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Review

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

Mireia Gascon[a,b,c,*], Mònica Guxens[a,b,c,d], Martine Vrijheid[a,b,c], Maties Torrent[e], Jesús Ibarluzea[c,g,h,i], Eduardo Fano[h,i], Sabrina Llop[c,j], Ferran Ballester[c,j], Mariana F. Fernández[c,k], Adonina Tardón[c,l], Ana Fernández-Somoano[c,l], Jordi Sunyer[a,b,c,m]

[a] ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
[b] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Spain
[d] Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Centre–Sophia Children's Hospital, Rotterdam, The Netherlands
[e] Àrea de Salut de Menorca, IB-SALUT, Menorca, Spain
[g] Subdirección de Salud Pública de Gipuzkoa, The Basque Government's Health Department, San Sebastián, Spain
[h] Faculty of Psychology, University of the Basque Country UPV/EHU, Donostia, Spain
[i] BIODONOSTIA, Health Research Institute, San Sebastián, Basque Country, Spain
[j] Epidemiology and Environmental Health Joint Research Unit, FISABIO—Universitat Jaume I—Universitat de València, València, Spain
[k] University of Granada, Complejo Hospitalario Universitario, Instituto de Investigación Biosanitaria (ibs.GRANADA), Granada, Spain
[l] Área de Medicina Preventiva y Salud Pública, Departamento de Medicina, Universidad de Oviedo, Asturias, Spain
[m] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Catalonia, Spain

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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.

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 childood); IRR, incidence rate ratio; MBzP, mono-benzyl phthalate; MDI, mental development index; MCSA, McCarthy scales of children's abilities; NO_2, NO_x, nitrogen dioxide; OR, odds ratio; PBDE47, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PDI, psychomotor developmental index; $PM_{2.5}$, PM_{10} PM_{coarse} 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.

* Corresponding author at: Parc de Recerca Biomèdica de Barcelona (PRBB), Doctor Aiguader, 88| 08003 Barcelona Catalonia, Spain.
E-mail address: mireia.gascon@isglobal.org (M. Gascon).

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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.

Contents

1. 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 (Ramón et al., 2017). 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) (Ribas-Fito et al., 2006a; Guxens et al., 2012a). 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 (Grandjean and Landrigan, 2014), 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.

2. Results

2.1. Tools to assess neuropsychological development in INMA

General cognition was evaluated with the Bayley Scales of Infant Development 1st edition (BSID-I) (Bayley, 1977) and the Griffiths Scales of Infant Development (GSID) (Griffiths, 1996) – first two years of life – and the McCarthy Scales of Children's Abilities (MCSA) (McCarthy, 1972) – 4–5 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 (Julvez et al., 2007a). 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 (Julvez et al., 2008). 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) (Scott et al., 2002). Although at the age of 7 years many tests were conducted

Table 1
List of neuropsychological tests conducted in the INMA Project across regions.

