

Letter to the Editor

Mannan-binding lectin in young children with asthma differs by level of severity

To the Editor:

Mannan-binding lectin (MBL) is a serum protein involved in opsonization and complement activation. Low levels have been linked with susceptibility to respiratory infections in children.^{1,2} Data on the association with asthma are conflicting, with both higher and lower levels being reported.^{3,4} One explanation for this might be the heterogeneity of asthma, this single term encompassing several distinct phenotypes. Some, but not all, studies showed an association between MBL and atopic, but not nonatopic, asthma,^{4,5} possibly because subjects with atopic asthma have more severe disease.^{6,7} We compared levels of MBL between healthy and wheezing children, classifying wheezers by severity defined by treatment step⁸ and by the presence or absence of atopy.

From an ongoing population-based cohort study of 8700 children born from 1993 through 1997 in Leicestershire, United Kingdom,^{7,9,10} all children aged 9 years or older whose parents had answered 2 or more previous questionnaires ($n = 2583$) were invited for a laboratory visit in 2004 through 2006. When the MBL project was closed, 389 children had attended the laboratory, and 154 had consented to venipuncture. Compared with the total cohort, this subgroup was older and consisted of proportionately more white children and preschool wheezers. Parents answered a questionnaire on respiratory symptoms in the past 12 months. MBL levels were measured by using a mannan-coated commercial ELISA kit with an anti-MBL antibody recognizing only functional oligomers (HK323; Hycult Biotechnology, Uden, the Netherlands). Children with parent-reported wheeze during the previous 12 months (41/154 [27%]) were classified as current wheezers. These were grouped by severity based on treatment steps recommended by the British Thoracic Society⁸ as untreated ($n = 14$), using only bronchodilators ($n = 12$), and using inhaled corticosteroids (ICSs; $n = 15$). Children without parent-reported wheeze ($n = 113$) served as healthy control subjects. Atopy was defined as a 3-mm skin prick test reaction to 1 or more of 4 allergens (dog, cat, grass pollen, and house dust mite; ALK-Abelló, Hungerford, United Kingdom). Because of skewness, we reported MBL levels as medians and interquartile ranges (IQRs) and used nonparametric tests to compare groups. For analysis by means of multivariable linear regression, data were log transformed to correct for skewness, and results were presented as unadjusted and adjusted ratios, comparing MBL levels of wheezers classified by severity with those of healthy children.

MBL levels were available for 124 white and 30 South Asian children with a mean age of 10.8 (SD, 0.79) years; 81 (53%) were boys. Overall, MBL levels were similar in children with and without wheeze, with medians of 0.92 $\mu\text{g/mL}$ (IQR, 0.30-2.37 $\mu\text{g/mL}$) and 0.90 $\mu\text{g/mL}$ (IQR,

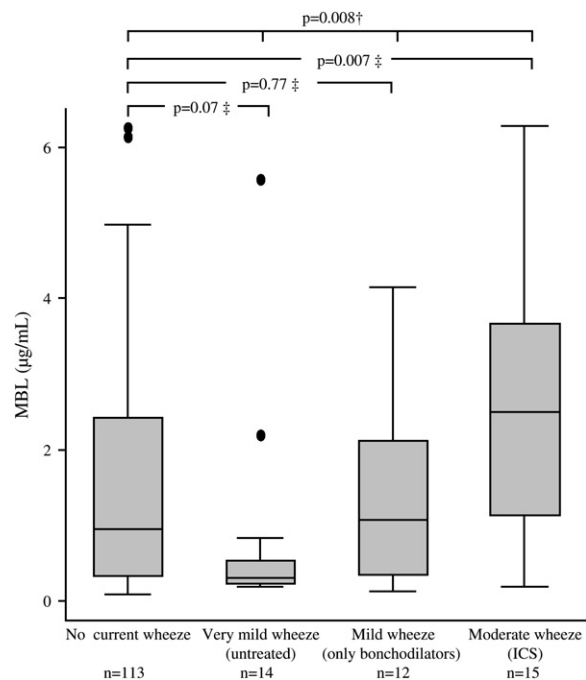


FIG 1. Box-plot representation of serum MBL levels among healthy children and those with current wheeze, grading wheezing children by severity based on the British Thoracic Society guidelines treatment step: median (horizontal line within box), 25th and 75th percentiles (lower and upper bound of box), and outliers (defined as points further than 1.5 times the height of the box above the 75th percentile). †Kruskal-Wallis test. ‡Mann-Whitney test.

