

# Hypothermia for traumatic head injury (Review)

Sydenham E, Roberts I, Alderson P



**THE COCHRANE  
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 4

<http://www.thecochranelibrary.com>



## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	3
METHODS . . . . .	3
RESULTS . . . . .	4
Figure 1. . . . .	5
Figure 2. . . . .	6
DISCUSSION . . . . .	8
AUTHORS' CONCLUSIONS . . . . .	8
ACKNOWLEDGEMENTS . . . . .	8
REFERENCES . . . . .	9
CHARACTERISTICS OF STUDIES . . . . .	13
DATA AND ANALYSES . . . . .	31
Analysis 1.1. Comparison 1 Immediate hypothermia versus normothermia, Outcome 1 Death at final follow-up. . . . .	32
Analysis 1.2. Comparison 1 Immediate hypothermia versus normothermia, Outcome 2 Death at final follow-up stratified by trial quality. . . . .	33
Analysis 1.3. Comparison 1 Immediate hypothermia versus normothermia, Outcome 3 Unfavourable outcome at final follow-up. . . . .	34
Analysis 1.4. Comparison 1 Immediate hypothermia versus normothermia, Outcome 4 Unfavourable outcome stratified by trial quality. . . . .	36
Analysis 1.5. Comparison 1 Immediate hypothermia versus normothermia, Outcome 5 Unfavourable outcome stratified by treatment duration. . . . .	37
Analysis 1.6. Comparison 1 Immediate hypothermia versus normothermia, Outcome 6 Unfavourable outcome at various times during follow-up. . . . .	38
Analysis 1.7. Comparison 1 Immediate hypothermia versus normothermia, Outcome 7 Pneumonia during the treatment period. . . . .	40
APPENDICES . . . . .	40
WHAT'S NEW . . . . .	45
HISTORY . . . . .	46
CONTRIBUTIONS OF AUTHORS . . . . .	48
DECLARATIONS OF INTEREST . . . . .	48
SOURCES OF SUPPORT . . . . .	48
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . . .	48
INDEX TERMS . . . . .	49

[Intervention Review]

# Hypothermia for traumatic head injury

Emma Sydenham<sup>1</sup>, Ian Roberts<sup>1</sup>, Phil Alderson<sup>2</sup>

<sup>1</sup>Cochrane Injuries Group, London School of Hygiene & Tropical Medicine, London, UK. <sup>2</sup>National Institute for Health and Clinical Excellence, Manchester, UK

Contact address: Emma Sydenham, Cochrane Injuries Group, London School of Hygiene & Tropical Medicine, Room 280, Keppel Street, London, WC1E 7HT, UK. [emma.sydenham@Lshtm.ac.uk](mailto:emma.sydenham@Lshtm.ac.uk).

**Editorial group:** Cochrane Injuries Group.

**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 4, 2009.

**Review content assessed as up-to-date:** 6 April 2009.

**Citation:** Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD001048. DOI: 10.1002/14651858.CD001048.pub4.

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Background

Hypothermia has been used in the treatment of head injury for many years. Encouraging results from small trials and laboratory studies led to renewed interest in the area and some larger trials.

### Objectives

To estimate the effect of mild hypothermia for traumatic head injury on mortality and long-term functional outcome complications.

### Search strategy

We searched the Cochrane Injuries Group Specialised Register, Current Controlled Trials *MetaRegister* of trials, Zetoc, ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) and Conference Proceedings Citation Index-Science (CPCI-S), CENTRAL (*The Cochrane Library*), MEDLINE and EMBASE. We handsearched conference proceedings and checked reference lists of all relevant articles. The search was last updated in April 2009.

### Selection criteria

Randomised controlled trials of hypothermia to a maximum of 35°C for at least 12 consecutive hours versus control in patients with any closed traumatic head injury requiring hospitalisation. Two authors independently assessed all trials.

### Data collection and analysis

Data on death, Glasgow Outcome Scale and pneumonia were sought and extracted, either from published material or by contacting the investigators. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each trial on an intention-to-treat basis.

### Main results

We found 23 trials with a total of 1614 randomised patients. Twenty-one trials involving 1587 patients reported data on deaths. There were fewer deaths in patients treated with hypothermia than in the control group (OR 0.85, 95% CI 0.68 to 1.06). Nine trials with good allocation concealment showed no decrease in the likelihood of death with hypothermia compared with the control group (OR 1.11, 95% CI 0.82 to 1.51). In both cases the result was not statistically significant. Twenty-one trials involving 1587 patients reported data on unfavourable outcomes (death, vegetative state or severe disability). Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.77, 95% CI 0.62 to 0.94). Nine trials with good allocation concealment showed patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group, but the

---

**Hypothermia for traumatic head injury (Review)**

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

reduction was small and non-significant (OR 0.93, 95% CI 0.70 to 1.23). Hypothermia treatment was associated with a slight increase in the odds of pneumonia (OR 1.35, 95% CI 0.95 to 1.91) but there was a reduction in pneumonia for trials with good allocation concealment (four trials analysed separately, 306 patients, OR 0.84, 95% CI 0.52 to 1.35) although in both cases the results are not statistically significant.

### Authors' conclusions

There is no evidence that hypothermia is beneficial in the treatment of head injury. Hypothermia may be effective in reducing death and unfavourable outcomes for traumatic head injured patients, but significant benefit was only found in low quality trials. Low quality trials have a tendency to overestimate the treatment effect. The high quality trials found no decrease in the likelihood of death with hypothermia, but this finding was not statistically significant and could be due to the play of chance. Hypothermia should not be used except in the context of a high quality randomised controlled trial with good allocation concealment.

## PLAIN LANGUAGE SUMMARY

### Hypothermia (body temperature cooling) for traumatic head injury

This review includes twenty-three randomised controlled trials involving 1614 patients with traumatic head injury. In each trial, the patients were randomly divided into two groups: one group remained at normal body temperature, and the other group was cooled to a maximum of 35 degrees Celsius (or 95 degrees Fahrenheit) for at least 12 consecutive hours. Cooling could be of the whole body (e.g. with a blanket with circulating cold water), or just the head (e.g. with a helmet with circulating cold water). Information on death, disability, and pneumonia were evaluated for each trial.

The review authors found that fewer people died or became severely disabled if they were treated with hypothermia, but this finding may be due to chance. It was also found that patients given hypothermia were more likely to develop pneumonia, and some patients died from pneumonia, but the increased risk of pneumonia could also be due to chance.

