

General

Dietary calcium, bone fractures, and osteoporosis

Meta-analyses of published studies have not shown a protective effect of higher calcium intake against bone fractures or osteoporosis. A Swedish population-based cohort study has shown that a calcium dietary intake of <700mg a day is associated with increased risk but increases above that intake do not further reduce the risk.

A cohort of 61433 women aged 39–73 on recruitment in 1987 were followed up for 19 years. A first fracture of any kind occurred in 14738 women (24%) during follow-up and 3871 (6%) had a first hip fracture. Dual energy X-ray absorptiometry was performed on 5022 women and 1012 (20%) were osteoporotic. Dietary calcium intake was assessed by food questionnaire. The risk of a first fracture of any kind was 17.2 per 1000 person-years at risk in the lowest quintile of dietary calcium intake (<751 mg per day) and 14.0 per 1000 person-years at risk in the third quintile. The hazard ratio (first vs third quintile) for a first hip fracture was 1.29 and the odds ratio for osteoporosis 1.47. Low vitamin D intake increased the risk in the first quintile of dietary calcium intake. In the highest quintile of dietary calcium intake there was no further reduction in risk of any fracture or osteoporosis but the risk of hip fracture was increased by 19%.

In middle-aged and older women low dietary calcium (<700mg/day) is associated with increased risk of fracture and of osteoporosis. Increased intake above that level does not further reduce the risk.

Warensjö E et al. Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. *BMJ* 2011; 342: 1194 (d1473).

Abortion of girls in India 1991–2011

In the first census ever performed in India (in the late 19th century) males outnumbered females. Currently (2011) there are only 915 girls (aged up to 6 years) for every 1000 boys of the same age. Present data show increasing numbers of female fetus abortions, particularly among the more affluent sectors of Indian society. Sex-selective abortion is illegal but highly profitable and unlikely to be punished. Data have been analysed for 250000 births during three rounds of a nationally representative survey (1990–2005) and birth cohorts of children aged 0–6 years

in the censuses of 1991, 2001, and 2011 have been studied.

Abortion of a girl fetus is more likely in the second pregnancy when the first pregnancy ended in the birth of a girl. After a female first birth, the sex ratio for second births was 906 girls per 1000 boys in 1990, 891 girls per 1000 boys in 1996, and 836 girls per 1000 boys in 2005. After a male first birth the sex ratios for second births in these years were 952, 973, and 1013 girls per 1000 boys.

The shortfall in girls in second births in families who already had a girl was confined to better-educated and wealthier mothers. The number of districts with a normal sex ratio (>950 girls per 1000 boys) has fallen in recent years and the estimated numbers of selective abortions of girls rose from around 2 million in the 1980s to between 3.1 and 6.0 million in the first decade of this century.

The strong preference for sons in India has resulted in increasing selective abortion of girls among people with access to the appropriate technology.

Jha P et al. Trends in selective abortions of girls in India: analysis of nationally representative birth histories from 1990 to 2005 and census data from 1991 to 2011. *Lancet* 2011; 377: 1921–8; Subramanian SV, Corsi DJ. Can India achieve a balance of sexes at birth? *Ibid*: 1893–4.

Global burden of disease in young people

There has been a recent surge in interest about the health of adolescents and young people. Around 27% of the world's population are aged 10–24 years (1.8 billion people). Data from the WHO 2004 *Global Burden of Disease Study* have illustrated the health problems of this age group.

Worldwide, the burden of disease, expressed as disability-adjusted life-years (DALYs) per 1000 population was greatest in the 0–4 years age group (about 700 DALYs per 1000 population, falling to <100 DALYs per 10000 in the 10–14 years age group, and then rising gradually through late adolescence, young adult life, and middle age to reach 300–350 DALYs per 1000 after the age of 60. The sex distribution of DALYs was equal until the late teens when there was a slight excess of DALYs in females, but from the mid-20s onwards men had an excess of DALYs over women. The total incidence of DALYs among people aged 10–24 years in 2004 was about 236 million. Thus this age-group, about 27% of the world's population, had about 15.5% of the disease burden.

Africa had 2.5 times more DALYs for

people aged 10–24 than high-income countries (208 vs 82 DALYs per 1000 population). In the 15–19 years age group girls had 12% more DALYs than boys. Across the world the three main causes of years lost because of disability (YLDs) in 10–24-year olds were neuro-psychiatric disorders, accidents, and infections and parasitic disease. The main risk factors for DALYs were alcohol, unsafe sex, iron deficiency, lack of contraception, and illicit drugs.

The health of adolescents and young adults is important and deserves more attention than it has been given.

