Asthma News This Week

Feb 1, 2019

Childhood Asthma Leadership Coalition

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JOURNAL articles

Sordillo, Joanne E., et al. **Longitudinal analysis of bronchodilator response in asthmatics and effect modification of age-related trends by genotype. *Pediatric Pulmonary*.** Feb 2019. doi: 10.1002/ppul.24219.

BACKGROUND AND OBJECTIVES: Genome Wide Association Studies (GWAS) have identified genetic polymorphisms associated with bronchodilator response (BDR), but it is unknown how these associations change across life stages. We examined the impact of genetic variants on BDR from childhood to adulthood in asthmatics to uncover potential effect modification by age. METHODS: We searched the National Human Genome Research Institute (NHGRI) catalog of published GWAS to obtain a list of genetic associations with BDR, and tested them for effect modification by age in 604 subjects from the Childhood Asthma Management Program (CAMP), a clinical trial with longitudinal measures of BDR (age range 5-30 years). We performed longitudinal analyses using linear mixed models and visualized

longitudinal changes in BDR using generalized additive models with repeated measures, adjusting for treatment group, sex, and main effects of age and additive genotype. RESULTS: Increasing age was associated with decreased BDR (-0.24% per year). Polymorphisms rs295137 (T allele) near SPATS2L and rs2626393 (C allele) near ASB3 demonstrated their strongest associations with BDR in early childhood through adolescence, with a large decrease in their magnitude of effect from adolescence onward. The effect estimate for % BDR associated with rs295137 genotype (Beta = 1.3; 95%CI 0.6-2.1) was diminished by age (interaction term = -0.06, P = 0.004). The effect estimate for rs2626393 (Beta = -0.92 (95%CI -1.7 to -0.2) was also modified by age (interaction term = 0.05, P = 0.0004). CONCLUSIONS: Polymorphisms associated with BDR in childhood may not be relevant for predicting adolescent and adult BDR, which could reflect age-related changes in asthma phenotypes.

Berger, K., et al. **Prenatal high molecular weight phthalates and bisphenol A, and childhood respiratory and allergic outcomes.** *Pediatric Allergy and Immunology.* Feb 2019. doi: [10.1111/pai.12992](10.1111/pai.12992).

BACKGROUND: The prevalence of asthma and allergy is increasing in US children. In utero exposure to chemicals used in personal care products and plastics may contribute to increase in these diseases. METHODS: We quantified urinary concentrations of eight phthalate metabolites and bisphenol A in mothers twice during pregnancy in 1999-2000 in Salinas, California. We assessed probable asthma, aeroallergies, eczema, and spirometry in their children at age 7, and measured T helper 1 and T helper 2 cells in blood at ages 2, 5, and 7 (N = 392). We employed Bayesian model averaging to select confounders from additional biomarkers measured in this population and controlled for them in logistic and linear regressions. RESULTS: Monocarboxyisooctyl phthalate was associated with increased odds for probable asthma (odds ratio: 1.54, 95% CI: 1.12, 2.12), and with lower forced expiratory volume in one second (β: -0.09 L, 95% CI: -0.15, -0.03) and forced expiratory flow from 25% to 75% of forced vital capacity (β: -7.06 L/s, 95% CI: -11.04, -2.90). Several other associations were attenuated in final models that controlled for additional biomarkers. CONCLUSION: Monocarboxyisooctyl phthalate was associated with lower respiratory health after controlling for related chemical exposure, which suggests that confounding by multiple chemical exposures should be considered in future research.

Kan, Mengyuan, et al. **Airway Smooth Muscle-Specific Transcriptomic Signatures of Glucocorticoid Exposure.** *American Journal of Cellular Molecular Biology.* Jan 2019. doi: 10.1165/rcmb.2018-0385OC.

Glucocorticoids, commonly used asthma controller medications, decrease symptoms in most patients, but some remain symptomatic despite high dose treatment. The physiological basis underlying glucocorticoid response, especially among asthma patients with severe, refractory disease is not fully understood. We sought to identify differences between fatal asthma and non-asthma donor-derived airway smooth muscle (ASM) cell transcriptomic response to glucocorticoid exposure, and to compare ASM-specific changes to those of other cell types. In cells derived from 9 fatal asthma and 8 non-asthma donors, RNA-Seq was used to measure ASM transcriptome changes after exposure to budesonide (100nM 24hr) or control vehicle (DMSO).

Differential expression results were obtained for this dataset, as well as 13 publicly available glucocorticoid response transcriptomic datasets corresponding to 7 cell types. Specific genes were differentially expressed in response to glucocorticoid exposure: 7,835 and 6,957 in non-asthma and fatal asthma donor-derived ASM cells, respectively (adjusted p-value <0.05). Transcriptomic changes in response to glucocorticoid exposure were similar in fatal asthma and non-asthma donor-derived ASM, with enriched ontological pathways that included cytokine- and chemokine-related categories. Comparison of glucocorticoid-induced changes of the non-asthma ASM transcriptome to that of 6 other cell types showed that ASM has a distinct glucocorticoid response signature that is also present in fatal asthma donor-derived ASM cells.

Course, Christopher W., et al. **Fractional exhaled nitric oxide in preterm-born subjects: A systematic review and meta-analysis.** *Pediatric Pulmonology*. Jan 2019. doi: 10.1002/ppul.24270.

BACKGROUND: Decreased lung function is common in preterm-born survivors. Increased fractional exhaled nitric oxide (FeNO) appears to be a reliable test for eosinophillic airway inflammation especially in asthma. We, systematically, reviewed the literature to compare FeNO levels in preterm-born children and adults who did or did not have chronic lung disease of prematurity (CLD) in infancy with term-born controls. METHODS: We searched eight databases up to February 2018. Studies comparing FeNO levels in preterm-born subjects (<37 weeks' gestation) in childhood and adulthood with and without (CLD) with term-born subjects were identified and extracted by two reviewers. Data were analysed using Review Manager v5.3. RESULTS: From 6042 article titles, 183 full articles were screened for inclusion. Nineteen studies met the inclusion criteria. Seventeen studies compared FeNO levels in preterm- and term-born children and adults; 11 studies (preterm n = 640 and term n = 4005) were included in a meta-analysis. The mean FeNO concentration difference between the preterm-born and term-born group was -0.74 (95% CI -1.88 to 0.41) ppb. For the six studies reporting data on CLD (preterm n = 204 and term n = 211) the mean difference for FeNO levels was -2.82 (95% CI -5.87 to 0.22) ppb between the preterm-born CLD and term-born groups. CONCLUSIONS: Our data suggest that preterm born children with and without CLD have similar FeNO levels to term-born children suggesting an alternative mechanism to eosinophilic inflammation for symptoms of wheezing and airway obstruction observed in preterm-born subjects.

Carr, T.F., et al. **Non-atopic rhinitis at age 6 is associated with subsequent development of asthma.** *Clinical and Experimental Allergy*. Jan 2019. doi: 10.1111/cea.13276.

BACKGROUND: It has been postulated that the association between allergic rhinitis and asthma is attributable to the progressive clinical expression of respiratory inflammation during childhood. The role of non-allergic rhinitis in early life in relation to subsequent asthma has not been extensively explored. We sought to determine whether rhinitis in early life was associated with risk of asthma development into adulthood, and whether this relationship is independent of allergic sensitization. METHODS: Participants were identified from the Tucson Children's Respiratory Study, a non-selected birth cohort. Allergy skin prick testing was performed at age 6 years using house dust mix, Bermuda, mesquite, olive, mulberry, careless weed, and Alternaria aeroallergens. Atopy was defined as ≥1 positive tests. Physician-diagnosed active asthma from

age 6 to 32 and physician-diagnosed rhinitis at age 6 were determined by questionnaire. Participants with asthma or active wheezing at age 6 were excluded from analyses. Risk estimates were obtained with Cox regression. RESULTS: There were 521 participants who met inclusion criteria. The hazard ratio for subsequently acquiring a diagnosis of asthma between the ages of 8 and 32 for those with non-atopic rhinitis was 2.1 (95% CI: 1.2, 3.4, P = 0.005), compared with the non-atopic no rhinitis group, after adjusting for sex, ethnicity, maternal asthma, maternal education and smoking, and history of 4+ colds per year at age 6. Among the atopic participants, both the active and no rhinitis groups were more likely to develop and have asthma through age 32. The relation between non-atopic rhinitis and asthma was independent of total serum IgE levels at age 6. CONCLUSION: Childhood rhinitis, even in the absence of atopy, confers significant risk for asthma development through adulthood. These findings underscore the importance of non-allergic mechanisms in the development of asthma.

