

Paediatrics

Early puberty and adult asthma risk

We are experiencing a worldwide shift towards earlier puberty in adolescence. The likely causative factors include increasing average weight and changes in childhood lifestyle. There has been some conflicting data surrounding the effects of early puberty with risk of adult asthma and one group has now set out to distinguish this association. Mendelian randomisation, an approach using genetic data, was used to analyse data on 240,000 women and 190,000 men who had provided self-reported information on asthma and age at puberty. Age at puberty was determined as age at menarche for females and age of voice-breaking in men. Early puberty was ranked as anytime below the age of 12 years and late puberty at greater than 14 years. Women and men with early puberty had an increased risk of asthma of 8% and 7%, respectively. Additionally, this study found no association between late puberty and asthma, as has been demonstrated in previous studies. Asthma may be a health consequence of early puberty, adding to an ever-increasing list.

Minelli C, van der Plaats DA, Leynaert B, et al. Age at puberty and risk of asthma: A Mendelian randomisation study. *PLoS Med* 2018; 15(8): e1002634. <https://doi.org/10.1371/journal.pmed.1002634>

Preventing obesity in children

Obesity is particularly prevalent in underserved populations where risk of chronic disease is highest. Targeting obesity during childhood is important for preventing chronic obesity leading into adulthood. One study has looked at the effect of a multicomponent behavioural intervention on child body mass index (BMI) with the aim to track BMI growth trajectories over a 36 month period. Participants were pre-school aged children (n=610) considered at risk for obesity but not yet obese, from underserved populations in Nashville, Tennessee. Child-parent pairs were given a 36-month intervention focused on health behaviours, or, a control activity (on school-readiness). The intervention included weekly skills-building sessions and monthly telephone coaching calls. At 36 months

there was no significant difference in BMI growth trajectories' found between those given the intervention and those in the control group. However, the intervention group did have a lower mean calorie intake. This multicomponent behavioural intervention did not change BMI trajectory in children from underserved communities considered at risk for obesity compared to a control programme.

Barkin SL, Heerman WJ, Sommer EC, et al. Effect of a Behavioral Intervention for Underserved Preschool-Age Children on Change in Body Mass Index: A Randomized Clinical Trial. *JAMA*. 2018;320(5):450-460. doi:10.1001/jama.2018.9128

Digital media use in adolescents and ADHD

The ever-increasing use of digital media and social networking platforms is being scrutinised for its negative impact, particularly in teenagers, on mental health parameters including anxiety. Attention-deficit/hyperactivity disorder (ADHD) can be a disruptive force in an individual's life. One team have investigated the relationship, if any, that exists between digital platform use and ADHD symptoms. Frequency of digital media use among 15 and 16 year olds was recorded alongside the participants self-rated frequency of ADHD symptoms. Fourteen digital media activities and 18 ADHD symptoms (of either inattentive or hyperactive-impulsive varieties) were included in the surveys given at baseline, 6, 12, 18 and 24-months. A two year follow-up revealed a statistically significant association between higher frequency of digital media use and subsequent (new) symptoms of ADHD. Increasing use of digital media and networking platforms may be associated with the development of ADHD symptoms in adolescents.

Ra CK, Cho J, Stone MD, et al. Association of Digital Media Use With Subsequent Symptoms of Attention-Deficit/Hyperactivity Disorder Among Adolescents. *JAMA*. 2018;320(3):255-263. doi:10.1001/jama.2018.8931

Paediatric multiple sclerosis

A low percentage of multiple sclerosis (MS) patients will present in childhood. Typically these patients will have a relapsing-remitting (RRMS) pattern. Those with a younger onset are likely to have twice as many relapse episodes during the first 6 years of diagnosis versus adults. Fingolimod is an oral sphingosine-1-phosphate-receptor modulator that has been shown to

be efficacious in adults with RRMS. A study has looked at the safety and efficacy of fingolimod in a paediatric population and compared it with interferon beta-1a in a randomised phase 3 trial. Participants, aged 10 to 17, with RRMS (n=215) were randomly assigned (1:1) to receive either oral fingolimod or intramuscular interferon beta-1a for 2 years. The annual relapse rate was 0.12 with fingolimod and 0.67 with interferon. Annual rate of new or newly enlarging lesions on MRI were significantly lower in those given fingolimod versus interferon. Serious adverse events were more frequent in the fingolimod group. Paediatric patients with RRMS may have lower rates of relapses and accumulation of lesions on MRI when given fingolimod versus interferon.

Chitnis T, Arnold DL, Banwell B, et al. Trial of fingolimod versus interferon beta-1a in paediatric multiple sclerosis. *N Engl J Med* 2018;379:1017-1027.

