RESEARCH

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Supervised exercise therapy versus usual care for patellofemoral pain syndrome: an open label randomised controlled trial

R van Linschoten,[1] M van Middelkoop,[1] M Y Berger,[1] E M Heintjes,[4] J A N Verhaar,[2] S P Willemsen,[1 3] B W Koes,[1] S M Bierma-Zeinstra[1]

[1]Department of General Practice, Erasmus University Medical Centre, Rotterdam, Netherlands
[2]Department of Orthopaedics, Erasmus University Medical Centre, Rotterdam, Netherlands
[3]Department of Epidemiology and Biostatistics, Erasmus University Medical Centre, Rotterdam, Netherlands
[4]PHARMO Institute, Utrecht, Netherlands
Correspondence to: R van Linschoten
r.v.linschoten@hccnet.nl

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ABSTRACT

Objective To assess the effectiveness of supervised exercise therapy compared with usual care with respect to recovery, pain, and function in patients with patellofemoral pain syndrome.

Design Open label randomised controlled trial.

Setting General practice and sport physician practice.

Participants Patients with a new episode of patellofemoral pain syndrome recruited by their general practitioner or sport physician.

Interventions The intervention group received a standardised exercise programme for 6 weeks tailored to individual performance and supervised by a physical therapist, and were instructed to practise the tailored exercises at home for 3 months. The control group were assigned usual care, which comprised a "wait and see" approach of rest during periods of pain and refraining from pain provoking activities. Both the intervention group and the control group received written information about patellofemoral pain syndrome and general instructions for home exercises.

Main outcome measures The primary outcomes were self reported recovery (7 point Likert scale), pain at rest and pain on activity (0-10 point numerical rating scale), and function (0-100 point Kujala patellofemoral score) at 3 months and 12 months follow-up.

Results A total of 131 participants were included in the study: 65 in the intervention group and 66 in the control group. After 3 months, the intervention group showed better outcomes than the control group with regard to pain at rest (adjusted difference −1.07, 95% confidence interval −1.92 to −0.22; effect size 0.47), pain on activity (−1.00, −1.91 to −0.08; 0.45), and function (4.92, 0.14 to 9.72; 0.34). At 12 months, the intervention group continued to show better outcomes than the control group with regard to pain (adjusted difference in pain at rest −1.29, −2.16 to −0.42; effect size 0.56; pain on activity −1.19, −2.22 to −0.16; effect size 0.54), but not function (4.52, −0.73 to 9.76). A higher proportion of patients in the exercise group than in the control group reported recovery (41.9% *v* 35.0% at 3 months and 62.1% *v* 50.8% at 12 months), although the differences in self reported recovery between the two groups were not statistically significant. Predefined subgroup analyses revealed that patients recruited by sport physicians (n=30) did not benefit from the intervention, whereas those recruited by general practitioners (n=101) showed significant and clinically relevant differences in pain and function in favour of the intervention group.

Conclusion Supervised exercise therapy resulted in less pain and better function at short term and long term follow-up compared with usual care in patients with patellofemoral pain syndrome in general practice. Exercise therapy did not produce a significant difference in the rate of self reported recovery.

Trial registration ISRCTN83938749.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Both exercise therapy and a "wait and see" approach are advocated in patients with patellofemoral pain syndrome

There is only limited evidence for the effectiveness of exercise therapy with respect to pain outcomes and conflicting evidence with respect to functional outcomes

WHAT THIS STUDY ADDS

Supervised exercise therapy for patients with patellofemoral pain syndrome is more effective than usual care with respect to pain at rest, pain on activity, and knee function

Supervised exercise therapy has no significant effect on self reported recovery

INTRODUCTION

Patellofemoral pain syndrome can be defined as pain around the patella that occurs during or after high loaded flexion and extension of the knee. There is no agreement about the aetiology of patellofemoral pain syndrome or the most appropriate treatment. Rest during periods of pain and refraining from pain provoking activities is advised and is considered usual care.[1] An active approach to treatment has been advocated but there is only limited evidence that exercise is more effective than no exercise with respect to pain reduction.[2] Evidence as to whether exercise provides functional improvement is conflicting. We investigated short term as well as long term effects of

Table 1 | Recovery at 3 and 12 months' follow-up

	Exercise therapy(n=65)			Control(n=66)			Adjusted odds ratio† (95% CI) at 3 months	Adjusted odds ratio† (95% CI) at 12 months
	Baseline	3 months (n/N (%))	12 months (n/N (%))	Baseline	3 months (n/N (%))	12 months (n/N (%))		
Recovered*	—	26/62 (41.9)	36/58 (62.1)	—	21/60 (35.0)	30/59 (50.8)	1.34 (0.65 to 2.79)	1.60 (0.77 to 3.34)

Frequencies are reported for those patients available at that time point. Adjusted odds ratios are reported for the total available in analysis.

