## **Paediatrics**

### Fish oils for childhood asthma

To follow-up the idea that a reduced intake of polyunsaturated fats may contribute to the prevalence of wheezing illnesses a study has assessed the effects of supplementation with n-3 LCPUFA (fish oil) when given to pregnant women on the wheezing profiles of their offspring. In a double-blind study 736 women at 24-weeks' gestation were given either fish oil or placebo (olive oil) every day. Persistent wheeze or asthma in offspring were primary endpoints. Just under 700 children were followed up within a three-year period. During this time there was a significant risk reduction of persistent wheeze or asthma in the fish oil group versus placebo totalling a relative risk reduction of 30% for those children of women given fish oils. A secondary outcome of lower respiratory tract infection was also significantly lowered in children born from women in the fish oil group.

Supplementation of fish oils given to women in their third trimester is associated with a lower risk of wheeziness or asthma in their children.

Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil–derived fatty acids in pregnancy and wheeze and asthma in offspring. *NEJM* 2016; 375 (26): 2530–2539.

### Foetal alcohol syndrome prevalence

Drinking alcohol when pregnant can result in a spectrum of birth defects encompassed in the disorder foetal alcohol syndrome (FAS). One study has set out to estimate the global prevalence of alcohol use during pregnancy and FAS in the population with the outcome of estimating the number of alcohol-consuming pregnancies per one case of FAS. A systematic review and meta-analysis was conducted on 328 studies for prevalence of alcohol use and 62 studies were used to assess FAS. It was estimated that just under 10% of pregnancies involved alcohol use. Prevalence of FAS in the population was calculated as 14.6 per 10 000 people. Analysis found that for every 67 alcohol-consuming pregnancies one child would be born with FAS. This translates to 119 000 FAS affected children born per year. FAS resulting from alcohol use during pregnancy is a prevalent issue and prevention strategies are needed to combat this preventable disorder.

Popova S, Lange S, Probst C, et al. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. Lancet Global Health 2017. DOI: 10.1016/S2214-109X(17)30021-9

## Intra-uterine MRI for foetal brain abnormality

A study has been conducted to assess if there is any extra benefit from using an in-utero MRI (iuMRI) to further assess potential diagnosis of foetal brain abnormalities, usually only assessed through ultrasound. The prospective cohort study based in the UK recruited women whose foetuses had ultrasounddetected brain abnormalities at 18 weeks. Following abnormal ultrasound an iuMRI was performed within 14 days and diagnostic accuracy and clinical impact were compared between the two imaging types. The participants were divided into two cohorts of gestational age 18-24 weeks (n=369) and 24 plus weeks (n=201). With iuMRI diagnostic accuracy was significantly improved by 23% and 29% for 18-24 and 24 plus weeks, respectively. Overall diagnostic accuracy was 68% with ultrasound alone and 93% with the iuMRI. In addition, the iuMRI provided extra diagnostic information in 49% of cases, changed prognostic information in 20%, and changed clinical management for three cases.

The use of iuMRI following abnormal foetal brain ultrasound may improve diagnostic accuracy and clinical decision making.

Griffiths PD, Bradburn M, Campbell MJ, et al. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. *The Lancet* 2016. DOI: 10.1016/S0140-6736(16)31723-8

# Cardiology

## Bleeding in patients with atrial fibrillation

To prevent the risk of thrombosis in patients with atrial fibrillation who have undergone percutaneous coronary intervention (PCI) with stent placement, a standard anticoagulation therapy of vitamin K antagonist plus dual antiplatelet therapy (DAPT) of P2Y12 inhibitor and aspirin is usually given. However, this comes with risk of increased bleeding. The PIONEER AF-PCI trial has investigated whether an oral factor Xa inhibitor, rivaroxaban, might decrease risk of bleeding in this setting. Over 2100 patients were randomly assigned either

low-dose rivaroxaban plus a P2Y12 inhibitor for 12 months; very-low-dose rivaroxaban plus DAPT for one, six, or 12 months; or the standard therapy for one, six, or 12 months. Both rivaroxaban groups significantly reduced the risk of major bleeding compared to the standard therapy vitamin K setting. Efficacy among all groups was similar although confidence intervals were wide.

Rivaroxaban given in either of these settings can reduce the risk of bleeding usually associated with vitamin K mediated anticoagulation therapy in atrial fibrillation patients who have undergone a PCI with stent fitting.

Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *NEJM* 2016; 375: 2423–2434.

