et al., Pediatrics, '07	455	Eating problems (Toddlers)	No	6 wks, 4, 8 & 12 mo	30 mo	Growth, Food preferences, Eating behavior	13 & 30 mo
	Wright et al., Pediatrics, '06	923	Eating Behavior	No	6 wks, 4, 8 & 12 mo	No	Weight Gain, Failure to thrive	13 mo

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Casiday et al., Eur J Clin Nutr, '04	502	Infant feeding patterns	No	1st wk of life	No	Weight gain, Feeding mode	6 wks
GENERATION R, Netherlands	van Rossem et al., Int J Pediatr Obes, '10	884	Breastfeeding	No	6 mo	No	Obesity (BMI)	3 yrs
KOALA, Netherlands	Gubbels et al., Int J Pediatr Obes, '10	2.834	Breastfeeding	No	3, 7 & 12 mo	1 & 2 yr (Child's eating style)	Weight gain, BMI & overweight	Up to 4 yrs
LISA/GINI, Germany	Rzehak et al., Eur J Epidemiol, '09	7.643	Breastfeeding Infancy	No	the first 4 mo	Yearly	Growth rates	6 yrs
	Rzehak et al., Am J Clin Nutr, '09	1.840	Infant feeding	No	the first 4 mo	Yearly	Growth (BMI)	Up to 6 yrs
	Kalies et al., Eur J Med Res, '05	2.624	Breastfeeding	No	Monthly in the 1st yr	No	Weight gain	2 yrs
MAS 5, Germany	Bergmann et al., Int J Obesity, 162 '03	480	Breastfeeding	No	Followed up to 6 yrs	No	Overweight, obesity	6 yrs
MCS, UK	Brophy et al., BMC Public Health, '09	17.561	Introduction of solid foods (< 3 mo)	No	No	Yes (Self report)	Obesity (BMI)	5 yrs
PIAMA, Netherlands	Scoltens et al., BJN, '09	244	Breastfeeding	No	3 mo	No	Weight, length, BMI	1 yr
	Scoltens et al.,	2.043	Breastfeeding	No	3 mo & 1yr	7 yrs	Overweight	8 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Obesity, '08							
	Scoltens et al., Am J Epidemiol, '07	2.347	Breastfeeding	No	3 mo & 1yr	No	Weight gain & overweight	1- 7 yrs
Southampton Women's Survey, UK	Robinson et al., J Clin Endocrinol Metab, '09	536	Infant feeding practices	No	6 & 12 mo Infants diet (FFQ)	No	Body composition	4 yrs
			Allergic Diseases					
ALSPAC, UK	Elliott et al., J Allergy Clin Immunol, '08	11.029, 7.245, 8.200, 7.081	Breastfeeding	No	During the first 4 yrs of life	No	Wheeze, allergy & lung function	3, 7, 7.5 , 8 yrs
	Shaheen et al., Thorax, '09	14.062	Dietary patterns Pregnancy	32 wk of gestation	No	No	Eczema, wheeze, asthma & pulmonary function	2.5, 3.5, 7 & 7.5, yrs
BAMSE, Sweden	Kull et al., Arch Dis Child, '02	3.791	Breastfeeding	No	1 & 2 yrs	No	Allergic Diseases	Up to 2 yrs
	Kull et al., Allergy, '06	2.965	Fish intake Infancy	No	No	1 yr	Allergic diseases	4 yrs
	Kull et all., J Allergy Clin Immunol, '04	2.965	Breastfeeding	No	2 mo & 1 yr	No	Asthma	4 yrs
	Kull et all., J Allergy Clin Immunol, '05	2.965	Breastfeeding	No	2 mo & 1 yr	2 & 4 yrs	Eczema	4 yrs
	Kull et all., J Allergy Clin	3.825	Breastfeeding	No	2 mo & 1 yr	2, 4 & 8 yrs	Asthma, wheeze,	8 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Immunol, '10						sensitization	
	Marmjö et al., Am J Clin Nutr, '09	2.423	Vitamin suppl. Intake childhood	No	2 mo	8 yrs	Allergic Diseases	8 yrs
	Rosenlund et al., J Allergy Clin Immunol '10.	2.447	Fruit & vegetable intake childhood	No	2 mo	8 yrs	Asthma, rhinitis, eczema	8 yrs
Birth Cohort (Aberdeen), UK	Martindale et al., Am J Resp Crit Care Med, '05	1.751	Vitamin E & C intake pregnancy	32 wk	No	No	Wheeze & eczema	2 yrs
	Devereux et al., Am J Resp Crit Care Med, '06	1.704	Vitamin E intake pregnancy	32 wk	No	3- 5 yrs	Wheeze, asthma & eczema	5 yrs
	Devereux et al., Am J Clin Nutr, '07	1.751	Vitamin D intake pregnancy	32 wk	No	5 yrs	Wheeze	5 yrs
	Willers et al., Thorax, '07	1.253	Vitamin E, C & zinc intake pregnancy	32 wk	No	3- 5 yrs	Wheeze, asthma	5 yrs
British Birth Cohort (1958), UK	Butland et al., Eur Respir J, '99	11.352	Fruit intake Adulthood	No	No	33 yrs	Asthma	33 yrs
DNBC, Denmark	Benn et al., Am J Epidemiol, '04	15.430	Breastfeeding	No	6 & 18 mo	No	Atopic Dermatitis	18 mo
INMA, Spain	Romieu et al., Clin Exp Al, '07	462	Fish intake pregnancy	3 mo after delivery	No	No	Asthma, eczema	1 & 6 yrs
	Chatzi et al.,	460	Diet in Childhood	No	6, 14 & 24 mo	6.5 yrs	Allergic Symptoms	6.5 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Pediatr Al Immunol, '07							
	Chatzi et al., Thorax, '08	460	Diet during pregnancy	3 mo after delivery	No	6.5 yrs	Allergic Symptoms	6.5
Isle of Wight Birth Cohort, UK	Karmaus et al., Asthma, '08	1.456	Breastfeeding	No	1 & 2 yrs	No	Asthma	1, 2, 4 & 10 yrs
KOALA, Netherlands	Kummeling et al., BJN, '08	2.764 mothers 2.598 children	Organic diet pregnancy & childhood	34 wk of gestation	No	2 yrs	Eczema & wheeze	2 yrs
	Snijders et al., J Pediatr, '07	2.516	Breastfeeding	No	3, 7 & 12 mo	No	Eczema & wheeze	7, 12 & 24 mo
	Snijders et al., Pediatrics, e115 '08	2.558	Introduction of solids	No	3, 7, 12 & 24 mo	During the first 2 yrs	Eczema, atopic dermatitis & wheeze	7, 12 & 24 mo
	Thijs et al., Allergy, '11	310	Fatty acids in breast milk	No	3, 7, 12 & 24 mo	During the first 2 yrs	Eczema & allergic sensitization	7, 12 & 24 mo
LISA/GINI, Germany	Sausenthaler et al., Pediatr Allergy Immunol, '06	2582	Margarine & Butter intake childhood	No	No	2 yrs	Eczema & allergic sensitization	2 yrs
	Zutavern et al., Pediatrics, '06	2612	Introduction of solid foods (> 4 mo)	No	6 mo	12, 18 & 24 mo	Atopic dermatitis & allergic sensitization	2 yrs
	Filipiak et al., J Pediatr, '07	4.753	Introduction of solid foods (up to 12 mo)	No	12 mo	No	Eczema	4 yrs
	von Berg et al, J Allergy Clin	2.252	Infant feeding practices (Hydrolysed	No	the first 4 mo	1, 2, 3, 4 & 6 yrs	Allergic Diseases	6 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Immunol, '08		formulas)					
	von Berg et al, J Allergy Clin Immunol, '03	945	Infant feeding practices (Hydrolysed formulas)	No	the first 6 mo	No	Allergic Diseases	1 yr
	von Berg et al, J Allergy Clin Immunol, '07	1.856	Infant feeding practices (Hydrolysed formulas)	No	the first 4 mo, 1 & 3 yrs	No	Atopic dermatitis & Asthma	3 yrs
	Lauberau et al., J Pediatr, '04	3.903	Breastfeeding	No	at 1 yr	No	Atopic dermatitis	3yrs
	Sausenthaler et al., AJCN, '07	2.641	Maternal diet pregnancy	Last Trimester	No	No	Eczema & Allergic sensitization	2 yrs
PACT, Norway	Storro et al., BMC Public Health, '10	7.845	Cod liver oil, Fish oil & Fish intake pregnancy & childhood (intervention program)	During pregnancy	6 wks after birth	1 & 2 yrs	Eczema, dermatitis	2 yrs
	Oien et al., J Epidemiol Community Health, '10	3.086	Fish & fish oil intake infancy	1 yr after birth	1 yr after birth	No	Asthma & eczema	2 yrs
PIAMA, Netherlands	Wijga et al., Thorax, '03	2.978	Milk products intake childhood	No	No	2 yrs	Asthma	3 yrs
	Wijga et al., J Allergy Clin.	265	Breast milk Fatty acids intake Infancy	No	3mo	No	Allergic Diseases	1 & 4 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Immunol., '06							
	Willers et al., Am J Resp Crit Care Med., '08	2.832	Maternal Diet (Milk & nut products) pregnancy	30-36 wk of gestation	No	2 yrs	Asthma, wheeze, dyspnea	1 to 8 yrs
PIPO Cohort, Belgium	Sariachvilli et al., Pediatr Allergy Immunol, '09	1.128	Introduction of solids	No	Yes (from 6 to 48 mo)	Yes (from 6 to 48 mo)	Eczema	4 yrs
			Neurodevelopment					
Aarhus Birth Cohort, Denmark	Linnet et al., Acta Paediatr, '09	24.068	Coffee intake pregnancy	16 wk of gestation	No	No	Hyperkinetic Disorder & ADHD	3-12 yrs
ALSPAC, UK	Feinstein et al., J Epidemiol Community Health, '08	7.703	Dietary patterns childhood	No	No	3, 4 & 7 yrs	School attainment	3, 4 & 7 yrs
	Wiles et al., Eur J Clin Nutr, '09	4.000	Childhood Diet (''junk food'' diet)	No	No	4 ½ yrs	Behavioural problems	7 yrs
	Northstone et al., J Epidemiol Community Health '11	3.966	Dietary patterns childhood	No	No	3, 4, 7 & 8.5 yrs	Cognitive outcomes (IQ)	8.5 yrs
	Daniels et al., Epidemiol, '04	7.421	Fish intake pregnancy	32 wk of gestation	15 mo	6 & 15 mo	Cognitive Development	15 & 18 mo
	Hibbelin et al., Lancet, '07	8.801 (5.549 at 8 yrs)	Fish intake pregnancy	32 wk of gestation	No	No	Behavioural & Cognitive outcomes	6 mo to 8 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Hibbelin & Davis, Prost, Leuk and Essent Fat Acids, '09	9.960	Seafood intake pregnancy	32 wk of gestation	No	No	Neurodevelopmental outcomes	18 & 32 wk of gestation
	Golding et al., Epidemiol, '09	9.960	Seafood intake pregnancy	32 wk of gestation	No	No	Depressive symptoms pregnancy	18 & 32 wk of gestation
British Birth Cohort ('46 & '58)), UK	Leask et al., Brit J Psychiatr, '00	4.746 ('46) 13.377 ('58)	Breastfeeding	No	2 yrs ('46) 7 yrs ('58)	No	Schizophrenia adulthood	28 yrs ('58) 43 yrs ('46)
British Birth Cohort ('46, '58 & '70), UK	Rudnicka et al., AJCN, '08	4.784 ('46), 14.498 ('58), 12.981 ('70)	Breastfeeding	No	2 yrs ('46) 7 yrs ('58) 5 yrs ('70)	No	Visual acuity	11 & 15 yrs ('46), 11 & 16 yrs ('58), 10 & 16yrs ('70)
DNBC, Denmark	Lauritzen et al., Lipids, '04	97	Maternal fish oil supplementation lactation	No	Lactating mothers diet	No	Visual acuity	2 & 4 mo
	Lauritzen et al., Reprod Nutr Dev, '05	148	Maternal fish oil supplementation lactation	No	Lactating mothers diet	No	Motor function & mental development	9 mo, 1 & 2 yrs
	Kesmodel et al., Scand J Public Health, '10	1.750	Maternal Diet (caffeine intake) Pregnancy	12 & 30 wk of gestation	No	No	Cognitive, behavioural & emotional functions	5 yrs
	Oken et al., Am J Clin Nutr, '08	25.466	Fish intake pregnancy & infancy	25 wk of gestation	6 & 18 mo	No	Developmental milestones	6 & 18 mo
Copenhagen Perinatal Cohort,	Sorensen et al., Acta Psychiatr,	6.841	Breastfeeding	No	1 yr	No	Maternal	_

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
Denmark	'05						Schizophrenia	
GENERATION R, Netherlands	Rosa et al., British J Nutr, '10	4.214	Folic acid intake pregnancy	< 18 wk of gestation	No	No	Behavioural problems	18 mo
INMA, Spain	Ribas-Fito, Am J Epidemiol, '07	343	Breastfeeding	No	1 & 4 yrs (Ribera d' Ebre) 6, 14 & 48 mo (Menorca)	No	Cognitive Development	4 yrs
	Julvez et al., Acta Paed, '07	500	Breastfeeding	No	1 & 4 yrs (Ribera d' Ebre) 6, 14 & 48 mo (Menorca)	No	ADHD	4 yrs
	Julvez et al., Paed Per epidemiol, '09	420	Folic acid pregnacy	End of 1st trimester	No	No	Neurodevelopment ADHD	4 yrs
	Mendez et al., PHN, '08	392	Fish intake pregnancy	3 mo after delivery	6 & 14 mo	No	Neurodevelopment	4 yrs
MCS, UK	Sacker et al., Pediatrics, '06	14.660	Breastfeeding	No	9 mo	No	Developmental delay	9 mo
MoBa, Norway	Bekkhus et al., Acta Paediatr, '10	25.343	Caffeine intake pregnancy	17 & 30 wk of gestation	No	No	Inattention/ Overactivity	18 mo
Southampton Women's Survey, UK	Gale et al., J Child Psychol Psychiatry, '09	241	Infant feeding	No	6 & 12 mo	No	Cognitive Function	4 yrs
	Gale et al., Arch	241	Breastfeeding	No	6 & 12 mo	No	Neuropsychological	4 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Dis Child , '10						Function	
	Gale et al., J Child Psychol Psychiatry, '08	217	Fish intake pregnancy	15 & 32 wk of gestation	No	No	Behavioural problems & intelligence	9 yrs
				Cardiovascular				
ALSPAC, UK	Martin et al., Circulation, '04	4.763	Breastfeeding	No	6 & 15 mo	No	Blood pressure	7.5 yrs
	Lawlor et al., Eur J Epidemiol, '08	3.612	Breastfeeding	No	4 wks, 6 & 7 mo	No	Cardiorespiratory fitness	9yrs
	Brion et al., Eur J Clin Nurt, '08	533 (4 mo), 710 (8 mo)	Sodium intake Infancy	No	No	4 & 8 mo	Blood pressure	7 yrs
	Leary et al., Arch Dis Child, '05	6.944	Maternal nutrient intake in pregnancy	32 wk of gestation	No	No	Blood pressure	7.5 yrs
	Brion et al., Am J Clin Nutr, '08	7.638	Iron intake pregnancy	32 wk of gestation	No	No	Blood pressure	7 yrs
DNBC, Denmark	Ulbak et al., Am J Clin Nutr, '04	73	Childhood diet	No	No	2.5 yrs	Blood pressure	2.5 yrs
	Larnkjaer et al., J Nutr, '06	150	Maternal fish oil supplementation lactation	No	4 mo after delivery	2.5 yrs	Blood pressure, pulse wave velocity, heart rate	2.5 yrs
	Asserhoj et al., J Nutr '08	98	Maternal fish oil supplementation	No	4 mo after delivery	2.5 & 7 yrs	Blood pressure, energy intake &	2.5 & 7 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
			lactation				physical activity	
GENERATION R, Netherlands	de Jonge et al., Early Human Develop, '10	933	Breastfeeding	No	2, 6 & 12 mo	No	Blood pressure, left cardiac structures & fractional shortening	1.5, 6 & 24 mo
	Bakker et al., Am J Hypertens '10	7.890	Maternal caffeine intake pregnancy	<18, 18-24 & ≥25 wk of gestation	No	No	Blood pressure, hypertension risk	During Pregnancy
Other Outcomes								
ABCD, Netherlands	van Eijsten et al., Brit J Nutr, '09	3.254	Maternal fatty acid intake pregnancy	12 wk of gestation	No	No	Ethnic differences	_
ABIS study, Sweden	Brekke et al., BJN, '07	10.762	High sugar intake Pregnancy, infancy	After Delivery	1 yr	1yr	Feeding patterns	1 yr
ALSPAC, UK	Coulthard et al., Public Health Nutr, '10	7.821	Fruit & vegetables intake Infancy (6 mo)	No	No	6 mo & 7 yrs	Fruit & vegetables intake Childhood (7 yrs)	6 mo & 7 yrs
	Micali et al., J Pediatr, '09	12.050	Eating disorders pregnancy	9 wk of gestation	1, 6 & 15 mo	No	Infant feeding & Growth	1, 6, 9 & 15 mo
	Glynn et al., J Hum Nutr Dietet, '05	663	_	No	No	17 yrs	Description of nutrient intake	7 yrs
	Shultis et al., J Epidemiol Community Health, '05	1.152, 998, 848 & 771	Birth weight	No	No	8, 18, 43 mo & 7yrs	Childhood diet	8, 18, 43 mo & 7 yrs
	Noble et al., J Hum Nutr Diet,	852	Breast & formula feeding Infancy	No	No	4 mo	Weaning practices	4 mo

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	'06							
	Cowin et al., J Hum Nutr Dietet, '07	1.026	_	No	No	18 mo	Nutrient intake comparison	18 mo
	Hopkins et al., Arch Dis Child, '07	928 & 782	Infant feeding	No	8 mo	No	Iron status	8 & 12 mo
	Northstone & Emmett, Br J Nutr, '08, 100(5)	6.177	_	No	No	3, 4, 7 & 9 yrs	Stability of dietary patterns	3, 4, 7 & 9 yrs
	Waylen et al., Acta Paediatrica, '09	8.242	Fatty acid intake pregnancy & childhood	32 wk	No	3 yrs	Childhood externalizing behaviour	7.9yrs
	Cowin et al., Eur J Clin Nutr, '01	796	Food & nutrient intake Infancy	No	No	18 mo	Haemoglobin & feritin levels	18 mo
	Emmett et al., Public Health Nutr, '02	863	_	No	No	18 & 43 mo	Food & nutrient intake	43 mo
	Northstone et al., Eur J Clin Nutr '02	1026	_	No	No	18 mo	Type of beverages consumed	18 mo
	Rogers et al., Eur J Clin Nutr, '03	993	Maternal smoking, age & education	No	No	18 mo	Food & Nutrient intake	18 mo
	Brion et al.,	5.717	Maternal diet	32 wk of	No	10 yrs	Offspring diet	10 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Am J Clin Nutr, '10	(prenatal) 5.593 (postnatal)	pregnancy	gestation				
	Tobias et al., Osteoporos Int, '05	4.451	Maternal diet pregnancy	32 wk of gestation	No	No	Bone Mass childhood	9 yrs
	Northstone et al., Eur J Clin Nutr, '08	12.053 (mothers)	Sociodemographic factors	32 wk of gestation	No	No	Dietary patterns pregnancy	_
	Northstone & Emmett, Br J Nutr, '08, 99(5)	8.953	_	32 wk of gestation	No	47 mo (Maternal Diet)	Dietary patterns assessment	47 mo
	Northstone, Emmett and Rogers, Br J Nutr, '08	12.035 (mothers)	Nutrient intake pregnancy	32 wk of gestation	No	No	Dietary patterns pregnancy	_
British Birth Cohort (1958), UK	Parsons et al., Eur J Clin Nutr, '05	11.341 (33 yrs) 11.361 (42 yrs)	Dietary patterns Adulthood	No	No	42 yrs	Dietary patterns Adulthood	33 yrs
British Birth Cohort (1970), UK	Crawley et al., BJN, '03	4.760	_	No	No	16-17 yrs	Dietary patterns	16-17 yrs
	Crawley et al., J Hum Nutr Diet, '93	4.760	_	No	No	16-17 yrs	Breakfast cereals intake	16-17 yrs

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Batty et al., Pediatrics '07	8.242	Mental Ability childhood	No	No	30 yrs	Food intake adulthood	10 yrs
DNBC, Denmark	Lauritzen et al., Lipids, '05	91	Maternal fish oil supplementation Lactation	No	Lactating mothers diet	No	Cytokin production	2.5 yrs
	Baker et al., Am J Clin Nutr, '07	37.459	High pre-pregnant BMI	No	6 mo	No	Early termination of breastfeeding	18 mo
	Sun et al., J Pediatr '11	69.750	Breastfeeding	No	6 & 18 mo	No	Risk of epilepsy	Up to 11 yrs (median, 7.7 yrs)
	Strom et al., Am J Clin Nutr '09	54.202	Maternal fish intake pregnancy	25 wk of gestation	No	No	Postpartum depression	1 yr
	Baker et al., Am J Clin Nutr, 1543 '08	36.030 (6mo), 26.846 (18mo)	Breastfeeding	No	6 & 18 mo	No	Postpartum weight retention	6 & 18 mo
	Klemmensen et al., Epidemiol, '09	49.373	Vitamin C and E intake pregnancy	25 wk of gestation	No	No	Pre-eclampsia	During pregnancy
	Knudsen et al., Public Health Nutr, '07	18.294	_	10-12 wk of gestation	No	No	Compliance with recommendations on folic acid use	During pregnancy
	Knudsen et al., Public Health Nutr, '10	54.371	_	25 & 30 wk of gestation	No	No	Compliance with recommendations on iron suppl. Use	During pregnancy
	Knudsen et al.,	3.098	Maternal fish oil	12 & 25 wk	No	No	Timing of	Birth

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	BJOG, '06		supplementation Pregnancy	of gestation			spontaneous delivery	
	Sun et al., Epilepsy Research, '10	65.754	Fatty acid intake pregnancy	25 wk of gestation	No	No	Risk of epilepsy	Up to 11 yrs
	Torp-Pendersen et al., Am J Epidemiol, '10	96.842	Coffee, tea intake pregnancy	12 -14, 30-32 wk & 6 mo	No	No	Risk of strabismus	Up to 10 yrs
	Bech et al., Am J Epidemiol, '05	55.379	Coffee intake Pregnancy	~ 16 wk of gestation	No	No	Pregnancy outcomes (Fetal death)	Pregnancy
GENERATION R, Netherlands	Timmermans et al., Preventive Med, '08	6.940	_	~14 wk of gestation	No	No	Determinants on folic acid use	During pregnancy
	Duijts et al., Pediatrics, '10	4.164	Breastfeeding	No	6 & 12 mo	No	Respiratory tract infection	1 yr
	van Rossem et al., J Epidemiol Community Health, '10	3.848	_	No	2 & 6 mo	No	Breastfeeding patterns among ethnic minorities	2 & 6 mo
GENERATION XXI, Portugal	Pinto et al., Public Health Nutr, '07	249	_	1st trimester & few days after birth	No	No	Maternal diet pregnancy	Before & during pregnancy
	Pinto et al., Ann Epidemiol,	320	_	Each trimester	No	No	Maternal fatty acid intake pregnancy	During pregnancy

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	'10							
Growing up in Scotland, UK	Skafida, PHN, '08	5.012 babies & 2.732 toddlers	Social class, Maternal education	No	Yes	No	Breastfeeding initiation	10 mo & 34 mo
INMA, Spain	Diez et al., Arch Environ Contam Toxicol, '09	218	Methylmercury (Fish intake)	10-13 & 28-32 wks of gestation	No	1 wks after birth & 4 yrs (neonates & preschool)	_	_
	Alvarez-Pedrerol et al., Clin Endocr, '10	600	Iodine intake pregnancy	During 3rd trimester	No	No	Iodine levels	During pregnancy
	Duarte-Salles et al., Public Health Nutr,'10	657	Smoking	During 1st trimester	No	No	Dietary intake of polycyclic aromatic hydrocarbons	During pregnancy
	Ramon et al., Science Total Environ, '08	253	Prenatal mercury exposure pregnancy	28-32 wk of gestation	No	No	_	During pregnancy
	Rebagliato et al., Epidemiology, '10	1.844	Iodine intake pregnancy	8- 23 wk of gestation	No	No	Maternal thyroid function	During pregnancy
	Murcia et al., J Epidemiol Community Health, '10	1.522	_	8- 22 wk of gestation	No	No	Iodine intake	During pregnancy
KOALA, Netherlands	Rist et al., BJN, '07	312	Organic diet pregnancy	34 wk of gestation	No	No	Fatty acids in breast milk	1mo postpartum

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
LISA/GINI, Germany	Sausenthaler et al., Clinical Nutrition, '10	833	Hydrolysed formula feeding Infancy	No	the first 4 mo	No	Taste preferences	10 yrs
MCS, UK	Kelly et al., Public Health Nutr, '05	18.125	_	No	1, 4 & 6 mo	Yes	Breastfeeding initiation	6 mo
	Quigley et al., Pediatrics, '07	15.890	Breastfeeding	No	~9 mo	No	Respiratory tract infection & diarrhea	8 mo
MoBa, Norway	Tandberg et al., Acta Paediatr, '10	196	Infants with Congenital Heart Defects infancy	No	6 mo	No	Infant feeding practices	Up to 6 mo
	Ystrom et al., J Pediatr, '08	27.753	Maternal Negative Affectivity	No	6 mo	No	Breastfeeding	6 mo
	Ystrom et al., Maternal Child Nutr, '09	27.763	Maternal Negative Affectivity	No	No	18 mo	Dietary patterns	18 mo
	Ystrom et al., Maternal Child Nutr '10	14.122	Maternal Negative Affectivity	No	No	3 yrs	Dietary patterns	3 yrs
	Brantsaeter et al., Ann Nutr Metab, '07	119	_	17-18 wk of gestation	No	No	Confirmation of dietary suppl. Use	During pregnancy
	Haugen et al., Ann Nutr Metab, '08	40.108	_	17-24 wk of gestation	No	No	Dietary supplement use	During pregnancy
	Nilsen et al.,	22.500	_	18 & 30 wk	No	No	Determinants on folic	During

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Diet During Pregnancy	Breastfeeding	Postnatal Diet	Main Outcome Measured	Age of Follow up
	Am J Clin Nutr, '06			of gestation			acid use	pregnancy
	Haberg et al., Arch Dis Child, '09	32.077	Folic acid intake pregnancy	17 & 30wk	No	6 & 18 mo	Respiratory tract infection	18 mo
	Siega-Riz et al., Am J Clin Nutr, '08	30.040	Maternal eating disorders pregnancy	15-22 wk of gestation	No	No	Nutrient & food intake	During pregnancy
	Dellava et al., Int J Eat Disord, '10	37.037	Maternal eating disorders Pregnancy	19 & 30 wk of gestation	No	No	Dietary supplement use	During pregnancy
	Reba-Harrelson et al., Eating Behaviors, '10	13.006	Maternal eating disorders pregnancy	17 wk of gestation	No	36 mo	Maternal & child feeding	36 mo
	Haugen et al., Epidemiology, '09	23.423	Vitamin D intake pregnancy	22 wk of gestation	No	No	Pre-eclampsia	During pregnancy
	Torjusen et al., BMC Public Health, '10	63.561	_	17-22 wk of gestation	No	No	Organic food intake	During pregnancy
	Niegel et al., J Develop & Beh Ped, '08	30.466	1.Temperament 2. Breastfeeding	No	0-6 & 6-14mo	No	1. Breastfeeding 2. Temperament	6- 18 mo (Temperament)
Southampton Women's Survey, UK	Crozier et al., J Nutr, '09	12.572	_	11 & 34 wk of gestation	No	No	Dietary patterns Before & during pregnancy	Before & during Pregnancy

Abbreviations: BMI, Body Mass Index; HC, Head Circumference; HCB, Hexachlorobenzene; IQ, Intelligence Quotient; ADHD, Attention Deficit Hyperactivity Disorder; SGA, Small for Gestational Age.

