All you need to read in the other general medical journals
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Obstructive sleep apnoea linked to cardiovascular death in women

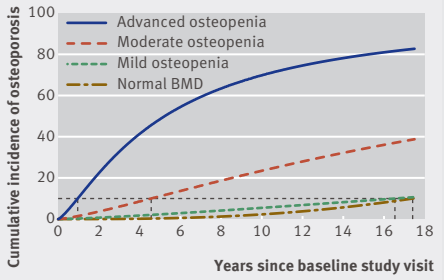
Men with obstructive sleep apnoea have an increased risk of death from cardiovascular disease, and so do some women, according to an exclusively female cohort from Spain. The authors tracked 1116 women referred to sleep clinics with suspected obstructive sleep apnoea. They reported 41 cardiovascular deaths (3.6%) during a mean follow-up of six years. The 95 women with severe and untreated disease were three times more likely to die of cardiovascular disease than those without obstructive sleep apnoea in fully adjusted analyses (18 deaths in 95 women *v* 5 deaths in 278 women; hazard ratio 3.5, 95% CI 1.23 to 9.98). Mild or moderate obstructive sleep apnoea was not linked to cardiovascular mortality in this study, and neither was treated obstructive sleep apnoea of any severity.

These findings, although preliminary, suggest that we should be paying as much attention to obstructive sleep apnoea in women as we do in men, say the authors. Between 2% and 3% of middle aged women have the disorder, but it is harder to recognise because symptoms tend to include depression, anxiety, or insomnia rather than the daytime sleepiness and witnessed apnoea seen in men.

Treatment with continuous positive airway pressure (CPAP) may reduce the cardiovascular risk associated with severe obstructive sleep apnoea in women, and confirmatory trials would be ideal, although difficult to perform. It wouldn't be ethical to withhold CPAP deliberately from women with severe obstructive sleep apnoea, say the authors.

Ann Intern Med 2012;156:115-22

Cumulative incidence of osteoporosis



Adapted from *N Engl J Med* 2012;366:225-33

How long is needed between DXA scans for older women?

US guidelines recommend screening older women for suboptimal bone mineral density using dual energy x ray absorptiometry (DXA). Women with frank osteoporosis can be treated, but how often should we recall the rest?

The goal of screening is to pick up osteoporosis before a fracture occurs, say researchers, who estimate that a screening interval of 15 years would be reasonable for women with a normal first scan or only mild osteopenia (T score −1.5 or higher). Women with moderate osteopenia should be rescanned in five years (T score −1.50 to −1.99), and women with advanced osteopenia should come back in one year (T score −2.00 to −2.49).

Their recommendations emerged from a cohort of nearly 5000 women. They were 67 years or older, had no osteoporosis or history of fractures when recruited, and had at least two DXA scans of the femoral neck or total hip during a maximum of 15 years of follow-up.

The researchers estimated how long it would take for 10% of the women to develop osteoporosis. It took 16.8 years (95% CI 11.5 to 24.6) for women with normal bone mineral density (BMD) at baseline, 4.7 years (4.2 to 5.2) for women with moderate osteopenia, and 1.1 years (1.0 to 1.3) for women with advanced osteopenia.

Older women made the transition to osteoporosis faster than younger women, so the authors suggest a screening interval of three rather than five years for women with moderate osteopenia who are 85 or older. Adjustment for other risk factors made little practical difference to the estimates.

N Engl J Med 2012;366:225-33

Treatments for hepatitis C take an important step forward

Treatment for hepatitis C has entered a new phase after the publication of an exploratory study establishing that some patients can be treated successfully without interferons, with all their associated side effects, says an editorial (p 273). The study tested a combination of two oral antiviral agents in 21 adults with hepatitis C who had not responded to standard treatment with peginterferon alfa and ribavirin. The two new drugs had complementary viral targets and complementary resistance profiles. Four of the 11 patients who received the combination for six months had no detectable hepatitis C RNA in their blood 12 weeks after the end of treatment, and it was still undetectable six months after the end of treatment.

