

Vascular

Sex differences in myocardial infarction

It is well recognised that the risk of cardiovascular disease is greater in men than in women. A group of researchers have investigated if sex differences in risk factors for myocardial infarction (MI) exist and if these vary with age. This prospective population based study used data from the UK Biobank on over 471,000 participants with no history of cardiovascular disease at point of entry. As expected, incidence of MI was found to be much higher in men than women (incidence per 10,000 person years 7.76 versus 24.35 in women and men, respectively). Incidence of MI in both men and women was associated with high blood pressure, smoking intensity, body mass index and diabetes but these results attenuated with age. However, some of these risk factors were more strongly associated with MI in women compared to men. With increasing age, the effect of these risk factors waned but the relative higher risk in women remained. Researchers argue that incidence of MI in women may catch up to that of men with time and increasing prevalence of lifestyle risk factors.

Millett E, Peters S, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. *BMJ* 2018; 363 :k4247

Dairy intake on cardiovascular outcomes

Whole-fat dairy products are often advised against due to a presumed adverse effect on blood lipids and cardiovascular health, however, evidence for this is scarce. A large multinational cohort study has assessed the associations between intake of total dairy and specific types of dairy with mortality and major cardiovascular disease. Country-specific validated food frequency questionnaires were used across 21 countries and five continents, resulting in over 136,000 individual's responses. At nine years follow-up, higher intakes of total dairy, corresponding to > 2 servings per day, were associated with lower risk of cardiovascular and non-cardiovascular mortality, cardiovascular disease and stroke compared to no dairy intake. There was no link found with myocardial infarction. Higher intakes of milk and yoghurt (> 1 serving versus no intake)

were associated with lower risk of the composite outcome but no association was found with cheese. Butter intake was reported as generally low and no significant associations were elicited. Dairy consumption was associated with a lower risk of mortality and major cardiovascular events in a diverse cohort.

Dehghan M, Mente A, Rangarajan S, et al. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* 2018; 392:2288-297

Heart failure with preserved ejection fraction

Exercise tolerance is a major burden for patients who have heart failure with preserved ejection fraction (HFpEF) and currently there are few medical strategies found to help. Some evidence suggests that impairments in nitric oxide availability may play a part in the pathophysiology of HFpEF. A study has investigated if inhaled nitrite might improve exercise capacity in HFpEF. The randomised trial compared exercise capacity in participants (n=105) by measuring peak oxygen consumption (mL/kg/min) in participants with HFpEF. Participants were randomised to receive either inhaled organic nitrite or placebo for 4 weeks followed by a washout period and then transition to the other arm of the study. There was no significant difference in the mean peak oxygen consumption between the nitrite or placebo phases of the trial. Additionally, no significant difference was observed concerning daily activity levels between the two treatment phases. The use of inhaled nitrites did not result in improved exercise capacity for patients with heart failure with preserved ejection fraction.

Borlaug BA, Anstrom KJ, Lewis GD, et al. Effect of Inorganic Nitrite vs Placebo on Exercise Capacity Among Patients With Heart Failure With Preserved Ejection Fraction: The INDIE-HFpEF Randomized Clinical Trial. *JAMA*. 2018;320(17):1764-1773. doi:10.1001/jama.2018.14852

Paediatrics

Childhood trauma exposure

Exposure to trauma in childhood is common and is associated with negative outcomes during childhood. By the age of 16 more than 60% of children are exposed to trauma and 30% have been exposed to multiple events. A population-based cohort study has investigated if there is an associa-

tion between cumulative childhood trauma exposure and adult psychiatric and functional outcomes. A sample of participants were assessed for lifetime trauma exposure with structured Child and Adolescent Psychiatric Assessment interviews up to 8 times during childhood (aged 9-16 years). Participants were then followed up 4 times in adulthood at ages 19, 21, 25 and 30 years. At age 16, cumulative childhood trauma exposure was associated with higher rates of adult psychiatric disorders and poor functional outcomes, including failure to hold a job and social isolation. When adjusting for other childhood risk factors, including psychiatric function and family adversities, trauma exposure continued to be associated with adverse outcomes.

