

## General

### Income inequality and mortality: meta-analysis

There have been many studies of the effect of income inequality in a community and health and mortality. Findings have varied, however, and there is uncertainty about the mechanisms involved and the contributions of poverty and feelings of unfairness leading to psychosocial stress. A meta-analysis of published papers has supported the suggestion that one factor leading to differences in study findings may be that there is a threshold of inequality below which the effect is not seen.

The meta-analysis included nine cohort studies and 19 cross-sectional studies (a total of almost 61 million people). Income inequality was measured using the Gini coefficient (0 = complete equality, 1 = complete inequality). For each increase in Gini coefficient of 0.05 units there was an 8% increase in mortality in cohort studies and a 4% increase in poor self-rated health in cross-sectional studies. The associations were stronger in studies with a Gini coefficient of at least 0.3 with data collected after 1990, with follow up >7 years, and with incorporation of time lags between income inequality and outcomes. It is calculated that if income-inequality causes increased mortality then up to 9.6% of deaths (14 million in 30 OECD countries) could be prevented by reducing the Gini coefficient to below 0.3. Estimated excess risk of premature mortality (compared with countries with Gini <0.3) was 3% in Japan (Gini 0.314), 11% in the USA (Gini 0.357), and 38% in Mexico (Gini 0.480).

Reducing income inequality could save many lives.

Kondo N et al. Income inequality, mortality, and self rated health: meta-analysis of multilevel studies. *BMJ* 2009; 339: 1178–81 (b4471); Pickett KE, Wilkinson RG. Greater equality and better health. *Ibid*: 1154–5. b4320 (editorial).

### Chronic diseases and disability in the elderly in developing countries

Worldwide 68% of the time lived with disability is attributable to chronic non-communicable diseases and most (84%) of this disease burden is in low- or middle-income countries. In these countries the people affected are often younger than in high-income countries. Nevertheless the proportion of the population

who are elderly is increasing around the world and more rapidly in developing countries. In the *Global Burden of Disease Report* of 1996 the main causes of disability in the elderly in developing countries were eye diseases, hearing loss, dementia, musculoskeletal diseases, and heart disease. A new study has placed dementia rather than eye diseases in top spot.

In 2003–2005 population surveys of all people aged >65 were performed at 11 sites in seven low- or middle-income countries (China, India, Cuba, Dominican Republic, Venezuela, Mexico, and Peru). Disability was assessed using the 12-item WHO disability assessment schedule (WHODAS 2.0). Other data were collected by clinical assessment or from self-reported diagnosis or impairment. In all regions except rural India and Venezuela the largest contribution to disability was from dementia (median population-attributable prevalence fraction (PAPF) 25%). The main other contributors were stroke (PAPF 11.4%), limb impairment (10.5%), arthritis (9.9%), depression (8.3%), eyesight problems (6.8%), and gastrointestinal impairments (6.5%). Chronic disease accounted for about two-thirds of disability prevalence.

In these populations the main contributor to disability is dementia. Chronic diseases of the brain and mind are not only leading causes of disability but they lead to dependence and present complex and long-term challenges in caring with very large societal costs.

Sousa RM et al. Contribution of chronic disease to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. *Lancet* 2009; 374: 1821–30; *Lancet*. Disability: beyond the medical model. *Ibid*: 1793 (editorial); Sabat SR. Dementia in developing countries: a tidal wave on the horizon. *Ibid*: 1805–6 (comment).

### Dabigatran vs warfarin for acute venous thromboembolism

Dabigatran is an orally administered direct inhibitor of thrombin. Unlike warfarin it is given as a fixed dose without coagulation monitoring. Now a multinational trial has shown that it is as effective and safe as warfarin for the treatment of venous thromboembolism (VTE).

A total of 2539 patients with acute VTE were initially treated for around 9 days with a parenteral anticoagulant (usually unfractionated or low-molecular-weight heparin) and then randomised, at 228 centres in 29 countries, to dabigatran 150 mg twice daily or dose-adjusted warfarin (target INR, 2.0–3.0) for 6

months. At 6 months the rates of recurrent VTE were 30/1274 (2.4%) in the dabigatran group and 27/1265 (2.1%) in the warfarin group, showing that dabigatran was not significantly inferior to warfarin.

