

## Weight loss by postmenopausal women linked to lower risk of breast cancer

Although obesity is an established risk factor for postmenopausal breast cancer, the results of studies into the possible link between weight loss and risk of breast cancer are inconsistent.

Researchers analysed information on 61 335 women participating in the World Health Initiative Observational Study who had no prior breast cancer and had normal mammogram results. The women's weight, height and body mass index were assessed at the start of the study and again 3 years later.

During an average 11.4-year follow up, 3061 new cases of invasive breast cancer were diagnosed (Chlebowski et al, 2018). Women with weight loss  $\geq 5\%$  had a 12% lower risk of breast cancer than women with stable weight. Weight gain of  $\geq 5\%$  was not associated with overall risk of breast cancer but was associated with a 54% higher incidence of triple negative breast cancer.

The findings suggest that weight loss may help lower postmenopausal women's breast cancer risk.

Chlebowski RT, Luo J, Anderson GL et al. Weight loss and breast cancer incidence in postmenopausal women. *Cancer*. 2018 Oct 8. <https://doi.org/10.1002/cncr.31687>

## Toolkit to prepare patients for surgery and recovery

The Royal College of Anaesthetists has launched an information toolkit which advises patients on how to prepare for going into hospital and encourages them to improve their health before surgery (<https://www.rcoa.ac.uk/fitterbettersooner>).

'Fitter Better Sooner' contains information such as how to cut down on smoking, reduce alcohol intake, diet and exercise. It also gives advice on how to manage other existing medical conditions such as diabetes and high blood pressure, as well as practical advice on what patients might need to take to hospital and what they might need at home when they leave.

## Impact of frailty on outcomes in patients with heart failure with preserved ejection fraction

The impact of frailty on outcomes in randomized trials in patients with heart failure with preserved ejection fraction has not been previously reported. An analysis sought to characterize frailty in a large contemporary trial cohort who had heart failure with preserved ejection fraction clinical and to evaluate its impact on patient relevant outcomes (Sanders et al, 2018).

Using data from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, a frailty index was constructed at baseline using 39 clinical, laboratory and self-reported variables. The relationship between frailty and outcomes and the role of frailty in modulating the benefits of spironolactone were examined in a subset of 1767 patients.

For the cohort as a whole (mean age 71.5 years, 49% female), the mean frailty index at baseline was  $0.37 \pm 0.11$ . Four frailty classes were defined, and overall 94% of subjects were considered frail. Body mass index, systolic blood pressure and pulse pressure all increased as frailty index increased. Both primary and



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secondary outcomes increased as frailty severity increased. There was no interaction between frailty class and treatment effect of spironolactone.

Frailty was very common in participants who had heart failure with preserved ejection fraction. Greater frailty was associated with a higher risk of cardiovascular outcomes and mortality. The benefit of spironolactone on outcomes in TOPCAT was not attenuated by frailty class.

Commenting on the findings, Dr Natalie Sanders, Assistant

Professor, Geriatrics Division, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA noted: 'A treatment benefit of spironolactone was observed in the most frail. This deserves further study but suggests that the presence of frailty should not be a reason to withhold treatment.'

Sanders NA, Supiano MA, Lewis EF et al. The frailty syndrome and outcomes in the TOPCAT trial. *Eur J Heart Fail*. 2018 Sep 18. <https://doi.org/10.1002/ejhf.1308>

## Apnoea–hypopnoea event duration predicts mortality in patients with obstructive sleep apnoea

Obstructive sleep apnoea is a risk factor for mortality, but the apnoea–hypopnoea index is a poor risk predictor – it does not capture the range of physiological variability within and between patients. A study examined whether respiratory event duration predicts all-cause mortality. Mortality risk as a function of event duration was estimated in the Sleep Heart Health Study, a prospective community-based cohort. Gender-specific hazard ratios were also calculated (Butler et al, 2018).

Among 5712 participants, 1290 deaths occurred over 11 years of follow up. After adjusting for demographic factors (mean age 63 years old; 52% female), apnoea–hypopnoea index, smoking and prevalent cardiometabolic disease, individuals with the shortest duration events had a significant hazard ratio for

all-cause mortality of 1.31 (95% confidence interval 1.11–1.54). This relationship was observed in both men and women and was strongest in those with moderate sleep apnoea.

The authors concluded that short respiratory event duration predicts mortality in men and women. People with shorter respiratory events may be predisposed to increased ventilatory instability and/or have augmented autonomic nervous system responses that increase the likelihood of adverse health outcomes. This highlights the need to assess physiological variation in obstructive sleep apnoea.

