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Article

Milk Other than Breast Milk and the Development of Asthma in Children 3 Years of Age. A Birth Cohort Study (2006-2011)

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Abstract: Prevalence of asthma in Australian children is amongst the highest in the world. Although breastfeeding positively influences infants' immunity, early introduction of Milk Other than Breast Milk (MOTBM) may also play an important role in the development of Asthma. The aim of this study was to investigate the association between the introduction of MOTBM in the first six months after birth and the development of reported persistent asthma in children 3-years old. A sample of 1,121 children was extracted from the Environments for Healthy Living longitudinal birth cohort study. Introduction of MOTBM during the first six months after birth increased the risk of development of persistent asthma by almost two-folds after adjusting for other covariates (Adjusted Relative Risk (ARR): 1.71, 95%CI: 1.03-2.83, p= 0.038). This study indicates that the introduction of MOTBM in the first six months of life is a risk factor for asthma incidence among children 3-years old. This result is important in explaining the benefits of breastfeeding as part of public health interventions to encourage mothers to increase breastfeeding initiation and duration and avoid introduction of MOTBM in the first six months after childbirth.

Keywords: asthma; breastfeeding; milk other than breast milk

1. Introduction

Asthma is a major public health issue predominantly facing developed countries, including Australia [1]. Asthma is the most common chronic disease among children. The World Health Organization (WHO) estimates 235 million people with the disease [2]. The worldwide prevalence of childhood asthma has been increasing considerably in the last few years [3]. The prevalence of asthma in Australian children is amongst the highest in the world [4]. Explanations for this increase are not yet clear thus limiting the opportunities to develop targeted primary prevention measures [3]

Asthma is a variable phenotype and its definition across studies is highly inconsistent. Clinically, asthma is defined as a chronic inflammatory disorder of lungs that is characterized by recurrent episodes of wheezing, shortness of breath, tightness of chest and coughing, associated with limitation of airflow in the respiratory system [5].

Asthma has a broad spectrum of possible determinants extending from genetics to lifestyle to environmental factors [3]. Inherited factors hypothesized to be associated with the risk of asthma include: maternal asthma [6], young maternal age [7], low level of mother's education [8], Aboriginality [9] and child sex [10]. In addition, several prenatal and postnatal factors and early childhood exposures have been reported to contribute to the development of asthma in the offspring.

Examples for these factors are maternal smoking during pregnancy [11], early gestational age [12], cesarean section [13], prematurity [14] and low birth weight [15]. Furthermore, the existence of eczema [16] and food allergy [17] has been associated with increased risk of asthma as reported by several reports.

Mostly, breastfeeding is the simplest method of infant feeding as well as the healthiest and the cheapest. However, in many cases Milk Other than Breast Milk (MOTBM) is introduced early in infant life for many reasons [18]. Breast milk offers ideal nutrition for a developing infant, with compositional changes that are adapted to the changing needs of the infant [19]. The components of breast-milk stimulate the infant's own immune system safeguarding him/her against the development of allergic disease [20]. Although breastfeeding provides health benefits, with particular impact on infant's immunity, it is not known whether or not breastfeeding decreases the risk of developing asthma. Another important question yet to be answered is the link between early introduction of MOTBM and development of Asthma. Many studies have attempted to assess the role of breastfeeding in decreasing the risk of development of asthma, however findings have been controversial [5,20–22]

A systematic review conducted by Matheson et al. reviewed 41 articles addressing the association between breastfeeding and protection against allergic diseases found that the protective effect of breastfeeding in the development of asthma was unclear with contradictory results were reported [20]. Another systematic review conducted by Lodge et al. that included 29 studies found some evidence that breastfeeding is associated with a 10% reduction in risk of asthma in children aged 5–18 years [22]. The authors however pointed to the poor quality of reviewed studies that might have an effect on the final conclusion [20–22].

On the other hand, numerous studies were conducted on MOTBM feeding and its effect on development of Asthma [23–26]. These studies however, were focusing on comparing the effects of various types of MOTBM, such as cow milk, goat milk, soymilk or hydrolyzed milk, on increasing or decreasing the risk of development of Asthma relative to each other. Some results showed that certain types of these MOTBM increased the risk of development of Asthma than the others [23,26,27]. However, the effect of any type of MOTBM in increasing the risk of development of Asthma relative to breast milk was not addressed.

Defining asthma through testing of lung function is challenging before the age of 5-years [28]. However, several studies monitored early signs of asthma during the first 3-years of infant's life to test for the impact of various factors on development of asthma in later life [29–31]. Furthermore, long term follow up studies in different populations have concluded that asthma, like other common chronic diseases, originates in early years of life and that impaired respiratory function at early childhood is usually associated with asthma in adulthood [29,30,32,33].

Hence, the aim of our study is to assess whether the introduction of any type of MOTBM during the first 6 months after birth increases the risk of later development of asthma among children age 3-years.

2. Materials and Methods

2.1. The Environments for Healthy Living study

The Environments for Healthy Living study (EFHL) is a prospective, multi-level, multi-year longitudinal birth cohort study with six recruitment years from 2006 to 2011. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000931077)[34].

The study recruited pregnant women from three geographically defined contiguous Health Districts in Australia (Logan City and the Gold Coast in Queensland, and the Tweed area in New South Wales) [35]. Perinatal data were obtained from maternal medical records following discharge from hospital, completed by the hospital midwives. Data items included maternal conditions, obstetric complications, delivery information and child information such as gender, gestational age and birth weight [34].

