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Asthma

Abdominal obesity (waist circumference) increases asthma risk in women

Brumpton *et al.* General and abdominal obesity and incident asthma in adults: the HUNT study. *Eur Respir J* 2013;41:323-9. <http://dx.doi.org/10.1183/09031936.00012112>

General obesity is well established as a risk factor for asthma in adults. Abdominal obesity (a raised waist circumference) is associated with all-cause mortality and is increasing at an even higher rate than general obesity. This is a prospective cohort study using data from the Nord-Trøndelag Health Study (HUNT) to assess the association between general obesity (BMI > 30 kg/m²), abdominal obesity (waist circumference > 88 cm in females and > 102 cm in males) and incident asthma in adults. The authors constructed a cohort population (n = 25,616) who participated in the HUNT 2 and HUNT 3 surveys (11 years apart) and who were aged < 65 years at the time of HUNT 3 (2006-2008). Incident asthma was self-reported new-onset cases during the 11 year follow-up. Using multivariate logistic regression, and after adjustment for covariates, odds ratios for incident asthma in subjects with general obesity (versus a normal BMI) were 1.96 [95% CI 1.52 to 2.52] in women and 1.84 [95% CI 1.30 to 2.59] in men. There was also a dose-response relationship between BMI and incident asthma. Adjusted odds ratios for abdominal obesity (versus normal waist circumference) were 1.88 [95% CI 1.51 to 2.34] in women and 1.55 [95% CI 1.08 – 2.21] in men. However, after adjusting for BMI, odds ratios for abdominal obesity remained significant in women [OR 1.46; 95% CI 1.04 to 2.05] but not in men [OR 0.88; 95% CI 0.53 to 1.47]. Therefore, in women, we should consider using both BMI and waist circumference to assess the risk of developing asthma rather than just BMI alone.

Obesity-associated severe asthma may be a distinct clinical phenotype

Gibeon *et al.* Obesity-associated severe asthma represents a distinct clinical phenotype: analysis of the British Thoracic Society Difficult Asthma Registry Patient Cohort according to BMI. *Chest* 2013;143:406-14.

<http://journal.publications.chestnet.org/article.aspx?articleid=1377967>

Continuing the theme of obesity and asthma, this study was designed to explore the role of obesity in severe asthma. The authors used data from the British Thoracic Society Difficult Asthma Registry to construct a cohort of 666 patients with severe asthma. Patients were divided into three groups according to BMI: normal weight (BMI 18.5 – 24.99 kg/m²), overweight (BMI 25.0 – 29.99 kg/m²), and obese (BMI > 30 kg/m²). The obese patients had a greater requirement for asthma medication than the overweight and normal weight groups, with use of maintenance oral corticosteroid therapy in 48.9%, compared to 40.4% and 34.5% in the overweight and normal weight groups, respectively. So too, use of short burst oral corticosteroid treatment and short-acting beta₂-agonists was increased in the obese group. Obese patients also had increased gastro-oesophageal reflux disease (GORD), with GORD occurring in 53.9% of obese patients compared with 48.1% and 39.7% in the

overweight and normal weight groups, respectively. The obese group had a reduced mean pre-bronchodilator FVC (80.1%; 95% CI 78.0 to 82.3) compared with the overweight (86.7%; 95% CI 83.7 to 89.8) and normal weight groups (86.20%; 95% CI 82.8 to 89.6). The mean carbon monoxide transfer coefficient was greater in the obese group (104.5%; 95% CI 102.1 to 106.9) than the normal weight group (97.0%; 95% CI 93.5 to 100.7). Total serum IgE levels were decreased in the obese group. The authors conclude that obese patients with severe asthma have particular characteristics, suggesting that obesity-associated severe asthma may represent a distinct clinical phenotype.

Omalizumab is associated with reduced hospitalisation in real-life practice

Grimaldi-Bensouda *et al.* Does omalizumab make a difference to the real-life treatment of asthma exacerbations?: results from a large cohort of patients with severe uncontrolled asthma. *Chest* 2013;143:398-405. <http://dx.doi.org/10.1378/chest.12-1372>

This is a prospective longitudinal cohort study involving 767 patients with uncontrolled severe asthma (despite optimal treatment with inhaled and oral corticosteroids and long-acting beta₂-agonists) who were not on treatment with omalizumab at study entry. During the study (mean follow-up 20.4 months) the 163 physicians involved treated the patients as per usual clinical protocols – i.e. this was real-life practice. 374 patients took omalizumab at least once. Risk of hospitalisation or an emergency department (ED) visit was assessed, controlling for age, sex, smoking history, BMI, GORD, allergic status, allergic rhinitis, asthma treatment, and hospitalisation or ED visits in the 2 months before omalizumab treatment. Omalizumab treatment was associated with a reduced risk of hospitalisation or ED visits for asthma [adjusted relative risk 0.57; 95% CI 0.43 to 0.78]. In addition, in those 374 patients who received omalizumab treatment, the adjusted risk of hospitalisation or an ED visit during the period of omalizumab treatment (versus periods of non-treatment) was 0.40 [95% CI 0.28 – 0.58]. Despite the limitations of this being an observational cohort study (rather than an RCT), omalizumab treatment seems to decrease significantly the risk of hospitalisation or ED visits in patients with severe asthma in real-life practice.

