Exposure to secondhand smoke is an established cause of coronary heart disease, lung cancer, and premature death. Mounting evidence also links such exposure to airway disease, including asthma, chronic obstructive pulmonary disease, and impaired lung function. On the basis of knowledge about these and other serious health effects, North America, Europe, and Australia have introduced smoke-free legislation. None the less, millions of people are still exposed to secondhand smoke in public places in many parts of the world. Globally, passive smoking is responsible for a substantial burden of disease, disability, and mortality. In this context, the linked study by Llewellyn and colleagues (doi:10.1136/bmj.b462) adds cognitive impairment to the list of adverse health effects related to secondhand smoke.

Although the serious negative health effects of exposure to secondhand smoke are established, we still have much to learn about the full spectrum of effects. In particular, we have only just begun to understand how it affects cognitive development and function over the life span. Emerging evidence suggests that parental smoking may impair cognitive development in children. Later in life, secondhand smoke may cause cardiovascular disease and stroke, which are themselves linked to cognitive decline. Until now, however, the suspicion that passive smoking is bad for the adult brain has not been scientifically confirmed.

Llewellyn and colleagues found that higher concentrations of salivary cotinine were associated with a concentration and cognitive impairment, which increases the likelihood that the association is a causal one. The study had many important strengths including population based sampling, use of an objective biomarker of secondhand smoke, the definition of cognitive impairment being based on neuropsychological testing, and careful control of confounding. The main limitation, which the authors acknowledged, is that salivary cotinine measurement reflects exposure over a short time period (two to three days). Because cognitive impairment develops over many years, the ideal metric to measure exposure would be one that captures cumulative lifetime exposure. Unfortunately, no existing biomarkers measure exposure to secondhand smoke for longer than several months. Although recent exposure probably correlates with longer term exposure, studies that examine the longitudinal effect of self reported lifetime exposure on cognitive impairment would strengthen the evidence of a causal association. Consequently, this study raises the strong possibility that secondhand smoke causes cognitive decline, but further research is needed to establish a causal effect.

If secondhand smoke is a known cause of serious disease and shortened life span, why are these latest findings about its effect on cognitive impairment important? Uncovering a link between passive smoking and dementia—the most severe form of cognitive impairment—could have important benefits for public health. Dementia has terrible consequences for quality of life, is greatly feared, and is not easy to prevent. Consequently, publicising the link between secondhand smoke and dementia may resonate powerfully with the public and increase awareness of the harms of passive smoking. Greater public awareness would eventually translate into political action aimed at passing smoke-free legislation in regions of the world where public smoking is still permitted.

Llewellyn and colleagues’ study contains another important public health message, that smokers may also be harmed by passive smoking. Their results strongly suggested that exposure to secondhand smoke was associated with cognitive impairment in former smokers. This observation supports a recent study showing that smokers and non-smokers had a decreased risk of acute coronary syndrome after Scotland’s smoking ban. Moreover, studies of bartenders, who are exposed to high amounts of secondhand smoke, have found that their respiratory health rapidly improved after their workplaces became smoke free, regardless of whether they were smokers or non-smokers. Taken together, these data challenge the conventional wisdom that the effects of passive smoking are overwhelmed by those of active smoking. They imply that secondhand smoke has deleterious health effects on smokers, and that smokers would also benefit from smoke-free legislation.

We are nearing the close of the first decade of the 21st century. Excitement and optimism have been generated by groundbreaking science aimed at decoding the human genome and uncovering the molecular mechanisms of disease. But millions of people continue to die worldwide from passive smoking. In addition to technologically sophisticated science, we should not forget the “low tech” intervention of clearing the air we breathe.
Risk of stroke and lifestyle
Smoking, exercise, alcohol, and diet are predictive factors

The current mortality and morbidity attributable to cerebrovascular disease is of concern nationally and globally. Moreover, the overall burden of stroke is expected to increase over the next two to four decades. More people will reach older age, when the risk of stroke rises sharply, and this will offset the fall in the age specific incidence of stroke reported by recent epidemiological studies. In the linked study (doi:10.1136/bmj.b349), Myint and colleagues prospectively assess the relation between lifestyle behaviours and incident stroke in men and women participating in the European Prospective Investigation into Cancer Study (EPIC). At baseline, between 1993 and 1997, patients completed a health and lifestyle survey, were examined by a nurse, and gave a blood sample. Over an average follow-up of 11.5 years, 599 strokes were ascertained from centrally collected death certificates and hospital discharge coding data. The authors constructed a five point lifestyle behaviour score on the basis of smoking, physical activity, alcohol intake, and plasma vitamin C concentrations, which are indicative of fruit and vegetable intake. An increasing score indicated more protective behaviour.