## A durable RNA inhibitor of PCSK9

An emerging target for the lowering of low-density lipoproteins (LDL) is via the inhibition of proprotein convertase subtilisin-kexin type 9 (PCSK9), a naturally occurring factor that limits the body's ability to remove LDL-C from the circulation. Inclisiran is an agent that achieves this inhibition via longacting RNA interference, inhibiting the synthesis of PCSK9. Safety of this agent has been assessed in a phase 1 trial. Healthy volunteers with LDL values of at least 100md/dL were randomly assigned inclisiran or placebo in either single of ascending doses. Side effects associated with inclisiran included cough, headache, diarrhoea and nasopharyngitis. These adverse events plus others associated were all moderate or mild and no serious adverse events were reported. When inclisiran was given at doses of 300mg or more in both single and multiple dose settings both PCSK9 and LDL levels were significantly reduced for a period of at least six months.

Inclisiran has a good safety profile and can effectively lower LDL for some longevity compared to placebo.

Fitzgerald K, White S, Borodovsky A, et al. A Highly Durable RNAi Therapeutic Inhibitor of PCSK9. *NEJM* 2017; 376: 41–51.

### **Evolocumab for coronary disease**

PCSK9 inhibitors have already showed efficacy in reducing LDL-C in patients on statins. A double-blind randomised trial has been conducted to assess if a PCSK9 inhibitor has any efficacy in reducing progression of coronary atherosclerosis in patients on statins. Over a 76-week period patients with coronary disease on statins were randomised to receive

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additional monthly subcutaneous injections of a PCSK9 inhibitor evolocumab (n=484) or placebo (n=484). Reduction in both LDL-C levels and percent atheroma volume (PAV) were used as measurements of efficacy. PAV was measured using serial intravascular ultrasonography imaging. A significant reduction in LDL was found in patients receiving evolocumab. Atheroma volume was also significantly lower in the evolocumab setting compared to placebo.

Patients with angiographic coronary disease currently on statins may benefit with the addition of evolocumab.

Nicholls SJ, Puri R, Anderson T, et al. Effect of Evolocumab on progression of coronary disease in statin-treated patients: The GLAGOV randomized clinical trial. *JAMA* 2016; 316 (22): 2373–2384. DOI: 10.1001/jama.2016.16951

### Infection

### **Mosquito control**

Control of mosquito numbers remains one of the most effective methods for prevention of mosquito-borne diseases. Control using treatments that decrease mosquito numbers is an effective method in theory, yet in practice numbers are hard to control due to the tendency of mosquitoes to breed in inaccessible sites, thereby avoiding treatment reach. One study has looked at the potential of using an insecticide that can be carried around by mosquitoes themselves with the idea that they might carry the treatment to these hard-to-reach breeding sites. Larvicide pyriproxyfen (PPF) was disseminated in a town in central Amazonia, Brazil. To measure efficacy mosquito numbers were measured before and after dissemination. For the juvenile mosquitoes, the researchers observed a decreased catchment of up to 90% compared to before PPF and adult mosquito numbers dropped by around 97%.

The use of mosquito-disseminated PPF may be a useful tool in reducing mosquito numbers with the potential benefit of reducing spread of mosquito-borne diseases.

Abad-Franch F, Zamora-Perea E, Luz SLB. Mosquitodisseminated insecticide for citywide vector control and its potential to block arbovirus epidemics: entomological observations and modeling results from Amazonian Brazil. *PLoS Med* 2017; 14 (1): e1002213. DOI: 10.1371/journal.pmed.1002213

#### **Antiviral therapy for hepatitis C**

An important host factor for the replication and survival of hepatitis C virus (HCV) is miR-122 (a microRNA) and as such it is being investigated as a therapeutic target. A double-blind, placebocontrolled randomised phase 1B study has assessed the safety and tolerability of an miR-122 antagonist, RG-101. HCV infected participants (n=32) were enrolled in one of two cohorts and in a 7:1 ratio randomly assigned either 2 mg/kg RG-101 or placebo; or 4 mg/kg RG-101 or placebo. At four weeks both doses of RG-101 resulted in a decreased viral load and a sustained response was demonstrated in three of the 28 treated participants by 76 weeks. At least one treatment-related side effect was reported by 26 of the 28 participants in both treatment cohorts including fatigue and insomnia. Resistance was associated with relapse on or before week 12 marked by resistance-associated substitutions in the HCV genome.

