

NINFEA (NASCITA ED INFANZIA: GLI EFFETTI DELL'AMBIENTE) STUDY: A WEB-BASED ITALIAN BIRTH COHORT

1. INTRODUCTION

The foetal and infant life are periods of fast development, characterised by a high susceptibility to exposures causing long-term health consequences, due to immaturity of physiological systems and the existence of specific exposure pathways. For this reason, several chronic diseases, including asthma, diabetes, hypertension, breast cancer, infertility, and impaired childhood physical and cognitive development have been proposed to have a perinatal origin, although their incidence is then modified by genetic susceptibility and postnatal exposures.

The study of the natural history of chronic diseases thus necessitates follow-up from foetal life to adulthood (1). Population-based birth cohorts comprising 10,000 to 100,000 participants exist or are planned in several countries, including Australia, Denmark, Norway, the United Kingdom, Spain, France, Canada and the USA. The aim of these studies is to measure various perinatal exposures, collect biological samples, and follow up participants from birth onwards. They are therefore regarded as research "platforms" for a multitude of future hypothesis-based studies aiming at investigating the aetiological role for early exposures and their interactions with genetic susceptibility and exposures occurring later in life (2). The main limitations of birth cohorts are their cost and organizational problems. The consequence is that recruitment is usually limited to selected areas and short periods.

The internet might be a powerful tool for conducting population-based birth cohorts efficiently. In a pilot study carried out in the city of Turin, we demonstrated the feasibility of an internet-based birth cohort by using a website to recruit more than 1200 pregnant women and follow up their children (3)

2. OBJECTIVES

The objective is to recruit and follow-up a birth cohort of at least 10,000 newborns in Italy.

The sample size will enable the study of the aetiology of various diseases and conditions with high impact on child and adult health: approximately 600-1000 cases of asthma, atopy, obesity, low birth weight, are expected to occur within the cohort. We will be able to study the effect of different types of exposures, including environmental factors (e.g. air pollution, passive smoking) life styles (e.g. breast feeding, maternal and infant diet, physical exercise) and medical conditions (e.g. maternal diabetes). It will be possible to investigate these exposures in interaction with the genetic susceptibility.

3. PILOT STUDY

We started a pilot study in July 2005 in the city of Turin (900,000 inhabitants). As part of the pilot, we constructed the study website, designed posters and leaflets, and

developed three online questionnaires to be completed during pregnancy and 6 and 18 months after giving birth.

The study was advertised in posters and leaflets, and 1200 pregnant women had participated by the end of December 2007. Approximately 90% of the first 800 women have completed the second questionnaire.

In July 2006, we surveyed women giving birth in the main obstetrics hospital of Turin to estimate the proportions with access to the internet and awareness of the study in the target population. Of 122 interviewed women, 66% had access to the internet and 42% were aware of the study. Eight women (6.5%) were members of the cohort. In January 2008 we started advertising in websites and forums. We estimated that about 15 women participate in the 2 weeks after the message is posted in a forum.

The study was approved by the local ethical committee.

4. METHODS

4.1. Population

The cohort will include babies born to pregnant women who have enough knowledge of the Italian language and the use of the internet to complete online questionnaires, who become aware of the study and volunteer to participate.

Participants will register on the study website (www.progettoninfea.it) and their children will be followed-up until adult life. In addition, mothers will be followed-up for complications in the late pregnancy and health status in the first years after delivery.

4.2. Recruitment

We will use both “active” (offline) and “passive” (online) approaches to advertise the study.

Active recruitment will involve advertising through standard methods (leaflets, posters, presentations at pre-delivery classes, etc.) in selected areas in Italy, through collaboration with local centers. Methods of advertisement are developed locally.

Passive recruitment will be managed centrally. We will post information about the study in Italian discussion forums on medical topics, websites dedicated to pregnant women, websites of the main Italian hospitals and Italian associations for diseases.

4.3. Questionnaires

Three online questionnaires (during pregnancy and 6 and 18 months after birth) were developed during the pilot phase on the basis of analogous questionnaires used in other birth cohorts. They obtain information about the mother and/or the child on environmental exposures, reproductive factors, medical history, anthropometrical measures, diet, supplements, health status in the first years of life, cognitive development, and several other factors. Each questionnaire requires about 30 minutes to be completed.

The questionnaires have been reviewed at the end of the pilot phase on the basis of the answers of the first 1000 women and will be reviewed periodically, according to emerging research questions.

4.4. Biological samples

At the end of the second questionnaire, women will be asked to donate a biological sample. Compliant women will receive by mail two kits (Oragene™), which have been specifically developed for collection of high quality DNA from saliva samples from adults and infants.

The kits contain a collection canister with a purifying agent, allowing the sample to be stored at room temperature for long time. Using a pre-paid envelop, women will mail the kits back to the Unit of Torino, which will be responsible for the collection and storage of biological samples.

The saliva of each kit will be aliquoted in four vials which will be frozen at -80°C and stored in a biobank for DNA extraction

4.5. Follow-up

Active follow-up will be managed centrally. Women will be invited via e-mail, telephone and mail to complete the second and third on-line questionnaires.

Newborns and their mothers will be also followed-up using health-related databases, such as the Birth Register, the Hospital Discharge Register, etc. The linkage will be carried out in collaboration with the Regional or National Institutions who are in charge of the Registries.

4.6. Sample size and statistical analysis

The expected sample size is at least 10.000 newborns. Several cases of relatively common diseases are expected to occur in this cohort, such as 600 cases of retarded foetal growth, 1000 cases of asthma, 600 cases of wheezing during the first 18 months of life, 1200 cases of atopic dermatitis, 500 cases of hypertension during pregnancy and 500 cases of childhood obesity.

Data will be analyzed using a standard nested case-control approach. The nested studies will be hypotheses-based and will investigate gene-environmental interactions when applicable. We will also carry out analyses following a life-course approach, such as those based on joint models in which baseline, intermediate and distal variables can be specified

4.7. Health promotion interventions

The use of the internet gives the possibility to nest in the cohort and evaluate health promotion interventions. Since July 2007, current smokers who participate to the pilot study are randomised to receive information on the closest centers for tobacco cessation. This intervention will apply also to participants in the enlarged cohort. The main endpoint is smoking 6 and 18 months after delivery. We will evaluate if it is possible to start analogous interventions and deliver them to the members of the cohort.

5. INTERNATIONAL COLLABORATION

The study will be linked with other “traditional” birth cohorts to analyze rare events and exposures. In additions, the same methodology (use of the internet for recruitment and follow-up) will be applied in other countries, to create and international network of web-based birth cohort studies.

6. UPDATE OF THE PROTOCOL

The present version of the protocol and all new versions will be available at the study website: www.progettoningfea.it.

7. ETHICAL ISSUES

The study has been approved by the Ethical Committee of the San Giovanni Battista Hospital, Turin Italy. A copy of the informed consent and Information about ethical issues are available at the website: www.progettoninfea.it.

REFERENCES

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- 3) Richiardi et al. Feasibility of recruiting a birth cohort through the internet: the experience of the NINFEA cohort. *Eur J Epidemiol* 2007 ;22:831-7.