Study design

Child health and the environment: the INMA Spanish Study

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Summary

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The INMA (INfancia y Medio Ambiente [Environment and Childhood]) is a population-based cohort study in different Spanish cities, that focuses on prenatal environmental exposures and growth, development and health from early fetal life until childhood. The study focuses on five primary areas of research: (1) growth and physical development; (2) behavioural and cognitive development; (3) asthma and allergies; (4) sexual and reproductive development; and (5) environmental exposure pathways. The general aims of the project are: (1) to describe the degree of individual prenatal exposure to environmental pollutants, and the internal dose of chemicals during pregnancy, at birth and during childhood in Spain; (2) to evaluate the impact of the exposure to different contaminants on fetal and infant growth, health and development; (3) to evaluate the role of diet on fetal and infant growth, health and development; and (4) to evaluate the interaction between persistent pollutants, nutrients and genetic determinants on fetal and infant growth, health and development.

Extensive assessments will be carried out on 3100 pregnant women and children. Data will be collected by physical examinations, questionnaires, interviews, ultrasound and biological samples. Pregnant women are being assessed at 12, 20 and 32 weeks of gestation to collect information about environmental exposures and fetal growth. The children will be followed until the age of 4 years.

Keywords: *longitudinal cohort study, prenatal exposures, pollution, diet, genetics, study design, biological samples, childhood growth, child development, endocrine disruptors.*

General description

The INMA – INfancia y Medio Ambiente (Environment and Childhood) is a network of research groups in Spain that built up a project aiming to study the role of the most important environmental pollutants in air, water and diet during pregnancy and early in life and their effects on child growth and development.

Scope of research

The INMA project will follow up a population sample of around 3100 pregnant mothers and newborns. New and existing cohorts of pregnant women will be incorporated from eight different Spanish regions (Table 1). The follow-up will continue until at least 2010, and, if resources are available, until 2020.

Genetic factors and nutritional, environmental and psychosocial exposures in the prenatal and postnatal periods will be evaluated. Outcomes will include prenatal and birth health events, growth, neurodevelopment, behavioural functioning, immunity and endocrine disruption. The results of these studies will become available within the next few years, and will help to assess pregnant women and childhood exposure as well as other health determinants in several areas of Spain and its immediate and later impacts on human health.

Rationale

The physical, social and intellectual development of children from conception to the end of adolescence requires an environment that is both protected and protective of their health. A growing number of diseases in children are linked to unsafe environments. Prenatal and early life exposures, including diet, are associated with child health and human development and predispose to late adult effects. Thus, the INMA project is based on three main rationales.

First, exposure to environmental pollutants through air, water and food is worldwide. Children are especially vulnerable to its effects as they are not just little adults, they are still growing, and their immune system and detoxification mechanisms are not fully developed. Children are then more vulnerable than adults to environmental exposures. Persistent pollutants like organochlorine compounds (OC) and some metals have been related to impaired intrauterine growth, prematurity, postnatal growth and neurodevelopment and minor behavioural disorders.[1–5] Air pollutants e.g. particulates have been associated with infant mortality and with child health problems such as asthma and allergies.[6,7]

Less epidemiological evidence exists about fetal damage, especially fetal growth, and there is a need for further evidence.[8] Also, chemical products in the water, namely disinfection by-products, have been associated with reproductive and child health outcomes;[9,10] this warrants further research to establish the validity of the fundings and, if so, develop effective preventive strategies. Little is known about the individual susceptibility to certain chemicals, and further studies integrating gene–environment interactions are needed.

Second, there is growing evidence of the importance of nutrition during pregnancy and the first months of life on fetal and infant growth and development, as well as on lifelong health and well-being. Specifically, intake of essential fatty acids (omega 3, omega 6) during pregnancy and early postnatal life is involved in fetal and infant growth, neurodevelopment and visual function.[11,12] Fish intake and supplementation with fish oil during pregnancy has also been associated with better postnatal neurodevelopment.[13–15] Moreover, low plasma levels of antioxidants and oxidative stress have been involved in pre-eclampsia and intrauterine growth retardation,[16–18] and it has been suggested that antioxidants in children have a protective influence on the risk of asthma.[19,20]

Third, some pollutants and nutrients have the same ingestion route. Fish, the principal source of omega 3, is also carrier of OCs and methyl-mercury. Breast feeding, the sole form of nutrition during the first month of life among breast feeders, carries both nutrients and pollutants. Although the mechanisms of toxicity for OCs are not well understood, the suggested underlying metabolic and hormonal mechanisms in neurotoxicity are also in the pathway of clinical effects due to deficiency of some essential fatty acids.[21,22] It remains to be elucidated whether nutrients can counteract the pollutants' negative effects on health.

