

General

Vitamin D supplementation and bone mineral density

Vitamin D has long been implicated in the prevention of osteoporosis but evidence from a recent meta-analysis disputes this claim, concluding that vitamin D supplementation without calcium co-administration was not preventative for fractures.

A systematic review and meta-analysis conducted in New Zealand assessed the efficacy of vitamin D supplementation on bone mineral density. The primary endpoint was the percentage change in density from baseline measured in five sites.

Six studies found vitamin D supplementation to be significantly beneficial, two showed it to be detrimental, whilst the remaining studies found the results to be insignificant. The only site found to marginally benefit from supplementation was the femoral neck.

The use of vitamin D for osteoporosis prevention without risks for vitamin D deficiency is unsuitable.

Reid I, Bolland M, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet* 2014; 383:146–55.

Sigmoid diverticulitis: a systematic review

Sigmoid diverticulitis is becoming increasingly common but is associated with high levels of mortality and morbidity. However, this rise in prevalence has been accompanied by significant advances in the understanding of the pathophysiology, and natural history resulting in management strategy changes.

In a systematic review, researchers concluded that altered gut motility, increased luminal pressure and disordered microenvironment all contribute to the pathophysiological processes but the natural course is mostly benign if uncomplicated. Surprisingly, evidence suggests that risk of septic peritonitis is reduced rather than increased with each recurrence. Studies have shown that 5–20% of patients managed surgically progress to chronic abdominal pain in contrast to 20–35% of medically managed patients. Of note, antibiotic and fibre treatment is less effective than originally thought, but mesalamine may be beneficial.

Evidence suggests that less aggressive antibiotic and surgical management may be more effective than previously thought.

Morris AM, Regenbogen SE, Hardiman KM, and Hendren S. Sigmoid diverticulitis: a systematic review. *JAMA* 2014; 311: 287–97.

Live kidney donation and end-stage renal disease

Previous research concluded the risk of end-stage renal disease (ESRD) is comparable to that of the general population. However, this may be an underestimation because the control groups used included unscreened, higher risk individuals compared with the donors.

Therefore, a study of 96217 donors was matched to an equal number of healthy non-donors and the risk of ESRD in kidney donors was assessed. The cohort was monitored over a median of 7.6 years for the development of ESRD. The primary outcome was the cumulative incidence and lifetime risk of ESRD.

The estimated risk of ESRD at 15 years after donation was 30.8 per 10000 in the donor group compared with 3.9 per 10000 in the controls, a significant difference. The lifetime risk of ESRD was estimated at 90 per 10000 for donors and 14 per 10000 for healthy nondonors.

Kidney donors have an increased risk of ESRD.

Muzaale AD, Massie AB, Wang M, et al. Risk of end-stage renal disease following live kidney donation. *JAMA* 2014; 311: 579–86.

Surgery

Perinatal outcomes after bariatric surgery

Obesity is a known risk factor for adverse pregnancy and perinatal outcomes. Therefore weight reduction is vital to reduce these risks, which in turn has prompted a ten-fold increase in the number of bariatric surgery procedures in some countries. A population based cohort study in Sweden investigated perinatal outcomes after bariatric surgeries.

Mothers with a history for bariatric surgery (n=2562) were matched to up to five control births. Secondary controls matched the surgery mothers to those that were eligible for surgery. The main outcomes measured preterm birth (<37 weeks) and small gestational age birth.

Post-surgery births were more likely to be preterm (9.7%) than in matched controls (6.1%) (odds ratio (OR), 1.7). A history of bariatric surgery was also associated with increased risk of preterm births. An increased risk for a small for gestational age birth was observed. No differences were noted for stillbirths or

neonatal death.

Women with a history of bariatric surgery are at increased risk of preterm and small for gestational age births.

Roos N, Neovius M, Cnattingius S, et al. Perinatal outcomes after bariatric surgery: nationwide population based matched cohort study. *BMJ* 2013; 347: 6460.

Coronary Revascularisation: CABG or PCI?

Coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) are the main therapeutic options for coronary revascularisation. However, the choice of which modality to use in some patient subgroups remains controversial.

A systematic review of literature aimed to determine the efficacy of each revascularisation technique in patients with unprotected left main disease (ULMD), >50% left main coronary stenosis, multivessel coronary artery disease (CAD), diabetes, and left ventricular dysfunction (LVD).

CABG is recommended in patients with ULMD, multivessel CAD, or LVD if the severity of the disease is complex due to the lower cardiac events associated with CABG. PCI is recommended in patients with less complex coronary disease, or in individuals deemed high surgical risk. Patients with diabetes and multivessel CAD should be recommended CABG. Overall, repeat revascularisation is higher among PCI patients, whereas stroke is more common after CABG.