Butler MP, Emch JT, Rueschman M, Sands SA, Shea SA, Wellman A, Redline S. Apnea-hypopnea event duration predicts mortality in men and women in the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2018 Oct 19. <https://doi.org/10.1164/rccm.201804-0758OC>

## Pre-eclampsia is associated with increased risk of dementia later in life

A nationwide register based cohort study was performed in Denmark to explore associations between pre-eclampsia and later dementia, overall and by dementia subtype and timing of onset (Basit et al, 2018).

The study included all women with at least one live birth or stillbirth between 1978 and 2015. The main outcome measure was hazard ratios comparing dementia rates among women with and without a history of pre-eclampsia.

The cohort consisted of 1 178 005 women with 20 352 695 person years of follow-up. Women with a history of pre-eclampsia had more than three times the risk of vascular dementia later in life, compared to women with no history of pre-eclampsia. The association with vascular dementia seemed to be stronger for late onset disease than for early onset disease. Adjustment for diabetes, hypertension and cardiovascular disease attenuated the hazard ratios only moderately; sensitivity analyses suggested that body mass index was unlikely to explain the association with vascular dementia. In contrast, only modest associations were seen for Alzheimer's disease and other/unspecified dementia.

The authors concluded that pre-eclampsia was associated with an increased risk of dementia, particularly vascular dementia. Cardiovascular disease, hypertension, and diabetes were unlikely to mediate the associations substantially, suggesting that pre-eclampsia and vascular dementia may share underlying mechanisms or susceptibility pathways.

Discussing the findings, Dr Heather Boyd, Senior Researcher and Research Group Leader, Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark, said: 'I hope the results of our study will serve to further spur research into how to identify previously pre-eclamptic women at greatest risk of cardiovascular and vascular morbidity later in life, so that we can develop protocols for post-pregnancy follow-up of these women and figure out which interventions are most effective at reducing their post-partum disease risk.'

Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. *BMJ*. 2018 Oct 17;363:k4109. <https://doi.org/10.1136/bmj.k4109>

## RCPCH flags up inequalities in key outcomes for most deprived children and young people

The health of today's children and young people will be one of the key factors in determining whether England is healthy and prosperous over the next 50 years.

A report from the Royal College of Paediatrics and Child Health (RCPCH) ([https://www.rcpch.ac.uk/sites/default/files/2018-10/child\\_health\\_in\\_2030\\_in\\_england\\_report\\_2018-10.pdf](https://www.rcpch.ac.uk/sites/default/files/2018-10/child_health_in_2030_in_england_report_2018-10.pdf)) used long-term historical data on key health outcomes and modelling methods to estimate outcomes for children and young people in 2030 in England compared with other wealthy European and western countries.

England has poorer health outcomes than the average across the EU15+ (the 15 EU countries in 2004 plus Canada, Australia and Norway) in most areas studied, and the rate of

improvement in England for many outcomes is lower than across the EU15+.

The marked inequalities seen in most key outcomes are likely to widen over the next decade as problems such as infant mortality and obesity are worsening more quickly among the most deprived section of the population.

The report's overarching recommendation calls for NHS England to develop a Children and Young People's Health Strategy for England, to be delivered by a funded transformation programme led by a dedicated programme board. This strategy should set out a governance and accountability framework for the commissioning, implementation and delivery of interventions to improve health outcomes for children and young people.



### Wearing a soft knee brace reduces dynamic knee instability in people with knee osteoarthritis

A small laboratory study from the Netherlands reports that wearing a soft knee brace (either tight or not tight) reduces objectively assessed dynamic knee instability beyond the subjectively reported improvement in people with knee osteoarthritis (<https://doi.org/10.1093/rheumatology/key162>).

### Doxylamine succinate/pyridoxine hydrochloride available for nausea and vomiting in pregnant women

Doxylamine succinate 10mg/pyridoxine hydrochloride 10mg (Xonvea) has been launched in the UK, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

### National Centre for Rural Health and Care launched

The National Centre for Rural Health and Care (<https://www.ncrhc.org/>) has been set up to improve health and care in rural areas across the UK. The centre has already started work to bring about improvements in health-care delivery in rural settings, through research, better use of data, workforce developments and improved technology. According to the 2011 census there are 9 million rural residents in England – about 18% of the population.

## Association between cataract and risks of osteoporosis and fracture

A nationwide population-based retrospective cohort study of individuals with ( $n=57\,972$ ) and without ( $n=57\,972$ ) cataracts from Taiwan's National Health Insurance Research Database was performed to evaluate the association between cataract and cataract surgery and risks of osteoporosis and fracture (<https://doi.org/10.1111/jgs.15626>).