Gore FM et al. Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet* 2011; 377: 2093–102; Stantelli JS, Galea S. The global burden of disease in 10–24-year-olds. *Ibid*: 2058–60.

Tropical

Bolus fluid therapy for critically ill children in Africa: increased mortality

Paediatric life-support training programmes recommend rapid, early fluid resuscitation for shocked children, given up to 60 ml of isotonic fluid per kg body weight within 15 minutes. Such fluid resuscitation is widely thought to have saved many lives but its evidence base is limited. In sub-Saharan Africa, hypovolaemic shock is a common presentation in children with malaria or severe sepsis and carries a high risk of death. WHO guidelines suggest fluid resuscitation for only advanced cases and it is not widely practised. A study in Uganda, Kenya, and Tanzania (in centres without intensive care units) has shown that rapid administration of fluid boluses may be associated with increased mortality.

The study included a total of 3170 children aged 60 days to 12 years with fever, impaired consciousness, and poor peripheral perfusion. There were 3141 children without severe hypotension (stratum A). They were randomised to one of three options: 20 ml/kg of 0.9% saline over the course of 1 hour (saline bolus), 20 ml/kg of 5% human albumin (albumin bolus), or no bolus (controls). Twenty-nine children had severe hypotension (stratum B). They were randomised to one of the bolus groups without a control group. The trial was stopped early because of increased mortality in the bolus groups compared with the controls. Malaria was diagnosed in 57% of

the children. Mortality at 48 hours was significantly higher in the two bolus groups than in the control group (10.6% in the albumin bolus group, 10.5% in the saline bolus group, and 7.3% in the controls) in stratum A, a 45% increase in risk of death with bolus therapy. At 4 weeks mortality was 12.2%, 12.0%, and 8.7%, respectively. The rates of neurological sequelae were similar (1.9–2.2%) in the three groups, as were rates of pulmonary oedema or increased intracranial pressure (1.7%–2.6%). In stratum B, 9 of 13 children in the albumin-bolus group and 9 of 16 in the saline bolus group died.

Both albumin and saline boluses were associated with increased mortality.

Maitland K et al. Mortality after fluid bolus in African children with severe infection. *NEJM* 2011; 364: 2483–95; Myburgh JA. Fluid resuscitation in acute illness – time to reappraise the basics. *Ibid*: 2543–4 (editorial).

Towards a malaria vaccine

An effective vaccine against *Plasmodium falciparum* malaria is needed urgently. Natural immunity to malaria declines quickly on leaving the endemic region. Dutch workers reported in 2009 that repeated exposure to infected mosquitoes whilst taking chloroquin prophylaxis provided protection from experimental challenge 2 months later with the same parasite strain. Chloroquin allows the parasites to develop in the liver but kills asexual parasites in the blood. Volunteers developed only low-level antiparasite antibodies but strong T-cell responses with interferon γ and interleukin 2 production in vitro. Now these researchers have reassessed the volunteers after a gap of 2.5 years.

The study included six immune subjects from the first trial and five newly recruited malaria-naïve volunteers. They were challenged by exposure to the bites of five *P. falciparum*-infected mosquitoes. Four of the six immune subjects remained microscopically negative after the challenge and rt PCR-based tests for blood parasites were negative throughout follow-up. Two of the six immune volunteers developed parasitaemia delayed by about 1 week compared with the nonimmune controls. The four protected subjects showed long-term persistence of parasite-specific pluripotent effective memory T-cell responses. They each reported symptoms, most commonly headache.

The artificially-induced immunity in these studies lasted for longer than immunity after natural exposure. Research

into mechanisms of malarial immunity and towards an effective vaccine continues.

Roestenberg M et al. Long-term protection against malaria after experimental sporozoite inoculation: an open label follow-up study. *Lancet* 2011; 377: 1770–6; Greenwood B, Targett G. The mysteries of immunity to malaria. *Ibid*: 1729–30 (comment).

Paediatrics

PCR CMV screening at birth

Congenital cytomegalovirus (CMV) infection may cause neurological defects including deafness. The infection may be diagnosed by rapid culture of urine and/or saliva, but these methods are not suitable for universal screening. Real-time PCR testing of dried blood spots has been tried for screening but failed to identify most congenital CMV infections. Now a multicentre US study has shown that PCR testing of saliva samples from neonates could be used for large-scale screening.