Adolescent cognitive ability and later-life risk of dementia

Dementia is a major cause of disability and dependence. Risk factors for dementia are present at various stages along the life-course. The influence of early-life cognitive performance measures of specific abilities has not been studied with regard to later-life risk of dementia. One study has investigated the associations, if any, between specific adolescent cognitive abilities and Alzheimer's disease and related disorders (ADRD) in later life. The cohort included over 85,000 men and women with data spanning from 1960 to 2013 aged 66-73 at age of collection. At analysis a gender difference was noted between the participants. In men, lower mechanical reasoning was associated with increased odds of ADRD. Whereas, in women, lower memory for words in adolescence was associated with increased odds of ADRD. Prominent but weaker associations were found for low performance on language, reasoning, visualisation and mathematic aptitudes in adolescence. Future risk of Alzheimer's disease may be influenced by low adolescent cognitive ability. The authors suggest at-risk subgroups may benefit from identification and intervention.

Huang AR, Strombotne KL, Horner EM, Lapham SJ. Adolescent Cognitive Aptitudes and Later-in-Life Alzheimer Disease and Related Disorders. *JAMA Network Open*. 2018;1(5):e181726. doi:10.1001/jamanetworkopen.2018.1726

Obs & Gynae

Prevalence of prenatal depression

Prenatal depression is associated with an increased risk of emotional, behavioural, and cognitive difficulties in the child and may extend beyond birth with consequences for both mother and child. Evidence suggests depression is increasing in young women, but not much is known about the prevalence in pregnant women. One study has investigated a potential generational change in the prevalence of prenatal depression in young mothers of today compared with their mothers generation. This longitudinal cohort study compared prenatal depressive symptoms in two generations of women given identical questionnaires. These women were the original mothers included in a parent and child study and their female offspring or female partners of their male offspring. In both cohorts the age range was limited to 19-24 years. The first generation cohort had a 17% prevalence of high depressive symptoms prenatally versus 25% in the second generation. This unique study found that there may be a higher incidence of prenatal depression today and as such this population may benefit from monitoring and intervention for depressive symptoms.

Pearson RM, Carnegie RE, Cree C, et al. Prevalence of Prenatal Depression Symptoms Among 2 Generations of Pregnant Mothers: The Avon Longitudinal Study of Parents and Children. *JAMA Network Open*.2018;1(3):e180725. doi:10.1001/jamanetworkopen.2018.0725

Platelet counts during pregnancy

An average of 5-10% of women with uncomplicated pregnancies will have a platelet count less than 150,000 per cubic millimetre around the time of delivery, this is known as 'gestational thrombocytopenia'. A study on platelet counts during pregnancy has been performed, comparing platelet counts throughout pregnancy with non-pregnant women. In uncomplicated pregnancies (n=4568) the mean first trimester platelet count was 251,000 per cubic millimetre versus 273,000 in the nonpregnant women (n=8885). At time of delivery, 10% of uncomplicated pregnancies had a platelet count below 150,000. During the total course of uncomplicated pregnancies 1% had

platelet counts below 100,000. Of 12 women with counts below 80,000, only five women demonstrated no alternative cause for the thrombocytopenia. Counts below 150,000 at time of delivery were commoner in women with pregnancy-related complications. Average platelet counts decrease during pregnancy in most women, however, counts of less than 100,000 may indicate that there is a cause other than pregnancy for thrombocytopenia.

Reese J, Peck J, Deschamps D, et al. Platelet counts during pregnancy. *NEJM* 2018. 379:32-43.

Environment

Climate change and nutritional inequality

Increasing carbon dioxide concentrations may increase inequalities in nutritional deficiencies, despite public health interventions. As atmospheric carbon dioxide concentrations rise, it is anticipated that the zinc and iron concentrations in crops will fall. A research group have modelled the potential extent and consequences of this scenario. For 137 countries, estimates of climate change, crop nutrient concentrations, dietary patterns, and disease risk were incorporated into a micro-simulation model of zinc and iron deficiency. Decreasing zinc and iron concentrations alone were estimated to induce over one thousand million disability-adjusted life years (DALYs) in the period from 2015 to 2050. When estimates of rising carbon dioxide were included an additional 125.8 million DALYs were added on to the total over the same period. This burden disproportionately affects South-East Asian and African regions where there are existing disease burdens from zinc and iron deficiencies. Attempts to alleviate this potential burden exacerbation include public health interventions, via supplementation, and importantly wider involvement from interventions such as the Paris Agreement.

