

## Stillbirth rate in twin pregnancies reduced by over 40% from 2014–16

The latest MBRRACE-UK report (<https://www.npeu.ox.ac.uk/mbrrace-uk/reports>) shows that the stillbirth rate associated with twin pregnancy in the UK has reduced by around 44% from 2014 to 2016. Rates of neonatal mortality associated with twin pregnancy have similarly reduced by a third. The increased risk of stillbirth and neonatal death in twin pregnancies compared to singleton pregnancies has also reduced by just less than a third.

Although the stillbirth and neonatal deaths rates overall are reducing over time the reduction in these rates between 2013 and 2016 is only around 6.5%. Targeted initiatives are required to reduce rates more rapidly if the current government ambition to halve the rates of stillbirth and neonatal death in England by 2025 is to be met.

## Inhaled nitric oxide decreases acute and chronic kidney disease after cardiac surgery

Administration of nitric oxide during and for 24 hours after heart surgery decreased the risk of patients developing acute and chronic kidney problems, found a randomized, controlled trial (<https://doi.org/10.1164/rccm.201710-21500C>).

Researchers studied 244 adults who underwent multiple cardiac valve replacement and required placement on cardiopulmonary bypass for at least 90 minutes.

Patients who received 80 parts per million of nitric oxide during and for 24 hours after surgery were less likely to develop acute kidney injury, with a decrease from 64% in the placebo-treated patients to 50% in those who received nitric oxide.

The risk of progressing to stage 3 chronic kidney disease was also reduced at 90 days, from 33% in the placebo-treated patients to 21% in those who received nitric oxide. After 1 year, 31% in the placebo group had serious kidney disease compared to 18% in the nitric oxide group.

## Children with neuroblastoma have an elevated risk of long-term psychological difficulties

Paediatric neuroblastoma patients are at elevated risk for long-term psychological impairment. In addition, those who experience such impairment as they get older tend to require special education services and to not go on to college (Zheng et al, 2018).

In the USA, neuroblastoma is diagnosed at a median age of 17.3 months. Treatment advances have prolonged survival for many affected children, but the young age at diagnosis and treatments used can make them vulnerable to health problems as their CNS develops.

To assess the long-term psychological effects of neuroblastoma and its treatment, Dr Nina Kadan-Lottick, of Yale University School of Medicine, and her colleagues studied 859 children who had been diagnosed with neuroblastoma at least 5 years earlier and were under 18 years old. Their median age at diagnosis was 0.8 years, and they were followed for a median of 13.3 years. These 859 neuroblastoma survivors were compared with 872 siblings of childhood cancer survivors.

Compared with siblings, neuroblastoma survivors had increased prevalence of impairment in the domains of anxiety and depression (19% vs 14%), headstrong behaviour



**Dr Nina Kadan-Lottick, Associate Professor of Pediatrics, Leader, Pediatric Oncology Clinical Trials, Section of Pediatric Hematology-Oncology, Yale University School of Medicine, New Haven, CT, USA**

(19% vs 13%), attention deficits (21% vs 13%), peer conflict or social withdrawal (26% vs 17%), and antisocial behaviour (16% vs 12%).

Common treatments – vincristine, cisplatin and retinoic acid – were not associated with impairment, but survivors who developed chronic health conditions as a result of their cancer treatment were at higher risk for developing worse outcomes.

‘Before recent advances in treatment, this survivor population was much smaller and we were not able to analyse these sorts of long-term outcomes,’ said Dr

Kadan-Lottick. ‘The goal is not simply to get our patients to be cancer-free but also to optimize their mental, emotional and social functioning as they move into adolescence and adulthood. Our hope is that these findings will help inform strategies for early screening and intervention to identify those survivors at highest risk for developing psychological and educational impairment later on in life.’

Zheng DJ, Krull KR, Chen Y et al. Long-term psychological and educational outcomes for survivors of neuroblastoma: A report from the Childhood Cancer Survivor Study. *Cancer*. 2018 Jun 11. <https://doi.org/10.1002/cncr.31379>

## Frailty is still fatal and an indicator of mortality

A new study (<https://doi.org/10.1093/ageing/afy07>) has found that the relationship between higher levels of frailty and mortality remains unchanged, despite death rates in the UK now being much lower than in the 1990s. Reduced mortality rates in older age appear to apply to those with little frailty, while older people with higher levels of frailty are not seeing a benefit.

The study drew its conclusions from two large studies of older people in England, conducted 20 years apart to test whether the amount of frailty has changed over time, and whether the relationship between frailty and death has changed.

Despite a slight increase in the frailty of the population, and a marked decrease in the mortality of the general population over the age of 65 years, the relationship between frailty and 2-year mortality has been relatively stable. This complex relationship may be partly accounted for by a reduction of mortality at lower levels of frailty and improved diagnosis.