*Recovered=fully or strongly recovered.

†Recovery was adjusted for duration of symptoms.

exercise therapy compared with usual care in patients with patellofemoral pain syndrome.

METHODS

Patients aged between 14 and 40 years consulting their GP or sport physician for patellofemoral pain syndrome were eligible. Inclusion criteria comprised the presence of at least three of the following: pain when walking up or down stairs; pain when squatting; pain when running; pain when cycling; pain when sitting with knees flexed for a prolonged period of time; grinding of the patella; and a positive clinical patellar test (such as Clarke's test or patellar femoral grinding test). Symptoms had to have persisted for longer than 2 months but not longer than 2 years. See bmj.com for exclusion criteria.

Patients were randomly allocated to the intervention (exercise therapy) or the control (usual care) group. They were stratified by age (14-17 years or 18 years and older) and by recruiting physician (GP or sport physician).

Interventions

The intervention group followed a standardised exercise protocol tailored to individual achievement and supervised by a physical therapist. It consisted of a general warm up, static and dynamic muscular exercises, and balance exercises and flexibility exercises for major thigh muscles. Patients exercised for 25 minutes.

The increment of the exercise protocol was monitored by the physical therapist. Patients visited the therapist nine times in 6 weeks. They were instructed to practise the exercises daily for 25 minutes over a period of 3 months. Patients received a tutorial with photographs, a text explaining the exercises, and a diary to register the amount of exercising.

Both the intervention group and the control group received standardised information and advice from their GP or sport physician about patellofemoral pain syndrome and advice to refrain from all sports activities that provoke pain. Patients were recommended to use a simple analgesic when pain was severe. Instructions for daily isometric quadriceps contractions were given to both groups according to national guidelines.[1] All this information was in a leaflet given to patients in both groups to promote standardisation (see web extra).

Other interventions—like the use of bandages, braces, insoles, ice application, or medication other than simple analgesics—were allowed in both groups, and information about their use was collected using self report questionnaires. Patients in the control group were instructed not to visit a physical therapist during the first 3 months.

Outcome measurement

Follow-up self report questionnaires were filled in by patients at baseline, at 6 weeks, and at 3 months, 6 months, 9 months, and 12 months after inclusion in the study. Primary outcomes measured at 3 and 12 months' follow-up were: perceived recovery compared with at the start of the study, functional disability, measured using the Kujala Patellofemoral Scale[3]; and pain severity at rest and on activity, measured using a numerical rating scale.[4]

Patients were deemed to have recovered if they rated themselves as "fully recovered" or "strongly recovered", whereas those who rated themselves as "slightly recovered" to "worse than ever" were deemed not to have recovered. This threshold was used to dichotomise perceived recovery into two clear categories: "recovered" and "not recovered."

Statistical analysis

From our sample size calculation we needed a study population of 136 patients, allowing for a potential dropout of 10%.

Subgroup analysis was performed for predefined subgroups based on age and type of recruiting physician. Differences in dichotomous outcomes (between "recovered" patients and "not recovered" patients) were analysed using logistic regression techniques for repeated measurements. Differences in continuous outcomes (pain scores and functional scores) were analysed with linear regression techniques for repeated measurements.

The influence of exercise therapy on each outcome was tested using a model that included prognostic variables with a P value of 0.1 or less and baseline values for pain at rest, pain on activity, and function score. For statistically significant dichotomous outcomes, the number needed to treat is given. For continuous data, we report effect sizes. See bmj.com.

RESULTS

Between April 2005 and April 2007, 131 patients were enrolled in the study and randomly assigned to the intervention group or the control group.

The exercise therapy group (n=65) and control group (n=66) had similar baseline characteristics. Almost twice as many women as men were included in the whole sample. Bilateral knee symptoms were more common than unilateral symptoms,

Table 2 | Function and pain scores at 3 and 12 months' follow-up

	Exercise therapy(n=65)			Control(n=66)				
	Baseline (mean (SD))	3 months (mean (SD))	12 months (mean (SD))	Baseline (mean (SD))	3 months (mean (SD))	12 months (mean (SD))	Adjusted difference* (95% CI) at 3 months	Adjusted difference* (95% CI) at 12 months
Function score (0-100)	64.4 (13.9)	78.8 (15.5)	83.2 (14.8)	65.9 (15.2)	74.9 (17.6)	79.8 (17.5)	4.92 (0.14 to 9.72)	4.52 (−0.73 to 9.76)
Pain at rest (0-10)	4.14 (2.3)	2.30 (2.5)	1.43 (2.2)	4.03 (2.3)	3.22 (2.8)	2.61 (2.9)	−1.07 (−1.92 to −0.22)	−1.29 (−2.16 to −0.42)
Pain on activity (0-10)	6.32 (2.2)	3.81 (2.9)	2.57 (2.9)	5.97 (2.3)	4.60 (3.0)	3.54 (3.38)	−1.00 (−1.91 to −0.08)	−1.19 (−2.22 to −0.16)

Mean scores are reported for those patients available at that time point. Adjusted differences are reported for the total available in analysis.

