

Original article

Neuropsychologic status at the age 4 years and atopy in a population-based birth cohort

Background: Mental health has been reported to be associated with allergy, but only a few cohort studies have assessed if neurodevelopment predicts atopy.

Objective: To investigate if neurobehavioral status of healthy 4-year-old children was associated with specific immunoglobulin E (IgE) at the same age and skin prick test results 2 years later.

Methods: A population-based birth cohort enrolled 482 children, 422 of them (87%) provided neurobehavioral data, 341 (71%) had specific IgE measured at the age of 4 years; and 395 (82%) had skin prick tests completed at the age of 6 years. Atopy was defined as IgE levels higher than 0.35 kU/l to any of the three tested allergens at the age of 4 or as a positive skin prick test to any of the six tested allergens at the age of 6. McCarthy Scales of Child Abilities and California Preschool Social Competence Scale were the psychometric instruments used.

Results: Twelve percent of children at the age of 4 and 17% at the age of 6 were atopic. Neurobehavioral scores were negatively associated with 6-year-old atopy after adjustment for socio-demographic and allergic factors. A relative risk of 3.06 (95% CI: 1.30–7.24) was associated with the lowest tertile (scorings ≤ 90 points) of the general cognitive scale. Similar results were found for verbal abilities, executive functions, and social competence. Asthma, wheezing, rhinitis, and eczema at the age of 6, but not at the age of 4, were associated with neurodevelopment at the age of 4.

Conclusions: Neuropsychologic functioning and later atopy are negatively associated in preschool age children.

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Key words: allergic disorders; atopy; children; immunoglobulin E sensitization; neurodevelopment; neuropsychologic status; population-based cohort study; skin prick test; social competence.

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Accepted for publication 7 January 2009

Little is known about the role that neurobehavior may play in atopy (1–3). Clinical studies have reported an increase of symptoms of attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), stress, anxiety, and depression in allergic children and adults (3–11). According to a recent meta-analysis (1), psychosocial factors (i.e. psychologic stress, poor social support, and behavioral problems) have been associated with the onset of 'atopic disorders' (mainly asthma) in 17 cohort studies. On the other hand, 'atopic disorders' have been linked to several mental health disturbances (i.e. psychologic distress, anxiety, panic disorders, and depressive symptoms) in six cohort studies (1).

However, the possible underlying mechanisms are unknown. One hypothesis is that both disorders share common pathophysiologic pathways. Thus, deregulation of the hypothalamus-pituitary-adrenal axis (HPA), the

basis of several psychologic disorders, including those related to stress management, may affect the immunological system (1, 3). But on another hand, the allergic symptoms could also affect the child neurodevelopment because of the clinical manifestations and corresponding treatments (1, 4). A way to improve our understanding is the study of intermediate phenotypes (preclinical makers) in allergy, i.e. levels of immunoglobulin E (IgE) in blood and skin prick test in healthy children would allow investigating this interrelationship without the influence of the clinical manifestations and management of atopic disorders. Only one previous cohort study in child mental health assessed IgE-mediated sensitization and did not find significant associations (12). Two other studies used IgE sensitization or skin prick test results as covariates (5, 13). Moreover, if we are able to assess that neurobehavior is independently associated with later atopy and

allergic symptoms, we will prove one direction of the association, which is from neurobehavior to atopy, indicating that the central nervous system (CNS) may exert some degree of influence. In addition, none of the previous studies assessed neurocognitive functions by psychologists using exhaustive individually administered scales instead of diagnostic mental questionnaires which are less precise instruments (1, 14).

Neurobehavioral assessment includes important areas such as neurocognitive functions, which are the cerebral functions related with complex mental and motor abilities like language, memory, perceptive-performance, gross and fine motor coordination, attention, and executive functioning (i.e. planning, abstract reasoning, organizing, and sequencing) (15). Measuring them give us a broad proxy of child's general neurodevelopment status. Additionally, social competence is an indicator of child's socio-affective maturation, which is also an important area of the child's neurobehavioral development (16).