Weyant C, Brandeau ML, Burke M, et al. Anticipated burden and mitigation of carbon-dioxide-induced nutritional deficiencies and related diseases: A simulation modelling study. *PLoS Med* 2018;15(7): e1002586. <https://doi.org/10.1371/journal.pmed.1002586>

Diabetes and myocardial infarction in extreme temperatures

We know that extremes of temperature are linked with increased mortality and with the rising prevalence of diabetes

mellitus (DM) researchers have become interested in the impact of having DM during times of extreme temperatures. In both high and low temperatures, mortality from acute myocardial infarction (AMI) is seen to rise. The effect of having DM on AMI occurrence during temperature extremes has now been studied. Data from over 50,000 AMI admissions from Hong Kong hospitals between 2002-2011 has demonstrated that when temperatures rose above 28.8°C there was a rise in AMI hospitalisations in patients with DM but not without. Cold temperatures saw an even greater association of DM AMI admissions versus patients without DM. These differences were more pronounced between groups in those younger than 75. While AMI is often fatal, if non-fatal the patient can still experience morbidity including heart failure. Researchers suggest those with DM avoid extreme temperatures to help mitigate this in the context of increasing worldwide temperatures and DM prevalence.

Lam HCY, Chan JCN, Luk AOY, et al. Short-term association between ambient temperature and acute myocardial infarction hospitalizations for diabetes mellitus patients: A time series study. *PLoS Med* 2018; 15(7): e1002612. <https://doi.org/10.1371/journal.pmed.1002612>

Prenatal exposure to pollution and new born thyroid function

The thyroid gland is vital for the growth and development of the foetus. Previous studies have demonstrated a potential association between prenatal particulate matter air pollution and reduced thyroid function in the new born. One study has set out to investigate if prenatal exposure to other air pollutants can influence thyroid function of the new born and if there is a critical windows of exposure for pollutants to have an influence. This cohort study included data from over 2,000 participants from the Children's Health Study in southern California. Prenatal monthly averages of ambient and traffic-related pollutant exposures were calculated using central monitoring data. Prenatal exposure to ambient and traffic pollutants was associated with high new born heel-stick blood spot total thyroxine (TT4). Two standard deviations' increase in prenatal exposure was associated with high new born thyroxine. Exposure in early-pregnancy and mid-pregnancy was particularly associated with higher new born TT4 concentrations. Particulate matter air

pollution may be toxic to foetal thyroid gland function.

Howe CG, Eckel SP, Habre R, et al. Association of Prenatal Exposure to Ambient and Traffic-Related Air Pollution With Newborn Thyroid Function Findings From the Children's Health Study. *JAMA Network Open*. 2018;1(5):e182172. doi:10.1001/jamanetworkopen.2018.2172

Cardiology

Vascular access in acute coronary syndrome management

Coronary angiography is used in those who have presented with acute chest syndrome as part of their management and is achieved with either femoral or radial vascular access. One study has compared the safety and efficacy of these two access approaches. This open-label, superiority trial included over 8,000 patients from 78 hospitals across Italy, the Netherlands, Spain and Sweden who presented with acute coronary syndrome between 2011 and 2014. Patients with ST-segment elevated myocardial infarction were randomised (1:1) to receive either access prior to coronary angiography. Clinical follow-up was performed at 30 and 100 days post procedure. Major adverse cardiovascular events were all-cause mortality, myocardial infarction, or stroke at 30 days. At the one-year follow-up, there was found to be no difference in major cardiovascular incidence between the radial and femoral access groups. However, net adverse clinical events, including major bleeding at 30 days, occurred at lower rates in the radial group. The researchers urge radial access be adopted as the default approach in acute coronary syndrome patients undergoing invasive management.

Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018; 392:835-848.

Novel approach to coronary artery disease

Drug eluting stents (DES) are commonly used in the therapeutic management of small coronary artery disease. A novel approach to managing coronary disease includes the use of drug-coated balloons (DCB). However, the safety and efficacy of DCB versus DES has poor literature. One

study has looked at this in an open-label, randomised, non-inferiority trial. Patients with coronary vessel disease (<3mm diameter) who were indicated for percutaneous coronary intervention were randomly allocated (1:1) to undergo angioplasty with DCB or with implantation of DES. Patients were also given dual antiplatelet therapy according to local guidelines. Non-inferiority was considered occurrence of major cardiac events (MACE) at 12 months, the pre-assigned margin of which was 4%. MACE included; cardiac death, non-fatal myocardial infarction, target-vessel revascularisation. At 12 months, the MACE profiles were found to be similar in both groups. DCB was found to be non-inferior to DES according to the pre-assigned margin (< 4%). DCB is non-inferior to DES in the management of small native coronary artery disease.