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The EFHL study was approved by the Griffith University Human Research Ethics Committee (Research ethics approval No is MED/16/06/HREC, MED/23/11/HREC). Additional ethical approval for participant recruitment was also obtained from each of the three participating public maternity hospitals (Logan Hospital HREC/06/QPAH/96, Gold Coast Hospital HREC/06/GCH/52, The Tweed Hospital NCAHS HREC 358N). A consent form was read and signed by each participant who agreed to release the hospital perinatal data related to the birth of her child, complete a maternal baseline questionnaire, and to individual follow- up [35].

When EFHL infants turned 1-year of age, the primary carers, predominantly the mothers, completed a questionnaire (wave 1) including questions about demographics, household socioeconomics, child feeding and diet, child health and development (including medically diagnosed asthma and food allergy). When the children reached 3-years and 5-years old, the primary carers were again contacted and completed similar questionnaires (wave 2 and 3).

2.2. Study population

Children age 3-years from the EFHL study were included in this study. These children were recruited between 2006 and 2010 with follow-ups at 1- and 3-years of the study waves 1 and 2 respectively (Figure 1). Twins were handled as unrelated children (17 children (1.7%)).

Recruitment		Follow-up questionnaire						
Year	Number	2007	2008	2009	2010	2011	2012	2013
2006	631	1-year		3-year				
2007	477		1-year		3-year			
2008	456			1-year		3-year		
2009	628				1-year		3-year	
2010	715					1-year		3-year
Total	2,907							

Figure 1: Study cohort, wave 1 (solid border) and wave 3 (dash border)

2.3. Study variables

The outcome variable, reported medically diagnosed persistent asthma, was derived from a question to the carer on whether the child has ever been diagnosed by a medical doctor with wheezing or asthma. A child was considered to have medically diagnosed persistent asthma if the carer indicated that the child was diagnosed with asthma at both 1-year (first wave) and 3-year (second wave) follow-ups. Those whose asthma status was not consistent at both waves were excluded from the study.

The main exposure variable is introduction of MOTBM at less than six months after birth, derived from the question: "How old was your child when he/ she first had any other type of milk in a cup or a bottle? (e.g. formula, cow's milk, soy milk)".

Covariates were selected from the literature [6,7,16,17,8–15]. Those related to the child included: whether stopped breastfeeding at <6 months of age, gender, delivered by caesarean section, low birth weight (weight<2500g), preterm delivery (gestational age <37 weeks), frequency of exposure to cigarettes smoke (derived from the question: "Indicate how regularly the baby is in a room or enclosed place where other people are smoking"), ever been diagnosed with eczema and ever diagnosed with food allergy. Those related to the mother were: age in years, level of education, place of birth, indigenous status, average number of cigarettes smoked each day on average at >20 weeks of pregnancy and treatment of asthma during pregnancy.

2.4. Statistical analyses

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Medically diagnosed persistent asthma was analyzed as a binary outcome variable. Percentages, means and standard deviations were used to describe the data. Logistic regression analyses were used to model the risk of medically diagnosed persistent asthma in relation to introduction of MOTBM at less than six months after birth and other potential confounding variables. Purposeful selection method was used to build the models. Initially, univariate logistic regression analyses were performed to select variables to be included in the multivariable logistic regression analyses. Variables with p-values < 0.25 were considered to develop an initial reduced model [36]. Using adjusted Wald tests, variables that tested insignificant (with p-values > 0.05) were then eliminated from this model. Insignificant variables were included one at a time and assessed for significance and for confounding effects using a 10 percent [37] change in the coefficients. Likelihood ratio tests were used to compare models. Variance inflation factors were used to assess multicollinearity among variables. Hosmer and Lemeshow goodness-of-fit tests [38] were used to assess goodness of fit of the final model. With a low incidence of the outcome, Relative Risks (RR), Adjusted Relative Risks (ARR) and their 95% confidence intervals were approximated from the corresponding Odds Ratios (OR) obtained from the logistic regression analyses. STATA 15.0 [39] was used for all analyses.

3. Results

Information was obtained on 2,907 children whose mothers were enrolled in the study from 2006 to 2010. A total of 1,342 children had complete information on reported medical diagnosis of asthma at 1-year (first wave) and 3-years (second wave) follow-up. Children with and without reported medically diagnosed persistent asthma at both waves were included (n=1,138) and those whose asthma status was not consistent at both waves were excluded (n=204). Out of the 1,138 children, 17 with missing information on MOTBM were also excluded. The analytical study cohort became 1,121 children.

Table 1. Characteristics of children: overall and those with persistent asthma at end of follow-up

	Total	Persistent asthma		Total
	%	No.	%	
Total	100.0	76	6.8	1,121
MOTBM introduced at < 6 months				
No	49.0	26	4.7	549
Yes	51.0	50	8.7	572
Stopped breastfeeding at < 6 months				
No	39.5	28	6.3	443
Yes	60.5	48	7.1	678
Gender*				
Male	47.8	56	10.4	536
Female	51.7	20	3.4	580
Delivered by caesarean section*				
No	68.4	49	7.7	767
Yes	31.2	27	6.4	350
Low birth weight (Weight<2500g)				
No	97.9	75	6.8	1,098
Yes	2.1	1	4.3	23
Preterm delivery (Gestational age<37 weeks)				
No	97.7	73	6.7	1095
Yes	2.3	3	11.5	26
Frequency exposed to cigarettes smoke*				
Sometimes	6.3	8	11.3	71
Not at all	93.6	68	6.5	1,049
Ever been diagnosed with eczema				
No	89.9	61	6.1	1,008
Yes	10.1	15	13.3	113