The risk of stroke decreased linearly with increasing scores in three models, with differing degrees of multivariate adjustment. In the final model, the risk of stroke was 2.3 times greater in people with a score of zero compared with those with a score of four (P trend <0.001), after adjusting for age, sex, body mass index, blood pressure, cholesterol, diabetes, use of aspirin, and social class. The associations between stroke and physical activity, stroke and alcohol consumption, and stroke and vitamin C concentrations differed between the sexes—each reached statistical significance in women but not in men.

The authors acknowledge some of the limitations of the study. Ischaemic and haemorrhagic strokes were not differentiated; vitamin C concentration was only a surrogate marker for fruit and vegetable intake; the elements of the score were dichotomised, which would remove any subtle association between individual factors and risk; and 9000 participants were excluded from the analysis because of missing data. Despite these limitations, the simple conclusion that the risk of stroke is associated with combined health behaviour is important. Importantly,

Adjunctive non-invasive ways of healing bone fractures

Moderate to poor quality evidence shows no benefit to clinically important outcomes

The treatment of bone fractures in the extremities traditionally includes cast immobilisation or surgery using internal or external fixation devices. Adjunctive non-invasive or extracorporeal treatments have also been developed to speed up bone healing in people with fractures or osteotomies. These treatments include electromagnetic stimulation, low intensity pulsed ultrasound, and extracorporeal shockwave therapy, which are generally referred to as “bone growth stimulators.”

A recent survey of Canadian orthopaedic surgeons showed that 16% of surgeons reported using bone growth stimulators for managing uncomplicated open and closed tibial shaft fractures and 45% used them for complicated tibial shaft fractures. Surgeons reported using low intensity pulsed ultrasound and electrical stimulation with equal frequency (21% each).1

In the linked systematic review (doi:10.1136/bmj.b351), Busse and colleagues assess the effectiveness of low intensity pulsed ultrasound for bone fractures.2 They find that the results are conflicting and that the quality of the evidence base is moderate to poor.

Mechanistic studies have indicated that electromagnetic stimulation affects several cellular pathways—including synthesis of growth factors, regulation of proteoglycans and collagen, and production of cytokines—which are all important in bone healing. This turned the use of electrical stimulation into a million dollar market in North America. However, a recent systematic review and meta-analysis found that current evidence from randomised controlled trials is insufficient to conclude that electromagnetic stimulation improves the rate of union in patients with a fresh fracture, osteotomy, delayed union, or non-union.3 This meta-analysis included 11 randomised controlled trials with methodological limitations and the heterogeneity between studies was substantial. The meta-analysis refuted the results of three previous methodologically weak systematic reviews that erroneously showed that electromagnetic stimulation had positive effects.4

Laboratory and animal studies indicate that low intensity pulsed ultrasound improves bone healing by potentially improving signal transduction, gene expression, blood flow, and tissue modelling and remodeling. Consequently, the Food and Drug Administration approved the use of low intensity pulsed ultrasound for fracture healing in 1994, and marketing campaigns increased its use in clinical practice. But the absence of high quality evidence of improvements in clinically important outcomes, such as decreased time to weight bearing and earlier return to function, makes the widespread use of bone growth stimulators questionable. Earlier systematic reviews of the clinical effectiveness of these techniques have proved questionable and, in the case of low intensity pulsed ultrasound, focused

Although this association is probably causal, so that lifestyle modifications will modify the risk of stroke, only interventional studies can prove this.

These findings should be interpreted in conjunction with other recent reports. The Health Professionals’ Follow-up Study and Nurses’ Health Study reported that the risk of stroke was associated with a similar lifestyle score to that used in EPIC, but that used body mass index instead of vitamin C concentrations.5 Among the 43 865 men and 71 243 women who had 1559 strokes during follow-up, the risk of stroke was 3.2 and 4.7 times greater in those with all risk factors than in those with none. The Women’s Health Study was a randomised controlled trial of 39876 women who had 450 strokes,6 and risk was 2.2 times higher in those with the highest lifestyle scores than in those with the lowest scores. The composition of these scores was similar to the EPIC score but used more detailed dietary information and body mass index.

It is encouraging that the association between the risk of stroke and combined health behaviour is consistent across different populations, and between observational and randomised controlled trials. The conclusion that lifestyle predicts the risk of stroke should help to inform individuals’ choices and policy makers’ decisions.

However, what is also consistent but less encouraging is the small proportion of participants with a lifestyle that protects against stroke—although lifestyle interventions could be of great benefit, a huge shift in behaviour will be needed to achieve this.

Systemic management of diabetic retinopathy

New evidence from trials has implications for clinical practice

Diabetic retinopathy is a major cause of blindness in adults. Ever since the United Kingdom Prospective Diabetes Study (UKPDS) and Diabetes Control and Complications Trials (DCCT),1,2 intensive control of blood glucose and blood pressure has been the mainstay of the systemic management of diabetic retinopathy. Because epidemiological studies indicated a direct and continuous relation between the degree of hyperglycaemia and the risk of diabetic retinopathy,4 the control of blood sugar and blood pressure has been guided by the belief that “lower is better.”

