Growth hormone in children with idiopathic short stature

The dose should be tailored to individual responsiveness to optimise growth and minimise harm

BSIP, MENDIL/SPL

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2011;342:d1248
doi: 10.1136/bmj.d1248

Does growth hormone affect the adult height of children with idiopathic short stature? Yes, according to the linked systematic review by Deodati and Cianfarani. The review included three randomised controlled trials of growth hormone, published between 1998 and 2008,[2-4] and seven non-randomised trials of growth hormone published between 1995 and 2002. Children with idiopathic short stature in the studies were defined as prepubertal short children, born at an appropriate size for gestational age. However, information on size at birth was rarely available, so children who were small for gestational age may have been included.[5]

The review found that the overall adult height of children treated with growth hormone was 0.65 standard deviation (SD) score higher than that of controls (about 4 cm) and they become 0.94 SD score taller than their parents. The overall height gain was 1.2 SD score in children treated with growth hormone versus 0.34 SD score in children not treated with growth hormone (difference 0.8 SD score), with a large interindividual variation in growth response, ranging from 0 to 3 SD score. At group level, growth hormone had a dose dependent effect on adult height and height in relation to parental height.

This meta-analysis of growth hormone treatment studies until adulthood summarises lessons that can be learnt from the past; such studies generally take 20 years to complete and were initiated in the 1980s, with all the limitations of the knowledge then available. The combined results of these long term trials can help refine current research questions. The large variation in individual responses indicates that mean height gain for the group cannot predict the growth response in a single individual. What does this tell us?

The growth hormone dependent growth of a child depends on the balance between hormone secretion and responsiveness to the hormone. Since the 1960s-70s, growth hormone secretion has been estimated by measuring the growth hormone response to a provocation or as spontaneous, mainly nocturnal, secretion. In addition, for the past decade growth hormone responsiveness has been estimated by using mathematical models to predict the growth response to growth hormone treatment.[6] This approach has been used to estimate the growth hormone dose needed for individual children to reach a predefined height goal and has been validated in a randomised controlled trial of growth hormone.[7] As in the reviewed trials, a fixed dose of growth hormone resulted in a broad range of growth responses, whereas individualised doses, using prediction model estimates, produced less variation around the predefined height goal of the trial (mid-parental height, calculated as mother's height (in SD score)+father's height (in SD score)/2). Thus, the use of prediction models to estimate response to growth hormone before deciding on treatment can be justified in terms of efficacy, safety, and cost, as well as for establishing the optimal dose.

Growth hormone affects more than just height—it is a major anabolic hormone with effects on most tissues. Responsiveness to growth hormone varies not only between individuals but also between tissues: brain, fat, and muscle may be more sensitive than bone.[8] Interestingly, an individualised dose of growth hormone not only results in less variation in growth, but also in less variation in fasting insulin values[8] and in psychological variables, such as internalising problems.[9] Thus, the interindividual variation in non-growth effects of growth hormone can also be reduced by using tailored doses, selected on the basis of mathematical models of responsiveness. This should reduce the risk of overtreatment or undertreatment, with consequent hormone imbalances, and hopefully also the long term risks of cardiovascular, metabolic, malignant, cognitive, and psychosocial disease.

The studies in the current review used the same dose (per kg or m^2) of growth hormone from early childhood until adulthood and did not take the different phases of growth (infancy, childhood, and puberty) into account. These growth phases are regulated differently. Fetal growth and growth during infancy are mainly nutrition dependent. This is followed by a growth hormone dose dependent phase during childhood, and finally the pubertal growth spurt—an effect of interplay between sex steroids and a twofold to fourfold increase in growth hormone secretion (more in girls than in boys).

A recently published study found that short children with a delayed transition from infancy to childhood respond better to growth hormone (compared to those with normal timing).[10] They were also the only ones to respond to the lower dose of growth hormone.[10] In fact, more than half of children with idiopathic short stature have such a delayed transition. Today, being small for gestational age and having a delayed transition from infancy to childhood are both known to cause short stature, possibly as a result of calorie restriction inducing epigenetic changes, and these causes can no longer be defined as "idiopathic." In the future, more subgroups of idiopathic short stature are likely to be defined. So far many genetic reasons for short stature are known, such as deletions in the *SHOX* gene, but they account for only a minority of cases of short stature.

