BREASTFEEDING AND ASTHMA IN A SAMPLE OF PORTUGUESE CHILDREN

Aleitamento materno e asma numa amostra de crianças portuguesas

Trabalho de Investigação

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À FCNAUP.
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Lista de Abreviaturas

OR – Odds Ratio;
CI – Confidence Interval;
Th1 – T helper cells type 1;
Th2 – T helper cells type 2;
IgE - Immunoglobulin E;
IQ - Intelligence Quotient;
SIDS - Sudden Infant Death Syndrome;
BMI - Body Mass Index.
Abstract

**Introduction:** Asthma is one of the most common chronic diseases worldwide. Some studies show that breastfeeding could be one of the solutions for this disease. However, the longstanding question of whether breastfeeding prevents or augments the incidence of asthma remains controversial. **Objective:** The aim of the present study is to quantify the association between the duration of breastfeeding and the occurrence of asthma in infancy. **Methods:** We invited 5867 Portuguese children randomly selected from elementary schools in Porto and their parents/caretakers to participate in the study. Of those schools who agreed to take part 3391 parents signed and returned the consent form fulfilled. Children were measured by two trained persons and their parents answered a questionnaire, regarding socio-demographic characteristics, asthma and breastfeeding. Overall, 2512 questionnaires were returned and children who did not meet the requirements were removed, living a final sample of 1976 children from 5 to 10 years old. Unconditional logistic regression models adjusting for confounders were performed to estimate the association between asthma and breastfeeding. **Results:** Our results show that boys suffered significantly more from asthma than girls (11.2% vs. 7.4%, p = 0.004) and that breastfeeding for more than 3 months was inversely related to the presence of asthma, only amongst boys [OR = 0.630 (95% CI: 0.398-0.997)]. **Conclusion:** Prolonged breastfeeding for more than 3 months amongst boys was associated with a reduced probability of having asthma in childhood.
Resumo

Introdução: Por todo o mundo, a asma é uma das doenças crónicas mais comuns. Alguns estudos mostram que o aleitamento materno poderá ser uma das soluções no combate a esta doença. No entanto, há estudos que demonstram que o aleitamento materno diminui a incidência de asma, outros que revelam que não tem efeito e outros ainda evidenciam que o aleitamento materno aumenta a incidência desta doença. Assim, esta questão permanece bastante controversa.

Objectivo: O objectivo deste estudo é quantificar a relação existente entre o aleitamento materno e a presença de asma na infância. Métodos: Foram convidadas para participar no estudo 5867 crianças seleccionadas aleatoriamente de escolas primárias do Porto, juntamente com os seus pais/encarregados de educação. Das escolas que aceitaram participar, 3391 pais/encarregados de educação assinaram e devolveram o termo de consentimento preenchido. Essas crianças foram medidas por dois profissionais treinados e os seus pais responderam a um questionário que incluía informação sócio-demográfica, diagnóstico médico de asma e duração de exposição a aleitamento materno. No final, 2512 questionários foram devolvidos e as crianças que não correspondiam aos requisitos foram eliminadas, deixando uma amostra final de 1976 crianças dos 5 aos 10 anos. Modelos de regressão logística ajustados para confundidores foram utilizados para estimar a associação entre a asma e o aleitamento materno.

Resultados: Os nossos resultados mostraram que a prevalência de asma é maior nos rapazes do que nas raparigas (11,2% vs. 7,4%, p = 0,004) e que o aleitamento materno por mais de 3 meses protege os rapazes de desenvolverem asma [OR = 0,630 (95% IC: 0,398-0,997)]. No que diz respeito às raparigas, não
houve nenhuma relação significativa. **Conclusão**: O aleitamento materno por mais de três meses associou-se a uma menor probabilidade de ocorrência de asma na infância, entre os rapazes.

**Key words e Palavras-chave**

Breastfeeding; Asthma; Children;

Aleitamento materno; asma; crianças;
Introduction

Asthma

Asthma is one of the most common chronic diseases that presently affects approximately 300 million people worldwide. Over the last 30 years, both the prevalence and severity of asthma have risen in affluent countries, but now appear to have stabilized, with more or less 10–12% of adults and 15% of children affected by the disease (1-4). In developing countries where the prevalence of asthma had been much lower, there is a rising incidence that seems to be associated with increased urbanization (1).

