

The SELMA Study: A Birth Cohort Study in Sweden Following More Than 2000 Mother–Child Pairs

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Abstract

Background: This paper describes the background, aim and study design for the Swedish SELMA study that aimed to investigate the importance of early life exposure during pregnancy and infancy to environmental factors with a major focus on endocrine disrupting chemicals for multiple chronic diseases/disorders in offspring.

Methods: The cohort was established by recruiting women in the 10th week of pregnancy. Blood and urine from the pregnant women and the child and air and dust from home environment from pregnancy and infancy period have been collected. Questionnaires were used to collect information on life styles, socio-economic status, living conditions, diet and medical history.

Results: Of the 8394 reported pregnant women, 6658 were invited to participate in the study. Among the invited women, 2582 (39%) agreed to participate. Of the 4076 (61%) non-participants, 2091 women were invited to a non-respondent questionnaire in order to examine possible selection bias. We found a self-selection bias in the established cohort when compared with the non-participant group, e.g. participating families did smoke less (14% vs. 19%), had more frequent asthma and allergy symptoms in the family (58% vs. 38%), as well as higher education among the mothers (51% vs. 36%) and more often lived in single-family houses (67% vs. 60%).

Conclusions: These findings indicate that the participating families do not fully represent the study population and thus, the exposure in this population. However, there is no obvious reason that this selection bias will have an impact on identification of environmental risk factors.

Keywords: *environmental factors, prospective birth cohort study, selection bias, Sweden.*

Exposure to toxic chemicals has historically mainly been an occupational problem with high exposure levels for workers in industrial and agricultural settings. This is still a major problem in low income countries while in high income countries the sources of exposure is more about leakage of hazardous compounds from commonly used articles and products. Among all the thousands of man-made chemicals that have been introduced to our environment during the last decades the endocrine disrupting chemicals (EDC) are of particular concern since they may alter the functions of the endocrine system with several adverse health outcomes as possible results. Recent

research has identified at least four circumstances as reasons for concern for EDC exposure and health outcome:

- The low dose effect during development
- The persistency of effects
- The large number of EDC sources in our daily life
- The wide spectrum of health effects

The low dose effect during development: Of great importance for understanding the health risks with EDC exposure is the growing knowledge that adverse effects may occur within a low dose range of exposure typical for the general population.^{1–3} The endogenous endocrine signalling system is working as hormones at very low levels and very limited changes in EDCs may have significant biological effects.¹ There is also growing knowledge indicating that such exposure is

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more important during development in the prenatal and infancy period and that 'timing' of exposure during development is more critical than the 'dose'.¹ *The persistency of effects:* Scientific reports during the last decade have shown that effects related to EDCs can be observed long time after the exposure did occur. This has been known for a long time due to experience from the use of the estrogenic compound diethylstilbestrol (DES) and of Thalidomide as drugs prescribed to pregnant women where no alarming health effects could be seen in the pregnant women who took the drug, but in their offspring, sometimes three decades later as in the case with DES.⁴ *The large number of EDC sources in our daily life:* Manmade chemicals with endocrine disrupting properties are used in a very large number of commonly used consumer products and they may leak into the surrounding environment.^{5,6} Examples of EDCs are: phthalates, widely used as plasticisers in polyvinyl chloride (PVC) and in numerous consumer products such as baby infant care products, toys, cosmetics, food packing materials and cleaning products;⁵⁻⁷ and bisphenol A (BPA), a high-volume production chemical used to make polycarbonate plastic and resins. Of particular concern is the use of BPA in food containers and baby bottles;⁸ and perfluorinated chemicals (PFCs), used in many products such as stain-resistant carpets and floor wax, and surface-active products that resist heat, oil, stains, grease and water (e.g. Gore-Tex and Teflon).⁵ These examples show that there are numerous of sources, that these sources are related to our daily life, and that 'everyone' is exposed including pregnant women and infants. *The wide spectrum of health effects:* Epidemiological and experimental studies have provided data on a possible relationship between EDC exposure and multiple chronic conditions such as reproduction and infertility,^{9,10} asthma and allergy,¹¹ weight gain, overweight/obesity,¹² and neurodevelopmental disorders such as autism spectrum disorders (ASD) and attention deficit hyperactivity disorder.^{13,14}

The Swedish *Environmental Longitudinal, Mother and child, Asthma and allergy* (SELMA) study aims to investigate the importance of early life exposure to environmental toxicants with focus on EDCs during the pregnancy and infancy period and life style factors for the development of multiple chronic diseases/disorders in offspring children, such as birth outcomes including weight gain and later on overweight/obesity problems, asthma and allergies, reproductive

effects (indicated by congenital defects in baby boys, anogenital distance (AGD), language delay and neurodevelopmental disorders (e.g. ASD).