Even been diagnosed with food allergy				
No	95.7	71	6.6	1,073
Yes	4.3	5	10.4	48

*0.1-0.4% missing data

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3.1. Characteristics of the study cohort

Among 1,121 children, about 7% of children had persistent asthma at the age of 3-years and 51% received MOTBM at less than six months after birth. There were slightly more females (51.7%) than males (47.8%). About one-third of the children (31.2%) were delivered by caesarean section and most were born full term (97.8%) and had normal birth weight (97.9%). Sixty-two percent of the mothers were aged 26-35 years and only a quarter completed university (24.8). Mothers were mostly born in Australia (72.2%), not Aboriginal/TSI (96.5%) and did not smoke cigarettes each day during pregnancy (89.2%). Key characteristics of the cohort are detailed in Tables 1 and 2.

Table 2. Characteristics of mothers: overall and those with children with persistent asthma at end of follow-up

	Total	Persistent asthma		Total
	%	No.	%	No.
Age in years				
16-25	17.9	22	10.9	201
26-30	30.9	19	5.5	346
31-35	31.1	26	7.4	349
36-45	20.1	9	4.0	225
Highest level of education*				
Did not complete high school	14.4	12	7.5	161
Completed high school	29.6	28	8.4	332
TAFE/trade or apprenticeship	30.8	27	7.8	345
University degree	24.8	8	2.9	278
Place of birth				
Elsewhere	27.8	18	5.8	312
Australia	72.2	58	7.2	809
Indigenous status**				
Aboriginal/TSI	1.4	0	0.0	16
Otherwise	96.5	75	6.9	1082
Average number of cigarettes smoked each day during pregnancy*				
0	89.2	62	6.2	1000
<=10	5.4	4	6.6	61
>10	4.7	10	18.9	53
Treatment for asthma during child's pregnancy (n=864)$				
No	75.4	66	7.9	839
Yes	2.2	4	16	25

*0.4-0.6% missing data, ** 2% missing data

$Question asked only to QLD state participants

3.2. Association between developing persistent asthma and MOTBM and other covariates

Tables 1 and 2 also report the associations between developing persistent asthma and MOTBM and other covariates. More children who were introduced to MOTBM at less than six months after birth (8.7%) persistent asthma compared to those who were not introduced (4.7%). Persistent asthma was much more prevalent among males (10.4%) compared to females (3.4%). Younger (16-25 years) (10.9%) and less educated mothers (8.0%) had higher percentages of children with persistent asthma than older ones (5.9%) and mothers who completed university (2.9%) respectively. Although only 10% of children were ever diagnosed with eczema, the diagnosis of persistent asthma was almost twice in this group (13.3%) compared to those who were not diagnosed with eczema (6.1%). Similar pattern was seen for children who were even been diagnosed with food allergy. The percentage of

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children with persistent asthma among those who were sometimes exposed to cigarettes smoke (11.3%) was much higher than those who were never exposed to smoke (6.5). Moreover, the level of passive smoking based on the total number of cigarettes smoked by mothers during their pregnancies per day did not show a dose-response effect. Persistent asthma was recorded in 18.9% of children who were exposed to tobacco smoke of more than 10 cigarettes/day while this percentage was about 6% for both children of mothers who smoked less than 10 cigarettes/day or did not smoke at all.

Table 3 summarizes the results of univariate and multivariable logistic regression modeling the likelihood of medically diagnosed persistent asthma in relation to other variables. Univariate analysis did not reveal any associations with child cesarean section delivery, low birth weight, preterm delivery, whether child stopped breastfeeding at less than 6 months or frequency child was exposed to cigarettes smoke. Although mother's level of education was significant in the univariate analysis it was included in the final multivariable model. The final model demonstrated that introduction of MOTBM in the first 6 months of life increases the risk of children having persistent asthma by 3-years of age by 71% after adjusting for other covariates (ARR: 1.71, 95%CI: 1.03-2.83, p-value=0.038). Children diagnosis with of eczema, being male, whose mothers are of young maternal age and smoke during pregnancy were associated with an increased risk of persistent asthma in children at the age of 3-years after adjusting for other covariates.

Table 3. Univariate and multivariable Logistic regression modeling the likelihood of medically diagnosed persistent asthma

	Univariate analysis		**Multivariable analysis**	
	RR [95% CI]	**p-value[1]**	**ARR [95% CI]**	**p-value[2]**
MOTBM introduced at < 6 months		0.009		
No	1.00		1.00	
Yes	1.93 [1.18,3.14]		1.71 [1.03,2.83]	0.038
Stopped breastfeeding at < 6 months		0.621		
No	1.00			
Yes	1.13 [0.70,1.83]			
Gender*		<0.001		
Male	1.00		1.00	
Female	0.31 [0.18,0.52]		0.31 [0.18,0.53]	0.000
Delivered by caesarean section		0.415		
No	1.00			
Yes	1.22 [0.75,1.99]			
Low birth weight (Weight<2500g)		0.642		
No	1.00			
Yes	0.62 [0.08,4.66]			
Preterm delivery (Gestational age<37 weeks)		0.336		
No	1.00			
Yes	1.83 [0.54,6.22]			
Frequency exposed to cigarettes smoke		0.126		
Sometimes	1.00			
Not at all	0.55 [0.25,1.19]			
Ever been diagnosed with eczema		0.005		
No	1.00		1.00	
Yes	2.38 [1.30,4.34]		2.15 [1.15,4.04]	0.017
Even been diagnosed with food allergy		0.310		
No	1.00			
Yes	1.64 [0.63,4.27]			
Age in years		0.028		
16-25	1.00		1.00	
26-30	0.47 [0.25,0.90]	0.022	0.47 [0.24,0.92]	0.028
31-35	0.65 [0.36,1.19]	0.164	0.67 [0.36,1.25]	0.206
36-45	0.34 [0.15,0.75]	0.008	0.33 [0.15,0.75]	0.009

