General

Agricultural interventions to improve diets of children in developing countries

It is accepted that for agricultural interventions to be fully successful in improving nutrition they should be initiated with that specific aim. Interventions aimed at improving the nutrition of children may include biofortification of crops, home gardening, aquaculture, small-scale fisheries, poultry development, animal husbandry, and dairy development. A systematic review has included 23 studies since 1990 that reported interventions in low- or middle-income countries aimed at improving child nutrition.

Overall, the studies provided insufficient evidence about the effectiveness of such interventions. They provided little information about programme participants or participation rates. Fifteen studies were of home gardens. Most studies had methodological flaws. They provided little evidence of an improvement in the diets of poor people and no evidence of increased household income.

There was no evidence of increased iron intake but some evidence of better vitamin A status. There was little evidence of an effect on the prevalence of undernutrition: eight studies reported undernutrition rates, one showed a significant reduction in stunting prevalence, three showed a significant reduction in the prevalence of underweight, and two showed a reduction in wasting. Most studies were underpowered to show an effect on undernutrition rates.

Studies of interventions aimed at improving child nutrition in low-or middle-income countries have been inadequate to show whether such interventions are effective.

Masset E et al. Effectiveness of agricultural interventions that aim to improve nutritional status of children: systematic review. *BMJ* 2012; 344 (11Feb): 16 (d8222); Dorward A, Dangour AD. Agriculture and health. Ibid: 8 (d7834) (editorial).

Specific exercises for subacromial impingement syndrome

Researchers in Sweden have shown that a specific exercise strategy may prove beneficial for patients with subacromial impingement syndrome.

The study included 102 patients with symptoms for more than 6 months and failure to respond to standard conservative treatment leading to them being put on a waiting list for surgery. Randomisation was to an exercise strategy targeting the rotator cuff and scapula stabilisers or to control exercises, for 12 weeks. The improvement in Constant–Murley shoulder score by 3 months was significantly greater in the specific exercise group and 69% in that group vs 24% in the control group described themselves as recovered or greatly improved. The proportion of patients opting for surgery was 20% (specific exercises) vs 63% (controls).

The specific exercise programme gave better results and reduced the number of operations performed.

Holmgren T et al. Effect of specific exercise strategy on need for surgery in patients with subacromial impingement syndrome: randomised controlled study. *BMJ* 2012; 304 (March 3): 15 (e787).

Pasireotide for Cushing's disease

Cushing's disease is caused by a corticotrophin-secreting pituitary adenoma. Transsphenoidal surgery is successful in 65–90% of patients but relapses are frequent. The options after relapse or surgical failure include further surgery, radiotherapy, bilateral adrenalectomy, and medical therapy. Somatostatin receptors (mostly subtype 5) are expressed by corticotroph adenomas and activation of these receptors inhibits corticotrophin secretion. Pasireotide, a somatostatin analogue, targets somatostatin receptor subtype 5 and, to a lesser degree, three of the other four subtypes. A multinational study of pasireotide in the treatment of Cushing's disease has been reported.

A total of 162 adults with Cushing's disease, either persistent or recurrent, or not suitable for pituitary surgery, were randomised to s.c. pasireotide 600 µg twice daily or 900 µg twice daily. At 3 months, non-responders received an extra 300 µg twice daily. The primary endpoint (normal urinary free cortisol at 6 months without an increase in dosage) was reached by 12/82 (14.6%) in the 600 µg group and 21/80 (26.3%) in the 900 µg group. In both groups the median urinary free cortisol level was reduced by about 50% after 2 months and then remained stable. Patients with a baseline urinary free cortisol level more than five times the upper limit of normal were less likely to achieve a normal level. Treatment resulted in reductions in serum and salivary levels of cortisol and in plasma levels of corticotrophin. Adverse events related to hyperglycaemia occurred in 73% of patients and 74 patients (46%) needed glucose-lowering medication.

Pasireotide shows promise as a second-line treatment for Cushing's disease.

Colao A et al. A 12-month phase 3 study of pasireotide in Cushing's disease. *NEJM* 2012; 366: 914–24.

Tropical

Worldwide malaria mortality 1980–2010

In 2011, the secretary general of the United Nations called for the total eradication of malaria by 2015. Since the turn of the century there has been a large increase in developmental assistance leading to advances in malaria control. A systematic analysis has collated all available data for malaria mortality for the period 1980–2010.

