Doctoral Thesis

Early life factors influencing neurodevelopment and the study of the interrelations between different behavioral areas

Jordi Julvez Calvo

2007

Jordi Julvez Calvo

C\ Guifré, 8 3er 1a

Barcelona 08001

jjulvez@imim.es

Doctoral Thesis

2007

Early life factors influencing neurodevelopment and the study of the interrelations between different behavioral areas

Departament de Ciències Experimentals i de la Salut

Programa de Doctorat en Ciències de la Salut i de la Vida

Universitat Pompeu Fabra

Thesis submitted by: Jordi Julvez Calvo

Thesis advisor: Jordi Sunyer Deu

Department: Centre for Research in Environmental Epidemiology

Institution: Municipal Institute of Medical Research (IMIM/PRBB) /

Pompeu Fabra University,

Barcelona, Spain

CONTENTS

ACKNOWLEDGEMENTS

En primer lloc voldria agrair al Jordi Sunyer la seva inestimable contribució tant en el àmbit professional com humà en la meva formació dels últims quatre anys llargs, que és diu molt ràpid!!!! Gràcies Jordi!!!

Com no!!! Núria Ribas!!! Et considero casi casi la meva segona tutora. No has parat d'ajudar-me ni en els teus últims dies al CREAL. Gràcies Núria!!!!!

Gràcies Maria Forns, Raquel Garcia i Maties Torrent, per haver contribuït de forma decisiva en la creació dels articles científics.

A la Lis Ellison Loschmann per la seva paciència en l'edició a l'Anglès dels articles i la tesi.

També als meus companys de feina, especialment als de la meva sala, més la Laura Bouso i la Gemma Perelló, gràcies per la vostra companyia diària durant tots aquests anys.

En l'àmbit extra-laboral:

A ma mare Eulàlia, al Wladi i a l'Arnau per tota la seva devoció en donar-me ànims, escoltar-me, aguantar-me, en fi, a compartir un ventall amplíssim d'emocions de tots colors.

També als meus amics de l'ànima com el Joan, l'Anna, el David, el Pau, la Iria, l'Almansara, la Mònica, l'Esther i la Laura. Em sento molt afortunat de poder gaudir de la seva companyia, de la seva estima i del seu suport en moments difícils; ostres ja fa una pila d'anys i alguns tota una vida!!!!!!!!!

Germanetes Mireia i Diana i germanet Ferran, Pare i Neus, també em sento molt agraït pel vostre especial interès a que les coses em sortissin bé.

També a vosaltres estimades àvies, no us oblidaré mai, ja fa temps que veu marxar, però encara noto el vostre amor. Tu també avi Pepito, no et posis gelós.

A tú molt especialment tieta Àngels que fa tant poc que ens has deixat, no tinc paraules per tu. Encara estic digerint la teva pèrdua, i m'entristeix haver-te vist tan poc en els últims temps.

PREFACE

The present doctoral thesis consists of the following sections: introduction, rationale, objectives, scientific papers (five), general discussion, overall conclusions and recommendations. The results presented here are part of the "Infància y Medio Ambiente (INMA)" project, which began in January 2004 supported by "Instituto de Salud Carlos III" (grant "Red de Grupos INMA (G03/176)"). These results are also part of "disrupció ambiental i salut" project, which started in December 2002, it has been supported in part by the "Fundació 'la Caixa'" (00/077-00), the "Instituto de Salud Carlos III, Red de Centros RCESP" (C03/09) and FIS 041436. The main objective of these projects was to investigate if specific environmental factors, particularly persistent pollutants, would affect children's development and health. I started as field worker performing the neuropsychological protocols and assessments in January 2001. I began working as PhD student coordinating the neuropsychological assessment of INMA project in December 2002. I wrote assessment protocols, supervised the fieldwork, did the management data with assistant colleagues, performed the statistical analyses and wrote four of the five scientific papers that constitute this thesis.

ACRONYMS

ADHD-DSM-IV: Attention-Deficit Hyperactivity Disorder Criteria of Diagnostic and Statistical Manual of the Mental Disorders, Fourth Edition.

CI: Confidence Interval.

CPSCS: California Preschool Social Competence Scale.

CFA: Confirmatory Factor Analyses.

DDE: 2,2-bis(*p*-chlorophenyl]-1,1-dichloroethylene.

DDT: bis[*p*-chlorophenyl]-1,1,1-trichloroethane.

GAMs: Generalized Adjusted Models.

LCPUFAs: Long-Chain Polyunsaturated Fatty Acids.

MCSA: McCarthy Scales of Children's Abilities.

nAChRs: Nicotinic Acetylcholine Receptors.

OCs : Organ-Chlorine Compounds.

SE: Standard Error.

SUMMARY

Background: Little is known about neurodevelopment among preschoolers and its susceptibility to determined environmental factors (i.e., social, psychological, biological and physical). Environmental neuroepidemiological studies among young children have generally focused the outcome assessments on global cognitive scores, without going further into more specific neurocognitive functions or assessing other behavioral areas.

Objectives: **(1)** Assess the psychometric characteristics of the behavioral outcomes, particularly California Preschool Social Competence Scale (CPCSC) in two population-based birth cohorts; **(2)** Assess the Attention Deficit Hyperactivity Disorder (ADHD) symptoms and analyze the concurrent neurocognitive and social competence outcomes in the two cohorts; **(3)** Assess early environmental exposures, duration of breastfeeding and maternal smoking associations with neurodevelopment in the cohorts.

Methods: Two prospective population-based birth cohorts, one from the island of Menorca (N=421) and the second from Ribera d'Ebre county (N=79), were followed up at the age of 4 years during a two year period (2001-2003). Children were assessed by three psychologists and their respective teachers for neuropsychological functions (McCarthy Scales or MCSA), inattention-hyperactivity behaviors (Attention-Deficit Hyperactivity Disorder Criteria of DSM-IV or ADHD-DSM-IV) and social behavior (California Preschool Social Competence Scale or CPSCS). Interviewer-administered questionnaires were completed with mothers to assess duration of exclusive breastfeeding; twice in the Ribera d'Ebre cohort, at age 1 year and age 4 years; and three times in the Menorca cohort, at

age 6 months, 14 months and 2 years after birth. Smoking habits (only Menorca cohort) were also assessed by interviewer-administered questionnaires during the third trimester of pregnancy and then every year up to age 4 years old of the child. Organ-chlorine compounds (OCs) were measured in cord serum. Child and parental general information were obtained through questionnaire. Confirmatory Factor Analyses (CFA) and other statistics were used to assess the outcome psychometric validities; multivariable linear or logistic regressions were used to assess the associations; and, to test the linearity of associations Generalized Adjusted Models (GAMs) were used.

Results: CPSCS showed acceptable psychometric characteristics when it was assessed for construct and criterion-related validities and test-retest reliability. All other standardized outcomes showed good psychometric characteristics in our cohorts.

Among the 467 children, 16 % showed DSM-IV symptom scores that fitted the diagnostic criteria for ADHD symptoms. The majority of the MCSA and CPSCS outcome scores were linearly associated with ADHD symptom scores (general cognitive β=-0.6 (-1.0 ; -0.3) per 1 symptom increment; global social competence β= -2.19 (-2.5 ; -1.9) / 1 sym). MCSA's executive function, perceptive-performance and quantitative sub-area scores were particularly associated with ADHD symptom scores.

Long-term breastfeeding was associated with executive function scores (an increase of 4.9 points after breastfeeding >20 weeks), and the improvement of social competence scores (relative risk for being in the lowest 20%, RR=0.57; 0.52-0.66, after >12 weeks) and attention-deficit hyperactivity symptom scores (RR=0.56; 0.37-0.85, after >12 weeks). Children who were breastfed for more than

20 weeks had a better cognitive performance regardless of their in utero exposure to DDT (adjusted β for high exposure to DDT (SE) = 0.30 (0.12) per week breastfed).

A high global consistency in maternal smoking habits was found (total agreement=88.7%). Maternal smoking during pregnancy (in cig./day) was associated with a decrease (in points) of children's global cognitive score (β=-0.60, (95% CI: -1.10; -0.09)); as well as global cognitive sub-areas like verbal score (β=-0.59, (95% CI: -1.11; -0.07)); quantitative score (β=-0.57, (95% CI: -1.08; -0.06)); executive function score (β=-0.71, (95% CI: -1.23; -0.20)); and working memory score (β=-0.46, (95% CI: -0.92; -0.01)).

Conclusions: The psychometric characteristics of the assessed outcomes are acceptable. Preschooler ADHD symptoms are associated with concurrent decrements in neurocognitive and social competence outcomes following patterns similar to those found in older children and adults with ADHD symptomlogy. Long-term breastfeeding is associated with fewer inattention and hyperactivity symptoms and an improvement in related behavioral areas (neuropsychological and socio-behavioral outcomes). Maternal smoking and DDT exposure during pregnancy lower neurocognitive development in preschoolers, however the benefits of long-term breastfeeding most probably outweigh the potential for harm due to environmental contaminants in breast milk.

1. INTRODUCTION

1.1. NEURODEVELOPMENT AMONG PRESCHOOLERS

Studying mental health in children is important since information in this area is sparse in comparison to that for the in adult population, with even fewer studies of this kind which have been done in preschoolers (Greenfield et al., 2005). The reasons for such a lack of scientific literature may be in part due to traditional conventions regarding socio-political interests in health science, in which social minorities (i.e., women, children and young children) had received lower priority in the past. Luckily this is slowly changing, since more recently, experts in the behavioral science areas are emphasizing the importance of studying children who may benefit better from preventive health policies (Kadesjö et al., 2001).

Maturation of the cortex (i.e., synaptic changes and axonal myelinization) during the first years of life is very intensive, and the frontal cortex is the last one to mature (after adolescence) (Herschkowitz et al., 2000; Grandjean et al., 2006). Preschoolers are very much influenced by socio-environmental interactions, particularly because their frontal cortex connections both internally and in relation to other cerebral areas (i.e., limbic system) are hyper-activated. This period of life is considered an important window for brain development, since its plasticity decreases with age (Couperus et al., 2006; Grandjean et al., 2006). The consequences of this are that preschoolers are rapidly learning how to manage the fundamentals of future complex behaviors, such as: personality, patterns of social interaction (social competence), controlling the attention (i.e., inattention) and the behavior (i.e., hyperactivity), along with other important cognitive areas

like verbal, perceptive-performance, memory, quantitative, and motor skills. Socio-environmental programs aiming to improve behavioral impairments in young children may be more beneficial in correcting the trajectory of the disabilities, than the programs applied to older children (Kadesjö et al., 2001). Special attention needs to be paid to some child disorders like Attention Deficit Hyperactivity Disorder (ADHD) which is the most predominant neuropsychiatric disorder in childhood (Furman, 2005). This disorder may negatively affect a child's learning abilities and social behavior compromising his/her future psychological development, including adolescence and adulthood (Kadesjö et al., 2001).

The works presented in this thesis are all based in two population-based birth cohorts of children of four years of age. The neurodevelopmental outcomes which ere assessed were cognitive development, social competence and ADHD symptoms. These three behavioral areas are of interest since they are indicators of different but interrelated parts of the psychological development. Cognitive assessment may be an indicator of maturation of the brain superior functions related with tasks involving verbal, perceptive-performance, memory, numerical, motor and executive abilities (Baron, 2004). Social behavior in young children may be indicative of their socio-emotional maturation and can be assessed through their responses to situations that require specific social demands, for example when they interact with the teacher or other classmates in the school context (Odom et al., 1999). ADHD symptom assessment involves the evaluation of behaviors that may be indicative of an alteration in the attention and/or activity areas, which are very important for normal development of the child in many other behavioral areas (Pelham et al., 2004). It is difficult to disentangle both how these behavioral areas interrelate and which is the direction the relation. Some studies,

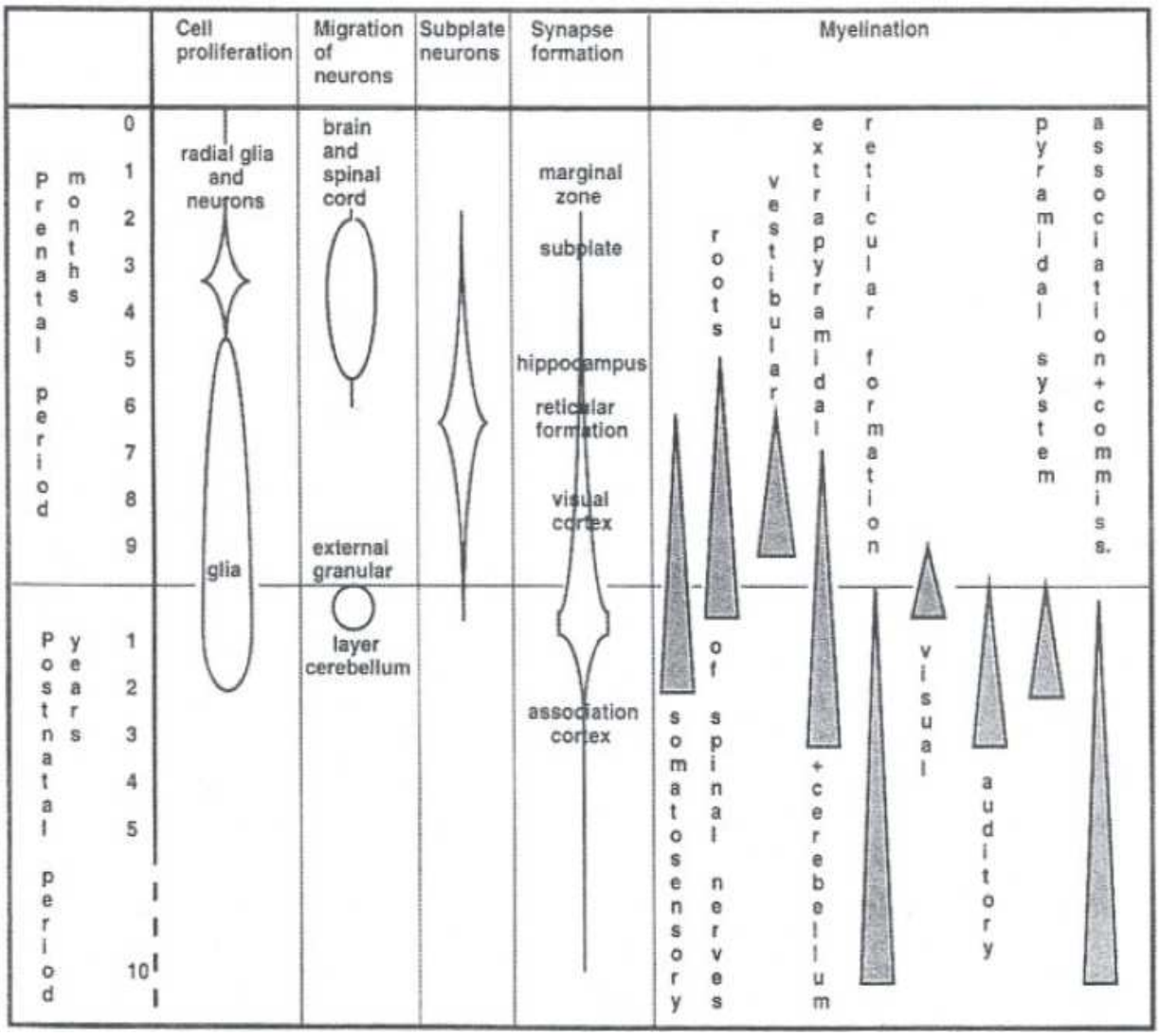
mostly done in older children, have documented that ADHD symptomlogy is caused principally by frontal lobe dysfunction, which, in turn, leads to impairments to those behavioral areas highly related with this dysfunction, such as executive functions and social competence (Stefanatos et al., 2001). Others have documented that ADHD, particularly the inattentive type, may also impair general cognitive development since it interferes to the learning processes (Greenfield et al., 2005; Baeyens et al., 2006). There remains a lack of literature describing ADHD symptoms and neuropsychological and socio-behavioral outcome associations, particularly among preschoolers (Berlin et al., 2003; Greenfield et al., 2005).

Practical problems relating to the need for large sample populations in epidemiological studies in order to adequately assess the associations between particular exposures and outcomes limit the range of neurodevelopmental variables which can be studied. Nonetheless, assessment of some of the neuropsychological, attention and social behaviors in young children would considerably enrich the current lack of literature in this important health area.

1.2. ENVIRONMENTAL EPIDEMIOLOGY AND NEURODEVELOPMENT

The developing brain has a target window period of development (from in utero up to the first two years of life) during which time it has an increased susceptibility to influence from some environmental determinants (Grandjean et al., 2006; Huizink et al., 2006). The brain has a high level of neurodevelopmental activity (i.e., cell proliferation, subplate neuron creation, neuron migration, synapse formation and myelinization) during this period (see figure 1) when factors like maternal smoking, breastfeeding or exposure to environmental neuroteratogenic pollutants may alter central nervous system functions that could manifest for extended periods, or even have more permanent effects (Mortensen et al., 2002; Jacobson et al., 2005; Grandjean et al., 2006). Obviously, there is an immensurable amount of neurodevelopmental determinants that may influence positively or negatively to the brain function and development. A child's long-term exposure to factors from a huge diversity of environments (social, psychological, biological and physical) with the addition of genetic influences may result in a particular outcome (Jacobson et al., 2005). The complexity of this area suggests caution when studying specific determinants and their influence on neurodevelopment, and we are only able to shed light on a small part this.

Figure 1. Development of nervous system during pre and postnatal period (Herschkowitz et al., 1997)



Neurodevelopment has been used as an outcome to trace environmental early effects during last decades, aiming to study the effects of lead, mercury and polychlorinated biphenyls (PCBs) in general population (Grandjean et al., 2006).

Bellinger et al. findings about lead neurotoxicity in Boston child cohorts (Bellinger et al., 1987) and Grandjean et al. description of methyl-mercury neurotoxicity in Faroese child cohorts (Grandjean et al., 1997). Subsequently, Ribas-Fito et al. set up a birth cohort study in Ribera d'Ebre (an industrially

polluted area) to assess if several organ-chlorine compounds (OCs) (particularly hexachlorobenzene) would affect neurodevelopment (see Appendix 3). Her findings showed that DDT (bis[*p*-chlorophenyl]-1,1,1-trichloroethane) and its metabolite DDE (2,2-bis(*p*-chlorophenyl]-1,1-dichloroethylene) were also present in cord serum and were the ones negatively associated with children's neurodevelopment at one year of age. She also described long-term breastfeeding as being a more important predictor of neurodevelopment than the DDT/DDE effects (Ribas-Fitó et al., 2003). DDT and DDE are environmental pollutants generally present everywhere in the environment (Skrbic et al., 2007), that accumulate in breast milk. Breastfeeding is an important factor that positively influences neurodevelopment, and is a potent biological pathway for environmental exposures passed from mother to child (Ribas-Fitó et al., 2003); it is necessary to assess if breastfeeding is beneficial regardless of DDT effects. Other toxic behaviors like maternal smoking habits also need to be studied, since tobacco smoking is, in part, similar to breastfeeding, in the sense that is a psychosocial behavior, and can be said to act like an environmental neurotoxic pollutant.

1.2.1. Duration of breastfeeding

There is no discussion about breastfeeding the infant for a long period is beneficial for his neurodevelopment, the controversy in the literature appears when explaining which are the intrinsic mechanisms (Mortensen et al., 2002). Some authors have concluded that when adjusting for maternal psychosocial factors like education, IQ, mental health or parenting skills, the apparent breastfeeding effects

diluted (Der et al., 2006). In this case breastfeeding the infant may be more an indicator of child's psychosocial environment than a causal factor per se. Other experimental, clinical trial and epidemiological studies concluded that breast milk contains long-chain polyunsaturated fatty acids (LCPUFAs) which are structural lipids critical for retina and cortical brain development during pre and early postnatal periods of life (Lauritzen et al., 2001). And then, the milk nutritive properties may be the major causal mechanisms that last with better mental abilities of children. A third hypothesis is based on factors associated with the feeding environment and physical and psychological contact between mother and child; they may contribute to the development of the infant's limbic system and its cortical connections (Feldman et al., 2003).

Organ-chlorine compounds (OCs) are persistent and ubiquitous environmental contaminants that were intensively used in the past (Ross et al., 2000). DDT (bis[*p*-chlorophenyl]-1,1,1-trichloroethane) and DDE (2,2-bis(*p*-chlorophenyl]-1,1-dichloroethylene) are both lipophilic chemicals resistant to degradation which bioaccummulate in the food chain (Ross et al., 2000; Ribas-Fitó et al., 2003; Wendo, 2004). Some studies have documented a link with DDT and DDE exposure in children and subsequent lower neurodevelopmental outcomes (Rogan et al., 1991; Hardell et al., 2002; Ribas-Fitó et al., 2003). Early life exposure occurs both in utero and via breastfeeding. Exposure to DDT in relation to neurodevelopment has been less studied (see Appendix 2). Animal studies have suggested that exposure to DDT during brain growth spurts affects the density of muscarinic cholinergic receptors of the cerebral cortex and can cause behavior abnormalities in adult life (Eriksson et al., 1992).

There are actually emerging new questions related to the fact that breast milk is also an important carrier of neurotoxic insults (i.e., DDT/DDE and nicotine) because of its fat composition (Jensen et al., 1991; Ribas-Fitó et al., 2005). If this is the case, irrespectively which are the intrinsic mechanisms of long-term breastfeeding for neurodevelopmental benefits; there is not a clear evidence that pediatricians still have to recommend long-term breastfeeding. It is generally unknown if long-term breastfeeding benefits are more important than the apparent negative effects of breast milk pollutants (Ribas-Fitó et al., 2003).