Table 3. General description of European birth cohorts with physical activity assessment during pregnancy or childhood

Country	Cohort	Source Population	Enrolment Period	N Children	Maternal Physical Activity	Type of Assessment	Childhood Physical Activity	Type of Assessment
Denmark	Copenhagen Cohort Study on Infant Nutrition and Growth	Region Based	1987-1988	143	No	-	Yes	24 h recall Questionnaire
	DNBC	Nation-Based	1996-2002	95.000	Yes	Questionnaire	Yes	Accelerometer
Finland	NFBC 1966,	Nation-Based	1966	12.058	No	-	Yes	Questionnaire
	NFBC 1986	Nation-Based	1985-1986	9.479	No	-	Yes	Questionnaire
	STRIP	Region Based	1990-1992	1.062	No	-	Yes	Questionnaire
Netherlands	ABCD, Amsterdam	Region-Based	2003-2004	6.161	Yes	Questionnaire	Yes	Questionnaire
	KOALA Birth Cohort Study	Nation-Based	2000-2003	2.834	Yes	Questionnaire	Yes	Questionnaire & Accelerometer
	PIAMA, Nationwide	Region-Based	1996-1997	4.000	Yes	Questionnaire	Yes	Questionnaire
Norway	MoBa	Nation- Based	1999-2008	108.500	Yes	Questionnaire	Yes	Questionnaire
Sweden	Stockholm Weight Development Study, SWEDES	Region- Based	1984-1985 (SPAWN)	2.342	No	-	Yes	Questionnaire & Accelerometer
United Kingdom	ALSPAC	Region-Based	1990-1992	14.000	Yes	Questionnaire	Yes	Questionnaire
	British Birth Cohort	Nation-Based	1970	17. 198	No	-	Yes	Questionnaire
	British Birth Cohort	Nation-Based	1946	5.362	No	-	Yes	Questionnaire

Country	Cohort	Source Population	Enrolment Period	N Children	Maternal Physical Activity	Type of Assessment	Childhood Physical Activity	Type of Assessment
	British Birth Cohort	Nation-Based	1958	751	No	-	Yes	Questionnaire
	Millennium Cohort Study	Nation-Based	2001	18.000	No	-	Yes	Questionnaire
	National Survey of Health and Development (MRC)	Nation-Based	1946	5.362	No	-	Yes	Questionnaire
	Southampton Women's Survey	Region- Based	1998-2002	12.583	Yes	Questionnaire	Yes	Questionnaire

Table 4. Overview of studies on physical activity during pregnancy/childhood within European cohort research

Cohort, Country	Author, Journal, Year	N Children	Main Exposure Measured	Main Outcome Measured	Physical Activity During Pregnancy	Postnatal Physical Activity	Age of Follow up
Birth Outcomes							
ALSPAC, UK	Both et al, Eur J Epidemiol, '10	11.759	P.A	Birth weight	Yes	No	1st & 2nd trimester
	Nieuwenhuijsen et al, Epidemiology, '02	11.462	Swimming	Birth weight	Yes	No	18 – 20 wk
DNBC, Denmark	Juhl et. al, Am J Obstet Gynecol, '10	79.692	P.A	Fetal growth	Yes	No	16 & 31 wk
	Madsen et al, BJOG, '07	92.671	P.A	Risk of miscarriage	Yes	No	12 – 16 wk
	Juhl et. al, Am J Epidemiol, '08	87.232	P.A	Risk of preterm birth	Yes	No	16 – 31 wk
	Juhl et. al, Epidemiology, '10	74.486	Swimming	Risk of preterm birth	Yes	No	12-16 and 30 wk
MoBa, Norway	Fleten et al, Obstet Gynecol, '10	43.705	P.A	Birth weight	Yes	No	17 & 30 wk
	Owe et al, Obstet Gynecol, '09	36.896	PA	Birth weight	Yes	No	17-30
Southampton Women Survey, UK	Bonzini et al, Occup Environ Med, '09	1327	Occupational P.A	preterm delivery, small for gestational age (SGA) and reduced head or abdominal circumference	Yes	No	34 wk

Postnatal Growth							
ALSPAC, UK	Tobias et al, Osteoporos Int, '05	4.451	P.A	Bone Mass	No	Yes	9 yrs.
	Clark et al, J Bone and Miner Res, '08	2.692	Vigorous P.A	Bone Mass	No	Yes	11 yrs
	Mattocks et al, BMJ, '07	5.451	Early life determinants of P.A	P.A	No	Yes	11 – 12 yrs
	Riddoch et al, BMJ, '09	4.150	P.A	BMI	No	Yes	12 -14 yrs
	Ness et al, PLoS Med, '07	5.500	P.A	BMI	No	Yes	12 yrs
	van Sluijs et al, Preventive Medicine, '09	4.688	Active travel to school	P.A	No	Yes	11 yrs
	Deere et al, Br J Sports Med, '09	4.880	Myopia	P.A	No	Yes	12 yrs
British Birth Cohort (1958), UK	Parsons et al, Int J Obes, '05	11.109	P.A	BMI	No	Yes	11, 16, 23, 33 and 42 yrs
	Parsons et al, Int J Epidemiol, '06	9.377	P.A	BMI	No	Yes	11, 16, 23, 33 and 42 yrs
KOALA, Netherlands	Gubbels et al, J Pediatr, '09	2.578	EBRBs	Obesity	No	Yes	2 yrs
MCS, UK	Brophy et al, BMC Public Health, '09	17.561	P.A	Obesity	No	Yes	3 yrs
	Hawkins et al, J Epidemiol Community Health	6.343	Maternal employment	Child's health behavior	No	Yes	3 yrs

	’09						
	Brophy et al., BMC Public Health, ’11	17.561	Parental factors	P.A	No	Yes	3 yrs
NFBC, Finland	Andersen et al, PLoS One, ’09	5.533	Birth weight	LTPA	No	Yes	15 - 16 yrs
	Auvinen et al, Med Sci Sports Exer, ’08	6.945	Level of P.A	Musculoskeletal pains	No	Yes	15 - 16 yrs
	Auvinen et al, Scand J Med Sci Sports, ’08	5.999	P.A	Low Back Pain	No	Yes	15 - 16 yrs
	Auvinen et al, Spine, ’07	5.993	P.A	Prevalence of NOP & SP	No	Yes	15 - 16 yrs
	Paalanne, Spine, ’08	874	Isometric Trunk Muscle Strength and Body Sway	Low Back Pain	No	Yes	19 yrs
	Tammelin et al, Med Sci Sports Exerc, ’07	6.928	P.A & Sedentary behavior	Recommended level of P.A	No	Yes	15 - 16 yrs
	Junno et al, Osteoporos Int, ’10	380	P.A	Vertebral size	No	Yes	16 - 19 yrs
	Paananen et al, European Journal of Pain, ’10	1.594	Psychosocial, mechanical, and metabolic factors	Musculoskeletal pains	No	Yes	16 – 18 yrs
NFBC, Finland, 1966	Ridgway et al, Plos One, ’09	9.009	Infant motor development	P.A	No	Yes	14 yrs
PIAMA, Netherlands	Wijga et al, J Obes, ’10	1.871	Diet, Screen Time & P. A	Childhood Overweight	No	Yes	5 & 7 yrs
STRIP, Finland	Hakanen, J Clin Endocrinol Metab,	640	FTO genotype, BMI, P.A	Risk of overweight	No	Yes	15 yrs

	'09						
SWEDES, Sweden	Ekelund et al, Am J Clin Nutr, '05	455	P.A	BMI	No	Yes	17 yrs
Neurodevelopment							
British Birth Cohort ('58 & '70), UK	Sacker et al,Eur J Public Health, '05	NCDS: 15.452& BCS70:14.018	Leisure time P.A	Psychological well-being	No	Yes	16
British Birth Cohort 1970, UK	Batty et al, Pediatrics, '07	8.282	P.A	Mental ability	No	Yes	30 yrs
NFBC, Finland	Kantomaa et. al, Med Sci Sports Exerc, '08	7.002	P.A	Emotional and behavioral problems	No	Yes	15 – 16 yrs
	Kantomaa et.al, Health Educ Res, '09	7.002	P.A	Educational performance	No	Yes	15 – 16 yrs
	Koivukangas et al, Schizophrenia Research, '10	6.987	P.A	Risk of psychosis	No	Yes	15 – 16 yrs
	Paananen et al, Eur J Pain, '10	6.986	P.A, Musculoskeletal pains	Psychological symptoms	No	Yes	15 - 16 yrs
MCS, UK	Griffiths et al, Int J of Beh Nutr Phys Act, '10	13.470	P.A, T.V viewing	Mental health	No	Yes	5 yrs
Cardiovascular							
ALSPAC, UK	Leary et al, Hypertension, '08	5.505	P.A	Blood Pressure	No	Yes	11 - 12 yrs
Copenhagen Cohort Study on	Schack-Nielsen et	106	P.A	Chronic disabling diseases	No	Yes	10 yrs

Infant Nutrition and Growth, Denmark	al, Br J Nutr, '05						
Other Outcomes							
ABCD, Netherlands	Vollebergt et al, Acta Obstet Gynecol Scand, '10	3.679	PA	Preeclampsia & gestational hypertension	Yes	No	< 24 wk
ALSPAC, UK	Riddoch et al, Arch Dis Child, '07	5.595	-	Level and pattern of P.A	No	Yes	11 yrs
British Birth Cohort (1958), UK	Parsons et al, Eur J Clin Nutr, '05	11.341 (33 yrs) & 11.361 (42yrs)		Change in diet, physical activity level over 8 yrs period	No	Yes	33yrs & 42 yrs
DNBC, Denmark	Osterdal et al, BJOG, '08	93.315	P.A	Risk of severe pre-eclampsia	Yes	No	12 -30 wk
	Juhl et. al, Scand J Med Sci Sports, '10	88.200	P.A	Change in exercise from early/mid to late pregnancy	Yes	No	16-30 wk
MoBa, Norway	Brantsaeter et al, Scand J Med Sci Sports, '10	112	-	Validation P.A Questionnaire	Yes	No	17-30 wk
	Owe et al, Scand J Med Sci Sports, '09	34. 508	P.A	Pregnancy-related factors	Yes	No	17-30 wk
	Magnus et al, Am J Epidemiol, '08	59.573	P.A	Preeclampsia	Yes	No	14-22 wk
	Nystad et al., Acta Paediatr	30.870	Baby swimming	LRTI	No	No	18 mo
NFBC, Finland	Kantomaa et. al, Prev Med, '07	5.457	P.A	Family income & parents education	No	Yes	15 - 16 yrs
National Survey of	Kuh et al, J	2.989	-	Patterns of P.A	No	Yes	53 yrs

Health and Development (MRC), UK	Epidemiol Community Health, '92						
SWEDES, Sweden	Ekelund et al, Public Health Nutr, '06	50	P.A	Validation P.A questionnaire	No	Yes	17 yrs

Abbreviations: PA, Physical Activity; LRTI, Lower Respiratory Tract Infections; BMI, Body Mass Index; LTPA, Leisure Time Physical Activity; NCDS, National Child Development Study; BCS70, British Cohort Study 1970; NOP, Neck or Occipital Pain; SP, Shoulder Pain; EBRBs, Energy Balance-Related Behaviors

References

1. Godfrey, K.M. and D.J. Barker, *Fetal nutrition and adult disease.* Am J Clin Nutr, 2000. **71**(5 Suppl): p. 1344S-52S.
2. Martinez, J.A., et al., *Interplay of early-life nutritional programming on obesity, inflammation and epigenetic outcomes.* Proc Nutr Soc, 2012. **71**(2): p. 276-83.
3. Gabory, A., L. Attig, and C. Junien, *Developmental programming and epigenetics.* Am J Clin Nutr, 2011. **94**(6 Suppl): p. 1943S-1952S.
4. Canani, R.B., et al., *Epigenetic mechanisms elicited by nutrition in early life.* Nutr Res Rev, 2011. **24**(2): p. 198-205.
5. Gluckman, P.D., et al., *Effect of in utero and early-life conditions on adult health and disease.* N Engl J Med, 2008. **359**(1): p. 61-73.
6. Symonds, M.E., et al., *Nutritional programming of the metabolic syndrome.* Nat Rev Endocrinol, 2009. **5**(11): p. 604-10.
7. Nurmatov, U., G. Devereux, and A. Sheikh, *Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis.* J Allergy Clin Immunol, 2011. **127**(3): p. 724-33 e1-30.
8. Dauncey, M.J. and R.J. Bicknell, *Nutrition and neurodevelopment: mechanisms of developmental dysfunction and disease in later life.* Nutr Res Rev, 1999. **12**(2): p. 231-53.
9. Hanley, B., et al., *Metabolic imprinting, programming and epigenetics - a review of present priorities and future opportunities.* Br J Nutr, 2010. **104 Suppl 1**: p. S1-25.
10. Tricon, S., et al., *Nutrition and allergic disease.* Clinical & Experimental Allergy Reviews, 2006. **6**(5): p. 117-188.
11. Allan, K. and G. Devereux, *Diet and asthma: nutrition implications from prevention to treatment.* J Am Diet Assoc, 2011. **111**(2): p. 258-68.
12. Marks, G.B., et al., *Prevention of asthma during the first 5 years of life: a randomized controlled trial.* J Allergy Clin Immunol, 2006. **118**(1): p. 53-61.
13. Dunstan, J.A., et al., *Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial.* J Allergy Clin Immunol, 2003. **112**(6): p. 1178-84.
14. Telama, R., et al., *Physical activity from childhood to adulthood: a 21-year tracking study.* Am J Prev Med, 2005. **28**(3): p. 267-73.
15. Hills, A.P., A.D. Okely, and L.A. Baur, *Addressing childhood obesity through increased physical activity.* Nat Rev Endocrinol, 2010. **6**(10): p. 543-9.
16. Keeton, V.F. and C. Kennedy, *Update on physical activity including special needs populations.* Curr Opin Pediatr, 2009. **21**(2): p. 262-268.
17. Sijtsma, A., et al., *Is directly measured physical activity related to adiposity in preschool children?* Int J Pediatr Obes, 2011. **6**(5-6): p. 389-400.
18. Dadvand, P., et al., *Green space, health inequality and pregnancy.* Environ Int, 2011.
19. Lumey, L.H., et al., *Cohort profile: the Dutch Hunger Winter families study.* Int J Epidemiol, 2007. **36**(6): p. 1196-204.
20. Huxley, R.R., et al., *Nutritional research in World War 2: the Oxford Nutrition Survey and its research potential 50 years later.* Br J Nutr, 2000. **84**(2): p. 247-51.
21. Osler, M., et al., *Cohort profile: the Metropolit 1953 Danish male birth cohort.* Int J Epidemiol, 2006. **35**(3): p. 541-5.
22. Stenberg, S.A. and D. Vagero, *Cohort profile: the Stockholm birth cohort of 1953.* Int J Epidemiol, 2006. **35**(3): p. 546-8.
23. Sayer, A.A., et al., *Falls, sarcopenia, and growth in early life: findings from the Hertfordshire cohort study.* Am J Epidemiol, 2006. **164**(7): p. 665-71.
24. Oien, T., O. Storro, and R. Johnsen, *Do early intake of fish and fish oil protect against eczema and doctor-diagnosed asthma at 2 years of age? A cohort study.* J Epidemiol Community Health, 2010. **64**(2): p. 124-9.

25. Storro, O., et al., *A primary health-care intervention on pre- and postnatal risk factor behavior to prevent childhood allergy. The Prevention of Allergy among Children in Trondheim (PACT) study.* BMC Public Health, 2010. **10**: p. 443.
26. Linnet, K.M., et al., *Coffee consumption during pregnancy and the risk of hyperkinetic disorder and ADHD: a prospective cohort study.* Acta Paediatr, 2009. **98**(1): p. 173-9.
27. Torp-Pedersen, T., et al., *In-utero exposure to smoking, alcohol, coffee, and tea and risk of strabismus.* Am J Epidemiol, 2010. **171**(8): p. 868-75.
28. Magnus, P., et al., *Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa).* Int J Epidemiol, 2006. **35**(5): p. 1146-50.
29. Keil, T., et al., *European birth cohort studies on asthma and atopic diseases: II. Comparison of outcomes and exposures--a GA2LEN initiative.* Allergy, 2006. **61**(9): p. 1104-11.
30. Halldorsson, T.I., et al., *Dietary predictors of perfluorinated chemicals: a study from the Danish National Birth Cohort.* Environ Sci Technol, 2008. **42**(23): p. 8971-7.
31. Ramon, R., et al., *Fish consumption during pregnancy, prenatal mercury exposure, and anthropometric measures at birth in a prospective mother-infant cohort study in Spain.* Am J Clin Nutr, 2009. **90**(4): p. 1047-55.
32. Olsen, S.F. and N.J. Secher, *Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study.* BMJ, 2002. **324**(7335): p. 447.
33. Mikkelsen, T.B., et al., *Relative validity of fruit and vegetable intake estimated by the food frequency questionnaire used in the Danish National Birth Cohort.* Scand J Public Health, 2007. **35**(2): p. 172-9.
34. Ramon, R., et al., *Vegetable but not fruit intake during pregnancy is associated with newborn anthropometric measures.* J Nutr, 2009. **139**(3): p. 561-7.
35. Bech, B.H., et al., *Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial.* BMJ, 2007. **334**(7590): p. 409.
36. Bakker, R., et al., *Maternal caffeine intake from coffee and tea, fetal growth, and the risks of adverse birth outcomes: the Generation R Study.* Am J Clin Nutr, 2010. **91**(6): p. 1691-8.
37. van Eijsden, M., et al., *Association between short interpregnancy intervals and term birth weight: the role of folate depletion.* Am J Clin Nutr, 2008. **88**(1): p. 147-53.
38. Nilsen, R.M., et al., *Infant birth size is not associated with maternal intake and status of folate during the second trimester in Norwegian pregnant women.* J Nutr, 2010. **140**(3): p. 572-9.
39. Scholtens, S., et al., *Long-chain polyunsaturated fatty acids in breast milk and early weight gain in breast-fed infants.* Br J Nutr, 2009. **101**(1): p. 116-21.
40. Bergmann, K.E., et al., *Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding.* Int J Obes Relat Metab Disord, 2003. **27**(2): p. 162-72.
41. Ong, K.K., et al., *Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis.* Pediatr Res, 2002. **52**(6): p. 863-7.
42. Gubbels, J.S., et al., *Association of breast-feeding and feeding on demand with child weight status up to 4 years.* Int J Pediatr Obes, 2011. **6**(2-2): p. e515-22.
43. Robinson, S.M., et al., *Variations in infant feeding practice are associated with body composition in childhood: a prospective cohort study.* J Clin Endocrinol Metab, 2009. **94**(8): p. 2799-805.
44. Ong, K.K., et al., *Dietary energy intake at the age of 4 months predicts postnatal weight gain and childhood body mass index.* Pediatrics, 2006. **117**(3): p. e503-8.
45. Johnson, L., et al., *Energy-dense, low-fiber, high-fat dietary pattern is associated with increased fatness in childhood.* Am J Clin Nutr, 2008. **87**(4): p. 846-54.
46. Brophy, S., et al., *Risk factors for childhood obesity at age 5: analysis of the millennium cohort study.* BMC Public Health, 2009. **9**: p. 467.
47. Baker, J.L., et al., *Maternal prepregnant body mass index, duration of breastfeeding, and timing of complementary food introduction are associated with infant weight gain.* Am J Clin Nutr, 2004. **80**(6): p. 1579-88.
48. Wilson, A.C., et al., *Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study.* BMJ, 1998. **316**(7124): p. 21-5.

49. Rogers, I.S., et al., *Diet throughout childhood and age at menarche in a contemporary cohort of British girls.* Public Health Nutr, 2010. **13**(12): p. 2052-63.
50. Elliott, L., et al., *Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC).* J Allergy Clin Immunol, 2008. **122**(1): p. 49-54, 54 e1-3.
51. Benn, C.S., et al., *Breastfeeding and risk of atopic dermatitis, by parental history of allergy, during the first 18 months of life.* Am J Epidemiol, 2004. **160**(3): p. 217-23.
52. Romieu I., T.M., Garcia-Esteban R., Ferrer C., Ribas-Fito N., Anto J. M. and Sunyer J., *Maternal fish intake during pregnancy and atopy and asthma in infancy.* Clinical and Experimental Allergy,, 2007. **37**: p. 518-525.
53. Chatzi L, T.M., Romieu I, Garcia-Esteban R, Ferrer C, Vioque J, Kogevinas M, Sunyer J., *Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood.* Thorax, 2008. **63**(6): p. 483-485.
54. Laubereau, B., et al., *Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life--results from the GINI-birth cohort study.* J Pediatr, 2004. **144**(5): p. 602-7.
55. Kull, I., et al., *Breast-feeding in relation to asthma, lung function, and sensitization in young schoolchildren.* J Allergy Clin Immunol, 2010. **125**(5): p. 1013-9.
56. Kummeling, I., et al., *Consumption of organic foods and risk of atopic disease during the first 2 years of life in the Netherlands.* Br J Nutr, 2008. **99**(3): p. 598-605.
57. Daniels, J.L., et al., *Fish intake during pregnancy and early cognitive development of offspring.* Epidemiology, 2004. **15**(4): p. 394-402.
58. Hibbelin, J.R., et al., *Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study.* Lancet, 2007. **369**(9561): p. 578-85.
59. Mendez, M.A., et al., *Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years.* Public Health Nutr, 2008. **12**(10): p. 1702-10.
60. Northstone, K., et al., *Are dietary patterns in childhood associated with IQ at 8 years of age? A population-based cohort study.* J Epidemiol Community Health, 2011.
61. Wiles, N.J., et al., *'Junk food' diet and childhood behavioural problems: results from the ALSPAC cohort.* Eur J Clin Nutr, 2009. **63**(4): p. 491-8.
62. Bekkhus, M., et al., *Intrauterine exposure to caffeine and inattention/overactivity in children.* Acta Paediatr, 2010. **99**(6): p. 925-8.
63. Martin, R.M., et al., *Does breast-feeding in infancy lower blood pressure in childhood? The Avon Longitudinal Study of Parents and Children (ALSPAC).* Circulation, 2004. **109**(10): p. 1259-66.
64. Lawlor, D.A., et al., *Associations of birth size and duration of breast feeding with cardiorespiratory fitness in childhood: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC).* Eur J Epidemiol, 2008. **23**(6): p. 411-22.
65. de Jonge, L.L., et al., *Breastfeeding is not associated with left cardiac structures and blood pressure during the first two years of life. The Generation R Study.* Early Hum Dev, 2010. **86**(8): p. 463-8.
66. Larnkjaer, A., et al., *Maternal fish oil supplementation during lactation does not affect blood pressure, pulse wave velocity, or heart rate variability in 2.5-y-old children.* J Nutr, 2006. **136**(6): p. 1539-44.
67. Both, M.I., et al., *The association of daily physical activity and birth outcome: a population-based cohort study.* Eur J Epidemiol, 2010. **25**(6): p. 421-9.
68. Juhl, M., et al., *Physical exercise during pregnancy and fetal growth measures: a study within the Danish National Birth Cohort.* Am J Obstet Gynecol. **202**(1): p. 63 e1-8.
69. Owe, K.M., W. Nystad, and K. Bo, *Correlates of regular exercise during pregnancy: the Norwegian Mother and Child Cohort Study.* Scand J Med Sci Sports, 2009. **19**(5): p. 637-45.
70. Bonzini, M., et al., *Occupational physical activities, working hours and outcome of pregnancy: findings from the Southampton Women's Survey.* Occup Environ Med, 2009. **66**(10): p. 685-90.
71. Riddoch, C.J., et al., *Prospective associations between objective measures of physical activity and fat mass in 12-14 year old children: the Avon Longitudinal Study of Parents and Children (ALSPAC).* Bmj, 2009. **339**: p. b4544.
72. Auvinen, J., et al., *Neck and shoulder pains in relation to physical activity and sedentary activities in adolescence.* Spine (Phila Pa 1976), 2007. **32**(9): p. 1038-44.

73. Auvinen, J., et al., *Associations of physical activity and inactivity with low back pain in adolescents.* Scand J Med Sci Sports, 2008. **18**(2): p. 188-94.
74. Brophy, S., et al., *Parental factors associated with walking to school and participation in organised activities at age 5: analysis of the Millennium Cohort Study.* BMC Public Health, 2011. **11**: p. 14.
75. Kantomaa, M.T., et al., *Emotional and behavioral problems in relation to physical activity in youth.* Med Sci Sports Exerc, 2008. **40**(10): p. 1749-56.
76. Koivukangas, J., et al., *Physical activity and fitness in adolescents at risk for psychosis within the Northern Finland 1986 Birth Cohort.* Schizophr Res, 2010. **116**(2-3): p. 152-8.
77. Griffiths, L.J., et al., *Associations between sport and screen-entertainment with mental health problems in 5-year-old children.* Int J Behav Nutr Phys Act, 2010. **7**: p. 30.
78. Leary, S.D., et al., *Physical activity and blood pressure in childhood: findings from a population-based study.* Hypertension, 2008. **51**(1): p. 92-8.
79. Schack-Nielsen, L., et al., *Arterial stiffness in 10-year-old children: current and early determinants.* Br J Nutr, 2005. **94**(6): p. 1004-11.
80. Mendez, M.A. and M. Kogevinas, *A comparative analysis of dietary intakes during pregnancy in Europe: a planned pooled analysis of birth cohort studies.* Am J Clin Nutr, 2011. **94**(6 Suppl): p. 1993S-1999S.

