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Asthma

Cod liver oil with high vitamin A content is associated with increased incidence of adult-onset asthma

Mai et al. Cod liver oil intake and incidence of asthma in Norwegian adults — the HUNT study. Thorax 2013;68:25-30. http://dx.doi.org/10.1136/thoraxjnl-2012-202061

This is the first large prospective cohort study to evaluate the association between cod liver oil intake and asthma development. In Norway before 1999, cod liver oil contained high concentrations of vitamin A (1000mcg per 5ml), which has been linked to an increased risk of diseases such as postmenopausal osteoporosis, gastric cancer and prostate cancer. Because of these risks, the Vitamin A concentration was reduced to the current level of 250mcg per 5ml in 2002. Data from the Nord-Trondelag Health (HUNT) studies were used to construct a cohort of 25,616 adults aged 19-55 who were followed-up from 1995-1997 (HUNT 2) to 2006-2008 (HUNT 3). 17,528 of this cohort were free of asthma in the HUNT 2 survey and had complete data on daily cod liver oil intake prior to this. The primary outcome was the incidence of new-onset asthma as reported in the HUNT 3 survey — i.e. after 11 years follow-up. 3076 of the 17,528 subjects (18%) had consumed cod liver oil daily for > 1 month in the year prior to baseline, and this was associated with an increased incidence of new-onset adult asthma [adjusted odds ratio 1.62; 95% CI 1.32 – 1.98] after adjustment for age, sex, smoking history, physical activity, education, socio-economic status, family history of asthma and body mass index. An interesting result; the authors conclude that further studies are needed to evaluate any relationship between the current cod liver oil formulation (containing 250mcg/5ml vitamin A) and asthma development.

High-altitude treatment improves severe refractory asthma

Rijssenbeek-Nouwen et al. High-altitude treatment in atopic and non-atopic patients with severe asthma. Eur Respir J 2012;40:1374-80. http://dx.doi.org/10.1183/09031936.00195211

High-altitude treatment in asthma has been used before, and its benefits have been attributed to the lower allergenic load — particularly reduced exposure to house dust mite — present at high altitudes. This is a prospective cohort study on 137 adults with severe refractory asthma, 92 of whom had proven allergic sensitisation, who were referred for high altitude treatment in Davos, Switzerland (height 1,600m). Treatment was for 12 weeks, and the aim was to investigate whether high altitude treatment was equally effective in patients with and without allergic sensitisation. Outcome measures included the asthma control questionnaire (ACQ), asthma-related quality of life questionnaire (AQLQ), prednisolone requirement, and post-bronchodilator FEV1. Both the sensitised and non-sensitised patients showed similar improvements in ACQ scores [-1.4 and -1.5, respectively, no significant difference between the two; P=0.79], AQLQ [1.5 and 1.5, P=0.94], and FEV1 [improvements of 6.1% and 5.8%, respectively; P=0.43]. Oral prednisolone use was similar [40% vs. 44%; P=0.51]. The authors conclude that high-altitude treatment improves clinical and functional parameters in patients with severe refractory asthma, whether they have allergic sensitisation or not.

Biological markers of stress are associated with onset of asthma in adolescent boys

Behreinian et al. Allostatic load biomarkers and asthma in adolescents. Am J Respir Crit Care Med 2013;187:144-52. http://dx.doi.org/10.1164/rccm.201201-0025OC

This is a prospective study of 352 children aged 7 – 10 years old who were recruited into the nested case-control arm of the Study of Asthma Genes and the Environment (SAGE). SAGE involved a population-based sample of 16,320 children born in Manitoba, Canada in 1995; initial recruitment involved stratification according to the presence of asthma (n=392), hay fever or food allergy (n=192), or neither (n=1002).

In this study, the authors have used the novel concept of ‘allostatic load’, a measure of physiological response to stress combining eight biomarkers — fasting glucose, total cholesterol, HDL, dehydroepiandrosterone sulphate (produced by the adrenal cortex; levels > 800 mcg/dl are highly suggestive of adrenal dysfunction), cortisol, systolic BP, diastolic BP, and waist-to hip ratio — and correlated it with the incidence and prevalence of asthma using logistic regression. Follow-up was for 4 years. Asthma prevalence was four times more likely in boys with a high (>3) versus a low (<2) allostatic load, after adjusting for age, ethnicity, current asthma/atopy, being overweight, and family history of asthma. Similarly, new-onset asthma was more common in boys with high allostatic load [adjusted odds ratio 4.35; 95% CI 1.19 – 15.9]. There was no correlation between asthma and allostatic load in girls. We already know that psychological risk factors including stress can impact on asthma control and the risk of asthma attacks, but here is an association between biomarkers of stress and an increased likelihood of asthma in adolescent boys. But why not girls as well…?