Age	Domains	Test	Ribera d'Ebre	Menorca	Granada	Asturias	Valencia	Gipuzkoa	Sabadell
1y–2y									
	Cognitive and psychomotor development	BSID-I	X	–	–	X	X	X	X
		GSID	X	–	–	–	–	–	–
4y–5y									
	Cognitive and psychomotor development	MCSA	X	X	X	X	X	X	X
	Attentional function	K-CPT	–	–	–	X	X	X	X
	ADHD symptoms	ADHD – DSM IV	X	X	X	X	X	X	X
	Behavioral problems	SDQ	–	–	–	–	–	X	–
	Social competence	CPSCS	X	X	X	X	X	X	X
	Autistic traits	CAST	–	–	–	X	X	X	X
		Batelle	–	–	–	X	–	–	X
7y–8y									
	Working memory	N-back test	–	–	–	X	X	–	X
	Processing speed	Finger tapping test	–	–	–	X	X	–	X
	Attentional function	ANT	–	–	–	X	X	–	X
	Behavioral problems	SDQ	–	–	–	X	X	X	X
		CSRS	–	–	–	X	X	–	X
8y–10y									
	Cognitive development	K-BIT	–	–	X	–	–	–	–
	Working memory	N-back test	–	–	–	–	–	X	X
		WISC-IV subtest (letter-number seq.)	–	–	X	–	X	–	--
	Mental flexibility	TMT – part B	–	–	X	–	–	X	X
	Processing speed	WISC-IV subtest (coding, symbol search)	–	–	X	–	X	X	X
		Finger tapping test	–	–	–	–	–	X	X
	Visuo-motor coordination	TMT – part A	–	–	X	–	–	X	X
	Verbal development	BEST	–	–	–	–	–	X	–
	Verbal and executive skills	TAVEC	–	–	X	–	X	X	X
	Attentional function	ANT	–	–	–	–	–	X	X
		CPT-II	–	X	X	–	–	–	–
		Stroop Test	–	–	X	–	–	–	–
		Go/no-go task	–	–	X	–	–	–	–
	Behavioral problems	CBCL	–	–	X	–	X	X	X
		CSRS	–	–	–	–	X	X	–
11y									
	Working memory	N-back test (num, 3-back)	–	–	–	–	X	–	X
	Decision making	Cups Task – Roulette version	–	–	–	–	–	–	X
	Processing speed	Finger tapping test	–	–	–	–	X	–	–
	Visuo-motor coordination	TMT – part A	–	–	–	–	X	–	–
	Non-verbal intelligence	PMA-R	–	–	–	–	–	–	–
		Raven's CPM	–	–	–	–	X	–	–
	Attentional function	Flanker task	–	–	–	–	–	–	X
		ANT	–	–	–	–	X	–	–
	Behavioral problems	SDQ	–	–	–	–	–	–	X
14y									
	Working memory	N-back test	X	X	–	–	–	–	–
	Mental flexibility	TMT – part B	X	X	–	–	–	–	–
	Processing speed	Finger tapping test	X	X	–	–	–	–	–
	Verbal and executive skills	TAVEC	X	X	–	–	–	–	–
18y									
	Working memory	N-back test	–	X	–	–	–	–	–
	Decision making	Cups Task – Roulette version	–	X	–	–	–	–	–
	Visuo-motor coordination and mental flexibility	TMT – part A and B	–	X	–	–	–	–	–
	Verbal and executive skills	Semantic Verbal Fluency Test	–	X	–	–	–	–	–

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 1), so far only those related to behavioral problems – the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997), the Conners' Parent Rating Scales (CPRS) (Gianarris et al., 2001) and the Child Behavior Checklist (CBCL/6-18) (Hudziak et al., 1999) – 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).

2.2. Prenatal and postnatal factors related to comorbidities

2.2.1. Prenatal determinants

2.2.1.1. 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 (POPs, 2017). However, due to their properties, humans are still exposed to low levels of these compounds (POPs, 2017).

In 2003 Ribas-Fitó et al. published the first paper of the INMA project about organochlorine exposure and cognitive and psychomotor development in children (Ribas-Fito et al., 2003). 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 (Ribas-Fito et al., 2006b). Further analysis including children of the new INMA birth cohorts did not observe associations with DDE (Forns et al., 2017a) 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 (Ribas-Fito et al., 2003). 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 [β (95%CI) = −1.24, (−2.41, −0.07)] but not of mental development measured at around 1 year of age (Forns et al., 2017a). 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 (Forns et al., 2012) (Table 2).

None of the studies evaluating the effects on cognitive and psychomotor development observed associations with HCB at the age of 1 year (Ribas-Fito et al., 2003; Forns et al., 2017a; Ribas-Fito et al., 2007a). 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)] (Ribas-Fito et al., 2007a) (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 detection (Puertas et al., 2010) (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 years (Gascon et al., 2011). 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 age (Gascon et al., 2012). 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 found (Gascon et al., 2011) (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.

2.2.1.2. Metals. Certain metals are considered developmental neurotoxicants, such as methylmercury, lead, arsenic and manganese (Grandjean and Landrigan, 2014). 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 (Ramon et al., 2011); 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) (Llop et al., 2012). 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)] (Llop et al., 2012). In the birth cohort of Sabadell, several metals (cobalt, cupper, arsenic, cadmium, antimony and lead) were measured in urine samples of mothers during the 1st and the 3rd trimesters of pregnancy (Forns et al., 2014a). Results showed no associations between low prenatal levels of these metals and cognitive and psychomotor development or behavioral symptoms (Forns et al., 2014a) (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 (Forns et al., 2014a). 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 (Julvez et al., 2016). In relation to prenatal low exposure to other metals and early neuropsychological development, the INMA project provided evidence of no associations.

2.2.1.3. 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 (Suades-González et al., 2015). However, research on the neuropsychological effects in humans,

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.