Jeger R, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet* 2018; 392:849-856.

Diclofenac use and cardiovascular outcomes

The cardiovascular safety of using the non-steroidal anti-inflammatory (NSAIDs), diclofenac, has been called into question. It has been considered unethical to conduct a widescale randomised clinical trial on the cardiovascular safety of diclofenac but more information is needed. A series of cohort studies that mimic a clinical trial (an emulated trial design) has now been performed comparing the use of diclofenac with other traditional NSAIDs, paracetamol, and no medicine initiation. A series of over 250 cohort studies were included, each mimicking a strict clinical trial design. Adults considered to have an existing low baseline risk were excluded from the studies (e.g those with cardiovascular, kidney and liver disease). Hazard ratios for major cardiovascular events at 30 days post initiation were calculated. Those who initiated diclofenac had an increased adverse event rate by 50%, 20% and 30% versus non-initiators, paracetamol or ibuprofen initiators, and naproxen initiators, respectively. Event rates for atrial fibrillation, stroke, myocardial infarction and cardiac death were increased with diclofenac. Diclofenac also increased upper gastrointestinal bleeding risk.

Schmidt M, Sørensen H, Pedersen L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies *BMJ* 2018;362 :k3426

Wearable device for atrial fibrillation diagnosis

Wearable technology may transform the way we access healthcare. Atrial fibrillation (AF) can have many complications, such as stroke, if undiagnosed and untreated. One study has looked at the benefits of wearing a home-based self-applied electrocardiogram (ECG) patch. The aim of the study was to see if, in an at-risk population, wearing the home-based monitor immediately would result in a different diagnosis rate of AF than if ECG monitoring was delayed for four months. The study followed a randomise control trial protocol. Participants were given an ECG monitoring patch (n=1364) either immediately after enrolment, to wear for four weeks, or were given it delayed at four months post enrolment (n=1291). Individuals at high risk for AF had higher diagnosis rates if given immediate monitoring with a home-based wearable ECG patch than those with delayed monitoring. Those given wearable ECG patches immediately also had a higher uptake and initiation of anticoagulants and healthcare resource utility at one year. This use of wearable ECG technology may help patients at risk of AF benefit from earlier diagnosis and intervention.

Steinhubl SR, Waalen J, Edwards AM, et al. Effect of a Home-Based Wearable Continuous ECG Monitoring Patch on Detection of Undiagnosed Atrial Fibrillation The mSToPS Randomized Clinical Trial. *JAMA*. 2018;320(2):146-155. doi:10.1001/jama.2018.8102

Antidepressants for long-term cardiac outcomes

Those who have experienced acute coronary syndrome (ACS) and have concurrent depression have poorer cardiac outcomes than those without depression. One study has investigated the long-term effect on medical outcomes in those with ACS and depression who have been treated with antidepressants. In this South Korean based randomised, placebo-controlled trial, 300 patients with recent ACS were randomised to receive either the antidepressant escitalopram or placebo for a 24-week course. Outcomes were major adverse cardiac events including mortality, myocardial infarction (MI) and percutaneous coronary intervention (PCI). At an average of eight years follow up, major adverse cardiac events occurred in 40.9% of those receiving escitalopram and 53.6% receiving placebo. Patients with

depression who experience an episode of ACS may significantly benefit from taking a course of escitalopram to help improve cardiac outcomes.

Kim J, Stewart R, Lee Y, et al. Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial. *JAMA*.2018;320(4):350–358. doi:10.1001/jama.2018.9422

Miscellaneous

Alcohol consumption and risk of dementia

Excessive consumption of alcohol is a leading risk factor for many diseases and is associated with increased mortality. As life expectancy increases we come to see the health effects of these modifiable life style behaviours in later life. The effects of alcohol consumption and risk of dementia have been investigated in a 23-year follow up of the Whitehall II cohort study. This included nine thousand civil servants in London who were aged 35-55 during the study's inception around 1985-88. Alcohol consumption behaviours were assessed as a mean of three assessments. Alcohol abstinence in midlife was associated with a higher risk of dementia compared to those drinking between 1-14 units of alcohol per week. From midlife to early old age, long term abstinence, decreased consumption, and long-term consumption of > 14 units of alcohol a week were all associated with a greater risk of dementia compared to those drinking 1-14 units a week. Analysis suggests drinking >14 units a week may be associated to dementia through greater cardiometabolic risks.

