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RESEARCH

THIS WEEK'S RESEARCH QUESTIONS

End of a short story?

AJ PHOTOS/HOP AMERICAIN/SPL

Although growth hormone therapy can increase growth rate, controversy continues over its use in children with idiopathic short stature, partly because this is a heterogeneous condition that includes normal variants of growth. Trials have also tended to be too small, short term, and inconsistent to ascertain the benefits for adult height. Because of this uncertainty, the European Agency for the Evaluation of Medicinal Products has not yet approved use of growth hormone for this indication.

Annalisa Deodati and Stefano Cianfarani systematically reviewed all randomised and non-randomised trials of growth hormone therapy in children with idiopathic short stature, defined as height >2 SD score below the mean (p 636). Of 10 studies included, only three were randomised controlled trials carried out to adulthood. The limited evidence indicated that growth hormone therapy does increase adult height, but the increase was small compared with those achieved in other conditions, and it varied greatly between individuals.

Reviewers thought the study provided "the ending of the story," since funding for further trials is unlikely. The authors suggest that debate should now shift to whether the gains seen here—around 4 cm—are of true value.

In an editorial (p 607), Kerstin Albertsson-Wikland emphasises that the response to growth hormone treatment can vary substantially between individuals and also at different stages of growth. Therefore, she says, it would be safer and more efficient to tailor doses to the individual, rather using a standard dose based on the child's size—the approach that is currently recommended by drug agencies and that was used in this study.

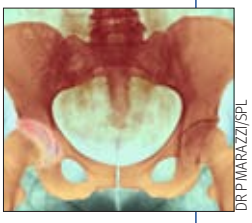
Reporting genetic risk: time to get a GRIPS

Genetic risk prediction studies usually analyse large numbers of genetic variations (from tens to tens of thousands) using statistical algorithms and models of variable complexity. All too often they are poorly reported, despite existing guidance on reporting observational study designs (STROBE statement), genetic association studies (STREGA), prediction models (REMARK), and test evaluation (REMARK and STARD).

So an international group of risk prediction researchers, epidemiologists, geneticists, methodologists, statisticians, and journal editors has developed the GRIPS (Genetic RIsk Prediction Studies) statement to help authors report this type of work fully (p 640, Research Methods and Reporting).

As well as covering the building, validation, and limitations of the statistical models, the 25 point GRIPS checklist asks for the down to earth stuff that often gets missed, such as "Report the numbers of individuals at each stage of the study. Give reasons for non-participation at each stage. Report the number of participants not genotyped and reasons why they were not genotyped" and "Discuss the generalisability and, if pertinent, the healthcare relevance of the study results." The supporting "explanation and elaboration" documentation for GRIPS is published in *PLoS Medicine*, and the statement is being co-published in nine journals, to ensure that it reaches both specialists and generalists.

Increased mortality with osteoarthritis



DR P MARAZZI/SPL

Eveline Nüesch and colleagues report that patients with osteoarthritis are at higher risk of premature death compared with the general population and that most of the excess is due to deaths from cardiovascular disease (p 638). In their cohort study, 1163 patients aged 35 years or over with symptomatic and radiographically confirmed osteoarthritis of the knee or hip showed a 55% excess in all cause mortality. Major risk factors included a history of cancer, diabetes, or cardiovascular disease, but the most striking association was with walking disability. In essence, "the more severe the restriction in walking ability the more likely a person was to die early," and most of the excess deaths associated with walking problems had cardiovascular causes. The authors recommend that management of patients with osteoarthritis and walking disability should focus on treatment of cardiovascular risk factors and increasing physical activity.

In their editorial, Cyrus Cooper and Nigel Arden (p 609) concur that evaluation and amelioration of cardiovascular risk factors (which already routinely occurs with rheumatoid arthritis) could usefully be extended to management of osteoarthritis. They also discuss the idea that osteoarthritis should be seen as a manifestation of biological ageing (as osteoporosis and sarcopenia already are), potentially with new approaches to prevention and treatment.