Some of the trials included in the review were of low methodological quality. Low quality trials have a tendency to overestimate the effect of a treatment. In this review, the lower quality trials showed hypothermia treatment to be somewhat effective in reducing death and disability among patients with head injury. However, the good quality trials showed no decrease in the likelihood of death with hypothermia treatment and a reduced likelihood of pneumonia. Some of the findings in this review are therefore contradictory, and this is probably due to the inclusion of data from low quality trials.

The review authors conclude that there is no evidence that hypothermia is beneficial in the treatment of head injury. Most of the positive and negative effects found may be due to chance. Hypothermia should not be used except in the context of a randomised controlled trial with good allocation concealment.

## BACKGROUND

Traumatic head injury is a major cause of death and disability amongst a predominantly young population. An estimated ten million people worldwide experience severe head injury every year (Langlois 2006). There is, however, a significant lack of evidence about effective therapies in the acute care of head injured patients, especially children (Adelson 2003). A long-term effort to review the literature and produce management guidelines by the American Association of Neurological Surgeons (Bullock 1996; Kirkpatrick 1997, Bullock 2007) could only make four definitive statements about treatment effectiveness that were supported by strong evidence from randomised studies. These recommendations included guidance on the management of blood pressure

and oxygenation, intracranial pressure, hyperventilation, and nutrition of head injured patients.

Mild to moderate hypothermia has been used in the treatment of head injury for over 50 years (Fay 1945). Although there were several promising experimental studies (Laskowski 1960; Clasen 1968) and case series (Sedzimir 1959; Shapiro 1974), no controlled clinical studies were performed and the therapy fell from favour. During the 1990s several investigators reported encouraging results of Phase II and III randomised clinical trials (Clifton 1995; Marion 1997; Shiozaki 1993), corroborated by consistent findings of high levels of cerebral protection associated with systemic cooling in well validated laboratory models of global is-

chaemia (Busto 1987). The early trials were small, single-centre investigations, which were sufficiently promising to lead to larger, multi-centre trials.

Originally it was thought that the primary mechanism of action of temperature control therapy was a reduction in cerebral metabolic rate (Bering 1961). There is now evidence that mild hypothermia might also influence the excessive post-traumatic release of excitatory neurotransmitters (Busto 1989), and attenuate the opening of the blood-brain barrier (Smith 1996). The main risks associated with induced systemic hypothermia are an increased risk of sepsis and pneumonia, coagulation abnormalities, and possible myocardial ischaemia and atrial fibrillation (Schubert 1995).

## OBJECTIVES

To determine whether the use of mild hypothermia in the treatment of traumatic head injury:

- reduces the risk of death (either during the treatment period or at the end of follow-up);
- reduces the proportion of patients who at final follow-up are either dead, in a vegetative state, or severely disabled;
- increases the risk of pneumonia.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We searched for all randomised controlled trials of mild hypothermia versus control.

#### Types of participants

Patients with any closed traumatic head injury requiring hospitalisation.

#### Types of interventions

Therapeutic cooling, either locally or systemically, by means of a fluid-filled cooling blanket, a 'bear-hugger' air-cooling device, ice water lavage, any combination of the above, or other methods, to a target temperature of at most 35°C for a period of at least 12 consecutive hours. Cooling could have begun immediately upon

admission to the intensive therapy unit or be deferred until intracranial pressure (ICP) became uncontrollable by conventional management.

## Types of outcome measures

### Primary outcomes

- All-cause mortality at the end of the follow-up period.
- Unfavourable outcome at the end of the follow-up period.

Unfavourable outcome was defined as a Glasgow Outcome Scale score of 'severe disability', 'persistent vegetative state', or 'death'; or an equivalent measure if a Glasgow Outcome Score was not presented.

### Secondary outcomes

- The frequency of pneumonia.

## Search methods for identification of studies

The searches were not restricted by language, date or publication status.

### Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group Specialised Register (12 Jan 2009);
- CENTRAL (*The Cochrane Library* Issue 1, 2009);
- MEDLINE (1950 to March 2009);
- PubMed (searched 6 April 2009);
- EMBASE (1980 to week 14, March 2009);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to April 2009 and Conference Proceedings Citation Index-Science (CPCI-S) 1990 to 7 April 2009;
  - Controlled Trials metaRegister of trials (mRCT) <http://www.controlled-trials.com/mrct/> (12 January 2009);
  - Zetoc (12 January 2009).

The latest search strategies are listed in [Appendix 1](#). The original search strategy from the first version of the review is in [Appendix 2](#).

### Searching other resources

In addition, we checked the reference lists of all relevant trials and review articles, and contacted leading investigators in the field for information about any other published, unpublished or ongoing trials.

## Data collection and analysis

### Selection of studies

Two authors screened the search results (ES and IR). We then retrieved the full text of relevant records. We independently compared the trial design with the inclusion criteria for this review. Disagreements were resolved by discussion.

### Data extraction and management

We extracted the following information from each trial: method of allocation concealment, blinding of outcome assessment, number of randomised patients, death or severe disability at various times during follow up, treatment duration, duration of follow up, loss to follow up, and number of patients with pneumonia during the treatment period. This information was entered into [Review Manager \(RevMan\)](#) by ES; IR checked for accuracy. We contacted trial report authors for additional information or clarification. There were a number of trials where it was not possible to determine the method of randomisation or allocation concealment from the trial report. We sought to contact the trial report authors, but were unable to reach them in some cases. These trials have been excluded from the review, and can be identified in the [Characteristics of excluded studies](#) table.

### Assessment of risk of bias in included studies

We assessed the quality of allocation concealment on the following scale ([Higgins 2008](#)):

- Yes: low risk of bias (e.g. sequentially numbered, sealed, opaque envelopes)
- No: high risk of bias (e.g. day of the week)
- Unclear: unclear or unknown risk of bias (method not stated).

### Data synthesis

We calculated Mantel-Haenzel odds ratios (ORs) and 95% confidence intervals (CIs) for death, unfavourable outcomes and pneumonia for each trial on an intention-to-treat basis. The odds ratio was chosen because of the large variation in baseline event rates between the trials (mortality in the control groups ranges from 0% to 82%), implying that the risk ratio would not be a good summary measure. Also, the Mantel-Haenzel approach was used because of the inaccuracy of Peto's approximation when the estimated treatment effect is large, as it was in several of the trials considered. Heterogeneity of treatment effect between trials was assessed using a standard  $\text{Chi}^2$  test,  $I^2$ , and if appropriate, we calculated a weighted estimate of the typical treatment effect across all studies.

## Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses to determine whether the treatment effect varies with: a) trial quality (quality of allocation concealment), b) duration of hypothermia, and c) length of follow-up.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

### Results of the search

We identified a total of 23 randomised controlled trials that met the inclusion criteria.