The estimated annual mortality from malaria was 995 000 (711 000 to 1 412 000) in 1980, rising to 1 817 000 (143 000 to 2 366 000) in 2004 and then falling to 1 238 000 (929 000 to 1 685 000) in 2010. The figure for Africa was 493 000 in 1980, 1 613 000 in 2004, and 1 133 000 in 2010. Malaria deaths outside Africa fell from 502 000 in 1980 to 104 000 in 2010. Among people aged 5 years and older malaria deaths in 2010 were greater than previous estimates (435 000 in Africa and 89 000 elsewhere).

The number of deaths from malaria in 2010 was greater than previous estimates, especially among older children and adults. Since 2004 malaria deaths in Africa have decreased by 30%. These investigators call for more donor support.

Murray CJL et al. Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet* 2012; 379: 413–31; The Lancet. New estimates of malaria deaths: concern and opportunity. Ibid: 385 (editorial).

Azithromycin for yaws in children

Yaws was almost eradicated in the 1970s as a result of a global control programme but in recent years it has reappeared in children in poor rural areas of Africa, Asia, and South America. Unless treated early it can become chronic and relapsing causing severe bone deformities. Intramuscular benzathine benzylpenicillin is the standard treatment but an oral treatment would have advantages. A trial in Papua New Guinea, has suggested that oral azithromycin might be suitable.

A total of 250 children aged 6 months to 15 years were randomised to single-dose treatment with either oral azithromycin, 30 mg/kg, or i.m. benzathine benzylpenicillin, 50 000 units/kg. The 6-month cure rate was 96% (azithromycin) vs 93% (benzathine benzyl penicillin), showing non-inferiority of azithromycin. Drug-related adverse events were

mild with either treatment.

Single-dose azithromycin is simpler than intramuscular benzathine benzylpenicillin. It may encourage the elimination of yaws through mass treatment campaigns.

Mitjà O et al. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. *Lancet* 2012; 379: 342–7; Mabey D. Oral azithromycin for treatment of yaws. Ibid: 295–7 (comment).

Cardiology

Antihypertensive drugs and gout

Up to 74% of people with gout are also hypertensive. A study based on a UK general practice database has provided data about the risk of gout with various antihypertensive drugs.

Data for 2000–2007 included 24 768 incident cases of gout and 50 000 matched controls. Among people with hypertension, diuretics were associated with a significant 2.4-fold increase in risk of gout. β-blockers significantly increased the risk by 48%, non-losartan angiotensin II receptor blockers were associated with a significant 29% increase in risk, and ACE inhibitors with a significant 24% increase. By contrast, calcium channel blockers were associated with a significant 13% reduction in risk, and losartan with a significant 19% reduction. Each of the latter drugs has urate-lowering properties.

Among people with hypertension, diuretics, β-blockers, ACE inhibitors, and non-losartan angiotensin II receptor blockers increase the risk of gout but calcium channel blockers and losartan reduce the risk.

Choi HK et al. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ* 2012; 344 (11 Feb): 18 (d8190); Ruilope LM. Antihypertensives in people with gout or asymptomatic hyperuricaemia. Ibid: 9 (d7961) (editorial).

The Y chromosome and coronary disease

Genes on the Y chromosome may be related to cardiovascular disease. The XYY karyotype is associated with increased cardiovascular mortality and a common polymorphism in the male-specific region (MSY) of the Y chromosome is associated with cardiovascular risk factors. A genetic study has illustrated the connection between the Y chromosome and coronary disease in men.

Genotyping was performed on 11 markers of the MSY in 3233 unrelated British men from three established cohorts. Each Y chromosome was tracked back to one of 13 ancient lineages (haplogroups) and the risk of coronary disease was related to haplogroup. Two haplogroups (R1b162 and I) accounted for 90% of Y chromosome variants. Carriers of haplogroup I had a 56% increase in risk of coronary disease compared with other haplogroups, independently of common cardiovascular and socioeconomic risk factors. Studies on macrophage transcriptome in men from one of the cohorts pointed to common genes related to inflammation and immunity.

The Y chromosome may play an important part in determining cardiovascular risk in men.

Charchar FJ et al. Inheritance of coronary artery disease in men: an analysis of the role of the Y chromosome. *Lancet* 2012; 379: 915–22; Miller VM. Family matters: sexual dimorphism in cardiovascular disease. Ibid: 873–5 (comment).