MICHAEL DONNE/SPL

LATEST RESEARCH: For this and other new research articles see www.bmj.com/research

Prevention of pain on injection of propofol
Leena Jalota and colleagues aimed to determine the most efficacious approach for preventing the pain caused by injection of propofol to induce anaesthesia. Their systematic review and meta-analysis suggests use of the antecubital vein, or pretreatment using lidocaine in conjunction with venous occlusion for the hand vein, but they also discuss other useful options (doi:10.1136/bmj.d1110).

Effect of statins on atrial fibrillation
Kazem Rahimi and colleagues pulled together evidence from both published and unpublished trials in a meta-analysis. Their results failed to back up the suggested beneficial effect of statins on atrial fibrillation shown in published shorter term studies (doi:10.1136/bmj.d1250).

Impact of growth hormone therapy on adult height of children with idiopathic short stature: systematic review

Annalisa Deodati, Stefano Cianfarani

EDITORIAL by Albertsson-Wikland

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STUDY QUESTION

What is the current evidence that long term growth hormone treatment in children with idiopathic short stature may improve their height as adults?

SUMMARY ANSWER

Growth hormone therapy in children with idiopathic short stature seems to be effective in partially reducing the deficit in height as adults, although the magnitude of effectiveness is on average less than that achieved in other conditions for which growth hormone is licensed.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Growth hormone therapy has been approved in the United States for children with idiopathic short stature, and a recent consensus conference proposed that children with height below −2.0 SD score warrant consideration for treatment. The results of this meta-analysis show that growth hormone therapy increases adult height of children with idiopathic short stature by about 4 cm.

Selection criteria for studies

We searched the Cochrane Central Register of Controlled Trials, Medline, and the bibliographic references from all retrieved articles describing such trials up to April 2010, using the search terms "growth hormone" and "final height" and "adult height" and "idiopathic short stature." Inclusion criteria were initial short stature, defined as height more than 2 SD scores below the mean; peak growth hormone responses greater than 10 µg/L; prepubertal stage; no previous growth hormone therapy; and no comorbid conditions that would impair growth.

Primary outcome(s)

The primary efficacy outcome measure was the difference in adult height between treated and untreated children. We considered a mean difference in adult height of more than 0.9 SD scores (about 6 cm) as a satisfactory response to growth hormone therapy.

Main results and role of chance

The adult height achieved by those in the treated group exceeded that of the controls, with a mean difference of 0.65 SD score (about 4 cm) (95% confidence interval 0.40 to 0.91; P<0.001.

Bias, confounding, and other reasons for caution

One potential limitation of any meta-analysis is the pooling of studies with heterogeneous populations. However, the rigorous entry criteria and review procedures for the current analyses were instituted to exclude studies in patients with known causes of short stature. A second potential limitation involves the effect of study dropouts on the validity of study findings. A third potential confounder is the small sample size, with its high chance of false positive results. A fourth potential limitation of any meta-analysis is the "file-drawer" effect, in which studies with negative results might remain unpublished thus biasing the literature towards positive findings.

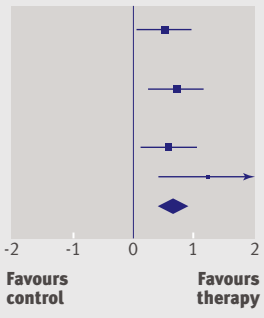
Study funding/potential competing interests

This study received no support from any organisation that might have an interest in the submitted work. SC received lecture fees from Ipsen, Eli Lilly, Novo Nordisk, and Pfizer, consulting fees from Ipsen, Eli Lilly, and Pfizer, and research funds from Merck-Serono, Pfizer, Eli Lilly, and Ferring.

