Asthma News This Week

Childhood Asthma Leadership Coalition

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JOURNAL ARTICLES

IN THE NEWS

JOURNAL articles

Bose, Sonali, et al. Prenatal nitrate air pollution exposure and reduced child lung function: Timing and fetal sex effects. *Environmental Research.* Nov 2018; 167: 591-597. https://doi.org/10.1016/j.envres.2018.08.019

Background: Prenatal particulate air pollution exposure may alter lung growth and development in utero in a time-sensitive and sex-specific manner, resulting in reduced lung function in childhood. Such relationships have not been examined for nitrate (NO3-).

Methods: We implemented Bayesian distributed lag interaction models (BDLIMs) to identify sensitive prenatal windows for the influence of NO3- on lung function at age 7 years, assessing effect modification by fetal sex. Analyses included 191 mother-child dyads. Daily ambient NO3- exposure over pregnancy was estimated using a hybrid chemical transport (Geos-Chem)/land-use regression model. Spirometry was performed at mean (SD) age of 6.99 (0.89) years, with forced

expiratory volume in one second (FEV1) and forced vital capacity (FVC) z-scores accounting for child age, sex, height and race/ethnicity.

Results: Most mothers were Hispanic (65%) or Black (22%), had ≤ high school education (67%), and never smoked (71%); 17% children had asthma. BDILMs adjusted for maternal age and education and child's asthma identified an early sensitive window of 6-12 weeks gestation, during which increased NO3- was significantly associated with reduced FEV1 z-scores specifically among boys. BDLIM analyses demonstrated similar sex-specific patterns for FVC.

Conclusion: Early gestational NO3- exposure is associated with reduced child lung function, especially in boys.

Naar, Sylvie, et al. Comprehensive Community-Based Intervention and Asthma Outcomes in African American Adolescents. *Pediatrics.* Oct 2018; 142(4): e20173737.
http://pediatrics.aappublications.org/content/pediatrics/early/2018/09/04/peds.2017-3737.full.pdf

Background: African American adolescents appear to be the most at risk for asthma morbidity and mortality even compared with other minority groups, yet there are few successful interventions for this population that are used to target poorly controlled asthma.

Methods: African American adolescents (age 12–16 years) with moderate-to-severe persistent asthma and ≥1 inpatient hospitalization or ≥2 emergency department visits in 12 months were randomly assigned to Multisystemic Therapy–Health Care or an attention control group (N = 167). Multisystemic Therapy–Health Care is a 6-month home- and community-based treatment that has been shown to improve illness management and health outcomes in high-risk adolescents by addressing the unique barriers for each individual family with cognitive behavioral interventions. The attention control condition was weekly family supportive counseling, which was also provided for 6 months in the home. The primary outcome was lung function (forced expiratory volume in 1 second [FEV1]) measured over 12 months of follow-up.

Results: Linear mixed-effects models revealed that compared with adolescents in the comparison group, adolescents in the treatment group had significantly greater improvements in FEV1 secondary outcomes of adherence to controller medication, and the frequency of asthma symptoms. Adolescents in the treatment group had greater reductions in hospitalizations, but there were no differences in reductions in emergency department visits.

Conclusions: A comprehensive family- and community-based treatment significantly improved FEV1, medication adherence, asthma symptom frequency, and inpatient hospitalizations in African American adolescents with poorly controlled asthma. Further evaluation in effectiveness and implementation trials is warranted.

Toftlund, L.H., et al. Improved lung function at age 6 in children born very preterm and fed extra protein post discharge. *Pediatric Allergy and Immunology.* Sept 2018; 29(6). [e-pub ahead of print]

Background: In very preterm-born children alveolar maturation is challenged and lung function is often compromised during childhood. So far, very few studies have focused on type of early nutrition and lung function in children born preterm.

Methods: This study is a six years follow-up of 281 very preterm-born infants (VPI) with a gestational age (GA) < 32+0 weeks. Infants breastfed at discharge from hospital were randomized to unfortified (UHM) or fortified (FHM) mother's (human) milk, whereas those not breastfed received a preterm formula (PF). The intervention lasted until 4 months corrected age. At six years of age fractional exhaled nitric oxide (FeNO), airway resistance and occlusion measurements with reversibility were performed. Data on predisposition to asthma and allergy as well as possible allergic symptoms of the child were obtained with questionnaires.

Results: Outcome data was fully or partially available on 160 (66.9%) of 239 children. This included 49 (30.6%) children fed UHM, 58 (36,3%) fed FHM, and 53 (33,1%) fed PF. Successful FeNO measurements were obtained in 119 (74.4%) children and airway resistance measurements in 160. FeNO results were not significantly different between feeding groups. Children fed a protein enriched diet (FMH/PF) had the lowest, i.e. best, airway resistance; FHM-fed had lower values than UHM-fed (p=0.042) before, and PF-fed had significantly lower values than UHM-fed after beta-2-agonist inhalation (P=0.050). The tendency of lower airway resistance when protein enriched were the same in gender specific analyses. In SGA children the same tendency was found between PF- and UHM-fed (P=0.007 before and P=0.046 after beta-2-agonist inhalation). All values were within reference limits.

