

Infection

Vitamin D for respiratory infections

Vitamin D supplementation has been investigated for beneficial potential in reducing risk of acute respiratory tract infection. Supplementation with vitamins D3 or D2 for any duration in randomised studies where acute respiratory tract infection was a primary efficacy outcome were included in a systematic review and meta-analysis. The analysis totalled 25 studies and more than 10 000 participants. Supplementation significantly reduced risk of acute respiratory tract infection in all participants. High protection was seen in patients receiving daily or weekly vitamin D without additional bolus doses. The highest benefit was found in participant groups who were very vitamin D deficient on entry who did not receive bolus doses. Supplementation with vitamin D was found to be safe and protective against acute respiratory tract infection.

Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017; 356 :i6583.

Vaccine for infant gastroenteritis

Worldwide, rotavirus gastroenteritis contributes to 37% of the deaths from diarrhoea in children, the effect of which is largest in sub-Saharan Africa. The efficacy of a potential vaccine in preventing rotavirus infection has been tested in a randomised trial in Niger. Healthy infants (n=3508) were randomised to receive either placebo or a live, oral bovine pentavalent vaccine (BRV-PV) at six, 19 and 14 weeks of age. The primary outcome was laboratory confirmed rotavirus gastroenteritis presenting at least 28 days after the third dose. A total of 31 cases of severe rotavirus presented in infants given the vaccination versus 87 in the placebo group demonstrating a vaccine efficacy of 67%. Safety profiles and death rates were similar between both groups. Three doses of BRV-PV provided increased protection against severe rotavirus gastroenteritis for infants in Niger. The vaccine is easily stored and low-cost, making it a good candidate for vaccine schedules in at-risk and resource-poor populations.

Isanaka S, Guindo O, Langendorf C, et al. Efficacy of a low-cost, heat-stable oral rotavirus vaccine in Niger. *NEJM* 2017; 376: 1121–1130. DOI: 10.1056/NEJMoa1609462

Biannual drug administration for filariasis

Current standard mass drug administration schemes of giving ivermectin and albendazole for lymphatic filariasis, caused by *Wuchereria bancrofti*, are not appropriate in central Africa. Ivermectin can cause severe adverse effects in those co-infected with *Loa loa microfilaraemia*, which is endemic in Central Africa and thus alternative strategies are needed. A three-year community trial of biannual mass administration of albendazole alone was conducted in a village in the Republic of Congo. Individuals aged two and above were offered albendazole every six months and were followed-up for changes in several infection rates between 2012 and 2015. In this time infections with *W bancrofti* and microfilaraemia rates both fell significantly within the community from 17.3% to 4.7% and 5.3% to 0.3%, respectively. After just one year there was no detection of hookworm infection. Rates of eggs expelled per faeces were also found to significantly decrease for *Ascaris lumbricoides* and *Trichuris trichiura*. Biannual mass administration of albendazole alone is an effective measure against lymphatic filariasis in areas co-endemic with loiasis where ivermectin cannot safely be given.

Pion SDS, Chesnais CB, Weil GJ, et al. Effect of 3 years of biannual mass drug administration with albendazole on lymphatic filariasis and soil-transmitted helminth infections: a community-based study in Republic of the Congo. *Lancet Infectious Diseases* 2017; DOI: 10.1016/S1473-3099(17)30175

Obs & Gyn

Ovarian conservation in cervical cancer

Hysterectomy is often accompanied by the removal of one or both ovaries. A retrospective analysis has been conducted to explore any difference in important health outcomes when both ovaries are removed versus conservation of one or both ovaries. The analysis included over 113 000 patients aged 35–45 who had received a hysterectomy for benign conditions, a third of which had bilateral ovarian removal. Researchers included ischaemic heart disease, cancer and all-cause mortality as important health outcomes. Patients with ovarian conservation had a significantly lower risk of hospital admission for both heart disease and cancer-related admissions following hysterectomy compared to those in the bilateral ovarian removal group. All-cause mortality was significantly

higher in the bilateral removal group and there were significantly fewer heart disease-related deaths in the ovarian conservation group. The analysis performed highlights the increased risk of several important health outcomes for women undergoing hysterectomy with bilateral ovarian removal for benign conditions and highlights the importance of balancing this risk of cervical cancer with the health outcomes above. Mytton J, Evison F, Chilton PJ, et al. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. *BMJ* 2017; 356: j372.