EFFECT OF LONG TERM GROWTH HORMONE THERAPY ON ADULT HEIGHT

Studies	Treated children: Mean SD score	SD	Total	Control children: Mean SD score	SD	Total	Weight (%)	Mean difference IV, random (95% CI)
Albertsson-Wikland 2008[11] (growth hormone 0.033 mg/kg/day)	-1.70	0.68	18	-2.20	0.75	19	30.0	0.50 (0.04 to 0.96)
Albertsson-Wikland 2008[11] (growth hormone 0.067 mg/kg/day)	-1.50	0.84	31	-2.20	0.75	19	31.7	0.70 (0.25 to 1.15)
Leschek 2004[10]	-1.77	0.80	22	-2.34	0.56	11	28.8	0.57 (0.10 to 1.04)
McCaughey 1998[9]	-1.14	1.06	8	-2.37	0.46	6	9.4	1.23 (0.41 to 2.05)
Total (95% CI)			79			55	100.0	0.65 (0.40 to 91)

Test for heterogeneity: τ^2=0.00, χ^2=2.48, df=3, P=0.48, I^2=0%
Test for overall effect: z=5.06, P<0.001



Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis

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EDITORIAL by Furukawa

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STUDY QUESTION

What is the relative efficacy and tolerability of drug treatments for generalised anxiety disorder?

SUMMARY ANSWER

Fluoxetine was ranked first for response and remission, sertraline first for tolerability; among UK licensed treatments, duloxetine was first for response (third overall); escitalopram first for remission (second overall); and pregabalin first for tolerability (second overall).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A range of drug treatments are available for people with generalised anxiety disorder, but the comparative efficacy and tolerability of treatments is uncertain. Though fluoxetine and sertraline are not licensed in the UK for this condition, fluoxetine was ranked first for response and remission, sertraline first for tolerability. For UK licensed drugs, duloxetine was ranked first for response, escitalopram first for remission, and pregabalin first for tolerability.

Selection criteria for studies

We searched for randomised controlled trials of any drug treatment for generalised anxiety disorder published from January 1980 to February 2009. A three person team initially reviewed the titles or abstracts, or both, of all identified publications, and then screened full text publications on those remaining after first pass. Data extracted for meta-analysis were independently reviewed and entered in the primary Bayesian probabilistic mixed treatment meta-analysis to establish drugs' ranking for three primary outcome measures (given as a percentage likelihood of being ranked first).

Primary outcome

The primary outcomes were response (proportion showing ≥50% reduction in Hamilton anxiety scale score), remission (proportion with final score of ≤7), and tolerability (proportion withdrawing from trials because of adverse events).

Main results and role of chance

Of 3249 citations, 46 trials met our inclusion criteria, 27 of which contained sufficient and appropriate data. Nine treatments (duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine, venlafaxine) were compared. Fluoxetine was ranked first for response and remission (probability of 62.9% and 60.6%, respectively). Sertraline was ranked first for tolerability (49.3%). Among UK licensed treatments, duloxetine was first for response (2.7%), escitalopram first for remission (26.7%), and pregabalin first for tolerability (7.7%). Ranking in the table does not match the decreasing percentage chance of being ranked first because that takes into account the number and quality of data for each treatment, whereas the ranking is based on mean results; treatments with few or heterogeneous data might have an increased chance of being the most efficacious. A secondary frequentist analysis supported the findings of the primary analysis.

Bias, confounding, and other reasons for caution

We included only a proportion of identified trials and did not systematically attempt to uncover unpublished studies (though searches of reference lists of published meta-analyses and pooled analyses identified some unpublished studies that we included), which could significantly affect results as unpublished studies are more likely to have negative or equivocal findings (publication bias). Funnel plots showed no evidence of publication bias for response and remission. All studies included were sponsored by manufacturers. Inclusion of such studies could lead to bias, though this might be balanced out by inclusion of studies from competing manufacturers.

Our analysis was based largely on placebo controlled studies, with fewer head to head studies. Assessment of outcome is hence based more on indirect than direct comparisons. Outcomes for response and remission were somewhat different, as not all studies gave data on remission. We could assess tolerability only by the blunt measure of withdrawals due to adverse events. Finally, the dose of drugs used in trials could have influenced outcome: most were given in recognised licensed doses but in some cases for conditions other than generalised anxiety disorder.

Study funding/potential competing interests

DB and DT have received funding from manufacturers of drugs used in generalised anxiety disorder. RW and RL worked for Complete Medical Group at the time the study was conducted. The study was funded by Lundbeck but was conducted and reported independently of the company. The authors were responsible for deciding to submit for publication. See the full version on bmj.com for details.