A comparator group treated with the new combination plus peginterferon alfa-2a and ribavirin did better (equally sustainable and complete viral responses in 10 of 11 patients). But those four patients who responded to oral agents alone establish an important principle, says the editorial. Oral drugs that target the hepatitis C virus directly but in different ways can be combined to maximise their effects while minimising resistance. Patients with this common and serious infection will not be dependent on injections of peginterferon forever.

The two direct acting drugs in this study, daclatasvir and asunaprevir, inhibit two different viral proteins, and other agents with different targets are in advanced stages of development. A safe and effective combination could be approved within three years, says the editorial.

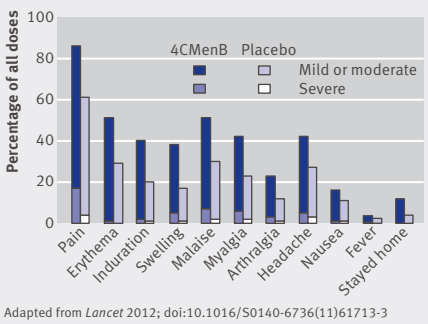
N Engl J Med 2012;366:216-24

New meningococcal vaccine passes early test in adolescents

Early testing of a long awaited vaccine against *Neisseria meningitidis* serogroup B has begun in adolescents in Chile. The new vaccine, 4CMenB, looked usefully immunogenic against three strains of group B meningococcus in a trial that tested one, two, or three doses against a placebo in 1631 children aged 11-17 years.

This is welcome news, says a linked comment (doi:10.1016/S0140-6736(11)61934-X). We already have vaccines against other major serogroups of this lethal pathogen, and group B has been holding out for a decade. Whereas other meningococcal vaccines were able to utilise

Reactions after vaccine and placebo



Adapted from *Lancet* 2012; doi:10.1016/S0140-6736(11)61713-3

"By the time that one is truly convinced of one's abiding wisdom, the chances are that Alzheimer's has properly set in"
Richard Lehman's blog at www.bmj.com/blogs

capsular polysaccharides to induce immunity, developers had to look elsewhere for suitable antigens from serogroup B. The capsular polysaccharides looked too much like a human molecule on neuronal cells to be used safely. Manufacturers Novartis settled on three different protein components plus the outer membrane vesicles from a strain responsible for an outbreak of invasive disease in New Zealand.

More than 90% of vaccinated adolescents mounted a clinically useful immune response, and two doses looked more effective than one (99-100%). Reactions at the injection site, malaise, headache, and fever were all significantly more common after the vaccine than after the placebo.

Serogroup B is a leading cause of invasive meningococcal infections in many countries, says the editorial. An effective vaccine is now one step closer.

Lancet 2012; doi:10.1016/S0140-6736(11)61713-3

Organic pollutants may weaken children's immune response to vaccinations

Fluorinated organic compounds are widespread in modern environments, where they persist for years. These pollutants, which come from packaging, textiles, and many other industrially produced goods, are in the human food chain and detectable in human serum. New research from the Faroe Islands suggests they could be a threat to children's immune responses to vaccinations.

In a cohort of 656 children, higher serum concentrations of perfluorinated compounds were associated with weaker antibody responses to diphtheria and tetanus vaccinations. The associations were strongest in children with postnatal exposure to the pollutants. A doubling of serum concentrations of the main perfluorinated compounds at age 5 was associated with a 50% drop in antibody concentrations (−49.4%, 95% CI −66.7% to −23.0%) and double the odds of a clinically inadequate humoral response to tetanus and diphtheria toxoids at age 7.

Two of the most common of these compounds, perfluoro-octanoic acid and perfluoro-octane sulfonic acid, seemed to be the main culprits. Both have elimination half lives in humans of more than four years, say the authors.

