

Infection

Existing vaccine linked with gonorrhoea incidence

Gonorrhoea is steadily becoming a global public health problem due to the combined effects of increasing antibiotic resistant strains and as-yet unsuccessful vaccine development. The disease is associated with significant morbidity and the development of effective management is well desired. Surveillance data has picked up a potential link between an existing vaccine and incidence of gonorrhoea. A retrospective case-control study conducted using individuals aged 15-30 years in New Zealand showed that exposure to three doses of the outer membrane vesicle meningococcal B vaccine (MeNZB) was associated with a reduced rate of gonorrhoea diagnosis. This is the first time a vaccination has been shown to impart any protection against the infection. Whilst producing differing disease manifestations, there is up to a 90% genetic homology between *Neisseria gonorrhoea* and *Neisseria meningitidis*, for which the vaccine was used against, and each share several equivalent virulence factors. This may provide biological backup for any link between vaccine exposure and decreased incidence of gonorrhoea. These findings encourage further research into the pathogenic factors that might be impacted by the vaccine.

Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet* 2017; 390:1603-1610

Brain imaging in congenital Zika syndrome

Following the 2015 outbreak of Zika virus in Brazil there is a growing population of children born with congenital Zika syndrome, the clinical course of which is not yet known. Early brain CT scans were performed on these children to assess for hydrocephalus. These scans have also demonstrated calcifications particularly present at the cortical-white matter junctions within the brain. One study has used follow up imaging to assess for changes in existing calcifications identified in 37 children with congenital Zika virus. The average time of initial scan was performed at 11 days of age followed up by repeat scan at an

average of 415 days of age. At follow-up, calcifications had diminished in size and number in 34 children. One scan had demonstrated complete resolution of calcifications and no change was seen in two scans. The improved calcification burden did not correlate with improvement of clinical signs. Detection or absence of calcifications may not be a useful tool in the late diagnosis of congenital Zika syndrome.

Petribu N, Aragao M, van der Linden V, et al. Follow-up brain imaging of 37 children with congenital Zika syndrome: case series study. *BMJ* 2017; 359:j4188

Persistence of Ebola virus in semen

Ebola virus is mainly transmitted via direct contact with blood or bodily fluids. With the presence of Ebola virus detected in the semen of men following recovery of Ebola, there has been concern about the risk of sexual transmission. There had been recommendations for Ebola survivors to abstain from sexual intercourse or use a condom for 3 months after recovery but these have been revised and lengthened following report of sexual transmission. A study has looked at semen samples from 220 male survivors of Ebola virus to assess duration of viral load in the semen by measuring Ebola virus RNA. Of this group 27% had positive initial samples. At 4 to 6 months the virus was detected in 62%, 25% with semen obtained at 7 to 9 months and 4% with a specimen taken from 16 to 18 months. Samples taken at 19 or more months were all negative for Ebola virus. The study did not directly evaluate risk of sexual transmission. Ebola virus may be present long-term in the semen of recovering men but declines with time.

Deen GF, Broutet N, Xu W, et al. Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors — Final Report. *NEJM* 2017; 377:1428-1437

Obs & Gyn

Frozen versus fresh embryo transfer

For nonovulatory women with polycystic ovarian syndrome undergoing in vitro fertilisation (IVF), elective use of frozen-embryos has proven to be more successful than fresh-embryo transfer but it is uncertain if the same stands for ovulatory women. A trial involving over 2100 women with regular menses has set out to investigate this.

Participants undergoing their first IVF cycle were randomised to receive either fresh-embryo transfer or cryo-preservation of the embryo followed by frozen embryo-transfer. Between the two groups the live-birth rate outcomes did not differ significantly. There were also no between group differences in rates of implantation, clinical pregnancy, on-going pregnancy or overall pregnancy loss. However, the risk of ovarian hyperstimulation syndrome (OHSS) was significantly lower in the frozen-embryo transfer group. OHSS can result in severe abdominal pain, cause blood clotting in the legs and can even be fatal.

