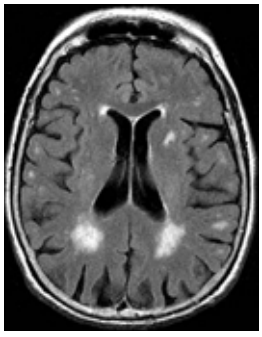
Do white matter hyperintensities on MRI matter clinically?

Yes, and they should prompt detailed screening for stroke and dementia risk factors



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Small vessel disease in the brain is one of the most common of all neurological disorders.[1] It is often present even in young otherwise healthy people,[2] and it leads to neurodegeneration, vascular cognitive disorder, and disability.[3] As yet, small vessel disease cannot be directly measured. However, a specific clinical syndrome or white matter lesions identified on imaging (such as white matter hyperintensities on magnetic resonance imaging) can be used as surrogate markers of small vessel disease. In the linked systematic review, Debette and Markus assess the association between white matter hyperintensities and the risk of stroke, cognitive decline, dementia, and death.[4]

Small vessel disease comprises different pathological processes mainly affecting arterioles that supply the deep part of the brain. The lack of anastomoses in the vascular architecture of the deep part of the brain makes tissue more susceptible to disease and easily compromised during haemodynamically unfavourable conditions.[5]

The most common small vessel disease in the brain is arteriolosclerosis with concentric hyaline thickening of the vessel wall associated with deep white matter lesions.[6] Others are lipohyalinosis with asymmetrical wall thickening associated with disturbances of the vascular tone and formation of lacunes, atherosclerosis of the proximal part of the arterioles with thromboembolic lesions, and cerebral amyloid angiopathy with Alzheimer's disease.

The clinical syndrome of small vessel disease is characterised by insidious onset and gradual progression (although sudden episodes of impairment may also occur), executive dysfunction, loss of initiative, mental slowness, slight gait deficits, and mild impairment of memory—symptoms that are not always easy to identify. Arteriolosclerotic small vessel disease with signs of white matter lesions and lacunes on magnetic resonance imaging are associated with protein changes in the cerebrospinal fluid different from those seen in Alzheimer's disease. The fully developed syndrome is often called subcortical ischaemic vascular dementia and is probably the most common and phenotypically homogeneous vascular cognitive disorder.[7]

Debette and Markus's review of prospective longitudinal studies assessed the clinical consequences of white matter hyperintensities on magnetic resonance imaging and found that they were associated with an increased risk of stroke (hazard ratio 3.3, 95% confidence interval 2.6 to 4.4), dementia (1.9, 1.3 to 2.8), and death (2.0, 1.6 to 2.7).[4]

The association with stroke remained significant after adjustment for vascular risk factors, which suggests that other, yet unknown, factors play a role in the association between changes on brain imaging and stroke.

Several mechanisms could account for the association of white matter hyperintensities with dementia. The authors' two most favoured causes are direct damage to the cortical-subcortical neuronal networks and an interaction between white matter lesions and related neuropathological changes, which would imply that the presence of one type of lesion accelerates the expression of the other.

Unexpectedly, the association with dementia was found only in the general population, not in hospital inpatients. The authors argue that once the disease has become clinically apparent the effect of white matter lesions may be less important, and that other factors such as Alzheimer related neuropathology may be more important in this phase of the disease. However, white matter hyperintensities only partially identify underlying white matter pathology but are associated with lesions developing in surrounding tissue, as measured by sensitive measures such as diffusion weighted imaging.[8] Thus, techniques that are better at detecting ongoing tissue damage may predict cognitive impairment also when the disease has become clinically evident.

Because white matter hyperintensities are clinically relevant, even when found incidentally on brain imaging, clinicians should perform a detailed screen for risk factors of stroke and dementia. If brain imaging equipment is not available it seems reasonable to suggest that the presence of predominant executive and speed dysfunction known to be associated with white matter lesions should also initiate screening for risk factors of stroke and dementia ("low tech approach").

From the research perspective, the evaluation of new imaging measures needs to be supplemented with neurochemical analyses of cerebrospinal fluid to measure markers of axonal, myelin, and vessel wall disease and markers related to Alzheimer's disease.[9] Such analyses would potentially answer some of the questions about the nature of white matter lesions, the mechanisms of disease, and whether the lesions are mainly related to arteriolosclerotic vessel wall damage, Alzheimer's disease, or both. Twin studies show a clear hereditary risk for white matter lesions,[10] but the genetic mechanisms need to be clarified. Trials of treatments for ischaemic small vessel disease using white matter lesions as surrogate markers of reduction of disease progression are also needed.[11]

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Calcium supplements in people with osteoporosis

Should not be given without concomitant treatment for osteoporosis

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In the linked systematic review, Bolland and colleagues assessed whether calcium supplements increase the risk of cardiovascular events in people with, or at risk of, osteoporosis.[1] They found that calcium supplements increased the risk of myocardial infarction (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67), but they found no significant difference in the risk of stroke, death, or the composite end point of myocardial infarction, stroke, or sudden death.