Copeland WE, Shanahan L, Hinesley J, et al. Association of Childhood Trauma Exposure With Adult Psychiatric Disorders and Functional Outcomes. *JAMA Netw Open*. 2018;1(7):e184493. doi:10.1001/jamanetworkopen.2018.4493

Humanitarian cardiac surgery

Most of the funds from international public health organisations and charitable corporations are channelled towards global health interventions that are considered highly cost-effective. Examples include infectious disease prevention and improvements in maternal and child mortality. However, surgical interventions are largely absent from the global health conversation. Humanitarian paediatric cardiac surgery is underfunded and one group have set out to determine its cost-effectiveness. The study determined the cost-effectiveness of multiple 2-week-long humanitarian paediatric cardiac surgery programme trips to various low- and middle-income countries (LMICs). During 2015, over 420 paediatric patients were served in 10 LMICs with an overall cost of \$3,210,873. Cost-effectiveness was considered \$171 per disability-adjusted life-year (DALY) that was averted. Each survivor (n=390 of 424) potentially gained an average of 40 DALYs averted, 3.5 years of schooling and \$159,533 in gross national income per capita during their extended life. The study concluded that humanitarian paediatric cardiac surgery in LMICs is highly cost-effective and may benefit from being promoted on the global humanitarian platform.

Cardarelli M, Vaikunth S, Mills K, et al. Cost-effectiveness of Humanitarian Pediatric Cardiac Surgery Programs in Low- and Middle-Income Countries. *JAMA Netw Open*. 2018;1(7):e184707. doi:10.1001/jamanetworkopen.2018.4707

School enrolment and ADHD

Within a single school year group, younger children are more likely to be diagnosed with attention deficit hyperactivity disorder (ADHD). The reason behind this may be due to the age variation in behaviour that is seen across a year group, with younger children having behaviour attributed to ADHD when it may instead be due to the comparative younger age of the child. Many schools have a September 1st cut-off for year entry and so children in one year group may have a year in age between them. Data taken from an insurance registry in the United States revealed that children born in August, therefore young for their school year, were more likely to be diagnosed with ADHD than those born just one month after in September but placed as the oldest in their school year. These differences were not seen across different adjacent month pairings, nor was it seen in states that did not adopt the September 1st cut off.

Layton T, Barnett M, Tanner R, et al. Attention deficit-hyperactivity disorder and month of school enrolment. *NEJM* 2018;379:2122-2130

Platelet transfusion thresholds in preterm infants

Preterm infants with low platelet counts are commonly given prophylactic platelet transfusions. There is wide variation among institutions regarding their threshold platelet values for giving prophylactic transfusions. A multicentre, randomised trial has compared outcomes for two different thresholds of platelet count. Infants born at less than 34 weeks with severe thrombocytopenia were randomised to receive platelet transfusions at platelet counts of either 50,000 per cubic millimetre (high-threshold n=328) or 25,000 per cubic millimetre (low-threshold n=331). The primary outcomes were death or new major bleed within 28 days. In the high threshold group 90% of infants had at least one transfusion compared with 53% of the low-threshold group. New major bleed or death occurred in 26% of the high-threshold group versus 19% of the low threshold group. Among preterm infants with severe thrombocytopenia, those assigned to receive platelet transfusions at higher thresholds of platelet count had worse outcomes than those assigned to have transfusions at lower, more restrictive, platelet counts.

Curley A, Stanworth S, Willoughby K, et al. Randomised trial of platelet transfusion thresholds in neonates. *NEJM* 2018; DOI: 10.1056/NEJMoa1807320

Respiratory

Smoked and vaporised cannabis

As cannabis smoking and vaporising is becoming legalised and a commercial commodity in many places worldwide it is important that we understand the effects of its use in a controlled setting. This has been investigated in healthy adults who infrequently use cannabis. Participants (n=17) were given cannabis, in relatively low concentrations, to vaporise and smoke in an outpatient setting. A dose of 25 mg of the active component of cannabis produced significant drug effects, increased incidence of adverse effects and caused a pronounced cognitive and psychomotor impairment compared with a vaporised placebo. A dose of 10 mg produced modest cognitive impairments. Vaporised cannabis resulted in stronger drug effects and higher peak concentrations of the active component in the blood, compared with equal doses of smoked cannabis. Heart rate and blood concentrations peaked within 30 minutes and returned to baseline within 4 hours. Subjective cognitive impairment persisted for up to 6 hours. Significant drug effects can occur at relatively low concentrations in infrequent cannabis users and this should be considered in the regulation of its retail products.

