

Benzodiazepine use not linked to increased dementia risk

Taking benzodiazepines (widely used to treat anxiety and insomnia) is not associated with an increased dementia risk in older adults, finds a study of 3434 participants aged 65 years and older without dementia at study entry, who were followed for an average of 7 years (Gray et al, 2016).

Although these results do not support a direct (causal) association between benzodiazepine use and dementia, clinicians are still advised to avoid using benzodiazepines in older adults to prevent important adverse health outcomes.

Gray SL, Dublin S, Yu O et al (2016) Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. *BMJ* 352: i90 (doi: 10.1136/bmj.i90)

PET scans overused to detect lung and oesophageal cancer recurrences

Positron emission tomography (PET) scans are frequently used to detect recurrence of cancer in asymptomatic patients.

In order to determine the efficacy of PET scans in detecting recurrence, a team from the University of Michigan looked at the national Surveillance, Epidemiology, and End Results and Medicare-linked data of 101 598 patients with primary lung and oesophageal cancers from 2005 to 2009, with follow-up through 2011. The researchers looked at lung and oesophageal cancers because of their comparable poor diagnoses and general anatomical location.

The researchers found a statistically significant difference in the use of PET in the lowest vs highest PET using hospitals, but no association between the use of PET and 2-year survival.

Healy MA, Yin H, Reddy RM, Wong SL (2016) Use of positron emission tomography to detect recurrence and associations with survival in patients with lung and oesophageal cancers. *J Natl Cancer Inst* (doi: 10.1093/jnci/djv429)

Weight gain between pregnancies increases risk of stillbirth and infant mortality

A study carried out in Sweden aimed to assess whether a change in body mass index between first and second pregnancies affected the risk of stillbirth and infant mortality in the second-born offspring (Cnattingius and Villamor, 2016).

In a Swedish population-based cohort of women who gave birth to their first and second child between 1 January 1992 and 31 December 2012, researchers investigated associations between change in maternal body mass index during early pregnancy from the first to second pregnancies and risks of stillbirth and neonatal, postneonatal, and infant mortality after the second pregnancy. Relative risks for each outcome according to body mass index change categories were calculated using binomial regression.

Professor Sven Cnattingius, Department of Medicine, Karolinska Institutet, Stockholm, Sweden



Complete information was available for 456 711 (77.7%) of 587 710 women who had their first and second single births during the study period. Compared with women with a stable body mass index (change between -1 kg/m² and <1 kg/m²)

between pregnancies, the adjusted relative risks for women who gained at least 4 body mass index units between pregnancies were 1.55 (95% confidence interval 1.23–1.96) for stillbirth and 1.29 (1.00–1.67) for infant mortality. Stillbirth risks increased linearly with increased body mass index gain.

Risks of infant mortality in second pregnancy only increased with body mass index gain in women who had a healthy body mass index (<25 kg/m²) during their first pregnancy; the adjusted relative risk for healthy weight women who gained 2 to less than 4 body mass index units was 1.27 (1.01–1.59) and for those who gained 4 body mass index units or more the adjusted relative risk was 1.60 (1.16–2.22). In overweight women (body mass index ≥ 25 kg/m²), weight loss before pregnancy reduced the risk of neonatal mortality.

Professor Sven Cnattingius of the Department of Medicine, Karolinska Institutet, Stockholm, Sweden, commented: ‘The take home message for clinicians and women is that after delivery, women should be advised to return to their prepregnancy weight – if they started off as overweight they should strive to reduce their weight even more.’

Cnattingius S, Villamor E (2016) Weight change between successive pregnancies and risks of stillbirth and infant mortality: a nationwide cohort study. *Lancet* 387(10018): 558–65 (doi: 10.1016/S0140-6736(15)00990-3)

Cancer death rates fall by 12% for men and 8% for women in 10 years

According to the latest analysis from Cancer Research UK the rate of cancer deaths has fallen, and this is largely the result of improvements in detection, diagnosis and treatments. Further encouraging news is seen in the narrowing gap between men and women’s cancer death rates.