The effort spent on detecting and treating osteoporosis is only worthwhile if it translates into a health benefit for patients. The most common argument for detecting and treating osteoporosis is a reduction in bone fractures that are either subtle and progressive (for example, those that cause loss of vertebral height) or overt (for example, fractures of the hip and wrist). Bone mineral density, which is often used as a measure of treatment success, is a surrogate measure for real clinical benefit.

Surrogate measures may be useful in pilot studies but become problematic when they become the goal of treatment.[2 3] Bone fractures in older people are an important cause of disability, and more than 20% of patients will die within one year of a low trauma hip fracture.[4 5] Accordingly, a safe and effective treatment that can prevent fractures should reduce mortality if given to a large enough population at sufficient risk.

Calcium supplements, given alone, improve bone mineral density,[4] but they are ineffective in reducing the risk of fractures and might even increase risk,[4 5] they might increase the risk of cardiovascular events,[1] and they do not reduce mortality.[1] They seem to be unnecessary in adults with an adequate diet. Given the uncertain benefits of calcium supplements, any level of risk is unwarranted.

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Why should calcium supplements increase cardiovascular risk? Calcium supplements may improve some conventional cardiovascular risk factors including blood pressure and lipids.[6] Accumulation of calcium in the arterial wall leading to reduced compliance would be expected to take years, but the increased risk of myocardial infarction reported by Bolland and colleagues occurred early after calcium supplementation (median follow-up of 3.6 years).

An alternative possibility is that the increased risk of myocardial infarction is not a true effect. If an intervention changes the rate of vascular events but is not associated with a commensurate change in mortality, the intervention may be changing the presentation rather than the incidence. Flecainide reduces the risk of non-fatal myocardial infarction by about 30% because infarctions are more likely to be fatal before patients reach hospital.[7] Similarly, long term treatment with aspirin seems to modify the presentation of vascular events with no effect on mortality and, possibly, with acceleration of the progression of vascular disease.[8] Although the risk of myocardial infarction seemed to increase substantially (by about 25%) with calcium supplementation this was not accompanied by an increase in mortality. Calcium supplements could simply be causing gastrointestinal symptoms that could be misdiagnosed as cardiac chest pain. However, even if calcium supplements really are safe, a neutral effect on mortality casts doubt on whether they are effective prophylaxis for fractures.

A combination of calcium and vitamin D is commonly used to treat osteoporosis. Vitamin D supplements might reduce the risk of falls, might have important clinical effects on cardiovascular function, do not increase mortality, and may mitigate the trend to excess mortality seen with calcium supplements alone.[9] However, no conclusive data are available to show that current doses of vitamin D supplements with or without calcium supplements reduce the rates of fracture, and meta-analyses found evidence of substantial reporting bias.[4 5 9]

Several agents that are, or might be, used to treat osteoporosis do reduce mortality, including bisphosphonates,[10 11] raloxifene,[10] and thiazides.[12] However, bisphosphonates and raloxifene were generally given in addition to calcium and vitamin D supplements. Other methods of reducing fractures should also be subject to scientific scrutiny. Reducing falls and bone trauma is, probably, the

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"Calcium supplements given alone do not improve bone mineral density: they reduce the rate of bone loss compared with placebo—a very important distinction."

Emma M Clark, consultant senior lecturer, University of Bristol

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most effective method of reducing fractures, but if it leads to a sedentary lifestyle it might impair both quality of life and longevity. Exercise might be a good way to increase bone strength, although it also carries risk.[12]

Requiring companies to show, before licensing, that treatments for chronic diseases such as osteoporosis, diabetes, and hypertension reduce long term disability and death could lead to a cessation of research in these areas. The cost and commercial risk would be too high. However, we do need to know whether treatments are safe, effective, and value for money. Extending the patent life of drugs to that of the copyright on a song (50 years according to the Berne Convention) would have many benefits and few drawbacks if properly managed. Regulators could insist that drugs show benefits on symptoms, disability, and mortality rather than surrogate outcomes, which would give doctors and patients greater certainty about the benefits and risks. Regulators could also insist that more trials examine the added value of new compared with old drugs. Lower prices for innovative drugs could be negotiated. Companies could plan a more comprehensive research programme with the knowledge that their income streams were more reliable, although still vulnerable to price competition from other companies and to being superseded by more innovative drugs. There would be fewer impediments to the adoption of innovations on financial grounds and less reason to persist with low cost generic drugs if they are inferior.