A total of 34 989 newborn infants had liquid or dried saliva specimens collected and tested for CMV using both PCR and culture and 177 (0.5%) had at least one positive test. Among 17 662 infants tested using liquid saliva 85 were positive on culture and all 85 were also positive on PCR testing. Using culture as the 'gold standard' PCR testing had a sensitivity of 100% and a specificity of 99.9%. Among the 17 327 infants tested using dried saliva, 76 were positive by culture and only two of these were negative on PCR, giving a sensitivity of 97.4% and a specificity of 99.9% for the PCR method.

PCR testing for CMV using liquid or dried saliva specimens showed high sensitivity and specificity. The methods could be used for large-scale neonatal screening. Dried specimens are easier to store and to transport.

Boppana SB et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. *NEJM* 2011; 364: 2111–8.

Fetal weight and birthweight percentiles – global reference values

Smallness-for-gestational-age at birth is defined as birthweight <10th percentile for gestational age. Deriving global standards for birthweight has proved difficult, especially for preterm births. Weight measured at birth gives lower 10th percentile values than estimated fetal weight (from ultrasound) for the same gestational ages in pregnancy. Thus

percentiles based on birthweight might underestimate the number of small-for-gestational-age infants.

Ultrasound-based fetal weight references were mostly developed in women of European ancestry, however, and may not be applicable to women in developing countries. Individualised references taking into account ethnic origin, maternal height and weight, parity, and fetal sex have been suggested but they have been based on ethnic groups living in developed countries and also may be unsuitable for use in developing countries.

Now global reference standards have been derived by adapting previous non-customised and individualised ultrasound fetal weight calculations and adjusting for mean birthweight at 40 weeks for any local population. Data from 24 countries in Africa, Latin America, and Asia (from the 2004–2008 WHO *Global Survey on Maternal and Perinatal Health* which included 237 025 births) were used for application and validation of the new reference standards. For each local reference the risks of adverse perinatal outcomes for small-for-gestational-age and not-small-for-gestational age infants were estimated. The odds ratios (small-for-gestational-age versus not-small-for-gestational age) using non-customised fetal weight reference standards, fully individualised reference standards, and the new country-specific standards were 1.59, 2.84, and 2.87, respectively.

The new reference standards are country-specific, and predict adverse perinatal outcomes more accurately than non-customised standards. They are much easier to use than individualised reference standards and equally predictive.

Mikolajczyk RT et al. A global reference for fetal-weight and birthweight percentiles. *Lancet* 2011; 377: 1855–61; Gardosi J. Fetal growth standards: individual and global perspectives. *Ibid*: 1812–4 (comment).

Hydroxycarbamide (hydroxyurea) for infants and toddlers with sickle cell disease

Hydroxycarbamide (formerly known as hydroxyurea) inhibits ribonucleotide reductase, increases the amount of fetal haemoglobin in red cells, improves nitric acid metabolism, reduces red cell-endothelial interaction, and decreases erythrocyte density. It is effective treatment for sickle-cell disease in school-age children and adults but there is little information about its use in younger children. Now a multicentre US trial has shown that hydroxycarbamide is effective treatment for infants and young children.

A total of 193 children aged 9–18 months with sickle-cell disease were randomised at 13 centres to hydroxycarbamide solution 20mg/kg/day, or placebo, for 2 years. Treatment with hydroxycarbamide significantly reduced painful crises (from 375 episodes in 75 control patients to 177 episodes in 62 patients) and dactylitis (from 123 episodes in 42 patients to 24 episodes in 14 patients). There were also significant reductions in acute chest syndrome and in transfusion requirements. There were fewer hospital admissions in the treatment group. Splenic function and glomerular filtration were similar in the two groups. The treatment was associated with increased haemoglobin levels, increased fetal haemoglobin, and reduced white cell counts with mild to moderate neutropenia.

Hydroxycarbamide is effective and inexpensive. These researchers suggest that it should be considered for all young children with sickle-cell anaemia.

Wang WC et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet* 2011; 377: 1663–72; Weatherall DJ. Hydroxycarbamide for sickle-cell anaemia in infancy. *Ibid*: 1628–30 (comment).

Infection

Meningococcal group A conjugate vaccine: immunogenicity and safety in Africans

Every 10–12 years, for more than a century, epidemics of group A *Neisseria meningitidis* meningitis have occurred in the so called 'African meningitis belt' that extends from Senegal in the west to Ethiopia in the east. People under the age of 30 are most likely to be infected and in 2009 there were >50 000 cases in Nigeria. Polysaccharide vaccines are effective in emergencies but a cheap vaccine is badly needed. A cheap vaccine (50 US cents per dose) has been tested in two studies; the first in Mali and Gambia and the second in Mali, Gambia, and Senegal. The vaccine (PsA-TT) consists of meningococcus group A polysaccharide conjugated to tetanus toxoid with aluminium phosphate as adjuvant.