This isn't the first time that researchers have noticed a link between perfluorinated compounds and immunological compromise in humans. And we know they can cause immune suppression in rats. This study reports the first prospective data in children, say the authors. The risk to children's immunity may also extend to antenatal exposure, although results from these analyses were inconsistent.

JAMA 2012;307:391-7

Vitamin D supplements fail to delay exacerbations of COPD

There are good biological reasons why vitamin D deficiency might contribute to poor outcomes for adults with chronic obstructive pulmonary disease (COPD). So researchers were disappointed when high dose supplements failed to prevent or delay exacerbations in a recent placebo controlled trial.

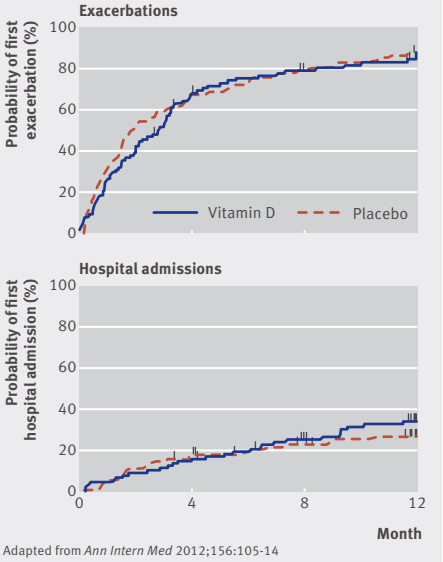
A dose of 100 000 IU a month increased serum concentrations of 25-hydroxyvitamin D substantially but made no difference to any clinical outcome, including time to first exacerbation, time to hospital admission, mortality, or quality of life. A small and exploratory subgroup analysis hinted at benefits for people with severe vitamin D deficiency at baseline (exacerbations per patient year 1.84 *v* 3.45; rate ratio 0.57, 95% CI 0.33 to 0.98). But with only 15 patients in each group, the authors and a linked editorial (p 156) caution against firm conclusions.

Vitamin D helps regulate inflammation and airway modelling, says the editorial. So we shouldn't give up on the idea that supplements might help at least some adults with COPD. Mortality is high and patients have few life saving options, except quitting smoking. These 182 participants had severe COPD, and 15 of them died within one year of randomisation.

Much bigger trials are already under way, with designs informed and improved by previous disappointments. There will be definitive answers eventually.

Ann Intern Med 2012;156:105-14

Time to first exacerbation or hospital admission



Adapted from *Ann Intern Med* 2012;156:105-14

Proton pump inhibitors do not help children with poorly controlled asthma

Doctors should think twice before prescribing proton pump inhibitors to children with poorly controlled asthma, say researchers. Lanzoprazole didn't improve control in a recent trial, and the results hinted at an increased risk of fractures. An editorial warns that more and more doctors are using these agents in children with asthma, encouraged by anecdotal reports of a link between poor control and reflux disease (p 406). This indication creep needs to stop, writes the author. The US regulator has already posted warnings about fractures in adults taking proton pump inhibitors. They should be prescribed with "great restraint" in children, with or without asthma.

The new trial compared lanzoprazole with a placebo in 306 children who had poorly controlled asthma despite treatment with inhaled corticosteroids. They had a mean age of 11 years. The drug made no difference to children's symptoms, lung function, or quality of life during the six month trial. Children treated with lanzoprazole reported significantly more respiratory infections than controls (63% (93/147) *v* 49% (74/150); relative risk 1.3, 95% CI, 1.1 to 1.6). Six children treated with lanzoprazole had fractures, compared with one control. The difference wasn't significant in the strict statistical sense (P=0.06) but it remains worrying, says the editorial.

Only three of the children in this trial had symptomatic gastro-oesophageal reflux. But asymptomatic reflux was common in the 115 children who had interpretable oesophageal pH measurements (49/115, 43%). Lanzoprazole did not work for this subgroup either.

JAMA 2012;307:373-81

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