Open Access: free full text available online
For the full versions of these articles see bmj.com

RESEARCH

Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients

MRC CRASH Trial Collaborators

EDITORIAL by Menon and Harrison

London School of Hygiene and Tropical Medicine, London WC1B 3DP
Correspondence to: P A Perel
Pablo.perel@lshtm.ac.uk

BMJ 2008;336:425-9
doi:10.1136/bmj.39461.643438.25

ABSTRACT

Objective To develop and validate practical prognostic models for death at 14 days and for death or severe disability six months after traumatic brain injury.

Design Multivariable logistic regression to select variables that were independently associated with two patient outcomes. Two models designed: "basic" model (demographic and clinical variables only) and "CT" model (basic model plus results of computed tomography). The models were subsequently developed for high and low-middle income countries separately.

Setting Medical Research Council (MRC) CRASH Trial.

Subjects 10 008 patients with traumatic brain injury. Models externally validated in a cohort of 8509.

Results The basic model included four predictors: age, Glasgow coma scale, pupil reactivity, and the presence of major extracranial injury. The CT model also included the presence of petechial haemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, midline shift, and non-evacuated haematoma. In the derivation sample the models showed excellent discrimination (C statistic above 0.80). The models showed good calibration graphically. The Hosmer-Lemeshow test also indicated good calibration, except for the CT model in low-middle income countries. External validation for unfavourable outcome at six months in high income countries showed that basic and CT models had good discrimination (C statistic 0.77 for both models) but poorer calibration.

Conclusion Simple prognostic models can be used to obtain valid predictions of relevant outcomes in patients with traumatic brain injury.

INTRODUCTION

The use of computer based prediction of outcome in patients with traumatic brain injury increases the use of certain therapeutic interventions in those predicted to have a good outcome and reduces their use in those predicted to have a poor outcome.[1] Many prognostic models have been reported (statistical models that combine data from patients to predict outcome) but none are widely used. A recent systematic review offers possible explanations.[2]

The Medical Research Council (MRC) CRASH (corticosteroid randomisation after significant head injury) trial is the largest clinical trial conducted in patients with traumatic brain injury and presents a unique opportunity to develop a prognostic model.[3 4] The trial prospectively included patients within eight hours of the injury, used standardised definitions of variables, and achieved almost complete follow-up at six months. Furthermore, the large sample size guarantees precise and valid predictions. The high recruitment of patients from low and middle income countries means that models developed with these data are relevant to these settings.

We have developed and validated prognostic models for death at 14 days and death and disability at six months in patients with traumatic brain injury.

METHODS

Patients—The study cohort was all 10 008 patients enrolled in the trial. Adults with traumatic brain injury, who had a score on the Glasgow coma scale of 14 or less, and who were within eight hours of injury, were eligible for inclusion in the trial.

Outcomes—Death of a patient was recorded on an early outcome form that was completed at hospital discharge, death, or 14 days after randomisation (whichever occurred first). Unfavourable outcome (death or severe disability) at six months was defined with the Glasgow outcome scale. For the purpose of this analysis, we dichotomised outcomes into favourable (moderate disability or good recovery) and unfavourable (dead, vegetative state, or severe disability).

Prognostic variables—For the prognostic model we considered age, sex, cause of injury, time from injury to randomisation, Glasgow coma score at randomisation, pupil reactivity, results of computed tomography, whether the patient had sustained a major extracranial injury, and level of income in country (high or low-middle income countries, as defined by the World Bank) (see bmj.com). We adjusted analyses for treatment within the trial as this was related to outcome, and we did not find interaction between treatment and the potential predictors.[3 4]

This article is an abridged version of a paper that was published on bmj.com on 12 February 2008. Cite this version as : *BMJ* 12 February 2008,doi:10.1136/bmj.39461.643438.25