We aimed to assess in a population-based birth cohort the association between neurobehavioral scores at the age of 4 years and IgE sensitization at the same age and skin prick test results 2 years later.

Material and methods

This study was based on a birth-cohort from Menorca, one of the Balearic Islands of the north-east coast of Spain. The Menorca cohort, established within the Asthma Multicenter Infant Cohort Study (17), recruited all women present for antenatal care (within 12 weeks of gestation) over a 12-month period starting in mid-1997. Their children were then followed from birth up to 6 years of age. Characteristics of the population have been described elsewhere (18). Briefly, 482 children (94% of those eligible) were enrolled and 422 (87%) of them provided neurobehavioral data up to the 4th yearly visit. Among them, 341 children (71%) had blood sample-specific IgE levels measured against several allergens (see below) at the age of 4 years and 395 children (82%) completed skin prick tests at the age of 6 (17). No differences in neurobehavioral scores between participants and nonparticipants were found. Socio-demographic characteristics were also similar, with the exception that participation rates were lower in the town of Mahó as compared with Ciutadella and the rest of smaller towns (data not shown). This study was approved by the ethics committee of the Institut Municipal d'Investigació Mèdica, Barcelona, and all mothers provided a signed informed consent. Our sample size was higher than the minimum number of 70 subjects that was required to assess a RR of 2.0 significant with a 95% confidence interval (19).

Psychologic testing of the children at the age of 4 (mean $\pm$ SD age 4.4 $\pm$ 0.16 years) was performed by two certified psychologists and the children's classroom teachers. Cognitive and motor development was assessed by the psychologists using the Spanish version of the McCarthy Scales of Children's Abilities (MCSA) (20). The General Cognitive scale and five subscales (verbal, perceptive-performance, memory, quantitative, and motor) were examined, and in addition some items were used to construct a new summary measure to assess those cognitive tasks associated with executive functions. Social competence was measured by the teachers using the California Preschool Social Competence Scale (21). Extensive information on the neurobehavioral assessments including scale and

subscale descriptions, evaluation procedures, and validity of the instruments has been reported in other papers (16, 18, 22).

We measured levels of specific IgE against house dust mite allergen (Der p 1), cat allergen (Fel d 1), and mixed grass pollen in the 4-year blood sample. Children with IgE levels higher than 0.35 kU/l to any of these three allergens were categorized as atopic (Der p 1, $n = 41$; Fel d 1, $n = 4$; mixed grass, $n = 7$). Immunoglobulin E levels to all allergens were analysed in a single laboratory using UniCap (Pharmacia, Morris Plains, NJ, USA) (17). In addition, children completed skin prick tests to six different allergens when they were 6-year old and were defined atopic if they had a wheal > 2 mm for any of the tested allergens (12). The allergens tested were Der p 1, Fel d 1, mixed graminæ, grass pollen, parietaria, and olea europea (number of children with a positive reaction were 62, 3, 4, 0, 3, and 12, respectively).

The atopic variables at the ages of 4 and 6 years were treated as two dichotomic outcomes (0 = no atopic reaction, 1 = atopic reaction to any of the allergens tested). Neurobehavioral variables (at the age of 4) were standardized to a mean of 100 with a standard deviation of 15 to homogenize all the scores and treated first as continuous variables in the univariate analysis (see Table 1). They were then dichotomized in the final regression models to further improve our clinical understanding. We added a cut-off point after the lowest tertile (reference group: children scoring > 90 points)

Table 1. Child and parental variables of interest by child atopy at the age of 4 and 6 years in the Menorca population birth cohort