Mirzakhani, H., et al. **Impact of Preeclampsia on the Relationship between Maternal Asthma and Offspring Asthma. An Observation from the VDAART Clinical Trial.** *American Journal of Respiratory and Critical Care Medicine.* Jan 2019. doi: 10.1164/rccm.201804-0770OC.

RATIONALE: Maternal asthma and preeclampsia have independently been reported to be associated with increased asthma incidence in children of affected mothers. Maternal asthma is also associated with increased risk of preeclampsia development. However, the joint effect of these maternal conditions on child asthma risk is unknown. OBJECTIVES: To study whether development of preeclampsia among pregnant women with asthma was associated with higher risk of childhood asthma in the VDAART (Vitamin D Antenatal Asthma Reduction Trial). CONCLUSIONS: Preeclampsia is associated with increased risk of early life childhood asthma in children less than 3 years old over and above that associated with maternal asthma alone. The results implicate the interplay between maternal factors as strong predictors of offspring asthma and in utero maternal-fetal immune perturbations and developmental dysregulations associated with preeclampsia.

Bacharier, L.B., et al. **Longitudinal phenotypes of respiratory health in a high-risk urban birth cohort.** *American Journal of Respiratory and Critical Care Medicine.* Jan 2019. doi: 10.1164/rccm.201801-0190OC.

Characterization of patterns of wheezing and allergic sensitization in early life may allow for identification of specific environmental exposures impacting asthma development OBJECTIVES: To define respiratory phenotypes in inner-city children and their associations with early-life environmental exposures. METHODS: Data were collected prospectively from 442 children in the URECA (Urban Environment and Childhood Asthma) birth cohort through age 7 years, reflecting symptoms (wheezing), aeroallergen sensitization, pulmonary function, and body mass index. Latent class mixed models identified trajectories of wheezing, allergic sensitization, and pulmonary function. Cluster analysis defined nonoverlapping groups (termed phenotypes). Potential associations between phenotypes and early-life environmental exposures were examined. MEASUREMENTS AND MAIN RESULTS: Five phenotypes were identified and mainly differentiated by patterns of wheezing and allergic sensitization (low wheeze/low

atopy; low wheeze/high atopy; transient wheeze/low atopy; high wheeze/low atopy; high wheeze/high atopy). Asthma was most often present in the high-wheeze phenotypes, with greatest respiratory morbidity among children with frequent wheezing and allergic sensitization. These phenotypes differentially related to early-life exposures, including maternal stress and depression, antenatal environmental tobacco smoke, house dust microbiome, and allergen content (all $P < 0.05$). Prenatal smoke exposure, maternal stress, and depression were highest in the high-wheeze/low-atopy phenotype. The high-wheeze/high-atopy phenotype was associated with low household microbial richness and diversity. Early-life aeroallergen exposure was low in high-wheeze phenotypes. CONCLUSIONS: Patterns of wheezing, allergic sensitization, and lung function identified five respiratory phenotypes among inner-city children. Early-life environmental exposure to stress, depression, tobacco smoke, and indoor allergens and microbes differentially associate with specific phenotypes.

Chang, D.V., et al. **Exhaled nitric oxide predicts loss of asthma control in children after inhaled corticosteroids withdrawal.** *Pediatric Pulmonary.* Jan 2019. doi: 10.1002/ppul.24268.

BACKGROUND: Exhaled nitric oxide (eNO) has been proposed for monitoring airway inflammation, diagnosis, and prediction of steroid responsiveness in asthma. However, its utility after elective suspension of asthma medication is still unclear. We aimed to determine the association between eNO values and the subsequent loss of asthma control (LAC) in asymptomatic asthmatic children after inhaled corticosteroids (ICS) withdrawal. METHODS: We conducted a prospective observational cohort study. Forty-two children (23 boys), mean age 11 years, with clinically controlled asthma, according to GINA guidelines, and receiving low-dose of ICS (budesonide 200 µg/day or equivalent) were included immediately after the withdrawal of ICS. eNO, Asthma Control Test (ACT) and spirometry were monthly assessed, during 54 weeks or until the presence of at least one of the following criteria of LAC: 1) asthma exacerbation, 2) obstructive spirometric pattern, 3) ACT ≤ 19. RESULTS: eNO baseline geometric mean (eNO_b), measured 4 weeks after discontinuation of ICS, was 23.7 ppb (SD: 1.16). An eNO_b cutoff point of 21.8 ppb was determined to better discriminate between high and low eNO groups. Twenty-five subjects (71.4%) had LAC. High eNO_b was associated to LAC (OR: 9.01; 95CI: 1.10-74.26). In addition, LAC occurred earlier in high eNO_b than in low eNO_b patients (8 vs 28 weeks, respectively; $P = 0.017$). CONCLUSIONS: Our findings suggest that eNO predicts loss of asthma control and may contribute for clinical follow up decisions during childhood asthma after ICS withdrawal.

Popovic, M., et al. **Differentially methylated DNA regions in early childhood wheezing: an epigenome-wide study using saliva.** *Pediatric Allergy Immunology.* Jan 2019. doi: 10.1111/pai.13023.

BACKGROUND: Epigenetics may play a role in wheezing and asthma development. We aimed to examine infant saliva DNA methylation in association with early childhood wheezing. METHODS: A case-control study was nested within the NINFEA birth cohort with 68 cases matched to 68 controls by sex, age (between 6 and 18 months, median: 10.3 months) and season at saliva sampling. Using a bump hunting region-based approach we examined associations between saliva methylome measured using Illumina Infinium HumanMethylation450k array and

wheezing between 6 and 18 months of age. We tested our main findings in independent publicly available datasets of childhood respiratory allergy and atopic asthma, with DNA methylation measured in different tissues and at different ages. RESULTS: We identified one wheezing-associated differentially methylated region (DMR) spanning ten sequential CpG sites in the promoter-regulatory region of PM20D1 gene (family wise error rate <0.05). The observed associations were enhanced in children born to atopic mothers. In the publicly available datasets, hypermethylation in the same region of PM20D1 was consistently found at different ages and in all analysed tissues (cord blood, blood, saliva and nasal epithelia) of children with respiratory allergy/atopic asthma compared with controls. CONCLUSION: This study suggests that PM20D1 hypermethylation is associated with early childhood wheezing. Directionally consistent epigenetic alteration observed in cord blood and other tissues at older ages in children with respiratory allergy and atopic asthma provides suggestive evidence that a long-term epigenetic modification, likely operating from birth, may be involved in childhood atopic phenotypes.

Kochis, S.R., et al. **Caregiver-reported asthma control predicts future visits, independent of guidelines-based control measures.** *Journal of Allergy and Clinical Immunology: In Practice.* Jan 2019. doi: 10.1016/j.jaip.2018.12.030.