1.2.2. Maternal smoking habits

It has been extensively documented that exposure to maternal tobacco smoking, especially in utero may lead to disruption in the behavioral development of the child during the early years of life (Huizink et al., 2006). Nevertheless, very few prospective cohort studies have been conducted beginning during pregnancy with yearly follow-up, as in the present study (Eskenazi et al., 1995; Trasti et al., 1999).

Various biological pathways of tobacco neurotoxicity have been described in animal experimental studies, for example, reduced uterine blood flow to the placenta resulting in chronic deprivation of nutrients and oxygen; or neuroteratogen affects where nicotine interacts with nicotinic acetylcholine receptors (nAChRs) affecting the frontal cortex, hippocampus and cerebellum where there are high density of these receptors present during pregnancy. Other effects due to nicotine such as increased oxidative stress and hypoactivity of the noradrenergic and dopaminergic systems have also been documented (Huizink et al., 2006). Nicotine exposure in the postnatal period appears to be less influential

on brain development in infants although there may be some residual effects from the intra-partum period on the nervous system (Linnet, 2003). One of the alternative biological pathways recently suggested for environmental exposure to tobacco is through breast milk (Huizink et al., 2006).

Yet another hypothesis has suggested that more important than the neurotoxic effects of tobacco smoke are the psychosocial characteristics of smokers, since they tend to show more depressive symptoms, lower levels of education or having lower IQ scores (Breslau et al., 2005; Jacobson et al., 2005). One way to clarify if smoking effects on offspring cognitive development are secondary to parental psychosocial disadvantages is formally comparing the maternal (during pregnancy) and paternal effects. If they are similar it would be indicative that the negative effects are probably confounding factors in the association, however, if the maternal and paternal effects are different, this may suggest an effect due to tobacco neurotoxicity (Lawlor et al., 2007).

1.3. STUDYING NEURODEVELOPMENT IN THE GENERAL POPULATION

One of the important aims in public health research is to assess if a particular environmental factor may have an affect on a specific health outcome in the general population. Assessing the whole population it is basically impossible, but we can select smaller population-based cohorts from specific regions that may be more or less representative of the general population. Most behavioral studies conducted to date have selected the children from clinical, scholar or especial group samples, with only a few them having a birth-cohort design (Linnet et al., 2003; Huizink et al., 2006). Thus, there is a need to design population-based birth cohort studies in order to assess factors that may affect behavioral development.

The studies presented in this thesis are based in two population-based birth cohorts, one from Ribera d'Ebre county and the other one from Menorca island. The two regions share some similarities and differences. They are both rich and developed semi-rural areas in which most of the people live in small cities or towns. However, Ribera d'Ebre county has been home to an important and old (since 1897) electrochemistry industry (actually named Ercros), which was formerly the most important economic sustenance of the region, but nowadays has become more focused on alternative activities like tourism. This electrochemistry industry has been releasing different kinds of pollutants into the environment for years, including OCs. Since one of the original aims in setting up these cohorts was to assess if specific OCs (particularly hexaclorobenze which is released by Ercros) affect children's health, a comparative population (Menorca) which had not been exposed to environmental pollutants to the same extent was chosen. Subsequent results showed that, in fact, DDT and DDE concentrations in cord

serum, in children from the Menorca cohort showed higher concentration levels than those from samples taken from the Ribera d'Ebre county children (Carrizo et al., 2006). The possible causes for these surprising results could be explained, in part, by cohort differences in dietary fish intake. It is well known that large fish have high concentration levels of OC and other persistent contaminants (i.e., methyl-mercury) (Fossi et al., 2006).

In conclusion, these two population-based birth cohorts are representative of four year old children from a general population sample from a developed country living in smaller towns and cities where there is some level of pollution associated with the industrial activity.

1.3.1. Psychometrical assessment in environmental epidemiology

Assessing human behavior is not easy since the levels of subjectivity of the observer tend to be higher than that of other health disciplines (Hoi et al., 2004). Nevertheless there are validated and standardized instruments that have been developed for several behavioral areas according to the type of observer (i.e., psychologist, teacher or parent).

The first step in assessing behavior is the actual selection of which behavioral areas are to be included. Most neuron-environmental studies of population-based-birth-cohorts choose cognitive tools like Bailey or McCarthy (MCSA) scales to assess children during the first years of life (0-6 years). The tools available for these early years are however few and un-specific, in part because the immature brain has had not enough time yet to specialize its potential behavioral outcomes to more concrete and sophisticated neuropsychological

outcomes (Baron, 2004). At around the three years of age, the brain of a child begins to show some basic proxies of future complex behaviors, and it is at this time that the more specific behavioral assessments can be undertaken. Commonly, many environmental studies which have assessed behavior during these ages have confined their analyses to only global cognitive scores. In the studies presented here we used the MCSA in a different way (by creating new neuropsychological outcomes), and in addition we have assessed other behavioral areas like social competence and ADHD symptoms as well as the more usual measure of global cognitive scores.

The second step is applying a strict protocol to reduce the variability related to either the instrument or to the observer. Sometimes the standardized instruments are sparse or not adequate (i.e., too long) for use in environmental epidemiology studies. In that case, we have to adapt and validate new tools to our particular socio-cultural context.

Assessing neuropsychological outcomes

a) Psychologists and quality controls

First it is necessary to decide how many psychologists will do the assessment, with the fewer the better being recommended in order to minimize inter-observer variability which may result in a lower validity of the measured outcomes. Second is training by an expert to administrate and interpret the scale. It is recommended that at the end of the training double-blinded techniques with a comparison of the final scores (which should not differ more than 5%) between all the psychologists (including the expert) is used. In addition to this, when the work field starts, the

psychologists should undertake two or three quality controls, which is the double-blind technique, but this time it is applied to children from the study sample. These results should be kept in the case that they differed more than 5% which may be used later during the data analyses phase. Psychologists should communicate with each other to clarify any issue arising during the training and fieldwork.

b) Assessing new outcome sub-areas

McCarthy Scales of Children's Abilities (MCSA) is the instrument used by the psychologists to assess cognitive and motor functions of the two cohorts presented in this thesis. It is a rich and comprehensive instrument which includes a large variety of tasks 'mapping' different cognitive areas (McCarthy, 1972). Since scientific knowledge has advanced in cognition and other similar disciplines like neuropsychology, assessment of new behavioral areas are needed in order to gain better understanding of the nature of outcomes. For this reason, we added new neurocognitive outcomes by reorganizing the scale items following neuropsychological knowledge (Baron, 2004; Lezak, 2004), and when it was statistically feasible, they were validated using Confirmatory Factors Analyses (CFA) (i.e., executive function sub-area).

Assessing other behavioral outcomes

Since most studies about environmental neuroepidemiology assessed only cognitive outcomes, it is necessary to extend the assessments to include other behavioral areas, like social competence or inattention-hyperactivity symptoms

(ADHD symptoms). These behaviors were reported by teachers using rating questionnaires like California Preschool Social Competence Scale (CPSCS) (Levin et al., 1969) and Attention-Deficit Hyperactivity Disorder Criteria of Diagnostic and Statistical Manual of the Mental Disorders, Fourth Edition (ADHD-DSM-IV) (American Psychiatric Association, 1994). CPSCS had to be translated and adapted to Catalan and Spanish since there were no screening scales adapted to our socio-cultural context. In addition to this, we further studied its psychometric characteristics in the present cohorts by using different statistical techniques (i.e., CFA).

These rating scales also needed to follow a strict protocol during the administration procedure to ensure their validity for assessing outcomes. These procedures included complementary instructions to make sure that teachers understood the statements, and, use of test-retest reliability assessment, involving a randomized subgroup of teachers responding again to both rating questionnaires after a one-month-interval.

2. RATIONALE

Preschoolers are a mystery; no one can doubt that they are the outsiders in terms of child behavioral studies. But paradoxically, some experts in human neurodevelopment are suggesting that when it is about detecting and solving troubles in behavioral development, it is better to do so during the early childhood period (Kadesjö et al., 2001). Study neurodevelopment in young children alone is, in itself, a sufficient reason to undertake the work presented here.

Environmental factors that may influence child's neurodevelopment, like duration of breastfeeding, maternal smoking habits or in utero exposure to persistent organ-chlorine pollutants needed to be analyzed since present knowledge in these areas is sparse and inconsistent. Although the effects of these factors on an individual child may be insignificant; when taking into account an entire population, these influences become important, because they may alter whole population IQ scores leading to higher or lower rates of cognitive impairments (Grandjean et al., 2006).

There is a need to use psychometrics tools to inform beyond general cognitive outcomes and to assess daily-life behavioral phenotypes such as attention, hyperactivity or social competence. These constructs have not been utilized so far in environmental epidemiology except in the study of lead.

Findings that clarify the effects and the underlying pathways of these and other neurodevelopmental determinants will contribute to an increased awareness by society as well as promoting the development of better prevention policies.

3. OBJECTIVES

3.1. General objectives

1. Validate California Preschool Social Competence Scale (CPSCS) adapted to Catalan and Spanish.
2. Assess the interrelationships between ADHD symptoms, neurocognitive and social competence outcomes in Menorca and Ribera d'Ebre cohorts.
3. Assess duration of breastfeeding and maternal smoking associations with neurodevelopment in Menorca and Ribera d'Ebre cohorts.

3.2. Specific objectives

1. Analyze the psychometric characteristics of the Spanish-Catalan version of CPSCS by studying its construct and criterion-related validities and analyzing its test-retest reliability in the Menorca and Ribera d'Ebre cohorts.
2. Analyze psychometric characteristics of ADHD-DSM-IV and MCSA (including new sub-areas as executive function) in the Menorca and Ribera d'Ebre cohorts.
3. Study the concurrent associations between teacher rated scores of ADHD symptoms (using ADHD-DSM-IV form list) and the neuropsychological (MCSA) and socio-behavioral (CPSCS) outcome scores in the Menorca and Ribera d'Ebre cohorts.

4. Study the association of the duration of breastfeeding with attention and hyperactivity and the related behavioral areas (neuropsychological and socio-behavioral outcomes) in the Menorca and Ribera d'Ebre cohorts.
5. Study the benefits of breastfeeding on cognition taking into account DDT concentrations at birth in the Menorca and Ribera d'Ebre cohorts.
6. Report the effects of pre- and post-natal maternal smoking habits on 4-year-old children's cognitive development in the Menorca cohort. Assess global cognitive outcome, and its specific sub-areas to gain a better understanding of the underlying pathways relating to smoking neurotoxicity.

4. PAPER # 1

Julvez J, Forns M, Ribas-Fitó N, Mazon C, Torrent M, Garcia-Esteban R, Ellison-Loschmann L, Sunyer J. Psychometric characteristics of the California Preschool Social Competence Scale in a Spanish Population Sample. *Early Education and Development* (under review).

PSYCHOMETRIC CHARACTERISTICS

OF THE CALIFORNIA PRESCHOOL SOCIAL COMPETENCE SCALE IN A SPANISH POPULATION SAMPLE

Submitted Date

09-2-2006

RUNING HEAD

Psychometric characteristics of CPSCS

WORD COUNT

Abstract: 215 words

Text: 3697 words

References: 54

Tables: 5

Appendix: 1

ABSTRACT

There are few rating scales that measure social competence in very young Spanish or Catalan children. We aimed to analyze the psychometric characteristics of the California Preschool Social Competence Scale (CPSCS) when applied to a Spanish and Catalan population. Children were rated by their respective teachers within six months following their fourth birthday in two population-based birth cohorts from Menorca Island and Ribera d'Ebre County, Spain (N=378; 66.3% of births during 1997-1999). A Confirmatory Factorial Analysis (CFA) was used to compare the underlying structure of the Spanish-Catalan version of the CPSCS with the original version. Cronbach's Alpha Coefficient was used to determine the internal consistency of each of the confirmed factors. Cohen's Kappa formula was used to calculate the test-retest reliability. Five correlated factors labeled as; Considerateness, Task Orientation,, Extraversion, Verbal Facility and Response to Unfamiliar, were optimally confirmed as a result of CFA. The first three factors had robust internal consistency (Alpha Coefficients > 0.75). The Kappa coefficient was satisfactory in 29 items (Kappas>0.60) out of 30. Children's cognitive abilities (IQ) and gender, maternal social class and level of education were related to the social competence scores as indicators of criterion-related factors. The bilingual version of the CPSCS has good psychometric properties allowing its use in further studies in either Spanish or Catalan populations.

KEYWORDS: CPSCS, preschoolers, young children, social competence, psychometrics, developmental psychology, scale validation, Confirmatory Factor Analyses, school, teachers, Spanish.

INTRODUCTION

The study of psychological development in children requires the assessment of social competence, thus, the majority of developmental tests include specific subtests to measure this behavioral area (Hart, Keller, Edelstein & Hofman, 1998). Social competence has been defined as the human capability to communicate and cooperate with other people, to negotiate options and make decisions, to adapt to new situations, to tolerate certain degrees of stress, and to control egocentric and primary emotions (Turner & Gartrell, 1978). Social competence is bi-directionally related to global cognitive development and plays an important role in the process of personality structuring (Hart, Keller, Edelstein & Hofman, 1998; Nigg, Quamma, Greenberg & Kusche, 1999).

Empirical evidence has shown that social competence scores are associated with global cognition (verbal and performance IQs) (Moffitt & Silva, 1988; Block & Kremen, 1996; Nigg, Quamma, Greenberg, & Kusche, 1999), and with neurocognitive functions, such as executive function and attention control (Rourke & Fuerst, 1991; Nigg, Hinshaw, Carte, & Trueting, 1998) in children. There is also some evidence suggesting an interrelation between temperament and social skills where children with behavioral problems appear to have poorer social competence scores than their counterparts (Izard et al., 2001). Higher levels of social stimulation in four year-old children has been found to be related to better McCarthy Scale scores six month later (Campion & Wohlfarth, 1989), and child's emotional knowledge (the ability to recognize and label emotional expressions) at five years of age may be a predictor of social behavior and academic competence at nine years of age (Izard et al., 2001).

Assessing social competence in very young children is not easy and discussion continues about the best strategies to use. Both the type of instrument to be used and the person doing the assessment (informant) are important and they appear to be related. Informants have different abilities for accessing, detecting and differentiating target behaviors, and also for providing objective or accurate data (Ladd & Profilet, 1996) thus,

the information obtained may differ depending on whether peers, parents, teachers or external observers are used. Peers rate sociometric questionnaires in which they express their general preferences for children in the classroom (Odom & McConnell, 1985); parents or teachers rate general social competence questionnaires based on their personal opinion and experiences of the child; and external observers describe rates of social interaction and social skills (Odom, McConnell, McEvoy et al., 1999).

We were interested in knowing how children behave in a peer social-context, thus we chose to obtain information from teachers. Teachers and educators have a wide knowledge of children behavior, covering different psychological domains (e.g. language, emotion, motor) and various situations (e.g. learning, playing, dressing, and toileting). Furthermore, teachers dedicate much of their daily time to guiding social development and observing behaviors including making comparisons between one child's behavior and that of other classmates (Ladd & Profilet, 1996).

There are few rating scales that analyze social competence in children in the pre-school social context and even less which have been developed for the Spanish context. The majority of social competence scales were constructed between the years 1965 to 1988: Devereux Elementary School Behavior Rating Scale (Spivack & Swift, 1967), California Preschool Social Competence Scale (Levine, *et al.,* 1969), Social Competence Scale and Symptom Checklist (Kohn & Rosman, 1974), Preschool Behavior Questionnaire (Behar & Stringfield, 1974), Classroom Behavior Inventory (Schaefer, 1975), Social Skills Rating Scale (Gresham & Elliott, 1986), Teacher-Child Rating Scale (Hightower, *et al*., 1986), Walker-McConnell Scale of Social Competence and School Adjustment (Walker & McConnell, 1988) and Social Competence and Behavior Evaluation (SCBE) (Dumas, Martínez, LaFreniere, et al.,1998). These scales are heterogeneous and embrace very different social competence constructs, such as: anxiety, apathy-withdrawal, assertiveness, self-control, cooperation-compliance, creative-initiative, learning competence, dependent / autonomous, depressive / happy, externalizing /

internalizing behaviors, hostility / considerateness, hyperactivity / distractibility / impatience, etc.

The only Spanish adaptation rating scale for social competence in preschoolers is SCBE (LaFreniere, et al, 1998). The SCBE comprises 80 items and is generally too long to be used as a screening tool. However the psychometric qualities of the Spanish version of SCBE showed good internal consistency, test-retest reliability and criterion-related validity, although no Confirmatory Factor Analyses have been used and it is not a teacher-rated scale.

The California Preschool Social Competence Scale (CPSCS) was designed in the USA by Levin, Elzey and Lewis in 1969, explicitly for use by teachers within the context of a preschool program. The CPSCS measures the adequacy of preschool children's interpersonal behavior and their degree social responsibility. The concept of independence, understood as interpersonal autonomy, is part of its definition (Levin, Elzey & Lewis, 1969). The original scale was designed to be unidimentional, but Flint (1981) analyzed the underlying structure using Exploratory Factorial Analyses and described 5 factors: Considerateness, Task Orientation, Extraversion, Verbal Facility and Response to Unfamiliar which are unique to the scale.

We have chosen this general social competence rating scale because it is short enough to be used in epidemiological studies in a school context. Additionally, the CPSCS items are orientated to assess basic constructs of social competence and takes into account aspects of social competence that are not cross-culturally and temporally dependent (Levin, Elzey & Lewis, 1969).

Many psychological and medical studies have used CPSCS to assess social behavior in young children (Doussard-Roosevelt, Porges, Scanlon, Alemi & Scanlon, 1997; Doussard-Roosevelt, McClenny, & Porges, 2001; NICHD, Allhusen, Appelbaum, Belsky, et al., 2001) however there are a few studies examining the construct validity and reliability of this scale (Flint, 1981; Brulle & Ivarie, 1989), and it has never been adapted into either Spanish or Catalan.

Empirical research suggests that boys show more aggressive-impulsive behaviors, less attention capabilities (Parke & Asher, 1983; Hynd, Hern, Kytja & Marshall, 1991) and thus, generally display lower scores in general social competence than girls who are perceived to be more altruistic than boys (Zahn, Radke & King, 1983; Zarbatany, Hartmann, Gelfand & Vinciguerra, 1985). Additionally, children from parents of high compared to low socioeconomic status have been described as being more socially competent (Levin, Elzey & Lewis, 1969; Dumas, Martínez, LaFreniere & Dolz, 1998; Bornstein & Bradleyet, 2003; Rimm-Kaufman, Pianta, Cox & Bradley, 2003).

Our aim was to analyze the psychometric characteristics of the Spanish-Catalan version of the CPSCS, on the specific objectives were: (a) to study the construct validity of CPSCS testing the unidimensional structure (Levin, Elzey & Lewis, 1969) and the multidimensional structure (Flint, 1981) of the scale using Confirmatory Factorial Analyses; (b) to examine criterion-related validity by assessing the association of the CPSCS'scales with children's cognitive abilities, comparing sex differences in impulsive-aggressive and attention behaviors derived from the scale's factor structure, and also by analyzing the effects of maternal socioeconomic status on children's social competence scores; and (c) to analyze test-retest reliability of the CPSCS after a one-month interval.

METHODS

Participants

The study participants were drawn from two population-based birth cohorts from Menorca Island and the County of Ribera d'Ebre, Spain. For the Ribera cohort, all singleton children born in the main hospital of the study area between March 1997 and December 1999 were recruited. 102 children were enrolled with 70 (68.6 %), having complete outcome data (psychometric assessment) from the visit at 4-years of age. The Menorca cohort was set up in 1997 and recruited all women presenting for antenatal care over a 12 month period. A total of 482 children (94 % of those eligible) were enrolled and complete outcome data was available for 308 (64%) children at the 4-years of age visit. All mothers provided signed consent forms and the study was approved by the ethics committee of the Institut Municipal d'Investigació Mèdica (Ribas-Fitó et al., 2006; Julvez et al., 2007).

Instruments

The California Preschool Social Competence Scale was designed to be used for evaluating the social competence of children aged 2.5 years to 5.5 years. It is composed of 30 items, with each one having four answer choices, as in a likert scale, ordered from 1 (lowest degree of social competence) to 4 (highest degree of social competence). The items cover a wide range of behaviors, such as response to routine, response to the unfamiliar, following instructions, making explanations, sharing, helping others, initiating activities, giving direction to activities, reaction to frustration, and accepting limits (see Appendix I). The total social competence score is the sum of all level ratings for the 30 items. Total social competence raw scores can thus range from 30 through to 120. The total score represents the child's global social competence (GSC), which is then converted to a percentile rank score, grouped into three score intervals for each group of chronological age, sex and occupational level. The mean and standard deviation of the raw scores at each age level for each group were used for the computation of the norms.

The normative sample of the scale approximates the proportion of preschool children in the major urban centers for each geographic region of the United States. The normative sample was based of 800 children. (Levin, Elzey & Lewis, 1969).

Information on socioeconomic background, maternal diseases, obstetric history, parity, child's gender, fetal exposure to alcohol (ever exposure during pregnancy) and cigarette smoking (at least one cigarette a day during the last trimester), type and duration of breastfeeding, education, and social class was obtained through questionnaires administered in person after delivery and at 4 years of age. The UK Registrar General's 1990 classification was used to group subjects by social class according to maternal occupation using the International Standard Classification of Occupations (ISCO-88) (http://www.warwick.ac.uk/ier/isco/isco88.html). Education level was defined as: (1) less than primary level (people that didn't finish the level that is formally required by law); (2) primary level (people who completed only the schooling level formally required by law); (3) secondary level (completed high school); (4) High level (people who finished college or did further study) (Dardet, 1995). We reduced the original education level categories for the regression models analyses and no differences were found in the final results.