Three new trials in the past year—Action in Diabetes and Vascular Disease (ADVANCE), the Diabetic Retinopathy Candesartan Trials (DIRECT), and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)—have provided new insights into the effectiveness and limitations of systemic treatment for diabetic retinopathy.

ADVANCE recruited 11 140 patients with type 2 diabetes and found that lowering glycated haemoglobin to 6.5% or less had no measurable effect on five year incident retinopathy (6.0% intensive treatment v 6.3% standard treatment).3 Systolic and diastolic blood pressures were also lowered by a mean of 5.6 mm Hg and 2.2 mm Hg, respectively, from a starting value of 145/81 mm Hg. However, this considerable reduction did not alter the four year incidence or progression of diabetic retinopathy (5.2% in both treatment and placebo arms).4 ADVANCE shows for the first time that tighter glucose control and lowering of blood pressure have limited effects on the risk of diabetic retinopathy.

Put into context, by lowering glycated haemoglobin to 7%, DCCT and UKPDS achieved risk reductions for diabetic retinopathy of 16-29% and 51-76%.1,5 In UKPDS, risk reduction was 34-47% when blood pressure was controlled to <150/85 mm Hg.7 Thus, a considerable proportion of diabetic retinopathy may not be amenable to improvements in the control of blood glucose or blood pressure.

Why does lowering glucose and blood pressure near normal values not reduce the development or progression of diabetic retinopathy? A recent meta-analysis provides some clues. In a sample of 11 423 community based participants,4 retinopathy signs characteristic of diabetes were detected in 7-13% of non-diabetic participants, and they were present even in those with glycated haemoglobin concentrations <5.0%. Raised blood pressure explained some but not all of this retinopathy.

Therefore, processes other than hyperglycaemia and...
hypertension probably contribute to the development of retinopathy and may need to be specifically targeted to reduce microvascular risk further.

Given the disappointing results of ADVANCE, what other systemic options are available once adequate blood glucose and blood pressure targets are met? Many systemic interventions—including antiplatelet agents (aspirin, ticlopidine), protein kinase C inhibitors (ruboxistaurin), aldose reductase inhibitors (sorbinil, tolrestat), and insulin-like growth factor inhibitors (octreotide)—have been examined in clinical trials, but no consistent evidence supports their use.

The DIRECT studies provide equivocal but more promising results. DIRECT sought to clarify results from an earlier trial, which indicated that blocking the renin-angiotensin system with lisinopril had a beneficial effect on diabetic retinopathy. DIRECT randomised 3231 normotensive or mildly hypertensive patients with type 1 or type 2 diabetes to daily placebo or 32 mg candesartan, an angiotensin II receptor blocker. After six years’ follow-up, use of candesartan in patients with type 1 diabetes modestly reduced the incidence of retinopathy by 18% but had no effect on the progression of existing retinopathy. In patients with type 2 diabetes, candesartan significantly increased regression of existing retinopathy by 34% and reduced its progression by 13%, although this last finding was not statistically significant. The greater effectiveness of candesartan in type 2 diabetes than in type 1 disease is consistent with observations that lowering blood pressure reduces diabetic retinopathy in type 2 diabetes only (UKPDS), and it hints at different pharmacological responses in these two forms of the disease.

In both DIRECT studies, these modest effects were achieved in participants with early retinopathy only and could be related to the blood pressure lowering effects of candesartan. Thus, although DIRECT indicates that candesartan reduces retinopathy in both types 1 and 2 diabetes, whether this effect is independent of tight blood pressure control and whether it translates into significant prevention of vision loss are still unclear. Although the DIRECT trials themselves have ended, longer observational follow-up of participants, as in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, may help to answer these questions.

A third major trial, the FIELD study, provides the most encouraging new findings. FIELD showed that fenofibrate, a lipid lowering fibrate, reduced the need for laser treatment of sight threatening diabetic retinopathy (either for macular oedema or proliferative retinopathy) by 31% over five years. Importantly, this result was achieved in patients with type 2 diabetes who already had good control of blood sugar and blood pressure. Fenofibrate also reduced the risk of total cardiovascular events and progression to nephropathy, and it had few adverse effects. Although fenofibrate has clear lipid lowering effects, lipid concentrations were similar in the intervention and control groups. This suggests that fenofibrate has other as yet unknown modes of action through lipid independent pathways, such as stimulating the secretion of vascular endothelial growth factor, apoptosis, or local inflammation. Whether statins are as effective as fenofibrate in reducing the need for diabetic retinopathy laser treatment is being examined in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) EYE study, which reports in 2009.

