

APSR Respiratory Research Review

Making Education Easy

Issue 22 – 2008

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Welcome to this edition of the Respiratory Research Review and thank you for the feedback.

The focus of this month's Research Review is asthma. We review excellent publications on the long term outcome of wheeze in preschool children, differences between obese and non-obese women with asthma, revisit the protective role of aspirin in asthma, as well as reviewing a randomised control trial on the effect on the management childhood guidelines in general practice.

Thank you for the feedback and suggestions for topics for the Research Reviews.

Kind regards,

Dr Lutz Beckert

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Long-term prognosis in preschool children with wheeze

Authors: Frank Pl et al

Summary: The prognosis and important predictive factors of wheeze among 628 preschool children (aged <5 years at recruitment) were investigated in this longitudinal study, with data collected at recruitment and at least 6 years' follow-up. Parents reported wheeze at baseline in 32% of the children, 27% of whom also reported wheeze at follow-up (persistent asthma). Baseline predictors of persistent asthma were exercise-induced wheeze (odds ratio 3.94; 95% CI 1.72, 9.00) and a history of atopic disorders (4.44; 1.94, 10.13). The presence of both these factors was associated with a 53.2% likelihood of developing asthma, and the likelihood decreased to 17.2% and 10.9% for one and none of these features, respectively. There was no apparent association between a family history of asthma and the development of persistent asthma among the study population.

Comment: This Manchester group answers an important clinical question: How many of the 25- 38% of preschool children who report wheezing will go on to develop asthma? This population study followed more than 600 children over a period of 6-11 years. The authors found that almost three quarters of 'wheezy children' had only transient symptoms. If children had exercise-induced wheeze and atopy then half of these children went on to develop asthma. These data are greatly reassuring for parents with preschool children who wheeze, as only a minority of these children will develop asthma.

Reference: *BMJ* 2008; 336(7658): 1423-6

<http://www.bmj.com/cgi/content/abstract/336/7658/1423>



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Randomised aspirin assignment and risk of adult-onset asthma in the Women's Health Study

Authors: Kurth T et al

Summary: Aspirin has previously been shown to slightly decrease the risk of adult-onset asthma among men, and this placebo-controlled RCT was conducted to investigate whether or not a similar effect is seen in women. Aspirin 100mg or placebo every alternate day was administered to 37,270 apparently healthy participants in the Women's Health Study. During 10 years' follow-up, there were 872 and 963 new cases of asthma diagnosed among the aspirin and placebo groups, respectively (hazard ratio 0.90; 95% CI 0.82, 0.99; $p = 0.027$). This effect was not significantly modified by age, exercise levels, postmenopausal hormone use, smoking status or randomised vitamin E assignment, but body mass index ≥ 30 kg/m² was associated with no effect with aspirin.

Comment: Data from the American Women's Health Study are shedding new light on the role of aspirin in the development of adult-onset asthma. The authors report a 10% lower risk of developing adult-onset asthma among woman taking 100mg of aspirin on alternate days. In earlier research, the Physicians' Health Study showed a 20% relative risk of newly reported adult-onset asthma in men taking 325mg of aspirin on alternate days. Bottom line: these are early data, but it appears that although aspirin can precipitate bronchospasm in patients with aspirin-intolerant asthma, it may be protective in preventing the development of asthma in adult women.

Reference: *Thorax 2008; 63: 514-8*

<http://thorax.bmj.com/cgi/content/abstract/63/6/514>

Observational studies on the effect of dietary antioxidants on asthma: a meta-analysis

Authors: Jinming GAO

Summary: This meta-analysis of observational studies investigated the relationship between antioxidant intake and asthma prevalence. Among the included studies investigating asthma or wheeze ($n = 13,653$), intake of vitamin C (7 studies), vitamin E (5) and β -carotene (5) were not associated with increased risks of having asthma (respective pooled odds ratios 1.06; 95% CI 0.79, 1.43, 0.88; 0.61, 1.25, and 1.12; 0.77, 1.62). Analyses of 3 studies investigating lung function revealed that vitamin C intake was associated with a mean increase in FEV₁ of 29.1mL (95% CI -0.4, 58.6; $p = 0.05$), while vitamin E and β -carotene intake did not significantly affect lung function.

Comment: This co-operation between researchers from China and Western Australia reviewed the protective effect of a 'good diet' on the development of asthma. They began with the plausible hypothesis that a modern western diet, low in antioxidants, may contribute to the development of asthma. After a thorough literature review the authors were not surprised to find that a diet high in antioxidants did not have a protective effect in the development of asthma. Their discussion is thought provoking, as the authors speculated that this outcome may be due to the fact that reactive oxygen is not necessarily harmful or that the reviewed studies were subject to re-call bias. Bottom line: keep an open mind on the effect of a 'good diet' on the development of asthma.