Fluticasone/formoterol combination therapy for asthma — efficacy and safety

Corren et al. Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma. Resp Med 2013;107:180-95. http://dx.doi.org/10.1016/j.rmed.2012.10.025

This is a 12-week, double-blind, randomised, parallel-group, placebo-controlled phase 3 efficacy and safety study. 557 adults and adolescents aged > 12 years with moderate to severe asthma were randomised to two different strength twice-daily (b.d.) fluticasone/formoterol combination inhalers (fluticasone 250 mcg/formoterol 10 mcg [n=110] and fluticasone 100 mcg/formoterol 10 mcg [n=114]), or to the separate components (fluticasone 250mcg b.d. [n=113] and formoterol 100mcg b.d. [n=112]), or to placebo (n=109). Primary endpoints were: mean change in morning pre-dose FEV1 from baseline to week 12; mean change in FEV1 from baseline morning pre-dose value to 12-week 2-hour post-dose value, and the number of patient withdrawals due to lack of treatment efficacy in each arm. Secondary endpoints included telephone diary data, morning and evening peak flow readings, asthma symptom scores, number and severity of asthma exacerbations, and the number of symptom-free days. 395/557 patients completed the study. The 250/100 fluticasone/formoterol combination inhaler was superior to all other treatment groups for the three primary endpoints as well as providing numerically greater (and mostly statistically significant) improvements in the...
secondary endpoints. Dropout numbers (percentages) were 23 (20.9%) and 18 (15.8%) for the 250/10 and 100/10 combination inhalers, respectively; 28 (24.8%) for fluticasone 250mcg b.d.; 41 (36.9%) for formoterol 10 mcg b.d., and 52 (47.7%) for placebo. Both strengths of the combination inhaler demonstrated a good safety profile, with no significant differences in numbers of adverse events between the groups. The fluticasoneformoterol combination inhaler is therefore a welcome addition to the asthma armamentarium.

COPD

How does the new GOLD classification predict the clinical course of COPD? Lange et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification. Am J Resp Crit Care Med 2012;186:975-81. http://dx.doi.org/10.1164/rcrm.201207-1299OC

The 2011 GOLD guideline classifies COPD into four categories based on symptoms, lung function and exacerbation history: Group A patients exhibit few symptoms (dyspnoea) and have a low risk of exacerbation; Group B have more severe symptoms and low exacerbation risk; Group C have few symptoms but high exacerbation risk; and Group D have severe symptoms and high exacerbation risk. See http://dx.doi.org/10.1164/rcrm.201207-1299OC for a recent discussion paper on the implications of this new classification. These authors investigated the ability of the new classification to predict the clinical course of COPD. In two similar population studies, data on exacerbations, hospital admission and death were collected on 6,628 COPD patients over an average of 4.3 years. During the first year, exacerbation rates were 2.2% in Group A, 5.8% in Group B, 25.1% in Group C, and 28.6% in Group D. One- and 3-year mortality rates were 0.6% and 3.8% respectively for Group A, 3.0% and 10.6% for Group B, 0.7% and 8.2% for Group C, and 3.4% and 20.1% for Group D. Groups B and D – with more severe dyspnoea – had up to an 8-fold higher mortality from cardiovascular disease and cancer than Groups A and C. The authors conclude that the new GOLD classification performs well by identifying individuals at risk of exacerbation. However, Group B, characterised by more severe dyspnoea but better lung function, had significantly poorer survival than Group C. Therefore, Group B patients warrant special attention.

Efficacy and safety of glycopyrronium bromide versus tiotropium and placebo Kerwin et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J 2012;40:1106-14. http://dx.doi.org/10.1183/09031936.00040712

Glycopyrronium bromide (NVA237) is a new once-daily long-acting muscarinic antagonist (LAMA), and this parallel-group RCT evaluated its efficacy and safety in patients with moderate-to-severe COPD over one year. 1,066 patients were randomised in a 2:1:1 ratio to glycopyrronium 50 mcg daily, placebo, or open-label tiotropium 18 mcg daily. The primary endpoint was trough FEV1 at 12 weeks, and there were various secondary endpoints. 810 patients completed the study. At 12 weeks, FEV1 increased by 97ml with glycopyrronium [95% CI 64.6 – 13.2] and 83ml with tiotropium [95% CI 45.6 – 121.4]. Glycopyrronium also produced significant improvements in dyspnoea [Transitional Dyspnoea Index at week 26, P=0.002] and health status (St George’s Respiratory Questionnaire, P<0.001) compared to placebo, and significantly reduced the risk of moderate-to-severe exacerbation by 34% [P=0.001] and the use of rescue medication [P=0.039], compared to placebo. Glycopyrronium-placebo and tiotropium-placebo differences were similar across groups. Therefore, glycopyrronium 50 mcg daily provided significant improvements in lung function, dyspnoea, health status, exacerbations and rescue medication use compared with placebo, and was comparable to tiotropium. No doubt this is another LAMA to be added to the armamentarium soon.