Major bleeding occurred in 1.6% vs 1.9%, a nonsignificant difference. The risk of any bleeding was significantly greater with warfarin (22% vs 16%). The two groups did not differ significantly as regards mortality, acute coronary syndromes, or abnormal liver function tests. Adverse events leading to discontinuation occurred 9.0% vs 6.5% (difference just significant).

In the treatment of VTE dabigatran has similar effectiveness and safety to warfarin but is easier to use.

Schulman S et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *NEJM* 2009; 361: 2342–52.

## Obs & Gyn

### Maternal-vaginal and neonatal chlorhexidine wipes to prevent neonatal sepsis: negative trial

There are about 900 000 neonatal deaths from sepsis in developing countries each year. Much neonatal sepsis occurs as a result of contamination during labour and delivery. Application of chlorhexidine to the mother's vagina during labour and to the skin of the neonate has been suggested as a way of preventing neonatal sepsis and there is evidence of its efficacy from non-randomised studies. Now, however, negative results have been reported from a randomised controlled trial in South Africa.

In Soweto, a total of 8011 women aged 12–51 years were randomised to chlorhexidine wipes during labour and chlorhexidine wiping of the whole of the skin (except face and ears) of the newborn baby or control (water wipes to the mother's external genitalia and chlorhexidine to the neonate's foot only). Neonatal sepsis in the first 3 days was diagnosed in 3% (chlorhexidine) vs 4% (controls), a nonsignificant difference. In a subset of 5144 mothers assessed bacteriologically the rates of colonisation of the newborn with group B streptococcus were 54% (chlorhexidine) vs 55% (controls).

Chlorhexidine as used had no effect on neonatal sepsis. Other interventions are needed. *Lancet* commentators, however, maintain that it is too early to abandon

this use of chlorhexidine: it might be effective in higher-risk settings

Cutland CL et al. Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised controlled trial. *Lancet* 2009; 374: 1909–16; Mullany LC, Biggar RJ. Vaginal and neonatal skin cleansing with chlorhexidine. *Ibid*: 1873–5 (comment).

### Lying still after intrauterine insemination

After intrauterine insemination spermatozoa may reach the fallopian tube (the site of fertilisation) within 2–10 minutes. There is uncertainty, however, about the need for women to be on their backs for a while after intrauterine insemination in order to improve the likelihood of pregnancy. Now a study in the Netherlands has shown that 15 minutes of supine lying improves pregnancy rates.

A total of 391 women were randomised to either remain supine for 15 minutes or to get up immediately after intrauterine insemination for three cycles. The ongoing pregnancy rate was 27% (immobilisation) vs 18% (mobilisation), a significant difference. The rates of live birth were 27% vs 17%. In the first, second, and third treatment cycles the ongoing pregnancy rates were 10%, 10%, and 7% vs 7%, 5%, and 5%.

These researchers conclude that 15 minutes of immobilisation after intrauterine insemination should be routine.

Custers IM et al. Immobilisation versus immediate mobilisation after intrauterine insemination: randomised controlled trial. *BMJ* 2009; 339: 1065–7 (b4080); Ledger WL. Supine positioning after intrauterine insemination. *Ibid*: 1040–1 (editorial).

### Pre-eclampsia and later hypothyroidism

It is believed that pre-eclampsia is probably caused by excess production of antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1). Blood levels of sFlt-1 increase in late pregnancy and the increase is much greater in women with pre-eclampsia. People treated with antiangiogenic factors for cancer may develop hypothyroidism. Now data from US and Norwegian studies have confirmed that women who have had pre-eclampsia may have an increased risk of hypothyroidism associated with excess production of antiangiogenic factors.

Data were analysed from 141 women in the US (CPEP) study of 1992–1995 and from 7121 women in the Norwegian Nord-Trøndelag Health Study of 1995–1997. In the CPEP study, serum TSH levels

increased by a factor of 2.4 after the onset of preeclampsia compared with a 1.5-fold increase in non-pre-eclamptic controls and there was a greater fall in levels of free triiodothyronine with pre-eclampsia. The increase in TSH levels was strongly associated with high sFlt-1 levels towards the end of pregnancy.