Shi Y, Sun Y, Hao C, et al. Transfer of Fresh versus Frozen Embryos in Ovulatory Women. *NEJM* 2018; 378:126-136

Biomarkers of ovarian reserve in fertility prediction

Biomarkers indicating ovarian reserve are increasingly being promoted as a marker of fertility among women, despite a lack of evidence. A study has investigated if low levels of antimüllerian hormone (AMH), suggesting low ovarian reserve, can indeed act as a useful marker for infertility in women of late reproductive age. The study included 750 women aged 30 to 44 years who had been trying to conceive for 3 months with no history of infertility. Participants were followed up for the outcome of conception achieved by 12 attempted cycles. The study found that women with low AMH levels did not significantly differ in probability of conception outcome from women with normal values at 6 cycles of attempt. Predicted probability of conception was also not significantly different between women with high versus normal levels of follicle stimulating hormone. Inhibin B levels were also found to not be a useful marker for infertility in women. These findings do not support the use of these biomarkers of ovarian reserve to predict fertility in women of late reproductive age.

Steiner AZ, Pritchard D, Stanczyk FZ, et al. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *JAMA*.2017;318(14):1367-1376. doi:10.1001/jama.2017.14588

Breast cancer recurrence following endocrine therapy

Standard adjuvant management of early oestrogen-receptor (ER) positive breast cancer is a five-year course of endocrine therapy. Extending the duration of endocrine therapy does further

reduce risk of recurrence but it can have additional side effects. A meta-analysis has analysed the progress of 63,000 female ER-positive breast cancer patients from 88 trials to assess association of original tumour size and nodal status with risk of recurrence at 20 years. Patients included were cancer free at 5 years when adjuvant endocrine therapy was ended. In the fifteen-year period following adjuvant endocrine therapy distant breast cancer recurrence rates steadily rose and were associated with the original tumour size and nodal status. The risk of recurrence ranged from 13 to 41% according to tumour size, nodal status and tumour grade. The largest risk of recurrence was at 41% in women with large tumours that had spread to at least 4 lymph nodes. This research supports the use of further methods to reduce long term recurrence which may include extended endocrine therapy.

Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *NEJM* 2017; 377:1836-1846.

Surveillance of cervical pre-invasive lesions

Cervical screening allows the early detection and intervention of pre-invasive and invasive lesions and subsequently there has been noticeable reduction in mortality from invasive cervical cancer. Largely, the pre-invasive and benign lesions are well characterised and understood, with clear management guidelines. In the middle of this non-invasive group is the classification known as cervical intraepithelial neoplasia 2 (CIN2) for which the natural course is not well understood. Either side of it sit histological classifications that have well described courses and as a result management protocols with CIN1 a benign diagnosis and CIN3 a true cancerous precursor. A meta-analysis has looked at the progression of CIN2 lesions managed conservatively for over 3 months. Using 36 studies that included over 3100 women, it was found that 50% of CIN2 lesions regressed, 32% persisted and 18% progressed. The authors argue that active surveillance women diagnosed with these lesions is justified, particularly among a young population who are likely to adhere to screening.

Tainio K, Athanasiou A, Tikkinen K et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. *BMJ* 2018; 360 :k499

Duration of lactation and diabetes

Glucose intolerance is fast becoming a global burden. It is important that we identify contributing factors and understand how we can manipulate the mechanisms involved to reduce the burden and the associated morbidity of diabetes. A protective association exists between lactation duration and diabetes. Previous studies have reported a reduced incidence of diabetes of between 3% and 15% per year of lactation. However, these studies have included older women and were based solely on self-reported diagnosis of diabetes. A study has now investigated if this protective link is biochemically supported. Data were taken from over 1,200 women in the Coronary Artery Risk Development in Young Adults (CARDIA) study which includes data spanning 30 years. Duration of lactation was strongly, and independently, associated with a lower incidence of diabetes with most benefit seen at the longest duration measured in the study of 12 or more months. Lactation duration is protective against development of diabetes.