PROBABILISTIC ANALYSIS SHOWING RANKING OF TREATMENTS BY OUTCOME MEASURE FOR GENERALISED ANXIETY DISORDER. FIGURES IN PARENTHESES INDICATE PERCENTAGE CHANCE OF BEING RANKED FIRST

Ranking	Response*	Remission†	Withdrawal‡
1	Fluoxetine§ (62.9)	Fluoxetine§ (60.6)	Sertraline§ (49.3)
2	Lorazepam§ (17.2)	Escitalopram (26.7)	Pregabalin (7.7)
3	Duloxetine (2.7)	Venlafaxine (3.5)	Fluoxetine§ (38.0)
4	Sertraline§ (5.8)	Paroxetine (2.9)	Paroxetine (1.7)
5	Paroxetine (7.7)	Sertraline§ (6.0)	Tiagabine§ (1.2)
6	Pregabalin (1.5)	Duloxetine (0.2)	Venlafaxine (0.7)
7	Venlafaxine (0.6)	Tiagabine§ (0.04)	Escitalopram (1.2)
8	Escitalopram (1.7)	NA	Duloxetine (0.1)
9	Tiagabine§ (0.04)	NA	Lorazepam§ (0.09)

NA=not available (not all studies reported on this outcome for all drugs).
*Proportion of patients who experienced reduction of ≥50% from their baseline Hamilton anxiety scale score.
†Proportion of patients with final HAM-A score ≤7.
‡Percentage of patients withdrawing from study because of adverse events.
§Not licensed for generalised anxiety disorder in UK.

All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study

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EDITORIAL by Cooper and Arden

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bmj.com
Clinical review: Osteoarthritis (*BMJ* 2006;332:639)

STUDY QUESTION

Are people with osteoarthritis of the knee or hip subject to an increased risk of death, and if so what are the main causes and potential risk factors?

SUMMARY ANSWER

Patients with osteoarthritis are at higher risk of death than the general population, and most of the excess is due to deaths from cardiovascular disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous data suggested that people with osteoarthritis have an excess mortality, but the causes and risk factors were not clear. Major risk factors associated with increased mortality in osteoarthritis patients are walking disability and a history of cancer, diabetes, and cardiovascular disease.

Participants and setting

Patients in our study were aged 35 years or over with symptoms and radiological confirmation of osteoarthritis of the knee or hip, who had been recruited from general practices in the south west of England.

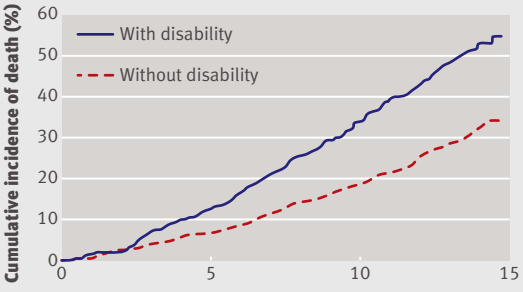
Design, size, and duration

We included 1163 patients from the Somerset and Avon Survey of Health, a population based cohort study. After a median of 14 years of follow-up, 438 (38%) participants had died and 725 (62%) were still alive. Participants used questionnaires to report comorbidities and walking disability at baseline. We compared causes of deaths obtained from death certificates with data for the general population. We studied associations between mortality and baseline characteristics by using multivariable Cox proportional hazards regression.

Main results and the role of chance

We found excess all cause mortality in patients with osteoarthritis compared with the general population (standardised mortality ratio 1.55, 95% confidence interval 1.41 to 1.70). We found an excess of all disease specific mortalities, but this was particularly pronounced for cardiovascular (1.71, 1.49 to 1.98) and dementia associated mortality (1.99, 1.22 to 3.25). Mortality increased with increasing age (P for trend <0.001), male sex (adjusted hazard ratio 1.59, 1.30 to 1.96), self reported history of diabetes (1.95, 1.31 to 2.90), cancer (2.28, 1.50 to 3.47), cardiovascular disease (1.38, 1.12 to 1.71), and walking disability (1.48, 1.17 to 1.86), but we found little evidence for increased mortality associated with previous joint replacement, depression, chronic inflammatory disease, eye disease, or presence of pain at baseline. The more severe the walking disability, the higher was the risk of death (P for trend <0.001). We found a protective effect of obesity on overall mortality.