The hygiene hypothesis as an explanation for increase in allergy, and therefore asthma, in westernised countries is a globally accepted theory (5). One of the possible explanations for the observed increase of atopic diseases in early childhood is the reduction of microbial exposure and, as a result, a different development of the T helper type 1 (Th1)/ T helper type 2 (Th2) immune response (6).

Asthma is a syndrome characterized by airflow obstruction due to excessive narrowing of the airways causing airflow reduction, symptomatic wheezing and dyspnea (1). It may be caused by different disorders. The reaction allergen-specific immunoglobulin E (IgE) that activates mast cells and initiates a complex and redundant inflammatory process, where cells, cytokines and adhesion molecules are involved at different stages is the triggering event in allergic subjects. Actually, mucosal eosinophilic inflammation is one of the typical characteristics of asthma and the particular T helper type 2 (Th2) phenotype of allergic patients favours it (7).
There are some risk factors that are known to be involved in asthma, some are endogenous factors (genetic predisposition, atopy, airway hyperresponsiveness, gender and maybe ethnicity) while others are environmental (indoor and outdoor allergens, occupational sensitizers, passive smoking, respiratory infections and maybe obesity and early viral infections) (1). Some of these factors are present in early life (2).

There is an effort to urgently reverse this trend of risen asthma (8), and breastfeeding could be one of the solutions. However, the longstanding question of whether breastfeeding prevents or reduces the incidence of asthma remains controversial.

**Breastfeeding**

Breastfeeding is universally recommended by the world’s health and scientific organizations as the best way of feeding infants (9-11). Years of investigation have shed light on the vast range of benefits not only for children but also for mothers and society.

For mothers, breastfeeding helps recovering from pregnancy and childbirth simultaneously offering them lifelong health advantages (10).

For society, breastfeeding provides an array of economic and environmental rewards (10).

For children, breastfeeding protects against acute and chronic illnesses and supports optimal development. Breastfeeding offers advantages for children that cannot be substituted by any other form of feeding. The benefits of breastfeeding begin right after childbirth and remain for many years after breastfeeding ends. Examples of these benefits are:
• higher scores on cognitive and IQ tests at school age, and also on tests of visual acuity (12-15);
• lower incidence of sudden infant death syndrome (SIDS) (10, 16);
• breastfed children are less likely to suffer from infectious illnesses and their symptoms (e.g., diarrhoea (17), ear infections (17, 18), respiratory tract infections, meningitis (10, 17));
• lower risk of the two most common inflammatory bowel diseases (Crohn’s disease, ulcerative colitis) (19);
• decreased incidence of some forms of cancer (10);
• possible lower risk of juvenile onset diabetes (19);
• possible lower risk of obesity in childhood and adolescence (20-23);
• fewer cavities and diminished need for braces (24).

Despite these important benefits, there is conflicting data regarding the impact of breastfeeding on the development of asthma.

**Previous Studies**

Whether breastfeeding protects against the development of allergy and asthma has been regularly studied and hotly debated for more than 70 years (25-32). Some studies provided evidence of a negative association consistent with protective effect (3, 25-27, 31-44), whereas some studies reported either no association (45-52), or a positive association between the duration of breastfeeding and the risk of asthma (53-58).

Regarding the cohort studies, there are some that show decreased risk of asthma: a prospective birth cohort study in Sweden found that longer breastfeeding duration reduced the risk of asthma during the first 4 years of life, especially
among infants without heredity for allergy (37) and an Australian cohort study found that exclusive breastfeeding for at least 4 months after birth significantly reduced the risk of asthma at age 6 years (3). No association was observed between breastfeeding and the risk of asthma in two cohort studies in Australia and in the United Kingdom (45, 52). On the other hand, breastfeeding for 4 weeks or longer was associated with an increased risk of asthma at 9–26 years in a New Zealand birth cohort (56). The Tucson Children’s Respiratory Study found that exclusive breastfeeding for 4 months or more was related to an increased risk of asthma and recurrent wheeze beginning at the age of 6 years although an association with recurrent wheeze early in life was preventive (58).