	Cognitive and psychomotor development		Poor social competence	ADHD symptoms	Behavioural problems	Conduct problems	Autism-spectrum traits
	1 year BSID/GSID	4–5 years MCSA	4–5 years CSPCS	4–5 years ADHD-DSM IV	7 years SDQ	4–5 years CAST	7 years CSRS
POPs							
DDT/DDE	↓X	↓					
PCBs	X ↓	↓					
HCB	X X		↑	↑			
Mirex		↓					
PBDEs	↓	X	X	X			
Metals							
Mercury (Hg)	X						
Others[a]		X		X			
Outdoor air pollution							
NO_2	X ↓	↓[b]				X[c]	
NO_x	X X	X[b]				X[c]	
Benzene	X						
$PM_{2.5}$	↓	X[b]				X[c]	
PM_{10}		X[b]				X[c]	
PM_{coarse}		X[b]				X[c]	
Residential indoor air pollution							
Use of gas appliances at home	↓	↓		↑			
NO_2		↓		↑			
Maternal smoking		↓					
Maternal fish intake	↑	X[d] ↑				↓	
Maternal dietetic supplements intake							
Folic acid	↓[e]	↑	↓	↓			
Iodine	↓ X						
Maternal determinants							
TSH concentrations		↓					
Low free thyroxine levels	↓						
Maternal intelligence (IQ)	X[f]						
Obesity	↓						
Vitamin D	↑			↓			
Bisphenol A (BPA)	↓	X		↑	X		X
Phthalates							
Σ_4DEHPs	X	X	↓	↓	X		↓
MBzP	X	↓	X	X	X		X
MEP	X	X	X	↓	X		X
MiBP	X	X	X	X	X		X
MnBP	X	X	X	X	X		X
Other determinants							
Pre- and perinatal head circumference	X						
TEXB-alpha	X[g]	X					
Use of non-persistent pesticides	↓						
Pet ownership		X	X				
Cell phone use	X						

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.
[a] Cobalt, cupper, arsenic, cadmium, antimony and lead.
[b] This study was conducted combining data of children from 1 to 6 years of age.
[c] This study was conducted combining data of children from 4 to 10 years of age.
[d] Associations observed only among children breastfeeding for <6 months.
[e] 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).
[f] Associations only observed in children of more disadvantaged occupational social classes.
[g] Only psychomotor effects observed in boys.

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_2 and benzene and mental development at the age of 14 months (Guxens et al., 2012b; Lertxundi et al., 2015). The associations were stronger among children whose mothers reported low intakes of fruits/vegetables during pregnancy (Guxens et al., 2012b). In children from Gipuzkoa cohort it was also found an inverse association between prenatal $PM_{2.5}$ exposure and the scores obtained for psychomotor development [β (90%CI) = −1.14 (−1.75, −0.53) for a 1 μg/m^3 increase of $PM_{2.5}$] (Lertxundi et al., 2015). In 2014 Guxens et al. expanded the work to 6 European birth cohorts including new data from INMA (Guxens et al., 2014). The study, including more than 9000 children, observed that NO_2 exposure during pregnancy was associated with reduced psychomotor development [β (95%CI) = −0.68 (−1.25, −0.11) per increase of 10 μg/m^3 in NO_2], with similar trends in most European regions. The study did not observe associations with cognitive development or between other air pollutants (NO_x, $PM_{2.5}$, PM_{10}, PM_{coarse}) and several neuropsychological domains evaluated between 1 and 6 years of age (Guxens et al., 2014). 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 (Guxens et al., 2016) (Table 2). Overall, the INMA project, together with other birth cohorts in Europe, has shown a consistent association between air pollutants, particularly NO_2, a marker of traffic related air pollution, and impaired neuropsychological development of children. However, no associations with autistic traits have been described.

2.2.1.4. 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 NO_2 concentrations at each participant's home (Morales et al., 2009a). The study found that both use of gas appliances and NO_2 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)] (Morales et al., 2009a). 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)] (Vrijheid et al., 2012). 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 covariates (Vrijheid et al., 2012) (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.

2.2.1.5. Smoking. Cigarette smoking reduces the health of smokers but also of those exposed to second-hand smoking (CDC, 2016). Association between maternal smoking during pregnancy with the neuropsychological development of children at age 4 were evaluated in the region of Menorca (Julvez et al., 2007b). In this study, maternal smoking (in cigarettes/day) was associated with a decrease of children's general cognitive development [β (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 *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) (Morales et al., 2009b) (Table 2).

2.2.1.6. 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 (Clarkson and Strain, 2003). 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 (Mendez et al., 2009). 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 ≤1 time/week [e.g. β (95%CI) = 11.0 (5.0 17.1) of the general cognitive score] (Mendez et al., 2009). 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 (Julvez et al., 2016). 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 blood (Julvez et al., 2016) (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.