Theophylline added to salmeterol/fluticasone reduces asthma exacerbations

Nie *et al.* Efficacy of theophylline plus salmeterol/fluticasone propionate combination therapy in patients with asthma. *Resp Med* 2013;107:347-54.

<http://dx.doi.org/10.1016/j.rmed.2012.12.004>

With an increasing number of asthma treatments in the armamentarium over the last 10-20 years, theophylline use has decreased considerably, not least because of its narrow therapeutic dose and potential for toxicity in higher doses. So it's interesting to see a new parallel-group RCT on the use of theophylline 200mg daily as an add-on therapy to salmeterol 50mcg/fluticasone 250mcg twice-daily. 325 patients were randomised to either theophylline or placebo, in addition to salmeterol/fluticasone, and study duration was 24 weeks. Primary outcome measures included asthma

control – as measured by the Asthma Control Test (ACT) – and exacerbation frequency (specifically the number of patients having at least one exacerbation). 29.6% of patients in the theophylline group had ≥ 1 exacerbation, whereas in the placebo group this figure was 46.9% [$P=0.004$]. Improvements in the FEF₂₅₋₇₅ value were greater in the theophylline group versus placebo [66.9 +/- 18.8% vs. 57.4 +/- 17.6%; $P<0.001$]. There were also significant decreases in sputum-induced eosinophil counts in the theophylline group. The authors conclude that the combination of theophylline with salmeterol/fluticasone reduces asthma exacerbations and significantly improves small airway function and airway inflammation.

SMART treatment with beclometasone-formoterol

Papi *et al.* Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind randomised controlled trial. *Lancet Respir Med* 2013;1:23-31. [http://dx.doi.org/10.1016/S2213-2600\(13\)70012-2](http://dx.doi.org/10.1016/S2213-2600(13)70012-2)

The extrafine beclometasone/formoterol combination inhaler has been licensed for the maintenance treatment of asthma since November 2007, but its long-acting beta₂-agonist (LABA) component, formoterol, is quick-acting and can potentially be used as reliever treatment; indeed, the budesonide/formoterol combination inhaler already has a licence for single-inhaler maintenance and reliever treatment (SMART) in moderate to severe asthma. Therefore, it's not surprising to see this double-blind multicentre Europe-wide RCT comparing beclometasone 100mcg/formoterol 6mcg [$n=857$, 852 completed] versus salbutamol [$n=857$, 849 completed] as reliever treatment in addition to maintenance beclometasone 100mcg/formoterol 6 mcg one puff twice-daily. Patients were aged ≥ 18 years, with inadequately controlled asthma, and FEV₁ $\geq 60\%$ predicted. After a 2-week run-in using salbutamol as reliever, follow-up was for 48 weeks. The primary outcome was time to first severe exacerbation, and secondary outcomes included overall numbers of severe and mild exacerbations, lung function and asthma control. Beclometasone/formoterol as SMART, versus maintenance beclometasone/formoterol with salbutamol as reliever, increased the time to first severe exacerbation from 134 to 209 days – a 36% reduction in risk [hazard ratio (HR) 0.64; 95% CI 0.49 to 0.82], and also reduced the number of days with mild asthma exacerbations from 65.1 to 56.0 days per patient per year [HR 0.86; 95% CI 0.76 to 0.98]. Both treatments showed improvements in all the other secondary outcomes, with no statistically significant difference between them. Therefore, the beclometasone/formoterol combination inhaler can be used as SMART treatment (no great surprise given the characteristics of formoterol), and we await further comparative studies...

Azithromycin may reduce severe exacerbations in non-eosinophilic severe asthma

Bruselle *et al.* Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax* 2013;68:322-9. <http://dx.doi.org/10.1136/thoraxjnl-2012-202698>

Macrolides have immune-modulatory and anti-inflammatory effects, and erythromycin and azithromycin have recently been shown to reduce exacerbations of COPD. This double-blind placebo-controlled RCT assessed whether long-term azithromycin could decrease the frequency of acute exacerbations and LRTIs in patients with severe asthma. Patients were randomised to receive azithromycin ($n=55$; 250mg daily for 5 days followed by 250mg three times a week) or placebo ($n=54$) in addition to their combination ICS/LABA inhaler for 6 months. The primary outcome was the rate of severe exacerbations and LRTIs requiring antibiotic treatment. Secondary outcomes included lung function, the Asthma Control Questionnaire (ACQ), and the Asthma Quality of Life Questionnaire (AQLQ). Because of the heterogeneity of asthma, the authors performed a pre-defined subgroup analysis based on blood eosinophilia at baseline. There was no significant difference in the primary outcome, with 0.75 exacerbations/LRTIs per patient [95% CI 0.55 to 1.01] in the azithromycin group versus 0.81 [95% CI 0.61 to 1.09] in the placebo group. However, in patients with non-eosinophilic asthma (blood eosinophil count $\leq 200 \times 10^9/l$), azithromycin produced a significant reduction in the rate of exacerbations/LRTIs (0.44 per patient [95% CI 0.25 to 0.78]) compared to placebo (1.03 per patient [95% CI 0.72 to 1.48]). Azithromycin also significantly improved the AQLQ score [0.32 increase; 95% CI 0.08 to 0.57] versus placebo [0.20 increase; 95% CI -0.01 to 0.41]. Therefore, azithromycin caused a significant reduction in exacerbation or LRTI rate only in patients with non-eosinophilic severe asthma, which (the authors conclude) warrants further study...