Concerning the reviews, a systematic review with meta-analysis of 12 prospective cohort studies came to the conclusion that exclusive breastfeeding during the first 3 months after birth protects child from asthma. The summary OR for the effect was 0.70 (95% CI 0.60, 0.81). This effect was greater in children with a family history of atopy [OR = 0.52 (95% CI: 0.35-0.79)] than in a combined population [OR = 0.73 (95% CI: 0.62-0.86)] (27). Friedman and Zeiger summarized in their recent review that exclusive breastfeeding should be encouraged for at least 4 to 6 months in infants at both high and low risk of atopy and independent of maternal asthma (25).

Some authors demonstrating a beneficial effect of breastfeeding on allergic disease indicate that both the duration (38, 41) and exclusivity (3) are important. However, there is scarce evidence of the role of long-term breastfeeding in the development of asthma.
Since most studies focus more on the exclusive breastfeeding for short-time rather than on its duration, and because there have been no studies showing the association between breastfeeding and asthma in Portugal, the present study examines that relationship amongst Portuguese school aged children.

**Objectives**

The aim of the present study was to quantify the association between the duration of breastfeeding (considering the duration of breastfeeding divided in 2 categories, &lt; 3 months) and the presence of asthma in a sample of 1976 children (5-10 years). Another purpose was to estimate the prevalence of asthma and breastfeeding in the present sample.

**Participants and Methods**

The study was a cross-sectional analysis, approved by each School Committee ("Agrupamento") and by the Ethical committee of São João Hospital, Porto.

**Study population**

Participants were selected at random from 40 elementary schools (38 public and 2 private ones were invited to participate in the study), throughout the city of Porto, Portugal, of which 35 schools (33 public and 2 private ones) accepted to take part. A total of 5867 children were therefore recruited.

Letters were distributed to all parents who agreed to take part outlining the aims of the study along with a consent form. Of those schools who agreed to take part
58% of parents signed and returned the form fulfilled. Therefore, the sample consisted of 3391 children. Anthropometric measurements were taken from all consenting children and questionnaires were distributed to parents of which 2512 were returned (74%). Children excluded from analysis included three subjects that presented congenital malformations, another 242 due to incomplete/incorrect questionnaire and 241 children for presenting extreme values of energy intake considering the Willet’s cut-off \(^{(59)}\). Furthermore, all pre-school children were removed (n = 50) leaving a final sample of 1976 children from 5-10 years old, of which 991 (50.2%) were girls and 985 (49.8%) were boys. However, data regarding asthma was available from 1946 (98%) children and data regarding both breastfeeding and asthma was available from 1922 children (97%).

**Measurements**

Information about child’s sex and date of birth, mothers age at birth, smoke inside the house, presence of asthma in children and in their parents, and breastfeeding were obtained through a structured questionnaire completed by the parents.

**Age**

The age of the children was then calculated based on the date of birth. Mother’s age at birth was calculated subtracting the age of the child to the current age of the mother.

**Presence of smoke inside the house**

The smoke inside the house was assessed by the question: “Does anyone smoke inside the house, presently?” (Yes / No / Don’t know).
Asthma

Asthma condition was defined as asthma ever diagnosed by a doctor. Parents answered the question: “Did a doctor ever tell you that your son had asthma?” (Yes / No / Don’t know). The atopic parents were identified by the answer to the question: “Did the child’s mother/father ever have asthma or allergic rhinitis?” (Yes / No / Don’t know).

Breastfeeding

Concerning the breastfeeding, parents were asked to indicate whether the mother had never breastfed or breastfed for less than one month, 1 to 3 months, 3 to 6 months, 6 to 12 months or more than one year. For the unconditional logistic regression models, we grouped the categories of the duration of breastfeeding into 2 categories: </> 3 months.

Anthropometrics

In each school, two trained persons performed anthropometric measurements using a standardized procedure. Anthropometric measurements were performed in light indoor clothing without shoes. Height was measured using a stadiometer, with the head in the Frankfort plane, and weight was measured using an electronic scale with an error of ± 100 g (Dry, Model 780, Germany). Body mass index (BMI) was then calculated. Prevalence of overweight and obesity were also determined and calculated as recommended by the International Obesity Task Force, making a correspondence between the traditional adult cut-offs (higher than 25 kg/m² to define overweight and 30 kg/m² to define obesity) and
specific values for children considering sex and age \(^{(61)}\). Children with low or normal weight were classified, for analyses, as non-overweight.

