The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project: more than 10 years contributing to environmental and neuropsychological research

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Abstract

Background: In 2003 the INMA—INfancia y Medio Ambiente (Environment and Childhood) Project, a Spanish national network of birth cohorts including more than 3500 participants, was set up with the aim to assess the health impacts of pre- and postnatal environmental exposures on children. The project has published more than 60 papers on maternal and environmental factors related to neuropsychological development in children, one of the main research interests within the project. With the present review, we evaluate the evidence provided by the INMA project on this topic and discuss how the data can contribute to cover the challenges that children’s environmental health research will face in the coming years.

Results: the INMA project has contributed to provide increasing evidence of the association between prenatal exposure to persistent organic pollutants (POPs) and child neuropsychological development, but it has also shown, using innovative methodologies, that postnatal exposure to these compounds does not play a role in this association. The project has also contributed to show the detrimental influence of certain air pollutants on child neuropsychological development, as well as how a balanced maternal fish intake can protect from the potential adverse effects of prenatal exposure to mercury. Also, the project has contributed to the understanding of impacts of nutritional factors including supplement intake and vitamin D levels during pregnancy and the role of breastfeeding on the neuropsychological benefits.

Conclusions: INMA findings underscore the importance of continued research on the delineation of the sensitive windows of exposure both during pregnancy and postnatally and on the combined effects of environmental exposures, denoted the exposome. In terms of health policy, INMA findings have important implications for the development of public health policies to advance the health and development of children.
Keywords: neuropsychological development; environmental epidemiology; pollutants; prenatal; postnatal; INMA project

Abbreviations

ADHD attention-deficit hyperactivity disorder
ADHD-DSM-IV criteria of the diagnostic and statistical manual of mental disorders 4th edition
BPA bisphenol A
BSID-I Bayley scales of infant development 1st edition
CAST childhood Asperger syndrome test
CBCL/6-18 child behavior checklist
CI confidence interval
CPSCS California preschool social competence scale
CSRS Conner’s parent rating scales
DDE dichlorodiphenyldichloroethylene
DDT dichlorodiphenyltrichloroethane
DEHPs di-(2-ethylhexyl) phthalate
GSID Griffiths scales of infant development
HCB hexachlorobenzene
INMA infancia y medioambiente (environment and childhood)
IRR incidence rate ratio
MBzP mono-benzyl phthalate
MDI mental development index
MCSA McCarthy scales of children’s abilities
NO2, NOx nitrogen dioxide
OR odds ratio
PBDE47 polybrominated diphenyl ethers
PCBs polychlorinated biphenyls
PDI psychomotor developmental index
PM2.5, PM10, PMcoarse particulate matter (2.5, 10, coarse)
POPs persistent organic pollutants
RR relative risk
SDQ strengths and difficulties questionnaire
SE standard error
TSH thyroid-stimulating hormone
Introduction

In 2003 the INMA—Infancia y MedioAmbiente (Environmental and Childhood) project, a Spanish national network of birth cohorts aimed at assess the health impacts of pre- and postnatal environmental exposures on children, was set up. The first cohorts started in 1997 in the locations of Ribera d’Ebre (n=102) and Menorca (n=482), in 2001 another birth cohort was set up Granada (n=668, including only boys). Based on the experience from these three cohorts, a new common research protocol was developed and four new cohorts were designed to evaluate the impact of environmental exposures and diet on children’s health: Valencia (n=787), Sabadell (n=622), Asturias (n=485) and Gipuzkoa (n=612). Overall, the project includes more than 3500 participant mother-child pairs.

Since 2001, the number of original papers published by the project has exponentially increased and so far more than 300 articles are contributing to the knowledge of the association between pre- and postnatal environmental exposures and child health. One of the main research interests within the INMA project has been the study of the neuropsychological development of children and, along the years, different tools, listed in Table 1, have been used in order to evaluate cognitive and psychomotor functions as well as behavioral outcomes.

Overall, the INMA project has published more than 60 papers on maternal and environmental factors related to neuropsychological development in children. Beyond the work conducted by other research teams, that contributes to the evidence of the associations between environmental factors and neuropsychological development in children, and beyond the mechanisms that explain these associations, which have been
discussed in other articles\textsuperscript{4}, with the present review we aim to evaluate the evidence provided by the INMA project up to January 2016 on which maternal and environmental determinants during pre- and postnatal life are associated with child’s neuropsychological development and to discuss how INMA data is contributing to cover the challenges that child health environmental research will face in the coming years.

**Results**

**Tools to assess neuropsychological development in INMA**

General cognition was evaluated with the Bayley Scales of Infant Development 1\textsuperscript{st} edition (BSID-I)\textsuperscript{5} and the Griffiths Scales of Infant Development (GSID)\textsuperscript{6} - first two years of life - and the McCarthy Scales of Children’s Abilities (MCSA)\textsuperscript{7} - 4 to 5 years of life. BSID yields two indices, the Mental Development Index (MDI) and the Psychomotor Developmental Index (PDI), whereas the GSID is divided into five subscales (locomotor, personal-social, hearing and language, eye-hand coordination, and performance). MCSA provides a global score for general cognition and scores for five subscales (verbal, perceptive-performance, memory, quantitative and motor). Additionally, within the INMA project, a new summary measure was constructed to assess those cognitive tasks associated with executive functions\textsuperscript{8}. At the age of 4-5 years, social competence was also evaluated with the California Preschool Social Competence Scale (CPSCS), which measures the appropriateness of preschool children’s interpersonal behavior and their degree of social responsibility, and includes the concept of independence, understood as interpersonal autonomy\textsuperscript{9}. Attention-deficit, hyperactivity and impulsivity, were also assessed with the Attention-Deficit Hyperactivity Disorder (ADHD) Criteria of the Diagnostic and Statistical Manual of
Mental Disorders 4th Edition (ADHD-DSM-IV), as well as autistic traits, determined with the Childhood Asperger Syndrome Test (CAST)\textsuperscript{10}. Although at the age of 7 years many tests were conducted (Table 1), so far only those related to behavioral problems - the Strengths and Difficulties Questionnaire (SDQ)\textsuperscript{11}, the Conners' Parent Rating Scales (CPRS)\textsuperscript{12} and the Child Behavior Checklist (CBCL/6-18)\textsuperscript{13} - have been included in publications. The SDQ, which covers common areas of emotional and behavioral difficulties, consists of 25 items that allow obtaining a global score and individual scores for five subscales (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behavior). The short form of the CPRS intends to assess problematic behavior in children and consists in summarizing the results into scores for three subscales (oppositional, cognitive problems/inattention and hyperactivity) and an ADHD index. The CBCL/6-18 provides several behavioural scales grouped by three composite scales (internalizing, externalizing and total problems scales).