Conclusions: Lung function in very preterm-born children may improve when fed a protein enriched nutrition post-discharge.

Buelo, Audrey, et al. At-risk children with asthma (ARC): a systematic review. *Thorax.* Sept 2018; 72(9): 813-824. http://dx.doi.org/10.1136/thoraxjnl-2017-210939

Introduction: Asthma attacks are responsible for considerable morbidity and may be fatal. We aimed to identify and weight risk factors for asthma attacks in children (5-12 years) in order to inform and prioritise care.

Methods: We systematically searched six databases (May 2016; updated with forward citations January 2017) with no language/date restrictions. Two reviewers independently selected studies for inclusion, assessed study quality and extracted data. Heterogeneity precluded meta-analysis. Weighting was undertaken by an Expert Panel who independently assessed each variable for degree of risk and confidence in the assessment (based on study quality and size, effect sizes, biological plausibility and consistency of results) and then achieved consensus by discussion. Assessments were finally presented, discussed and agreed at a multidisciplinary workshop.

Results: From 16 109 records, we included 68 papers (28 cohort; 4 case-control; 36 cross-sectional studies). Previous asthma attacks were associated with greatly increased risk of attack (ORs between 2.0 and 4.1). Persistent symptoms (ORs between 1.4 and 7.8) and poor access to care (ORs between 1.2 and 2.3) were associated with moderately/greatly increased risk. A

moderately increased risk was associated with suboptimal drug regimen, comorbid atopic/allergic disease, African-American ethnicity (USA), poverty and vitamin D deficiency. Environmental tobacco smoke exposure, younger age, obesity and low parental education were associated with slightly increased risk.

Discussion: Assessment of the clinical and demographic features identified in this review may help clinicians to focus risk reduction management on the high-risk child. Population level factors may be used by health service planners and policymakers to target healthcare initiatives.

Rogers, Valerie E., et al. Inflammation and asthma control in children with comorbid obstructive sleep apnea. *Pediatric Pulmonology.* Sept 2018; 53(9): 1200-1207. https://doi.org/10.1002/ppul.24074

Objectives: A bi-directional relationship exists between asthma and obstructive sleep apnea (OSA) in which presence of one is associated with increased prevalence and severity of the other. Our objective was to determine whether OSA accounted for differences in airway and systemic inflammation in asthmatic children and whether inflammation was associated with asthma control. We hypothesized that greater severity of SDB would correlate with increased upper airway and systemic inflammation and result in reduced asthma control.

Methods: Non-obese children aged 4-12 years with persistent asthma, with or without OSA were recruited. Asthma control was measured with the Childhood Asthma Control Test. Children underwent polysomnography and blood sampling, and children with OSA underwent clinically indicated adenotonsillectomy. Tonsils and sera were analyzed for 11 cytokines.

Results: Twenty-seven children (20 with OSA, seven without OSA) participated, mean age 7.9 years, 55.6% female, 92.6% African American. Levels did not differ for any cytokine between children with and without OSA. Lower nadir oxygen saturation was associated with higher levels of tonsil TNF-α ($P < 0.001$) and IL-10 ($P < 0.05$). Higher REM-related apnea-hypopnea index was associated with higher levels of tonsil TNF-α ($P < 0.05$). Children with uncontrolled asthma had significantly higher levels of serum IL-10, IL-13, and TNF-α, and tonsil TNF-α (all $P < 0.05$) than well-controlled asthmatic children. There was no association between OSA, or any polysomnography variable, and asthma control.

Conclusions: Despite the presence of OSA-associated airway inflammation, and asthma control-associated airway and systemic inflammation, OSA was not related to level of asthma control in this non-obese, largely minority, low income sample.

Orfanos, Sarah, et al. Obesity increases airway smooth muscle responses to contractile agonists. *American Journal of Physiology.* August 2018. https://doi.org/10.1152/ajplung.00459.2017

Background: The asthma-obesity syndrome represents a major public health concern that disproportionately contributes to asthma severity and induces insensitivity to therapy. To date, no study has shown an intrinsic difference between human airway smooth muscle (HASM) cells

derived from non-obese subjects and those derived from obese subjects. The objective of this study was to address whether there is a greater response to agonist-induced calcium mobilization, phosphorylation of myosin light chain (MLC) and greater shortening in HASM cells derived from obese subjects.

Methods: HASM cells derived from non-obese and obese subjects were age and gender matched. Phosphorylation of MLC was measured after having been stimulated by carbachol. Carbachol or histamine-induced mobilization of calcium and cell shortening was assessed in HASM cells derived from non-obese and obese donors.

Results: Agonist-induced MLC phosphorylation, mobilization of calcium and cell shortening was greater in obese as compared to non-obese-derived HASM cells. The MLC response was comparable in HASM cells derived from obese non-asthma and non-obese fatal asthma subjects. HASM cells derived from obese female subjects were more responsive to carbachol than HASM cells derived from obese male subjects. Insulin pre-treatment had little effect on these responses.