HPV vaccine safety in pregnancy

The human papillomavirus (HPV) vaccine is recommended for all girls and women aged nine to 26 years old to prevent viral complications, including cervical cancer. It is not recommended for pregnant women yet many women will have received it inadvertently whilst pregnant. The safety of this vaccine on pregnancy outcomes is not known as pregnant women have not been included in HPV vaccine clinical trials. A cohort study has been conducted to look at several adverse pregnancy outcomes in women who had received quadrivalent HPV vaccine at several stages of gestation, bivalent HPV vaccine was excluded. Vaccinated pregnancies were matched with pregnancies not exposed to the HPV vaccine in thousands of women in Denmark. Matched analyses revealed that there was no significant difference in HPV-vaccinated and non-vaccinated pregnancies for risk of major birth defect, miscarriage, preterm delivery, low-birth weight, and still birth. Quadrivalent HPV vaccine was not associated with significantly higher risks of adverse pregnancy outcomes in this Danish, nationwide study.

Schelle, NM, Pasternak B, Mølgaard-Nielsen D, et al. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. *NEJM* 2017; 376: 1223–1233.

Maternal obesity and cerebral palsy

Maternal obesity is associated with many adverse pregnancy-related outcomes, including preterm delivery and asphyxia, these outcomes alone are associated with increased risk of cerebral palsy.

A study in Sweden has questioned whether there is an increased risk of cerebral palsy in infants of mothers who are overweight or obese at early preg-

nancy, and whether gestational length is significant. Pregnancy body mass index (BMI) was recorded in expectant mothers and over 1.4 million infants in Sweden were subsequently followed-up for an average of eight years. For infants born at full term, there was a significantly increased risk of cerebral palsy associated with high maternal pregnancy BMI. Risk increased as BMI increased with maternal BMI of 40 or greater associated with the highest risk. Of these, 45% could be attributed to asphyxia related mechanisms. However, there was no significant relationship found in infants who were born preterm. Maternal overweight is associated with an increased risk of cerebral palsy in full-term infants, partially mediated through asphyxia-related complications.

Villamor E, Tedroff K, Peterson M, et al. Association between maternal body mass index in early pregnancy and incidence of cerebral palsy. *JAMA* 2017; 317 (9): 925–936. DOI: 10.1001/jama.2017.0945

Cardiovascular

Pneumonia and risk of heart failure

Community-acquired pneumonia (CAP) is a common illness and despite being classed as an acute condition it can have long ranging consequences. There is increasing interest in the link between pneumonia and subsequent cardiovascular effects and one prospective cohort study has investigated this by looking at incidence of heart failure following CAP. The Canadian study included nearly 5000 adults with CAP and no history of heart failure and matched them according to age, sex and treatment setting with adults who had not had CAP or heart failure in a ratio of 1:5. Over an average of 10 years follow-up the incidence of heart failure was nearly 12% in the CAP patient cohort and just over 7% in the control group. The risk of heart failure may be substantially increased following an episode of CAP and as such this should be considered in the patient's post-discharge plans.

Eurich DT, Marrie TJ, Minhas-Sandhu JK, et al. Risk of heart failure after community acquired pneumonia: prospective controlled study with 10 years of follow-up. *BMJ* 2017; 356: j413.

Stress, brain activity and heart disease

The amygdalar region of the brain is associated with the processing of stress and other emotional reactions, and it is well established that emotional stress is

associated with an increased risk of cardiovascular disease. A novel study was set up to assess whether resting activity in the amygdala could be assessed as a predictor for cardiovascular events. The researchers assessed participant's (n=293) perceived stress levels, amygdalar activity (through imaging), arterial inflammation and C-reactive protein (CRP) levels. At an average of four years follow-up, 22 participants had cardiovascular disease events. Amygdalar activity was significantly linked to increased bone marrow activity, arterial inflammation, and risk of cardiovascular events. Perceived stress was also significantly linked with amygdalar activity, arterial inflammation and CRP levels. The study has shown for the first time that cardiovascular outcomes are linked with high amygdalar activity, subsequent to perceived emotional stress, and appear to be mediated via increased bone marrow activity and arterial inflammation.

Tawakol A, Ishai A, Takx RA, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* 2017; 389: 834–845.