Information about children's cognitive and psychomotor development was obtained by professional psychologists through McCarthy Scales (MCSA) assessment which was performed during the same time period as the social competence assessment (McCarthy, 1972).

Procedures

The first step was the translation and adaptation of the original scale to Spanish and Catalan by a psychologist and two epidemiologists, following two standardized techniques (Brislin, 1970):

(a) Committee translation which required that the instrument be independently translated by two or more bilingual people (English-Spanish/Catalan); (b) Back-translation to the original language.

Children from both cohorts were rated by their respective teachers (CPSCS) and three trained psychologists (MCSA) during a three-year-period (2001-2003). The bilingual version of CPSCS (Spanish and Catalan) was filled up by the teacher during the school year after the child's fourth birthday. In Spain, schooling is compulsory from age 5-16 years with a structured preschool program available for children aged 3-5 years old. Preschool teachers spend approximately five hours per day with the children.

Two small subgroups of children from both cohorts (Menorca n=12; Ribera d'Ebre n=34) were randomly selected for the one-month test-retest reliability of the Spanish-Catalan CPSCS instrument. Teachers from both subgroups had to complete the CPSCS twice within a one-month period and without access to the information they had supplied during the first assessment.

Statistical analyses

There were no significant differences in the CPSCS scores for the two cohorts, thus the results were pooled to gain statistical power.

Confirmatory factorial analyses (CFA) was used to determine if the underlying structure of the Spanish-Catalan version was similar to the original version of CPSCS (Flint, 1981). We tested five different theoretical models:

Model-0 (30 items) comprised of the unidimentional (one factor) scale as per the original version of the CPSCS (Levin, Elzey & Lewis, 1969).

Model-1 (29 items) comprised of the scale with five uncorrelated factors as derived by Flint (1981), using Exploratory Factor Analyses (EFA) with a factor loading of the English version >0.40. Item 3 was excluded because it didn't accomplish the criterion for any of the five factors.

Model-2 (29 items) reproduced Model-1, taking into account that all the factors were correlated.

Model-3 (26 items) reproduced Model-2, but excluded those items showing factorial loadings of the Spanish-Catalan version ≤ 0.40, thus, item 4, item 11 and item 26 were subsequently excluded from this model.

Model-4 (23 items) was as per Model-3 but excluded items with factorial loadings < 0.45, thus, items 1, 2 and 27 were then also excluded.

Composite Reliability or Cronbach's Alpha Coefficient was used to determine the internal consistency of each factor confirmed by CFA. Cronbach's Alpha scores range from 0 to 1, a high score indicating that the scale items of that factor measure true and similar variability, and that the factor has good internal consistency. An acceptable Alpha would be >0.70 (Copyright StatSoft, Inc., 1984-2003).

Children's age, sex and General Cognitive Index and maternal education and socioeconomic status were variables considered to be potentials predictors of CPSCS scores. Multivariable logistic regression analyses were done for each of these variables to determine their effects in the Spanish-Catalan version of CPSCS. This analysis took into account the Global Social Competence score (GSC) and the five factor scores identified from Model-3. The variables were dichotomized due to their non-normal distribution; the reference group per each outcome was those children scoring over percentile 20 (PC20). This criterion is commonly used in clinical assessment to distinguish between 'normal' and 'low' responses (Jacobson and Jacobson, 2005).

Cohen's Kappa formula was used to calculate the test-retest reliability. We followed the Brulle et al. (1988) coding formula before applying Absolute Simple Kappa Index in order to assess the inter-observer reliability of the English version of CPSCS. An acceptable Kappa coefficient of agreement would be > 0.60 (Feinstein, 1981).

All data analyses were carried out using Stata 8.0 Special Edition and AMOS 5.0.

RESULTS

The distribution of children's gender in the different studied covariates was very similar (table 1). Most of the children were 4.5 years old when teachers filled out the questionnaire. Children's crude global cognitive scores (MCSA) were also very similar by gender. But when the different scores of our CPSCS version (global & subscales) were compared there were significant differences in all of them except for Response to Unfamiliar subscale. Male children worsen them, except for Extraversion subscale, in which showed better scores.

(Table 1 should be placed here)

Goodness-of-fit indices for the five CPSCS models are shown in Table 2. Models 1 and 2 did not reach the minimum points in their indices for an acceptable goodness of fit. Model-3 showed an acceptable goodness of fit in almost all indices except for CFI that was just below the 0.90 cutoff-point. Model-4 was also similarly acceptable, but without significant improvement from the Model-3 indices. Model-3 theorizes that the Spanish-Catalan CPSCS fits acceptably with the factorial structure of the five factors proposed by Flint (1981), that all the factors are correlated, and, that any items (3, 4, 11 and 26) with low weights (≤ 0.40) should be excluded from the model.

(Table 2 should be placed here)

Table 3 describes the standardized factor loadings and their composite reliabilities for Model-2 and for the best fitting model (Model-3). Most of the factor loadings of Model-2 were significantly associated with a moderate to high level of weights, and the Composite Reliabilities (Cronbach's Alpha Coefficient) were acceptable (> 0.81) for all factors except for Response to the Unfamiliar factor (F5). All the factor loadings from Model-3 were significantly associated with a high-moderate level of weights (between 0.41 and 0.86), but their composite reliabilities, calculated by Cronbach's Alpha Coefficient, was satisfactory for factor 1 (Considerateness), 2 (Task Orientation) and 3 (Extraversion), and unsatisfactory for factor 4 (Verbal Facility) and 5 (Response to Unfamiliar).

(Table 3 should be placed here)

Table 4 describes the inter-correlations between factors assessed in Model-3. The highest correlations were found between F1 (Considerateness) and F4 (Verbal Facility), F2 (Task Orientation) and F4 (Verbal Facility), F2 (Task Orientation) and F3 (Extraversion), and, F3 (Extraversion) and F5 (Response to Unfamiliar). Some correlations like F1 with F2, F1 with F5, F2 with F3, F2 with F5 and F3 with F5 were relatively similar to the ones found by Flint (1981), but others like F1 with F4, F2 with F4 and F4 with F5 were relatively different in their study.

(Table 4 should be placed here)

ºThe multivariable regression models showed that children's IQs, gender, mother's social class and level of education were associated with Global Social Competence. Having a low IQ score was associated with lower scores in all CPSCS subscales. Being a male was associated with a lower score in F1, F2, F4 and Global Social Competence (table 5). The children from mothers of higher social class or higher education level presented better scores in Global Social Competence, F2 and F4. Children's age was only associated with F2.

(table 5 should be placed here)

Test-retest Kappa Index analyses of the Spanish-Catalan CPSCS version showed an unacceptable coefficient of agreement (<0.60) for item 2 only. The other item indexes ranged from 0.62 to 0.85, with a median of 0.78.

DISCUSSION

The aim of the current study was to validate a screening tool to assess young children's social competence. There are few rating scales for preschoolers with similar properties to the CPSCS which are also short enough to be used in epidemiological studies (Hogan, Scott & Bauer, 1992; Dumas Martínez, LaFreniere & Dolz, 1998; Damián, 2000; Carney & Merrell, 2002; Castro, Mendez & Fantuzzo, 2002.). Additionally, the Spanish-Catalan version of the CPSCS fills an important gap in social competence screening instruments for preschoolers in Spain and other Spanish speaking countries.

We found that the five factors assessed by Flint (1981) using the original version of CPSCS were statistically acceptable (Gonzalez-Gutierrez et al., 2005; Hu, & Bentler, 1999) in the Spanish and Catalan version of the CPSCS. The best fitting model that we tested was Model 3 which considered five inter-correlated factors and excluded 4 items (3, 4, 11 and 26) from the original form. In addition, our analyses did not confirm the CPSCS as a unidimentional scale (Levin, Elzey & Lewis, 1969). It also confirmed that it cannot be conformed by five independent factors as it was conceived by Flint (1981), when he prioritized the formal result presentation of a varimax rotation EFA instead of oblique EFA results, even though his results were similar in both analyses. Varimax rotation technique option assumes that the factors under exploration are independent and oblique rotation technique assumes that these factors are inter-correlated. Internal reliability (Cronbach's Alpha coefficient) was consistent in the three first factors but slightly below the cutoff criteria (<0.70) for the other two factors possibly due to the reduced number of items (Becker, 2000). However, CFA showed suitable goodness-of-fit indices with the inclusion of five factors and additionally, the decision to retain all five factors fitted conceptually with one of the primary aims of the study given the important role that 'Verbal Facility' has on child socialization and because 'Response to Unfamiliar' is considered a useful mechanism of social and personal adaptation.

The intercorrelations between the factors obtained in the current study show a similar pattern to those obtained by Flint (1981), with one difference, our data indicated that 'Verbal Facility' is highly correlated with all other factors. This fact can be explained by the role that verbal abilities have on social development (Nigg et al., 1999).

Inclusion of the first three factors, Considerateness, Task Orientation and Extraversion, are consistent with previous work reviewing social-emotional behavior (Kohn & Rosman, 1973; Behar & Stringfield, 1974; Schaefer, Baker & Zawel, 1975; Flint, 1981). The most conceptually significant concordances are the three factors found in Schaefer's Classroom Inventory EFA, listed as: Task Orientation/Distractibility; Hostility/Considerateness and Introversion/Extraversion.

Our findings regarding the criterion-related validity of the scale, were consistent with previous studies. We found a high positive association for all CPSCS scores and MCSA IQs scores assessed during the same period. This is expected since cognitive development is part of a child's psychological development and is closely related to other behavioral areas like social competence (Rourke & Fuerst, 1991; Nigg, et at. 1998). When we compared children's gender, boys showed lower levels in all scores except for 'Extraversion' (F3), and 'Response to Unfamiliar' (F5) while clue factors like 'Considerateness' (F1) or 'Task Orientation' (F2) showed the highest score difference between genders. Children with parents being of lower social class and education level, obtained lower scores in Global Social Competence, and, 'Task Orientation' (F2) and 'Verbal Facility' (F4) subscales which are probably the factors having most verbal cognitive influence and highly affected by a child's socio-cultural environment (Schmidt, & Lawson, 2002).

Overall, the bilingual version of CPSCS appears to have good construct and criterion-related validity, however, these findings are not enough to conclude that our scale has robust psychometric characteristics, since an analysis of the test-retest reliability would also be needed. Andrew Brulle (1989) studied inter-observer reliability of the CPSCS, and concluded that the reliability of the scale was not satisfactory since it

measured teacher's opinion more than objective statements of social competence. However, data obtained in present study shows satisfactory test-retest reliability.

There are several limitations to the study which need to be considered. Firstly, since we only tested the scale in 4 year olds, we cannot be sure of the appropriateness of this scale to children of other preschool ages although it would not be unreasonable to expect to find very similar psychometric characteristics for other age groups. Secondly, the fact that inter-observer reliability was not tested means we cannot be certain that the scale measures objective statements of social competence. Thirdly, our sample size was sufficient but small for Confirmatory Factor Analyses. The consequences of having a smaller sample include more convergence failures and lowered accuracy of parameter estimates and, in particular standard errors (Loehlin, 1992). Finally, we were unable to assess cross-cultural differences between the bilingual version and the original scale to determine the effects of time (1973); Culture (New York State) with specific characteristics of the sample (children with learning and behavioral problems).

In conclusion, the Spanish and Catalan version of the CPSCS has good psychometric properties and should be considered for use in further studies concerned with factors relating to social competence in Spanish or Catalan pre-school children.

Acknowledgments

All teachers of preschool classes from Ribera D'Ebre County and Menorca Island.

All the psychologists that have coordinated the fieldwork.

The nurses and administrative personal from Primary Health Care Center of Mahó and Primary Health Care Center of Flix.

All the people that gave me support from the Respiratory and Environmental Health ResearchUnit, especially Lis Ellison-Loschmann and Dave MacFarlane for editing assistance, Estel Plana, Laura Bouso & Gemma Perelló.

Funding

"Instituto de Salud Carlos III" INMA Project (G03/176). This study has also been supported in part by the "Fundació "La Caixa"" (00/077-00).

REFERENCES

Álvarez-Dardet, C., Alonso, J., Domingo, A., & Regidor, E. (1995). *La Medición de la clase social en ciencias de la salud : informe de un grupo de trabajo de la Sociedad Española de Epidemiología*. Barcelona, Spain: SG Editores S.A.

Ballester, F., Sala, M., Sunyer, J., & Grimalt, J. (2000). Serum concentrations of hexachlorobenzene in family members of workers in an electrochemical factory. *Scandinavian Journal of Work, Environment & Health,* 26(1), 67-70.

Behar, L., & Stringfield, S. (1974). A behavior rating scale for the preschool child. *Developmental Psychology,* 10(5), 601-610.

Becker, G. (2000). Creating comparability among reliability coefficients: The case of Cronbach alpha and Cohen kappa. *Psychological Reports*, 87(3, Pt 2), 1171-1182.

Block, J., & Kremen, A.M. (1996). IQ and Ego-Resiliency: Conceptual and Empirical Connections and Separateness*. Journal of Personality and Social Psychology*, 70, 349-361.

Bornstein, M.H., & Bradley, R.H. (2003). *Socioeconomic status, parenting, and child development*. Mahwah, NJ, US: Lawrence Erlbaum Associates.

Brislin, R.W. (1970). Back-translation for cross-cultural research. *Journal of Cross-Cultural Psychology,* 1(3), 185-216.

Brulle, A.R., & Ivarie, J. (1989). Teacher Checklists: A reliability Analysis. *Special Services in the School,* 5(1-2), 67-75.

Carney, A.G., & Merrell, K.W. (2002). Reliability and comparability of a Spanish-language form of the Preschool and Kindergarten Behavior Scales. *Psychology in the Schools*, 39(4), 367-373.

Campion J., & Wohlfarth R. (1989). Theory and Research in Practice: an Oportunity Group for Young Children with Developmental Difficulties*. Child Care, Health and Development*, 15(5), 343-361.

Castro, M., Mendez, J.L., & Fantuzzo, J. (2002). A validation study of the Penn Interactive Peer Play Scale with urban Hispanic and African American preschool children. *School Psychology Quarterly,* 17(2), 109-127.

Copyright StatSoft, Inc. (1984-2003). Reliability and Item Analysis. *Electronic Textbook StatSoft*.

Damián, M.D. (2000). Escala del desarrollo comunicativo-social aplicada a niños españoles y mexicanos./Scale of Social Development applied to Spanish and Mexican children. *Psicothema,* 12(Suppl2), 163-165.

Doussard-Roosevelt, J.A., Porges, S.W., Scanlon, J.W., Alemi, B., & Scanlon K.B. (1997). Vagal regulation of heart rate in the prediction of developmental outcome for very low birth weight preterm infants. *Child Development,* 68, 173-186.

Doussard-Roosevelt, J.A., McClenny, B.D., Porges, S.W. (2001). Neonatal cardiac vagal tone and school-age developmental outcome in very low birth weight infants. *Developmental Psychobiology,* 38(1), 56-66.

Dumas, E.J., Martínez, A., LaFreniere, J.P., & Dolz, L. (1998). La versión española del cuestionario “Evaluación de la Conducta y la Competencia Social en Preescolares" (Social Competence and Behavior Evaluation SCBE): Adaptación y validación. *Psicológica,* 19(2), 107-121.

Feinstein, A.R. (1981). Clinical biostatistics. LVI. The t test and the basic ethos of parametric statistical inference (conclusion). *Clinical Pharmacology & Therapeutics,* 30(4), 133-146.

Flint, L.D. (1981). Dimensionality of the California Preschool Social Competency Scale. *Applied Psychological Measurement,* 4(2), 203-212.

Gonzalez-Gutierrez, J., Moreno-Jimenez, B., Garrosa-Hernández, E., & López-López, A. (2005). Spanish version of the Swedish Occupational Fatigue Inventory (SOFI): Factorial replication, reliability and validity. *International Journal of Industrial Ergonomics,* 35, 737-746.

Gresham, F., Elliott, S., & Black, F. (1987). Teacher-rated social skills of mainstreamed mildly handicapped and nonhandicapped children. *School Psychology Review*, 16(1), 78-88.

Hart, D., Keller, M., Edelstein, W., & Hofman, V. (1998). Childhood personality influences on social-cognitive development: A longitudinal study. *Journal of Personality and Social Psychology,* 74(5), 1278-1289.

Hightower, A., Cowen, E., Spinell, A., Lotyczewski, B., & et al (1987). The Child Rating Scale: The development of a socioemotional self-rating scale for elementary school children. *School Psychology Review*, 16(2), 239-255.

Hogan, A.E., Scott, K.G., & Bauer, C.R. (1992). The Adaptive Social Behavior Inventory (ASBI): A new assessment of social competence in high-risk three-year-olds. *Journal of Psychoeducational Assessment,* 10(3), 230-239.

Hosmer, D., & Lemeshow, S. (2000). *Applied logistic regression*. 2nd ed., New York; Chichester, Wiley.

Hoyle, R. (1995). *Structural Equation Modeling: concepts, issues and applications.* Thousand Oaks, CA: Sage Publications.

Hynd, W.G., Hern, L.K., Kytja, K.V., & Marshall, M.R. (1991). Neurobiological basis of attention-deficit hyperactivity disorder (ADHD). *School Psychology Review,* 20(2), 174-186.

Hu, L., & Bentler, P.M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling,* 6(1), 1-55.

Izard, C.; Fine, S.; Schultz, D.; Mostow, A., et al. (2001). Emotion knowledge as a predictor of social behavior and academic competence in children at risk. *Psychological Science*, 12 (1), 18-23.

Jacobson, J.L., & Jacobson, S.W. (2005), Methodological issues in research on developmental exposure to neurotoxic agents. Neurotoxicology and Teratology 27,395-406.

Julvez J, Ribas-Fitó N, Forns M, Garcia-Esteban R, Torrent M, Sunyer J (2007a), Attention behaviour and hyperactivity at age four and duration of breastfeeding. *Acta Paediatr* (in press).

Kohn, M., & Rosman, L.B. (1972). A social competence scale and symptom checklist for the preschool child: Factor dimensions, their cross-instrument generality, and longitudinal persistence. *Developmental Psychology*, 6(3), 430-444.

Kohn, M., & Rosman, L.B. (1973). Cross-situational and longitudinal stability of social-emotional functioning in young children. *Child Development,* 44(4), 721-727.

Ladd, W.G., & Profilet, M.S. (1996). The Child Behavior Scale: A teacher-report measure of young children's aggressive, withdrawn, and prosocial behaviors. *Developmental Psychology,* 32(6), 1008-1024.

Levin, S., Elzey, F.F., & Lewis, M. (1969). *California Preschool Social Competency Manual*. San Francisco, CA: Consulting Psychologists Press, INC.

Loehlin, J.C. (1992). *Latent variable models.* Hillsdale, NJ: Lawrence Erlbaum Publishers.

McCarthy, D. (1972) *Manual for the McCarthy Scales of Children's Abilities*. New York, NY, Pa: Psychological Corp 1972. (Spanish Adaptation (1996): Madrid, Spain, Pa: TEA Ediciones, S.A.).

Moffitt, T.E., & Silva, P. (1988). Self-Reported Delinquency Neuropsychological Deficit, and History of Attention Deficit Disorder*. Journal of Abnormal Child Psychology*, 16, 553-569.

NICHD Early Child Care Research Network, Allhusen, V., Appelbaum, M., Belsky, J., Booth, C.L., Bradley, R., Brownell, C., Burchinal, P., Caldwell, B., Campbell, S., Clarke-Stewart, A., Cox, M., DeHart, G., & Friedma (2001). Nonmaternal care and family factors in early development: An overview of the NICHD Study of Early Child Care. *Journal of Applied Developmental Psychology,* 22(5), 457-492.

Nigg, T.J, Hinshaw, S.P., Carte, E., & Trueting, J. (1998) Neuropsychological Correlates of Antisocial Behavior and Comorbid Disruptive Behavior Disorders in Children with ADHD*. Journal of Abnormal Psychology*, 107:468-480.

Nigg, T.J., Quamma, P.J., Greenberg, T.M., & Kusche, A.C. (1999). A two-year longitudinal study of neuropsychological and cognitive performance in relation to behavioral problems and competences in elementary school children. *Journal of Abnormal Child Psychology,* 27(1), 52-63.

Odom, S.L., & McConnell, S.R. (1985). A performance-based conceptualization of social competence of handicapped preschool children: Implications for assessment. *Topics in Early Childhood Special Education,* 4(4), 1-19.

Odom, S.L., McConnell, S.R., McEvoy, M.A., Peterson, C., Ostrosky, M., Chandler, L.K., Spicuzza, R.J., Skellenger, A., Creighton, M., & Favazza, P.C. (1999). Relative

effects of interventions supporting the social competence of young children with disabilities. *Topics in Early Childhood Special Education,* 19(2), 75-91.

Parke, D.R., & Asher, R.S. (1983). Social and personality development. *Annual Review of Psychology,*34, 465-509.

Ribas-Fitó, N., Torrent, M., Carrizo, D., Munoz-Ortiz, L., Julvez, J., Grimalt, J., & Sunyer, J. (2006). In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. *Am J Epidemiol,* 164, 955-62.

Rimm-Kaufman, E.S., Pianta, C.R., Cox, J.M., & Bradley, H.R. (2003). Teacher-rated family involvement and children's social and academic outcomes in kindergarten. *Early Education & Development,* 14(2), 179-198.

Rourke, B.P., & Fuerst, D.R. *Learning Disabilities and Psychosocial Functioning: A Neuropsychological Perspective.* New York: Guilford Press; 1991.

Schaefer, C., Baker, E., & Zawel, D. (1975). Major replicated dimensions of adjustment and achievement: Cross-cultural and longitudinal research. In J. M. O'Malley (Chair), *Dimensions of competence in classrooms.* Symposium presented at the annual meeting of American Educational Research Association, Washington, DC.