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Developing a Child Cohort Research Strategy for Europe

Working group

Life-style and substance exposures

Researchers involved: Per Magnus, Siri Håberg, Katrine Strandberg-Larsen and Vincent Jaddoe

Summary

This working group explores health consequences of tobacco smoking, alcohol intake and illicit drug use as studied in European birth cohorts. Questionnaire information on use of tobacco and alcohol before, during and after pregnancy is included in most of the cohorts, while illicit drug use is more rarely a part of the data sets. In addition, data on paternal use of tobacco and alcohol are also often included. Paternal use is sometimes only reported by the woman.

A substantial number of publications from European birth cohorts have examined these variables as the main exposure of interest with many different outcomes. In this report we can only recite some findings. However, we list a series of papers that address substance exposures and health outcomes using birth cohorts in order to demonstrate the high research activity. It should also be pointed out that substance use is included in many other publications as a confounder or an effect-modifying variable.

We believe that better information on the health consequences of substance use, both short-term and long-term, will benefit from the analysis of data in birth cohorts. The value of having many cohorts is the replication of findings across varied contexts. To estimate the attributable risks associated with substance use, more studies are needed, in particular on the long-term neuropsychiatric development of children. For preventive efforts, better understanding of the complex causal pattern behind initiation and continuation of substance is needed. This includes substance use during pregnancy.

The most important stimulant for the further development of European birth cohorts is the funding of the infrastructure. There have been calls to fund bio-bank infrastructure. However, bio-banks are of limited value unless they are linked to active cohorts following participants to include new data on exposures, such as substance use, as well as endpoints.

Our recommendations are: a) to fund the infrastructure of birth cohorts in general, b) to set out calls for research questions that can be responded to by collaborating birth cohorts, and c) to encourage researchers to apply to the European Research Council for the resolution of new and innovative research questions through the use of data from existing birth cohorts.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

Smoking and heavy intake of alcohol in pregnancy has been linked to maternal and child disease to an extent that is sufficient to give a clear public health advice of complete abstinence. The evidence of detrimental effects comes from different types of study, e.g. animal experiments, not only from birth cohorts. However, observational birth cohorts have given the best and most precise information on the consequences of smoking and heavy alcohol intake during pregnancy. Randomized, controlled trials are not feasible or ethical to perform, unless they are designed as trials to reduce substance exposure.

The most controversial scientific issue is the effect of low and moderate intake of alcohol during pregnancy on child outcomes. Confounding as a systematic error in the studies is difficult to exclude, see for instance: Strandberg-Larsen K, Andersen A-MN. Alcohol and fetal risk: a property of the drink or the drinker? Acta Obstet Gynecol Scand 2011;90:207-9. A main unresolved issue is the long term effects on children's cognitive and neuropsychiatric development. More use of genetic factors as instrumental variables are needed to reduce confounding. Another systematic error is selection bias since heavy drinkers may be less likely to participate in birth cohorts, and there may be selective loss to follow up.

In addition, an uncertainty that pertains to all substances is the true value of the reported exposure. Cultural traditions as well as policy differences between countries can be reflected in patterns of actual and reported exposure between cohorts. Presumably, the reported intake will in most cases be lower than the actual intake, and better ways to validate questionnaire information using biological specimens are needed.

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

Substance exposure has been associated with many diseases and traits in studies of birth cohorts. The space does not allow a full exposé of findings from birth cohorts, but here are three examples:

Example 1: Studies on smoking and pregnancy outcome

There is quite an extensive list of publications on the effects of smoking in pregnancy on fetal growth, starting from Simpson's original observation in 1957 (1). Indeed, one expects to find in birth cohorts that birth weight is reduced with about 200 grams if the mother is a smoker, and a major deviation from this expectation casts doubt on the validity of the study. In the Generation R Study, a recent analysis suggests that the effect of smoking on birth weight is modified by intake of folate (2). From the Danish National Birth Cohort (DNBC), a study has been performed with the intention of understanding whether smoking can explain the difference in birth weight between mothers with high and low socioeconomic status. It was

found that smoking during pregnancy was a main mediator. Together with BMI, smoking explained the educational gradient in birth weight at term (3). If the prevalence of smoking drops further and the educational gradient in BMI persists, women with low socioeconomic status will turn out to have babies with larger birth weight in the future. On the other hand, no effect of smoking on the risk of congenital malformations in the Danish cohort was found (4). In the Norwegian Mother and Child Cohort Study (MoBa) a question was included that asked the pregnant woman whether she had been exposed to tobacco in utero, i.e. whether her mother had smoked while pregnant. A small effect of in utero exposure with later reduction in fertility has been found (5), while no certain effect of fetal loss was reported (6).

1. Simpson WJ. A preliminary report on cigarette smoking and the incidence of prematurity. Am J Obstet Gynecol 1957;73:808.
2. Bakker R, Timmermans S, Steegers AEP, Hofman A, Jaddoe VWV. Folic acid supplements modify the adverse effect of maternal smoking on fetal growth and neonatal complications. J Nutr 2011;141:2172-9.
3. Mortensen LH, Diderichsen F, Smith GD, Andersen AM. The social gradient in birthweight at term: quantification of the mediating role of maternal smoking and body mass index. Hum Reprod 2009;24:2629-35.
4. Morales-Suarez-Varela MM, Bille C, Christensen K, Olsen J. Smoking habits, nicotine use and congenital malformations. Obstet Gynecol 2006;107:51-7.
5. Ye X, Skjærven R, Basso O, Baird DD, Eggesbø M, Cupul-Uicab LA, Haug K, Longnecker MP. In utero exposure to tobacco smoke and subsequent reduced fertility in females. Huma Reprod 2010;25:2901-6.
6. Cupul-Uicab LA, Baird DD, Skjærven R, Saha-Chaudhuri P, Haug K, Longnecker MP. In utero exposure to maternal smoking and women's risk of fetal loss in the Norwegian Mother and Child Cohort (MoBa). Human Reprod 2011;26:458-65.

Example 2: Studies on moderate alcohol intake and pregnancy outcome

It is well established that high doses of alcohol during pregnancy can lead to the fetal alcohol syndrome. One of the features of this syndrome is growth retardation (1). The consequences of light or moderate alcohol intake on birth weight are more uncertain. Even for binge drinking, the effect on birth weight is not clear (2). In the Generation R Study, a detailed follow-up of ultrasound measures of fetal growth did not find any association to alcohol intake. Compared with mothers who did not drink alcohol at all, a small increase in fetal weight gain was observed among drinkers (3). This kind of paradoxical observation is quite typical for studies of light to moderate alcohol intake in pregnancy, and is usually thought to be a reflection of rest-confounding. However, biological effects cannot be excluded. For preterm birth, a DNCB study has

shown that the risk increases when alcohol consumption increases past 4 drinks per week. On the other hand, women drinking 2-4 drinks per week had a reduced risk: the relative risk was 0.77 (95 % CI: 0.64 – 0.93) for preterm birth when compared to non-drinkers (4). Binge drinking three or more times during pregnancy is associated with increased risk of stillbirth, but not with the risk of spontaneous abortions in the Danish cohort (5,6).

1. Sokol RJ, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. JAMA 2003;290:2996-9.
2. Henderson J, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. J Epidemiol Comm Health 2007;61:1069-73.
3. Bakker R, Pluimgraaff LE, Steegers EAP, Raat H, Tiemeier H, Hofman A, Jaddoe V. Associations of light and moderate maternal alcohol consumption with fetal growth characteristics in different periods of pregnancy: The Generation R Study. Int J Epidemiol 2010;39:777-89.
4. Andersen K, Andersen AMN, Olsen J, Grønbæk M. Alcohol consumption during pregnancy and the risk of preterm delivery. Am J Epidemiol 2004;159:155-161.
5. Strandberg-Larsen K, Nielsen NR, Grønbæk M, Andersen PK, Olsen J, Andersen AMN. Binge drinking in pregnancy and risk of fetal death. Obstet Gynecol 2008;11:602-9.
6. Strandberg-Larsen K, Grønbæk M, Andersen AMN, Andersen PK, Olsen J. Alcohol drinking pattern during pregnancy and risk of infant mortality. Epidemiology 2009;20:884-91.

Example 3: Effects of illicit drug use

Parental cannabis use and reported frequencies of other illicit drug use are often very low among participants in the selected cohorts. There are only a few studies on illicit drug use in pregnancy and health outcomes in the child, all based on two cohorts: ALSPAC and Generation R. In ALSPAC, maternal use of cannabis during preganancy was not associated with late fetal or perinatal death (1). A study in ALSPAC that investigated parental drug use as a predictor for child drug use at age 10, found maternal drinking, but not cannabis use, to be predictive. In the Generation R, cannabis exposure in pregnancy was found to be more frequent if the biological father of the child also used cannabis or if the mother was single or unmarried (2). In utero exposure to cannabis was associated with changes in hemodynamic programming of the vascular system of the fetus in late pregnancy and with growth restriction in mid-and late pregnancy and with lower birth weight (3, 4). Also, gestational exposure to cannabis was found to be associated with behavioral problems in early childhood (up to 18 months of age) but only in girls and only in the area of increased aggressive behavior.

1. Fergusson DM, Horwood LJ, Northstone K. Maternal use of cannabis and pregnancy outcome. BJOG 2002;
2. El Marroun H, Tiemeier H, Jaddoe VW, Hofman A, Mackenbach JP, Steegers EA, Verhulst FC, van den Brink W, Huizink AC. Demographic, emotional and social determinants of cannabis use in early pregnancy: the Generation R study. Drug Alcohol Depend 2008;98:218-26.
3. El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, van den Brink W, Huizink AC. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatr 2009;48:1173-81.
4. El Marroun H, Tiemeier H, Steegers EA, Roos-Hesselink JW, Jaddoe VW, Hofman A, Verhulst FC, van den Brink W, Huizink AC. A prospective study on intrauterine cannabis exposure and fetal blood flow. Early Hum Develop 2010;86:231-6.

Table 1 displays results from selected birth cohorts with substance use as main exposure. A list of references belonging to the various birth cohorts are also listed (not complete).

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

By establishing a series of birth cohorts across Europe, it is now possible to estimate the health consequences of alcohol intake, tobacco smoking and the use of illicit drugs. Eighty birth cohorts are registered (www.birthcohorts.net). Some of the larger cohorts have a very general approach to causal research and have tried to include as many exposure and end-point variables as possible, while the smaller cohorts often have been set up to solve more specific problems, for instance the role of mercury exposure versus child health as is the case in the cohorts of the Faroe Islands. Most of them have included alcohol intake and tobacco smoking as variables, not necessarily because they represented the main exposures of interest, but they are often considered as confounding or effect-modifying factors.

The cohorts have varying sample sizes and are placed in populations where the recommendations and cultural contexts surrounding the use of tobacco and alcohol for women of childbearing age are different. From a scientific point of view, this diversity across Europe is an advantage. If the same observation is found, regardless of the confounder structure in the different data sets, a biological association becomes more probable. An analogy can be drawn to the observation that moderate intake of alcohol in adults above 40-50 years is associated with reduced risk of coronary heart disease (Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ 2011;342:d61doi:10.1136/bmj.d671). This observation has been found in very diverse populations. This is used as an argument in favour of causation, even though observational investigations, such as cohorts, always will lack complete confounder control.

There will be differences between cohorts as regards the wording of questions as well as the periods covered prenatally and postnatally. These measurement issues should be taken into account when studies are compared across cohorts. In addition to cohort data, information from other sources is valuable. Some birth registries will for instance include smoking behaviour, while alcohol intake is usually not included. Together with cross-sectional studies they provide valuable information on the prevalences of exposures. The estimation of associations to health outcomes in the birth registries themselves, as well as through linkage to other disease registries, will add to the information on relative and attributable risks. A more detailed presentation of cohorts is given in Tables 2-4, linked to the case study described below.

1.4 Identification of gaps

For public health purposes, it is necessary to have scientifically based knowledge that will estimate the burden of disease linked to the use of these substances in pregnancy. Thus, better evidence on the prevalence of exposure as well as better estimates of relative risk of diseases linked to substance use is needed. Also, experts should provide advice on the actions that can be taken to reduce the extent of exposure. These actions can be regulations (laws, taxation, rules and restrictions for access, import policies) or actions targeted at smaller groups and individuals.

There are several gaps that need to be filled for politicians to have the best guidance. The efficiency of specific targeted interventions requires randomized, controlled trials. An interventional design embedded within a birth cohort is a design that has not been used yet in this area. Interventions with communities as the unit of randomization could also be tested out.

There has been a substantial reduction in the proportion of women who smoke during pregnancy during the past decades. At present, a strong socioeconomic gradient is found as regards smoking. From a public health point of view, a major challenge is to prevent smoking for women with low socioeconomic background, and a better understanding of the underlying causes of social inequalities in substance use is needed.

As the birth cohorts evolve, they will provide important information on the determinants of substance use in adolescence. This information is largely lacking today, and will be important for the guidance of policy. The value of the birth cohorts is the rich nature of the total exposures and backgrounds collected from conception and onwards

For the prediction or causal analysis as to why some people drink moderate or large amounts of alcohol, while others do not drink at all, the cohorts will provide rich information.

In addition, the effects of these substances may give insight into disease mechanisms. For instance, tobacco smoking significantly reduces the risk of hyperemesis gravidarum and preeclampsia, and it is controversial whether moderate alcohol intake is associated with a reduced risk of preterm birth. In depth studies, using available biological materials from cohorts will be valuable for the exploration of the pathophysiology of some diseases.

The cohort studies have limitations. Selection, information bias and rest-confounding can distort the picture and make estimates of absolute, relative and attributable risks flawed. For the self-reported intake of these substances, a major problem is misclassification. In addition, one may reasonably assume that heavy drinkers/smokers will less often take part in the cohorts. This makes the estimation of the prevalence of exposures as well as the estimation of population attributable risks, uncertain. In addition, confounding is a major issue, as drinking and smoking behaviour is associated with socioeconomic background factors as well as with other life-styles, such as nutrition and physical activity. However, cohorts represent the best available sources of empirical information.

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

Katrine Strandberg-Larsen and coworkers from Denmark proposed a case study with the aim to examine whether the observed beneficial effects of light drinking is likely to be causal or an artifact attributable to behavior modification bias or confounding by environment, genes or lifestyles. To resolve this scientific problem they suggest to pool data from European birth cohorts and reanalyze the association between alcohol and birth weight and alcohol and preterm delivery, respectively. When reanalyzing the pooled data they want to explore whether the observed beneficial effects can be replicated when: 1) restricting the analyses to first-time pregnancies with a short waiting time to pregnancy, 2) comparing differently exposed siblings or cousins in order to obtain more alike comparison groups and 3) doing parental-offspring comparisons.

Several European cohorts have information on alcohol consumption and smoking. Table 2 shows cohorts with information on alcohol intake during pregnancy. Table 3 shows eligibility criteria for inclusion into the case study, and Table 4 shows cohorts with more than 1000 participants, available biological material and information on substance exposure.

3. Recommendations

Tobacco and alcohol consumption are major contributors to the global burden of disease. Birth cohorts can give valuable new information on the effects of these substances on the growing fetus, effects that may have long-lasting consequences. Furthermore, the follow-up of these children into adolescence and adulthood will provide insights into the determinants of substance use, information that will be essential for public health actions. We recommend that birth cohorts should be supported to give the scientific basis for political decisions in this important area by funding the infrastructure of birth cohorts in general, by setting out calls within the EU framework research programs for research questions that can be responded to by collaborating birth cohorts, and to encourage researchers to apply to the European Research Council for the resolution of new and innovative research questions through the use of data from existing birth cohorts.

Birth cohort papers with alcohol, tobacco and illicit drug use as main exposure:

Norwegian Mother and Child Cohort Study (MoBa)

1. Cupul-Uicab LA, Ye X, Skjaerven R, Haug K, Longnecker MP. Reproducibility of reported in utero exposure to tobacco smoke. Ann Epidemiol. 2011;21:48-52.
2. Ye X, Skjærven R, Basso O, Baird D, Eggesbø M, Uicab LEC, Haug K, Longnecker MP. In utero exposure to tobacco smoking and subsequent reduced fertility in females. Human Reprod 2010;25:2901-06.
3. Håberg SE, Bentdal YE, London SJ, Kværner KJ, Nystad W, Nafstad P. Prenatal and postnatal parental smoking and acute otitis media in early childhood. Acta Paediatr 2010;99:99-105.
4. Stene-Larsen K, Borge AIH, Vollrath ME. Maternal smoking in pregnancy and externalizing behavior in 18-month-old children: Results from a population-based prospective study. J Am Acad Child Adoles Psychiatr 2009;3:48.
5. Håberg SE, Stigum H, Nystad W, Nafstad P. Effects of pre- and postnatal parental smoking on early childhood respiratory health. Am J Epidemiol 2007;166:679-86.
6. Magnus P, Irgens LM, Haug K, Nystad W, Skjærven R, Stoltenberg C and the MoBa study group. Cohort profile: The Norwegian Mother and Child Cohort Study. Int J Epidemiol 2006; 35:1146-50.
7. Rønningen KS, Paltiel L, Meltzer HM, Nordhagen R, Lie KK, Hovengen R, Haugen M, Nystad W, Magnus P, Hoppin JA. The biobank of The Norwegian Mother and Child Cohort Study. Eur J Epidemiol 2006;21:619-25.
8. Vikanes Å, Grjibovski A, Vangen S, Gunnes N, Samuelsen SO, Magnus P. Maternal body composition, smoking, and hyperemesis gravidarum. Ann Epidemiol 2010;20:592-8.

9. Cupul-Uicab LA, Baird DD, Skjærven R, Saha-Chaudhuri P, Haug K, Longnecker MP. In utero exposure to maternal smoking and women's risk of fetal loss in the Norwegian Mother and Child Cohort (MoBa). Human Reprod 2011;26:458-65.

RHEA cohort:

1. Vardavas, C. I., L. Chatzi, E. Patelarou, E. Plana, K. Sarri, A. Kafatos, A. D. Koutis and M. Kogevinas (2010). Smoking and smoking cessation during early pregnancy and its effect on adverse pregnancy outcomes and fetal growth. Eur J Pediatr 2010;169:741- 8.

Generation R cohort:

1. Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, Witteman JC, Hofman A. The Generation R Study: Design and cohort profile. Eur J Epidemiol 2006;21:475-84.
2. Bakker R, Pluimgraaff LE, Steegers EA, Raat H, Tiemeier H, Hofman A,Jaddoe VW. Associations of light and moderate maternal alcohol consumption with fetal growth characteristics in different periods of pregnancy: the Generation R Study. Int J Epidemiol 2010;39:777-89.
3. Bakker R, Steegers EA, Mackenbach JP, Hofman A, Jaddoe VW. Maternal smoking and blood pressure in different trimesters of pregnancy: the Generation R Study. J Hyperten 2010;28:2210-8.
4. Mook-Kanamori DO, Steegers EA, Eilers PH, Raat H, Hofman A, JaddoeVW. Risk factors and outcomes associated with first-trimester fetal growth restriction. JAMA. 2010;303:527-34.
5. Patra J, Bakker R, Irving H, Jaddoe V, Malini S, Rehm J. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. BJOG 2011;118:1411-21.
6. Jaddoe VW, Bakker R, Hofman A, Mackenbach JP, Moll HA, Steegers EA,Witteman JC. Moderate alcohol consumption during pregnancy and the risk of low birth weight and preterm birth. The Generation R Study. Ann Epidemiol 2007;17:834-40.
7. Jaddoe VW, Verburg BO, de Ridder MA, Hofman A, Mackenbach JP, Moll HA,Steegers EA, Witteman JC. Maternal smoking and fetal growth characteristics in different periods of pregnancy: the Generation R Study. Am J Epidemiol 2007
8. Jaddoe VW, Troe EJ, Hofman A, Mackenbach JP, Moll HA, Steegers EA, Witteman JC. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. Paediatr Perinat Epidemiol 2008;22:162-71.

9. Cents RA, Tiemeier H, Velders FP, Jaddoe VW, Hofman A, Verhulst FC, Lambregtse-van den Berg MP, Hudziak JJ. Maternal smoking during pregnancy and child emotional problems: The relevance of maternal and child 5-HTTLPR genotype. Am J Med Genet B Neuropsychiatr Genet 2012;159B:289-97.
10. Bakker R, Kruithof C, Steegers EA, Tiemeier H, Mackenbach JP, Hofman A, Jaddoe VW. Assessment of maternal smoking status during pregnancy and the associations with neonatal outcomes. Tob Res 2011;13:1250-6.
11. Bakker R, Timmermans S, Steegers AEP, Hofman A, Jaddoe VWV. Folic acid supplements modify the adverse effect of maternal smoking on fetal growth and neonatal complications. J Nutr 2011;141:2172-9.
12. Taal HR, Geelhoed JJ, Steegers EA, Hofman A, Moll HA, Lequin M, van der Heijden AJ, Jaddoe VW. Maternal smoking during pregnancy and kidney volume in the offspring: the Generation R Study. Pediatr Nephrol 2011;26:1275-83.
13. Durmus B, Kruithof CJ, Gillman MH, Willemsen SP, Hofman A, Raat H, Eilers PH, Steegers EA, Jaddoe VW. Parental smoking during pregnancy, early growth, and risk of obesity in preschool children: the Generation R Study. Am J Clin Nutr 2011;94:164-71.
14. Geelhoed JJ, El Marroun H, Verburg BO, van Osch-Gevers L, Hofman A, Huizink AC, Moll HA, Verhulst FC, Helbing WA, Steegers EA, Jaddoe VW. Maternal smoking during pregnancy, fetal arterial resistance adaptations and cardiovascular function in childhood. BJOG. 2011 May;118(6):755-62.
15. Durmuş B, Ay L, Hokken-Koelega AC, Raat H, Hofman A, Steegers EA, Jaddoe VW. Maternal smoking during pregnancy and subcutaneous fat mass in early childhood. The Generation R Study. Eur J Epidemiol 2011;26:295-304.
16. El Marroun H, Tiemeier H, Steegers EA, Roos-Hesselink JW, Jaddoe VW, Hofman A, Verhulst FC, van den Brink W, Huizink AC. A prospective study on intrauterine cannabis exposure and fetal blood flow. Early Hum Develop 2010;86:231-6.
17. El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, van den Brink W, Huizink AC. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatr 2009;48:1173-81.
18. El Marroun H, Tiemeier H, Jaddoe VW, Hofman A, Mackenbach JP, Steegers EA, Verhulst FC, van den Brink W, Huizink AC. Demographic, emotional and social determinants of cannabis use in early pregnancy: the Generation R study. Drug Alcohol Depend 2008;98:218-26.

ALSPAC cohort:

1. Golding J. Children of the nineties. A longitudinal study of pregnancy and childhood based on the population of Avon (ALSPAC). West Engl Med J 1990;105: 80-2.
2. Passaro KT, Little RE, Savitz DA, Noss J. The effect of maternal drinking before conception and in early pregnancy on infant birthweight. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Epidemiology 1996;.
3. Passaro KT, Little RE, Savitz DA, Noss J. Effect of paternal alcohol consumption before conception on infant birth weight. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Teratology 1998;
4. Rogers I, Emmett P, Baker D, Golding J. Financial difficulties, smoking habits, composition of the diet and birthweight in a population of pregnant women in the South West of England. ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Eur J Clin Nutr 1998;
5. Rogers I, Emmett P. The effect of maternal smoking status, educational level and age on food and nutrient intakes in preschool children: results from the Avon Longitudinal Study of Parents and Children. Eur J Clin Nutr 2003;57:854-64.
6. Fergusson DM, Horwood LJ, Northstone K. Maternal use of cannabis and pregnancy outcome. BJOG 2002;
7. Hull MG, North K, Taylor H, Farrow A, Ford WC. Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. Fertil Steril 2000;74:725-33.
8. Lux AL, Henderson AJ, Pocock SJ. Wheeze associated with prenatal tobacco smoke exposure: a prospective, longitudinal study. ALSPAC Study Team. Arch Dis Child 2000;83:307-12.
9. Henderson AJ, Sherriff A, Northstone K, Kukla L, Hruba D, 'Pre- and postnatal parental smoking and wheeze in infancy: cross cultural differences. Avon Study of Parents and Children (ALSPAC) Study Team, European Longitudinal Study of Pregnancy and Childhood (ELSPAC) Co-ordinating Centre.', Eur Respir J 2001; 18 (2): 323-9
10. Henderson AJ, Newson RB, Rose-Zerilli M, Ring SM, Holloway JW, Shaheen SO. Maternal Nrf2 and gluthathione-S-transferase polymorphisms do not modify associations of prenatal tobacco smoke exposure with asthma and lung function in school-aged children. Thorax 2010;65:897-902.
11. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. Pediatr Res 2002;52:863-7.
12. Little RE, Northstone K, Golding J. Alcohol, breastfeeding, and development at 18 months. Pediatrics 2002;109:E72-2.
13. Donath SM, Amir LH. The relationship between maternal smoking and breastfeeding duration after adjustment for maternal infant feeding intention. Acta Paediatr 2004;93:1514-8.

14. Heron J, Ness A. Lack of association between smoking behavior and the sex ratio of offspring in the Avon longitudinal study of parents and children. Fertil Steril 2004;81:700-2.
15. Leary S, Davey Smith G, Ness A. Smoking during pregnancy and components of stature in offspring. Am J Hum Biol 2006;18:502-12.
16. Leary SD, Smith GD, Rogers IS, Reilly JJ, Wells JC, Ness AR. Smoking during pregnancy and offspring fat and lean mass in childhood. Obesity (Silver Spring) 2006;14:2284-93.
17. Sayal K, Heron J, Golding J, Emond A. Prenatal alcohol exposure and gender differences in childhood mental health problems: a longitudinal population-based study. Pediatrics 2007; 119:e426-34.
18. Brion MJ, Leary SD, Smith GD, Ness AR. Similar associations of parental prenatal smoking suggest child blood pressure is not influenced by intrauterine effects. Hypertension 2007;49: 1422-8.
19. Alati R, Macleod J, Hickman M, Sayal K, May M, Smith GD, Lawlor DA. Intrauterine exposure to alcohol and tobacco use and childhood IQ: findings from a parental-offspring comparison within the Avon Longitudinal Study of Parents and Children. Pediatr Res 2008;64:659-66.
20. Macleod J, Hickman M, Bowen E, Alati R, Tilling K, Smith GD. Parental drug use, early adversities, later childhood problems and children's use of tobacco and alcohol at age 10: birth cohort study. Addiction 2008;103:1731-43.
21. Munafo MR, Heron J, Araya R. Smoking patterns during pregnancy and postnatal period and depressive symptoms. Nicotine Tob Res 2008;10:1609-20.
22. Brion M-J, Leary SD, Lawlor DA, Davey Smith G, Ness AR. Modifiable maternal exposures and offspring blood pressure: A review of epidemiological studies of maternal age, diet and smoking. Pediatric Res 2008;63:593-8.
23. Brion MJ, Victora C, Matijasevich A, Horta B, Anselmi L, Steer C, Menezes AM, Lawlor DA, Davey Smith G. Maternal smoking and child psychological problems: Disentangling causal and noncausal effects. Pediatrics 2010;126:e57-e65.
24. Macdonald-Wallis C, Tobias JH, Davey Smith G, Lawlor DA. Parental smoking during pregnancy and offspring bone mass at age 10 years: findings from a prospective birth cohort. Osteoporos Int 2010;
25. Zammit S, Thomas K, Thompson A, Horwood J, Menezes P, Gunnell D, Hollis C, Wolke D, Lewis G, Harrison G. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. Br J Psychiatry 2009;195:294-300.
26. Zuccolo L, Fitz-Simon N, Gray R, Ring SM, Sayal K, Smith GD, Lewis SJ. A non-synonymous variant in ADH1B is strongly associated with prenatal alcohol use in a European sample of pregnant women. Hum Mol Genet 2009;18:4457-66.
27. Freathy RM, Ring SM, Shields B, Galobardes B, Knight B, Weedon MN, Smith GD, Frayling TM, Hattersley AT. A common genetic variant in the 15q24 nicotinic acetylcholine receptor gene cluster

(CHRNA5-CHRNA3-CHRNB4) is associated with a reduced ability of women to quit smoking in pregnancy. Hum Mol Genet 2009;18:2922-7.