In the Norwegian study, women who had pre-eclampsia in their first pregnancy were 1.7 times more likely to have a raised TSH level later. This rise in TSH was not accompanied by thyroid peroxidase antibodies suggesting that it was not due to autoimmune thyroid disease. Pre-eclampsia in both first and second pregnancies increased the risk still further (nearly six-fold).

Increase in sFlt-1 levels in pre-eclampsia may be associated with subclinical hypothyroidism with a risk of later clinical hypothyroidism.

Levine R et al. Pre-eclampsia, soluble fms-like tyrosine kinase 1, and the risk of reduced thyroid function: nested case-control and population based study. *BMJ* 2009; 339: 1355–9 (b4336); North RA, Taylor RN. Subclinical hypothyroidism after preeclampsia. *Ibid*: 1323–4 (editorial).

## Paediatrics

### Child disability in developing countries

Little is known about the prevalence, causes, types, and severity of disability in children in developing countries. The Multiple Indicator Cluster Survey of 2005–2006 (MICS3) has provided data about disability in children aged 2–9 years from 18 low- and middle-income countries.

The screening tool used was the Ten Questions screen depending on Yes/No answers by parents or guardians to questions about developmental milestones, vision, hearing, comprehension, movement, seizures, learning, speech, communication, and intellectual impairment. Positive screening rates in the 18 countries varied from 3% to 48% (median 23%). Factors associated with lower positivity rates were breastfeeding, vitamin A supplementation, and early-learning activities. Factors associated with higher screening positivity rates were stunting and underweight. Older children (aged 6–9 years) who screened positive were less likely to attend school. The causal implications of these associations and the role of reverse causality are uncertain. The screening test assesses

only increased risk for disability but previous work has suggested that up to 33% of children who screen positive may have severe disability and the screening tool picks up 80% to 100% of all children with severe disability.

The Ten Questions screen provides a simple way of assessing disability prevalence in children in developing countries. Further progress will depend on assessment of causal factors and improving services for disabled children. Lack of opportunity and discrimination that turn impairment into disability need to be improved.

Gottlieb CA et al. Child disability screening, nutrition, and early learning in 18 countries with low and middle incomes: data from the third round of UNICEF's Multiple Indicator Cluster Survey (2005–06). *Lancet* 2009; 374: 1831–9; The *Lancet*. Disability: beyond the medical model. *Ibid*: 1793; Trani J-F. Screening children for disability. *Ibid*: 1806–7 (comment).

### Mexico's Oportunidades programme: 10 year effects

Conditional cash transfer (CCT) programmes provide cash payments to poor families on condition that they meet certain requirements such as attendance at health and education sessions. Mexico was one of the first countries to provide such a programme, the Oportunidades, which has become a model for other countries. After 3–5 years, children in this programme were shown to have benefited in terms of growth, cognition, and language development. Now the results of assessment at 10 years have been reported.

The programme began between April 1998 and October 1999 when 506 low-income communities were randomised to enrolment either immediately (320 communities) or after 18 months (186). The present report gives details of assessments in 2007 when the children were aged 8–10 years. A total of 1093 children had been in the programme from birth and 700 from the age of 18 months. The early involvement group had fewer behavioural problems but the two groups were similar as regards growth, BMI, language, and cognition. Children of mothers with no formal education were about 1.5 cm taller if enrolled early. Some effects were independent of money but the money itself had significant effects on most outcomes.

Early enrolment in a CCT programme has beneficial effects on children growth and development.

Fernald LCH et al. 10-year effect of Oportunidades, Mexico's conditional cash transfer programme, on child growth, cognition, language, and behaviour: a longitudinal follow-up study. *Lancet* 2009; 374:

1997–2005; Cueto S. Conditional cash-transfer programmes in developing countries. *Ibid*: 1952–3. (comment).

