

## Report on European Children's and Birth Cohort Studies, Part A Study Precedents

### Contents

1. Survey Summary .....	3
2. Study Results.....	5
2-1. Types of Cohorts and Study Characteristics.....	5
A. National Cohort—The Norwegian Mother and Child Cohort Study (MoBa).....	5
B. National Cohort—Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study .....	5
C. Hospital-Based Cohort—Generation R Study .....	6
D. Research-Based Cohort—Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study .....	7
2-2. Cohort Study Design and Status.....	8
A. The Norwegian Mother and Child Cohort Study (MoBa) .....	8
B. Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study.	10
C. Generation R Study .....	12
D. Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study.....	18
3. Issues for Discussion.....	21
3-1. Cohort Design .....	21
A. Important Considerations for Cohort Design.....	21
B. National-Scale Cohorts .....	22
C. Multicenter Cohorts.....	22
D. Cohorts and Subcohorts .....	22
3-2. Cohort Administration.....	23
A. Administrative Organization .....	23
B. Computer Usage.....	24
3-3. Data Management and Use .....	24
A. Information Access.....	24
B. Biological Samples.....	24
3-4. Cooperative Framework and Incentives.....	25
3-5. Foreseeable Issues .....	26
A. Ethical Guidelines and Informed Consent .....	26
B. Ethical Guidelines and Study Design.....	27
C. Pros and Cons of Intervention.....	27

D.	Protection of Personal Information and Information Security .....	28
3-6.	Contributions of Later Cohorts .....	28
A.	Linking Data to Other Cohorts .....	28
B.	Unique Contribution.....	28

# 1. European Child Cohort Studies Survey Summary

## Survey Panel

Manabu, Hasegawa	Ministry of the Environment
Fujio, Kayama	Jichi Medical University
Rie, Masho	Center for Environmental Information Science
Motoyuki, Yuasa	Hokkaido University

## Period of Survey

November 4–14, 2007

## Purpose of Survey

To obtain an understanding of cohort precedents from other countries, as part of the planning and review process for Japan to implement a children's and birth cohort, with a particular focus on gaining an awareness of the status of large-scale birth cohorts implemented as national projects. The survey panel will also seek to identify important technical considerations through interviews with persons involved in maintaining and managing cohorts, and who are engaged in other cohort tasks such as collection and storage of data and biological samples.

In addition, the survey panel will interview a medical officer in charge of children's environmental health from the World Health Organization (WHO), in order to understand WHO's initiatives in this area.

## Studies Surveyed in Person

The scope of the survey focuses on large-scale birth cohorts with a sample size of 100,000 or more subjects that were conducted by Norway and Denmark. These studies were chosen in order to understand the circumstances that led to the establishment of a large-scale birth cohort implemented at the national level, and to grasp their current status. Also included in the scope of candidate studies were birth cohorts by hospitals and researchers that are comparatively large in scale and involved the taking and storage of biological samples. Of the candidate studies, the actual investigation abroad was restricted to studies that agreed to receive a visit from the survey panel and whose schedule permitted a visit during the investigative trip to Europe. The survey panel was aware of other cohort studies in the United States and Australia and in other parts of Europe that could have been included in the scope of the study, but time and expense considerations prevented the survey panel from scheduling visits to these studies.

The actual studies that were surveyed in person were, in chronological order of visit, as follows:

**A. Generation R Study**

**Erasmus University Rotterdam (Hospital-Based)**

Cohort Name: Generation R

Principal investigator: Albert Hofman  
Department of Epidemiology & Biostatistics, Erasmus Medical  
Center  
Erasmus University

Website: <http://www.generationr.nl>

**B. Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study  
Utrecht University (Researcher-Based Cohort)**

Cohort name: PIAMA

Principal investigator: Bert Brunekreef  
The Institute for Risk Assessment Sciences (IRAS)  
Centre for Prevention and Health Services Research  
Utrecht University

Website: None

**C. The Norwegian Mother and Child Cohort Study (MoBa)  
Norwegian Institute of Public Health (National Cohort)**

Cohort name: The Norwegian Mother and Child Cohort Study

Principal investigator: Per Magnus  
Norwegian Institute of Public Health  
Division of Epidemiology

Website: <http://www.fhi.no/tema/morogbarn>

**D. Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study  
Danish State Serum Institute (National Cohort)**

Cohort name: Bedre sundhed for mor og barn

Principal investigator: Mads Melbye  
Statens Seruminstitut

Website: <http://www.bsmb.dk>

**E. Children's Environmental Health  
World Health Organization (WHO)**

Medical Officer: Dr. Jenny Pronczuk  
Public Health and Environment, World Health Organization

Website: <http://www.who.int/ceh/en/>

## 2. Study Results

### 2-1. Types of Cohorts and Study Characteristics

#### **A. National Cohort—The Norwegian Mother and Child Cohort Study (MoBa)**

#### **B. National Cohort—Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study**

The characteristics of the large-scale national birth cohort studies conducted by Norway and Denmark are summarized below.

#### Social Background

- Norway has a population of 4,698,000. The total fertility rate is 1.80 with 56,000 births per year (UN survey, 2000–2005).
- Denmark has a population of 5,442,000. The total fertility rate is 1.76 with 65,000 births per year (UN survey, 2000–2005).

The majority of people in both countries are registered with general practitioners (GPs) who are supported through a publicly funded health care system. GPs receive public funds based on the number of registered patients they have and the actual treatment they provide. There is no cost to the patient for medical care related to childbirth. When a woman is pregnant, she is diagnosed by her GP, who refers her to a midwife. Almost all births take place in a hospital. Various registry systems such as for birth, medical care, and hospital discharges have been established through legislation. The registry system for hospital discharges is currently being prepared.

#### Advantages for Study Subjects

Subjects who join the study are entered for a chance to win prizes in drawings. Subjects also gain satisfaction from knowing that they are contributing to health policies that will improve the health of future children. (Data are not returned to subjects.)

#### Framework of Cohort Study

- Cohort size: 90,000 subjects for MoBa Study (1999 to September 2007), and 101,042 subjects for BSMB Study (1997–2002).
- Recruitment of subjects: For the MoBa Study, pregnant women who scheduled an ultrasound examination were mailed an application package (with questionnaire and consent form) inviting them to participate in the cohort. For the BSMB Study, pregnant women who were diagnosed as being pregnant by their GP received an application package from the GP inviting them to participate in the cohort.
- Biological samples: Maternal blood samples were taken by a GP during routine checkups, which were then sent to the study center by GPs. Umbilical cord blood samples were taken at birth at hospitals and were sent to the study center by hospitals.
- Survey forms (consent forms): Mothers sent their consent forms to the study centers. For the MoBa Study, the children themselves were notified upon reaching 15 years of age, and were required to fill out their own consent form at 18 years of age. The BSMB Study is

designed to keep data and conduct follow-up study using registries until the child reaches 20 years of age.