CUMULATIVE INCIDENCE OF ALL CAUSE MORTALITY UP TO 15 YEARS IN PATIENTS WITH AND WITHOUT WALKING DISABILITY AT BASELINE EXAMINATION



No at risk				
Without disability	711	663	578	111
With disability	288	251	189	22

Bias, confounding, and other reasons for caution

We took account of missing values in baseline data by using multiple imputation. Comorbidities and consumption of analgesics were reported by patients, and we used information given on death certificates to derive estimates for disease specific mortality. Both of these could have biased our results.

Generalisability to other populations

Because of the population based nature of the study, we believe that the results are generalisable to patients with osteoarthritis in different countries or settings.

Study funding/potential competing interests

The Somerset and Avon Survey of Health was originally funded by the Department of Health and the South and West NHS Research and Development Directorate. This work was funded by the Swiss National Science Foundation and by Arthritis Research UK.

Adequacy of reporting monitoring regimens of risk factors for cardiovascular disease in clinical guidelines: systematic review

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STUDY QUESTION

How well do clinical practice guidelines aimed at cardiovascular disease management report recommendations for monitoring cardiovascular disease (CVD) risk factors?

SUMMARY ANSWER

More than half of the guidelines in our sample did not address the monitoring of one or more of the main CVD risk factors and less than one third addressed all three (dyslipidaemia, hypertension, and smoking cessation).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Management and monitoring of CVD and its risk factors is one of the most common consultations in healthcare. Clinical guidelines are often referred to by providers looking for recommendations on treatment and monitoring of these conditions. Only a small proportion (20%) of the guidelines we identified and appraised in a systematic review addressed monitoring for all three main CVD risk factors, and the recommendations were often vague, confusing, and contradictory, making them difficult to implement in clinical practice.

Selection criteria for studies

All guidelines published in the English language between January 2002 and February 2010 addressing CVD prevention or treatment, found on Medline, Trip database, National Guideline Clearinghouse, and databases containing guidelines.

Primary outcome(s)

Whether, and to what extent, was monitoring for any of the CVD risk factors addressed in each guideline.

Main results and role of chance

We identified 117 guidelines, 84 of which contained a section on lipids. Half of these (53%, 44 guidelines) did not provide specific recommendations for what to monitor, 51% (n=43) for when to monitor, and 64% (n=54) for what action to take if the target was out of range. The guidelines mentioning hypertension (n=79) and smoking (n=65) were little better, with 63% (n=50) and 54% (n=35), respectively, not providing a recommendation for what to monitor. For both these risk factors, about two thirds recommended when to monitor, and what action to take. The number of guidelines that explicitly referenced the level of evidence for monitoring was low, with most of the recommendations based on weak levels of evidence.

Bias, confounding, and other reasons for caution

We restricted our systematic review to guidelines published in English, but our findings are likely to be relevant to many parts of the world. We looked only at dyslipidaemia, hypertension, and tobacco use as CVD risk factors. Although many other risk factors exist, we chose these three as the most important for consideration in consultations about healthcare.

Study funding/potential competing interests

The study was not funded. We have no competing interests.

PROPORTION OF GUIDELINES DEALING WITH MANAGEMENT OF RISK FACTORS FOR CARDIOVASCULAR DISEASE, AND COMPLETENESS OF MONITORING RECOMMENDATION

Risk factor	No (%) with section on risk factor management	No (%) including monitoring	No (%) with specific section on monitoring	Completeness of monitoring recommendation: What to monitor			When to monitor			What to do if target is out of range		
				Not reported	Non-specific*	Specific	Not reported	Non-specific*	Specific	Not reported	Non-specific*	Specific
Lipid level	84 (72)	53 (63)	34 (40)	31†	13	40	31†	12	41	31	23	30
Hypertension	79 (68)	40 (51)	26 (32)	39	11	29	39	12	28	39	16	24
Smoking	65 (55)	37 (57)	19 (29)	35	—	30	28	17	20	28	14	23

*Not useful in practice.
†44 guidelines provided no information or non-specific information.