The first study included 601 children aged 12–23 months who were randomised to PsA-TT, a meningococcal polysaccharide vaccine (PsACWY), or *Haemophilus influenzae* type b conjugate vaccine (control). A four-fold or greater increase in serum bactericidal

antibody (SBA) titre occurred in 96.0% (PsA-TT) vs 63.7% (PsACWY). At 40 weeks the PsA-TT group had higher antibody titres and immunological memory after a polysaccharide booster vaccine. In the second study a four-fold or greater increase in SBA titre occurred in 78.2% (PsA-TT) vs 46.2% (PsACWY). There were no serious vaccine-related events in either study. Tenderness and induration at the injection site were more frequent after PSA-TT.

The PsA-TT vaccine could be effective in controlling epidemics of group A meningococcal meningitis in Africa.

Sow SO et al. Immunogenicity and safety of a meningococcal A conjugate vaccine in Africans. *NEJM* 2011; 364: 2293–304.

Telaprevir for chronic HCV infection

Standard treatment for chronic hepatitis C virus (HCV) genotype 1 infection is with at least 48 weeks of pegylated interferon and ribavirin. Sustained virological response occurs in 40–50% of treatment-naïve patients. Telaprevir is an HCV genotype 1 protease inhibitor that has produced better response rates when added to standard treatment. It promotes early viral suppression and rates of relapse after stopping treatment are low, suggesting that shorter treatment durations might be successful. Two studies, one of previously untreated patients and one of previously treated patients who did not respond adequately or relapsed, have been reported in successive papers in the *New England Journal of Medicine*.

A total of 1088 previously untreated patients were randomised at 123 centres in an international study to one of three groups. All three groups received peginterferon and ribavirin (PR) for the first 12 weeks. One group (t12PR) also received telaprevir during the first 12 weeks and peginterferon plus ribavirin for the next 12 weeks unless HCV RNA testing was positive at either week 4 or 12, or both, when peginterferon plus ribavirin would be continued for the next 36 weeks (48 weeks in all). Another group (T8PR) received telaprevir, peginterferon, and ribavirin for 8 weeks followed by peginterferon and ribavirin alone (with placebo) for another 4 weeks and then peginterferon and ribavirin for 12 or 36 weeks as in the T12PR group. The third group (PR) received peginterferon and ribavirin for 48 weeks with placebo in the first 12 weeks. Both telaprevir groups (T8PR and T12PR) had significantly greater rates of sustained virological response (negative HCV RNA testing 24 weeks after last

planned dose of study treatment) (69% and 75%) than the peginterferon plus ribavirin only group (44%). A majority (58%) of patients in the telaprevir groups were eligible to stop treatment after 24 weeks. Anaemia, gastrointestinal side effects, and rashes were more common in the telaprevir groups. Treatment was discontinued because of adverse events in 10% of the two telaprevir groups and 7% of the control group. The addition of telaprevir increased the rate of sustained virological response and allowed treatment to be shortened to 24 weeks in most cases.

The trial with patients previously treated with peginterferon and ribavirin included 663 patients. Randomisation was again to three groups: peginterferon and ribavirin for 48 weeks with telaprevir in the first 12 weeks (t12PR48), 4 weeks of peginterferon plus ribavirin followed by 12 weeks of added telaprevir and then peginterferon and ribavirin alone for another 32 weeks (lead-in T12PR48), or peginterferon and ribavirin alone for 48 weeks (controls). The rates of sustained virological response were 83% (T12PR48), 88% (lead in T12PR48), and 24% (controls), significantly higher in the telaprevir groups than in the control group, among patients who had previously relapsed. Among patients with previous partial response to treatment the corresponding figures were 59%, 54%, and 15%, and among patients who had previously not responded 29%, 33%, and 5%. Telaprevir caused more anaemia, neutropenia, and leukopenia.

The addition of telaprevir to treatment with peginterferon and ribavirin improved rates of sustained virological response in both of these trials.

Jacobson IM et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *NEJM* 2011; 364: 2405–16; Zeuzem S et al. Telaprevir for retreatment of HCV infection. *Ibid*: 2417–28; Rosen HR. Chronic hepatitis C infection. *Ibid*: 2429–38 (clinical practice).

Dengue vector control strategies

It is estimated that around the world there are about 50 million dengue infections each year, mainly in urban areas in developing countries. Dengue control is mainly via insecticide-based vector control. A dengue transmission model has been developed that takes into account the evolution of insecticide resistance in vector mosquitoes and human population immunity. The model integrates a dynamic model with economic assessment and is based on data from Rio de Janeiro.