### Included studies

The 23 included randomised controlled trials involved 1614 randomised patients. All trials except two ([Ishikura 1998](#), [Meissner 2003a](#)) reported the number of deaths in the intervention and control groups at final follow-up. Fifteen trials reported Glasgow Outcome Scale (GOS) scores specifically at three, six or 12 months post-injury. Eleven trials reported the occurrence of pneumonia.

### Risk of bias in included studies

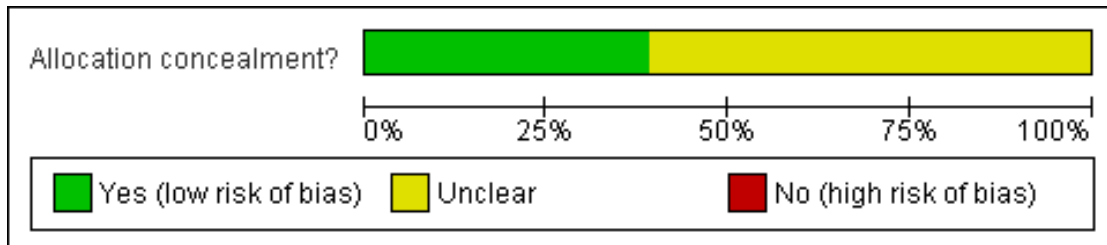
#### Allocation

Adequate allocation concealment is an important dimension of trial quality.

Nine trials had a reasonable standard of allocation concealment ([Adelson 2005 HYPO1](#); [Adelson 2005 HYPO2](#); [Clifton 1992](#); [Clifton 1993](#); [Clifton 2001](#); [Harris 2009](#); [Hutchison 2008](#); [Marion 1997](#); [Qiu 2007](#)). Twelve trials had unclear allocation concealment (e.g. 'by lot') ([Aibiki 2000](#); [Biswas 2002](#); [Hashiguchi 2003](#); [Hirayama 1994](#); [Jiang 2000](#); [Meissner 2003b](#); [Shiozaki 1993](#); [Shiozaki 1999](#); [Shiozaki 2001](#); [Smrcka 2005](#); [Yan 2001](#); [Zhang 2000](#)). Two trials did not present mortality or GOS scores in the treatment and control groups ([Ishikura 1998](#); [Meissner 2003a](#)) and had unclear allocation concealment.

[Figure 1](#) and [Figure 2](#) show the proportion of trials that were judged by the review authors to have had adequate allocation concealment.

**Figure 1. Methodological quality graph: review authors' judgements on whether there was allocation concealment, presented as percentages across all included studies.**



**Figure 2. Methodological quality summary: review authors' judgements on whether there was allocation concealment for each included study.**

	Allocation concealment?
Adelson 2005 HYPO1	+
Adelson 2005 HYPO2	+
Aibiki 2000	?
Biswas 2002	?
Clifton 1992	+
Clifton 1993	+
Clifton 2001	+
Harris 2009	+
Hashiguchi 2003	?
Hirayama 1994	?
Hutchison 2008	+
Ishikura 1998	?
Jiang 2000	?
Marion 1997	+
Meissner 2003a	?
Meissner 2003b	?
Qiu 2007	+
Shiozaki 1993	?
Shiozaki 1999	?
Shiozaki 2001	?
Smrcka 2005	?
Yan 2001	?
Zhang 2000	?

## Effects of interventions

### Death at final follow-up

#### Analysis 1.1

Twenty-one trials involving 1587 patients reported deaths. Patients treated with hypothermia were somewhat less likely to die than those in the control group, but the reduction was not significant (OR 0.85, 95% CI 0.68 to 1.06). There was no evidence of statistical heterogeneity between trials ( $\text{Chi}^2 = 21.91$ ,  $\text{df} = 19$  ( $P = 0.29$ );  $I^2 = 13\%$ ).

### Death at final follow-up stratified by trial quality

#### Analysis 1.2

Nine trials involving 891 patients used good allocation concealment methods. Hypothermia treatment was associated with no decrease in the likelihood of death, which was statistically non-significant compared with the control group (OR 1.11, 95% CI 0.82 to 1.51). There was no evidence of statistical heterogeneity between trials ( $\text{Chi}^2 = 4.33$ ,  $\text{df} = 8$  ( $P = 0.83$ );  $I^2 = 0\%$ ).

Twelve trials involving 696 patients did not conceal allocation, or used 'unclear' concealment methods according to Higgins 2008. Patients treated with hypothermia were less likely to die than those in the control group (OR 0.62, 95% CI 0.44 to 0.86). There was no evidence of statistical heterogeneity between trials ( $\text{Chi}^2 = 11.14$ ,  $\text{df} = 10$  ( $P = 0.35$ );  $I^2 = 10\%$ ).

### Unfavourable outcome at final follow-up

#### Analysis 1.3

Twenty-one trials involving 1587 patients reported death or severe disability. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.77, 95% CI 0.62 to 0.94). There was some evidence of statistical heterogeneity between trials ( $\text{Chi}^2 = 38.20$ ,  $\text{df} = 20$  ( $P = 0.008$ );  $I^2 = 48\%$ ).

### Unfavourable outcome stratified by trial quality

#### Analysis 1.4

Nine trials involving 891 patients used good allocation concealment methods. Hypothermia treatment was associated with a statistically non-significant small reduction in unfavourable outcome compared with the control group (OR 0.93, 95% CI 0.70 to 1.23). There was no statistical heterogeneity between trials ( $\text{Chi}^2 = 9.77$ ,  $\text{df} = 8$  ( $P = 0.28$ );  $I^2 = 18\%$ ).

Twelve trials involving 696 patients did not conceal allocation, or used 'unclear' concealment methods according to Higgins 2008. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.60, 95% CI 0.44 to 0.82). There was some statistical heterogeneity between trials ( $\text{Chi}^2 = 24.64$ ,  $\text{df} = 11$  ( $P = 0.01$ );  $I^2 = 55\%$ ).

### Unfavourable outcome stratified by treatment duration

#### Analysis 1.5

Fourteen trials reported deaths or severe disability according to the duration of treatment.

Four trials involving 321 patients treated the hypothermia group for 24 hours. There was a slight, non-significant, increase in the likelihood of unfavourable outcome for patients given hypothermia (OR 1.03, 95% CI 0.65 to 1.65). There was some statistical heterogeneity between trials ( $\text{Chi}^2 = 7.86$ ,  $\text{df} = 3$  ( $P = 0.05$ );  $I^2 = 62\%$ ).