In the meantime, on the basis of the limited evidence available, patients with osteoporosis should generally not be treated with calcium supplements, either alone or combined with vitamin D, unless they are also receiving an effective treatment for osteoporosis for a recognised indication. Research on whether such supplements are needed as an adjunct to effective agents is urgently required.

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Pharmacological enhancement of performance in doctors

The benefits have not been proved, and more evidence is needed

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In recent years society's attitude to various types of personal enhancement has shifted. Examples include the popularity of multivitamins and diet pills, the widespread use of caffeine (despite side effects such as anxiety, tremor, and tachycardia), and the unregulated off-label use of methylphenidate (Ritalin), fluoxetine (Prozac), and sildenafil (Viagra).

Since the serendipitous discovery that drugs used to treat narcolepsy (modafinil) and attention deficit hyperactivity disorder (such as methylphenidate and atomoxetine) can improve the brainpower of healthy people, public and scientific interest has grown. Although the current level of use among doctors is unknown, data indicate that a large proportion of other groups in society (such as students and more senior academics) are currently choosing to use these substances.[1]

The scientific, moral, and ethical questions about cognitive enhancement are complex and have been acknowledged as such by the Royal Society and the Academy of Medical Sciences; both have held workshops and public events on the topic. In addition, the BMA has produced a discussion paper about the ethical aspects of cognitive enhancement, which highlights the many challenging problems facing the medical profession should personal enhancement be widely adopted.[2]

Fatigue is linked to impairment of human performance; people who are fatigued have frequent lapses of attention and impaired functioning in several important cognitive domains.[3] Although measures to reduce doctors' working hours have been instituted on both sides of the Atlantic, they are not a panacea. Surgeons performing long, arduous operations remain susceptible to the effects of fatigue, and frequent transitions from day to night work expose junior doctors to the risk of impaired psychomotor performance.[4] Given the continued need for innovation in this area, pharmacological methods could conceivably be used to combat fatigue at some time in the future. However, they cannot be recommended until the benefits and risks associated with their use have been fully assessed.

Modafinil, licensed for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnoea, and shift work sleep disorder, is the most suitable agent for promoting wakefulness. It is well tolerated by patients with these disorders,[5] has a low risk of misuse, and is effective in combating the effects of fatigue on healthy individuals, military helicopter pilots, and emergency physicians.[6-8]

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Although these findings are promising, the impact of modafinil on clinically relevant measures of performance currently remains unknown.

Beyond increasing wakefulness, performance enhancing drugs may have benefits for healthy, non-fatigued individuals. Studies involving healthy subjects found that modafinil improved performance on tests of working memory and forward planning,[9] methylphenidate improved performance on tests of working memory,[10] and atomoxetine improved performance on tests of response inhibition (suppression of inappropriate actions).[11] Given these findings, it is possible to speculate that doctors who take these drugs may be able to plan an intervention more effectively or show greater cognitive flexibility when approaching a challenging clinical problem. However, for the size and pattern of effects on clinical performance to be fully understood, small, well designed controlled studies, which draw on recent advances in the fields of simulation and neuropsychological assessment, must be performed. These studies will be the first step towards quantifying the effects of cognitive enhancing agents on the performance of doctors.

When deciding whether or not to use these drugs, doctors must give primacy to the potential benefits and risks for patients and society. However, although most neurocognitive enhancers seem to be safe and are tolerated well by the clinical populations for whom they are prescribed, the risks they pose to a healthy population are not yet well understood. Therefore, in taking enhancing agents for the greater good of society, doctors will almost inevitably place themselves at risk of harms at an individual level. As a result, only when potential personal benefits of enhancement, such as a reduced risk of needle stick injuries or motor vehicle accidents in fatigued people, are considered is the risk-benefit ratio likely to be acceptable. If the benefits are found to outweigh the risks then employers, professional bodies, and policy makers will need to work together to develop standards, guidelines, and legislation to protect clinicians from the possibility of explicit or implicit coercion. The public must also be involved in the debate, and their views acted on. Early indications are that members of society are more likely to agree with cognitive enhancement if motivations for using them are seen to be unselfish.[12]

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Promoting self care for minor illness

Is worthwhile but hard to achieve

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A recent survey commissioned by the Proprietary Association of Great Britain that investigated the attitudes and behaviours of consumers and professionals around self care of minor illnesses reported that little has changed over the past 20 years.[1] More than half (52%)of people with a new minor ailment self treated and 22% did nothing. Within the sample of people who had received a prescription from a doctor the last time they had a minor ailment, 62% visited a doctor.