0.27-2.46 $\mu\text{g/mL}$), respectively. However, among wheezers, MBL levels were associated with severity classified by treatment steps (Fig 1). MBL levels were significantly higher in moderate wheezers receiving ICSs (median, 2.46 $\mu\text{g/mL}$) compared with healthy children (0.90 $\mu\text{g/mL}$, $P = .007$) and untreated wheezers (0.27 $\mu\text{g/mL}$, $P = .001$). MBL levels in children with untreated wheeze tended to be even lower than those in healthy children ($P = .07$). Results remained unchanged after adjustment for sex, ethnicity, age, exposure to tobacco smoke, frequency of colds, and frequency of otitis media as markers of susceptibility to infections (Table I). Because parental understanding of “wheeze” is variable,¹⁰ we performed a sensitivity analysis including only children whose parents correctly defined wheeze ($n = 125$). Results were similar, with an MBL ratio of 0.52, 0.95, and 2.61 ($P = .033$) in wheezing children with no treatment, only bronchodilators, and ICSs, respectively, compared with that seen in nonwheezers. When the children were reclassified by using other markers of severity, such as frequency of wheezing episodes, the results were similar but less pronounced.

In contrast, MBL levels did not differ between atopic ($n = 47$) and nonatopic ($n = 90$) children either within the whole population (0.92 $\mu\text{g/mL}$ [IQR, 0.20-2.89 $\mu\text{g/mL}$]

TABLE I. Ratio of MBL levels in children with current wheeze, classified according to severity of wheeze, compared with that seen in healthy children (n = 154)

	n	Unadjusted		Adjusted*	
		MBL ratio	P value	MBL ratio	P value
Healthy	113	1		1	
Wheezing					
Very mild wheeze (untreated)	14	0.58	.155	0.53	.112
Mild wheeze (only bronchodilators)	12	1.13	.762	0.95	.899
Moderate wheeze (ICSs)	15	2.75	.006	2.41	.031

In the unadjusted model MBL levels (geometric means) in healthy children were 0.69 $\mu\text{g/mL}$. In the adjusted model children with baseline characteristics (white female, age of 8-9 years, no smokers in household, <3 colds in the last 12 months, and no otitis) had an MBL level of 0.57 $\mu\text{g/mL}$.

*Adjusted for sex, age, frequency of colds, ethnicity, recurrent otitis media, and environmental tobacco smoke.

and 1.01 $\mu\text{g/mL}$ [IQR, 0.37-2.46 $\mu\text{g/mL}$], respectively, $P = .67$) or within the group of current wheezers (0.92 $\mu\text{g/mL}$ [IQR, 0.22-3.10 $\mu\text{g/mL}$] and 1.17 $\mu\text{g/mL}$ [IQR, 0.48-2.46 $\mu\text{g/mL}$], respectively, $P = .51$). Similar results were found using other markers of atopy, such as the presence of eczema, hay fever, or both. Ethnic group, age, sex, frequency of colds, and ear infections were not independently associated with MBL levels.

Levels of MBL in this population-based cohort study were no different in children with and without wheeze but were significantly higher in children with moderate wheeze using ICSs compared with levels in children with very mild wheeze receiving no treatment and healthy children. Our results were robust to adjustment for possible confounders, such as sex, age, ethnicity, environmental tobacco smoke, frequency of colds, and recurrent ear infections. However, because our study was relatively small, our findings will need to be confirmed in independent samples. Because the subgroup who attended the laboratory was older and included proportionately more white children and preschool wheezers, median MBL levels in the whole sample might not be representative of the general population. However, adjusted differences between nonwheezers and wheezers of different severity groups are likely to be robust.

