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Early exposure to dichlorodiphenyldichloroethylene, breastfeeding and asthma at age six

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Summary

Our aims were to assess association of dichlorodiphenyldichloroethylene (DDE) with childhood asthma measured up to age 6 and the effect of DDE on the protective effect of breastfeeding on asthma. In addition, we attempted to assess the relevant time-window of DDE exposure (i.e. at birth or at 4 years).

All women presenting for antenatal care in Menorca, Spain over a 12-month period beginning in mid-1997 were invited to take part in a longitudinal study that included a yearly visit. Four hundred eighty-two children were enrolled and 462 provided complete outcome data after 6.5 years of follow-up. Organochlorine compounds were measured in cord serum of 402 (83%) infants and in blood samples of 285 children aged 4. We defined asthma as the presence of wheezing at age 6 and during any preceding year or doctor-diagnosed asthma, and used skin prick test at age 6 to determine atopic status.

Results At birth and 4 years of age, all children had detectable levels of DDE (median 1 ng/mL and 0.8 ng/mL, respectively). From birth to age 4, the mean DDE level among children with artificial feeding decreased by 72%, while among breastfed children it increased by 53%. Diagnosed asthma and persistent wheezing were associated with DDE at birth [odds ratio (OR) for an increase in 1 ng/mL, OR = 1.18, 95% confidence interval (95% CI) = 1.01–1.39 and OR = 1.13, 95% CI = 0.98–1.30, respectively], but not with DDE at 4 years. Neither breastfeeding nor atopy modified these associations ($P > 0.3$). Breastfeeding protected against diagnosed asthma (OR = 0.33, 95% CI = 0.08–0.87) and wheezing (OR = 0.53, 95% CI = 0.34–0.82) in children with low and high DDE levels at birth.

Conclusion In a community without known dichlorodiphenyltrichloroethane environmental releases, this study strengthens the evidence for an effect of DDE on asthma by measuring the disease at age 6 and does not support the hypothesis that DDE modifies the protective effect of breastfeeding on asthma.

Keywords asthma, breastfeeding, childhood, DDE, exposure

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Introduction

Breastfeeding is the ideal form of infant nutrition. Exclusive breastfeeding for at least 4 months protects against the development of early childhood wheezing irrespective of maternal history of asthma [1] and this protection may extend up to adolescence [2]. At the same time, breastfeeding mobilizes organochlorine compounds stored in the fat tissue of the mother and via breast milk increases the accumulation of organochlorine com-

pounds in children [3,4]. Organochlorine compounds [5], and particularly dichlorodiphenyldichloroethylene (DDE) have been associated with asthma in infants [6] and school-aged children [7]. Currently, the epidemiologic evidence is unclear as to whether the benefits of breastfeeding are counterbalanced by negative effects resulting from the accumulation of organochlorine compounds [8]. An analysis of the time window of exposure may contribute to our understanding of this issue. If the negative effect of DDE in the development of asthma is restricted to

the pre-natal period, as suggested by our group recently [6], then the effect of breastfeeding should not be modified by post-natal mobilization of organochlorine compounds. Our previous investigation, however, was limited by the lack of repeated measures of DDE after birth and the short follow-up time. Here, the cohort was enlarged up to 6.5 years and measures of organochlorine compounds were repeated at age 4.

No causal pathway between DDE and asthma has been identified, though the hormone-like activity of DDE could be an explanation. DDE might interfere with mast cells in airways that express estrogen/progesterone receptors [9], favoring the role of DDE in TH2 immune differentiation and effect on patterns of T cell signaling [10]. Alternatively, the hormone-like activity of DDE may have a direct effect on the airway through altering β_2 -adrenergic responsiveness [11] and increasing the production of prostaglandins [12].

Our aims were to assess the association of DDE on childhood asthma measured up to age 6 and the influence of DDE on the protective effect of breastfeeding on childhood asthma. In addition, we attempted to assess the relevant time-window of DDE exposure (i.e. at birth or at 4 years).

Methods

All women presenting for antenatal care in Menorca over a 12-month period starting in mid-1997 were recruited. Four hundred and eighty-two children were subsequently enrolled and 462 (97%) provided complete outcome data after 6.5 years of follow-up; organochlorine compounds were measured in cord serum of 402 (84%) children. Blood was drawn in 360 children at 4 years of age, 285 of whom had organochlorine compounds measured. The study was approved by the corresponding ethical committees and written informed consent was obtained from the parents of all children [13].