Gunderson EP, Lewis CE, Lin Y, et al. Lactation Duration and Progression to Diabetes in Women Across the Childbearing Years: The 30-Year CARDIA Study. *JAMA Intern Med.* 2018;178(3):328–337. doi:10.1001/jamainternmed.2017.7978

Neurology

Brain structure following space flight

There have been reports of visual impairment and raised intracranial pressure in astronauts on return from space missions but the cause is not known and the effect of microgravity on the brain during space travel has not been extensively studied. An imaging study has now looked at the configuration of the brain following space flight in astronauts using MRI. Imaging was taken on return of astronauts from missions of both long (average 164 days) and short duration (average 13 days), and compared with previous imaging. In 17 of the 18 astronauts who had been on long duration flights the central sulcus of the brain had narrowed. This was seen in 3 of 16 short duration astronauts. Following all long duration missions there was an upward shift of the brain and narrowing of cerebrospi-

nal fluid (CSF) spaces but not following short duration missions. Three of the long duration group had optic-disc oedema on return, and all three had an MRI demonstrating a narrowed central sulcus. The clinical significance of these changes remains unclear.

Roberts DR, Albrecht MH, Collins HR, et al. Effects of spaceflight on astronaut brain structure as indicated on MRI. *NEJM* 2017; 377:1746-1753.

Gene replacement therapy for muscular atrophy

The motor neuron disease ‘spinal muscular atrophy’ (SMA) is a severe childhood monogenic disorder that results in a failure to achieve motor milestones, need for ventilation, or death in young children. It is caused by loss or dysfunction of the gene encoding survival motor neuron 1 (SMN1). A study has looked at if single gene replacement therapy can benefit infants born with this disorder, primarily investigating safety of the technique. Motor milestones in infants who were given a single dose of therapy (n=15) were compared to historical cohorts. At 20-months of age all infants were still alive versus a survival rate of 8% in the historical cohort. Motor milestones, quantified by a scale of motor function, had improved at 3 months compared to a decline in the historical cohort. Results included infants able to sit unassisted, speak and two that could walk independently. A single intravenous infusion of adeno-associated viral vector containing DNA coding for SMN resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts

Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *NEJM* 2017; 377:1713-1722.

Remyelinating therapy in MS

The disease process behind multiple sclerosis (MS) involves an inflammatory, autoimmune demyelination of the nerve cells of the central nervous system (CNS). This leads to dysfunction of neuronal transmission and the resultant symptoms of MS, including visual nerve dysfunction. Currently therapies target the inflammatory and immune mediated damage yet there are no effective treatments that address re-myelination. A double-blind randomised study has assessed safety and efficacy of using clemastine fumarate, an over the counter antihistamine that has been shown to stimulate the

production of CNS myelinating cells. Participants were patients (n=50) who have been diagnosed with relapsing MS for less than 15 years. The primary outcome was assessing change in visual nerve transmission. By the end of the study, clemastine fumarate treatment had significantly reduced latency delay nerve transmission in eyes. No serious adverse events were reported but treatment was associated with fatigue. This is the first controlled study to demonstrate myelin repair in those with chronic demyelinating MS, even after prolonged damage.

Green AJ, Gelfand JM, Cree BA, et al. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. *Lancet* 2017; 390: 2481-2489.

Nerve grafting for spastic limb paralysis

Spastic limb paralysis caused by stroke, brain injury or a cerebral palsy is a long-term disability. Spastic posture can provoke major impairment to activities of daily living such as hygiene and dressing, as well as causing pain. A study has investigated if grafting of the contralateral C7 nerve (from the unaffected side) can restore some function in patients. Patients with unilateral arm paralysis (n=36) present for more than 5 years were randomised (1:1) to either undergo C7 nerve transfer plus rehabilitation, or rehabilitation alone. Any improvement was measured using a scoring scale and primary outcome was improvement on this scale from baseline at 12 months. The surgical grafting cohort had a significantly higher mean improvement than the rehabilitation alone group ($p < 0.001$) and imaging techniques supported success of nerve connectivity. There was no reduction in power, tactile threshold or sensation in the hand of the donor side. Grafting of C7 resulted in a reduction in spasticity and improvement in function when combined with rehabilitation versus rehabilitation alone.

