General

Sugar intake and body weight

The exact relationship between high sugar intake and obesity is unclear. Now a systematic review and meta-analysis of published studies has confirmed a direct link between sugar intake and body weight.

The study included 38 cohort studies and 30 randomised trials. In trials on adults there was a significant relationship between reduced sugar intake and weight loss (about 0.8 kg) and a similar relationship between increased sugar intake and weight gain (about 0.75 kg). Exchanging dietary sugars for other carbohydrates of equal caloric value resulted in no change in weight. In children, trials of recommendations to reduce intake of sugary foods and drinks showed no weight reduction but compliance was poor. Prospective studies of intakes of sweetened drinks showed a significant 55% increase in risk of overweight or obesity after 1 year among groups with the highest intakes.

Reducing sugar intake might result in weight loss.

Te Morenga L et al. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ* 2013; 346 (Jan 19): 12 (2012; 345: e7492); Jackson T. How science is going sour on sugar. Ibid: 2013; 346: f307(editor's choice); Willett WC, Ludwig DS. Science souring on sugar. Ibid: 7 (e8077) (editorial); Watts G. Sugar and the heart: old ideas revisited. Ibid: 16 (e7800) (public health, feature).

Fat intake and body weight

A similar systematic review and meta-analysis to the one reported above has reported on the effects of changes in fat intake on body weight. The meta-analysis included 33 randomised trials and 10 cohort studies in adults. Compared with usual fat intakes, lower intakes were associated with an average reduction in body weight of 1.6 kg, a reduction in BMI of 0.51 kg/m2, and, in one trial, a reduction in waist circumference in women of 0.3 cm. For each 1% reduction in fat intake there was a reduction in body weight of 0.2 kg (in populations with intakes of 28% to 43% of energy from fat and in studies of 6 months to >7 years duration). Limited evidence in children and young adults supported these findings.

Reducing dietary intake of fat causes weight loss.

Hooper L et al. Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies. *BMJ* 2013; 346 (Jan 19): 13 (2012; 345: e7666).

Nutrition in ICU

Early resort to enteral nutrition (EN) is the aim for most patients in the intensive care unit (ICU) but many patients are unable to tolerate EN and undernutrition may result as well as chest complications from aspiration. Researchers in Geneva and Lausanne, Switzerland have evolved a strategy of individualised supplemental parenteral nutrition (SPN) in patients inadequately fed with EN.

The study included 305 ICU patients on day 3 of ICU admission who on EN had received <60% of their energy target, were expected to stay more than 5 days in ICU and to survive longer than 7 days. Energy targets were calculated with indirect calorimetry on day 3 or from ideal body weight (25 kcal/kg/day for women and 30 kcal/kg/day for men). Randomisation was to EN or SPN. Between day 4 and day 8 mean energy delivery was 103% of target (28 kcal/kg/day) in the SPN group and 77% of target (20 kcal/kg/day) in the EN group. Patients in the SPN group had significantly fewer nosocomial infections between days 9 and 28 compared with the EN group (27% vs 38%). The SPN group had fewer days on antibiotics.

Individually optimised supplementation of energy provision with SPN reduced the rate of nosocomial infections. Overall 28 day mortality, length of stay in ICU, length of stay in hospital, frequency of hyperglycaemia or hypoglycaemia, and need for renal replacement therapy were all similar in the two groups.

Heidegger CP et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet* 2013; 381: 385–93; Vincent J-L, Preiser J-C. When should we add parenteral to enteral nutrition? Ibid: 354–5 (comment).

Oncology

Breast and colorectal cancer screening: 10 year lag to benefit

A meta-analysis of randomised trials of mammographic and faecal occult blood screening for breast and colorectal cancers in the USA, Sweden, the UK, and Denmark has concentrated on the time lag until benefit from reduced cancer mortality is seen.

The study included trials identified by Cochrane reviews, and US Preventive Services Task Force reviews as being of high quality. For faecal occult-blood screening it was estimated that to prevent 1 cancer death in 5000 people screened would take 4.8 years; prevention of 1 cancer death in 1000 people screened would take 10.3 years; and prevention of 1 death in 500 people screened would take 14.6 years to become apparent. The corresponding time lags for mammographic screening would be 3.0, 10.7, and 15.5 years.

The time lag to the prevention of 1 cancer death per 1000 people screened by mammography or faecal occult blood testing is 10–11 years. It is suggested that screening should be offered only to people with a life expectancy longer than this but a *BMJ* editorialist rejects this suggestion as arbitrary and misguided.