Spindle TR, Cone EJ, Schlienz NJ, et al. Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis: A Crossover Trial. *JAMA Netw Open.* 2018;1(7):e184841. doi:10.1001/jamanetworkopen.2018.4841

Oxygen therapy in acute respiratory failure

High flow nasal oxygen therapy is increasingly being used for acute hypoxemic respiratory failure (AHRF). Immunocompromised patients with AHRF are treated in an intensive care setting and suffer poor outcomes. They tend to be more severely hypoxemic and so improving oxygen saturations is crucial for this group and avoiding invasive ventilation is a major treatment goal. Whether high flow therapy reduces mortality in immunocompromised patients with AHRF is uncertain. A randomised trial recruited immunocompromised patients with AHRF (n=776) across 32 intensive care units (ICU) in France. Patients were randomised to receive either continuous high-flow oxygen therapy or standard oxygen therapy. There was no differ-

ence in mortality between the groups at 28 days, neither did intubation rates or length of ICU stay differ. Additionally, there was no difference in subjective dyspnoea and comfort found between the groups. Immunocompromised patients with acute respiratory failure have similar outcomes when given either high flow oxygen therapy or standard oxygen therapy.

Azoulay E, Lemiale V, Mokart D, et al. Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure The HIGH Randomized Clinical Trial. *JAMA.* 2018;320(20):2099-2107. doi:10.1001/jama.2018.14282

Indwelling pleural catheter draining

Malignant pleural effusions are often managed with indwelling pleural catheters to help drain the effusion. The optimal regimen of draining these indwelling catheters is debated. The options are aggressive drainage, performed daily, or drainage only when the patient is symptomatic. In the AMPLE-2 study, patients with symptomatic malignant pleural effusions from 11 centres spanning Australia, New Zealand, Hong Kong and Malaysia were randomised to receive either daily (n=43) or symptom-guided (n=44) drainage for 60 days. The study found no differences between aggressive and symptom-guided indwelling pleural catheter drainage regimens for mean daily breathlessness scores.

Quality of life measures were better in the aggressive drainage group and spontaneous pleurodesis occurred at higher rates in the aggressive group. There were no differences in pain scores, total days in hospital or mortality between the two groups. Daily indwelling catheter drainage may promote better quality of life than symptomatic pleural drainage in malignant pleural effusions managed with an indwelling pleural catheter.

Muruganandan S, Azzopardi M, Fitzgerald D, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. *NEJM* 2018; 6:671680

Obs & Gyn

Caesarean delivery and early childhood weight

The use of caesarean section at delivery continues to increase. Whilst it can be a life-saving procedure for both mother and infant, there are both immediate and long-term complications. The use of

elective caesarean has triggered many questions as to the long term implications of what may be considered an unnecessary medical procedure for some. We know that infants born from caesarean delivery (CD) have been linked to increased rates of obesity in childhood and one group have now questioned if there is a difference in the risk between elective and emergency caesareans. This cohort study looked at the 12-month body mass index-for-age of infants born from either emergency or elective procedures, taken from Growing Up in Singapore Toward Healthy Outcomes (GUSTO) database. Infants born from elective CD were significantly associated with risk of overweight at age 12 months whereas no significant association was found with those born from emergency CD. The authors argue that parents should be educated on these potential long term metabolic outcomes when deciding choice of elective delivery.

Cai M, Loy SL, Tan KH, et al. Association of Elective and Emergency Caesarean Delivery With Early Childhood Overweight at 12 Months of Age. *JAMA Netw Open*. 2018;1(7):e185025. doi:10.1001/jamanetworkopen.2018.5025

Screening and treating bacterial vaginosis

Bacterial vaginosis (BV) can double the risk of pre-term birth. Management with antibiotics can reduce poor outcomes, including preterm birth. A study has investigated whether treating bacterial vaginosis can decrease late miscarriage or spontaneous very preterm birth. The study was conducted across 40 French centres and included over 5,000 women, at gestation < 14 weeks, with bacterial vaginosis on screening. Participants considered low-risk pregnancies were randomised in 3 groups to receive either single-or triple course 300 mg clindamycin twice-daily for 4 days, or placebo. High risk pregnancies were randomised for either single or triple course clindamycin. There was no significant difference in outcomes in either the low-risk or high risk groups. Clindamycin was associated with more adverse effects, including diarrhoea and abdominal pain, compared to placebo. Systematic screening and subsequent treatment for bacterial vaginosis in women with low-risk pregnancies shows no evidence of risk reduction of late miscarriage or spontaneous very preterm birth. The authors suggest reconsidering the use of antibiotics for preventing preterm birth in an asymptomatic patient population.