\textit{Prenatal and postnatal factors related to comorbidities}

\textit{Prenatal determinants}

\textit{Persistent organic pollutants (POPs)}

Because of their persistency and the health effects associated, the production and use of most POPs are currently banned in the majority of countries, which has led to a general reduction of the exposure levels in the environment and human tissues\textsuperscript{14}. However, due to their properties, humans are still exposed to low levels of these compounds\textsuperscript{14}.

In 2003 Ribas-Fitó \textit{et al.} published the first paper of the INMA project about organochlorine exposure and cognitive and psychomotor development in children\textsuperscript{15}.  

The study, conducted in the vicinity of an electrochemical plant in Ribera d’Ebre (Catalonia) and including 92 mother-infant pairs, observed that for each doubling of cord blood dichlorodiphenyldichloroethylene (DDE) concentration the cognitive and the psychomotor scores decreased in 3.50 points (SD: 1.39) and 4.01 points (SD: 1.37), respectively, at the age of 13 months. Later, children 4 years old from Ribera d’Ebre and Menorca (N=475) with dichlorodiphenyltrichloroethane (DDT) concentrations in cord serum above 0.20 ng/ml had decreased a mean of 7.86 (SE, 3.21) points in the verbal scale and 10.86 (SE, 4.33) points in the memory scale compared with those with DDT concentrations below 0.05 ng/ml, with stronger associations among girls. At this age, very weak associations with DDE were observed. Further analysis including children of the new INMA birth cohorts did not observe associations with DDE at the age of 1 year (Table 2).

In the first study conducted in Ribera d’Ebre, polychlorinated biphenyl (PCBs) were only marginally associated with psychomotor development at the age of 13 months. Forns et al., in a study including 1391 children of the new INMA birth cohorts, observed that prenatal PCB exposure, and particularly to congeners 138 and 153, resulted in impairment of psychomotor \[ \beta (95\%CI) = -1.24, (-2.41, -0.07) \] but not of mental development measured at around 1 year of age. A subsequent study conducted in Menorca observed that prenatal exposure to PCB153, but not other congeners, was associated with decreased scores of all scales, except the motor scale, at the age of 4 years (Table 2).

None of the studies evaluating the effects on cognitive and psychomotor development observed associations with HCB at the age of 1 year. However, in the birth
cohorts of Ribera d’Ebre and Menorca, children with concentrations of HCB > 1.5 ng/mL at birth had a statistically significant increased risk of having poor social competence and ADHD scores [(RR 95%CI = 4.04 (1.76-9.58) and 2.71 (1.05-6.96), respectively]¹⁹ (Table 2).

Prenatal exposure to mirex, measured in 104 children from Granada (only 26% of children had detectable levels), was related with a decrease of 5.15 points in working memory and of 7.33 points in the quantitative area of the MCSA at the age of 4 years, with respect to children with prenatal mirex values below the limit of detection²⁰ (Table 2).

In Menorca, where children were classified as exposed and non-exposed to polybrominated diphenyl ether 47 (PBDE47) according to the limit of quantification (only 45% had detectable levels), no associations were observed between prenatal exposure and cognitive development at the age of 4 years²¹. However, in Sabadell and Gipuzkoa, the sum of different PBDE congeners were associated with decreasing mental development scores in the first year of life (β per log ng/g lipid = -2.25, 95%CI -4.75, 0.26), being PBDE209 the main congener responsible for this association. No relationship with psychomotor development was observed at that age²². The association between prenatal PBDEs exposure and behavioral outcomes (ADHD symptoms and social competence) was also assessed in children from Menorca, but no associations were found²¹ (Table 2).

In summary, the INMA project has provided evidence of the neuropsychological impacts of prenatal exposure to some organochlorine compounds, particularly DDT/DDE and PCBs in relation to cognitive development and HCB in relation to
behavior problems. For other POPs (mirex, PBDEs), some effects on cognitive and psychomotor development have been also described.

**Metals**

Certain metals are considered developmental neurotoxicants, such as methylmercury, lead, arsenic and manganese. Medium-high prenatal exposure to mercury has been described in the INMA cohorts, with a high proportion of newborns with elevated concentrations of total mercury in cord blood; however, these high concentrations did not associate with neither a mental [β (95%CI)=0.1 (-0.68, 0.88)] or a psychomotor [β (95%CI)=-0.05 (-0.79, 0.68)] delay at the age of 14 months (n=1683). A stratified analysis by sex suggested an impaired but not statistically significant effect on psychomotor development only in girls [β (95%CI)=−1.09 (-2.21, 0.03) (interaction p-value= 0.033)]. In the birth cohort of Sabadell, several metals (cobalt, copper, arsenic, cadmium, antimony and lead) were measured in urine samples of mothers during the 1st and the 3rd trimesters of pregnancy. Results showed no associations between low prenatal levels of these metals and cognitive and psychomotor development or behavioral symptoms (Table 2). One of the limitations of this study was that the matrix and technique used to measure lead were not the most appropriate (whole blood is the most suitable biological matrix), and therefore many children were classified as having non-detectable levels. Overall, the INMA project has shown that in this Mediterranean population, what is considered “elevated” levels of exposure to mercury during pregnancy do not seem to have a detrimental effect on the neuropsychological development of the infants. This, as we will discuss later, might be explained by the protective effects of maternal fish consumption, the main source of mercury in this cohort, among other factors. In relation to prenatal low exposure to other metals and
early neuropsychological development, the INMA project provided evidence of no
associations.

