

PostScript

LETTERS TO THE EDITOR

Consumption of milk fat and reduced asthma risk in pre-school children

We read the paper by Wijga *et al*¹ published in the July 2003 issue of *Thorax* with great interest. The authors found that the consumption of specific food items such as full cream milk, butter, and brown bread can contribute to a decrease in the risk of asthma and wheezing in pre-school children. These findings agree with previous studies in adults,² but there are a few methodological problems in the analyses used in the study which may have influenced the results obtained.

Our first area of concern is that trans-generational traditions of families with atopic diseases are not taken into consideration. For instance, families with a history of atopy tend to smoke less, which is described as a "healthy passive smoker effect".^{3,4} Grandparents and parents who have asthma tend not to smoke, but their children are more likely to develop atopic manifestations than children from smoking families without asthma. It is also likely that atopic parents change their exposure to pets which may lead to a similar "healthy pet keeping effect".⁵ For related reasons, families may also alter their diets resulting in a "healthy cow's milk effect". These potential changes within families are supported by avoidance strategies propagated by various national medical associations. Children of atopic parents therefore tend to experience different exposures. Hence, before using statistical models we need to investigate the extent to which the diet of children differs according to the atopic status of their parents. An additional table is therefore needed, comparable to table 2, with consumption frequencies in columns for allergic and non-allergic parents as well as "allergic mothers" and "allergic fathers". In this respect, we were surprised to see the different proportion of mothers (14.2%) and fathers (29.1%) with allergy. Previous studies have reported the proportions of fathers in both mothers and fathers to be consistently around 30-35%.⁶⁻⁸

This leads to our second area of concern which deals with the logistic regression

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model used in table 3. By modelling, the authors attempted to control for the effects of maternal and paternal atopy by considering them as confounding variables. We see the child's diet acting as an intervening variable in the association between parental atopy history and the risk of the child developing asthma (fig 1). The standard epidemiological rule is that intervening variables should not be considered as confounders.⁹ By neglecting this rule the authors may have achieved biased odds ratios. In addition, children with a parental history of allergy are likely to have a different genetic make up. It is therefore very likely that they react differently—for instance, to cow's milk—which requires the investigation of interactive effects of parental atopy and diet on asthma in the offspring. To overcome these two challenges the authors need to present another table stratifying for parental allergy. The child's risk of wheezing should be estimated for each stratum. This would then adequately control for the intervening effects of parental allergy and provide an indication of any interaction. Additionally, information on the risk of exposure to cow's milk in children with and without parental atopy would help either to change or—since we expect no protective effect in atopic families—to sustain the recommendation to avoid early exposure to cow's milk.

To add to this argument, the authors also failed to differentiate between allergic and non-allergic (transient?) wheezing. We look forward to seeing additional informative tables.

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Authors' reply

The first point made by Karmaus and Fussman is that the association we observed between consumption of products containing milk fat (full cream milk, milk products, butter) and a reduced risk of asthma in pre-school children¹ could be the result of a "healthy cow's milk effect". We think this is unlikely as avoidance of cow's milk is uncommon in the Netherlands. Dutch guidelines do not advise avoidance of cow's milk for children with familial allergy after the age of 12 months unless the child has cow's milk allergy.² The popular belief is that young children need milk for healthy growth and few parents see milk as potentially harmful. 99% of Dutch children aged 1-4 years use milk (products).³ In the PIAMA population, too, nearly all children used milk—either full cream or semi-skimmed. Apart from 64 children with cow's milk allergy who were excluded from the analyses, only 27 children (<1%) had not used milk (products) in the previous month. Of these children, 16 had an allergic parent and 11 had non-allergic parents. The data requested by Karmaus and Fussman do not show an association between parental allergy and the prevalence of daily consumption of the foods that we found to be associated with reduced risk of asthma or wheeze: full cream milk, milk products (mainly flavoured and unflavoured yoghurt, either full cream or low fat), butter and brown bread (table 1, first column).

Karmaus and Fussman correctly point out the imbalance between the percentages of allergic mothers and allergic fathers in the study. This imbalance is due to the study design. Maternal allergy was used as the criterion to allocate participants to subgroups of the PIAMA study and in the natural history part of the study non-allergic mothers were oversampled.