BACKGROUND: It is unknown whether caregiver perception of a child's asthma control, independent of guideline-based asthma control assessment, is a predictor of future acute visits. OBJECTIVE: To determine if caregiver-reported asthma control is an indicator of future risk of acute visit. METHODS: Two study populations of low income, minority 5-17 year old children with persistent asthma were included. Questionnaires administered at baseline, 3, 6, 9, and 12 months captured symptoms, short-acting beta-agonist use, acute visits in the previous 3 months, and caregiver-reported asthma control. Well controlled, not well controlled, and very poorly controlled asthma were defined using National Asthma Education and Prevention Program (NAEPP) guideline-based assessment. Relationships between caregiver-reported control and acute visits in the subsequent 3 months were examined. RESULTS: At baseline, both populations were predominantly Black/African American (91% and 79%) with public insurance (85% and 88%) and very poorly controlled asthma (47% and 50%). In both populations, the majority of caregivers reported that their child's asthma was well controlled (73% and 69%). In both populations, participants whose caregivers reported that their child had uncontrolled asthma had greater odds of having an acute visit in the following 3 months as compared to participants whose caregivers reported that their child's asthma was well controlled, independent of guideline-based control, age, sex, race, controller medication, insurance and atopy (OR [95% CI]: 2.4 [1.4 - 4.2] and 1.6 [1.1 - 2.4]). CONCLUSION: Among predominantly low-income minority children with asthma, caregiver-reported asthma control may provide information about the risk of future acute visit for asthma that is complementary to guideline-based control assessment.

Nagy, M.R., et al. **Association between asthma, obesity, and health behaviors in African American youth.** *Journal of Asthma*. Jan 2019. doi: 10.1080/02770903.2019.

BACKGROUND: There is a clear relationship between obesity and asthma, with obesity recognized as a risk factor for asthma. There is mounting evidence, however, that asthma may predict obesity risk via behavioral pathways. OBJECTIVES: The purpose of this study was to

assess the cross-sectional relationships between asthma, body mass index (BMI) percentile, and behavioral factors including caloric intake, dietary inflammatory index, moderate-vigorous physical activity (MVPA), and sedentary time (SED) among African American adolescents. METHODS: A community-based sample of 195 African American youth (ages 11-18 years) were included in this analysis. Asthma status was based on self-report using the International Study of Asthma and Allergies in Children's Phase Three questionnaire. MVPA and SED were measured via accelerometry, and caloric intake and dietary inflammatory index were evaluated with the Food Frequency Questionnaire. Weight status was assessed via BMI percentile using measured weight, height, and CDC growth charts. RESULTS: Adolescents with a history of asthma were significantly more overweight (62% vs. 43%, $p = 0.04$) and consumed a higher inflammatory diet (1.6 ± 0.3 vs. 1.0 ± 0.2, $p = 0.02$) than their peers who never had asthma. After adjusting for all covariates, activity and dietary variables, odds ratio analysis revealed adolescents who reported ever having asthma were 3.1 ± 1.5 times as likely to be overweight or obese than adolescents with no asthma history ($p = 0.02$). CONCLUSIONS: Presence of asthma history was associated with increased obesity risk in African American adolescents, independent of behavioral factors. Longitudinal studies are needed to better understand the relationship between asthma and obesity in African American adolescents.

Das, R.R., et al. **Role of breathing exercises and yoga/ pranayama in childhood asthma: A systematic review.** *Current Pediatric Reviews.* Jan 2019. doi: 10.2174/1573396315666190121122452.

BACKGROUND: Various complementary or alternative medicines (including breathing exercises and yoga/pranayama) have been tried as an attractive option to pharmacotherapy in childhood asthma. OBJECTIVE: To evaluate the role of breathing exercise and yoga/pranayama as add on therapy to the "pharmacologically recommended treatment" of childhood asthma. METHODS: We searched the published literature through the major databases: Medline via Ovid, PubMed, CENTRAL, Embase, and Google Scholar till June 2018. Randomized trials comparing breathing exercises and yoga/ pranayama versus control or as part of a composite intervention versus control were included. The primary outcome measures were quality of life and change in asthma symptoms. Secondary outcomes were: decrease in medication use, number of exacerbations, change in lung function and immunological parameters, school absenteeism, and adverse events. RESULTS: A total of 10 trials (466 children, 6-14 years age) were included. The severity of asthma varied among the trials. The data for primary outcome measures could not be pooled, there were mixed results for both primary and secondary outcomes. No significant benefit was obtained in acute asthma, and the lung function tests [except PEFR % at 4-6 weeks, PEF absolute at 3 months, and FVC absolute at 3 months] in chronic asthma. One trial compared breathing exercise versus yoga, and found no difference. Adverse events were not significant. CONCLUSIONS: Breathing exercise and yoga/ pranayama may have some additive role in the treatment of childhood asthma. However, at present it cannot be recommended as a standard of care due to insufficient data.

Marsland, A.L., et al. **A randomized pilot trial of a school-based psychoeducational intervention for children with asthma.** *Clinical & Experimental Allergy*. Jan 2019. doi: 10.1111/cea.13337.

BACKGROUND: Asthma is a common childhood illness with high morbidity and mortality among minority and socioeconomically disadvantaged children. Disparities are not fully accounted for by differences in asthma prevalence, highlighting a need for interventions targeting factors associated with poorer asthma control. One such factor is psychological stress. OBJECTIVE: Here, we examine the feasibility and acceptability of "I Can Cope (ICC)," a school-based stress management and coping intervention for children with asthma. METHODS: A parallel randomized pilot trial was conducted. One hundred and four low income children (mean age 10 years; 54% male; 70% African American) with persistent asthma were recruited from 12 urban schools and randomized to: (1) ICC or one of two control conditions: (2) "Open Airways for Schools (OAS)" - an asthma education intervention or (3) no treatment. RESULTS: 71% of eligible children participated in the study, with a dropout rate of 12%. ICC was rated as highly acceptable by participating children and parents. Preliminary efficacy data suggest that when compared with no treatment, ICC resulted in decreased symptoms of depression, perceived stress, and child-reported symptoms of asthma, and improvements in sleep quality and child-reported asthma control. There were no intervention-related changes in objective measures of asthma morbidity. The magnitude of intervention effects on psychological function did not differ between the ICC and OAS groups. CONCLUSIONS: Results support the feasibility and acceptability of utilizing school-based interventions to access hard to reach children with asthma. Preliminary findings offer support for future, large-scale efficacy studies of school-based interventions designed to target multiple factors that contribute to asthma disparities.

Colicino, S., et al. **Validation of childhood asthma predictive tools: a systematic review.** *Clinical & Experimental Review*. Jan 2019. doi: 10.1111/cea.13336.

BACKGROUND: There is uncertainty about the clinical usefulness of currently available asthma predictive tools. Validation of predictive tools in different populations and clinical settings is an essential requirement for the assessment of their predictive performance, reproducibility and generalizability. We aimed to critically appraise asthma predictive tools which have been validated in external studies. METHODS: We searched MEDLINE and EMBASE (1946-2017) for all available childhood asthma prediction models and focused on externally validated predictive tools alongside the studies in which they were originally developed. We excluded non-English and non-original studies. PROSPERO registration number is CRD42016035727. RESULTS: From 946 screened papers, 8 were included in the review. Statistical approaches for creation of prediction tools included chisquare tests, logistic regression models and the least absolute shrinkage and selection operator. Predictive models were developed and validated in general and high-risk populations. Only three prediction tools were externally validated: the Asthma Predictive Index, the PIAMA, and the Leicester asthma prediction tool. A variety of predictors has been tested, but no studies examined the same combination. There was heterogeneity in definition of the primary outcome among development and validation studies, and no objective measurements were used for asthma diagnosis. The

performance of tools varied at different ages of outcome assessment. We observed a discrepancy between the development and validation studies in the tools' predictive performance in terms of sensitivity and positive predictive values. CONCLUSIONS: Validated asthma predictive tools, reviewed in this paper, provided poor predictive accuracy with performance variation in sensitivity and positive predictive value.

