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COHORT PROFILE

Cohort Profile: The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project

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How did the study come up?

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. Pre-natal and early life exposures are associated with child development and health and predispose to late adult effects.

The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project is a network of birth cohorts in Spain that aim to study the role of environmental pollutants in air, water and diet during pregnancy and early childhood in relation to child growth and development. INMA was based on the experiences acquired by three birth cohorts: the cohort of Ribera d'Ebre ($n = 102$), which assessed neurological development in an area with high levels of organochlorine compounds (OCs) and mercury originating from the emission of a chlor-alkali plant; the cohort of Menorca ($n = 530$), which studied associations of early life exposure to air-borne irritants and allergens on allergy and asthma; and the cohort of Granada ($n = 668$), which studied the incidence of infant reproductive health disorders at birth in relation to environmental endocrine disruptors. Based on the experience from these cohorts, a common protocol was developed for four new birth cohorts: Valencia ($n = 855$), Sabadell ($n = 657$), Asturias ($n = 494$) and Gipuzkoa ($n = 638$) cohorts. The protocol also aimed to unify the three older and four newer cohorts.

What does it cover?

The INMA project is a prospective population-based cohort study concerned with the associations between pre- and post-natal environmental exposures and growth, health and development from early fetal life until adolescence.

The general aims of the project are:

(i) To describe the degree of individual pre-natal exposure to environmental pollutants and the internal dose of these chemicals during pregnancy, at birth and during childhood;
(ii) To evaluate the impact of exposures to different contaminants on fetal and infant growth, health and development;

(iii) To evaluate the interaction between pollutants, nutrients and genetic variants on fetal and infant growth, health and development.

Who is in the sample?

The studied population includes pregnant women of general population resident in each study area [Ribera d'Ebre, Menorca, Granada, Valencia, Sabadell, Asturias and Gipuzkoa (Figure 1)] and their children. Criteria for inclusion of the mothers were: (i) to be resident in one of the study areas, (ii) to be at least 16 years old, (iii) to have a singleton pregnancy, (iv) to not have followed any programme of assisted reproduction, (v) to wish to deliver in the reference hospital and (vi) to have no communication problems.

Figure 1 Geographical location of INMA cohorts in Spain

Each cohort had a different period of recruitment (Figure 2). In the Ribera d'Ebre and Granada cohorts, mothers were recruited during hospital admission for delivery. Recruitment took place between March 1997 and December 1999 in the Ribera d'Ebre cohort and between October 2000 and July 2002 in the Granada cohort. In the Menorca cohort, all eligible pregnant women presenting for pre-natal care at all general practices of the island (in public or private health centres) were invited to participate in the study over a 12-month period starting in mid 1997. In the four new cohorts, recruitment took place during the first pre-natal visit (10–13 weeks of gestation) in the main public hospital or health centre of each study area. The recruitment period in Valencia was from November 2003 to June 2005. In Sabadell, it took place from July 2004 to July 2006. Recruitment in Asturias was carried out from May 2004 to July 2007, and in Gipuzkoa from April 2006 to January 2008. A common characteristic of these areas is that the vast majority of the population attends the public health sector. From 45% to 98% of the eligible pregnant women agreed to participate (96% in Ribera d'Ebre, 98% in Menorca, 54% in Valencia, 60% in Sabadell, 45% in Asturias and 68% in Gipuzkoa; information not available for Granada). In Sabadell, the