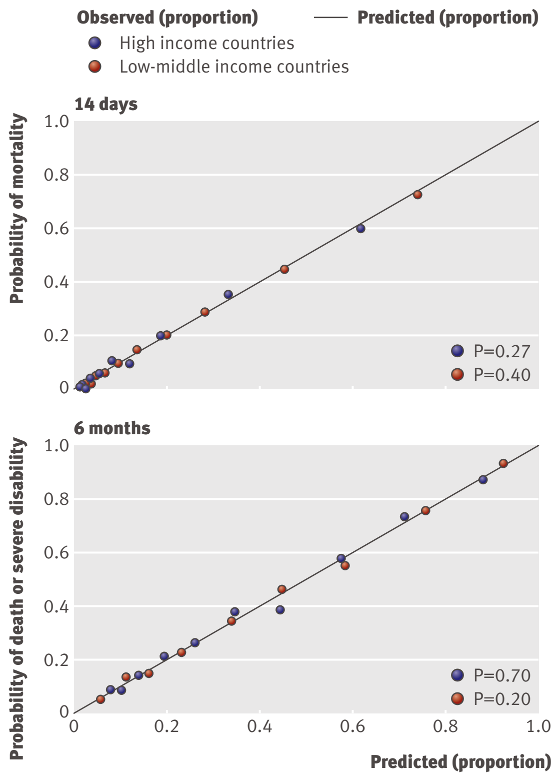

Fig 1 | Calibration of basic models using expected and observed probabilities of mortality at 14 days (top) and death or severe disability at six months (bottom) in patient with traumatic brain injury according to income level of country

Analysis—We included all variables collected in the CRASH trial in a first multivariable logistic regression analysis. We excluded variables that were not significant at 5% level. We quantified each variable's predictive contribution by its z score (the model coefficient divided by its standard error). We explored linearity between age and mortality at 14 days and Glasgow coma score and mortality at 14 days. Interactions between country income level and all the other predictors were evaluated with a likelihood ratio test.

Prognostic models—We developed different models for each of the two outcomes: a basic model, which included only clinical and demographic variables, and a CT model, which also included results of computed tomography.

Performance of the model—We assessed performance of the models in terms of calibration and discrimination. Calibration was assessed graphically and with the Hosmer-Lemeshow test. Discrimination was assessed with the C statistic (an equivalent concept to area under the receiver operator characteristic curve).

Internal validation—The internal validity of the final model was assessed by the bootstrap re-sampling technique. This showed no overoptimism in any of the final model's predictive C statistics.

External validation—We externally validated the models in an external cohort of 8509 patients with moderate and severe traumatic brain injury from 11 studies conducted in high income countries (the IMPACT (international mission for prognosis and clinical trial) dataset).[5]

Score development—We developed a clinical score based on regression coefficients. A web based version of the model was developed to be accessible to clinicians internationally.

RESULTS

General characteristics

More of the patients were men (81%) and more came from low-middle income countries (75%). More than half (58%) of participants were included within three hours of injury. Road traffic crashes were the most common cause of injury (65%) and 79% of the participants underwent computed tomography. A total of 1948 patients (19%) died in the first two weeks, 2323 patients (24%) were dead at six months, and 3556 patients (37%) were dead or severely dependent at six months. See bmj.com.

The relation between age and the log odds of death within 14 days showed no association until the age of 40 and a linear increase afterwards. The relation between Glasgow coma score and mortality at 14 days was reasonably linear and we therefore included the coma score as a continuous variable. The relation with unfavourable outcome at six months showed similar patterns.

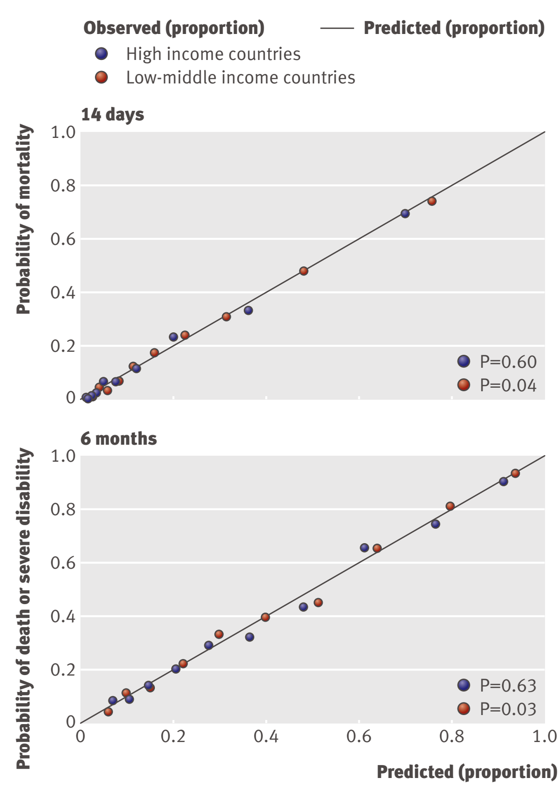

Fig 2 | Calibration of computed tomography models using expected and observed probabilities of mortality at 14 days (top) and death or severe disability at six months (bottom) in patient with traumatic brain injury according to income level of country