Gauderman, W.J., et al. **A unified model for the analysis of gene-environment interaction.** *American Journal of Epidemiology*. Jan 2019. doi: <u>10.1093/aje/kwy278.</u>

Gene-environment (G × E) interaction is important for many complex traits. For a case-control study of a disease trait, logistic regression is the standard approach to model disease as a function of a gene (G), environmental factor, G × E interaction, and adjustment covariates. We propose an alternative model with G as the outcome and show how it provides a unified framework for obtaining all of the common G × E tests. These include the 1-degree-of-freedom (df) test of G × E interaction, the 2-df joint test of G and G × E, the case-only and empirical-Bayes tests, and several two-step tests. In the context of this unified model, we propose a novel 3-df test and demonstrate that it provides robust power across a wide range of underlying G × E interaction models. We demonstrate the 3-df test in a genomewide scan of G × Sex interaction for childhood asthma using data from the Children's Health Study. This scan identifies a strong G × Sex interaction at the phosphodiesterase (PDE) 4D locus, a known asthma-related locus, with a strong effect in males (odds ratio = 1.70 per allele, P = 3.8×10-8) and virtually no effect in females. We describe a software program, GxEScan, which can be used to fit standard and unified models for genomewide G × E studies.

Wang, A.L., et al. **DNA methylation is associated with improvement in lung function on inhaled corticosteroids in pediatric asthmatics.** *Pharmacogenetics and Genomics.* Jan 2019. doi:<u>10.1097/FPC.0000000000000366.</u>

Asthma is the most common chronic disease in children. Inhaled corticosteroids (ICS) are the first-line treatment for asthma control, but up to one-third of children have a poor treatment response. The mechanism of ICS resistance is poorly understood, and the role of DNA methylation in ICS treatment response is not known. We examined the association between peripheral blood DNA methylation and ICS treatment response in 152 pediatric persistent asthmatics from the Childhood Asthma Management Program. Response to ICS was measured by the percentage change in forced expiratory volume in 1 s (FEV1) 8 weeks after treatment initiation. The top CpG sites with a nominal P value less than 0.001 were correlated with gene expression using Pearson's and partial correlations. In 152 participants, mean±SD age was 9.8±2.0 years and median change in FEV1 after ICS initiation was 4.6% (interquartile range: 10.4%). A total of 545 CpG sites were differentially methylated (nominal P<0.05), and seven CpG sites had a nominal P value less than 0.001. Relative hypermethylation of cg20434811, cg02822723, cg14066280, cg27254601, and cg23913400 and relative hypomethylation of cg24937126 and cg24711626 were associated with an increase in FEV1 on ICS treatment. One CpG site was associated with gene expression. Relative hypermethylation of cg27254601 was associated with both an increase in FEV1 and BOLA2 expression (ρ=0.25, P=0.02). We identified a novel association between BOLA2 methylation, gene expression, and ICS response

as measured by lung function. Pharmacoepigenetics has the potential to detect treatment sensitivity in persistent childhood asthma.

Lau, N., et al. **Association between traffic related air pollution and the development of asthma phenotypes in children: a systematic review.** *International Journal of Chronic Diseases*. Jan 2019. doi: 10.1155/2018/4047386.

INTRODUCTION: Traffic related air pollution (TRAP) has long been associated with the onset of childhood asthma. The relationship between TRAP exposure and the development of childhood asthma phenotypes is less understood. To better understand this relationship, we performed a systematic review of the literature studying childhood TRAP exposure and the development of childhood asthma and wheezing phenotypes (transient, persistent, and late-onset asthma/wheezing phenotypes). METHODS: A literature search was performed in PubMed, Embase, and Scopus databases for current literature, returning 1706 unique articles. After screening and selection, 7 articles were included in the final review. Due to the low number of articles, no meta-analysis was performed. RESULTS: TRAP exposure appears to be associated with both transient and persistent asthma/wheezing phenotypes. However, there was little evidence to suggest a relationship between TRAP exposure and late-onset asthma/wheezing. The differing results may be in part due to the heterogeneity in study methods and asthma/wheezing phenotype definitions, in addition to other factors such as genetics. CONCLUSION: TRAP exposure may be associated with transient and persistent asthma/wheezing phenotypes in children. The low number of studies and differing results suggest that further studies are warranted.

Wadden, D., et al. **Sex-specific association between childhood BMI trajectories and asthma phenotypes.** *International Journal of Pediatrics*. Jan 2019. doi: 10.1155/2018/9057435.

BACKGROUND: Asthma and obesity are two common health problems in the pediatric population. Obesity is associated with several comorbidities which are of great consequence. Excess adipose tissue has been linked to asthma in a number of studies. However, little is known about childhood body mass index (BMI) trajectories and the development of asthma phenotypes. OBJECTIVE: The current study aims to investigate the significance of BMI trajectories over childhood and the risk of asthma phenotypes. METHODS: The current study is a prospective cohort of children aged 0-2 years who were followed every two years for eight years through cycles one to five in the National Longitudinal Survey of Children and Youths (NLSCY). Statistical analysis: a latent class growth modelling (LCGM) method was used to identify BMI trajectory patterns from cycles one to five. Multiple imputation (number of imputations=5) was carried out to impute children with missing values on height or weight information. Sampling weights and 1,000 bootstrap weights were used in SAS PROC SURVEYLOGISTIC to examine the association between BMI trajectory and asthma phenotypes (persistent or transient asthma) in a multivariate analysis. RESULTS: The study consisted of 571,790 males and 549,230 females. Among them, 46% of children showed an increasing trajectory in terms of change in BMI percentile during childhood, followed by the stable-trajectory group (41%) and decreasing-trajectory group (13%). After controlling for confounding factors, females in the increasing BMI trajectory group were four times more likely to be associated with persistent asthma (OR = 4.09;

95% CI:1.04-16.15; p = 0.0442) than females in the stable BMI trajectory group. No such relationship was found in males. The BMI trajectory was not significantly associated with risk of transient asthma for either sex. CONCLUSION: We report a female-specific association between increasing adiposity, measured by BMI, and persistent asthma.

Bjur, K.A., et al. **Socioeconomic status, race/ ethnicity, and health disparities in children and adolescents in a mixed rural-urban community-Olmsted County, Minnesota.** *Mayo Clinic Proceedings.* Jan 2019. doi: 10.1016/j.mayocp.2018.06.030.

OBJECTIVE: To characterize disparities in childhood health outcomes by socioeconomic status (SES) and race/ethnicity in a mixed rural-urban US community. METHODS: This was a retrospective population-based study of children 18 years and younger residing in Olmsted County, Minnesota, in 2009. The prevalence rates of childhood health outcomes were determined using International Classification of Diseases, Ninth Revision codes. Socioeconomic status was measured using the HOUsing-based SocioEconomic Status index (HOUSES), derived from real property data. Adjusting for age and sex, logistic regression models were used to examine the relationships among HOUSES, race/ethnicity, and prevalence of childhood health outcomes considering an interaction between HOUSES and race/ethnicity. Odds ratios were calculated using the lowest SES quartile and non-Hispanic white participants as the reference groups. RESULTS: Of 31,523 eligible children, 51% were male and 86% were of non-Hispanic white race/ethnicity. Overall, lower SES was associated with higher prevalence of bronchiolitis, urinary tract infection, asthma, mood disorder, and accidents/adverse childhood experiences (physical and sexual abuse) in a dose-response manner (P<.04). Prevalence rates of all childhood conditions considered except for epilepsy were significantly different across races/ethnicities (P<.002). Racial/ethnic disparities for asthma and mood disorder were greater with higher SES. CONCLUSION: Significant health disparities are present in a predominantly affluent, non-Hispanic white, mixed rural-urban community. Socioeconomic status modifies disparities by race/ethnicity in clinically less overt conditions. Interpretation of future health disparity research should account for the nature of disease.

Licari, A., et al. **Vitamin D3 in children with allergic asthma in clinical practice.** *Pediatric Pulmonary.* Jan 2019. doi: 10.1002/ppul.24229.

Asthma is a chronic inflammatory disorder; type 2 inflammation is the most common asthma endotype in childhood. T regulatory cells are functionally and allergen-specifically defective in allergic patients. Vitamin D3 exerts many functions on immune system, mainly concerning T regulatory function. Asthma control is the goal of the asthma treatment. We aimed to stratified a group of 76 consecutive children (50 males, 26 females, mean age 10.4 + 2.2 years) with allergic asthma and visited for the first time at a third-level paediatric clinic during a 3-month period, considering the Vitamin D3 serum levels. The three Vitamin D3 classes were not able to discriminate significant difference for all the parameters considered. In conclusion, Vitamin D3 serum assessment seems to be scarcely useful to pheno/endotyping allergic asthmatic children in clinical practice.