Reference: *Respirology 2008; 13(4): 528-36*

<http://www3.interscience.wiley.com/journal/120088486/abstract>

Predictors for wheezing phenotypes in the first decade of life

Authors: Midodzi WK et al

Summary: Prenatal, perinatal and early childhood predictors of wheezing phenotypes were investigated in this prospective analysis of five surveys conducted every 2 years during the first decade of life in 2711 children. Significant risk factors for preschool, intermittent and persistent wheeze included child's allergy, early respiratory tract infection and parental asthma. Risk factors for preschool wheeze also included breastfeeding, daycare attendance and parental smoking, and breastfeeding was also a risk factor for intermittent wheeze. Protective factors for primary school wheeze included crowding at home and daycare attendance, and crowding at home was also a protective factor for primary school wheeze. The investigators noted that their findings suggest it is possible there are different aetiologies for asthma among children.

Comment: This Canadian group reports the findings for five different phenotypes of wheezing. Like the British study, they found a high prevalence of wheezing but a low (9%) prevalence of persistent wheezing. Breastfeeding was found to be a risk factor for preschool and intermittent wheezing but not for persistent wheezing. This study found the following risk factors for persistent wheeze: presence of allergy, parental asthma, male gender and maternal smoking in pregnancy. We will await their follow-up data with interest as these children develop into adolescents and adults.

Reference: *Respirology 2008; 13(4): 537-45*

<http://www3.interscience.wiley.com/journal/120088484/abstract>

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Assessing adherence and factors associated with adherence in young children with asthma

Authors: Burgess SW et al

Summary: In this study, 1 month's electronic monitoring of preventive asthma medication (Smartinhaler) was compared with reported medication usage in 51 asthmatic children (aged 18 months to 7 years). Medication usage was overestimated in verbal reports and questionnaire responses at 85.1% and 84.2%, respectively, compared with 70.5% with electronic monitoring. The main barriers to adherence were parents 'forgetting' and their child's 'reaction to being given medication'. Stress associated with parenting significantly affected adherence ($p = 0.05$).

Comment: Adherence to prescribed therapy is one of the most important aspects of asthma therapy. This Australian group investigated adherence to therapy in young children with asthma. The authors compared the electronic monitoring devices with the parents report and the physician's estimate. Even under study conditions, the children's adherence was only 70%. The treating physician only identified 12 out of 21 subjects within 10% of their actual dose. Two out of three least adherent children were prescribed the highest dose of medication. Bottom line: suboptimal adherence should be suspected in all cases of poorly controlled asthma.

Reference: *Respirology* 2008; 13(4): 559-63

<http://www3.interscience.wiley.com/journal/120088488/abstract>

Dynamic hyperinflation with bronchoconstriction: differences between obese and nonobese women with asthma

Authors: Sutherland TJT et al

Summary: This study investigated whether changes in airway calibre and lung volumes that are associated with acute bronchoconstriction differ between obese and nonobese women with asthma ($n = 30$), and if they affect the intensity and/or quality of symptoms. Following adjustment for baseline airway calibre and hyper-responsiveness, body mass index was found to be independently associated with changes in lung volume. Additionally, obese participants had increased functional residual capacity ($p < 0.001$) and decreased inspiratory capacity ($p = 0.003$). The investigators noted that their findings indicate that there is potential for altered perception and assessment of asthma severity in obese asthmatics.

Comment: This systematic study from Dunedin, NZ helps us to understand the challenging co-existence of asthma and obesity. The authors found that spirometry results in obese patients with asthma often show restrictive or 'pseudonormal' patterns. For the same degree of methacholine-induced bronchoconstriction, obese asthmatic patients report more dynamic hyperinflation and report more shortness of breath. Bottom line: In obese patients, abnormal airway function is less likely to be identified and dynamic hyperinflation may explain the patient's perception of greater asthma severity.

Reference: *Am J Respir Crit Care Med* 2008; 177(9): 970-5

<http://ajrccm.atsjournals.org/cgi/content/abstract/177/9/970>

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Longitudinal evaluation of airway function 21 years after preterm birth

Authors: Narang I et al

Summary: This longitudinal study explored the evolution of respiratory symptoms, spirometry and airway hyper-responsiveness (AHR) in 60 index ex-preterm participants (median age 21.7 years) who had excess respiratory symptoms, airway obstruction and increased AHR identified during mid-childhood. Compared with 50 healthy term controls, respiratory symptoms were significantly more common among index participants (odds ratio 4.2; 95% CI 1.3, 13.5; $p = 0.01$), but differences in spirometry parameters and AHR between the index and control groups were not statistically significant.

Comment: This group of British researchers followed a cohort of 317 preterm subjects into adulthood. In mid-childhood, this group reported increased respiratory symptoms (especially cough), increased airway obstruction and evidence of AHR. In adulthood, this group continued to have more respiratory symptoms but showed no ongoing low lung functions or AHR. This improvement is in keeping with other longitudinal studies. Bottom line: It is reassuring to see that lung functions normalise in adult life. However, this group is thought to be at increased risk of premature deterioration of lung function and will need continued surveillance.

