3 days) compared with controls (median 2 days; IQR 1–5 days) ($p=0.04$) [5], suggesting a more rapid onset of symptoms in children at greater risk of hospital presentation for pneumonia. We now show that the same cases were less likely to have visited a GP for other illnesses in the previous year. The lack of association between these two variables ($p=0.8$) suggests the two findings are unrelated.

We therefore hypothesise that a child presenting to general practice promptly after illness onset, with a history of infrequent consulting, may be at increased risk for pneumonia or empyema. This is consistent with common knowledge regarding any illness that needs prompt and decisive action by the GP. However, our findings cannot inform GP decision making because they may be influenced by response bias. Larger, prospective studies are needed to test our hypothesis.

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Asymmetric dimethylarginine and asthma: results from the Childhood Asthma Prevention Study

To the Editor:

Asymmetric dimethylarginine (ADMA) is a naturally occurring analogue of L-arginine and functions as an endogenous inhibitor of nitric oxide synthase (NOS). ADMA is an established risk factor for cardiovascular disease and contributes to chronic endothelial dysfunction [1]. Recently, it has been proposed that ADMA is also a mediator of allergic airways disease, with animal studies indicating a possible role in the development of airway hyperresponsiveness, lung inflammation and fibrosis. Exogenous administration of ADMA has been shown to augment airway responsiveness to methacholine in murine models of asthma and increased ADMA levels were observed in lung homogenates and sputum specimens from humans with asthma [2]. However, human data on the relationship between ADMA and asthma are limited. Therefore, we examined the relationship between systemic ADMA levels and current asthma in a cohort from the Childhood Asthma Prevention Study (CAPS).

Study subjects included 314 8-year-old children from Sydney, Australia. They were originally enrolled prenatally into a randomised controlled trial of house dust mite avoidance and dietary fatty acid modification implemented from birth to 5 years. All subjects had one or more parents or an older sibling with asthma or wheezing illness. The details of this trial have been published elsewhere [3]. Of the 616 subjects who were enrolled prenatally, 314 had clinical and laboratory

TABLE 1 Baseline characteristics and L-arginine metabolic parameters in study subjects

	No current asthma	Current asthma	p-value
Subjects n	242	72	
Lung function			
FEV1 % pred	105.4±11.1	104.9±10.9	0.75
FVC % pred	99.2±10.4	99.7±11.1	0.75
FEV1/FVC	0.93±0.05	0.92±0.06	0.089
*F*eNO ppb	8.9±9.3	11.1±7.7	0.007#
DRR %·μmol^{-1}	1.7±5.8	11.4±25.9	0.002#
Inhaled steroid use %	0.8	20.8	p<0.0001
Atopy %	38.2	68.1	p<0.0001
L-Arginine metabolism			
ADMA μmol·L^{-1}	0.91±0.23	0.92±0.20	0.88
L-Arginine μmol·L^{-1}	106.1±31.5	104.5±30.6	0.70
L-Arginine/ADMA	127.4±68.0	122.2±59.7	0.68

Data are presented as mean±SD, unless otherwise stated. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; *F*eNO: fraction of expired nitric oxide; DRR: dose-response ratio; ADMA: asymmetric dimethylarginine. #: p-values derived from t-test of log transformed data.

data available for analysis at age 8 years for the present study. The study was approved by the local human research ethics committee and the parent or legal guardian gave written informed consent.

Current asthma at 8 years of age was defined as the presence of wheezing in the previous 12 months together with a reported doctor's diagnosis of asthma or the presence of airway hyperresponsiveness. Spirometry, airway hyperresponsiveness