Ten trials involving 683 patients treated the hypothermia group for 48 hours. Hypothermia treatment was associated with a very slight, non-significant, reduction in unfavourable outcome compared with the control group (OR 0.96, 95% CI 0.70 to 1.31). There was no statistical heterogeneity between trials ( $\text{Chi}^2 = 12.13$ ,  $\text{df} = 9$  ( $P = 0.21$ );  $I^2 = 26\%$ ).

### Unfavourable outcome at various times during follow-up

#### Analysis 1.6

Fifteen trials reported Glasgow Outcome Scale (GOS) scores at three, six or 12 months post-injury. Some trials reported GOS scores at more than one time point.

Six trials involving 271 patients reported GOS scores at three months post-intervention. Hypothermia treatment was associated with a statistically non-significant reduction in unfavourable outcome compared with the control group (OR 0.85, 95% CI 0.52 to 1.39). There was some statistical heterogeneity between trials ( $\text{Chi}^2 = 10.29$ ,  $\text{df} = 5$  ( $P = 0.07$ );  $I^2 = 51\%$ ).

Nine trials involving 839 patients reported GOS scores at six months post-intervention. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group, but the reduction was not significant (OR 0.76, 95% CI 0.57 to 1.01). There was significant statistical heterogeneity between trials ( $\text{Chi}^2 = 27.77$ ,  $\text{df} = 8$  ( $P = 0.0005$ );  $I^2 = 71\%$ ).

Four trials involving 262 patients reported GOS scores at 12 months post-intervention. Patients treated with hypothermia were less likely to have an unfavourable outcome than those in the control group (OR 0.52, 95% CI 0.31 to 0.87). There was no statistical heterogeneity between trials ( $\text{Chi}^2 = 3.62$ ,  $\text{df} = 3$  ( $P = 0.31$ );  $I^2 = 17\%$ ).

### Pneumonia during the treatment period

#### Analysis 1.7

Eleven trials involving 559 patients reported pneumonia cases. Patients treated with hypothermia were somewhat more likely to have pneumonia than those in the control group, but the increase was not significant (OR 1.35, 95% confidence interval 0.95 to 1.91).

Pneumonia was stratified by trial quality:

Four trials with good allocation concealment involving 306 pa-

tients reported pneumonia cases. Hypothermia treatment was associated with a statistically non-significant decrease in pneumonia (OR 0.84, 95% confidence interval 0.52 to 1.35). There was no statistical heterogeneity between trials ( $\text{Chi}^2 = 1.47$ ,  $\text{df} = 3$  ( $P = 0.69$ );  $I^2 = 0\%$ ).

Seven trials with non-concealed allocation involving 253 patients reported pneumonia cases. Patients treated with hypothermia were more likely to have pneumonia than those in the control group (OR 2.47, 95% confidence interval 1.44 to 4.23). There was no statistical heterogeneity between trials ( $\text{Chi}^2 = 9.34$ ,  $\text{df} = 5$  ( $P = 0.10$ );  $I^2 = 46\%$ ).

## DISCUSSION

### Summary of main results

There is no evidence that hypothermia is beneficial in the treatment of head injury. Hypothermia may be effective in reducing death and unfavourable outcomes for traumatic head injured patients, but significant benefit was only found in low quality trials. The high quality trials found no decrease in the likelihood of death with hypothermia, but this finding was not statistically significant. Some of the findings in this review are therefore contradictory, and this is probably due to the inclusion of data from low quality trials. Most of the positive and negative effects of hypothermia found may be due to the play of chance.

### Quality of the evidence

Numerous trials of hypothermia treatment have been conducted in recent years. The majority of trials found were of low quality, with unclear allocation concealment. These low quality trials may overestimate the effectiveness of hypothermia treatment versus control.

In trials with good allocation concealment, patients receiving hypothermia were slightly more likely to die, but this may be due to the play of chance. There was a non-significant reduction in pneumonia in trials with good allocation concealment.

### Potential biases in the review process

This systematic review addresses a focused research question using predefined inclusion criteria and methodology to select and appraise eligible studies.

As with all systematic reviews, the possibility of publication bias should be considered as a potential threat to validity. However, in light of our extensive and sensitive searching we believe that the risk of such a bias affecting the results is minimal.

## Agreements and disagreements with other studies or reviews

The conclusions of this review are broadly consistent with those of [Peterson 2008](#). The majority of trials identified for this review and [Peterson 2008](#) were of low methodological quality. Both reviews found there may be an increased likelihood of pneumonia with hypothermia.

A broader review by [Polderman 2008](#) summarises the findings of some of the trials included in this review.

P. David Adelson describes how paediatric patients may respond to hypothermia treatment differently than adult patients ([Adelson 2009](#)).

## AUTHORS' CONCLUSIONS

### Implications for practice

There is no evidence that hypothermia is beneficial in the treatment of head injury. Hypothermia may be effective in reducing death and unfavourable outcomes for traumatic head injured patients, but significant benefit was only found in low quality trials. Low quality trials have a tendency to overestimate the treatment effect. The high quality trials found no decrease in the likelihood of death with hypothermia, but this finding was not statistically significant and could be due to the play of chance. Hypothermia should not be used except in the context of a high quality randomised controlled trial with good allocation concealment.

### Implications for research

More high quality randomised controlled trials are needed to determine the benefit of hypothermia for traumatic head injury.

## ACKNOWLEDGEMENTS

Thanks to:

- Brenda Thomas (Stroke Review Group) for help and advice with the original EMBASE search strategy.
- Ian Whittle, Kate Signorini, Elena Telaro, Yoichi Nagayama, Irene Kwan, Frank Del Vecchio, Lisa Xue and Cynthia To for help with manuscripts in languages other than English.
- Reinhard Wentz and Irene Kwan of the Injuries Group for the original searches.
- Katharine Ker of the Injuries Group for work on previous versions of the review.

- Karen Blackhall, Trials Search Co-ordinator of the Cochrane Injuries Group for updating the searches in 2003, 2005, 2008 and 2009.
- Odette Harris and Monique Surles for providing additional data for the Harris 2009 trial.

## REFERENCES

### References to studies included in this review

#### Adelson 2005 HYPO1 *{published data only}*

Adelson PD, Ragheb J, Muizelaar JP, Kanev P, Brockmeyer D, Beers S, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery* 2005;**56**(4): 740–54. [DOI: 10.1227/01.NEU.0000156471.50726.26]

#### Adelson 2005 HYPO2 *{published data only}*

Adelson PD, Ragheb J, Muizelaar JP, Kanev P, Brockmeyer D, Beers S, et al. Phase II clinical trial of moderate hypothermia after severe traumatic brain injury in children. *Neurosurgery* 2005;**56**(4): 740–54. [DOI: 10.1227/01.NEU.0000156471.50726.26]

#### Aibiki 2000 *{published data only}*

Aibiki M, Maekawa S, Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. *Critical Care Medicine* 2000;**28**(12):3902–6.

