

## Metformin exposure in first trimester of pregnancy does not increase risk of congenital anomalies

A population-based exploratory case-control study investigated whether exposure to metformin during the first trimester of pregnancy increased the risk of all or specific congenital anomalies (Given et al, 2018). Cases of 29 specific subgroups of non-genetic anomalies, and all non-genetic anomalies combined, were compared with controls (all other non-genetic anomalies or genetic syndromes). The study included data from 11 European congenital anomaly registries surveying 1 892 482 births in Europe between 2006 and 2013. A total of 50 167 babies was affected by congenital anomaly. Of these, 168 babies affected by congenital anomaly (141 non-genetic, 27 genetic) were exposed to metformin (3.3 per 1000 births). No evidence was found for a higher proportion of exposure to metformin during the first trimester among babies with all non-genetic anomalies combined compared with genetic controls.

Given JE, Loane M, Garne E et al. Metformin exposure in first trimester of pregnancy and risk of all or specific congenital anomalies: exploratory case-control study. *BMJ*. 2018 Jun 25;361:k2477. <https://doi.org/10.1136/bmj.k2477>

## Council of Europe's new protocol on genetic testing

The Council of Europe's protocol on genetic testing for health purposes has into force (<https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/203>). The protocol, an addition to the Convention on Human Rights and Biomedicine, lays down rules on the conduct of genetic tests, including direct-to-consumer testing. It specifies the conditions under which tests may be carried out on persons not able to consent, with particular attention to children, and addresses privacy issues and the right to information obtained through genetic testing. It also covers counselling and screening.

## Cancer increases the risk of heart attacks, strokes and vascular occlusions

It is well known that pre-existing cancer is a significant risk factor for venous thrombosis, but a new study has shown that the risk of arterial thromboses and their consequences is also higher in patients with cancer (Grilz et al, 2018).

The study aimed to quantify the risk and explore clinical risk factors of arterial thromboembolism in patients with cancer, and also investigate its potential impact on mortality. Patients with newly-diagnosed cancer or progression of disease after remission were included in a prospective observational cohort study and followed for 2 years. The study included 1880 patients (54.3% male; median age 61 years). During a median follow-up of 723 days, 48 (2.6%) patients developed arterial thromboembolism, 157 (8.4%) developed venous thromboembolism, and 754 (40.1%) patients died.

The cumulative 3-, 6-, 12- and 24-month risks of arterial thromboembolism were 0.9%, 1.1%, 1.7% and 2.6% respectively. Male sex, age, hypertension, smoking, lung



Dr Ella Grilz, PhD Student, Pabinger & Ay Laboratory, Clinical Division of Haematology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

cancer and kidney cancer were associated with a higher risk of arterial thromboembolism. The occurrence of arterial thromboembolism was associated with a 3.2-fold increased risk of all-cause mortality.

'We were able to show that, although the risk of arterial thrombosis in patients with malignant tumours is significantly lower than that of venous thrombosis, there is a great variation, depending upon the type of tumour,' said lead author Dr Ella Grilz, from the Pabinger & Ay

Laboratory, Clinical Division of Haematology, Department of Medicine I, Medical University of Vienna, Vienna, Austria, describing the new findings.

Follow-on investigations will now look for potential biomarkers for heart attacks, strokes and vascular occlusions in patients with cancer.

Grilz E, Königsbrügge O, Posch F et al. Frequency, risk factors, and impact on mortality of arterial thromboembolism in patients with cancer. *Haematologica*. 2018 May 24. <https://doi.org/10.3324/haematol.2018.192419>

## When should emergency physicians order imaging tests for patients with epileptic seizures?

Patients who go to the emergency department with seizures often undergo neuroimaging, usually computed tomography scans. Such imaging in adults presenting with new onset ('index') seizures leads to a change in care for 9–17% of patients, but it was unclear if such changes are made following imaging in the emergency department for seizures in adults with known seizure disorders ('non-index' seizures).

In a study of 822 emergency department visits for non-index seizures (Salinsky et al, 2018), neuroimaging was performed in nearly half of all patients (381/822; 46%). Of these, 11 (3%) of imaging tests led to an acute change in patient management,

8 (2%) after excluding false positive scans. Acute head trauma, prolonged alteration of consciousness and a focal neurological examination at presentation were associated with an increased yield of emergency department neuroimaging. Without any of these three clinical factors, the true positive yield of neuroimaging was zero.

The findings support a more conservative use of emergency department neuroimaging for patients with non-index seizures, based on clinical factors at the time of presentation.