Both CABG surgery and PCI are reasonable options for patients with advanced CAD but recommendations should consider all factors including the severity of the CAD.

Deb S, Wijeyesundera H, Ko D, et al. Coronary artery bypass graft surgery vs percutaneous interventions in coronary revascularization: A systematic review. *JAMA* 2013; 310: 2086–95.

Adhesion barriers in abdominal surgery

Adhesions are the most common complication following peritoneal surgery causing high levels of morbidity. The gross underestimation of the burden of adhesions burden in thought to be, in part due to the lack of preventative barriers.

A systematic review and meta-analysis evaluating the benefits and harms of four adhesion barriers were studied, including: oxidised regenerated cellulose (ORC), hyaluronate carboxymethylcellulose (HC), icodextrin and polyethylene glycol (PG). The primary outcome measured the incidence of reoperation for adhesive small bowel obstruction.

The HC barrier resulted in a substan-

tial reduction in reoperations for small bowel obstruction (RR, 0.49). However; this was not true for icodextrin where the incidence of reoperation did not differ significantly between Icodextrin patients and the controls (no barrier). No data were found regarding either ORC or PG on reoperation for adhesive small bowel obstruction, but evidence suggests that ORC significantly reduced abdominal adhesions (relative risk (RR), 0.51).

The clinical effects of adhesions can be safely reduced by ORC and HC.

Ten Broek R, Stommel M, Strik C, et al. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. *Lancet* 2014; 383: 48–59.

Treatment of ruptured abdominal aortic aneurysms

Observational studies suggest a lower mortality following endovascular strategies for ruptured abdominal aortic aneurysms (AAA) versus open repair. However, evidence from randomised trials failed to show any survival benefit for endovascular repair.

A multinational randomised trial investigated mortality between endovascular and open repair. Patients with a diagnosis of ruptured AAA were randomised to receive either endovascular repair (n=316) or open repair (n=297). The primary outcome was mortality at 30 days.

Results showed a similar and non-significant difference in mortality between the groups. A total of 35.4% of patients in the endovascular group reached the primary endpoint compared with 37.4% of open repair patients. However, patients receiving endovascular repair were more likely to be discharged directly home. Interestingly, subgroup analysis showed that women benefit significantly more from endovascular repair than men.

Mortality for repair of ruptured AAA is similar between endovascular and open repair.

IMPROVE Trial Investigators. Endovascular or open repair strategy for ruptured abdominal aortic aneurysm: 30 day outcomes from IMPROVE randomised trial. *BMJ* 2014;348:7661.

Five-year follow-up of the first tissue-engineered airway transplant

In 2008, the first completely tissue engineered trachea was transplanted into a patient suffering from malacia with an end-staged left main bronchus. Now with a 5-year follow-up, the results have been published, assessing airway function and the tumorigenic risks of the implanted stem cells.

Since the transplantation, three monthly CT scans and bronchoscopy assessments

have been conducted alongside quality-of-life checks and other tests of function and histology.

By 12 months, despite the tissue-engineered trachea remaining patent and histologically healthy, a progressive cicatricial stenosis of the native trachea developed requiring stenting surgery. Respiratory function and cough reflex remained normal and no evidence of stem-cell teratoma or anti-donor antibodies was found. The quality of life was reported as ‘excellent’ or ‘very good’ and the patient was not hindered in any aspect of activities of daily living.

Early indications of tissue-engineering of the human trachea suggest it is safe and outcomes give promising results.

Gonfiotti A, Jaus M, Barale D, et al. The first tissue-engineered airway transplantation: 5-year follow-up results. *Lancet* 2014; 383: 238–44.

Obs & Gyn

Pelvic floor muscle training for pelvic organ prolapse

It is estimated that 40% of women over 50 years of age have some degree of pelvic organ prolapse. Conservative management often encourages women to perform pelvic floor muscle exercises but evidence showing the benefit of these exercises is minimal.

A multinational trial aimed to assess the effectiveness of pelvic floor exercises in reducing prolapse symptoms. Women with newly diagnosed pelvic prolapse (symptomatic stage I, II or III) were randomised to receive either one-to-one pelvic muscle training programme (intervention group, n=225) or a lifestyle advice leaflet or no muscle training (control, n=222). The primary outcome was change in prolapse symptoms at 12 months.

Results showed that women in the intervention group reported significantly fewer prolapse symptoms at 12 months than those in the control group.

Individualised pelvic floor muscle training programme is effective at reducing prolapse symptoms.