Outdoor air pollution

Outdoor air pollution is a global public health threat. Animal studies have shown that air
pollutants might reach the brain directly via the olfactory bulb and may themselves be
proinflammatory\textsuperscript{27}. However, research on the neuropsychological effects in humans,
particularly in children, only started some years ago. A study including 1889 children
from the four youngest INMA cohorts observed an inverse non-significant association
between prenatal exposure to NO\textsubscript{2} and benzene and mental development at the age of
14 months\textsuperscript{28,29}. The associations were stronger among children whose mothers reported
low intakes of fruits/vegetables during pregnancy\textsuperscript{28}. In children from Gipuzkoa cohort it
was also found an inverse association between prenatal PM\textsubscript{2.5} exposure and the scores
obtained for psychomotor development [\( \beta \) (90\%CI) = -1.14 (-1.75, -0.53) for a 1 \( \mu g/m^3 \)
increase of PM\textsubscript{2.5}]\textsuperscript{29}. In 2014 Guxens et al. expanded the work to 6 European birth
cohorts including new data from INMA\textsuperscript{30}. The study, including more than 9000
children, observed that NO\textsubscript{2} exposure during pregnancy was associated with reduced
psychomotor development [\( \beta \) (95\%CI) = -0.68 (-1.25, -0.11) per increase of 10 \( \mu g/m^3 \) in
NO\textsubscript{2}], with similar trends in most European regions. The study did not observe
associations with cognitive development or between other air pollutants (NO\textsubscript{x}, PM\textsubscript{2.5},
PM\textsubscript{10}, PM\textsubscript{coarse}) and several neuropsychological domains evaluated between 1 and 6
years of age\textsuperscript{30}. Guxens et al. also evaluated the association between these air pollutants
and autistic traits in a study including more than 8000 children from four to ten years of
age in four European birth cohorts and no associations were observed\textsuperscript{31} (Table 2).
Overall, the INMA project, together with other birth cohorts in Europe, has shown a
consistent association between air pollutants, particularly NO₂, a marker of traffic related air pollution, and impaired neuropsychological development of children. However, no associations with autistic traits have been described.

Residential indoor air pollution

In children from the region of Menorca, cognitive functioning and attention-hyperactivity behaviours were evaluated at age 4 years in relation to prenatal use of gas appliances, obtained by questionnaire, and indoor NO₂ concentrations at each participant’s home. The study found that both use of gas appliances and NO₂ concentrations were inversely associated with cognitive outcomes [β (95%CI) for general cognition=−5.10 (-9.92, -0.28) and =−0.27 (-0.48, -0.07, respectively] and ADHD symptoms [OR (95%CI) for inattention symptoms=3.59 (1.14, 11.33)] and 1.06, (1.01, 1.12)]32. A second study, including more than 1800 children of 14 months of age, observed that children whose mothers used gas cooking during pregnancy had a small decrease in the mental development score compared with those using other cookers [β (95%CI)=−2.5 points (-4.0, -0.9)]33. This decrease was stronger when gas cooking was combined with less frequent use of an extractor fan, and was relatively consistent across strata defined by social class, education, among other covariates33 (Table 2). The INMA data published on indoor air pollution are consistent with those obtained for outdoor air pollution, although few papers have been published within the same project.

Smoking

Cigarette smoking reduces the health of smokers but also of those exposed to second-hand smoking. Association between maternal smoking during pregnancy with the neuropsychological development of children at age 4 were evaluated in the region of
Menorca\textsuperscript{35}. In this study, maternal smoking (in cigarettes/day) was associated with a decrease of children’s general cognitive development [$\beta$ (95%CI)=$-0.60$ (-1.10, -0.09)], as well as other subareas of the test (verbal, quantitative, working memory and executive function scores). An extension of this study observed this association was modified by a polymorphism in the \textit{GSTM1} gene, being children with null allele for this gene those who had the strongest effects (beta = $-4.73$, 95% CI -9.45 to -0.02)\textsuperscript{36} (Table 2).

\textit{Maternal fish intake}

Fish is an important source of n-3 fatty acids, iodine, vitamin D, and other nutrients which are essential for brain development but is also a potential source of neurotoxins, such as POPs or methylmercury\textsuperscript{37}. Fish consumption during pregnancy and during childhood was obtained in INMA through semi-quantitative food frequency questionnaires. In the cohort of Menorca no associations were observed between maternal fish consumption and the scores obtained in the MSCA at 4 years of age\textsuperscript{38}. However, among children breastfed for <6 months, maternal fish intakes of >2–3 times/week (but not >3 times/week) were associated with significantly higher scores on several subscales compared with maternal intakes of \leq 1 time/week [e.g. $\beta$ (95%CI)=11.0 (5.0 17.1) of the general cognitive score]\textsuperscript{38}. A second study including more than 1500 children observed that consumption of seafood during pregnancy was associated with increments in neuropsychological scores, although the associations were not fully linear\textsuperscript{26}. The intake of 600 and 854 g/week increased 2.90 (0.72, 5.09) points in the cognitive development at the age of 14 months and 2.84 (0.74, 4.94) at the age of 4-5 years. For consumptions above 854 g/week associations were weaker. Intake of small fatty fish explained part of the positive associations at 14 months of age, and lean
and large fatty fish appeared to be predictors of child neuropsychological function at the age of 4-5 years. Additionally, the study observed a reduction in autistic traits in relation to total, lean, and large fatty fish consumption [> 854 g/week of total fish maternal consumption decreased −0.55 (−1.06, −0.04) points of autism-spectrum traits]. Overall, coefficients diminished 15%–30% after adjustment for mercury exposure or long-chain polyunsaturated fatty acid concentrations in cord blood26 (Table 2). Studies from the INMA project show the potential benefits of balanced consumption of fish, and that these might be more evident in children breastfeeding less time than what is established by the current recommendations.