*Function score was adjusted for baseline score, age, and duration of symptoms. Pain at rest was adjusted for baseline score and age. Pain on activity was adjusted for baseline score, age, and gender. Positive adjusted differences for the function score, and negative difference for pain scores, are in favour of the exercise group.

and the study population had a high level of sports participation.

Primary outcome measures

Tables 1 and 2 show the primary outcome measures.

Both the intervention and control groups had a lower pain score at 3 months' follow-up than at baseline. The adjusted analysis at 3 months showed a significant difference in pain at rest and pain on activity in favour of the exercise group. The function score was higher in the exercise than in the control group. Effect sizes for exercise therapy ranged from 0.47 (pain at rest) and 0.45 (pain on activity) to 0.34 (function).

There was no significant difference in self reported recovery, as defined by the outcome measurement "recovered," between the groups at 3 months. When we used the outcome measurement "improved" (that is, "fully recovered," "strongly recovered," or "slightly recovered"), we found that recovery at 3 months was significantly more likely in the exercise group than in the control group (81% improved *v* 53% improved; adjusted odds ratio 4.07, 95% CI 1.86 to 8.90; number needed to treat 3.6).

At the 12 month follow-up, further improvement on pain and function scores from baseline was noted for both groups. The adjusted differences in pain scores between the groups still showed a significant difference in favour of the exercise group. The effect sizes for exercise therapy on pain were 0.56 and 0.54, respectively.

Subgroup analysis

Among patients recruited by a GP, those in the exercise group had significantly higher and clinically relevant differences on the pain and functional outcome parameters compared with the control group at both 3 and 12 months' follow-up (effect size pain at rest 0.67 (P<0.01) at 3 months and 0.79 (P<0.01) at 12 months; effect size pain on activity 0.62 (P<0.01) and 0.65 (P=0.02); and effect size function 0.57 (P<0.01) and 0.55 (P<0.01)). Among patients recruited by a sport physician, however, those in the exercise group did not show better outcomes than those in the control group at either follow-up point. No significant differences were found between the treatment and intervention groups for recovery at 3 and 12 months.

The effect estimates for recovery, pain, and function at 3 and 12 months for patients aged 14-17 years and for those aged 18 years or older were similar to those in the whole cohort. There were no significant differences between the exercise therapy and control groups according to age, except for pain on activity at 3 months and pain at rest at 12 months in patients aged 18 years or older. See bmj.com.

Additional interventions

The use of oral NSAIDs and topical agents during the first 3 months in the control group was two to four times higher than in the intervention group (P=0.096 and P=0.051, respectively).

At analysis for the following 9 months, the self reported use of NSAIDs and topical agents was about three times higher in the control group than in the intervention group (P=0.059 and P=0.09, respectively), whereas the use of supportive aids (bandages/braces) was about two times higher in the control group (P=0.09).

DISCUSSION

In patients with patellofemoral pain syndrome, exercise therapy produces better results regarding pain and function at 3 months and at 12 months than usual care.

We did not find a significant difference between the exercise therapy group and the control group in self reported "recovery" (that is "fully recovered" or "strongly recovered") at either 3 months or 12 months. Recovery at 3 months was significantly more likely in the exercise group than in the control group when we used the outcome measurement "improved" (that is, "fully recovered," "strongly recovered," or "slightly recovered"). After 12 months, nearly all patients had improved and the difference between the groups was no longer significant.

We conclude that although exercise therapy is effective for improving pain and function, these benefits are not clearly reflected in patients' self reported recovery. Although perceived recovery is relevant as a clinical outcome, understanding what exactly comprises recovery from the patient's point of view is difficult.

Clinically relevant and statistically significant effects of exercise on pain and function were found in patients recruited by the GP. The confidence intervals

for this analysis were wide, so coincidental findings owing to the small numbers of patients recruited by sport physicians cannot be excluded. The use of additional interventions was higher in the control group, however, implying that differences in outcome measurements between the groups are more likely to be underestimated than overestimated.

Comparison with other studies

Early studies without a control group indicated that rehabilitation including exercise therapy could be beneficial for patients with patellofemoral pain syndrome.[5 6] Systematic reviews have reported that most studies are of poor methodological quality, lack randomisation, a control group, or clearly defined outcomes.[2 7] Six randomised studies, including our own study, have compared exercise therapy with non-exercise therapy. See bmj.com for details.

