Injury and attention-deficit/hyperactivity disorder
Monitoring children with early injuries could reduce later risk

The cause of attention-deficit/hyperactivity disorder (ADHD) is uncertain and has provoked considerable debate. The Department of Health in the United Kingdom is currently commissioning a systematic review of its causation.\(^1\) In the linked retrospective cohort study, Keenan and colleagues examine the hypothesis that head injury in young children might be a causative factor in the development of ADHD.\(^2\)

Concern has been expressed internationally about the increased prescribing of stimulants to treat ADHD in children.\(^3\) Prescriptions in England rose from 220,000 in 1994 to 418,300 in 2004.\(^4\) International estimates of prevalence vary considerably. The American Psychiatric Association estimates that 3–5% of school age children have ADHD,\(^5\) but studies vary considerably from as low as 0.85% of girls in the UK to 19.8% of boys in Colombia.\(^6\) A UK survey of 10,438 children aged 5–15 found that 3.62% of boys and 0.85% of girls had ADHD.\(^7\)

Recently published guidelines from the National Institute for Health and Clinical Excellence and the American Academy of Child and Adolescent Psychiatry conclude that risk factors may interact rather than act in isolation.\(^8\) They indicate that genetics is important, but that environmental influences—such as injury, maternal smoking, maternal alcohol consumption, heroin use in pregnancy, fetal hypoxia, exposure to toxins, and zinc deficiency—may contribute too.

To be diagnosed with ADHD, a child must have levels of inattention, hyperactivity, and impulsivity higher than expected for their developmental stage. These must be pervasive in a range of situations and associated with impaired social or academic development.\(^9\) No validated test is available to confirm the diagnosis. Because these traits are present in normal children, the validity of a diagnosis of ADHD is constantly debated.\(^10\)

The precise association between head injury and ADHD is not clearly established, but increasing severity of head injury is associated with the appearance of ADHD symptoms—so called “secondary ADHD.”\(^11\) ADHD symptoms may also be more severe and persist longer in children with a diagnosis of ADHD after head injury, and lower socioeconomic status also predicts a worse prognosis.\(^12\)

Keenan and colleagues’ study comprised 62,088 children from the database of the health improvement network, which contains data from 308 general practitioner practices over the period 1988 to 2003. To ascertain whether head injury increases the incidence of ADHD occurring after a head injury, they compared children with head injuries (2782) with non-injured controls (58,190) and added another injury comparison group—children with burns (1116). Children in either injury group were identified as having a “medically attended” head injury or burn, and were injured before 2 years of age and diagnosed with ADHD before 10 years. The control group was used to tease out head injury as a key factor from the influences of injury itself.

The results showed no significant association between head injury and an increase in ADHD symptoms. Both injury groups had similar and significantly higher rates of a diagnosis of ADHD after injury compared with non-injured controls. The risk for children with burns or head injury was twice that of non-injured controls and remained higher after adjusting for factors such as sex, prematurity, and socioeconomic status. The results indicate that young children who get injured might have more behavioural traits that subsequently attract a diagnosis of ADHD.\(^2\)

Another interesting correlation was found with children older than 2. Children who had a head injury between the ages of 2 and 10 had a higher likelihood of receiving a diagnosis of ADHD before their 10th birthday. This was true for each of the three groups that had previously been observed after head injury, burn, or no injury before the age of 2. This strengthens the hypothesis that the ADHD core symptoms—excessive inattention, hyperactivity, and impulsivity—might be key factors associated with an increased rate of injury.

The study has limitations, as acknowledged by the authors. Firstly, the extent and degree of head injury could not be ascertained from the database, so it was not possible to explore the known association between increased severity of traumatic brain injury and development of secondary ADHD. Secondly, it is not known precisely how the diagnoses of ADHD were made or by whom. Therefore, the reliability of the diagnoses is uncertain.

None the less, the findings are important. They indicate that primary care clinicians should assess children with injuries for symptoms of ADHD and continue to monitor them over time.