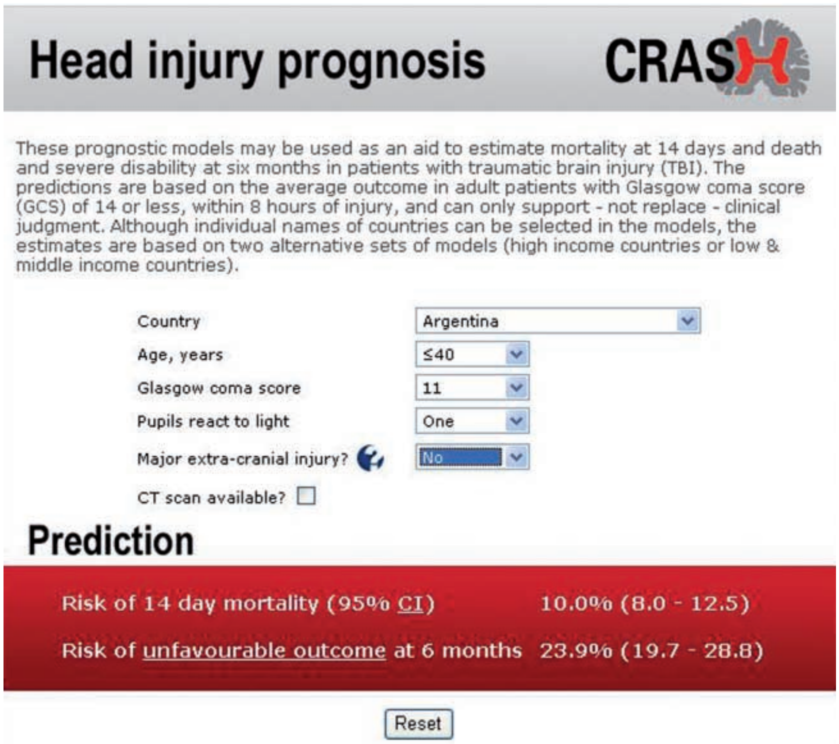

Fig 3 | Screenshot of web based calculator available at www.crash2.lshtm.ac.uk/. If CT scan available box is ticked, calculator displays additional CT variables

Low-middle *v* high income countries

In comparison with patients from high income countries, those from low-middle income countries were younger, more likely to be male, were recruited later, had less severe traumatic brain injury (as defined by Glasgow coma score and pupil reactivity), and more often had abnormal results on computed tomography. Road traffic crashes were a more common cause of traumatic brain injury. Although patients from low-middle income countries experienced higher mortality at 14 days (odds ratio 1.94, 95% confidence interval 1.64 to 2.30), there was no significant difference in unfavourable outcome at six months.

There were significant interactions between the country's income level and several predictors and so we developed two models, one for low-middle income countries and another for high income countries. Older age was a stronger predictor of 14 day mortality in high income countries (interaction $P<0.001$), and lower Glasgow coma score was a stronger predictor in low-middle income countries (interaction $P=0.003$). Obliteration of the third ventricle and a non-evacuated haematoma were both associated with a higher risk in high income countries (interaction $P<0.001$ and $P=0.03$, respectively).

Multivariable predictive models

We developed eight models altogether: basic and CT models for predicting two outcomes in two settings (low-middle and high income countries).

Basic models—Glasgow coma score was the strongest predictor of outcome in low-middle income countries and age was the strongest predictor in high income countries, while the absence of pupil reactivity was the third strongest predictor in both regions.

CT models—Obliteration of the third ventricle and midline shift were the strongest predictors of mortality at 14 days, and non-evacuated haematoma was the strongest predictor of unfavourable outcome at six months.