Sabia S, Fayosse A, Dumurgier J, et al. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study *BMJ* 2018; 362 :k2927

Biomarkers for targeted cancer therapies

Cancer therapeutics have been transformed by the discovery of immune targets and the development of immune mediated drugs. However, many of these drugs are expensive and have a harsh side-effect profile. Drugs inhibiting two particular targets have shown great efficacy but their long-term effects are only seen in a few patients. Identifying biomarkers may help determine which patients would benefit best from these drugs. Inhibitors for two

targets, programmed cell death 1 (PD-1) and programme cell death ligand 1 (PD-L1), have been tested in patients whose cancers were either positive or negative for the marker PD-L1. The efficacy of these inhibitors was evaluated in a meta-analysis including over 4,100 patients from eight randomised trials. Both PD-1 and PD-L1 inhibitors were associated with significantly prolonged survival compared to conventional cancer therapies, in both PD-L1 positive and negative patients. Whilst this analysis demonstrated the efficacy of targeting PD-L1 and PD-1 in cancers, the use of PD-L1 expression may not be helpful in determining which patients may benefit most or should be offered these therapies.

Shen X, Zhao B. Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis. *BMJ* 2018; 362 :k3529

Traumatic brain injury and suicide risk

Traumatic brain injuries (TBIs) have long been a leading cause of death and disability. Long-term consequences can include psychiatric problems. One study has looked at the association between TBI and suicide, a relationship that has been scarcely studied. This retrospective cohort study included data on over 7 million individuals over a 35-year period. Of this cohort 7.6% had medical contact for TBI. TBIs considered ranged from mild TBI (concussion), skull fracture without documented TBI, and severe TBI (evidence of structural brain injury). Of the 34,500 individuals who died by suicide, 10% had a history of TBI. The majority of these had a mild TBI (2701 individuals). The absolute suicide rate was 41 per 100,000 person years with a history of TBI versus 20 per 100,000 in those without. Suicide risk increased in those with more than one contact with TBI. Risk of suicide was highest in the first six months post TBI. Individuals with a history of traumatic brain injury may have increased suicide rates compared to the general population.

Madsen T, Erlangsen A, Orlovská S, et al. Association Between Traumatic Brain Injury and Risk of Suicide. *JAMA*. 2018;320(6):580–588. doi:10.1001/jama.2018.10211

Stress related disorders and autoimmune disease

Extreme life stressors and subsequent psychiatric reactions are often associated with a down regulated immune system. One team have investigated if there is a potential link between stress-

related disorders and development of autoimmune disorders. The Sweden based study followed a register-based retrospective cohort format and included patients with stress-related disorders (n=106,464) and matched unexposed individuals (n=1,064,640). Stress-related disorders included post-traumatic stress disorder, acute stress reaction, adjustment disorder, to name a few. At an average follow-up of 10 years an overall increased risk of autoimmune disease was found in those already diagnosed with a stress-related disorder. The incidence rate of autoimmune diseases was 9.1 per 1000 person-years in those exposed to stress-disorders versus 6.0 per 1000 person-years in the unexposed matched cohort. The effects were most pronounced in younger patient groups with hazard ratios at 1.48 in those <33 years versus a hazard ratio of 1.23 in those > 51 years. Stress-related disorders may increase the risk of developing an autoimmune disease.

Song H, Fang F, Tomasson G, et al. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. *JAMA*. 2018;319(23):2388–2400. doi:10.1001/jama.2018.7028

Fatty acids as anxiolytics

Anxiety is one of the most commonly experienced psychiatric symptoms and the prevalence of any anxiety disorders is 1 in 3. There is some evidence that omega-3 polyunsaturated fatty acids (PUFAs) may be of some benefit in those suffering with anxiety symptoms but to date no systematic reviews have been performed. A systematic review and meta-analysis has now evaluated the efficacy of omega-3 PUFAs in reducing anxiety symptoms. The analysis included data from participants given omega-3 PUFA treatment (n=1203) and those not given any in a control setting (n=1037). Omega-3 PUFAs were found to have a significant anxiolytic effect when given at high doses of at least 2000 mg/d versus placebo, but not when given at doses below. Subgroup analysis also revealed that reduction in anxiety symptoms was greater with omega-3 PUFAs in those with a specific clinical anxiety diagnosis compared to individuals who had subclinical diagnoses. Omega-3 PUFAs may be effective at reducing anxiety symptoms in a clinical setting.

Su K, Tseng P, Lin P, et al. Association of Use of Omega-3 Polyunsaturated Fatty Acids With Changes in Severity of Anxiety Symptoms: A Systematic Review and Meta-analysis. *JAMA Network Open*.2018;1(5):e182327.