RG-101 was found to be well tolerated and show efficacy in reducing GCV viral load.

van der Ree MH, de Vree JM, Stelma F, et al. Safety, tolerability, and antiviral effect of RG-101 in patients with chronic hepatitis C: a phase 1B, double-blind, randomised controlled trial. *The Lancet* 2017. DOI: 10.1016/S0140-6736(16)31715-9

#### **Ebola vaccine candidate**

Despite an intense research drive there are still no licensed Ebola virus vaccines. One promising candidate, rVSV-ZEBOV, has been assessed for Ebola prevention in a phase 3 efficacy, ring-vaccination trial in Guinea, west Africa. Contacts of laboratory confirmed Ebola cases were given either a single intra-muscular dose of vaccine immediately after randomisation (n=2119) or a delayed vaccination at 21 days later (n=2041). The primary outcome assessed was laboratory confirmed Ebola at 10 days or more following randomisation. No cases of Ebola occurred at 10 days or more for those immediately vaccinated versus 16 cases among the delayed group. Vaccination in additional non-randomised clusters also produced similar results. Mild adverse events were reported in 53% of the total number of vaccinated individuals and two serious adverse vaccination-associated events, one febrile reaction and one anaphylaxis, were reported.

The results from the Guinea study show that the rVSV-ZEBOV vaccine may offer significant protection against Ebola virus disease and as such it is a promising vaccination candidate.

Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). The Lancet 2016. DOI: 10.1016/S0140-6736(16)32621-6

### **Community-wide helminth control**

Deworming strategies are the main methods for helminth control for children in at-risk populations. These campaigns are often aimed at children rather than community-wide. A meta-analysis and systematic review has investigated if there is any difference in helminth prevalence in children when deworming strategies are implemented at a community-wide level compared to children-directed strategies. The meta-analysis included 38 studies and concluded that strategies that were aimed at a community level significantly reduced both hookworm and Ascaris lumbricoides (giant roundworm) in children compared to school-age children directed strategies. However, no effect was seen for Trich-uris trichuria (whipworm) and significant heterogeneity was found across studies.

The meta-analysis suggests that community-wide deworming strategies are more effective at reducing the child-hood burden of helminth infection compared to childhood-directed methods.

Clarke NE, Clements AC, Doi S, et al. Differential effect of mass deworming and targeted deworming for soil-transmitted helminth control in children: a systematic review and meta-analysis. *The Lancet* 2017; 389: 287–297.

# Mental health

## Problem-based therapy in primary care

Mental illness is common in the population yet it can be ill recognised and treated in resource-poor settings. A Zimbabwe-based study has investigated the use of a lay health worker (LHW) delivered problem-solving based therapy for individuals with common mental disorders in a primary care setting. The randomised trial investigated the use of the primary care based intervention, which consisted of individual problem-based solving therapy given by a trained LHW plus education and continued peer support. Individuals with common mental disorders as defined by locally validated criteria were randomly assigned either the problem-solving therapy given by LHWs (n=286) or standard care enhanced with education (n=287) and followed up for six months. Those in the intervention group reported significantly lower symptom scores compared to the control and reported a significantly lower risk of depressive symptoms (both p<0.001). Individuals suffering with mental illness benefitted

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from LHW-provided problem solving therapy in a primary care based setting demonstrated by improved mental health scores at six months.

Chibanda D, Weiss HA, Verhey R, et al. Effect of a primary care–based psychological intervention on symptoms of common mental disorders in Zimbabwe: A randomized clinical trial. *JAMA* 2016; 316 (24): 2618–2626.

### **Counselling for alcohol problems**

There is often poor access in primary care to appropriate psychological help for those who might benefit. One example is access to intervention for harmful drinkers. A study has assessed the cost and effectiveness of using a brief psychological treatment, Counselling for Alcohol Problems (CAP), that is delivered by lay counsellors to patients with harmful drinking behaviours. The randomised trial compared primary outcomes of remission and mean daily alcohol consumed between CAP with enhanced usual care (EUC) and EUC alone in male participants with harmful drinking behaviours in Goa, India. A total of 36% of 164 participants in the CAP plus EUC group achieved remission versus 26% of 172 in the EUC alone group. Abstinence over the past 14 days was significantly higher in the CAP plus EUC group. For harmful drinkers CAP plus EUC significantly reduced harmful drinking behaviour compared to EUC alone and was considered cost-effective in the study.