These findings support previous studies that have reported high levels of MBL in both adults and children with asthma, although this is the first time that an association with severity has been reported. An important difference between earlier studies and our results is that our children were recruited from the total population rather than from hospitals. Therefore our wheeze group includes a broader range of phenotype and severity of asthma, revealing important differences in levels of MBL.

Our findings suggest that MBL might play a modulatory role in the progression of asthma and thus be a marker of susceptibility to more severe disease or a marker for a

distinctive asthma phenotype. Two authors reported an association between MBL levels and eosinophilia, supporting our hypothesis of a role for MBL in different asthma phenotypes.^{3,4} We did not measure eosinophil counts, but our data do not confirm earlier reports that atopy might be the main distinguishing feature of wheezing children with high MBL levels.

Although classification of severity was based on use of ICSs, it is unlikely that ICSs directly affect MBL levels. Cumulative doses of ICSs taken by individuals from population-based studies are low, and pulmonary absorption is minimal, making it unlikely that ICSs could affect hepatic synthesis of MBL.

The recent discovery of a polymorphism associated with high levels of MBL and the fact that homozygosity for this mutation was found only in asthmatic subjects⁴ provide further evidence that MBL plays a modulatory role in asthma development and, as our data suggest, predisposes to more severe disease.

We thank Professor Richard Camp and Melinda Dean for their useful suggestions.

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Supported by Asthma UK (grant no. 05-030), the Swiss National Science Foundation (PROSPER grant 3233-069348 and 3200-069349 and SNF grant 823B-046481), Trent NHS Executive (Trent Research Scheme, RBF no. 98XX3), and Deutsche Forschungsgemeinschaft (STO430/1-2).

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

- Cedzynski M, Szymraj J, Swierczko AS, Bak-Romaniszyn L, Banasik M, Zeman K, et al. Mannan-binding lectin insufficiency in children with recurrent infections of the respiratory system. *Clin Exp Immunol* 2004; 136:304-11.
- Koch A, Melbye M, Sorensen P, Homoe P, Madsen H, Molbak K, et al. Acute respiratory tract infections and mannose-binding lectin insufficiency during early childhood. *JAMA* 2001;285:1216-321.
- Uguz A, Berber Z, Coskun M, Halide Akbas S, Yegin O. Mannose-binding lectin levels in children with asthma. *Pediatr Allergy Immunol* 2005; 16:231-5.
- Kaur S, Gupta VK, Shah A, Thiel S, Sarma PU, Madan T. Elevated levels of mannan-binding lectin (MBL) and eosinophilia in patients of bronchial asthma with allergic rhinitis and allergic bronchopulmonary aspergillosis associate with a novel intronic polymorphism in MBL. *Clin Exp Immunol* 2006;143:414-9.
- Aittoniemi J, Soranummi H, Rovio AT, Hurme M, Pessi T, Nieminen M, et al. Mannose-binding lectin 2 (MBL2) gene polymorphism in asthma and atopy among adults. *Clin Exp Immunol* 2005;142: 120-4.
- Kurukulaaratchy RJ, Fenn M, Matthews S, Arshad SH. Characterisation of atopic and non-atopic wheeze in 10 year old children. *Thorax* 2004; 59:563-8.
- Kuehni CE, Strippoli M-PF, Silverman M. Food intolerance and wheezing in young South Asian and white children: prevalence and clinical significance. *J Allergy Clin Immunol* 2006;118:528-30.

8. British Thoracic Society. British guideline on the management of asthma. *Thorax* 2003;58(suppl 1):i1-94.
9. Kuehni CE, Davis A, Brooke AM, Silverman M. Are all wheezing disorders in very young (preschool) children increasing in prevalence? *Lancet* 2001;357:1821-5.
10. Michel G, Silverman M, Strippoli M-PF, Zwahlen M, Brooke AM, Grigg J, et al. Parental understanding of “wheeze” and its impact on asthma estimates. *Eur Respir J* 2006. In press.

doi:10.1016/j.jaci.2006.09.028