The outcome of interest was wheezing reported on each interviewer-led annual questionnaire (at years 1, 2, 3, 4 and 6.5) being described as, 'whistling or wheezing from the chest, but not noisy breathing from the nose.' One or more episodes of wheezing over 12 months constituted wheezing during any given year. The outcome was the presence or absence of wheeze each year and persistent wheezing at age 6.5 (wheezing at this age and in a preceding year). A second outcome of interest was doctor diagnosed asthma at age 6.5 as reported by parents.

Mothers were interviewed 6, 14 months and 2 years after delivery regarding the type and duration of exclusive breastfeeding. No significant differences on breastfeeding patterns were found between the surveys. Number of asthmatic parents, maternal smoking, parity, education and social class came from a questionnaire administered to the pregnant mothers [13]. Gestational age and birth

weight was extracted from clinical records and maternal body mass index (BMI) during pregnancy (first trimester) and child BMI at 6.5 years were calculated from the weight and height measured with the same instrument in all subjects using standardized protocol.

Three hundred and eight out of the 402 children underwent skin prick testing at 6.5 years of age. A weal of 2 mm or greater in the presence of a positive histamine control and a negative uncoated control constituted a positive skin test. A positive skin test to at least one allergen (*Der p 1*, *Der f 1*, cat, dog, grass pollen, mixed tree, mixed gramineae, parietaria) was considered indicative of atopy. Selection of a more specific cut-off (3 mm) did not change the results. Maternal atopy to common aeroallergens was measured using prick test [13].

DDE and dichlorodiphenyltrichloroethane (DDT) were measured in cord serum by gas chromatography (GC) with electron capture detection and GC coupled to chemical ionization negative-ion mass spectrometry [14].

Analysis of the relationship between organochlorine compound exposures and dichotomous outcome variables (e.g. persistent wheeze at age 6 or not) was conducted using logistic regression. To assess the role of organochlorine compound exposure on the risk of wheezing during each year, adjusted for wheezing status in all previous years, we used generalized estimating equations (GEE) with an unstructured correlation matrix and an interaction term between year and the exposure variable. Multivariate models were used to adjust for confounding variables and to test for interactions. All variables significantly related with wheezing in the bivariate models ($P < 0.2$) were included in the multivariate model, and only retained if they had a statistically significant association (< 0.1) or modified the coefficient of organochlorine compounds by a 5%. The shape of the dose-response relationships were assessed using GAM modelling. Analyses were conducted using Stata software, version 8.0 (StataCorp, College Station, TX, USA). Statistical tests of hypotheses were two-tailed with significance set at $P < 0.05$.

Results

At birth and at 4 years of age all children had detectable levels of DDE while for DDT the figures were 92% at birth and 60% at 4 years (Table 1). Levels of DDE exceeded by ten times or more the levels of DDT. Levels of DDE at age 4 were clearly related to breastfeeding. Among those who were not breastfed there was an approximately fourfold decrease in levels of DDE and DDT, while for breastfed children DDE showed a small increase and DDT a small reduction. The ratio DDE at 4 years of age compared with DDE at birth was 0.58 among children with artificial feeding while it was 1.53 among breastfed children ($P < 0.01$).

Table 1. Levels of DDE and DDT at birth and 4 years

	% detectable	Minimum	p25	p50	p75	Maximum
DDE (ng/mL)						
At birth (<i>n</i> = 402)	100.0	0.043	0.571	1.028	1.940	19.54
At 4 years (<i>n</i> = 285)	99.3	0.088	0.440	0.810	1.765	43.88
Breastfed (<i>n</i> = 202)	100.0	0.122	0.593	1.113	2.005	43.88
Not breastfed (<i>n</i> = 43)	97.7	0.088	0.179	0.354	0.586	1.765
DDT (ng/mL)						
At birth (<i>n</i> = 402)	92.1	0.008	0.037	0.080	0.202	2.283
At 4 years (<i>n</i> = 285)	60.4	0.038	0.024	0.049	0.105	0.658
Breastfed (<i>n</i> = 202)	67.8	0.038	0.030	0.059	0.114	0.658
Not breastfed (<i>N</i> = 43)	37.2	0.040	0.008	0.027	0.065	0.570

DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethylene.