**Statistical analysis**

Data were described as counts and proportions for categorical variables. Chi-square tests were used to compare proportions of several variables. A P-value of less than 0.05 was considered statistically significant.

Unconditional logistic regression models were fitted, separately for boys and girls, to estimate the magnitude of the association between breastfeeding (considering the duration of breastfeeding divided in 2 categories, \(<\!/\!/> 3\) months) and the presence of asthma, adjusting for confounders (age, BMI, atopic parents, smoke inside the house, mother’s age at birth).

Data analysis was performed using the statistical package SPSS, 16.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Characteristics of the study population**

The prevalence of asthma was significantly higher among boys (11.2% vs 7.4%, p=0.004) (table 1). There is no statistically significant difference between the prevalence of asthma amongst ages (table 1).

Children who have atopic mother have higher prevalence of asthma (13.0% vs. 5.1%, p < 0.001 for girls; 15.5% vs. 8.9%, p = 0.004 for boys), as do so children
who have atopic father (10.7% vs. 5.9%, p = 0.029 for girls; 17.3% vs. 9.6%, p = 0.005 for boys) (table 1).

Table 1 also shows the distribution of the study population by classes of breastfeeding duration and the prevalence of asthmatic children in each class, divided by sex. There is no statistically significant difference in the duration of breastfeeding between boys and girls. The prevalence of asthmatic boys decreased with increasing duration of breastfeeding (p for trend = 0.022). No such significant association was observed in girls.

Table 1 - Prevalence of asthma in the sample according to different categories of possible confounders.

<table>
<thead>
<tr>
<th></th>
<th>Girls</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>N</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>978</td>
<td>72</td>
<td>7.4</td>
<td>968</td>
<td>108</td>
<td>11.2</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>2</td>
<td>13.3</td>
<td>16</td>
<td>4</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>212</td>
<td>12</td>
<td>5.7</td>
<td>240</td>
<td>20</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>265</td>
<td>20</td>
<td>7.5</td>
<td>246</td>
<td>29</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>210</td>
<td>17</td>
<td>8.1</td>
<td>209</td>
<td>29</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>236</td>
<td>16</td>
<td>6.8</td>
<td>214</td>
<td>23</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>5</td>
<td>12.5</td>
<td>43</td>
<td>3</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p for trend = 0.498</td>
<td>p for trend = 0.942</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-overweight</td>
<td>579</td>
<td>37</td>
<td>6.4</td>
<td>566</td>
<td>62</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>overweight</td>
<td>263</td>
<td>19</td>
<td>7.2</td>
<td>243</td>
<td>26</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>obesity</td>
<td>106</td>
<td>13</td>
<td>12.3</td>
<td>135</td>
<td>16</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p for trend = 0.058</td>
<td>p for trend= 0.833</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Atopic mother

<table>
<thead>
<tr>
<th></th>
<th>yes</th>
<th>246</th>
<th>32</th>
<th>13.0</th>
<th>245</th>
<th>38</th>
<th>15.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>702</td>
<td>36</td>
<td>5.1</td>
<td>683</td>
<td>61</td>
<td>8.9</td>
</tr>
</tbody>
</table>

p < 0.001  
p = 0.004

### Atopic father

<table>
<thead>
<tr>
<th></th>
<th>yes</th>
<th>169</th>
<th>18</th>
<th>10.7</th>
<th>162</th>
<th>28</th>
<th>17.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>723</td>
<td>43</td>
<td>5.9</td>
<td>710</td>
<td>68</td>
<td>9.6</td>
</tr>
</tbody>
</table>

p = 0.029  
p = 0.005

### Mothers age at birth

<table>
<thead>
<tr>
<th>Tertile</th>
<th>1&lt;sup&gt;st&lt;/sup&gt;</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>number</td>
<td>number</td>
</tr>
<tr>
<td></td>
<td>Tertile</td>
<td>365</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Tertile</td>
<td>344</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Tertile</td>
<td>262</td>
<td>21</td>
</tr>
</tbody>
</table>

p for trend = 0.813  
p for trend = 0.446

### Smoke inside the house

<table>
<thead>
<tr>
<th></th>
<th>yes</th>
<th>295</th>
<th>18</th>
<th>6.1</th>
<th>259</th>
<th>30</th>
<th>11.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>677</td>
<td>54</td>
<td>8.0</td>
<td>708</td>
<td>78</td>
<td>11.0</td>
</tr>
</tbody>
</table>