Strengths and limitations of study

Patients in the intervention group cannot be blinded for the exercise therapy. A blinded external observer could be used to provide objective and observational measures of functional outcomes. However, as no validated objective outcome measures for patellofemoral pain syndrome are available, the use of validated subjective outcome measures seems appropriate.

The attention of a physical therapist as well as the use of an exercise diary may have influenced the outcome in the intervention group. However, the attention from the physical therapist is an integral part of the supervised exercise therapy. The exercise diary may have caused a bias owing to awareness of being involved in a study.

Additional analysis of the data excluding the participants who violated the protocol during the first 3 months of follow-up showed greater differences in the outcome parameters on pain and function at 3 and 12 months. This change indicates that the effects of exercise therapy may indeed be even higher than those reported in our primary analysis.

Patients were recruited by GPs and sport physicians, which reflects common practice and therefore increased the clinical applicability of our results.

Contributors: See bmj.com

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Competing interests: None declared.

Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at m.vanmiddelkoop@erasmusmc.nl.

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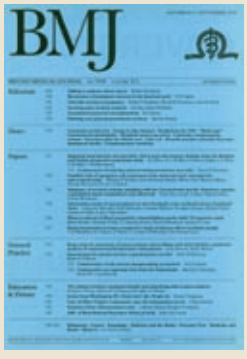
From our archive

Variant Creutzfeldt-Jakob disease: early warning (1988)



Press announcements released last year about an outbreak of a brain disease, spongiform encephalopathy, in the cattle of south west Britain were received with alarming indifference by the medical profession as well as by the general public. Fears that transmission of the disease to man might occur through the sale of animal products were immediately allayed by reassurances largely from the veterinary profession, but no contribution was made from the food industry, and the basis for this confidence was not adequately explained. It has generally been accepted that the slaughter of animals showing characteristic signs of infection—such as behaviour changes—as well as the usual processes of sterilisation and pasteurisation, are enough to remove any risk to the consumer. Unfortunately, this is a view that is naive, uninformed, and potentially disastrous…

In summary, we are faced with the fact that spongiform encephalopathy, whether or not we are at risk from it ourselves, is now established in the cattle of this country. This is a disease for which there is no serological marker, and the incubation period is probably long. There is no way of telling which cattle are infected until features develop, and if transmission has already occurred to man it might be years before affected individuals succumb. It is possible, but unproved, that many asymptomatic cattle are nevertheless as infective as those symptomatic animals which are immediately destroyed for public health reasons. So should not the use of brains in British foods be either abolished outright or more clearly defined? Then in the absence of more compelling evidence those of us who wish to exclude it from our diets at least have that choice.

Holt TA, Phillips J. Bovine spongiform encephalopathy. *BMJ* 1988;296:1581-2.

Eight years later came confirmation of the link between bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease in humans (*BMJ* 1996;312:795).

The entire archive of the *BMJ*, going back to 1840, is now available at www.bmj.com/archive.

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Acceptability of A/H1N1 vaccination during pandemic phase of influenza A/H1N1 in Hong Kong: population based cross sectional survey

Joseph T F Lau, Nelson C Y Yeung, K C Choi, Mabel Y M Cheng, H Y Tsui, Sian Griffiths

School of Public Health and Primary Care, Faculty of Medicine, Prince of Wales Hospital, Shatin, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China

Correspondence to: J T F Lau
jlau@cuhk.edu.hk

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STUDY QUESTION What is the intention of the Hong Kong general population to take up vaccination against influenza A/H1N1 under five hypothetical scenarios including personal cost and availability of clinical evidence on the vaccine?

SUMMARY ANSWER The prevalence of intention to take up vaccination against influenza A/H1N1 would be sensitive to personal cost and availability of data on efficacy and safety.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Over half of the healthcare workers surveyed in Hong Kong in May 2009, when pandemic level 5 was declared, were unwilling to take up vaccination against influenza A/H1N1. Uptake by the Hong Kong general population seems to be sensitive to personal cost and would be low in the absence of data on efficacy and safety.

Participants and setting

A random sample of 301 Chinese adults living in Hong Kong was anonymously interviewed by telephone using a structured questionnaire.

Design

The study used a cross sectional population based design.

PROPORTION OF PARTICIPANTS HIGHLY LIKELY TO TAKE UP VACCINATION AGAINST INFLUENZA A/H1N1 ACCORDING TO HYPOTHETICAL SCENARIO

Scenario	No (%) of participants (n=301)
Vaccination is free	135 (45)
Vaccination costs <$HK100	108 (36)
Vaccination costs $HK101-200	72 (24)
Vaccination costs >$HK200	45 (15)
No clinical evidence on vaccine efficacy and safety	14 (5)

Primary outcome(s)

Intention to take up vaccination against influenza A/H1N1.