The SELMA study is a continuation of our earlier Dampness in Building and Health (DBH) study that was initiated in Värmland in year 2000, with an overall aim to identify health-relevant exposures in Swedish buildings, largely focusing on asthma and allergy in children. More information as well as publications is available on the study's website (<http://www.dbhstudien.se>). The background, general description of the methods and some preliminary findings of the DBH study are described in Bornehag *et al.*¹⁵ A number of interesting findings emerged from the DBH study, establishing a basic framework for the current SELMA study.^{11,14,16,17} However, the DBH study suffered from a number of limitations which made the results difficult to assess. First, the second phase of the study, a case-control study, including both the health examinations and the exposure measurements, were conducted with a cross-sectional design with limited possibilities for explaining relationship between exposure and health. Second, while monitoring early life exposure is important when searching for risk factors for chronic diseases later on,¹⁸⁻²⁰ the DBH study did not include the pregnancy and infancy exposure as the study children were one year of age or older at baseline. Third, the study did not include measurements of human uptake of environmental exposures, e.g. biomarkers for chemical exposures, which is essential for investigating this problem. The SELMA study is designed to overcome such methodological problems faced in the DBH studies.

The current paper presents the outline of the SELMA study, its design and rationale. This paper also emphasises the description of the recruitment procedure since this is essential for successfully conducted birth cohort studies as well as identification of possibly involved selection bias.

Methods

The study area

The SELMA study is a population-based longitudinal prospective cohort study of mother-child pairs recruited and followed from the 10th week of pregnancy up to school age in the ongoing first phase.

Information about the study is available at <http://www.selmastudy.se>.

The study area is the county of Värmland located in the western part of Sweden about 250 km west from Stockholm. The county includes 16 municipalities with a mixture of rural areas, green suburbs and the moderate-sized town Karlstad with about 85 000 inhabitants. The county has a total population size of 273 265, according to the Statistics Sweden (SCB) database in 2010 within a 17 586 km² area (Figure 1).

The county of Värmland was selected as the study area because of the close collaboration between the SELMA study group and the local primary health care providers. This collaboration made it possible to make study planning, to get access in existing health databases, and coordinating the data collection

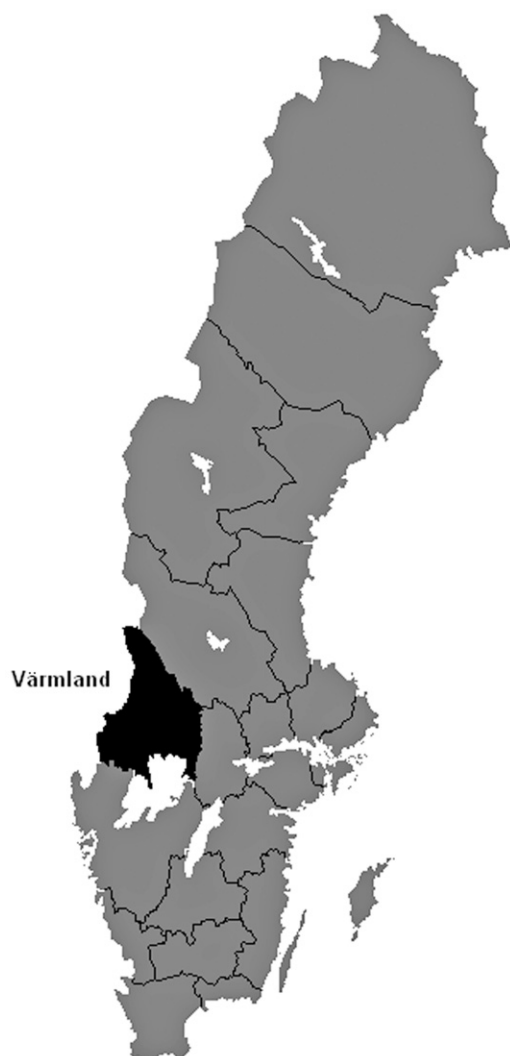


Figure 1. Map of Sweden is showing Värmland in dark colour.

procedures. However, the population characteristics including health and socio-economic status in Värmland are representative for general Swedish population.²¹

Study selection criteria

In Sweden almost all pregnant women visit an antenatal care centre (ACC) around week 10 of pregnancy and are then monitored continuously throughout the pregnancy period. In the county of Värmland there are 25 ACCs. The women who were registered at an ACC around pregnancy week 10 were invited to participate in the SELMA study.