Dysfunctional breathing present in 5% of children with severe or difficult-to-control asthma

De Groot *et al.* Dysfunctional breathing in children with asthma: a rare but relevant comorbidity. *Eur Respir J* 2013;41:1068-73. <http://dx.doi.org/10.1183/09031936.00130212>

Functional breathing problems such as hyperventilation can result in significant morbidity, and are surprisingly common. In 2001, a UK cross-sectional survey reported a prevalence of dysfunctional breathing of 29% in adults with asthma (*BMJ* 2001;322:1098-100). A subsequent survey in adults without asthma reported a prevalence of 8% (see <http://dx.doi.org/10.1016/j.pcrj.2004.10.007>). This cross-sectional survey of 206 children (aged 5-18 years) from the Netherlands is the first to report the prevalence of dysfunctional breathing in children with asthma. All children were on maintenance inhaled corticosteroids (ICS), underwent spirometry, and had measurement of exhaled fraction of nitric oxide (FeNO) and specific IgE for five major aero-allergens. They also completed the Nijmegen Questionnaire and 203/206 children completed the paediatric version of the Asthma Control Questionnaire (ACQ). The Nijmegen Questionnaire has 16 questions on symptoms of dysfunctional breathing (such as 'feeling tense', 'difficulty in breathing', 'palpitations in the chest') with a score of 0 ('never') to 4 ('very often') for each item; a score of ≥ 23 signifies dysfunctional breathing. Dysfunctional breathing was present in 11 (5.3%) of the children, more commonly in girls (8/62 = 12.9%) than in boys (3/144 = 2.1%) [$P=0.002$]. Poor asthma control was more common in the children with dysfunctional breathing (10/11 = 90.9%) than in those without (65/192 = 32.3%) [odds ratio (OR) 19.3; 95% CI 3.14 to 430.7]. Median ACQ scores in children with dysfunctional breathing were higher (i.e. worse asthma control) [median 2.0; range 1.5-3.2] than in children without [0.5; range 0.2-1.2; $P<0.001$]. Therefore, we need to consider dysfunctional breathing as a possible factor in children with severe or difficult-to-control asthma.

Perimenstrual asthma is common in women with severe and difficult-to-control asthma

Rao *et al.* Characteristics of perimenstrual asthma and its relation to asthma severity and control: data from the Severe Asthma Research Program. *Chest* 2013;143:984-92. <http://dx.doi.org/10.1378/chest.12-0973>

The aims of this study were to identify factors associated with perimenstrual asthma (PMA), including its association with asthma severity and control. Women who reported PMA symptoms on recruitment to the National Heart, Lung, and Blood Institute Severe Asthma Research Program were included. Data were collected on clinical symptoms, demographics, and various immuno-inflammatory and physiological markers. Self-reported PMA was present in 92 subjects (19%), and was associated with a higher BMI, lower FVC % predicted, and gastro-oesophageal reflux disease (GORD). 52% of women with PMA fulfilled the criteria for severe asthma, compared with 30% of women without PMA. Using multivariate analysis, and whilst controlling for asthma severity, sensitivity to aspirin and a lower FVC% predicted were also associated with PMA. The authors conclude that perimenstrual asthma is common in women with severe asthma, is associated with poor disease control, and is also associated with aspirin sensitivity and a lower FVC % predicted after adjusting for potential confounders. Interestingly, the authors suggest that this particular asthma phenotype may be characterised by alterations in prostaglandin metabolism...

COPD

30 metres – the minimal clinically important difference for change in 6-minute walking distance over 1 year

Polkey *et al.* Six-minute-walk test in chronic obstructive pulmonary disease. Minimal clinically important difference for death or hospitalisation. *Am J Resp Crit Care Med* 2013;187:382-6. <http://dx.doi.org/10.1164/rccm.201209-1596OC>

COPD is a multi-system disease characterised by a number of different symptoms, particularly dyspnoea. The impact of bronchodilators, the fundamental treatment for dyspnoea, can be assessed by spirometry. However, the effects of other sorts of treatment (such as pulmonary rehabilitation and inhaled corticosteroids) require different forms of assessment such as quality of life questionnaires, monitoring of exacerbation rates, and measurement of exercise capacity using various measures such as the 6-minute walk test. These authors used data from the ECLIPSE cohort [$n=2,112$] to determine the minimal clinically important difference over a 1-year period for change in the 6-minute walk distance (6MWD) in relation to death and hospitalisation. They also compared change in 6MWD with changes in lung function and health status (as

measured by the St George's Respiratory Questionnaire). Of those patients who had a change in their 6MWD, 323 were hospitalised and there were 94 deaths. A reduction in the 6MWD of 30 metres or more was associated with an increased risk of death [hazard ratio (HR) 1.93; 95% CI 1.20 to 2.90], but there was no association between change in 6MWD and hospitalisation. There was only weak correlation between the 6MWD and lung function or health status. Therefore, 30 metres appears to be the clinically significant minimal important difference in 6MWD.