Variables of interest	Atopy† at the age of 4		Atopy‡ at the age of 6	
	Yes ($n = 43$)	No ($n = 298$)	Yes ($n = 67$)	No ($n = 328$)
Children at the age of 4 years				
Atopy (IgE > 0.35 kU/l), Yes (%)	—	—	60.0*	3.0
Asthma, Yes (%)	13.9*	3.4	13.4*	4.0
Wheeze, Yes (%)	30.2*	10.1	17.9	10.7
Rhinitis, Yes (%)	16.3*	2.3	11.9*	2.7
Eczema, Yes (%)	18.6	13.1	19.4	11.9
General cognitive, MCSA (median)	92.8*	99.3	90.6*	100.1
Verbal cognitive, MCSA (median)	95.3*	99.8	94.1*	100.5
Perceptive-performance, MCSA (median)	94.5	100.3	94.5*	100.3
Quantitative, MCSA (median)	92.8	95.9	92.8*	95.9
Memory, MCSA (median)	94.6	98.6	94.6*	100.5
Motor skills, MCSA (median)	94.1*	100.7	96.3*	100.7
Executive function, MCSA (median)	92.9*	99.6	92.9*	99.6
Social competence, CPSCS (median)	100.4	103.6	99.4*	104.6
Children at the age of 6 years				
Asthma, Yes (%)	21.9*	2.4	16.4*	3.7
Wheeze, Yes (%)	33.3*	5.5	28.4*	5.2
Rhinitis, Yes (%)	14.6*	0.7	11.9*	1.2
Eczema, Yes (%)	21.9	22.8	32.8*	21.9
Parents				
Maternal atopy, Yes (%)	37.2	34.2	47.8*	35.2
Maternal asthma, Yes (%)	4.6	7.4	6.0	6.1
Paternal asthma, Yes (%)	7.0	5.4	7.5	5.2

* P -value < 0.05 for χ^2 tests of differences of percentages or F -tests of mean differences, both, by atopy categories.

†Positive if at least one IgE to Der p1, Fel d 1, Mixed grass pollen > 0.35 kU/l.

‡Positive if at least one specific (house dust mite, cat ...) skin prick test positive (> 2 mm).

following what conventionally is considered the cut-off point of children with normal but low scores (14, 15, 18).

Information on lower tract respiratory infections, atopic disorders – such as asthma, wheeze, rhinitis, and eczema – and corresponding medical treatments were obtained from parents through yearly face-to-face standardized questionnaires (23). For this study, we used data from the 4th and 6th year reports. Maternal atopy (positive skin prick tests completed in the household visit 3 months after giving birth) and parental asthma (by questionnaire) were also obtained (17, 23).

Additional information on maternal and paternal education in years, maternal, and paternal socioeconomic status (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, Cesarean, With Forceps, or Other'; delivery complications 'Yes/No'), parity, dietary intakes during pregnancy collected using a semi-quantitative food frequency instrument, alcohol consumption during pregnancy (any consumption 'Yes/No'), having pets at home, child's exposure to cigarettes smoke (maternal and paternal daily smoking 'Yes/No' during pregnancy and at child's 4th year of age), age during kindergarten attendance, dietary intake (at the age of 4, using the same dietary questionnaire applied during pregnancy), hours per day at school (at the age of 4), watching TV

(at the age of 6), sleeping (at the age of 6), playing with sedentary games such as computer (at the age of 6), and doing physical activity (at the age of 6), was obtained prospectively as pregnancy through yearly face-to-face questionnaires. Gestational age and anthropometric measures at birth were collected from clinical records, and anthropometric measures at the age of 4 years were collected using standard methods. Full descriptions of covariates have been published in other papers (17, 18, 23).

The associations between child neurodevelopment at the age of 4 years and the atopic outcomes were assessed using log-binomial regressions, which is appropriate for cohort studies to derive relative risk (RR). Final multivariate models were adjusted for additional variables that produced at least a 10% change in the RRs for the association between neurodevelopment measures and the outcome of interest (24).