Schmidt, C., & Lawson, C. (2002). Caregiver attention-focusing and children's attention-sharing behaviours as predictors of later verbal IQ in very low birthweight children. *Journal of Child Language*, 29(1), 3-22.

Spivack, G., & Swift, M.S. (1966). The Devereaux Elementary School Rating Scale: a study of the nature and organization of achievement related to disturbed classroom behavior. *journal of special education*, 1(1), 71-90.

Turner, J., & Gartrell, W.J. (1978). Social factors in psychiatric outcome: Toward the resolution of interpretive controversies. *American Sociological Review,* 43(3), 368-382.

Walker, H.M., & McConnell, S.R. (1988). *The Walker-McConnell Scale of Social Competence and School Adjustment.* Austin, TX: Pro-Ed.

Zahn, C., Radke, M., & King, K. (1983). Early altruism and guilt. *Academic Psychology Bulletin,* 5(2), 247-259.

Zarbatany, L., Hartmann, P.D., Gelfand, M.D., & Vinciguerra, P. (1985). Gender differences in altruistic reputation: Are they artifactual? *Developmental Psychology,* 21(1), 97-101.

Table 1. Description of mother and child characteristics at birth (n=378) and social competence scores (CPSCS) by gender

	BOYS	**GIRLS**
COVARIATES		
Children's Cohorts; %	49.8	50.2
Ribera d'Ebre (70)	48.1	51.9
Menorca (308)	50.1	49.9
Children's Age in Years	4.58(±0.30)	4.59(±0.26)
Children's IQ, MCSA (Mean & SD)	100 (15)	101 (15)
Maternal Social class; %		
Professional	2.7	3.6
Managerial & Technician	11.3	10.8
Manual & Non-Manual Skilled	43.2	48.0
Partly Skilled	13.1	9.4
Unskilled	5.4	4.5
Unemployed	24.3	23.8
Maternal Education Level; %		
High (>15 years)	12.4	10.6
Secondary (12 years)	30.3	34.8
Primary (8 years)	46.3	41.4
Less than Primary (<8 years)	11.0	13.2
CPSCS (Median & Range)		
Global score*	89 (48-116)	97 (55-114)
Considerateness (Factor 1)*	19 (7-24)	21 (9-24)
Task Orientation (Factor 2)*	23 (9-32)	25 (11-32)
Extraversion (Factor 3)*	14 (6-20)	14 (2-20)
Verbal Facility (Factor 4)*	14 (7-16)	15 (7-16)
Response to Unfamiliar (Factor 5)	9 (4-12)	9 (4-12)

*** P-value<0.05** for X^2 tests of differences of percentages or F tests of mean differences, both, by child's gender.

Table 2. Fitting indexes of five models assessed by confirmatory factor analyses

Summary of Maximum Likelihood Confirmatory Factor Analysis Results

	Model 0	**Model 1**	**Model 2**	**Model 3**	**Model 4**
χ^2	2085.7	1874.3	1103.0	813.8	674.71
Number of Parameters (NPAR)	57	65	75	62	56
Degree of Freedom	378	370	360	289	220
Fitting indices (cutoff point criteria)*					
Model-Sample Discrepancy Measures					
χ^2/df (<3)	5.518	5.066	3.064	2.816	3.067
GFI (>0.85)	0.624	0.712	0.815	0.852	0.864
AGFI (>0.80)	0.568	0.661	0.777	0.821	0.829
RMR (<0.10)	0.103	0.181	0.066	0.058	0.061
Measures Based on Population Discrepancies					
RMSEA (<0.08)	0.109	0.104	0.074	0.069	0.074
Comparisons to Baseline Models					
CFI (≥0.90)	0.653	0.694	0.849	0.878	0.888
Information-Theoretic Measures					
AIC (low scores)	2199.7	2004.3	1253.0	937.8	786.71

Model 0 (30 items): Hypothesized, 1 factor

Model 1 (29 items): Hypothesized, 5 uncorrelated factors

Model 2 (29 items): Hypothesized, 5 correlated factors

Model 3 (26 items): Revised Model 2: items with factorial loadings ≤ 0.40 excluded

Model 4 (23 items): Revised Model 3: items with factorial loadings < 0.45 excluded

* It refers the cutoff point criteria per each of the fitting indices for excluding H_o, this means limit point criterion for not accepting the proposed model.

χ^2 (Chi-square); GFI (Goodness of Fit Index); AGFI (Adjusted GFI); RMR (Root Mean Square Residual); RMSEA (Root Mean Square Error of Approximation); CFI (Comparative Fit Index).

Table 3. Standardized factor loadings and composite reliabilities of Model 2 and Model 3

Factor, item	Maximum Likelihood Estimates Model 2		Maximum Likelihood Estimates Model 3	
	Standardized Factor loadings	Composite Reliability Ŧ	Standardized Factor loadings	Composite Reliability Ŧ
Considerateness (F1)		0.84		0.85
It4cs	0.40		-	
It7cs	0.02*		-	
It13cs	0.87		0.86	
It14cs	0.82		0.81	
It15cs	0.70		0.71	
It21cs	0.57		0.55	
It22cs	0.46		0.62	
It24cs	0.71		0.72	
Task Orientation (F2)		0.89		0.88
It6cs	0.56		0.56	
It7cs	0.70		0.73	
It8cs	0.73		0.70	
It9cs	0.79		0.80	
It10cs	0.82		0.83	
It11cs	0.39		-	
It22cs	0.22		-	
It23cs	0.64		0.64	
It25cs	0.63		0.64	
It30cs	0.64		0.63	
Extraversion (F3)		0.82		0.78
It11cs	0.18		-	
It16cs	0.55		0.54	
It17cs	0.67		0.68	
It18cs	0.72		0.73	
It19cs	0.74		0.74	
It20cs	0.61		0.59	
It28cs	-0.06*		-	
Verbal facility (F4)		0.81		0.63
It1cs	0.44		0.43	
It2cs	0.42		0.42	
It5cs	0.61		0.60	
It8cs	-0.03*		-	
It9cs	-0.22*		-	
It11cs	0.24		-	
It12cs	0.75		0.73	
Response to the Unfamiliar (F5)		0.63		0.60
It26cs	0.40		-	
It27cs	0.44		0.41	
It28cs	0.67		0.63	
It29cs	0.72		0.76	

Ŧ α-Cronbach

* P-value>0.05

Table 4. Estimated correlations between the factors of Model 3

	Model 3			
	F2	F3	F4	F5
F1	0.62 (0.65)	0.34 (0.35)	0.79 (0.01)	0.30 (0.46)
F2		0.71 (0.55)	0.85 (0.27)	0.69 (0.53)
F3			0.65 (0.38)	0.81 (0.56)
F4				0.66 (0.14)

Between brackets are the factor correlations of original CPSCS described in Flint et al. (1981) study.

Table 5. Association † (odds ratio 'OR' and 95% confidence interval) between mother and child covariates and cognitive development and the Spanish and Catalan version of the California Preschool Social Competency Scale (CPSCS)

	Global Social Competence	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Child's Global Cognitive (McCarthy Scales)						
> Percentile 75	1	1	1	1	1	1
Percentile 75-Percentile 50	**3.09** (1.04 ; 9.30)	1.90 (0.81 ; 4.40)	**3.26** (0.98 ; 10.87)	**4.83** (1.30 ; 17.98)	1.70 (0.68 ; 4.27)	**5.01** (1.76 ; 14.30)
Percentile <50-Percentile 25	**3.51** (1.17 ; 10.51)	1.18 (0.46 ; 3.01)	**4.26** (1.28 ; 14.24)	**5.68** (1.53 ; 21.13)	**2.89** (1.19 ; 6.98)	**4.45** (1.52 ; 13.05)
< Percentile 25	**12.23** (4.14 ; 36.26)	**3.97** (1.65 ; 9.56)	**14.18** (4.28 ; 46.96)	**16.09** (4.40 ; 58.83)	**9.39** (3.84 ; 22.94)	**8.70** (2.98 ; 25.37)
Child's Age per Years	0.34 (0.08 ; 1.42)	0.50 (0.13 ; 2.00)	**0.16** (0.03 ; 0.78)	0.71 (0.17 ; 2.94)	0.50 (0.14 ; 1.77)	1.20 (0.33 ; 4.32)
Child's Sex						
Females	1	1	1	1	1	1
Males	**2.73** (1.52 ; 4.93)	**2.60** (1.4 ; 4.6)	**3.59** (1.88 ; 6.84)	1.68 (0.93 ; 3.04)	**2.32** (1.38 ; 3.91)	1.05 (0.61 ; 1.82)
Child's Cohort						
Ribera d'Ebre	1	1	1	1	1	1
Minorca	1.73 (0.78 ; 3.83)	0.68 (0.34 ; 1.33)	2.08 (0.89 ; 4.89)	1.01 (0.45 ; 2.25)	1.28 (0.63 ; 2.59)	1.00 (0.47 ; 2.15)
Maternal Social Class						
Professional, Technician & Managerial	1	1	1	1	1	1
Skilled Manual & Non-Manual	2.42 (0.77 ; 7.57)	0.90 (0.37 ; 2.25)	2.11 (0.67 ; 6.66)	2.88 (0.90 ; 9.12)	**2.79** (1.01 ; 7.71)	1.41 (0.59 ; 3.36)
Part Skilled & Unskilled	**4.40** (1.33 ; 14.70)	1.60 (0.60 ; 4.2)	**3.63** (1.06 ; 12.38)	2.81 (0.81 ; 9.80)	**4.05** (1.37 ; 12.0)	0.97 (0.34 ; 2.76)
Not working	**5.80** (1.80 ; 18.60)	2.2 (0.88 ; 5.53)	**4.79** (1.47 ; 15.64)	2.79 (0.83 ; 9.32	**4.06** (1.41 ; 11.71)	1.30 (0.50 ; 3.36)
Maternal Education						
High & Secondary	1	1	1	1	1	1
Primary & Less	**2.22** (1.23 ; 4.02)	1.60 (0.91 ; 2.81)	**2.17** (1.16 ; 4.04)	1.05 (0.57 ; 1.95)	**2.01** (1.19 ; 3.39)	1.11 (0.63 ; 1.94)

†Each column is a multivariable regression model including age, sex, cohort and alternatively maternal social class or maternal education.

APPENDIX I

Original Items of California Preschool Social Competence Scale (CPSCS)

1. Identification: 1. Can state first name only; 2. Can state full name; 3. Can state full name and age as of last birthday; 4. Can state name, age and address.
2. Using Names of Others: 1. Uses no proper names in interacting with those around him; 2. Uses the names of no more than five children or adults; 3. Uses the name of from five to ten children; 4. Uses the names of virtually all children and adult.
3. Greeting New Child, when a new child joins the group: 1. He inadvertently physically overpowers child in greeting him (i.e. hugs, bumps, pulls); 2. He makes a limited and brief physical contact (i.e. pats, pokes, rubs) with child and some verbal contact; 3. He usually makes verbal contact and sometimes touches child; 4. He nearly always makes verbal contact with child without physical contact.
4. Safe Use of Equipment: 1. He proceeds with activity, ignoring hazards involving height, weight, and distance (climbing on unstable equipment, stacking boxes too high, jumping onto off-balanced structures); 2. He proceeds with hazardous activity, sometimes seeking help sometimes getting into difficulty; 3. He proceeds with hazardous activity but frequently seeks help when he is in difficulty; 4. He corrects hazards or seek help before proceeding with activity.
5. Reporting Accidents, when he has an accident (e.g., spilling, breaking): 1. He does not report accidents; 2. He sometimes reports accidents; 3. He frequently reports accidents; 4. He nearly always reports accidents.
6. Continuing in Activities: 1. He wanders from activity to activity with no sustained participation; 2. He continues in his own activity but easily diverted when he notices activities of others; 3. He continues in his own and leaves only when he is interrupted by others; 4. He continues in his own activity in spite of interruptions.
7. Performing Tasks: 1. He usually has to be asked two or three times before he will begin a task; 2. He usually begins task the first time he is asked but dawdles and has to be reminded; 3. He begins task the first time he is asked but is slow in completing task; 4. He begins task the first time he is asked and is prompt in completing task.
8. Following Verbal Instructions, he can follow verbal instructions: 1. When they are accompanied by demonstrations; 2. Without demonstrations, if one specific instruction is involved; 3. Without demonstrations, when it involves two specific instructions; 4. Without demonstrations, when it involves three or more specific instructions
9. Following New Instructions: 1. He carries out one familiar instruction; 2. He carries out one new instruction the first time it is given; 3. He follows new instructions given one at a time, as well as familiar ones; 4. He follows several new instructions given at a time, as well as familiar ones.
10. Remembering Instructions: 1. He nearly always needs to have instructions or demonstration repeated before he can perform the activity on his own; 2. He frequently requires repetition, a reminder, or affirmation that he is proceeding correctly; 3. He occasionally needs repetition of instruction for part of the activity before completing the activity; 4. He performs the activity without requiring repetition of instructions.
11. Making Explanation to Other Children, when attempting to explain to another child how to do something (put things together, play a game, etc.): 1. He is unable to do so; 2. He gives an incomplete explanation; 3. He gives a complete but general explanation; 4. He gives a complete explanation with specific details.
12. Communicating Wants: 1. He seldom verbalizes his wants; acts out by pointing, pulling, crying, etc; 2. He sometimes verbalizes but usually combines actions with words; 3. He usually verbalizes but sometimes acts out his wants; 4. He nearly always verbalizes his wants.
13. Borrowing: 1. He takes objects when in use by others without asking permission; 2. He sometimes asks permission to use other's objects; 3. He frequently asks

permission to use other's objects; 4. He nearly always asks permission to use other's objects.
14. Returning Property, when he has borrowed something: 1. He seldom attempts to return the property to its owner; 2. He occasionally attempts to return the property to its owner; 3. He frequently attempts to return the property to its owner; 4. He nearly always returns the property to its owner.
15. Sharing: 1. He does not share equipment or toys; 2. He shares but only after adult intervention; 3. He occasionally shares willingly with other children; 4. He frequently shares willingly with other children.
16. Helping Others, when another child is having difficulty (such as using equipment, dressing): 1. He never helps the other child; 2. He helps another child only when they are playing together; 3. He sometimes stops his own play to help another child; 4. He frequently stops his own play to help another child**.**
17. Playing with Others: 1. He usually plays himself; 2. He plays with others but limits play to one or two children; 3. He occasionally plays with a larger group (three or more children), 4. He usually plays with a larger group (three or more children).
18. Initiating Involvement, when other children are involved in an activity which permits the inclusion of additional children: 1. He seldom initiates getting involved in the activity; 2. He sometimes initiates getting involved in the activity; 3. He frequently initiates getting involved in the activity; 4. He nearly always initiates getting involved in the activity.
19. Initiating Group Activities: 1. He nearly always initiates activities which are solely for his own play; 2. He initiates his own activities and allows one child to join him; 3. He sometimes initiates activities which include two or more children; 4. He frequently initiates activities which are of a group nature.
20. Giving Direction to Play, when playing with others: 1. He typically follows the lead of others; 2. He sometimes makes suggestions for the direction of the play; 3. He frequently makes suggestions for the direction of the play; 4. He nearly always makes suggestions for the direction of the play.
21. Taking Turns: 1. He frequently interrupts or pushes others to get ahead of them in an activity taking turns; 2. He attempts to take turn ahead of time but does not push or quarrel in order to do so; 3. He waits for turn, but teases or pushes those ahead of him; 4. He waits for turns or waits to be called.
22. Reaction to Frustration, when he does not get what he wants or things are not going well: 1. He has a tantrum (screams, kicks, throws, etc.); 2. He finds a substitute activity without seeking help in solving the problem; 3. He seeks help from others in solving the problem without making an attempt to solve it himself; 4. He seeks help from others in solving the problem after making an effort to solve it himself.
23. Dependence upon Adults: He will continue in an activity on his own without having an adult participate with him or encourage him: 1. Hardly ever; 2. Sometimes; 3. Frequently; 4. Nearly always.
24. Accepting Limits, when an adult sets limits on the child's activity (play, space, use of material, type of activity) he accepts the limits: 1. Hardly ever; 2. Sometimes; 3. Frequently; 4. Nearly always.
25. Effecting Transitions, in changing from one activity to another: 1. He requires personal contact by adult (i.e., holding hands, leading); 2. He will not move toward new activity until the physical arrangement have been completed; 3. He moves toward new activity when teacher announces the activity; 4. He moves toward new activity without physical or verbal cues.
26. Changes in Routine, the child accepts changes in routine (daily schedule, room arrangements, adults) without resistance or becoming upset: 1. Hardly ever; 2. Sometimes; 3. Frequently; 4. Nearly always.
27. Reassurance in Public Places, when taken to public places he must be given physical or verbal reassurance: 1. Nearly always; 2. Frequently; 3. Sometimes; 4.

Hardly ever.

28. Response to Unfamiliar Adults: 1. He avoids or withdraws from any contact with unfamiliar adults; 2. He, when initially approached by unfamiliar adults, avoids contact, but if approached again, is responsive; 3. He responds to overtures by unfamiliar adults but does not initiate contact; 4. He readily moves toward unfamiliar adults.

29. Unfamiliar Situations: 1. He restricts himself to activities in which he has previously engaged; 2. He joins in an activity which is new for him only if other children are engaged in it; 3. He joins with other children in an activity which is new to everyone; 4. He engages in an activity which is new for him even though other children are not involved.

30. Seeking Help, when he is involved in an activity in which he needs help: 1. he leaves the activity without seeking help; 2. He continues in the activity but only if help is offered; He persists in the activity and finally seeks help; 4. He seeks help from others after making a brief attempt.

5. PAPER # 2

Julvez J, Forns M, Ribas-Fitó N, Torrent M, Sunyer J. Attention behavior and hyperactivity and concurrent neurocognitive and social competence outcomes in four year olds from two population-based birth cohorts. *The Journal of Child Psychology and Psychiatry* (under review).

ATTENTION BEHAVIOR AND HYPERACTIVITY AND CONCURRENT NEUROCOGNITIVE AND SOCIAL COMPETENCE OUTCOMES IN FOUR YEAR OLDS FROM TWO POPULATION-BASED BIRTH COHORTS

Submitted Date

18-4-2007

RUNNING HEAD

ADHD symptoms and neurodevelopment in preschoolers

WORD COUNT

Abstract: 246 words

Text: 3306 words

Tables: 4

Figures: 1

References: 39

ABSTRACT

Objective. Little is known about Attention Deficit Hyperactivity Disorder (ADHD) symptoms in preschoolers. We aimed to study the concurrent associations between ADHD symptom and the neurodevelopmental scores in two population-based birth cohorts.

Methods. The cohorts, one from the island of Menorca (N=386) and the second from Ribera d'Ebre county (N=81) in Spain were followed up at the age of 4 years during a two year period (2001-2003). Children were assessed by three psychologists and their respective teachers for neuropsychological functions (McCarthy Scales, MCSA), inattention-hyperactivity behaviors (Attention-Deficit Hyperactivity Disorder Criteria of DSM-IV, ADHD-DSM-IV) and social behavior (California Preschool Social Competence Scale, CPSCS). Multivariable linear and logistic regressions were used to adjust for covariates.

Results. 16 % of the 467 children showed DSM-IV symptom scores that fitted the diagnostic criteria for ADHD symptoms. The majority of the MCSA outcome scores were linearly associated with ADHD symptom scores (general cognitive β=-0.6 (-1.0 ; -0.3) per 1 symptom increment), specifically inattention symptom scores (general cognitive β= -1.8 (-2.3 ; -1.2) / 1 sym.). Most of the CPSCS outcome scores were also linearly associated with ADHD symptoms (global social competence β= -2.19 (-2.5 ; -1.9) / 1 sym.). MCSA's executive function, perceptive-performance and quantitative sub-area scores were associated with ADHD symptom scores after adjustments for the MCSA complementary sub-area scores.

Conclusions. Preschooler ADHD symptoms are associated with concurrent decrements in neurocognitive and social competence outcomes. The association patterns are similar to those found in older children and adults with ADHD symptomology.

Key words: ADHD symptoms, cognitive development, social competence, preschoolers, population-based birth cohort.

INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is considered the most common neurobehavioral disorder in childhood.[1] The clinical prevalence of ADHD is usually estimated at 3-10 % in school age children and is more common in boys than girls (from 3:1 to 9:1 depending upon target population).[2] Nowadays, there is a growing interest in the study of its symptomology (ADHD symptoms) among younger age groups, specifically preschoolers.[3-4] Some authors have suggested that ADHD symptoms may be discerned as early as 6-8 years of age and possibly during the pre-school years.[4-6] Prompt symptom identification may lead to earlier preventive action to minimize related difficulties like learning problems, socio-affective development and/or other outcome impairments.[7]

Behavioral research in preschoolers is still modest compared with that in older children;[4] with even fewer studies on ADHD symptoms and the co-occurrence of other neurodevelopmental outcomes in population-based birth cohorts.[8-11] Studying behavior in children without clinical diagnoses may contribute to a better understanding of how these psychological areas interrelate with each other in the general population.

Executive function may play an important role in ADHD[6,12] along with other psychological impairments including perceptual-performance cognition and social skills,[12-13] but these observations have been documented primarily in school age children and adults.

We aimed to study the concurrent associations between teacher rated scores of ADHD symptoms (using ADHD-DSM-IV form list) and the neuropsychological (McCarthy scales, MCSA) and social competence (California Preschool Social Competence Scale, CPSCS) outcome scores in two population-based birth cohorts.