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	Univariate analysis		Multivariable analysis	
	RR [95% CI]	**p-value[1]**	**ARR [95% CI]**	**p-value[2]**
Highest level of education		0.015		
Did not complete high school	1.00			
Completed high school	1.14 [0.57,2.31]	0.709		
TAFE/trade or apprenticeship	1.05 [0.52,2.14]	0.884		
University degree	0.37 [0.15,0.92]	0.032		
Place of birth		0.404		
Elsewhere	1.00			
Australia	1.26 [0.73,2.18]			
Average number of cigarettes smoked each day during pregnancy		0.016		
0	1.00		1.00	
<=10	1.06 [0.37,3.02]		0.89 [0.30,2.61]	0.831
>10	3.52 [1.69,7.33]		4.23 [1.91,9.37]	<0.001
Treatment for asthma during child's pregnancy (n=864)**		0.004	-	-
No	1.00		-	-
Yes	2.23 [0.74,6.69]		-	-

[1] Likelihood ratio p-value; [2] Wald test p-value

*Question asked only to QLD state participants (not included in multivariable analysis)

Multivariable analysis: RR are approximated by OR. Hosmer and Lemshow goodness and fit test p-value=0.929, 93% correct classification

4. Discussion

All screened studies compared the effects of different types of MOTBM on increasing or decreasing the risk of asthma; however, all of these studies compared the effects of different types of MOTBM relative to each other. To our knowledge, this research is the first to assess whether MOTBM, regardless of its source, increases the risk of development of asthma or not.

There are three major types of infant formula: standard cow's milk-based formulas, soy-based formulas and hypoallergenic formulas (hydrolysed cow's milk formulas) [40]. Previous studies assessing standard cow-based formulas found that these formulas were not protective against asthma during infancy or childhood [26,41]. Similarly, soy-based formula did reduce the risk of asthma when compared with standard cows-based milk formula in infants and children [26]. The literature evidence supporting the preventive effects of hydrolysed infant formulas for asthma is inconsistent and insufficient. Some studies suggest that certain partially or extensively hydrolysed formulas may reduce the risk of asthma compared to non-hydrolysed formulas for children with a family history of atopic disease [26,41,42]. In contrast, it was reported by others that infants who received hydrolysed cow's milk formula did not have a lower risk of asthma compared with those who received human breast milk or standard cow's milk formula [23].

Although several studies examined the association between different infant formulas and asthma [23,26,27,41,43], this study uniquely distinguished between breast milk and any type of MOTBM. Our result revealed that in comparison with infants who received breast milk only, those who received MOTBM during the first 6 months after birth had a 71% increased risk of persistent asthma at age of 3 years (ARR: 1.71, 95%CI: 1.03-2.83, p=0.038). This association was independent of established maternal and environmental risk factors.

Previous findings regarding duration of breastfeeding and the risk of asthma are contradictory. Although several studies showed that breastfeeding prevents asthma [44,45] there were also several disagreeing studies [46,47]. This study found no significant association between duration of breastfeeding up to 6 months and development of persistent asthma in the first 3 years of life (RR: 1.13, 95%CI: 0.70-1.83). This finding is consistent with previous studies carried out in Denmark and Sweden which showed that breastfeeding does not lower the risk of childhood asthma (OR: 1.08, 95% CI: 0.93-1.25) and (OR: 0.99, 95% CI: 0.96-1.02) respectively [47,48]

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Mode of delivery, gender, maternal and household smoking as well as maternal asthma are potential risk factors for asthma in children as demonstrated by several studies [49–54]. Gender appears to be a factor in the development of asthma, where boys in general are reported to have more severe asthma than girls [50] and higher rates of admission to hospitals [52,55]. Researchers have attributed this to airway hyper-responsiveness in childhood that is more common and more severe among males than females. Moreover, boys have smaller airway diameters relative to lung volume than girls [56,57]. Consistent to what was observed in these studies [50,52] more males (10.4%) than females (3.4%) in our study were diagnosed with persistent asthma and there is strong association between sex differences and development of asthma (p-value <0.001).

There is strong evidence in literature for a causal link between parental smoking and childhood asthma. Maternal smoking during pregnancy has been consistently associated with early childhood asthma [51,58]. Passive exposure of fetus to tobacco smoke during pregnancy has been reported by numerous studies to result in reduced lung function in the early months of infant's life, with a dose–response relationship between exposure and decreased airway calibre in early life [59,60]. Although, our results did not show dose response relationship, there was a strong association between smoking during pregnancy and the development of childhood asthma. Children who were exposed to high level of tobacco smoke of more than 10 cigarettes/day had higher risk for development of asthma (ARR: 4.23, 95% CI: 1.91-9.37, p<0.001). These results are consistent with what was previously reported by Tariq et al. [58], where the authors found that smoking during pregnancy was associated with the development of childhood asthma at two years of age (OR: 2.2, 95% CI: 1.5-3.4, p<0.001).