INMA cohort:

1. Guxens M, Ballester F, Espada M, Fernández MF, Grimalt JO, Ibarluzea J, Olea N, Rebagliato M, Tardón A, Torrent M, Vioque J, Vrijheid M, Sunyer J on behalf of INMA Project: Cohort Profile: The INMA – INfancia y Medio Ambiente (Environment and Childhood) Project. Int J Epidemiol 2011;
2. Iñiguez C, Ballester F, Amorós R, Murcia M, Plana A, Rebagliato M. Active and passive smoking during pregnancy and ultrasound measures of fetal growth in a cohort of pregnant women. J Epidemiol Community Health 2011;
3. Sunyer J, Garcia-Esteban R, Castilla AM, Aurrekoetxea JJ, Iñiguez C, Tardón A, Espada M, Lertxundi A, Chatzi L, Rebagliato M, Kogevinas M; on behalf of the INMA project. Exposure to second hand smoke and reproductive outcomes depending on maternal asthma. Eur Respir J. 2012:

Danish National Birth Cohort (DNBC):

1. Andersen K, Andersen AMN, Olsen J, Grønbæk M. Alcohol consumption during pregnancy and the risk of preterm delivery. Am J Epidemiol 2004;159:155-161.
2. Strandberg-Larsen K, Nielsen NR, Grønbæk M, Andersen PK, Olsen J, Andersen AMN. Binge drinking in pregnancy and risk of fetal death. Obstet Gynecol 2008;11:602-9.
3. Strandberg-Larsen K, Grønbæk M, Andersen AMN, Andersen PK, Olsen J. Alcohol drinking pattern during pregnancy and risk of infant mortality. Epidemiology 2009;20:884-91.
4. Mortensen LH, Diderichsen F, Smith GD, Andersen AM. The social gradient in birthweight at term: quantification of the mediating role of maternal smoking and body mass index. Hum Reprod 2009;24:2629-35.
5. Strandberg-Larsen K, Andersen A-MN. Alcohol and fetal risk: a property of the drink or the drinker? Acta Obstet Gynecol Scand 2011;90:207-9.

Tables and Annexes are provided on the following pages.

Table 1 Results from selected European birth cohorts with published work on smoking, alcohol and illicit drug use

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Journal*
MoBa	Cupul-Uicab LA, et al	2011	In utero exposure to maternal smoking	Fetal loss	Hum Reprod
MoBa	Ye X, et al.	2010	In Utero Exposure to Tobacco Smoking	Subsequent Reduced Fertility in Females	Human Repro.
MoBa	Håberg SE, et al	2010	Prenatal and postnatal parental smoking	acute otitis media in early childhood	Acta Paediatr.
MoBa	Stene-Larsen K, et al	2009	Maternal smoking in pregnancy	externalizing behavior in 18-month-old children	J Am Acad Child Adoles Psychiatr
MoBa	Håberg SE, et al		pre- and postnatal parental smoking	early childhood respiratory health	Am J Epidemiol
ALSPAC	Rogers I, et al	2003	maternal smoking status, educational level and age	food and nutrient intakes in preschool children	Eur J Clin Nutr
ALSPAC	Rogers I, et al	1998	'Financial difficulties, smoking habits, composition of the diet	Birth weight	Eur J Clin Nutr
ALSPAC	Freathy RM, et al	2009	genetic variant	ability of women to quit smoking in pregnancy	Hum Mol Genet
ALSPAC	Munafo MR, et al	2008	'Smoking patterns during pregnancy and postnatal period	depressive symptoms	Nicotine Tob Res
ALSPAC	Brion MJ et al	2007	parental prenatal smoking	child blood pressure	Hypertension
ALSPAC	Hull MG, et al	2000	active and passive smoking	Delayed conception	Fertil Steril
ALSPAC	Lux AL, et al	2000	prenatal tobacco smoke exposure	Wheeze	
ALSPAC	Henderson AJ, et al	2001	Pre- and postnatal parental smoking	wheeze in infancy	Eur Respir J
ALSPAC	Henderson AJ, et al	2010	Gene polymorphisms modify associations of prenatal tobacco	lung function in school-aged children	Thorax
ALSPAC	Ong KK, et al	2002	maternal smoking, parity and infant breast-feeding	Size at birth and early childhood growth	Pediatr Res
ALSPAC	Donath SM, et al	2004	maternal smoking	breastfeeding	Acta Paediatr
ALSPAC	Heron J, et al	2004	Smoking behavior	sex ratio of offspring	Fertil Steril

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Journal*
ALSPAC	Leary SD, et al	2006	Smoking during pregnancy	components of stature in offspring	Am J Hum Biol
ALSPAC	Leary SD, et al	2006	Smoking during pregnancy	offspring fat and lean mass in childhood	Obesity
ALSPAC	Alati R, et al	2008	Intrauterine exposure to alcohol and tobacco use	childhood IQ	Pediatr Res
ALSPAC	Brion M-J, et al	2008	maternal age, diet and smoking	offspring blood pressure	Pediatric Research
ALSPAC	Brion MJ, et al	2010	Maternal Smoking	Child Psychological Problems	Pediatrics
ALSPAC	Macdonald-Wallis C, et al	2010	'Parental smoking during pregnancy	offspring bone mass at age 10 years	Osteoporos Int
DNBC	Morales-Suarez-Varela MM, et al	2006	Smoking habits, nicotine use	Congenital malformations	Obstet Gynecol
DNBC	Lassen TH, et al	2010	Maternal use of nicotine replacement therapy (NRT) during pregnancy	Birthweight	Paediatr Perinat Epidemiol
DNBC	Strandberg-Larsen K, et al	2008	Use of nicotine replacement therapy during pregnancy	Stillbirth	BJOG
GENERATION R	Cents RA, et al	2012	Maternal smoking during and relevance of maternal and child 5-HTTLPR genotype	child emotional problems	Am J Med Genet B Neuropsychiatr Genet
GENERATION R	Bakker R, et al	2011	maternal smoking status during	neonatal outcomes	Tob Res.
GENERATION R	Taal HR, et al	2011	Maternal smoking during pregnancy	kidney volume	Pediatr Nephrol
GENERATION R	Durmuş B, et al	2011	Parental smoking during pregnancy	obesity in preschool children	Am J Clin Nutr.
GENERATION R	Geelhoed JJ, et al	2011	Maternal smoking during pregnancy	fetal arterial resistance adaptations and cardiovascular function in childhood	BJOG
GENERATION R	Durmuş B, et al	2011	Maternal smoking during pregnancy	subcutaneous fat mass in early childhood	Eur J Epidemiol.
GENERATION R	Jaddoe VW,et al	2007	Maternal smoking	fetal growth characteristics in	Am J Epidemiol

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Journal*
				different periods of pregnancy	
GENERATION R	Jaddoe VW, et al	2008	Active and passive maternal smoking during pregnancy	low birthweight and preterm birth	Paediatr Perinat Epidemiol
GENERATION R	Bakker R, et al	2010	Maternal smoking	blood pressure in different trimesters	J Hypertens
INMA	Sunyer J, et al	2012	Exposure to second hand smoke	Birth weight	Eur Respir J.
INMA	Iñiguez C, et al	2011	Active and passive smoking during pregnancy	Fetal Growth	J Epidemiol Community Health.
RHEA	C. Vardavas et al.	2010	Smoking & smoking cessation	Fetal growth, birth weight, preterm birth	European Journal of Pediatrics
ALSPAC					
ALSPAC	Little RE, et al	2002	Alcohol, breastfeeding	development at 18 months	Pediatrics
ALSPAC	Sayal K, et al	2007	Prenatal alcohol exposure	gender differences in childhood mental health problems	Pediatrics
ALSPAC	Alati R, et al	2008	Intrauterine exposure to alcohol and tobacco use	childhood IQ	Pediatr Res
ALSPAC	Zammit S, et al	2009	'Maternal tobacco, cannabis and alcohol use during pregnancy	adolescent psychotic symptoms in offspring	Br J Psychiatry
ALSPAC	Zuccolo L, et al	2009	Genetic variant	prenatal alcohol use	Hum Mol Genet
ALSPAC	Passaro KT, et al	1996	maternal drinking before conception and in early pregnancy	Birth weight	Epidemiology
ALSPAC	Passaro KT, et al	1998	paternal alcohol consumption before conception	Birth weight	Teratology
DNBC	Strandberg-Larsen K, et al	2008	Binge drinking in pregnancy	Fetal death	Obstet Gynecol
DNBC	Albertsen K, et al	2004	Alcohol consumption during pregnancy	Preterm delivery	Am J Epidemiol
DNBC	Strandberg-Larsen K, et al	2011	Maternal alcohol drinking pattern during pregnancy	An isolated congenital heart defect	Birth Defects Res A Clin Mol Teratol
GENERATION R	Bakker R, et al	2010	Maternal alcohol	Fetal growth characteristics	Int J Epidemiol

Cohort	*Author*	*Year*	*Exposure*	*Outcome*	*Journal*
			consumption	in different periods of pregnancy	
GENERATION R	Jaddoe VW, et al	2007	Moderate alcohol consumption during pregnancy	low birth weight and preterm birth	Ann Epidemiol.
GENERATION R	Patra J, et al	2011	alcohol consumption	low birthweight, preterm birth and small for gestational age	BJOG
ALSPAC	Fergusson DM, et al	2002	Maternal use of cannabis	Late fetal and perinatal death	BJOG
ALSPAC	Macleod J, et al	2008	Parental drug use, early adversities, later childhood problems	use of tobacco and alcohol at age 10	Addiction
DNBC					
DNBC					
GENERATION R	El Marroun H, et al	2009	Intrauterine cannabis exposure	fetal growth trajectories:	J Am Acad Child Adolesc Psychiatry
GENERATION R	El Marroun H, et al	2010	Intrauterine cannabis exposure	fetal blood flow	Early Hum Dev.
GENERATION R	El Marroun H, et al	2008	Demographic, emotional and social determinants	cannabis use in early pregnancy	Drug Alcohol Depend

Table 2 European cohorts with women enrolled while pregnant and information on alcohol and birth outcomes

Cohort (web site)	Country	N mother-child pairs	Gestational age at enrolment in weeks	Year of enrolment	Alcohol consumption	BW	GA	Gravidity	TTP	Intention of pregnancy
1. Aarhus Birth Cohort (N/A)	Denmark	93,000	12-19	1990 and ongoing	X	X	X	X	X	(X)
2. ABCD (www.abcd-studie.nl)	Netherlands	7,863	12-14	2003-04	X	X	X	?	X	?
3. ABIS (www.abis-studien.se)	Sweden	17,000	13-18	1997-99	X	X	X	?	?	?
4. ALSPAC (www.alspac.bristol.ac.uk)	United kingdom	14,000	1-12	1991-92	X	X	X	X	X	(X)
5. APREG(N/A)	Hungary	2,800	4-8	2000-06	-	X	X	?	X	?
6. BIB- Born in Bradford (www.borninbradford.nhs.uk)	United kingdom	13,000	26-28	2007-10	X	X	X	X	_	?
7. CHEF (Children´s health and the environment in the faroes) (www.chef-project.dk)	Faroes	1,860	32-34	1986-87,1994-95, and 1997-00	X	X	X	?	-	?
8. Determination of maternal caffeine intakes associated with increased risk to the fetus (N/A)	United kingdom	1,500	1-12	2003-06	X	X	X	?	?	?
9. DNBC (www.dnbc.dk)	Denmark	100,418	6-24	1996-02	X	X	X	X	X	X
10. Duisburg (N/A)	Germany	232	28+	2000-03	?	X	X	?	-	?
11. EDEN (N/A)	France	1,800	<24	2003-06	X	X	X	X	X	(X)
12. Generation R (www.generationr.nl)	Netherlands	9,778	1-12	2001-06	X	X	X	X	X	X
13. Generation XXI (N/A)	Portugal	8,493 (only a subgroup during pregnancy)	1-12 or at birth	2004-2006	X	X	X	X	X	(X)
14. Healthy Habits for two -HHf2 (N/A)	Denmark	11,300	28+	1984-86	X	X	X	X	X	X
15. INMA in Asturias,Gipuzkoa, Menorca, Sabadell, and Valencia (www.proyectoinma.org)	Spain	3,100	12	1997,98, and 2004-2008	X	X	X	X	X	(X)

16. INUENDO (www.inuendo.dk)	Sweden, Poland, Ukraine, Greece	2,269 women 1,322 children	6-38 weeks	2002-2004	-	X	X	X	X	?
17. IVAAQ (N/A)	Denmark, Greenland	400	13-18	1999-2005	X	X	X	?	?	?
18. Kaunas cohort – KANC (N/A)	Lithuania	4,000	12	2007-09	X	X	X	?	X	?
19. KOALA Birth Cohort Study, The Netherlands (www.koala-study.nl)	Netherlands	2,834	14	2000-03	X	X	X	X	X	(X)
20. Krakow cohort (N/A)	Poland	480	Not stated	2001-03	X	X	X	?	?	?
21. Lifeways Cross-Generation Cohort Study (N/A)	Ireland	1,061	1-12	2001-03	X	X	X	X	?	?
22. LUKAS (N/A)	Findland	442	20-34	2002-05	?	(X)	X	?	-	?
23. Methyr Allergy Study (N/A)	United kingdom	497	19-28	1982-84	X	X	?	?	?	?
24. MoBa (www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5895:0:15,3046:1:0:0:::0:0)	Norway	107,000	17-18	1999-08	X	X	X	X	X	X
25. NFBC-1986 (http://kelo.oulu.fi/NFBC/)	Findland	9,362	1-12	1985-86	X	X	X	X	X	X
26. NINFEA (https://www.progettoninfea.it/)	Italy	7,500	13-18	2005+	X	X	X	X	X	(X)
27. North Cumbria Community Genetics Project (N/A)	United kingdom	8,000	During pregnancy	1996-2001	?	?	?	?	?	?
28. PELAGIE (N/A)	France	3,421	13-18	2002-06	X	X	X	X	X	(X)
29. PIAMA (http://piama.iras.uu.nl/en/index.php)	Netherlands	4,000	28+	1996-97	X	X	X	X	-	?
30. Polish Mother and Child cohort study -REPRO_PL (www.repropl.com)	Poland	1,300	8-12	2007-11	X	X	X	X	X	(X)
31. RHEA study (http://rhea.med.uoc.gr/)	Greece	1,500	13-18	2007-08	X	X	X	X	X	(X)
32. SEATON (http://www.abdn.ac.uk/seatonstudy/)	United kingdom	1,924	During pregnancy is the only information on the webpage	1997-?	X	X	X	X	?	?
33. Southamptom Women's Survey (www.mrc.soton.ac.uk/sws/)	United kingdom	3,159	Before pregnancy	1988-02	X	X	X	X	?	?
34. TI-MOUN (N/A)	France	300	19-28	2005-08	X	X	X	X	?	?
35. Trieste child development cohort (N/A)	Italy	700	19-28	2007-09	X	X	X	X	?	?

Table 3 Eligibility criteria for the European cohorts to fulfill, in order to be included in the alcohol case study

Ordering of requisites	Required data	Level of detail	Timing of data collection
1	Maternal alcohol consumption during pregnancy	Average number of drinks per week or possible to divide into: Abstainers, less than 1, 1-2, 3-4,5-6, 7+ drinks/week	During pregnancy
2	Birth weight	Continuously recorded in grams, kg, or pounds and ounces	At birth
3	Gestational age at birth	In days or weeks estimated from the LMP*, EDD, ultrasound or clinical estimations	During pregnancy or at birth
4	Gestational age at enrolment into the cohort	In days	Enrolment before <37 completed weeks of gestation
5	Gravidity	First vs. multiple	During pregnancy or at birth
6	Time-to-pregnancy	In months or possible to divide into: None, 1-<3, 3-<6, 6-<12, 12+ months	During pregnancy or at birth
	Will request if available, but not required	**Level of detail**	**Timing of data collection**
7	Family relations within the cohorts	Link between full and half siblings of the mothers and the children in the cohorts	Irrelevant
8	Paternal alcohol consumption during pregnancy	Average number of drinks per week or possible to divide into: Abstainers, less than 1, 1-4, 5-7,8-13, 14-20, 21+ drinks/week	During pregnancy
9	Maternal alcohol consumption before pregnancy	Average number of drinks per week or possible to divide into: Abstainers, less than 1, 1-2, 3-4, 5-6, 7-14, 14+ drinks/week	During pregnancy
10	Maternal diabetes	Yes/no and type of diabetes	During pregnancy or at birth
11	Maternal age	In years at conception or at birth	Irrelevant
12	Smoking during pregnancy	No, ex, and amount of current smoking or possible to divide into: 1-10 and 10+ cigarettes/day	During pregnancy
13	Coffee consumption during pregnancy	Cups per day or possible to divide into: none, 1-4, 5-8, 8+ cups/day	During pregnancy
14	Maternal education/SES*	Years of education or occupational status	During pregnancy or at birth
15	Pre-pregnancy BMI*	Continuous or possible to divide into: <18,5, 18,5-24,25-29,30+ (kg/m^2)	During pregnancy
16	Maternal ethnicity	Country of origin	Irrelevant
17	Material status	Married, cohabiting, single	During pregnancy or at birth
18	Other reproductive experience	Parity, Infertility treatment, history of spontaneous or requested abortions, stillbirths, preterm delivery	During pregnancy

*LMP is last menstrual period, EDD is estimated day of delivery, SES is socioeconomic status, BMI is Body mass index (kg/m^2)

Table 4 General description of CHICOS birth cohorts with data on smoking, alcohol and other drug use, 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	Greece	Heraklion	2007-2008	1500
INMA	Spain		2004-2006	2600
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

chicos

Developing a Child Cohort Research Strategy for Europe

Working Group

Other Environmental exposures

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Summary

The foetus and infant are especially vulnerable to the effects of environmental risk factors that disrupt developmental processes. Chemical, physical and biological hazards in the environment include indoor and outdoor air pollution, water contamination, pesticides, heavy metals, persistent organic pollutants (POPs), environmental tobacco smoke (ETS), noise pollution, radiations, allergens, and biological organisms. Each of these may lead to serious health problems ranging from premature birth, low birth weight and congenital anomalies, to respiratory diseases, cancer, learning disabilities, behavioural problems, and possibly even obesity during childhood. In Europe, there are a total of 43 birth cohorts that are collecting a wealth of information on environmental exposures and child health. The distribution of these birth cohorts is not homogeneous across Europe, with more and larger cohorts mostly located in the north and west of Europe, and fewer and smaller cohorts in the south and east. All these cohorts have some information on second hand tobacco smoke exposure and many cohorts assessed occupational exposures, exposure to allergens and biological organisms and outdoor air pollution. Few cohorts have assessed water contaminants, metals, pesticides, radiations, POPs and noise. All cohorts have information on birth outcomes. A considerable number of cohorts have assessed child neuropsychological development, growth and obesity and allergies, asthma and respiratory infections. Metabolic syndrome indicators, childhood cancer and sexual maturation have been assessed in few cohorts. Overall, a good evidence exist on the association between second hand smoke and occupational hazards & adverse birth outcomes; high levels of lead (Pb), mercury (Hg), polychlorinated biphenyls (PCBs), and dioxines & neuropsychological development and cognitive function; traffic-related air pollution exposure and domestic visible mould & asthma and related symptoms. The evidence is limited for the association of disinfection-by-products, low levels of Hg and Pb, PCBs & adverse pregnancy outcomes; and traffic-related air pollution & neuropsychological development and cognitive function. No evidence exists for an association between chronic noise exposure & pregnancy outcomes, because the number of studies is small. Recommendations for next 15 years birth cohort research can be summarized as follows: (i) further combining of existing environment and health data to provide more informative, better and robust evidence for any associations, explore any cultural, geographical and socio-economic differences; (ii) follow up of existing cohorts to determine health effects in later life of pre natal and early childhood exposure; (iii) standardization and improvement of existing environmental exposure assessments, taking into account mobility and explore the interaction with physical activity; (iv) more work on the effects of new and emerging chemical exposures, indoor pollutants, and pesticides; (v) more research on the risks and benefits of environmental factors such as green space, solar UV, electromagnetic fields/mobile phones and soundscape/noise; (vi) strengthening the evidence base for ETS, outdoor air pollution, POPs, and metals; (vii) evaluate the role of mixtures of exposure on child health outcomes; and (viii) initiate new birth cohorts to capture new exposures and new exposure scenarios.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

It is well recognised that the foetus and infant are especially vulnerable to the effects of environmental risk factors that disrupt developmental processes. This is due to critical windows of vulnerability that occur during the rapid growth and development of organs and systems, to immaturities in children's metabolism, and to greater intake and absorption of chemicals from air, water, and food relative to their body weight (Grandjean et al. 2008). Chemical, physical and biological hazards in the environment include indoor and outdoor air pollution, water contamination, pesticides, heavy metals, persistent organic pollutants (POPs), environmental tobacco smoke (ETS), noise pollution, radiations, allergens, and biological organisms. Each of these may lead to serious health problems ranging from premature birth, low birth weight and congenital anomalies, to respiratory diseases, cancer, learning disabilities, behavioural problems, and possibly even obesity during childhood.

Many epidemiological studies have shown associations between environmental hazards and adverse child health outcomes. In this context, birth or mother-child cohort studies have been crucial in understanding these associations because they start the recruitment during pregnancy and follow children up for many years. In Europe, there are many pregnancy and birth cohort studies that are collecting a wealth of information on environmental exposures and child health. Therefore, the main aim of this WG is to evaluate existing environmental exposure information in European birth cohorts and develop recommendations for future research in Europe.

Specific objectives:

a) To review the existing information on environmental exposures in CHICOS birth cohorts (exposure assessment, methods used, comparability of different types of assessment, etc.); CHICOS will build on the work carried out in ENRIECO;

b) To identify gaps in knowledge in priority topics of policy interest;

c) To evaluate the role of cohorts as part of the development of a future research strategy;

d) 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. Persistent Organic Chlorines (POCs) exposure during pregnancy and birth outcomes
   2. Selected maternal occupations and birth outcomes
   3. Persistent Organic Chlorines (POCs) exposure during pregnancy and respiratory infections

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

Birth cohort versus other study design

Early exposures to environmental toxicants cause adverse effects on health that can often manifest themselves over generations. Many chemicals that the body has difficulties in metabolizing and eliminating tend to accumulate and can be transferred from mothers to children across the placenta or in breast milk such as lead, mercury, or polychlorinated biphenyls (PCBs). Children may be exposed to the same chemical from multiple sources and also may also be exposed simultaneously to several compounds at the same time with additive toxic effects. Different epidemiological studies have tried to disentangle these effects; however, many of these studies are weakened in methodology. Cross-sectional studies for instance cannot enhance our understanding of the developmental process. On the other hand, in retrospective cohort studies the assessment of exposure may be difficult and limited by recall bias and although they can collect information during pregnancy retrospectively they cannot provide biological samples from this period – which are crucial to study the effects of some environmental chemicals such as POPs or metals. Therefore, only prospective epidemiological studies, such as birth cohorts, which collect data on many co-variates, and follows children up for many years after birth, can provide insights in developmental problems of children in the first years of life as well as in later life.

Contribution of European birth cohorts

In 2009, the European Commission funded the ENRIECO project (**EN**vironmental Health **RI**sks in **E**uropean Birth **Co**horts – www.enrieco-org) to coordinate birth cohort research in Europe in the area of environmental exposures. This project has identified more than 30 existing cohorts with data on over 350,000 children. An inventory web-based database has been created with environmental exposures and health information collected by these cohorts (www.birthcohortsenrieco.net) (Vrijheid et al. 2011). Further, as part of ENRIECO the relationship between certain environmental exposures and health outcomes based on epidemiological studies (particularly birth cohort studies) were evaluated. Table 1 shows all the studies published by the European birth cohorts on environmental exposures described in the ENRIECO reports. All these reports are available on the project website (www.enrieco.org). Given the time limitations and limited resources some exposure-response relationships were not evaluated (ie. obesity and endocrine disruptor chemicals).

General conclusions (mostly from ENRIECO WP4 reports available in www.enrieco.org):

Birth outcomes

- *Second hand smoke*: there is very strong evidence for an association between exposure to second hand smoke during pregnancy and adverse birth outcomes, and part of this research has its origins in European birth cohort studies.
- *Occupation*: there is good evidence that occupational hazards can adversely affect reproduction and pregnancy outcomes; however prospective birth cohorts have not contributed largely in establishing these occupational risk factors.
- *Air pollution*: an association is suggested between air-pollution levels (particularly carbon monoxide, nitrogen dioxide, sulphur dioxide, and particulate matter) and birth weight, gestational duration and preterm births; but the evidence for congenital anomalies and air pollutants (ie. ozone, polyaromatic hydrocarbons) is weak. Some European birth cohorts have reported some associations, but the main evidence is coming from other sources.
- *Drinking water contaminants*: there is growing evidence for a weak association between drinking water exposure to disinfection by-products (DBPs), particularly trihalomethanes and some birth outcomes such as small for gestational age, but less for other birth outcomes. Most of this evidence came from registry based studies. Only 2 studies were identified from European birth cohorts; however, no data on direct exposure to disinfection-by-products was evaluated.
- *Persistent organic pollutants*: there is some evidence for an association between PCBs exposure and birth weight, whereas associations between other persistent organic pollutant exposures and birth weight/gestational age have been less consistent. Several of the studies come from European birth cohorts, while most other information come from North American birth cohorts.
- *Metals*: there is growing evidence for an association between mercury, lead, cadmium, arsenic, and manganese and low birth weight. Furthermore, there is some evidence for an association between preterm birth and high levels of mercury and lead. The European birth cohorts have mainly studied the effects of mercury present in fish and in amalgam fillings, whereas studies in non-European regions have focused on mercury and other metals such as arsenic and cadmium.
- *Pesticides*: little is known on the possible impact of agricultural and household pesticide exposure in the European area on foetal development –results from only one European birth cohort (DNBC). There are some consistent results showing a negative impact on foetal development of the occupational exposure to pesticides and exposure via drinking water contamination by atrazine during pregnancy. For other types of exposure to pesticides, evidence is still inadequate to conclude to an adverse effect on foetal growth and development.