METHODS

Subjects

This study is based on two Spanish birth-cohorts, one from Menorca Balearic Island in the northwest Mediterranean Sea, and the other from Ribera d'Ebre county, situated in Catalonia, north-eastern Spain, is a rural area with some industry concentrated in one small town. Children from Menorca (N=386 out of 468 newborns during the years 1997-1998) and Ribera d'Ebre (N=81 out of 102 newborns during the years 1997-1999) were followed-up to the age of 4 years old with psychometrical assessments performed during the period 2001-2003. In total, 467 children (82%) were included in the final data analyses.[14-16] Participants did not differ in most of the covariates (p>0.07) from non-participants, except for home location and children's age during assessment. After explaining the study to parents, written informed consent was obtained. The ethical committee of the "Insitut Municipal d'Investigació Mèdica" approved the study.

Assessment Instruments

A standardized version of the McCarthy Scales of Children's Abilities (MCSA) adapted to the Spanish population by TEA (official editorial company for adapting tests in Spain) was used to evaluate motor and cognitive capabilities.[17] Three neuropsychologists were trained to administer and interpret the MCSA. A strict protocol was applied to avoid inter-observer variability, including inter-observer-trainings and three sets of quality controls (inter-observer-reliability-tests) undertaken during the fieldwork. The inter-observer variability was lower than 5%. MCSA subtests were reorganized into new outcome sub-area scores according to those tasks highly associated with specific neurocognitive function.[18-19] We created these new outcomes instead of using separate subtest scores[20] with the intention of minimizing the difficulty associated with a low level of score reliability that, in turn, could affect the power of the analyses (type II error).[21] The original MCSA contains eighteen subtests grouped into one general scale or five global sub-area scales

(general cognitive scale, or verbal, perceptual, quantitative, memory and motor skills). The new outcome sub-areas were created by the reorganization of these eighteen subtests as follows: verbal memory (items 3 and 7_{II}); working memory (5, 14_{II}); memory span (6, 7_{I}, 14_{I}); gross (9, 10, 11) and fine (12, 13) motor skills; global executive function (2, 5, 6, 14_{II}, 15, 17,18); verbal (5, 14_{II},15, 17) and perceptive-performance (2, 6, 18) executive functions and cognitive functions of posterior cortex (1, 3, 4, 7_{I}, 7_{II}, 12, 13 and 16).[14,16] We analyzed the internal construct validity of global executive function sub-area using Confirmatory Factor Analyses; which showed an acceptable goodness of fit ($\chi 2/df$ = 21.4743/14 = 1.53; Bentler's comparative fit index 'CFI' = 0.9464; Bentler and Bonnett's non-normed fit index 'NNFI' = 0.9495).[22] Additionally, we analyzed the Cronbach's Alpha Coefficient for internal consistency of global executive function and cognitive functions of posterior cortex sub-areas which were 0.68 and 0.69 respectively.

The California Preschool Social Competence Scale (CPSCS) was designed for evaluation of social competence in children aged from 2.5 years to 5.5 years. It is composed of 30 items, with each item having four possible answers ordered as a likert scale (from 1 to 4). The items cover a wide range of behaviors such as response to routine, response to the unfamiliar, following instructions, making explanations, sharing, helping others, initiating activities, giving direction to activities, reaction to frustration, and accepting limits.[23] The scale is also composed of five factors describing different social competence sub-areas: Considerateness (F1), Task Orientation (F2), Extraversion (F3); Verbal Facility (F4) and Response to Unfamiliar (F5).[24] The scale has been successfully adapted into a bilingual version (Spanish/Catalan) able to be used by both monolingual and/or bilingual teachers (Julvez et al. 2007. *Under review*). Cronbach's Alpha Coefficient analysis was 0.92 for scale's global score, 0.85 for F1, 0.88 for F2, 0.78 for F3, 0.63 for F4, and 0.60 for F5.

Attention-Deficit Hyperactivity Disorder Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (ADHD-DSM-IV) is an internationally recognized questionnaire comprising 18 items designed to evaluate attention-deficit (1-9),

hyperactivity and impulsivity (10-18) symptoms in children.[25] The original DSM-IV form list was used which rates items as “Yes=1” or “No=0”. Cronbach’s Alpha Coefficient analyses were 0.90 for general symptoms, 0.89 for attention-deficit and 0.81 for hyperactivity-impulsivity. ADHD-DSM-IV symptom scores were treated as categorical and continuous variables. Three exclusive categories were created for primary analyses: reference group (0) children without any symptom score reported (n=212); moderate group (1) children with some symptoms but without achieving scores for diagnostic criteria of ADHD-DSM-IV (n=178); and general diagnostic-criteria group (2) children achieving scores for symptom diagnostic criteria in inattention subscale or hyperactivity one or both (n=75). Diagnostic criteria group subjects were further separated into three different groups for more specific analyses: (a) Inattention type group included those children achieving scores only for inattention symptom diagnostic criteria (n=40); (b) Hyperactive type group included those children achieving scores for only hyperactivity symptom diagnostic criteria (n=20); (c) Mixed type group included those children achieving scores for both (inattention and hyperactivity) symptom diagnostic criteria at the same time (n=15). Finally ADHD-DSM-IV symptom scores were also treated as continuous variables (1 point = 1 symptom) for general, inattention and hyperactivity symptoms.

Proceedings

Following neuropsychological testing (MCSA), behavioral scales (CPSCS, ADHD-DSM-IV) were completed by the children’s teachers. In Spain, schooling is compulsory from age 5-16 years with a structured preschool program available for children aged 3-5 years old. Preschool teachers spend approximately five hours per day with the children. To assess one-month inter-test reliability two small subgroups of children from both cohorts (n=12 and n=34) were randomly selected. The test-retest reliability by Kappa Formula was satisfactory for all items (mean>0.70) except item 2 (using names of others) of CPSCS.

Information on maternal and paternal education in years, maternal and paternal socioeconomic background (using The UK Registrar General’s 1990 classification

according to parental occupation by ISCO88 code), marital status, maternal health and obstetric history (pregnancy complications 'Yes/No'; type of delivery 'Vaginal, Caesarean, With Forceps or Other'; delivery complications 'Yes/No'), parity, alcohol consumption during pregnancy (any consumption 'Yes/No'), child's exposure to cigarettes smoke (maternal and paternal daily smoking 'Yes/No' during pregnancy and at child's 4th year of age), duration of breastfeeding, age during kindergarten attendance and dietary fish intake (weekly at age 4 years) was obtained through questionnaire. Gestational age and anthropometric measures at birth were collected from clinical records, and anthropometric measures at age 4 years were collected using standard methods.

Statistical Analyses

Continuous outcomes were standardized to a mean of 100 with a standard deviation of 15 to homogenize all the scales. A cut-off point corresponding to the 20th percentile (PC20) was created to categorize those outcomes with a non-normal distribution. This criterion is commonly used in clinical assessment to distinguish between 'normal' and 'low' responses.[21] Logistic regressions were used to measure the association for binary outcomes with ADHD-DSM-IV symptom scores while regression coefficients were used to measure the associations of continuous normally distributed outcomes with ADHD-DSM-IV symptom scores.

The initial analysis was stratified by cohort, but due to non-heterogeneity ($p>0.50$), the results of the two cohorts were pooled and adjusted for geographic location. Final multivariable models were adjusted for maternal variables of; social class, parity at child's age 4 years, marital status, alcohol consumption during pregnancy, tobacco smoking during pregnancy and at child's age 4 years, for child's variables of; gender, duration of breastfeeding, age when starting kindergarten, and age and school season during test assessment, the paternal variable of education level and evaluator (psychologist). The variables of; child's gestational age, birth weight and height , cranial perimeter and Apgar test scores, child's weight and height at age 4 years, child's dietary fish intake, child's

having older siblings at age 4 years, mother's type of delivery, mother's age and height after delivery, maternal weight, father's age and alcohol consumption after delivery and number of rooms in the home were not retained because their inclusion one by one in a model with ADHD symptom scores did not change the coefficient of the latter by more than 5%.

Adjusted General Additive Models (GAM) were used to evaluate the linearity of the relation between ADHD-DSMV symptom scores and MCSA's general cognitive outcome scores, through non-parametric depiction of the predictor on the outcome, when the effects of the other variables had been taken into account. We reported the statistic GAIN, which is the difference in the normalized deviance between the GAM and a model with a linear term for that predictor. A large gain indicates a lot of nonlinearity, in terms of statistical significance. The associated *P*-value is based on a chi-square approximation to the distribution of the gain if the true marginal relationship was linear.

Finally, we assessed whether the association between general ADHD-DSM-IV symptom scores and an outcome was confounded by any one of the other outcomes, thus, MCSA global sub-area outcomes (excluding those with shared items) were treated as potential confounders. For every one of the MCSA outcomes we reran the multivariate models, including the complementary outcome(s) as a covariate each time. First adjusting set included verbal, perceptive-performance and quantitative scores, which they are the three MCSA conventional sub-areas, and the sum of all their subtests represents the general cognitive area. Second adjusting set included executive function and cognitive function of posterior cortex sub-area scores, which the sum of both of them also includes all the subtests that account for general cognitive area.

RESULTS

16 % of the 467 children rated by their respective teachers in ADHD-DSM-IV symptom scores fitted the diagnostic criteria for general ADHD symptoms. 8.5 % for inattentive type, 4.3 % for hyperactive type and 3.2 for mixed type. The boys' symptom score (fitting diagnostic-criteria) prevalence was more than three times that of the girls' one being 24.4 % and 7.4 % respectively. Table 1 shows detailed distributions of the covariates of interest by ADHD-DSM-IV symptom score groups. There were significant differences in child's gender, duration of breastfeeding, and home location and mother's social class. There were higher rates of ADHD-DSM-IV symptom scores for diagnostic criteria with lower social class and duration of breastfeeding and higher parity; particularly among children who met diagnostic criteria for inattentive type symptoms.

There were significant differences (using crude analyses) in almost all outcome variables, when comparing the group without any ADHD-DSM-IV symptom scores to that with symptom scores achieving general diagnostic criteria. But when it was considered the different symptom type groups, the results showed that the children scoring lower neurocognitive outcomes were only the ones achieving diagnostic criteria for inattention symptoms (see table 2).

There was a linear relationship, using adjusted GAMs, between MCSA general cognitive scores and general ADHD (GAIN = 2.14; p-value for linearity (null hypothesis) = 0.14.), inattention (0.21; 0.65) and hyperactivity (1.91; 0.17) symptom scores (see figure 1), but only inattention symptom scores showed a clear linear pattern. The findings were similar for each one of the MCSA global sub-areas (data not shown). When CPSCS global social competence scores was the dependent variable there was a clear linear relationship with all three ADHD-DSM-IV symptom scores: general ADHD (GAIN = 0.34; p-value = 0.60), inattention (1.21; 0.27) and hyperactivity (1.3; 0.26).

Table 3 shows the adjusted associations between ADHD-DSM-IV symptom score groups (including continuous variables) and the psychological outcome scores. All of

them, except verbal memory, were negatively associated with the general ADHD symptom diagnostic criteria group. Also when the general ADHD symptoms were taken into account one by one, as a continuous variable, there was a significant linear trend in all the outcomes except the MCSA's scores of global verbal and global memory (including its span and verbal sub-areas). The inattention type group showed worse scores in all outcomes apart from verbal memory. When inattention type symptom scores were treated as continuous variable the results were unchanged, showing a significant negative linear trend with the same outcomes. The hyperactive type group showed a negative association only with CPSCS scores, specifically with global social competence and considerateness, task orientation and verbal facility factors. The results were similar when it was treated as continuous variable. The mixed type group was not included in the table since its sample size was small (n=15), but it showed a similar pattern of results to those of the inattentive type group (data not shown).

Table 4 presents the results after MCSA outcome mutual adjustments. Using the same adjusted models as table 3 for general ADHD-DSM-IV symptom diagnostic criteria group, we included the selected MCSA outcomes as covariates each time. Global executive and global perceptive-performance scores, and to lesser a degree, global quantitative scores showed a significant association after being adjusted for their complementary outcome global sub-areas. When the same model was retested for the inattention type group, the results were essentially unchanged.

DISCUSSION

In the current study, an increased prevalence of ADHD symptoms in preschoolers was associated with male gender and shorter duration of breastfeeding, as well as with having mothers with high parity or lower social class. There was a negative linear association between ADHD symptoms and most of the neurodevelopmental and socio-behavioral outcomes; this was especially true for inattention symptoms. When we analyzed the same associations taking into account the three DSM-IV diagnostic criteria groups, only inattentive and mixed types showed a significant negative association with most of the neurocognitive outcomes. Executive function, perceptive-performance and quantitative sub-area scores remained significantly associated with the general ADHD symptom diagnostic criteria group after adjusting for other complementary MCSA outcomes. Social competence outcomes showed the same pattern of association with all ADHD symptoms, including hyperactivity symptoms.

Overall the prevalence of general ADHD symptoms based on DSM-IV diagnostic criteria scores was 16 %, with 8.5 %, 4.3 % and 3.2 % for inattention, hyperactivity and mixed types, respectively. The prevalence of children meeting diagnostic criteria for general ADHD symptoms is similar to a recent community-based study that examined the prevalence of general ADHD symptoms reported by teachers in a large representative sample (n=3,006) of children including a preschooler group (n=413).[8] It is also similar to teacher-rate levels found in other population-based studies, which in some cases included older children.[26-28] But when the prevalence was examined separately for inattentive, hyperactive and mixed symptom type groups, it differed from rates in Nolan et al. (2001)[8] for preschoolers; in their findings the higher rates were in hyperactive and combined symptom types, which is the opposite of the present results. Nevertheless, our findings are in concordance with results of this study for the total sample. In addition, other population-based studies, which included older children, also reported higher rates for the inattentive type, and similar lower rates for hyperactive and combined types.[12,26-27,29] Our

findings of higher rates of ADHD-symptom diagnostic criteria in boys than in girls are also in concordance with literature.[5,12] There is less known about the relationship between mother's psychosocial status and ADHD symptoms, but it is suggested that lower socio-educational families have higher prevalence levels.[1,30]

Our findings of lower concurrent neurocognitive scores in children with high scores of ADHD symptoms, especially for inattention symptoms, are in concordance with findings from other studies in older children.[11,29,31-33] Also, it is interesting to note that hyperactivity symptoms were not associated with cognitive scores, but were negatively associated only with social competence scores, especially the factor of considerateness, which has been documented as being consistent with more externalized behavioral problems in children with hyperactivity symptoms.[4,33]

Specific associations were found between being in the general ADHD symptom diagnostic criteria group (particularly with inattention symptomology) and neurocognitive development, in which significant associations with executive function, perceptive-performance and quantitative scores persisted, when adjusted for the complementary outcomes; this statistical technique was used with the intention to discriminate which outcomes may be more statistically associated with ADHD symptoms, since they are all intercorrelated. These results are similar to findings from other studies describing the neuropsychological outcomes of children and adults with ADHD symptoms.[3,6,11-13,34-35] In neurobiological terms, these behavioral areas may be related to activation of the prefrontal cortex and right hemisphere which may be dysfunctional with ADHD.[13,36] In addition, the fact that social competence scores, which are an important indicator of the socio-emotional maturation of the child,[37] were associated with all types of ADHD symptoms, points to the important role that limbic system maturation may be playing with ADHD symptoms.[13,38]

The linearity of the association between children's inattention symptoms and the cognitive scores suggests a consistent decrease in points of cognition scores with increasing inattention symptoms. This is an interesting finding which may be indicating a

true causal association (dose-response relationship).[21] In addition, these results raise the question of whether it is always necessary to have a cutoff point to separate children with or without ADHD symptom diagnostic criteria in studies of the general population. This suggests that use of a dimensional approach to study ADHD symptoms in preschoolers may be more appropriate.[4]

One limitation of the study is that although based in a cohort sample, this is a cross-sectional study design. There is no longitudinal data available on the psychological assessments, thus, causal inferences for the interpretation of the associations between outcomes must be made with caution. Another limitation is that we were only able to account for one measure of ADHD symptoms, and the instrument used has not yet been validated for preschoolers. Nevertheless some authors have suggested that where children of at least 4 years of age have attended structured school programs similar to primary school, as in the present study, the ADHD-DSM-IV instrument is adequate in reported by their respective teachers.[4-5]

The strengths of this study are that it is based on two population-based birth cohorts with an 82 % follow up. Also, the fact that these cohorts are not from a clinical population increases the potential for generalizability of the findings.[9] We validated the CPSCS questionnaire and assessed test-retest reliability for ADHD-DSM-IV scores as validation measures of the psychometrical tests used. The two general outcomes (cognitive, social competence) were statistically related to maternal social class and education level, and based on the literature, these findings may be interpreted as a good indicator of the outcome's criterion-related validity.[39]

Clinical implications

These results support that ADHD symptoms are already present in preschoolers. Early preventive action may reduce the risk of future ADHD symptoms and related problems that could compromise the child's development, as well as impacting their adolescence and adulthood.

Future research in preschoolers, including longitudinal data is needed to replicate our findings.

In conclusion, our findings show that preschoolers' ADHD symptoms are associated with concurrent decrements in their neurocognitive and social competence outcomes. The association patterns are similar to the ones found in older children and adults with ADHD symptomology.

Acknowledgement

All teachers and parents of the children from Ribera d'Ebre County and Menorca Island for patiently answering our questionnaires.

All the psychologists that have coordinated the fieldwork.

Raquel Garcia-Esteban for statistical support.

The nurses and administrative personal from the Primary Health Care Center of Mahó and Primary Health Care Center of Flix for administrative, technical and material support.

Lis Ellison-Loschmann for editing assistance.

Funding

This study was supported by "Instituto de Salud Carlos III, Red de Grupos INMA" (G03/176). This study has also been supported in part by the "Fundació 'la Caixa'" (00/077-00), the "Instituto de Salud Carlos III, Red de Centros RCESP" (C03/09) and FIS 041436.

BIBLIOGRAPHY

[1]Furman L. What is attention-deficit hyperactivity disorder (ADHD)? *J Child Neurol* 2005;20:994-1002.

[2]Pineda D, Ardilla A, Rosselli M, et al. Prevalence of Attention-Deficit/Hyperactivity Disorder Symptoms in 4- to 17-year-old children in the general population. *J Abnorm Child Psychol* 1999;27:455-462.

[3]Sonuga-Barke EJ, Dalen L, Remington B. Do executive deficits and delay aversion make independent contributions to preschool attention-deficit/hyperactivity disorder symptoms? *J Am Acad Child Adolesc Psychiatry* 2003;42:1335-42.

[4]Greenfield E, Fischel J. The impact of preschool inattention, hyperactivity, and impulsivity on social and academic development: A review. Clin Child Psychol Psychiatry, 2005;46:755-773.

[5]Pelham W-JR, Chacko A, Wymbs T. Diagnostic and Assessment Issues of Attention Deficit/Hyperactivity Disorder in the Young Child. *Handbook of infant, toddler, and preschool mental health assessment* 399-420. New York, NY, US: Oxford University Press; 2004.

[6]Seidman L. Neuropsychological functioning in people with ADHD across the lifespan. *Clin Psychol Rev* 2006;26:466-485.

[7]Kadesjö C, Kadesjö B, Hägglöf B, Gillberg C. ADHD in Swedish 3- to 7- year-old children. *J Am Acad Child Adolesc Psychiatry* 2001;40:1021-1028.

[8]Nolan EE, Gadow KD, Sprafkin J. Teacher reports of DSM-IV ADHD, ODD, and CD symptoms in schoolchildren. *J Am Acad Child Adolesc Psychiatry* 2001;40:241-9.

[9]Gadow KD, Sprafkin J, Nolan EE. DSM-IV Symptoms in community and clinic preschool children. *J Am Acad Child Adolesc Psychiatry* 2001;40:1383-92.

[10]Gadow KD, Nolan EE. Differences between preschool children with ODD, ADHD, and ODD+ADHD symptoms. *J Child Psychol Psychiatry* 2002;43:191-201.

[11]Berlin L, Bohlin G, Rydell A-M. Relations between inhibition, executive functioning, and ADHD symptoms: A longitudinal study from age 5 to 8 1/2 years. *Child Neuropsychol* 2003;9:255-266.

[12]Baeyens D, Roeyers H, Walle JV. Subtypes of attention-deficit/hyperactivity disorder (ADHD): distinct or related disorders across measurement levels? *Child Psychiatry Hum Dev* 2006;36:403-17.

[13]Stefanatos GA, Wasserstein J. Attention deficit/hyperactivity disorder as a right hemisphere syndrome: Selective literature review and detailed neuropsychological case studies. In Wasserstein JJ & Wolf LE (Eds.), *Adult attention deficit disorder: Brain mechanisms and life outcomes* (pp. 172-195). New York, NY: New York Academy of Sciences; 2001.

[14]Ribas-Fito N, Torrent M, Carrizo D, et al. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. *Am J Epidemiol* 2006;164:955-62.

[15]Julvez J, Ribas-Fitó N, Forns M, Garcia-Esteban R, Torrent M, Sunyer J. Attention behaviour and hyperactivity at age four and duration of breastfeeding. *Acta Paediatr* 2007a (in press).

[16]Julvez J, Ribas-Fitó N, Torrent M, Forns M, Garcia-Esteban R, Sunyer J. Maternal smoking habits and cognitive development of children at age four years in a population-based birth cohort. *Int J Epidemiol* 2007b (in press).

[17]McCarthy D. *Manual for the McCarthy Scales of Children's Abilities*. New York, NY: Psychological Corp.; 1972. Spanish Adaptation (1996), Madrid, Spain: TEA Ediciones, S.A.; 1996.

[18]Baron SI. *Neuropsychological Evaluation of the Child*, 1st ed. New York, NY: Oxford University Press; 2004. 429 pp.