**Maternal dietetic supplements intake**

Folic acid supplements intake during pregnancy are recommended in order to reduce the incidence of neural tube defects and improve overall foetal growth. In fact, some studies indicate that a dose of 400 μg/day of folic acid is needed to avoid neural tube defects39. In a study conducted in Menorca, the use of folic acid during pregnancy was associated with higher subscale scores for verbal [β (SE) = 3.98 (1.69)], motor [β (SE) = 4.54 (1.66)] and verbal-executive function [β (SE) = 3.97 (1.68)] subscales at the age of 4 years40. Also, teacher ratings for social competence [β (SE) = 3.97 (1.61)] and inattention symptoms [OR (95%CI)=0.46 (0.22, 0.95)] were associated with the folic acid intake, independently of the intake of other vitamins40. Detailed information on the daily doses of folic acid supplements was gathered from the mothers to assess a dose-response analysis in a second study41. Authors observed that, at the age of 1 year, children whose mothers used folic acid supplement dosages higher than 5000 μg/day during pregnancy had a statistically significantly lower mean psychomotor scale score [β (95%CI) =-4.35 (-8.34, -0.36)] than children whose mothers used a recommended
dosage of folic acid supplements (400-1000 μg/day). An increased risk of delayed psychomotor development (psychomotor scale score <85) was also evident among children whose mothers took folic acid supplement dosages higher than 5000 μg/day, although the association was not statistically significant [OR (95%CI)=1.59 (0.82, 3.08)]. Regarding intakes <400 μg/day children obtained better mental scores [β (95%CI) =2.30 (0.38, 4.22)] than those of mothers who ingested between 400 and 1000 μg/day\(^4\) (Table 2). These results suggested that high folic acid supplementation (≥ 5000 μg/day) could be harmful for child neuropsychological development but it should be confirmed in further studies.

In the INMA project two studies have evaluated the effects of iodine supplementation during pregnancy\(^2\), which is often recommended in order to ensure a proper thyroid function (the WHO recommends a iodine intake for pregnant and lactating women of 250 μg/day if iodized salt is not accessible for around of the 80% of the households\(^4\)). In the birth cohort of Valencia, maternal intake of ≥150 μg/day of iodine supplements, compared with <100 μg/day, was associated with a 5.2-point decrease in psychomotor development (95%CI=−8.1,−2.2) at the age of 1 year\(^2\). However, when the analyses were extended to other cohorts, the association was not statistically significant [β (95%CI)=−0.9 (−6.9, 5.0) for psychomotor score, and a decrease of 1.8 point in mental score was observed (95%CI=−5.6, 2.0)] at the age of 1 year\(^3\). The results of these studies indicate that, at least in these Spanish regions, iodine supplementation does not improve infant neuropsychological development in the first year of life (Table 2).

Maternal thyroid hormone levels
Maternal thyroid hormones play an important role in many fundamental processes underlying brain development and maturation of the fetus\textsuperscript{45}. In Granada birth cohort, which only includes boys, higher thyroid-stimulating hormone (TSH) cord blood concentrations were associated with a decrease of 3.51 and 3.15 points on cognitive and executive function scores, respectively, and an increased risk of scoring low in the quantitative scale at the age of 4 years [OR (95%CI)=2.64 (1.16, 5.54)]\textsuperscript{46}. In a second study including more than 1700 children, low free thyroxine (fT4) levels (<5th percentile) in healthy pregnant women were associated with a moderate delay in child neurodevelopment [β (95%CI)= -3.4 (-6.7, -0.2) points of mental scores of the BSID]\textsuperscript{47}. Self-reported prepregnancy thyroid disorder without medical treatment was also associated with child neurodevelopment [β (95%CI)= -5.5 (-8.9, -2.0) points of mental scores of the BSID]\textsuperscript{47} (Table 2).

**Vitamin D**

Vitamin D has a crucial role in maintaining the musculoskeletal health and also has influences on the immune system and brain development and maintenance\textsuperscript{48}. In 2012 Morales et al. observed that increasing circulating concentration of maternal vitamin D during pregnancy was associated with improved mental [β (95%CI)=0.79 (0.14, 1.45)] and psychomotor [β (95%CI)=0.88 (0.22, 1.54)] development in 1820 infants of 1 year\textsuperscript{49}. Moreover, infants of mothers with vitamin D concentrations >30 ng/mL (clinically considered as optimal levels) showed an advantage of 2.6 and 2.3 points in mental and psychomotor scores, respectively, in comparison with those of mothers with vitamin D concentrations <20 ng/mL (considered as deficient levels)\textsuperscript{49}. Three years later, in a study including 1650 children, Morales et al. observed that prenatal vitamin D concentrations were also associated with a reduced risk of total ADHD-like symptoms.
in children at the age of 4 years [IRR (95%CI)= 0.89 (0.80, 0.98) per 10 ng/ml increment of maternal vitamin D]\(^{50}\). Using clinical cut-off points, the risk of ADHD DSM-IV was of RR (95%CI)=0.87 (0.72, 1.06) per 10 ng/ml increment of vitamin D\(^{50}\) (Table 2). Above results indicate neuropsychological benefits by increasing vitamin D levels up to those clinically considered as optimal.

*Phthalates and Bisphenol A (BPA)*

Phthalates and BPA are non-persistent compounds that have been suggested to have effects on the neuropsychological development, based on some animal and child studies, but results are not consistent and there are still discrepancies among them\(^{51,52}\). The INMA project has been the first birth cohort to use two biological samples in order to measure phthalates and BPA exposure during pregnancy, reducing potential misclassification, in relation to different neuropsychological items (mental, psychomotor and behavioural) in children at different ages (1, 4 and 7 years). Results have not provide consistent associations across ages\(^{51,52}\). For instance, the study evaluating the effects of exposure to low and high molecular weight phthalates only observed an association between prenatal MBzP phthalate exposure and psychomotor score at the age of 4 years [\(\beta (95\% CI)=-1.49 (-2.78, -0.21)\)] but not with the cognitive domain in children at the age of both 1 and 4 years\(^{52}\). Associations between DEHPs concentrations and social competence, ADHD symptoms or behavioural outcomes were also inconsistent across ages. Furthermore, there were few associations showing increasing scores with increasing exposure to some of the compounds analyzed\(^{52}\). The study evaluating effects of prenatal BPA exposure observed a decreased on
psychomotor development at the age of 1 year [β (95%CI), comparing tertiles=-4.28 (-8.15, -0.41)], but not at the age of 4 [β (95%CI)=2.50 (-1.18, 6.18)], and an increased in hyperactivity at the age of 4 years [IRR (95%CI)=1.72 (1.08, 2.73)] that did not occur at the age of 7 [IRR (95%CI)= 0.97 (0.63, 1.49)]51 (Table 2).