Lanz, M.J., et al. **Can early intervention in pediatric asthma improve long-term outcomes? A question that needs an answer.** *Pediatric Pulmonary*. Jan 2019. doi:

OBJECTIVE: Although many children with asthma do not experience persistence into adulthood, recent studies have suggested that poorly controlled asthma in childhood may be associated with significant airflow obstruction in adulthood. However, data regarding disease progression are lacking, and clinicians are not yet able to predict the course of a child's asthma. The goal of this article was to assess the current understanding of childhood asthma treatment and progression and to highlight gaps in information that remain. RESULTS: Uncontrolled asthma in early childhood can potentially have lasting effects on lung development, but it is unclear whether traditional interventions in very young children preserve lung function. Although not all children respond to standard interventions, certain asthma phenotypes have been identified that can help to understand which children may respond to a particular treatment. CONCLUSION: Clinicians should monitor children's asthma control and pulmonary function over time to assess the long-term impact of an intervention and to minimize the effect of uncontrolled asthma, especially exacerbations, on lung development. New biologic therapies have shown promise in treating adults with severe, uncontrolled asthma, and some of these therapies are approved in the United States for children as young as age 6. However, knowledge gaps regarding the efficacy and safety of these treatments in younger children hamper our understanding of their effect on long-term outcomes.

Heflin, C., et al. **SNAP benefits and childhood asthma.** *Social Science & Medicine.* Jan 2019. doi:.

Anecdotal and descriptive evidence has led to the claim that some low-income households may face a "eat or breathe" tradeoff, but quantitative evidence is scarce. We link Medicaid claims data to monthly Supplemental Nutritional Assistance Program (SNAP) participation data from the state of Missouri from 2010 to 2013 to explore monthly patterns in children's emergency room (ER) claims for asthma and to examine whether these patterns are sensitive to the timing and amount of SNAP benefits. This allows us to empirically test whether SNAP households with Medicaid insurance face trade-offs between food and medicine that increases the likelihood that a child in a SNAP and Medicaid household will go to the ER for asthma at the end of the month. While we do not find overwhelming evidence that the timing of SNAP benefits receipt are associated with the timing of asthma-related ER visits, we do find clear evidence that increased SNAP benefits are associated with a reduction in the overall probability of an asthma-related ER visit.

Goldstein, A., et al. **The impact of adenotonsillectomy on pediatric asthma.** *Pediatric Pulmonology.* Jan 2019. doi:

OBJECTIVE: To determine asthma outcomes in children undergoing adenotonsillectomy (T&A) for treatment of sleep-disordered breathing (SDB). HYPOTHESIS: Asthmatic children will demonstrate improvement in asthma control after T&A compared to asthmatic children not undergoing surgical treatment. PATIENT-SUBJECT SELECTION: 80 children with diagnosed asthma, aged 4-11, undergoing T&A and 62 controls matched to the T&A subjects by age, sex,

and asthma severity classification. METHODOLOGY: Parents and children completed the Childhood Asthma Control Test (C-ACT) and the Pediatric Sleep Questionnaire (PSQ). Parents were queried regarding the number of asthma exacerbations, the frequency of the use of systemic steroids, the number of emergency room visits and the number of hospitalizations in the prior 6 months. The identical questionnaires and interviews were completed 6 months after entry. RESULTS: The adjusted mean (95% CI) C-ACT score was 21.86 (20.94-22.68) at entry and 25.15 (24.55-25.71) at follow-up for the T&A group compared with 22.42 (21.46-23.28) and 23.59 (22.77-24.33) for the control group. There was a significant group by time interaction (P < 0.001). Simple effects analysis showed that group means did not differ at entry (P = 1.00) but did differ at follow-up (P = 0.006). Baseline PSQ was a significant predictor of improvement in C-ACT scores. Statistical modeling did not demonstrate significant group by time interactions for any of the asthma clinical outcomes, although these outcomes were very infrequent in both groups. CONCLUSION: Treatment of SDB improves asthma outcomes as measured by the C-ACT.

Litonjua, A.A. **Vitamin D and childhood asthma: causation and contribution to disease activity.** *Current Opinion in Clinical Immunology.* Jan 2019. doi: 10.1097/ACI.0000000000000509.

PURPOSE OF REVIEW: To review the literature of the past 18 months (April 2017 through September, 2018) relating to vitamin D and childhood asthma. RECENT FINDINGS: A combined analysis of two clinical trials of maternal vitamin D supplementation trials showed a significant protective effect of vitamin D supplementation trials in the primary prevention of asthma and recurrent wheeze up to age 3 years. Secondary analyses from these trials have also suggested that initial maternal vitamin D status could affect the response to supplementation during pregnancy, with the biggest protective effect in children born to mothers with initial 25hydroxyvitamin D (25OHD) levels of at least 30ng/ml. A postnatal, 6-month vitamin D supplementation trial in black, premature babies showed a 34% decreased risk of recurrent wheezing at 1 year among the infants who received supplementation. An individual patient data meta-analysis of published clinical trials concluded that vitamin D supplementation decreased the risk of asthma exacerbations in those with 25OHD levels less than 10ng/ml. Results of observational analyses on primary prevention of asthma and in prevention of exacerbations remain mixed, with the bulk of the evidence suggesting that there is a protective effect of higher vitamin D levels. SUMMARY: Evidence continues to accumulate that vitamin D supplementation helps to prevent the development of asthma and recurrent wheeze in early life, and may also help in the management of asthma. The level(s) of circulating vitamin D that maximizes these effects remains to be identified.

Peloza, D.L. and D.J. Jackson. **Strategies to prevent exacerbations of childhood asthma.** *Current Opinion in Pulmonary Medicine.* Jan 2019. doi: 10.1097/MCP.0000000000000539.

PURPOSE OF REVIEW: The goal of this review is to discuss strategies to prevent asthma exacerbations in children, focusing on recent advances in knowledge and understanding. RECENT FINDINGS: Asthma exacerbations are common, and their prevention is an important goal to avoid detrimental impacts such as loss of disease control and lung function and

significant healthcare costs. A number of strategies have been studied as tools for prevention of asthma exacerbations. Daily inhaled corticosteroids (ICSs) are effective for many children with asthma. However, alternative strategies such as intermittent ICS therapy, antileukotrienes, and biologics have been studied as means to lessen corticosteroid exposure. Further, recent studies have examined add-on strategies for children not controlled with ICS alone. Finally, personalizing therapy with targeted approaches has provided significant benefit to those with moderate-severe disease. SUMMARY: Recent research highlights many potentially effective treatment strategies to prevent asthma exacerbations in children. We have reviewed and summarized the data on treatment approaches to help provide a better understanding of the methods that can be utilized. An individualized approach with careful monitoring is essential to identify the most effective strategies to prevent asthma exacerbations in each child.

Bi, C., et al. **Phthalates and organophosphates in settled dust and HVAC filter dust of U.S. low-income homes: Association with season, building characteristics, and childhood asthma.** *Environment International*. Dec 2018. doi: 10.1016/j.envint.2018.09.013.