Members of the SELMA study group visited all the ACCs in Värmland and instructed the midwives on how to invite the pregnant women in the study. When a pregnant woman visited an ACC for the first meeting with a midwife she was invited to participate in the study. The midwife provided information about the study and also handed out a package of information that could be read at home. The information package explained the study objectives and the data collection procedures. At the next visit the woman was asked whether she was interested to participate or not. In addition to the verbal invitations, posters were hung to the midwives' office rooms and waiting rooms at the ACCs. If the women had questions during the study period they could ask the midwives. If the midwives were not able to answer the questions, they could directly contact the SELMA study group.

Recruitment period was from September 2007 to March 2010. Pregnant women who did not understand a written Swedish questionnaire or was not a resident in the county were excluded. Women beyond week 22 in their pregnancy and moving outside the study area were also excluded from the SELMA study. Participation in the study was voluntary and no incentive was given to the participants.

The women who did not give consent to participate in the study received a non-respondent questionnaire. This questionnaire included five questions regarding the age of the women, smoking habits in the family, type of housing, highest education for both the parents, and asthma and allergy symptoms in the family. To return to the study participants, local mass media is used to disseminate the study progress and the findings. Two letters have already been sent to the

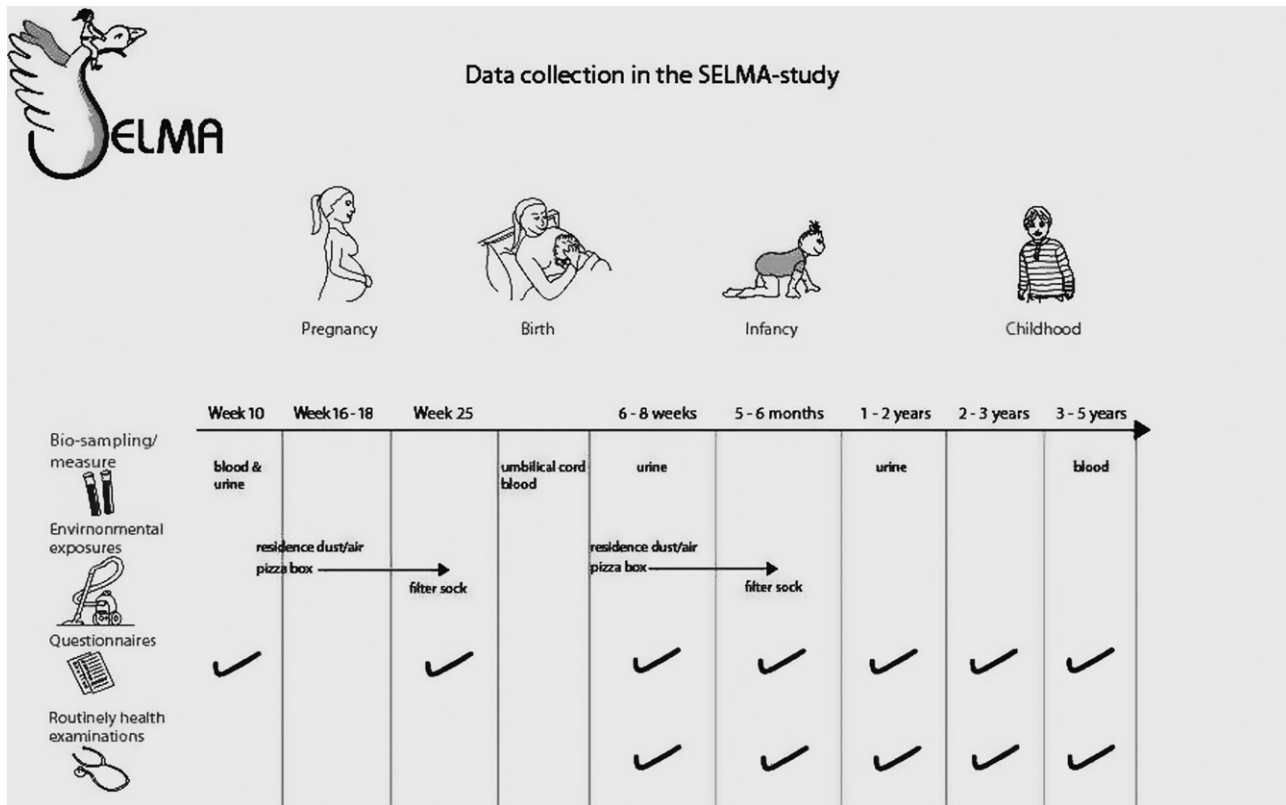


Figure 2. Data collection procedure in the SELMA study.

active participants with information about the study. The participants are also allowed to contact the study group to follow the study update.

Planning and piloting

Data collection procedure designs for the SELMA study went through multiple phases, including development of questionnaires, education of ACC staffs, visiting hospitals and practitioners, and testing questionnaire materials. For biological sampling, particularly, a pilot study regarding exhaled nitric oxide and phthalate uptake including 103 children between aged 2 and 6 months was designed with special emphasis on sampling biological specimens and to test the data collection procedure for urine sampling among young children as well as to test dust and air sampling procedures.