- Study centers: All survey forms and biological samples were comprehensively managed by a central institution (Norwegian Institute of Public Health and Danish State Serum Institute respectively). Phone inquiries from study subjects were also handled by the central institution.
- Scientific study projects: Researchers and other parties can apply for access to the data and samples, subject to review of the application.

### **C. Hospital-Based Cohort—Generation R Study**

The characteristics of the hospital-based birth cohort conducted by the Erasmus University Medical Center of the Netherlands are summarized below.

#### **Social Background**

The Netherlands has a population of 16,419,000 (UN survey, 2007). The total fertility rate is 1.73 with 199,000 births per year (UN survey, 2000–2005). National health care basically covers all costs related to birth. When it is discovered that a woman is pregnant, the family doctor refers the woman to a local midwife center, where pregnant women receive advice and routine checkups. Childbirth typically takes place at the home, with the assistance of a midwife.

The cohort target area was Rotterdam, which has a population of approximately 600,000 including a sizable population of immigrants. (Only 56% of the population in the target area are of Dutch origin). There are 4,300 births per year in Rotterdam.

#### **Advantages for Subjects**

Subjects are informed of the overall status of the cohort through newsletters, symposiums, and other avenues. Children receive a birthday gift when turning 5 years of age. In addition, subjects receive various giveaways that are provided by sponsors of the study, such as discount coupons for amusement facilities. Subjects also gain the satisfaction of knowing that they are contributing to health policies that will improve the health of future children.

Subjects who choose to take part in the focus cohort are referred to a specialist if their tests reveal any irregularities.

#### **Framework of Cohort Study**

- Cohort size: 9,778 including 1,232 subjects for the focus cohort (2002–2006).
- Recruitment of subjects: Recruitment was concentrated on women from the target study area who became pregnant during the study period and visited a midwife or obstetrician. These women received a Generation R Study information package from the midwife or physician. The study staff then contacted the pregnant women by phone in order to have them fill out a consent form at the first ultrasound examination. Subjects were asked to fill out written consent forms leading up to each of four study phases (at birth, 1–4 years of

age, 4–12 years of age, and 12–20 years of age). Fathers were recruited for the study (for questionnaires and blood samples) through the mothers.

- Focus cohort: Of the subjects in the regular study, subjects born to two generations of Dutch-born citizens (parents and grandparents, on both the maternal and paternal side) were recruited for a focus cohort prior to postnatal week 25.
- Biological samples: Blood and urine samples were taken during routine checkups.
- Survey forms: Forms were sent to mothers by postal mail.
- Study centers: The contact center for subjects was the Generation R Study office within the Erasmus University Medical Center. A Generation R Study examination room was established within the Sophia Children's Hospital and equipped with facilities for performing ultrasound examination, taking blood samples, and testing for sinus infections. A behavioral observation room for children was also established and equipped with one-way mirrors and video cameras.

Measurements were taken at two centers.

Storage and analysis of samples is performed at the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam Medical Diagnostic Center.

- Scientific study projects: Projects are conducted by researchers and graduate students from the university. Joint research is also conducted with researchers from outside the university.

#### **D. Research-Based Cohort—Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study**

The characteristics of the birth cohort conducted by researchers from Utrecht University of the Netherlands are summarized below.

##### **Social Background**

Same as for BSMB Study.

##### **Advantages for Subjects**

Parents with concerns about allergies and asthma gain the reassurance of having these aspects investigated from participating in the study. Subjects also receive a newsletter and a gift on their child's birth. In addition, subjects gain the satisfaction of knowing that they are contributing to promoting better health for future children.

##### **Framework of Cohort Study**

- Cohort size: 4,146 including 855 subjects for intervention study (1996–1997). Subjects are tracked for at least 8 years.
- Recruitment of subjects: Subjects were recruited from throughout the Netherlands by midwives. Participation started from the third month of pregnancy.
- Intervention study: Involved a double-blind test using mite-impermeable bedding (mattress and pillow covers) and placebos (standard cotton bedding).

- Biological samples: Heel-prick blood (for phenylketonuria screening), venous blood, and DNA of parents and children.
- Environmental exposures: Analysis of indoor dust and assessment of exposures from nearby roads.
- Survey forms: Forms were filled out by subjects.
- Study centers: The study was mainly implemented by the Institute for Risk Assessment Sciences of Utrecht University and the Netherlands' National Institute of Public Health and the Environment (RIVM), with the cooperation of university hospitals (Utrecht University, University of Groningen and Erasmus University, Rotterdam) and Sanquin Research of Amsterdam.
- Scientific study projects: Projects are conducted by researchers and graduate students of the cooperating institutions.

## 2-2. Cohort Study Design and Status

### A. The Norwegian Mother and Child Cohort Study (MoBa)

#### Purpose

To collect as much data as possible concerning exposures and health outcomes, in order to respond to hypotheses that may arise in the future. The study is not aimed at proving specific etiological hypotheses.

#### Statistical Premise

No basis was given for specific hypotheses.

**Table 1**  
*Examples of exposures and health outcomes to be investigated in the Norwegian Mother and Child Cohort Study.*

<b>Examples of exposures</b>	<b>Examples of diseases</b>
Medication	Pelvic pain
Hereditary factors	Congenital malformations
Infections	Stillbirth
Dietary factors	Premature birth
Environmental toxins	Cancer
Physical activity	Diabetes
Work situation	Asthma/allergy
Occupational hazards	Rheumatism
Interpersonal relationships	Depression
Personal habits	Breast cancer

Source: Protocol—the Norwegian Mother and Child Cohort Study



## Recruitment of Subjects

Recruitment was concentrated on pregnant women who scheduled an ultrasound examination at hospitals or clinics that met the criteria of handling at least 100 childbirths annually. The women were mailed an invitation to participate in the study that also included a brochure, consent form, first questionnaire, and paternal questionnaire.

## Profile of Subjects

All births in the Netherlands were eligible for the study. Invitations were sent at each pregnancy, with a 42.7% rate of return. The participation rate was 45% among those recruited. At postnatal 18 months, the interview response rate was 77%.

## Data Collection

### *Mailed Questionnaires:*

- The study was conducted by mailing questionnaires at the following stages:
  - 13–17th week of pregnancy (questions about previous outcomes of pregnancy, history of medication and medical treatment, occupation, exposures in workplace and home, lifestyle and habits, and mental condition)
  - 22nd week of pregnancy (frequency of food intake)
  - 30th week of pregnancy (health condition during pregnancy, changes in lifestyle and occupation)
  - Postnatal 6 months (health and nutritional status of child, status of mother's physical and mental health),
  - Postnatal 18 months (status of child's development),
  - 3 years (status of child's development),
  - 7 years (to be implemented)
- The paternal questionnaire contained questions about the father's workplace exposures, lifestyle, and clinical history.
- The survey forms were automatically tabulated by scanning.
- The survey forms to be used at 7 years of age are currently being prepared, with an option for respondents to choose from a mailed written survey or an online survey.