#### Biswas 2002 *{published data only}*

Biswas AK, Bruce DA, Sklar FH, Bokovoy JL, Sommerauer JF. Treatment of acute traumatic brain injury in children with moderate hypothermia improves intracranial hypertension. *Critical Care Medicine* 2002;**30**(12):2742–51. [DOI: 10.1097/01.CCM.000038209.56308.9E]

#### Clifton 1992 *{published and unpublished data}*

Clifton GL, Allen S, Berry J, Koch SM. Systemic hypothermia in treatment of brain injury. *Journal of Neurotrauma* 1992;**9**:S487–95.

#### Clifton 1993 *{published data only}*

Clifton GL. Hypothermia and hyperbaric oxygen as treatment modalities for severe head injury. *New Horizons* 1995;**3**:474–8.  
Clifton GL. Hypothermia in the management of patients with head injury. Abstracts of the 2nd International Neurotrauma Symposium. Glasgow, 1993; Vol. July 4–9.  
Clifton GL. Systemic hypothermia in treatment of severe brain injury. *Journal of Neurosurgical Anesthesiology* 1995;**7**:152–6.  
Clifton GL. Systemic hypothermia in treatment of severe brain injury: A review and update. *Journal of Neurotrauma* 1995;**12**: 923–7.  
\* Clifton GL, Allen S, Barrodale P, Plenger P, Berry J, Koch S, Fletcher J, Hayes RL, Choi SC. A phase II study of moderate hypothermia in severe brain injury. *Journal of Neurotrauma* 1993; **10**:263–73.

#### Clifton 2001 *{published data only}*

Clifton GL. Hypothermia in Neurotrauma. Abstracts of the 3rd International Neurotrauma Symposium. Toronto, Canada, 1995: July 22–27.

\* Clifton GL, Miller ER, Choi SC, Levin HS, McCauley S, Smith KR, et al. Lack of effect of induction of hypothermia after acute brain injury. *New England Journal of Medicine* 2001;**344**(8): 556–63.

#### Harris 2009 *{published and unpublished data}*

Harris OA, Muh CR, Suries MC, Pan Y, Rozycki G, Macleod J, Easley K. Discrete cerebral hypothermia in the management of traumatic brain injury: a randomized controlled trial. *Journal of Neurosurgery* 2009 Feb 27 (epub ahead of print).

#### Hashiguchi 2003 *{published data only}*

Hashiguchi N, Shiozaki T, Ogura H, Tanaka H, Koh T, Noborio M, et al. Mild hypothermia reduces expression of heat shock protein 60 in leukocytes from severely head-injured patients. *The Journal of Trauma Injury, Infection, and Critical Care* 2003;**55**:1054–60. [DOI: 10.1097/01.TA.0000033252.43742.8B]

#### Hirayama 1994 *{published data only}*

Hayashi N, Hirayama T, Udagawa A, Daimon W, Ohata M. Systemic Management of Cerebral Edema Based on a New Concept in Severe Head Injury Patients. *Acta Neurochirurgica* 1994;**60**(supplement):541–3.  
Hayashi N, Shibuya T, Kinoshita K, Jo S, Azuhata T, Mera K, Tanjo K. The cerebral thermal dysregulation and hypothermia treatment in severe brain injury patients. Abstracts of the Tenth International Symposium on Intracranial Pressure and Neuromonitoring in Brain Injury. Williamsburg USA, 1997: May 25–29.  
\* Hirayama T, Katayama Y, Kano T, Hayashi N, Tsubokawa T. Impact of Moderate Hypothermia on Therapies for Intracranial Pressure Control in Severe Traumatic Brain Injury. In: Nagai H, Ishii S, Maeda M editor(s). *Intracranial Pressure IX*. Tokyo: Springer-Verlag, 1994:233–6.  
Hirayama T, Katayama Y, Maeda T, Kawamata T, Tsubokawa T. Effects of moderate hypothermia on the evolution of cerebral contusion. Abstracts of the 3rd International Neurotrauma Symposium. Toronto, Canada, 1995: July 22–27.

#### Hutchison 2008 *{published data only}*

Hutchison J, Ward R, Lacroix J, Hebert P, Barnes M, et al. Hypothermia therapy after traumatic brain injury in children. *The New England Journal of Medicine* 2008;**358**:2447–56.

#### Ishikura 1998 *{published data only}*

Ishikura H, Yamagami K, Akahori M, Shoji Y, Fukui H, Tanaka T. Changes in Blood Platelet Count and Serum Thrombopoietin (TPO) level under Moderate Hypothermic Therapy in Traumatic

Severe Closed Head Injury. *Critical Care Medicine* 1998;**26** (Supplement 1):A82.

**Jiang 2000** {published data only}

\* Jiang JY, Yu MK, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *Journal of Neurosurgery* 2000;**93**: 546–9.

Jiang JY, Zhu C. The mild hypothermia significantly decreases mortality of severe traumatic brain injured patients. Abstracts of the International Conference on Recent Advances in Neurotraumatology, Riccione, Italy, Sept 8-11 1996. 1996.

**Marion 1997** {published data only}

Clark RSB, Kochanek PM, Obrist WD, Wong HR, Billiar TR, Wisniewski SR, Marion DW. Cerebrospinal fluid and plasma nitrite and nitrate concentrations after head injury in humans. *Critical Care Medicine* 1996;**24**:1243–51.

Darby JM, Marion DW, Peitzman A, Carlier P, Obrist WD. Pulmonary complications in brain-injured patients treated with hypothermia. *Anesthesiology* 1992;**77**:A295.

Marion DW, Carlier P. Moderate therapeutic hypothermia improves outcome following severe traumatic brain injury. Abstracts of the 3rd International Neurotrauma Symposium. Toronto, Canada, 1995; July 22-27.

Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. *Journal of Neurosurgery* 1993; **79**:354–62.

Marion DW, Palmer AM, DeKosky ST, Kochanek PM, Carlier PM. Effect of moderate hypothermia on neurochemical mediators of secondary brain injury. *Journal of Neurosurgery* 1995;**82**:344A.

Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST. Treatment of traumatic brain injury with moderate hypothermia. Abstracts of the Tenth International Symposium on Intracranial Pressure and Neuromonitoring in Brain Injury. Williamsburg USA, 1997; May 25-29.

\* Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST. Treatment of traumatic brain injury with moderate hypothermia. *New England Journal of Medicine* 1997;**336**:540–6.