Once-daily indacaterol versus tiotropium or twice-daily long-acting beta2-agonists for stable COPD: a systematic review Rodrigo et al. Comparison of indacaterol with tiotropium or twice-daily long-acting beta2-agonists for stable COPD: a systematic review. Chest 2012;142:1104-10. http://dx.doi.org/10.1378/chest.11-2252

The use of bronchodilators is fundamental to the management of COPD. This systematic review assessed the efficacy and safety of once-daily indacaterol compared to tiotropium (the other currently available once-daily bronchodilator) and twice-daily long-acting beta2-agonists (LABAs). Five RCTs (involving 5,920 patients) were included. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in rescue medication use and dyspnoea [43% greater likelihood of achieving a minimal clinically important difference (MCID) in the Transient Dyspnoea Index (TDI); number needed to treat = 10]. The MCID in health status was achieved more readily with indacaterol than with tiotropium [odds ratio (OR) 1:43; 95% CI 1:12 – 1:68]. Trough FEV1 was significantly higher after treatment with indacaterol than with twice-daily LABAs [P< 0.001], as was dyspnoea [61% greater likelihood of achieving an MCID in the TDI; P=0.008] and health status [21% greater likelihood of achieving an MCID in the St George’s Respiratory Questionnaire, P=0.04]. Indacaterol had a safety profile similar to both comparators. The authors conclude that indacaterol is a useful alternative to tiotropium or twice-daily LABAs.

Lung volume reduction surgery leads to weight gain in under-weight and normal weight patients Kim et al. Weight gain after lung reduction surgery is related to improved lung function and ventilatory efficiency. Am J Resp Crit Care Med 2012;186:1109-16. http://dx.doi.org/10.1164/rccm.201203-0538OC

These authors set out to characterise the types of patients who put on weight after lung volume reduction surgery (LVRS) for emphysema. Over 1,000 patients previously enrolled into the US National Emphysema Treatment Trial were divided into groups according to their body mass index (BMI): underweight (< 21 kg/m²), normal weight (21-25 kg/m²), overweight (25-30 kg/m²), and obese (>30 kg/m²). Data on baseline characteristics, treatment (LVRS versus medical management), and change in weight, were collected. Lung function was assessed in patients with and without significant weight gain (> 5% increase in BMI) at 6 months. Weight gain was greater in the LVRS patients as compared to medical patients, in the underweight and normal weight groups. The LVRS patients with significant weight gain at 6 months also showed significant improvements in lung function compared to those patients without significant weight gain: change in FEV1 = 11.53 (SD +/- 9.31)%; versus 6.58 +/- 8.68% [P<0.0001], change in FVC = 17.51 +/- 15.20% vs. 7.55 +/- 14.88% [P<0.0001], and change in 6-minute walk distance = 38.70 +/- 69.57m vs. 7.57 +/- 73.37m [P<0.0001]. The authors conclude that lung volume reduction surgery leads to weight gain in non-obese patients, that this is associated with improvements in lung function, exercise capacity and respiratory muscle strength, and that these physiological changes may actually be responsible for the weight gain.

Once-daily QVA149 (indacaterol/glycopyrronium) versus twice-daily salmeterol/fluticasone for symptomatic COPD Vogelmeier et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med; published online 6th December 2012. http://dx.doi.org/10.1016/S2213-2600(12)70052-8

This multi-centre, randomised, double-blind, double-dummy, parallel group study was an efficacy and safety head-to-head comparison between once-daily QVA149 – a new fixed-dose indacaterol 110mcg/glycopyrronium (a long-acting muscarinic agonist) 50mcg combination inhaler – and the twice-daily fixed-dose combination of salmeterol 50mcg and fluticasone 500mcg (SFC). 523 patients aged 40 or over with moderate to severe COPD (GOLD stages II-III) were randomised to receive QVA149 (n=259) or SFC (n=264), with stratification by smoking status. The primary endpoint, aiming to demonstrate the superiority of the combination bronchodilator QVA149, was the standardised area under the curve (AUC) from 0 to 12 hours post-dose (AUCO-12h) for FEV1 at 26 weeks – which is of questionable clinical importance... Nonetheless, this was significantly higher with QVA149 than with SFC [difference = 0.138L; 95% CI 0.100 – 0.176]. The incidence of adverse events, including COPD exacerbations, was similar between the two groups, with 143/258 (55.4%) for QVA149 [132/258 (5.0%) serious events] and 159/264 (60.2%) for SFC [14/264 (5.3%) serious events]. The authors conclude that once-daily QVA149 provides significant improvements in lung function versus twice-daily SFC, with significant symptomatic benefit. However, this really isn’t surprising, since the primary endpoint was specifically chosen to favour the dual bronchodilator action of QVA149 compared to the single bronchodilator (salmeterol) action of SFC. So this wasn’t really a fair comparison.
Comprehensive self-management versus routine monitoring for COPD
Bischoff et al. Comprehensive self-management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: a randomised controlled trial. BMJ 2012; 345:e7642. Published online 28th November 2012. http://dx.doi.org/10.1136/bmj.e7642