- *Noise*: there is no evidence for an association between chronic noise exposure during pregnancy and pregnancy outcomes but the number of studies are small.

Neuropsychological development/Cognitive Function

- *Metals*: there is good evidence for an association between high levels of lead and mercury and neurobehavioural/cognitive effects. Several of these studies come from European birth cohorts, whilst most other information comes from North and South America, and Seychelles islands. There is some evidence for an association between cognitive effects and manganese and cadmium.
- *Persistent organic pollutants*: there is good evidence for an association between exposure high levels of PCBs and dioxins and neurodevelopment impairment. However, the evidence is limited for low levels of exposure to PCBs and dioxins or for high and low levels of the other old POPs (DDT, DDE, HCB) and new POPs (PBDEs, Mirex, PFOS/A and others). Most of the evidence has come from United States of America, some from European birth cohorts and, in lesser extent, from Canada, Mexico and Japan.
- *Air pollution*: several observational studies in the general population have observed the neuropsychological developmental hazards of air pollution in children. Some of this evidence comes from European birth cohorts but most information comes from USA and China. All these effects, however, are not conclusive given the limited number of studies, their small size and their methodological constraints.

Allergy and Asthma

- *Air pollution*: there is good evidence for an association between traffic-related air pollution exposure and the prevalence of asthma and related symptoms and growing evidence for an association between traffic-related air pollution exposure and the incidence of asthma and allergic sensitization. Furthermore, there is some evidence for an association between traffic-related air pollution and eczema and suggestive evidence for associations with symptoms of rhinitis. Most of the evidence has come from the European birth cohort studies as well as the North American studies.
- *Allergens and biological organisms*: there is good evidence for an association between exposure to domestic visible mould and allergic health outcomes such as wheeze, asthma and allergic rhinitis symptoms among European and non-European investigations; however, most of these studies come from cross-sectional based study design. In order to assign the direction of causality, there is especially a need for prospective birth cohort studies. The HITEA project (Health Effects of Indoor Pollutants: Integrating microbial, toxicological and epidemiological approaches) is a collaborative project of four European birth cohort studies investigating the long term health impacts of biological agents such as mould components.

Contribution of birth cohort collaboration

Even though cohort studies are essential to prospectively evaluate possible exposure response relationships, sample sizes are often too small to lead to conclusive results on their own, or have led to inconsistent and sometimes opposite results. Whilst it is clear that individual cohorts can, and have, made important contributions to understanding environmental causes of childhood disease and ill-health, it is also becoming increasingly clear that their full potential can only be realised with collaboration across large regions in Europe. Several collaborative projects have recognised this and are combining birth cohorts from different countries: GA2LEN (asthma), ESCAPE (air pollution), NewGeneris (genotoxicity), HIWATE (water chlorination byproducts), INUENDO (persistent organic pollutants), OBELIX (obesogenic pollutants), ArcRisk (mercury and organic pollutants in the Arctic Circle) and HITEA (indoor biological agents).

As part of the ENRIECO project 5 different case studies were conducted trying to combine exposure and health data from different cohorts: 1) Occupational exposures during pregnancy (under ENRIECO a protocol was prepared but data from cohorts will be analyzed within CHICOS); 2) POPs and birth weight; 3) Dampness and the association with asthma and allergy in European birth cohorts; 4) Foetal tobacco smoke exposure and asthma among 4-6 year olds; and 5) Foetal tobacco smoke exposure and wheezing among 0-2 year olds. These case studies were conducted using two different approaches: a *decentralized* approach was applied in case study 2 using data from 14 cohorts, whereas a *centralized* approach was applied in cases studies 3, 4 and 5 using data from 19 cohorts. Strengths and weaknesses of each approach are described in the final ENRIECO report (available in www.enrieco.org).

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

Identification of cohorts

Cohorts have been included following these criteria:

- birth and mother-child cohorts
- population-based (not strict)
- recruitment at the latest during the first year of life (if data on outcome of pregnancy available)
- at least one follow-up point during first years of life
- sample size: at least 200 (same criterion as ENRIECO)
- start year: 1985 onwards
- located in one of the EU member states

Birth cohorts with data on environmental pollutant exposures have been mainly identified from the ENRIECO inventory (www.birthcohortsenrieco.net) linked to the birthcohorts.net webpage (www.birthcohorts.net). This inventory provides detailed data of more than 30 birth cohorts, studying more than 350,000 mother-child pairs (Vrijheid et al. 2011). Birth cohorts included in this inventory and some other ones identified later from birthcohrts.net webpage are listed in table 2. The geographical distribution of these cohorts is shown in figure 1. They are situated in 19 European countries principally in Northern, and Western Europe. We identified 6 cohorts in Eastern Europe and 10 in the Southern Europe. The distribution of these birth cohorts is not homogeneous across Europe, with more and larger cohorts mostly located in the north and west of Europe, and fewer and smaller cohorts in the south and east. Three studies, the Aarhus Birth Cohort, the Danish National Birth Cohort (DNBC), and the Norwegian Mother and Babies study (MoBa) have recruited more than 100,000 mother-child pairs each. Ten studies have recruited between 5,000 and 20,000 pairs, 21 between 1,000 and 5,000, and nine cohorts concern less than 1000 subjects. Even though one of the initial inclusion criteria for CHICOS birth cohorts was to have a sample size of at least 1,000 subjects, we have considered important to include these ones because they provide valuable information on specific environmental risk factors or specific health outcomes.

In 19 cohorts children are aged between 5-10 years, children in 16 cohorts are over 10 years old, and in eight cohorts they are less than 5 years old. Most of the cohorts start recruitment of mothers during pregnancy; the rest start at birth. Most cohorts have multiple follow-up points after birth, and the majority has follow-up points in each of the child age periods specified in the questionnaire (1-6 months, 6 to 18 months, 18 months to 5 years, 5 to 10 years, over 10 years) (figure 2).

More information of these birth cohorts can be found in the ENRIECO inventory webpage www.birthcohortsenrieco.net and in the recently published paper of Vrijheid et al (Vrijheid et al. 2011).

Current work in the European birth cohorts

A detailed evaluation of existing environmental exposure and health information in the European birth cohorts was conducted as part of the ENRIECO project. ENRIECO WP2 (Exposures) was divided in 11 exposure groups: outdoor air pollution, water contamination, allergens and microbial agents metals, pesticides, emerging pollutants (e.g. bisphenol A, phthalates and phenols), smoking and second hand tobacco smoke, POPs, noise, and occupational exposures. ENRIECO WP3 (Health outcomes) was divided in 5 health groups: pregnancy-related outcomes, asthma and allergy, neurobehaviour assessment, childhood cancer, and child growth, obesity and puberty. These small working groups consisted of experts in the field and they evaluated the information for the different exposures and health topics and make recommendations for future research in European birth cohorts. The full working group reports are

available on the ENRIECO website (www.enrieco.org). Table 4 gives an overview of the available number of subject for specific exposure-health analyses in European birth cohorts.

It is worthy to note that these reports were prepared based on the information of a total 34 European birth cohorts (counting the cohorts of the Faroes, the old INMA cohorts and the new INMA cohorts as one cohort each). Identification of cohorts and receipt of the inventory questionnaires is ongoing and hence, some cohorts listed in table 2 could not be included in the reports. Moreover, through the CHICOS questionnaire developed by WP1 we will be able to identify more cohorts that have measured some environmental exposures and they were not initially included in ENRIECO. Questions about smoking, outdoor air pollution, indoor contaminants and occupation have been included in this questionnaire.

Exposures: Table 3 summarizes the contribution of these 34 birth cohorts to the different exposure topics. All cohorts have some information on second hand tobacco smoke exposure and many cohorts assessed occupational exposures (n=29), exposure to allergens and biological organisms (n=27) and outdoor air pollution (n=23). Assessment of exposure to water contaminants (n=11), metals (n=14), pesticides (n=17), radiations (n=14), persistent organic pollutants (n=13) and noise (n=16) is limited to fewer cohorts. A more detailed summary on the exposure assessment in the cohorts is provided in Annex 1.

Health outcomes: All cohorts have information on birth outcomes. A considerable number of cohorts have assessed child neuropsychological development (n=25), growth and obesity (n=33) and allergies, asthma and respiratory infections (n=32). Metabolic syndrome indicators, such as blood pressure or cholesterol levels, are collected in around half of the cohorts. Childhood cancer and sexual maturation have, to date, been assessed in few cohorts (n=12 and n=14, respectively).

Strengths and Limitations

Exposures:

- *Standardization*

  Overall, there is little standardization of exposure assessment methods between cohorts and even if the same method is used, protocols vary largely between cohorts. Some exceptions include studies in which a standardized exposure assessment is part of a collaborative effort such as TRAPCA, ESCAPE, HIWATE, AIRALLERG, and HITEA. Similarly, there is little standardization of the timing of the exposure assessment varying from pregnancy to early childhood and infancy.

- *Validity*

  Exposure assessment by means of individual environmental or biological measurements is costly and therefore usually not feasible in large cohort studies. Often, questionnaires are used instead to assess exposures. For some exposures such as the assessment of pet allergen and mould exposure

or for SHS exposure, questionnaire reports are found to be an inexpensive and valid estimate of residential environmental tobacco smoke exposure. Furthermore, often little is known about the long(er)-term validity of a single exposure assessment for a longer period.

- *Timing of exposure assessment*

  For many exposures, we presently know very little about the relevance of the timing of the exposure in addition to the level of exposure, and it is unclear whether exposure during a specific period when organs develop and are considered being more susceptible, is more important than later exposure. Prospective birth cohort studies with repeated exposure and health outcome assessments offer a unique possibility to increase our knowledge with regard to the timing of exposure.

- *Time-activity pattern, exposure at non-residential addresses and residential mobility*

  Environmental exposure assessment for air pollution, water contaminants, noise and pesticides is very often limited to residential exposure although study participants regularly spend considerable amounts of their time outside. Consequently, little is known about the role of residential and non-residential exposure in the association between exposure and health to improve exposure assessment.

Health outcomes

- *Harmonization*

  The degree of harmonization of the methods and tools used by cohorts is different for each type of health outcome assessed: highest harmonization → time to pregnancy, birth weight, preterm births, wheeze or asthma and allergy (using e.g. ISAAC-based questionnaires), postnatal changes in body mass index, waist circumference, occurrence of obesity; lowest harmonization → specific congenital malformations, stillbirth, IQ, ADHD and occurrence of puberty.

1.4 Identification of gaps

- Standardization of exposure methods between cohorts. However, this may reduce the possibility of comparing different methods, and this may not in all cases be beneficial.
- More research on the timing of exposure to define the critical windows of exposure
- Validation studies to compare estimated residential exposures with personal exposures (particularly for air pollution, water contamination, noise and pesticides). In order to improve

exposure assessment, time-activity pattern exposure, at non residential addresses and residential mobility, should be included in future studies.

- Development of biomarker studies for cancer research
- Serial measures of child growth covering the different periods
- Few Eastern European countries and low-income countries
- Continuation of the follow-up until adulthood
- Slow response to key policy questions
- Slow response to concerns about “new” environmental exposures
- Understand geographical and cultural inequalities in disease, exposure, and health related behaviours
- Need for replication of findings with important public health implications in different settings
- Need for improving methodological approaches, including protocols of biological and environmental sample collection and analysis.
- Combined analyses to improve statistical power

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

As part of the CHICOS case studies 3 environmental case studies were conducted: POPs and birth weight and gestational age; POPs and respiratory infections; and maternal occupation and birth weight and gestational age. Two of these case studies were an extension of the work started in the ENRIECO project. Although initial discussions took place for the occupational case study, no analyses where conducted. A decentralised meta-analysis was conducted for the POPs and birth weight and a paper was published; based on this experience we attempted to perform pooled analyses in the POPs CHICOS case study. Therefore, we conducted a centralized approach for all these 3 environmental case studies: individual cohorts prepared a dataset with all the variables required and sent it to CREAL for harmonization and data analysis.

For the POPs case study we contacted 11 cohorts of which 10 agreed to participate including 7839 mother-child pairs. The aim of this case study was to examine exposure-response associations between biological markers of persistent organic chlorines (POC) and selected pregnancy outcomes (birth weight, weight for gestational age, sex ratio) in order to (i) discuss causal inference; (ii) detail exposure-response relations, if

any; (iii) identify thresholds and no-effect levels, if any; (iv) identify vulnerable subgroups, if any; and (v) examine interactive effects of exposures and characteristics.

For the occupational case study we initially contacted 17 cohorts of which 14 agreed to participate – the REPRO_PL cohort, that was not initially identified, also joint the case study. More than 200.000 mother-child pairs were included in the analysis. The aim of this case study was to evaluate the risk of adverse birth outcomes (reductions in birth weight and gestational age) for specific "at risk" maternal occupations using combined data from European birth cohorts and evaluate the heterogeneity between countries in such effects. Based on the occupational codes for job titles, a specific job-exposure matrix will be developed.

Finally, for the POPs and respiratory infections case study we contacted 11 birth cohorts and 7 finally participated. The main objective of this case study was to examine exposure-response associations between biological markers of POPs and respiratory infections and wheezing at early ages (from 0 to 8 years) in order to (i) evaluate the similarity of effects between different cohorts; (ii) calculate summary risk estimates (meta-analysis) and evaluate causal inference; (iii) study possible interactions with other factors (smoking, maternal history of asthma, breastfeeding, fish consumption, etc); and (iv) model dose-response relationships (pooled analysis), if possible.

The overall time framework of case studies was 2 years (end of 2012) and the work has been coordinated by Maribel Casas (POPs and birth outcomes and occupation and birth outcomes) and Mireia Gascon at CREAL, Barcelona (POPs and respiratory infections).

Preliminary results

POPs and birth outcomes

- Multiple imputation of missing values were performed generating 10 datasets for each cohort. Then, a pooled datasets was created.
- Because PCB153 and DDE are measured in different matrices this complicates pooling the data of different cohorts. Therefore, cohort specific conversion factors have been calculated. Generic conversion factors, the same as used in Govarts et al paper, will be applied in a sensitivity analysis to compare results.
- An increase in the level of PCB153 decreases birth weight by 70 g (95% CI -109, -30) but does not effect gestational age. For PCB153 and birth weight there was no threshold and the exposure response was linear. DDE has no effect on birth weight and gestational age.

Maternal occupation and birth outcomes

- Nine occupational sectors were defined as potentially exposed based on ISCO 88 code: health, day-care, cleaning, agriculture, electricity, lab work, food industry, printing and painting, and hairdressers.
- Between 75 and 92% of women declared working during pregnancy on the cohorts and those women appeared to have higher birth weight compared to non-working women. The nine occupational sectors accounted for 44% of total workforce. Cleaning work appeared to be negatively associated with birth weight.

Lessons learned

- Many cohorts were interested and committed to this collaborative project of combined data analyses. European birth cohorts provide in aggregate a unique research resource that can and should be exploited to obtain added value for research objectives that require large datasets.
- Combining data from various cohorts requires careful consideration of the aims, protocols, data, ethical issues, analyses and management, and it is time and labour intensive but potential fruitful
- The combination of data from different cohorts and/or regions around Europe provides an increase in power and more robust results. It allows the evaluation of specific regional effects.
- Most of the cohorts were willing to provide their data in exchange for being part of the work and being included in the paper(s), but some could not participate because of the lack of funding to pay for the data extraction.
- Cohorts were in favour of a centralized pooled approach; it allows combined analyses addressing variables with very heterogeneous assessments across cohorts where a flexible handling of data is essential and an established basis of trust and work experience between participating partners already exists.
- To increase the willingness of birth cohorts to participate in collaborative projects on combined data analyses, financial reimbursement for time and effort to provide previously collected datasets should be considered.

3. Conclusions and Recommendations

Conclusions (extracted from ENRIECO final report):

- There are many pregnancy and birth cohorts in Europe with information on environmental exposures and health outcomes.
- The sizes of the cohorts vary considerably. In the context of the project, it should be noted, however, that studies of environmental contaminant exposures, specially those measuring

exposure biomarkers, cannot cover generally large numbers of subjects, but can still make an important contribution.

- There is fairly good cover of Europe, except Eastern Europe.
- There is considerable expertise and experience associated with the cohorts.
- The cohorts have provided important environmental exposure, health and environmental exposure-response data
- The amount and detail of information provided by cohorts on environment and health differs considerably
- Greater and more efficient use needs to be made of the existing cohort data at the European level to:
    - Provide speedy response to key policy questions
    - Provide speedy response to concerns about “new” environmental exposures
    - Improve understanding of geographical and cultural inequalities in disease, exposure, and health related behaviours
    - Replicate findings with important public health implications in different settings
    - Link with routinely collected environmental and health data
    - Improve methodological approaches, including validated exposure assessment tools, protocols of biological and environmental sample collection and analysis.
    - Improve statistical power through combined analyses
- Cohorts tend to report individually, but recent initiatives have tried to combine data from various cohorts to increase e.g. power (overall and subgroups)
- Existing European birth and mother-child cohorts provide a real potential for combined analyses on pregnancy-related outcomes and child health outcomes in relation to environmental exposures. Table 4 provides an indication of the number of subjects available for exposure-health analyses.
- Combining information from different cohorts appears to be beneficial and increase the value of the cohorts and resulting information
- Combining data from various cohorts requires careful consideration of the aims, protocols, data, ethical issues, analyses and management, and it is time and labour intensive but potential fruitful
- There are currently limited resources to combine existing studies/data

- Follow up of existing cohorts is essential to determine health effects in later life of pre natal and early childhood exposure, for which there is some but not conclusive evidence
- New pregnancy and birth cohorts are needed to evaluate any potential health effects of new environmental exposures, or existing environmental exposures under new conditions. The International Programme of Chemical Safety (http://www.who.int/ipcs/en/) publishes a list of 241 environmental chemicals and the corresponding recommendations for improving research (ie. analytical methods, sources)
- (http://www.who.int/ipcs/publications/ehc/ehc_numerical/en/index.html). Birth cohorts in Europe should use this list to identify new chemicals that could have an effect on children's health.

Recommendations for next 15 years birth cohort research

- Further combining of existing environment and health data to provide more informative, better and robust evidence for any associations, explore any cultural, geographical and socio-economic differences;
- Follow up of existing cohorts to determine health effects in later life of pre natal and early childhood exposure;
- Standardization and improvement of existing environmental exposure assessments. The exposome concept may provide a good framework. Take into account mobility and explore the interaction with physical activity, where appropriate;
- Further work is needed on new and emerging chemical exposures such as phthalates, bisphenol A, PFOS/PFOA, indoor pollutants, and pesticides in relation to growth and obesity, neuropshycological development and cognitive function, allergies, asthma and respiratory infections and puberty and fertility;
- Further work is needed on the risks and benefits of environmental factors such as green space, solar UV, EMF/mobile phones and soundscape/noise in relation to birth outcomes, growth and obesity, neuropsychological development and cognitive function, allergies, asthma and respiratory infections and puberty and fertility;
- Strengthening the evidence base for ETS, outdoor air pollution, POPs, metals in relation to relevant outcomes such as growth and obesity, neuropsychological development and cognitive function, allergies, asthma and respiratory infections and explore the role in puberty and fertility;

- Evaluate the role of mixtures of exposure on birth outcomes, growth and obesity, neuropsychological development and cognitive function, allergies, asthma and respiratory infections and puberty and fertility;
- Initiate new birth cohorts to capture new exposures and new exposure scenarios.

Tables & Annexes

Table 1. European birth cohorts with published work on Environmental exposures (from ENRIECO WP4 reports – available in www.enrieco.org)

Cohort, Country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied outcome*	*Main outcome measured*
BIRTH OUTCOMES						
Second hand tobacco smoke						
Finland	Jaakkola 2001 (Jaakkola et al. 2001)	389	pregnancy	ETS, hair nicotine	birth	Small for gestational age, birth weight
Netherlands	Jaddoe 2008 (Jaddoe et al. 2008a)	7098	pregnancy	Number of cigarettes	birth	Birth weight, gestational age
Poland	Adamek 2005 (Adamek et al. 2005)	1528	pregnancy	ETS	birth	Birth weight
	Jedr ychowski 2004 (Jedrychowski et al. 2004)	362	pregnancy	ETS, $PM_{2.5}$	birth	Birth weight and length, head circumference
	Hanke 2004 (Hanke et al. 2004)	183	pregnancy	ETS, cotinine	birth	Gestational age, birth weight
Smoke-free Newborn Study, Denmark	Hegaard 2006 (Hegaard et al. 2006)	1612	pregnancy	ETS, cotinine	birth	Birth weight
Occupation						
ABCD, Netherlands	Vrijkotte 2009 (Vrijkotte et al. 2009)	7135	pregnancy	Maternal occupation (Dutch Job Content Questionnaire: job demands and job control)	birth	Birth weight, small for gestational age
DNBC, Denmark	Suarez-Varela 2009 (Suarez-Varela et al. 2009)	66866	pregnancy	Hospital workers	birth	Pregnancy outcomes
	Zhu 2006 (Zhu et al. 2006b)	9062	pregnancy	Laboratory work (JEM)	birth	Late fetal loss, multiple births, sex ratio, preterm birth, small for gestational age, birth weight, congenital malformations
	Zhu 2006 (Zhu et al. 2006c)	3766	pregnancy	Hairdressers	birth	Late fetal loss, multiple births, sex ratio, preterm birth, small for gestational age, birth weight, congenital malformations

Cohort, Country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied outcome*	*Main outcome measured*
	Zhu 2005 (Zhu et al. 2005)	7079	pregnancy	Laboratory work (JEM)	birth	Time to pregnancy
	Zhu 2004 (Zhu et al. 2004a)	41769	pregnancy	Shift work; Job stress (DISCO-88)	birth	Late fetal loss
	Zhu 2004 (Zhu et al. 2004b)	10237	pregnancy	Shift work (DISCO-88)	birth	Birth weight, small for gestacional age, preterm birth
	Zhu 2003 (Zhu et al. 2003)	11438	pregnancy	Shift work (DISCO-88)	birth	Time to pregnancy
Generation R, Netherlands	Jansen 2010 (Jansen et al. 2010)	6111	pregnancy	Employment status; weekly working hours	birth	Pregnancy complications
PÉLAGIE, France	Garlantezec 2009 (Garlantezec et al. 2009)	3421	pregnancy	Maternal occupation exposure to solvents; JEM (occupational and industrial code)	birth	Congenital malformations
Prospective Cohort Southampton Women's Survey, UK	Bonzini 2009 (Bonzini et al. 2009)	1327	pregnancy	Working activities (hours, standing/walking, kneeling/squatting, trunk bending, lifting and night shifts)	birth	Preterm delivery, small for gestational age, reduced head or abdominal circumference
				Air pollution		
ABCD, Netherlands	Gehring 2010 (Gehring et al. 2011a)	7600	pregnancy	LUR: NO_2 at the birth address	birth	Birth weight, small for gestational age
				Drinking water		
ALSPAC, UK	Nieuwenhuijsen et al. 2002 (Nieuwenhuijsen et al. 2002)	11462	pregnancy	Amount of swimming hours	birth	Birth weight
DNBC, Denmark	Juhl et al. 2010 (Juhl et al. 2010)	74486	pregnancy	Self-reported exercise data (swimming, bicycling, or no exercise)	birth	Gestational age, congenital malformations
				Persistent Organic Pollutants		
DNBC, Denmark	Halldorsson 2008 (Halldorsson et al. 2008)	100	pregnancy	PCB in serum	birth	Birth and placenta weight
Duisburg, Germany	Cao 2008 (Cao et al. 2008)	104	pregnancy	PCDD, PCB in blood	birth	Testosterone and estradiol in cord blood
HUMIS, Norway	Eggesbø 2009 (Eggesbo et al.	326	birth	HCB in breast milk	birth	Birth weight

Cohort, Country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied outcome*	*Main outcome measured*
	2009)					
INMA-old, Spain	Fernandez 2007 (Fernandez et al. 2007)	164	birth	DDT, lindane, mirex in placenta	birth	Cryptorchidism or hypospadias
INUENDO, Greenland, Poland, Ukraine	Toft 2010 (Toft et al. 2010)	678	pregnancy	PCB, DDE in serum	birth	Fetal loss
INUENDO, Greenland, Poland, Ukraine	Wojtyniak 2010 (Wojtyniak et al. 2010)	1322	pregnancy	PCB, DDE in serum	birth	Birth weight and gestational age
PCB cohort, Slovakia	Sonneborn 2008 (Sonneborn et al. 2008)	1057	pregnancy	PCB in serum	birth	Birth weight
			Metals			
ALSPAC, UK	Daniels 2007 (Daniels et al. 2007)	8415	pregnancy, birth	Maternal dental history (mercury), mercury in cord tissue	birth	Gestational age, birth weight
EDEN, France	Drouillet-Pinard 2010 (Drouillet-Pinard et al. 2010)	691	pregnancy	Mercury and selenium in maternal hair, Food Frequency Questionnaire	birth	Birth weight and length, head circumference, tricipital skin folds, subscapular skin folds, ultrasound
INMA-new, Spain	Ramón 2009 (Ramon et al. 2009)	554	pregnancy, birth	Mercury in cord blood, Food Frequency Questionnaire	birth	Birth weight and length, small for gestational age
UK	Marriott 2007 (Marriott et al. 2007)	68	birth	Zinc, Selenium, Manganese, Copper in blood	birth	Birth weight, head circumference
			Pesticides			
DNBC, Denmark	Zhu 2006 (Zhu et al. 2006a)	62604	pregnancy	Gardeners and farmers (pesticides)	birth	Late fetal loss, multiple births, sex ratio, preterm birth, small for gestational age, birth weight, congenital malformations
Poland	Hanke 2003 (Hanke et al. 2003)	104	pregnancy	Use of pesticides (occupational and non-occupational)	birth	Birth weight
			Noise			
ELSPAC, Czech republic	Hruba 1999 (Hruba et al. 1999)	3897	pregnancy	Occupational noise	birth	Intrauterine growth retardation, head circumference, congenital malformations
Finland	Hartikainen-Sorri 1994	292	pregnancy	Occupational noise	birth	Birth weight, gestational age