p = 0.305  
p = 0.805

### Breastfeeding

<table>
<thead>
<tr>
<th>Duration</th>
<th>Never</th>
<th>54</th>
<th>6</th>
<th>11.1</th>
<th>61</th>
<th>8</th>
<th>13.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td>152</td>
<td>11</td>
<td>7.2</td>
<td>125</td>
<td>19</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>1 to 3 months</td>
<td>267</td>
<td>22</td>
<td>8.2</td>
<td>227</td>
<td>29</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>3 to 6 months</td>
<td>210</td>
<td>13</td>
<td>6.2</td>
<td>234</td>
<td>25</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>6 to 12 months</td>
<td>187</td>
<td>13</td>
<td>7.0</td>
<td>206</td>
<td>17</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>95</td>
<td>6</td>
<td>6.3</td>
<td>104</td>
<td>8</td>
<td>7.8</td>
<td></td>
</tr>
</tbody>
</table>

p for trend = 0.329  
p for trend = 0.022

N – number of children in each class

n – number of asthmatic children in each class
Association between breastfeeding and asthma

Breastfeeding for more than 3 months was inversely related to the occurrence of asthma amongst boys [OR = 0.645 (95% CI: 0.430 – 0.967]. For girls, this association was not statically significant [OR = 0.774 (95% CI: 0.476 - 1.258). When adjusting for possible confounders (child’s age, mother’s age at birth, asthmatic mother, asthmatic father, presence of smoke inside the house and BMI), the ORs remained similar – boys: OR = 0.630 (95% CI: 0.398 – 0.997) and girls: OR = 0.886 (95% CI: 0.512 - 1.533) (Table 2).

Table 2 - Odds ratios (crude and adjusted for confounders) for asthma according to categories of breastfeeding duration.

<table>
<thead>
<tr>
<th>Breastfeeding</th>
<th>Crude</th>
<th>Adjusted</th>
<th>Crude</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Girls</td>
<td>Boys</td>
<td>Girls</td>
<td>Boys</td>
</tr>
<tr>
<td>≤ 3 months</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>≥ 3 months</td>
<td>0.774 (0.476-1.258)</td>
<td>0.645 (0.430-0.967)</td>
<td>0.886 (0.512-1.533)</td>
<td>0.630 (0.398-0.997)</td>
</tr>
</tbody>
</table>
Discussion

Brief summary of the results and comparison with literature

We found a lower prevalence of asthma amongst girls than boys (7.4% vs. 11.2%, p = 0.004). These findings are similar to those described in literature (62, 63). No single straightforward mechanism can explain the gender differences found in asthma due to the complexity of the disease. Nevertheless, it seems to be related to biological sex differences as well as sociocultural and environmental differences (64). Concerning the duration of breastfeeding, there is no statistically significant difference between boys and girls. However, in the international literature, most studies show that girls are usually breastfed for longer periods than boys (65-68), but also the opposite is found (69, 70).

We found a 35.5% (CI: 3.3% - 57.0%) decrease in the probability of having asthma, and 37.0% (CI: 0.3% - 60.2%) when adjusted for possible confounders amongst boys who were breastfed for a longer period (> 3 months vs. < 3 months). Nevertheless, for girls the decreased occurrence of asthma was not statistically significant. This result was comparable to those found by van Merode T. et al (71). However, they only studied high-risk infants and asthma-like symptoms while our study involves all type of children and the diagnose of asthma by a doctor.

Despite child’s BMI, mother’s age at birth and smoke inside the house being described in literature as risk factors for asthma, it didn’t happen in this population (table 1).
Biological explanation of the results

Breastfeeding is of considerable relevance to the development of the immune system in infancy and as a result it may influence the incidence and severity of subsequent asthma and atopy later in childhood \(^{(40)}\). There are at least five reasons to expect that breastfed children may show a reduced incidence of asthma and atopic disease \(^{(72)}\):

1. Breastfeeding makes children less exposed to foreign dietary antigen \(^{(72)}\), including those in cow’s milk \(^{(73)}\). Nevertheless, there are also antigens in mother milk, like β-lactoglobulin, but these antigens may induce tolerance instead of allergic sensitisation \(^{(74)}\).