Men’s death rates have fallen by 12% from 2003 to 2013, compared to an 8% drop for women over the same period. This equates to around 85 000 men and 77 000 women dying from cancer each year in the UK.

Four cancers – lung, bowel, breast and prostate – cause almost half (46%) of all

cancer deaths in the UK and accounted for over half (53%) of all new cancer cases in the UK in 2013. The combined death rate for these four cancers mirrors the overall fall, dropping by around 11% over the last 10 years, from 146 people per 100 000 in 2003 to 131 people per 100 000 in 2013.

However, for some cancers, such as liver and pancreatic, the rates of people dying from the disease have increased over the last decade.

The full report can be accessed at www.cancerresearchuk.org/health-professional/cancer-statistics

Effects of iron replacement on gut microbiota in patients with inflammatory bowel disease

Iron deficiency is a common complication in patients with inflammatory bowel disease and oral iron therapy is thought to exacerbate inflammatory bowel disease symptoms. An international and interdisciplinary research group has investigated how the intestinal microbiota responds to oral or intravenous iron replacement (Lee et al, 2016).

An open-labelled clinical trial compared the effects of oral *vs* intravenous iron replacement therapy. The study included patients with Crohn's disease ($n=31$), ulcerative colitis ($n=22$) and control subjects with iron deficiency (non-inflamed, $n=19$). After randomization, participants received iron sulfate (oral) or iron sucrose (intravenous) over 3 months. Clinical parameters, faecal bacterial communities and metabolomes were assessed before and after intervention.

Both oral and intravenous treatments ameliorated iron deficiency, but higher ferritin levels were seen with intravenous iron. Changes in disease activity were independent of iron treatment types. Faecal samples in patients with inflammatory bowel disease were characterized by marked interindividual

differences. Metabolite analysis also showed separation of both ulcerative colitis and Crohn's disease from control anaemic participants. Bacterial diversity changed substantially in about half of all participants after iron replacement therapy, but patients with Crohn's disease were most susceptible.

Clear intravenous-specific and oral-specific fingerprints were evident at the level of metabolomes, with changes affecting cholesterol-derived host substrates. Shifts in gut bacterial diversity and composition associated with iron treatment were pronounced in participants with inflammatory bowel disease. Despite similar clinical outcomes, oral or intravenous administration affects bacterial phylotypes and faecal metabolites in different ways.

Commenting on the results, Professor Dirk Haller of the Technical University of Munich, said: 'The study shows how fragile the stability of the microbial community is, especially in patients with Crohn's disease.'

Lee T, Clavel T, Smirnov K et al (2016) Oral versus intravenous iron replacement therapy distinctly alters the gut microbiota and metabolome in patients with IBD. *Gut* (doi: 10.1136/gutjnl-2015-309940)

Professor Dirk Haller, Chair of Nutrition and Immunology, ZIEL Institute for Food & Health, Technical University of Munich, Munich, Germany



Pregnant women hold key to beating Gambian sleeping sickness

It has long been assumed that the most common strain of the sleeping sickness – chronic Gambian sleeping sickness – is spread solely through tsetse flies. But Gambian sleeping sickness is rarely detected in tsetse flies and a team at the University of Edinburgh has proposed an alternative human to human mode of transmission (Welburn et al, 2016).

In humans, the disease can lie dormant for many years without causing symptoms. These 'silent carriers' have a natural tolerance to the disease, which women would ordinarily pass on to their baby if they become pregnant.

The researchers suggest that in times of famine, changes occur in a pregnant woman's

genetic profile that mean that her tolerance is not passed on to her children but the dormant infection is.

Professor Sue Welburn, Professor of Medical and Veterinary Molecular Epidemiology at the University of Edinburgh said: 'Our priority should now be to concentrate on screening women of child-bearing age in high risk locations to ensure they receive adequate nutrition during periods of drought and famine.'