## AIDS

### HIV vaccine assessed

An HIV vaccine regimen has been tested in Thailand in a community at high risk for HIV infection.

The regimen consisted of a primer vaccine (a recombinant canarypox vector vaccine, ALVAC-HIV [VCP1521]) and a booster vaccine (a recombinant glycoprotein 120 subunit vaccine, AIDSVAX B/E). The primer was given as four injections at baseline and around 4 weeks, 12 weeks, and 24 weeks, and the booster as two injections at 12 and 24 weeks. The participants were 16402 healthy men and women aged 18–30 years who were mostly at risk of requiring HIV infection through heterosexual sex.

They were randomised to vaccines or placebo and followed up for 3 years after the last doses of vaccine. HIV infection occurred in 51/7960 subjects over 26507 person-years in the vaccine group (0.192 per person-year) and in 74/7988 over 26478 person-years in the placebo group (0.279 per person-year). Vaccine efficacy was 26.4% in the intention-to-treat analysis, 26.2% in the per-protocol analysis, and 31.2% in the modified intention-to-treat analysis (just significant only in the modified intention-to-treat analysis). Among subjects who became infected with HIV, vaccination status did not affect viral levels or CD4+ cell counts.

These researchers conclude that their results show only a modest benefit but provide a signpost to the direction of future research.

Reks-Ngarm S et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *NEJM* 2009; 361: 2209–20; Dolin R. HIV vaccine trial results – an opening for further research. *Ibid*: 2279–80 (editorial).

### Abacavir-lamivudine vs tenofovir-emtricitabine for initial therapy

Recommended initial therapy for HIV-1 infection is with two nucleoside reverse-transcriptase inhibitors (NRTIs) with a non nucleoside reverse-transcriptase inhibitor or a ritonavir-boosted protease inhibitor. In a multicentre trial US researchers have obtained better results with tenofovir disoproxil fumarate plus emtricitabine (TE) rather than abacavir

plus lamivudine (AL) as the two fixed-dosage NRTIs.

A total of 1858 patients were randomised to one of four treatment regimens: AL plus efavirenz, AL plus ritonavir-boosted atazanavir, TE plus efavirenz, or TE plus ritonavir-boosted atazanavir. At scheduled interim review there were significant differences in efficacy between the TE and the AL groups among the 797 patients with initial HIV-1 RNA levels of 100000 copies per ml or greater. With a median follow-up of 60 weeks the time to virological failure in this subgroup was significantly shorter in the AL groups and the rates of virological failure were 14% (AL) vs 7% (TE). The time to first adverse event was also significantly shorter in the AL groups. There were no significant differences in change in CD4+ cell count. Among patients with initial HIV-1 RNA levels of 100000 copies per ml or greater results were better with tenofovir DHF plus emtricitabine as the two NRTIs.

Sax PE et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *NEJM* 2009; 361: 2230–40.

## Diabetes

### Lifestyle changes to prevent diabetes

The US Diabetes Prevention program lasted for 2.8 years and showed that, among adults with impaired glucose tolerance or raised fasting plasma glucose, intensive lifestyle intervention (weight loss and regular exercise) reduced the incidence of type 2 diabetes by 58% and metformin treatment was associated with a 31% reduction. Now the 10-year follow-up results have been reported.

A total of 2766 subjects were followed up; 910, 924, and 932 from the original lifestyle, metformin, and placebo groups. During follow-up all three groups received lifestyle intervention and metformin was continued in the original metformin group.

In the initial study the incidence of diabetes was 4.8, 7.8, and 11.0 cases per 100 person-years in the lifestyle, metformin, and placebo groups. During the follow-up study the corresponding rates were 5.9, 4.9, and 5.6 cases per 100 person-years. Over the 10 years since randomisation the incidence of diabetes was 34% lower in the original lifestyle group, and 18% lower in the original metformin group, compared with the original placebo group.

The preventive effects of life style intervention or metformin may last for 10 years or more.

Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; 374: 1677–86; The *Lancet*. Type 2 diabetes epidemic: a global education. *Ibid*: 1654 (editorial); Misra A. Prevention of type 2 diabetes: the long and winding road. *Ibid*: 1655–6 (comment).