Hagen S, Stark D, Glazener C, et al. Individualised pelvic floor muscle training in women with pelvic organ prolapse (POPPY): a multicentre randomised controlled trial. *Lancet* 2014.

Thrombotic risk during the post-partum period

Increased risk of thrombosis is recognised to occur not only during pregnancy but also during the postpartum period, defined as the 6 weeks post-delivery. However, no evidence exists on the risks of

thrombotic events beyond the first 6 weeks after delivery, therefore a large population study of Californian women aimed to establish the duration of risk.

Of the 1 687 930 women included, 1015 had a thrombotic event (248 cases of stroke, 47 myocardial infarctions, and 720 cases of venous thromboembolism) during the study period. The risk of primary thrombotic events was higher in the 6 weeks postpartum, with 411 events recorded versus 38 for the corresponding period a year later (significant OR, 10.8). A modest but significant increase was observed during the 7–12 weeks post-delivery (95 events versus 44 events a year later; OR 2.2). No significant increase of events was calculated beyond 12 weeks after delivery.

Elevated risk of thrombosis may persist until 12 weeks post-delivery.

Kamel H, Navi B, Sriram N, et al. Risk of a Thrombotic Event after the 6-Week Postpartum Period. *NEJM* 2014. DOI: 10.1056/NEJMoa1311485.

Dextrose gel for neonatal hypoglycaemia treatment

Neonatal hypoglycaemia is common and often affects otherwise healthy babies but without treatment brain damage can occur. Dextrose gel has been proposed as an effective management strategy but little literature exists on assessing the efficacy in neonates. A recent trial studied the value of dextrose gel in reversing hypoglycaemia compared with breastfeeding for at-risk neonates.

Over 2 years, 519 babies at risk of hypoglycaemia (aged 35–42 weeks) were randomised to receive either 40% dextrose gel (200 mg/kg) or placebo. The primary outcome measured treatment failure, (blood glucose concentration of less than 2.6 mmol/L).

A total of 47% of the randomised babies become hypoglycaemic. Results showed that dextrose gel significantly reduced treatment failure when compared with placebo (14% vs 24% respectively; RR 0.57). No serious adverse events were observed.

Treatment with dextrose gel is effective, easily administered and should be considered as first line treatment for management of hypoglycaemia.

Harris D, Weston P, Signal M, Chase J, and Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 382: 2077–83.

CPD Challenge
See page 53 to test yourself on this article

Infection

Serogroup A meningococcal conjugate vaccine

Serogroup A meningococcal polysaccharide-tetanus toxoid conjugate vaccine (PsA-TT) was first granted pre-qualification by the World Health Organization in 2010. Results after a 6-week vaccination programme in Burkino Fasso yielded excellent results and the vaccine now being tested across parts of Africa. A community study in Chad assessed the efficacy of the PsA-TT on meningococcal meningitis during an epidemic.

Approximately 1.8 million people aged between 1 and 29 years were vaccinated with a single dose of PsA-TT across three regions of Chad. The incidence of meningitis was obtained for before and after a vaccination programme.

The incidence of meningitis in the three vaccinated regions was 2.48 per 100 000 in comparison to 43.8 per 100 000 in the non-vaccinated areas. A crude incidence difference of 94% was calculated in addition to an incidence ratio of 0.096, both of which were significant. No reports of serogroup A meningococcal meningitis in the vaccinated regions were made.

PsA-TT is highly effective in preventing serogroup A invasive meningococcal disease.

Daugla D, Gami J, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet* 2014;383:40–7.

Cholera vaccine: 5-year follow-up

An estimated 2.8 million cases and 91 000 deaths from cholera occur every year in endemic countries. In 2009, a bivalent killed whole-cell oral cholera vaccine was licensed, now the 5-year follow-up results have been published.

Participants from a slum area of Kolkata, India were randomly allocated to receive two doses of either modified bivalent killed whole-cell oral cholera vaccine (n=31932) or placebo (n=34968). The primary endpoint was prevention of cholera during 14 days and 1825 days after the second dose.

A total of 69 and 219 recipients of the vaccine group and placebo groups, respectively, developed cholera during the 5 year follow-up. This yielded incidences of 2.2 per 1000 in the vaccine group and 6.3 per 100 in the placebo. Cumulative protective efficacy of the vaccine at 5 years was significant at 65% with no evi-

dence of decline in protection efficacy.

Unlike previous oral cholera vaccines, this vaccine remains effective after 5 years.

Bhattacharya S, Sur D, Ali M. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis* 2013;13:1050–6.