### *Dietary Survey*

The frequency of food intake was studied through the questionnaire at the 22nd week of pregnancy.

### *Biological Samples*

Blood samples were taken at the time of ultrasound examination (17th week) for women who had already mailed in their consent forms. Paternal blood samples were also taken if the father attended the examination and consented to giving a sample. The mother's consent form was filled out at this time if it was not already mailed in. Maternal and umbilical cord blood samples were taken at birth. Blood and DNA samples are stored at the Norwegian

Institute of Public Health and preserved at temperatures of  $-85^{\circ}\text{C}$  and  $-25^{\circ}\text{C}$ , respectively. Blood samples were dispensed in multi-well trays.

#### *Information from Registries*

Registry information for childbirth, medication, cancer, cause of death, and immunizations can be accessed. Norway is also preparing a patient discharge registry, whose information can eventually be linked.

### Information Management

All working information was managed for each pregnancy using an Oracle database. The database is also linked to the registries.

## **B. Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study**

### Purpose

To learn about childhood disease and fetal development and their determinants from the perspective of complications at pregnancy and early exposures. The study places a particular emphasis on learning about the impacts of medication and infectious disease. The scope of the study covers all diseases that could be due to fetal exposures affecting childhood and beyond. The study establishes both a medication database and a biobank.

### Statistical Premise

*Table 1. Smallest detectable relative risk (RR) in a case-control analysis nested within the cohort, using four controls per case<sup>a</sup>*

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

The estimates are based on 80% power to detect the indicated relative risk (or higher) at a testing level of 0.05 in a cohort of 100,000 newborns.

<sup>a</sup>*Sources:* Sundhedsstyrelsen Sundhedsstatistik 1999: 3 and Basso et al. Am J Epidemiol 1999; 150: 598–604.

Source: Scand. J. Public Health 29 300-307. 2001.

## Recruitment of Subjects

Ninety-five percent of female subjects received an application package from a GP inviting them to participate in the cohort study, at the time of receiving a medical examination from a GP for pregnancy diagnosis (6–12th week of pregnancy). The remainder of the female subjects received an application package from a midwife.

## Profile of Subjects

Recruitment was concentrated on all pregnant women who visited a GP and intended to carry through with their pregnancy, and who possessed an adequate knowledge of the Danish language. The participation rate was approximately 30% among those recruited. At postnatal 18 months, the interview response rate was 75%.

## Data Collection

### *Phone Interviews*

Computer-assisted phone interviews were conducted at four stages in order to collect information not recorded in medical histories. The four stages and average duration of phone interviews were as follows: 12th week of pregnancy (18 minutes), 30th week of pregnancy (10 minutes), postnatal 6 months (16 minutes), and postnatal 18 months (10 minutes).

### *Dietary Survey*

Survey forms were sent to all subjects at the 25th–26th week of pregnancy, containing questions about intake of supplements and diet during the previous month. The survey forms were automatically tabulated by scanning.

### *Social and Occupational Status*

Data concerning social and occupational status were obtained from registries.

### *Air Quality, Drinking Water Quality*

Associations with air quality and drinking water quality can be analyzed based on address data.

### *Biological Samples*

Maternal blood samples were taken by a GP during routine checkups conducted at the 6th, 12th, and 24th weeks of pregnancy. Whole blood samples were mixed with EDTA and sent to the study center by standard postal mail. Umbilical cord blood samples were taken immediately after birth at the hospital by a midwife or nurse and were kept in refrigerated storage until they were sent by standard postal mail.

When blood samples were received by the Danish State Serum Institute, four whole blood spots are put on filter paper. The blood sample is then separated. Plasma and buffy coats are put into liquid nitrogen and in freezers at  $-20^{\circ}\text{C}$ .

## Information Management

All working information is managed by computer and consists of interview schedules, deadlines for mailing letters, addresses, phone numbers, and changes to this information. The computing platform is keyed by the participant ID number, and is also linked to biobank and questionnaire data. It can also be linked to registry data based on national ID numbers.

## Framework for Implementation

### *Management Body*

Comprises approximately four researchers responsible for implementation of the study.

### *Steering Committee*

Comprises representatives of the Danish National Research Foundation, National Board of Health, Danish State Serum Institute, county governments, and midwives organizations. The project leader is Jorn Olsen.

### *Advisory Board*

Comprises representatives of professional organizations for midwives, GPs, obstetricians, pediatricians, child nurses, and a member from a parenthood organization.

## C. Generation R Study

### Purpose

To identify environmental and genetic factors that impact development and health from the fetal period through adolescence. The study has four main areas of focus: (1) Growth and physical development, (2) behavior and development of cognitive skills, (3) childhood illness, and (4) health status and health management of pregnant women and children.

The major purposes of the study are as follows:

- Record growth from fetal period through adolescence
- Identify biological, environmental, and social factors that have an impact on growth from the fetal period through adolescence
- Verify the effectiveness of current methodologies for early identification and prevention of high-risk groups

### Statistical Premise

No premise is provided for concrete hypotheses. The general discourse is as follows:

**Table 9.** Effects sizes in standard deviation that minimally can be detected according to the prevalence of the exposure

Proportion exposed (%)	Whole cohort (n = 7000)	Focus cohort (n = 700)
50	0.067	0.212
25	0.077	0.276
10	0.112	0.353
5	0.154	0.486
1	0.337	1.064

The presented effect sizes are detectable proportions of the standard deviation with a type I error of 5% and a type II error of 20% (power 80%).

**Table 10.** Relative risks that minimally can be detected according to the prevalence of the exposure

Proportion exposed (%)	Incidence (1 year) of outcome of interest					
	Whole cohort (n = 7000)			Focus cohort (n = 700)		
	10%	5%	1%	10%	5%	1%
50	1.23	1.33	1.83	1.83	2.28	4.94
25	1.26	1.38	1.94	1.96	2.46	5.41
10	1.39	1.56	2.42	2.48	3.26	7.92
5	1.55	1.80	3.09	3.20	4.39	11.74
1	2.36	3.04	6.83	7.75	11.61	37.55

The presented effect sizes are detectable relative risks with a type I error of 5% and a type II error of 20% (power 80%).

Source: European Journal of Epidemiology 21, 475-484. 2006.

## Recruitment of Subjects

Pregnant women received a Generation R Study information package from a midwife or physician. Study staff then contacted the pregnant women by phone and interviewed the women at the first ultrasound examination in order to have them fill out a consent form. Fathers were indirectly recruited for the study (questionnaires and blood samples) through the mothers. The participation rate among pregnant women (prior to birth) was 91%.

## Profile of Subjects

Recruitment was concentrated on individuals who were residents of the target study area (Rotterdam) at the time of giving birth, and who gave birth during the period of the study between April 2002 and January 2006. The study sought to recruit subjects during early pregnancy, but pregnant women were also recruited up until the time of birth. The participation rate was 61% among those recruited.