Inter-arm difference in systolic blood pressure and cardiovascular risk

A reduced ankle-brachial pressure index is taken as evidence of peripheral vascular disease. Similarly, a difference in systolic blood pressure between the two arms of >15 mmHg may be evidence of atherosclerosis. Guidelines recommend measuring the blood pressure in both arms in patients presenting with hypertension but it is rarely done in UK general practice. A systematic review and meta-analysis has included 20 studies. In five angiographic studies subclavian stenosis of >50% was associated with a mean difference in systolic pressure between the arms of 36.9 mmHg and a difference of 10 mmHg or greater was associated with a nine-fold increase in likelihood of subclavian stenosis. Pooled data from non-invasive studies showed that a between-arms difference of 15 mmHg or greater was associated with a 2.5-fold increase in peripheral vascular disease, a 60% increase in pre-existing cerebrovascular disease, a 70% increase in cardiovascular mortality, and a 60% increase in all-cause mortality. A difference of 10 mmHg or greater was associated with a 2.4-fold increase in peripheral vascular disease.

A difference in systolic blood pressure of 10 mmHg or more between arms may be an indicator of vascular disease needing investigation and treatment.

Clark CE et al. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. *Lancet* 2012; 379: 905–14; McManus RJ, Mant J. Do differences in blood pressure between arms matter? Ibid: 872–3 (comment).

Obs & Gyn

Ulipristal acetate for fibroids

Ulipristal acetate is a selective progesterone-receptor modulator that acts on myometrial and endometrial tissue and inhibits ovulation. Two small trials have suggested that ulipristal acetate might benefit patients with uterine fibroids. Now two successive reports in the *New England Journal of Medicine* have shown that ulipristal acetate is more effective than placebo and non-inferior to leuprolide acetate, a gonadotropin-releasing hormone (GnRH) agonist, with a lesser tendency to cause hot flushes.

In a placebo-controlled trial, a total of 242 women with fibroids, excessive uterine bleeding, and anaemia (haemoglobin 10.2 g/dl or less) were randomised (2:2:1) to oral ulipristal acetate 5 mg per day, or 10 mg per day, or placebo, for 13 weeks, together with iron supplementation. At 13 weeks, uterine bleeding was controlled in 91% (ulipristal acetate 5 mg), 92% (10 mg), and 19% (placebo). Amenorrhea occurred in 73%, 82%, and 6% respectively. Median total fibroid volume decreased by 21% and 12% in the treated groups and increased by 3% in the placebo group. Ulipristal acetate induced benign changes in endometrial histology that resolved within 6 months of stopping treatment. One patient in the ulipristal 10 mg group developed uterine haemorrhage and one in the placebo group had a fibroid protruding through the cervix. Headache and breast tenderness occurred at the same rates in both treatment and placebo groups.

In an active-control trial a total of 307 patients with symptomatic fibroid and excessive uterine bleeding were randomised to oral ulipristal acetate 5 mg daily oral ulipristal acetate 10 mg daily, or i.m. leuprolide acetate 3.75 mg once a month, for 3 months. Uterine bleeding was controlled in 90% (ulipristal 5 mg), 98% (ulipristal 10 mg), and 89% (leuprolide). Amenorrhea occurred after an average of 7 days, 5 days, and 21 days respectively and moderate to severe hot flushes were reported by 11%, 10%, and 40%.

Ulipristal acetate is effective for the treatment of uterine fibroids prior to surgery.

Donnez J et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *NEJM* 2012; 366: 409–20; Donnez J et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. Ibid: 421–32; Stewart EA. Uterine fibroids and evidence-based-medicine - not an oxymoron. Ibid: 471–3 (editorial).

Neurodevelopmental outcomes after intrauterine or neonatal insult

Although the millennium development goals have concentrated attention on neonatal and early childhood mortality there has been less attention paid to morbidity resulting from intrauterine or neonatal insult. A total of 153 studies has been included in a systematic review of the global effects of such insults on child neurodevelopment.

The studies included 22 161 survivors of intrauterine or neonatal insults (sepsis, meningitis, hypoxia, ischaemic encephalopathy, preterm birth, jaundice, tetanus, and infections with cytomegalovirus, herpes virus, rubella, toxoplasma, or syphilis. The outcomes assessed were cognition, motor ability, hearing, vision, seizures, behaviour, and multidomain. With at least one of any of these insults the risk of at least one neurodevelopmental sequel was 39%. The risk of severe impairment was 19%, of at least one moderate impairment 5%, and of at least one mild impairment 10%. Almost 60% of children with sequelae had learning difficulties, cognitive defects, and developmental delay. Cerebral palsy occurred in 21%, hearing impairment in 20%, and visual impairment in 18%. Multiple impairments were present in 32% of impaired survivors. There were few studies from developing countries and more studies are needed.