Phthalates and organophosphates are ubiquitous indoor semi-volatile organic contaminants (SVOCs) that have been widely used as plasticizers and flame retardants in consumer products. Although many studies have assessed their levels in house dust, only a few used dust samples captured by filters of building heating, ventilation, and air conditioning (HVAC) systems. HVAC filters collect particles from large volumes of air over a long period of time (potentially known) and thus provide a spatially and temporally integrated concentration. This study measured concentrations of phthalates and organophosphates in HVAC filter dust and settled floor dust collected from low-income homes in Texas, United States, in both the summer and winter seasons. The most frequently detected compounds were benzyl butyl phthalate (BBzP), di-(2-ethylhexyl) phthalate (DEHP), di-n-octyl phthalate (DnOP), tris (1-chloro-2-propyl) phosphate (TCIPP), triphenyl phosphate (TPHP), and tris (1,3-dichloroisopropyl) phosphate (TDCIPP). The median level of TCIPP in settled dust was 3- to 180-times higher than levels reported in other studies of residential homes. Significantly higher concentrations were observed in HVAC filter dust as compared to settled dust for most of the frequently detected compounds in both seasons, except for several phthalates in the winter. SVOC concentrations in settled dust in winter were generally higher than in summer, while different seasonality patterns were found for HVAC filter dust. Settled dust samples from homes with vinyl flooring contained significantly higher levels of BBzP and DEHP as compared to homes with other types of floor material. The concentration of DEHP and TDCIPP in settled dust also significantly associated with the presence of carpet in homes. Cleaning activities to remove dust from furniture actually increased the levels of certain compounds in HVAC filter dust, while frequent vacuuming of carpet helped to decrease the concentrations of some compounds in settled dust. Additionally, the size and age of a given house also correlated with the levels of some pollutants in dust. A statistically significant association between DEHP concentration in HVAC filter dust in summer and the severity of asthma in children was observed. These results suggest that HVAC filter dust represents a useful sampling medium to monitor indoor SVOC concentrations with high sensitivity; in contrast, when using settled dust, in addition to consideration of seasonal influences, it is critical to know

the sampling location because the type and level of SVOCs may be related to local materials used there.

Reese, Sarah E., et al. **Epigenome-wide meta-analysis of DNA methylation and childhood asthma.** *Journal of Allergy and Clinical Immunology*. Dec 2018. doi: <u>10.1016/j.jaci.2018.</u>

BACKGROUND: Epigenetic mechanisms, including methylation, can contribute to childhood asthma. Identifying DNA methylation profiles in asthmatic patients can inform disease pathogenesis. We sought to identify differential DNA methylation in newborns and children related to childhood asthma. METHODS: Within the Pregnancy And Childhood Epigenetics consortium, we performed epigenome-wide meta-analyses of school-age asthma in relation to CpG methylation (Illumina450K) in blood measured either in newborns, in prospective analyses, or cross-sectionally in school-aged children. We also identified differentially methylated regions. RESULTS: In newborns (8 cohorts, 668 cases), 9 CpGs (and 35 regions) were differentially methylated (epigenome-wide significance, false discovery rate < 0.05) in relation to asthma development. In a cross-sectional meta-analysis of asthma and methylation in children (9 cohorts, 631 cases), we identified 179 CpGs (false discovery rate < 0.05) and 36 differentially methylated regions. In replication studies of methylation in other tissues, most of the 179 CpGs discovered in blood replicated, despite smaller sample sizes, in studies of nasal respiratory epithelium or eosinophils. Pathway analyses highlighted enrichment for asthma-relevant immune processes and overlap in pathways enriched both in newborns and children. Gene expression correlated with methylation at most loci. Functional annotation supports a regulatory effect on gene expression at many asthma-associated CpGs. Several implicated genes are targets for approved or experimental drugs, including IL5RA and KCNH2. CONCLUSION: Novel loci differentially methylated in newborns represent potential biomarkers of risk of asthma by school age. Cross-sectional associations in children can reflect both risk for and effects of disease. Asthma-related differential methylation in blood in children was substantially replicated in eosinophils and respiratory epithelium.

Shankar, Michelle, et al. **Depressive symptoms among urban adolescents with asthma: A focus for providers.** *Academic Pediatrics*. Dec 2018. doi: <u>10.1016/j.acap.2018.12.004.</u>

OBJECTIVES: Asthma is the most common chronic disease of childhood in the United States, disproportionately affecting urban, poor, and minority children. Adolescents are at high risk for poor asthma outcomes and for depressive symptoms. The purpose of this study is to investigate associations between depressive symptoms and asthma-related clinical and functional outcomes among urban teens. METHODS: We used baseline data from a 3-arm randomized trial, School-Based Asthma Care for Teens, in Rochester, NY. We used the Center for Epidemiological Studies Depression Scale with a standard cutoff score of 16 to identify subjects at risk for clinical depression. We used structured in-home surveys and validated scales to assess clinical and functional outcomes and conducted bivariate and multivariate analyses to evaluate differences between groups. RESULTS: We identified 277 eligible teens (ages 12 to 16, 80% participation, 54% black, 34% Hispanic, 45% female, 84% on Medicaid). Overall, 28% reported depressive symptoms. Teens with depressive symptoms experienced greater asthma symptom severity and more acute health care utilization for asthma (all P < .001); however, there was no difference in

preventive care use between groups. Teens with depressive symptoms also reported lower asthma-related quality of life (P < .001), less sleep (P < .001), and more limitation in mild (adjusted odds ratio [aOR], 2.60; 95% confidence interval [CI], 1.34-5.02) and moderate (aOR, 2.56; 95% CI, 1.41-4.61) activity and in gym (aOR, 2.33; 95% CI, 1.30-4.17). CONCLUSIONS: Depressive symptoms are prevalent among urban teens with asthma and are associated with worse asthma-related clinical outcomes, functional limitation, and quality of life. Providers should consider depression as a significant comorbidity that may impact multiple aspects of daily life for this population.

Bobolea, I. **Early life origins of asthma: A review of potential effectors. Journal of** *Investigational Allergology and Clinical Immunology.* Dec 2018. doi: 10.18176/jiaci.0361.

There is currently growing evidence that events occurring early in life, both before and after birth, are significantly associated with the risk of asthma, COPD and low lung function later in life. In fact, from conception to death there are continuous, dynamic numbers of gene-environment interactions that determine two fundamental biologic processes, lung development and lung ageing. Over 130 birth cohorts have been initiated in the last 30 years. These birth cohorts have improved our understanding of asthma inception, progression and persistency. In this review, we summarize the main data upon those early life events proven to determine later development and persistence of asthma, such as maternal atopy or smoking, preterm birth/ bronchopulmonary dysplasia, or infections, nutrition and obesity, smoking and other environmental exposures in childhood and adolescence. Some of these factors are obviously impossible to prevent or eliminate; others, in exchange, have been proven to have a protective role, and current research is aimed to optimally enhance them. The available prophylactic measures are also revised here. In case of environmental pollution for instance, large scale political interventions successfully managed to decrease contamination levels, leading to improved lung function and lower asthma prevalence in the respective geographical areas. Future research should focus on better understanding these complex interactions, in order to develop and enhance effective preventive therapeutic measures.

Altman, M.C., et al. **Allergen-induced activation of natural killer cells represent an early-life immune response in the development of allergic asthma.** *Journal of Allergy and Clinical Immunology.* Dec 2018. doi: 10.1016/j.jaci.2018.02.019.

BACKGROUND: Childhood asthma in inner-city populations is a major public health burden, and understanding early-life immune mechanisms that promote asthma onset is key to disease prevention. Children with asthma demonstrate a high prevalence of aeroallergen sensitization and TH2-type inflammation; however, the early-life immune events that lead to TH2 skewing and disease development are unknown. OBJECTIVE: We sought to use RNA sequencing of PBMCs collected at age 2 years to determine networks of immune responses that occur in children with allergy and asthma. METHODS: In an inner-city birth cohort with high asthma risk, we compared gene expression using RNA sequencing in PBMCs collected at age 2 years between children with 2 or more aeroallergen sensitizations, including dust mite, cockroach, or both, by age 3 years and asthma by age 7 years (cases) and matched control subjects who did not have any aeroallergen sensitization or asthma by age 7 years. RESULTS: PBMCs from the cases

showed higher levels of expression of natural killer (NK) cell-related genes. After cockroach or dust mite allergen but not tetanus antigen stimulation, PBMCs from the cases compared with the control subjects showed differential expression of 244 genes. This gene set included upregulation of a densely interconnected NK cell-like gene network reflecting a pattern of cell activation and induction of inflammatory signaling molecules, including the key TH2-type cytokines IL9, IL13, and CCL17, as well as a dendritic cell-like gene network, including upregulation of CD1 lipid antigen presentation molecules. The NK cell-like response was reproducible in an independent group of children with later-onset allergic sensitization and asthma and was found to be specific to only those children with both aeroallergen sensitization and asthma. CONCLUSION: These findings provide important mechanistic insight into an early-life immune pathway involved in TH2 polarization, leading to the development of allergic asthma.