### Insulin plus metformin vs insulin plus repaglinide for non-obese patients with type 2 diabetes

Whilst metformin is an established drug for the treatment of type 2 diabetes in obese patients its use in non-obese patients has been questioned. Researchers in Denmark have compared insulin plus metformin with insulin plus repaglinide (an insulin secretagogue) for the treatment of non-obese patients with type 2 diabetes.

A total of 133 non-obese (BMI 27 or less) patients with type 2 diabetes were treated for 4 months with repaglinide plus metformin. After this run-in period, 102 patients with HbA<sub>1c</sub> concentration >6.4% were randomised to biphasic insulin aspart (70/30) daily, plus either metformin or repaglinide. Insulin dosage frequency was adjusted according to fasting blood glucose and HbA<sub>1c</sub> measurements. Ninety-seven patients completed the 12-month trial. During the course of treatment HbA<sub>1c</sub> levels fell from 8.15% to 6.72% in the insulin plus metformin group and from 8.07% to 6.9% in the insulin plus repaglinide group, a non-significant difference. The fall in HbA<sub>1c</sub> occurred mainly in the first month. The total daily dose of insulin and risk of hypoglycaemia were similar in the two groups. Weight gain was greater in the repaglinide group.

Glycaemic control was similar in the two groups. Weight gain was less with metformin.

Lund SS et al. Combining insulin with metformin or an insulin secretagogue in nonobese patients with type 2 diabetes: 12 month, randomised, double blind trial. *BMJ* 2009; 339: 1121–5 (b4324); Kooy A. Continuation of metformin after introduction of insulin in type 2 diabetes. *Ibid*: 1093–4 (b4227).

### Rituximab preserves beta-cell function in newly diagnosed diabetes

The destruction of pancreatic beta cells in type 1 diabetes is mainly T-lymphocyte-mediated. B-lymphocytes, however, may be important in T-lymphocyte-mediated diseases. Rituximab is an anti-CD20 monoclonal antibody that causes selective depletion of B-lymphocytes. Now a multicentre trial in the USA and Canada

has shown that treatment with rituximab preserves beta-cell function in patients with newly diagnosed type 1 diabetes.

A total of 87 patients aged between 8 and 40 years with newly diagnosed type-1 diabetes were randomised to rituximab by infusion, or placebo, weekly for four doses from day 1 of the study and followed up for 1 year. At 1 year the mean area under the curve (AUC) for serum C-peptide concentration during the first 2 hours of a mixedmeal tolerance test was significantly greater in the rituximab group (0.56 vs 0.47 pmol/ml) indicating better beta-cell function. The treated group also had lower levels of glycated haemoglobin and needed less insulin. The rate of decline of C-peptide levels between 2 and 12 months was less in the rituximab group. CD19+ B lymphocyte counts fell to zero within 1 month but there was 69% recovery by 12 months. There were mild or moderate reactions after the first infusion but only minimal reactions after subsequent infusions.

Treatment with rituximab was associated with partial preservation of beta-cell function. B-lymphocytes may play a part in beta-cell destruction.

Pescovitz MD et al. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function. *NEJM* 2009; 361: 2143–52.

## Cardiology

### Salt intake and cardiovascular risk: meta-analysis

A meta-analysis of data about the relationship between salt intake and risk of stroke and other cardiovascular disease has included 13 studies, 19 independent cohorts, and 177 025 people in six countries.

Over periods of follow-up varying from 3.5 to 19 years there were 5346 strokes and 5161 cardiovascular events. An increase in salt intake of 85 mmol (5g) per day was associated with a significant 23% increase in risk of stroke and a 17% increase in risk of cardiovascular disease.

Increasing intakes of salt are associated with progressively increased risk of stroke. There is also an association between salt intake and cardiovascular disease in general.

Strazzullo P et al. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009; 339: 1296 (Pico) (b4567); Appel LJ. The case for population-wide salt reduction gets stronger. *Ibid*: 1266–7 (editorial).