Performance of models—All models showed excellent discrimination, with C statistics over 0.80. Calibration in all models was adequate and six out of the eight models had good calibration when evaluated with the Hosmer-Lemeshow test (figs 1 and 2).

Clinical score—Individual scores and their respective probability of outcome can be obtained from our web based calculator (www.crash2.lshtm.ac.uk/) (fig 3). A good agreement is evident between observed and predicted outcome by the web calculator (figs 1 and 2).

External validation—Because an external cohort of patients from low-middle income countries was not available we validated the models in patients from high income countries only for unfavourable outcome at six months using the IMPACT dataset. The calibration was excellent for the CT model but poorer for the basic model (figs 4 and 5).

DISCUSSION

We have developed web based prognostic models for predicting two clinically relevant outcomes in patients with traumatic brain injury using variables available at the bedside. The models have excellent discrimination and good fit with both internal and external validation. We have reported on differences in outcomes and on the

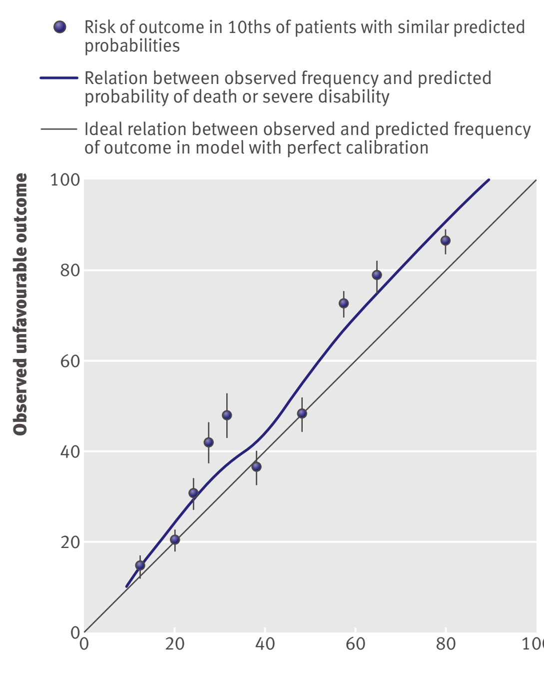

Fig 4 | External validation of basic model for death or severe disability at six months in IMPACT database

strength of predictors of outcomes, according to whether patients are from high or low-middle income countries.

Older age, low Glasgow coma score, absent pupil reactivity, and the presence of major extracranial injury predict poor prognosis. All have been previously identified as prognostic factors for poor outcome in traumatic brain injury. The presence of "obliteration of third ventricle or basal cisterns" on computed tomography was associated with the worst prognosis at 14 days. This is supported by recent findings that absence of basal cisterns is the strongest predictor of six month mortality.[6] We also found—as previously reported—the independent prognostic value of traumatic subarachnoid haemorrhage.[7]

Patients from low-middle income countries had worse early prognosis than those from high income countries, although regional differences in outcome after traumatic brain injury have been reported the difference in mortality between low-middle and high income countries has not.[8]

A low Glasgow coma score had an even worse prognosis in patients from low-middle income countries compared with patients from high income countries. This might relate to quality of care or low Glasgow coma score in high income countries being associated with greater use of sedation, rather than severity of traumatic brain injury. Increasing age had a worse prognosis in high income countries compared with low-middle income countries. This is because of even lower risks at younger ages in high income countries, while both have similar risks at older ages. Regarding computed tomography, some abnormal findings were stronger predictors in high income countries. This could be because of better technology and more accurate diagnosis.

A systematic review identified over 100 prognostic models for patients with traumatic brain injury. As with our models, two of the more methodologically robust models showed similarly good discrimination but worse calibration.[9 10] They too included Glasgow coma score, age, pupil reactivity, and results of computed tomography as predictors, but, unlike our models, they did not include the presence of major extracranial injury, and none included patients from low-middle income countries.