The aim of this 24-month, multicentre, 3-arm, randomised controlled trial (RCT) was to compare comprehensive self-management versus routine monitoring for primary care COPD patients in the Netherlands. Recruitment took place from 2004 to 2006, and patients with very severe COPD (GOLD IV) were excluded. 165 patients were randomised to self-management (patients received a self-management programme, educational modules, a written exacerbation action plan, and 4 sessions of individual teaching from a practice nurse with ongoing telephone support; n=55), routine monitoring (2-4 structured practice nurse consultations/year; n=55), or usual care (patient-initiated GP consultations without any practice nurse input; n=55). Randomisation was stratified according to COPD severity, smoking status, and number of exacerbations in the preceding 2 years. The primary outcome was change in quality of life as measured by the Chronic Respiratory Questionnaire (CRQ) score, and secondary outcomes included frequency of (and patients' ability to manage) exacerbations. There were no significant differences in mean CRQ score between the three groups after 24 months. The only secondary outcome that showed a difference was the management of exacerbations, more of which were managed in the self-management group by bronchodilators and prednisolone [odds ratio (OR) 2.81; 95% CI 1.16 – 6.82], antibiotics, or both [OR 3.98; 95% CI 1.10 – 15.58]. Therefore, comprehensive self-management didn’t show any quality of life benefits over usual care, though the self-management group seemed more capable of managing their exacerbations. However, the authors do comment that the structure of primary care COPD management in the Netherlands has changed considerably since this study took place, with more attention being paid to the components of chronic care that increase the chance of self-management success – and in which case we need to bear this in mind when interpreting the findings of this study.

Systematic review of the safety of inhaled treatments for COPD: tiotropium Soft Mist inhaler has a higher risk of death
Dong et al. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax 2013; 68:46-56. http://dx.doi.org/10.1136/thoraxjnl-2012-201926

This is an extensive systematic review of the safety of all inhaled medications used for the treatment of COPD, with particular emphasis on cardiovascular death. The authors identified RCTs of tiotropium Soft Mist inhaler, tiotropium Handihaler, long-acting beta2-agonists (LABAs), inhaled corticosteroids (ICS), and LABA/ICS combination inhalers, all with treatment periods > 6 months. They then performed mixed treatment comparison meta-analyses to estimate the odds ratios of death for each treatment versus the others. 42 trials involving 52,516 patients were included. The tiotropium Soft Mist inhaler showed an increased overall risk of death compared to placebo [odds ratio (OR) 1.51; 95% CI 1.06 – 2.19], tiotropium Handihaler [OR 1.65; 95% CI 1.13 – 2.34], LABA [OR 1.63; 95% CI 1.10 – 2.44], and LABA/ICS combination inhalers [OR 1.90; 95% CI 1.28 – 2.86]. For cardiovascular death the risks of tiotropium Soft Mist inhaler were even more pronounced; odds ratios were 2.07 [95% CI 1.09 – 4.16] compared to placebo, 2.38 [95% CI 1.20 – 4.99] compared to tiotropium Handihaler, 3.04 [95% CI 1.48 – 6.55] compared to LABAs, and 2.79 [95% CI 1.37 – 6.02] compared to LABA/ICS combination inhalers. The authors conclude that tiotropium Soft Mist inhaler has a higher risk of mortality and that it should be used with caution. This study follows the call by Beasley et al. in 2010 to compare comprehensively all inhaled medications used for COPD. This is an extensive systematic review of the safety of all inhaled medications used for COPD, with particular emphasis on cardiovascular death. The authors identified RCTs of tiotropium Soft Mist inhaler, tiotropium Handihaler, long-acting beta2-agonists (LABAs), inhaled corticosteroids (ICS), and LABA/ICS combination inhalers, all with treatment periods > 6 months. They then performed mixed treatment comparison meta-analyses to estimate the odds ratios of death for each treatment versus the others. 42 trials involving 52,516 patients were included. The tiotropium Soft Mist inhaler showed an increased overall risk of death compared to placebo [odds ratio (OR) 1.51; 95% CI 1.06 – 2.19], tiotropium Handihaler [OR 1.65; 95% CI 1.13 – 2.34], LABA [OR 1.63; 95% CI 1.10 – 2.44], and LABA/ICS combination inhalers [OR 1.90; 95% CI 1.28 – 2.86]. For cardiovascular death the risks of tiotropium Soft Mist inhaler were even more pronounced; odds ratios were 2.07 [95% CI 1.09 – 4.16] compared to placebo, 2.38 [95% CI 1.20 – 4.99] compared to tiotropium Handihaler, 3.04 [95% CI 1.48 – 6.55] compared to LABAs, and 2.79 [95% CI 1.37 – 6.02] compared to LABA/ICS combination inhalers. The authors conclude that tiotropium Soft Mist inhaler has a higher risk of mortality and that it should be used with caution. This study follows the call by Beasley et al. in November for the worldwide withdrawal of the tiotropium Soft Mist inhaler (BMJ 2012; 345:e7390) – and it seems to back them up…