Forty-three insecticide-based vector

control strategies were assessed, targeting adult and larval stages of the vector and various insecticide strategy efficacies and application frequencies. All strategies would cause the emergence of insecticide resistance and loss of herd immunity, tending to increase the extent of future epidemics. One or more applications a year of high-efficacy (90% killing) larval control would reduce the dengue burden for up to 2 years. Three or more applications a year of adult vector control would reduce dengue burden for up to 4 years. For two high-efficacy adult vector control applications a year the incremental cost-effectiveness ratio would be US\$ 615 per disability-adjusted life-year (DALY) saved and for six applications a year it would be \$ 1267 per DALY saved. The six-applications strategy would probably meet the WHO standard for a cost-effective or very cost-effective intervention.

Year-round larval control is likely to be counter-productive. Policies based on larval control should be reassessed.

Luz PM et al. Dengue vector control strategies in an urban setting: an economic modelling assessment. *Lancet* 2011; 377: 1673–80; Massad E, Coutinho FAB. The cost of dengue control. *Ibid*: 1630–1 (comment).

Obs & Gyn

Caesarean section in developing countries: clinical officers vs doctors

Clinical officers in developing countries are not medically qualified but trained to a standard at which they can carry out many of the tasks usually performed by doctors. Out of 47 sub-Saharan African countries 19 allow clinical officers to provide obstetric care but in only 5 are they allowed to perform caesarean sections. In some countries, however, they perform up to 80% of caesarean sections. A systematic review and meta-analysis has addressed the question of the relative effectiveness and safety of clinical officers and medical doctors in the performance of caesarean sections.

The review included six non-randomised controlled studies (16018 patients). Data from all six studies showed a non-significant 46% increase in maternal mortality after caesarean sections performed by clinical officers rather than doctors. Data from five of the studies showed a non-significant 31% increase in perinatal mortality. There were significant increases in wound infection and wound dehiscence after clinical officer

caesarean sections.

The different names and training given to non-medically qualified clinicians in different countries make it difficult, or impossible, to perform a valid comparison between countries. There must be many other potentially confounding factors that could not be fully taken into account.

Wilson A et al. A comparison of clinical officers with medical doctors on outcomes of caesarean section in the developing world: meta-analysis of controlled studies. *BMJ* 2011; 342: 1134 (d2600); Bergström S. "Non-physician clinicians" in low-income countries. *Ibid*: 1094–5 (d2499) (editorial).

Perinatal outcomes after 2009/ H1N1 infection in pregnancy

During the 2009 influenza A H1N1 pandemic, pregnant women had more severe infections and higher mortality. A UK study has shown that perinatal outcomes were also worse.

The study included all women with confirmed H1N1 infection in pregnancy admitted to obstetrician-led maternity units in the UK during the second wave of the pandemic between September 2009 and January 2010. There were 256 pregnant 'cases' and 1220 pregnant controls without H1N1 infection. The cases had significant increases in preterm and very preterm delivery and perinatal mortality. Perinatal mortality was 39 per 1000 births in cases and 7 per 1000 births in controls, a highly significant difference. The increase was mostly in stillbirths (27 vs 6 per 1000 births). Preterm birth was increased four-fold in cases compared with controls and very preterm birth was increased almost five-fold. Preterm birth was associated with third trimester infection, intensive care unit admission, and secondary pneumonia.

H1N1 infection in pregnancy increased rates of perinatal mortality and preterm birth. Editorialists suggest that vaccination is the key to reducing the damage.

Pierce M et al. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ* 2011; 342: 1351 (d3214); Joseph KS, Liston RM. H1N1 influenza in pregnant women. *Ibid*: 1322-3 (d3237) (editorial)

Thyroid autoantibodies, miscarriage, and preterm birth: meta-analysis

Thyroid autoantibodies are common, being found in 6–20% of women of reproductive age. They may increase the risk of miscarriage or preterm birth. A meta-analysis of published evidence has con-

firmed this increased risk and shown that levothyroxine treatment of women with thyroid autoantibodies and apparently normal thyroid function might reduce it.

The meta-analysis included 31 studies (12 126 women) concerning miscarriage and five studies (12 566 women) concerning preterm birth. The presence of thyroid autoantibodies increased the risk of miscarriage by a factor of 3.9 in 19 cohort studies and 1.8 in 12 case-control studies. Among women with thyroid autoantibodies and apparently normal thyroid function there was some evidence of elevated levels of thyroid stimulating hormone (TSH). The studies on risk of preterm birth showed a two-fold increase in risk in the presence of thyroid autoantibodies. Two small trials suggested that the risks of miscarriage and preterm birth could be reduced by treating women with thyroid autoantibodies and apparently normal thyroid function with levothyroxine.