To characterise individual exposure levels during pregnancy and childhood, to identify the role of diet and other associated risk factors on reproductive outcomes and child health, and to understand the interactions between multiple factors and susceptibility will contribute to early identification of environmental risks and to the development of protective and preventive strategies.

Aims

The general aims of the project are:

1. To describe the degree of individual prenatal exposure to environmental pollutants, and the internal dose of chemicals during pregnancy, at birth and during childhood in Spain;
2. To evaluate the impact of the exposures to different contaminants on fetal and infant growth, health and development; and
3. To evaluate the role of diet on fetal and infant growth, health and development; and
4. To evaluate the interaction between persistent pollutants, nutrients and genetic variants on fetal and infant growth, health and development.

Design

Overview

The INMA Study is a prospective population-based cohort study concerned with the effects of pre- and postnatal environmental exposures on growth, development and health from early fetal life until young adulthood.

Investigations are carried out in pregnant women and children. Pregnant women are assessed at 12, 20 and 32 weeks of gestation to collect information about environmental exposures and fetal growth. Children will be assessed at birth, at the age of 1 year and at the age of 4 years.

Table 1. INMA cohorts

Population	Inclusion year	Target number of infants	4 years
Old cohorts			
Ribera de l'Ebre	1997/99	102	2001/03
Menorca	1997/98	482	2002
Granada	2001/02	668	2005/06
New cohorts			
Valencia	2003/04	1000	2007
Asturias	2004/06	500	2008
Sabadell	2004/06	800	2008
Madrid	2005	50	2009
Basque Country	2005/06	800	2009

Study cohorts (Table 1)

The INMA is based on experience acquired by groups studying the cohorts of Ribera d'Ebre ($n = 102$), which evaluated the relation between organochlorines and methyl-mercury exposure and neurological development, Menorca ($n = 482$), which studied the relation between allergy, development and asthma with air pollution, and Granada ($n = 668$), which studied the incidence of infant reproductive health disorders in relation to potential environmental exposures.

Based on experience from these previous studies, a new research protocol was developed based on the work of different working groups: exposures, effects and design. The new cohorts have been designed to evaluate the impact of environmental exposures and diet on children's health: Valencia ($n = 1000$), Sabadell ($n = 800$), Asturias ($n = 500$), Madrid ($n = 50$) and the Basque Country ($n = 800$).

Enrolment

Midwives and obstetricians give eligible participants oral information about the study and hand out an information package to the pregnant women in the 12th week. After the visit, all eligible pregnant women who visit the public health centre of each area have an interview with INMA staff to obtain additional information; they are then enrolled in the study. The inclusion criteria of the mothers are: (a) to belong to the study area (specific in each cohort), (b) to be at least 16 years old, (c) to have a singleton pregnancy, (d) to have their first prenatal visit (10–13 weeks of gestation) in the main public hospital or health centre of the area, (e) to not have followed any programme of assisted reproduction, (f) to wish to deliver in the reference hospital, and (g) to have no communication problems. A characteristic of these areas is that a vast majority of the population attend the public health sector.

Informed consent

The study has been approved by the Ethical Committee of the Institut Municipal d'Investigacio Medica and by the Ethical Committees of the hospitals involved in the study. Pregnant women receive written and oral information about the study. Participants are asked for their written informed consent twice: once for their participation in the prenatal visits and the other time for the inclusion of their child into the follow-up study.

Data collection

A list of all assessments planned until the age of 4 years is shown in Tables 2 and 3. More detailed information on the INMA protocols is available upon request.

Information is collected using a variety of sources. Some general considerations about measurement tools are: questionnaires are administered in an interview format by trained interviewers; for biological samples, total blood, plasma and serum samples are divided in small aliquots and stored at –80°C, urine and placentas are stored at –20°C until delivery to the specialised laboratories.