Main results and the role of chance

Overall, 45% (n=135/311) of the participants thought it highly likely that they would take up free vaccination against influenza A/H1N1. The prevalence of intention (highly likely to take up vaccination) decreased with increasing cost: 36% (n=108) would take up vaccination if it cost less than $HK100 (£8; €9; $13), 24% (n=72) for $HK101-200, and 15% (n=45) for more than $HK200. In the absence of data on vaccine efficacy and safety this decreased further to 5% (n=14). The response rate was 80%.

Bias, confounding, and other reasons for caution

This study was cross sectional and cannot establish causality. We could only document the willingness of people to accept vaccination against A/H1N1, which may not reflect their actual behaviour. We did not record participants' chronic disease status; such participants may have a different prevalence of intention to take up vaccination against influenza A/H1N1.

Generalisability to other populations

Hong Kong went through a unique experience with the outbreak of severe acute respiratory syndrome. The results of the current study may not be applicable to the situations in other countries. Some similarities in terms of sensitivity to cost and scientific evidence may, however, be shared among countries.

Study funding/potential competing interests

This study was supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong Special Administrative Region, and the Li Ka Shing Institute of Health Sciences. We have no competing interests.

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Migraine and cardiovascular disease: systematic review and meta-analysis

Markus Schürks,[1 9] Pamela M Rist,[1 2] Marcelo E Bigal,[3 4] Julie E Buring,[1 2] Richard B Lipton,[3 5 6] Tobias Kurth[1 2 7 8]

EDITORIAL by Loder

[1]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue East, Boston, MA 02215-1204, USA
[2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
[3]Department of Neurology, Albert Einstein College of Medicine, NY, USA
[4]Merck Research Laboratories, Whitehouse Station, NJ, USA
[5]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, NY, USA
[6]Montefiore Headache Center, Bronx, NY, USA
[7]INSERM Unit 708—Neuroepidemiology, Paris, France
[8]Faculty of Medicine, University Pierre et Marie Curie, Paris, France
[9]Department of Neurology, University Hospital Essen, Germany

Correspondence to: M Schürks
mschuerks@rics.bwh.harvard.edu

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STUDY QUESTION What is the published evidence on the association between migraine, including migraine aura status, and ischaemic stroke, myocardial infarction, and death due to cardiovascular disease?

SUMMARY ANSWER Migraine almost doubles the risk of ischaemic stroke, a finding driven by the subgroup of people who have migraine with aura, but does not seem to change the risk of myocardial infarction or death due to cardiovascular disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Migraine has been consistently associated with increased risk of ischaemic stroke. Our meta-analysis indicates that this risk is apparent only among people who have migraine with aura, whereas any migraine does not alter the risk of myocardial infarction and death due to cardiovascular disease.

Selection criteria for studies

We searched PubMed, Embase, the Cochrane Library, and reference lists of studies published until January 2009 for case-control and cohort studies investigating the association of any migraine or specific migraine subtypes with cardiovascular disease including ischaemic stroke, myocardial infarction, and death due to cardiovascular disease. Identified studies were grouped according to a priori categories on migraine and cardiovascular events.

Primary outcome(s)

Ischaemic stroke, myocardial infarction, and death due to cardiovascular disease.

Main results and role of chance

We included 25 studies. These were heterogeneous for participant characteristics and definition of cardiovascular disease. The risk for ischaemic stroke was increased among people with migraine (nine studies; pooled relative risk 1.73, 95% confidence interval 1.31 to 2.29). Additional analyses indicated that the risk was doubled among people who had migraine with aura (2.16, 1.53 to 3.03), but not among people who had migraine without aura (1.23, 0.90 to 1.69; meta-regression for aura status P=0.02). Furthermore, women seemed to be at greater risk (2.08, 1.13 to 3.84) compared with men (1.37, 0.89 to 2.11). The risk was further increased by age less than 45 years, smoking, and oral contraceptive use. In contrast, the risk for myocardial infarction (eight studies; 1.12, 0.95 to 1.32) and death due to cardiovascular disease (five studies; 1.03, 0.79 to 1.34) was not increased among people with migraine. Too few studies are available to evaluate reliably the impact of modifying factors, such as migraine aura, on the associations with specific cardiovascular disease other than ischaemic stroke.