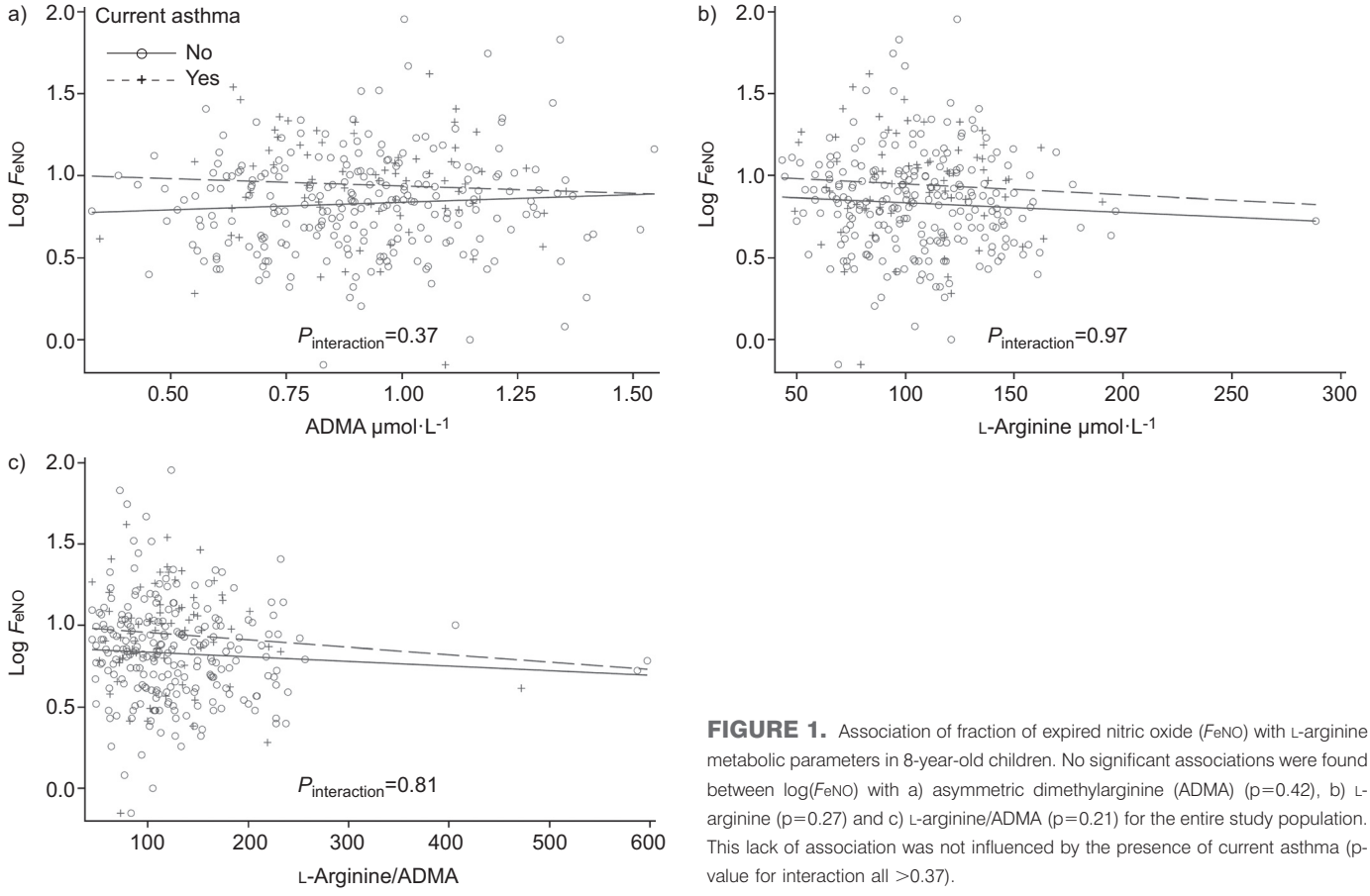

FIGURE 1. Association of fraction of expired nitric oxide (*F*eNO) with L-arginine metabolic parameters in 8-year-old children. No significant associations were found between log(*F*eNO) with a) asymmetric dimethylarginine (ADMA) (p=0.42), b) L-arginine (p=0.27) and c) L-arginine/ADMA (p=0.21) for the entire study population. This lack of association was not influenced by the presence of current asthma (p-value for interaction all >0.37).

to methacholine, fraction of exhaled nitric oxide (F_{ENO}) and atopic status were assessed, as described previously [4]. Serum was stored at -80°C and analysed for ADMA by ELISA (Immunodiagnostik AG, Bensheim, Germany) and for L-arginine by high-performance liquid chromatography. Both ADMA and L-arginine were measured in duplicate and the averages were recorded.

Independent sample t-test (two-tailed) was used for comparisons between people with and without current asthma. Baseline variables that demonstrated skewing were logarithmically transformed prior to parametric testing. The associations between parameters of L-arginine metabolism and F_{ENO} were analysed using general linear models, and the interaction with current asthma was examined. Statistical significance was determined by p-value of <0.05.