The statistical power for the study was originally estimated for asthma and allergy diseases in children. At 4–5 years of age the prevalence of doctor diagnoses asthma is around 5% with higher prevalence for rhinitis, eczema and IgE sensitisation¹⁷ as well as several

other health effects focused on in the SELMA study. This means that case groups can be expected to have a size of at least 100–200 children. This means that an odds ratio of 2.0 can be detected with a power of 80% and 95% confidence interval.

Outline for data collection

The data collection and sampling procedures of the study population were performed in connection to the routinely performed examinations at ACCs and child health centres (CHCs). Manuals for different sampling procedures, such as used questionnaires, are available on the study's website (<http://www.selmastudy.se>). The multiple data collection and sampling procedure during pregnancy, birth and infancy/childhood period included the following items (Figure 2):

- Biological sampling of blood and urine from the pregnant women and the infant/child
- Environmental sampling of indoor dust and air in the home during the pregnancy and the infancy period

- Self-administered questionnaires conducted several times during the pregnancy, the infancy and the childhood period
- Physicians' examination of the infant/child at the routine visits at CHCs

Biological sampling

Maternal samples of blood were collected during the routine visits. A group of staffs at the Primary Health Cares who have special training in collecting biological sampling was responsible for taking blood samples. Blood was not collected as fasting sample. A polypropylene tube was used to collect the blood. Urine samples for pregnant women were collected by the women at the same day before visiting the ACCs. The women were asked to collect early morning urine and kept it to below the room temperature before handing out to the health care labs. Urine samples for children were collected by a phthalate-free sanitary towel, put in the infant's diaper in the night before the visit at the children health care centre. Urine was squeezed out of the towel in the morning by the parents and collected in laboratory tubes. Urine was kept cold before frozen. Urine collection by plastic bags was rejected as being an avoidable source of phthalate contamination. Quality controls of the sampling such as patients identified, labelling and equipment maintenance are regularly maintained by the health care system. The blood and urine samples were collected as:

- 1 blood and urine from the pregnant women at their first visit at ACC during the 10th week of pregnancy;
- 2 cord blood at delivery;
- 3 two urine samples from the child; one at 2 months and one at 12 months of age. In both cases the urine was collected by the parents (supplied with materials and a written manual) and later brought to the CHC or a clinical laboratory. The child urine samples were collected by putting a small pad in the child diaper.

All biological samples were stored frozen (-80°C for serum and -20°C for urine) in a bio-bank at the Central Hospital in Karlstad.

Environmental sampling

Indoor settled dust was collected by the families themselves in all participating homes during both the

pregnancy and the infancy period. The sampling procedure was described in details in manuals distributed together with sampling boxes to the families. Sampling sites were the parent's bedroom during pregnancy and the room where the child slept during infancy. Dust was sampled with two methods: first, a 'pizza box' was placed on a shelf above floor level for a period of 15 weeks in order to collect settled dust.²² The reason for sampling dust above floor level was to get a smaller particle size, i.e. representing dusts that have been airborne and therefore inhalable. Thereafter, the dust in the box was transferred onto a filter and stored frozen (-20°C) until analysis. Second, a filter sock was placed on the vacuum hose of the family's vacuum cleaner and dust was collected from doorframes and skirting boards above the floor level.²² The filter socks are stored frozen (-20°C) until analysis.

In addition to the dust sampling, 216 pregnant women were invited to do a passive air sampling between November 2009 and March 2010, in which 165 families completed the sampling. Two different methods were used to collect different types of chemical organic compounds. Volatile organic compounds (VOCs) were collected by passive sampling on Tenax adsorbent tubes in parents' bedrooms²³ with a sampling period of 2 weeks. Polyurethane foam (PUF) disks were used for passive sampling of semi-volatile organic compounds (sVOCs) where the duration of this sampling was 8 weeks.²⁴ The collected VOCs samples on adsorbent tubes were analysed after arrival to the analytical laboratory using thermal desorption followed by gas chromatography for separation with mass selective detector for identification and flame ionisation detection for quantification of the compounds (TD-GC/MS/FID). The analytical method for Tenax adsorbent tubes followed an accredited method available at the laboratory. The chromatograms are stored and awaiting further evaluations. The PUF samplers are stored prior to the analyses.

Self-administered questionnaires

Questionnaires to the families have been distributed two times during the pregnancy, three times during the infancy period, and several times during the childhood period (Figure 2). All so far used questionnaires are available in Swedish on the SELMA study's website (<http://www.selmastudien.se>).

