

## Ethnic differences in need for pacemakers

A team of researchers at the NIHR Leicester Biomedical Research Centre has found evidence that south Asian people (from India, Pakistan, Bangladesh and Sri Lanka) are less likely to require a pacemaker to treat bradycardia than white people of European origin (<https://doi.org/10.1136/heartjnl-2017-312374>).

The researchers looked at the number of permanent pacemakers implanted in Leicestershire over an 8-year period. During that time, 4883 people had a permanent pacemaker implanted, which represents about five people in every 1000 of the local population. However, the rate of permanent pacemakers fitted in white people was nearly six times higher than in south Asian people, even when factors such as risk of heart disease and age were taken into account.

## Seasonal variations in exceeding maximum daily dose of paracetamol

Between 2011 and 2016, 14 481 American adults who used paracetamol in the preceding 30 days were sampled from national online panels and completed a detailed online daily diary of paracetamol medication use for 7 days. Respondents were not told that the study concerned paracetamol. Cold/flu season was contrasted to off-season in terms of symptoms, use of paracetamol medications and consumption exceeding 4 g (the recommended daily maximum). (Dates varied from year to year, cold/flu season lasted roughly from September/October to March/April, while off-season lasted from June to late August.)

Overall, 6.3% of users exceeded 4 g on at least one day; 3.7% of usage days exceeded 4 g. This was not the result of differences in characteristics of individuals using paracetamol during cold/flu season, but mainly a result of increased use of over-the-counter combination therapies designed to treat upper respiratory cold/flu symptoms (<https://doi.org/10.1111/bcp.13551>).

## Low dose dexmedetomidine given at night may prevent delirium in critically ill patients

Skrobik et al (2018) have reported what is believed to be the first investigation to identify a drug to prevent adults in the intensive care unit from developing delirium.

The study enrolled 100 intensive care unit patients at two hospitals, in Quebec and Boston. The patients did not have delirium at the time of enrollment. Half the patients were randomly assigned to receive intravenous dexmedetomidine; the others were infused with the placebo.

Compared to the placebo arm, those receiving dexmedetomidine during their intensive care unit stay:

- Were more likely to remain free of delirium throughout their intensive care unit stay: 80% *vs* 54%
- Spent more days free of delirium in the intensive care unit: 8 *vs* 6 days
- Were less likely, if in pain, to experience severe pain: 44% *vs* 66%.

Following a previous study of a select group of critically ill patients, the authors expected that dexmedetomidine would also improve sleep quality. In the current study, however, there was no difference in sleep quality between the



**Dr Yoanna Skrobik, Associate Investigator, Injury Repair Recovery Program, McGill University, Montreal, Quebec, Canada**

two groups, as assessed by a self-reported questionnaire.

Lead author Dr Yoanna Skrobik, Associate Investigator, Injury Repair Recovery Program, McGill University, Montreal, Quebec, Canada, said that the sleep findings should be interpreted in light of two caveats: sleep in the intensive care unit is almost always abnormal, and there is no validated instrument to identify when an intensive care unit patient is experiencing normal *vs* abnormal sleep.

There was also no difference in length of intensive care unit or hospital stay, or in intensive care unit mortality. However, reduced opiate requirements confirmed other studies describing dexmedetomidine's potential to relieve pain.

'We believe this is a practice-altering study and that dexmedetomidine should be used with patients at high risk for delirium,' concluded Dr Skrobik.

Skrobik Y, Duprey MS, Hill NS, Devlin JW (2018) Low-dose nocturnal dexmedetomidine prevents ICU delirium: a randomized, placebo-controlled trial. *Am J Respir Crit Care Med* <https://doi.org/10.1164/rccm.201710-1995OC>

## Survivors of childhood cancer at greater risk of cardiovascular disease in adulthood

Survivors of childhood cancer are at increased risk of suffering prematurely from cardiovascular disease in adulthood, according to a new study (Faber et al, 2018).

A total of 951 adult long-term survivors of childhood cancer underwent a clinical examination that included assessing factors that might put them at higher risk of cardiovascular disease. The researchers also checked their medical history, whether or not they smoked and whether there was any family history of cardiovascular disease. Their ages ranged from 23 to 48 years at the time of follow up. The results were compared with over 15 000 people from the general population.

Survivors of childhood cancer had an

increased risk of having high blood pressure and dyslipidaemia, which occurred 6 and 8 years earlier respectively than in the general population.

Childhood cancer survivors also had a nearly two-fold increased risk of cardiovascular diseases such as congestive heart failure and venous thromboembolism. Cardiovascular disease was found in 4.5% of survivors and in most cases occurred before they reached 40 years of age, nearly 8 years earlier than the general population.