Welburn SC, Molyneux DH, Maudlin I (2016) Beyond tsetse – implications for research and control of human African trypanosomiasis epidemics. *Trends Parasitol* 32(3): 230–41 (doi: 10.1016/j.pt.2015.11.008)

Screening all English hospital admissions for MRSA is not cost effective

Mathematical modelling (doi: 10.1016/S1473-3099(15)00417-X) has shown that screening all patients admitted to hospital for methicillin-resistant *Staphylococcus aureus* (MRSA) is unlikely to be cost effective in England at the current NHS willingness-to-pay threshold. Screening admissions to high-risk specialties is likely to be more cost effective in terms of cost per quality-adjusted life-year gained.

Safety of ivacaftor in children with cystic fibrosis

In an open-label, single-arm study ivacaftor at doses of 50 mg and 75 mg seems to be safe in children aged 2–5 years with cystic fibrosis with a gating mutation followed up for 24 weeks (doi: 10.1016/S2213-2600(15)00545-7). The frequency of elevated liver function tests suggests that careful monitoring of young children is needed, particularly those with a history of elevated liver function tests.

National smoking bans have reduced harm from passive smoking

An updated Cochrane review has found that populations of countries where smoking bans have been imposed have benefited from reduced exposure to passive smoke, specifically decreasing cardiovascular disease (doi: 10.1002/14651858.CD005992.pub3).

DNA 'molecular scissors' are vital in preventing cancers

'Molecular scissors' that repair damaged and abnormal DNA are critical for keeping cancers at bay (Lachaud et al, 2016).

A protein called FAN1 plays an important role during the copying of chromosomes that occurs whenever cells divide. In particular, the ability of FAN1 to recognize and cut special types of abnormal structures inside cells during the copying of DNA is important for preventing cancers, particularly of the lungs, liver and pancreas. Moreover, it appears that certain cancers may be caused by failure of FAN1 to cut DNA in the way it is supposed to.

Professor John Rouse, of the University of Dundee's Medical Research Council Protein Phosphorylation and Ubiquitination Unit, commented: 'Other scientists have reported that Fan1 is mutated in pancreatic cancers, and we showed that in these cancers Fan1 is not able to recognise the abnormal structures that need to be cut. This leads the genome of these cells to become abnormal accounting for the cancers.'

Lachaud C, Moreno A, Marchesi F, Toth R, Blow JJ, Rouse J (2016) Ubiquitinated Fancd2 recruits Fan1 to stalled replication forks to prevent genome instability. *Science* (doi: 10.1126/science.aad5634)

Testosterone gel improves sexual function, walking ability and mood in men aged over 65 years

Serum testosterone concentrations decrease as men age, but benefits of raising testosterone levels in older men have not been established. The Testosterone Trials are a coordinated set of seven double-blind, placebo-controlled trials being conducted at 12 sites across the USA.

Participants received testosterone gel or placebo gel for 1 year. Efficacy was assessed at baseline and at 3, 6, 9 and 12 months. Data on adverse events were collected during the treatment period and for 12 months afterward.

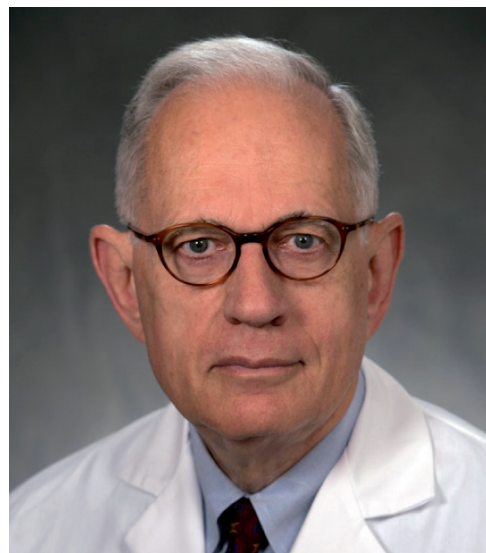
They found that testosterone treatment increased the blood testosterone level in men

65 years and older to levels comparable to mid-normal for young men (Snyder et al, 2016). Testosterone improved all aspects of sexual function, including sexual activity, sexual desire and the ability to get an erection. Testosterone treatment did not significantly improve distance walked in 6 minutes when only men enrolled in the physical function trial were considered, but did increase the distance walked when all men in the TTrials were considered. Testosterone did not improve energy, but did improve mood and depressive symptoms.