Muscle strength is not associated with Vitamin D levels in COPD

Jackson *et al.* Vitamin D and skeletal muscle strength and endurance in COPD. *Eur Respir J* 2013;41:309-16. <http://dx.doi.org/10.1183/09031936.00043112>

Up to 25% of COPD patients develop significant muscle weakness, principally due to decreased activity. Previous studies have shown an association between 25-hydroxyvitamin D (25(OH)D) and muscle strength in healthy older people. However, patients with COPD are at increased risk of Vitamin D deficiency because of inadequate intake and reduced time outdoors. The aim of this study was to see whether vitamin D levels contribute to muscle dysfunction in COPD. 104 COPD patients [mean (+/- standard deviation) FEV₁ = 44 (+/-22) % predicted] and 100 age- and sex-matched controls were recruited. Vitamin D (both 25-hydroxy and 1,25-hydroxy) levels and parathyroid hormone (PTH) levels were measured and compared with quadriceps strength and endurance. 25(OH)D levels were similar in both groups (COPD group 48.5 +/- 25.5 nmol/L versus 55.4 +/-28.3 nmol/L; P=0.07) but PTH was higher in the COPD group (5.2 +/- 2.3 pmol/L vs. 4.4 +/- 2.0 pmol/L; P=0.01). In the COPD patients, 25(OH)D, 1,25(OH)₂D, and PTH levels were not associated with any measure of muscle strength, whereas in control patients 25(OH)D was significantly associated with a number of measures of muscle strength including twitch quadriceps force and handgrip strength. The authors conclude that, in contrast with healthy controls, muscle strength is not associated with vitamin D levels in COPD. The subset analysis of 26 patients who had quadriceps biopsy performed and assays of mRNA expression led the authors to postulate that this may be due to vitamin D resistance in COPD patients.

Case-finding for COPD: BOLD results

Jithoo *et al.* Case-finding options for COPD: results from the Burden of Obstructive Lung Disease Study. *Eur Respir J* 2013;41: 548-55. <http://dx.doi.org/10.1183/09031936.00132011>

This is another interesting paper from the BOLD study, which adds to the continuing debate on the best way to perform COPD case-finding. Different case identification strategies were developed, with case identification algorithms using questionnaire data alone, questionnaire data plus pre-bronchodilator peak expiratory flow (PEF) data, or questionnaire data plus both pre- and post-bronchodilator PEF data. The screening efficiency of these different algorithms was assessed – i.e. their ability to identify subjects at risk for COPD who should then have diagnostic spirometry. Data were obtained from 14 countries where population-based samples of adults (n=9,390; age ≥40 years) completed the BOLD questionnaires and had spirometry performed. 756/9,390 subjects (8.1%) met the criteria for moderate to severe COPD. In this group, use of questionnaire data alone had high sensitivity (97%) for a diagnosis of COPD – but confirmatory spirometry was required in 80% of cases. Use of PEF required confirmatory spirometry in only 22% of cases, with 84% sensitivity. For severe COPD, using PEF for case-finding achieved up to 93% sensitivity with only 9% requiring confirmatory spirometry. The authors conclude that PEF is a simple cost-effective initial screening tool for COPD case-finding in adults aged ≥40 years old, and that these findings should be validated in primary care settings. The linked editorial by Steenbruggen *et al.* (<http://dx.doi.org/10.1183/09031936.00153512>) makes the point that this is potentially a major breakthrough, but also that other opportunistic strategies – such as the use of microspirometry – have not been considered here.

Early diagnosis of COPD in primary care: screening all smokers or more selective case-finding?

Sansores *et al.* Prevalence and diagnosis of chronic obstructive pulmonary disease among smokers at risk. A comparative study of case-finding vs. screening strategies. *Resp Med* 2013;107:580-6. <http://dx.doi.org/10.1016/j.rmed.2012.12.010>

And another study with a COPD case-finding theme, this time from Mexico. These authors set out to compare a symptom-based case-finding strategy with a population screening strategy, using spirometry to determine the relative effectiveness of the two different models. Case-finding took place as part of a COPD Day campaign, and was aimed at smokers with respiratory symptoms (n = 1999). Screening involved smokers who were attending a smoking cessation programme (n = 782). In both approaches, subjects completed a respiratory symptoms questionnaire and performed spirometry.

COPD prevalence was assessed using GOLD criteria, and was 10.1% in the case-finding group and 13.3% in the screening group [P<0.01]. Prevalence of cough (61.5% versus 37.0%; P<0.01) and wheeze (56.7% vs. 15.1%; P<0.001) was higher among smokers in the case-finding group compared to the screening group. Using multivariate logistic regression, dyspnoea was (not unexpectedly) a common predictor of COPD in both groups [odds ratio 2.98; 95% CI 1.41 to 3.1]. The authors conclude that a screening strategy aimed at all smokers may be more effective in a primary care setting than a case-finding strategy...