At the first visit to ACC (approximately 10 week of pregnancy) the first questionnaire was handed to the pregnant woman. This first questionnaire mainly identified features of indoor environmental factors by previously validated questions, e.g. type of dwelling, type of flooring, ventilation, moisture problems and odour.²⁵ Furthermore, data on family health status, e.g. allergic problems were assessed by ISAAC questions,²⁶ family life style (i.e. pet ownership, smoking habits, food habits, etc), medication, socio-economic indicators, housing conditions including dampness and ventilation, pet keeping and smoking habits, were collected. The latter are questions designed to estimate in time how difficult or easy it was for the couple to become pregnant.

The second questionnaire was distributed in mid-pregnancy period, around the 25th week. This questionnaire was focused on food habits, smoking and health of the mother, attitude to breast feeding, medication, hair care and dental care.

During the child's first year the families received three questionnaires. The first questionnaire was distributed when the child was 2 months and focused mainly on family life style, infant and mother health status and child housing. The second questionnaire, when the child was 6 months concerned mother and child health, breast feeding and housing conditions. The third questionnaire was distributed when the child was 1 year mainly concerned the features related to the child's health status, breast feeding, smoking and different housing conditions, e.g. type of dwelling, type of flooring, ventilation, moisture problems, odour and re-painting.

A questionnaire when the child was 2 years old included questions on asthma and allergic symptoms in the family, food reactions in the child, housing condition and family structure, smoking and pet keeping. In total, five questionnaires were sent out or planning to send between the child birth and the child was 4 years old. Furthermore, an annual questionnaire is intended to send to the families, up to school age of the child (i.e. until 6 years old), investigating mainly the health status of the child and housing conditions.

If a completed questionnaire was not returned to the SELMA officials in about 2 months after it was handed out, a first reminder was sent out, and approximately 2 months later a second reminder was sent out in case of further delay of returning a completed questionnaire.

Physicians' examination

The national voluntary child health promotion program is attended by virtually all children in Sweden and each child visits the CHCs about 20 times until it has reached the normal school age of 7 years. The practical responsibility resides mainly with nurses but there were also regular scheduled examinations by physicians at the ages 2, 6, 12 and 18 months. The SELMA study was coordinated with these examinations to collect relevant data and health examinations coincide also to a large extent with the regular national vaccination scheme that is provided to all children. At all these occasions, length, weight and head circumference was measured and compared with normal growth curves. In order to increase the quality of such data validations are routinely made in the health care system. Apart from a clinical examination of eyes, heart, lung, skin, hips and abdomen, different level of age-specific development was assessed, for instance the ability to focus the eyes at 2 month of age and the ability to walk and speak at least 10 words at 18 months of age. All this information was stored in a structured electronic medical record database (County Council Health Care) and was made available for the SELMA study group. If a child shows signs of disease, referral to secondary care was arranged. Minor illnesses, in particular skin conditions were, however, cared for at the health centre. Vaccinations were recorded in a national database, Swevac, separate from the electronic medical record system mentioned above.

Four ongoing health-related research tracks

Four ongoing research tracks in the SELMA study were focusing on the importance of prenatal EDC exposure for (1) language delay and neurodevelopmental disorders, (2) alterations in expected growth, height and weight, (3) asthma and allergy, and (4) changes related to lower *in utero* androgens in 300 randomly selected baby boys, i.e. AGD. Regarding neurodevelopmental disorders data from a routinely made language delay screening at age of 30 months was used as well as data from clinical diagnoses and questionnaires later on. Data on weight gain and height were routinely and frequently collected in the CHC system and available for the study. Information on asthma and allergy problem in the family and the child was collected by questionnaires and by routinely

health examinations at CHC. IgE sensitisation was investigated at the age of 5 year of the children. Finally, a random sample of 300 boys aged about 20 months was examined where AGD was measured. The method for AGD measurements were described in Mendiola *et al.*²⁷

Statistical analysis

For statistical analyses, cross-tabulation was used to analyse the distribution of health and socio-economic characteristics of participants and non-participants families in the SELMA study. Differences between participants and non-participants were tested by chi-squared test at $**<0.01$ and $*<0.05$ levels.

Ethical approval

Participating families had to provide a written consent for participation in the SELMA study and for collecting blood and urine samples both for the pregnant women and for the child. The SELMA study has been

approved by the regional ethical committee, Uppsala, Sweden (2007-05-02, Dnr: 2007/062).

Results

Recruitment of the pregnant women

The recruitment process started in September 2007 and ended in March 2010 when 2582 pregnant women had been recruited. A flow diagram shows the relative number of participants and non-participants at different steps of the SELMA study until present publication (Figure 3).