Home monitoring of ventilation rate might identify COPD exacerbations earlier
Yanez et al. Monitoring breathing rate at home allows early identification of COPD exacerbations. Chest 2012;142:1524-9. http://dx.doi.org/10.1378/chest.11-2728

Given that ventilation rate (VR) increases during an infective exacerbation of COPD, these authors monitored the VR of 89 patients with severe COPD (mean FEV1 +/- SD = 42.3 +/- 14.0% predicted), all of whom were receiving home oxygen for 9.6 +/- 4.0 hours. The aim was to see if an increase in VR could be elicited before the patient was hospitalised for an exacerbation. 30 patients (33.7%) required hospitalisation, and in 21/30 (70%) there was a detectable increase in VR from 15.2 +/- 4.3 to 19.1 +/- 5.9 [P< 0.05]. There was no increase in VR in those patients who were not admitted to hospital. 24 hours before hospitalisation, a mean increase in VR of 4.4 breaths/min provided the best sensitivity (66%) and specificity (93%) for predicting hospitalisation [ROC analysis showing area under the curve (AUC) = 0.79; P<0.05]. Two days before, a mean increase of 2.3 breaths/min gave 72% sensitivity and 77% specificity [AUC=0.76; P<0.05] for predicting hospitalisation. Therefore, in patients receiving home oxygen treatment, VR increases prior to admission for a COPD exacerbation. Not particularly surprising, but the authors conclude that monitoring of VR in patients on home oxygen might flag up an impending exacerbation and permit early intervention.

Reduced lung function due to biomass smoke exposure in Nepal
Kurmi et al. Reduced lung function due to biomass smoke exposure in young adults in rural Nepal. Eur Respir J 2013;41:25-30. http://dx.doi.org/10.1183/09031936.002511

Previous studies from developing countries assessing the risk of COPD in populations exposed to biomass smoke have shown a higher prevalence of respiratory symptoms and reduced lung function associated with solid fuel use in both children and adults, particularly in women (who tend to do the cooking). However, many of these studies have suffered from methodological limitations, including non-validated questionnaires, poor quality spirometry, lack of a control population, and limited control for confounding factors such as cigarette smoking. The authors of this cross-sectional study have used validated objective and subjective outcome measures to assess lung function changes due to biomass fuel use (in this case 98.9% wood) in individuals aged > 16 years in four out of nine randomly selected districts in Kathmandu, Nepal. Exposure to liquefied petroleum gas (LPG) was used as the control. 1,648 participants were enrolled, and 1,392 (856 males, 736 females) had valid spirometry results for analysis. FEV1, FVC, and FEV1/FVC ratio were all reduced in biomass fuel users of all ages, after adjusting for height, age, sex, BMI, literacy, income, smoking history and environmental tobacco exposure. Airflow obstruction was twice as common compared to LPG users [8.1% versus 3.8%; P<0.001] based on lower limit of normal criteria. Lung function was reduced even in the youngest age group (16-25 years), with a mean FEV1 of 2.65 litres [95% CI 2.57 – 2.73] in biomass users versus 2.83 litres [95% CI 2.74 – 2.91] in LPG controls. This confirms previous findings, and highlights the fact that exposure to biomass smoke is associated with reduced lung function even in the late teenage years...

Addition of antibiotics to steroids helps patients hospitalised with COPD exacerbations
Stefan et al. Association between antibiotic treatment and outcomes in patients hospitalised with acute exacerbation of COPD treated with systemic steroids. Chest 2013;143:82-90. http://journal.publications.chestnet.org/article.aspx?articleid=1216510

The aim of this retrospective cohort study was to evaluate the impact of antibiotic treatment in addition to standard treatment regimens including oral steroids in patients hospitalised with an exacerbation of COPD. The cohort consisted of 53,900 COPD patients aged > 40 years who were admitted to 410 acute care hospitals throughout the USA over a 2-year period from January 2006 to December 2007. Three commonly used antibiotic regimes were studied: quinolones (50%), macrolides plus cephalosporins (22%), and macrolides alone (9%). Patients who received antibiotics had lower mortality [1% versus 1.8%; P<0.0001]. Using multivariate analysis, antibiotic treatment in hospital was associated with a 40% reduction in the risk of in-hospital death [relative risk (RR) 0.60; 95% CI 0.50 – 0.73] and a 13% reduction in the risk of 30-day readmission for COPD [RR 0.87; 95% CI 0.79 – 0.96]. There was little difference between the three different antibiotic regimes. The authors conclude that adding antibiotics to treatment with oral steroids for an acute exacerbation of COPD has a beneficial effect on various outcomes including in-hospital death and 30-day readmission. Given the size of the cohort, this is a reasonable assumption. However, we can only draw limited inference from an observational retrospective study. We now need a prospective RCT.
Depression has the most impact on quality of life in COPD: Burgeil et al. Impact of comorbidities on COPD-specific health-related quality of life. Resp Med 2013;107:233-41. http://dx.doi.org/10.1016/j.resmed.2012.10.002