Effect of anti-platelet drugs and beta-blockers on mortality in severe oxygen-dependent COPD

Ekstrom *et al.* Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease: a time-dependent analysis. *Am J Resp Crit Care Med* 2013;187:715-20. <http://dx.doi.org/10.1164/rccm.201208-1565OC>

This was a prospective national cohort study of all COPD patients in Sweden who started treatment with long-term oxygen therapy (LTOT) between October 2005 and June 2009. 2,249 patients were included, of whom 1,129 (50%) died during follow-up. Using a Cox regression analysis which involved adjustment for age, sex, PaO₂, PaCO₂, World Health Organization performance status, body mass index, comorbidities (including cardiovascular disease) and any other medications, the authors estimated the time-dependent effects of various cardiovascular drugs on mortality. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), antiplatelet drugs, beta-blockers and statins were all studied. Antiplatelet drugs were associated with reduced mortality [hazard ratio (HR) = 0.86; 95% CI 0.75 to 0.99], and there was a non-significant trend towards reduced mortality for ACE inhibitors and ARBs [HR = 0.90; 95% CI 0.79 to 1.04] and statins [HR 0.86; 95% CI 0.72 to 1.03]. However, beta-blockers were associated with increased mortality [HR = 1.19; 95% CI 1.04 to 1.37]. The authors have been assiduous in their attempts to exclude bias and account for confounding factors, and the results are therefore fairly convincing. We now need randomised controlled trial (RCT) evidence on the possible benefits of anti-platelet drugs in severe COPD...

Over 60% of patients have echocardiographic abnormalities at their first hospital admission for an exacerbation of COPD

Freixa *et al.* Echocardiographic abnormalities in patients with COPD at their first hospital admission. *Eur Respir J* 2013;41:784-91. <http://dx.doi.org/10.1183/09031936.00222511>

Over the last decade, it has become increasingly recognised that COPD is a multisystem disease and that patients often have a number of major co-morbidities. Of these, one of the most common is cardiovascular disease. In this prospective study, patients were recruited from January 2004 to March 2006 in nine hospitals in Spain during their first admission for an exacerbation of moderate to severe COPD. 342 (57% of those eligible; FEV₁ = 52 +/- 16% predicted; mean age (±SD) = 67.9 (±8.6) years; 93% male) entered the study and had transthoracic echocardiography three months after discharge. Patients also completed a questionnaire on socio-demographic data, lifestyle information, previous treatments and diagnoses, and quality of life (St George's Respiratory Questionnaire, SGRQ). The Charlson index of co-morbidity and all previous diagnoses were obtained from medical records. Notable risk factors included self-reported hypertension, hypercholesterolaemia (>240 mg/dL), and diabetes. There were significant echocardiographic abnormalities in 64% of patients – the most common being right ventricular (RV) enlargement in 30%, followed by left atrial dilatation (29%), pulmonary hypertension (19%), left ventricular (LV) systolic dysfunction (13%), LV diastolic dysfunction (12%), and LV enlargement (6%). Echocardiographic abnormalities were unrelated to COPD severity, were more common in patients with self-reported cardiac disease, but were also present in 63% of patients with no known cardiac risk factors other than smoking. Therefore, the authors propose that echocardiography should be considered for all patients with clinically significant COPD. A formal evaluation of screening echocardiography is now needed...

Prevalence of three different COPD phenotypes

Izquierdo-Alonso *et al.* Prevalence and characteristics of three clinical phenotypes of chronic obstructive pulmonary disease (COPD). *Resp Med* 2013;107:724-31. <http://dx.doi.org/10.1016/j.rmed.2013.01.001>

The Spanish have been at the forefront of moves to identify and characterise the various COPD clinical phenotypes; for a summary of the new Spanish COPD guidelines (GesEPOC) see <http://dx.doi.org/10.4104/pcrj.2013.00016>. This was an observational multicentre study on 331 COPD patients recruited from various Spanish hospital chest clinics in order to determine the prevalence of the three common COPD clinical

phenotypes: emphysema (type 1); chronic bronchitis (type 2); and the COPD-asthma phenotype (type 3). Using various imaging techniques, full pulmonary function testing, and questionnaires, 43.2% were classified as the emphysema phenotype, 44.7% as chronic bronchitis, and 12/1% as the COPD-asthma phenotype. The emphysema patients had lower FEV₁ values than the other two phenotypes, with an average FEV₁ (+/- SD) of 46.6 (+/- 21.1)% predicted, versus 55.2 (+/- 21.2)% for chronic bronchitis patients and 54.4 (+/- 21.8)% in the COPD-asthma patients [P<0.05]. There were no significant differences in exacerbation rates, numbers of emergency room visits or hospital admission rates between the three different phenotypes. However, patients with the chronic bronchitis phenotype (type 2) did have a higher prevalence of cardiovascular co-morbidity and obstructive sleep apnoea than types 1 and 3 [P<0.001]. The authors conclude that emphysema patients have worse pulmonary function and dyspnoea, but that the greater co-morbidity in the chronic bronchitis patients may need specific attention.