Other determinants

The INMA project has also evaluated other potential determinants of the neuropsychological development in children such as maternal intelligence53 and weight54, head circumference during pregnancy55, prenatal exposure to other endocrine disruptors56, the use of non-persistent pesticides at home57, the presence of dampness, pet ownership and farm animal at home58 and the use of cell phones (electromagnetic radiation exposure) during pregnancy59 (Table 2).

A study including the children from Sabadell birth cohort observed that maternal IQ plays an important role in the first stages of cognitive development in children of more disadvantaged occupational social classes, but that for other groups the effects of maternal IQ on cognitive development were mostly explained by maternal education53. Maternal pre-pregnancy obesity was associated with reduced infant cognitive development at the age of 14 months [score reduction (95%CI)= 2.72 (-5.35, -0.10)]54 in a study including more than 2000 Spanish children and around 400 Greek children. This association showed a dose-response relationship with continuous maternal body mass index (BMI), whereas no associations with paternal overweight/obesity were observed54 (Table 2). Besides, in another study prenatal and perinatal head circumference of children was not associated with mental and psychomotor scores at the age of 14.
months, suggesting that head circumference growth during uterine life among healthy infants may not be an important marker of early-life neuropsychological development\(^5\).

Neuropsychological effects of in utero exposure to mixtures of xenoestrogens were evaluated in a study involving 489 children\(^6\). Total Effective Xenoestrogen Burden (TEXB), a quantitative biomarker of the cumulative effect of xenoestrogens measured in placentas, was not associate with mental development at the age of 14 months \([\beta (95\% CI)=0.48 (2.23), p-val=0.83]\), and only boys with the highest TEXB levels scored on average 5.2 points less than those with the lowest, on psychomotor development at 14 months \([\beta (95\% CI)=-5.19 (2.65), p-val=0.05]\). These associations did not persist at the age of 4 years\(^6\) (Table 2).

The use of non-persistent pesticides at home during pregnancy has been obtained in INMA through questionnaires\(^7\). Researchers observed that the use of insecticide sprays during pregnancy was associated with a decrement in psychomotor development \([\beta (95\% CI)=-1.9 (-3.4, -0.5)]\) during the first year of life. These negative effects were enhanced in girls and in children with higher levels of prenatal PCB and mercury exposure and belonging to the lowest social class\(^7\) (Table 2).

Another study collecting information on pet ownership, as a marker of exposure to allergens, during pregnancy in the Menorca birth cohort showed no associations with cognitive and psychomotor development or social competence at the age of 4 years\(^8\) (Table 2).
Finally, a study including participants from Sabadell evaluated whether the use of cell phones during pregnancy had an impact on the neuropsychological development of children at the age of 14 months\textsuperscript{59}. The study observed no association between cell phone use and mental [\( \beta (95\%\text{CI}) = 0.8 \ (-0.6, 2.2) \)] or psychomotor development scores [\( \beta (95\%\text{CI}) = -0.8 \ (-2.2, 0.6) \)]. Furthermore, there was no trend with amount of cell phone use within users\textsuperscript{59} (Table 2).

**Postnatal determinants**

*Persistent organic pollutants*

Postnatal exposure to POPs in INMA cohorts has been evaluated in a lesser extent compared to prenatal exposure. PCBs exposure, measured at the age of 4 years (N=285), did not show any associations with the cognitive or psychomotor development\textsuperscript{18}. Another study estimating postnatal exposure to PCB153, DDE and HCB through PBPK models (N=1175) showed that although breastfeeding increased children’s blood POPs levels during postnatal life, deleterious effects of PCB153 on neuropsychological development in the first year of life were mainly attributable to prenatal exposure\textsuperscript{60}. In addition, postnatal exposure to PBDE47 (244 children were classified as exposed according to the limit of quantification) was not associated with cognitive development at the age of 4 years\textsuperscript{21}. However, higher exposure was related with a higher risk of attention deficit problems [RR (95\%CI)=1.8 (1.0, 3.2)] and poor social competence [RR (95\%CI)=2.6 (1.2, 5.9)]\textsuperscript{21} (Table 3).

*Metals*
Granada cohort evaluated the effects of postnatal exposure to metals on cognitive development of children in a cross-sectional study\(^6^1\). After adjustment for fish intake, increasing total mercury levels measured in 72 children’s hair at the age of 4 years were associated with decrements in the general cognitive \([\beta (95\%CI)=-6.6 \text{ points} (-13.04, -0.15)]\), memory \([-8.4 \text{ points} (-15.96, -0.83)]\), and verbal \([-7.5 \text{ points} (-14.99, -0.02)]\) scores\(^6^1\) (Table 3).

**Outdoor air pollution**

Granada cohort also evaluated the potential detrimental effects of outdoor air pollution on neuropsychological development of children\(^6^2\). The study, including 210 children, observed a decrease of 4.19 points in the general cognitive score and decreases of 6.71, 7.37 and 8.61 points in quantitative, working memory and gross motor areas, respectively, in relation to NO\(_2\) levels assessed during their fifth year of life. However, most of associations were not statistically significant\(^6^2\) (Table 3).

**Smoking**

The relation between postnatal maternal smoking and neuropsychological development of INMA children has been also evaluated\(^3^5\). The study included mothers that smoked both during pregnancy and after birth and mothers that only smoked in one of these periods (N=420), and observed no associations between smoking and their child cognition, at the age of 4 years, among mothers smoking only after birth\(^3^5\) (Table 3).