Further trials are planned.

Thangaratinam S et al. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ* 2011; 342: 1065 (d2616); Negro R, Stagnaro-Green A. Thyroid autoantibodies, preterm birth, and miscarriage. *Ibid*: 1035–6 (d2260) (editorial).

AIDS

Preventing tuberculosis in adults with HIV infection

Trials have shown that prophylaxis with isoniazid for 6–12 months or isoniazid plus rifampicin (rifampin) for 3 months, for people with HIV infection, reduces the risk of tuberculosis by 32–64%. Such treatment is rarely given, however, because of concerns about poor compliance, reinfection, and mycobacterial drug resistance.

Researchers in Soweto, South Africa have compared four different prophylactic regimens including the standard 6 months of isoniazid. In an area with a high prevalence of both HIV infection and tuberculosis a total of 1148 patients with HIV infection and a positive skin test (median age 30 years, median CD4 cell count 484 per cumm) were randomised, whilst not taking antiretroviral therapy, to one of four regimens: rifapentine 900mg plus isoniazid 900mg weekly for 12 weeks, rifampicin 600mg plus isoniazid 900mg twice weekly for 12 weeks, isoniazid 300mg daily for up to 6 years (continuous isoniazid), or isoniazid 300mg daily for 6 months

months (controls). The incidence rates of active tuberculosis or death were 3.1, 2.9, 2.7, and 3.6 per 100 person-years in these groups respectively, with no significant group differences. Serious adverse reactions were more common with continuous isoniazid than with any other regimen. Multi-drug resistance occurred in 3.4% of isolates of *Mycobacterium tuberculosis*.

All regimens were judged to be effective and none was superior to 6 months of isoniazid.

Martinson NA et al. New regimens to prevent tuberculosis in adults with HIV infection. *NEJM* 2011; 365: 11–20; Nardell E, Churchyard G. What is thwarting tuberculosis prevention in high-burden settings? *Ibid*: 79–81 (editorial).

HIV/AIDS care education of staff in primary care clinics in South Africa

A trial in South Africa has shown that an educational outreach programme for staff in primary care clinics improved the care of patients with HIV/AIDS.

A total of 15 clinics were randomised to usual care alone (seven clinics) or usual care plus outreach education (6–20 visits by a trainer, covering HIV/AIDS and antiretroviral treatment (ART). All clinics were run by specialist HIV nurses. At intervention clinics newly diagnosed HIV-infected patients were 95% more likely than patients at control clinics to receive prophylactic co-trimoxazole (41% vs 32%), and 25% more likely to have tuberculosis diagnosed (7% vs 6%). HIV testing leading to increased enrolment in the HIV/AIDS and ART programme did not increase significantly in the intervention group.

The outreach education programme improved HIV/AIDS care but did not improve access to care.

Zwarenstein M et al. Outreach education for integration of HIV/AIDS care, antiretroviral treatment, and tuberculosis care in primary care clinics in South Africa: PALSA PLUS pragmatic cluster randomised trial. *BMJ* 2011; 342: 1066 (D2022).

Isoniazid prophylaxis in HIV-exposed, tuberculosis-exposed children: not effective

Tuberculosis is the cause of death in 12–18% of African children who die with HIV infection. In many areas of South Africa both HIV infection and tuberculosis are common. In a four-centre study (Johannesburg, Cape Town, and Durban in South Africa and Gaborone in Botswana) isoniazid prophylaxis for children exposed to HIV

was not effective.

The study included 1352 infants of HIV-infected mothers. HIV-1 DNA PCR testing before and 24 weeks after randomisation showed that 548 infants were HIV-infected and 804 HIV-uninfected. All infants received BCG vaccination in the first 30 days of life. All sites had a programme for prevention of mother-to-child HIV infection and all HIV-infected infants received antiretroviral treatment. All infants had been exposed to a case of tuberculosis or were born to a mother on antituberculosis treatment. At 91–120 days of age the infants were randomised to isoniazid (10–20mg/kg per day) or placebo, for 96 weeks. Among the HIV-infected children tuberculosis or death occurred in 19.0% of the isoniazid group and 19.3% of the placebo group. Among HIV-uninfected children the rates of tuberculosis infection, tuberculosis disease, or death were 10% and 11%. The incidence of tuberculosis was 121 cases per 1000 child-years in HIV-infected children and 41 per 1000 years in HIV-uninfected children. Toxicity was similar in the two groups.