Conclusion: Our results show an increase in agonist-induced calcium mobilization associated with an increase in MLC phosphorylation and an increase in ASM cell shortening in favor of agonist-induced hyperresponsiveness in HASM cells derived from obese subjects. Our studies suggest that obesity induces a retained phenotype of hyperresponsiveness in cultured human airway smooth muscle cells.

Gerald, J.K., et al. School-Supervised Use of a Once-Daily Inhaled Corticosteroid Regimen: A Cluster Randomized Trial. *Allergy and Clinical Immunology.* Aug 2018. [e-pub ahead of print].

Background: School-supervised use of a once-daily inhaled corticosteroid regimen (supervised therapy) can improve medication adherence and asthma control.

Objective: To evaluate the effectiveness of supervised therapy in a unique setting and population.

Methods: We conducted a cluster-randomized trial of supervised therapy in 20 elementary schools with a disproportionate enrollment of low income Latino students. Schools were purposively selected, matched, and randomized to receive 9-months of supervised therapy with mometasone furoate or usual care. All English- or Spanish-speaking students with self-reported asthma were eligible. The Asthma Control Questionnaire (ACQ) was interviewer-administered quarterly at school. Students in supervised therapy schools were hypothesized to have lower ACQ scores than students in usual care schools.

Results: Of 393 enrolled students, 189 immediate intervention and 143 delayed intervention students provided ≥1 ACQ data point, were between 6 - 10 years of age, and were included in the primary analysis. At baseline, 39% of students reported taking a controller medication and 24% had well-controlled asthma. Eighty percent of immediate intervention students were prescribed mometasone. Schools administered 98% of prescribed doses when students attended school. Absences, weekends, and holidays reduced calendar adherence to 53%. During the first year, the mean ACQ score for immediate and delayed intervention students was 1.55 (95% CI 1.41, 1.70)

and 1.64 (95% CI 1.47, 1.80), respectively. The estimated treatment effect was -0.08 (95% CI -0.31, 0.14).

Discussion: Compared to usual care, supervised therapy did not improve asthma control among this population of Latino students. Additional research is warranted to confirm these results.

Vereen, Shanda, et al. Association Between Maternal 2nd Trimester Plasma Folate Levels and Infant Bronchiolitis. *Maternal and Child Health Journal.* 2018. https://doi.org/10.1007/s10995-018-2610-2 [e-pub ahead of print]

Objectives: Viral bronchiolitis is the most common cause of infant hospitalization. Folic acid supplementation is important during the periconceptional period to prevent neural tube defects. An area of investigation is whether higher prenatal folate is a risk factor for childhood respiratory illnesses. We investigated the association between maternal 2nd trimester plasma folate levels and infant bronchiolitis.

Methods: We conducted a retrospective cohort analysis in a subset of mother-infant dyads (n = 676) enrolled in the Conditions Affecting Neurocognitive Development and Learning in Early Childhood study and Tennessee Medicaid. Maternal folate status was determined using 2nd trimester (16-28 weeks) plasma samples. Bronchiolitis diagnosis in the first year of life was ascertained using International Classification of Diagnosis-9 codes from Medicaid administrative data. We used multivariable logistic regression to assess the adjusted association of prenatal folate levels and infant bronchiolitis outcome.

Results: Half of the women in this lower-income and predominately African-American (84%) study population had high levels of folate (median 2nd trimester level 19.2 ng/mL) and 21% of infants had at least one bronchiolitis healthcare visit. A relationship initially positive then reversing between maternal plasma folate and infant bronchiolitis was observed that did not reach statistical significance (poverall = .112, pnonlinear effect = .088). Additional adjustment for dietary methyl donor intake did not significantly alter the association.

Conclusions for Practice: Results did not confirm a statistically significant association between maternal 2nd trimester plasma folate levels and infant bronchiolitis. Further work is needed to investigate the role of folate, particularly higher levels, in association with early childhood respiratory illnesses.

In the NEWS
- ❖ Asthma Inhaler Device Market is Expected to Exhibit a Strong 5.2% CAGR Between 2018 and 2022. *Market Watch.* Sept 7, 2018.
- ❖ O'Neill, Eilis. Researchers explore a pesticide link to asthma in farmworkers' children. *WUNC 91.5 North Carolina Public Radio.* Sept 7, 2018.
- ❖ Cross, Daile. Is it asthma? Perth researchers developing urine test to diagnose disease. *WA Today (Australia).* Sept 7, 2018.

- ❖ Cone, Allen. Excessive airway nerves linked to severe asthma in study. *UPI.* Sept 6, 2018.
- ❖ Barcelona Institute for Global Health. Growth in first 3 years of life affects respiratory health in children. *Science Daily.* Aug 31, 2018.
- ❖ Hurley, Dan. Improving Outcomes For Low-Income Kids With Asthma. *WVXU (Cincinatti).* Aug 28, 2018.