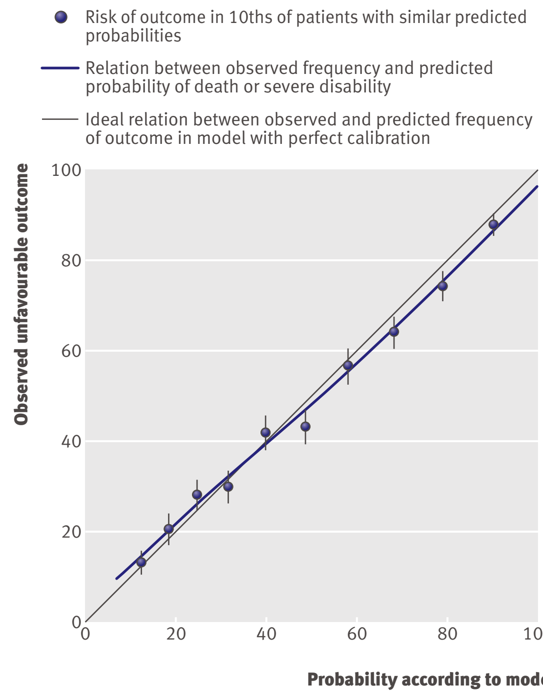

Fig 5 | External validation of CT model for death or severe disability at six months in IMPACT database

Strengths and weakness of the study

We used a well described cohort of patients, with prospective and standardised collection of data on prognostic factors, low loss to follow-up, used a validated outcome measure at a fixed time after the injury, and with a large sample size in relation to the number of prognostic variables. The external validation confirmed the discriminatory ability of the models in patients from high income countries and showed good calibration for the computed tomography model. We also included the complete spectrum of patients with traumatic brain injury, ranging from mild to severe. Finally, the data required to make predictions are easily available.

There are some limitations. The data from which the models were developed come from a clinical trial and this could therefore limit external validity. Also for the validation we were forced to exclude the variables major extracranial injury and petechial haemorrhages because they were not available in the IMPACT sample. The external validation showed good discriminatory ability, but this was somewhat lower than in the original data. This may be explained by a more homogeneous selected case mix in these other trials, which included only patients with moderate and severe Glasgow coma score.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Traumatic brain injury is a leading cause of death and disability worldwide with most cases occurring in low-middle income countries

Prognostic models may improve predictions of outcome and help in clinical research

Many prognostic models have been published but methodological quality is generally poor, sample sizes small, and only a few models have included patients from low-middle income countries

WHAT THIS STUDY ADDS

In a basic model prognostic indicators included age, Glasgow coma scale, pupil reactivity, and the presence of major extracranial injury

In a CT model additional indicators were the presence of petechial haemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid bleeding, mid-line shift, and non-evacuated haematoma

The strength of predictors of outcomes varies according to whether patients are from high or low-middle income countries

These prognostic models, that include simple variables, are available on the internet (www.crash2.lshtm.ac.uk/)

Implications of the study

It may be inappropriate to extrapolate from models for high income countries to poorer settings. We have developed a methodologically valid, simple, and accurate model that may help decisions about health care for individual patients. These prognostic models can also help in the design and analysis of clinical trials, and in clinical audit by allowing adjustment for case mix.

The writing committee comprised: Pablo Perel (Chair), Miguel Arango, Tim Clayton, Phil Edwards, Edward Komolafe, Stuart Pocock, Ian Roberts, Haleema Shakur, Ewout Steyerberg, and Surakrant Yutthakasemsunt. Details of theCRASH trial collaborators are on bmj.com.
Contributors: See bmj.com.
Funding: The MRC CRASH trial was funded by the UK Medical Research Council.
Competing interests: None declared.
Ethical approval: All MRC CRASH collaborators obtained local ethics or research committee approval.
Provenance and peer review: Not commissioned; externally peer reviewed.