Nadkarni A, Weobong B, Weiss HA, et al. Counselling for Alcohol Problems (CAP), a lay counsellor-delivered brief psychological treatment for harmful drinking in men, in primary care in India: a randomised controlled trial. *The Lancet* 2017; 389: 186–195.

## **Diabetes**

#### **Continuous glucose monitoring**

Continuous glucose monitoring (CGM) has shown efficacy in the management of blood glucose for those with type 1 diabetes (T1DM) on insulin treatment. However, many of the studies demonstrating this have involved participants using insulin pumps, whereas the use of insulin injections is far more common in adults with T1DM. A randomised trial in the United States has set out to establish whether this efficacy is repeated for T1DM patients who use insulin injections for glucose management. Haemoglobin A1c (HbA1c) levels were used to assess glucose management in insulininjecting patients randomised to either personal continuous glucose monitoring devices (n=105) or usual care of home

blood glucose monitoring (n=53). At 24 weeks, there was a significant reduction in HbA1c compared to baseline in participants in the CGM group versus the control group. Duration of hypoglycaemic episodes as a secondary outcome was also found to be significantly lower in the CGM group. For T1DM patients who inject insulin, continuous glucose monitoring helps with the management of glycaemic control.

Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections. The DIAMOND randomized clinical trial. *JAMA* 2017; 317 (4): 371–378.

## Screen and treat for type 2 diabetes

To help combat the rising prevalence of type 2 diabetes mellitus (T2DM) 'screen and treat' methods of screening and treating prediabetes are becoming common practice.

A systematic review and metaanalysis has looked at the accuracy of screening and efficacy of interventions in preventing the onset of T2DM. The analysis reviewed 49 screening studies and 50 intervention trials. The review concluded that the use of HbA1c for the detection of prediabetes was neither sensitive nor specific enough for use in this setting. Fasting glucose was not sensitive but it was considered specific for prediabetes detection. The analysis also found that glycaemic abnormalities such as a deviant HbA1c may present in the absence of other abnormal measurements. Analysis of interventions demonstrated that lifestyle changes were effective in delaying progression to T2DM. However, the researchers suggested that the inaccuracy of screening diagnoses may result in incorrect diagnosis and subsequent intervention data may be implicated.

The findings suggest that 'screen and treat' regimes alone are not sufficient to impact the T2DM epidemic.

Barry E, Roberts S, Oke J, et al. Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and metanalysis of screening tests and interventions. *BMJ* 2017; 356: i6538.

### Bihormonal bionic pancreas for type 1 diabetes

A study has investigated the safety and efficacy of using a bihormonal pancreas in an at-home setting in type 1 diabetics. The device regulates automatic subcutaneous release of insulin and glucagon with only the patient's body mass index used to for calibration. Participants (n=43) were

randomly assigned to receive either the bionic pancreas or their usual glycaemic control methods for 11 days, and then switch to the opposite for a further 11 days and were told to participate in their usual daily activities. Mean glucose concentrations were assessed via continuous glucose monitoring. The bionic pancreas resulted in a significantly lower mean glucose concentration compared to the usual control setting. There was also a shorter duration of time spent in hypoglycaemic periods for those when in the bionic pancreas period. Nausea was reported at a higher mean score in the bionic period but there were no serious adverse events associated.

The bihormonal bionic pancreas resulted in superior glycaemic control for type 1 diabetics when in a home setting. El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. *The Lancet* 2017; 389: 369–380.

# Obs & Gyn

## Subclinical hypothyroidism in pregnancy

Fifteen percent (15%) of pregnancies in Europe present with subclinical hypothyroidism, in line with current diagnostic criteria. A retrospective cohort study has looked at the safety of thyroid hormone treatment in pregnant women with subclinical hypothyroidism. Over 5400 pregnant women with untreated thyroid stimulating hormone (TSH) at 2.5-10 mIU/L were included in the study. The primary outcome was pregnancy loss. A total of 843 women were given treatment for their hypothyroidism (mean baseline TSH of 4.8 mIU/L) during their pregnancy, and the remainder of women who weren't given treatment had a mean baseline TSH of 3.3. The study found that there was a significantly lower rate of pregnancy loss in treated women versus the untreated group (p<0.01). However, it was also observed that preterm delivery, gestational diabetes and pre-eclampsia were all at higher odds for women in the treated groups. Subclinical hypothyroidism in pregnancy may benefit from treatment to reduce risk of pregnancy loss; however, other risks require further research.

Maraka S, Mwangi R, McCoy RG, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. *BMJ* 2017; 356: i6865.