Xpert MTB/RIF testing for tuberculosis

The use of Xpert MTB/RIF testing for tuberculosis (TB) has shown to be more accurate than smear microscopy testing. However, little is known about its efficacy outside the laboratory, its effect on implementing same-day treatment, or TB-related morbidity.

A trial conducted in five southern African countries compared the feasibility, accuracy, and clinical effect of Xpert MTB/RIF testing in primary healthcare facilities. Participants were randomly assigned to receive either the smear microscopy (n=758) or nurse-performed MTB/RIF (n=744). The primary outcome was TB-related morbidity in culture-positive patients.

Results showed that morbidity was non-significant between groups at both 2 and 6 months. Importantly, point-of-care MTB/RIF testing had similar sensitivity but higher specificity than laboratory-based MTB/RIF. More patients from the MTB/RIF group received same-day diagnosis and same-day treatment initiation compared with the microscopy group, although by day 56 the proportion of patients on treatment was similar between the groups.

Xpert MTB/RIF can be accurately administered by nurses in primary care clinics.

Theron G, Zijenah L, Chanda D, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet* 2014;383:424–35.

Oncology

HPV-based screening as prevention for invasive cervical cancer

Incidence of advanced cervical cancer has been shown to be lower in women receiving HPV screening. However, little research has investigated HPV-based screening as an alternative to cytology-based cervical screening for the prevention of invasive cervical cancer.

To assess this, a follow-up study investigated any difference between the incidence of invasive cervical carcinoma

between the two screening methods.

A total of 176 464 women (aged 20–64) were assigned to undergo either HPV-based or cytology-based screening. A rate ratio of 0.60 for invasive cervical carcinomas was calculated. No significant difference between the two groups in the first 30 months was observed but thereafter the rate was significantly lower in the HPV screening. The cumulative incidence of invasive carcinoma was 8.7 per 10⁵ at 5.5 years in the HPV group and 36 per 10⁵ in the cytology group.

HPV gives greater protection against invasive cervical carcinoma.

Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJF, Arbyn M. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* 2014 Feb 14;383(9916):524–32.

Mastectomy for BRCA1 and BRCA2 mutations

Women carrying the BRCA1 or BRCA2 mutations have a lifetime risk of breast cancer of 60–70% and once diagnosed the chances of secondary cancers remains high. Previous research has demonstrated that contralateral (bilateral) mastectomy versus unilateral mastectomy reduce risk of breast cancer, but the effects of contralateral or unilateral mastectomy for BRCA-associated breast cancer has not been quantified.

A longitudinal cohort study consisting of 390 women diagnosed with BRCA1 or BRCA2 breast cancer (stage I or II) managed with contralateral mastectomy or unilateral mastectomy. The primary outcome measured survival between the two groups.

The median follow-up duration was 14.3 years, in which 18 women in the bilateral mastectomy group died versus 61 in the unilateral group. After 20 years, the survival rate was 88% for the contralateral group compared with 66% in those with unilateral mastectomy. Calculations estimated a significant 48% reduction in death from breast cancer with contralateral mastectomy.

BRCA associated breast cancer treated with contralateral mastectomy have an increased survival.

Metcalfe K, Gershman S, Ghadirian P, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. *BMJ* 2014;348:226.

Follow-up strategies after colorectal cancer

Rigorous follow-up regimens after colorectal cancer (CRC) surgery are common practice and but evidence showing the prolonged survival benefit of this has

been described as unconvincing.

A trial consisting of 1202 participants investigated different follow-up regimens on incidence of surgery for CRC recurrence. Regimens consisted of blood carcinoembryonic antigen (CEA) measurements every 3 months for 2 years and then biannually for 3 years; computed tomography (CT) scans of the chest, abdomen, and pelvis were performed biannually for 2 years and then annually for 3 years, or the intensive combination of both. A minimal follow-up group received follow-up if symptoms recurred.

Overall, 5.9% of patients were surgically treated for recurrence. The lowest recurrence rate was 2.3% in the minimal follow-up group. The CEA group recurrence rate was calculated at 6.7%, 8% in the CT group, and 6.6% in the combination group (significant ORs; 3.00, 3.63, and 3.10 respectively).

Intensive follow-up provides no survival advantage.

Primrose J, Perera R, Gray A, et al. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: The facts randomized clinical trial. *JAMA* 2014;311:263–70.

Respiratory

Safety of benzodiazepines and opioids in severe respiratory disease

Both opioids and benzodiazepines are commonly prescribed in very severe respiratory disease but little is known about the safety of these drugs. The primary reason of this study was to establish if the two classes of drugs increased the risk of hospital admission or death in 2249 patients with chronic respiratory failure.