Faber J, Wingerter A, Neu MA et al (2018) Burden of cardiovascular risk factors and cardiovascular disease in childhood cancer survivors: data from the German CVSS-study. *Eur Heart J* <https://doi.org/10.1093/eurheartj/ehy026>

## Impact of cytomegalovirus infection on outcomes of allogeneic haematopoietic cell transplantation

Peter D Steinberg

Despite pre-emptive therapy, cytomegalovirus infection significantly impacts outcomes and resource utilization in allogeneic haematopoietic cell transplantation recipients, particularly among those with recurrent episodes of cytomegalovirus infection.

In a retrospective analysis of data from 172 allogeneic haematopoietic cell transplantation recipients, 57% of patients who suffered a first cytomegalovirus infection had  $\geq 2$  recurrent episodes, and 20% had  $\geq 4$  recurrences. The study was presented by Professor Rafael F Duarte, from the Department of Haematology, Hospital Universitario Puerta de Hierro, Madrid, Spain, at the 44th Annual Meeting of the European Society for Blood and Marrow Transplantation in Lisbon, Portugal.

In the first year post-haematopoietic cell transplantation, hospital length of stay was  $>30$  days longer in patients with cytomegalovirus infection than in



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those without; this increase was  $>40$  additional days in patients with  $\geq 2$  recurrent cytomegalovirus infections, significantly longer than those with only one episode of cytomegalovirus infection (19 days;  $P < 0.001$ ).

‘Given their impact on outcomes and length of stay in haematopoietic cell transplantation recipients, recurrent cytomegalovirus

infections may require sustained prophylaxis, although no clinical trial or large registry study has evaluated this strategy in patients experiencing two or more episodes,’ said Professor Duarte.

In January, the European Medicines Agency approved the antiviral letermovir to prevent cytomegalovirus from becoming active and causing disease in adults receiving an allogeneic haematopoietic stem cell transplant. Many people have cytomegalovirus in their body but it is usually inactive and it does not cause harm unless the immune system is weakened.

## Half of patients with rare autoimmune rheumatic diseases face 3-year wait for diagnosis

People living with rare autoimmune rheumatic diseases are facing major obstacles to diagnosis, treatment and lifestyle.

A new report, *Reduce, Improve, Empower*, published by the Rare Autoimmune Rheumatic Diseases Alliance ([www.rheumatology.org.uk/Portals/0/Policy/Policy%20Report/RAIRDA%20Report\\_Web.pdf](http://www.rheumatology.org.uk/Portals/0/Policy/Policy%20Report/RAIRDA%20Report_Web.pdf); ver=2018-02-27-132208-213), reflects the experiences of more than 2000 people across the UK who are living with lupus, scleroderma or vasculitis. It found that almost half of those people had to wait more than 3 years between experiencing the first symptom of their condition and being correctly diagnosed, and they have continued to face ongoing struggles since.



Two-thirds of people living with one of these conditions reported needing to visit multiple hospitals in order to get the treatment and care they need. The impact of these rare conditions can be significant – one in five people reported missing more than 3 months of work in the past year as a result of their condition, with a similar proportion having

to give up work entirely.

Commenting on the results, Dr Peter Lanyon, chair of the Rare Autoimmune Rheumatic Diseases Alliance, said: ‘These findings are a stark reminder of the challenges that people living with these conditions face, from getting a diagnosis, to accessing treatment and to coping with the impacts on home, work and family life.’

### Discovery of new genes associated with osteoarthritis may pave the way for targeted therapies

To understand more about the genetic basis of osteoarthritis, 16.5 million DNA variations from the UK Biobank resource were studied (<https://doi.org/10.1038/s41588-018-0079-y>). Following combined analysis in up to 30 727 people with osteoarthritis and nearly 300 000 people without osteoarthritis in total, scientists discovered nine new genes that were associated with osteoarthritis, a significant breakthrough for this disease.

### Using topological data analysis to define asthma subtypes

Researchers have identified biological variations in lung tissue samples that for the first time can help identify people with mild asthma from those with moderate or severe asthma using topological data analysis (<https://doi.org/10.1016/j.jaci.2017.12.982>).

### Ontruzant is first breast cancer biosimilar launched in the UK

Ontruzant (trastuzumab), a biosimilar referencing Herceptin (trastuzumab), has been launched for the treatment of early breast cancer, metastatic breast cancer and metastatic gastric cancer. This is the first trastuzumab biosimilar to receive regulatory approval in Europe and is the first to launch in the UK.

## Long-term use of proton pump inhibitors does not increase risk of hip fracture in people with Alzheimer's disease

Hip fractures are a major health concern among older persons with Alzheimer's disease, who usually use many concomitant drugs for several diseases. Evidence of the association between proton pump inhibitor use and risk of hip fracture is contradictory.