Infections

Tuberculosis is more severe in patients with diabetes – with higher rates of treatment failure and relapse

Jimenez-Corona *et al.* Association of diabetes and tuberculosis: impact on treatment and post-treatment outcomes. *Thorax* 2013; **68**:214-20. <http://dx.doi.org/10.1136/thoraxjnl-2012-201756>

The March issue of *Thorax* has a tuberculosis (TB) theme to coincide with World TB Day. In their introduction, the Editors make the point that TB shows every sign of weathering the storm of potent anti-TB medications, and is now emerging in ever-increasingly drug-resistant forms – making *Mycobacterium tuberculosis* the most successful human pathogen of all time. This is a prospective study of patients with primary TB in Mexico who had positive sputum samples between 1995 and 2010 [n=1262]. The prevalence of diabetes (previous diagnosis or receiving oral hypoglycaemics or insulin treatment) was 30% [n=374]. Patients with TB and concomitant diabetes had more severe clinical manifestations [odds ratio (OR) for cavities on the chest x-ray = 1.80; 95% CI 1.35 to 2.41], and a higher probability of treatment failure [OR 2.93; 95% CI 1.18 to 7.23] and relapse [OR 1.83; 95% CI 1.04 to 3.23]. Using molecular analysis, the authors ascertained that subsequent episodes of TB among patients with diabetes were largely caused by bacteria with the same genotype, but in 5/26 cases reinfection occurred by a different bacterial genotype. Therefore, diabetes seems to have an aggravating effect on TB. The reasons are unknown, but immune system changes when both diseases are coexistent have been described, including reduction in activation of alveolar macrophages, reduced production of interleukin-10, reduction in Th1 cytokines, and alterations in the overall immune response.

Hydration of infants with bronchiolitis: nasogastric tube or intravenously?

Oakley *et al.* Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. *Lancet Respir Med* 2013; **1**:113-20. [http://dx.doi.org/10.1016/S2213-2600\(12\)70053-X](http://dx.doi.org/10.1016/S2213-2600(12)70053-X)

One of the major reasons for admitting infants with bronchiolitis is to ensure they are properly hydrated and monitored. The two main active hydration methods are by nasogastric tube or intravenously (i.v.), but comparative data between the two methods are lacking. Under the auspices of the Paediatric Research in Emergency Departments International Collaborative (PREDICT), this multicentre open randomised trial included all infants aged 2-12 months who were admitted to hospitals in Australia and New Zealand with bronchiolitis between April to October in the three-year period 2009-2011. Infants were randomised to nasogastric hydration [n=381] or i.v. hydration [n=378] by computer-generated sequence, stratified by hospital site and age group (2-6 months versus 6-12 months). The primary outcome was length of hospital stay, and secondary outcomes included intensive care unit (ICU) admission rates, adverse events, and success rates for tube insertion versus intravenous access. There was no difference in length of hospital stay between the two groups: 86.6 hours [SD 58.9] for nasogastric hydration vs. 82.2 hours [SD 58.8] for i.v. hydration [absolute difference 4.5 hours; 95% CI -3.9 to 12.9]. Rates of ICU admission and adverse events were also similar. However, where data were available on insertion success rates, these were higher in the nasogastric group [only one attempt needed in 275/323 infants (85%)] compared to the i.v. group (only one attempt needed in 165/294 infants (56%)). The authors conclude that both methods were equally effective for hydration of infants with bronchiolitis, but success rates for nasogastric insertion were higher.

Cardiovascular events after clarithromycin for lower respiratory tract infections

Schembri *et al.* Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. *BMJ* 2012; **346**:f1235. Published online 22nd March 2013. <http://dx.doi.org/10.1136/bmj.f1235>

This is a secondary analysis of two prospective cohort studies involving large datasets. The first is the EXODUS (Exacerbations of Obstructive Lung Disease managed in UK Secondary care) dataset of patients aged > 40 years admitted with acute exacerbations of COPD between 2009 and 2011 (n = 1343). The second is the Edinburgh pneumonia study cohort of patients admitted with radiologically-confirmed community acquired pneumonia (CAP) to hospitals in Edinburgh between 2005 and 2009 (n = 1631). The primary outcome was the association between clarithromycin use and first hospital admission for a cardiovascular event (acute coronary syndrome, decompensated cardiac failure, serious arrhythmia, or sudden cardiac death) and admissions for acute coronary syndrome (myocardial infarction and unstable angina). Secondary outcomes were all-cause and cardiovascular mortality at one year. 268 cardiovascular events occurred in the COPD cohort and 171 in the CAP cohort. After multivariable adjustment, clarithromycin was associated with an increased risk of cardiovascular events [hazard ratio (HR) 1.50; 95% CI 1.13 to 1.97] and acute coronary syndrome [HR 1.67; 95% CI 1.04 to 2.68] in acute exacerbations of COPD. For CAP, clarithromycin use was associated with an increased risk of cardiovascular events [HR 1.68; 95% CI 1.18 to 2.38] but not acute coronary syndrome [HR 1.65; 95% CI 0.97 to 2.80]. Clarithromycin use was also associated with increased cardiovascular mortality [adjusted HR 1.52; 95% CI 1.02 to 2.26] but not all-cause mortality [HR 1.16; 95% CI 0.90 to 1.51] in acute exacerbations of COPD, but there was no association with mortality when used in CAP. The authors conclude that clarithromycin may be associated with increased cardiovascular events when used to treat acute exacerbations of COPD or CAP, and that this now needs to be confirmed through studies using other datasets.