Resnick DK, Marion DW, Darby JM. The effect of hypothermia on the incidence of delayed traumatic intracerebral hemorrhage. *Neurosurgery* 1994;**34**:252–6.

**Meissner 2003a** {published data only}

Meissner W, Fritz H, Dohm B, Krapp C, Reinhart K. Hormonal and haemodynamic consequences of moderate hypothermia in head injured patients. *Neurosciences* 2003:102–3.

**Meissner 2003b** {published data only}

Meissner W, Krapp C, Kauf E, Dohrn B, Reinhart K. Thyroid hormone response to moderate hypothermia in severe brain injury. *Intensive Care Medicine* 2003;**29**:44–8. [DOI: 10.1007/s00134-002-1556-3]

**Qiu 2007** {published data only}

Qiu W, Zhang Y, Sheng H, Zhang J, Wang W, Liu W, et al. Effects of therapeutic mild hypothermia on patients with severe traumatic

brain injury after craniotomy. *Journal of critical care* 2007;**22**: 229–36.

**Shiozaki 1993** {published and unpublished data}

Shiozaki T, Sugimoto H, Taneda M, Yoshida H, Iwai A, Yoshioka T, Sugimoto T. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. *Journal of Neurosurgery* 1993;**79**:363–8.

**Shiozaki 1999** {published data only}

Shiozaki T, Kato A, Taneda M, Hayakata T, Hashiguchi N, Tanaka H. Little benefit from mild hypothermia therapy for severely head injured patients with low intracranial pressure. *Journal of Neurosurgery* 1999;**91**:185–91.

**Shiozaki 2001** {published data only}

Shiozaki T, Hayakata T, Taneda M, Nakajima Y, Hashiguchi N, Fujimi S, et al. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. *Journal of Neurosurgery* 2001;**94**:50–4.

**Smrcka 2005** {published data only}

Smrcka M, Vidlak M, Maca K, Smrcka V, Gal R. The influence of mild hypothermia on ICP, CPP and outcome in patients with primary and secondary brain injury. *Acta Neurochirurgica* 2005;**95** (Suppl):273–5.

**Yan 2001** {published data only}

Yan Y, Tang W. Changes of evoked potentials and evaluation of mild hypothermia for treatment of severe brain injury. *Chinese Journal of Traumatology* 2001;**4**:8–13.

**Zhang 2000** {published data only}

Zhang K, Wang JX. Comparative study on mild hypothermia in patients with severe head injury and the most severe head injury. *Inner Mongolia Medical Journal* 2000;**32**:4–6.

## References to studies excluded from this review

**Bayir 2009** {published data only}

Bayir H, Adelson PD, Wisniewski SR, Shore P, Lai Y, Brown D, Janesko-Feldman KL, et al. Therapeutic hypothermia preserves antioxidant defenses after severe traumatic brain injury in infants and children. *Critical care medicine* 2009;**37**(2):689–95.

**Chen 2001** {published data only}

Chen L, Piao Y, Zeng F, Lu M, Kuang Y, Li X. Moderate hypothermia therapy for patients with severe head injury. *Chinese Journal of Traumatology (English edition)* 2001;**4**(3):164–7.

**Chouhan 2006** {published data only}

Chouhan RS, Dash HH, Bithal PK, Chaturvedi A, Pandia MP, Radhakrishnan M, et al. Intraoperative mild hypothermia for brain protection during intracranial aneurysm surgery. *Journal of Anaesthesiology and Clinical Pharmacology* 2006;**22**(1):21–8.

**Fukuoka 2004** {published data only}

Aibiki M. Personal communication with author. September 10, 2008.

\* Fukuoka N, Aibiki M, Tsukamoto T, Seki K, Morita S. Biphasic concentration change during continuous midazolam administration in brain-injured patients undergoing therapeutic moderate hypothermia. *Resuscitation* 2004;**60**:225–30.