2. There are factors in human milk that encourage gastrointestinal mucosa maturation, thus allowing early “closure” of macromolecular absorption \(^{(72)}\). In many mammals, the most remarkable effect of diet onto intestinal development occurs immediately following the first feed of mother’s milk. This may be caused by an expression of genes triggered by the constituents of the milk. A range of growth factors, hormones, and other similar biologically active substances present in human milk act synergistically in growth modulation \(^{(75)}\).

3. The possibility of sensitisation may be reduced by decreasing the incidence of infection and possibly altering the gut microflora that can act as an adjuvant for ingested food proteins \(^{(72)}\). Soluble and cellular host defence components as well as nonspecific lymphoid components and nonlymphoid antiinfectious elements, which are present in human colostrum and milk, protect the neonate from infection in a hostile environment \(^{(76-78)}\).

4. Macromolecular uptake is restricted by functional immunomodulatory and antiinflammatory factors contained in human milk \(^{(72)}\). Long lasting systemic
immunomodulating properties that may be present in human milk \(^{(79)}\) can protect against a number of diseases \(^{(80-84)}\).

5. Cytokines and growth factors in human milk may play a significant role in modulating the development of asthma \(^{(72)}\).

**Controversies**

Until some time ago, the role of breastfeeding in preventing asthma and allergy was unquestionable, along with consistent evidence from many cross-sectional and cohort studies \(^{(3, 85-87)}\). However, in 2000, data from a US cohort study in Tucson showed that breastfeeding was generally protective against atopic illness although breastfeeding mothers who had high IgE levels had children with higher rates of asthma and allergy \(^{(58)}\). This was followed by a New Zealand cohort study in Dunedin, which showed that children who were breastfed for more than 4 weeks were more likely to have asthma as young adults \(^{(56)}\).

The methodologic quality of both cohort studies was critically appraised by Peat et al. \(^{(88)}\). Regarding the Dunedin cohort, their major concern was that, like in our study, breastfeeding data were obtained retrospectively (at 3 years of age), so there could be mistaken or biased recall. The rates and duration of breastfeeding were also low compared to the latest trends in Australia \(^{(89)}\). The Tucson cohort was drawn from a population of children who obtained care from paediatricians attached to a specific insurance provider and hence represent a middle-class population. Both cohorts were criticized for not defining the level of exclusive breastfeeding and a lack of scientific plausibility for their results.

Nevertheless, these studies have various strengths. The Tucson cohort had good outcome measures of asthma and atopy and was well powered, and some have
argued that there are biologically possible explanations for their findings. In order to defend their cohort, Sears et al. (56) indicated that there was a high degree of agreement of breastfeeding data with more recent child health records and that the cohort met the most of the criteria proposed by Kramer (30) for determining the effect of breastfeeding on asthma. It was also suggested that a plausible explanation for an association between breastfeeding and increased atopic disease could be the hygiene hypothesis.

**Reasons for different results in literature**

The duration of follow up and ages at which outcomes are assessed are the main reasons why in some studies breastfeeding protect against atopy and asthma, whereas in others the risk increases. Studies in which early childhood outcomes (eczema or wheezing illness before the age of 2) were assessed demonstrate protection from prolonged or exclusive breastfeeding, while those in which outcomes in later childhood were assessed show increased atopy and asthma risk. However, there are other reasons for the heterogeneity of these results. A key issue is the distribution of the duration of breastfeeding in the study population. The range of duration varies considerably. In some study populations, like the U.S. (33) and New Zealand (56), many children were not breastfed while in others, for instance in Norway (39) and Sweden (38), practically all children are fed with breast milk. This becomes important when fitting a dichotomous variable if the true relation is non-linear.

The extent of follow-up and the age of onset of asthma are other important issues. If breastfeeding delays the onset of asthma, the present prevalence of asthma would be lower amongst breastfed than non-breastfed in early childhood, but
similar in later life. A stronger protective effect (summary OR = 0.47, 95 % CI 0.34 - 0.66) in studies with less than a 2-year follow-up period compared to those with 2 or more years follow-up period (summary OR = 0.72, 95 % CI 0.62 - 0.82) are shown in the meta-analysis of Gdalevich et al. (27). In the present study, we tried to understand the long-term effects of breastfeeding and utilized as outcomes the occurrence of asthma at the age of 5 to 10 years old.