The second point of concern raised by Karmaus and Fussman deals with our logistic regression model. They state that, by treating parental allergy as a confounder, we neglected the epidemiological rule that intervening variables should not be considered as confounders. However, in their fig 1, parental

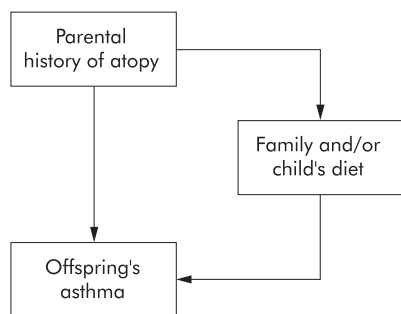


Figure 1 Causal transmission of trans-generational risks for asthma.

Table 1 Percentages and (numbers) of 2 year old children who consumed different foods on 6 or 7 days/week, crude prevalences of asthma and wheeze at age 3 in children who, at age 2, used different foods on a daily basis ("daily use") compared with children with lower consumption frequencies (others) and adjusted odds ratios† for the relationship between daily consumption‡ of different foods at age 2 and prevalence of asthma and wheeze at age 3, stratified for parental allergy

Foods	Percentage (n) daily users	"Ever asthma"			Recent asthma			Recent wheeze		
		Crude % prevalence			Crude % prevalence			Crude % prevalence		
		"Daily use"	Others	Adjusted OR (95% CI)	"Daily use"	Others	Adjusted OR (95% CI)	"Daily use"	Others	Adjusted OR (95% CI)
<i>Neither parent allergic (n=1816)</i>										
Full cream milk	31.2 (n=567)	3.3*	6.0	0.44 (0.22 to 0.91)*	2.3*	4.5	0.37 (0.16 to 0.84)*	9.9*	14.0	0.67 (0.41 to 1.07)
Milk products	75.1 (n=1364)	4.6	6.7	0.70 (0.43 to 1.14)	3.5	4.8	0.73 (0.41 to 1.30)	11.5*	16.2	0.70 (0.51 to 0.96)*
Brown bread	82.8 (n=1503)	4.7	7.3	0.67 (0.39 to 1.15)	3.5	5.2	0.69 (0.36 to 1.30)	12.4	14.2	1.05 (0.72 to 1.54)
Butter	7.0 (n=126)	4.0	5.2	0.80 (0.29 to 2.18)	2.4	3.9	0.59 (0.17 to 2.05)	8.2	13.0	0.53 (0.26 to 1.08)
<i>Mother and/or father allergic (n=1162)</i>										
Full cream milk	33.5 (n=389)	6.6§	9.8	0.62 (0.32 to 1.18)	5.0	7.3	0.65 (0.31 to 1.38)	17.6	18.5	1.00 (0.61 to 1.62)
Milk products	74.1 (n=861)	8.1	10.4	0.77 (0.48 to 1.24)	6.4	7.0	0.92 (0.53 to 1.62)	17.0§	21.7	0.67 (0.47 to 0.96)*
Brown bread	85.2 (n=990)	7.8*	14.3	0.49 (0.28 to 0.83)*	5.8*	10.8	0.47 (0.26 to 0.87)*	17.9	20.0	0.91 (0.58 to 1.44)
Butter	6.3 (n=73)	1.4*	9.2	0.13 (0.02 to 0.98)*	0*	7.0	0	6.8*	19.0	0.43 (0.15 to 1.23)
<i>Only mother allergic (n=295)</i>										
Full cream milk	32.9 (n=97)	5.4	11.1		5.4	9.6		8.5*	19.2	
Milk products	73.9 (n=218)	8.9	10.1		8.4	7.5		16.0	14.8	
Brown bread	84.8 (n=250)	8.1	15.6		6.9§	15.6		14.5	22.2	
Butter	7.1 (n=21)	0	9.9		0	8.8		1.0	16.8	

*p<0.05, §p<0.10 for difference in asthma or wheeze prevalence between daily users and less frequent consumers.