Enhancing people's ability to self care should be a priority for the NHS. Average annual general practitioner consultation rates per person in the United Kingdom have increased from 3.9 in 1995 to 5.3 in 2006, an ongoing increase of 70 million more general practitioner consultations each year in England.[2] This is unsustainable, particularly in the current economic climate. Recent NHS policy has thus been aimed at promoting effective self care, both for minor ailments (see http://www.nhsdirect.nhs.uk/help/) and for long term conditions.

Promoting self care can be highly beneficial to the NHS and its users. Minor illnesses form 18% of the general practitioner workload and cost the NHS £1.9bn (€2.2bn;

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"By continually educating patients about their condition, nurses can help patients improve their health outcomes, build positive attitudes regarding their treatment, and become independent."

Monique J Grant-Coke, nursing programme coordinator and assistant professor, Northern Caribbean University, Jamaica

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$2.9bn) a year.[1] Moreover, consultations with professionals for minor ailments can reduce the time and quality of care available for more serious illnesses. Consumers prefer the convenience of self care and supporting them in this endeavour can empower them to self treat in the future.[1] Theoretically, promoting self care could lead to delays in diagnosing more serious illnesses, but no data are available to support this view.[3]

Most people attempt self management before consulting their general practitioner. Consultations were triggered by failure of self care, the need for reassurance, involvement of young children, fear of more severe illness, or encouragement from family or friends.[1] This finding mirrors previous work which showed that most patients go through a process of evaluating, monitoring, and re-evaluating their symptoms before consulting.[4]

Despite the survey's conclusion that little has changed over 20 years, other data suggest that, like other health behaviours, self care including the decision on whether to consult a clinician changes over time and varies between different countries and cultures. A recent study examining consulting habits of 100 000 patients registered with UK general practices reported a 25% decrease in consultation rates for acute respiratory tract infections between 1997 and 2006.[5] In a cross sectional observational study of patients presenting with acute cough in 13 different countries across Europe, the mean symptom score at presentation varied twofold, with patients in Spain and Italy presenting with the lowest scores, and those in Sweden presenting with the highest scores (higher scores indicated more severe and greater number of symptoms).[6]

Several attempts have been made to promote self care for minor illness, particularly respiratory tract infections. The provision of leaflets or booklets with self care guidance, either within a consultation or through general dissemination to households, has little effect on future consultation rates for respiratory tract infections and other minor ailments.[7 8] However, not prescribing antibiotics, or offering a delayed prescription to be used if symptoms fail to improve within a specified time, can lead to a small but significant reduction in future consultation rates for similar symptoms.[9 10] Similarly, the use of an interactive booklet covering prognosis, treatment options, and symptoms that should prompt reconsultation can also reduce future consultation rates.[11]

These data are in accordance with the literature on changing health behaviours, which shows that mere provision of information has little effect. Changing behaviour often requires multiple interventions that work at several levels: the individual, the immediate family or social circle, and society in general.[12]

Concepts derived from psychological models of changing individual behaviour that may apply to promoting self care for minor illness include helping people to develop accurate knowledge about the consequences of their health behaviour (outcome expectancies)—for example, providing information about the lack of effect of antibiotics on duration or severity of symptoms in acute respiratory tract infection[8]; enhancing self efficacy (people's belief in their ability to self care effectively); changing subjective norms (enhancing social approval for self care); changing personal and moral norms (promoting commitment to self care); and promoting concrete plans through action planning.[12]

Several types of intervention may be needed including education (one to one advice, media campaigns), policy changes (changes to requirements for sick certificates), additional resources (the recent pharmacy minor illness management service, which allows patients who do not pay for prescriptions to obtain certain drugs free without a prescription from their doctor), and use of technologies (telephone triage, online support).[12] However, the relative effectiveness of each of these interventions, either separately or together, is unknown. Research on the effectiveness of such interventions to promote self care on minor illness is needed, and should follow National Institute for Health and Clinical Excellence guidance of using a theory based, well planned, staged approach to evaluation.[12]