**Breastfeeding**

INMA studies have reported the health benefits of breastfeeding in a number of studies. The first, conducted in the Ribera d’Ebre birth cohort, showed that at the age of 13
months the mental (10.71 points) and the psychomotor (8.97 points) development of children breastfeeding for more than 16 weeks was better compared to those breastfeeding for a shorter period of time\textsuperscript{15}. When children of Ribera d'Ebre and Menorca became 4 years, breastfeeding for a period longer than 28 weeks was also associated with better cognitive scores [\(\beta (95\% \text{CI}) \text{ for general cognition}= 3.9 \ (0.0, 7.9)\)]\textsuperscript{8}. Furthermore, breastfeeding was shown to counterbalance the detrimental effects of prenatal DDE/DDT exposure in two INMA studies\textsuperscript{15,63}. Also, the benefits of breastfeeding on cognitive and executive function were described to be stronger in children whose mothers had lower education level (\(\beta=7.02\)) compared to those with a higher education level (\(\beta=2.59\))\textsuperscript{8}. Results also showed benefits of breastfeeding on social competence [\(\text{RR} (95\% \text{CI}) \text{ for poor social competence}=0.44 \ (0.27, 0.72)\)] and attention and hyperactivity symptoms [\(\text{RR} (95\% \text{CI})= 0.61 \ (0.44, 0.86)\)]\textsuperscript{8}. In the birth cohort of Sabadell the benefits of breastfeeding were only statistically significantly associated to mental score at 14 months among those children breastfeeding for a longer time and with a higher n3/n6 colostrum long-chain polyunsaturated fatty acid (LC-PUFA) ratio [\(\beta (95\% \text{CI})=5.50 \ (1.05, 9.94)\)]\textsuperscript{64}. No relation was found between breastfeeding and psychomotor score\textsuperscript{64}. At the age of 4 years of these children, full breastfeeding (above 6 months) was associated with child general cognitive [\(\beta (95\% \text{CI})=7.5 \ (2.9, 12.1)\)] and executive function [\(\beta (95\% \text{CI})= 6.9 \ (2.1, 11.7)\)] after adjusting for a range of social, psychological, and nutritional factors\textsuperscript{65}. However, omega-3 (n3) fatty acid levels were not associated with child neuropsychological scores\textsuperscript{65}. Menorca and Sabadell birth cohorts analysed polymorphisms in genes encoding the key enzymes involved in LC-PUFA synthesis in mothers and their offspring\textsuperscript{66}. The study observed maternal genetic variants involved in colostrum n-3 LC-PUFA levels, associated with higher cognitive scores in their children. In infants,
the study found that certain genetic variants modified the effects of breastfeeding on cognition, confirming gene-breastfeeding interactions66 (Table 3).

**BPA**

A cross-sectional study conducted in Granada (N=269 boys) observed that at the age of 9-11 years higher urinary BPA concentrations (only one sample) were associated with lower behavioural scores on some of the Child Behaviour Checklist (CBCL/6–18) scales (somatic complaints and social and thought problems), but no associations were observed with other scores, including ADHD problems67 (not shown in tables).

**Other determinants**

Postnatal use of non-persistent pesticides at home did not associate with the mental or psychomotor development of children at the age of 1 year in a study including more than 2000 mother-children pairs57 (Table 3).

In relation to home conditions, persistent home dampness during early life significantly decreased the general cognitive score by 4.9 points (95%CI=−8.9, -0.8) and the social competence by 6.5 points (95% CI=−12.2, -0.9) at the age of 4 years in the birth cohort of Menorca58. However, pet ownership and the measured microbial compounds at the age of 3 months were not related with the psychometric tests scores. On the contrary, occasional farm animal contact increased the general cognitive score [β (95%CI)= 5.6 (1.8, 9.3)]58 (Table 3).
The effects of radiofrequency electromagnetic fields (non-ionizing radiation) were cross-sectionally evaluated in a subsample of boys of the Granada birth cohort at the age of 9-11 years.\textsuperscript{68} The study observed that all exposure measurements were lower than reference guideline limits. Additionally, for most of the cognitive and behavioural parameters no associations were observed; only children living in areas with radiofrequency-electromagnetic fields exposure above median levels had statistically significant lower scores for verbal expression/comprehension and higher scores for internalizing and total problems, and obsessive-compulsive and post-traumatic stress disorders, in comparison to those living in areas with lower exposure\textsuperscript{68} (not shown in tables).

Finally, the INMA project also evaluated the relationship between stress (using cortisol in saliva of children as biomarker), and neuropsychological development at the age of 14 months.\textsuperscript{69} Forns \textit{et al.} observed that higher levels of cortisol were associated with better scores in the mental scale [children in the highest tertile of cortisol levels had higher scores compared with the reference group (β=4.60; p-value=0.03)].\textsuperscript{69}

\textit{Comorbidities}

The INMA project has also investigated the link between different health outcomes in order to better understand whether these are correlated as well as the potential mechanisms of the associations observed with certain exposures. In relation to neuropsychological development, studies have evaluated its link with thyroid hormones, atopic disorders and weight status of children.
A cross-sectional study conducted in the birth cohorts of Menorca and Ribera d’Ebre observed that at the age of 4 years (N=342), children with TSH concentrations in the upper quartile of the normal range performed lower on cognitive scores and were at higher risk for attention deficit and hyperactivity/impulsivity symptoms compared to those in the lower quartile\textsuperscript{70}. In contrast, high free T4 concentrations were associated with decreased risk of having 1–5 attention deficit symptoms [OR=0.25; p< 0.01)]\textsuperscript{70}. Similar results were found in the cohort of Granada with a cross-sectional study, including 300 boys at 10 years of age; children with TSH levels in the higher tertile had worse verbal memory, whereas children with higher free T4 levels had better attention, lower impulsivity and better cognitive scores\textsuperscript{71}.