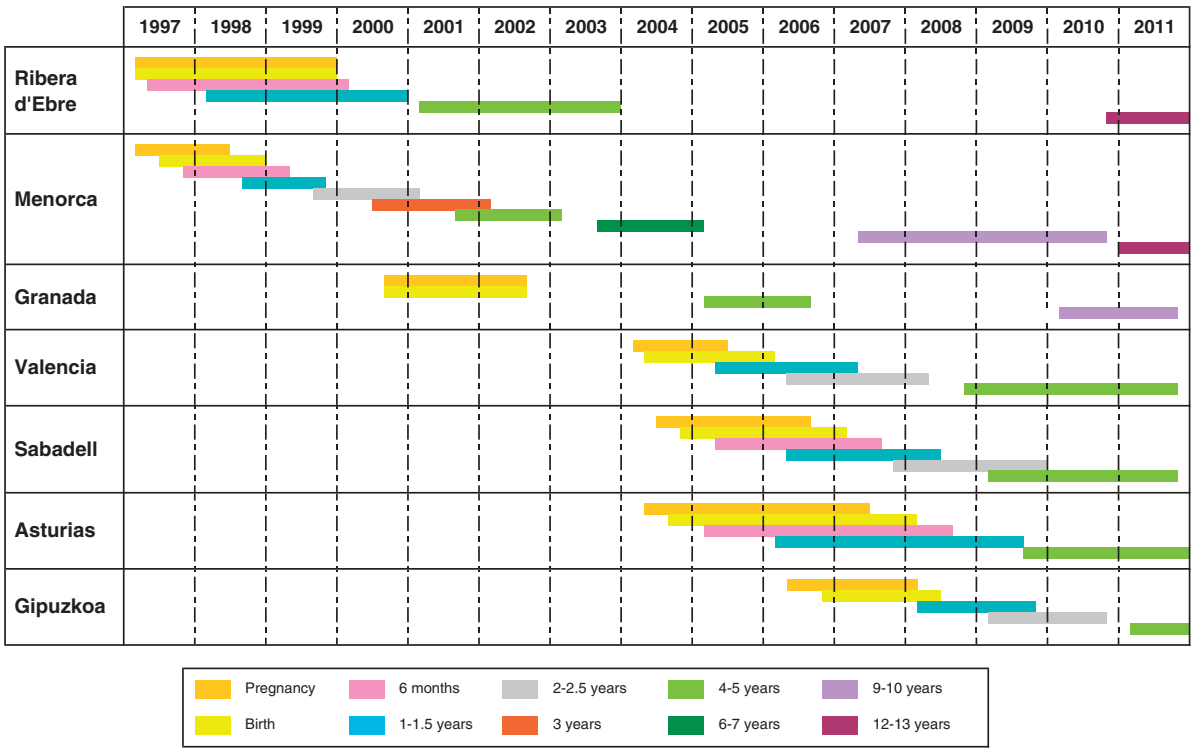

Figure 2 Follow-up periods of INMA cohorts

educational achievement of women who refused was lower than that of the participants, but there were no differences in age. In Valencia, a higher proportion of older women and of working women agreed to participate. There were no differences in age between participants and non-participants in Asturias. In Gipuzkoa, a high proportion of working women were included. Information comparing basic characteristics of participants and non-participants was not available for Ribera d'Ebre, Menorca and Granada. Two cohorts (Sabadell and Gipuzkoa) were able to collect information regarding reasons for non-participation, which were as follows: 27.6% did not want to participate, 30.3% said they did not have time, 9.3% reported no interest and 32.7% could not be located for the baseline interview, after being identified as eligible by their attending physician.

How often have participants been followed up?

Each cohort varies to some degree in the follow-up time-points and methods, although follow-up surveys were performed in all cohorts at the main time-points (pregnancy, birth and 4 years) (Figure 2). In Ribera d'Ebre, the follow-up examinations took place at birth and at 8 weeks, 8 months and 1 and 4 years. In Granada, the surveys were performed at birth and at 4 years. Although women were not studied during pregnancy in these cohorts, a retrospective questionnaire about pregnancy data was administered at birth. In Menorca, the follow-up started during pregnancy, and surveys were carried out at birth, at 3 months and at the ages of 1, 2, 3, 4, 6, 9.5 and 10.5 years. Currently, in 2010, follow-up surveys of 9.5-year-olds in Granada and of 12- to 13-year-olds in Ribera d'Ebre and Menorca are starting. In the four new cohorts, the recruitment survey in the first trimester of pregnancy was followed by surveys during the third trimester, at birth, at 6 months (only for Sabadell and Asturias), at 1–1.5 years, at 2–2.5 years (except for Asturias) and at 4–5 years (currently ongoing). Follow-up of the children will continue until at least adolescence, if resources are available.

What has been measured?

Extensive assessments were carried out in pregnant women and children. The information was gathered from a variety of sources: *ad hoc* administered questionnaires in face-to-face interviews by trained INMA personnel, clinical data, physical examinations, ultrasound scans, biological samples (blood, placenta, urine, saliva, hair, nails and mother's milk), biomarkers, diet determinants and environmental measurements (air pollution, water pollution and persistent and semi-persistent pollutants). Data collected at each wave varied slightly among cohorts according to internal interests, but the main common variables were included in all cohorts. For example, all cohorts have collected data on parental socio-demographical and occupation characteristics, parental smoking habits, maternal and child diet, child anthropometry, respiratory symptoms and cognitive assessment at different ages, and levels of persistent pollutants during pregnancy.