†Adjusted for consumption frequencies of foods shown in the table, consumption frequency of semi-skimmed milk, consumption frequency of margarine, sex, birth weight, presence of older sibling(s), maternal education, having been breast fed for ≥8 weeks, and parental smoking in the home.

‡For full cream milk and butter odds ratios are shown for daily consumption (on 6–7 days/week) compared with consumption less than once a week; for milk products and brown bread the prevalence of consumption less than once a week is less than 5% and therefore odds ratios are shown for daily consumption versus all others.

allergy is not an intervening variable between the exposure of interest (diet) and the effect studied (child's asthma). Parental allergy would only be an intervening variable when the child's diet at age 2 is a cause of parental allergy. Instead, in their figure parental allergy is a classical confounder—that is, it is a factor that is a cause of both the exposure and the disease of interest* and was therefore dealt with correctly in our analyses.

We agree with Karmaus and Fusmann, however, that effect modification might be present in that children of allergic parents might react differently to dietary exposures, but there was no evidence of effect modification in our data. The prevalences of asthma and of wheeze were lower in daily users in most parental allergy subgroups although, because of the small numbers, even large differences were not statistically significant in most cases (table 1, data shown for only three subgroups). Adjusted logistic regression analysis was carried out in only two subgroups because numbers were too small in the other groups. The adjusted odds ratios for daily consumption of full cream milk, milk products, and butter were consistently below 1 both in children of allergic and in children of non-allergic parents; however, because of the small numbers, the confidence intervals were wider than in the analysis of the group as a whole (see table 3 in our paper).

The last point made by Karmaus and Fussman is that they would have liked us to differentiate between allergic and non-allergic (transient?) wheezing. IgE measurements were not available for these children and they were too young for us to be able to differentiate between transient and persistent wheezers. We look forward to future analyses when a more reliable asthma diagnosis can be made.

We conclude that there is no evidence in our population for a "healthy full cream cow's milk effect", that we adjusted correctly for parental allergy in our analyses, and that

our data do not suggest that the reported associations between daily consumption of products containing milk fat and reduced risk of asthma and wheeze are only present in children of non-allergic parents.

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BIS/BTS SARS guidelines

The guidelines on severe acute respiratory syndrome (SARS) published by the British Infection Society (BIS) and the British Thoracic Society (BTS) in July 2003 recommend giving adult patients with suspected or probable SARS an N95 or equivalent mask and request that they wear this continuously.¹ This recommendation was apparently provided to prevent the spread of the SARS coronavirus from the patient to the surrounding environment.

An N95 respirator (mask) is a negative pressure respirator which only filters air entering the mask, not leaving it.² Those wearing this respirator will experience an additional burden on the breathing system in moving air in and out of the respirator.³ For this reason, occupational protection agencies such as the United States Occupational Safety and Health Administration⁴ require those using these types of respirator to be medically qualified because of physiological⁵ and psychological⁶ stresses that may occur. Patients with SARS coronavirus will certainly not meet these requirements and use of a respirator will only add to their pulmonary stress. Since there will be no filtration of air leaving the wearer of this respirator, little protection besides that of a barrier will occur, allowing viral spread from the patient with limited impedance. It has also been suggested⁶ that N95 respirators, even when properly used by healthcare workers, do not provide adequate protection against the SARS virus.

The recommendation should be changed to eliminate the requirement of the patient using a respirator and instead shifting this requirement to healthcare workers. This will provide the best protection against the spread of SARS coronavirus. It has recently been

suggested⁷ that a high ventilation rate in hospital wards with SARS patients results in lower infectivity of healthcare workers. The most adequate form of protection is therefore proper use of personal protective equipment, including respirators, by healthcare workers together with a high ventilation rate.⁶ The guidelines should be adjusted to recommend that patients should not wear a respirator.

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Authors' reply

We thank Mr Lange for his comments on the BTS/BIS SARS guidelines of July 2003. He and other *Thorax* readers will be pleased to know that the guidelines have been rewritten over the last few months and are now on the BTS website under the title "Hospital management of adults with SARS if SARS re-emerges".¹

The new BTS/BIS/HPA guidelines recommend that all possible or probable SARS patients should wear a surgical face mask rather than an N95 respirator, and that healthcare workers should wear a respirator complying with the European standard EN149:2001 FFP3 or higher filtration. Healthcare workers should note that wearing a respirator is just one way of preventing the spread of SARS; other important precautions include good personal hygiene (especially hand hygiene) and gloves, aprons, gowns, visors, and goggles when appropriate.² For further up to date information please visit the UK Health Protection Agency (HPA) website.³

The UK Health Protection Agency continues to urge healthcare workers to remain vigilant to the possibility of SARS even though the level of risk in the UK remains very low.