As demonstrated by several studies [6,12]; maternal asthma was also associated with an increased risk of childhood asthma. Inconsistently, our univariate analysis did not show any association between maternal asthma and development of childhood asthma before the age of 3 years. It is worth mentioning that maternal asthma was not included in our multivariable analysis as the variable regarding this issue was asked only to QLD state participants.

A low level of maternal education is another risk factor for development of asthma as revealed by our study. Children born to mothers with university degree were 63% less susceptible to asthma than children born to mothers who did not complete high school (RR: 0.37 95% CI: 0.15-0.92, p=0.032). Researchers argue that maternal education affects child health in various ways. Mothers who have low levels of education can hardly get social support in addition to limited access to health information. Overall, this increases the exposure to risk factors that affects mothers and consequently their children health negatively [8,61].

It has been hypothesized that caesarean section might increase the risk for developing asthma compared to vaginal delivery, as a result of depriving the newborn of exposure to maternal microflora [49]. A number of studies found that complicated modes of delivery and caesarean section might have a positive association with development of asthma [49,53,54]. In the present study we did not observe similar association between caesarean section and persistent asthma diagnosed at the age of 3 years (OR: 1.22, 95% CI: 0.75-1.99).

There is evidence that suggests the existence of a complex relationship between eczema and asthma, where it was found that the majority of infants with early eczema develop asthma in childhood; an example of the so called "atopic march" [62]. Researchers suggested that understanding the relationship between eczema and asthma might help in preventing asthma developing in these vulnerable children, to prevent the atopic march. Demehri and his colleagues reported the existence of many theories about the link between eczema and asthma. One theory suggests that the impairment of skin, which is body's protective external barrier, might stimulate the immune system to over-react to any potential allergen present in the body, including the surface of the airways in the lungs [63]. In line with several previous studies [62,64,65], we found that eczema in infancy was strongly associated with the development of asthma in children at age of 3. Multivariable analyses showed that existence of eczema at baseline increased the risk of developing asthma by two fold (RR: 2.15, 95% CI: 1.15-4.04, p=0.017) relative to children without eczema at the beginning of the study.

There are several limitations of this study. Firstly, the recruitment was through three public maternity hospitals only in the participating districts (Logan, Gold Coast and the Tweed Hospitals).

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Secondly, the use of self-report questionnaires to collect the information from primary carers may lead to recall bias as evidenced in previous cohort studies [20,66]. The strengths of this study lie in its large sample size, its prospective design and the use of carefully constructed questionnaires to maximize accuracy and completeness through asking specific questions, which made results less subject to recall bias. In addition, asthma was diagnosed by a physician and not by parental self-report of symptoms.