Sleep disorders

Management of obstructive sleep apnoea: specialist care versus primary care models

Chai-Coetzer *et al.* Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: a randomized trial. *JAMA* 2013; **309**:997-1004. <http://dx.doi.org/10.1001/jama.2013.1823>

As with many other areas of clinical activity, and largely because of the cost-effectiveness of the primary care setting, there has been interest in the possibility of transferring much of the management of obstructive sleep apnoea (OSA) from secondary care into primary care. This is a randomised, non-inferiority study comparing the efficacy and costs of primary care management of OSA in three rural regions of South Australia (n = 81) versus secondary care management in a university hospital sleep medicine centre in Adelaide (n = 74). In both settings, management included continuous positive airway pressure (CPAP) treatment and/or mandibular advancement splints. The primary outcome measure was change in the Epworth Sleepiness Scale (ESS; 0 points [no daytime sleepiness] to 24 points [severe daytime sleepiness]) over 6 months, and the a priori declared non-inferiority margin was 2 points. Various secondary outcomes included quality of life measures, OSA symptoms, patient satisfaction, and cost. In both groups, there were significant improvements in ESS scores: in the primary care group the ESS score decreased from 12.8 to 7.0 [P<0.001] and in the secondary care group it decreased from 12.5 to 7.0 [P<0.001]. The improvement in the primary care group was non-inferior to specialist management, with a mean change in ESS score of 5.8 versus 5.5 [adjusted difference -0.13; P=0.43]. There were no differences in secondary outcome measures. The authors conclude that, with appropriate training and resources, primary care management of OSA was non-inferior to secondary care management.

Fibrotic lung disease

No association between statin use and risk of interstitial lung disease

Saad *et al.* Statins and the risk of interstitial lung disease: a cohort study. *Thorax* 2013;68:361-4.

<http://dx.doi.org/10.1136/thoraxjnl-2012-201823>

This is an important negative study, since previous reports have suggested that statins may be associated with an increased risk of interstitial lung disease (ILD – of which the commonest is idiopathic pulmonary fibrosis). It's a nested case-control study within a large population cohort of 1.41 million patients who were covered by the RAMQ drug plan in Quebec, Canada, and who had collected at least one prescription for a respiratory medication (any bronchodilator, inhaled corticosteroid, leukotriene receptor antagonist or cromone) between January 1990 and December 2005. 6665 cases of ILD were identified within the cohort – with a confirmed diagnosis of ILD from a pulmonologist or rheumatologist or hospitalisation with ILD as the primary discharge diagnosis, and with confirmation of the diagnosis within the next 90 days. There were 4 matched controls (by age, gender and month of cohort entry) for each case, randomly chosen from the cohort, giving a total of 26,660 controls. All prescriptions for statins were recorded in the 2-year period prior to the index date – i.e. date of ILD diagnosis. After adjustment for confounders and any variables identified as known or potential risk factors for ILD, as well as comorbidities, there was no association between current use of statins and subsequent risk of ILD [adjusted odds ratio 0.99; 95% CI 0.91 to 1.08]. Given the widespread use of statins, and the precision of the estimate, this is a reassuring finding.

Miscellaneous

Social deprivation is associated with worse growth and lung function in children with cystic fibrosis

Taylor-Robinson *et al.* The effect of social deprivation on clinical outcomes and the use of treatments in the UK cystic fibrosis population: a longitudinal study.

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[http://dx.doi.org/10.1016/S2213-2600\(13\)70002-X](http://dx.doi.org/10.1016/S2213-2600(13)70002-X)

This was a longitudinal study of all 8055 UK cystic fibrosis (CF) patients under the age of 40. The aim was to assess the association between social deprivation and individual patients' clinical and healthcare outcomes. Data on weight, height, body mass index (BMI), percent predicted FEV₁, risk of *Pseudomonas* colonisation and major treatments employed, were collected between January 1996 and December 2009. Compared with the least deprived quintile, children in the most deprived quintile had a lower BMI [mean difference -0.13; 95% CI -0.22 to -0.04], were shorter [mean difference -0.31cm; 95% CI -0.40 to -0.21], and were more likely to have *Pseudomonas* colonisation [odds ratio (OR) 1.89; 95% CI 1.32 to 2.66] and a lower FEV₁ [mean difference -4.12%; 95% CI -5.01 to -3.19]. These differences were present in early childhood, but did not widen as patients got older. In terms of treatments employed, after adjustment for disease severity the most deprived quintile were more likely to receive intravenous antibiotics [OR 2.52; 95% CI 1.92 to 3.17] and nutritional treatments [OR 1.78; 95% CI 1.44 to 2.20] than the least deprived quintile. The authors conclude that children with CF from socially deprived areas have worse growth and lung function compared to children from affluent areas, but these inequalities don't widen with increasing age.