Individuals with and without cataracts were matched 1:1 for age, sex and index year. Those with cataracts were further divided into cataract surgery and non-surgery groups.

During mean follow up of 6.4 years, 17 450 participants with cataracts and 12 627 without developed osteoporosis or fractures. Having cataracts was significantly associated with risk of developing osteoporosis or fracture. Participants who underwent cataract surgery were at significantly lower risk of osteoporosis or fracture than those who did not.

The authors concluded that having cataracts was independently associated with increased risks of osteoporosis and fracture. There might be an association between cataract surgery and lower risks of osteoporosis and fracture.

## Patient complaints reveal quality and safety 'blind spots' in health-care delivery

Health-care complaints made by patients can provide unique insight on aspects of health-care delivery not easily evaluated by hospitals, a new study has found (Gillespie and Reader, 2018).

The study analysed over 1000 complaints from patients across the UK and found they highlighted quality and safety issues difficult to capture through staff reports, surveys and hospital inspections.

The researchers used the free Healthcare Complaints Analysis Tool which they have developed to analyse and systemise complaints (<https://doi.org/10.1136/bmjqs-2015-004596>). The tool conceptualises complaints in clinical, management and relationship domains. It also identifies problems at different levels of severity, enabling complaints to be organized by their level of seriousness. This coding system is designed to be able to extract the unique insights available in complaints.

The researchers found complaints were particularly valuable in identifying problems before admission to hospital – such as cancelled medical appointments – or after discharge, such as a lack of follow-up care. A third (32%) of the 2074 problems reviewed by the study occurred either during admission or after



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discharge which, because they take place outside hospital, are often not monitored by other means.

Patients were also uniquely placed to report cases where there was an omission of care such as neglect of patient hygiene. Errors of omission are notoriously difficult to detect as people rarely observe or take responsibility for what has not happened.

Commenting on the findings, Dr Alex Gillespie, Associate Professor from the Department of Psychological and Behavioural Science, London School of Economics and Political Science,

said: 'Over one third of the problems reported in complaints were omissions, usually staff not doing something... When omissions occur, it is often patients who compensate and error-correct, for example, following up appointments, ensuring care plans are followed, and even providing basic hygiene on the ward. Complaints thus provide unique insight into what is not done and the largely invisible processes of correcting these errors.'

Gillespie A, Reader TW. Patient-centered insights: using health care complaints to reveal hot spots and blind spots in quality and safety. *Milbank Q.* 2018 Sep;96(3):530–567. <https://doi.org/10.1111/1468-0009.12338>

## Benzodiazepine use in patients with chronic obstructive pulmonary disease and post-traumatic stress disorder may increase suicide risk

Long-term use of benzodiazepine medications in patients with chronic obstructive pulmonary disease as well as post-traumatic stress disorder may lead to increased suicide risk (Donovan et al, 2018).

Researchers reported on 44 555 veterans who received medical care between 2010 and 2012. Of these, 23.6% received benzodiazepines long term (90 days or longer).

Benzodiazepines are commonly prescribed for symptoms of chronic obstructive pulmonary disease, including

anxiety, shortness of breath and insomnia, and are also commonly prescribed to those with post-traumatic stress disorder to treat anxiety and insomnia.

To better understand the risks posed by benzodiazepines, the researchers matched patients in their analysis by taking over 44 patient characteristics into account.

The researchers found that long-term use of benzodiazepines in patients with chronic obstructive pulmonary disease who also had post-traumatic stress disorder more than doubled their risk of suicide. These patients also had higher rates

of psychiatric admissions. Short-term benzodiazepine use, but not long-term use, was associated with increased mortality.

Interestingly, the researchers did not find that long-term use of benzodiazepines in these patients increased their risk of death from all causes or respiratory events, as previous studies have suggested.

Donovan LM, Malte CA, Spece LJ et al. Risks of benzodiazepines in chronic obstructive pulmonary disease with comorbid posttraumatic stress disorder. *Ann Am Thorac Soc.* 2018 Oct 12. <https://doi.org/10.1513/AnnalsATS.201802-145OC>

## Combined hormonal contraceptives linked to reduced risk of ovarian cancer in women of reproductive age

A prospective, nationwide cohort study was undertaken to investigate the association between contemporary combined hormonal contraceptives (including progestogen types in combined preparations and all progestogen-only products) and overall and specific types of ovarian cancer (Iversen et al, 2018).