A known barrier to referral of children with ADHD to specialist services by primary care doctors is non-recognition of the disorder’s symptoms.\(^13\) Early assessment and referral to preventive programmes, such as parent training, can reduce symptoms.\(^14\) Referral to a specialist team may be useful where problems persist.

A focus on the risk to these children cuts across the separate and sometimes distracting debate about the existence of ADHD. We should concentrate on early...
Maternal undernutrition before and during pregnancy is linked to poor pregnancy outcomes. Maternal micronutritional deficiency can jeopardise the intrauterine growth or development of the fetus and increase perinatal morbidity and mortality by disrupting protein metabolism, gene transcription, endocrine functions, and transport of nutrients.¹

About 20% and 50% of women in south Asia and sub-Saharan Africa, respectively, have low body mass index (<18.5), a known risk factor for poor pregnancy outcomes.² During pregnancy, 50-70% of women in developing countries have anaemia and might blindness, a sign of vitamin A deficiency.³ In the linked randomised controlled trial, Zeng and colleagues compare the effect of antenatal supplementation with multiple micronutrients, iron and folic acid, or folic acid alone on birth weight, duration of gestation, and maternal haemoglobin in the third trimester.⁴

Politics, social class, social milieu, cultural practices, access to and use of health care (including perinatal care), and dietary practices are key determinants of maternal malnutrition and poor perinatal survival. ⁵ Clearly, even with renewed interest it might take years to implement well informed policies that would have a sustainable effect on these determinants. In most settings increasing dietary energy intake or providing additional micronutrients (either as supplements or by fortifying local foods) is the best way to improve the nutritional status of women.⁶,⁷ The beneficial effects of vitamin A, iodine, folic acid, and iron supplementation on the outcomes of pregnancy and the health of the newborn, or both, has been well documented in most populations.

The World Health Organization advocates the routine use of iron-folic acid supplements in antenatal care, and most governments strive to implement this policy. Lately, interest has focused on the effects of multiple micronutrient supplements on pregnancy and birth outcomes in areas where deficiency of multiple micronutrients is prevalent.⁸ A meta-analysis of nine high quality studies including 15,378 women living in low income countries found that, although multiple micronutrient supplements significantly decreased the risk of infants having low birth weight, being small for gestational age, and having anaemia when compared with no supplements, placebo supplements, and supplements of only one or two micronutrients, they provided no additional benefits over iron-folic acid supplements.⁹

Zeng and colleagues evaluated the effect of daily supplements of iron-folic acid (60 mg of iron, 400 µg folic acid) or a combination of 15 multiple micronutrients (with 30 mg of iron, as recommended by Unicef) on maternal anaemia, duration of gestation, birth weight, neonatal mortality, and perinatal mortality in rural China. The comparison arm consisted of women randomly allocated to receive folic acid supplements, the only antenatal supplement promoted by the Ministry of China to prevent neural tube defects. The current antenatal care policy in China gave the authors a unique opportunity to study the effects of iron supplementation on pregnancy and birth outcomes. Moreover, pregnant women randomly allocated to two intervention groups received 60 mg/day or 30 mg/day of iron, which enabled the authors to evaluate any possible dose dependent effects of iron supplementation on the outcomes of interest. Iron-folic acid supplementation significantly reduced the risk of early preterm delivery (<34 weeks), and early neonatal mortality compared with folic acid alone (relative risk 0.50, 95%
The UK quality and outcomes framework
Has improved quality of care and reduced health inequalities

In the linked study, Ashworth and colleagues report on the relation between the quality and outcomes framework and health inequalities in general practice in the United Kingdom by assessing the effects of social deprivatation on levels of blood pressure monitoring and control. Tackling health inequalities has been a consistent part of the political rhetoric in the UK for more than a decade, with primary care seen as a key player in improving life expectancy in areas with the worst health record and highest deprivation.

Perhaps the most substantive government intervention in primary care in recent years has been the renegotiation of the general practitioner contract in 2003, which included—at its heart—a system of financial incentives for delivering quality care. This pay for performance scheme—the quality and outcomes framework—now links achievement on 129 indicators covering clinical domains; organisational domains; and additional services domains, such as contraception and patients’ experience, to the practice’s income. The framework was originally designed to improve health outcomes and not as a tool to tackle aspects of health inequality. In the first year of its implementation (2004-5), practices serving deprived populations achieved slightly lower quality scores and therefore received less financial remuneration than those in more affluent areas.