ASSOCIATION BETWEEN MIGRAINE AND CARDIOVASCULAR EVENTS AND HETEROGENEITY

Migraine type and cardiovascular disease event	No of studies	Relative risk (95% CI)*	I^2 (%)
Any migraine type and ischaemic stroke	9	1.73 (1.31 to 2.29)	65
Migraine with aura and ischaemic stroke	8	2.16 (1.53 to 3.03)	39
Migraine without aura and ischaemic stroke	8	1.23 (0.90 to 1.69)	39
Any migraine type and myocardial infarction†	8	1.12 (0.95 to 1.32)	59
Any migraine type and death due to cardiovascular disease	5	1.03 (0.79 to 1.34)	54

*From random effects model
†Four study cohorts from one paper

Bias, confounding, and other reasons for caution

Both migraine and cardiovascular disease, including ischaemic stroke, myocardial infarction, and death due to cardiovascular disease, are biologically heterogeneous, which may obscure a potential association. We tried to reduce this bias by grouping studies according to strict a priori criteria on migraine and cardiovascular disease subtypes. However, some of the studies provided results only for combined outcomes such as ischaemic stroke plus transient ischaemic attacks and coronary heart disease or used specific outcomes such as "angina leading to hospitalization." These studies could not be grouped with other studies into our prespecified categories. We still chose this approach to reflect more accurately the medical reality in clinical practice. Despite this, residual low to moderate heterogeneity remains among the studies in these categories. Furthermore, migraine was ascertained by different methods, including clinical diagnosis, self administered questionnaires, and health insurance databases. All these methods have, however, been shown to be valid. Finally, there was some indication of publication bias from Egger's test for the overall analysis between migraine and ischaemic stroke.

Study funding/potential competing interests

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The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial

B H Cuthbertson,[1] J Rattray,[2] M K Campbell,[3] M Gager,[4] S Roughton,[3 5] A Smith,[2] A Hull,[6] S Breeman,[3] J Norrie,[7] D Jenkinson,[3] R Hernández,[3 8] M Johnston,[9] E Wilson,[10] C Waldmann,[4] on behalf of the PRaCTICaL study group

EDITORIAL by Beraldo

[1]Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto
[2]School of Nursing and Midwifery, University of Dundee, Dundee
[3]Health Services Research Unit, University of Aberdeen, Aberdeen AB32
[4]Intensive Care Unit, Royal Berkshire and Battle Hospital, Reading
[5]Intensive Care Unit, Aberdeen Royal Infirmary, Aberdeen
[6]Department of Mental Health, Murray Royal Hospital, Perth
[7]Robertson Centre for Biostatistics, University of Glasgow, Glasgow
[8]Health Economics Research Unit, University of Aberdeen
[9]Health Psychology Unit, University of Aberdeen
[10]Department of Anaesthesia and Intensive Care Medicine, Ninewells Hospital and Medical School, Dundee

Correspondence to: B H Cuthbertson brian.cuthbertson@sunnybrook.ca

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STUDY QUESTION Do nurse led follow-up programmes improve patient rehabilitation after discharge from intensive care?

SUMMARY ANSWER No, such programmes showed no evidence of being effective or cost-effective in improving patients' quality of life in the year after discharge.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Follow-up programmes after discharge from intensive care, aimed at reduction in morbidity, are now widespread but evidence for their effectiveness is lacking. This study shows that nurse-led follow-up clinics after intensive care were neither effective nor cost-effective, and their place in practice should be reviewed.

Design
A pragmatic, non-blinded, multicentre, randomised controlled trial of nurse led follow-up programmes versus standard care of patients after discharge from intensive care. The follow-up programmes included a manual based physical rehabilitation programme, clinic review at three and nine months after discharge, and medical and psychiatric review as indicated during the first year after discharge.

Participants and setting
Adult patients were recruited at three UK hospitals after discharge from level 3 dependency (intensive care unit) care. The 286 who survived until hospital discharge were included in the study, with 192 completing the primary outcome.

Primary outcome
Health related quality of life at 12 months measured using the SF-36 questionnaire.

Main results and the role of chance
The primary outcome analysis shows no difference between the groups (see table). There were also no differences in any of the secondary outcome measures, including health related quality of life at six months, quality adjusted life years at 12 months, incidence and severity of other psychological morbidities at six and 12 months, and mortality in the 12 months after discharge. Sensitivity analysis suggests these results are robust. The follow-up programme was significantly more costly than standard care, with a mean cost of care of £7126 for the intervention compared with £4810 for standard care (difference £2316 (95% credible interval £269 to £4363)) and are unlikely to be considered cost effective.

Harms
There was no evidence of harm in this study.

Bias, confounding, and other reasons for caution
The study has a low risk of bias and high internal validity because of the rigorous randomised trial design using intention to treat analysis and an accompanying sensitivity analysis.

Generalisability to other populations
These results have reasonable generalisability to similar patient groups who require level 3 intensive care in other healthcare settings. However, our patients may have had a higher severity of illness than patients treated in intensive care units in other countries, and our results should be interpreted in light of these differences in case mix and timing.

Study funding/potential competing interests
The study was funded by the Chief Scientists Office for Scotland. There are no competing interests.