Upon starting long-term oxygen therapy, 24% of the patients used benzodiazepines, where as 23% received opioids. During the follow-up period (5 years), 76% of patients were admitted to hospital where 50% died. Neither drug was associated with increased hospital admissions. However, mortality was increased significantly with the use of benzodiazepines significantly (hazard ratio of 1.21) but only higher doses (above 0.3 defined daily doses per day) of opioids were associated with significant increased mortality (adjusted hazard ratio 1.21).

Neither drugs increased hospital admissions but benzodiazepines and high dose opioids increased mortality.

Ekstrom M, Bornefalk-Hermansson A, Abernethy A,

and Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014;348:445.

Upper-airway stimulation for obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is characterised by recurrent narrowing and closure of the upper airway during sleep. OSA is commonly managed with continuous positive airway pressure (CPAP), an intervention not tolerate by some patients. A recent study assessed the efficacy of the novel technique, upper airway stimulation, for moderate-to-severe OSA.

A multicentre cohort consisting of 126 patients underwent surgical implantation of a stimulation device. The primary outcome measured the change in apnoea events per hour and the oxygen desaturation index (ODI; the number of times per hour whereby the oxygen levels drop by >4% from baseline).

At 12 months, the median decrease in apnoeic events decreased significantly from 29.3 events per hour to 9.0 per hour and the ODI by 78% from 25.4 events per hour to 7.4 events per hour. The rate of serious adverse events from the procedure was less than 2% and measures indicated an improved quality of life.

Upper-airway stimulation reduces OSA severity.

Strollo P, Soose R, Maurer J, et al. Upper-Airway Stimulation for Obstructive Sleep Apnea. *NEJM* 2014;370:139–49.

Air pollution and low birth weight

Ambient air pollution has been linked to restricted foetal growth and in turn adverse respiratory health in childhood. A European cohort study assessed the effects of maternal exposure to low concentrations of ambient air pollution on birthweight.

Data was pooled from 14 studies across Europe giving a sample population of 74 178 women. The primary outcome was low birthweight at term defined as weight <2500g at birth after 37 weeks gestation.

An increase of 5 µg/m³ in PM_{2.5} concentration was associated with an increased risk of low birthweight (significant OR, 1.18). An increased risk was also observed for pregnancy in concentrations lower than the European Union annual PM_{2.5} limit of 25 µg/m³. High traffic density on the nearest street was also associated with low birthweight at term. Results indicate that a reduction of 10 µg/m³ in PM_{2.5} would result in an estimated 22% decrease of low birthweight at term.

Ambient air pollutant exposure during

pregnancy is associated with restricted foetal growth.

Pedersen M, Giorgis-Allemand L, Bernard C, et al. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). *Lancet Resp Med* 2013; 9: 695–704.

Malaria

Detecting artemisinin-resistant *Plasmodium Falciparum*

The discovery of resistance of *P falciparum* in parts of South-East Asia has led to concerns over the spread of resistance across the region and to Africa. Importantly, artemisinin resistance results in lengthening of half-life parasite clearance during treatment. A Cambodian study investigated whether an in-vitro ring-stage assay (RSA) could identify *P falciparum* from patients with slow- or fast-clearing infections.

Parasite samples were obtained from a previous study and novel in-vitro survival assays explored the stage-dependant susceptibility of slow-clearing and fast-clearing parasites to dihydroartemisinin. In 2012, RSA parasite clearance studies measured the ex-vivo responses of parasites from patients with malaria to assess identification of artemisinin-resistance *P falciparum* infections.

In vitro survival rates of parasites from 13 slow-clearing and 13 fast-clearing infections differed significantly when assays were done on 0-3 hour ring-stage parasites (10.88% vs 0.23%) whilst ex-vivo survival rates correlated with in-vivo parasite clearance half-lives.

In-vitro RSA allows for characterisation of artemisinin resistance and ex-vivo RSA can be used for resistance surveillance.

Witkowski B, Amaratunga C, Khim N, et al. Novel phenotypic assays for the detection of artemisinin-resistant *Plasmodium falciparum* malaria in Cambodia: in-vitro and ex-vivo drug-response studies. *Lancet Infect Dis* 2013;13:1043–9.

The logo features a stylized orange sun rising over a dark blue horizon. Below the sun, the word "Africa" is written in a large, white, serif font, and "HEALTH" is written in a smaller, white, sans-serif font. At the bottom, a purple banner contains the text "CPD Challenge" in white, with "See page 53 to test yourself on this article" in smaller white text below it.