Results

Twelve percent of the children were atopic at the age of 4 years and 17% at the age of 6 years. Most of the children (60%) that were atopic at the age of 4 were also atopic at the age of 6. Among children who were not

Table 2. Adjusted associations between child general psychologic scores and atopic and allergic outcomes at the age of 4 and 6 years (Menorca population-based birth cohort)

Outcome	RR (95% CI) At the age of 4 years	
	General cognitive (MCSA)	General social competence (CPSCS)
At the age of 4 years	Scorings ≤ 90 points† vs Scorings >90 points ^{Re(RR = 1)}	
Atopy (IgE >0.35 kU/l)	2.26 (1.49–3.44)**	1.25 (0.72–2.17)
Atopy, 4-year-old allergic symptom‡ adjusted	1.67 (0.94–2.98)	1.19 (0.60–2.34)
Asthma	1.96 (0.86–4.47)	1.86 (0.72–4.82)
Asthma, 4-year-old atopy§ adjusted	2.39 (0.82–6.91)	3.35 (0.93–12.09)
Wheeze	1.45 (0.84–2.52)	1.51 (0.84–2.71)
Wheeze, 4-year-old atopy§ adjusted	1.52 (0.84–2.75)	1.14 (0.59–2.20)
Rhinitis	1.07 (0.42–2.76)	1.62 (0.53–4.94)
Rhinitis, 4-year-old atopy§ adjusted	0.99 (0.29–3.41)	1.56 (0.40–6.13)
Eczema	0.91 (0.51–1.63)	1.94 (1.07–3.52)*
Eczema, 4-year-old atopy adjusted	0.89 (0.47–1.66)	1.99 (1.07–3.69)*
At the age of 6 years		
Atopy (prick test >2 mm)	2.51 (1.65–3.81)**	2.05 (1.29–3.27)**
Atopy, 4-year-old allergic symptom‡ adjusted	2.46 (1.31–4.62)**	1.83 (1.11–3.02)*
Asthma	3.06 (1.30–7.24)*	1.42 (0.54–3.76)
Asthma, 4-year-old atopy§ adjusted	5.05 (1.36–18.81)*	1.81 (0.43–7.63)
Wheeze	4.41 (2.25–8.66)**	1.81 (0.90–3.64)
Wheeze, 4-year-old atopy§ adjusted	3.22 (1.56–6.66)**	1.37 (0.62–3.06)
Rhinitis	1.12 (0.35–3.61)	5.76 (1.51–22.00)*
Rhinitis, 4-year-old atopy§ adjusted	4.02 (0.55–29.57)	32.47 (1.27–828.16)*
Eczema	0.84 (0.55–1.27)	1.76 (1.22–2.54)**
Eczema, 4-year-old atopy adjusted	0.95 (0.59–1.51)	2.14 (1.45–3.15)**

Relative Risks (RR) from multivariate log-binomial regression models are presented.

P*-value < 0.05; *P*-value ≤ 0.005.

†The cut-off point corresponded to the lowest tertile for both general scorings (MCSA and CPSCS). The results were unchanged when including the neuropsychologic scorings as continuous variables (data not shown). All models are adjusted for psychologist, child's gender, school season, chronologic age during testing, birth weight, gestational age and duration of breastfeeding, maternal level of education and social class, parity, smoking during and after pregnancy, and home location.

‡Allergic symptoms includes: asthma symptoms, wheeze, rhinitis, and eczema.