## Data Collection

### *Medical Examinations*

- The study sought to learn the health status of mothers through three sets of medical examinations conducted in early (for subjects who joined in early pregnancy), mid-, and late pregnancy.

- Children's growth was recorded through ultrasound examination at each routine checkup and by collecting information from examinations conducted at birth. Additional information is currently being collected from physical examinations, questionnaires, and routine checkups conducted through 4 years of age. For the focus cohort, additional ultrasound examinations (to measure brain, heart and kidney development) were conducted as well as taking biological samples (blood and saliva).
- At 5 years of age, a session lasting from 2.5 to 3 hours is implemented for ultrasound examination and behavioral observation, and for taking biological samples (saliva, mucous, etc.).

#### *Questionnaires*

Information was collected through questionnaires sent by postal mail. Subjects who joined in early pregnancy were sent separate questionnaires at the 12th, 15th, 20th, and 30th weeks of pregnancy.

#### *Complications During Pregnancy, Pregnancy Outcomes*

A coding system was used to classify complications and outcomes from hospital and midwife records.

#### *Information on Paternal Exposures*

Information was collected through medical examinations and questionnaires for the fathers. Biological samples (blood) were also taken.

#### *Dietary Survey*

The survey forms included questions about the mother and child's diet.

#### *Biological Samples*

- Maternal blood samples were taken in early pregnancy (35 ml) and mid-pregnancy (20 ml). Paternal blood samples were taken prior to birth (10 ml). The plasma and serum volume were distributed into 250  $\mu$ l aliquots and stored at  $-80^{\circ}\text{C}$ . DNA was extracted from buffy coat and stored leukocytes.
- Children's DNA was extracted from umbilical cord blood. DNA was supplemented by obtaining mucous samples from the cheek after birth.
- Samples of maternal urine were taken only during the period from February 2004 to November 2005. The samples have been stored.

**Table 1.** Main outcomes per research area

---

<b>Growth and physical development</b>
Fetal growth patterns and organ development
Pregnancy complications
Postnatal growth patterns
Obesity
Risk factors for development of cardiovascular disease
Risk factors for type 2 diabetes
<b>Behavior and cognitive development</b>
Maternal and paternal psychopathology
Fetal and postnatal brain development
Behavior, psychopathology and cognition
Neuromotor development
Chronic pain
Attachment
Stress reactivity
<b>Diseases in childhood</b>
Infectious diseases in childhood
Development of the immune system
Asthma and asthma related symptoms
Paroxysmal neurological disorders
<b>Health and healthcare</b>
Quality of life
Health care utilization
Effectiveness of screening programs

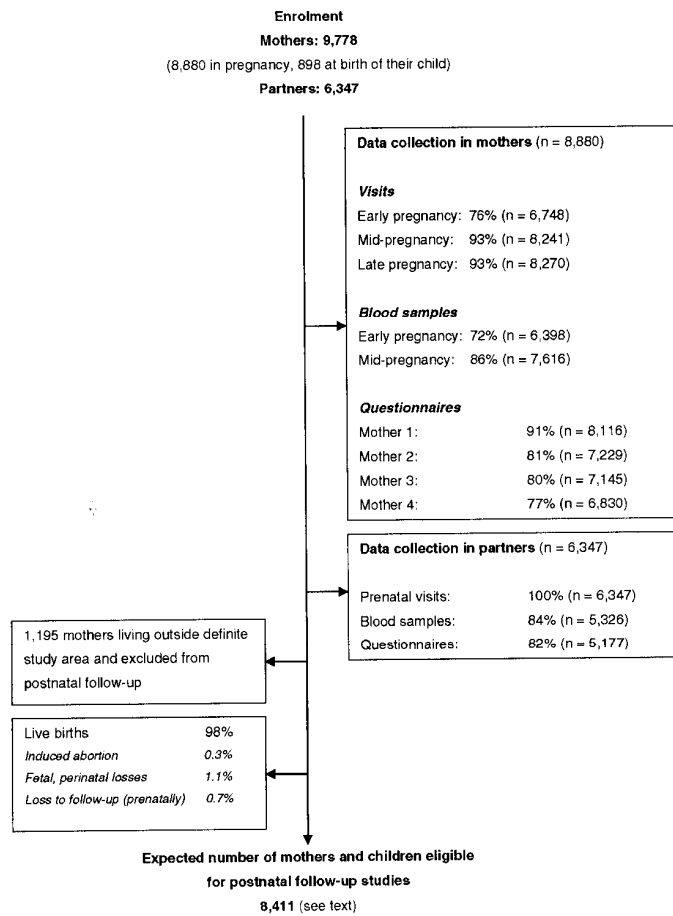
---

**Table 2.** Main determinants

---

<b>Biological determinants</b>
Parental anthropometrics and blood pressure
Fetal and postnatal growth characteristics
Endocrine and immunological factors
Genetic variants
<b>Environmental determinants</b>
Maternal and childhood diet
Parental life style habits (including smoking, alcohol consumption)
Housing conditions
<b>Social determinants</b>
Parental education, employment status and household income
Parental marital status
Ethnicity

---



**Figure 2.** Participant enrolment and measurements in the first phase.

**Table 3.** Assessments in the prenatal phase

**Assessments in mothers**

Physical examinations: height, weight, blood pressure  
 Questionnaires: socio-economic status, ethnicity, housing, living conditions, diet, medical history, family history, drug use, life style habits, use of medical services  
 Interviews: expectations of parents to be (only in focus cohort)  
 Biological samples: blood and urine samples (storage, DNA)  
 Fetal ultrasounds: gestational age, fetal growth and in the focus cohort fetal brain, heart and kidney development, fetal blood flow distribution and placental function

**Assessments in partners**

Physical examinations: height, weight, blood pressure  
 Questionnaires: socio-economic status, ethnicity, housing, living conditions, medical history, family history, drug use, life style habits, Use of medical services  
 Interviews: expectations of parents to be (only in focus cohort)  
 Biological samples: blood samples (storage, DNA)

**Assessments in newborns at birth**

Physical examinations: weight  
 Cord blood sample (storage, DNA)



**Table 4.** Assessments in mothers, their partners and their children in the prenatal phase

	Early pregnancy	Mid-pregnancy	Late pregnancy	Birth
<i>Mother</i>				
Physical examination	+	+	+	
Questionnaire	+	+		
Interview			F	
Fetal ultrasound examination	+	+	+	
Additional detailed fetal ultrasound			F	
Blood sample	+	+		
Urine sample	+	+	+	
<i>Partner</i>				
Physical examination	+			
Questionnaire		+		
Interview			F	
Blood sample	+			
<i>Child</i>				
Physical examination				+
Cord blood sample				+

+ = Assessment in whole cohort.