The growth of a child is an integrated marker of health. Therefore, low growth rate resulting in short stature needs to be identified, investigated, and treated if possible. Tailoring the growth hormone dose according to individual responsiveness to growth and non-growth effects, and also taking the growth period (infancy, childhood, puberty, or adulthood) into account, will hopefully normalise growth and minimise long term risks. Currently, authorities, such as the European Medicines Agency and Food and Drug Administration, accept only fixed growth hormone dosing regimens based on the size of the child. An individualised growth hormone dosing regimen is still not recommended despite the potential efficacy, cost, and not least safety justifications for such a treatment regimen.

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Drug treatment for generalised anxiety disorder

More head to head trials are needed to confirm apparent differences in effectiveness

RESEARCH, p 637

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Competing interests: The author has completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declares: no support from any organisation for the submitted work; he has received honorariums for speaking at CME meetings sponsored by Astellas, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Kyorin, MSD, Meiji, Otsuka, Pfizer, Shionogi, and Yoshitomi; he is on advisory boards for Sekisui Chemicals and Takeda Science Foundation; he has received royalties from Igaku-Shoin, Seiwa-Shoten, Nihon Bunka Kagaku-sha, and American Psychiatric Publication.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2011;342:d1216
doi: 10.1136/bmj.d1216

Generalised anxiety disorder is characterised by excessive worrying over everyday things and is associated with irritability; restlessness; difficulties in concentrating; and somatic symptoms such as muscle tension, fatigue, or sleeplessness. In the linked systematic review Baldwin and colleagues assess the relative effectiveness and tolerability of different drugs in the treatment of patients with this disorder.[1]

Generalised anxiety disorder first appeared in the American diagnostic classification system in 1980 as a residual category after diagnostic criteria for more specific anxiety disorders such as panic disorder, phobias, and obsessive-compulsive disorder had been delineated. Since then, conceptualisations of this disorder have been successively refined, and it is now generally recognised as an independent diagnostic entity. It can be distinguished from other, often coexisting, mental disorders, and its symptoms are uniquely associated with functional impairment and distress. Generalised anxiety disorder is one of the more common mental disorders in the general population, with 12 month prevalence estimates of around 3% and lifetime prevalence estimates of around 6%. It is also a common clinical diagnosis in primary care.[2]

Various drug and non-drug treatments have been shown to be effective including benzodiazepines, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors, anticonvulsants, and cognitive behavioural therapy. The existence of several treatment options is clinically desirable but raises the difficult question of which is likely to be the most effective and acceptable for an individual patient.

Systematic reviews and meta-analyses of individual drugs can provide partial answers when they make head to head comparisons with active drugs or make comparisons with a common comparator such as placebo. However, evaluating relative superiority among alternative drugs requires larger sample sizes than are needed for comparisons with placebos. In other words, even with comprehensive searches for relevant trials and the use of meta-analytical pooling, the results will still often have wide confidence intervals that may encompass both the point of null effects and the point of minimally important clinical difference. Many reviews then erroneously conclude, or at least imply, that the two treatments have similar effectiveness.

A more refined use of the available evidence is now possible. Multiple treatment meta-analysis, also known as mixed treatment comparison or network meta-analysis, is a relatively new approach to systematic reviews, which combines evidence from both direct head to head comparisons and indirect comparisons via intermediate comparators. It preserves the comparison of randomised treatments within each trial and offers many advantages. Firstly, it can produce tighter confidence intervals than found with other analyses because it uses both direct and indirect estimates. Secondly, it can estimate relative effectiveness between treatments that have never been directly compared. In addition, when conducted within a Bayesian framework, it can rank treatments on the basis of—for example, the probability of each treatment being the best among all the alternatives.