In summary, the current study indicates that introduction of MOTBM during the first six months after birth is a risk factor for asthma in children 3-years of age. Although more studies and further analyses are needed to confirm these findings and to better understand the underlying mechanisms, public health interventions promoting the risk of early introduction of MOTBM and encouraging mothers to refrain from using it during the first six months after birth may help in reducing the morbidity and prevalence of childhood asthma. In support of previous research, the current data did not show a correlation between breastfeeding and protection against asthma.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Asthma Australia, Statistics: People and asthma.
2. World Health Organization 2018, Media centre: Asthma.
3. Oddy, W. H. Breastfeeding, Childhood Asthma, and Allergic Disease. *Ann. Nutr. Metab.* **2017**, doi:10.1159/000457920.
4. *Australian Centre for Asthma Monitoring 2009. Asthma in Australian children: findings from Growing Up in Australia, the Longitudinal Study of Australian Children. Cat. no. ACM 17. Canberra: AIHW.;*
5. Miliku, K.; Azad, M. Breastfeeding and the Developmental Origins of Asthma: Current Evidence, Possible Mechanisms, and Future Research Priorities. *Nutrients* **2018**, doi:10.3390/nu10080995.
6. Lim, R. H.; Kobzik, L.; Dahl, M. Risk for asthma in offspring of asthmatic mothers versus fathers: A meta-analysis. *PLoS One* **2010**, doi:10.1371/journal.pone.0010134.
7. Sherriff, A.; Peters, T. J.; Henderson, J.; Strachan, D. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3 1/2 years. *Int. J. Epidemiol.* **2001**, doi:10.1093/ije/30.6.1473.
8. Lewis, K. M.; Ruiz, M.; Goldblatt, P.; Morrison, J.; Porta, D.; Forastiere, F.; Hryhorczuk, D.; Zvinchuk, O.; Saurel-Cubizolles, M. J.; Lioret, S.; Annesi-Maesano, I.; Vrijheid, M.; Torrent, M.; Iniguez, C.; Larranaga, I.; Harskamp-van Ginkel, M. W.; Vrijkotte, T. G. M.; Klanova, J.; Svancara, J.; Barross, H.; Correia, S.; Jarvelin, M. R.; Taanila, A.; Ludvigsson, J.; Faresjo, T.; Marmot, M.; Pikhart, H. Mother's education and offspring asthma risk in 10 European cohort studies. *Eur. J. Epidemiol.* **2017**, doi:10.1007/s10654-017-0309-0.
9. Valery, P. C.; Purdie, D. M.; Chang, A. B.; Masters, I. B.; Green, A.; Valery PC1, Purdie DM, Chang AB, Masters IB, G. A. Assessment of the diagnosis and prevalence of asthma in Australian indigenous children. *J Clin Epidemiol* **2003**, *56*, 629–35, doi:10.1016/S0895-4356(03)00081-7.
10. Chen, Y. C.; Dong, G. H.; Lin, K. C.; Lee, Y. L. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: A systematic review and meta-analysis. *Obes. Rev.* 2013.
11. Burke, H.; Leonardi-Bee, J.; Hashim, A.; Pine-Abata, H.; Chen, Y.; Cook, D. G.; Britton, J. R.; McKeever, T. M. Prenatal and Passive Smoke Exposure and Incidence of Asthma and Wheeze: Systematic Review and Meta-analysis. *Pediatrics* **2012**, doi:10.1542/peds.2011-2196.
12. Metsälä, J.; Kilkkinen, A.; Kaila, M.; Tapanainen, H.; Klaukka, T.; Gissler, M.; Virtanen, S. M. Perinatal factors and the risk of asthma in childhood--a population-based register study in Finland. *Am. J. Epidemiol.* **2008**, doi:10.1093/aje/kwn105.
13. Thavagnanam, S.; Fleming, J.; Bromley, A.; Shields, M. D.; Cardwell, C. R. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin. Exp. Allergy* **2008**, doi:10.1111/j.1365-2222.2007.02780.x.
14. Been, J. V.; Lugtenberg, M. J.; Smets, E.; van Schayck, C. P.; Kramer, B. W.; Mommers, M.; Sheikh, A. Preterm Birth and Childhood Wheezing Disorders: A Systematic Review and Meta-Analysis. *PLoS Med.* **2014**, doi:10.1371/journal.pmed.1001596.
15. Mu M, Ye S, Bai MJ, Liu GL, Tong Y, Wang SF, S. J.; Mu, M.; Ye, S.; Bai, M.-J.; Liu, G.-L.; Tong, Y.; Wang, S.-F.; Sheng, J. Birth Weight and Subsequent Risk of Asthma: A Systematic Review and Meta-Analysis. *Hear. Lung Circ.* **2014**, *23*, 511–9, doi:10.1016/j.hlc.2013.11.018.
16. van der Hulst, A. E.; Klip, H.; Brand, P. L. P. Risk of developing asthma in young children with atopic eczema: a systematic review. *J. Allergy Clin. Immunol.* **2007**, doi:10.1016/j.jaci.2007.05.042.
17. Caffarelli, C.; Garrubba, M.; Greco, C.; Mastrorilli, C.; Povesi Dascola, C. Asthma and Food Allergy in Children: Is There a Connection or Interaction? *Front. Pediatr.* **2016**, doi:10.3389/fped.2016.00034.

18. Nasser, A.; Omer, F.; Al-Lenqawi, F.; Al-Awwa, R.; Khan, T.; El-Heneidy, A.; Kurdi, R.; Al-Jayyousi, G.; Nasser A, Omer F, Al-Lenqawi F, Al-Awwa R, Khan T, El-Heneidy A, Kurdi R, A.-J. G. Predictors of continued breastfeeding at one year among women attending primary healthcare centers in Qatar: A cross-sectional study. *Nutrients* **2018**, *10*, doi:10.3390/nu10080983.
19. World Health Organization 2016, the world health report: Chapter 4; childhood and maternal undernutrition.
20. Matheson, M. C.; Allen, K. J.; Tang, M. L. K. Understanding the evidence for and against the role of breastfeeding in allergy prevention. *Clin. Exp. Allergy* 2012.
21. Dogaru, C. M.; Nyffenegger, D.; Pescatore, A. M.; Spycher, B. D.; Kuehni, C. E. Breastfeeding and childhood asthma: Systematic review and meta-Analysis. *Am. J. Epidemiol.* 2014.
22. Lodge, C.; Tan, D.; Lau, M.; Dai, X.; Tham, R.; Lowe, A.; Bowatte, G.; Allen, K.; Dharmage, S. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. *Acta Paediatr* **2015**, doi:10.1111/apa.13132.
23. Boyle, R. J.; Ierodiakonou, D.; Khan, T.; Chivinge, J.; Robinson, Z.; Geoghegan, N.; Jarrold, K.; Afxentiou, T.; Reeves, T.; Cunha, S.; Trivella, M.; Garcia-Larsen, V.; Leonardi-Bee, J. Hydrolysed formula and risk of allergic or autoimmune disease: Systematic review and meta-analysis. *BMJ* **2016**, doi:10.1136/bmj.i974.
24. Osborn, D. A.; Sinn, J. K. Soy formula for prevention of allergy and food intolerance in infants. *Cochrane Database Syst. Rev.* **2006**, doi:10.1002/14651858.CD003741.pub4.
25. Szajewska, H.; Horvath, A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. *Curr. Med. Res. Opin.* **2010**, doi:10.1185/03007990903510317.
26. Felix SF Ram, J. F. S. Development of childhood asthma and formula milk. *Br. J. midwifery* **2004**, *12*.
27. Scott, M.; Roberts, G.; Kurukulaaratchy, R. J.; Matthews, S.; Nove, A.; Arshad, S. H. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. *Thorax* **2012**, doi:10.1136/thoraxjnl-2012-202150.
28. Miller, M. R.; Hankinson, J.; Brusasco, V.; Burgos, F.; Casaburi, R.; Coates, A.; Crapo, R.; Enright, P.; van der Grinten, C. P. M.; Gustafsson, P.; Jensen, R.; Johnson, D. C.; MacIntrye, N.; McKay, R.; Navajas, D.; Pedersen, O. F.; Pellegrino, R.; Viegi, G.; Wagner, J. Standardisation of spirometry. *Eur. Respir. J.* 2005.
29. Goksör, E.; Gustafsson, P. M.; Alm, B.; Åmark, M.; Wennergren, G. Reduced airway function in early adulthood among subjects with wheezing disorder before two years of age. *Pediatr. Pulmonol.* **2008**, doi:10.1002/ppul.20798.
30. Piippo-Savolainen, E.; Korppi, M. Wheezy babies--wheezy adults? Review on long-term outcome until adulthood after early childhood wheezing. *Acta Paediatr.* **2008**, doi:10.1111/j.1651-2227.2007.00558.x.
31. Azad, M. B.; Vehling, L.; Lu, Z.; Dai, D.; Subbarao, P.; Becker, A. B.; Mandhane, P. J.; Turvey, S. E.; Lefebvre, D. L.; Sears, M. R.; and the CHILD Study Investigators Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. *Eur. Respir. J.* **2017**, doi:10.1183/13993003.02019-2016.
32. Stern, D. A.; Morgan, W. J.; Halonen, M.; Wright, A. L.; Martinez, F. D. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* **2008**, doi:10.1016/S0140-6736(08)61447-6.
33. Sears, M. R.; Greene, J. M.; Willan, A. R.; Wiecek, E. M.; Taylor, D. R.; Flannery, E. M.; Cowan, J. O.; Herbison, G. P.; Silva, P. a; Poulton, R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N. Engl. J. Med.* **2003**, doi:10.1056/NEJMoa022363.
34. Cameron, C. M.; Scuffham, P. A.; Shibl, R.; Ng, S.; Scott, R.; Spinks, A.; Mihala, G.; Wilson, A.; Kendall,