F = assessment only in focus cohort.

Early pregnancy: gestational age < 18 weeks; mid-pregnancy: gestational age 18–25 weeks; late pregnancy: gestational age ≥25 weeks.

Source: European Journal of Epidemiology 21, 475-484. 2006.

## Environmental Exposures

A geographic information system (GIS) was used to obtain the distance from roads using address data. This was combined with models for dispersion of noise and pollutants, in order to analyze the association between exposures from vehicle traffic and the impact on health.

## Information Management

Subjects were assigned a unique code for management of study data and other information. Data were stored in a separate database from the personal information database.

## Framework for Implementation

Measurements were taken at two centers.

Storage and analysis of biological samples is performed at the STAR, Rotterdam medical diagnosis center.

Research based on the cohort is conducted by a number of teams from the Erasmus University Medical Center, with the cooperation of Erasmus University and the Public Health Service of the Rotterdam Region. Outside requests for research are reviewed by the Generation R Study Research and Management Group, and the ethical committee of the Erasmus University Medical Center.

## **D. Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study**

### **Purpose**

To study the effect of reductions in allergens on childhood development of asthma, by recruiting mothers with allergic anamnesis and conducting a double-blind test of their children involving the use of mite-impermeable bedding. Also, to evaluate the role of environmental and dietary risk factors in relation to childhood development of allergic diseases, by recruiting mothers with and without allergic anamnesis and observing the development of asthma in their children.

### **Statistical Premise**

Of the placebo group, 50% of subjects developed allergies until 8 years of age. It was postulated that treatment through the use of mite-impermeable bedding would have a 1.5-fold effect on reducing the development of allergies, lowering the rate of developing allergies to 33%. In order to detect these effects, it was determined that at least 200 subjects were needed in each group. Consequently, the design of the study enabled a statistical tolerance of up to 50% variation without bias.

### **Recruitment of Subjects**

Questionnaires were distributed for screening purposes at approximately 50 prenatal health clinics (altogether handling roughly 12,000 births per year). The questionnaires were distributed by midwives at the first prenatal examination. The total number of usable returns was 10,232 (out of 10,819 responses), of which 2,949 persons were found to match the criteria of atopic mothers, for a rate of 28.8% of all usable returns. Of this group, 1,986 persons were invited to participate in the intervention study and 965 persons were invited to participate in the follow-up study. The rate of consent for participating in the study was 42% (855 persons) and 49% (472 persons), respectively, in the intervention study and follow-up study. Of the 5,084 persons who matched the criteria of non-atopic mothers, 55% (2,819 persons) consented to participate. Participation in the cohort took place in the third month of pregnancy.

### **Profile of Subjects**

Recruitment was concentrated on individuals who were residents of the target study area at the time of giving birth, and who gave birth during the period of study between the summer of 1996 and fall of 1997. The rate of ongoing participation was high, at greater than 90% at 3 years of age. The dropout rate was slightly higher in the intervention study group, which is thought to be related to the higher demands for subjects in the intervention study. One of the reasons for the high rate of ongoing participation overall is due to the study's emphasis on requiring long-term cooperation from subjects. This point was stressed at the time of recruitment, and individuals were advised not to participate if they could not fulfill the long-term obligation.

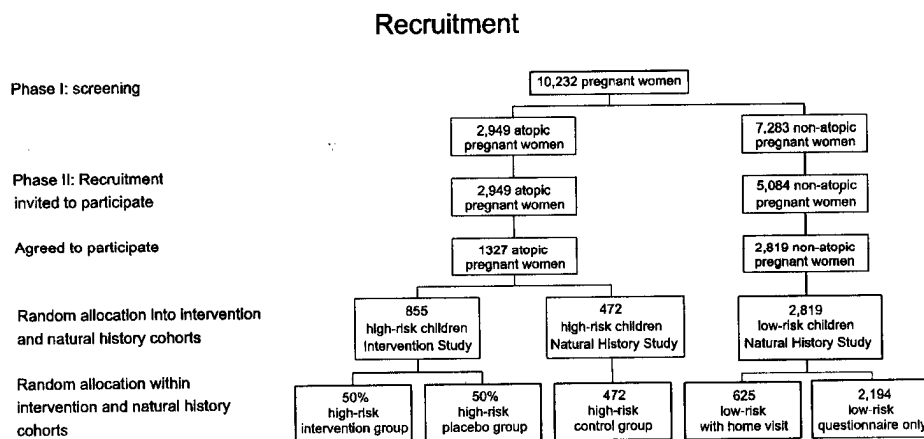


Fig. 2. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) recruitment scheme.

Source: Brunekreef B. et al. (2002) The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results. *Pediatr. Allergy Immunol* 2002; 13 (Suppl. 15): 55-60.

- Recruited: 3291
- entry questionnaire: 3289
- 3 months q sent: 3283
- 3 months q rec'd: 3174
- 1 yr q sent: 3243
- 1 yr q received: 3029
- 2 yr q sent: 3167
- 2 yr q received: 3053
- definitely lost: 8
- definitely lost: 40 (+8=48)
- definitely lost: 76 (+48=124)

Fig. 4. Loss to follow-up in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) 'natural history' cohort.

Source: Brunekreef B. et al. (2002) The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results. *Pediatr. Allergy Immunol* 2002; 13 (Suppl. 15): 55-60.

## Data Collection

### *Medical Examinations*

Medical examinations were implemented by taking venous blood samples for IgE measurement, taking measurements of height and body weight, and checking for atopic inflammation of the skin. Pulmonary functions in the form of peak flow, respiratory NO, and airway resistance (Rint) were also measured.

### *Records*

Records of allergy symptoms and symptoms of respiratory tract infection were obtained from parents until the first year after birth. Records were also kept of medical examinations, diagnosis, treatments, and medications.

### *Questionnaires*

Questionnaires were implemented at each home visit and included questions about the family history of allergies, nutrition, passive smoking, breastfeeding, home situation, and daycare use.

### *Dietary Survey*

Questions about diet were included in the questionnaires.

### *Biological Samples*

Heel-prick blood samples (for phenylketonuria screening) were taken from the intervention study group during a home visit conducted at postnatal 12 months. The samples were subjected to IgE analysis. DNA samples were also taken from parents and children.

### *Survey Forms*

Survey forms were filled out by the subjects.