Zheng MX, Hua XY, Feng JT, et al. Trial of contralateral Seventh Cervical Nerve Transfer for Spastic Arm Paralysis. *NEJM* 2018. 378:22-34

Paediatrics

Neuroprotection for preterm infants

Preterm birth increases the risk of both death within the first week of life and cerebral palsy. Effective therapies to re-

duce the risk of adverse neonatal neurological outcomes are well needed. Magnesium sulphate may reduce the risk of such adverse outcomes when given to pregnant women at risk of preterm birth. Researchers have compiled data from five randomised trials including data on over 6,100 preterm (<37 weeks' gestation) infants whose at-risk mothers were given magnesium sulphate or control treatment prior to preterm birth. Antenatal magnesium sulphate given to women at risk of preterm birth was found to reduce the risk of infant death or cerebral palsy in infants born preterm. These benefits were seen regardless of the reason for risk of preterm birth. This highlights a potential strategy for combating the burden of death and cerebral palsy in babies born prematurely that is both inexpensive and effective.

Crowther CA, Middleton PF, Voysey M, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis. *PLoS Med* 2017; 14(10): e1002398. <https://doi.org/10.1371/journal.pmed.1002398>

First trimester weight gain associated with birth weight

Gestational weight gain partly determines infant birth weight but we do not know if the chronology of maternal weight gain during pregnancy is important and previous studies have provided conflicting data on this. A preconception cohort study in China has set out to evaluate the influence of pregravid weight and weight gain throughout pregnancy on infant birth weight. The study included over one thousand newly married women who underwent weight measurements starting at an average of 19 weeks prior to pregnancy followed by measurements at 10 gestational intervals. Pregravid weight was found to be strongly associated with infant birth weight. However, among the 10 gestational intervals, only the weight gain up to 18 weeks was associated with infant birth weight. For pregravid to 14 weeks, birthweight was associated with 14 g per kilogram of maternal weight gain and for 14-18 weeks the association was 26 g per kilogram of maternal weight gain. Understanding that early weight gain is influential in infant birth weight may help provide a critical window for interventions to help influence infant birth weight.

Retnakaran R, Wen SW, Tan H et al. Association of Timing of Weight Gain in Pregnancy With Infant Birth Weight. *JAMA Pediatr*.

Long-term consequences of childhood kidney disease

Early intervention for those at risk may help reduce the global burden of chronic kidney disease and end-stage renal disease (ESRD). Childhood kidney disease can progress to a chronic disease whilst still in childhood and we know that this group can go on to develop ESRD. However, there is a population of children with kidney disease who go into adolescence disease-free. Data on the long-term renal health of this healthy adolescent population has previously been unclear. A historical cohort study of Israeli adolescents included data taken from between 1967 to 1997. Childhood kidney disease included congenital abnormalities, pyelonephritis and glomerular disease. At adolescence, all children included in the study had normal renal function and no hypertension. Adults with normal renal function in teenage years on a background of childhood kidney disease had a significantly increased risk of ESRD, suggesting long term implication of childhood renal disease. This highlights a group who could benefit from early identification and intervention.