Baldwin and colleagues' analysis is the first multiple treatment meta-analysis of various drugs for generalised

anxiety disorder. The authors found that fluoxetine seemed to be more effective than other treatments and sertraline was better tolerated. They recommend that, among five treatments specifically licensed for generalised anxiety disorder in the United Kingdom, duloxetine, escitalopram, and pregabalin may offer some advantages over venlafaxine and paroxetine.

Although the authors make the best possible use of the available evidence, some caveats are worth consideration. Firstly, of the 46 eligible trials, only half could contribute to the multiple treatment meta-analysis for response, defined as 50% or greater reduction in severity of anxiety, and less than a third to that for remission, defined as achieving minimally symptomatic status. This raises concerns about selective outcome reporting bias.[3] Secondly, the available evidence was scanty, especially for direct comparisons between active drugs. For example, fluoxetine was ranked first in effectiveness to bring about response and remission, but data came from 33 patients in one trial only. Thirdly, as the authors argue, few significant differences were seen in terms of response among the active treatments. Yet they base their recommendations on the rankings according to the Bayesian model, which may in itself be a justifiable practice. However, their conclusion that of the five treatments having licensed indications for generalised anxiety disorder in the UK, duloxetine, escitalopram, and pregabalin offer some advantages over venlafaxine and paroxetine may be tenuous at best, particularly when the same rankings show that venlafaxine and paroxetine may be superior to duloxetine, escitalopram, and pregabalin in at least one of their three primary outcomes. Using GRADE criteria, the evidence for these relative rankings should be downgraded two or three levels for publication bias, imprecision, inconsistency, and indirectness.[4]

With these methodological caveats in mind, evidence suggests that fluoxetine and sertraline have some advantages over others in the short term treatment of generalised anxiety disorder. However, the weaknesses noted above make it difficult to draw firm conclusions. Researchers and the medical community need access to all the outcome data from all of the trials so that more robust multiple treatment meta-analyses can be done. Another unanswered clinical question awaiting rigorous pooling of available evidence is relative effectiveness and tolerability of these drugs in the long term.

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Excess mortality in osteoarthritis

Provides evidence for a unified approach to musculoskeletal ageing

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RESEARCH, p 638

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Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2011;342:d1407
doi: 10.1136/bmj.d1407

Osteoarthritis is the most common joint disorder worldwide. It comprises a group of overlapping disorders that may have different causes, but which result in joint failure subsequent to morphological changes in articular cartilage, subchondral bone, synovium, and other joint structures. Osteoarthritis typically affects the hands, knees, hips, spine, and feet.[1] Although osteoarthritis can be defined pathologically, radiographically, or clinically, most epidemiological studies have relied upon radiographic features to characterise the disease. Radiographic features have a graded (although sometimes discordant) association with clinical features—joint pain and functional impairment—with notable disability arising from involvement of the knee and hip. The lifetime risk of osteoarthritis specific morbidity is about 25% for the hip[2] and 45% for the knee,[3] and the disorder is a major contributor to the 57 000 knee and 55 000 hip arthroplasties undertaken each year in the United Kingdom.[4] In the linked study, Nüesch and colleagues assess all cause and disease specific mortality in patients with knee or hip osteoarthritis.[5]

In contrast to the well established morbidity attributable to osteoarthritis, relatively little is known about the effect on mortality. Rheumatoid arthritis, the most common inflammatory joint disorder, is associated with a twofold to threefold excess mortality, specifically attributable to cardiovascular disease, infection, respiratory disease, and gastrointestinal disease.[6] However, conventional thinking has been that osteoarthritis itself does not cause death. Previous studies have attributed higher death rates in patients with osteoarthritis to concomitant risk factors for the disorder (most notably obesity) or to treatment with non-steroidal anti-inflammatory drugs.[7 8] These studies have important limitations (patients were recruited from hospital settings, they were confined to various categories of employment, standardised clinical and radiographical definitions were not always incorporated, and patients were investigated after surgery).