All information collected in the different follow-up surveys is shown in Tables 1 and 2. Biomarkers analysed during pregnancy, at delivery and in children's biological samples are listed in Table 3. Planned measurements for future follow-up surveys will be similar to previous ones, focusing on measurement of air, water and diet contaminants, child growth patterns, sexual maturation, respiratory function, atopy and neurodevelopment.

What is attrition like?

Figure 3 illustrates a flowchart of the main phases in the INMA project until 1–1.5 years (the follow-up point that all participants have completed), including the sources of attrition in the sample and the impact on sample size. Differences in maternal and newborn characteristics of participants lost at 1–1.5 years are shown in Table 4. Predictors of sources of attrition were: maternal age (younger mothers), foreign country of origin, lower educational level and social class, higher smoking use during pregnancy, higher parity and with history of pre-term births ($P < 0.05$).

Wide-ranging efforts were made to maintain subjects in the INMA cohorts such as releasing periodic bulletins, creating a new web page and maintaining a personal and regular contact with mothers by our nurses. Periodic bulletins are being sent to all INMA families in order to keep them updated with the project. The bulletins are used to inform them about project progress and results. There is also information on forthcoming follow-ups and related topics. Priority was given to the web page (www.proyectoinma.org) to maintain active communication with the families. On the web page, there is general information on the study, all protocols and questionnaires, all published papers, news and press releases related with the project and a list of all researchers involved with a short description of their work and their email addresses. Moreover, as the most important aim of the web page is to approach the families, the web page is translated into the four languages spoken by INMA study participants: Spanish, Catalan/Valencian, Basque and Asturian. A very important aspect of maintaining participation in INMA is the ongoing contact by our nurses aimed at creating a familiar, personal and confidential relationship with the families.

Table 1 Questionnaire data collected in different study phases

Variables	Pre-natal period		Post-natal period						
	1st trimester	3rd trimester	Birth	6 months	1–1.5 years	2–2.5 years	4–5 years	6–7 years	9–10 years
Social and environmental factors									
Socio-demographic factors	✓	✓		✓	✓	✓	✓	✓	
Occupation characteristics		✓			✓				
House characteristics		✓		✓	✓	✓	✓	✓	✓
Bedroom characteristics		✓		✓	✓	✓	✓	✓	
Kitchen characteristics		✓		✓	✓	✓	✓	✓	
Chemical products use		✓			✓		✓		✓
Domestic activities		✓			✓		✓		
Pets		✓		✓	✓	✓	✓	✓	✓
Mobile phone use		✓					✓		
Noise		✓			✓		✓		
Traffic data		✓			✓		✓		
Time-activity patterns		✓			✓	✓	✓		
Water use		✓			✓	✓	✓		
Lifestyles									
Parental smoking, alcohol and drugs use	✓	✓		✓	✓	✓	✓	✓	✓
Diet (mother and child)	✓	✓		✓	✓	✓	✓	✓	✓
Physical activity (mother and child)	✓	✓				✓	✓	✓	✓
Maternal health and diseases									
Pregnancy history	✓	✓							
Chronic diseases	✓					✓			
Family history of diseases	✓					✓			
Radiation	✓								
Dentist	✓	✓							
Transfusion	✓								
Medication	✓	✓		✓					
Vaccination	✓	✓							
Health services use	✓	✓							
Childhood health and diseases									
Symptoms and diagnosis				✓	✓	✓	✓	✓	✓
Medication				✓	✓		✓	✓	✓
Vaccination					✓		✓		
Health services use					✓	✓	✓	✓	

What has it found? Key findings and publications

The INMA project is still ongoing with the analysis of data now in progress, particularly at an early stage in the four new cohorts. Nevertheless, findings related with the first three cohorts and the first articles of the four new cohorts are already available. The INMA website gives updated references with a Pubmed link to all INMA publications (http://www.proyectoinma.org/presentacion-inma/resultats_en/). Major findings obtained so far are highlighted below.

Our results suggest that environmental contaminants that are common in soil, water and food are present in tissues of mothers and children. Several compounds have been found in placentas, cord blood, mother's and child's blood, mother's and child's urine, child's hair and mother's milk[1–37] (see Table S1 of supplementary data). Their ubiquity supports the plausibility of embryo-fetal exposure during pregnancy. Moreover, concentrations of environmental chemical pollutants were also measured in tap water, swimming pool water, indoor and outdoor air and personal samples[10,38–50] (see Table S2 of supplementary data).