E.; Sipe, N.; McClure, R. J. Environments For Healthy Living (EFHL) Griffith birth cohort study: characteristics of sample and profile of antenatal exposures. *BMC Public Health* **2012**, doi:10.1186/1471-2458-12-1080.

35. Cameron, C. M.; Scuffham, P. A.; Spinks, A.; Scott, R.; Sipe, N.; Ng, S. K.; Wilson, A.; Searle, J.; Lyons, R. A.; Kendall, E.; Halford, K.; Griffiths, L. R.; Homel, R.; McClure, R. J. Environments for Healthy Living (EFHL) Griffith birth cohort study: Background and methods. *Matern. Child Health J.* **2012**, doi:10.1007/s10995-011-0940-4.
36. Hosmer DW, Lemeshow S, S. R. *Applied Logistic Regression, 3rd Edition*; 2013; ISBN 978-0-470-58247-3.
37. Lemeshow, S.; Moeschberger, M. L. Review of regression methods in biostatistics: Linear, logistic, survival, and repeated measures models by Vittinghoff, Glidden, Shiboski, and McCulloch. *Stata J.* 2005.
38. Hosmer, D. W.; Lemeshow, S. Goodness of fit tests for the multiple logistic regression model. *Commun. Stat. - Theory Methods* **1980**, doi:10.1080/03610928008827941.
39. StataCorp Stata Statistical Software: Release 15 2017.
40. Martin, C.; Ling, P.-R.; Blackburn, G. Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. *Nutrients* **2016**, doi:10.3390/nu8050279.
41. von Berg, A.; Filipiak-Pittroff, B.; Krämer, U.; Link, E.; Bollrath, C.; Brockow, I.; Koletzko, S.; Grübl, A.; Heinrich, J.; Wichmann, H. E.; Bauer, C. P.; Reinhardt, D.; Berdel, D. Preventive effect of hydrolyzed infant formulas persists until age 6 years: Long-term results from the German Infant Nutritional Intervention Study (GINI). *J. Allergy Clin. Immunol.* **2008**, doi:10.1016/j.jaci.2008.04.021.
42. Osborn, D. A.; Sinn, J. K. H.; Jones, L. J. Infant formulas containing hydrolysed protein for prevention of allergic disease and food allergy. *Cochrane Database Syst. Rev.* 2017.
43. Cabana, M. D. The Role of Hydrolyzed Formula in Allergy Prevention. *Ann. Nutr. Metab.* **2017**, doi:10.1159/000460269.
44. Kull, I.; Almqvist, C.; Lilja, G.; Pershagen, G.; Wickman, M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J. Allergy Clin. Immunol.* **2004**, doi:10.1016/j.jaci.2004.07.036.
45. Kull, I.; Melen, E.; Alm, J.; Hallberg, J.; Svartengren, M.; van Hage, M.; Pershagen, G.; Wickman, M.; Bergström, A. Breast-feeding in relation to asthma, lung function, and sensitization in young schoolchildren. *J. Allergy Clin. Immunol.* **2010**, doi:10.1016/j.jaci.2010.01.051.
46. Sears MR Willan AR,et al.Lancet., G. J. M. Long-term relation between breasfeeding and development of Atopy and Asthma in children and young adults: A longitudinal study. *Lancet.* **2002**, doi:10.1016/S0140-6736(02)11025-7.
47. Jelding-Dannemand, E.; Malby Schoos, A. M.; Bisgaard, H. Breast-feeding does not protect against allergic sensitization in early childhood and allergy-associated disease at age 7 years. *J. Allergy Clin. Immunol.* **2015**, doi:10.1016/j.jaci.2015.02.023.
48. Ek, W. E.; Karlsson, T.; Hernándes, C. A.; Rask-Andersen, M.; Johansson, Å. Breast-feeding and risk of asthma, hay fever, and eczema. *J. Allergy Clin. Immunol.* **2018**, doi:10.1016/j.jaci.2017.10.022.
49. Park, Y. H.; Kim, K. W.; Choi, B. S.; Jee, H. M.; Sohn, M. H.; Kim, K. E. Relationship between mode of delivery in childbirth and prevalence of allergic diseases in Korean children. *Allergy, Asthma Immunol. Res.* **2010**, doi:10.4168/aair.2010.2.1.28.
50. Subbarao, P.; Mandhane, P. J.; Sears, M. R. Asthma: Epidemiology, etiology and risk factors. *CMAJ* 2009.
51. Dezateux, C.; Stocks, J.; Dundas, I.; Fletcher, M. E. Impaired airway function and wheezing in infancy: The influence of maternal smoking and a genetic predisposition to asthma. *Am. J. Respir. Crit. Care Med.* **1999**, doi:10.1164/ajrccm.159.2.9712029.