Lee SJ et al. Time lag to benefit after screening for breast and colorectal cancer: meta-analysis of survival data from the United States, Sweden, United Kingdom, and Denmark. *BMJ* 2013; 346 (Jan 19): (2012; 345: e8441); Patrick J. Benefits of cancer screening take years to appreciate. Ibid: 10 (2012; 346: f299).

Abiraterone for metastatic prostate cancer without previous chemotherapy

Abiraterone inhibits cytochrome P-450c17, thereby inhibiting testosterone synthesis. Together with low-dose prednisone the drug prolongs survival in patients with metastatic castration-resistant prostate cancer who have previously been treated with docetaxel. Now a multinational trial in Europe and North America has shown that treatment with abiraterone and prednisone benefits patients with metastatic castration-resistant prostate cancer who have not had prior chemotherapy.

A total of 1088 patients with metastatic, castration-resistant prostate cancer and no previous chemotherapy were randomised to oral abiraterone acetate 1000 mg, or placebo, daily. All patients received prednisone 5 mg twice daily. Median radiographic-progression-free survival was 16.5 months (abiraterone) vs 8.3 months (placebo), a highly significant difference. After an average follow-up of 22 months, overall survival was significantly better in the abiraterone group, but not crossing the efficacy boundary. The abiraterone group did better as regards time to starting chemotherapy, opiate use for pain, PSA progression, and performance decline. Adverse events were more common with abiraterone.

Abiraterone with prednisone benefitted patients with metastatic, castration-resistant prostate cancer who had not had previous chemotherapy.

Ryan CJ et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *NEJM* 2013; 368: 138–48.

Psychology

Early psychological intervention to prevent psychosis

People who go on to develop schizophrenia usually go through a prodromal period after which 22–44% of ultra-high-risk individuals proceed to manifest schizophrenia. A systematic review and meta-analysis of randomised controlled trials has suggested that psychological intervention during the prodromal stage could reduce the risk of progression.

The analysis included 11 trials (1246 participants) of intervention (psychological, pharmacological, nutritional, or combined) during the prodromal stage. After 1 year of treatment there was evidence (moderate quality) that cognitive behavioural therapy (CBT) reduced the risk of progression to schizophrenia significantly by 46% compared with supportive counselling. Evidence that dietary omega-3 fatty acid supplementation or integrated psychotherapy reduced the risk was of very low quality and evidence that integrated psychotherapy was better than standard treatment was of low quality.

CBT, with or without family therapy given during the prodromal period could reduce the rate of progression to schizophrenia. The writers of an editorial however, questioned the validity of defining ultra-high risk and of the concept of transition, calling into question the interpretation of this study.

Stafford MR et al. Early interventions to prevent psychosis: systematic review and meta-analysis. *BMJ* 2013; 346 (Jan 26): 12 (f185); Van Os J, Murray RM. Can we prevent psychotic illness by treating "schizophrenia lite"? Ibid: 9 (f304) (editorial).

Socioeconomic change and common mental disorder in Taiwan

The relationship between socioeconomic societal changes and the prevalence of common mental disorders (CMDs, non-psychotic, depressive, and anxiety disorders) is uncertain and ill understood. In Taiwan since 1990 there have been rapid socioeconomic changes with a move towards high technology and economic growth accompanied by rising unemployment and increased inequality.

The 12-item Chinese Health Questionnaire has been used in surveys of Taiwanese adults at 5-year intervals since 1990. Questionnaires were completed by 9079 people. The prevalence of probable CMDs increased from 11.5% in 1990 to 23.8% in 2010. At all five time-points increases in CMD prevalence paralleled increases in national rates of unemployment, divorce, and suicide. Significant risk factors for CMDs included female sex, fewer years of education, unemployment, and limitation of daily activities because of poor health, but after adjustment for these factors the CMD time trends were still significant.

Socioeconomic changes in society are important determinants of common mental disorders.

Fu T S-T et al. Changing trends in the prevalence of common mental disorders in Taiwan: a 20-year repeated cross-sectional survey. *Lancet* 2013; 381: 235–41; Stuckler D, McKee M. The progress of nations: what we can learn from Taiwan. Ibid: 185–7 (comment).

Addition of CBT for drug-resistant depression

Antidepressant drug treatment is fully successful in only a third of patients. What to do about non-responders is debated. A multicentre trial in UK general practices has shown that adding cognitive behavioural therapy (CBT) is effective.