Subtil D, Brabant G, Tilloy E, et al. Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial. *Lancet* 2018; 392:2171-2179.

Cervical screening self-sampling

Cervical screening has considerably reduced rates of cervical cancer. However, there is an inconsistency in access to screening and where these gaps exist, cervical cancer remains a burden. A meta-analysis has investigated whether self-sampling kits, which are then sent off for clinical testing, could be as sensitive as clinically-provided samples at accurately testing for high-risk human papillomavirus (hrHPV) when then verified by colposcopy or biopsy. The aim was to see if under-screened women could be reached via a more accessible means of testing. Firstly, the analysis found that self-sample for hrHPV and clinician samples were similarly accurate when assays were based on validated polymerase chain reaction but not signal amplification. Secondly, directly sending self-sample kits to women's addresses generated greater response rates than sending out invitation letters. Opt-in strategies where women had to request self-sample kits were not more effective than invitation letters. Participation rates in under-screened communities were >75% where direct offer of self-sampling devices was available. Offering self-sample kits for cervical screening may help participation rates in under-screened communities.

Arbyn M, Smith SB, Temin S, et al. Detecting cervical precancer and reaching underscreened women by using HPV testing on self-samples: updated meta-analyses *BMJ* 2018; 363 :k4823

Smoking cessation and the menopause

Both cigarette smoking and early menopause are associated with increased risk of chronic disease including cardiovascular disease and osteoporosis. We know that current female smokers are at an increased risk of an early (age 40-44 years) and premature (age <40 years) menopause but information on risk of early menopause in previous smokers is unclear. Researchers pooled data from 17 observational studies and looked at smoking behaviours including status, intensity, duration, pack-years, age started and years since quitting and analysed this information with the individuals age at natural menopause. Former smokers were found to have a 15% higher risk of premature and early menopause compared with never

smokers. This result was much lower compared to current smokers who were found to have double the risk compared to never smokers. Smokers who had quit for more than 10 years had a similar risk to never smokers. Early smoking cessation can help reduce risk of smoking-associated early menopause and may also reduce the increased risk of chronic disease associated with both smoking and early menopause.

Zhu D, Chung H-F, Pandeya N, et al. Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies. *PLoS Med* 2018; 15(11): e1002704.

Pre-eclampsia linked to vascular dementia

Pre-eclampsia during pregnancy can have morbid outcomes and may also influence health of women much later on. Women who have experienced pre-eclampsia during pregnancy are at increased risk of hypertension, cardiovascular disease and diabetes. It is thought that these diseases share a similar pathophysiology. Now scientists have investigated if there is a link between pre-eclampsia and dementia. A register based cohort study included data from over 1,000,000 women in Denmark. Women with a history of pre-eclampsia were found to have more than three times an increased risk of vascular dementia, particularly late-onset, compared to women who had never experienced pre-eclampsia. Adjustment for vascular dementia risk factors (diabetes, hypertension and cardiovascular disease) had only moderately changed the risks scores. Other dementias including Alzheimer's disease had only modest associations with pre-eclampsia. Pre-eclampsia and vascular dementia may be independently associated and possibly share a common disease pathway. Researchers suggest eliciting histories of pre-eclampsia in women to help identify those who may benefit from early clinical intervention.

Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. *BMJ* 2018; 363 :k4109

Misc

Single corticosteroid injection for mild carpal tunnel

Carpal tunnel syndrome (CTS) is a nerve disturbance resulting in discomfort and disruption in activities of daily living.

Mild CTS is managed with either supportive splints or corticosteroid injections, the aim of which is to improve hand function and reduce symptoms. Surgery is only considered in severe and refractory cases. A study has now been performed working under the impression that the comparative effectiveness of the two more conservative management strategies has not been evaluated in primary care. The randomised, open-label, study included participants aged 18 and over who had a minimum of a 6 week history of mild or moderate CTS. Participants (n=234) were randomly assigned to receive either a single injection of 20mg methylprednisolone acetate or a night-resting splint to be worn for 6 weeks. The Boston Carpal Tunnel Questionnaire (BCTQ) was used to assess symptom burden. At the end of 6 weeks the group who received the single dose of steroid at the beginning experienced a significant improvement in BCTQ score compared to the splint group.