Isoniazid prophylaxis was not effective in HIV-infected or HIV-uninfected children. The reason is not known.

Madhi SA et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. *NEJM* 2011; 365: 21–31; Nardell E, Churchyard G. What is thwarting tuberculosis prevention in high-burden settings. *Ibid*: 79–81 (editorial).

Diabetes

Trends in fasting plasma glucose and diabetes since 1980

Overweight, obesity, hyperglycaemia, and diabetes have all increased in prevalence in many parts of the world. Variations in previous studies have made comparisons and overall conclusions difficult. A new systematic analysis has attempted to overcome these difficulties in assessing data from 199 countries to establish trends during the period 1980–2008.

Data were obtained from health examination surveys and epidemiological studies. Global age-standardised mean fasting plasma glucose (FPG) rose by 0.07mmol/L in men and 0.09mmol/L in women per decade to reach 5.50 and 5.42mmol/L respectively by 2008. The age-standardised prevalence of diabetes in adults rose from 8.3% (men) and 7.5% (women) in 1980 to 9.8% and 9.2% in

2008. The number of people with diabetes more than doubled, rising from 153million to 347million. High diabetes prevalence and high mean FPG values in 2008 were found in south Asia, Latin America, the Caribbean, central Asia, north Africa, and the Middle East, but Oceania had the highest rates of increase and the highest values in 2008 (mean FPG 6.09 and 6.08, diabetes prevalence 15.5% and 15.9%). Mean FPG and diabetes prevalence changed little in east and south-east Asia and in central and eastern Europe. In 2008 mean FPG was lowest in sub-Saharan Africa, east and south-east Asia, and high-income Asia-Pacific. Among high-income sub regions the slowest rise in FPG (0.07 and 0.03mmol/L per decade) was in western Europe and the fastest (0.18 and 0.14mmol/L per decade) in north America.

Mean FPG values and diabetes prevalence are rising around the world. More effective prevention is needed.

Danaei G et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011; 378: 31–40; Tobias M. Global control of diabetes: information for action. *Ibid*: 3–4 (comment).

Pulmonary

Beta-blockers in COPD

Beta-blockers have been regarded as contraindicated in chronic obstructive pulmonary disease (COPD) because of the risk of inducing bronchospasm. Now a study of Scottish data has shown that beta-blocker treatment may be beneficial.

The retrospective cohort study included 5977 patients with COPD. Beta-blocker use was associated with a 22% reduction in all-cause mortality overall and reduced mortality at all severities of COPD as judged by stage of treatment. Compared with patients who were treated only with inhaled short-acting β -agonists or antimuscarinics, increasing intensity of treatment was associated with a 57% reduction in overall mortality and the addition of a beta-blocker increased this reduction to 72%. Beta-blockers did not reduce pulmonary function when given with a long-acting β -agonist or a long-acting antimuscarinic.

Why beta-blockers should have this effect is unclear. Many patients with COPD also have coronary disease and

beta-blockers are beneficial for patients with coronary disease but that does not explain all of the benefit in COPD. It is suggested that in COPD long-term beta-blocker treatment may be bronchoprotective, anti-inflammatory, and mucus-resolving. Prospective trials are needed before beta-blocker therapy can be accepted as standard in COPD.

Short PM et al. Effect of β -blockers in treatment of chronic obstructive pulmonary disease: retrospective cohort study. *BMJ* 2011; 342: 1068 (d2549); Kazani S, Israel E. Treatment with β -blockers in people with COPD. *Ibid*: 1037–8 (d2655) (editorial).

Airway remodelling in asthma: effect of bronchoconstriction without inflammation

The pathological changes in asthma include airway inflammation and airway remodelling. The latter is characterised by goblet cell hyperplasia, subepithelial collagen deposition, and hypertrophy of smooth muscle and it has been thought to be a consequence of eosinophilic inflammation. There is evidence, however, from in vitro research, that mechanical stress resulting from bronchoconstriction may play an important part in the development of airway remodelling. Now researchers in Southampton, England have shown that bronchoconstriction without eosinophilic inflammation causes remodelling.