2.2.1.7. 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 defects (Prevention of neural tube defects: results of the Medical Research Council Vitamin Study, 1991). 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 years (Julvez et al., 2009a). 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 vitamins (Julvez et al., 2009a). Detailed information on the daily doses of folic acid supplements was gathered from the mothers to assess a dose-response analysis in a second study (Valera-Gran et al., 2014). 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 (Valera-Gran et al., 2014) (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 (Murcia et al., 2011; Rebagliato et al., 2013), which is often recommended in order to ensure a proper thyroid function (the WHO recommends an 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 (WHO, 2016)). 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 (Murcia et al., 2011). 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 (Rebagliato et al., 2013). 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).

2.2.1.8. Maternal thyroid hormone levels. Maternal thyroid hormones play an important role in many fundamental processes underlying brain development and maturation of the fetus (Moog et al., 2015). 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)] (Freire et al., 2010a). 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] (Julvez et al., 2013). 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] (Julvez et al., 2013) (Table 2).

2.2.1.9. 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 (Wimalawansa, 2012). 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 (Morales et al., 2012). 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) (Morales et al., 2012). 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] (Morales et al., 2015). 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 (Morales et al., 2015) (Table 2). Above results indicate neuropsychological benefits by increasing vitamin D levels up to those clinically considered as optimal.

2.2.1.10. 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 (Casas et al., 2015; Gascon et al., 2015). 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 (Casas et al., 2015; Gascon et al., 2015). 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 [β (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 (Gascon et al., 2015). 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 (Gascon et al., 2015). 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)] (Casas et al., 2015) (Table 2).

2.2.1.11. Other determinants. The INMA project has also evaluated other potential determinants of the neuropsychological development in children such as maternal intelligence (Forns et al., 2017b) and weight (Casas et al., 2013a), head circumference during pregnancy (Álamo-Junquera et al., 2015), prenatal exposure to other endocrine disruptors (Vilahur et al., 2014), the use of non-persistent pesticides at home (Llop et al., 2013), the presence of dampness, pet ownership and farm animal at home (Casas et al., 2013b) and the use of cell phones (electromagnetic radiation exposure) during pregnancy (Vrijheid et al., 2010) (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 education (Forns et al., 2017b). 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)] (Casas et al., 2013a) 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 observed (Casas et al., 2013a) (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 (Álamo-Junquera et al., 2015).

Neuropsychological effects of in utero exposure to mixtures of xenoestrogens were evaluated in a study involving 489 children (Vilahur et al., 2014). 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 [β (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 [β (95%CI) = −5.19 (2.65), p-val = 0.05]. These associations did not persist at the age of 4 years (Vilahur et al., 2014) (Table 2).

The use of non-persistent pesticides at home during pregnancy has been obtained in INMA through questionnaires (Llop et al., 2013). Researchers observed that the use of insecticide sprays during pregnancy was associated with a decrement in psychomotor development [β (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 (Llop et al., 2013) (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 (Casas et al., 2013b) (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 (Vrijheid et al., 2010). The study observed no association between cell phone use and mental [β (95%CI) = 0.8 (−0.6, 2.2)] or psychomotor development scores [β (95%CI) = −0.8 (−2.2, 0.6)]. Furthermore, there was no trend with amount of cell phone use within users (Vrijheid et al., 2010) (Table 2).

2.3. Postnatal determinants

2.3.1. 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 showed any associations with the cognitive or psychomotor development (Forns et al., 2012). 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 (Gascon et al., 2013). 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 (Gascon et al., 2011). 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)] (Gascon et al., 2011) (Table 3).

2.3.2. Metals

Granada cohort evaluated the effects of postnatal exposure to metals on cognitive development of children in a cross-sectional study (Freire et al., 2010c). 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 [β (95%CI) = −6.6 points (−13.04, −0.15)], memory [−8.4 points (−15.96, −0.83)], and verbal [−7.5 points (−14.99, −0.02)] scores (Freire et al., 2010c) (Table 3).

2.3.3. Outdoor air pollution

Granada cohort also evaluated the potential detrimental effects of outdoor air pollution on neuropsychological development of children (Freire et al., 2010b). 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 (Freire et al., 2010b) (Table 3).

2.3.4. Smoking

The relation between postnatal maternal smoking and neuropsychological development of INMA children has been also evaluated (Julvez et al., 2007b). 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 (Julvez et al., 2007b) (Table 3).