Chesterton L, Blagojevic-Bucknall M, Burton C. The clinical and cost-effectiveness of corticosteroid injection versus night splints for carpal tunnel syndrome (INSTINCTS trial): an open-label, parallel group, randomised controlled trial. *Lancet* 2018; 392:1423-1433

Nurse-led care for gout

Gout is a painful condition caused by build-up of urate in the joints. It can be managed medically given the access to resources. In the UK, only 40% of patients receive urate-lowering therapies and those that do often miss out on dose titration that would allow target serum urate concentrations. A group have investigated if the use of nurse-led management for gout may result in different outcomes than when it is traditionally managed within primary care by general practitioners (GPs). Research nurses were trained in best management of gout and participants who had a gout flare within the previous 12 months were randomly assigned to receive either nurse-led care from these trained nurses (n=255), or continued GP-led care (n=262). The primary outcome was percentage of patients achieving a serum urate concentration below 360 µmol/L at 2 years. A significantly higher number of patients receiving the nurse-led care achieved the primary outcome compared to those receiving usual care. The use of nurse-led gout management was considered both efficacious and cost-effective compared to usual care.

Doherty M, Jenkins W, Richards H, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a

treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *Lancet* 2018; 392: 1403-1412

Incretin drugs and cholangiocarcinoma

Cholangiocarcinoma is a rare but fatal cancer. Some evidence suggests that the incretin system may be involved in the development of cholangiocarcinoma and this may implicate incretin-based drugs. Such drugs include dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor antagonists, used in the management of type 2 diabetes. A population based cohort study has investigated if there is an association between these drugs and an increased risk of cholangiocarcinoma. The study included over 150,000 adults newly treated with antidiabetic drugs. At 615,000 person years follow-up, 105 incidents of cholangiocarcinoma had been recorded. Use of DPP-4 inhibitors was associated with an increased hazard of cholangiocarcinoma. GLP-1 receptor agonists were associated with increased hazard but with a wide confidence interval. Both drug groups had increased reporting odds ratios for cholangiocarcinoma versus sulphonylureas and thiazolidinediones (also used in type 2 diabetes). Risk of cholangiocarcinoma in type 2 diabetics may be increased by using DPP-4 inhibitors, and possibly GLP-1 receptor agonists.

Abrahami D, Douros A, Yin H, et al. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study. *BMJ* 2018; 363 :k4880

Mobile video analysis for autism detection

The diagnosis and incidence of autism spectrum disorder (ASD) has risen by approximately 700% since the mid 1990's and it is said to affect 1 in 59 children in the United States. The current diagnostic standard requires direct clinician contact and several hours of observation. As it stands there are long wait lists for a child to be diagnosed and subsequently receive appropriate support. As a result, children are often diagnosed at later ages. A study has applied machine learning models to analyse two-minute home videos of children with (n=33) or without ASD (n=33). The study demonstrated that behavioural features, including social smile and eye contact, could be picked up by the machine learning models accurately. Home videos may provide sufficient information for machine learning models to detect autism traits or flag

inconclusive cases, acting as a means of triage in autism diagnosis. This may help speed up the diagnosis process and allow for earlier intervention for children needing extra support.

Tariq Q, Daniels J, Schwartz JN, et al. Mobile detection of autism through machine learning on home video: A development and prospective validation study. *PLoS Med* 2018; 15(11): e1002705.

Modelling sugar reduction and obesity outcomes

High sugar intakes are associated with obesity and many countries across the world are facing an obesity epidemic. One such country is Mexico, where adults on average consume 12.6% of their everyday total energy (calorie intake) from added sugars. The World Health Organisation recommends that < 10% of total energy intake (TEI) comes from added sugars. To help combat sugar consumption the Mexican government have imposed a 10% sugar-sweetened beverage tax. A research group have estimated that in order for Mexico to achieve <10 TEI sugar-sweetened beverages (SSBs) would have to have their added sugars halved. Mathematical models calculated that with this sugar reduction in SSBs within 12 years, the Mexican population would have an average reduced weight of 1.3kg and 12.5% less obesity. The positive effects would be felt greatest among young adults, makes and the middle socioeconomic groups. The study supports the notion of a national reduction of added sugars in sugar-sweetened beverages to help curb the obesity epidemic.

Basto-Abreu A, Braverman-Bronstein A, Camacho-Garcia-Formenti D, et al. Expected changes in obesity after reformulation to reduce added sugars in beverages: A modeling study. *PLoS Med* 2018; 15(10): e1002664. <https://doi.org/10.1371/journal.pmed.1002664>



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