Table 2. Median levels of DDE and DDT (ng/mL) according to asthma diagnosis and persistent wheezing at age 6.5, and variables of interest

Variables	At cord			At 4 years		
	N	DDE	DDT	N	DDE	DDT
Asthma diagnosis at 6.5 years						
No	372	1.027	0.080	270	0.870	0.051
Yes	12	1.379	0.061	7	0.538	0.027
Wheezing						
Never	207	1.025	0.083	140	0.939	0.048
Persistent (at 6.5 and any previous year)	34	1.340	0.095	26	0.660	0.036
Prick test > 2 mm						
Negative	299	1.092	0.081	227	0.807	0.051
Derp1	52	1.007	0.076	37	1.099	0.049
Any	57	1.007	0.081	40	1.111	0.055
Breastfeeding in weeks						
0	70	0.988	0.087	43	0.354	0.027
> 0–20	166	1.162	0.089	99	0.746	0.046
> 20	166	1.003	0.062	103	1.719	0.071
Maternal BMI (kg/m ²)						
< 22	195	0.941	0.061	139	0.807	0.049
22–25	117	1.089	0.087	84	0.941	0.058
> 25	79	1.289	0.091	53	0.805	0.041
Maternal age in years						
≤ 25	87	0.671	0.065	47	0.729	0.043
25–30	182	1.089	0.081	109	0.851	0.057
> 30	133	1.395	0.102	89	0.957	0.058
Sex						
Males	205	0.994	0.080	136	0.910	0.050
Females	197	1.118	0.080	149	0.770	0.049

BMI, body mass index; DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethylene.

Children with diagnosed asthma or wheezing at age 6 had higher levels of cord DDE than children without asthma or persistent wheezing, but not of DDE at age 4 or DDT (Table 2). DDE and DDT did not show any significant variation with atopy. At 4 years there was a strong

increase in levels of DDE and DDT by breastfeeding duration. Among the maternal variables (age, smoking, asthma, atopy, BMI and education) and the child variables (sex, birth weight, gestational age, BMI at 6 and parity) considered, only maternal age ($P < 0.05$), maternal BMI ($P < 0.05$) and child's sex ($P = 0.19$) showed some association with any of the organochlorine levels.

Asthma diagnosis and persistent wheezing showed an association with DDE at birth, the association with wheezing approaching statistical significance ($P = 0.08$, both in the crude and adjusted models, Table 3). DDE was treated as a continuous variable in the crude and adjusted models since GAM models confirmed a linear relationship between asthma or wheezing with DDE (P for gain using non-linear shape = 0.17). In fact, of the children with diagnosed asthma or persistent wheezing, approximately 50% had levels of DDE above the upper tertile (odds ratio per inter-quartile change = 1.91). The association between wheezing at any age and DDE at birth varied by age, with a statistically significant interaction at years 3 and 4 with respect to years 1 and 2. Wheezing occurring at 4 showed a statistically significant association with DDE at birth. Only two children started wheezing after 4 years of age, and those whose wheezing persisted at age 6 had higher levels of DDE than those whose wheezing ceased (median 1.30 and 1.18 ng/mL, respectively; though differences were not statistically significant). Inclusion in the models of variables related to asthma such as maternal asthma, atopy, smoking, BMI, family size, birth weight, and child BMI did not change any of the results. Stratification by child atopy measured with prick test did not show any interaction in the association between DDE and wheezing or asthma (P for interaction > 0.5), and if any the association was stronger among those without atopy. Breastfeeding duration did not modify the association between DDE at birth and asthma and wheezing (P for interaction > 0.3). Adjustment for DDT did not confound any result. When the analysis was conducted with DDT at birth instead of DDE, no association was found. No association was found with DDE at 4 years, the ratio DDE

Table 3. Association (odds ratio and 95% confidence interval) between DDE (in ng/mL) at birth and asthma and wheezing, stratified by atopic status in 402 children

	Odds ratio per each increase in 1 ng/mL of DDE at birth			
	Crude	Adjusted [†]	Non-atopics [‡]	Atopics [‡]
Asthma diagnosis at 6.5 years	1.18 (1.02–1.37)	1.18 (1.01–1.39)	1.25 (1.01–1.54)	0.92 (0.37–2.27)
Persistent wheezing at 6.5	1.11 (0.97–1.26)	1.13 (0.98–1.30)	1.15 (0.98–1.34)	1.71 (0.85–3.42)
Wheeze per year [‡]				
Year 1	0.91 (0.79–1.06)	0.92 (0.80–1.07)	0.91 (0.77–1.07)	0.97 (0.77–1.23)
Year 2	1.01 (0.91–1.12)	1.02 (0.92–1.13)	0.97 (0.86–1.10)	1.00 (0.81–1.23)
Year 3	1.05* (0.95–1.17)	1.07* (0.96–1.19)	1.10* (0.97–1.23)	0.99 (0.79–1.24)
Year 4	1.13* (1.01–1.26)	1.14* (1.02–1.28)	1.10* (0.96–1.26)	1.02 (0.84–1.25)
Year 6.5	0.98 (0.80–1.18)	0.99 (0.82–1.19)	1.00 (0.77–1.29)	0.99 (0.80–1.22)

[†]Adjusted for maternal age, duration of breastfeeding and sex.