Table 2 Clinical, cognitive and behavioural measurements in different study phases

		Pre-natal period		Post-natal period					
General category	**Details**	1st trim	3rd trim	Birth	6 mo	1–1.5 years	4–5 years	6–7 years	9–10 years
Physical health measures									
Mother									
Anthropometry	Weight	✓		✓			✓		
	Height	✓					✓		
	Waist circumference, bioimpedance						✓		
Blood pressure	Diastolic, systolic						✓		
Allergy	Prick test				✓				
Father									
Anthropometry	Weight, height	✓							
Allergy	Prick test				✓				
Child									
Fetal growth	Ultrasounds	✓	✓						
Birth characteristics	Type of delivery, Apgar, gestational age,			✓					
	cord blood gasometry, haematocrit, placenta weight			✓					
Anthropometry	Weight, height			✓		✓	✓	✓	✓
	Head circumference			✓		✓	✓		
	Waist circumference						✓		✓
	Skin fold						✓		
	Bioimpedance						✓		✓
Blood pressure	Diastolic, systolic						✓		✓
Respiratory function	Oscillometry						✓		✓
	Spirometry						✓		✓
	Peak flow							✓	
	Exhaled NO								✓
Allergy	Prick test							✓	
Sexual development	Tanner stages, genital malformations			✓			✓		✓
Skin anomalies				✓	✓	✓			✓
Cognition and behaviour									
Mother	Mother-to-child attachment					✓	✓		
	Mental health					✓	✓		
	Intelligence quotient					✓	✓		✓
Father	Father-to-child attachment					✓			
	Mental health					✓	✓		
	Intelligence quotient					✓	✓		
Child	Dubowitz test			✓					
	Bayley Scales of infant development					✓			
	Etxadi-Gangoiti Scale of family context					✓	✓		
	McCarthy Scales of children's abilities						✓		
	California Preschool Social Competence Scale						✓		
	ADHD Criteria of DSM-IV						✓		✓
	Communication domain of Battelle Developmental Inventory						✓		
	Childhood Asperger Syndrome test						✓		
	Computer performance test						✓	✓	✓

trim = trimester; mo = months; NO = nitric oxide

Table 3 Biomarkers measured at different study phases

	Pre-natal period		Post-natal period		
Biomarkers	1st trimester	3rd trimester	Birth	1–1.5 years	4–5 years
Organochlorine compounds	Mother's blood	Mother's blood	Cord blood	Child's blood	Child's blood
			Mother's milk		
			Placenta		
Polybrominated compounds			Mother's milk		Child's blood
Mercury		Mother's urine	Cord blood		
			Placenta		
			Child's hair		Child's hair
Lead	Mother's urine	Mother's urine	Cord blood		
Other metals	Mother's urine	Mother's urine			
Bisphenol A and phenols	Mother's urine	Mother's urine	Placenta		Child's urine
Phtalates	Mother's urine	Mother's urine			Child's urine
Hydroxypyrene		Mother's urine			Child's urine
Thyroid hormones	Mother's blood		Cord blood		Child's blood
C-reactive protein	Mother's blood				
F2-isoprostanes	Mother's urine	Mother's urine			
IgE (total, cat, dust, pollen)	Mother's blood	Father's blood			Child's blood
Fatty acids	Mother's blood		Cord blood		
			Mother's milk		
Lipids	Mother's blood		Cord blood		
Folic acid	Mother's blood				
Ferritine	Mother's blood				
Vitamin B12	Mother's blood				
Vitamin C	Mother's blood		Mother's milk		
Vitamin E			Mother's milk		
Vitamin D	Mother's blood	Mother's blood			
Iodine	Mother's urine	Mother's urine			
Porphirines			Child's urine		Child's urine
Cortisol				Mother's saliva	Mother's saliva
				Child's saliva	Child's saliva
Genetics	Mother's blood		Cord blood		Child's blood

Pre-natal exposure to several of these environmental contaminants has been related with an alteration of maternal and child thyroid hormones levels,[1,2,20,51–53] an increased risk for congenital anomalies,[15,28,54] an impairment of the fetal and child growth,[18,25,55–60] a delay in child cognitive and behavioural development[8,16,19,22,23,44,61–63] and an increased risk of child respiratory symptoms and atopy.[26,27,46,64–68] However, long-term breastfeeding and some maternal diet factors during pregnancy, such as fish consumption or high adherence to a Mediterranean diet score may counteract some of these pollutants' negative effects on child health.[19,69–79] Moreover, genetic differences have shown to lead to different effects of environmental factors on child health outcomes.[14,44,80]

What are the main strengths and weaknesses?