Ashworth and colleagues provide a longer term perspective on the relation between the quality and outcomes framework and health inequalities. They used data collected during the first three years of the framework’s implementation, from more than 97% of practices in England, and they found that the small differences between values of blood pressure monitoring and control in the least and most deprived areas in 2003 were dwarfed by the overall improvement in values over the time period. Crucially, they also found that the achievement gap between practices in the least and most deprived areas had almost disappeared. This important study supports the findings of a methodologically similar paper published recently in the Lancet, which examined the relation between socioeconomic inequalities and overall achievement in 48 of the clinical indicators of the quality and outcomes framework during the same three year time period. Doran and colleagues also found that median achievement scores increased across the board, and that the gap in median achievement narrowed from 4.0% to 0.8% between practices in the most deprived and least deprived areas.

The evidence therefore suggests that the quality and outcomes framework contributed to an improvement in the process of care and intermediate health outcomes for patients with a range of clinical conditions, although the size of the contribution is unclear. Low scoring
practices in deprived areas also seem just as able to improve the quality of their care (as measured by the framework) as low scoring practices in more affluent areas. This offers the tantalising prospect that the quality and outcomes framework is a truly equitable public health intervention.7

However, several important caveats exist. For example, inequalities in health care might already have increased (as predicted by the inverse equity hypothesis8) in response to other quality improvement initiatives that pre-dated the introduction of the quality and outcomes framework. We know that the quality of care was improving in several clinical conditions before 2004, and this could have created a “ceiling effect” in terms of achievement for practices in more affluent areas. Inequalities could also have widened in uncentrised areas of health care, although two recently published studies in the United States and UK suggest that practices have delivered the same quality of care for conditions not included within a pay for performance scheme.9 10

This emerging evidence has several implications for policy makers and practitioners. In future, perhaps pay for performance schemes should be actively designed with health inequalities in mind.. For example, Massachusetts is considering including pay for performance targets for reducing ethnic inequalities in healthcare provision in their Medicaid programme.11 Perhaps future schemes should more directly reward absolute quality scores and improvement over time.12 Evaluations could also plan at the outset to consider and then monitor the consequences of pay for performance on health inequalities.

On balance, however, the message of Ashworth and colleagues’ paper is a hopeful one. High blood pressure is the most important risk factor worldwide for developing cardiovascular disease, a condition that contributes greatly to the gap in life expectancy between deprived and affluent areas. The problem of reducing blood pressure is now being tackled more effectively in practices across the land. Perhaps the greatest contribution that the quality and outcomes framework has made to changing practice will therefore be the largely unintended consequence of generating more equitable health care.


Statins and primary prevention of cardiovascular events

No change in strategy is needed despite the hype surrounding the recent JUPITER study

Earlier this month, the New England Journal of Medicine published the randomised controlled trial JUPITER,1 which compared rosuvastatin (20 mg daily) with placebo in 18000 patients with no apparent vascular disease, low density lipoprotein cholesterol (LDL-C) of less than 3.4 mmol/l (130 mg/dl), and high sensitivity C reactive protein concentrations of 2.0 mg/l or higher. The combined primary end point was myocardial infarction, stroke, arterial revascularisation, hospital admission for unstable angina, or death from cardiovascular causes. The trial was stopped after a median of two years after a highly significant improvement in the primary end point with rosuvastatin (hazard ratio 0.56; 95% confidence interval 0.46 to 0.69; P<0.0001). It is hardly surprising that the JUPITER study is seen by many as opening the door to new avenues to prevention.