The findings also agree with previous reports that women have higher frailty scores but lower mortality than men, indicating that although men generally have better health in older age, women tend to live longer.

## Mothers with mental illness can prevent mental disorders reoccurring in their children

International research has established for the first time that a child whose mother has a mental illness but has been part of a nurturing family environment, pre- and post-pregnancy, is less likely to suffer from a mental disorder in later life than those who grew up in a less supportive environment (Essau et al, 2018).

The study used data from the Oregon Adolescent Depression Project, a 16-year study of a large cohort of high school students and their mothers who were randomly selected from nine high schools in western Oregon, USA. Over 300 participants completed all four stages of the research. Information about the mothers was obtained by a detailed questionnaire.

The psychiatric disorders of the mothers included in the research included anxiety disorders, post-traumatic stress disorder, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, alcohol abuse and drug dependency.



**Professor Cecilia A Essau, Professor of Developmental Psychopathology, Department of Psychology, Roehampton University, London**

Commenting on the results Professor Cecilia A Essau, Professor of Developmental Psychopathology at the University of Roehampton, London, said: 'For decades many mothers suffering from addictions and mental illness believed there was little they could do to prevent their own children from suffering a similar fate. Many women will have been put off having children in the fear that they will pass on their illness to their offspring.'

She continued: 'Our research now shows that women can prevent passing on their illness by providing a supportive family environment. It's a heartening signal of hope to women with mental illness who will be able to enjoy the love of the children without fearing that they were inflicting on them a life of poor health.'

Essau CA, Sasagawa S, Lewinsohn PM, Rohde P. The impact of pre- and perinatal factors on psychopathology in adulthood. *J Affect Disord.* 2018 Aug 15;236:52-59. <https://doi.org/10.1016/j.jad.2018.04.088>

## Immunocompromised patients with sepsis may have lower mortality at hospitals treating more cases

Immunosuppressed patients with sepsis appear more likely to die if they are treated in a hospital caring for a relatively small number of these patients (Greenberg et al, 2018).

Researchers analysed the medical records of 350 183 patients with sepsis at 60 American hospitals. One of five of those patients was classified as being immunocompromised.

The study found 15% of immunosuppressed patients with sepsis died during hospitalization compared to 12% of non-immunosuppressed patients with sepsis at all hospitals. At hospitals seeing fewer than 225 immunosuppressed patients with sepsis each year, these patients were 38% more likely to die while hospitalized, compared to 21% more likely to die at hospitals that saw 225 or more of these patients yearly.

Immunosuppressed patients with sepsis were more likely than non-immunosuppressed

patients to return to their homes after discharge, rather than another health facility (60% *vs* 50%). This was a surprise – the authors believe that non-immunosuppressed patients may have been more likely to be experiencing declining states of health before sepsis than immunosuppressed patients.

The results do not explain why immunosuppressed patients fared better at hospitals treating large numbers of such patients. The authors speculate that 'immunosuppressed patients with sepsis had improved survival at hospitals where clinicians had greater familiarity caring for immunosuppressed patients.'

Greenberg JA, Hohmann SF, James BD, Shah RC, Hall JB, Kress JB, David MZ. Hospital volume of immunosuppressed sepsis patients and sepsis mortality. *Ann Am Thorac Soc.* 2018 Jun 1. <https://doi.org/10.1513/AnnalsATS.201710-819OC>

### Exposure to smoking before and after birth linked to hearing impairment in toddlers

Exposure to tobacco smoke pre- and postnatally was associated with hearing impairment in young children in Japan (<https://doi.org/10.1111/ppe.12477>). The prevalence of hearing impairment at 3 years of age was 4.6%. The increased relative risk of hearing impairment was 1.26 in children exposed to only maternal past smoking during pregnancy, rising to 2.35 in those exposed to smoking during pregnancy and second-hand smoke at 4 months.

### Surgery more effective than physiotherapy for groin pain

The first randomized trial to compare hip arthroscopy and physiotherapy in the treatment of femoroacetabular impingement syndrome ([https://doi.org/10.1016/S0140-6736\(18\)31202-9](https://doi.org/10.1016/S0140-6736(18)31202-9)) found a greater, clinically significant, improvement with surgery than physiotherapy.

### First two-drug regimen for HIV launched in the UK

Dolutegravir/rilpivirine has been launched in the UK for the treatment of HIV infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/ml) on a stable antiretroviral regimen for at least 6 months, with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

55th ERA-EDTA Congress Copenhagen, Denmark, 24–27 May

**Ferric citrate extends dialysis-free life in patients with advanced chronic kidney disease**

In a single-centre study, the phosphate binder ferric citrate improved mineral metabolism and haemoglobin in patients with advanced chronic kidney disease, regardless of baseline serum phosphate, haemoglobin or iron sufficiency.