§Significant associations (*P*-value < 0.05) between atopy and the allergic outcome in the multivariate models, showing RRs (Re: nonatopics) with similar magnitude to the RRs found in the neurobehavioral determinants (data not shown).

atopic at the age of 4, 22 (7.7%) became atopic at the age of 6. There was similar atopic prevalence by gender at the age of 4, but prevalence of atopy increased among boys up to 21% by age 6, while girls stood stable at 12%. No statistically significant associations were found between children's atopy and maternal socio-demographic factors. However, atopy was borderline less frequent among children of mothers with higher educational level, higher social class, higher frequency of fish intakes during pregnancy, and higher parity. Children's atopy also showed borderline associations with the child's birth weight (positive), gestational age (positive), and frequency of fish intakes at the age of 4 (negative). Prevalence of asthma, wheeze, and rhinitis were higher among atopic than nonatopic children at both ages, whereas eczema prevalence was higher among atopic children only at the age of 6 years (see Table 1). Atopic children at both ages showed lower scores of several important neurobehavioral scales and subscales. Among parental characteristics, only maternal atopy was associated with the child's atopy at the age of 6 years.

Atopy at the age of 4 was negatively associated with general cognitive scores in the adjusted models (see Table 2), with a RR of being atopic increased 126% for children among the lowest tertile (scorings ≤ 90 points) in the general cognitive scale. The association weakened 50% of its magnitude (P -value = 0.087) when 4-year-old allergic outcomes were included to the same model. No associations were found between general cognitive scores and asthma, wheeze, rhinitis, or eczema at 4 years. Atopy at the age of 6 was negatively associated with both general cognitive and general social competence scores (RR, 95% CI: 2.51, 1.65–3.81; and 2.05, 1.29–3.27 respectively). Furthermore, asthma (RR, 95% CI: 3.06, 1.30–7.24 in general cognitive scores), wheeze (4.41, 2.25–8.66 in general cognitive scores), rhinitis (5.76, 1.51–22.00 in general social competence scores), and eczema (1.76, 1.22–2.54 in general social competence scores) at the age

of 6 were all negatively associated with the neurobehavioral variables. In addition, to ensure that the associations between neurobehavioral scores and atopy at the age of 6 were not confounded by allergic outcomes at the age of 4, we performed a rerun of the final models and adjusted them for asthma, wheeze, rhinitis, and eczema at 4 years instead of the same allergic outcomes at 6 years, and the associations did not change. Similar results were obtained when models were adjusted for allergic outcomes at the age of 6 years (data not shown). When asthma, wheeze, rhinitis, and eczema were adjusted for atopy at the age of 4 as a confounder, the results were unchanged. Results were similar when atopy at the age of 6 years was included as a confounder (data not shown).

Verbal cognition (RR, 95% CI: 2.19, 1.17–4.14) and executive functioning (RR, 95% CI: 1.65, 1.13–2.41) were the MCSA sub-area scores that showed negative associations with atopy at the age of 6 after multivariate adjustments including allergic symptoms at the age of 4.

Table 3 shows the associations of atopy at the age of 6 as the outcome, after excluding children with atopy at the age of 4. The results did not change at all the association patterns observed in Table 2, showing a significant negative association between general cognitive abilities at the age of 4 and atopic outcome 2 years later (RR, 95% CI: 3.34, 1.49–7.50). Neurobehavioral scorings also showed predictive associations with wheeze and eczema outcomes.

Furthermore, stratification by asthma, wheezing, early wheezing (before the age 2 years), or rhinitis did not modify the association with neurobehavior and 6-year-old atopy, with a similar magnitude in both strata (P for interaction = 0.20). We did not find any gender interaction between the neurobehavioral and atopic associations (data not shown). In addition, we did not find any significant association between lower tract respiratory infection diseases, asthma treatments, and any other

Table 3. Adjusted associations between child psychologic scores and atopic and allergic outcomes at the age of 6 years after excluding 4-year-old atopic children (Menorca population-based birth cohort, $n = 283$)

Outcome	RR (95% CI) At the age of 4 years	
	General cognitive (MCSA)	General social competence (CPSCS)
At the age of 6 years	Scorings ≤ 90 points† vs Scorings >90 points ^{Re(RR = 1)}	
Atopy (prick test >2 mm)‡	3.34 (1.49–7.50)**	2.20 (0.86–5.62)
Asthma§	6.12 (0.91–41.30)	5.60 (0.41–76.61)
Wheeze§	3.25 (1.37–7.72)*	3.12 (1.08–8.99)*
Eczema§	1.05 (0.65–1.70)	2.09 (1.36–3.21)**

Relative risks (RR) from multivariate log-binomial regression models are presented.