As shown in the figure, 8394 women were reported to be pregnant at 25 ACCs in Värmland during the recruitment period. Of those, 7119 pregnant women were selected to be invited to participate in the Selma study, which corresponds to 85% of the total number of pregnant women in the county during the recruitment period. A number of 1275 (15%) pregnant women were never invited to the study. Two ACCs had difficulties to set up the study protocol and start

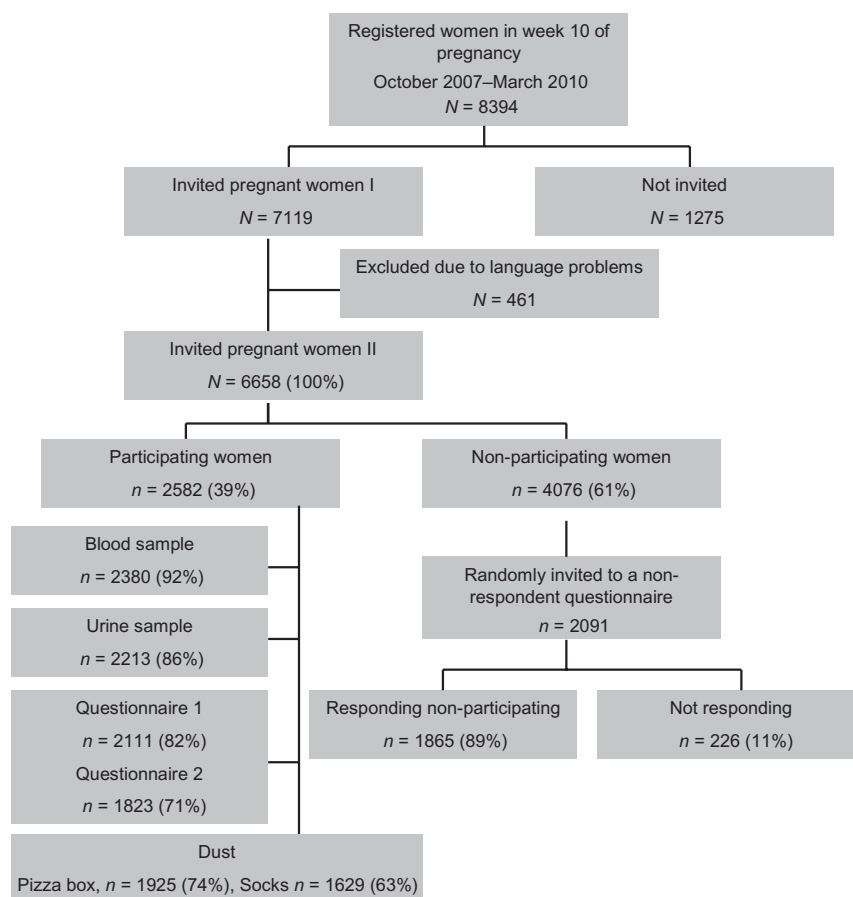


Figure 3. The recruitment process in the SELMA study.

recruiting the SELMA-participants at the beginning of the recruitment process and families were therefore not invited. However, these 1275 non-participating families can be seen as rather randomly distributed and not a source for selection bias.

Among the invited 7119 women, 461 were excluded due to language problems at the beginning of the recruitment process. This means that a number of 6658 eligible pregnant women who resided in Värmland at the first visit at ACCs around 10 weeks of pregnancy were invited during the recruitment period.

Out of the invited pregnant women, 2582 consented to participate in the study, corresponding to a recruitment rate of 39%. A number of 4076 (61%) pregnant women decided not to participate in the study or were excluded by the midwives due to that the women were beyond week 22 in their pregnancy (10 women) and/or moving outside the study area (6 women). Women who had difficulties with their pregnancy were also excluded from the SELMA study.

Among the participating women, so far, we have stored biological samples of blood from 2380 (92%) and urine from 2213 (86%) women. We have stored indoor dust from 1925 (75%) pregnant women's bedrooms and data from the baseline questionnaire from 2111 (82%) families. Urine samples for the children were not reported here, as the reporting of child biological samples is underway.

Characteristics of the participants and non-participants

In order to control for the selection bias in the SELMA study the pregnant women who refused participation were requested to answer a short questionnaire. We used five questions focusing on the age of the pregnant woman, family history of asthma and allergy, type of housing, smoking habits and educational status for both the parents to be.