Nüesch and colleagues report the pattern and causes of incident mortality in a large population based sample of men and women with osteoarthritis of the knee and hip.[5] The 1163 participants (denominator population 26 046) aged 35 years and over who had symptomatic radiographically defined osteoarthritis at these two joint sites showed a significant excess in all cause mortality (standardised mortality ratio 1.55, 95% confidence interval 1.41 to 1.70); cause specific mortality was particularly high for cardiovascular disease and dementia. The authors suggest that this association may result from low grade systemic inflammation, long term use of non-steroidal anti-inflammatory drugs, or a lack of physical activity. An alternative possibility is abnormal vascular pathology of the subchondral bone, which has been shown to contribute to the initiation and progression of osteoarthritis.[9] These results have important implications for the clinical management of osteoarthritis, as well as for understanding its pathogenesis.

In rheumatoid arthritis, the recognised association with death from cardiovascular disease has led to routine evaluation of cardiovascular risk factors, the use of drugs to normalise the serum lipid profile and blood pressure, and a focus on lifestyle changes. Although such strategies are already recommended in the context of arthroplasty, the current study suggests that they should be incorporated into primary care algorithms for the management of symptomatic osteoarthritis not severe enough to warrant surgery. The use of exercise regimens to enhance joint function is also likely to benefit other parts of the musculoskeletal system, such as bone and muscle.

The findings also shed new light on biological ageing of the musculoskeletal system. Population based studies have suggested that systems seem to age together in individuals.[10] Changes in two other musculoskeletal tissues (bone and muscle) have been well characterised throughout the life course, and the morbidities associated with their involution (osteoporosis and sarcopenia) are established contributors to physical frailty. Like osteoarthritis, the prevalence of both disorders rises steeply with age, and interactions between joint structure and muscle weakness in the causation of lower limb disability have long been recognised.

It is now also clear that low bone density and muscle strength are markers of premature death[11 12]—not only are they associated with a host of attributes that independently predispose to reduced survival, but they may also mirror the biological rates of cellular ageing that characterise all individuals. Biological ageing may be assessed at the molecular level (DNA repair, oxidative damage, or epigenetic modification), system level (endocrine or metabolic system), or whole organism level. Theories of ageing may also be categorised according to whether the process is principally genetically determined or occurs as a response to random events over time. A distinction may also be drawn as to whether ageing has evolved as a beneficial process in its own right (adaptive theories) or as a byproduct of other pathways (non-adaptive theories). These models of biological ageing are not mutually exclusive, and there is growing support for characterising musculoskeletal ageing from a life course perspective, in terms of recognising important influences operating from conception to death. The notion that osteoarthritis should join osteoporosis and sarcopenia as a manifestation of biological ageing opens a major avenue for future research aimed at identifying biomarkers of the underlying cellular and molecular processes and at evaluating behavioural interventions and drugs targeted at optimising bone, muscle, and articular health.

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Reduction of childhood mortality through millennium development goal 4

Will not be maximised unless injury prevention is integrated into the overall plan

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Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
Cite this as: *BMJ* 2011;342:d357
doi: 10.1136/bmj.d357

Millennium development goal 4 aims to reduce mortality in children under 5 years by two thirds between 1990 and 2015. Unfortunately, as of 2010, among the 67 countries with high child mortality (≥40 deaths/1000 live births), only 10 are on track to meet this target.[1] At the millennium development goal summit in September 2010, the general assembly of the United Nations adopted an outcome document that expressed "deep concerns that [progress] falls short of what is needed."[2] The lack of focus on prevention of childhood injury in many countries is exacerbating the failure to meet the target.

About 830 000 children under 18 years die each year as a result of unintentional injuries, including road traffic injuries, poisoning, falls, burns, and drowning. In addition, tens of millions of children require acute hospital care or long term rehabilitation for non-fatal injuries. Globally, injuries are the leading cause of death for children aged 10-19 years, and road traffic injuries and drowning account for nearly half of all unintentional injuries to children.[3]

More than 260 000 children die as a result of road traffic injuries each year, and up to 10 million more are non-fatally injured.[3] Both sexes are affected, although twice as many boys as girls die from road traffic injuries.[4] The global cost of road traffic injuries has been estimated at $500bn (£320bn; €385bn) annually.[3] More than 450 children drown each day worldwide, and thousands have serious lifelong disabilities, including brain damage, as a result of non-fatal drowning events.[3] In Bangladesh, for example, 20-29% of deaths in the 1-4 year age group are caused by drowning.[5] Burns kill 96 000 children annually and