Table: PIAMA Observation Scheme

<b>Study Population Study Time Frame</b>	<b><u>Intervention Study Intervention Group</u></b>	<b><u>Intervention Study Placebo Group</u></b>	<b><u>Natural History Study Atopic control</u></b>	<b><u>Natural History Study non-atopic: with home visit</u></b>	<b><u>Atopic control non-atopic: Questionnaire only</u></b>
<b>2 Month before Birth</b>	Questionnaire, Covers, Dust, Visit	Questionnaire, Covers, Dust, Visit	Questionnaire	Questionnaire	Questionnaire
<b>3 Month after Birth</b>	Questionnaire, Dust, Visit	Questionnaire, Dust, Visit	Questionnaire, Dust, Visit	Questionnaire, Dust, Visit	Questionnaire
<b>1 Year after Birth</b>	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire	Questionnaire	Questionnaire
<b>2 Years</b>	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
<b>3 Years</b>	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
<b>4 Years</b>	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire
<b>5 Years</b>	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
<b>6 Years</b>	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
<b>7 Years</b>	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
<b>8 Years End of Study</b>	Questionnaire, Examination	Questionnaire, Examination	Questionnaire, Examination	Questionnaire, Examination	Questionnaire, Examination

Source: Fig. 3 The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) observation scheme. Brunekreef B. et al, (2002) The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results. *Pediatr. Allergy Immunol* 2002; 13 (Suppl. 15): 55-60.

## Environmental Exposures

### *Dust Samples*

For the intervention study group, dust samples were obtained from floors and mattresses during home visits conducted prior to birth and at 3 and 6 months after birth. For the follow-up study group, dust samples were obtained from floors and mattresses during home visits, but at one-third of the frequency (taken at 3 months after birth only).

### *Use of Geographic Information System*

A geographic information system (GIS) was used for assessment of environmental exposures (distance from nearby roads).

### *Use of Registries*

Information about medications dispensed by pharmacies was accessed from registries.

Table: Strengths and Limitations of PIAMA Study Topics

Topic	Strength	Limitation
• Diet and physical activity	• Included in questionnaire	• Not validated
• Environmental exposures: home characteristics, pets, combustion products, siblings, daycare, passive smoking	• Includes passive smoking Validated Rest: used frequently	
• Circumstances of birth	• Registered during check-up	
• Respiratory and eczema ISAAC	• Validated for 7-12 years of age Standardized application	• Not validated at early age Worldwide Longitudinality not validated “Too European?”
• Respiratory, allergy, and eczema in parents and siblings ISAAC and European Community Respiratory Health Survey	• Validated and standardized	
• Other: quality of life, health services use, and so on		

Source: National Children’s Study Workshop Methods for the Assessment of Asthma-Related Health Outcomes. May 27–28, 2004. Rosen Centre Hotel Orlando, FL  
[http://www.nationalchildrensstudy.gov/events/ncs\\_assembly/2004\\_May/Asthma-outcomes052004.cfm](http://www.nationalchildrensstudy.gov/events/ncs_assembly/2004_May/Asthma-outcomes052004.cfm)

## Framework for Implementation

The study was mainly implemented by the Institute for Risk Assessment Sciences of Utrecht University and the Netherlands’ National Institute of Public Health and the Environment (RIVM), with the cooperation of university hospitals (Utrecht University, University of Groningen and Erasmus University, Rotterdam) and Sanquin Research of Amsterdam.

## 3. Issues for Discussion

### 3-1. Cohort Design

#### A. Important Considerations for Cohort Design

At each visit by the survey panel, it was indicated that the cohort design had increased in importance at the present juncture. The panel was therefore advised to publish a research paper on the cohort design in conjunction with launching the cohort.

The survey panel was also advised that it is necessary to spend sufficient time at the design stage to discuss the rationale and logic of the research. In particular, the PIAMA Study staff advised that it is necessary to clearly identify the purposes of the cohort study and information that had to be obtained for these purposes in designing the cohort. The PIAMA Study staff further emphasized that the purposes of the study should not be changed after they are initially established.

Each of the cohort staff advised that there is a tendency from their perspective to seek as much information as possible by increasing the frequency of asking questions and sample-taking and the volume of questions and samples. At the same time, there is a tendency for study subjects to drop out of the study if the demands of the study take up too much time. Since participation tends to decline when cohort staff demand too much from subjects, the cohort design should also consider the reactions of subjects as well as the scientific validity.

Regarding the feasibility of implementing the cohort as it was designed, it was repeatedly stressed that cohort staff should conduct thorough verification and make any adjustments that are needed during the pilot study. Of course, any circumstances that require changes to the cohort design (after the actual study launch) can endanger the feasibility for continuing the cohort. It is therefore necessary to identify all possible issues and carefully consider the countermeasures during the pilot study, while accounting for the differences in scale between the pilot study and actual study.

## **B. National-Scale Cohorts**

Comprehensive, nationwide studies are best conducted as national projects. The national cohort projects implemented by Norway and Denmark both were successful in collecting homogeneous, nationwide data by implementing the same schedule and identical survey forms across their respective countries. The large-scale, nationwide cohorts implemented by Norway and Denmark were also successful because they were comprehensively managed by an independent central institution.

Relating to the discussion below, it is also possible to execute a nationwide cohort by dividing the cohort into geographic regions and establishing study centers in each region, with each study center responsible for starting and managing the cohort. However, this can result in multiple parallel cohorts, so that the overall project ceases to exist as a large-scale cohort. Furthermore, a comprehensive cohort cannot be achieved if the study centers adopt different study designs for their own research purposes.

## **C. Multicenter Cohorts**

In the case of the PIAMA Study, the target study area was spread across three geographically separate regions. A university in each region was responsible for implementing the study in that region under comprehensive design guidelines. The PIAMA cohort staff indicated that there were serious issues with the standardization of various procedures and methodologies, and the cohesiveness of the criteria used for diagnosis. In addition, the PIAMA cohort staff suggested that standardization throughout the cohort could be achieved by adopting an internationally standardized set of diagnosis criteria, if such criteria were available.

The PIAMA cohort staff advised that comparison and cooperation with other cohorts could be better facilitated by adopting a standardized methodology for epidemiological investigation that is used extensively worldwide, such as the International Study of Asthma and Allergies in Childhood (ISAAC), using it also for the contents of questionnaires. Furthermore, it was indicated that in the case of a multicenter cohort, it is important to bring together all field staff responsible for data collection to receive training in one central location.

## **D. Cohorts and Subcohorts**

The Generation R Study was established for the purposes of educational and research institutions, in contrast with the Norwegian and Danish cohorts that were conducted as national projects. At the outset of the Generation R Study, a subcohort comprising around 10% of the overall cohort were chosen as a focus cohort study in order to study supplemental items. One reason for establishing a subcohort was to eliminate possible disparities in child development caused by differences in ethnic background, by focusing on subjects born to two

generations of Dutch-born citizens. In addition, it was decided to designate a single technician to take all measurements, in order to eliminate disparities from having different technicians take ultrasound organ measurements. This decision effectively limited the number of measurements that could be taken and was another reason for establishing a subcohort.

Both the PIAMA Study and the Generation R Study were conducted for research purposes. The PIAMA Study was initially intended as an intervention study and is therefore divided into an intervention study and follow-up study. The intervention study is further divided into an intervention group and placebo group that together comprise approximately 20% of the overall sample size.