The study randomized 203 patients to either ferric citrate 210 mg (two per meal) or standard of care. Compared with standard of care, by month 9 ferric citrate resulted in significant increases in mean transferrin saturation, ferritin and haemoglobin and significant reductions in mean serum phosphate and intact FGF23. Time to renal replacement therapy or death was significantly longer in the ferric citrate group both overall and in patients with diabetes.

Lead investigator Professor Geoffrey Block, associate clinical professor in medicine, University of Colorado Health Sciences Center, Denver, USA, concluded that the results justify a larger, randomized, placebo-controlled trial to validate the effects on patient outcomes.

Block G, Block M, Smits G et al. Randomized trial of the effects of ferric citrate in patients with advanced chronic kidney disease. Abstract LB05

**Abatacept does not improve remission rate in lupus nephritis, but leads to faster falls in proteinuria**

In the phase 3 ALLURE study, compared with placebo, the T-cell co-stimulation modulator abatacept did not improve the rate of complete remission in active class III or IV lupus nephritis. However, abatacept-treated patients had more rapid improvement in proteinuria, which led to earlier sustained complete remission.

Lead investigator Professor David Jayne, Professor of Clinical Autoimmunity, University of Cambridge, Cambridge, said: ‘The disparity between effects on the biology of the disease and on disease-related biomarkers, while failing to show improvements on 1-year remission endpoints, remains a major challenge for assessing newer therapies in lupus nephritis... We must now wait for the complete longitudinal data after 2 and 3 years to establish whether there are any long-term differences between the groups.’

The largest lupus nephritis trial to date, ALLURE was a 24-month, randomized, multicentre, double-blind study that assigned 405 patients to placebo or abatacept on a background of mycophenolate and

© ERA-EDTA 2018



**Professor David Jayne, Professor of Clinical Autoimmunity, University of Cambridge, Cambridge**

corticosteroids. On the primary endpoint, there was no significant difference in the proportion of patients achieving complete remission at 1 year (abatacept 35.1% vs placebo 33.5%,  $P=0.73$ ).

Sustained complete remission occurred earlier and more frequently in abatacept-treated patients. These benefits were driven by improved proteinuria, seen as early as 3 months and driven by a rapid effect on urine protein concentration (day 15 mean change from baseline: abatacept -717

(standard error 186), placebo -51 (standard error 180)).

Abatacept had no adverse effect on renal function. Safety was consistent with the known profile of abatacept, with rates of serious adverse events similar to placebo. Deaths were similar at year 2 (abatacept 7, placebo 6).

Jayne D, Dooley MA, Wofsy D et al. A phase III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept or placebo on standard of care in patients with active class III or IV lupus nephritis. Abstract LB03

**Type 2 diabetes doubles cardiac disease risk in chronic kidney disease**

Type 2 diabetes doubled the risk of cardiovascular disease in patients with chronic kidney disease in a Danish study. The odds ratio of cardiovascular disease in diabetes patients was 1.9 (95% confidence interval 1.13–3.27) vs 0.67 (95% confidence interval 0.44–1.02) in patients with normal fasting blood glucose and no history of diabetes.

According to investigator Professor Bo-Feldt Rasmussen, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark: ‘Chronic kidney

disease patients who also have diabetes mellitus are seriously ill, high-risk patients. They have a worse prognosis than many cancer patients. We have to do everything we can to prevent chronic kidney disease patients from developing diabetes and raise kidney patients’ awareness of preventive measures.’

The study involved 496 patients, including 78 (15.7%) with known type 2 diabetes, 28 (5.7%) with previously undiagnosed type 2 diabetes and 87 (17.5%) with pre-diabetes. Cardiovascular

disease prevalence was highest among chronic kidney disease patients with known type 2 diabetes (51.3%) and lowest in patients without diabetes (23.1%).

Mean body mass index was higher and activity levels lower in the known diabetes group compared with the no-diabetes group. There were no significant differences between the four groups in systolic or diastolic blood pressure.

Dyhr RL, Hornum M, Trankaer H et al. Diabetes and cardiovascular disease in the Copenhagen Chronic Kidney Disease Cohort. Abstract SP427

Sue Lyon

© 2018 MA Healthcare Ltd

## Antidepressant use and incidence of weight gain during 10-year follow up

A population-based cohort study has evaluated the long-term association between antidepressant prescribing and body weight (Gafoor et al, 2018).

The study included 136 762 men and 157 957 women with three or more records for body mass index from general practices contributing to the UK Clinical Practice Research Datalink, 2004–14.