- Gal 2002** *{published data only}*  
Gal R, Cundrle I, Zimova I, Smrcka M. Mild hypothermia therapy for patients with severe brain injury. *Clinical Neurology and Neurosurgery* 2002;**104**:318–21.
- Gentilello 1997** *{published data only}*  
Gentilello LM, Jurkovich GJ, Stark MS, Hassantash SA, O'Keefe GE. Is hypothermia in the victim of major trauma protective or harmful?. *Annals of Surgery* 1997;**226**:439–49.
- Guo 2004** *{published data only}*  
Guo W, Wang L-L, Cai K-H. A control study on mild hypothermia in treatment of severe craniocerebral injury. *Journal of Xinxiang Medical College* 2004;**21**(4):269–71.
- Hayashi 2002** *{published data only}*  
Hayashi S, Inao S, Takayasu M, Kajita Y, Ishiyama J, et al. Effect of early induction of hypothermia on severe head injury (abstract). *Acta Neurochirurgica* 2002;**81**(Suppl):83–4. [PUBMED: 12168365]
- Hayashi 2005** *{published data only}*  
Hayashi S, Takayasu M, Inao S, Yoshida J. Balance of risk of therapeutic hypothermia. *Acta Neurochirurgica* 2005;**95**(Suppl):269–72.
- Legros 1985** *{published data only}*  
Legros B, Lapiere F, Laudat P, Krettly PH, Fournier P, Meny J, et al. Barbiturate hypothermia treatment for post-traumatic brain injury: infectious complications and mortality [Barbiturici-ipotermia nella protezione metabolica cerebrale post-traumatica: complicazioni infettive e mortalita]. *Minerva Anestesiologica* 1985;**51**:525–30.
- Li 2008** *{published data only}*  
Li G, XU R-X, Ke Y-Q, Jiang X-C, Zhang S-F, Deng B-L, Yu X. Effect of sub-hypothermia therapy on coagulopathy after severe head injury. *Chinese medical journal* 2008;**121**(22):2350–2.
- Liu 2005** *{published data only}*  
Liu W, An Y-H, Liu E-Z, Yu C-J. Effect of mild hypothermia combined with hibernation on the homeostasis of patients with severe head injury. *Chinese Journal of Clinical Rehabilitation* 2005;**9**(33):175–7.
- Liu 2006** *{published data only}*  
Liu WG, Qiu WS, Zhang Y, Wang WM, Lu F, Yang XF. Effects of selective brain cooling in patients with severe traumatic brain injury: a preliminary study. *The Journal of International Medical Research* 2006;**34**:58–64.
- Meissner 1998** *{published and unpublished data}*  
Meissner W, Fritz H, Dohrn B, Specht M, Reinhart K. Influence of Hypothermia on Cytokine Concentrations in Head Injured Patients. *Critical Care Medicine* 1998;**26**(Supplement 1):A82.
- Mrlan 2006** *{published data only}*  
Mrlan A, Smrcka M, Klabusay M. The use of controlled mild hypothermia and immune system status in patients with severe brain injury. *Bratisl Lek Listy* 2006;**107**(4):113–7.
- Nara 1997** *{published data only}*  
Nara I, Shioyai T, Saruta K, Hara M, Saito I. Comparative effects of hypothermia, barbiturates, and osmotherapy for cerebral oxygen metabolism, intracranial pressure and cerebral perfusion pressure in patients with severe head injury. Abstracts of the Tenth International Symposium on Intracranial Pressure and Neuromonitoring in Brain Injury. Williamsburg USA, 1997:May 25-29.
- Nordby 1984** *{published data only}*  
Nordby HK, Nesbakken R. The effect of high-dose barbiturate compression after severe head injury: a controlled clinical trial. *Acta Neurochirurgica* 1984;**72**:157–66.
- Qiu 2005** *{published data only}*  
Qiu WS, Liu WG, Shen H, Wang WM, Zhang SL, Zhang Y, et al. Therapeutic effect of mild hypothermia on severe traumatic head injury. *Chinese Journal of Traumatology* 2005;**8**(1):27–32.
- Qiu 2006** *{published data only}*  
Qiu W, Wang W, Du H, Liu W, Shen H, Shen L, et al. Thrombocytopenia after therapeutic hypothermia in severe traumatic brain injury. *Chinese Journal of Traumatology* 2006;**9**(4):238–41.
- Schulman 2005** *{published data only}*  
Schulman C, Namias N, Doherty J, Manning R, Li P, Alhaddad A, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. *Surgical interventions* 2005;**6**(4):369–75.
- Shen 2000** *{published data only}*  
Shen JH, Shen MW. Application of mild hypothermia in treatment of severe brain injury. *Hebei Med J* 2000;**6**:498–500.
- Wang 2005** *{published data only}*  
Wang WP, Ren HJ, Chi JY, Xu FL, Quan Y. Effects of mild hypothermia on patients with lower intracranial pressure following severe brain injury. *Chinese Journal of Traumatology* 2005;**8**(1):54–6.
- Wang 2007** *{published data only}*  
Wang Q, Li AL, Zhi DS, Huang HL. Effect of mild hypothermia on glucose metabolism and glycerol of brain tissue in patients with severe traumatic brain injury. *Chinese Journal of Traumatology* 2007;**10**(4):246–9.
- Wusi 2006** *{published data only}*  
Wusi Q, Hong S, Ying Z, Weimin W, Weiguo L, Qizhou J, et al. Noninvasive selective brain cooling by head and neck cooling is protective in severe traumatic brain injury. *Journal of Clinical Neuroscience* 2006;**13**:995–1000.
- Xia 2005** *{published data only}*  
Xia YQ, Yan LL, Xu RX, Wang QH. Evaluation of improvement of subhypothermia in cerebral vasospasm after severe craniocerebral injury. *Chinese Journal of Clinical Rehabilitation* 2005;**9**(41):138–41.
- Yamagami 1997** *{published data only}*  
Yamagami K, Iwase M, Matsubara M, Matsuo N, Tanaka T. Nitric oxide production and arginine consumption in traumatic brain injury are correlated with severity. Abstracts of the 26th Meeting of the Society for Critical Care Medicine. Critical Care Medicine. 1997; Vol. 25, issue supplement 1:A72.
- Yan 2007** *{published data only}*  
Yan Y, Tang W, He J, Gao J, Dan W, Zhong D, et al. Clinical research about brain oxygen metabolism and

neuroelectrophysiology during mild hypothermia in patients with severe head injury. *Chinese Journal of Surgery* 2007;**45**(2):109–13.

**Zhi 2003** {*published data only*}

Zhi D, Zhang S, Lin X. Study on the therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surgical Neurology* 2003;**59**:381–5. [DOI: 10.1016/S0090-3019(03)00148-4]

## References to ongoing studies

**Adelson 2007** {*unpublished data only*}

Pediatric traumatic brain injury consortium: hypothermia.. Ongoing study November 2007.

**Beca 2006** {*unpublished data only*}

Pilot Study of Early and Prolonged Hypothermia in Severe Traumatic Brain Injury in Children.. Ongoing study November 2006.

**Clifton 2002** {*unpublished data only*}

National Acute Brain Injury Study: Hypothermia II (NABISH II).. Ongoing study 4/1/02 – 6/30/08.

**Maekawa 2002** {*unpublished data only*}

Therapeutic Strategy for Severe Head Trauma Patients With Mild Hypothermia and Estimation of Medical Expenses in Japan.. Ongoing study December 2002.

## Additional references

**Adelson 2003**

Adelson PD, Bratton SL, Carney NA, Chestnut RM, Coudray HEM, Goldstein B, Kochanek PM, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. *Pediatric critical care medicine* 2003;**4**(3 (Suppl)):S1–75. [DOI: 10.1097/01.CCM.0000067635.95882.24]

**Adelson 2008a**

Adelson D. [Personal communication with author]. 5 October 2008.

**Adelson 2008b**

Adelson D. [Personal communication with author]. 17 October 2008.

**Adelson 2009**

Adelson PD. Hypothermia following pediatric traumatic brain injury. *Journal of Neurotrauma* 2009;**26**:429–36. [DOI: 10.1089/neu.2008.0571]

**Bering 1961**

Bering EA Jr. Effect of body temperature change on cerebral oxygen consumption of the intact monkey. *American Journal of Physiology* 1961;**200**:417–9.

**Bullock 1996**

Bullock R, Chesnut RM, Clifton G, Ghajar J, Marion DW, Narayan RK, et al. Guidelines for the management of severe head injury. *Journal of Neurotrauma* 1996;**13**:639–734.

**Bullock 2007**

Bullock MR, Povlishock JT. Guidelines for the management of severe head injury. *Journal of Neurotrauma* 2007;**24**(Supplement 1):S1–106. [DOI: 10.1089/neu.2007.9976]

**Busto 1987**

Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intra-ischemic brain temperature critically determine the extent of ischemic neuronal injury. *Journal of Cerebral Blood Flow Metabolism* 1987;**7**:729–38.

**Busto 1989**

Busto R, Globus MY, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of mild hypothermia on ischemia-induced release of neuro-transmitters and free fatty acids in rat brain. *Stroke* 1989;**20**:904–10.

**Clasen 1968**

Clasen RA, Pandolfi S, Russell J, Stuart D, Hass GM. Hypothermia and hypotension in experimental cerebral edema. *Archives of Neurology* 1968;**19**:472–86.