Table 2. Main exposures and determinants assessed in the new INMA (n = 3300)

	Prenatal period			Postnatal period		
	12 weeks	20 weeks	32 weeks	Birth	1 year	4 years
Exposures						
PAHs, ozone, VOCs and NO_2	Outdoor		Outdoor Indoor (VOCs, NO_2)[a] Questionnaire		Questionnaire GIS	Questionnaire GIS
Particulates					Personal	
Hydroxypyrene	Maternal urine					Child urine
Trihalomethanes	Outdoor		Indoor[a] Questionnaire		Questionnaire	Questionnaire
Organochlorines, polybrominated diphenyl ethers, phthalates, phenols	Maternal serum		Questionnaire	Cord serum Mecomium[b]		Child serum
Other endocrine disrupters			Questionnaire	Placenta		
Lead				Cord blood		Child blood
Arsenic	Maternal nail					Child nail
Mercury				Newborn hair		Child hair
Maternal occupation			Questionnaire			
Other determinants						
Diet	Questionnaire		Questionnaire		Questionnaire	Questionnaire
Antioxidants	Maternal serum			Maternal milk[c]		Child serum
Folate	Maternal serum					
Oxidative stress markers	Maternal serum Maternal urine		Matenal urine		Child urine	
Fatty acids	Maternal plasma			Maternal milk[c] Cord blood		Child plasma
Genetic study	Maternal blood			Cord blood		
Parental psychopathology					Questionnaire	

[a]In subsamples.
[b]Only in the Valencia cohort.
[c]Only in the Sabadell cohort.
GIS, Geographic Information System; PAH, polycyclic aromatic hydrocarbon; VOC, volatile organic compound.

The amount of venous maternal blood to be taken is 20 mL at 12 weeks of gestation, 15 mL from the newborn (cord blood) and 10 mL at the age of 4 years. DNA will be extracted from blood with ethylenediamine tetraacetic acid (EDTA). A 100 mL urine sample is collected from the mother at 12 weeks' gestation and the child at the age of 4 years. A nail sample is collected from mothers at 12 weeks' gestation and from children at the age of 4 years. Hair samples will be obtained at birth and at the age of 4 years. Placentas will be collected from one out of five women. Breast milk (20 mL) will be taken at the end of the first feeding on the third day after delivery and will be stored at –80°C.

Assessment of determinants (Table 2)

Air pollution:

- Questionnaire: assessment of the exposures to traffic and environmental tobacco smoke during pregnancy (28–32 weeks) and at the ages of 1 and 4 years through a questionnaire.
- Biological samples: measurement of hidroxypyrene in urine in a subsample of pregnant women (at 10–12 weeks of gestation), and children at the age of 4 years.
- Measurement of the environment: measurement of volatile organic compounds (VOCs), and NO_2 in

Table 3. Main outcomes to be assessed in the new INMA cohorts (n = 3300)

	Prenatal period			Postnatal period		
	12 weeks	20 weeks	32 weeks	Birth	1 year	4 years
Intrauterine growth	Ultrasound	Ultrasound	Ultrasound			
Sexual development				Physical examination	Physical examination	Physical examination
Postnatal growth				Physical examination	Physical examination	Physical examination
Neurodevelopment				Dubowitz test	Bayley scales	McCarthy scales Hyperactivity, social competence
Thyroid hormones	Maternal serum			TSH screening		Child serum
Asthma/atopy	Maternal serum				Questionnaire Physical examination	Child serum Questionnaire

TSH, thyroid stimulating hormone.

outdoor and indoor samples. Measurement of particulates, polycyclic aromatic hydrocarbons, ozone and other pollutants in outdoor samples. Measurement of particulates, VOCs, NO_2 and ozone in air quality registries. Measurement of personal exposure to particulates in children aged 1 year. Prediction of individual exposures through the Geographic Information System.

Water pollution:

- Questionnaires: water consumption during pregnancy and childhood using a questionnaire at 28–32 weeks of gestation and at the ages of 1 and 4 years. Measurement of the environment: thrihalomethanes and other disinfection by-products in water of a subsample of residences.