Mwaniki MK et al. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet* 2012; 379: 445–52; Thompson LC, Gillberg C. Behavioural problems from perinatal and neonatal insults. Ibid: 392–3 (comment).

Infection

Group B streptococcal infection in early infancy

In developed countries the most common cause of sepsis in early infancy is the group B streptococcus (*Streptococcus agalactiae*). Affecting infants in the first 3 months of life, group B streptococcal infection may be early onset (in the first 6 days of life) or late onset (at age 7–89 days). Early onset is taken to imply vertical transmission from the mother and late onset, maternally or environmentally acquired infection. Intrapartum antibiotic prophylaxis given to high-risk or known carrier mothers is effective but the disease is still an important cause of infant morbidity and mortality. A systematic review and meta-analysis has included 74 studies, only five from low-income countries.

The mean incidence of group B streptococcal infection in infants up to 89 days of age was 0.53 cases per 1000 livebirths and the mean case fatality ratio was 9.6% (0.43 per 1000 and 12.1% for early onset disease, 0.24 per 1000 and 6.8% for late onset disease). Case fatality was 4.6% in high-income countries and 12.6% in low-income countries. There were no serotype data from low-income countries but in high-income countries the most common serotypes were III, Ia, Ib, II, and V. A vaccine including these serotypes should be effective. Where intrapartum antibiotic prophylaxis was common the average incidence of group B streptococcal disease was 0.23 per 1000 live births but where such prophylaxis was not commonly used the incidence was 0.75 per 1000 livebirths.

Group B streptococcal infection in early infancy remains important. A vaccine is in preparation. More data from developing countries are needed.

Edmond KM et al. Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis. *Lancet* 2012; 379: 547–56; Cotton MF. Rabie H. Group B streptococcal disease in infants. Ibid: 502–3 (comment).

Prevention of sexually transmitted infections

Community-based interventions to prevent sexually transmitted infection (STIs) in Africa and elsewhere have had mixed results. A trial in Peru has shown possible benefits.

Twenty Peruvian cities were randomised to intervention (an S-PLUS programme of four components: (strengthened STI management by pharmacy workers and clinicians, mobile-team outreach to female sex workers (FSWs), presumptive treatment of FSWs for trichomoniasis, and condom promotion for FSWs and the general public) or standard care. STI screening was performed at baseline and random sample follow-up surveys were performed after 2 or 3 years. Full follow-up data were obtained for 12 930 people aged 18–29 years. Testing was for infection with *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, or positive syphilis serology. During the course of the trial there was a non-significant reduction in the four STIs together from 8.4% to 8.1% in control cities and from 7.6% to 6.3% in intervention cities. Significant reductions were noted in young women and FSWs overall, and for *T vaginalis* among young women and *T vaginalis* and *N gonorrhoeae* among FSWs.

The intervention was followed by significant reductions in some STIs in young women and FSWs.

Garcia PJ et al. Prevention of sexually transmitted infections in urban communities (Peru PREVEN): a multicomponent community-randomised controlled trial. *Lancet* 2012; 379: 1120–8; Donovan B, Guy R. Developments in research for STI prevention in Peru. Ibid: 1081–2 (comment).

Paediatrics

Oral amoxicillin for severe early childhood pneumonia in rural Pakistan

In 2008, pneumonia accounted for 18% of all deaths in children under the age of 5 years. Almost half of all deaths in young children occur in Pakistan, India, China, Nigeria, and the Democratic Republic of the Congo. Delayed treatment is responsible for many child pneumonia deaths and in 2004 WHO and UNICEF recommended antibiotic treatment at home given by trained health workers, instead of hospital referral, for non-severe pneumonia in rural areas. Meta-analyses have confirmed the effectiveness of this policy. Now a trial in rural Pakistan has shown that the policy is effective for children with severe pneumonia.

A cluster-randomised trial in rural Sindh province, Pakistan included 4410 children aged 2–59 months with WHO-defined severe pneumonia. The children were screened by lady health workers (LHWs). Those with severe pneumonia were prescribed oral amoxicillin syrup (45 mg/kg twice daily) for 5 days at home (intervention clusters) or given a single dose of oral co-trimoxazole and referred to the nearest health facility for i.v. antibiotic treatment (control clusters). The children were followed up at 2, 3, 6, and 14 days. Treatment failure by day 6 occurred in 8% (intervention) and 13% (control), a non-significant difference. There were three deaths, two in the intervention group and one in the control group.

Home treatment with oral amoxicillin

was at least as effective as current WHO policy for severe pneumonia.