What do the results mean? Do we really have to change our ways of targeting our preventive efforts—for example, measure high sensitivity C reactive protein on a regular basis? Although the relative risk reduction is impressive, the absolute risk puts the results into perspective. Of 100 people in the control arm, 1.36 experienced a primary outcome within one year, and this was reduced to 0.77 by the intervention. Although this was significant, its clinical relevance is doubtful. Participants were free of vascular disease, but half of them had a Framingham risk score >10%, and more than a third had the metabolic syndrome. A closer look at subgroup analyses (size of plots, exact numbers are not reported) indicates that most events occurred in high risk groups. Wouldn’t old fashioned risk estimation by traditional methods have produced similar results?

The relative risk reduction (44%) was also much higher than in previous trials. Although the authors suggest that measuring C reactive protein allows the selection of a group of patients who benefit more than others,
Influenza vaccine in the over 65s

Probably has important benefits, despite recent doubts about its effectiveness

The annual influenza vaccination campaign is one of the United Kingdom’s most successfully implemented public health programmes—uptake in those over 70 is estimated at 78%, the highest in Europe.¹ The rationale for the programme is based on the knowledge that the vaccine is effective and cost effective. Although age-related deterioration of immune function makes vaccines less effective in older people than in younger ones, the one available good quality randomised controlled trial shows good overall vaccine efficacy for serologically confirmed influenza (58%, 95% confidence interval 26% to 77%) and clinical influenza (47%, 27% to 61%) in those over 60.²

Large observational studies from the United States have also provided evidence for benefits against less influenza specific outcomes. These studies found that in the over 65s the vaccine reduces hospital admissions for pneumonia and influenza by 27% and all cause mortality by 48%.³ However, in the past few years, some researchers have questioned the plausibility of these less specific findings,⁴ and several prominent media articles have suggested that the vaccination programme is not worthwhile.

So what does the evidence to date say? A systematic review published in 2005 with multiple meta-analyses evaluated the effectiveness of the influenza vaccine in people aged 65 and over.⁵ Much of the evidence came from large cohorts within Health Maintenance Organisation (HMO) databases in the US. Overall the results of the cohort studies showed that, after adjusting for alternative explanations such as non-compliance, recall bias, and secular trends, the vaccine is effective and cost effective. Although the JUPITER investigators talk about a “strategy” based on measurement of LDL-C and C reactive protein, this is not what they studied. In fact, they present a conventional drug trial on a highly selected group of patients. Testing a strategy in a pragmatic trial would have to involve measuring high sensitivity C reactive protein in addition to detecting conventional risk factors to identify patients like the ones included in JUPITER. In a control arm only the usual risk factors would be used to target treatment at high risk patients. A trial of this kind conducted in relevant settings, such as primary care, is needed before a strategy that includes measuring high sensitivity C reactive protein can be routinely recommended. Only then can we know whether the additional complexity and cost (high sensitivity C reactive protein is measured differently from conventional C reactive protein) would translate into reduced disease outcomes. Furthermore, from a recent analysis of the Framingham study we learn that the additional prognostic value of laboratory measurements is negligible.⁶ Against the hype of new tests and drugs we should not forget that to work at a population level interventions have to be simple and easily reproducible.

So what can we learn from the JUPITER trial? Firstly, that rosuvastatin is efficacious and safe. This is important because a previous trial with rosuvastatin 10 mg versus placebo was negative, with a non-significant relative risk reduction of only 8%.⁷ However, because rosuvastatin was not compared directly with simvastatin and other statins, we do not know whether it is really better. Until we know that, established (and cheaper) statins should be preferred. Secondly, statins work independently of LDL-C concentrations, but in low risk populations the effects on absolute risk are small. Thirdly, this study—in which almost half of the subjects were below the target level for LDL-C lowering in ischaemic heart disease—makes the whole concept of lipid lowering to a specific LDL-C target look more obsolete than before. Instead of lowering lipids we should talk about global cardiovascular risk assessment. Statins with their multiple actions are an effective means to improve the prognosis of high risk patients, as are aspirin and antihypertensive drugs. Possible effects should be discussed with patients,⁸ and if doctor and patient agree that a statin is indicated, a fixed dose should be given.⁹

All this is hardly new. No change in practice is warranted on the basis of the JUPITER study. Future studies should evaluate alternative strategies of risk assessment and intervention in usual care settings that may include measuring high sensitivity C reactive protein. Current preventive practices should be reconsidered only if an effect can be shown in a pragmatic study.

for confounders, the reduction in less specific measures, such as hospital admission for pneumonia and influenza, was smaller but still significant (vaccine efficacy 27%, 21% to 33%) and that the effect on all cause mortality was large (47%, 39% to 54%).