Migraine history and perioperative stroke

A fifth of the general public are likely to have experienced migraine. There is some known association between history of migraine and increased risk of ischaemic stroke. A research group has looked at whether there is increased risk of ischaemic stroke in a perioperative setting. This prospective hospital registry study included surgical patients from the Massachusetts General Hospital. The primary outcome was perioperative ischaemic stroke within the 30 days following surgery in patients with and without histories of migraine and migraine plus aura. The patients were also assessed for hospital readmission within 30 days. Of the 124 000 patients included, 8% had history of migraine, 12% of which experienced migraine with aura. Patients with a history of migraine had an odds ratio of 1.75 for risk of stroke versus those without migraine history. The risk was even higher in patients whose migraine history included aura. Readmission rates were also higher (OR 1.31) for patients with migraine.

Patients with a history of migraine may have an increased risk of perioperative ischaemic stroke.

Timm FP, Houle TT, Grabitz SD, et al. Migraine and risk of perioperative ischemic stroke and hospital readmission: hospital based registry study. *BMJ* 2017; 356: i6635.

Anti-coagulants and subdural haematoma risk

There has been a reported increasing incidence of subdural haematoma in the public, the cause of which is not known. A study has set out to investigate if this increase in incidence could be linked to the (increasing) use of anticoagulant agents. The case-control observational study was based in Denmark and included over 10 000 patients aged 20 to 89 years and matched them with over 400 000 controls. Information on subdural haematoma incidence and anticoagulant drug use was collected and analysed. Of the 10 000 subdural haematoma patients, nearly 50% were taking anticoagulant medications. Higher risk of subdural haematoma was associated with any use of low-dose aspirin, clopidogrel, direct oral anticoagulants, and a vitamin K antagonist. The highest risk of subdural haematoma was associated with combined use of vitamin K antagonist and an antiplatelet drug. Data showed there was both an increased prevalence of anticoagulant use among the population and an increased risk of subdural haematoma between the years 2000 and 2015. Researchers associated the increased incidence of haematoma with the increased use of anticoagulant therapies.

Gaist D, Garcia Rodriguez LA, Hellfritsch M, et al. Association of antithrombotic drug use with subdural hematoma risk. *JAMA* 2017; 317 (8): 836–846. DOI: 10.1001/jama.2017.0639

Paediatrics

Increasing survival in premature infants

A study has been conducted to assess the extent to which infants born prematurely and considered 'perivable' have experienced increased survival rates. The researchers looked at survival and neurodevelopmental outcomes for infants born between 22 and 24 weeks gestation and evaluated outcomes at 18 to 22 months of corrected age. The study was carried out with infants born in the United States between three different year groups, 2000–2003, 2004–2007 and finally 2008–2011. Data from over 4000 infants was provided from 11 centres taking part in the study. Survival rates significantly increased from 30% of infants in the earliest year group to 36% in the 2008–2011 cohort. Likewise, there was a significant increase in survival without neurodevelopmental impairment across the earliest and latest

birth cohorts from 16% to 20%. There was no observed difference in infant survival with neurodevelopmental impairment (15% in 2000–2003 and 16% in 2008–2011). Overall, both survival with and without neurodevelopmental impairment increased compared to death between 2000 and 2011 in premature infants considered periviable at birth.

Younge N, Goldstein RF, Bann CM, et al. Survival and Neurodevelopmental outcomes among periviable infants. *NEJM* 2017; 376: 617–628.

Endotracheal tubes versus laryngeal masks in paediatrics

The most common critical incidents occurring in paediatric anaesthesia are perioperative respiratory adverse events (PRAE). Data from children older than one-year-old has already shown that using laryngeal mask airways (LMAs) reduces PRAE incidence compared with endotracheal tubes. As PRAE occurs more often with infants (<1 year old) it is important to know which of these methods might result in a decreased rate of such events. A group in Australia has investigated whether there is any difference in PRAE for infants (<1 year old) with LMA or endotracheal tubes when undergoing minor elective surgery with general anaesthesia. Infants were randomly assigned either LMA (n=85) or endotracheal tube (n=95). PRAE occurred in 53% of infants in the endotracheal group versus 18% in the LMA group. Major PRAE events including laryngospasm and bronchospasm occurred in 19% in the endotracheal group versus only 4% of infants in the LMA group. Infants undergoing elective procedures under general anaesthesia experienced significantly lower rates of major perioperative respiratory adverse events with LMAs than with endotracheal tubes.

Drake-Brockman T, Ramgolam A, Zhang G, et al. The effect of endotracheal tubes versus laryngeal mask airways on perioperative respiratory adverse events in infants: a randomised controlled trial. *Lancet* 2017; 389: 701–708.