Trial registration number
ISRCTN 24294750

EFFECT OF INTERVENTION ON PATIENTS' HEALTH RELATED QUALITY OF LIFE (SF-36 SCORE)

	Intervention		Standard care			
SF-36 score at 12 months after discharge	No of patients	Mean (SD) score	No of patients	Mean (SD) score	Effect size (95% CI)	P value
Physical component score	90	42.0 (10.6)	97	40.8 (11.9)	1.1 (−1.9 to 4.2)	0.46
Mental component score	90	47.1 (12.7)	97	46.8 (12.4)	0.4 (−3.0 to 3.7)	0.83

Results analysed on the basis of intention to treat

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Risk of bias versus quality assessment of randomised controlled trials: cross sectional study

Lisa Hartling, Maria Ospina, Yuanyuan Liang, Donna M Dryden, Nicola Hooton, Jennifer Krebs Seida, Terry P Klassen

Alberta Research Centre for Health Evidence, Department of Pediatrics, University of Alberta, Aberhart Centre One, Edmonton, AB, Canada T6G 2J3

Correspondence to: L Hartling
hartling@ualberta.ca

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STUDY QUESTIONS What is the inter-rater reliability of a new tool introduced by the Cochrane Collaboration for assessing the internal validity of randomised trials and what is its concurrent validity compared with two other approaches to quality assessment: the Jadad scale and the Schulz approach to allocation concealment? Is there a relation between risk of bias and study effect estimates?

SUMMARY ANSWER The inter-rater agreement varied from slight to substantial across domains of the risk of bias tool, and the correlation between risk of bias assessments and the other two tools was low. The risk of bias tool may be more appropriate for assessing a trial's internal validity, but it requires more personal judgment and more time to use.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS In February 2008 the Cochrane Collaboration introduced the risk of bias tool to assess the internal validity of randomised controlled trials. Inter-rater agreement was fair and the time to complete the tool was significantly longer than other approaches. A significant difference in effect sizes was observed between studies with a high or unclear risk of bias and those with a low risk of bias.

Participants and setting
We studied a convenience sample of 163 randomised controlled trials in child health.

Design
The study design was cross sectional.

Primary outcome(s)
Our main outcome measures were inter-rater agreement, concurrent validity, and the relation between risk of bias and effect estimates.

Main results and the role of chance
Inter-rater agreement on individual domains of the risk of bias tool ranged from slight for selective reporting (κ=0.13) to substantial for sequence generation (κ=0.74). Inter-rater agreement for the other domains was moderate for allocation concealment (κ=0.50) and fair for blinding (κ=0.35), incomplete data (κ=0.32), "other sources of bias" (κ=0.31), and overall risk (κ=0.27). Discrepancies were largely driven by reliance on reporting compared with judgment on risk of bias. Hence domains that involved a greater degree of subjective judgment about potential risk of bias, such as blinding, tended to have poorer inter-rater agreement than domains that were more objective, such as sequence generation. The mean time to complete the risk of bias tool was significantly longer than for the Jadad scale and Schulz approach, individually or combined (8.8 minutes (SD 2.2) per study *v* 2.0 (SD 0.8), P<0.001). There was low correlation between risk of bias overall compared with the Jadad scores (τ=0.059, P=0.395) and Schulz approach (τ=0.138, P=0.064). The lack of correlation suggests that the different tools are measuring different constructs; hence the risk of bias tool may be more appropriate for assessing a trial's internal validity. Effect sizes differed between studies assessed as being at high or unclear risk of bias (0.52) compared with those at low risk (0.23). This provides some preliminary validation of the risk of bias tool's usefulness to identify studies that may exaggerate treatment effects.

Bias, confounding, and other reasons for caution
The differences in effect sizes were based on a small number of studies in the reference (low risk) category. The sample of trials was heterogeneous for outcomes, interventions, and diseases.

Generalisability to other populations
The sample included trials only in children and therefore results may not be generalisable to trials in other age groups.

Study funding/potential competing interests
This study received no funding. We have no competing interests.

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INTER-RATER AGREEMENT USING RISK OF BIAS TOOL

	Risk of bias assessments			
Domain	High	Unclear	Low	Weighted κ (95% CI)
Sequence generation	4	107	52	0.74 (0.64 to 0.85)
Allocation concealment	5	105	53	0.50 (0.36 to 0.63)
Blinding	16	49	98	0.35 (0.22 to 0.47)
Incomplete data	25	52	86	0.32 (0.19 to 0.45)
Selective reporting	16	19	128	0.13 (−0.05 to 0.31)
Other sources of bias	15	85	63	0.31 (0.17 to 0.44)
Overall risk of bias	61	96	6	0.27 (0.13 to 0.41)

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Mortality in renal transplant recipients given erythropoietins to increase haemoglobin concentration: cohort study

Georg Heinze,[1] Alexander Kainz,[2] Walter H Hörl,[2] Rainer Oberbauer[2 3 4]

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[1]Core Unit of Medical Statistics and Informatics, Medical University of Vienna, 1090 Vienna, Austria
[2]Department of Nephrology, Medical University of Vienna, 1090 Vienna, Austria
[3]Austrian Dialysis and Transplant Registry, 4010 Linz, Austria
[4]Department of Nephrology, KH Elisabethinen, 4010 Linz, Austria
Correspondence to: R Oberbauer, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria rainer.oberbauer@meduniwien.ac.at

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STUDY QUESTION What is the optimal range of haemoglobin concentrations achieved with treatment with erythropoietins that is not associated with increased mortality in renal transplant patients?