Across the three trials, adverse events were similar in men who received testosterone and those who received placebo. However, the number of men in the TTrials was too small to draw conclusions about the risks of testosterone treatment.

'The results of the TTrials show for the first time that testosterone treatment of older men ... does have some benefit,' said lead author and principal investigator of the TTrials Dr Peter J Snyder, a professor in the Division of Endocrinology, Diabetes and Metabolism at Penn. 'However, decisions about testosterone treatment for these men also will depend on the results of the other four trials ... and the risks of testosterone treatment.'

Dr Peter J Snyder, Medical Director, Penn Pituitary Center, Perelman Center for Advanced Medicine, Philadelphia, Pennsylvania, USA



Snyder PJ, Bhasin S, Cunningham GR et al; Testosterone Trials Investigators (2016) Effects of testosterone treatment in older men. *N Engl J Med* 374(7): 611–24 (doi: 10.1056/NEJMoa1506119)

Air pollution and lung function in ethnic minority children with asthma

Adverse effects of exposure to ambient air pollution on lung function are well documented but evidence in ethnic minority children is lacking. An American study (Neophytou et al, 2016) looked at 1449 Latino and 519 African American children with asthma, aged 8–21 years old, from five different geographical regions in mainland USA and Puerto Rico.

The researchers examined five pollutants (particulate matter $\leq 10 \mu\text{m}$ (PM10) and $2.5 \mu\text{m}$ in diameter (PM2.5), ozone, nitrogen dioxide and sulphur dioxide), derived from participant residential history and ambient air

monitoring data, and assessed over several time windows. Among others, they tested for interaction terms between exposures and genetic ancestry.

A $5 \mu\text{g}/\text{m}^3$ increase in average lifetime PM2.5 exposure (the most common cause of health problems from air pollution) was associated with a 7.7% decrease in forced expiratory volume in 1 second (95% confidence interval = -11.8%, -3.5%) in the overall study population. Global genetic ancestry did not appear to significantly modify the effect that environmental exposures had on lung function, but percent African

ancestry was a significant predictor of lung function.

Early-life particulate exposures were associated with reduced lung function in Latino and African American children with asthma. This is the first study to report an association between exposure to fine particulate matter and reduced lung function in minority children in which ethnic status was measured by genome-wide genetic ancestry.

Neophytou AM, White MJ, Oh SS et al (2016) Air pollution and lung function in minority youth with asthma in the GALA II & SAGE II studies. *Am J Respir Crit Care Med* (doi: 10.1164/rccm.201508-1706OC)

Symptoms of knee instability are risk factors for recurrent falls

Symptoms of knee instability in older adults may indicate an increased risk of falling and of experiencing the various physical and psychological consequences of falling (Nevitt et al, 2016). Determining effective treatments for knee instability should be an important priority as clinicians care for aging patients.

Dr Michael Nevitt, Professor in the Department of Epidemiology and Biostatistics, University of California, San Francisco, and his colleagues prospectively studied 1842 participants in the Multicenter Osteoarthritis Study (MOST) who were an average of 67 years old at the start and who had, or were at high risk for, knee osteoarthritis.

At the end of 5 years 16.8% reported knee buckling, and at the end of 7 years 14.1% had recurrent (≥ 2) falls. Patients who reported knee instability at year 5 had a 1.6–2.5-times higher likelihood of recurrent falls, fear of falling and poor balance confidence at year 7. Those who fell when a knee buckled at the start of the study had four and a half times the likelihood of recurrent falls, were twice as likely to have significant fall injuries, and had three times higher risk of fall injuries that limited activity 2 years later, and were four times more likely to have poor balance.