Of the 314 children, 160 (51%) were males and 72 (23%) fulfilled our criteria for current asthma. Post-bronchodilator forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio were not significantly different between subjects with and without current asthma. However, children with asthma had higher F_{ENO} concentrations, higher dose response ratio to methacholine (more airway responsiveness), a higher prevalence of atopy and were more likely to be taking inhaled corticosteroids than children without asthma (table 1).

ADMA and L-arginine levels were not significantly different between children with and without asthma. As ADMA competes with L-arginine for NOS utilisation, the L-arginine to ADMA ratio may be a better reflection of L-arginine bioavailability for nitric oxide production [5]. L-Arginine to ADMA ratio was also not significantly different between children with and without asthma (table 1).

Log(F_{ENO}) was not significantly associated with ADMA ($\beta=0.06$, 95% CI -0.09–0.2; $p=0.42$), L-arginine ($\beta=-0.001$, 95% CI -0.002–0.0005; $p=0.27$) and L-arginine to ADMA ratio ($\beta=-0.0003$, 95% CI -0.0009–0.0002; $p=0.21$). No significant interaction with current asthma was present in these relationships (fig. 1).

Of those with current asthma, 21% had received daily inhaled corticosteroids therapy in the past 12 months. Inhaled corticosteroid use did not modify the results of any of the associations examined (p-value for interaction all >0.17).

This study does not support the view that circulating levels of ADMA or L-arginine are related to the presence of asthma or airway inflammation in children. To the best of our knowledge, this is the largest study to examine ADMA and its relationship to asthma in children. The key strength of the study is its relatively large size in a well characterised group of 8-year-old children, thus enabling robust conclusions to be made regarding our results.

Recent studies have demonstrated a potential contribution of imbalances in L-arginine metabolism to the development of airway hyperresponsiveness and airflow obstruction in asthma [6–8]. ADMA is an endogenous inhibitor of all isoforms of NOS and is produced by the methylation of L-arginine residues by protein methyltransferases. The understanding of its possible role in asthma pathogenesis is evolving and has been supported predominantly by animal models of allergen-induced asthma. SCOTT *et al.* [2], using a murine model of allergic airway disease, found upregulation of ADMA levels following ovalbumin challenge. Furthermore, exogenous administration of ADMA to challenge-naïve mice exaggerated their airway hyperresponsiveness to methacholine challenge. In another murine model, WELLS and co-workers [7, 8] showed that elevated circulating ADMA levels increased lung collagen deposition and exacerbated airway inflammation.

The results of our study appear to be in contrast to the currently available human data. A recent study from the Severe Asthma Research Programme found higher ADMA levels in adults with severe asthma, and measures of systemic L-arginine bioavailability correlated with the degree of airflow obstruction [6].This effect was confined to those with severe asthma, but not observed in those with mild-to-moderate asthma. MORRIS *et al.* [9], in a mixed paediatric and adult population, demonstrated a striking reduction in systemic L-arginine levels in asthmatics (less than 50% of control values) during acute exacerbations. More recently, RICCIONI *et al.* [10] also found lower blood L-arginine and ADMA levels in a paediatric asthma clinic population compared to controls. The discrepancy between our results and prior studies may be explained by the following. First, our study was a population-based cohort and, overall, those children with asthma in our study had a mild phenotype as evidenced by their well-preserved lung function. Secondly, although all children with current asthma had wheezing in the previous 12 months (by definition), they were not assessed during an acute exacerbation, and it is conceivable that systemic L-arginine metabolism may alter during disease exacerbations. Finally, the role of ADMA in asthma pathogenesis may also differ between children and adults.

We were only able to evaluate systemic ADMA and L-arginine levels as respiratory specimens were not collected in our study subjects. One important limitation of our study is that we cannot exclude the possibility that dysregulation of ADMA/L-arginine metabolism may be compartmentalised to the airways and thus, no systemic spillover effects were detected in blood samples. Nevertheless, we believe that our study provides an important contrast to previous smaller clinic-based studies as alterations in systemic L-arginine metabolism were not evident in our population-based study of children with mild asthma. Finally, a recent small randomised controlled trial failed to demonstrate any beneficial clinical effects of oral L-arginine supplementation in moderate-to-severe asthma [11].

In conclusion, current asthma and airway inflammation were not associated with alterations in systemic ADMA and L-arginine levels in a large cross-sectional study of 8-year-old children. However, further studies involving examination of airway specimens are needed to clarify the role of ADMA in asthma pathogenesis.

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