Omalizumab for the treatment of chronic idiopathic urticaria

Maurer *et al.* Omalizumab for the treatment of chronic idiopathic or spontaneous urticarial. *New Engl J Med* 2013;368:924-35

<http://www.nejm.org/doi/full/10.1056/NEJMoa1215372>

Chronic urticaria is a debilitating condition that can prove very difficult to manage since patients are often unresponsive to existing pharmacotherapies. Omalizumab is a recombinant DNA-derived IgG monoclonal antibody that selectively binds to human IgE. It has an anti-inflammatory action via its effects on mast cell and basophil function. It already has a licence for use in severe allergic asthma, and phase 2 trials have shown some effect in chronic urticaria.

This was a multicentre, phase 3, double-blind randomised controlled trial (RCT) on the efficacy and safety of omalizumab in patients with moderate-to-severe chronic idiopathic urticaria previously unresponsive to licensed doses of antihistamines. 323 patients were randomised to three 4-weekly injections of omalizumab 75mg, 150mg, 300mg, or placebo. Follow-up was for 16 weeks. The primary outcome was change in the weekly itch-severity score (range 0 – 21; the higher the score, the worse the itching). The average baseline score was 14 in each group. After 12 weeks, the mean changes (+/- SD) from baseline in the weekly itch-severity score were -5.1 +/- 5.6 (placebo group), -5.9 +/- 6.5 (75mg group; P=0.46), -8.1 +/- 6.4 (150mg group; P=0.01), and -9.8 +/- 6.0 (300mg group; P<0.001). Adverse event rates were similar in the four groups, and the frequency of serious adverse events was low – albeit higher in the 300mg group (6%) than in the other groups (placebo = 3%; 75mg and 150mg groups = 1%). The authors conclude that omalizumab reduces symptoms and signs of chronic idiopathic urticaria previously unresponsive to antihistamine therapy.

Cough in patients with GORD: careful patient selection required before starting acid-suppressive treatment

Kahrilas *et al.* Response of chronic cough to acid-suppressive therapy in patients with gastroesophageal reflux disease.

Chest 2013;143:60512.

<http://journal.publications.chestnet.org/article.aspx?articleid=1388071>

Gastro-oesophageal reflux disease (GORD) is a known cause of persistent non-productive cough, and we published a series of perspectives on the management of cough recently (see, for example, <http://dx.doi.org/10.4104/pcrj.2012.00077>). However, there is some debate regarding the benefit of anti-reflux treatment for GORD presenting as persistent cough. This systematic review identified nine RCTs of various design in which patients with acid reflux with chronic cough were treated with acid suppression (eight used proton pump inhibitors (PPIs), one used ranitidine). In all the studies, pH manometry was used to confirm and characterise the nature of the acid reflux. In two crossover studies, PPI treatment significantly improved cough compared to placebo, but only in the arm receiving placebo first. In seven studies, the therapeutic gain of acid suppression treatment was greater if there was increased acid exposure as confirmed by pH manometry. The authors conclude that we need to be much more selective when choosing those patients who are likely to respond to acid suppression therapy – and perhaps this means a lower threshold for primary care referral to secondary care for further investigation including pH studies...?

Using socio-demographic and clinical features to improve detection of lung cancer

Iyen-Omofoman *et al.* Using socio-demographic and early clinical features in general practice to identify people with lung cancer earlier. *Thorax* 2013;68:451-9.

<http://dx.doi.org/10.1136/thoraxjnl-2012-202348>

In this large case-control study, the authors identified all incident cases of lung cancer diagnosed between January 2000 and July 2009 in The Health Improvement Network (THIN) database of 8.2 million patients from 446 UK general practices. Patients aged < 40 years were excluded. 10 controls for each case (aged 40 or over) were randomly selected from the same general practice as the case. In total, 12,074 cases of lung cancer and 120,731 controls were studied. Using logistic regression analysis, features that were independently associated with lung cancer were age [unadjusted odds ratio (OR) for age > 80 versus age 40-45 = 48.8; 95% CI 39.7 to 60.0], sex [OR for men vs. women = 1.6; 95% CI 1.5 to 1.6], socioeconomic status [OR for Townsend 5th deprivation quintile (most deprived) vs. 1st quintile = 1.9; 95% CI 1.8 to 2.1] and smoking history [OR for very heavy smoker (40+/day) vs. non-smoker = 12.5; 95% CI 11.1 to 14.1]. The authors then derived a risk-prediction model and assessed it in an independent dataset of 1,826,293 patients from the THIN database. From 4 to 12 months before diagnosis, a number of other variables were independently predictive of lung cancer, including frequency of consultations [OR for 11-20 consultations vs. 0-10 = 2.7; 95% CI 2.6 to 2.8], haemoptysis [OR 20.2; 95% CI 16.2 to 25.0], a diagnosis of COPD [OR 7.8; 95% CI 7.2 to 8.5], weight loss [OR 6.2; 95% CI 5.2 to 7.4] and dyspnoea [OR 4.7; 95% CI 4.4 to 5.1]. The authors conclude that this model outperforms the current UK National Institute for Health and Clinical Excellence (NICE) referral guidelines, and that its use would facilitate earlier diagnosis of lung cancer in primary care.

Available online at <http://www.thepcrj.org>