The trial included 48 adult volunteers with asthma controlled with an as-required short-acting beta agonist, a skin prick reaction to house mite, and abnormal airway reactivity to metacholine. They underwent full assessment followed, after at least 14 days, by bronchoscopy. They were then randomised to four groups of 12 for challenge tests. Each group underwent its own inhaled challenge (house dust mite allergen, methacholine, saline, or metacholine after salbutamol, on days 0, 2, and 4; bronchial biopsy was performed at the initial pre-challenge bronchoscopy and at repeat bronchoscopy at least 4 days after the last challenge. The allergen was chosen to produce both bronchoconstriction and eosinophilic airway inflammation, the metacholine to produce bronchoconstriction without inflammation, and the saline and the metacholine after salbutamol acted as control challenges. Both allergen and metacholine caused immediate bronchoconstriction of the same degree but eosinophilic inflammation occurred only in the allergen group. Airway remodelling was seen in both of these challenge groups but not in the control challenge groups. Sub-epithelial

collagen-band thickness increased by 2.17 μm in the allergen group and by 1.94 μm in the metacholine group, but did not increase significantly in the control groups. There were similar findings for mucus gland hyperplasia. The active challenges produced similar degrees of bronchoconstriction and of airway remodelling and significantly more airway remodelling than the control challenges.

Bronchoconstriction without additional airway inflammation caused airway remodelling. These findings may have important implications for treatment. Emphasis has been on controlling airway inflammation with inhaled steroid but control of bronchoconstriction may be equally important.

Grainge CL et al. Effect of bronchoconstriction on airway remodelling in asthma. *NEJM* 2011; 364: 2006–15; Tschumperlin DJ. Physical forces and airway remodelling in asthma. *Ibid*: 2058–9 (editorial).

Cardiology

Arsenic and cardiovascular mortality in Bangladesh

Millions of people around the world are exposed to dangerous concentrations of arsenic in water. As well as being a carcinogen, arsenic has also been related to increased risk of cardiovascular disease. The health risks of arsenic may be increased in smokers. In Bangladesh around 57 million people have been chronically exposed to increased levels of arsenic in groundwater. A study there has shown a dose-dependent relationship between arsenic levels in drinking water and cardiovascular mortality, exaggerated among smokers.

The study included 11746 people aged 18–75 who had lived in the study area for at least 5 years before recruitment in 2000–2002. Arsenic concentrations in well water (5966 contiguous wells in an area of 25 km²) ranged between 0.1 and 864 $\mu\text{g/L}$. Follow-up averaged 6.6 years with visits every 2 years. Causes of death were ascertained using a validated verbal autopsy procedure and medical records. There were 198 deaths from cardiovascular disease (43% of all deaths). The hazard ratios for death from heart disease according to increasing quartiles of well water arsenic levels were 1.0 (reference), 1.22, 1.35, and 1.92 (quartile ranges of well water arsenic concentration 0.1–12.0, 12.1–62.0, 62.1–148.0, and 148.1–864.0 $\mu\text{g/L}$). Baseline urinary arsenic concentrations were similarly

related to heart disease mortality. There was a 29% increase in heart disease mortality for every 1 SD increase in well water arsenic concentration. Cerebrovascular mortality, however, was not related to well water arsenic levels. There was a synergistic effect between raised arsenic concentrations in well water and smoking, the risks of the two combined being greater than the sum of the risks of each.

Arsenic in drinking water increases the risk of dying from heart disease and smoking has a synergistic effect. It has been estimated that around the world about one in ten deaths is due to high levels of arsenic in drinking water.

Chen Y et al. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. *BMJ* 2011; 342: 1067 (d2431); Smith AH, Steinmaus CM. Arsenic in drinking water. *Ibid*: 1036–7 (d2248) (editorial).

PPIs plus aspirin and first myocardial infarction: increased cardiovascular risk

Proton pump inhibitors (PPIs) may reduce the platelet inhibition associated with aspirin treatment. A study in Denmark has shown that outcomes may be worse after a first myocardial infarction among patients taking both aspirin and a PPI. The retrospective cohort study based on national registry data included all 19925 patients aged 30 years or older admitted to hospital in Denmark in 1997–2006 with a first myocardial infarction who survived for at least 30 days after discharge and filled a prescription for aspirin within that 30-day period. A total of 4306 patients also took a PPI and 4159 of these were matched with 4159 controls (not treated with a PPI). Over 1 year of follow-up the combined endpoint of repeat myocardial infarction, stroke, or cardiovascular death was 46% or 61% (depending on the method of analysis) more common in patients taking a PPI. There was no increase in risk related to use of H₂ receptor blockers.

The combination of aspirin and a PPI in patients admitted to hospital with a first myocardial infarction was associated with increased cardiovascular risk compared with aspirin without a PPI.

Chalot M et al. Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: nationwide propensity score matched study. *BMJ* 2011; 342: 1135 (d2690).



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