A nested case-control study in Finland used the nationwide MEDALZ data (<https://doi.org/10.1111/apt.14589>). Community-dwelling people with Alzheimer's disease who encountered incident hip fracture ( $n=4818$ ; mean age 84.1 years) were included as cases. Four controls were matched for each case at the date of hip fracture ( $n=19235$ ; mean age 84.0 years). The association between hip fracture and duration of current proton pump inhibitor use (ongoing use during 0–30 days before the index date), and cumulative duration of use during 10 years before was investigated with conditional logistic regression.

The increased risk of hip fracture was evident only in short-term proton pump inhibitor use, but no association was found for long-term or cumulative use.

## Death rate from colorectal cancer predicted to have fallen by 7% since 2012

The decline in deaths from colorectal cancer is one of the major success stories of the past 30 years in Europe say researchers, as they predict that in 2018 death rates from the disease will continue to fall by around 7% compared to 2012 (Malvezzi et al, 2018).

They predict that death rates in the European Union for most cancers will continue to fall this year, compared to 2012, with the exceptions of deaths from cancers of the pancreas and lung in women, which will continue to rise.

Professor Carlo La Vecchia, Professor at the Faculty of Medicine, University of Milan, Italy, who led the research, says: 'Colorectal cancer is the most common cause of cancer death among non-smokers in both men and women. The fall in mortality that we are predicting for 2018 has been one of the major success stories in clinical oncology. This improvement in death rates in Europe comes in the absence of a single major breakthrough and is the result of improved diagnosis and management of the disease.'

The researchers looked at cancer death rates in the European Union 28 member states as a whole and also in the six largest



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countries – France, Germany, Italy, Poland, Spain and the UK – for all cancers, and, individually, for stomach, intestines, pancreas, lung, breast, uterus (including cervix), ovary, prostate, bladder and leukaemias for men and women. They say that in 2018 alone, about 392 300 cancer deaths will be avoided compared to the highest rates in the 1980s – 275 000 in men and 117 000 in women.

In their predictions for cancer deaths in the European Union for 2018, Professor La Vecchia and his colleagues predict that colorectal cancer will account for the second highest number of deaths with 177 400 (98 000 in men, 79 400 in women) dying from the disease. The numbers of deaths have risen since 2012 because of the growing population of elderly people; however, compared with 2012, the age standardized rates will fall by 6.7% in men to 15.8 per 100 000 of the population and 7.5% in women to 9.2 per 100 000.

Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C, Negri E (2018) European cancer mortality predictions for the year 2018 with focus on colorectal cancer. *Ann Oncol* <https://doi.org/10.1093/annonc/mdy033>

## Order of surgical procedures in operating list may affect operating time

In a new study of trained surgeons, the order in which surgical procedures were performed had a relationship with their duration (Pike et al, 2018).

A linear mixed-effects model and matched analysis were used to estimate the impact of list order and the cost of switching between procedures on a list while controlling for key prognosticators. The influence of procedure method (open *vs* minimally invasive) and complexity was also explored.

The linear mixed-effects model included 255 757 procedures, and the matched analysis 48 632 pairs of procedures. Repeating the same procedure in a list resulted in an overall time saving of 0.98% for each increase in list position.

Switching between procedures increased the duration by an average of 6.48%. The overall reduction in operating time from completing the second procedure straight after the first was 6.18%. This pattern was consistent across procedure method and complexity. Repeating the same procedure in a list resulted in shorter operating times, while switching between different procedures resulted in increased operating times. The effects were similar for open and minimally invasive procedures, and for procedures of differing complexity.

Commenting on the findings, Dr Faisal Mushtaq from the Faculty of Medicine and Health, University of Leeds, Leeds, said: 'This study demonstrates the existence of a natural "warm-up" effect as surgeons

work their way through their operating lists. Reductions in operating time come from repeating the same procedure, but this saving is lost when surgeons are asked to perform a different type of procedure on the same list.'

The authors concluded that there is a robust relationship between operating list composition and surgical performance (indexed by duration of operation). An evidence-based approach to structuring a theatre list could reduce total operating time.

Dr Mushtaq added: 'This is an important development in our understanding of how to optimize surgical performance.'

Pike TW, Mushtaq F, Mann RP et al (2018) Operating list composition and surgical performance. *Br J Surg* <https://doi.org/10.1002/bjs.10804>

## Pre-eclampsia screening method found superior to current tests

New research (Tan et al, 2018) highlights a more accurate way to screen for pre-eclampsia in pregnant women than currently recommended methods.