A total of 469 patients aged 18–75 years with drug-treatment-resistant depression (on antidepressants for 6 weeks or longer) were randomised at 73 general practices to CBT plus usual care or usual care alone. A response (at least 59% reduction in Beck depression inventory (BDI) score) at 6 months occurred in 46% (CBT) vs 22% ((controls), a significant difference (odds ratio 3.26). Remission (BDI score <10) occurred in 28% vs 15%. At 12 months the response rate was 55% vs 31% and the remission rate 40% vs 18%. The mean BDI score was 17.0 vs 21.7.

Adding CBT to usual care (including antidepressants) is effective treatment for patients with depression who have not responded to drug treatment.

Wiles N et al. Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. *Lancet* 2013; 381: 375–84; Otto MW, Wisniewski SR. CBT for treatment resistant depression. Ibid: 352–3 (comment).

Neurology

Antidepressants and prolonged QTc

The US Food and Drug Administration has warned about a prolongation of corrected QT interval (QTc) with use of the anti-depressant, citalopram. Prolonged QTc is associated with increased risk of ventricular arrhythmias. Now a study in a large healthcare system in New England, USA has confirmed prolongation of QTc with citalopram, escitalopram, and amitriptyline.

The study included 38§397 patients who had an ECG after being prescribed an antidepressant or methadone between February 1990 and August 2011. The antidepressants studied were the selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, paroxetine, and sertraline, and non-SSRI antidepressants, amitriptyline, nortriptyline, bupropion, duloxetine, mirtazapine, and venlafaxine. The opioid, methadone was included to confirm assay sensitivity since it is known to prolong QTc. There were significant dose-related associations between citalopram, escitalopram, and amitriptyline and prolonged QTc and between bupropion and shortened QTc. None of the other seven antidepressants had a significant effect on QTc.

Prolonged QTc was associated with use of citalopram, escitalopram, and amitriptyline. The risk is greater with older and more ill patients.

Castro VM et al. QT interval and antidepressant use: a cross sectional study of health records. BMJ 2013; 346 (Feb 9): 15 (f288).

New genetic variant in Alzheimer's disease

Rare variants in the genes encoding amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) have been associated with early onset (<60 years) Alzheimer's disease. The ε4 allele of apolipoprotein E (Apo E) is the most important variant affecting the risk of late onset Alzheimer's disease, the most common form. Now two studies reported in a single issue of the *New England Journal of Medicine* have strongly implicated a rare variant in the gene encoding the triggering receptor expressed on myeloid cells 2 (TREM2) in Alzheimer's disease. Gene sequencing of 2261 Icelanders pointed to the rs75932628-T missense mutation that increased the risk of Alzheimer's disease almost three-fold (odds ratio 2.92). The frequency of this mutation among people who had reached the age of 85 without Alzheimer's disease was 0.46%. The same association (odds ratio 2.9) was found in Norwegian, American, and Dutch populations.

A study in Europe and North America showed 22 variant alleles in exon2 of TREM2 in 1092 patients with Alzheimer's

disease and five variant alleles in 1107 controls, the most common variant in Alzheimer's disease was the rs75932628 variant.

The rs79532628-T variant in the TREM2 gene is associated with increased risk of Alzheimer's disease. The TREM2 gene has an anti-inflammatory role in the brain, suggesting that the predisposition to Alzheimer's disease may be mediated by inflammation.

Jonsson T et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *NEJM* 2013; 368: 107–16; Guerreiro R et al. TREM2 variants in Alzheimer's disease. Ibid: 117–27; Neumann H, Daly MJ. Variant TREM2 as risk factor for Alzheimer's disease. Ibid: 182–4 (editorial).

Cardiology

Biodegradable biolimus-eluting stent versus durable everolimus-eluting stent

The current standard drug eluting stent is the thin-strut everolimus-eluting stent coated with a durable biocompatible polymer. This stent has been compared with a biodegradable polymer-coated biolimus-eluting stent in a multinational European study.

A total of 27 202 patients eligible for PCI were randomised (2:1) to the biolimus-eluting or the everolimus-eluting stent. The biolimus group included 1795 patients (2638 lesions) and the everolimus group 912 patients (1387 lesions). The primary endpoint (cardiac death or nonfatal myocardial infarction, or clinically indicated target vessel revascularisation at 12 months) occurred in 5.2% (biolimus) vs 4.8% (everolimus) showing noninferiority of the biolimus stent.