This is a cross-sectional analysis of data from the French COPD cohort initiatives study. The aim was to ascertain the most important co-morbidities contributing to impairment of health-related quality of life (HRQoL) as measured by the St George’s Respiratory Questionnaire (SGRQ), in 326 patients with COPD (77% male; median [interquartile range] age 65 (57 – 72) years; FEV1 48.9 [34.7 – 65.9]% predicted). Data included spirometry, modified MRC scores, hospital anxiety-depression (HAD) scale, BMI, exacerbations, and physician-diagnosed co-morbidities. Multiple regression analysis was used to assess the association between co-morbidities and SGRQ score. There was a positive correlation between SGRQ total score, dyspnoea, and the number of COPD exacerbations per year. SGRQ total scores were increased (i.e. worse) in women, and in those patients with a low BMI, anxiety or depression (P< 0.001). Multivariate analysis showed that dyspnoea, exacerbations per year, and depression all had an independent and significant effect on the total SGRQ score, whereas the effects of low BMI, coronary artery disease and FEV1; on total SGRQ score were only modest. The authors conclude that, in the presence of dyspnoea and exacerbations, depression has the most impact on quality of life in COPD when compared to other co-morbidities.

Infections

Vitamin D deficiency is common in bronchiectasis: Chalmers et al. Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. Thorax 2013;68:39-47. http://dx.doi.org/10.1136/thoraxjnl-2012-202125

Vitamin D has immune-modulatory and anti-inflammatory effects, and deficiency is associated with asthma, poorer lung function in adults and children (see the December 2012 Journalwatch@pcrj reviews on the papers by Chen Wu et al. http://dx.doi.org/10.1136/thoraxjnl-2012-20351OC and Lange et al. http://dx.doi.org/10.1164/rccm.201110-1868OC ); and an increased risk of respiratory infections. These authors measured 25-hydroxyvitamin-D levels in 402 patients with bronchiectasis, and categorised the patients as vitamin D deficient (< 25 nmol/l, n=201, 50%), insufficient (25-74 nmol/l, n=173, 43%), or sufficient (> 75 nmol/l, n=28, 7%). In contrast, only 12% of age and sex matched controls were vitamin D deficient (P<0.0001). Using logistic regression, vitamin D deficiency was independently associated with chronic bacterial colonisation [odds ratio 1.67; 95% CI 1.10 – 2.56]; 21.4% of the vitamin D deficient bronchiectasis controls were vitamin D deficient (P<0.0001). Using logistic regression, vitamin D increased risk of respiratory infections. These authors measured 25-hydroxyvitamin-and Lange http://dx.doi.org/10.1164/rccm.201202-0448OC

Sleep disorders

CPAP treatment for obstructive sleep apnoea in the elderly: effect on cardiovascular mortality: Martinez-Garcia et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment. Am J Respir Crit Care Med 2012; 186:909-16. http://dx.doi.org/10.1164/rccm.201203-0448OC

This was a prospective cohort study of 939 patients aged > 65 years considered to be at-risk of obstructive sleep apnoea (OSA), recruited over a 10-year period (1998-2007) with a median follow-up of 69 months. OSA was defined using the Apnoea-Hypopnoea Index [AHI], an AHI of 15-29 constituted mild-to-moderate OSA, an AHI > 30 constituted severe OSA, and patients with an AHI < 15 formed the control group. OSA patients were subdivided into those treated with continuous positive airway pressure (CPAP) adherence > 4 hours/day and those who were nonadherent (CPAP not prescribed, or adherence < 4 hours/day). The impact of CPAP and CPAP treatment on cardiovascular mortality was then determined using a multivariate Cox survival analysis. The adjusted hazard ratio (HR) for cardiovascular death compared to the control group for patients with untreated severe OSA was 2.25 [95% CI 1.41 – 3.61], suggesting an association between severe untreated OSA and increased cardiovascular mortality in the elderly. For both the CPAP-treated severe OSA group [HR 0.93; 95% CI 0.46 – 1.89] and the untreated mild-to-moderate OSA group [HR 1.38; 95% CI 0.73 – 2.64] the 95% confidence intervals for HR (cardiovascular death compared to controls) cross 1.0, suggesting that CPAP treatment (for > 4 hours/day) has reduced the cardiovascular risk in severe OSA and that mild-to-moderate OSA does not increase cardiovascular risk.