The findings from these trials should be interpreted within the context of systemic interventions on a broader range of diabetic complications, including death from cardiovascular disease. For example, the effect of tight glucose control on cardiovascular mortality was examined in two similar trials, ADVANCE and ACCORD. In ACCORD, tight glucose control to achieve a median glycated haemoglobin of 6.4% resulted in a 22% higher risk of death over 3.5 years. This contrasted with ADVANCE, where a similar glycated haemoglobin goal resulted in no difference in mortality but a 21% reduction in nephropathy as the only significant benefit achieved. The underlying causes of these contradictory findings are unclear but may be related to the generally less healthy participants, more rapid lowering of glycated haemoglobin, and higher rates of insulin treatment and hypoglycaemic episodes in ACCORD. Nonetheless, ACCORD’s results suggest caution in aggressive glucose control, especially because the benefits seem to be limited to nephropathy.

References:
The National Dementia strategy in England

A “smorgasbord” of evidence, economics, and obligation

Public awareness of dementia is currently high, thanks to touching personal accounts of the illness through individual experience, such as that of the writer Sir Terry Pratchett.1 In the United Kingdom, dementia affects about 700 000 people at an estimated cost of £17bn (£19bn; $24bn) a year.2 The National Dementia strategy for England—the product of extensive consultation with an estimated funding of £150m—was launched in February 2009.3 The main outputs are 17 recommendations coalesced around three areas—raising awareness, diagnosing the disease early on, and improving quality of care. The mantra of “a memory clinic in every town” was one of the publicity sound bites,4 but it raised legitimate questions about the evidence behind the strategy. How many of the 17 recommendations are evidence based? How many can be? The answer to both questions is—some of them.

The recommendations include a mix of long awaited priority setting and reaffirmation of existing legislation. Some are obvious—for example, good quality information for people with dementia and their carers and improved community support and implementation of the Carers’ strategy—aspirations that simply provide a stimulus for local initiatives. The benefits of early diagnosis and intervention are highlighted—for economic reasons and for individual wellbeing. The need to improve the quality of care for people with dementia in general hospitals and in institutional care is stressed. The research base needs to be expanded, with coordination between the Dementia and Neurodegenerative Diseases Network, charities, and the research councils. The cited justification for the recommendations includes economic necessity, empirical research, and patients’ preferences (and sometimes all three). The strategy does not suggest the introduction of screening but that awareness needs to be raised. Memory clinics are not buildings but pathways to coordinated multidisciplinary care.

The management of dementia is supported by a substantial body of evidence in several key areas. The clinical efficacy of drugs for dementia is accepted, although their cost effectiveness in the early stages of the illness has not been proved to the satisfaction of the National Institute for Health and Clinical Excellence.5 Effective interventions to relieve stress on carers are available, with effect sizes comparable to drug treatments.6 Early intervention and home support delay entry into institutional care.7 Drug treatments for behavioural problems can treat symptoms but concerns exist about their safety, particularly in the long term.8 Standards in nursing and residential homes can be measured and improved with specific attention.9 Detection of dementia in primary care can be improved.10 New treatments are emerging and preventive strategies may soon become a reality.11 Memory assessment services can lead to improved quality of care. What is lacking is the longer term outcome studies of particular types of service and the benefits of a holistic approach (combinations of health and social care, dementia care mapping, and integrated drug and psychosocial approaches).

Similar plans are being developed for UK devolved nations, and countries across Europe are beginning to prepare for the emerging health and social care challenges presented by dementia. Many have specific dementia plans (Norway, Ireland, and Germany in particular), and the French dementia plan has received high level political backing from President Sarkozy, together with €1.6bn over five years. This plan is characterised by transparency and unitary governance, although it spans the education, health, research, and social ministries. Its main objectives are to improve knowledge about dementia, reduce stigma, provide better education and training for professionals, ensure that people with dementia are properly diagnosed, and develop a range of services for people with dementia and their carers.12 The three measures that have similarities to the English plan are that specific units for people with behavioural problems will be created; the plan will be underpinned by an increase in research aiming at providing a better evidence base; and information from all the memory consultations will be captured by an electronic database.

The intermingling of research evidence with current best practice is a logical way forward, and the strategy should be in the context of other initiatives such as the Carer’s strategy, the Care Quality Commission, and Putting People First.13 The National Dementia strategy is a reminder of the importance of dementia, the imperative to raise awareness about the needs of carers, and the potential of drug and non-drug interventions. It is not about drugs, screening, or buildings. It is about people and their carers. Like every other strategy, its worth will be shown by how it is used locally. Improvements in dementia care will come from interweaving awareness, evidence, and implementation.

1 TerryPratchett. www.terrypratchett.co.uk.
4 Santry C. Dementia plans: high hopes but who will pay? Health Serv J 19 Feb 2009.