Soofi S et al. Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Matiari district, rural Pakistan: a cluster-randomised controlled trial. *Lancet* 2012; 379: 729–37; Black RE, El Arifeen S. Community-based treatment of severe childhood pneumonia. Ibid: 692–4 (comment).

Pulmonary hypertension in children

The overall population prevalence of pulmonary hypertension (PH) in Western countries is around 25–50 per million. It is probably much less prevalent in children than in adults and there may be considerable differences between the adult and paediatric disease. A global registry at 31 centres in 19 countries has provided data about paediatric pulmonary hypertension (PPH). PH is classified into five groups, the most common of which is pulmonary arterial hypertension (PAH), which can be idiopathic (IPAH), heritable (HPAH), or associated with conditions such as congenital heart disease (APAH).

The study included 362 children (59% girls) aged 3 months to 18 years (median 7 years) at the time of diagnosis. All had confirmed pulmonary hypertension (mean pulmonary artery pressure at least 25 mmHg, pulmonary capillary wedge pressure at least 12 mmHg, pulmonary capillary wedge pressure at least 12 mmHg, and pulmonary vascular resistance index at least 3 WU/m-2). Most (317 patients, 88%) were classified as PAH, among whom 182 had idiopathic or familial PAH and 135 had PAH associated with other disorders (115 with congenital heart disease). Of the remaining 45 cases, 42 had lung disease or hypoxaemia and three had chronic thromboembolic pulmonary hypertension or 'miscellaneous causes'. Most (93%) of the children with congenital heart disease had a systemic-to-pulmonary shunt. Eighty-six (24%) of the total cohort had an additional disorder, trisomy 21 in 42 cases. Twenty-one patients had lived at high altitude (>2000 metres) for >6 months, 47 had been born preterm, and eight had had persistent pulmonary hypertension of the newborn. Exertional dyspnoea was the presenting symptom in 65% of the cohort. Syncope occurred in 20%, 31% of patients with idiopathic or familial PAH and 18% of those with repaired congenital heart disease. Right heart function was often preserved, 64% of patients being in functional class I or II.

Paediatric pulmonary hypertension differs from PH in adults and separate paediatric data are needed.

Berger RF et al. Clinical features of paediatric pulmonary hypertension: a registry study. *Lancet* 2012; 379: 537–46; a registry study. *Lancet* 2012; 379: 537–46; Mallory GB. Pulmonary hypertension in early life. Ibid: 500–1 (comment).

Moderate or late preterm birth and health outcomes

The UK Millennium cohort study is nationally representative prospective cohort study including 18 818 infants born in 2000–2002 and still living in the UK at the age of 9 months. Health outcomes in relation to gestational age at birth were assessed at ages 3 and 5 years and included growth, hospital admissions, longstanding illness, wheezing, use of prescribed drugs, and parental rating of children's health. In general, there was an inverse relationship between gestational age at birth and frequency of adverse health outcomes. The greatest number of such outcomes was among children born at moderate or late preterm (32–36 weeks) or at early term (37–38 weeks). Birth at 32–36 weeks accounted for 5.7% of children with three or more hospital admissions at ages 9 months to 5 years. Birth before 32 weeks accounted for 3.8% of such children and birth at 37–38 weeks for 7.2%. For a limiting longstanding illness the corresponding population attributable fractions were 5.4% for birth at 32–36 weeks, 2.7% for birth before 32 weeks, and 5.4% for birth at 37–38 weeks.

Modestly preterm birth and early term birth contribute more to the burden of adverse health outcomes than does very preterm birth.

Bryle EM et al. Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. *BMJ* 2012; 344 (March 17): 17 (e896).

Surgery

Surgeons: too young and too old?

A study at five large centres in France (Lille, Lyon, Marseille, Paris, and Poitiers) has suggested that increased complication rates may occur with both younger, less experienced, surgeons and surgeons in the later years of their careers.

The study included all 3679 thyroidectomies performed in the five centres between April 2008 and December 2009. Of these operations, 3574 (97%) were performed by 28 surgeons over the course of 1 year. Overall, the rates of recurrent laryngeal nerve palsy and hypoparathyroidism were 2.08% and 2.69% respectively. The rate of recurrent laryngeal nerve palsy fell during the first 4 years of surgical practice but rose considerably after 20 or more years of experience. The rate of postoperative hypoparathyroidism fell little in the early years of practice but rose considerably after 20 or more years. The optimal age of surgeons appeared to be 35–50 years.

Older surgeons may have poorer results. These results need to be confirmed and possible reasons explored.