1 Murray LS, Teasdale GM, Murray GD, Jennett B, Miller JD, Pickard JD, et al. Does prediction of outcome alter patient management? *Lancet* 1993;341:1487-91.
2 Perel P, Edwards P, Wentz R, Roberts I. Systematic review of prognostic models in traumatic brain injury. *BMC Med Inform Decis Mak* 2006;6:38.
3 CRASH Trial Collaborators. Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;364:1321-8.
4 CRASH Trial Collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet* 2005;365:1957-9.
5 Maas AI, Marmarou A, Murray GD, Teasdale SG, Steyerberg EW. Prognosis and clinical trial design in traumatic brain injury: the IMPACT study. *J Neurotrauma* 2007;24:232-8.
6 Maas AI, Hukkelhoven CW, Marshall LF, Steyerberg EW. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery* 2005;57:1173-82.
7 Wardlaw JM, Easton VJ, Statham P. Which CT features help predict outcome after head injury? *J Neurol Neurosurg Psychiatry* 2002;72:188-92.
8 Hukkelhoven CW, Steyerberg EW, Farace E, Habbema JD, Marshall LF, Maas AI. Regional differences in patient characteristics, case management, and outcomes in traumatic brain injury: experience from the tirilazad trials. *J Neurosurg* 2002;97:549-57.
9 Signorini DF, Andrews PJD, Jones PA, Wardlaw JM, Miller JD. Predicting survival using simple clinical variables: a case study in traumatic brain injury. *J Neurol Neurosurg Psychiatry* 1999;66:20-5.
10 Hukkelhoven CW, Steyerberg EW, Habbema JD, Farace E, Marmarou A, Murray GD, et al. Predicting outcome after traumatic brain injury: development and validation of a prognostic score based on admission characteristics. *J Neurotrauma* 2005;22:1025-39.

Accepted: 5 December 2007

Effect of training and lifting equipment for preventing back pain in lifting and handling: systematic review

Kari-Pekka Martimo,[1] Jos Verbeek,[2] Jaro Karppinen,[3] Andrea D Furlan,[4] Esa-Pekka Takala,[1] P Paul F M Kuijer,[5] Merja Jauhiainen,[6] Eira Viikari-Juntura[1]

EDITORIAL by Wedderkopp and Leboeuf-Yde

[1]Musculoskeletal Disorders Group, Centre of Expertise for Health and Work Ability, Finnish Institute of Occupational Health, Helsinki, Finland
[2]Knowledge Transfer in Occupational Health and Safety Group, Centre of Expertise for Good Practices and Competence, Finnish Institute of Occupational Health, Kuopio, Finland
[3]Musculoskeletal Disorders Group, Centre of Expertise for Health and Work Ability, Finnish Institute of Occupational Health, Oulu, Finland
[4]Institute for Work and Health, Toronto, Canada
[5]Coronel Institute of Occupational Health, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
[6]Knowledge Transfer in Occupational Health and Safety Group, Centre of Expertise for Good Practices and Competence, Finnish Institute of Occupational Health, Helsinki, Finland

ABSTRACT

Objectives To determine whether advice and training on working techniques and lifting equipment prevent back pain in jobs that involve heavy lifting.

Data sources Medline, Embase, CENTRAL, Cochrane Back Group's specialised register, CINAHL, Nioshtic, CISdoc, Science Citation Index, and PsychLIT were searched up to September-November 2005.

Review methods The primary search focused on randomised controlled trials and the secondary search on cohort studies with a concurrent control group. Interventions aimed to modify techniques for lifting and handling heavy objects or patients and including measurements for back pain, consequent disability, or sick leave as the main outcome were considered for the review. Two authors independently assessed eligibility of the studies and methodological quality of those included. For data synthesis, we summarised the results of studies comparing similar interventions. We used odds ratios and effect sizes to combine the results in a meta-analysis. Finally, we compared the conclusions of the primary and secondary analyses.

Results Six randomised trials and five cohort studies met the inclusion criteria. Two randomised trials and all cohort studies were labelled as high quality. Eight studies looked at lifting and moving patients, and three studies were conducted among baggage handlers or postal workers. Those in control groups received no intervention or minimal training, physical exercise, or use of back belts. None of the comparisons in randomised trials (17 720 participants) yielded significant differences. In the secondary analysis, none of the cohort studies (772 participants) had significant results, which supports the results of the randomised trials.

Conclusions There is no evidence to support use of advice or training in working techniques with or without lifting equipment for preventing back pain or consequent disability. The findings challenge current widespread practice of advising workers on correct lifting technique.

INTRODUCTION

Heavy lifting at work increases the risk of back pain.[1] Optimal working techniques are encouraged to prevent back pain and injuries when lifting heavy loads or patients cannot be avoided.[2 3] In addition, lifting equipment has been developed to relieve some of the workload. Back pain is highly prevalent. The resulting disability has enormous consequences in terms of distress and economic costs of absence from work and reduced productivity.[4] Employers must ensure that workers receive proper training on how to handle loads correctly.[5] Specific techniques have been advocated to reduce the load on the back.[6 7]