Data presented in Table 1 compare differences in characteristics of the 1865 participating and 990 not participating families in the SELMA study. The participating mother tended to be older than the non-participating mother (i.e. mean ages 32 vs. 31 years). A higher level of education was associated with the participation in the study, especially educational level of the mother. More than 50% of the women in the participating group had college or university education, while only about 36% of the non-participants had such

education level. Furthermore, non-participants had a higher prevalence of current smoking status than participants (19% vs. 14%). The major differences in parental smoking were observed for daily smoking. A higher prevalence of parental daily smoking habit was associated with non-participation. Families living in single-family houses were more inclined to participate when compared with families living in multi-family houses. Finally, a significant difference in self-reported allergy symptoms in the family was observed between participating and non-participating families, where reported allergy symptoms were more prevalent in the participant families than the non-participant families.

Comments

The SELMA study includes a comprehensive multi-stage data collection procedure on various exposures in early life and in childhood, which appears to be a powerful instrument for any aetiological investigation.²⁸ In order to establish relevant information on environmental toxicants and related health effects we are following a so-called 'full chain model' described in Figure 4. The framework is divided into three main parts. The most left triangle describes the environmental exposure (A) focusing on chemical substances in air and dust, their sources and factors that modify the exposure. The most right triangle (C) is focusing on different human health effects that can be related to EDCs and biological mechanisms. Finally, the triangle in the middle (B) describes the interface between the environment and humans with focus on human uptake of chemicals and pathways. Data from such a full chain are essential inputs for risk management activities (D) described in the top of the model. The SELMA study is using this model in order to establish new scientific data for chemicals with endocrine disrupting properties by following them from sources to health effects and uses the information for development of risk management activities aiming to reduce relevant exposures and health risks. The 'full chain model' is further described in Bornehag and Sundell.²⁹

One of the key advantages that the SELMA study enjoys is its close integration with the primary health care system that routinely monitors the pregnant women and children and records their medical history. Almost all of the pregnant women in Sweden

Table 1. Distribution of health and socio-economic characteristics of participants and non-participants families in the SELMA study (bold text symbolise reference)

Family characteristics	Categories	Non-participants <i>n</i> = 1865 (%)	Participants <i>n</i> = 990 (%) ^a	<i>P</i> -value
Age	<25 years	306 (7.19)	87 (8.8)	
	25–35 years	903 (1.58)	618 (4.62)	0.000
	>35 years	344 (2.22)	285 (8.28)	0.000
Education mother	College/university	675 (36.4)	502 (51.3)	
	High school	947 (51.1)	356 (36.4)	0.000
	Contemporary school	160 (8.6)	43 (4.4)	0.000
	Other	71 (3.8)	77 (7.9)	0.030
Education father	College/university	473 (26.1)	339 (35.2)	
	High school	1119 (61.8)	505 (52.5)	0.000
	Contemporary school	153 (8.4)	58 (6.0)	0.000
	Other	66 (3.6)	60 (6.2)	0.000
Smoking in the family	Yes	357 (19.2)	132 (13.5)	0.000
Smoking mother	No	1659 (89.1)	931 (95.2)	
	Yes, sometimes	29 (1.6)	15 (1.5)	0.799
	Yes, daily	174 (9.3)	32 (3.3)	0.000
Smoking father	No	1599 (86.0)	873 (89.3)	
	Yes, sometimes	60 (3.2)	52 (5.3)	0.016
	Yes, daily	200 (10.8)	53 (5.4)	0.000
Type of dwelling	Single-family house	1109 (60.0)	667 (69.4)	
	Multi-family house	737 (40.0)	294 (30.6)	0.000
Allergy in the family	Yes	703 (37.8)	563 (57.6)	0.000

attend the voluntary antenatal care program, meaning most pregnant women have access to the same health care system regardless of their social status, colour or ethnicity. The close coordination with the primary health care staffs and access to regularly collected medical records strengthen the quality and reproducibility of the health data that are to be analysed in the study.

In order to identify possible selection bias in the recruitment process, related to low recruitment of pregnant women in the SELMA study, participants' and non-participants' characteristics were compared with regard to sociodemographic, life style and health variables. The analysis showed significant differences in characteristics between participating and non-participating families, where participants were more likely to have higher level of education, and to live in single-family houses. Also, participants were less likely to smoke, and were more likely to have

asthma or allergy in the family. These results show that the participating families do not fully represent the general population of pregnant women in the study area and there is a source for selection bias. However, such a selection bias may not be a main problem when examining the importance of early life exposure of environmental toxicants for development of adverse health effects in offspring children. Yet, the challenges the study group may face are low response rate and to maintain representativeness throughout the continuous monitoring of the mother–child pairs and follow-up data collection, which has been a great concern for longitudinal study design.³⁰

Two important mother–child birth cohorts in Scandinavia are showing participation rates in the range of about the same as the current SELMA study. The Norwegian Mother and Child Cohort Study, which invited more than 150 000 pregnant women, had a participation rate of 42.7%,³¹ and the participant rate