The relative risk of ovarian cancer was calculated among users of any contemporary combined hormonal contraceptives and by progestogen type in combined preparations and all progestogen-only products, including non-oral preparations. Separate analyses examined women followed up to their first contraception type switch and those with full contraceptive histories. Duration, time since last use and tumour histology were examined and the population prevented fraction calculated.

During 21.4 million person years, 1249 incident ovarian cancers occurred. Among ever users of hormonal contraception, 478 ovarian cancers were recorded over 13 344 531



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person years. Never users had 771 ovarian cancers during 8 150 250 person years.

Use of contemporary combined hormonal contraceptives is associated with a reduction in ovarian cancer risk in women of reproductive age – an effect related to duration of use, which diminishes after stopping use. These data suggest no protective effect from progestogen-only products.

First author Dr Lisa Iversen, Research Fellow, Academic

Primary Care, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, commented: ‘Our findings are reassuring to both women currently of reproductive age and prescribers; contemporary combined oral contraceptives are also associated with a reduced risk of ovarian cancer.’

Iversen L, Fielding S, Lidegaard Ø, Mørch LS, Skovlund CW, Hannaford PC. Association between contemporary hormonal contraception and ovarian cancer in women of reproductive age in Denmark: prospective, nationwide cohort study. *BMJ*. 2018 Sep 26;362:k3609. <https://doi.org/10.1136/bmj.k3609>

## Financial cost of bullying and harassment to the NHS in England estimated as £2.281 billion per annum

Bullying and harassment in the NHS in England could be costing over £2 billion per year (Kline and Lewis, 2018).

The first comprehensive estimate of the financial costs of bullying and harassment in the NHS, the study used data from NHS Digital to gauge the impact of bullying upon sickness absence, employee turnover, productivity, sickness presenteeism and employment relations. The financial cost of each of these factors was combined to produce the overall figure of £2.281 billion per year.

Of each individual component, sickness presenteeism was estimated to have the biggest financial impact. Described as the productivity lost when staff continue to come to work while being bullied and are more prone to making mistakes, presenteeism as a result of bullying was estimated to cost £604.4 million – double the cost of sickness absence because of bullying.

Study authors Professor Duncan Lewis and Dr Roger Kline described the overall cost as ‘extremely cautious’, as several costs lack reliable evidence to estimate accurately. Professor Lewis, Professor of Management at Plymouth University Business School, added: ‘Estimating the financial cost of bullying should not come at the expense of the moral reasons for tackling bullying and harassment. Nonetheless, if our paper means that NHS Trust executives realize the heinous costs of bullying, they may then think about where the additional resources currently wasted through bullying and harassment might be better deployed, which ultimately means more effective patient care.’

Kline R, Lewis D. The price of fear: estimating the financial cost of bullying and harassment to the NHS in England. *Public Money & Management* 2018 Oct 24. <https://doi.org/10.1080/09540962.2018.1535044>

## Safety and efficacy of intravenous iron dosing in patients undergoing haemodialysis

The results of PIVOTAL, a randomized controlled trial designed to investigate the effects of two intravenous iron dosing strategies among patients on maintenance haemodialysis, have been published (Maddougall et al, 2018).

The reactive, low-dose intravenous iron arm was intended to maintain patients near the lowest acceptable iron limits (serum ferritin of 200 µg/litre and transferrin saturation of 20%), while the proactive, high-dose intravenous iron regimen encouraged more liberal iron dosing and permitted higher ferritin and transferrin saturation levels (up to 700 µg/litre and 40% respectively), as has been seen in the USA. Although liberal intravenous iron dosing is known to improve response to erythropoiesis-stimulating agents and to allow for reduced doses of erythropoiesis-stimulating agents, the effect of this strategy on other objective outcomes was previously unclear.

The trial followed 2141 patients from 50 sites in the UK for up to 4.5 years. The trial met its primary endpoint by demonstrating non-inferiority of the proactive dosing regimen. The proactive iron dosing regimen was also associated with a 22% reduced risk of death or cardiovascular events when analysed as recurrent events ( $P < 0.01$ ). As suggested by previous data, higher doses of iron allowed for a nearly 20% reduction in median doses of erythropoiesis-stimulating agents ( $P < 0.001$ ). The proactive dosing strategy, and attendant increases in serum ferritin concentrations and transferrin saturation, was not associated with any increase in the risk of hospitalization, infection or vascular access thrombosis.

Maddougall IC, White C, Anker SD et al; PIVOTAL Investigators and Committees. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med*. 2018 Oct 26. <https://doi.org/10.1056/NEJMoa1810742>