'Falls, injury from falls and poor balance confidence are extremely common and debilitating problems in older people. The

present study has demonstrated for the first time that knee instability and knee buckling are important causes of these problems in the very large segment of the older population suffering from knee pain,' said Dr Nevitt. 'Fortunately, it may be possible to treat knee instability and prevent knee buckling with targeted exercises. Joint replacement surgery can also improve knee stability.'

Dr Nevitt added that pain is the predominant symptom of knee osteoarthritis, and symptoms of instability such as knee buckling and falls may be overlooked by clinicians. He recommends that health professionals should ask patients with knee osteoarthritis about instability, buckling and falls, and work with them to take preventive actions, including proper use of walking aids, leg strengthening and appropriate footwear.

Nevitt MC, Tolstykh I, Shakoor N, Nguyen US, Segal NA, Lewis C, Felson DT for the Multicenter Osteoarthritis Study Investigators (2016) Symptoms of knee instability are risk factors for recurrent falls. *Arthritis Care Res* (doi: 10.1002/acr.22811)



Dr Michael Nevitt, Professor in the Department of Epidemiology and Biostatistics, University of California, San Francisco

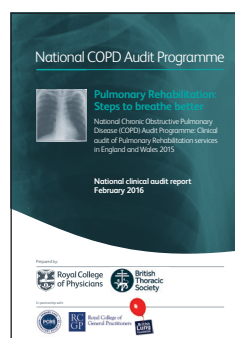
Pulmonary rehabilitation delivers significant health benefits but too many patients are missing out

The National Chronic Obstructive Pulmonary Disease (COPD) Audit Programme's pulmonary rehabilitation report reveals substantial health benefits are received by patients who complete pulmonary rehabilitation treatment yet many patients are not being referred, and many patients (40%) find it difficult to complete the pulmonary rehabilitation programme.

Over a third of patients (37%) in England and Wales are waiting longer than the 3 months recommended in the British Thoracic Society quality standards.

Pulmonary Rehabilitation: Steps to breathe better reviews the quality of care received by 7413 patients across 210 pulmonary rehabilitation services in the primary, secondary and community care sectors.

Overall, the report reveals many areas of good quality pulmonary rehabilitation treatment for patients with COPD, including widespread provision of walking (95%), cycle (70%) and aerobic and resistance exercise therapy (89%). The full report can be found at: www.rcplondon.ac.uk/COPD



Explaining the alcohol harm paradox

New research from a collaboration including Bangor University, Liverpool John Moores University and Alcohol Research UK explains why people in deprived communities have higher levels of alcohol-related ill health than people in non-deprived communities, despite drinking the same amounts of alcohol – the alcohol harm paradox (Bellis et al, 2016).

The study found that people who are heavier drinkers and live in low-income communities are more likely to combine such drinking with other health-damaging behaviours than people in more affluent communities. These combinations do not just add to the dangers from alcohol consumption but effectively multiply the risks of ill health.

People living in deprived areas who drank at levels consistent with increased risks to health were nearly 11 times more likely than people living in non-deprived areas to combine drinking with smoking, excess weight, poor diet and little exercise. In combination, these behaviours multiply the risk of alcohol-related conditions.

For those drinkers at increased risk, 66.9% of those living in non-deprived areas were found to have at least one other health risk behaviour, compared with 83.2% of those living in deprived areas.

Mark Bellis, one of the researchers from Bangor University, said: 'About 9% of increased risk drinkers surveyed in poorer communities also smoked, were overweight and had unhealthy lifestyles. Together these combinations can create enormous stresses on people's bodies, overwhelming their ability to limit the health harms caused by alcohol. In affluent areas less than 1% of people drinking at increased risk levels also reported all three other health risks.'

Bellis MA, Hughes K, Nicholls J, Sheron N, Gilmore I, Jones L (2016) The alcohol harm paradox: using a national survey to explore how alcohol may disproportionately impact health in deprived individuals. *BMC Public Health* (doi: 10.1186/s12889-016-2766-x)