* P -value < 0.05 ; ** P -value ≤ 0.005 .

†The cut-off point corresponded to the lowest tertile for both general scorings (MCSA and CPSCS). All models are adjusted for the same list of covariates listed in Table 2 footnotes.

‡Results were unchanged when allergic outcomes (4 and 6 years of age) were included in the multivariate models (data not shown).

§Atopy at the age of 6 years was not significantly associated with any allergic outcome in the multivariate models, with the exception of eczema (data not shown). Rhinitis outcome was excluded of analyses because only two new cases were observed.

disease treatments (i.e. antibiotics) and the neurobehavioral scores (data not shown).

Discussion

In this cohort study, we found that scorings of general cognition and social competence at the age of 4 were inversely associated with atopy at the age of 6 after adjusting for allergic symptoms at the age of 4. The association with general cognition remained the same after excluding children with atopy at the age of 4. Asthma, wheezing, and rhinitis at the age of 6, but not at the age of 4, were also inversely associated with neurodevelopment independent of the atopic status. This is the first report to assess neurodevelopment as a whole in the relationship with atopy, using an extensive scale of general cognition and motor abilities and a complementary teacher rating scale of social competence. Both scales followed standardized techniques for the assessment process and validity analyses, and showed acceptable psychometric characteristics (16, 18, 22).

The pathways between neurobehavior and atopy are not clearly elucidated, but several hypotheses have been raised (1, 5, 11). One of the hypotheses is that atopic children are more likely to have clinical disturbances, such as symptoms of asthma or wheezing (and their corresponding treatments) that may affect behavior. These factors could modify the psychosocial environment of the child and create a vicious cycle, worsening the child neurodevelopment (1, 5, 8, 11). However, our results appear to argue against this hypothesis, because the associations persisted after controlling for a wide range of variables that are markers of these factors (i.e. allergic disorders, treatments, daily life behaviors such as hours spent at school); and such associations showed similar results among subjects without allergy disorders. Moreover, in the case that clinical disturbances had a primary role, the results would have shown a different association pattern, with predominant associations being observed with allergic disorders at the age of 4 instead of with allergic disorders at the age of 6.

Another hypothesis suggests that lower behavior scores might be indicators of chronic or acute stresses in the child's life that may affect atopy as well (1, 3, 5, 25). However, we took into account many variables that indicate factors that could influence child stress or its management, such as sleeping hours, physical activity and ways of entertainment, parental social class and level of education, smoking, alcohol consumption, maternal parity, and marital status. None of these factors confounded the associations' strength (data not shown). These findings may suggest that the association between neurobehavior and atopy could be something more complex than what stress hypothesis suggests. As we did not measure any direct indicator of stress, stretching anything beyond the above speculation would amount to overstating our findings.