Calderon-Margalit R, Golan E, Twig G, et al. History of Childhood Kidney Disease and Risk of Adult End-Stage Renal Disease. *NEJM* 2018; 378:428-438 DOI: 10.1056/NEJMoa1700993

Miscellaneous

Health benefits of coffee

Coffee is one of the most widely consumed beverages worldwide. As such, it makes sense that we understand what, if any, health impacts its consumption has. A review has looked at over 200 meta-analyses of observational research and 17 analyses of interventional research where health outcomes associated with coffee consumption were interpreted. It was found that coffee consumption was more often linked with benefit to consumers than harm. For several outcomes, including overall cause mortality and cardiovascular mortality, consumption of three to four cups of coffee a day versus none was associated with a greater reduction in risk. High coffee consumption was associated with an 18% lower risk of incident cancer than with low coffee

consumption. Coffee drinkers were also found to benefit from a lower risk of several specific cancers, neurological, metabolic and liver conditions. However, high coffee consumption was found to be associated with adverse birth outcomes including preterm birth in pregnant women. Coffee drinking was also associated with risk of fracture in women.

Poole R, Kennedy OJ, Roderick P, et al. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ* 2017; 359 :j5024

Ultra-processed foods and cancer risk

Lifestyle habits have a major influence over the development of cancers. A study has looked at the impact of processed food intake on risk of overall, breast, prostate and colorectal cancers. Food items were categorised according to their degree of processing by the NOVA classification. Ultra-processed foods may contain high levels of fat, sugar and salt with a lower density of nutrients. They may also contain controversial additives and be contained in packaging that contains carcinogenic material. The study found that ultra-processed food intake was associated with an overall higher risk of cancer. Several surveys have found that this group of foods may contribute to between 25% and 50% of total daily energy intake. Even a 10% increase in the proportion of ultra-processed foods in an individual's diet was associated with an increased risk of greater than 10% for overall and breast cancers. These are modifiable risk factors and by identifying them and reducing our involvement with them we can reduce our risk of several cancers.

Fiolet T, Srour B, Sellem L, al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. *BMJ*2018; 360 :k322

Oral capsule delivered faecal microbiota

Clostridium difficile infection (CDI) is the major cause of hospital acquired infectious diarrhoea. Recurrent CDI (RCDI) has been shown to be effectively reduced with faecal microbiota transplantation (FMT) with an efficacy of between 60-90% following a single treatment. Previous studies have already shown that frozen-and-thawed FMT is non-inferior to fresh FMT against RCDI. A team in the Canada have investigated if the route of delivery has any consequence

on efficacy in a non-inferiority trial. Participants were randomly assigned to receive FMT either by oral capsule or by colonoscopy. A follow up at 12 weeks post the single-dose treatment revealed that 96% of participants in each group were recurrence free. Participants significantly preferred the oral capsule delivery and the risk of minor adverse events was lower at 5% with capsule versus 12% with colonoscopy. Faecal microbiota transplantation delivered by oral capsule is non-inferior to colonoscopy and may be an attractive alternative to colonoscopy delivered methods in the treatment of recurrent *Clostridium difficile* infection.

Kao D, Roach B, Silva M, Effect of Oral Capsule–vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. *JAMA*. 2017;318(20):1985–1993. doi:10.1001/jama.2017.17077

Cardiopulmonary responses to walking in pollution

Air pollution is a major environmental health risk. We know that long term exposure to pollutants can decrease lung function in older individuals and those with chronic obstructive pulmonary disorder (COPD). In addition, shorter term exposure to pollution has been associated with increased mortality in ischaemic heart disease (IHD) and COPD. Walking has been shown to result in beneficial cardiorespiratory effects. A study has compared outcomes of healthy volunteers and volunteers with COPD or ischaemic heart disease aged 60 and older walking on either heavily polluted streets or urban green space. The aim was to assess the effects on respiratory and cardiovascular responses to walking down a busy street that is high in pollution versus a traffic free area. In all participant groups walking in the green low-pollution environment led to an increase in lung function. These positive responses were negated by walking in the high pollution area. Short-term exposure to traffic pollution prevents the beneficial cardiopulmonary effects of walking in people with COPD, IHD and those free from cardiopulmonary disease.

Sinharay R, Gong J, Barratt B et al. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. *The Lancet* 2018; 391;339 - 349



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