Beck-Sague, C.M., et al. **Trends in racial and ethnic disparities in childhood asthma in Miami, Florida: 2005-2013.** *Journal of Immigrant and Minority Health*. Dec 2018. doi: 10.1007/s10903-017-0686-1.

Nationally, racial and ethnic disparities in childhood asthma plateaued from 2005 to 2013. We assessed trends in childhood asthma in Miami, Florida using Youth Risk Behavior Surveillance System (YRBSS) data and emergency department (ED) utilization and hospitalization rates by zip code population characteristics. Asthma prevalence in Miami did not vary significantly by race/ethnicity in YRBSS respondents in 2005 (16.2-17.2%, all groups), but rose in African-Americans and Hispanics and declined in Whites by 2013 to 27.9, 20.9 and 12.6%, respectively (P = 0.02). Median asthma ED visit rates rose from 106.8 (2006-2008) to 138.2 (2011-2013; P = 0.004) per 10,000 children. High-poverty and majority African-American zip codes were 6.3 and 7.3 times more likely to have asthma ED visit rates > 200 than others (P < 0.001). In high-poverty zip codes, majority African-American population was not associated with significantly higher ED utilization. In low-poverty zip codes, the association became stronger. Greater poverty explains much, but not all of Miami African-Americans' higher asthma risk.

Berger, K., et al. **Associations between prenatal maternal urinary concentrations of personal care product chemical biomarkers and childhood respiratory and allergic outcomes in the CHAMACOS study.** *Environment International*. Dec 2018. doi: 10.1016/j.envint.2018.09.027.

BACKGROUND: Personal care product chemicals may be contributing to risk for asthma and other atopic illnesses. The existing literature is conflicting, and many studies do not control for multiple chemical exposures. METHODS: We quantified concentrations of three phthalate metabolites, three parabens, and four other phenols in urine collected twice during pregnancy from 392 women. We measured T helper 1 (Th1) and T helper 2 (Th2) cells in their children's blood at ages two, five, and seven, and assessed probable asthma, aeroallergies, eczema, and lung function at age seven. We conducted linear and logistic regressions, controlling for additional biomarkers measured in this population as selected by Bayesian Model Averaging. RESULTS: The majority of comparisons showed null associations. Mono-n-butyl phthalate (MnBP) was associated with higher Th2% (RR: 10.40, 95% CI: 3.37, 17.92), and methyl paraben was associated with lower Th1% (RR: -3.35, 95% CI: -6.58, -0.02) and Th2% at borderline significance (RR: -4.45, 95% CI: -8.77, 0.08). Monoethyl phthalate was associated with lower

forced expiratory flow from 25 to 75% of forced vital capacity (FEF25-75%) (RR: -3.22 L/s, 95% CI: -6.02, -0.34). Propyl paraben (OR: 0.86, 95% CI: 0.74, 0.99) was associated with decreased odds of probable asthma. CONCLUSIONS: While some biomarkers, particularly those from low molecular weight phthalates, were associated with an atopic cytokine profile and poorer lung function, no biomarkers were associated with a corresponding increase in atopic disease.

Cherkasov, S.V., et al. **Oral microbiomes in children with asthma and dental caries.** *Oral Diseases.* Dec 2018. doi: [10.1111/odi.13020.](10.1111/odi.13020.)

OBJECTIVE: Recently, a significant association between dental caries and the severity of bronchial asthma in children has been revealed. This finding indicates a possible relationship between the oral microbiome and the pathogenesis of asthma. The purpose of our study was to estimate differences in the dental plaque microbiota of asthmatic children with and without dental caries by 16S rDNA sequencing. MATERIAL AND METHODS: Dental plaque samples were obtained with a spoon excavator from the occlusal surface of one deciduous tooth (the second mandibular left molar in caries-free children and the most affected tooth in caries-affected children). Total DNA was extracted from dental plaque. DNA libraries were analysed by 16S rRNA gene sequencing on the MiSeq (Illumina) platform. RESULTS: There were no significant differences in the composition of bacterial communities from both caries-affected and caries-free children with asthma. The "caries-enriched" genus was Veillonella (Veillonellaceae, Selenomonadales, Negativicutes). Relative abundance of Neisseria was significantly higher in caries-free children with asthma ($p < 0.05$). CONCLUSIONS: The most significant difference in compared bacterial communities was a higher relative abundance of Veillonella in caries-affected plaques that suggests its involvement in pathogenesis of caries. Potential respiratory pathogens are present in oral cavity of both caries-affected and caries-free asthmatic children.

Biagini Myers J.M., et al. **A pediatric asthma risk score to better predict asthma development in young children.** *Journal of Allergy and Clinical Immunology*. Dec 2018. doi: 10.1016/j.jaci.2018.09.037.

BACKGROUND: Asthma phenotypes are currently not amenable to primary prevention or early intervention because their natural history cannot be reliably predicted. Clinicians remain reliant on poorly predictive asthma outcome tools because of a lack of better alternatives. We sought to develop a quantitative personalized tool to predict asthma development in young children. METHODS: Data from the Cincinnati Childhood Allergy and Air Pollution Study (n = 762) birth cohort were used to identify factors that predicted asthma development. The Pediatric Asthma Risk Score (PARS) was constructed by integrating demographic and clinical data. The sensitivity and specificity of PARS were compared with those of the Asthma Predictive Index (API) and replicated in the Isle of Wight birth cohort. RESULTS: PARS reliably predicted asthma development in the Cincinnati Childhood Allergy and Air Pollution Study (sensitivity = 0.68, specificity = 0.77). Although both the PARS and API predicted asthma in high-risk children, the PARS had improved ability to predict asthma in children with mild-to-moderate asthma risk. In addition to parental asthma, eczema, and wheezing apart from colds, variables that predicted asthma in the PARS included early wheezing (odds ratio [OR], 2.88; 95% CI,

1.52-5.37), sensitization to 2 or more food allergens and/or aeroallergens (OR, 2.44; 95% CI, 1.49-4.05), and African American race (OR, 2.04; 95% CI, 1.19-3.47). The PARS was replicated in the Isle of Wight birth cohort (sensitivity = 0.67, specificity = 0.79), demonstrating that it is a robust, valid, and generalizable asthma predictive tool. CONCLUSIONS: The PARS performed better than the API in children with mild-to-moderate asthma. This is significant because these children are the most common and most difficult to predict and might be the most amenable to prevention strategies.

Oksel, C., et al. **Causes of variability in latent phenotypes of childhood wheeze.** *Journal of Allergy and Clinical Immunology*. Dec 2018. doi: 10.1016/j.jaci.2018.10.059.

BACKGROUND: Latent class analysis (LCA) has been used extensively to identify (latent) phenotypes of childhood wheezing. However, the number and trajectory of discovered phenotypes differed substantially between studies. OBJECTIVE: We sought to investigate sources of variability affecting the classification of phenotypes, identify key time points for data collection to understand wheeze heterogeneity, and ascertain the association of childhood wheeze phenotypes with asthma and lung function in adulthood. METHODS: We used LCA to derive wheeze phenotypes among 3167 participants in the ALSPAC cohort who had complete information on current wheeze recorded at 14 time points from birth to age 16½ years. We examined the effects of sample size and data collection age and intervals on the results and identified time points. We examined the associations of derived phenotypes with asthma and lung function at age 23 to 24 years. RESULTS: A relatively large sample size (>2000) underestimated the number of phenotypes under some conditions (eg, number of time points <11). Increasing the number of data points resulted in an increase in the optimal number of phenotypes, but an identical number of randomly selected follow-up points led to different solutions. A variable selection algorithm identified 8 informative time points (months 18, 42, 57, 81, 91, 140, 157, and 166). The proportion of asthmatic patients at age 23 to 24 years differed between phenotypes, whereas lung function was lower among persistent wheezers. CONCLUSIONS: Sample size, frequency, and timing of data collection have a major influence on the number and type of wheeze phenotypes identified by using LCA in longitudinal data.