52. Kao, C. C.; See, L. C.; Yan, D. C.; Ou, L. S.; Huang, J. L. Time trends and seasonal variations in hospital admissions for childhood asthma in Taiwan from 1990 to 1998. *Asian Pacific J. Allergy Immunol.* **2001**.

53. Bager, P.; Melbye, M.; Rostgaard, K.; Stabell Benn, C.; Westergaard, T. Mode of delivery and risk of allergic rhinitis and asthma. *J. Allergy Clin. Immunol.* **2003**, doi:10.1067/mai.2003.34.

54. Bager, P.; Wohlfahrt, J.; Westergaard, T. Caesarean delivery and risk of atopy and allergic disesase: Meta-analyses. *Clin. Exp. Allergy* **2008**, doi:10.1111/j.1365-2222.2008.02939.x.

55. Terry, D.; Robins, S.; Gardiner, S.; Wyett, R.; Islam, M. R. Asthma hospitalisation trends from 2010 to 2015: Variation among rural and metropolitan Australians. *BMC Public Health* **2017**, doi:10.1186/s12889-017-4704-y.

56. Le Souef PN, Sears MR, S. D.; Le Souëf, P. N.; Sears, M. R.; Sherrill, D.; Le Souef PN, Sears MR, S. D. The Effect of Size and Age of Subject on Airway Responsiveness in Children. *Am. J. Respir. Crit. Care Med.* **1995**, *152*, 576–9, doi:10.1164/ajrccm.152.2.7633710.

57. Mandhane, P. J.; Greene, J. M.; Cowan, J. O.; Taylor, D. R.; Sears, M. R. Sex differences in factors associated with childhood- and adolescent-onset wheeze. *Am. J. Respir. Crit. Care Med.* **2005**, doi:10.1164/rccm.200412-1738OC.

58. Tariq, S. M.; Hakim, E. A.; Matthews, S. M.; Arshad, S. H. Influence of smoking on asthmatic symptoms and allergen sensitisation in early childhood. *Postgrad. Med. J.* **2000**, doi:10.1136/pmj.76.901.694.

59. Health, C.; Health, C. The Environment and Childhood Asthma (ECA) Study in Oslo: ECA-1 and ECA-2. *Pediatr Allergy Immunol* **2002**, doi:10.1034/j.1399-3038.13.s.15.2.x.

60. Hwang, S.-H.; Hwang, J. H.; Moon, J. S.; Lee, D.-H. Environmental tobacco smoke and children's health. *Korean J. Pediatr.* **2012**, doi:10.3345/kjp.2012.55.2.35.

61. Prickett, K. C.; Augustine, J. M. Maternal Education and Investments in Children's Health. *J. Marriage Fam.* **2016**, doi:10.1111/jomf.12253.

62. von Kobyletzki, L. B.; Bornehag, C.-G.; Hasselgren, M.; Larsson, M.; Lindström, C. B.; Svensson, Å. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. *BMC Dermatol.* **2012**, doi:10.1186/1471-5945-12-11.

63. Demehri, S.; Morimoto, M.; Holtzman, M. J.; Kopan, R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. *PLoS Biol.* **2009**, doi:10.1371/journal.pbio.1000067.

64. Burgess, J. A.; Lowe, A. J.; Matheson, M. C.; Varigos, G.; Abramson, M. J.; Dharmage, S. C. Does eczema lead to asthma? *J. Asthma* 2009.

65. Burgess, J. A.; Dharmage, S. C.; Byrnes, G. B.; Matheson, M. C.; Gurrin, L. C.; Wharton, C. L.; Johns, D. P.; Abramson, M. J.; Hopper, J. L.; Walters, E. H. Childhood eczema and asthma incidence and persistence: A cohort study from childhood to middle age. *J. Allergy Clin. Immunol.* **2008**, doi:10.1016/j.jaci.2008.05.018.

66. Berti, P. R.; Mildon, A.; Siekmans, K.; Main, B.; MacDonald, C. An adequacy evaluation of a 10-year, four-country nutrition and health programme. *Int. J. Epidemiol.* **2010**, doi:10.1093/ije/dyp389.