CPAP treatment for mild obstructive sleep apnoea: improves sleepiness but not cardiovascular risk: Craig et al. Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. Thorax 2012;67:1090-6. http://dx.doi.org/10.1136/thoraxjnl-2012-202178

This was a multicentre parallel-group hospital-based RCT which assessed the role of CPAP treatment for patients with mild obstructive sleep apnoea (OSA). 391 patients with confirmed OSA (oxygen desaturation index > 7.5/hour) but with insufficient symptoms to warrant treatment with continuous positive airway pressure (CPAP) were randomised to 6 months of automatically-adjusted CPAP therapy or normal care. Primary endpoints were change in the Epworth Sleepiness Score (ESS), and predicted 5-year mortality using a cardiovascular risk score which incorporated age, sex, height, blood pressure, smoking history, diabetes, cholesterol, creatinine, left ventricular hypertrophy, previous myocardial infarction or stroke. Secondary endpoints included several of the cardiovascular components, sleepiness, and self-assessed health status. 341/391 patients attended for their 6-month follow-up visit and had complete ESS data. CPAP significantly improved subjective daytime sleepiness (adjusted treatment effect on ESS -2.0 [95% CI -2.6 to -1.4] and self-assessed health status but did not improve calculated cardiovascular risk. Of course, these results aren’t surprising when compared to the study by Martinez-Garcia et al. in the Blue journal where we’ve already reviewed (see above, http://dx.doi.org/10.1164/rccm.201203-0448OC). It looks as though there is an increased cardiovascular risk for patients with severe OSA (which may be reduced by CPAP treatment), but no increased cardiovascular risk (and therefore no potential for reducing the risk by CPAP) for patients with mild OSA.

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Moderate to severe obstructive sleep apnoea increases the likelihood of type 2 diabetes
Wang et al. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirology* 2013;18:140-6. http://dx.doi.org/10.1111/j.1440-1843.2012.02267.x

This is a sound meta-analysis which summarises the current ‘state of play’ on the association between varying degrees of severity of obstructive sleep apnoea (OSA) and type 2 diabetes. Only six studies met the inclusion criteria: they needed to be well-conducted prospective cohort studies in which OSA was assessed by objective measurements, the incidence of type 2 diabetes was a primary outcome measure, and in which a risk estimate for type 2 diabetes was reported together with 95% confidence intervals. Pooled relative risks (RR) were calculated. The six studies included a total of 5953 patients, and follow-up ranged from 2.7 to 16 years. There were 332 incident cases of type 2 diabetes. Severity of OSA was defined according to the apnoea-hypopnoea index (AHI) and oxygen desaturation levels. Patients with moderate to severe OSA (AHI ≥ 15) had a greater risk of diabetes [RR 1.63; 95% CI 1.09 – 2.45] compared to those without OSA. However, there was no significant association between mild OSA and type 2 diabetes [RR 1.22; 95% CI 0.91 – 1.63]. These findings therefore support the hypothesis that moderate to severe OSA is an independent risk factor for the development of type 2 diabetes.

Fibrotic lung disease
Serum carcinoembryonic antigen correlates with severity of idiopathic pulmonary fibrosis
Fahim et al. Serum carcinoembryonic antigen correlates with severity of idiopathic pulmonary fibrosis. *Respirology* 2012;17:1247-52. http://dx.doi.org/10.1111/j.1440-1843.2012.02321.x

Idiopathic pulmonary fibrosis (IPF) is the commonest interstitial lung disease. There is previous epidemiological evidence which suggests that patients with IPF have an increased risk of developing lung cancer. Given that carcinoembryonic antigen (CEA) has a close association with epithelial malignancy, these authors assessed serum CEA concentrations in 41 non-smoking patients (mean age 73 +/- 7 years) with IPF and correlated the concentrations with lung function. The mean (+/- standard deviation) FVC was 88 +/- 20% predicted, and the mean diffusing factor for carbon monoxide (DLCO) was 52 +/- 10% predicted. 21 patients (51%) had a serum CEA concentration higher than the upper limit of normal (5ng/ml). CEA concentration was significantly negatively correlated with lung function (P<0.005), and raised CEA level also correlated significantly with the extent of fibrosis. The authors conclude that serum CEA concentrations are elevated in approximately half of patients with IPF, and that this correlates with disease severity. We await further studies on a possible future role for serum CEA measurement in the assessment of IPF in routine clinical practice...