Although we cannot rule out the above-mentioned hypotheses and the existence of residual confounding, we have found that children with socio-behavioral problems (i.e. low scores in social competence) also showed lower scores in neurocognitive functioning. Moreover, the same areas were also negatively associated with child atopy. This suggests the existence of direct physiologic pathways involved in the association between neurobehavior and atopy, maybe sharing genetic influences. Altered HPA function and allergic disorders may be part of these pathways, probably secondary to gene-environment interactions (1, 3, 5). Recently, it has been found the G Protein-Coupled Receptor 154 gene (GPR154), on human chromosome 2p15-p14, is associated with asthma and high serum total IgE. Additionally, the same gene has the neuropeptide S as an endogenous ligand, which is highly expressed in the brain and interacts with HPA responses to stress and anxiety (26). In this framework, many complex mechanisms could be involved. For example, elevated endogenous cortisol produced by HPA may affect the developing immune system with subsequent atopic responses and consequent allergic disorders (27). Moreover, HPA dysfunction has been involved in a range of psychologic problems, such as affective disorders (i.e. anxiety, stress management, depression), ADHD, and CD (28–30). It is well documented that these psychologic problems are, in turn, related to the impairment of social competence and neurocognitive functions, such as executive functions, attention, and concentration skills (31–34). Accordingly, the interrelationships among the neurobehavioral areas and atopy might proceed from HPA dysfunctions that slowly deregulate the developing immune system with erratic IgE responses and development of allergic disorders (1, 3). In fact, we found independent and direct associations between neurobehavior and atopy, and between neurobehavior and allergic disorders. In addition, we found independent associations between atopy and allergic disorders (data not shown), but most of their magnitudes were diluted when we excluded the 4-year-old atopic children from the final models, while the neurobehavioral associations were always present with invariant magnitude. All these findings argue in favor of the possibility that the CNS may be playing the major role in the complexity of these interrelationships during preschool ages.

Nevertheless, it is necessary to clarify more precisely the role of other potential factors not analysed in this study, such as maternal mental health (stress, emotional, or psychiatric problems) and educational practices (control and stimulation) (35–37). An important limitation of our study is the small number of incident cases of atopy between the ages of 4 and 6 (only 22) that precludes a true longitudinal analysis to properly disentangle the temporal order between the events. Nevertheless, we were able to detect a negative association between neurodevelopment and atopy after excluding the atopic children at

the age of 4, which was statistically significant with a P -value < 0.005 . Additionally, the fact that the strength of the association with atopy at 6 years of age was similar after excluding the subjects with atopy at baseline suggests that lower neurobehavioral scorings may precede atopy. Even though, we think that with this limitation this study cannot totally resolve the temporal sequence between neurodevelopment and atopy. Other study limitation was the participating rate. However, it probably did not influence the results because the majority of demographic factors were equally distributed between participants and nonparticipants. In addition, the observations that children who were atopic at the ages of 4 and 6 years were associated with most of the 6-year-old allergic outcomes; that mothers with high levels of IgE sensitization had higher risk to have children showing the same pattern at the age of 6; and that atopic gender differences were found, in which male incidence increased by 9% between the ages of 4 and 6, while female incidence stood stable, argue against a strong selection bias operating in our population-based cohort (2, 38–40).

In conclusion, this study shows associations between neurodevelopment and atopy. The child's general status of neuropsychologic functioning, including several specific areas such as verbal and executive functions and social competence was negatively related with atopy 2 years later after adjusting for a range of socio-demographic and allergic disorder factors. These results suggest that there is room for investigating further whether these interrelations are caused by complex interactions between neurologic and immunologic systems during the development of the child. Future cohort studies with longitudinal data, following the child until

adulthood are needed to elucidate the existence of these associations and to investigate which neurobehavioral areas are mostly implicated to better understand the neurobiology underlying atopy and allergic disorders.

Acknowledgments

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.

We would like to thank all teachers and parents of the children from Menorca Island for patiently answering our questionnaires, all the psychologists who have coordinated the fieldwork, the nurses and administrative personnel from the Primary Health Care Center of Mahó for administrative, technical and material support and Dr. Anna Choi for language editing assistance.

Author contributions

Study concept and design: Julvez and Sunyer. Acquisition of data: Torrent and Julvez. Analysis and interpretation of data: Julvez and Sunyer. Drafting of the manuscript: Julvez. Critical revision of the manuscript for important intellectual content: Julvez, Sunyer, Torrent, Guxens, Antó and Guerra. Statistical analyses: Julvez. Obtaining funding: Sunyer. Administrative, technical, or material support: Torrent and Julvez.

Competing interest

There are no competing interest with authors and funding.

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