2.3.5. 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 (Ribas-Fito et al., 2003). 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 [β (95%CI) for general cognition = 3.9 (0.0, 7.9)] (Julvez et al., 2007a). Furthermore, breastfeeding was shown to counterbalance the detrimental effects of prenatal DDE/DDT exposure in two INMA studies (Ribas-Fito et al., 2003; Ribas-Fito et al., 2007b). Also, the benefits of breastfeeding on cognitive and executive function were described to be stronger in children whose mothers had lower education level (β = 7.02) compared to those with a higher education level (β = 2.59) (Julvez et al., 2007a). Results also showed benefits of breastfeeding on social competence [RR (95%CI) for poor social competence = 0.44 (0.27, 0.72)] and attention and hyperactivity symptoms [RR (95%CI) = 0.61 (0.44, 0.86)](Julvez et al., 2007a). 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 [β (95%CI) = 5.50 (1.05, 9.94)] (Guxens et al., 2011). No relation was found between breastfeeding and psychomotor score (Guxens et al., 2011). At the age of 4 years of these children, full breastfeeding (above 6 months) was associated with child general cognitive [β (95%CI) = 7.5 (2.9, 12.1)] and executive function [β (95%CI) = 6.9 (2.1, 11.7)] after adjusting for a range of social, psychological, and nutritional factors (Julvez et al., 2014). However, omega-3 (n3) fatty acid levels were not associated with child neuropsychological scores (Julvez et al., 2014). Menorca and Sabadell birth cohorts analysed polymorphisms in genes encoding the key enzymes involved in LC-PUFA synthesis in mothers and their offspring (Morales et al., 2011). 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 interactions (Morales et al., 2011) (Table 3).

2.3.6. 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 problems (Pérez-Lobato et al., 2015a) (not shown in tables).

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].

	Cognitive and psychomotor development		Poor social competence	ADHD symptoms
	1 year BSID/GSID	4–5 years MCSA	4–5 years CSPCS	4–5 years ADHD-DSM IV
POPs				
DDT/DDE	X			
PCBs	X	X		
HCB	X			
Mirex				
PBDEs		X	↑	↑
Metals				
Mercury (Hg)		↓		
Outdoor air pollution				
NO_2		X		
Maternal smoking				
		X		
Breastfeeding				
Breastfeeding >4 to 6 months	↑↑	↑↑	↓	↓
LC-PUFA	↑			
Omega n3 fatty acid		X		
Other determinants				
Use of non-persistent pesticides	X			
Persistent home dampness		↓	↓	
Pet ownership		X	X	
Farm animal contact		↑	X	
Measured microbial compounds		X	X	
Cortisol	↑			

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).

2.3.7. 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 pairs (Llop et al., 2013) (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 Menorca (Casas et al., 2013b). 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)] (Casas et al., 2013b) (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 (Calvente et al., 2016). 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 (Calvente et al., 2016) (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 (Forns et al., 2014b). Forns 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)] (Forns et al., 2014b).

2.4. 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 (Alvarez-Pedrerol et al., 2007). In contrast, high free T4 concentrations were associated with decreased risk of having 1–5 attention deficit symptoms [(OR = 0.25; p < 0.01)] (Alvarez-Pedrerol et al., 2007). 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 (Pérez-Lobato et al., 2015b).

Other studies focused on the association between atopy and related outcomes and neuropsychological development (Julvez et al., 2009b; Sunyer et al., 2010). 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 (Julvez et al., 2009b). 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)] (Julvez et al., 2009b). In the same cohort associations between genes related to atopy and neuropsychological development was observed (Sunyer et al., 2010), but the associations observed between certain environmental pollutants and cognitive development were not explained by the immunological status (atopy) of the children (Sunyer et al., 2010).

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 (Guxens et al., 2009). 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 (985%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 (Guxens et al., 2009).

3. 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 (Grandjean and Landrigan, 2014). 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 (Suades-González et al., 2015). This is a very relevant area of research given the health burden of urban air pollution (Cohen et al., 2017). 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 (Stahlhut et al., 2009; Hauser and Calafat, 2005; Egeghy et al., 2011). 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 pollutnats and impaired neurodevelopment, as well as for exposure to some POPs. Using innovative methodologies (Gascon et al., 2013), 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 (Grandjean, 2013). 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 (Vrijheid et al., 2014), 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 (Vrijheid et al., 2014; Wild, 2012). 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.

4. 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.

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