The main outcomes were antidepressant prescribing, incidence of  $\geq 5\%$  increase in body weight, and transition to overweight or obesity. Adjusted rate ratios were estimated adjusting for age, sex, depression recording, comorbidity, coprescribing of antiepileptics or antipsychotics, deprivation, smoking, and advice on diet.

In the year of study entry, 17 803 (13.0%) men and 35 307 (22.4%) women with a mean age of 51.5 years (standard deviation 16.6 years) were prescribed antidepressants. During 1 836 452 person years of follow up, the incidence of new episodes of  $\geq 5\%$  weight gain in participants not prescribed antidepressants was 8.1 per 100 person years and in participants prescribed antidepressants was 11.2 per 100

person years (adjusted rate ratio 1.21, 95% confidence interval 1.19–1.22,  $P < 0.001$ ). The risk of weight gain remained increased during at least 6 years of follow up.

Professor Martin Gulliford, Professor of Public Health, King's College London, London, commented: 'From a clinical perspective, these observations reinforce the need for active weight management to accompany prescribing of antidepressant treatments. These results should be set in the context of increasing body mass index in the general population. Very widespread use of antidepressants may be contributing to increasing overweight and obesity at population level.'

Gafoor R, Booth HP, Gulliford MC. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study. *BMJ*. 2018 May 23;361:k1951. <https://www.bmj.com/content/361/bmj.k1951>



**Professor Martin Gulliford,**  
Professor of Public Health,  
King's College London, London

## More weight loss is better in overweight and obese adults with knee osteoarthritis

Researchers previously showed that overweight and obese individuals with knee osteoarthritis can reduce pain by 50% and significantly improve function and mobility with a 10% or more weight loss over an 18-month period. The investigators' latest findings reveal that a 20% or more weight loss has the added benefit of continued improvement in physical health-related quality of life along with an additional 25% reduction in pain and improvement in function (Messier et al, 2018).

The results come from a secondary analysis of diet-only and diet plus exercise groups in the Intensive Diet and Exercise for Arthritis (IDEA) randomized controlled trial. A total of 240 overweight and obese older community-dwelling adults with pain and knee osteoarthritis were divided into four groups according to weight loss achieved over 18 months: less than 5%, between 5 and 9.9%, between 10 and 19.9%, and 20% and greater.

The greater the weight loss, the better participants fared in terms of pain, function, 6-minute walk distance, physical and mental health-related quality of life, knee joint compression force, and IL-6 (a marker of inflammation). Comparing the two highest groups, the  $\geq 20\%$  group had 25% less pain and better function than the  $\geq 10\%$  group, and significantly better health-related quality of life.

Lead author Dr Stephen Messier, of Wake Forest University, Winston-Salem, North Carolina, USA, commented: 'The importance of our study is that a weight loss of 20% or greater – double the previous standard – results in better clinical outcomes, and is achievable without surgical or pharmacological intervention.'

Messier SP, Resnik AE, Beavers DP et al. Intentional weight loss for overweight and obese knee osteoarthritis patients: is more better? *Arthritis Care Res (Hoboken)*. 2018 Jun 18. <https://doi.org/10.1002/acr.23608>

## Right ventricular function during exercise in children after heart transplantation

Right ventricular dysfunction is a common problem after heart transplant. A research team from Toronto, Canada evaluated right ventricular systolic and diastolic reserve in paediatric heart transplant recipients (Cifra et al, 2018).

Thirty-nine paediatric heart transplant recipients and 23 controls underwent stepwise semi-supine bicycle ergometry stress echocardiography. A range of parameters were measured at incremental heart rates. The relationship with increasing heart rate was evaluated for each parameter.

At rest, heart transplant recipients had higher heart rate with lower tissue Doppler imaging velocities and right ventricular myocardial acceleration during isovolumic contraction values, while right ventricular free wall longitudinal strain was similar between groups. At peak exercise, heart rate was higher in controls and all measurements of right ventricular function were significantly lower in heart transplant recipients, except for right ventricular free wall longitudinal strain. When assessing the increase in each parameter vs heart rate, the slopes were not significantly different between patients and controls except for myocardial acceleration during isovolumic contraction, which was lower in heart transplant recipients.

In paediatric heart transplant recipients right ventricular systolic and diastolic functional response to exercise is preserved. The blunted myocardial acceleration during isovolumic contraction response possibly indicates a mildly decreased right ventricular contractile response but this requires further investigation.

Cifra B, Morgan CT, Dragulescu A et al. Right ventricular function during exercise in children after heart transplantation. *Eur Heart J Cardiovasc Imaging*. 2018 Jun 1;19(6):647-653. <https://doi.org/10.1093/ehjci/jex137>