Duclos A et al. Influence of experience on performance of individual surgeons in thyroid surgery: prospective cross sectional multicentre study. *BMJ* 2012; 344 (11 Feb): 19 (d8041).

Oncology

Algorithm for ovarian cancer risk in general practice patients

Researchers in Nottingham, England have produced a new algorithm to estimate risk of ovarian cancer among women presenting in general practice.

A total of 375 practices (1 158 723 women) contributed to the derivation cohort and 189 practices (608 862 women) to the validation cohort. The women were aged 30–84 with no previous diagnosis of ovarian cancer. The risk factors examined were age, family history of ovarian cancer, previous other cancers, BMI, smoking, alcohol, deprivation, loss of appetite, loss of weight, abdominal pain, abdominal distension, rectal bleeding, postmenopausal bleeding, urinary frequency, diarrhoea, constipation, tiredness, and anaemia. During 2.03 million person-years of follow-up, 976 women developed a first ovarian cancer. A family history of ovarian cancer increased the risk 9.8-fold. Other significant risk factors were anaemia (x 2.3), abdominal pain (x 7), abdominal distension (x 23), rectal bleeding (x 2), postmenopausal bleeding (x 7), loss of appetite (x 5), and weight loss (x 2). Of all ovarian cancers occurring with 2 years of assessment, 63% were in women with a predicted risk in the highest 10%.

The algorithm could be used, after independent validation in an external cohort, to facilitate early diagnosis and referral. A calculator is available at www.qcancer.org/ovary. Further research is needed into the cost-effectiveness of the algorithm and its effect on clinical outcomes.

Hippisley-Cox J, Coupland C. Identifying women with suspected ovarian cancer in primary care: derivation and validation of algorithm. *BMJ* 2012; 344 (Jan 28): 17 (d 8009); Hamilton W. Computer assisted diagnosis of ovarian cancer in primary care. Ibid: 9 (d7628) (editorial).

Vemurafenib for advanced melanoma

About half of melanomas carry an activating mutation in the gene encoding the serine-threonine protein kinase B-RAF (BRAF), the BRAF V600 mutation. This causes activation of the mitogen-activated protein kinase (MAPK) pathway, enhancing cell proliferation and inhibiting apoptosis. Vemurafenib is a potent kinase inhibitor acting preferentially on cancer cells with the BRAF V600 mutation. Initial studies have suggested that vemurafenib might be active against such melanomas. A multicentre, phase II trial has provided confirmation.

A total of 132 patients were treated at ten US centres and three centres in Australia. All had previously treated metastatic melanoma with the BRAF V600 mutation (184 of 328 patients (56%) had tested positive for the mutation). Median follow-up was 12.9 months. The overall confirmed response rate was 53% with 6% having a complete response. Responses lasted 6.7 months on average and the median progression-free survival was 6.8 months. Only 14% had primary progression. Some patients responded only after 6 months or more of treatment. Median overall survival was 15.9 months. The most common adverse effects were arthralgia, rash, photosensitivity, fatigue, and alopecia. A quarter of the patients (26%) developed squamous cell skin cancers.

Among patients with metastatic melanoma with a BRAF V600 mutation vemurafenil produced a clinical response in 53% and an overall median survival of 16 months.

Sosman JA et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *NEJM* 2012; 366: 707–14.

PSA testing and prostate cancer mortality

In 2008, a US task force recommended that prostate-specific antigen (PSA) screening for prostate cancer should not be offered to asymptomatic men. Now follow-up in the European Randomised Study of Screening for Prostate Cancer has been extended to 11 years.

The study included 182 160 men aged 50–74 years (162 388 aged 55–69 years) in eight European countries. Randomisation was to PSA screening or no PSA screening. After an average follow-up of 11 years in the 55–69 age group there was a significant 21% relative reduction in prostate cancer deaths in the screening group compared with controls (a 29% reduction after allowing for noncompliance). Screening saved 1.07 deaths per 1000 men randomised. To prevent one death from prostate cancer over the 11-year period it would be necessary to invite 1055 men for screening and to detect 37 cancers. There was no significant difference between screening and control group in all-cause mortality.

PSA screening reduced prostate-cancer mortality but not all-cause mortality. These researchers call for more information before general recommendations about screening can be made. An editorialist tends towards a negative approach.

Schröder FH et al. Prostate-cancer mortality at 11years of follow-up. *NEJM* 2012; 366: 981–90; Miller AB. New data on prostate-cancer mortality after PSA screening. Ibid: 1047–8 (editorial).