Salinsky M, Wong VSS, Motika P, Meuse J, Nguyen J. Emergency department neuroimaging for epileptic seizures. *Epilepsia*. 2018 Jul 18. <https://doi.org/10.1111/epi.14518>

## Relapse in former smokers may be linked to sense of lost social identity

As well as being physically addictive, smoking has a range of emotional, behavioural and social triggers. New findings (Notley and Collins, 2018) suggest that smokers who have quit often relapse because they want to recapture a sense of lost social identity, and that many ex-smokers experience quitting as a 'loss'.

Lead researcher Dr Caitlin Notley, Senior Lecturer in Mental Health in the Norwich Medical School, University of East Anglia, Norwich, said: 'Although many people do manage to quit, relapse is very common. We wanted to understand other social factors that might also be important.'

The research team studied in-depth interviews with people who had quit and relapsed. A total of 43 participants described their history of smoking and previous quit attempts, their current quit attempt, and discussed any smoking relapses. The researchers then more closely studied 23 participants who provided the most detailed information about relapsing to smoking.



**Dr Caitlin Notley, Senior Lecturer in Mental Health, Faculty of Medicine and Health, Norwich Medical School, University of East Anglia, Norwich**

Dr Notley said: 'What we have found is that relapse is associated with a whole range of emotional triggers. It is often tied up with people wanting to recapture a lost social identity – their smoker identity.'

'People want to feel part of a social group, and recover a sense of who they are – with smoking having been part of their identity, for most, since their teenage years.'

'A loss of smoker identity may mean giving up previous social groups, and finding a new identity as a non-smoker.'

She added: 'People often go back to smoking because they feel it helps them cope with stressful events. Many saw slipping back into smoking as inevitable. They also talked about a sense of relief at regaining their identity as a smoker – so there are a lot of emotional reactions related to relapse such as pleasure, but also guilt and shame.'

Notley C, Collins R. Redefining smoking relapse as recovered social identity – secondary qualitative analysis of relapse narratives, *Journal of Substance Use* 2018. <https://doi.org/10.1080/14659891.2018.1489009>

## Long-term trends of health service usage among patients with heart failure

A study was undertaken to identify subgroups of patients with heart failure with different trajectories of long-term readmission rates (Rao et al, 2018), and to assess common causes and their sequences of readmissions for each subgroup.

Patients with a primary diagnosis of heart failure during 2008–9 were identified using nationally representative primary care data linked to national hospital data, and followed up for 5 years. The model categorised patients with heart failure ( $n = 9466$ ) into five subgroups: low-impact (66.9%); two intermediate ones (27.4%); chronic high-impact (2.3%) with steady high annual readmission rates; and short-term high-impact (3.4%) with rapid decline in readmission rates. The groups were defined by their trends of yearly number of readmissions.

All-cause 5-year mortality was highest in the short-term high-impact group. Compared with low-impact users, high-impact users had higher mortality, bereavement episodes and more out-of-hours GP visits. The chronic high-impact users had distinct sequences of causes of emergency admissions, most often chest infection, ischaemic heart disease, and cardiopulmonary signs and/or symptoms.

Chronic high-impact users were a small proportion of patients, but with increasingly high use of health-care services. Short-term high-impact users were largely patients at the end of life, who required prompt palliative care involvement to reduce unnecessary readmissions.

Rao A, Kim D, Darzi A, Majeed A, Aylin P, Bottle A. Long-term trends of use of health service among heart failure patients. *Eur Heart J Qual Care Clin Outcomes*. 2018 Apr 28. <https://doi.org/10.1093/ehjqcco/qcy013>

### Vanguards have not delivered intended depth and scale of change

The vanguard programme, which has developed new care models to integrate health and social care services, has not delivered the depth and scale of transformed services it aimed for at the start of the programme, says a report by the National Audit Office (<https://www.nao.org.uk/wp-content/uploads/2018/06/Developing-new-care-models-through-NHS-Vanguards.pdf>).

### Marker for favourable prognosis in gastric and oesophageal cancer

Patients with non-metastatic adenocarcinomas of the gastroesophageal transition have a better prognosis if their tumour cells produce the signal molecule PD-L1 (programmed cell-death-protein-1 ligand) (<https://doi.org/10.1080/2162402X.2018.1435226>).

### Heat-stable carbetocin could save thousands of lives

Heat-stable carbetocin is as effective as oxytocin in preventing postpartum haemorrhage following vaginal birth and does not require refrigeration (<https://doi.org/10.1056/NEJMoa1805489>). This could save thousands of lives in low- and lower-middle income countries, where 99% of postpartum haemorrhage-related deaths occur, and where refrigeration of medicines can be difficult to achieve and maintain.