[19]Lezak, MD, Howieson DB, Lorin DW, Hannay JH, Fischer JS. *Neuropsychological Assessment,* 4th ed. London: Oxford University Press; 2004. 1016 pp.

[20]Andrews K, Moore IM, Kaufmann PM, Kramer JH, Matthay K, Hutter JJ. Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: A prospective study. *J Pediatr Psychol* 2001;26:1-9.

[21]Jacobson JL, Jacobson SW. Methodological issues in research on developmental exposure to neurotoxic agents. *Neurotoxicol Teratol* 2005;27:395-406.

[22]Yuan KH, Bentler PM. Normal theory based test statistics in structural equation modelling. *Br J Math Stat Psychol* 1998;51:289-309.

[23]Levin S, Elzey FF, Lewis M (1969), *California Preschool Social Competency Manual*, 1st ed. San Francisco, CA: Consulting Psychologist Press; 1969. 16 pp.

[24]Flint, L.D. Dimensionality of the California Preschool Social Competency Scale. *Applied Psychological Measurement* 1981;4:203-212.

[25]American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).* Washington, DC: American Psychiatric Association; 1994.

[26]Baumgaertel A, Wolraich ML, Dietrich M. Comparison of diagnostic criteria for attention deficit disorders in a German elementary school sample. *J Am Acad Child Adolesc Psychiatry* 1995;34:629-38.

[27]Wolraich ML, Hannah JN, Pinnock TY, Baumgaertel A, Brown J. Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *J Am Acad Child Adolesc Psychiatry* 1996;35:319-24.

[28]Goldman L, Genel M, Bezman R, Slanetz P. Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *JAMA* 1996;279:1100-1108.

[29]Gadow KD, Nolan EE, Litcher L, et al. Comparison of attention-deficit/hyperactivity disorder symptom subtypes in Ukrainian schoolchildren. *J Am Acad Child Adolesc Psychiatry* 2000;39:1520-7.

[30]Campbell S, Ewing L. Follow-up of hard-to-manage preschoolers: Adjustment at age 9 and predictors of continuing symptoms. *J Child Psychol Psychiatry* 1990;31:871-889.

[31]Morgan AE, Hynd GW, Riccio CA, Hall J.Validity of DSM-IV ADHD predominantly inattentive and combined types: relationship to previous DSM diagnoses/subtype differences. *J Am Acad Child Adolesc Psychiatry* 1996;35:325-33.

[32]Faraone SV, Biederman J, Mennin D, Russell R, Tsuang MT. Familial subtypes of attention deficit hyperactivity disorder: a 4-year follow-up study of children from antisocial-ADHD families. *J Child Psychol Psychiatry* 1998;39:1045-53.

[33]Willcutt EG, Hartung CM, Lahey BB, Loney J, Pelham WE. Utility of behavior ratings by examiners during assessments of preschool children with attention-deficit/hyperactivity disorder. *J Abnorm Child Psychol* 1999;27:463-72.

[34]Marks DJ, Berwid OG, Santra A, Kera EC, Cyrulnik SE, Halperin JM. Neuropsychological correlates of ADHD symptoms in preschoolers. *Neuropsychology* 2005;19:446-55.

[35]Yochman A, Ornoy A, Parush S. Co-occurrence of developmental delays among preschool children with attention-deficit-hyperactivity disorder. *Dev Med Child Neurol* 2006;48:483-8.

[36]Krain A, Castellanos X. Brain development and ADHD*. Clin Psychol Rev* 2006;26:433-444.

[37]Izard C, Fine S, Schultz D, et al. Emotion knowledge as a predictor of social behavior and academic competence in children at risk. *Psychol Sci* 2001;12:18-23.

[38]Mesulam M. Behavioral Neuroanatomy: Large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations. In Mesulam M (ed.), *Principles of behavioral and cognitive neurology,* 2nd ed. (pp. 172-195). London: Oxford University Press; 2000.

[39]Bornstein MH, Bradley RH. *Socioeconomic status, parenting, and child development.* Mahwah, NJ: Lawrence Erlbaum Associates, Publishers; 2003. 287 pp.

Table 1. Covariates of interest (percentage) by ADHD-DSM-IV symptom score groups (n=467)

COVARIATES FROM PREGNANCY TO 4TH YEAR		ADHD-DSM-IV Symptom Groups				
		No Symptoms (n=214)	Symptoms without Criteria (n=178)	Diagnostic Criteria for General ADHD Symptoms (n=75)	Diagnostic Criteria for Inattention Symptoms (n=40)	Diagnostic Criteria for Hyperactivity Symptoms (n=20)
CHILD						
Sex**	Female	60.8	46.9	23.0	22.5	20.0
Low gestational age	<37 weeks	3.3	5.1	5.4	5.0	10.0
Low birth weight	<2.5 kg	7.1	5.1	6.8	2.5	10.0
Duration of Breastfeeding >20 weeks**		47.9	31.4	32.9	35.9	35.0
Age during test administration (median)		4.6	4.5	4.5	4.5	4.6
Kindergarten before one year of age		21.7	17.9	20.8	13.2	35.0
Location*	Menorca (n=386)	87.7	76.4	82.7	87.5	80.0
MOTHER						
Social Class**	Highly Skilled	15.9	12.4	11.3	0.0	20.0
	Skilled	50.0	42.6	39,4	47.4	20.0
	Partly skilled and Unskilled	12.5	17.7	23.9	26.3	35.0
	Unemployed	21.6	27.2	25.3	26.3	25.0
Education level*	Secondary & High, >=12 years	48.6	42.1	33.8	34.3	36.8
	Less than Secondary, <12 years	51.4	47.9	66.2	65.7	63.2
Parity**	Older brothers or sisters at study child's age 4yrs	46.2	52.5	55.4	57.5	45.0
	Number of siblings at study child's 4 yrs of age (excludes study child)					
	2 or more	13.3	19.3	22.0	28.9	10.0
Marital status at age 4	Without a stable partner	6.1	7.4	8.2	10.5	5.0
Smoking	During pregnancy	17.9	23.2	27.0	25.0	30.0
	At age 4	28.3	33.5	38.7	35.0	30.0
Alcohol consumption during pregnancy		23.1	25.4	27.0	32.5	20.0
FATHER						
Social Class (%)	Highly Skilled	17.9	15.5	20.0	10.8	30.0
	Skilled	66.5	58.2	60.0	64.9	50.0
	Partly skilled and Unskilled	15.6	25.9	20.0	24.3	20.0
Education level (%)	Secondary & High, >=12 years	38.7	37.9	33.3	22.2	47.4
	Less than Secondary, <12 years	61.3	62.2	66.7	77.8	52.6
Age in years at child's birth (mean)		32.5	32.7	33.1	34.0	31.4

** P-value<0.05 and * P-value<0.10 for X^2 tests of differences of percentages or F tests of mean differences, both, by ADHD-DSM-IV symptom categories.

Children with diagnostic criteria for Mixed type symptoms (n=15) are not shown in the table (which showed similar covariate distributions as Inattentive type group).

Table 2. Crude medians of child's psychological outcome variables at 4 years of age by five ADHD-DSM-IV symptom score groups (Ribera d'Ebre & Menorca, N=467)

OUTCOME SCORES AT 4 YEARS OF AGE (N)	No Symptoms (214)	ADHD Symptoms but no Criteria (178)	Diagnostic Criteria for General ADHD Symptoms (75)	Diagnostic Criteria for Inattention Symptoms (40)	Diagnostic Criteria for Hyperactivity Symptoms (20)
GLOBALS					
Cognitive (MCSA) ‡	100.8	100.1	**94.2**	**89.1**	104.5
Social Competence (CPSCS) †	109.0	**98.3**	**81.4**	**78.8**	**95.6**
SUBSCALES					
Developmental Neuropsychology (MCSA)					
Verbal (Global) ‡	101.7	101.7	**96.6**	**92.1**	103.0
Perceptual-performance (Global) ‡	102.2	**100.3**	**94.5**	**87.7**	106.1
Quantitative (Global) ‡	99.0	95.9	**92.8**	**89.7**	94.4
Memory (Global) ‡	100.5	100.5	**98.6**	**92.6**	104.5
Span	102.1	102.1	**98.6**	**93.3**	102.1
Working Memory †%	24%	21%	**8%**	**5 %**	15 %
Verbal Memory †	99.4	104.4	99.4	**94.5**	106.8
Motor skills (Global) ‡	102.9	**98.5**	**98.5**	**90.8**	108.4
Gross Motor skills †	100.1	98.3	100.1	**94.9**	108.8
Fine Motor Skills	101.1	97.6	**94.2**	**87.3**	106.3
Executive Function (Global)	102.3	99.6	**92.9**	**86.8**	102.3
Verbal Executive Function	101.0	99.2	**93.8**	**89.3**	98.3
Visual-perceptive Executive Function	104.1	100.5	**93.3**	**88.0**	104.1
Cognitive Functions of Posterior Cortex (CFPC) (Global)	99.7	102.7	**95.3**	**86.4**	107.1
Verbal CFPC †	100.6	102.8	98.4	**94.0**	107.2
Visual-performance CFPC	100.0	100.0	**96.9**	**87.5**	107.9
Social Competence (CPSCS)					
F1 (Considerateness)	108.3	**101.2**	**80.1**	**87.2**	**78.4**
F2(Task Orientation)	108.2	**99.8**	**80.1**	**77.2**	**102.6**
F3 (Extraversion)	101.3	101.3	**86.9**	**86.8**	108.6
F4 (Verbal Facility) †	110.5	**102.7**	**87.1**	**79.3**	**94.9**
F5 (Response to Unfamiliar) †	107.2	**98.6**	**90.0**	**90.0**	102.9

Children with diagnostic criteria for Mixed type symptoms (n=15) are included in the models but data not shown. They showed similar results as Inattentive type group.

All normal distributed MCSA data is standardized (Mean:100; SD:15).

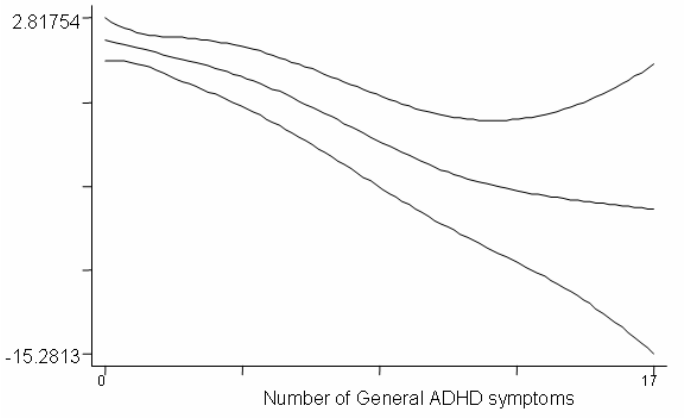
Bold = P-value <0.05.

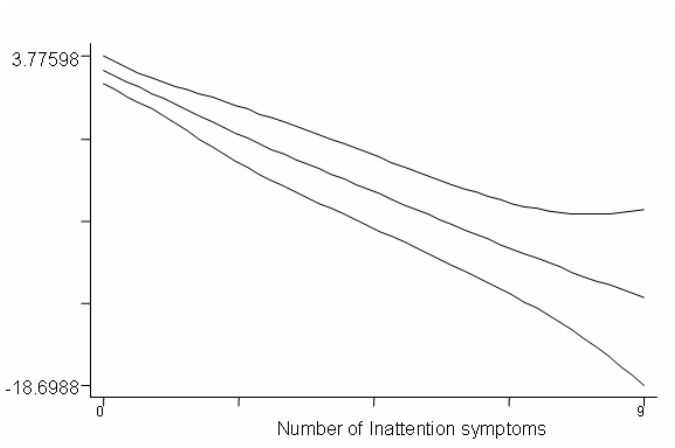
† Non-normal distribution.

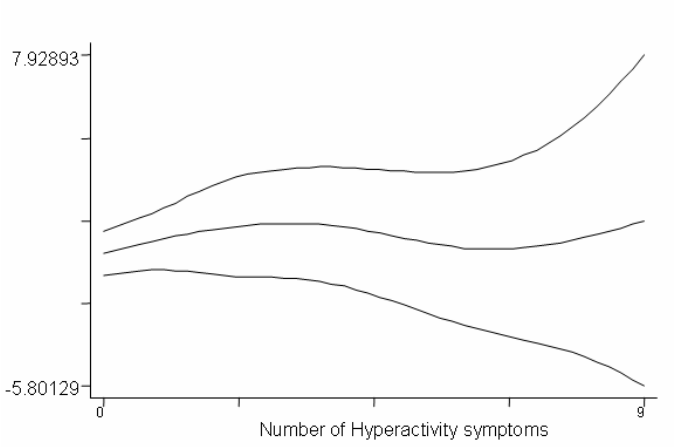
% Percentage, cut-off point corresponds percentile 80.

‡ MCSA conventional indexes.

Figure 1. Adjusted non-parametric associations between ADHD-DSM-IV symptom scores (General, Inattention and Hyperactivity) and children's MCSA's general cognitive outcome scores







Adjusted for: mother's social class and father's education level, mother's parity at child's age 4 years, mother's marital status, maternal alcohol consumption and tobacco smoking during pregnancy, maternal smoking at child's age 4 years, child's gender, child's duration of breastfeeding, child's age when started kindergarten, child's age and school season during test assessment, evaluator (psychologist) and child's home location at age 4 years.

Table 3. Adjusted children's outcome scores[†] (coefficient (β) or odds ratio (OR)) of ADHD-DSM-IV symptom scores (Ribera d'Ebre & Menorca, N=467)

	ADHD-DSM-IV Symptom Score					
	CATEGORICAL			CONTINUOUS (N=467)		
Neuropsychological Functions (MCSA)	**Diagnostic Criteria for General ADHD Symptoms (n = 75)**	**Diagnostic Criteria for Inattention Symptoms (n = 40)**	**Diagnostic Criteria for Hyperactivity Symptoms (n = 20)**	**General ADHD Symptoms**	**Inattention Symptoms**	**Hyperactivity Symptoms**
GENERAL COGNITIVE [‡] [β]	**-8.7**	**-13.7**	-0.5	**-0.6**	**-1.8**	0.1
GLOBAL VERBAL [‡] [β]	**-5.6**	**-10.8**	0.7	-0.3	**-1.3**	0.6
GLOBAL PERCEPTUAL-PERFORMANCE [‡] [β]	**-8.6**	**-12.9**	1.0	**-0.7**	**-1.7**	-0.2
GLOBAL QUANTITAVE INDEX [‡] [β]	**-9.4**	**-11.3**	-5.1	**-0.9**	**-1.8**	-0.5
GLOBAL MEMORY [‡] [β]	**-4.7**	**-9.3**	0.5	-0.2	**-1.2**	0.5
VISUAL & VERBAL SPAN [β]	**-5.0**	**-9.0**	-0.6	-0.3	**-1.2**	0.4
WORKING MEMORY [β]	**4.6**	**5.0**	3.8	**1.1**	**1.3**	1.1
VERBAL MEMORY [OR]	0.8	1.2	0.7	1.0	1.0	**0.9**
GLOBAL MOTOR SKILLS [‡] [β]	**-6.5**	**-12.2**	4.2	**-0.5**	**-1.4**	0.4
GROSS MOTOR SKILLS [OR]	**2.7**	**4.0**	0.3	**1.1**	**1.2**	1.0
FINE MOTOR SKILLS [β]	**-6.0**	**-9.9**	2.1	**-0.5**	**-1.2**	-0.2
GLOBAL EXECUTIVE FUNCTION [β]	**-9.4**	**-13.0**	-2.1	**-0.7**	**-1.7**	-0.1
VERBAL EXECUTIVE FUNCTION [β]	**-7.9**	**-10.8**	-2.4	**-0.5**	**-1.5**	0.0
VISUAL-PERFORMANCE EXECUTIVE FUNCTION [β]	**-9.1**	**-12.7**	-0.8	**-0.7**	**-1.7**	-0.1
GLOBAL COGNITIVE FUNCTIONS OF POSTERIOR CORTEX (CFPC) [β]	**-6.6**	**-12.4**	1.7	**-0.5**	**-1.6**	0.3

Table 3. (cont.)

	ADHD-DSM-IV Symptom Score					
	CATEGORICAL			CONTINUOUS (N=467)		
	Diagnostic Criteria for General ADHD Symptoms (n = 75)	Diagnostic Criteria for Inattention Symptoms (n = 40)	Diagnostic Criteria for Hyperactivity Symptoms (n = 20)	General ADHD Symptoms	Inattention Symptoms	Hyperactivity Symptoms
Social Competence (CPSCS) [β]	**-24.5**	**-26.9**	**-13.0**	**-2.2**	**-4.1**	**-1.9**
F1 (CONSIDERATENESS) [β]	**-23.3**	**-18.2**	**-23.6**	**-2.4**	**-3.2**	**-3.6**
F2 (TASK ORIENTATION) [β]	**-21.8**	**-28.2**	**-5.7**	**-1.8**	**-4.0**	**-1.0**
F3 (EXTRAVERSION) [β]	**-9.5**	**-15.1**	3.7	**-0.7**	**-2.2**	0.4
F4 (VERBAL FACILITY) [OR]	**15.5**	**20.5**	**8.8**	**1.2**	**1.5**	**1.2**
F5 (RESPONSE TO UNFAMILIAR) [OR]	**6.0**	**7.9**	1.3	**1.2**	**1.4**	1.1

Reference group for categorical ADHD-DSM-IV Symptom Score Groups (Re, n = 212) always refers to those children without any symptom during fourth year assessment.

Children with symptom scores but without meeting diagnostic criteria for DSM-IV (n=178) and children with diagnostic criteria for Mixed type symptoms (n=15) are included in the models but data not shown.

Odds ratio equals 1 for Re in logistic regressions.

Average outcome score for reference group (intercept) was approximately 105 for all linear regressions.

Bold = P-value<0.05

For ORs the cut-off corresponds to percentile 20 (reference group >PC20), except for Working Memory outcome that is percentile 80 (reference group>PC80).

All normal distributed data is standardized (Mean: 100; SD: 15).

† Each line is five models adjusted for same covariates as Figure 1.

‡ MCSA conventional indexes.

Table 4. Mutual adjusted MCSA outcome scores (coefficient (β)) of general ADHD-DSM-IV symptom diagnostic criteria score group (Ribera d'Ebre & Menorca, n=467)

(n, Re = 212)	**GENERAL ADHD-DSM-IV SCORE GROUP (n = 75)**	
MCSA OUTCOMES:	**Coefficient**	**Coefficient †**
Global Verbal	**-5.6**	0.6
Global Perceptive-Performance	**-8.6**	**- 4.4**
Global Quantitative	**-9.4**	**- 1.4**
Global Executive Function	**-9.4**	**- 4.8**
Global Cognitive Functions of Posterior Cortex	**-6.6**	- 0.4

Reference group (Re) always refers to those children without any ADHD-DSM-IV symptom score. Children with symptom scores but without meeting diagnostic criteria for DSM-IV (n=178) are included in the model but data not shown.

Re = around 105, it is the same as in table3.

All multivariable models were also adjusted for the corresponding covariates listed in Figure 1.

Bold = P-value<0.05.

† It shows the adjusted coefficients for each other outcomes. The first set includes the first three outcomes in a unique regression model. The second set includes the last two outcomes in a unique regression model.

6. PAPER # 3

Julvez J, Ribas-Fitó N, Forns M, Garcia-Esteban R, Torrent M, Sunyer J. Attention behavior and hyperactivity at age 4 and duration of breast-feeding. *Acta Paediatrica* 2007 Jun;96(6):842-7.

Julvez J, Ribas-Fitó N, Forns M, Garcia-Esteban R, Torrent M, Sunyer J.
Attention behaviour and hyperactivity at age 4 and duration of breast-feeding.
Acta Paediatr. 2007 Jun;96(6):842-7.

Comment in:
Acta Paediatr. 2007 Jun;96(6):796-7.

7. PAPER # 4

Ribas-Fitó N, Julvez J, Torrent M, Grimalt JO, Sunyer J. Benefits of Breastfeeding on Cognition regardless DDT concentrations at birth. *American Journal of Epidemiology* (accepted).

Dear Dr. Nuria Ribas-Fito,

I am pleased to tell you that your manuscript (AJE-00297-2007.R2) entitled, "Benefits of Breastfeeding on Cognition regardless DDT concentrations at birth", has been accepted for publication in the American Journal of Epidemiology.

The American Journal of Epidemiology editorial office staff will be in touch with you to discuss further plans for publication.

Congratulations,

Dr. Mark Klebanoff
Editor, AJE

American Journal of Epidemiology
410-223-1649
410-223-1620 (FAX)
http://mc.manuscriptcentral.com/aje

BENEFITS OF BREASTFEEDING ON COGNITION REGARDLESS DDT CONCENTRATIONS AT BIRTH

Accepted Date

13-6-2007

UNING HEAD

Breastfeeding, DDT and cognitive functioning at age 4

WORD COUNT

Abstract: 190 words

Text: 1885 words

References: 27

Tables: 2

ABSTRACT

RATIONALE: We have previously reported that intrauterine exposure to background concentrations of DDT reduces the cognitive performance among preschoolers. Breastfeeding has been associated to both an increased exposure during infancy to certain pollutants and to a better performance in the cognitive tests. OBJECTIVE: To examine the role of breastfeeding on cognitive function among preschoolers taking into account the prenatal DDT exposure. METHODS: Two birth cohorts in Ribera d'Ebre and Menorca (Spain) were recruited between 1997-1999 (n=391). Infants were assessed at age 4 years using the McCarthy Scales for Infant Development. Organochlorine compounds were measured in cord serum. Information on type and duration of breastfeeding was obtained through questionnaire when the child was one year. RESULTS: Children who were breastfed for more than 20 weeks had a better cognitive performance regardless their in utero exposure to DDT. A linear dose response between breastfeeding and cognition was observed in all DDT groups (adjusted β for high exposed to DDT (SE) = 0.30 (0.12) per week breastfed).
CONCLUSIONS: Despite the possibility of harm from environmental contaminants in breast milk, breastfeeding for long periods should be still recommended as the best infant feeding method.