[‡]Also adjusted for autocorrelation. Reference group were those without wheezing at any age.

Atopy was defined according to prick test at 6 years. The reference group are children without wheezing at any age and no-atopy at age six.

**P* for interaction with year < 0.10.

DDE, dichlorodiphenyldichloroethylene.

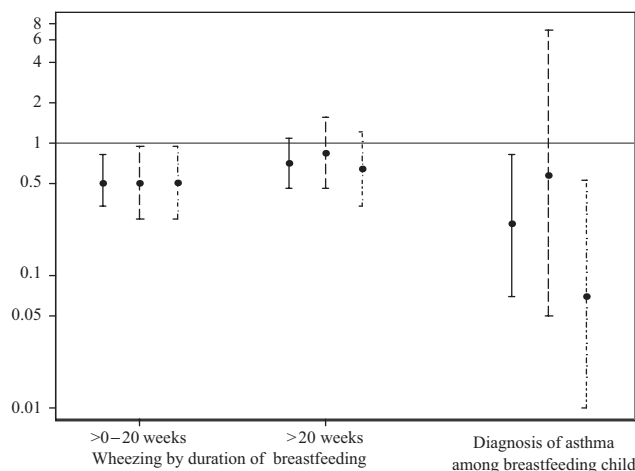


Fig. 1. Association [odds ratio (95% confidence interval) adjusted for maternal asthma, atopy, smoking, body mass index; sex, parity and birth weight in the y-axis] of persistent wheezing and diagnosis of asthma at age 6 and half with breastfeeding duration among all children (—), children with cord serum dichlorodiphenyldichloroethylene < 1 ng/mL (---) or > 1 ng/mL (-.-).

at 4/DDE at birth or when atopy was the outcome instead of wheezing or asthma.

Breastfeeding had a protective association with wheezing and diagnosed asthma (Fig. 1). The association between breastfeeding and wheezing was not modified for age of wheezing presentation (*P* for interaction with year > 0.20). Breastfeeding was negatively associated with wheezing, particularly among children breastfed for less than 20 weeks (OR = 0.53; 95% CI = 0.34–0.82), and with asthma diagnosis (OR = 0.33; 95% CI = 0.08–0.87) in comparison with children who did not breastfeed (Fig. 1). The associations remain similar after stratifying for high or low DDE levels at birth (*P* for interaction > 0.6). When

DDE was treated as a continuous variable instead of categorical the effect modification was also non-significant (*P* for interaction > 0.5).

Discussion

DDE at birth increased the risk of asthma diagnosed and of persistent wheezing at age 6, but this was not the case for DDE measured at 4 years of age. DDE levels did not modify the protective effect of breastfeeding on childhood asthma. These results suggest an effect of prenatal DDE exposure on childhood asthma probably via its hormone-like effect [10]. An alternative explanation such as residual confounding or chance seems unlikely given the cofactors assessed [6,13] and the strong prior evidence provided by animal studies [15] as well as human studies [16]. Nevertheless, Menorca is an area of low prevalence of asthma [13] and generalization of our results require studies in areas with higher frequency of asthma.

The present results suggest that in a community without known current DDT releases, the major source of DDE in children comes from maternal exposures since children with artificial feeding had a decrease in their body burden. The lack of an effect with DDE measured at 4 years of age suggests that the critical time window occurred early in life. The time window of exposure is becoming a key aspect in the study of diseases involving systems with a long developmental length such as the immunological and respiratory system. A recent study on the effect of air pollution on asthma showed that only early exposures to traffic increased the risk of wheezing among children aged 5–7, but not more recent exposures [17]. In the pesticides field, early exposure to herbicides has been related with wheezing at age 5 [5]. Low levels of organochlorine compounds have been shown to more selectively inhibit type I immune responses [18], compatible with an effect in

the development of the immune system in the pre-natal and early post-natal life [10]. Moreover, we found no modification according to DDE levels on the protective effect of breastfeeding in asthma. Breastfeeding is an important way of ingesting organochlorine compounds during infancy. The lack of effect after stratification of breastfeeding duration by pre-natal levels of DDE suggested that the post-natal effects of DDE (incorporated through breastfeeding) on asthma are probably less relevant than pre-natal exposure, as some authors have also suggested for neurodevelopment [19].