This biolimus-eluting stent was as safe and effective as the everolimus-eluting stent. More patients need to be followed-up for longer to assess whether the biolimus-eluting stent is associated with less risk of stent thrombosis after 1 year.

Smits PC et al. Abluminal biodegradable polymer biolimus-eluting stent versus durable polymer everolimus-eluting stent (COMPARE II): a randomised, controlled, non-inferiority trial. Lancet 2013; 381: 651–60; Mehilli J. Degradable polymer drug-eluting stents: a durable benefit? Ibid: 607–9 (comment).

Biodegradable biolimus-eluting stent versus durable sirolimus eluting stent

A biolimus-eluting biodegradable polymer stent has been compared with a sirolimus-eluting permanent polymer stent at three sites in western Denmark.

A total of 2468 patients (3087 lesions) were randomised to one or other stent. The primary endpoint (cardiac death, myocardial infarction, definite stent thrombosis, or target-vessel revascularisation, at 9 months) was reached by 4.1% (biolimus) vs 3.1% (sirolimus), borderline nonsigificance (p=0.06) for non-inferiority of the biolimus-eluting stent. Definite stent thrombosis by 12 months occurred in 0.7% (biolimus) vs 0.2% (sirolimus), a significant difference. Per-protocol analysis showed that a significantly greater proportion of patients in the biolimus-eluting stent group reached the primary endpoint.

Results at 1-year were not better with this biolimus-eluting stent than with the sirolimus-eluting stent. Longer term data are needed.

Christiansen EH et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. *Lancet* 2013; 381: 661–9; Kastrati A, Neumann F-J. SORT OUT V: a new episode in the DES wars. Ibid: 609–11 (com-

Paclitaxel-eluting balloons versus paclitaxel-eluting stents versus balloon angioplasty for restenosis after a drug-eluting stent.

Restenosis after use of a drug-eluting stent for coronary lesions is a major problem and the best management is subject to debate. Researchers in Germany have compared three options: paclitaxel-eluting balloons (PEB), paclitaxel-eluting stents (PES), and balloon angioplasty.

A total of 402 patients with at least 50% restenosis after use of a limus-eluting stent were randomised to PEB, PES, or balloon angioplasty. The results of angiography at 6–8 months after the procedure were available for 338 patients (84%). Both PEB and PES gave better results than balloon angioplasty and PEB was noninferior to PES. There were no group differences in mortality, myocardial infarction, or target lesion thrombosis.

It is concluded that PEB could be useful because it eliminates the need for repeat stent implantation.

Byrne RA et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent. (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet* 2013; 381: 461–7; Alfonso F, Pérez-Vizcayno MJ. Drug-eluting balloons for restenosis after stent implantation. Ibid: 431–3 (comment).

CPD Challenge

See page 53 to test yourself on this article

Diabetes

Type 2 diabetes – weekly exenatide versus daily liraglutide

Glucagon-like peptide-1 (GLP-1) receptor agonists stimulate glucose dependent insulin secretion, inhibit glucagon secretion, reduce food intake, and slow gastric emptying. Exenatide in a slow-release formulation is given by injection weekly and liraglutide is given by injection daily: both are GLP-1 receptor agonists. The two preparations have been compared for the treatment of type 2 diabetes in a multinational study.

A total of 912 patients with type 2 diabetes, poorly controlled on oral antidiabetic drugs, were randomised to injections of liraglutide, 1.8 mg, once daily, or exenatide, 2.0 mg once weekly. The least-squares mean change in HbA_{1c} was significantly greater with liraglutide (-1.48%) than with exenatide

(-1.28%). An HbA_{1c} level of <7% was achieved by 60% (liraglutide) vs 53% (exenatide), a significant difference. Weight loss occurred in both groups but was greater with liraglutide. Nausea, diarrhoea, and vomiting were less frequent with exenatide. Adverse events leading to discontinuation occurred in 5% (liraglutide) and 3% (exenatide). There were no episodes of major hypoglycaemia and minor hypoglycaemia occurred at a similar rate in both groups.

Weekly exenatide and daily liraglutide gave similar clinical results, though the reduction in HbA_{1c} levels was greater with liraglutide.

Buse JB et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 2013; 381: 117–24; Thethi T, Fonseca V. Comparing diabetes drugs – helping clinical decisions? Ibid: 93–4 (comment).