Breast milk is itself naturally complex immunologically and has allergens that may in some cases be sensitizing and in other cases protective, depending on a diversity of factors. Besides, the IgE concentrations diverge in breast milk. There may be also genetic differences in infant/mother pairs that have an effect on whether breastfeeding would be protective or sensitizing.

The relation between breastfeeding and asthma could also be changed by exposures to environmental factors. Data from the third US National Health and Nutrition Examination Survey indicated that in children exposed to environmental tobacco smoke, breastfeeding might reduce the prevalence of asthma and recurrent wheezing, but not in unexposed children (33). In the present study, we adjusted for the presence of smoke inside the house, but it did not modify the relationship.

The use of different cut points for established breastfeeding and different confounding factors may also be relevant.

**Confounders**

A review of the literature recognized an array of possible confounding factors and we adjusted for some of them:
- atopic father or mother – if one of the parents is atopic or asthmatic, their infants are more likely to develop asthma; in addition, if asthmatic women were more likely to breastfeed their children, this may have resulted in an increased prevalence of asthma in breastfed children\(^{(35, 90)}\).
- mothers age at birth – the beneficial effect of breastfeeding on asthma might depend on the high concentration of sCD14 in the mother’s milk; as higher levels of sCD14 are associated with younger age, it is expected that younger mothers that breastfed have less risk to have children with asthma\(^{(44)}\).
- BMI – children with higher BMI have increased risk of developing asthma\(^{(40, 91-93)}\), and this trend almost reached statistical significance in girls; nevertheless, BMI was considered a confounding variable in logistic regression.
- presence of smoke inside the house – tobacco smoke is one environmental risk factor for asthma\(^{(94-96)}\); besides, women who smoked during pregnancy and in the postnatal period have children with reduced lung function in both infancy and later childhood, increased lower respiratory tract infections in infancy, and suffer more frequent exacerbations of asthma and may have an increased risk of developing asthma\(^{(97)}\); there is also a strong association between smoking and both the decision to breastfeed and the duration of breastfeeding\(^{(98)}\).

**Limitations and Strengths**

This study has some limitations. First, the number of parents who return the consent form and the questionnaires fulfilled maybe considered low (42.8 %), and those who didn’t answer may be different from those who answered introducing a selection bias. It is also known from previous research into survey participation that population-based samples may under-represent the most socio-economically
disadvantaged and overrepresent the advantaged (99). Moreover, from the final sample composed of 1976 children, data regarding both breastfeeding and asthma was only available for 1922 (97%). Secondly, it was a retrospective study, so there may be also a recall bias. When assessing the outcomes, we only relied on the reports of the parents, which may have led to a misclassification of the children both regarding the diagnosis of asthma as the categories of breastfeeding. Besides, the degree of exclusive breastfeeding is not known. As most studies relate the time of exclusive breastfeeding with asthma, it was difficult to compare our results with them. Thirdly, although we adjusted for age, atopic parents, mother’s age at birth, child’s BMI and presence of smoke inside the house it is acknowledged that there may be other confounders that were not measured and cannot be taken into account, such as the age of onset of asthma, mothers who smoked during pregnancy and in the postnatal period or the presence of indoor domestic pets.

However, this study has important strengths as is the relatively high number of participants involved. Also, of the 3391 questionnaires distributed, 2512 returned completed, so our response rate was relatively high (74%). Since being male is a known risk factor for asthma (100) we stratified the population based on sex and then adjusted for known confounders. It is essential to control confounders (factors that will change rates of both breastfeeding and asthma) in an observational study such as this. We compared asthma with the extent of breastfeeding while most studies focus more on the exclusive breastfeeding for short-time rather than on its duration. Besides, there are scarce studies regarding these issues (asthma and breastfeeding) in Portugal. This means that this is a pioneer study in this area.
Conclusions

Our findings support the hypothesis that prolonged breastfeeding for more than 3 months among boys may reduce their chance of having asthma in childhood. However, further studies are essential to confirm these benefits and to understand better the mechanisms concerned. Nevertheless, public health interventions promoting an increased duration of breastfeeding may help to reduce the prevalence of childhood asthma, especially in boys.
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