Persistent and semi-persistent pollutants:

- Questionnaires: exposure during pregnancy and childhood using a questionnaire at 28–32 weeks of gestation and at the ages of 1 and 4 years.
- Biological samples: measurement of OCs, polybrominated diphenyl ethers, phthalates and phenols in maternal serum at 12 weeks of gestation, cord serum and child serum at the age of 4 years. Arsenic in maternal and child nails at the age of 4 years. Lead (in child serum) and methyl-mercury (in child hair) at birth and at the age of 4 years. Measurement of different endocrine disrupters with oestrogenic activity in placentas.

Diet determinants:

- Questionnaires: maternal diet assessment by a food frequency questionnaire at two point interviews (10–13 and 28–32 weeks of gestation). Infant and child diet assessment by a breast-feeding questionnaire at the age of 1 year and a food frequency questionnaire at the age of 4 years.
- Biological samples: measurement of fatty acids, vitamins C and E, and folate in maternal serum, fatty acids in cord blood, vitamins E and C in breast milk, and measurement of fatty acids and vitamins at the age of 4 years.

Other determinants:

- Oxidative stress (as underlying mechanism): measurement of lipid hydroperoxides in maternal serum (12 weeks' gestation) and F2 isoprostanes in urine at 12 and 32 weeks' gestation, and child urine at the age of 1 year.
- Questionnaires: sociodemographic data, relevant data about biological father, medical and obstetric history, family history of allergies, use of drugs and vaccinations during pregnancy, complications of the current pregnancy at 12 and 32 weeks of gestation.
- Genetic determinants: total blood will be stored to measure genetic determinants for the different outcomes in the future.
- Parental psychopathology: mental health of both parents and maternal and paternal attachment to the infant measured using a questionnaire at the age of 1 year.

Assessment of outcomes (Table 3)

Reproductive outcomes:

- Intrauterine growth measured by fetal biometry assessed longitudinally by ultrasound scans at 12,

20 and 32 weeks' gestation in all women. The measurements will include femur length, head circumference, biparietal diameter and abdominal circumference.

- Anthropometric measures at birth (length, weight, head circumference and abdominal circumference) obtained by clinical examination.
- Preterm delivery and pre-eclampsia: information based on clinical records.

Postnatal growth and sexual development:

- Child growth: height and weight examination at the ages of 1 and 4 years. Clinical records of height and weight every 6 months.
- Sexual development: clinical examination performed by INMA researchers with a standardised protocol at birth, at the age of 1 year and at the age of 4 years.

Neurodevelopment:

- Neurodevelopment: Dubowitz test at birth; mental and psychomotor measurement at the ages of 1 and 4 years with the Bayley Scales of Infant Development and the McCarthy Scales respectively. Measurement of child hyperactivity (based on the DSM-IV) and social competence (California Preschool Social Competence Scales) through a questionnaire administered to the teachers at the age of 4 years.
- Thyroid status: measurement of thyroid stimulating hormone (TSH) at birth, and of free-T4, TSH and total-T3 at the age of 4 years.

Asthma and atopy:

- Measurement of specific IgE in maternal serum during pregnancy to assess maternal atopy.
- Assessment of asthma symptoms through questionnaire.

Atopy: physical dermal examination at the age of 1 year and measurement of total IgE at the age of 4 years.

Data quality, control and management

The INMA field staff such as interviewers, laboratory technicians and project paediatricians have been specifically trained for the project. All measurements have been tested for inter- and intra-reproducibility.

An electronic database has been prepared to monitor the cohort in order to facilitate the follow-up and to minimise the loss to follow-up. Information regarding maternal identification, inclusion number, information required for the follow-up (such as enrolment date, date of last menstrual period or expected date of delivery), and the calendar for the visits and the sampling procedures is collected by the INMA staff. Some information is also gathered on refusals in order to compare basic sociodemographic characteristics between both groups.

Confidentiality is guaranteed by keeping the monitoring data file separated from the questionnaire information and the biological samples.

Communication

The INMA Study aims to guarantee helpful communication to the participants of the INMA by collective meetings and periodic bulletins, to communicate the results to the general population through the web page and other sources, to guarantee that INMA data are published in the scientific press, and to provide useful information to health professionals, health officers and politicians.

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