Improved quality of life and reduction in all-cause mortality following co-trimoxazole for idiopathic pulmonary fibrosis
Shulgin et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole. *Thorax* 2012; published online 10th November 2012. http://dx.doi.org/10.1136/thoraxjnl-2012-202403

Idiopathic pulmonary fibrosis (IPF) is the commonest interstitial lung disease, with approximately 5000 new cases diagnosed each year in the UK alone. Prognosis is poor, with 5-year survival rates of 20-40%. There are limited treatment options, and only last year we reviewed an important randomised controlled trial (RCT) in the NEJM which showed that the previously widely-used triple therapy of prednisolone, azathioprine and N-acetylcyesteine was unsafe and of no benefit (see http://www.nejm.org/doi/full/10.1056/NEJMoa1113354 and http://dx.doi.org/10.4104/pcrj.2012.00079. If the cough persists despite best management (i.e. it is refractory), not surprisingly this results in substantial quality of life impairment. Given the central reflex sensitisation similarities between chronic cough and neuropathic pain, these authors studied the use of the neuromodulator gabapentin in patients with refractory chronic cough. In this double-blind randomised controlled trial (RCT), 62 patients with refractory chronic cough (i.e. > 8 weeks’ duration) were randomised to receive gabapentin 1800mg daily [n=32] or placebo [n=30] for 10 weeks. The primary endpoint was change in the Leicester Cough Questionnaire (LCQ) from baseline to week 8 (which seems rather odd when treatment was given for a 10-week period…). Gabapentin significantly improved quality of life compared to placebo according to the LCQ [between-group difference in LCQ score = 1.80, 95% CI 0.56 – 3.04]. Side-effects occurred in 10/32 patients (31%) given gabapentin and in 3/30 (10%) given placebo. The authors conclude that treatment of refractory chronic cough with gabapentin was effective and generally well tolerated, and that this supports the idea that central reflex sensitisation is an important mechanism in refractory chronic cough.

Further reassurance on varenicline
Svanstrom et al. Use of varenicline for smoking cessation and risk of serious cardiovascular events: a nationwide cohort study. BMJ 2012;345:e7176. http://dx.doi.org/10.1136/bmj.e7176

A recent BMJ systematic review and meta-analysis on varenicline use was published recently and reviewed here (see http://dx.doi.org/10.4104/pcrj.2012.00079 and http://dx.doi.org/10.1136/bmj.e2856). This is further evidence that varenicline is safe when used appropriately for smoking cessation. These authors report a nationwide cohort study to assess the risk of serious cardiovascular events with varenicline use compared to bupropion. Data were collected on drug prescriptions and cardiovascular events. The primary outcomes at 6 months after start of treatment were acute coronary syndrome, ischaemic stroke, and cardiovascular death. 17,926 new users of varenicline and 17,926 new users of bupropion were studied. There were 57 major cardiovascular events in the varenicline group (6.9 cases per 1000 person-years) compared with 60 events among bupropion users (7.1 cases per 1000 person-years), and the hazard ratio (HR) for any major event was 0.96 (95% CI 0.67 – 1.39). Varenicline use was not associated with an increased risk of acute coronary syndrome [HR 1.20; 95% CI 0.75 – 2.19], ischaemic stroke [HR 0.77; 95% CI 0.40 – 1.48], or cardiovascular death [HR 0.51; 95% CI 0.13 – 2.02]. When the authors performed subgroup analysis, the risk of any major cardiovascular event was not significantly different between patients with and without a history of cardiovascular disease (HR 1.24 [95% CI 0.72 – 2.12] and 0.83 [95% CI 0.51 – 1.36], respectively). Therefore, this study found no increased risk of cardiovascular events following varenicline treatment versus bupropion for smoking cessation.

Miscellaneous
Gabapentin for refractory chronic cough
Ryan et al. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;380:1583-9. http://dx.doi.org/10.1016/S0140-6736(12)60776-4

Management of chronic cough involves careful assessment and judicious use of trials of treatment to aid diagnosis, for a recent series of international perspectives on the management of chronic cough see http://dx.doi.org/10.4104/pcrj.2012.00075. If the cough persists despite best management (i.e. it is refractory), not surprisingly this results in substantial quality of life impairment. Given the central reflex sensitisation similarities between chronic cough and neuropathic pain, these authors studied the use of the neuromodulator gabapentin in patients with refractory chronic cough. In this double-blind randomised controlled trial (RCT), 62 patients with refractory chronic cough (i.e. > 8 weeks’ duration) were randomised to receive gabapentin 1800mg daily [n=32] or placebo [n=30] for 10 weeks. The primary endpoint was change in the Leicester Cough Questionnaire (LCQ) from baseline to week 8 (which seems rather odd when treatment was given for a 10-week period…). Gabapentin significantly improved quality of life compared to placebo according to the LCQ [between-group difference in LCQ score = 1.80, 95% CI 0.56 – 3.04]. Side-effects occurred in 10/32 patients (31%) given gabapentin and in 3/30 (10%) given placebo. The authors conclude that treatment of refractory chronic cough with gabapentin was effective and generally well tolerated, and that this supports the idea that central reflex sensitisation is an important mechanism in refractory chronic cough.