KEY WORDS

DDT, neurodevelopment, children, mental, cognitive, preschoolers, intelligence, breastfeeding

INTRODUCTION

Breastfeeding is the preferred and promoted mode of feeding during the firsts weeks of life and has been described to be beneficial for children's cognitive development (1-4). Beast milk contains all the necessary nutrients and immunological components that the infant needs (5). However, due to its fat composition, accumulates and harbors persistent organohalogens, including persistent organic pollutants (POPs), heavy metals, and volatile solvents (6,7).

Some organochlorine compounds (OCs) are recognized causes of neurodevelopmental impairments and subclinical brain dysfunction. Exposure to these chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brain function (8). The role of breastfeeding in the relationship between exposure to chemicals and children's neurodevelopment is yet to be clarified.

We have previously reported that the longer time a child has been breastfed, the higher their concentrations of DDT at age 4 are (9) and that intrauterine exposure to background concentrations of DDT reduces the cognitive performance among preschoolers (10) while breastfeeding increases (11). Since breastfeeding plays an important role in both children exposure to environmental pollutants and children's cognitive performance, we aim to assess the role of breastfeeding on intelligence while taking into account concentrations of DDT at birth.

METHODS

Characteristics of the population have been described elsewhere (10,11). Two different Spanish cohorts were included in this analysis. The Ribera d'Ebre cohort recruited all healthy singleton children born in the main hospital of the study area from March 1997 to December 1999. 102 children were enrolled and 76 provided complete outcome data for the four year visit (75%). The Menorca cohort was set up in 1997 within the Asthma Multicenter Infants Cohort study (12) and recruited all women presenting for antenatal care over 12 months starting in mid 1997. 482 healthy children were subsequently enrolled and 402 (83%) provided complete outcome data up to the fourth year visit. Among children from both cohorts with completed data, cord serum could be obtained from 391 neonates (82%). Serum at 4 years was obtained from 343 children. This study was approved by the ethics committee of the Institut Municipal d'Investigació Mèdica and all mothers provided a signed informed consent.

Neuropsychological testing of the children at age 4 (mean age 4.4 yrs in Ribera d'Ebre and 4.3 yrs in Menorca) was performed by three certified psychologists (one for the Ribera d'Ebre cohort and two for the Menorca cohort) (10). The staff involved in the neuropsychological testing did not know the degree of exposure to organochlorine compounds of the child or the type and duration of feeding. Cognitive development was measured with the Spanish version of the McCarthy Scales of Children's Abilities (MCSA) (13) that provides information on cognitive and motor abilities.

A gas chromatograph with electron capture detection (Hewlett Packard 6890*N* GC-ECD) was used to quantify *p,p'*-DDT, p,p'-DDE and other organochlorine compounds as described elsewhere (9). Quantification was performed using external standards, with the PCB142 injection standard used to correct for volume. Recovery of TBB and PCB209 (75-115%) was used to correct results. Limits of detection (LOD) were 0.02 ng/ml. A value of 0.01 ng/ml was given for the non quantifiable concentrations. Serum samples were stored

at – 40 ^{0}C until analysis. All the analyses were carried out in the Department of Environmental Chemistry (IIQAB-CSIC) in Barcelona, Spain.

Interviewer-administered questionnaires were completed with mothers to assess duration of exclusive breastfeeding; twice in the Ribera d'Ebre cohort, at age 1 year and age 4 years; and three times in the Menorca cohort, at age 6 months, 14 months and 2 years after delivery. No significant differences were found between the surveys. Duration of breastfeeding was categorized in three groups. The reference group included all children that were not breastfed or breastfed for less than 2 weeks. The other two 'breastfeeding' groups were defined according to the median (between 2 and 20 (short-term), and more than 20 weeks (long-term)). Information on other covariates have been described elsewhere (10).

Neurodevelopment scores followed a normal distribution, while serum OC levels were skewed to the right and were normalized by logarithmic transformation. DDT concentrations at birth were categorized in 3 categories (≤ 0.05 ng/ml; > 0.05 to 0.20; and > 0.20 ng/ml). The scores obtained from the McCarthy test were examined in relation to level of OCs and the study variables using linear regression models.

Gender, scholar trimester, psychologist, age at examination in days, maternal social class, maternal education and maternal consumption of alcohol and tobacco during pregnancy were the variables that met the criteria for confounding (when adjustment for an additional variable altered the breastfeeding coefficient by 10% or more in the models). Interaction between breastfeeding and DDT (or DDE) was checked by including an interaction term in the models. Dose-response relationship was assessed using Generalized Additive Models (GAM) modeling. All statistical analyses were conducted with the STATA 8.0 statistical software.

RESULTS

The percentage of children breastfeeding for more than 2 weeks was 70.8% with a duration average of 22.9 weeks. McCarthy scoring at age 4 and concentrations of DDT and DDE at birth according to type and duration of breastfeeding are presented in table 1. Children with longer periods of breastfeeding performed better in the cognitive scales of the McCarthy test. Concentrations of DDT and DDE at birth were not different between the breastfeeding groups. At 4 years, the DDT and DDE concentrations increased according to duration of breastfeeding. Maternal social class, education level and smoking during pregnancy were associated with duration of breastfeeding.

Table 2 shows the adjusted association between breastfeeding and the general cognitive, the verbal and the memory McCarthy scoring according to exposure to DDT. Breastfeeding improved child cognitive development among all infants and both children in the lowest, medium and highest group of DDT exposure had better cognitive skills after long-term breastfeeding, although only statistically significant among those children with higher exposures. Long term breastfeeding was also found to be beneficial for the quantitative and perceptual-performance scales among those children with high exposures ($\beta_{quantitative}$ (SE) = 2.99 (1.39) and $\beta_{perceptual\text{-}performance}$ (SE) = 5.56 (2.34)). A linear dose response between breastfeeding and cognition was observed regardless the DDT exposure of the child (non-linearity chi-square using GAM modeling > 0.10; β for high exposed to DDT (SE) = 0.30 (0.12) per week breastfed). DDE was not found to affect the child intelligence. There was no statistically significant interaction between duration of breastfeeding and prenatal exposure to DDT (p=0.14). The benefits of breastfeeding were significant in both genders. No association was found between DDT (p=0.65) or DDE (p=0.46) at 4 years and child cognitive scoring.

DISCUSSION

Breastfeeding is associated with an increase in the preschoolers' cognition performance while DDT is associated with a lower performance in the McCarthy Scale. The benefit of breastfeeding on child cognition was present regardless the child DDT exposure.

As described in multiple studies (1-4), breastfeeding alone was found to be beneficial for children's neurodevelopment. Children who were formula fed or breastfed for less than two weeks performed worst in the cognitive areas. The reasons for this difference might be because breast milk contains superior nutrients (14-16) than formula milk or by the frequency of physical and psychological contact between mothers their infants during the breastfeeding process (17). Alternatively, it has been suggested that variables such as maternal education, intelligence or income might mediate much of the observed association between breastfeeding and cognition (18).

The role of breastfeeding on children's health has become a controversial issue due to the possibility of harm from environmental contaminants in breast milk (19). Children that are breastfed have a continuous exposure to the contaminant than those who are formula fed (9) and the concentrations of DDT and DDE at 4 years are much higher among those children who are longer-term breastfed. It is difficult to disentangle the negative role of breastfeeding (the contaminants) versus its positive role (the nutrients). One study found that despite the high PCB and dioxin levels transferred via breast milk, breastfeeding seemed to have a beneficial effect on neurologic status compared with formula feeding (20,21). Walkowiak et al. (22) found that mental and motor development between 7 and 42 months of age has a significant negative association with PCB concentration in early human milk. We described in a previous study with children from the Ribera d'Ebre cohort that long-term breastfeeding was found to be beneficial to neurodevelopment at one year, potentially counterbalancing the impact of exposure to these chemicals through breast milk (23). In this study, when children were 4 years of age, we also found that long term breastfeeding was beneficial for child development

regardless the concentration of DDT in cord serum. These results suggest that breastfeeding did not increase the neurotoxicological risk through a potential DDT exposure via breast milk. One explanation could be that the breast milk nutrients could be counterbalancing the negative effect of DDT. Another explanation could be related to the kinetics of these contaminants in colostrum, transitional milk or mature milk. Unfortunately, we did not collect colostrum and mature milk from this mother-infant pairs to understand the patterns of exposure. In any case, concentrations of DDT at 4 years were not associated with a decrease in the cognitive skills and only the prenatal exposures were the ones associated with a potential harm on neurodevelopment.

A potential limitation of the present study is the non-response rate (17%). However, in most cases, subjects were not included (n=77) because of the small quantity of sera in the repository aliquots of cord serum. Geographical differences between Menorca and Ribera d'Ebre were eliminated by analyzing the data by cohort. The results using the Menorca cohort alone showed no differences compared to the two-cohort analyses, and the results from the Ribera d'Ebre cohort alone were in the same direction but not statistically significant (10). This lack of significance could be explained by the small size of the cohort. Recall bias cannot be discarded since information was obtained retrospectively. However, one study found more than 98% agreement between responses at age 3 and data recorded prospectively by nurses (24). Information for this study was obtained at 6 or 12 months. Duration of breastfeeding was obtained through questionnaires and a reporting bias also needs to be considered. The results could be biased if better-educated mothers can report their breastfeeding behaviors more accurately. We are unaware of any literature that documented a connection between breastfeeding recall and education. Education was included in all models.

Residual confounding cannot be discarded since inclusion of social class and education level in the models might not have removed part of parental IQ variance associated with their children's IQ (25). Unfortunately parental IQ could not be measured in the Menorca cohort. In the Ribera d'Ebre maternal IQ was not associated with child

neurodevelopment. We neither assessed the home environment with a standardized tool such as the HOME Inventory (26) because of cross-cultural differences.

More information regarding DDT and other pollutants in breast milk and their effect on infant development is needed to provide recommendations for clinical practice, and promote environmental and public health policies that reduce human exposure to dangerous pollutants (27). Overall, despite the possibility of harm from environmental contaminants in breast milk, breastfeeding for long periods should be still recommended as the best infant feeding method, even in developing countries where DDT spraying is currently being undertaken and population impregnation is much higher.

Acknowledgements

We thank all the study participants for their generous collaboration. We are also indebted to Carlos Mazón, Mrs. Rosa M. Sabaté and Mrs. Maria Victoria Iturriaga for their assistance in contacting the families and administering the questionnaires. This study was funded by grants from the Spanish Ministry of Health (FIS-97/1102, FIS-97/0588, FIS-00/0021-02 and FIS-PI041436, Instituto de Salud Carlos III (Red RCESP C03/09 and Red INMA G03/176), “Fundació La Caixa” (97/009-00 and 00/077-00), European Comission (Concerted Action, contract number QLK4-2000-00263) and the Generalitat de Catalunya-CIRIT 1999SGR 00241.

We declare no conflict of interest.

References

1. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. Am J Clin Nutr. 1999;70:525-535
2. Jain A, Concato J, Leventhal JM. How good is the evidence linking breastfeeding and intelligence? Pediatrics. 2002;109:1044-53.
3. Reynolds A. Breastfeeding and brain development. Pediatr Clin North Am. 2001;48:159-171
4. Drane DL, Logemann JA. A critical evaluation of the evidence of the association between type of infant feeding and cognitive development. Paediatr Perinat Epidemiol. 2000;14:349-356
5. Newton ER. Breastmilk: the gold standard. Clin Obstet Gynecol. 2004;47:632-42
6. Jensen AA. Levels and trends of environmental chemicals in human milk. In: Jensen AA and Sorach SA, Editors. Chemical contaminants in human milk, CRC Press, Boca Raton (FL). 1991; 24–198
7. Ribas-Fitó N, Grimalt JO, Marco E et al. Breastfeeding and concentrations of HCB and p,p'-DDE at the age of 1 year. Environ Res. 2005;98:8-13.
8. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet. 2006;368:2167-78
9. Carrizo D, Grimalt JO, Ribas-Fito N et al. Physical-chemical and maternal determinants of the accumulation of organochlorine compounds in four-year-old children. Environ Sci Technol. 2006;40:1420-6
10. Ribas-Fitó N, Torrent M, Carrizo D et al. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. Am J Epidemiol. 2006;164:955-62
11. Júlvez J, Ribas-Fito N, Forns M et al. Attention behaviour and hyperactivity ata ge 4 and duration of breast-feeding. Acta Paediatr. 2007; 96:842-7

12. Polk S, Sunyer J, Munoz-Ortiz L et al. A prospective study of Fel d1 and Der p1 exposure in infancy and childhood wheezing. Am J Respir Crit Care Med. 2004;170:273-8.
13. McCarthy D. Manual for the McCarthy Scales of Children's Abilities. New York, NY, Pa: Psychological Corp; 1972. (Spanish Adaptation: Madrid, Spain, Pa: TEA Ediciones, S.A.; 1996)
14. Uauy R, Periano P. Breast is best: human milk is the optimal food for brain development. Acta Paediatr Suppl. 203;92:11-18
15. Carlson SE. Long-chain polyunsaturated fatty acids and development of human infants. Acta Paediatr Suppl. 1999;88:72-7
16. Gustafsson PA, Duchen K, Birberg U et al. Breastfeeding, very long polyunsaturated fatty acids (PUFA) and IQ at 6 ½ years of age. Acta Paediatr. 2004;93:1280-7
17. Feldman R, Eidelman AI. Direct and indirect effects of breast milk on the neurobehavioral and cognitive development of premature infants. Dev Psychobiol 2003;43:109-119
18. Gibson-Davis CM, Brooks-Gunn J. Breastfeeding and verbal ability of 3-year-olds in a multicity sample. Pediatrics. 2006;118:e1444-1451
19. Solomon GM, Weiss PM. Chemical contaminants in breast milk: time trends and regional variability. Environ Health Perspect. 2002; 110: A339−A347
20. Koopman-Esseboom C, Weisglas-Kuperus N, deRidder MAJ et al. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants mental and psychomotor development. Pediatrics 1996; 97:700–706
21. Patandin S, Lanting CI, Mulder PGH et al. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr. 1999; 134:33–41.
22. Walkowiak J, Wiener J, Fastabend A et al. Environmental exposure to polychlorinated biphenyls and quality of the home environment Effects on psychodevelopment in early childhood. Lancet. 2001; 358:1602–1607

23. Ribas-Fitó N, Cardo E, Sala M et al. Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. Pediatrics. 2003; 111:e580-5.
24. Sears MR, Taylor DR, Poulton R. Breastfeeding and asthma: appraising the controversy--a rebuttal. Pediatr Pulmonol 2003;36:366-8
25. MgGue M, Bouchard Jr TJ , Iacono WG et al. Behavioral genetics of cognitive ability: a life-span perspective. In: Plomin R, McClearn EG, eds. Nature, Nurture and Psychology. Washington, DC, Pa: American Psychological Association; 1993:59-76
26. Bradley RH, Caldwell BM. Home Observation for Measurement of the Environment: Administration Manual. Little Rock, AR: University of Arkansas; 1984
27. Nickerson K. Environmental contaminants in breast milk. J Midwifery Womens Health.2006;51:26-34

Table 1. Crude McCarthy scoring at four years and concentrations of DDT at birth (median (IQ range)) according to duration of breastfeeding

	Duration of Breastfeeding in Weeks			
	< 2	2-20	> 20	p-trend
	n=77	n=162	n=152	
Mc Carthy				
General Cognitive	104 (93-118)	106 (92-118)	110 (101-126)	0.001
Verbal	46 (39-58)	48 (40-56)	51 (45-60)	0.012
Perceptual-Performance	39 (34-45)	40 (36-44)	42 (38-49)	0.003
Memory	22 (19-27)	23 (19-28)	25 (20-30)	0.033
Quantitative	17 (14-19)	17 (15-21)	18 (15-22)	0.005
Motor	34 (31-39)	34 (31-39)	36 (30-40)	0.41
Concentrations of DDT and DDE				
At birth				
DDT (ng/ml)	0.07 (0.04-0.27)	0.07 (0.04-0.23)	0.06 (0.03-0.14)	0.09
DDE (ng/ml)	0.94 (0.49-1.94)	1.07 (0.56-2.02)	1.01 (0.62-1.77)	0.69
At 4 years†				
DDT (ng/ml)	0.02 (0.01-0.04)	0.04 (0.01-0.08)	0.06 (0.03-0.14)	0.001
DDE (ng/ml)	0.37 (0.22-0.54)	0.72 (0.41-1.29)	1.57 (0.80-2.49)	0.001

† N were 68, 138 and 137, respectively

Table 2. Adjusted change¶ (coefficient and 95% confidence intervals) in the general cognitive, the verbal and the memory McCarthy areas scoring by breastfeeding (in weeks) according to exposure to DDT at birth

	All population	Low exposed < 0.05 ng/ml	Mid exposed 0.05-0.20 ng/ml	High exposed > 0.20 ng/ml
	n=391	n=162	n=138	n=91
General Cognitive				
Reference †	*103.98*	109.04	100.32	91.91
Short-term Breastfeeding	*1.90 (2.57)*	2.11 (4.21)	0.35 (4.74)	3.79 (5.09)
Long-term Breastfeeding	*7.66 (2.66)**	5.69 (4.53)	6.90 (4.86)	13.04 (5.83)*
Verbal				
Reference †	*48.26*	50.97	46.74	38.61
Short-term Breastfeeding	*0.28 (1.54)*	0.48 (2.54)	-0.91 (2.80)	2.27 (3.07)
Long-term Breastfeeding	*3.10 (1.60)*	2.21 (2.74)	2.41 (2.70)	5.92 (3.53)
Memory				
Reference †	*21.26*	23.46	19.33	15.73
Short-term Breastfeeding	*0.37 (1.01)*	0.87 (1.63)	-0.24 (1.89)	1.15 (2.06)
Long-term Breastfeeding	*2.03 (1.05)*	0.85 (1.75)	2.22 (1.81)	3.13 (2.37)

* p-value < 0.05

¶ Adjusted for gender, scholar trimester at examination, psychologist, maternal social class, maternal education and maternal consumption of alcohol and tobacco during pregnancy.

† Scoring in infants who were breastfed for less than 2 weeks

8. PAPER # 5

Julvez J, Ribas-Fito N, Torrent M, Forns M, Garcia-Esteban R, Sunyer J. Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. *International Journal of Epidemiology* 2007 Jun 5;[Epub ahead of print].

Julvez J, Ribas-Fitó N, Torrent M, Forns M, Garcia-Esteban R, Sunyer J.
Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort.
Int J Epidemiol. 2007 Aug;36(4):825-32. Epub 2007 Jun 5.

Comment in:
Int J Epidemiol. 2007 Aug;36(4):832-3.

9. GENERAL DISCUSSION

Overall, we have been able to find a range of scores of mental health in preschoolers consistent with cognitive development, ADHD symptoms and social competence. Breastfeeding appears to improve all these outcomes, some of which were assessed for the first time, while maternal smoking during pregnancy impairs some of them. Studying neurodevelopment from early life appears to be a powerful tool for assessing the early effects of environment.

9.1. Psychometric characteristics of the outcomes

Because a Catalan-Spanish version of the California scale (CPSCS) was non-existent prior to the commencement of this work, we translated and adapted it to our cultural context, and then, studied its psychometric characteristics among the two cohorts. It showed acceptable goodness of fit indexes for construct validity, after using CFC to test if the original underlying structure fitted into our data. The scale was composed of five factors: Considerateness, Task Orientation, Extraversion, Verbal Facility and Response to Unfamiliar (Flint, 1981). CPSCS criterion-related validity was also demonstrated since the scale showed significant associations with some determinants commonly documented to be associated with children's social competence scores: children's IQ scores, and gender, maternal social class and level of education (Rourke et al., 1991; Nigg et al., 1998;). Finally, the one month interval test-retest reliability was also found to be acceptable, indicating that the scale scores were consistent.

The other assessed outcomes, standardized for use in our socio-cultural context, were also submitted to some degree of validity analysis. All the ADHD-DSM-IV scale scores showed good internal consistency and reliability. MCSA global cognitive score also showed good internal consistency. The newly created MCSA subscales following a-priori neuropsychological knowledge (i.e., verbal memory, memory span, working memory, gross and fine motor skills, executive functions and cognitive functions of posterior cortex) and have enhanced the interpretation of the findings, since they were sensitive to the specificity of the associations obtained. MCSA executive function was also statistically validated and showed good fitting indexes when its construct validity was assessed by CFA.

9.2. Neurodevelopment among preschoolers

Neurodevelopment among preschoolers is less documented than for that of their older counterparts (Greenfield et al., 2005). ADHD is the most common disorder in childhood and some authors have suggested that the symptoms of this disorder may be detected in children before age six years old (Furman et al., 2005; Greenfield et al., 2005). Thus, it is important to study if children with ADHD symptoms from the cohorts showed similar neurobehavioral patterns to those documented in older children.