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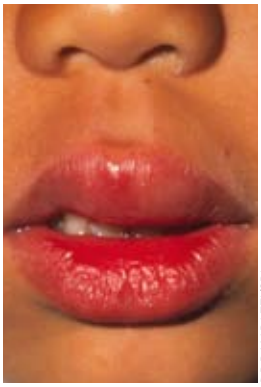
Oral immunotherapy for peanut allergy

A potentially important advance, but long term effectiveness and safety need to be established



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Preliminary findings from studies investigating the effectiveness of oral immunotherapy for peanut allergy are encouraging and suggest that a possible cure for peanut allergy may be within sight. Although the excitement about this new treatment approach is understandable, we are still some distance from reliably establishing its effectiveness, cost effectiveness, and safety, all of which are prerequisites for its use in routine clinical practice.

Peanut allergy affects up to one in 200 people in economically developed countries, and unlike many other types of food allergy is usually lifelong.[1] It often causes considerable psychological distress, to both those affected and their carers.[2] It may also have ramifications for other people, such as fellow pupils at school,[3] because accidental exposure to even very small amounts of peanut can be enough to trigger anaphylaxis, which may prove fatal.[4]

Until recently the only treatment for peanut allergy was meticulous avoidance of peanuts and preparedness to treat a reaction promptly with self administered adrenaline if accidental exposure occurred. Although improved labelling of peanut containing foods has certainly helped,[5] the 700% increase in the numbers of hospital admissions for anaphylaxis between 1990-1 and 2003-4 as a result of exposure to peanuts (and other triggers) suggests that avoidance is still far from straightforward.[6]

Immunotherapy involves giving allergic people very small but gradually increasing doses of the protein to which they are allergic until a stable maintenance dose can be reached. Although the mechanisms are not clearly understood, immunological changes are thought to be induced, which reduce the risk of a reaction on further exposure. The aim is first to induce a state of desensitisation—the ability to tolerate relatively small doses of peanut allergen when given regularly—and ultimately immunological tolerance, so that peanuts can be eaten at any time and in whatever quantity desired.[7]

Although immunotherapy with grass pollen is widely used for people with severe hay fever, until recently there has been surprisingly little interest in using this approach for food allergy. This is even more surprising because as early as 1908, increasing doses of egg allergen given to a child with severe egg allergy were reported to improve his ability to tolerate egg-containing foods.[8] A resurgence of interest in immunotherapy based approaches for food allergy was seen in the early 1990s, but this was dampened by the observation that serious adverse reactions were common in those receiving subcutaneous immunotherapy for peanut allergy.[9]

Recent studies have focused on the role of oral immunotherapy for peanut allergy.[10 11] The early reports relate to small case series conducted in highly motivated, carefully selected patients and families. Different protocols of administration are being evaluated, but the common feature is very close monitoring of patients when administering the allergen and later on. Such monitoring takes the form of round the clock expert support and availability of emergency rescue drugs.

The early results from these case series indicate that most people enrolled can substantially increase the amount of protein they are able safely to consume. However, these are preliminary results from studies at potentially high risk of bias and should not be taken up in routine clinical settings. Reports that a few clinicians in the United States have taken this leap are thus very worrying.[12]

Fundamental questions remain about the effectiveness and safety of immunotherapy for oral peanut allergy, which should begin to be answered by the trials that are currently under way. We crucially need to know whether the benefits are maintained when treatment is discontinued, what the optimum treatment length is, whether booster doses are needed, and, if so, at what intervals. These approaches require intensive monitoring so commissioners will also want data on cost effectiveness. Importantly, after several deaths triggered by injection immunotherapy in people with severe hay fever, the Committee on the Safety of Medicines banned the use of this once popular treatment in UK general practice. Despite subsequent improvements in the safety of immunotherapy and the protocols used, the repercussions of this decision are still being felt in that access to injection immunotherapy remains very restricted for those with severe hay fever.

Although it is early days, we may be on the cusp of a major new breakthrough for the management of people with peanut allergy. It is important, however, that our excitement about this advance, which has the potential to transform the lives of millions of people worldwide, does not get the better of us, and that we wait for the science to lead the way.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.orge/coi_disclosure.pdf (available on request from the corresponding author) and declare: (1) Support in the form of a grant from the Chief Scientist's Office of the Scottish Government for the submitted work; (2) No relationships with any company that might have an interest in the submitted work in the previous three years; (3) No spouses, partners, or children with financial relationships that may be relevant to the submitted work; and (4) No non-financial interests that may be relevant to the submitted work.

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