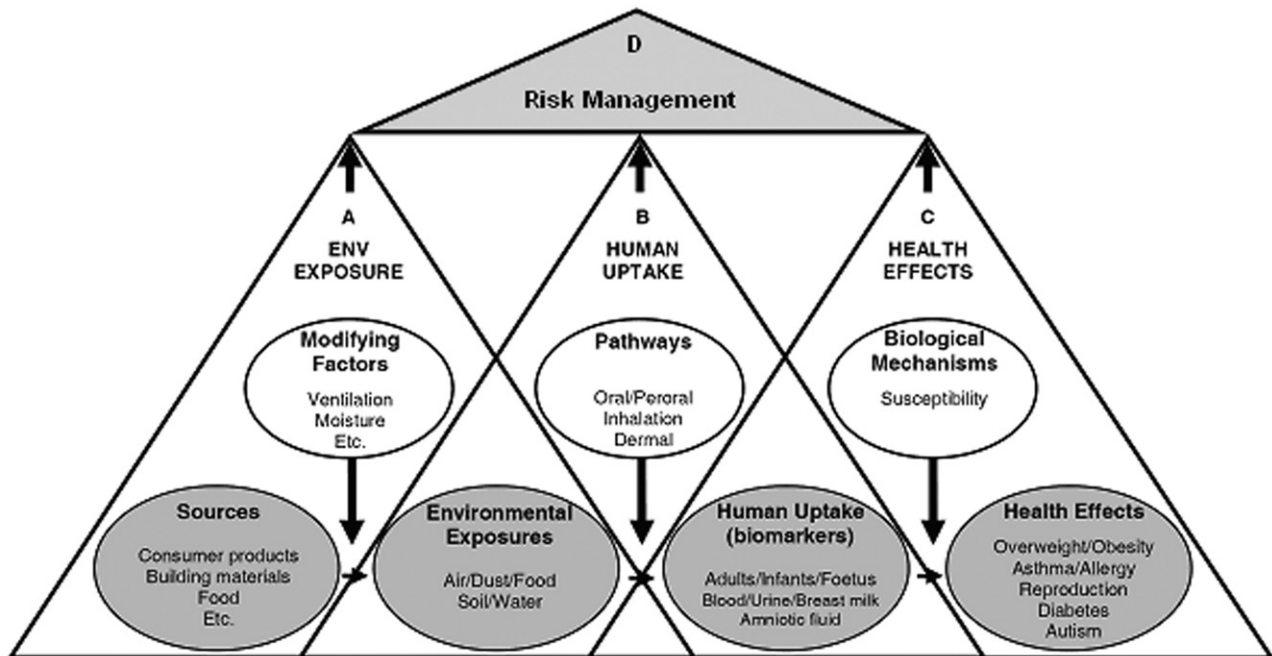


Figure 4. The full chain model following chemicals from sources that may leak EDCs to the environment where such environmental exposure can be taken up by humans and finally, give rise to health effects.

for the Danish National Birth Cohort from more than 100 000 recruited pregnant women was 30%.^{32,33} With such participation rates (well below 50%), there is of course a risk for selection bias, and it is doubtful if the study population represent the entire population. However, the overall aim with the SELMA study is to investigate associations between early life exposure for environmental factors and diseases in offspring in latter life. It is not obvious that a selection bias will influence such analyses. But there is a risk that the study population in the SELMA study is not fully represented the total population.

Vrijheid and colleagues have summarised 35 European birth cohort studies that have focused on environmental risk factors and its impact on health.³⁴ The current SELMA study has similarities with its data collection designs with the most of European birth cohorts described in the study that the most cohorts started with recruiting pregnant mother, collected biological samples and assessed environmental exposure. However, considerable differences have also been noticed between the studies; one of the key differences between the SELMA study and another Swedish study BAMSE (The Stockholm Children Allergy and Environmental Prospective Birth Cohort) is that the BAMSE study did not collect any biological sample from the mother during pregnancy ([http://](http://www.birthcohorts.net)

www.birthcohorts.net). The SELMA study is smaller, specialised type of cohort study with its special focus on exposure for EDCs in early life.

The needs for further European collaboration have been suggested for the existing birth cohort studies.^{34,35} The current SELMA study has an ambition to find and develop such collaboration with other ongoing birth cohorts in Europe, US and South East Asia with special focus on exposure for EDCs in early life and the importance for such exposure for multiple health effects in offspring. This type of collaboration is needed to reduce publication bias, facilitate replication of findings, and identify standardised methods for comparison studies.^{35,36}

In summary, due to multiple data collection procedures involved in the SELMA study, the study should be able to provide valuable information concerning several hypotheses related to prenatal exposure for EDCs and adverse health effects in children. Major challenges are to keep families actively participating in the study and to handle the participation rate as well as the involved self-selection bias in the study.

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