Antibiotics for uncomplicated appendicitis

Acute appendicitis is a common paediatric emergency which, historically, has been favourably managed by surgical appendectomy. We now know that uncomplicated acute appendicitis can be treated conservatively with antibiotics in adults with safe and effective results. However, this non-surgical approach of giving primary antibiotics

remains controversial in paediatric cases. A meta-analysis has compiled information from five studies and over 400 paediatric patients assessing safety and efficacy of antibiotic versus appendectomy for acute uncomplicated appendicitis in patients aged five to 15 years. Of the 168 patients who had primary antibiotics there was a 90% success rate. However, when the appendicitis presented with appendicolith (presence of calcium deposit in the appendix) there was a higher failure rate of treatment than with appendectomy. Primary antibiotic therapy may be a feasible and conservative approach to managing uncomplicated appendicitis in paediatric patients when there is no appendicolith.

Huang L, Yin Y, Yang L, et al. Comparison of antibiotic therapy and appendectomy for acute uncomplicated appendicitis in children - A meta-analysis. *JAMA Pediatr* 2017; DOI: 10.1001/jamapediatrics.2017.0057

Neurodevelopmental outcomes with hydrocortisone

Infants born preterm are at an increased risk of bronchopulmonary dysplasia. Therapeutic intervention using dexamethasone resulted in only short-term benefits and caused neurodevelopmental deficits. Subsequently this method was recommended against. Low-dose hydrocortisone therapy is now interesting researchers and its efficacy has been demonstrated previously. Researchers have now investigated the effect of low-dose hydrocortisone therapy on neurological development at two years. Preterm infants across 21 French neonatal units were randomly allocated either low-dose hydrocortisone (n=256) for 10 days or placebo (n=267) and followed-up for an average of 22 months to assess any difference in neurological outcome. No significant difference was found between placebo and low-dose hydrocortisone for neurodevelopmental development. Incidence of cerebral palsy and other major neurological impairments were similar between the two groups. For preterm infants, early administration of low-dose hydrocortisone therapy for prevention of bronchopulmonary dysplasia did not result in a significant difference in adverse neurodevelopmental outcomes compared to placebo.

Baud O, Trousson C, Biran V, et al. Association between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. *JAMA* 2017; 317 (13): 1329–1337.

Gastroenterology

Faecal transplant for ulcerative colitis

The natural gut microbiota plays an important role in both health and disease. There is evidence that gut bacteria are implicated in ulcerative colitis. Faecal transplants have proven an effective therapy for many gastrointestinal illnesses, but its use in ulcerative colitis is not well researched. A double-blind randomised trial has been set up to assess the efficacy of faecal transplants in the management of ulcerative colitis. Patients were randomly allocated to receive either faecal microbiota transplant (intensive-dose and multi-donor) (n=42) or a placebo colonoscopic infusion (n=43). The primary outcome was steroid-free clinical remission and endoscopic response at week eight. Microbial changes were monitored throughout. Primary outcome was achieved in 27% of faecal transplant patients versus 8% with placebo. No difference was observed in adverse outcomes. Gut microbiota diversity increased and persisted following transplantation and specific species were linked with certain outcomes. Intensive-dose, multi-donor faecal transplantation provides significant symptomatic and endoscopic improvement in patients with active ulcerative colitis.

Paramsothy S, Kamm MA, Kaakoush N, et al. Multi-donor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017; 389: 1218–1228.

Transfusion policies for gastrointestinal bleeds

Blood transfusions are a universally accepted management for acute upper gastrointestinal bleeding. However, there is variation and debate among institutions regarding the thresholds for bleeding that must occur before a transfusion is indicated. A meta-analysis and systematic review has compiled information from trials comparing hospital approaches that differ in how restrictive or liberal institutions are in giving transfusions to patients with upper gastrointestinal bleeding. Outcomes including mortality, re-bleeding, ischaemic events and average red blood cell transfusion number were compared between groups considered restrictive and liberal regarding transfusion policy. Nearly 2000 patient records were included from five randomised trials (one of which was unpublished).

The restrictive group was associated with a lower rate of blood transfusion units and also with a significantly lower risk of mortality and re-bleeding events than the liberal transfusion group. No difference was observed for risk of ischaemic events. This study supports the implementation of more restrictive transfusion thresholds for adults with upper gastrointestinal bleeds.