Diabetes

Glucagon-like peptide-1 receptor agonists and weight loss

Glucagon-like-peptide-1 (GLP-1) is secreted in the lower gastrointestinal tract after meals and stimulates insulin secretion depending on blood glucose levels. It inhibits glucagon release, delays gastric emptying, and reduces appetite. GLP-1 is not satisfactory for clinical use because it is rapidly degraded but two GLP-1 receptor agonists (exenatide and liraglutide) are currently approved. A systematic review and meta-analysis has concentrated on the weight loss associated with GLP-1 receptor agonist therapy.

The meta-analysis included 21 randomised controlled trials (6411 overweight or obese patients) with randomisation to a GLP-1 receptor agonist (exenatide or liraglutide) or control (placebo, oral antidiabetic drugs, or insulin). In eighteen trials the patients had type 2 diabetes and in three they did not. Overall the GLP-1 receptor agonist groups lost, on average, 2.9 kg more than controls. Average weight loss with a GLP-1 receptor agonist was 3.2 kg greater than in controls for patients without diabetes and 2.8 kg greater for patients with diabetes. GLP-1 receptor agonist treatment was also associated with improvements in systolic and diastolic blood pressure, serum cholesterol levels, and blood glucose control. It did not affect liver enzyme levels and was not associated with hypoglycaemia. Side-effects included nausea, vomiting, and diarrhoea.

Treatment with a GLP-1 receptor agonist is associated with weight loss as well as other benefits. A *BMJ* editorialist cautions against using these drugs for weight loss in people without diabetes at present. They might be used as an addition to metformin for control of type 2 diabetes but there are concerns about safety that need to be addressed in further trials. Pancreatitis, pancreatic metaplasia, and thyroid C cell tumours have occurred in animal studies.

Vilsbøll T et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2012; 344 (January 28): 14 (2011; 343: d7771); Padwal R. Glucagon-like peptide-1 agonists. Ibid: 7 (2011; 343: d7282) (editorial).

GAD65 antigen therapy for new diabetes: negative trial

Type 1 diabetes follows the immunological destruction of pancreatic beta cells. Various attempts have been made to moderate this immune response in patients with new type 1 diabetes with mixed results. Glutamic acid decarboxylase (GAD) is an important antigen in the pathogenesis of type 1 diabetes and induction of immune tolerance with the 65-kD isoform (GAD65) gave promising initial results. Now a trial at 63 centres in nine European countries has shown no benefit from this treatment.

A total of 334 patients aged 10–20 years with type 1 diabetes, serum antibodies against GAD65, and fasting C-peptide levels >0.1 nmol per litre (0.3 ng per ml) were randomised within 3 months of diagnosis to three groups: s.c. GAD65 with alum (GAD-alum) on days 1, 30, 90, and 270, GAD-alum on days 1 and 30 and placebo on days 90 and 270, or placebo on days 1, 30, 90, and 270. Levels of stimulated C-peptide decreased similarly in all three groups and the change in stimulated C-peptide level between baseline and 15 months did not differ significantly between the groups. Levels of glycated haemoglobin, insulin dosage, and rates of hypoglycaemia were similar in the three groups. There were few adverse events.

GAD-alum did not alter the course of early type 1 diabetes.

Ludvigsson J et al. Gad65 antigen therapy in recently diagnosed type 1 diabetes mellitus. *NEJM* 2012; 366: 433–42.

Psychology

Behaviour problems and dementia: mortality risks with different antipsychotics

The use of antipsychotics for elderly people with dementia and behavioural disturbances is generally discouraged because of the risk of increased mortality. For some patients however, their use might be considered because the patient's behaviour poses a risk to themselves or to others. US data have shown the relative risks with different antipsychotics.

The study included data for 75 445 people aged 65 or older living in nursing homes in 45 states and newly prescribed an antipsychotic in 2001–2005. Within the first 180 days of treatment there were 6598 non-cancer deaths (37.1 deaths per 100 person–years.) Compared with risperidone, there was a significant doubling of mortality risk with haloperidol and a significant 20% reduction in risk with quetiapine. Aripiprazole, olanzapine, and ziprasidone were associated with risks similar to that of risperidone. The effects of haloperidol and quetiapine were most marked soon after the initiation of treatment.

Quetiapine seemed to be the safest of the antipsychotics.

Huybrechts KF et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population-based cohort study. *BMJ* 2012; 344 (March 17); 16 (e977); McCleery J, Fox R. Antipsychotic prescribing in nursing homes. Ibid: 7 (e1093) (editorial).