SUMMARY ANSWER Mortality increases in patients who are treated with erythropoietins and achieve haemoglobin concentrations above 125 g/l.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Recent data suggest that use of erythropoietins might increase mortality under some circumstances. In a cohort of renal transplant patients haemoglobin concentrations above 125 g/l achieved with treatment with erythropoietins are associated with a higher risk of mortality.

Participants and setting

We included 1794 patients in Austria who received their first renal allograft between 1992 and 2004 and survived at least three months.

Design, size, and duration

In this retrospective cohort observational study we followed up patients until death, re-transplantation, or the end of the study (December 2004). We had baseline data on characteristics of recipients and donors and follow-up data on comorbidities, medication, immunosuppressive regimen, and laboratory readings. Multivariable Cox regression was used to evaluate the association of haemoglobin concentration and treatment with erythropoietins with time to death, conditional on at least three months' survival. Restricted cubic splines were used to estimate non-linear associations. Analysis was adjusted for confounding variables, identified by a purposeful selection algorithm. Results are reported as absolute mortality rates and confounder adjusted hazard ratios and as survival at 10 years.

Main results and the role of chance

The median follow-up was 5.6 years. Of 1794 eligible patients, 805 received erythropoietins. In total 345 patients died, including 59 during the first 90 days after transplantation. The absolute mortality rates per 100 person years were 5.4 for those who received erythropoietins and 2.6 for those who did not. Seventy eight per cent of patients who did not receive erythropoietins survived 10 years compared with only 57% of those who did receive erythropoietins.

After adjustment for confounders, haemoglobin concentrations lower than 125 g/l were correlated with an increased risk of mortality. Whereas concentrations higher than 125 g/l lead to reduced mortality in patients who did not receive erythropoietins, we found an increased risk in those who did receive erythropoietins, with significance reached at 140 g/l. Mortality was similar in both groups of patients for similar haemoglobin concentrations up to about 147 g/l. With concentrations above 147 g/l patients who received erythropoietins had a significantly higher risk than patients who did not.

Bias, confounding, and other reasons for caution

Despite refined selection of confounders, we cannot completely rule out residual unmeasured confounding. Furthermore, we had no data on dose and type of erythropoietins, and thus we cannot speculate on the reasons of increased mortality. A potential dilution effect might have occurred by non-response among patients who received erythropoietins. As in all non-randomised trials, a causal relation cannot be confirmed.

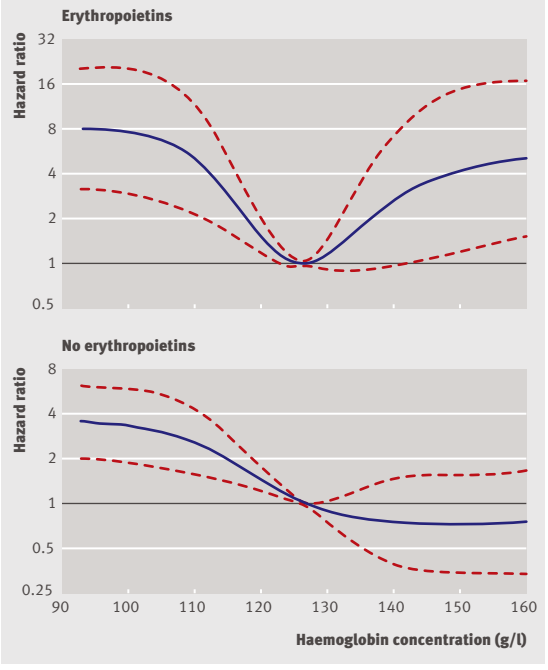
Generalisability to other populations

This study included Austrian patients who underwent kidney transplantation and is potentially generalisable to populations with similar demographic structure and health policies. Our results are in accordance with those of large randomised controlled trials in haemodialysis patients that showed no benefit from higher target haemoglobin concentrations.

Study funding/potential competing interests

This study was funded by the Austrian Science Fund (P-18325-B13 to RO) and Austrian Academy of Science.

MULTIVARIABLE COX REGRESSION FOR RISK OF DEATH



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