The results showed an increased prevalence of ADHD symptoms was associated with male gender, a negative linear association was found between ADHD symptoms (particularly inattentive type) and most of the neurocognitive outcomes (especially executive function and perceptive-performance functions); and, the social competence was strongly associated with all types of ADHD

symptoms. These findings suggest the possibility that ADHD symptoms consolidate before a child reaches six years of age since they showed similar prevalence and neurobehavioral patterns that have been previously described in other observational studies among primary school children, adolescents and adults (Stefanatos et al., 2001). Nevertheless, longitudinal data is needed to confirm this hypothesis, since our outcomes were assessed following a cross-sectional design. If this is confirmed by future longitudinal data analyses, we could assume that ADHD symptom assessments can be done in younger aged children, who may show increased improvements with especial programs compared to their older counterparts (Kadesjö et al., 2001). The fact that we found a linear association pattern may be indicative that a dichotomist approach for diagnosing children (with or without the cutoff number of ADHD symptoms) is not appropriate. A dimensional assessment approach may reflect a closer view to study the complexity of this behavioral area, unless among preschoolers from the general population (Greenfield et al., 2005).

9.3. Duration of breastfeeding and maternal smoking habits

Duration of breastfeeding was found to be positively associated with the children's neurodevelopment at age of four years. ADHD symptoms, social competence and executive functions were the areas which benefited most following adjustment for those outcomes that had shown a significant association in the multivariable models. Similar outcomes have been described as dysfunctional in previous ADHD observational studies among older children. These findings suggest that long-term breastfeeding has specific effects on some behavioral areas which may,

in turn, affect global outcomes. In addition, these results provide additional confirmatory information in relation to two of the three hypotheses described earlier (see introduction) regarding the breast milk nutrients (i.e., LCPUFAs) and the associated physical and psychological contact effects. Some epidemiological, control trial and animal experimental studies have studied the effect of fatty acids and/or the effect of maternal-filial contact promoted during the breastfeeding process, and in both cases, the neurobehavioral areas or the brain functional structures affected were similar to the ones found in our results (Braun et al., 2000; Lauritzen et al., 2001; Feldman et al., 2003; Smith at al., 2003; Richardson et al., 2005). The intrinsic mechanisms underlying these associations could be an interaction of various factors, such as: a direct effect of long-term supply of LCPUFAs from breast milk, which is especially necessary during early brain development. In addition to this, indirect effects through long-term maternal-filial physical and psychological contacts, which promotes the regular release of oxitocine and leptine, and which in part helps to consolidate their affective link, is very important for the offspring's limbic system maturation during this period (Feldman et al., 2003). All these factors directly or indirectly promoted by long-term breastfeeding may be the major causal mechanisms that explain the link with improved neurodevelopment among children. But if this is true, are these effects permanent or do they dissipate during adolescence or adulthood? Those are questions that we cannot answer with the present results. One study has found also positive associations with IQ scores among adults, but they didn't adjust for some important maternal psychosocial factors (Mortensen et al., 2002). We were also unable to adjust for important maternal psychosocial factors like IQ, mental

health and parenting skills, and thus, we cannot conclusively rule out that breastfeeding effects may be confounded by these factors.

Children's uterine exposure to DDT and DDE background concentrations (in low levels) were associated with a decrease in verbal, memory, quantitative, and perceptual-performance skills at age of four years (see Appendix 2). Nevertheless, further findings showed that the benefit of breastfeeding on child cognition was present regardless of DDT exposure; even though when it was taking into account the child's serum levels at age four years. These results suggest that breastfeeding did not increase the neurotoxical risk through a potential DDT exposure via breast milk. One explanation could be that the breast milk nutrients counterbalance the negative effect of DDT. Another explanation could be related to the kinetics of these contaminants in colostrum, transitional milk or mature milk. Pre-natal exposure of DDT is toxic, but not post-natal (via breast milk).

Maternal smoking habits, particularly during pregnancy, were negatively associated with children's cognitive development in the Menorca cohort. Some cognitive areas, especially verbal, quantitative, executive and working memory scores, showed a higher negative association. Maternal smoking behavior was highly consistent through the years, with only a small reported decrease in the prevalence and intensity (cig/day) during pregnancy. These findings are consistent with the literature, including animal experimental studies (Weitzman et al., 2002; Linnet et al., 2003; Huizink et al., 2006). The evidence for biological plausibility to explain smoking neurotoxicity effects during pregnancy is more solid (i.e., decreasing uttering blood flow, fetus with 15 % higher nicotinic levels, nicotinic interactions with acetylcholine receptors, oxidative stress) (Huizink et al., 2006). Again, as for the breastfeeding analyses, we were unable to adjust for important

cofactors (same as breastfeeding), and thus, one could assume that some o the observed effects may be attributed to smokers' characteristics, since some studies have reported that smokers show poorer mental health and/or IQ scores than non-smokers (Breslau et al., 2005; Jacobson et al., 2005; Huizink et al., 2006). To further examine the potential effect if this on these results we formally compared maternal smoking (during pregnancy) effects on offspring cognitive development with paternal smoking effects on offspring cognitive development (Lawlor et al., 2007). The comparison showed statistically significant differences between the two coefficients for children's global cognitive scores, even when we took into account up to 15% of apparent non-paternity. This suggests that a major part of the negative association with four-year-old children's cognitive scores may be due to the neuroteratogenic effect of tobacco smoke exposition during the in utero period.

9.4. Limitations

The non-participant rate was low and we found no differences in smoking habits and duration of breastfeeding, and, in the case DDT aliquots without enough serum, no significant differences were seen with MCSA general cognitive scores. However non-participants were more likely to have lower level of maternal education which was statistically significant.

The nurses who assessed the determinants by in-person questionnaires, the lab personnel who analyzed the serum concentrations of OCs and the teachers and psychologists who assessed the outcomes, were all unaware of any of the children's condition which could have contributed to differential diagnostic bias.

One of the major weaknesses of the studies presented here which has been, previously mentioned in the general discussion as well as within the individual papers, was that important maternal variables such as IQ, mental health and home rearing environment could not be assessed. Other covariates like education level, social class, marital status, smoking or drinking alcohol during pregnancy, child age starting kindergarten, paternal education, drinking and smoking habits, were however included in the analyses. We would suggest that the inclusion of these covariates may have acted to reduce some of the residual confounding effects resulting from the unadjusted covariates, because they are indirect indicators of parental IQ, mental health, rearing skills and genetic background (Weitzman et al., 2002; Linnet et al., 2003; Jacobson et al., 2005). In addition to this, particularly when maternal smoking effects were analyzed, the fact that paternal smoking was included in the final models and showed no significant or differentiated effects from maternal ones is consistent with biological plausibility as an explanation for maternal effects.

Longitudinally repeated measurements of the outcomes, particularly for those assessed by teachers would have enhanced outcome validity (Jacobson et al., 2005). Nevertheless we assessed the reliability properties of these scales by re-testing them in a randomized sub-sample of the two cohorts.

Additionally, the measurement of maternal cotinine levels in blood during pregnancy or child levels of LCPUFAs in blood or milk during the breastfeeding period would have enhanced the interpretations of the results. However, our reports of smoking and breastfeeding have shown to be consistent.

9.5. Implications in psychology

There are a number of different implications that should be highlighted:

1) The adaptation and validation of a screening instrument to assess social competence in the preschool context, given that there are currently so few of them, is important. This screening tool can subsequently be used by preschool personnel to easily assess all children, and, identify those for more extensive assessment who may be at risk for developing socio-behavioral problems. Also it could be used, as we have shown, in epidemiological studies to efficiently evaluate other behavioral areas apart from cognitive functions.
2) Our results in relation to ADHD symptoms and concurrent neurocognitive and social competence outcomes may indicate that preschoolers show consistent symptomology, and, if this is confirmed by further longitudinal data analysis, ADHD symptom assessments could begin during this earlier period of life.
3) The detailed neurocognitive assessments (i.e., executive functions, cognitive functions of posterior cortex, working memory, memory span, etc) may help to identify more precisely those cognitive areas in children which are impaired or have benefited by from exposure to a specific factor. Furthermore, detailed knowledge of the effects (i.e., child exposed to heavy maternal smoking during pregnancy) may contribute to the improvement of reinforcement programs.
4) In addition to the neurocognitive assessments, the fact to evaluate other behavioral areas (i.e., social competence and ADHD

symptoms) has enriched the interpretation of the findings, and, possibly it has contributed to further understand the intrinsic mechanisms; their inclusion has raised new important questions that would require more research in the future (see Appendix 1).

9.6. Implications in public health

The findings presented in this thesis have led us to think about several public health implications:

Neurodevelopment can be considered as a key target for assessment of hidden environmental health effects, particularly in terms of being an early detector of the silent pandemic of developmental neurotoxicity from industrial chemicals as described by Grandjean et al. (2006). Young children (including during the in utero period) are more vulnerable than adults to low dose exposures to neurotoxic substances. The nervous system in this period, in addition to its complexity is immature and does not yet have natural protections in place. All these characteristics provide an open window for neurodevelopmental disruption that may have long term effects through to later life (Grandjean et al., 2006).

ADHD symptom and social competence assessments in preschoolers have shown consistent results that, particularly in environmental epidemiology raise new questions related to the assessment of cognitive development. Additionally, these findings concur with other authors' suggestions that special attention in detecting ADHD symptoms should be given to children during the early years of life.

Long-term breastfeeding is strongly recommended, irrespective of whether there is a potential increase in background exposure to neurotoxins. The effects from breastfeeding appear to assist children's development and aid in aversion of potential insults from the effects of exposure to neurotoxins. In addition to cognitive function, long-term breastfeeding improves other areas (i.e., social competence and ADHD symptoms) which are fundamental for a child's psychological development.

Finally, the findings relating to maternal smoking habits provide further evidence of the need to avoid smoking, particularly during pregnancy and even where smoking is limited to a few cigarettes per day.

10. CONCLUSIONS

10.1. About psychometrical assessment

1. The Catalan-Spanish version of CPCSC showed acceptable psychometrical properties that make it a valid tool for use by teachers or educators in the social competence assessment of preschool pupils.
2. New MCSA neurocognitive outcomes were found to be useful for further assessing the specificity of the effects and in helping to interpret the underlying pathways.
3. The assessment of other behavioral areas (social competence and ADHD symptoms) in addition to cognitive development has enriched the findings through use of a more comprehensive approach.

10.2. About neurodevelopment among preschoolers

1. Preschoolers' ADHD symptoms are associated with concurrent decrements in their neurocognitive and social competence outcomes.
2. The association patterns are similar to the ones found in older children and adults with ADHD symptomology.
3. Since these results suggest that ADHD symptoms are already present in preschoolers, it may be that early preventive actions are required to reduce the risk of future ADHD symptoms and related problems that could compromise child development.

10.3. About early life determinants

1. Long-term breastfeeding is positively associated with preschoolers' psychological development.
2. Long-term breastfeeding is particularly associated with early behavioral and neuropsychological indicators of ADHD symptoms at school age.
3. Despite the possibility of harm from environmental contaminants in breast milk (i.e., DDT), breastfeeding for long periods remains beneficial to child cognitive development.
4. Maternal smoking habits during pregnancy are negatively associated with subsequent cognitive development in the child.
5. Paternal and postnatal maternal smoking habits are not associated with offspring cognitive development.
6. The neurocognitive sub-areas associated with maternal smoking during pregnancy are consistent with other documented findings among humans and animals.

10.4. Implications

The results of this study indicate that preschoolers would benefit from an increased input from professionals responsible for their mental development. Society in general has to inform, encourage and support pregnant women to avoid exposure to some environmental factors. Long-term breastfeeding and not smoking during pregnancy should be strongly recommended.

.

11. APPENDICES

11.1. Appendix 1.

Mortensen EL. Neuro-developmental effects of breastfeeding. Acta Paediatrica 2007 Jun;96(6):796-7**.**

Mortensen EL.
Neuro-developmental effects of breastfeeding.
Acta Paediatr. 2007 Jun;96(6):796-7.

11.2. Appendix 2.

Ribas-Fito N, Torrent M, Carrizo D, Munoz-Ortiz L, Julvez J, Grimalt JO,Sunyer J. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. *American Journal of Epidemiology* 2006 Nov 15;164(10):955-62.

Ribas-Fitó N, Torrent M, Carrizo D, Muñoz-Ortiz L, Júlvez J, Grimalt JO, Sunyer J.
In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers.
Am J Epidemiol. 2006 Nov 15;164(10):955-62.

11.3. Appendix 3.

Ribas-Fito N, Torrent M, Carrizo D, Julvez J, Grimalt JO, Sunyer J. Exposure to hexachlorobenzene during pregnancy and children's social behavior at 4 years of age. *Environmental Health Perspectives*. 2007 Mar;115(3):447-50.

Ribas-Fitó N, Torrent M, Carrizo D, Júlvez J, Grimalt JO, Sunyer J.
Exposure to hexachlorobenzene during pregnancy and children's social behavior at 4 years of age.
Environ Health Perspect. 2007 Mar;115(3):447-50.

12. REFERENCES

Agency for Toxic Substances and Disease Registry. Toxicological profile for DDT, DDE, and DDD: update. Syracuse Research Corporation, ed. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Public Health Service, US Department of Health and Human Services, 2000.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).* Washington, DC: American Psychiatric Association; 1994.

Baeyens D, Roeyers H, Walle JV. Subtypes of attention-deficit/hyperactivity disorder (ADHD): distinct or related disorders across measurement levels? *Child Psychiatry Hum Dev* 2006;36:403-17.

Baron SI. *Neuropsychological Evaluation of the Child*, 1st ed. New York, NY: Oxford University Press 2004. 429 pp.

Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med* 1987;316:1037-43.

Berlin L, Bohlin G, Rydell A-M. Relations between inhibition, executive functioning, and ADHD symptoms: A longitudinal study from age 5 to 8 1/2 years. *Child Neuropsychol* 2003;9:255-266.

Braun K, Lange E, Metzger M, *et al*. Maternal separation followed by early social deprivation affects the development of monoaminergic fiber systems in the medial prefrontal cortex of Octodon degus. *Neuroscience* 2000;95:309-318.

Breslau N, Paneth N, Lucia VC, Paneth-Pollak R. Maternal smoking during pregnancy and offspring IQ. *Int J Epidemiol* 2005;34:1047-53.

Carrizo D, Grimalt JO, Ribas-Fito N et al. Physical-chemical and maternal determinants of the accumulation of organochlorine compounds in four-year-old children. Environ Sci Technol. 2006;40:1420-6.

Chen CW, Hurd C, Vorojeikina DP, Arnold SF, Notides AC. Transcriptional activation of the human estrogen receptor by DDT isomers and metabolites in yeast and MCF-7 cells. *Biochem Pharmacol* 1997;53:1161-72.

Couperus J, Nelson C. Early Brain Development and Plasticity. *Blackwell handbook of early childhood development* 2006; 85-105.

Der G, Batty GD, Deary IJ. Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis. *BMJ* 2006;333(7575):945.

Dorner G, Plagemann A. DDT in human milk and mental capacities in children at school age: an additional view on PISA 2000. *Neuro Endocrinol Lett*. 2002;23:427-31.

Eriksson P, Ahlbom J, Fredriksson A. Exposure to DDT during a defined period in neonatal life induces permanent changes in brain muscarinic receptors and behaviour in adult mice. *Brain Res* 1992;582:277-81.

Eskenazi B, Trupin LS. Passive and active maternal smoking during pregnancy, as measured by serum cotinine, and postnatal smoke exposure. II. Effects on neurodevelopment at age 5 years. *Am J Epidemiol* 1995;142:S19-29.

Feldman R, Eidelman AI. Direct and indirect effects of breast milk on the neurobehavioral and cognitive development of premature infants. *Dev Psychobiol* 2003;43:109-119.

Flint LD. Dimensionality of the California Preschool Social Competency Scale. *Applied Psychological Measurement* 1981;4: 203-212.

Fossi MC, Casini S, Marsili L. Endocrine Disruptors in Mediterranean top marine predators. *Environ Sci Pollut Res Int* 2006;13:204-7.

Furman L. What is attention-deficit hyperactivity disorder (ADHD)? *J Child Neurol* 2005;20:994-1002.

Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R, Jorgensen PJ. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol* 1997;19:417-28.

Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006;368:2167-78.

Greenfield E, Fischel J. The impact of preschool inattention, hyperactivity, and impulsivity on social and academic development: A review. Clin Child Psychol Psychiatry 2005;46:755-773.

Hardell L, Lindstrom G, Van Bavel B. Is DDT exposure during fetal period and breast-feeding associated with neurological impairment? *Environ Res* 2002;88:141-4.

Herschkowitz N, Kagan J, Zilles K. Neurobiological bases of behavioral development in the first year. *Neuropediatrics* 1997;28:296-306.

Herschkowitz N. Neurological bases of behavioral development in infancy. *Brain Dev* 2000;22:411-6.

Hoi K. Suen; Sarah E. Rzasa. Psychometric foundations of behavioral assessment.. *Comprehensive handbook of psychological assessment, Vol. 3: Behavioral assessment.* 2004; 37-56.

Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neurosci Biobehav Rev* 2006;30:24-41.

Jacobson JL, Jacobson SW. Methodological issues in research on developmental exposure to neurotoxic agents. *Neurotoxicol Teratol* 2005;27:395-406.

Jensen AA. Levels and trends of environmental chemicals in human milk. In: Jensen AA and Sorach SA, Editors. Chemical contaminants in human milk, CRC Press, Boca Raton (FL). 1991; 24–198.

Kadesjö C, Kadesjö B, Hägglöf B, Gillberg C. ADHD in Swedish 3- to 7- year-old children. *J Am Acad Child Adolesc Psychiatry* 2001;40:1021-1028.

Kotimaa A, Moilanen I, Thomsen PH, Olsen J, Jarvelin MR. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry* 2003;160:1028-40.

Lauritzen L, Hansen HS, Jorgensen MH, *et al*.. The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. *Prog Lipid Res* 2001;40:1-94.

Lawlor DA, Smith GD, O'Callaghan M, Alati R, Mamun AA, Williams GM, Najman JM. Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. *Am J Epidemiol* 2007 165:418-24.

Levin S, Elzey FF, Lewis M (1969), *California Preschool Social Competency Manual*, 1st ed. San Francisco, CA: Consulting Psychologist Press; 1969. 16 pp.

Lezak, MD, Howieson DB, Lorin DW, Hannay JH, Fischer JS. *Neuropsychological Assessment.* 4th ed. London, Pa: Oxford University Press; 2004. 1016 pp.

Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, Kotimaa A, Moilanen I, Thomsen PH, Olsen J, Jarvelin MR. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry* 2003;160:1028-40.

McCarthy D. *Manual for the McCarthy Scales of Children's Abilities*. New York, NY, Pa: Psychological Corp; 1972. (Spanish Adaptation: Madrid, Spain, Pa: TEA Ediciones, S.A.; 1996).

Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM. The association between duration of breastfeeding and adult intelligence. *JAMA* 2002;287:2365-71.

Nigg TJ, Hinshaw SP, Carte E, Trueting J. Neuropsychological Correlates of Antisocial Behavior and Comorbid Disruptive Behavior Disorders in Children with ADHD. *Journal of Abnormal Psychology* 1998;107:468-480.

Odom SL., McConnell SR, McEvoy MA, et al., Relative effects of interventions supporting the social competence of young children with disabilities. *Topics in Early Childhood Special Education* 1999;19:75-91.

Pelham W-JR, Chacko A, Wymbs T. Diagnostic and Assessment Issues of Attention Deficit/Hyperactivity Disorder in the Young Child. *Handbook of infant, toddler, and preschool mental health assessment* 399-420. New York, NY, US: Oxford University Press 2004.

Ribas-Fito N, Cardo E, Sala M, Eulalia de Muga M, Mazon C, Verdu A, Kogevinas M, Grimalt JO, Sunyer J. Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. *Pediatrics* 2003;111:580-5.

Ribas-Fitó N, Grimalt JO, Marco E et al. Breastfeeding and concentrations of HCB and p,p'-DDE at the age of 1 year. Environ Res. 2005;98:8-13.

Richardson AJ, Montgomery P. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* 2005;115:1360-1366.

Rogan WJ, Gladen BC. PCBs, DDE, and child development at 18 and 24 months. *Ann Epidemiol*. 1991;1:407-13.

Ross PS, Vos JG, Birnbaum LS, Osterhaus AD. PCBs are a health risk for humans and wildlife. *Science* 2000;15;289:1878-9.

Rourke, B.P., & Fuerst, D.R. *Learning Disabilities and Psychosocial Functioning: A Neuropsychological Perspective.* New York: Guilford Press; 1991.

Skrbic B, Durisic-Mladenovic N. Principal component analysis for soil contamination with organochlorine compounds. *Chemosphere* 2007.

Smith MM, Durkin M, Hinton VJ, *et al*.. Influence of breastfeeding on cognitive Outcomes at age 6-8 years: follow-up of very low birth weight infants. *Am J Epidemiol* 2003;158:1075-1082.

Stefanatos GA, Wasserstein J. Attention deficit/hyperactivity disorder as a right hemisphere syndrome: Selective literature review and detailed neuropsychological case studies. In Wasserstein JJ & Wolf LE (Eds.), *Adult attention deficit disorder: Brain mechanisms and life outcomes* (pp. 172-195). New York, NY: New York Academy of Sciences 2001.

Trasti M, Vik T, Jacobsen G, Bakketeig L. Smoking in pregnancy and children's mental and motor development at age 1 and 5 years. *Early Hum Dev* 1999;55:137-147.

van Wendel de Joode B, Wesseling C, Kromhout H, Monge P, Garcia M, Mergler D. Chronic nervous-system effects of long-term occupational exposure to DDT. Lancet. 2001 Mar 31;357(9261):1014-6.

Weitzman M, Byrd RS, Aligne CA, Moss M. The effects of tobacco exposure on children's behavioral and cognitive functioning: implications for clinical and public health policy and future research. *Neurotoxicol Teratol* 2002;24:397-406.

Wendo C. Uganda considers DDT to protect homes from malaria. Health officials claim DDT will help save money, but critics warn of environmental costs. *Lancet* 2004;363:1376.