The staff of the PIAMA Study and Generation R Study chose to establish subcohorts for focus study within the overall cohort. The staff of these studies indicated that this approach is better for conducting statistical analysis based on the large sample size of the overall cohort, while also obtaining detailed data from the small sample size of the subcohort.

However, there is a strong possibility that the response to the study can be affected by subjects' knowledge of the subcohort. For example, subjects' responses can be affected by their knowledge that the subcohort follows different operational guidelines from the overall cohort, such as a greater volume of questions, examinations, and samples, and different types of questions and examinations. The response can also be affected by subjects knowing that their selection for the subcohort is relevant to their health, such as belonging to a high-risk group for a specific disease. Consequently, the cohort must be carefully designed in order to determine that establishing the subcohort is essential for the purposes of the study, and that the subcohort can be implemented so that it does not confuse the overall study results.

## 3-2. Cohort Administration

### A. Administrative Organization

The Norwegian and Danish cohorts were implemented as national projects with approximately 60,000 subjects. The administration staff involved with these cohorts recommended that daily decision making should be handled by a management body comprising several operational managers working closely together. Due to the nature of the work, the operational managers must work in close physical proximity to each other. In the case of the Norwegian and Danish cohorts, all operational tasks were conducted within one institution.

For the Norwegian and Danish cohorts, a steering committee and/or an advisory board was established in order to advise the operational managers and reflect the opinions of the parties concerned. The steering committee comprises staff such as from study sponsors and government organizations, while the advisory board comprises staff from organizations that conduct the actual field work of recruiting study subjects and taking samples. Of course, all actions relating to the operation of the cohorts are first approved by the ethical committees of the respective organizations and institutions, and with the approval of the state data inspectorate.

All contact and forwarding addresses for the cohort operation are consolidated under the institution to which the operational managers are assigned. This includes telephone help lines for subjects, forwarding addresses for completed questionnaires, and forwarding addresses for physicians to send biological samples.

At the time of the visit by the survey panel, all of the studied cohorts had finished recruiting subjects. Consequently, the cohorts only needed a staff of several working members supervised by operational managers, in order to field calls, enter data, and maintain databases, despite the large scale of the cohorts. When the cohorts were first launched, the staff size was several times larger in order to perform tasks such as conducting phone interviews and asking subjects to return questionnaires that had been forwarded to them.

## **B. Computer Usage**

(The following information applies to cohorts other than the PIAMA Study, since the PIAMA Study is not yet at the phase of collecting detailed information.)

All of the cohorts utilize computer management for operating schedules, operations information, and samples. Computer information management is exclusively conducted using unique ID numbers that are assigned to each participant, in order to facilitate cohort information management. Access to link keys for personal information and registry information is strictly controlled.

The cohorts use computers and peripheral equipment to improve operational efficiency and reduce human error. For example, the Danish cohort uses computers to manage contact information for subjects and work schedules (such as for contacting subjects). Phone interviews are also conducted with the assistance of computers. In addition, the Norwegian and Danish cohorts use scanning equipment to automatically tabulate survey forms.

The Norwegian cohort will give subjects a choice of receiving mailed survey forms or filling out survey forms online, starting from the next survey forms to be implemented at 7 years of age. The Norwegian cohort staff indicate that there are many advantages to using computerized survey forms, since they can be easily tabulated and designed to eliminate errors from illogical answers. Computerized survey forms also reduce the number of unnecessary questions that subjects have to view, by automatically skipping over questions based on answers to previous screening questions. It will be interesting to see how the study subjects respond to this implementation.

### **3-3. Data Management and Use**

#### **A. Information Access**

Databases are used to manage all personal information of cohort subjects, in addition to information from survey forms and for biological samples. For the Norwegian and Danish cohorts, researchers can apply to access cohort information. For the Generation R Study, access to cohort information is restricted to joint research projects only.

In all of the above examples, access to information requires the submission of a study planning document and approval through a screening process.

#### **B. Biological Samples**

All of the cohorts studied were engaged in sample-taking and storage of blood for use as biological samples.

For the Generation R Study, the actual cohort implementation was done by the staff of hospitals who performed medical examinations on mothers. With the exception of the



Generation R Study, the rest of the cohorts advised that two major precautions had to be observed for taking biological samples. One is to define the procedures for taking and sending samples, and to stress the significance of observing the procedures to ensure the success of the cohort study. The other is to convey these procedures to physicians, nurses, and other staff who actually take samples (blood samples at routine checkups or umbilical cord blood samples after birth), and to gain their cooperation and understanding of the importance of the procedures.

Factors such as the container material used to hold the blood sample, type of reagent added, temperature during transport, and length of time after taking the sample can limit the scope of analyzable items. Furthermore, after samples are received, they must be dispensed and separated according to a later schedule for analysis, and each sample must be stored at an appropriate temperature. Therefore, it was pointed out that it is necessary to draw up detailed and long-term plans for handling of biological samples at the research design phase.

It was also advised that the cohort information database should include information about the history of samples, for storage purposes. This includes information about the length of time in transport, and the timing and frequency when samples are thawed for partial use.

Actual biological samples are almost never provided to outside parties for research purposes. However, in cases of requests by an outside party and backing by research funds, an outside party may be permitted to conduct additional analysis at the institution where the samples are stored. In terms of precedence, samples from the Norwegian cohort were analyzed for a research project by the U.S. National Institute of Environmental Health Sciences (NIEHS).

### 3-4. Cooperative Framework and Incentives

All of the cohort study staff stressed the need to offer incentives at the initial phases of the study and at each subsequent phase, for all parties involved.

Examples of incentives provided for subjects include the provision of newsletters and birthday gifts, and discount coupons provided by study sponsors. Additional incentives were offered for the Norwegian and Danish cohorts, in the form of a cash prize of 5,000 krone (equivalent to approximately 100,000 yen) for the 10,000th enrollment in the cohort, and prizes in a drawing for a family ski vacation.

For the Norwegian MoBa Study and the Dutch Generation R and PIAMA Studies, subjects were first informed of the cohort study by either a physician or a midwife. Consequently, it was advised that it is important for physicians and midwives to understand the importance of the cohort study, so that they believe that it is worthwhile to recruit subjects for the study. The Norwegian cohort staff led thorough discussions with organizations and unions representing physicians and midwives so that they would embrace the study. They also went to great lengths by visiting extensively with local maternity centers to hold briefing sessions during lunch breaks for physicians and midwives in the field.

Compensation is provided for work involved in implementing the cohort study. For the Norwegian and Danish cohort studies, there are no medical fees to be paid by subjects, but physicians are compensated for taking blood samples for the cohort study. Non-graduate and graduate students who assist the cohort operation can gain access to data, which they can use for their own research or dissertations, by working for the cohort study.