## Drinking changes young adults' metabolite profile

Adolescent drinking is associated with changes in the metabolite profile, a new study shows (Heikkinen et al, 2018). Some of these changes correlated with reduced brain grey matter volume, especially in young women who are heavy drinkers. The findings could contribute to the development of new treatments.

The study was a 10-year follow-up study among adolescents living in eastern Finland. The researchers determined the metabolite profiles of heavy- and light-drinking young adults, and used magnetic resonance imaging to measure their brain grey matter volumes. These two methods have not been used in combination before, although previous studies have shown an association between heavy drinking and metabolite profile changes.

The researchers observed metabolite profile changes even in young people who consumed alcohol at a level that is socially acceptable. Moreover, none of the study participants had a diagnosis of alcohol dependence.

Heikkinen N, Kärkkäinen O, Laukkanen E et al. Changes in the serum metabolite profile correlate with decreased brain grey matter volume in moderate-to-heavy-drinking young adults. *Alcohol*. 2018. <https://doi.org/10.1016/j.alcohol.2018.05.010>

## Computer therapy can help people with aphasia find lost words

Computer therapy can help people with aphasia learn new words even years after a stroke, a new study has revealed ([www.journalslibrary.nihr.ac.uk/programmes/hta/122101](http://www.journalslibrary.nihr.ac.uk/programmes/hta/122101)). Researchers found a number of significant benefits to using computer therapy for people affected by aphasia, in comparison to usual speech and language therapy alone.

The 5-year study offered people with aphasia the opportunity to take part in self-managed speech and language therapy using a computer at home, in addition to any face to face therapy available to them. More than 270 people from 21 NHS speech and language departments across the UK took part in the trial – all were between 4 months and 36 years post-stroke.

Results showed that computer therapy enabled patients to increase their speech and language practice – 28 hours on average compared with 3.8 hours of usual speech and language therapy over a 6-month period.

Participants also significantly improved their ability to say the words they chose to practise. This showed that people with aphasia can learn new words even after a long time post-stroke with computer therapy. They could still say



**Dr Rebecca Palmer, Reader in Communication and Stroke Rehabilitation, Rehabilitation and Assistive Technology Group, SCHARR (School of Health and Related Research), The University of Sheffield, Sheffield**

the words 6 months after the computer therapy had finished.

The approach tested, which included a combination of tailoring the programme to the individual with aphasia by a speech and language therapist, independent practise at home by the person with aphasia, and volunteer or speech and language therapy assistant support, cost half as much as providing the same amount of extra therapy face to face.

Dr Rebecca Palmer from the Rehabilitation and Assistive Technology Group, School of Health and Related Research,

The University of Sheffield, Sheffield and chief investigator, said: 'Our study showed that 61% of people continued to use the computer therapy after the end of the trial period showing that people with aphasia want to continue learning words and can do this independently.'

She added: 'Although people were able to say more words they didn't always automatically use these words in conversation. One in three were able to use some of the words they had learnt but the majority of people weren't automatically making that transition. This would suggest we need to do something to help people practise more in everyday communication situations.'

## Fatigue is a common but underestimated symptom of endometriosis

Fatigue is a common but underestimated symptom of endometriosis, according to findings from an international study (Ramin-Wright et al, 2018).

The researchers recruited 1120 women, 560 with endometriosis matched with 560 without it, from practices in Switzerland, Germany and Austria. The women completed a questionnaire that asked about various factors relating to quality of life and endometriosis, as well as medical and family histories, lifestyle and mental disorders. Fatigue and insomnia were categorised into five different levels ranging from 1 (never) to 5 (very often).

They found that 50.7% of women diagnosed with endometriosis suffered from frequent fatigue compared to 22.4% of women without the condition. Fatigue with endometriosis was also associated with a more than seven-fold increase in insomnia, a four-fold increase in depression, a two-fold increase in pain and a nearly 1.5-fold increase in occupational stress. Age, time since first diagnosis and the stage of the disease were not linked to fatigue.

The prevalence of fatigue remained significant after the results were adjusted for other factors that might play a role in fatigue, such as pain, insomnia,

occupational stress, depression, body mass index and motherhood.

'These findings suggest that endometriosis has an effect on fatigue that is independent of other factors and that cannot be attributed to symptoms of the disease,' said Professor Brigitte Leeners, deputy head of the Department of Reproductive Endocrinology at the University Hospital Zurich, Switzerland, who led the research.