Lithium toxicity

Lithium is effective in the treatment of bipolar disorder, providing protection against both depression and mania, but there are concerns about potential toxicity, in particular its effects on the kidneys and risk of teratogenicity. Present guidelines suggest avoiding lithium in pregnancy but the degree of risk is unknown, as is the extent of renal toxicity. A systematic review and meta-analysis has clarified some issues.

The analysis included 385 studies, including 22 randomised, controlled trials, 197 case-control, uncontrolled cohort, or cross-sectional studies, and 166 case reports. Overall, lithium reduced glomerular filtration rate by 6.22 mL/min and urinary concentrating ability by 15% of normal maximum. The risk of chronic renal failure was low, with 0.5% of patients needing renal replacement therapy. The risk of hypothyroidism was increased almost six-fold. There was also an increased risk of hyperparathyroidism with an average increase in blood calcium levels of 0.09 mmol/L and in parathyroid hormone levels of 7.32 pg/mL. Weight gain was greater with lithium than with placebo but not greater than with olanzapine. In this study there were no significant increases in risk of congenital malformations, alopecia, or other skin disorders.

Lithium treatment increases the risks of hypothyroidism and hyperparathyroidism. The risk of end-stage renal failure is low but urinary concentrating ability may be impaired, leading to clinical nephrogenic diabetes insipidus. The risk of teratogenicity is uncertain but there was no significant increase in congenital malformations in this study. Serum calcium levels should be checked before and during treatment. Lancet editorialists conclude that these data confirm that, on balance, lithium is the treatment of choice for bipolar disorder.

McKnight RF et al. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* 2012; 379: 721–8; Malhi GS, Berk M. Is the safety of lithium no longer in balance? Ibid: 690–2 (comment).

Neurology

Deep brain stimulation and memory

Deep brain stimulation has been used to treat Parkinson's disease, dystonia, depression, and obsessive-compulsive disorder. Animal experiments have suggested that stimulation of entorhinal-hippocampal pathways may improve memory. Studies in humans have shown negative effects on memory but it is possible that stimulation at certain sites during information processing could enhance memory. Now studies on patients with implanted electrodes for seizure diagnosis prior to epilepsy surgery have shown some enhancement of memory when applied during learning.

Seven subjects each completed a spatial learning task (learning destinations within a virtual environment). Four had entorhinal electrodes and five had at least one hippocampal electrode (four had both). Focal electrical stimulation below the after discharge threshold was given in half of the learning trials. Entorhinal stimulation during learning improved memory for location and enabled subjects to reach landmarks quicker and by shorter routes. It also resulted in a resetting of the phase of the theta rhythm on hippocampal electroencephalogram. Direct stimulation of the hippocampus had no effect. No adverse events occurred.

Entorhinal stimulation enhanced spatial memory. Much more research will be needed to determine the clinical implications of this research.

Sulthana N et al. Memory enhancement and deep-brain stimulation of the entorhinal area. *NEJM* 2012; 366: 502–10; Black SE. Brain stimulation, learning, and memory. Ibid: 563–5 (editorial).

Dutasteride for localised prostate cancer

Localised prostate cancer is relatively benign and many men may receive unnecessary treatment. Treatment with a 5α-reductase inhibitor might reduce the need for more aggressive therapy. Researchers in North America have suggested that dutasteride treatment might benefit men with low-risk prostate cancer.

The trial, at 65 centres in the USA and Canada, included 289 men aged 48–82 with low-volume, Gleason score 5–6 prostate cancer and at least one repeat biopsy during follow-up. They had all chosen active surveillance rather than more aggressive treatment. Randomisation was to dutasteride 0.5 mg daily or placebo, and follow-up was for 3 years with repeat biopsies at 18 months and 3 years. At 3 years, the rate of prostate cancer progression was 38% (dutasteride) vs 48% (placebo), a significant difference. The rates of adverse events were similar in the two groups. Sexual adverse events or breast enlargement occurred in 24% vs 15%. There were no deaths from prostate cancer and no subject developed metastatic disease. Cardiovascular adverse events occurred in 5% of each group.

Dutasteride might benefit men with low-risk prostate cancer who choose active surveillance. A *Lancet* commentator, however, points to previous evidence that dutasteride might have no effect on prostate cancer mortality (or might even increase the risk) and concludes that dutasteride, or any other treatment, cannot be recommended for these men. He believes that neither treatment nor diagnosis should be attempted for low-risk disease.

Fleshner NE et al. Dutasteride in localised prostate cancer management: the REDEEM randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 379: 1103–11; Parker C. What (if anything) to do about low-risk prostate cancer. Ibid: 1078–80 (comment).