Cohort, Country	Author, Year	N children	Age exposure assessment	Main exposure measured	Age studied outcome	Main outcome measured
	(Hartikainen et al. 1994)					
NEUROPSYCHOLOGICAL DEVELOPMENT/COGNITIVE FUNCTION						
			Metals			
ALSPAC, UK	Daniels 2007 (Daniels et al. 2007)	7375	prenatal	maternal dental history, mercury levels	15 mo	language development
	Chandramouli 2009 (Chandramouli et al. 2009)	488	30 mo	lead levels	7-8 yrs	development, behaviour, education
Faroes, Faroe Islands	Julvez 2010 (Julvez et al. 2010)	878	birth, 7, 14 yrs	mercury levels	14 yrs	attention function, time speed processing
	Choi 2008 (Choi et al. 2008)	1204	birth	mercury levels	7 yrs	different neuropsychological domains
INMA-old, Spain	Freire 2010 (Freire et al. 2010)	72	4 yrs	mercury levels, fish intake	4 yrs	cognitive development
Krákow cohort, Poland	Jedrychowski 2008 (Jedrychowski et al. 2008)	452	birth	lead levels	6 mo	visual recognition memory
	Jedrychowski 2009 (Jedrychowski et al. 2009b)	444	birth	lead levels	12, 24, 36 mo	cognitive development
	Jedrychowski 2009 (Jedrychowski et al. 2009a)	457	birth	lead levels	12, 24, 36 mo	cognitive development
			Persistent Organic Pollutants			
DNBC, Denmark	Fei 2008 (Fei et al. 2008)	1400	pregnancy	PFOS, PFOA levels	birth, 6-18 mo	development milestones
Dutch PCB/Dioxin study, The Netherlands	Huisman 1995 (Huisman et al. 1995a)	418	pregnancy, birth	PCBs, PDCC/Fs levels	10-24 d	neurological optimality
	Huisman 1995 (Huisman et al. 1995b)	418	pregnancy, birth	PCBs levels	18 mo	neurological optimality
	Koopman-Essenboom 1996 (Koopman-Esseboom et al. 1996)	207	pregnancy, birth	PCBs levels	3, 7, 18 mo	cognitive development
	Lanting 1998 (Lanting et al. 1998)	394	pregnancy, birth	PCBs levels	42 mo	motor development, neurological optimality
	Patandin 1999 (Patandin et al. 1999)	395	pregnancy, birth	PCBs levels	42 mo	cognitive development
	Vreugdenhil 2002 (Vreugdenhil et al. 2002a)	372	pregnancy, birth	PCBs levels	6.5 yrs	cognitive development
	Vreugdenhil 2002	207	pregnancy,	PCBs levels	6.8 yrs	play behaviour

Cohort, Country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied outcome*	*Main outcome measured*
	(Vreugdenhil et al. 2002b)		birth			
	Vreugdenhil 2004 (Vreugdenhil et al. 2004)	83	pregnancy, birth	PCBs levels	9 yrs	different neuropsychological domains
	Walkowiak 2001 (Walkowiak et al. 2001)	171	pregnancy, birth	PCBs levels	7, 18, 30, 42 mo	cognitive development, home environment
Duisburg, Germany	Wilhelm 2007 (Wilhelm et al. 2008)	189	pregnancy, birth	PCBs, PDCC/Fs levels	2 w & 18 mo	neurological optimality, cognitive development
Faroes, Faroe Islands	Steuerwald 2000 (Steuerwald et al. 2000)	182	birth	PCBs levels	2 w	neurological optimality
	Grandjean 2001 (Grandjean et al. 2001)	435	birth	PCBs levels	7 yrs	different neuropsychological domains
Germany	Winneke 2005 (Winneke et al. 2005)	70	pregnancy, birth	PCBs levels	72 mo	home environment, cognitive development
Groningen infant COMPARE, The Netherlands	Roze 2009 (Roze et al. 2009)	62	pregnancy	organohalogens including BFRs levels	5-6 yrs	cognition, motor performance, behaviour
INMA-old, Spain	Gascon 2011 (Gascon et al. 2011)	482	birth	PBDEs levels	4 yrs	cognition, ADHD-like symptoms, social competence
	Puertas 2009 (Puertas et al. 2010)	104	birth	mirex levels	4 yrs	cognitive development
	Ribas-Fitó 2007 (Ribas-Fito et al. 2007)	475	birth	HCB levels	4 yrs	behaviour, ADHD-like symptoms
	Ribas-Fitó 2006 (Ribas-Fito et al. 2006b)	475	birth	DDT/DDE levels	4 yrs	cognitive development
	Ribas-Fitó 2003 (Grandjean et al. 2001; Ribas-Fito et al. 2003)	92	birth	DDE, PCBs, HCB levels	13 mo	cognitive development
PCB cohort, Slovakia	Park 2009 (Park et al. 2009)	147	birth	6 congeners of OH-PCBs levels	16 mo	cognitive development
	Park 2010 (Park et al. 2010)	760	birth	dioxin-like PCB, non-dioxin-like PCB, antiestrogenic PCBs levels	16 mo	cognitive development
ALLERGY AND ASTHMA						
Visible mould						
AirAllerg, Germany & Netherlands	Tischer 2010 (Tischer et al. 2011)	358	6y	Visible mould; (1,3)-ß-D-glucan and EPS from children's mattress	6 yrs	Asthma, wheeze, allergic rhinitis, Rhinoconjunctivitis
ALSPAC, UK	Baker and Henderson 1999	1954	6m	Visible mould	6 mo	Wheeze

Cohort, Country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied outcome*	*Main outcome measured*
	(Baker and Henderson 1999)					
BAMSE, Sweden	Emenius 2004 (Emenius et al. 2004)	4089	1y	Visible mould	2 yrs	Wheeze
PASTURE, Finland	Karvonen 2009 (Karvonen et al. 2009)	396	2m	Mould spots indoor, visible mould indoor	1 yrs	Wheeze, cold
PIAMA, Netherlands	Douwes 2006 (Douwes et al. 2006)	696	3m	(1,3)-ß-D-glucan from living-room floor; EPS-Pen/Asp	0-4 yrs	Asthma, wheeze
				Air pollution		
GINIplus and LISAplus, Germany	Krämer 2009 (Kramer et al. 2009)	2753	birth, 6y	LUR: NO_2, $PM_{2.5}$, soot at the home address, distance of home from major road	6 yrs	Asthma/asthmoid/spastic/obstructive bronchitis, hay fever, atopic eczema, allergic sensitization
Oslo birth cohort, Norway	Oftedal 2009 (Oftedal et al. 2009)	3533	birth, 12m	Dispersion model: NO_2, and distance of home from major road	9 yrs	Asthma, wheeze, dry cough
PIAMA, Netherlands	Gehring 2010 (Gehring et al. 2010)	3863	birth, 6y	LUR: NO_2, $PM_{2.5}$, soot at the home address, distance of home from major road	1-8 yrs	Asthma, hay fever, atopic eczema, allergic sensitization, wheeze, bronchial hyperresponsiveness
	Kerkhof 2010 (Kerkhof et al. 2010)	916	birth, 6y	LUR: NO_2, $PM_{2.5}$, soot at the home address, distance of home from major road	1-8 yrs	Asthma
	Gehring in press (Gehring et al. 2011b)	4146 women 3863 children	pregnancy; 0-8y	LUR: NO_2, $PM_{2.5}$, soot at the birth address	1-8 yrs	Dry night cough
Poland	Jedrychowski 2007	275	3y	Indoor moulds	3 yrs	Wheeze
				OBESITY		
				Endocrine-disrupting chemicals		
INMA-old, Spain	Smink 2008 (Smink et al. 2008)	482	pregnancy	HCB levels	birth, to 6.5 yrs	Birth weight and height
Belgium	Verhulst 2008 (Verhulst et al. 2009)	138	birth	HCB, DDE, PCBs and dioxin-like compounds levels	1- 3 yrs	BMI

Cohort, Country	*Author, Year*	*N children*	*Age exposure assessment*	*Main exposure measured*	*Age studied outcome*	*Main outcome measured*
The Netherlands	Patandin 1998 (Patandin et al. 1998)	207	pregnancy	PCBs levels		Birth weight and height, head circumference

Table 2. General description of European birth cohorts with data on Environmental exposures (n=43)

	Birth Cohort	*Full name and key reference*	*Country*	*Regions covered*	*Enrolment period*	*N children*
1.	Aarhus Birth Cohort	(Hedegaard et al. 1993)	Denmark	Denmark	1990-ongoing	93000
2.	ABCD	Amsterdam Born Children and their Development study (van Eijsden et al. 2010)	Netherlands	Amsterdam	2003-2004	7863
3.	ALSPAC	The Avon Longitudinal Study of Parents and Children (Golding et al. 2001)	UK	Bristol	1991-1992	14062
4.	ArcRisk-Norway	Impacts on health in the Arctic and Europe owing to climate-induced changes in contaminant cycling	Norway	Troms, Finnmark and Nordland	2007-2009	430
5.	BAMSE	The Stockholm Children Allergy and Environmental Prospective Birth Cohort Study (Wickman et al. 2002)	Sweden	Stockholm	1994-1996	4089
6.	BiB	Born in Bradford (Raynor 2008)	UK	Bradford	2007-2010	13000
7.	Children of Ukraine	(Hryhorczuk et al. 2009)	Ukraine	Kyiv, Dniprodzerzhynsk, Mariupol	1992-1996	4510
8.	Co.N.ER	Cohort of newborns in Emilia Romagna (Porta 2006)	Italy	Bologna	2004-2005	654
9.	Czech	Czech Republic Early Childhood Health	Czech Republic	Teplice and Prachatice	1994-1999	7577
10.	DARC	The Danish Allergy Research Centre cohort (Johnke et al. 2005)	Denmark	Odense	1998-1999	562
11.	DNBC	Danish National Birth Cohort (Olsen et al. 2001)	Denmark	Denmark	1996-2002	96986

	Birth Cohort	*Full name and key reference*	*Country*	*Regions covered*	*Enrolment period*	*N children*
12.	Duisburg	Duisburg cohort (Wilhelm et al. 2008)	Germany	Duisburg	2000-2003	234
13.	EDEN	Study of determinants of pre and postnatal developmental, psychomotor development and child health (Drouillet et al. 2009)	France	Nancy, Poitiers	2003-2006	1873
14.	ELFE	French longitudinal study of children (Vandentorren et al. 2009)	France	France	2011-2012	20000
15.	Faroes [a]	Children's Health and the Environment in the Faroes (Grandjean et al. 1992; Grandjean et al. 1997)	Faroe Islands	Faroe Islands	1986-2009	2351
16.	FLEHS I	Flemish Environment and Health Survey (Koppen et al. 2009)	Belgium	Flanders	2002-2004	1196
17.	GASPII	Gene and Environment: Prospective Study on Infancy in Italy (Porta et al. 2007))	Italy	Rome	2003-2004	708
18.	Generation R	Generation R (Jaddoe et al. 2008b)	Netherlands	Rotterdam	2001-2006	9778
19.	Generation XXI	Generation XXI (Pinto et al. 2009)	Portugal	Porto	2004-2006	8666
20.	GINIplus	German Infant Nutritional Intervention study - plus (Zirngibl et al. 2002)	Germany	Münich, Wesel	1995-1998	5991
21.	HUMIS	Norwegian Human Milk Study (Eggesbo et al. 2009)	Norway	Norway	2002-2009	2500
22.	INMA old [b]	Environment and Childhood (Ribas-Fito et al. 2006a)	Spain	Granada, Menorca, Ribera d'Ebre	1997-2002	1252
23.	INMA new [c]	Environment and Childhood (Ribas-Fito et al. 2006a)	Spain	Asturias, Gipuzkoa, Sabadell, Valencia	2003-2008	2505
24.	INUENDO [d]	Biopersistent organochlorines in diet and human fertility (Toft et al. 2005)	Greenland, Sweden, Poland, Ukraine	Greenland, Sweden (east & west coast), Warsaw (Poland), Kharkiv (Ukraine)	2002-2004	1322
25.	KANC	Kaunas cohort (Grazuleviciene et al. 2009)	Lithuania	Kaunas	2007-2009	4000
26.	KOALA	Child, parents and health: lifestyle and genetic constitution (Kummeling et al. 2005)	Netherlands	Southern Netherlands	2000-2003	2834
27.	Kraków	Krákow cohort (Jedrychowski et al. 2003)	Poland	Kraków	2001-2004	505
28.	Leicester [e]	Leicester Respiratory Cohorts (Kuehni et al. 2007)	UK	Leicestershire and Rutland	1985-1993	10350
29.	LISAplus	Influences of life-style related factors on the immune system	Germany	Münich, Wesel, Leipzig, Bad Honneff	1997-1998	3097

	Birth Cohort	Full name and key reference	Country	Regions covered	Enrolment period	N children
		and the development of allergies in childhood - plus (Heinrich et al. 2002)				
30.	LUKAS	LUKAS (Karvonen et al. 2009)	Finland	Kuopio, Jyväskylä, Joensuu and Iisalmi	2002-2005	442
31.	MAS	Multicentre Allergy Study (Bergmann et al. 1994)	Germany	Berlin, Duesseldorf, Freiburg, Mainz, Munich	1990	1314
32.	MAAS	The National Asthma Campaign Manchester Asthma and Allergy Study (Custovic et al. 2002)	UK	Manchester	1995-1997	1211
33.	MoBa	The Norwegian Mother and Child Cohort Study (Magnus et al. 2006)	Norway	Norway	1999-2008	107000
34.	MUBICOS	Multiple Births Cohort Study	Italy	Turin, Trieste, Bologna, Pisa, Rome, Foggia and Palermo	2009	1000
35.	NINFEA	Birth and Infancy: Effects of the Environment (Richiardi et al. 2007)	Italy	Italy	2005+	7500
36.	Northern Adriatic Cohort	(Barbone et al. 2004)	Italy	North Eastern Italy	1999-2001	243
37.	PARIS	Pollution and Asthma Risk: an Infant Study(Clarisse et al. 2007)	France	Paris	2003-2006	3840
38.	PCB cohort	Early Childhood Development and PCB exposures in Slovakia (Sonneborn et al. 2008)	Slovakia	Michalovce, Stropkov, Svidnik	2001-2003	1134
39.	PÉLAGIE	Endocrine disruptors: Longitudinal study on pregnancy abnormalities, infertility, and childhood (Guldner et al. 2007)	France	Brittany	2002-2006	3460
40.	PIAMA	Prevention and Incidence of Asthma and Mite Allergy (Brunekreef et al. 2002)	Netherlands	Northern, Western and Central parts	1996-1997	3963
41.	REPRO_PL	Polish Mother and Child Cohort (Polanska et al. 2009)	Poland	Lodz, Wroclaw, Lask, Kielce, Katowice, Legnica, Lublin, Szczecin, Piekary Slaskie	2007-2011	1800
42.	RHEA	Mother Child Cohort in Crete (Chatzi et al. 2009)	Greece	Heraklion, Crete	2007-2008	1500
43.	Trieste	PHIME study: Trieste cohort	Italy	Trieste	2007-2009	900

[a] The Faroes cohorts consist of 4 sub-cohorts: cohort 1 (enrolment: 1986-1987; N=1022), cohort 2 (enrolment: 1994-1995; N=182), cohort 3 (enrolment: 1997-2000, N=656), cohort 5 (enrolment: 2007-2009, N=491)

[b] INMA-old consists of 3 sub-cohorts: Granada (enrolment: 2000-2002; N=668), Menorca (enrolment: 1997-1998; N=482), Ribera Ebre (enrolment: 1997-1999; N=102)

[c] INMA-new consists of 4 sub-cohorts: Asturias (enrolment: 2004-2007; N=485), Gipuzkoa (enrolment: 2006-2008; N=611), Sabadell (enrolment: 2004-2007; N=622), Valencia (enrolment: 2003-2005; N=787)

[d] INUENDO consists of 4 sub-cohorts: Greenland, Sweden (east & west coast), Warsaw (Poland), Kharkiv (Ukraine)

[e] The Leicestershire Respiratory Cohorts consist of 2 subcohorts: The Leicester 1990 cohort (enrolment 1985-1989; N=1650) and the Leicester 1998 cohort (enrolment 1993-1997; N=8700)

Table 3. Assessment of exposures in the European birth cohorts included in the ENRIECO inventory (n=34)

Cohort	*Outdoor air pollution*	*Water contamin.*	*Allergens & biol. organisms*	*Metals*	*Pesticides* [b]	*POPs* [c]	*Other chemicals* [d]	*Radiation*	*Smoking &SHS* [e]	*Noise*	*Occupation*
ABCD	M			Q	Q			Q*, M*, E*	Q		Q
ALSPAC			Q	B	Q	B*		Q, G	B,Q	E,Q	Q
ArcRisk-Norway				B		B			Q		Q
BAMSE	E, M,S		E,Q						B, E ,Q		Q
BiB	E,M	E, Q, B							Q		Q
Co.N.ER	S*		Q						Q	Q	Q
Czech	E								B,Q		Q
DARC	S		Q						Q		Q
DNBC	M, S		Q		Q		B	Q	Q		Q
Duisburg	S	Q	Q*	B		B	B		B*, Q		Q
EDEN	E, M, S	E*, Q		B			B	Q	B,Q		Q
ELFE	E*, M*	E*, Q*	E*	B*, Q*	B*,Q*	B*	B*, E*,Q*	G*,M*, Q*	B*, Q*		Q*
Faroes											
Cohort I				B, Q		B			Q		Q
Cohort II				B,Q		B			Q		Q
Cohort III				B		B			Q		Q
Cohort V				B*, Q	Q	B*	B*		Q		Q
FLEHS	E, S		Q	B, Q	Q	B			Q		Q
GAPS II	M, S		Q						Q	M,Q	
Generation R	M		Q		B*,E,Q	B*	B, Q		Q	M,Q	B,Q
Generation XXI			Q						Q		Q
GINIplus	M		E,Q						B, E,Q		
HUMIS	S		Q	Q	Q	B	B	Q	Q		Q
INMA old											
Granada	E, M, S	E, Q, B	Q	B, Q	Q	B	B, Q	Q	B,Q	Q	Q
Menorca	M*		Q, E	B*		B	B	Q	Q		Q
Ribeira Ebre		E	Q	B*		B	B*	Q*	B*,Q		Q
INMA new											

Asturias	E, M, S	E, Q	E,Q	B, Q	Q	B	B, Q	Q	B* ,Q	Q	Q
Gipuzkoa	E, M, S	E, Q	Q	B, Q	Q	B	B, Q	Q	B* ,Q	Q	Q
Sabadell	E, M, S	E, Q	E,Q	B, Q	Q	B	B, Q	Q	B* ,Q	Q	Q
Valencia	E, M, S	E, Q	Q	B, Q	Q	B	B, Q	Q	B* ,Q	Q	Q
INUENDO				B*	Q*	B*	B		B* ,Q		Q
KANC	M	E, Q							Q	M*,Q	Q
KOALA		Q	Q					Q*	Q	Q	Q
Krákow	E,S		E,Q	B	Q	B	E		B,Q		Q
Leicester	M, S		Q						Q		Q
LISAplus	M, S		E,Q		Q*				B, E,Q	M*,Q	
LUKAS			E,Q	B	Q	B	B, Q		Q		Q
MAS			E,Q						B,Q	Q	Q
MoBa	M*	Q	Q	B*, Q	B,Q	B*	B	Q	Q	Q	Q
NINFEA	M*, S		Q	Q	Q		Q*	Q*	Q	Q*	Q
PARIS	E,M	Q	E,Q						E,Q		Q
PCB cohort				B	Q	B	B*		Q		Q
PÉLAGIE		B,E,Q		B	B,E,Q	B	B		Q		Q
PIAMA	M, S		E,Q						E,Q		
REPRO_PL	B, E*, S		Q	B		B*			B,Q	Q	Q
RHEA	M, S	E,Q	Q	B	Q	B*	B*	Q	B,Q	Q	B,Q

[a] Information presented in the table may differ from information presented in the full working group reports because the latest version of the inventory database was used here and reports were based on an earlier version of the database

[b] Organochlorine pesticides are under POPs; [c] Persistent Organic Pollutants; [d] brominated flame retardants, perfluorinated compounds, phthalates and phenols; [e] SHS = second hand tobacco smoke, includes prenatal and postnatal active and passive smoking

B: biomonitoring, E: Environmental monitoring (routine data and/or individual measurements), G: Geographical data; M: Modelling, Q: questionnaires; S: surrogate variables from questionnaires and/or Geographical Information Systems;

* planned

Table 4. Available number of subject for specific exposure-health analyses in European birth cohorts

Outcomes\ Exposures		Air pollution Outdoor (dispersion and/or LUR)		Water contamination	Allergens & biological organisms		Metals		Pesticides		POPs		Other chemicals		Radiations		Smoking	Noise		Occupation	
		NO_2/NO_x	$PM_{2.5}$	DBPs	Pets	House dust mite	Hg	Pb	House home use	Occupational exposure	PCBs	DDT/ DDE	BPA	Phthalates	EMF	Ioninzing		Objective	Subjective	History	Exposures
Birth outcomes	Time to pregnancy	55569	49454	18286	152541	2731	12638	7370	17797	10598	4777	4776	2358	2605	71438	144869	176453		72838	182211	9692
	Congenital malfo.	79046	70432	4010	164745	?	7208	7208	16179	10478	2179	2179	1597	1096	102641	196308	221500		100719	232570	10871
	Fetal loss (≥ 26 weeks)	78448	68021	6527	150766	0	3941	3320	5493	12866	4105	3648	1597	1696	104517	199702	204164		109002	216872	6511
	Preterm birth	62362	42935	22904	177893	376	10759	9416	18055	20644	6433	4954	1488	1187	103913	205080	234338		109491	263690	19511
	Premature rupture of membranes	58399	34972	14880	100863	858	10438	9416	23445	20050	5269	2250	1698	981	1883	103050	143067		11329	141262	16533
	Birth weight	91836	30448	44988	120120	5765	8767	10692	27055	22144	6771	7278	3917	3696	104517	119408	168340		110367	182447	19913
Neuro development	Intelligence quotient	1520	?	220	985	482	861	378	1324	635	1322	1122	760	482	?	?	3747	0	220	4047	1111
	Attention deficit and hyperactivity	4453	3233	220	13165	482	1502	680	1171	482	1764	1764	482	482	?	6750	16074	?	9470	12841	7232
Asthma/ Allergy	Wheeze (0-3 years)	45879	43748	220	89443	5806	582	100	1857	855	1155	1155	482	852	0	7125	134787	1899	5504	117355	9107
	Asthma (7-10 years)	28800	28799	?	84445	4788	1035	580	8700	?	1035	1035	0	?	0	0	122349	1398	12939	108217	0
	Spirometry (6-10 years)	5859	5639	220	9199	2115	482	0	5482	482	355	355	482	482	0	?	11121	80	5220	7937	482
	Eczema (2-5 years)	43724	41904	880	107825	5879	2308	680	18913	855	2801	2855	1080	1402	?	7125	149964	1979	25811	127976	14131
	Allergic rhinitis (6-10	12746	29823	?	141366	5465	1150	680	15000	250	1641	1599	104	386	0	0	170837	80	16700	164284	1136
	Allergic sensitization (6-10 years)	5759	5759	?	11498	2929	90	90	7176	176	90	90	90	266	0	?	13455	0	7520	10186	90
Child growth and puberty	BMI (2-5 years)	50227	46892	2220	130599	4729	1650	810	3954	280	1610	2133	864	966	?	6750	175176	600	11570	159317	16391
	Waist circum. (2-5 years)	5594	5000	594	6294	?	500	0	594	0	200	?	480	350	?	0	7594	0	594	8394	6094
	Puberty	23962	23742	?	52333	2983	900	580	?	?	900	900	?	0	0	0	55900	0	700	53300	0

Figure 1. Geographical distribution of European birth cohorts with data on Environmental exposures (n=42)