### Uterine relaxants for external cephalic version

Breech birth occurs in 4% of pregnancies and can result in complications. External cephalic version (ECV) is a method that involves turning the foetus to a head first position before labour begins. Uterine relaxants are needed for this and often fenoterol is used. However, this class of drug is associated with adverse maternal cardiovascular effects. A randomised trial has compared the efficacy of fenoterol with an oxytocin receptor antagonist that has fewer cardiac side effects, atosiban. Women at 34 plus weeks' gestation with a foetus in breech were given either fenoterol (n=414) or atosiban (n=416) for uterine relaxation prior to ECV. The investigation compared numbers of cephalic presentations 30 minutes after ECV and at delivery. There were no differences in adverse neonatal outcomes between groups. Atosiban resulted in a significantly lower number of cephalic positions 30 minutes after ECV versus fenoterol, but no significant difference was found between cephalic presentations at birth between the groups.

The study concluded with continued support for the use of fenoterol for external cephalic version.

Velzel J, Vlemmix F, Opmeer BC, et al. Atosiban versus fenoterol as a uterine relaxant for external cephalic version; randomised controlled trial, BMJ 2017: 356: i6773

### **Pelvic floor muscle training** for prolapse

There is a known association between pelvic floor muscle exercise and reduced prolapse severity and symptoms. One study has looked at whether pelvic floor exercise intervention can reduce the risk of second prolapse and need for future treatment. The study included women of any age who had experienced prolapse before, but not sought treatment. Participants were randomised to receive either personal pelvic floor physiotherapy sessions plus extra pelvic floor training classes and a DVD for intervention (n=207) or a leaflet for lifestyle advice for those with prolapse (n=207). Participants were assessed for self-reported prolapse symptom scores two years. The study found that the intervention group did result in a statistically significant reduction in prolapse symptoms. However, the researchers considered the reduction in symptoms 'small, but probably important'.

Pelvic floor muscle exercise and training can help with the reduction of secondary prolapse symptoms.

Hagen S, Glazener C, McClurg D, et al. Pelvic floor muscle training for secondary prevention of pelvic organ prolapse (PREVPROL): a multicentre randomised controlled trial. The Lancet 2017: 389:393-402

## Gastroenterology

### Clinical remission in Crohn's disease

Crohn's disease is a chronic inflammatory bowel disease that can be debilitating. One method for alleviating the disease burden is to tackle the inflammatory response involved, one component of which is the janus kinase-1 (JAK-1) pathway. One study has looked at the effect on Crohn's activity using selective inhibition of JAK-1 by the drug filgotinib. The FITZROY randomised phase 2 study compared filgotinib with placebo to assess efficacy in reduction of Crohn's disease activity. Participants were active Crohn's sufferers who were given either filgotinib at 200 mg once a day (n=130) or placebo (n=44) for 10 weeks. At week 10, 47% of the filgotinib patients achieved clinical remission versus 23% in the placebo group (p=0.0077). A further observational period of 10 weeks with participants given either placebo, 100mg or 200mg of the drug based on responder status was performed. Within the total 20 weeks, 9% of filgotinib treated participants versus 3% of placebo receiving participants reported serious adverse effects.

Filgotinib was associated with a significantly higher rate of clinical remission in Crohn's sufferers than placebo. Vermeire S, Schreiber S, Petryka R, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebocontrolled trial. The Lancet 2017; 389: 266-275.

### Prevention of Clostridium difficile recurrence

The most common cause of infectious diarrhoea in hospitalised patients is Clostridium difficile infection. The infection is usually treated with antibiotics; however recurrences following therapy are common. Two double-blind randomised trials have looked at the efficacy of C. difficile directed monoclonal antibody therapies actoxumab and bezlotoxumab that target C. difficile toxins A and B, respectively. Over 2600 adults receiving standard-of-care antibiotics for a C. difficile infection were given either bezlotoxumab, actoxumab plus bezlotoxumab, or placebo and were assessed for recurrence at 12 weeks. Recurrent

infection was significantly lower in the bezlotoxumab alone group versus placebo and in the combined drug group versus placebo. Actoxumab addition did not improve efficacy of treatment. Sustained cure (no recurrence) was highest at 64% for the bezlotoxumab alone group. Safety profiles were similar across all groups. Addition of bezlotoxumab to standard antibiotic intervention for C. difficile infection can help reduce rate of infection recurrence.

Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent Clostridium difficile Infection. NEJM 2017; 376: 305-317.

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