Main weaknesses

Loss to follow-up is the main limitation of a prospective cohort study, since loss is not random. Although attrition rates in the INMA project were low, non-participants were more likely to have a lower socio-economic status. Big efforts were constantly made to retain all subjects in the INMA cohorts by periodic bulletins, the web page and personal and regular contact with the families by our nurses.

When the INMA project was conceived, three cohorts already existed and four new cohorts were set up. A new common protocol was designed, based on the experience of the three existing cohorts. In order

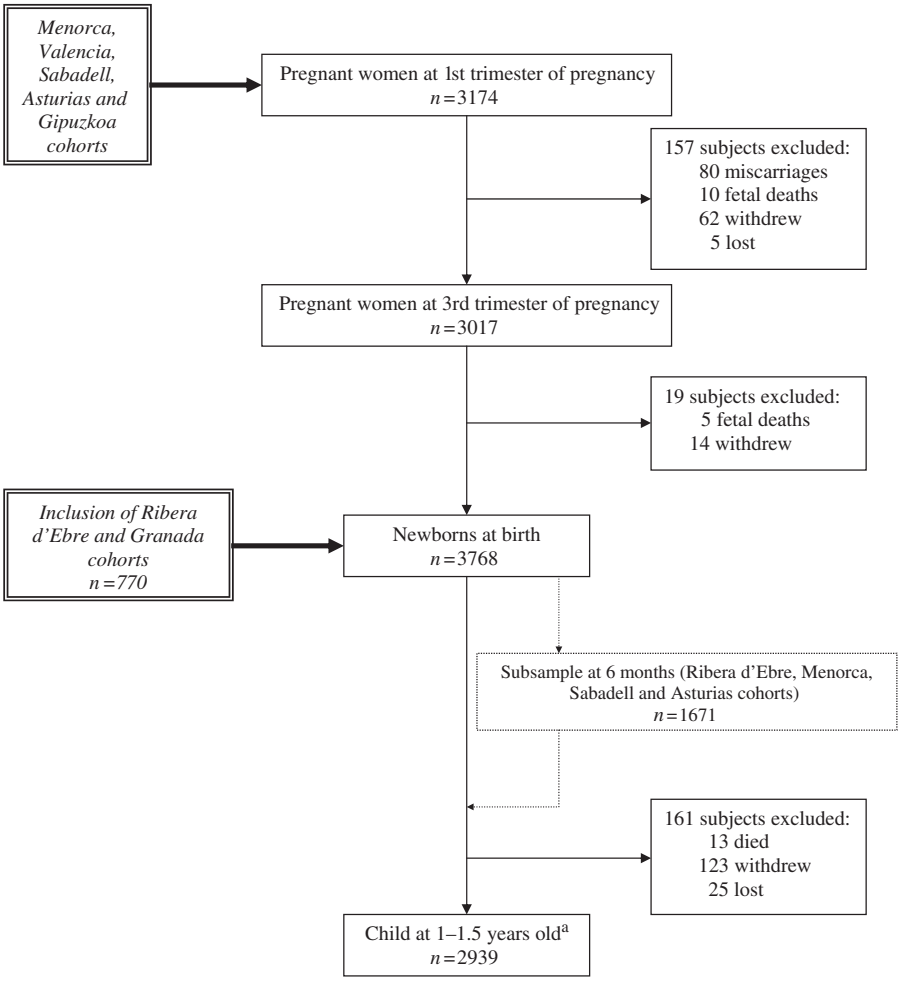

Figure 3 Flowchart illustrating the main phases in the INMA project until child is aged 1–1.5 years. [a]Not taking into account Granada cohort as there was no follow-up at 1–1.5 years ($n = 668$ newborns at birth)

to address issues of comparability across the sub-cohorts, all INMA researchers collaborate closely in working groups on different topics, such as growth, neurodevelopment, respiratory health and others. Joint analyses are our priority and new follow-up surveys are always developed together keeping in mind the global project. An active and up-to-date-intranet of the project was built in order to improve INMA researchers' communication and work.