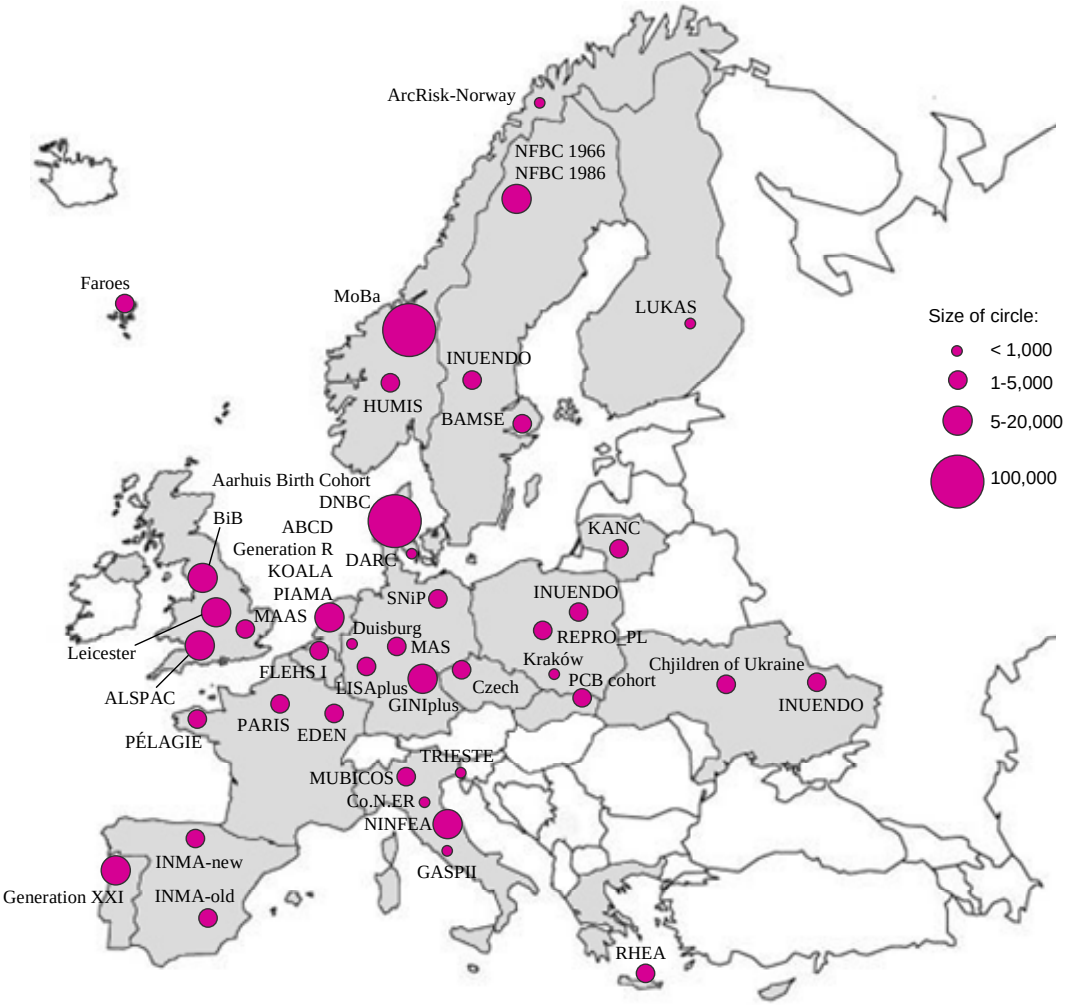
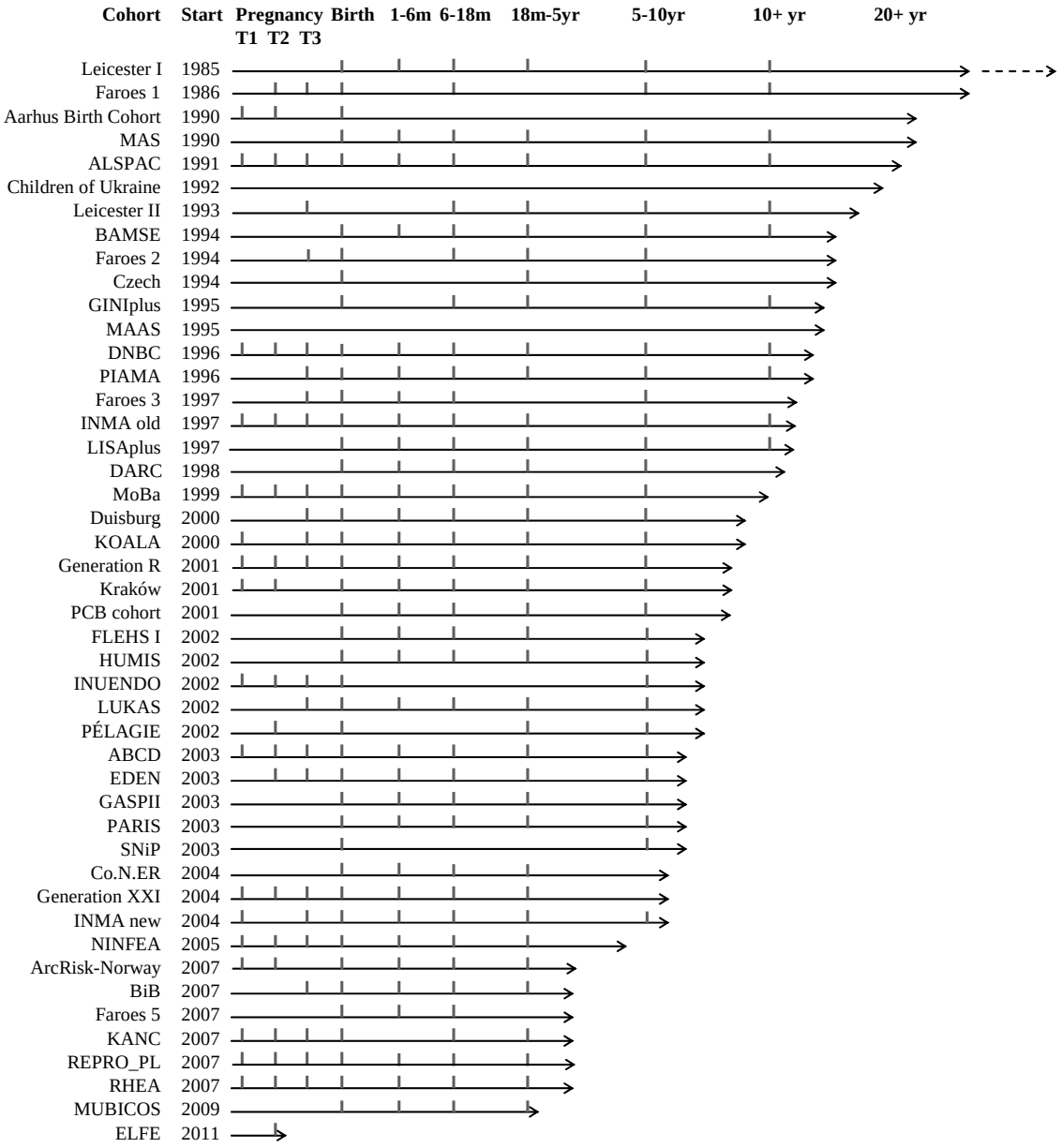


Figure 2. Start of enrolment and time points of follow-up [a] (vertical bars) of European birth cohorts with data on Environmental exposures (n=39*)



[a] These are points in predefined periods. Some cohorts have many more (e.g. yearly) follow-points that are not reflected in this figure. The 4 Faroes cohorts and the 2 Leicester cohorts are shown separately as they have different time lines.

* Children of Ukraine, MASS, Northern Adriatic Cohort, and Trieste cohorts not included.

Annex 1 Exposure assessment in European birth cohorts

Table 1. Description of exposure assessment in the European birth cohorts included in the ENRIECO inventory by exposure topic

Exposure topic	*N* [a]	*Description*
Outdoor air pollution	23	• Many cohorts assessed outdoor air pollution exposure • Air pollution modeling is becoming increasingly the method of choice: land-use regression modeling (15 cohorts) and dispersion modeling (8 cohorts) • Fourteen cohorts are currently participating in the collaborative EU-funded ESCAPE project that adds land-use regression modeling of nitrogen oxides, particulate matter, soot and particle composition to existing cohort studies using a standardized protocol • Most cohorts currently have data on exposure during pregnancy and/or early life
Water contamination	11	• Disinfection by-products were studied most • Exposure assessment usually by means of a combination of questionnaires and individual measurements or routinely collected measurement data • Validation by means of biomonitoring in a small number of subjects • Most studies assessed exposure during pregnancy
Allergens & biological organisms	27	• Exposure to cat and dog allergen was assessed by means of questionnaires in all cohorts; by means of measurements in house dust samples in 7 cohorts • Mite allergen levels were measured in settled house dust samples in 7 cohorts • Mould exposure was mainly assessed by means of questionnaires (14 cohorts) • Exposure was assessed during infancy and/or early childhood in most studies
Metals	14	• Most cohorts have analyzed the effects of low-level environmental exposure to Hg and Pb; little attention to other metals (As, Cd, etc) • There are well-standardized protocols for most of the metals • The ICP-MS and the AAS analytical techniques were used most • Most measurements were performed in cord blood; other non-invasive matrices such as hair and urine are gaining attention

Exposure topic	*N* [a]	*Description*
Pesticides	17	• Many studies assessed household use (13cohorts); fewer studies assessed occupational (10 cohorts) or dietary exposure (7 cohorts) • Exposure was mainly assessed by means of questionnaires
Emerging exposures	17	• Few cohorts have measured emerging contaminants, but this is a rapidly developing field and many cohorts are planning to assess exposure to emerging contaminants • There is heterogeneity with regard to the type of biological media used and the timing of the exposure measurements
Radiations	11	*Non-ionizing radiations* • *Mainly assessed by questionnaire:* maternal occupational exposures (3 cohorts), prenatal medical ionising radiation exposures (6 cohorts); 2 cohorts currently plan to ask questions about medical radiation exposures in children • 1 cohort is planning to assess residential radon exposure using geographical methods • No standardised questionnaires or protocols in this field *UV* • Only *six* cohorts are collecting UV-related data through questionnaire questions on sunburn in children, use of sunbeds during pregnancy, and time spent outdoors. • *None* of the cohorts collect data on maternal and child skin type, sunscreen use, or clothing. • Standard questionnaires are not available. *Non-ionizing radiations* • Very few cohorts assess exposure to non-ionising radiations: 2 cohorts include occupational EMF exposure in their questionnaires, 2 cohorts assess ELF exposure to overhead high-voltage power lines through geographical information from electricity companies, 2 cohorts include questions about mobile phone use of the mother during pregnancy and 4 on children's mobile phone use. • A few cohorts have started using base-station maps combined with information from home appliances and personal RF exposimeters, in order to estimate whole body RF/ELF-EMF exposure. • There are no standardised or validated questionnaires, models or protocols in use at this moment.
Smoking and second hand tobacco smoke	34	• All cohorts have information about exposure during pregnancy and 30 cohorts in addition assessed exposure at different periods during infancy and childhood

Exposure topic	*N* [a]	*Description*
		• Assessment mainly by questionnaire; cotinine measurements in biological samples (mainly urine) in 9 cohorts
Persistent organic pollutants	13	• Exposure assessment by means of high performance liquid chromatography (HPLC) measurements in biological samples with adjustment for lipid content • Variation between studies with regard to sampling medium, timing of sample collection and lipid adjustment • Most data available for polychlorinated biphenyl (PCB) and dichlorodiphenyltrichloroethane (DDT)
Noise	16	• All cohorts used questionnaire assessments, mainly annoyance (n=15) • 5 cohorts used noise propagation modeling or noise maps • Traffic is the source of noise that has been studied most • Most cohorts assessed exposure during pregnancy
Occupational exposures	29	• All cohorts have information on maternal occupation and most cohorts (n=25) have information on paternal occupation at least one point in time • Data mainly collected by means of questionnaires (most often job title; sometimes checklist occupation) • Coding of maternal job title by Job Exposure Matrices (JEM) planned/done in a number of studies (n=16)

[a]N = Number of ENRIECO cohorts with exposure assessment

Reference list

Adamek R, Florek E, Piekoszewski W, Anholcer A, Kaczmarek E. 2005. [Effect of exposure to tobacco smoke and selected socioeconomic factors in occurrence of low birth weight]. Przegl Lek 62:965-969.

Baker D, Henderson J. 1999. Differences between infants and adults in the social aetiology of wheeze. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. J Epidemiol Community Health 53:636-642.

Barbone F, Valent F, Pisa F, Daris F, Fajon V, Gibicar D et al. 2004. Prenatal low-level methyl mercury exposureand child development in an Italian coastal area. Seychelles Medicaland Dental Journal Special Issue 7.

Bergmann RL, Bergmann KE, Lau-Schadensdorf S, Luck W, Dannemann A, Bauer CP et al. 1994. Atopic diseases in infancy. The German multicenter atopy study (MAS-90). Pediatr Allergy Immunol 5:19-25.

Bonzini M, Coggon D, Godfrey K, Inskip H, Crozier S, Palmer KT. 2009. Occupational physical activities, working hours and outcome of pregnancy: findings from the Southampton Women's Survey. Occup Environ Med 66:685-690.

Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM et al. 2009. Prenatal bisphenol A exposure and early childhood behavior. Environ Health Perspect 117:1945-1952.

Brunekreef B, Smit J, de Jongste J, Neijens H, Gerritsen J, Postma D et al. 2002. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. Pediatr Allergy Immunol 13 Suppl 15:55-60.

Cao Y, Winneke G, Wilhelm M, Wittsiepe J, Lemm F, Furst P et al. 2008. Environmental exposure to dioxins and polychlorinated biphenyls reduce levels of gonadal hormones in newborns: results from the Duisburg cohort study. Int J Hyg Environ Health 211:30-39.

Chandramouli K, Steer CD, Ellis M, Emond AM. 2009. Effects of early childhood lead exposure on academic performance and behaviour of school age children. Arch Dis Child 94:844-848.

Chatzi L, Plana E, Daraki V, Karakosta P, Alegkakis D, Tsatsanis C et al. 2009. Metabolic syndrome in early pregnancy and risk of preterm birth. Am J Epidemiol 170:829-836.

Choi AL, Budtz-Jorgensen E, Jorgensen PJ, Steuerwald U, Debes F, Weihe P et al. 2008. Selenium as a potential protective factor against mercury developmental neurotoxicity. Environ Res 107:45-52.

Clarisse B, Nikasinovic L, Poinsard R, Just J, Momas I. 2007. The Paris prospective birth cohort study: which design and who participates? Eur J Epidemiol 22:203-210.

Custovic A, Simpson BM, Murray CS, Lowe L, Woodcock A. 2002. The National Asthma Campaign Manchester Asthma and Allergy Study. Pediatr Allergy Immunol 13 Suppl 15:32-37.

Daniels JL, Rowland AS, Longnecker MP, Crawford P, Golding J. 2007. Maternal dental history, child's birth outcome and early cognitive development. Paediatr Perinat Epidemiol 21:448-457.

Douwes J, van Strien R, Doekes G, Smit J, Kerkhof M, Gerritsen J et al. 2006. Does early indoor microbial exposure reduce the risk of asthma? The Prevention and Incidence of Asthma and Mite Allergy birth cohort study. J Allergy Clin Immunol 117:1067-1073.

Drouillet P, Kaminski M, Lauzon-Guillain B, Forhan A, Ducimetiere P, Schweitzer M et al. 2009. Association between maternal seafood consumption before pregnancy and fetal growth: evidence for an association in overweight women. The EDEN mother-child cohort. Paediatr Perinat Epidemiol 23:76-86.

Drouillet-Pinard P, Huel G, Slama R, Forhan A, Sahuquillo J, Goua V et al. 2010. Prenatal mercury contamination: relationship with maternal seafood consumption during pregnancy and fetal growth in the 'EDEN mother-child' cohort. Br J Nutr 104:1096-1100.

Eggesbo M, Stigum H, Longnecker MP, Polder A, Aldrin M, Basso O et al. 2009. Levels of hexachlorobenzene (HCB) in breast milk in relation to birth weight in a Norwegian cohort. Environ Res 109:559-566.

Emenius G, Svartengren M, Korsgaard J, Nordvall L, Pershagen G, Wickman M. 2004. Indoor exposures and recurrent wheezing in infants: a study in the BAMSE cohort. Acta Paediatr 93:899-905.

Fei C, McLaughlin JK, Lipworth L, Olsen J. 2008. Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and maternally reported developmental milestones in infancy. Environ Health Perspect 116:1391-1395.

Fernandez MF, Olmos B, Granada A, Lopez-Espinosa MJ, Molina-Molina JM, Fernandez JM et al. 2007. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case-control study. Environ Health Perspect 115 Suppl 1:8-14.

Freire C, Ramos R, Lopez-Espinosa MJ, Diez S, Vioque J, Ballester F et al. 2010. Hair mercury levels, fish consumption, and cognitive development in preschool children from Granada, Spain. Environ Res 110:96-104.

Garlantezec R, Monfort C, Rouget F, Cordier S. 2009. Maternal occupational exposure to solvents and congenital malformations: a prospective study in the general population. Occup Environ Med 66:456-463.

Gascon M, Vrijheid M, Martinez D, Forns J, Grimalt JO, Torrent M et al. 2011. Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. Environ Int 37:605-611.

Gehring U, van Eijsden M, Dijkema MB, van der Wal MF, Fischer P, Brunekreef B. 2011a. Traffic-related air pollution and pregnancy outcomes in the Dutch ABCD birth cohort study. Occup Environ Med 68:36-43.

Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M et al. 2010. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. Am J Respir Crit Care Med 181:596-603.

Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M et al. 2011b. Traffic-related air pollution and dry night cough during the first 8 years of life. Pediatr Allergy Immunol 22:85-86.

Golding J, Pembrey M, Jones R. 2001. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. Paediatr Perinat Epidemiol 15:74-87.

Grandjean P, Bellinger D, Bergman A, Cordier S, Davey-Smith G, Eskenazi B et al. 2008. The faroes statement: human health effects of developmental exposure to chemicals in our environment. Basic Clin Pharmacol Toxicol 102:73-75.

Grandjean P, Weihe P, Burse VW, Needham LL, Storr-Hansen E, Heinzow B et al. 2001. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. Neurotoxicol Teratol 23:305-317.

Grandjean P, Weihe P, Jorgensen PJ, Clarkson T, Cernichiari E, Videro T. 1992. Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead. Arch Environ Health 47:185-195.

Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K et al. 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 19:417-428.

Grazuleviciene R, Danileviciute A, Nadisauskiene R, Vencloviene J. 2009. Maternal smoking, GSTM1 and GSTT1 polymorphism and susceptibility to adverse pregnancy outcomes. Int J Environ Res Public Health 6:1282-1297.

Guldner L, Monfort C, Rouget F, Garlantezec R, Cordier S. 2007. Maternal fish and shellfish intake and pregnancy outcomes: a prospective cohort study in Brittany, France. Environ Health 6:33.

Halldorsson TI, Thorsdottir I, Meltzer HM, Nielsen F, Olsen SF. 2008. Linking exposure to polychlorinated biphenyls with fatty fish consumption and reduced fetal growth among Danish pregnant women: a cause for concern? Am J Epidemiol 168:958-965.

Hanke W, Romitti P, Fuortes L, Sobala W, Mikulski M. 2003. The use of pesticides in a Polish rural population and its effect on birth weight. Int Arch Occup Environ Health 76:614-620.

Hanke W, Sobala W, Kalinka J. 2004. Environmental tobacco smoke exposure among pregnant women: impact on fetal biometry at 20-24 weeks of gestation and newborn child's birth weight. Int Arch Occup Environ Health 77:47-52.

Hartikainen AL, Sorri M, Anttonen H, Tuimala R, Laara E. 1994. Effect of occupational noise on the course and outcome of pregnancy. Scand J Work Environ Health 20:444-450.

Hedegaard M, Henriksen TB, Sabroe S, Secher NJ. 1993. Psychological distress in pregnancy and preterm delivery. BMJ 307:234-239.

Hegaard HK, Kjaergaard H, Moller LF, Wachmann H, Ottesen B. 2006. The effect of environmental tobacco smoke during pregnancy on birth weight. Acta Obstet Gynecol Scand 85:675-681.

Heinrich J, Bolte G, Holscher B, Douwes J, Lehmann I, Fahlbusch B et al. 2002. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. Eur Respir J 20:617-623.

Hruba D, Kukla L, Tyrlik M. 1999. Occupational risks for human reproduction: ELSPAC Study. European Longitudinal Study of Pregnancy and Childhood. Cent Eur J Public Health 7:210-215.

Hryhorczuk D, Dardynskaia I, Lukyanova E, Matwyshyn-Fuoco M, Friedman L, Shkiryak-Nizhnyk Z et al. 2009. Risk factors for wheezing in Ukrainian children: Ukraine European Longitudinal Study of Pregnancy and Childhood Group. Paediatr Perinat Epidemiol 23:346-351.

Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, van der Paauw CG, Tuinstra LG et al. 1995a. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum Dev 41:111-127.

Huisman M, Koopman-Esseboom C, Lanting CI, van der Paauw CG, Tuinstra LG, Fidler V et al. 1995b. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. Early Hum Dev 43:165-176.

Jaakkola JJ, Jaakkola N, Zahlsen K. 2001. Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration. Environ Health Perspect 109:557-561.

Jaddoe VW, Troe EJ, Hofman A, Mackenbach JP, Moll HA, Steegers EA et al. 2008a. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. Paediatr Perinat Epidemiol 22:162-171.

Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA et al. 2008b. The Generation R Study: design and cohort update until the age of 4 years. Eur J Epidemiol 23:801-811.

Jansen PW, Tiemeier H, Verhulst FC, Burdorf A, Jaddoe VW, Hofman A et al. 2010. Employment status and the risk of pregnancy complications: the Generation R Study. Occup Environ Med.

Jedrychowski W, Bendkowska I, Flak E, Penar A, Jacek R, Kaim I et al. 2004. Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland. Environ Health Perspect 112:1398-1402.

Jedrychowski W, Perera F, Jankowski J, Mrozek-Budzyn D, Mroz E, Flak E et al. 2009a. Gender specific differences in neurodevelopmental effects of prenatal exposure to very low-lead levels: the prospective cohort study in three-year olds. Early Hum Dev 85:503-510.

Jedrychowski W, Perera F, Jankowski J, Rauh V, Flak E, Caldwell KL et al. 2008. Prenatal low-level lead exposure and developmental delay of infants at age 6 months (Krakow inner city study). Int J Hyg Environ Health 211:345-351.

Jedrychowski W, Perera FP, Jankowski J, Mrozek-Budzyn D, Mroz E, Flak E et al. 2009b. Very low prenatal exposure to lead and mental development of children in infancy and early childhood: Krakow prospective cohort study. Neuroepidemiology 32:270-278.

Jedrychowski W, Whyatt RM, Camann DE, Bawle UV, Peki K, Spengler JD et al. 2003. Effect of prenatal PAH exposure on birth outcomes and neurocognitive development in a cohort of newborns in Poland. Study design and preliminary ambient data. Int J Occup Med Environ Health 16:21-29.

Johnke H, Vach W, Norberg LA, Bindslev-Jensen C, Host A, Andersen KE. 2005. A comparison between criteria for diagnosing atopic eczema in infants. Br J Dermatol 153:352-358.

Juhl M, Kogevinas M, Andersen PK, Andersen AM, Olsen J. 2010. Is swimming during pregnancy a safe exercise? Epidemiology 21:253-258.

Julvez J, Debes F, Weihe P, Choi A, Grandjean P. 2010. Sensitivity of continuous performance test (CPT) at age 14years to developmental methylmercury exposure. Neurotoxicol Teratol.

Jurewicz J, Hanke W. 2011. Exposure to phthalates: reproductive outcome and children health. A review of epidemiological studies. Int J Occup Med Environ Health 24:115-141.

Karvonen AM, Hyvarinen A, Roponen M, Hoffmann M, Korppi M, Remes S et al. 2009. Confirmed moisture damage at home, respiratory symptoms and atopy in early life: a birth-cohort study. Pediatrics 124:e329-e338.

Kerkhof M, Postma DS, Brunekreef B, Reijmerink NE, Wijga AH, de Jongste JC et al. 2010. Toll-like receptor 2 and 4 genes influence susceptibility to adverse effects of traffic-related air pollution on childhood asthma. Thorax 65:690-697.

Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MA, van der Paauw CG, Tuinstra LG, Sauer PJ. 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97:700-706.

Koppen G, Den Hond E, Nelen V, Van De ME, Bruckers L, Bilau M et al. 2009. Organochlorine and heavy metals in newborns: results from the Flemish Environment and Health Survey (FLEHS 2002-2006). Environ Int 35:1015-1022.

Kramer U, Sugiri D, Ranft U, Krutmann J, von Berg A, Berdel D et al. 2009. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. J Dermatol Sci 56:99-105.

Kuehni CE, Brooke AM, Strippoli MP, Spycher BD, Davis A, Silverman M. 2007. Cohort profile: the Leicester respiratory cohorts. Int J Epidemiol 36:977-985.

Kummeling I, Thijs C, Penders J, Snijders BE, Stelma F, Reimerink J et al. 2005. Etiology of atopy in infancy: the KOALA Birth Cohort Study. Pediatr Allergy Immunol 16:679-684.

Lanting CI, Patandin S, Fidler V, Weisglas-Kuperus N, Sauer PJ, Boersma ER et al. 1998. Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. Early Hum Dev 50:283-292.

Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. 2006. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 35:1146-1150.

Marriott LD, Foote KD, Kimber AC, Delves HT, Morgan JB. 2007. Zinc, copper, selenium and manganese blood levels in preterm infants. Arch Dis Child Fetal Neonatal Ed 92:F494-F497.

Nieuwenhuijsen MJ, Northstone K, Golding J. 2002. Swimming and birth weight. Epidemiology 13:725-728.

Oftedal B, Nystad W, Brunekreef B, Nafstad P. 2009. Long-term traffic-related exposures and asthma onset in schoolchildren in oslo, norway. Environ Health Perspect 117:839-844.

Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM et al. 2001. The Danish National Birth Cohort--its background, structure and aim. Scand J Public Health 29:300-307.

Park HY, Hertz-Picciotto I, Sovcikova E, Kocan A, Drobna B, Trnovec T. 2010. Neurodevelopmental toxicity of prenatal polychlorinated biphenyls (PCBs) by chemical structure and activity: a birth cohort study. Environ Health 9:51.

Park HY, Park JS, Sovcikova E, Kocan A, Linderholm L, Bergman A et al. 2009. Exposure to hydroxylated polychlorinated biphenyls (OH-PCBs) in the prenatal period and subsequent neurodevelopment in eastern Slovakia. Environ Health Perspect 117:1600-1606.

Patandin S, Koopman-Esseboom C, de Ridder MA, Weisglas-Kuperus N, Sauer PJ. 1998. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res 44:538-545.

Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, Weisglas-Kuperus N. 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134:33-41.

Philippat C, Mortamais M, Chevrier C, Petit C, Calafat AM, Ye X et al. 2011. Exposure to Phthalates and Phenols during Pregnancy and Offspring Size at Birth. Environ Health Perspect.

Pinto E, Barros H, dos SS, I. 2009. Dietary intake and nutritional adequacy prior to conception and during pregnancy: a follow-up study in the north of Portugal. Public Health Nutr 12:922-931.

Polanska K, Hanke W, Gromadzinska J, Ligocka D, Gulczynska E, Sobala W et al. 2009. Polish mother and child cohort study--defining the problem, the aim of the study and methodological assumption. Int J Occup Med Environ Health 22:383-391.

Porta D, Forastiere F, Di Lallo D, Perucci CA. 2007. [Enrolment and follow-up of a birth cohort in Rome]. Epidemiol Prev 31:303-308.

Porta DFMPGaCESG. 2006. Prospective cohort studies of newborns in Italy to evaluate the role of environmental and genetic characteristics on common childhood disorders. Italian Journal of Pediatrics 32:350-357.

Puertas R, Lopez-Espinosa MJ, Cruz F, Ramos R, Freire C, Perez-Garcia M et al. 2010. Prenatal exposure to mirex impairs neurodevelopment at age of 4 years. Neurotoxicology 31:154-160.

Ramon R, Ballester F, Aguinagalde X, Amurrio A, Vioque J, Lacasana M et al. 2009. Fish consumption during pregnancy, prenatal mercury exposure, and anthropometric measures at birth in a prospective mother-infant cohort study in Spain. Am J Clin Nutr 90:1047-1055.

Raynor P. 2008. Born in Bradford, a cohort study of babies born in Bradford, and their parents: protocol for the recruitment phase. BMC Public Health 8:327.

Ribas-Fito N, Cardo E, Sala M, Eulalia dM, Mazon C, Verdu A et al. 2003. Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. Pediatrics 111:e580-e585.

Ribas-Fito N, Ramon R, Ballester F, Grimalt J, Marco A, Olea N et al. 2006a. Child health and the environment: the INMA Spanish Study. Paediatr Perinat Epidemiol 20:403-410.

Ribas-Fito N, Torrent M, Carrizo D, Julvez J, Grimalt JO, Sunyer J. 2007. Exposure to hexachlorobenzene during pregnancy and children's social behavior at 4 years of age. Environ Health Perspect 115:447-450.

Ribas-Fito N, Torrent M, Carrizo D, Munoz-Ortiz L, Julvez J, Grimalt JO et al. 2006b. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. Am J Epidemiol 164:955-962.

Richiardi L, Baussano I, Vizzini L, Douwes J, Pearce N, Merletti F. 2007. Feasibility of recruiting a birth cohort through the Internet: the experience of the NINFEA cohort. Eur J Epidemiol 22:831-837.

Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF. 2009. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ Health Perspect 117:1953-1958.