Other studies focused on the association between atopy and related outcomes and neuropsychological development\textsuperscript{72,73}. Thus, in almost 400 children from Menorca 4 years old, it was observed that only eczema was associated with social competence at that age [general cognitive score, RR (95%CI)= 1.99 (1.07, 3.69)]. No associations with other atopy related symptoms (asthma, wheeze, rhinitis or atopy) were observed, neither with general cognition\textsuperscript{72}. However, atopy, asthma, and wheeze at age 6 years were associated with cognitive development at age 4 years [RR (95%CI)=2.46 (1.31, 4.62) for atopy] and eczema with social competence [RR (95%CI)= 2.14 (1.45, 3.15)]\textsuperscript{72}. In the same cohort associations between genes related to atopy and neuropsychological development was observed\textsuperscript{73}, but the associations observed between certain environmental pollutants and cognitive development were not explained by the immunological status (atopy) of the children\textsuperscript{73}. 
The relationship between child weight and neuropsychological development has been also evaluated within the INMA project. Guxens et al. investigated the association between neuropsychological development at the age of 4 years and overweight at the age 6 years in the birth cohort of Menorca with a cross-sectional design\textsuperscript{74}. Although authors did not observe a relation between cognitive function scores and concurrent measures of BMI at age 4 years, higher general cognitive abilities at age 4 years, particularly executive function, verbal, quantitative, and memory skills scores, were associated with a lower likelihood of being overweight at age 6 years, after adjustment for a large list of covariates, including socioeconomic factors and maternal BMI [OR (95\%CI)=0.47 (0.25, 0.88) for general cognitive score]. Furthermore, the risk of maintaining an unhealthy weight status (at risk of overweight or overweight) between 4 and 6 years of age, as well as of worsening their weight status over time (incidence of being at risk of overweight or overweight) was lower among children with better cognitive scores at age 4 years\textsuperscript{74}.

Discussion

The current review provides an overview of the main determinants of child’s neuropsychological development studied within the INMA project and the main findings obtained, related with prenatal and postnatal exposures to maternal, environmental and dietary determinants and co-morbidities.

In terms of the environmental pollutants, INMA has provided substantial evidence for the inclusion of DDT in the current list of known developmental neurotoxicants\textsuperscript{4}. In addition, our data have provided new knowledge on the relation between urban air pollution and impaired neurodevelopment, specially on executive functions, motor
development and attention and autism spectrum effects. This is a very relevant area of research given the health burden of urban air pollution. INMA project has also contributed to show the detrimental influence of certain indoor air pollutants.

Furthermore, INMA is a very pertinent cohort to assess the effects of fish consumption and related pollutants, given the high and variable intake among the Spanish population, and some micronutrients. Thus, our results have shown that a balanced maternal fish intake could protect from the potential adverse effects of prenatal exposure to mercury. The longitudinal nature of INMA will allow the following up for a potential delayed relationship between prenatal exposure and neurodevelopment as well as the role of other factors (diet, co-exposures or genetics) on it.

We have also found an important deficit of Vitamin D, with a high prevalence in a sunny country due to the current dominant indoor lifestyle. This issue raises an important public health concern that merits promoting global preventive interventions. The project has also contributed to the understanding of the role of breastfeeding on the neuropsychological benefits.

The results relating exposure to non-persistent contaminants (such as BPA, phthalates, non-persistent pesticides) and neurodevelopment are still scarce and less consistent, not only within the INMA birth cohort but also in other studies, mainly because proper exposure assessment to these compounds is much more complicated, due to their exposure is highly changing along short periods of time. Nevertheless, the INMA study has been one of the pioneering cohorts to evaluate these compounds and to study their association with neuropsychological impairment.
Interesting data have also been revealed concerning critical windows of exposure. During prenatal period, when brain structures are forming and growing considerably, the effect of environmental exposures may be more important than exposures during postnatal life. Thus, INMA project has contributed to provide increasing evidence of the association between prenatal exposure to urban air pollutants and impaired neurodevelopment, as well as for exposure to some POPs. Using innovative methodologies\textsuperscript{60}, INMA cohort data have shown that postnatal exposure to POPs compounds does not seem to play a role on this association and that the critical period of exposure during prenatal life. The identification of critical periods of exposure is fundamental for preventive purposes; however, to date, the windows of sensitivity to environmental exposures, air pollution for example, are still unknown\textsuperscript{79}. The review also highlights the amount of information that has been gathered within the project and can be used to answer current or new research questions, especially of in relation to postnatal exposures.

Most of the research included in this review has been limited to hypothesis testing studies based on individual exposures of interest. The future work of the INMA Project, as part of the HELIX project\textsuperscript{80}, will focus in the analysis of the exposome. The exposome has been proposed as a new paradigm to encompass the totality of human environmental (meaning all non-genetic) exposures from conception to old ages\textsuperscript{80,81}. In addition, taking profit of all the information gathered on neuropsychological development, we also aim to evaluate the relationship between the neuropsychological evaluations conducted at each year of follow-up in order to establish individual trajectories of cognitive growth and measure changes in the growth function underlying
the brain development. Thirdly, we will evaluate comorbidities by assessing the relationship between neuropsychological development, atopy, and obesity using information obtained at different time-points, including biomarkers of metabolic syndrome as well. A final new line of research refers to the assessment of the effect of the economical crisis doing pre-post studies, including social determinants, diet, exercise, and stress given the dramatic changes that had occurred after the period 2010-15.

**Conclusions**

The updated findings presented in this Review confirm and add evidence of the role of a range of maternal and environmental exposures on early childhood neuropsychological development. The findings underscore the importance of continued research on the delineation of the sensitive windows of exposure during pregnancy and postnatally and on the combined effects of toxicant exposures, denoted the exposome, since environmental exposure to multiple pollutants are the norm rather than the exception. In terms of health policy, these findings have important implications for the development of public health policies to advance the health and development of children.

**Acknowledgments**

The authors are indebted to all participants, without whom this work would not have been possible. We are grateful to all the personnel that have made INMA Project a reality.