It is not possible to measure all factors related with pregnancy and child health, or to measure all with complete accuracy; residual confounding by unmeasured or incompletely measured factors may occur in specific analyses. Nevertheless, information on a large number of covariates has been collected in this project, as shown above. We believe that collection of the maximum number of relevant variables is important to better understand the complexities of the origins of child diseases. Moreover, relevant and novel biomarkers are and will be analysed in relation with the main purposes of the studies.

Finally, environmental epidemiology faces the challenge of studying effects that are usually more functional than pathological at lower exposure levels, unlike those found at higher accidental or occupational exposure levels. Studies examining low exposure levels and subtle functional effects inevitably suffer from lack of statistical power, which may limit the deduction of clear conclusions regarding causality. The participation of the INMA project in different multi-national studies will improve statistical power to check hypotheses on rare events and effect modifications, as well as allow cross-country comparisons.

Main strengths

INMA project is a large prospective birth cohort that includes families living in different socio-economic and environmental areas of Spain, with exhaustive follow-ups both for the extensive environment measurements, questionnaire data and physical and neurodevelopment evaluations as well as for the time-periods. This project will allow not only the exploration of different associations between environmental factors and reproductive and child outcomes, but also the description of levels of contaminants

Table 4 Differences in maternal and newborn characteristics of participants lost at 1–1.5 years old in the INMA project[a]

Maternal characteristics	Participants included at pregnancy ($n=3174$)	Participants followed at 1–1.5 years ($n=2843$)	Participants lost at 1–1.5 years ($n=331$)	*P*-value of difference
Age (years)[b]	30.4 (4.4)	30.6 (4.3)	29.2 (5.3)	<0.001
Overweight/obese (%)	25.5	25.1	30.1	0.081
Country of origin (foreign) (%)	7.7	7.2	13.6	<0.001
Parity (%)				0.022
0	55.1	55.6	50.2	
1	37.0	37.0	37.7	
⩾2	7.8	7.5	12.1	
Education level (%)				<0.001
Primary or less	30.1	29.1	41.5	
Secondary	39.5	39.3	41.1	
High	30.4	31.6	17.4	
Maternal occupation at pregnancy (%)				0.001
I/II managers/technicians	35.6	36.3	28.1	
III/IV skilled manual/non-manual	44.5	44.5	44.1	
V/VI semi-skilled/unskilled	19.9	19.2	27.7	
Smoking use during pregnancy (%)	30.0	29.5	38.6	0.016
Alcohol consumption during pregnancy (%)	18.6	18.2	22.9	0.063
Newborn characteristics	**Participants included at birth ($n=2998$)**	**Participants followed at 1–1.5 years ($n=2843$)**	**Participants lost at 1–1.5 years ($n=155$)**	***P*-value of difference**
Sex (females) (%)	48.3	48.4	46.5	0.644
Gestational age (weeks)[b]	39.7 (1.8)	39.7 (1.7)	39.1 (3.3)	<0.001
Premature (<37weeks) (%)	4.5	4.2	10.9	<0.001
Birthweight (g)[b]	3244 (483)	3247 (471)	3188 (661)	0.142

[a]Excluding Granada cohort that do not have a follow-up at 1–1.5 years, and Ribera d'Ebre cohort with the inclusion of participants was at birth.
[b]Mean (SD).

in large samples of pregnant women and children of Spain.

Moreover, it is a population-based study in which the population is selected by exposure or health effect. Furthermore, the nurses who assessed health determinants by in-person questionnaires, the lab personnel who analysed the samples and nurses, psychologists, and teachers who assessed the health outcomes were all unaware of any of the children's conditions which could contribute to differential bias in assessment of determinants or outcomes.

Can I get hold of the data? Where can I find out more?

External collaborations are welcomed. Researchers who have an interest in using INMA data for research purposes can apply for access to data. There are mechanisms for submitting research proposals to our INMA steering committee (see more details in our study website (http://www.proyectoinma.org/presentacion-inma/politica-colaboracion/en_politica-colaboracion.html). Any delivery of data will be considered as a sub-project within INMA and a formal agreement will be signed. Proposals are evaluated by the INMA steering committee although in specific cases outside experts can be consulted. We encourage interested researchers to contact us.

Supplementary Data

Supplementary Data are available at *IJE* online.

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