### High-dose losartan for heart failure

Angiotensin-receptor blockers reduce morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (LVEF) but optimum doses are not established. Now an international trial has shown that losartan at a dose of 150 mg daily gives better results than 50 mg daily.

The trial included a total of 3846 patients at 255 sites in 30 countries. They had heart failure (NYHA class II-IV), LVEF 40% or less, and intolerance to ACE inhibitors.

Randomisation was to losartan at a dose of either 50 mg or 150 mg daily. After an average follow-up of 4.7 years the primary endpoint (death or admission for heart failure) was reached by 43% in the 150 mg group and 46% in the 50 mg group, a significant difference. Mortality was not significantly different between the two groups (33.1% vs 34.8%) but the reduction in admissions for heart failure in the 150 mg group was significant (23.4% vs 26.3%). Renal impairment, hypotension, and hyperkalaemia were more frequent in the 150 mg group.

Patients with heart failure may benefit from a relatively high dose of losartan.

Konstam MA et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009; 374: 1840–8; Krum H. Optimising management of chronic heart failure. *Ibid*: 1808–9 (comment).

### Bleeding risk and antithrombotic treatments after acute myocardial infarction

Several combinations of antithrombotic drugs are used after acute myocardial infarction but little is known about their safety. National registers in Denmark have provided further data.

Data were analysed from 40 812 patients admitted to hospital with a first myocardial infarction between 2000 and 2005. From prescriptions at hospital discharge treatment group was determined: monotherapy with aspirin, clopidogrel, or vitamin K antagonist; dual therapy with aspirin plus clopidogrel, aspirin plus vitamin K antagonist, or clopidogrel with vitamin K antagonist; or triple therapy with all three drugs. The yearly incidence of hospital admission for bleeding was 2.6% (aspirin alone), 4.6% (clopidogrel alone), 4.3% (vitamin K antagonist alone), 3.7% (aspirin plus clopidogrel), 5.1% (aspirin plus vitamin K antagonist), 12.3% (clopidogrel plus vitamin K antagonist), and 12% (triple

therapy). Compared with aspirin alone the increased risks were 33%, 23%, 47%, 84%, 3.52-fold, and 4.05-fold for the other treatments respectively. The numbers-needed-to-harm were 81 (aspirin plus clopidogrel), 45 (aspirin plus vitamin K antagonist), 15.2 (clopidogrel plus vitamin K antagonist), and 12.5 (triple therapy). Among patients with non-fatal bleeding 38% either died or had recurrent myocardial infarction during the study.

On leaving hospital after a first myocardial infarction the risk of readmission for bleeding increases with the number of antithrombotic drugs used. Triple therapy or dual therapy with clopidogrel and a vitamin K antagonist particularly increase the risk.

Sørensen R et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009; 374: 1967–74; Grove EL, Story RF. The right oral antithrombotics in acute coronary syndromes. *Ibid*: 1947–8 (comment).

## Oncology

### What to do about lung nodules on CT screening

When noncalcified lung nodules are found in CT-based screening programmes it may be difficult to decide on the best course of action. Current practice is usually to refer the patient for further investigation if the nodule is >5 mm in diameter. Now researchers in the Netherlands and Belgium have assessed a strategy based on nodule volume and volume-doubling time.

A total of 7557 subjects with increased risk of lung cancer had CT screening in years 1, 2, and 4. A positive result was obtained in 2.6% and 1.8% in rounds 1 and 2. In round 1 the sensitivity for lung cancer was 94.6% and the negative predictive value 99.9%. Among 7361 subjects with a negative scan in round 1 20 lung cancers were detected after 2 years of follow-up.

Among high-risk subjects screened in three rounds of CT scanning, paying attention to nodule volume and volume-doubling time the chances of finding lung cancer at 1 and 2 years after a negative first-round test were 1 in 1000 and 1 in 3000.

Van Klaveren RJ et al. Management of lung nodules detected by volume CT scanning. *NEJM* 2009; 361: 2221–9; Mulshine JL, Jablons DM. Volume CT for diagnosis of nodules found in lung-cancer screening. *Ibid*: 2281–2 (editorial).