Lang, J.E., et al. **Being overweight or obese and the development of asthma.** *Pediatrics.* Dec 2018. doi: 10.1542/peds.2018-2119.

OBJECTIVES: Adult obesity is linked to asthma cases and is estimated to lead to 250 000 new cases yearly. Similar incidence and attributable risk (AR) estimates have not been developed for children. We sought to describe the relationship between overweight and obesity and incident asthma in childhood and quantify AR statistics in the United States for overweight and obesity on pediatric asthma. METHODS: The PEDSnet clinical data research network was used to conduct a retrospective cohort study (January 2009–December 2015) to compare asthma incidence among overweight and/or obese versus healthy weight 2- to 17-year-old children. Asthma incidence was defined as ≥2 encounters with a diagnosis of asthma and ≥1 asthma controller prescription. Stricter diagnostic criteria involved confirmation by spirometry. We used multivariable Poisson regression analyses to estimate incident asthma rates and risk ratios and accepted formulas for ARs. RESULTS: Data from 507 496 children and 19 581 972 encounters

were included. The mean participant observation period was 4 years. The adjusted risk for incident asthma was increased among children who were overweight (relative risk [RR]: 1.17; 95% confidence interval [CI]: 1.10–1.25) and obese (RR: 1.26; 95% CI: 1.18–1.34). The adjusted risk for spirometry-confirmed asthma was increased among children with obesity (RR: 1.29; 95% CI: 1.16–1.42). An estimated 23% to 27% of new asthma cases in children with obesity is directly attributable to obesity. In the absence of overweight and obesity, 10% of all cases of asthma would be avoided. CONCLUSIONS: Obesity is a major preventable risk factor for pediatric asthma.

Lee, C.C., et al. **Associations between patient-reported outcome measures of asthma control and psychosocial symptoms.** *Clinical Pediatrics.* Nov 2018. doi: 10.1177/0009922818812479.

There is growing emphasis on using patient-reported outcome measures to enhance clinical practice. This study was a retrospective review of scores on the Childhood Asthma Control Test (C-ACT) and the Pediatric Symptom Checklist-17 (PSC-17) at a pediatric primary care center in Boston, Massachusetts. A total of 218 patients were selected at random using billing codes for well-child (WC) care and asthma, excluding complex medical conditions. Cutoff scores were used to identify uncontrolled asthma (C-ACT $\leqslant$ 19) and clinically significant psychosocial symptoms (+PSC-17). Multiple logistic regression was used to measure associations between C-ACT $\leqslant$ 19 and +PSC-17, adjusting for covariates. In multivariable analysis, C-ACT $\leqslant$ 19 at WC visits was associated with +PSC-17 at WC visits (adjusted odds ratio = 3.2 [95% confidence interval = 1.3-8.6]). C-ACT $\leqslant$ 19 at non-WC visits was also associated with +PSC-17 at WC visits (adjusted odds ratio = 3.1 [95% confidence interval = 1.2-8.9]). Patient-reported outcome measures of asthma control and psychosocial symptoms were positively correlated in this sample.

Wang, A.L., et al. **Remission of persistent childhood asthma: Early predictors of adult outcomes.** *Journal of Allergy and Clinical Immunology*. Nov 2018. doi: 10.1016/j.jaci.2018.09.038.

BACKGROUND: Few data exist on the predictors of asthma remission by early adulthood in North America. OBJECTIVE: The predictors of adult asthma remission were determined in a multiethnic population of patients with mild-to-moderate persistent childhood asthma. METHODS: Asthma remission in early adulthood was measured by using 2 definitions: a clinical and a strict definition. Both included normal lung function and the absence of symptoms, exacerbations, and medication use. The strict definition also included normal airways responsiveness. Predictors were identified from 23 baseline measures by using multivariate logistic regression. The probability of remission was modeled by using decision tree analysis. RESULTS: In 879 subjects the mean ± SD baseline age was 8.8 ± 2.1 years, 59.4% were male, and 68.7% were white. By adulthood, 229 (26.0%) of 879 participants were in clinical remission, and 111 (15.0%) of 741 participants were in strict remission. The degree of FEV1/forced vital capacity (FVC) ratio impairment was the largest predictor of asthma remission. More than half of boys and two thirds of girls with baseline FEV1/FVC ratios of 90% or greater were in remission at adulthood. Decreased airways responsiveness was also a predictor for both remission definitions (clinical remission odds ratio, 1.23 [95% CI, 1.09-1.39]; strict remission

odds ratio, 1.52 [95% CI, 1.26-1.84]). The combination of normal FEV1/FVC ratio, airways responsiveness, and serum eosinophil count at baseline yielded greater than 80% probability of remission by adulthood. CONCLUSION: A considerable minority of patients with persistent childhood asthma will have disease remission by adulthood. Clinical prognostic indicators of asthma remission, including baseline lung function, can be seen from an early age.

In the NEWS

Najarro, Claudia. Guest Column: [Families will suffer if Wheeler becomes EPA chief](#). *Las Vegas Sun.*. Feb 4, 2019.

Zimlich, Rachael. [New tool improves asthma prediction, prevention](#). *Contemporary Pediatrics.* Feb 1, 2019.

[All About Children Pediatric Partners joins Penn State Health Medical Group](#). *Penn State News.* Feb 1, 2019.

Stepler, Kellen. [Duquesne professor helps children at risk for asthma](#). *The Duquesne Duke.* Jan 31, 2019.

Morrison, John. [Putting Psychological Flexibility into (ACT)ion for Asthma](#). *American Academy of Pediatrics Blog.* Jan 30, 2019.

Miller, Randy. [Asthma Van Helps Keep Atlanta Students Healthy — And In School](#). *WABE: Georgia Health News.* Jan 25, 2019.

Ivanhoe Newswire. [Doctors say some children's asthma may actually be acid reflux](#). *KTVA The Voice of Alaska.* Jan 24, 2019.

Morton, M. [Benefits of FENO-guided asthma management passes from mother to child](#). *Infectious Diseases in Children.* Jan 21, 2019.

Bahrenburg, Caitlyn. [Study Shows Plausible Link Between Fertility Care and Asthma Risk](#). *MD Magazine.* Jan 10, 2019.

Brewster, Carisa D. [New Tool Better Predicts Pediatric Asthma Development](#). *MD Magazine.* Jan 2, 2019.

Clinical Pharmacist. [Obesity increases risk of childhood asthma by 29%, say researchers](#). *The Pharmaceutical Journal.* Jan 2, 2019.

[Loma Linda University researchers see link between rail yard pollution and children with asthma-related problems](#). *Herald News.* Dec 27, 2018.

Cronan, Kate. [Being overweight or obese may account for 10 percent of children's asthma cases](#). *The Philadelphia Inquirer.* Dec 20, 2018.

Children's Hospital of Philadelphia. Children's Hospital of Philadelphia Expands Community Asthma Prevention Program in Partnership with Philadelphia Housing Development Corporation. *PR Newswire.* Dec 18, 2018.

Rule, Kelly. CHOP teams up with local contractors to renovate homes of children with asthma. *Fox 29.* Dec 17, 2018.

Bonis, Liz. New tool developed by Cincinnati Children's may help predict asthma in kids. *Local 12.* Dec 14, 2018.

Brewster, Carisa. Back to all news Lower SNAP Benefits May Increase ER Visits for Pediatric Asthma. *MD Magazine.* Dec 14, 2018.

Oliver, Elizabeth. IVF linked to child asthma risk. *BioNews.* Dec 10, 2019.

Blaiss, Michael. Asthma Mythbusters: No, Chihuahuas Can't Cure Your Kid's Asthma. *U.S. News and World Report.* Dec 4, 2018.