Odutayo A, Desborough M, Trivella M, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. *Lancet Gastro & Hep* 2017; DOI: 10.1016/S2468-1253(17)30054-7

Peptic ulcer disease and fibromyalgia

Fibromyalgia is a complex syndrome and it is often a long time before any diagnosis is made after symptoms present. The syndrome can occur with multiple non-musculoskeletal features including gastrointestinal upset. A cohort study has been conducted to see if there is any correlation between fibromyalgia and incidence of peptic ulcer disease. The cohort study analysed data from over 25 000 patients aged 20 and over, diagnosed with fibromyalgia between 2000 and 2011. These patients were matched with a cohort containing over 100 000 controls without fibromyalgia. None of the patients had a diagnosis of peptic ulcer disease at diagnosis. Peptic ulcer disease was found to have a significantly higher incidence per 1000 person-years in patients with fibromyalgia versus the control group. Those with fibromyalgia were at a 1.40 fold higher risk of peptic ulcer disease compared to the control population. Further analysis eliminated fibromyalgia medications from any link with the higher incidence of ulcer disease. Peptic ulcer disease occurs at a higher rate in those with fibromyalgia.

Wang KA, Wang JC, Lin CL, et al. Association between fibromyalgia syndrome and peptic ulcer disease development. *PLoS ONE* 2017; 12 (4): e0175370. DOI: 10.1371/journal.pone.0175370

Misc

Dementia and heavy traffic

The incidence of major neurodegenerative disorders is increasing and this is largely attributed to the increasing longevity of the population. It is important that we identify modifiable risk factors for these devastating illnesses. A group of researchers have conducted a study based on the growing concern that living near major roads negatively impacts

cognition. Incidence rates for dementia, Parkinson's disease and multiple sclerosis were investigated for association to proximity of major roads. The population-based cohort study included over 6.5 million neurological disease-free adults in Ontario, Canada and assessed their residential postcodes for proximity to major roads and followed-up the participant population between 2001 and 2012 for diagnosis of the above diseases. For dementia, the hazard ratio (HR) for dementia risk increased from HR 1 at 201–300 metres distance to HR 1.07 for less than 50m. No association was found with Parkinson's disease or multiple sclerosis.

Living close to heavy traffic was associated with a higher incidence of dementia in this large population-based cohort.

Chen H, Kwong JC, Copes R, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet* 2017; 389: 718–726.

Antiandrogen therapy in prostate cancer

There is a 30% risk of recurrence for men who have undergone radical prostatectomy for prostate cancer. Additional radiotherapy given to men demonstrating biochemical recurrence (through monitoring of prostate-specific antigen) is beneficial, however there is still risk of recurrence. A double-blind, placebo-controlled trial has investigated if the addition of an antiandrogen therapy might further benefit men in this category and improve overall survival. Eligible patients (n=760) who had undergone prostatectomy and radiotherapy were randomly assigned either the antiandrogen drug bicalutamide or daily placebo for 24 months. After follow-up at 12 years there was a significantly lower incidence of death in the bicalutamide group versus the control (6% vs 13%). Metastases occurred in 14% of those given bicalutamide versus 23% given placebo. Late radiotherapy associated adverse events were similar among both groups. However, there was a significantly higher risk of gynaecomastia in the bicalutamide group (70% vs 11%). Prostatectomy with salvage radiation therapy provides an increased overall survival for men with prostate cancer when complimented with 24 months of antiandrogen therapy.

Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *NEJM* 2017; 376: 417–428.

Prevention of sickle cell pain crises

A common feature of sickle cell disease is the occurrence of pain crises resulting from vaso-occlusion that is exacerbated by cell-cell interactions subsequent to upregulation of adhesion molecule P-selectin. Safety and efficacy of an antibody drug that acts against P-selectin, crizanlizumab, has been assessed in a phase 2, double blind trial. Sickle cell patients (n=198) were randomised to receive either high dose crizanlizumab at 5mg per kg weight or placebo 14 times over a 52-week period. Those who were treated with crizanlizumab experienced a 45% lower average rate of crises over the year period compared to those on placebo. Time to first crisis was significantly longer with crizanlizumab than placebo at four months versus 1.4 months. Crises without complication occurred at a 63% lower rate in the high-dose treatment group compared to placebo but some adverse effects including diarrhoea and vomiting were higher in the treatment group.

Sickle cell patients receiving crizanlizumab experienced a significantly lower rate of pain crises than those given placebo.

Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *NEJM* 2017; 376: 429–439.



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