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are more common in girls because they are more likely be exposed to fire at home, a result of socially defined gender roles. Each year, another 45 000 and 47 000 children die from poisoning and falls, respectively, around the world, and the toll of these injuries on the health system is even higher because of the millions of non-fatal events.[3]

Although 40% of all deaths in children in high income countries are caused by injuries, 95% of childhood deaths from injury occur in low and middle income countries.[3] Rates of death from injury in children are more than four times higher in low and middle income countries than in high income countries.[6] This inequity means that regions like sub-Saharan Africa and South Asia, which are among the most populous and poorest regions in the world, have some of the highest incidence rates and fatality rates for childhood injury.[7]

Children are highly susceptible to injuries, which are preventable causes of death and disability.[1] Yet low and middle income countries generally have few data on childhood injuries, lack national policies on the prevention of such injuries, and have very few funded programmes or research in this area.[3] This oversight not only increases loss of healthy life, with consequent social and economic effects, but may also have serious implications for the achievement of millennium development goals related to child health.

Given the size of the problem, the relative lack of global attention to childhood injuries in terms of public policies and resource investment is surprising.[8] Although the World Health Organization and United Nations Children's Fund (Unicef) released a world report at the end of 2008 on childhood injuries, they seem to have little budgetary support to act on it. The almost 1000 attendees at the September 2010 World Conference on Injury Prevention and Safety Promotion (www.safety2010.org.uk) in London also highlighted insufficient global interest and called on governments to be proactive in confronting this burden on the world's children.

Childhood injuries are not simply "accidents"—many of them can be prevented or the severity of their effects reduced.[8] Experience in developed nations has shown that interventions for preventing injury can be effective; high income countries have reduced deaths from childhood injury by 30-50% over the past 30 years by implementing multi-sectoral approaches to the prevention of childhood injury.[3 5] Effective preventive methods include implementing and enforcing safety legislation and standards; promoting home and transport safety; modifying products and the environment where children live and play; and improving care and rehabilitation of injured children.[6]

Specific injury prevention and control interventions are available. For example, approaches to reducing childhood road traffic injuries include introducing laws on minimum drinking age; implementing lower blood alcohol limits for teenage drivers; making motorcycle helmets, seat belts, and child restraints mandatory; reducing speed around schools; and introducing graduated driver licensing (whereby a full licence is not given until a specified number of hours have been driven).[3] Interventions to prevent drowning include removing or covering water hazards; fencing swimming pools; providing personal flotation devices; and ensuring immediate resuscitation.[3] These interventions are effective and cost effective, giving high returns for investments (table).[9 10]

Benefits of investments for injury prevention and control interventions[3 9 10]

Intervention	Average cost/ disability adjusted life year (DALY)	Return for every $1 investment
Road safety improvements		$3
Improved enforcement	$5	
Speed bumps (at top 25% of dangerous junctions)	$9	
Motorcycle helmets	$467	
Bicycle helmets	$107	$29
Child restraints		$29
Burn safety measures		
Smoke alarms		$65
Poisoning safety measures		
Poison control services		$7
Safety promotion		
Prevention advice from paediatricians		$10

1$=£0.64; €0.77.

Despite this knowledge, the lack of implementation—especially in low and middle income countries—is staggering. Governments, civil society, and the private sector must create safer physical and social environments for children and safer products, such as toys and musical instruments. A comprehensive approach to the prevention of childhood injury should include developing national policies to promote action, improving legislation to ensure safety, investing in evidence based programmes, and supporting relevant research to adapt and modify interventions to local contexts. Health and medical professionals, especially in low and middle income countries, need to accept that the acute transfer of energy (instead of a biological agent) through human bodies causes injuries; the use of public health sciences helps identify the causes of injuries; and solutions for injury prevention and control are multisectoral and come from within and outside of the health sector.[6]