**Funding**
This study was supported by Instituto de Salud Carlos III (Red INMA G03/176, CB06/02/0041, 97/0588, 00/0021-2, PI04/1436, PI06/1756, PI08/1151, PS09/01958, PI12/01890, PI14/00677, MS13/00054, CP13/00054 including FIS-FEDER funds 03/1615, 04/1509, 04/1112, 04/1931, 05/1079, 05/1052, 06/1213, 07/0314, 09/02311, 09/02647, 11/0178, 11/02591, 11/02038, 13/1944, 13/2032, 13/02429, 14/0891, 14/1687, and 16/1298) and Miguel Servet-FEDER MS15/00025, Spanish Ministry of Health - CIBERESP (FIS-97/1102, FIS-PS09/00362, FIS-07/0252, FIS-PI11/00610, FISPI07/0252, FISPI11/0610, FIS-PI04/2018, FIS-PI09/02311, FIS-PI13/02429, FIS-PI06/0867, FIS-PS09/00090, FIS-PI13/02187, PI13/02406, MS13/00054), Spanish Ministry of Economy and Competitiveness (SAF2012-32991 incl. FEDER funds), EU Comission (QLK4-CT-2000-00263, QLK4-1999-01422, QLK4-2002-00603) and CONTAMED FP7-ENV-212502, FP7-ENV-2011 cod 282957, 261357, 308333 and 603794 and HEALTH.2010.2.4.5-1), Generalitat de Catalunya-CIRIT 1999SGR 00241, Generalitat de Catalunya-AGAUR (2009 SGR501, 2014 SGR 822), Department of Health of the Basque Government (2005111093, 2009111069, 2013111089 and 2015111065), the Provincial Government of Gipuzkoa (DFG06/002, DFG08/001 and DFG15/221), Consejería de Salud de la Junta de Andalucía (grant number 183/07 and SAS-PI-0675-2010), Conselleria de Sanitat, Generalitat Valenciana, Andalusia Regional Government - Consejería de Salud (Grants P09-CTS-5488 Project of Excellence, and SAS PI-0133-2007; PI-0675–2010), Agence Nationale de Securite Sanitaire de l'Alimentation de l'Environnement et du Travail (1262C0010), beca de la IV convocatoria de Ayudas a la Investigación en Enfermedades Neurodegenerativas de La Caixa, Fundació La Caixa (97/009-00 and 00/077-00), Fundació La Marató de TV3 (090430), Obra Social Cajastur/Fundación Liberbank and University of Oviedo, and
annual agreements with the municipalities of the area of study (Zumarraga, Urretxu, Legazpi, Azkoitia y Azpeitia y Beasain).

References

compounds and neuropsychological development up to two years of life. 
*EnvironInt.* Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; Hospital del Mar Research Institute (IMIM), Barcelona, Spain; CIBER Epidemiologia y Salud Publica (CIBERESP), Barcelona, Spain; 2012 Sep;45 (1873–6750 (Electronic)):72–77.


81. Wild CP. The exposome: from concept to utility. *IntJEpidemiol*. International Agency for Research on Cancer, 150 cours Albert Thomas, 69008 Lyon, France. director@iarc.fr; 2012 Feb;**41**(1464–3685 (Electronic)):24–32.
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Bayley Scales of Infant Development 1st edition (BSID-I)
Griffiths Scales of Infant Development (GSID)
McCarthy Scales of Children’s Abilities (MSCA)
Conners’ Kiddie Continuous Performance Test (K-CPT)
Attention-Deficit Hyperactivity Disorder Criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (ADHD-DSM-IV)
California Preschool Social Competence Scale (CPSCS)
Childhood Asperger Syndrome Test (CAST)
Strengths and Difficulties Questionnaire (SDQ)
Conners' Parent Rating Scales (CSRS)
Trail Making Test (TMT)
Child behavior checklist (CBCL)
Attention Network Test (ANT)
Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV)
Kaufman Brief Intelligence Test (K-BIT)
Basque, English, Spanish Test (BEST) - based on MINT and Colorized Snodgrass and Vanderwart Pictures
Semantic Verbal Fluency Test (TAVEC)
Continuous Performance Test (CPT)
Primary Mental Abilities Test- Reasoning (PMA-R)
Raven’s Coloured Progressive Matrices (Raven’s CPM)
Table 2. Studies and associations observed by each study between prenatal determinants and cognitive and psychomotor development and behavioural outcomes between 1 and 7 years.

<table>
<thead>
<tr>
<th>Cognitive and psychomotor development</th>
<th>Poor social competence</th>
<th>ADHD symptoms</th>
<th>Behavioural problems</th>
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<td>4-5 years CSPCS</td>
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*Other determinants include metallothionein (MT), indoor air pollutants, and others.*
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<td><strong>Phthalates</strong></td>
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<td>Use of non-persistent pesticides</td>
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<th>Obesities</th>
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Attention-Deficit Hyperactivity Disorder Criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (ADHD-DSM-IV); Bayley Scales of Infant Development (BSID); California Preschool Social Competence Scale (CPSCS); Childhood Asperger Syndrome Test (CAST); Conners’ Parent Rating Scales (CSRS); Griffiths Scales of Infant Development (GSID); McCarthy Scales of Children’s Abilities (MCSA); Strengths and Difficulties Questionnaire (SDQ); Total Effective Xenoestrogen Burden

↑ = increased risk/coefficient
↓ = decreased risk/coefficient
X = no associations found
Empty space indicates no studies available

*Cobalt, copper, arsenic, cadmium, antimony and lead

This study was conducted combining data of children from 1 to 6 years of age.

This study was conducted combining data of children from 4 to 10 years of age.

Associations observed only among children breastfeeding for <6 months.

Association observed in mothers with intakes of folic acid of >5000 μg/day compared to mothers with intakes of the recommended dose (400-1000 μg/day).

Associations only observed in children of more disadvantaged occupational social classes.

Only psychomotor effects observed in boys.
Table 3. Studies and associations observed by each study between postnatal determinants and cognitive and psychomotor development and behavioural outcomes between 1 and 5 years$^a$.

<table>
<thead>
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<tr>
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Attention-Deficit Hyperactivity Disorder Criteria of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (ADHD-DSM-IV); Bayley Scales of Infant Development (BSID); California Preschool Social Competence Scale (CPSCS); Childhood Asperger Syndrome Test (CAST); Child Behaviour Checklist (CBCL/6–18); Conners’ Parent Rating Scales (CSRS); Griffiths Scales of Infant Development (GSID); Long-chain polyunsaturated fatty acid (LC-PUFA); McCarthy Scales of Children’s Abilities (MCSA); Strengths and Difficulties Questionnaire (SDQ)

↑=increased risk/coefficient
↓=decreased risk/coefficient
X=no associations found
Empty space indicates no studies available

$^a$No studies available neuropsychological evaluating outcomes at the age of 7 years, only two studies evaluated neuropsychological outcomes at the age of 9-11 years (see text).