Diagnosis of asthma in childhood is controversial. Early wheezing frequently occurs during low-respiratory tract infections while wheezing occurring at age 6 has been shown to be a good surrogate of childhood asthma [20]. In our study, only two out of the 402 children had wheezing at 6 years but not previously, which precludes any chance to evaluate wheezing occurring at this age in comparison with wheezing at 4, as those who persist wheezing after 4 had very similar DDE levels to those who wheeze at four, and slightly higher than those who wheeze up to four (Table 2). The fact that results on diagnosed asthma and persistent wheezing at age 6 were consistent with results on wheezing occurring after the period when lower respiratory tract infections has the higher incidence (i.e. after age 3), suggests that the association of DDE on wheezing at age four could be extended to childhood asthma.

Some elements in breast milk act to protect the infant from developing allergies such as the content in IgA, cytokines like IFN- γ , long chain polyunsaturated fatty acids, or specific antibodies against viral diseases [1]. Our study and previous studies conducted among school-aged children [21] both suggest that the protective effect of breastfeeding on wheezing extends up to 6 years of age, beyond the period when wheezing is generally a marker of viral infections. Furthermore, in contrast to a previous study we did not find any modification of the breastfeeding effect by levels of DDE [8]. In 343 children cross-sectionally assessed at school age, the protective effect of breastfeeding on asthma disappeared in the group with high levels of DDE [8]. The major problem of that study was that DDE levels were assessed at school age when the effect of breastfeeding duration in the DDE body-burden could not be disentangled (although we did not find an effect modification of the role of breastfeeding using DDE levels at age 4. In our study, DDE levels at birth, as well as other variables were similar ($P > 0.3$) among children with or without blood measurements at age 4). The high risk group in that study (i.e. 0.44 ng/mL) was lower than median levels in the present study (i.e. 1 ng/mL). Furthermore, in our study the interaction did not happen after considering DDE as a continuous variable, indicating that divergences in the selection of a threshold level might not be an explanation.

We found an effect for DDE but not for DDT. One explanation could be that DDT levels were ten times lower

than DDE levels, probably due to the lack of recent local environmental releases. A second explanation refers to the different biological properties of these compounds. DDE binds with the androgen receptor in rats and inhibits the binding of androgen to the androgen receptor at levels that can inhibit human androgen receptor [22]. However, epidemiological studies in a small group of sprayers in Mexico [23] and in farmers in North Carolina (USA) [24] failed to find a cross-sectional association between androgen levels and DDE, while a decrease of testosterone was found. P,p'-DDT may have an opposite effect than the antiandrogen activity of p,p'-DDE [25] though pp'DDE and particularly op'DDE may also have an estrogenic effect [26, 27]. Our DDE measure was the addition of the isomers o,p'-DDE and p,p'-DDE, the latter providing the largest amount although the two isomers are highly correlated ($r = 0.89$). Why DDT did not show any association could in part be due to the opposite effects of DDE and DDT, but also to the lower levels of DDT than DDE in our population. Finally, a cohort study in Michigan showed that among non-smoking mothers, duration of breastfeeding was shorter in mothers with higher levels of DDE among first born [28], coinciding with an old study with much higher levels [29], because DDE might reduce milk. We also found higher DDE levels at birth among mothers who breastfed for a shorter time among those mothers who breastfed, though differences were not significant. When we selected only first-born children, DDE levels at birth among children with shorter breastfeed duration were much higher than among mothers with longer duration, although we did not find any modification by smoking (data not shown). This effect adds support for the estrogenic effect of DDE.

As we reported previously with IgE at 4 years [6], we found no association with atopy measured with prick test at age 6 in contrast to a study in school children measuring total IgE [7,8]. This finding reduces the possibility that a lack of association with IgE in our study was due to the young age of our children, as we speculated when the cohort only spanned up to 4 years. Furthermore, this finding might indicate that the association between DDE and asthma does not involve the immunological cells related with specific IgE production. The unmodified association between DDE and wheezing found among non-atopic children (and if any stronger association) strengthen this possibility, although we had a small power to test interaction given the low prevalence of asthma. Similarly, two studies on other organochlorine compounds, such as PCBs and dioxins, found a negative association with allergic reactions in children [30] and IgE sensitization in rats [31].

Overall, this study strengthens the evidence for an effect of DDE on asthma by measuring the disease at age 6 and does not support a DDE effect modification of the protective effect of breastfeeding on asthma. Moreover, it suggests the early exposure as a more relevant

time-window than exposure at age four. Furthermore, it reinforces the lack of effect of DDE on atopy. The hormone-like activity of DDE appears as the best explanation which deserves further research at mechanistic level.

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