Private companies that sponsor the study realize an advertising benefit by gaining a higher public profile. The benefit for governments is that they gain a scientific base for health care

policies and access to a reference group, information database, and biobank for diverse future uses. Taxpayers benefit directly through the implementation of better government policies for health care that will benefit their own health, while benefitting indirectly from cost reductions that may be achieved.

For the Norwegian and Danish cohorts, the participation rate was observed to decline as the recruitment period progressed. The return rate for questionnaires also continued to decline as the tracking period progressed. Since both Norway and Denmark possess extensive registry systems, the cohorts in those countries can access a wide variety of information about cohort subjects from registries even if the cohorts stop receiving responses from the subjects. This includes information about social status, records of medication, and records of eyewear and hearing aid prescriptions. Moreover, since Norway and Denmark require mandatory military service, all citizens are required to undergo a detailed examination of their physical and mental health at 18 years of age, which can be linked to the cohort data. Norway and Denmark are also able to continue tracking the addresses of subjects.

In contrast, Japan has no such registry systems at this point, so it is not possible to similarly link a cohort to such registry information. Once the cohort loses contact with the participant, it may not be possible to collect further information.

For the PIAMA Study, the participation rate was maintained at rates between 85% and 90% after eight years. The high sustained participation rate is likely due to the large number of mothers participating in the cohort who have a specific interest in the issue of children's allergies.

The cohort staff were of the common opinion that it is essential to maintain the public profile of the cohort by continuing to release the results of the study beginning from the study launch, and to receive regular and continual public exposure such as from scientific papers and media coverage. These initiatives are necessary in order to recruit subjects and keep them participating in the cohort, and to continue securing adequate funding for the cohort.

### 3-5. Foreseeable Issues

#### **A. Ethical Guidelines and Informed Consent**

All of the cohorts studied are operated under the respective ethical guidelines established by the countries and institutions that implement the cohorts. These guidelines cover issues such as respect for human rights, verification of the purposes of research and validity of research methodology, and the framework for approving research plans.

Ethical guidelines typically require that researchers obtain informed consent and take steps to protect personal information from the standpoint of human rights.

All of the cohort staff indicated that they encountered difficulties with gaining consent for participation, due to the particulars of their respective birth cohort studies. These issues center around the prolonged length of the study (which can span several decades if children are tracked into adulthood), and the inability of designating study items that will become critical in the future.

Regarding the prolonged length of the study, the Norwegian cohort requires that the cohort must personally inform children once they reach 15 years of age, in addition to obtaining consent from the mother at initial participation in the study. In addition, new consent forms must also be obtained once the child reaches 18 years of age. For the Danish cohort, data may

be kept until the child turns 20 years of age, and follow-up study using registry information may be conducted based on the mother's consent given at the time of joining the cohort.

For the Dutch Generation R Study, the institution implementing the study divided the cohort into four phases (prenatal, 1–4 years, 4–12 years and 12–20 years) and obtained written consent from the mother at each phase.

In all of the above examples, the subjects and mothers do not have the right to access their personal data. However, by withdrawing their consent to participate in the cohort, they can request that their personal data (information and biological samples) be destroyed.

## **B. Ethical Guidelines and Study Design**

Regarding the inability to designate study items that will become critical in the future, this issue affects the validity of the research (cohort study design). Accordingly, all of the cohort studies except for the PIAMA Study do not outline specific hypotheses in their cohort design, nor do they propose an epidemiological means of study for elucidating the hypotheses. The cohorts only outline general hypotheses and do not venture beyond discussing the need to secure a sufficient sample size in order to verify hypotheses.

For the Norwegian cohort, the research design clearly states that the purpose of the cohort study is “to collect as much data as possible concerning exposures and health outcomes, in order to respond to hypotheses that may arise in the future. The study is not aimed at proving specific etiological hypotheses.”

Research projects that use these cohorts are all implemented under the approval of an individual screening process, based on proposals for funding obtained independently from the cohort study.

## **C. Pros and Cons of Intervention**

The biggest ethical issue that is likely to arise from research that uses cohort data is whether or not to inform the participant if a health issue is identified. For all of the cohorts studied, the informed consent for participation in the cohort clearly states that personal data will not be returned.

(The details of informed consent are not known for the PIAMA Study. According to Dr. Bert Brunekreef, the principal investigator of the PIAMA Study, some information must be provided to subjects in order to gain their loyalty to the cohort. However, it was our impression that Dr. Brunekreef did not want to discuss this issue in further detail.)

Regarding this issue, the Norwegian and Danish cohort staff indicated that there was some opposition to the implementation of the cohort study, based on the argument that it was unethical and did not benefit the subjects.

The Norwegian cohort staff indicated that there was a research project in Norway that conducted analysis of risk genes for Type I diabetes as part of the project and proceeded to inform mothers of children in the high-risk group. However, a lawsuit later arose under the claim that informing the subjects had incited fear. The research in question was eventually cancelled due to this pressure.

For the Generation R Study, the focus cohort study specifies that subjects are referred to a specialist if a health issue is discovered.

## **D. Protection of Personal Information and Information Security**

All of the cohorts studied have taken careful steps to protect personal information and implement information security. Subjects are identified only by a unique ID number, and sensitive data including personal information are separately managed. There are also extensive restrictions on linking IDs to data. Similar measures are in place to protect against linking to various registries.

Information security measures are used for maintaining and managing databases and data. Restrictions are in place for both physical and electronic access. Security measures are also in place for the maintenance and management of biobanks and stored biological samples.

## **3-6. Contributions of Later Cohorts**

### **A. Linking Data to Other Cohorts**

All cohort staff pointed out that there were certain possibilities that could be gained from linking data with existing internal and outside cohorts, such as to enable broader statistical analysis and perceive variations by region (ethnicity). It was commonly understood that data must be standardized for this purpose, including standardization of the content of questions, sample types, sample-taking method, items for analysis, and diagnosis. The PIAMA Study staff indicated that one solution is to develop and use a globally standardized methodology for epidemiological investigation, such as ISAAC.

### **B. Unique Contribution**

The prospects of a Japanese cohort were met with strong words of encouragement. It was specifically advised that later cohorts should endeavor to learn from the failures of earlier cohort groups in order to adopt better designs and methodologies, which in turn will deliver greater benefits with less funding and labor.

Regarding the possibility of Japan's making its own unique contribution to the global framework for health care policy, it was advised that Japan should endeavor to design a cohort that addresses the weaknesses of other cohorts, if possible. The specific examples given were as follows:

- Capitalize on advanced analytical technology by taking the initiative to implement measurements such as that of environmental pollutants in biological samples.
- Endeavor to establish a methodology for utilizing a strong track record of environmental monitoring in exposure assessments.
- Endeavor to take and bank RNA samples. Although DNA is easily handled, it is difficult to judge the results of DNA analysis. RNA samples require careful handling but provide direct markers for biological gene expressions. It was also suggested to establish a cDNA bank specifically focusing on developmental periods in order to become aware of the specific expression proteins at each stage of children's development.