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Urinary leukotriene LTE₄ levels in non-responders to antileukotriene therapy

I read with interest the recent article by Green *et al*¹ showing that, in acute asthma, activation of leukotriene pathways correlated with the degree of airflow obstruction and a reduction in leukotriene levels was associated with resolution of asthma exacerbation. However, no analysis was performed on patients categorised as being in the treatment failure group which was reported to be as high as 10% of patients receiving intravenous montelukast.² The importance of this analysis cannot be understated as not everyone with asthma responds to antileukotriene therapy^{3,4} and non-responders have been reported to be as high as 50% in chronic asthma.⁵

It would have been interesting to observe urinary leukotriene LTE₄ levels in the treatment failure group as it has been shown that cysteinyl leukotriene release from leukocytes of responders was higher than from non-responders which, in turn, correlated with the response to antileukotriene therapy.⁵

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Authors' reply

We thank Dr Lee for his interest in our reports.^{1,2} However, he appears to confuse the terms "treatment failure" and "non-responder". "Treatment failure", as defined in the original report for our study,¹ referred to a clinical outcome (a composite end point of hospitalisation, need for excluded medication, or need for prolonged acute asthma treatment in the emergency setting). In contrast, "non-responder" generally refers to a subset of patients who fail to surpass a defined threshold of response. As we have commented previously using chronic asthma as an example, simplistic "responder/non-responder" analyses often fail to account for clinically important aspects of disease varia-

bility and the impact of a treatment intervention.³ Moreover, in our initial report of intravenous montelukast in acute asthma,¹ a systematic analysis of baseline variables did not identify any factor which predicted response to intravenous montelukast in terms of either forced expiratory volume in 1 second (FEV₁) or treatment failures, with the exception of baseline FEV₁.

The present report² addressed the relationship between FEV₁ and cysteinyl leukotriene production as measured by LTE₄ excretion. A similar analysis of treatment failures and LTE₄ levels is complicated by the fact that, unlike baseline FEV₁ which was measured before administration of the study drug, treatment failures tended to be reduced by intravenous montelukast.¹ Nevertheless, 27 of 201 patients (15 (11.1%) in the montelukast group and 12 (18.2%) in the placebo group) met one or more of the criteria for treatment failure during the study. Of these, 20 patients had LTE₄ data for analyses. Compared with patients who did not meet the criteria for treatment failures and who had LTE₄ data available (n = 161), LTE₄ levels were numerically higher at baseline in the treatment failure group although this did not reach statistical significance (121.6 pg/mg creatinine (95% CI 91.5 to 161.6) v 111.6 pg/mg creatinine (95% CI 100.0 to 128.5)). If Dr Lee's hypothesis is correct, LTE₄ levels should have been lower among the treatment failures. The data therefore suggest that, rather than serving as a useful predictor of clinical outcome, increased LTE₄ levels are more likely to be a marker of worsened acute asthma severity, consistent with our analyses of LTE₄ levels and FEV₁.² Taken together, the data provide a strong biological rationale for the observed benefit of antileukotriene therapy in acute asthma.¹

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NOTICE

Rare Pulmonary Diseases and Orphan Drugs in Respiratory Medicine

A meeting on "Rare Pulmonary Diseases and Orphan Drugs in Respiratory Medicine" organised by the Department of Pneumology, Hospital San Giuseppe, Milan and the RIPID Study will take place on 25/26 February 2005 at the Congress Center Palazzo delle Stelline, Milan, Italy. For further information contact the Organizing Secretariat at: Victory Project Congressi, Via G Modena 3a, 20129 Milan, Italy. Telephone: 02 89 05 35 24. Fax: 02 20 13 95. Email: info@victoryproject.it.