Ramin-Wright A, Kohl Schwartz AS, Geraedts K et al. Fatigue - a symptom in endometriosis. *Hum Reprod*. 2018 Jun 26. <https://doi.org/10.1093/humrep/dey115>

## Depression during pregnancy rises in a generation

Anxiety and depressive symptoms during pregnancy have risen by 51% within a generation according to findings from a major study (Pearson et al, 2018).

Using unique data from two generations who took part in Bristol's Children of the 90s longitudinal study, researchers examined responses to questions completed by the women during pregnancy to compare levels of depressive symptoms more than 20 years apart.

Looking at the responses of 2390 of the original women who were recruited to the study in the early 1990s and then 180 of their daughter's generation who became pregnant by the age of 24 years, researchers found that having high depressive symptoms was 51% more common in the current generation. Today 25% of young mums have high depressive symptoms compared to 17% in the 1990s according to the research.

If their mother was depressed in pregnancy, daughters were also more than three times as likely to be depressed in their pregnancy.

Dr Rebecca Pearson, Lecturer in Psychiatric Epidemiology, Bristol Medical School, Bristol, commented: "Thanks to the Children of

the 90s data we can now make valuable comparisons between generations on the experienced levels of depression. While there is a perception that mental health is rising, this may be a result of greater awareness and less stigma. These new data give a more accurate picture of what our current population of young pregnant women are facing.

She added: 'Interestingly, however, the research shows that depression in today's young women may be driven by rises in feeling overwhelmed and stress rather than feelings of being down and flat.'

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



**Dr Rebecca Pearson, Lecturer in Psychiatric Epidemiology, Bristol Medical School, Bristol**

## Comparison of embolization vs resection for treatment of benign prostatic hyperplasia

A randomized, open label, non-inferiority trial was performed to compare prostatic artery embolization with transurethral resection of the prostate in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia in terms of patient-reported and functional outcomes (Abt et al, 2018).

A total of 103 patients aged  $\geq 40$  years with refractory lower urinary tract symptoms secondary to benign prostatic hyperplasia were randomized; 48 and 51 patients reached the primary endpoint (change in international prostate symptoms score) 12 weeks after prostatic artery embolization and transurethral resection of the prostate respectively.

Secondary outcomes included further questionnaires, functional measures, magnetic resonance imaging findings, and adverse events; changes from baseline to 12 weeks were compared between treatments with two-sided tests for superiority.

The improvement in lower urinary tract symptoms secondary to benign prostatic hyperplasia seen 12 weeks after prostatic artery embolization was close to that seen after transurethral resection of the prostate. Prostatic artery embolization was associated with fewer complications than transurethral resection of the prostate but has disadvantages regarding functional outcomes, which should be considered when selecting patients for this procedure.

Further comparative study findings, including longer follow up, should be evaluated before prostatic artery embolization can be considered as a routine treatment.

Abt D, Hechelhammer L, Müllhaupt G et al. Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: randomised, open label, non-inferiority trial. *BMJ.* 2018 Jun 19;361:k2338. <https://doi.org/10.1136/bmj.k2338>

## Current rectal cancer treatment does not have a survival benefit for younger patients

A new study (Kolarich et al, 2018) reveals that individuals younger than 50 years of age who are diagnosed with rectal cancer do not experience an overall survival benefit from currently recommended treatments. Specifically, the addition of chemotherapy and radiation to surgery does not prolong life for these patients. The findings suggest that early onset disease may differ from later onset disease in terms of biology and response to therapy.

The overall incidence of rectal cancer is decreasing in patients over 50 years of age, likely as a result of improved screening adherence; however, there is a disproportionate increase in the incidence of rectal cancer in patients under the age of 50 years. The mortality rate from rectal cancer among younger patients has also increased in the past few decades.

Current guidelines – which recommend a combination of chemotherapy, radiation and surgery for stages II and III rectal cancer – are predominantly based on data from patients older than 50 years of age. To examine how younger patients fare, researchers examined 2004–2014 information from the National Cancer Database. A total of 52 519 patients were analysed.

Patients younger than 50 years old who have been diagnosed with rectal cancer represent a unique group. These younger patients do not see a survival benefit from receiving the currently recommended treatment for stages II and III rectal cancer. The study also revealed age-specific survival data for younger patients. Younger patients were more likely to be female and minorities, to be diagnosed at a higher stage, and to have travelled further to be treated at academic/integrated centres.

Kolarich A, George TJ Jr, Hughes SJ et al. Rectal cancer patients younger than 50 years lack a survival benefit from NCCN guideline-directed treatment for stage II and III disease. *Cancer.* 2018 Jul 9. <https://doi.org/10.1002/cncr.31527>