Title

Metabolomics of asthma

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To the Editor:

Two recent publications in this Journal provided interesting reading regarding the metabolomics of asthma. Fitzpatrick et al. (1) and Loureiro et al. (2) identified metabolites and metabolic pathways suggesting that oxidative stress is a factor contributing to asthma severity in children and asthma exacerbation in adults, respectively. Although these findings support a role for oxidative stress in asthma, these studies have some limitations.

It is not clear, due to the design of the studies, whether the reported and highlighted metabolites are a proxy for oxidative stress contributing to severe asthma and asthma exacerbation or a consequence of the disease. It is also not completely clear if the findings are driven by use of medication – this is common to both studies, but particularly relevant in the study by Loureiro et al. since samples from the exacerbation period were collected after the treatment provided at the emergency room. The two groups of children from the study by Fitzpatrick et al. are not totally comparable, since the group with severe asthma was almost exclusively non-white, unlike the control group (mild asthma), and racial differences in biological predictors of severe asthma have been previously reported (3). In addition, the use of non-fasting samples raises the question whether the results might have been influenced by diet, since several food items have been shown to associate with specific metabolites (4), and the short-term effects of diet on the metabolome is uncertain. Finally, like most of the previous studies on metabolomics of asthma (table 1), these were pilot studies (small by nature) that could not adjust for potential confounders.

Fitzpatrick et al. and Loureiro et al., together with previous studies, have shown several metabolites and pointed out several pathways that could characterize asthma or asthma exacerbation. Not all studies used the same methods (some used NMR, others MS) or sample types (some used serum, others urine or exhaled breath condensate) nor collected fasting samples nor controlled for the use of asthma- and non-asthma-related drugs or comorbidities. This should remind us of what we have seen when large genome-wide association studies failed to replicate tens of SNPs that were previously found associated with disease in small candidate gene studies. Nevertheless, the present findings, as those from previous studies, are excellent candidate metabolites to be replicated in future and larger studies.

In summary, on the basis of the publications by Fitzpatrick et al. and Loureiro et al., some may conclude that we have enough information to move to the development of treatments targeting the oxidative stress-related pathways. Unfortunately, we are still far from understanding the real meaning of these metabolites, and we cannot exclude that some of current findings might be false positives that will not be replicated in larger and better controlled studies. Randomized trials and animal model studies showing the effects of controller drugs on the metabolic profile should provide important information that will help to disentangle the effect of such drugs on the metabolome.

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Table 1. Summary of previous publications on metabolomics of asthma and their main findings and issues.

First author [year]	Study population	Type of sample	Analytical method	Main findings	Main issues
Children					
Carraro [2007] E1	- 25 asthmatics (17 persistent asthma treated with ICS; 8 intermittent asthma with no ICS in previous month) - 11 healthy age-matched controls	Exhaled breath condensate	NMR	- Acetylated products (1.7-2.2 ppm spectral region) and oxidized compounds (3.2-3.4 ppm spectral region) discriminated asthmatics from non-asthmatics	- Small sample size - Not clear what metabolites have been identified - Role of ICS in the findings not clear
Saude [2011] E2	- 73 with stable atopic asthma, 67% with ICS - 20 with unstable asthma in emergency room; 50% with ICS - 42 healthy age- and sex-matched (10 confirmed non-atopic)	Urine	NMR	- Several metabolites, from several pathways, discriminated asthma exacerbation from stable asthma	- Small sample size - Role of ICS in the findings not clear - Treatment given at emergency not mentioned
Mattarucchi [2012] E3	- 41 atopic asthmatics (14 with SABA; 16 with low conc. ICS + LABA; 11 with high conc. ICS + LABA) - 12 age-matched non-atopic non-asthmatics	Urine	LC-MS	- Low levels of urocanic acid, methyl-imidazoleacetic acid, and a metabolite like isoleucyl-proline in asthmatics	- Small sample size - Role of ICS in the findings not clear
Sinha [2012] E4	- 58 asthmatics - 2 healthy, non-asthmatics	Exhaled breath condensate	NMR	- Asthmatics showed lack of ammonium ions	- Small sample size - No mention on the use of ICS or any other treatment
Carraro [2013] E5	- 42 atopic asthmatics [31 with non-severe asthma (17 with low-medium conc. ICS alone or combined with LABA mainly; 14 ICS naive); 11 with severe asthma with high conc. ICS (and others) + LABA - 15 healthy	Exhaled breath condensate	NMR	- High levels of retinoic acid- and deoxyadenosine-related metabolites in severe asthmatics - Low levels of ercalcitriol in severe asthmatics - Low levels of 20-hydroxy-PGF2a, 6-keto-prostaglandin F1a, and thromboxane B2 in severe asthmatics	- Small sample size - Role of ICS in the findings not clear
Gahleitner [2013] E6	- 25 asthmatics (17 persistent asthma treated with ICS; 8 intermittent asthma with no ICS in previous month) - 11 healthy age-matched controls	Exhaled breath condensate (fasting)	GC-MS	- Eight metabolites discriminated asthmatics from healthy children: 1-(methylsulfanyl)propane, ethylbenzene, 1,4-dichlorobenzene, 4-isopropenyl-1-methylcyclohexene,	- Small sample size - Role of ICS in the findings not clear

				2-octenal, octadecyne, 1-isopropyl-3-methylbenzene, and 1,7-dimethylnaphtalene	
Adults					
Sinha [2012] E4	- 7 asthmatics (non-smokers) - 10 healthy non-asthmatics (non-smokers)	Exhaled breath condensate	NMR	- Lack of ammonium ions in asthmatics	- Small sample size - No mention on the use of ICS or any other treatment
Ibrahim [2013] E7	- 79 asthmatics (77% with ICS) - 34 controls	Exhaled breath condensate	NMR	- Five spectral regions distinguished asthmatics from controls (AUC = 0.91)	- Small sample size - Role of ICS in findings not clear - Controls were about 14 years younger than asthmatics
Jung [2013] E8	- 39 asthmatics (77% with ICS - they stopped their medication for at least 3 days before sample collection; 44% were atopic) - 26 healthy controls	Serum	NMR	- High levels of methionine, glutamine, histidine, and lower levels of formate, methanol, acetate, choline, O-phosphocholine, arginine, and glucose in asthmatics	- Small sample size - Medication stopped 3 days before sample collection, but ICS-related DNA methylation effect should not be excluded
Loureiro [2013] E9	- Woman with severe persistent allergic asthma treated with omalizumab	Urine	GC-MS	- Previous to treatment, main metabolites were alkanes. 12 weeks after, aldehydes were the main metabolites	- Just one case
Ried [2013] E10	- 260 asthmatics from the KORA cohort (asthmatics with three definitions: 260 ever asthmatics; 147 non-medicated current asthmatics; 104 medicated asthmatics) - 2,778 never asthmatics (controls)	Serum (fasting)	ESI-MS/MS	- High levels of phosphatidylcholines and low levels of lyso-phosphatidylcholines in current asthmatics (similar results for medicated asthma) - Changes in levels of polyunsaturated phosphatidylcholines were associated with asthma and affected by asthma risk alleles (in *PSMD3* and *MED24*)	- Causality could not be established

ESI-MS/MS = Electrospray ionization tandem mass spectrometry; ICS = inhaled corticosteroids; LC-MS = liquid chromatography mass spectrometry; GC-MS = gas chromatography mass spectrometry; NMR = nuclear magnetic resonance; SABA = short-acting beta agonists; LABA = long-acting beta agonist.

For full list of citations (E1 to E10) in this table please see this article's Online Repository available at www.jacionline.org.

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