Reference: *Am J Respir Crit Care Med* 2008; 178(1): 74-80

<http://ajrccm.atsjournals.org/cgi/content/abstract/178/1/74>



*Independent commentary
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intended for Medical Professionals*

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Clinical outcomes of pulmonary arterial hypertension in carriers of *BMPR2* mutation

Authors: Sztrymf B et al

Summary: The impact of *BMPR2* mutations on clinical outcomes in pulmonary arterial hypertension (PAH) was explored in this study. The investigators found a number of differences between the *BMPR2* mutation carriers (n = 68) and noncarriers (155), including higher mean pulmonary artery pressure (64 vs. 56mm Hg; p < 0.0001), lower cardiac index (2.13 vs. 2.50 L/min/m²; p = 0.0005), increased pulmonary vascular resistance (17.4 vs. 12.7mm Hg/L/min/m²; p < 0.0001) and lower mixed venous oxygen saturation (59 vs. 63%; p = 0.02). *BMPR2* mutation carriers were also younger at PAH diagnosis (36.5 vs. 46.0 years; p < 0.0001) and progressed to lung transplantation or death sooner (p = 0.044). Overall survival was similar between the two groups (p = 0.51).

Comment: This is a further report from the large French database of patients with PAH. The authors found 68 *BMPR2* mutations in their cohort of 195 patients with idiopathic PAH. When comparing the outcome of patients with *BMPR2* mutations with idiopathic PAH, they found that the patients with mutations developed disease earlier and with more severe haemodynamic compromise. This study highlights a more severe form of PAH with *BMPR2* mutations, and Lewis Rubin in the editorial reminds us that “we still have a long way to go” in looking after these patients as the median time of survival is only about 10 years.

Reference: *Am J Respir Crit Care Med* 2008; 177(12): 1377-83

<http://ajrccm.atsjournals.org/cgi/content/abstract/177/12/1377>

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Pulmonary manifestations in patients with POEMS syndrome

Authors: Allam JS et al

Summary: This retrospective review of pulmonary manifestations of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin abnormalities) included 137 patients (mean age 51.6 years) diagnosed with the syndrome. Respiratory symptoms occurred in 28% of the patients, and included pulmonary hypertension, respiratory muscle weakness, restrictive lung disease and isolated diminished diffusing capacity. Pleural effusions, diaphragm elevation and increased cardiac silhouette were seen on x-ray in 23% of patients. Median overall survival was reduced by respiratory muscle weakness (87 vs. 139 months; p < 0.05), and the presence of cough.

Comment: This group of authors from the Mayo clinic report on pulmonary complications of POEMS syndrome based on 137 patients investigated over 20 years. Of these, 38 patients (28%) had respiratory symptoms within 2 years of the diagnosis: 20% had dyspnoea, 10% had chest pain and 8% had cough. In addition, 28% had significant radiological abnormalities and 33% had minor abnormalities. The authors concluded that pulmonary complications like neuromuscular weakness, pulmonary hypertension and restrictive lung disease are common in this illness, which is a hallmark of severe peripheral neuropathy.

Reference: *Chest* 2008; 133(4): 969-74

<http://www.chestjournal.org/cgi/content/abstract/133/4/969>

Dexmethylphenidate hydrochloride for the treatment of sarcoidosis-associated fatigue

Authors: Lower EE et al

Summary: The efficacy of dexmethylphenidate hydrochloride (d-MPH) in treating sarcoidosis-associated fatigue was investigated in this study. Ten participants received 8 weeks' treatment with d-MPH and placebo in a randomised crossover fashion. Patients had a significant improvement in fatigue as assessed using both Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F] and Fatigue Assessment Score [FAS] instruments (p < 0.001 and p < 0.02, respectively) after receiving d-MPH. Median FVC was greater following d-MPH treatment compared with baseline (2.56 vs. 2.38L; p < 0.01; median FVC was 2.41L following placebo), but 6-minute walk distance was not significantly affected by d-MPH treatment.

Comment: In this small 'proof of concept' study, the authors attempted to investigate the effectiveness of d-MPH in treating patients with sarcoidosis-associated fatigue. The patients were randomised to either placebo or active treatment groups. The active treatment group was treated with the d-threo-methylphenidate hydrochloride isomer (d-MPH) of methylphenidate, which has fewer side effects such as jitteriness, palpitations and headache than methylphenidate. The authors found a 36% improvement of fatigue in the active treatment group, a similar improvement as demonstrated in a cancer chemotherapy study. This finding needs to be validated in larger studies, but raises the possibility of a treatment for the troublesome sarcoidosis-associated fatigue.

Reference: *Chest* 2008; 133(5): 1189-95

<http://www.chestjournal.org/cgi/content/abstract/133/5/1189>

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