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Poor inpatient care for older people

Good care for frail older people should be part of mainstream clinical practice

BSIP, LECA/SPL

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Competing interests: None declared.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2011;342:d373
doi: 10.1136/bmj.d373

In 1963, in a message to Congress, John F Kennedy said that a society's quality and durability can best be measured by the respect and care given to its elderly citizens.[1] By this measure, the recent report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) on the perioperative care of older people gives our society cause for concern.[2] The report has been widely received as demonstrating inadequate care for older people undergoing surgery, and its findings described as shocking, disturbing, and unacceptable.[3]

The report describes an observational study of more than 800 patients over the age of 80 years who died within 30 days of a variety of surgical procedures. There was nothing extraordinary about these patients—they were typical in many ways of the population accessing acute care in the modern NHS. They were older; nearly all had comorbidity (94%); disabilities were common, as was delirium or dementia, or both; and many (66%) were identifiably frail. A key finding was that only 38% of patients received care that was regarded as good by the NCEPOD assessors. Around 20% of NHS sites and 46% of private hospitals did not have on-site specialist medical support for the care of older people (geriatricians), and most sites (87%) did not have a policy for appropriate medical pre-assessment.

The report makes a series of recommendations that are relevant to all providers and practitioners of surgical care for frail older people, including assessment of nutrition; assessment and management of frailty and comorbidity; medication review and pain management; assessment of capacity; and the perioperative monitoring and control of body temperature, blood pressure, and fluid balance. In making these recommendations, the NCEPOD advisers have had to focus on some very basic areas of care.

It is reasonable to expect no less than competence in these fundamental dimensions of clinical care—we would all want these things done for ourselves, our family, and our patients—but the recommendations go further. In addition to encouraging basic competence in clinical care, the report recommends the involvement of more senior doctors in the assessment process. This may be helpful, particularly if the senior involved has the appropriate knowledge, skills, and attitudes to help unpick the complex clinical picture often seen in frail older patients. In this regard, the report also calls for more involvement of geriatricians, such as making routine daily input from geriatric medical specialist services integral to inpatient care pathways for older people undergoing surgery.

This may be an attractive quick fix, but what will these specialists do? Most research on the organisation and delivery of quality care for frail older people emphasises the importance of careful and comprehensive assessment in multiple domains, and the organisation and delivery of care to meet the assessed needs. These multidimensional approaches can improve health outcomes and minimise harm in older people in hospital.[4] Such models should include the maintenance and recovery of physical function, the prevention and management of delirium,[5] nutritional assessment and support, the management of pain, and careful review and management of drugs. Examples include stroke and orthogeriatric units,[6] in addition to acute inpatient care.[7 8] Not all of this knowledge is currently being generally applied, and this has been described as discriminatory.[9]

These kinds of approaches have been regarded as more or less specialised forms of care, practised by practitioners with skills in the assessment and management of frail older people. The NCEPOD report's authors imply that every older patient undergoing surgery deserves routine daily clinical review from practitioners who are able to assess and meet their clinical needs. However, as the demographic transition proceeds and we look forward to a future with many more people over 80 years needing acute medical and surgical care, is this really a role just for specialists? Shouldn't we all be doing it?

Most hospital admissions, bed days, readmissions, and discharge delays are experienced by older people, so it would make sense to recommend that all practitioners be trained to a high standard in the care of older people. Shouldn't the basic skills, knowledge, and attitudes necessary for effective evidence based care of older people be embedded in the training of all healthcare professionals, at all levels? Of course this has implications for undergraduate medical education,[10-12] specialist training curriculums, and professional development in almost all surgical and non-surgical specialties.

Geriatricians are needed for complex referrals and to teach and reinforce good practice, but the NCEPOD report shows that the essential skills for providing good clinical care for frail older people need to be much more widely disseminated than at present. It is time to bite the bullet and transform the healthcare workforce into one that is underpinned by the knowledge, skills, and positive attitudes needed to make evidence based high quality care for frail older people a central component of mainstream clinical practice. The NCEPOD report is the ideal catalyst for this.

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