The Screening ProgRamme for prE-Eclampsia (SPREE) study compares first trimester screening for pre-eclampsia by this alternative approach with the current National Institute for Health and Care Excellence guideline. The alternative approach combines known risk factors with the results of various maternal biophysical and biochemical measurements taken at 11–13 weeks' gestation: mean arterial pressure, uterine artery pulsatility index and serum placental growth factor; known as the first-trimester combined test.

Pre-eclampsia occurring at any point during pregnancy (all-PE) was found in 473 (2.8%) of 16 747 pregnancies and preterm pre-eclampsia was seen in 142 (0.8%). The detection rates of the National Institute for Health and Care Excellence checklist for all-PE and preterm pre-eclampsia were 30.4% and 40.8% respectively. Screening carried out by the first-trimester combined test increased the detection rates for all-PE and preterm pre-eclampsia to 42.5% and 82.4% respectively.

Furthermore, compliance with the National Institute for Health and Care Excellence recommendation that women at high risk for pre-eclampsia should be treated with aspirin from the first trimester was only 23%.

'The SPREE study has provided definitive proof to support risk-based screening for preterm-PE using various biomarkers. It is now time to revise the professional guidelines and to move away from using a checklist-based method for screening' said co-senior author Dr Liona Poon, Clinical Senior Lecturer in Women's Health, King's College London, London.

Tan MY, Wright D, Syngelaki A et al (2018) Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol* <https://doi.org/10.1002/uog.19039>



**Dr Liona Poon, Clinical Senior Lecturer in Women's Health, King's College London, London**

## Extrafine inhaled triple therapy vs dual bronchodilators in patients with chronic obstructive pulmonary disease

A randomized, parallel-group, double-blind trial compared a single inhaler triple combination of beclometasone dipropionate, formoterol fumarate and glycopyrronium *vs* a single inhaler dual bronchodilator combination of indacaterol plus glycopyrronium in terms of the rate of moderate-to-severe chronic obstructive pulmonary disease exacerbations over 52 weeks of treatment (Papi et al, 2018).

Eligible patients had symptomatic chronic obstructive pulmonary disease, severe or very severe airflow limitation, at least one moderate or severe exacerbation in the previous year, and were receiving inhaled maintenance medication. After a 2-week run-in period, patients were randomly assigned to receive 52 weeks of treatment with two inhalations of extrafine triple therapy twice per day or one inhalation of dual bronchodilator therapy per day. The primary endpoint was the rate of moderate-to-

severe chronic obstructive pulmonary disease exacerbations across 52 weeks of treatment in all randomized patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment.

The authors concluded that in patients with symptomatic chronic obstructive pulmonary disease, severe or very severe airflow limitation, and an exacerbation history despite maintenance therapy, extrafine triple therapy significantly reduced the rate of moderate-to-severe exacerbations compared with dual bronchodilator therapy without increasing the risk of pneumonia.

Papi A, Vestbo J, Fabbri L et al (2018) Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* **391**(10125): 1076–1084. [https://doi.org/10.1016/S0140-6736\(18\)30206-X](https://doi.org/10.1016/S0140-6736(18)30206-X)

## Challenging the obesity paradox in Caucasian adults

The idea that it might be possible to be overweight or obese but not at increased risk of heart disease, otherwise known as the 'obesity paradox', has been challenged by a study of nearly 300 000 people (Iliodromiti et al, 2018).

This research shows that the risk of heart and blood vessel problems, such as heart attacks, strokes and high blood pressure, increases as body mass index increases beyond 22–23 kg/m<sup>2</sup>. The risk also increases steadily the more fat a person carries around his/her waist.

The study was conducted in 296 535 adults of white European descent who are taking part in the UK Biobank study, and who were healthy at the time they enrolled with the study. UK Biobank recruited from 2006 to 2010, and follow-up data on participants were available up to 2015 for this latest analysis.

Researchers at the University of Glasgow, led by Dr Stamatina Iliodromiti, a clinical lecturer in obstetrics and gynaecology and MRC Fellow, found that people with a body mass index between 22 and 23 kg/m<sup>2</sup> had the lowest risk of cardiovascular disease. As body mass index increased above 22 kg/m<sup>2</sup>, the risk of cardiovascular disease increased by 13% for every 5.2 kg/m<sup>2</sup> increase in women and 4.3 kg/m<sup>2</sup> in men.

Dr Iliodromiti commented: 'This is the largest study that provides evidence against the obesity paradox in healthy people. It is possible that the story may be different for those with pre-existing disease because there is evidence that in cancer patients, for instance, being slightly overweight is associated with lower risk, especially as cancer and its treatments can lead to unhealthy weight loss.'

Iliodromiti S, Celis-Morales CA, Donald M, Lyall DM et al (2018) The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: a cohort study of 296 535 adults of white European descent. *Eur Heart J* <https://doi.org/10.1093/eurheartj/ehy057>