Smink A, Ribas-Fito N, Garcia R, Torrent M, Mendez MA, Grimalt JO et al. 2008. Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years. Acta Paediatr 97:1465-1469.

Sonneborn D, Park HY, Petrik J, Kocan A, Palkovicova L, Trnovec T et al. 2008. Prenatal polychlorinated biphenyl exposures in eastern Slovakia modify effects of social factors on birthweight. Paediatr Perinat Epidemiol 22:202-213.

Steuerwald U, Weihe P, Jorgensen PJ, Bjerve K, Brock J, Heinzow B et al. 2000. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. J Pediatr 136:599-605.

Suarez-Varela MM, Kaerlev L, Zhu JL, Bonde JP, Nohr EA, Llopis-Gonzalez A et al. 2009. Hospital work and pregnancy outcomes: a study in the Danish National Birth Cohort. Int J Occup Environ Health 15:402-409.

Tang-Peronard JL, Andersen HR, Jensen TK, Heitmann BL. 2011. Endocrine-disrupting chemicals and obesity development in humans: a review. Obes Rev 12:622-636.

Tischer C, Gehring U, Chen CM, Kerkhof M, Koppelman G, Sausenthaler S et al. 2011. Respiratory health in children, and indoor exposure to (1,3)-beta-D-glucan, EPS mould components and endotoxin. Eur Respir J 37:1050-1059.

Toft G, Axmon A, Giwercman A, Thulstrup AM, Rignell-Hydbom A, Pedersen HS et al. 2005. Fertility in four regions spanning large contrasts in serum levels of widespread persistent organochlorines: a cross-sectional study. Environ Health 4:26.

Toft G, Thulstrup AM, Jonsson BA, Pedersen HS, Ludwicki JK, Zvezday V et al. 2010. Fetal loss and maternal serum levels of 2,2',4,4',5,5'-hexachlorbiphenyl (CB-153) and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) exposure: a cohort study in Greenland and two European populations. Environ Health 9:22.

van Eijsden M, Vrijkotte TG, Gemke RJ, van der Wal MF. 2010. Cohort Profile: The Amsterdam Born Children and their Development (ABCD) Study. Int J Epidemiol.

Vandentorren S, Bois C, Pirus C, Sarter H, Salines G, Leridon H. 2009. Rationales, design and recruitment for the Elfe longitudinal study. BMC Pediatr 9:58.

Verhulst SL, Nelen V, Hond ED, Koppen G, Beunckens C, Vael C et al. 2009. Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. Environ Health Perspect 117:122-126.

Vreugdenhil HJ, Lanting CI, Mulder PG, Boersma ER, Weisglas-Kuperus N. 2002a. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J Pediatr 140:48-56.

Vreugdenhil HJ, Mulder PG, Emmen HH, Weisglas-Kuperus N. 2004. Effects of perinatal exposure to PCBs on neuropsychological functions in the Rotterdam cohort at 9 years of age. Neuropsychology 18:185-193.

Vreugdenhil HJ, Slijper FM, Mulder PG, Weisglas-Kuperus N. 2002b. Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. Environ Health Perspect 110:A593-A598.

Vrijheid M, Casas M, Bergstrom A, Carmichael A, Cordier S, Eggesbo M et al. 2011. European Birth Cohorts for Environmental Health Research. Environ Health Perspect.

Vrijkotte TG, van der Wal MF, van Eijsden M, Bonsel GJ. 2009. First-trimester working conditions and birthweight: a prospective cohort study. Am J Public Health 99:1409-1416.

Walkowiak J, Wiener JA, Fastabend A, Heinzow B, Kramer U, Schmidt E et al. 2001. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. Lancet 358:1602-1607.

Wickman M, Kull I, Pershagen G, Nordvall SL. 2002. The BAMSE project: presentation of a prospective longitudinal birth cohort study. Pediatr Allergy Immunol 13 Suppl 15:11-13.

Wilhelm M, Wittsiepe J, Lemm F, Ranft U, Kramer U, Furst P et al. 2008. The Duisburg birth cohort study: influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months. Mutat Res 659:83-92.

Winneke G, Kramer U, Sucker K, Walkowiak J, Fastabend A, Heinzow B et al. 2005. PCB-related neurodevelopmental deficit may be transient: follow-up of a cohort at 6 years of age. Environ Toxicol Pharmacol 19:701-706.

Wojtyniak BJ, Rabczenko D, Jonsson BA, Zvezday V, Pedersen HS, Rylander L et al. 2010. Association of maternal serum concentrations of 2,2', 4,4'5,5'-hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (p,p'-DDE) levels with birth weight, gestational age and preterm births in Inuit and European populations. Environ Health 9:56.

Zhu JL, Hjollund NH, Andersen AM, Olsen J. 2004a. Shift work, job stress, and late fetal loss: The National Birth Cohort in Denmark. J Occup Environ Med 46:1144-1149.

Zhu JL, Hjollund NH, Andersen AM, Olsen J. 2006a. Occupational exposure to pesticides and pregnancy outcomes in gardeners and farmers: a study within the Danish National Birth Cohort. J Occup Environ Med 48:347-352.

Zhu JL, Hjollund NH, Boggild H, Olsen J. 2003. Shift work and subfecundity: a causal link or an artefact? Occup Environ Med 60:E12.

Zhu JL, Hjollund NH, Olsen J. 2004b. Shift work, duration of pregnancy, and birth weight: the National Birth Cohort in Denmark. Am J Obstet Gynecol 191:285-291.

Zhu JL, Knudsen LE, Andersen AM, Hjollund NH, Olsen J. 2005. Time to pregnancy among Danish laboratory technicians who were a part of the National Birth Cohort. Scand J Work Environ Health 31:108-114.

Zhu JL, Knudsen LE, Andersen AM, Hjollund NH, Olsen J. 2006b. Laboratory work and pregnancy outcomes: a study within the National Birth Cohort in Denmark. Occup Environ Med 63:53-58.

Zhu JL, Vestergaard M, Hjollund NH, Olsen J. 2006c. Pregnancy outcomes among female hairdressers who participated in the Danish National Birth Cohort. Scand J Work Environ Health 32:61-66.

Zirngibl A, Franke K, Gehring U, von Berg A, Berdel D, Bauer CP et al. 2002. Exposure to pets and atopic dermatitis during the first two years of life. A cohort study. Pediatr Allergy Immunol 13:394-401.

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Developing a Child Cohort Research Strategy for Europe

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Summary

This working group explores the availability and potential of biological and genetic materials from mothers, fathers and children in European birth cohorts. Many cohorts collect biological samples, such as DNA, blood, urine, and bacterial cultures in both children and parents. Most studies do have samples in children. The number of studies have biological samples in fathers is limited. Biomarkers are frequently used for asessing causal associations. Biomarkers might be related to envrionmental exposures, nutritional determinants (eg folate, vitamine levels), life style related habits such as smoking (cotinin levels), and hormones (thyroid hormone, cortisol. Information about these exposures might overcome the potential for bias from studies using self reported data, increase power for association studies, and might give insight in the underlying causal mechanisms. More specfically, biological samples in pregnancy, birth and child cohorts enable studies on biological and causal pathways leading to various outcomes related to growth, development and physical and mental health in fetal life, childhood and adulthood. Some examples are given in this report. Since 2010, European birth cohorts had major contributions to identification of common genetic variants related to various health outcomes in childhood and adulthood. Many of these birth cohorts closely work together in the Early Growth & Longitudinal Epidemiology (EAGLE) Consortium and Early Growth Genetics Consortium. Our **major findings** are;

a. Many birth cohorts collect biological and genetic samples and had major investments for establishing biobanks, most cohorts are Western European;
b. Collaboration on logistics of biological and genetic sample collection, storage and use is scarce;
c. Many birth cohorts do have biological samples available but cannot make optimal use of them because of financial restrictions;
d. Scientific collaboration using especially genetic samples has proven to be extremely successful. Thee collaborations are not funded yet

Our **major recommendations specifically focused on research on** biological and genetic materials in birth cohort studies are:

a. Strengthen collaboration of birth cohort studies for establishing biobanks for biological and genetic sample collections and storage in Western and Eastern Europe
b. Specific funding opportunities for both collaborative studies on biological and genetic samples, especially in European consortia. These should be focused on promising research fields (epigenetics, expression and metabolomics);

In conclusion, European birth cohorts developed unique, large scale and expensive biobanks. For the upcoming years, a major challenge will be how to fund measurements in materials from these biobanks for collaborative studies for assessment of risk factors of various child health outcomes.

1. Review of cohort contribution and existing cohort data

1.1. Description of current state of scientific knowledge

Biological and genetic information is an essential part for birth cohorts studies. Biomarkers are essential for assessing causal associations and biological pathways. Biomarkers might be related to envrionmental exposures, nutritional determinants (eg folate, vitamine levels), life style related habits such as smoking (cotinin levels), and hormones (thyroid hormone, cortisol). Information about these exposures might overcome the potential for bias from studies using self reported data, and increase power for association studies. More specfically, biological samples in pregnancy, birth and child cohorts enable studies on biological and causal pathways leading to various outcomes related to growth, development and physical and mental health in fetal life, childhood and adulthood. Recently, high troughput methods have become available to measure up to thousends of genetic, epigenetic and metabolomic markers in subjects participating large-scale epidemiological studies. Also, studies on genetic and epigenetic associations might lead to new insights in the development of common diseases in fetal life, childhood and adulthood.

Genome wide association studies (GWAS) have become available, which make use of a hypothesis free approach without any *a priori* assumptions on biologic pathways. Miillions of genetic variants are screened for their associations with common health and diseases outcomes and their risk factors. This method is based on known structural information about the human DNA. The full genome is characterized by single nucleotide polymorphisms (SNPs). Current high throughput genotyping methodologies enable genotyping of up to 1 million SNPs per subject. With imputation techniques, analyses of another 2.5 to 10 million SNPs can be performed. SNPs closely related to a genetic variant involved in a disease, will be overrepresented in affected individuals. Because of the potential small effect sizes and the chances of having false positive findings, rigid adjustments for multiple testing are necessary and analyses are based on large sample sizes up to 10,000s of subjects. This has initiated major collaborative projects. Meta-analyses from GWAS have identified over 1500 genetic loci related to common diseases and their risks factors in adulthood, such as obesity, type 2 diabetes, cardiovascular disease, Crohn's disease, asthma, schizophrenia and prostate cancer and in children identified genetic loci related to rare diseases such as leukemia, neuroblastoma and birth defects and more common health outcomes such as birth weight.

Genome wide genetic and epigenetic studies in children are challenging for several reasons. First, diseases in childhood might be common, but symptoms are frequently atypical. Examples of common, but not well defined symptoms in children are upper airway symptoms, fever of unknown origin, and wheezing. Also, diagnostic options are often limited. Misclassification of disease related outcomes leads to loss of power, and increases the numbers of patients needed to show any genotype-phenotype associations. One approach to overcome this limitation is to study the variance in the normal distribution of risk factors, well-defined proxies and specific intermediate phenotypes, rather than studying specific childhood diseases.

This approach has also proven to be successful in GWAS in adulthood, as it seems easier to identify genes involved in blood pressure and lipid levels than as genes involved in hypertension or dyslipidemia. Studying intermediate phenotypes of diseases in childhood instead of the diseases themselves might give clues for new pathways. Second, it is important to identify not only biological factors related to diseases, but also to normal variation of outcomes such as physical growth, developmental milestones, school performance, food and taste preferences, and puberty stages. Identification of variants of these traits might lead to clues of biological pathways of normal variation within childhood and adolescence. Third, a specific characteristic of many phenotypes in childhood is the change over time. Most prospective cohort studies follow their children from early life into adolescence or adulthood. Outcomes in these studies might be defined as non-linear or linear changes over time. Advanced statistical methods are needed to perform genome wide genetic and epigenetic studies on repeatedly measured outcomes. Fourth, practical issues when dealing with young children such as blood sampling or other objective assessments are challenging and time-consuming and a multi-center approach is needed when large sample sizes are required.

Thus, studies on biological and genetic markers in parents and children are needed to identify complex pathways leading to health outcomes in fetal life, childhood and adulthood. Birth cohort studies are especially needed in this field of research because of the possibility to study intergenerational effects and the longitudinal developmental trajectories.

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

Many birth and child cohorts have collected biological samples, including blood, DNA, urine, saliva, urine and bacterial cultures. Using these samples, European birth cohort studies had a major contribution to child health research. For example, recent studies showed associations of various biomakers related to maternal nutrition, angiogenesis, inflammation and blood clotting with birth outcomes. Also, studies on fatty acids showed associations with birth weight and postnatal outcomes. Similarly, two studies providing information on bacterial carriage, showed associations of early bacterial carriage with the risk of childhood asthma and eczema. A full review of findings from all European birth cohort studies is beyond the scope of this exploration. The potential and power of European collaborations on biomarker and genetic studies is illustrated by recent genome wide association studies focused on childhood obesity, asthma, atopy, and birth weight.

Results from genome wide association studies in child cohort studies

Several European birth cohort studies with genome wide data or DNA have combined their efforts and established the EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium and Early Growth Genetics (EGG) Consortium. These consortia comprises of pregnancy and birth cohorts that aim to investigate the genetic and epigenetic basis of phenotypes in fetal life, childhood and adulthood. These consortia cover a

broad range of pathways and phenotypes. European birth cohort studies involved in these collaborations are the 1958 British Birth Cohort Study, London, United Kingdom (58BC), Avon Longitudinal Study of Parents and Children, Bristol, United Kingdom (ALSPAC); Copenhagen Study on Asthma in Childhood, Copenhagen, Denmark (COPSAC); Generation R Study, Rotterdam, the Netherlands (Generation R); Helsinki Birth Cohort Study, Helsinki, Finland (HBCS); INMA Study, Barcelona, Spain (INMA); Influences of Lifestyle-related Factors on the Immune System and the Development of Allergies in Childhood Study, Munich, Germany (LISA); Netherlands Twin Register, Amsterdam the Netherlands (NTR), Northern Finland Birth Cohort Study 1966, London, United Kingdom (NFBC66); Norwegian Mother and Child Cohort Study, Oslo, Norway (MOBA). Collaboration has also established with the Western Australian Pregnancy Cohort Study, Perth, Australia (Raine) and the Children's Hospital of Philadelphia (CHOP). Results from this collaboration have led to identification of common genetic variants and their related pathways leading to low birth weight, smaller infant head circumference, childhood obesity and childhood eczema. Below, we give summary of results which are largely based on the data and collaboration from European birth cohorth studies.

To identify genetic variants associated with **birth weight,** the consortium meta-analyzed six genome-wide association (GWA) studies (n = 10,623 Europeans from pregnancy/birth cohorts) and followed up two lead signals in 13 replication studies (n = 27,591). rs900400 near LEKR1 and CCNL1 (P = 2 x 10(-35)) and rs9883204 in ADCY5 (P = 7 x 10(-15)) were robustly associated with birth weight. Correlated SNPs in ADCY5 were recently implicated in regulation of glucose levels and susceptibility to type 2 diabetes, providing evidence that the well-described association between lower birth weight and subsequent type 2 diabetes has a genetic component, distinct from the proposed role of programming by maternal nutrition. Using data from both SNPs, we found that the 9% of Europeans carrying four birth weight-lowering alleles were, on average, 113 g (95% CI 89-137 g) lighter at birth than the 24% with zero or one alleles (P(trend) = 7 x 10(-30)). The impact on birth weight is similar to that of a mother smoking 4-5 cigarettes per day in the third trimester of pregnancy.

To identify genetic variants associated with **head circumference in infancy**, the consortium performed a meta-analysis of seven genome-wide association studies (GWAS) (N = 10,768 individuals of European ancestry enrolled in pregnancy and/or birth cohorts) and followed up three lead signals in six replication studies (combined N = 19,089). rs7980687 on chromosome 12q24 (P = 8.1 × 10(-9)) and rs1042725 on chromosome 12q15 (P = 2.8 × 10(-10)) were robustly associated with head circumference in infancy. Although these loci have previously been associated with adult height, their effects on infant head circumference were largely independent of height (P = 3.8 × 10(-7) for rs7980687 and P = 1.3 × 10(-7) for rs1042725 after adjustment for infant height). A third signal, rs11655470 on chromosome 17q21, showed suggestive evidence of association with head circumference (P = 3.9 × 10(-6)). SNPs correlated to the 17q21 signal have shown genome-wide association with adult intracranial volume, Parkinson's disease and other

neurodegenerative diseases, indicating that a common genetic variant in this region might link early brain growth with neurological disease in later life.

To identify genetic variants associated with **childhood obesity**, the consortium performed collaborative meta-analysis of 14 studies consisting of 5,530 cases (≥95th percentile of body mass index (BMI)) and 8,318 controls (<50th percentile of BMI) of European ancestry. Taking forward the eight newly discovered signals yielding association with P < 5 × 10(-6) in nine independent data sets (2,818 cases and 4,083 controls), we observed two loci that yielded genome-wide significant combined P values near OLFM4 at 13q14 (rs9568856; P = 1.82 × 10(-9); odds ratio (OR) = 1.22) and within HOXB5 at 17q21 (rs9299; P = 3.54 × 10(-9); OR = 1.14). Both loci continued to show association when two extreme childhood obesity cohorts were included (2,214 cases and 2,674 controls). These two loci also yielded directionally consistent associations in a previous meta-analysis of adult BMI.

The consortium conducted a genome-wide association meta-analysis on **childhood eczema** of 5,606 affected individuals and 20,565 controls from 16 population-based cohorts and then examined the ten most strongly associated new susceptibility loci in an additional 5,419 affected individuals and 19,833 controls from 14 studies. Three SNPs reached genome-wide significance in the discovery and replication cohorts combined, including rs479844 upstream of OVOL1 (odds ratio (OR) = 0.88, P = 1.1 × 10(-13)) and rs2164983 near ACTL9 (OR = 1.16, P = 7.1 × 10(-9)), both of which are near genes that have been implicated in epidermal proliferation and differentiation, as well as rs2897442 in KIF3A within the cytokine cluster at 5q31.1 (OR = 1.11, P = 3.8 × 10(-8)). The consortium replicated association with the FLG locus and with two recently identified association signals at 11q13.5 (rs7927894; P = 0.008) and 20q13.33 (rs6010620; P = 0.002). These results underline the importance of both epidermal barrier function and immune dysregulation in atopic dermatitis pathogenesis.

This overview of studies demonstrates the power of both the data and collaborations of birth cohort studies. None of the studies would have been able to perform this research by themselves.
Also, for these studies, not only classical birth cohort studies, but also registry data with for example dried blood spots have been used. Remarkably, this successful collaboration was not funded.

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

Many birth cohorts collect biological and genetic samples. Most of these studies are in Western European countries. A full overview of biological samples that are available in European birth cohorts is given in on *www.birthcohorts.net*. Obviously, major investments for establishing biobanks have been made. Not all studies did measurements in these biological samples, mainly because of financial restrictions.

Table 2 European cohorts with mothers and children with biological samples available.

Cohort (web site)	Country	N mother-child pairs	Gestational age at enrolment in weeks	Year of enrolment
1. Aarhus Birth Cohort (N/A)	Denmark	93,000	12-19	1990 and ongoing
2. ABCD (www.abcd-studie.nl)	Netherlands	7,863	12-14	2003-04
3. ABIS (www.abis-studien.se)	Sweden	17,000	13-18	1997-99
4. ALSPAC (www.alspac.bristol.ac.uk)	United kingdom	14,000	1-12	1991-92
5. APREG(N/A)	Hungary	2,800	4-8	2000-06
6. BIB- Born in Bradford (www.borninbradford.nhs.uk)	United kingdom	13,000	26-28	2007-10
7. CHEF (Children´s health and the environment in the faroes) (www.chef-project.dk)	Faroes	1,860	32-34	1986-87,1994-95, and 1997-00
8. DNBC (www.dnbc.dk)	Denmark	100,418	6-24	1996-02
9. EDEN (N/A)	France	1,800	<24	2003-06
10. Generation R (www.generationr.nl)	Netherlands	9,778	1-12	2001-06
11. Generation XXI (N/A)	Portugal	8,493	1-12 or at birth	2004-2006
12. Healthy Habits for two -HHf2 (N/A)	Denmark	11,300	28+	1984-86
13. INMA in Asturias,Gipuzkoa, Menorca, Sabadell, and Valencia (www.proyectoinma.org)	Spain	3,100	12	1997,98, and 2004-2008
14. INUENDO (www.inuendo.dk)	Sweeden, Poland, Ukraine, Greece	2,269 women 1,322 children	6-38 weeks	2002-2004
15. IVAAQ (N/A)	Denmark, Greenland	400	13-18	1999-2005
16. Kaunas cohort – KANC (N/A)	Lithuania	4,000	12	2007-09
17. KOALA Birth Cohort Study, The Netherlands (www.koala-study.nl)	Netherlands	2,834	14	2000-03
18. Lifeways Cross-Generation Cohort Study (N/A)	Ireland	1,061	1-12	2001-03
19. MoBa (www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5895:0:15,3046:1:0:0:::0:0)	Norway	107,000	17-18	1999-08
20. NFBC-1986 (http://kelo.oulu.fi/NFBC/)	Findland	9,362	1-12	1985-86
21. NINFEA (https://www.progettoninfea.it/)	Italy	7,500	13-18	2005+
22. North Cumbria Community Genetics Project (N/A)	United kingdom	8,000	During pregnancy	1996-2001
23. PELAGIE (N/A)	France	3,421	13-18	2002-06
24. PIAMA (http://piama.iras.uu.nl/en/index.php)	Netherlands	4,000	28+	1996-97
25. Polish Mother and Child cohort study -REPRO_PL (www.repropl.com)	Poland	1,300	8-12	2007-11
26. RHEA study (http://rhea.med.uoc.gr/)	Greece	1,500	13-18	2007-08
27. Southamptom Women's Survey (www.mrc.soton.ac.uk/sws/)	United kingdom	3,159	Before pregnancy	1988-02

1.4 Identification of gaps

- Many birth cohorts collect biological and genetic samples and had major investments for establishing biobanks. Most of these cohorts are in Western European countries; Therefore, knowledge about the role of biological factors on child health outcomes in Eastern European countries is limited;
- There is hardly collaboration on the logistics of biological and genetic sample collection, and storage. There is a huge potential for collaboration on this part of the data collection;

- Many birth cohorts do have biological samples available but cannot make optimal use of them because of financial restrictions;
- Scientific collaboration using especially genetic samples has proven to be extremely successful. Thee collaborations are not funded yet;

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

See overview genome wide association studies.

3. Recommendations

Our **major recommendations specifically focused on research on** biological and genetic materials in birth cohort studies are:

c. Create better distribution of high quality birth cohort studies with biobanks across Europe;
d. Harmonization of protocols for data collection, storage and analysis;
e. Strengthen collaboration of birth cohort studies for establishing biobanks for biological and genetic sample collections and storage in Western and Eastern Europe;
f. Specific funding opportunities for both collaborative studies on biological and genetic samples, especially in European consortia. These should be focused on promising research fields (epigenetics, expression and metabolomics);

Working group

Multiple Determinants

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Working group on Interactions between multiple child health determinants

Pathways of causality are typically complex and always multifactorial. A variety of external and internal factors influence the susceptibility and exposure of fetuses, infants, and children to environmental hazards. Both research and policies aimed at improving and protecting children's health (and that of women of reproductive age) therefore need to consider determinants at the individual and community level and the interactions between social, environmental and biological factors.

Birth cohorts are essential to understanding this full picture as information on multiple risk factors and disease/health related outcomes are collected prospectively. This field has not received much emphasis and is methodologically complex. However, any strategy for child cohort research across Europe should consider these issues, particularly since they will necessitate large sample sizes and replication across different cohorts.

The working group on multiple determinants has assessed the various challenges involved in moving towards more integrative methods, assessing impacts of multiple risk factors on child health. These challenges include:

1. Complete data on many risk factors to be collected at multiple time points in the cohorts;
2. Development of biomarkers which will allow characterisation of global exposures without characterizing each exposure separately.
3. Development of statistical methods for the analysis of complex interactions between multiple risk factors.
4. Development of scenarios for multiple risk factor assessment in children as part of Health Impact Assessment methods.

At the same time, recent years have seen a call for more "integrative" methods in exposure assessment, epidemiology and impact assessment, to work towards a more comprehensive view of how exposures may co-exist and jointly impact on health. The "exposome" concept was first introduced in 2005 by C Wild to encompass the totality of exposures from conception onwards, complementing the genome. The EC followed this by a call in FP7 on the exposome topic. A group of birth cohorts closely related to CHICOS and involving the leaders of this working group, used this opportunity to submit a proposal entitled "The Human Early-Life Exposome (HELIX) – novel tools for integrating early-life exposures and child health across Europe". The project started in January 2013. HELIX aims to use novel exposure assessment, biomarker, and statistical tools to characterise early-life (pre and postnatal) exposure to multiple environmental

hazards and associate these with child health outcomes. The main focus of the project is on tackling the challenges outlined above:

1. In order to build a true exposome HELIX will integrate a wide range of chemical, physical, social, dietary and other life-style exposures, using 6 European birth cohorts.

2. HELIX will employ state-of-the-art omics techniques in biological samples in the cohorts – this will be done to measure molecular signatures associated with environmental exposures through analysis of profiles of metabolites, proteins, RNA transcripts, and DNA methylation. The use of this sequential set of omics approaches will lead to the comprehensive evaluation of biological alterations due to exposure changes in early-life – it will allow characterising how the external exposome impacts on the internal exposome. Ultimately, this could lead to the characterization of global exposures without characterizing each exposure separately. Biological pathways will be used to inform analyses of the relationship between multiple exposures and child health.

3. HELIX will develop novel statistical approaches for the analysis of the association of patterns of multiple and combined exposures and child health outcomes. A multi-step statistical approach will be developed to analyse complex, multiple exposure data, using novel statistical techniques including: agnostic exposure-wide association study (EWAS) analysis, structural equation modelling, and Bayesian profile regression. This approach will serve as a proof-of-concept approach for the statistical analysis of future multiple exposure studies. Risk estimates for child health diseases and disorders related to integrated multiple exposures are not currently available thus severely limiting health impact assessments.

4. HELIX will estimate the burden of common childhood diseases that may be attributed to multiple environmental exposures in Europe. This will be achieved using integrated health impact assessment tools, prevalence data from over 35 European birth cohorts (>300,000 subjects) and surveys, and exposure-response results from HELIX. This will provide burden of disease estimates for children in Europe based on improved exposure information, and allows us to prioritise the importance of environmental exposures in terms of (likely) disease burden. Novel aspects include the focus on pregnancy and early childhood, and on complex scenarios of multiple exposures.

Because this new and large exposome initiative has only just started, the CHICOS working group on multiple exposures considers that it is currently too early to develop recommendations for a cohort research agenda in this field. The exposome approach needs developing, testing, and evaluating, before we can give such recommendations.