Several authors have suggested that such a large benefit for all cause mortality is not plausible, because it would mean that most deaths in winter—and not the 5-10% previously suggested—are related to influenza. An explanation put forward was that the cohort studies could be reporting biased results, as a result of unadjusted confounders—for example, vaccine recipients might be more “healthy” than those not receiving the vaccine. A “frailty” bias has been suggested, where patients who were either in hospital, more frail, or terminally ill in the autumn were less likely to receive vaccine, but also more likely to die that winter.17

One of the problems of HMO datasets is that patients’ details are limited to those routinely recorded in the databases (for example, standard international classification of diseases codes for comorbidities), so functional status, disease severity, and smoking status cannot be fully accounted for. A recent case-control analysis of one of the HMO datasets where the researchers obtained more detailed information showed that by adjusting for measures of “frailty,” and compared with the pre-influenza period, the effectiveness of the vaccine was attenuated in preventing community acquired pneumonia (odds ratio 0.92, 0.77 to 1.10) and hospital admissions for pneumonia (0.85, 0.62 to 1.15) in those influenza seasons.5 However, influenza activity was relatively low in the study years, so a smaller proportion of pneumonia may have been caused by influenza. A UK study using pooled data over 10 years, which controlled for the presence and severity of underlying illness and compared this with the peri-influenza period, did show a significant reduction in hospital admissions for acute respiratory diseases (vaccine efficacy 21%, 17% to 26%) and respiratory mortality (12%, 8% to 16%), but did not show a clear effect on all cause mortality.9

However, winter mortality as a result of influenza may be greater than was previously thought because methods of estimating the burden of influenza are indirect and may underestimate the complications. In addition, methods of adjusting for confounding in these studies may be flawed, partly because the vaccine might provide some benefit either side of epidemic periods. This is because lower amounts of the virus are still present outside of the influenza season and they might have a prolonged effect on mortality in the elderly.10 More frail patients in hospital during autumn may also receive their vaccine after discharge, and confounding by indication (having the opposite effect) may be stronger than frailty selection bias.10 A recent study to assess the potential role of confounders found that functional status (assessed by the 20 item short form general health survey) was actually higher in unvaccinated participants.11 Nichols and colleagues also tried to model a hypothetical confounder and found that even in the most extreme scenario, the vaccine still reduced mortality by 33%.5

Establishing the full effectiveness of the influenza vaccine is fraught with difficulty—influenza seasons vary in timing and magnitude; the vaccine may not fully match the circulating strain that year; different strains may affect different age groups according to susceptibility (for example, natural immunity); few studies measure influenza specific outcomes (serologically confirmed influenza)—a wide range of less specific end points is usually reported; and observational studies, with their potential for bias and unmeasured confounding, are the norm. Randomised controlled trials, such as that quoted above for the influenza specific outcomes,2 would be the gold standard, but in countries where the vaccine is recommended it might be difficult to obtain ethical approval.

So, should elderly people be vaccinated this autumn? Despite their divergent positions, most experts agree on one thing—that although the evidence base needs strengthening, influenza vaccine has some benefit and programmes should continue.12 Resources need to be targeted at additional approaches. These include developing more effective vaccines and better forms of delivery for the elderly (for example, adjuvants and intradermal injections), and ensuring that more healthcare workers and carers who come into contact with vulnerable elderly people are vaccinated. Influenza causes substantial mortality and morbidity in older people and, even if the more general all cause mortality benefit may be lower than first thought, the current vaccine programme offers older people valuable protection against illness, hospital admission, and mortality specific to influenza, should they be exposed this winter.

1 Blank PR, Schwenglenks M, Szucs TD. Influenza vaccination coverage rates in five European countries during season 2006/7 and trends over six consecutive seasons. BMC Public Health 2008;8:272.