**Clifton 1995**

Clifton GL. Systemic Hypothermia in Treatment of Severe Brain Injury: A Review and Update 1995. *Journal of Neurotrauma* 1995;**12**:923–7.

**Clifton 2009**

Clifton G, Drever P, Valadka A, Zygun D, Okonkwo D. Multicenter trial of early hypothermia in severe brain injury. *Journal of Neurotrauma* 2009;**26**:393–7. [DOI: 10.1089/neu.2008.0556]

**Fay 1945**

Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. *Assoc Res Nerv Ment Dis Proc* 1945;**24**:611–9.

**Higgins 2008**

Higgins JPT, Green S (editors). The Cochrane Handbook of Systematic Reviews. The Cochrane Collaboration 2008; Vol. Version 5.0.0 [updated February 2008]:Available from www.cochrane-handbook.org.

**Kirkpatrick 1997**

Kirkpatrick PJ. On guidelines for the management of severe head injury. *Journal of Neurology, Neurosurgery and Psychiatry* 1997;**62**:109–11.

**Langlois 2006**

Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *The Journal of Head Trauma Rehabilitation* 2006;**21**(5):375–8.

**Laskowski 1960**

Laskowski EJ, Klato I, Baldwin M. Experimental study on the effects of hypothermia on local brain injury. *Neurology* 1960;**10**:499–505.

**Peterson 2008**

Peterson K, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. *Journal of Neurotrauma* 2008;**25**:62–71. [DOI: 10.1089/neu.2007.0424]

**Polderman 2008**

Polderman K H. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet* 2008;**371**:1955–69.

**Review Manager (RevMan)**

The Nordic Cochrane Center. Review Manager (RevMan). 5.0.0. Copenhagen: The Cochrane Collaboration, 2008.

**Schubert 1995**

Schubert A. Side effects of mild hypothermia. *Journal of Neurosurgical Anesthesiology* 1995;**7**:139–47.

**Sedzimir 1959**

Sedzimir CB. Therapeutic hypothermia in cases of head injury. *Journal of Neurosurgery* 1959;**16**:407–14.

**Shapiro 1974**

Shapiro HM, Wyte SR, Loeser J. Barbiturate-augmented hypothermia for reduction of persistent intracranial hypertension. *Journal of Neurosurgery* 1974;**40**:90–100.

**Smith 1996**

Smith SL, Hall ED. Mild pre- and posttraumatic hypothermia attenuates blood-brain barrier damage following controlled cortical impact injury in the rat. *Journal of Neurotrauma* 1996;**13**:1–9.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Adelson 2005 HYPO1

Methods	Multicentre, randomised, controlled trial.	
Participants	Patients less than 13 years of age, with a Glasgow coma scale (GCS) score of $\leq 8$ .	
Interventions	Hypothermia patients: Cooling to 32-33C within 6 hours of injury for 48 hours. Passively rewarmed by 1C every 3-4 hours. Normothermia patients: no intervention/not reported.	
Outcomes	ICP CPP Mortality Infection Arrhythmia Coagulopathy Pneumonia	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	'The investigators were blinded to the allocation. The statistician and data systems manager controlled the randomisation protocol and were blinded to the site.' <a href="#">Adelson 2008b</a>

#### Adelson 2005 HYPO2

Methods	Single centre, randomised, controlled trial.	
Participants	Patients less than 17 years of age, with a GCS score of $\leq 8$ .	
Interventions	Hypothermia patients: Cooling to 32-33C for 48 hours. Passively rewarmed by 1C every 3-4 hours. Normothermia patients: no intervention/not reported.	
Outcomes	ICP CPP Mortality Infection Arrhythmia Coagulopathy Pneumonia	

**Adelson 2005 HYPO2** (Continued)

Notes	The time between injury and randomisation was more than 6 hours. In some cases there was an unknown time of injury (e.g. child abuse).	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	'The investigators were blinded to the allocation. The statistician and data systems manager controlled the randomisation protocol and were blinded to the site.' <a href="#">Adelson 2008b</a>

**Aibiki 2000**

Methods	Randomised controlled trial. Four patients were excluded from the normothermic group after randomisation because of abdominal or chest injuries.	
Participants	Patients aged 4 to 76, within 8 hours of traumatic brain injury. GCS score of $\leq 8$ on admission to emergency room.	
Interventions	Hypothermia patients: Cooling to 32-33C within 4 hours of injury for 3-4 days. Rewarming at 1C per day. Normothermia patients: maintained at 36-37C.	
Outcomes	Death and Glasgow Outcome Scale (GOS) score at 6 months. Thromboxane A2 and prostaglandin I2 levels during study. Complications during treatment.	
Notes	GOS assessed by "independent neurosurgeon who were not aware of the study". p.3904	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	'Patients were assigned randomly to each group.' p.3903 No mention of allocation concealment.

**Biswas 2002**

Methods	Randomised controlled trial.	
Participants	Children up to 18 years old, with closed traumatic brain injury and a GCS score of $\leq 8$ .	
Interventions	Hypothermia patients (n=10): cooled to 32 to 34 degrees Celsius for 48 hours, by cooling blanket placed underneath the body. Rewarming over a period of 12 hours. Control patients (n=11): rectal temperature was maintained between 36.5 and 37.5 degrees Celsius.	

**Biswas 2002** (Continued)

Outcomes	Death. GOS score at three, six and 12 months. ICP and CPP.	
Notes	GOS score assessed blind to allocation. Analysis on an intention-to-treat basis. Two patients in the hypo group were lost to follow-up at the end of the study period. (2/10 lost to follow-up.) Five patients in the control group were lost to follow-up at the end of the study period. (5/11 lost to follow-up.)	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Not described.

**Clifton 1992**

Methods	Randomised controlled trial.	
Participants	Patients with GCS score of 4-8 with closed head injury but no major systemic injuries, in whom cooling could begin within 6 hours of injury.	
Interventions	Hypothermia patients: cooling to 30-32C for 24 hours using cooling blankets and iced saline stomach lavage. Rewarming over a period of 24 hours. Control patients: No active temperature management.	
Outcomes	Death and GOS score at 3 months. Complications during treatment phase.	
Notes	GOS score was not assessed blind to treatment allocation.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	By 'sealed envelopes'.

**Clifton 1993**

Methods	Randomised controlled trial.	
Participants	Patients age 16 to 60, GCS score of 4-7 with closed head injury but no major systemic injuries, in whom cooling could begin within 6 hours of injury.	

**Clifton 1993** (Continued)

Interventions	Hypothermia patients: cooling to 32-33C for 48 hours using cooling blankets. Rewarming over a period of 48 hours. Control patients: Cooling blankets were used to maintain body temperature at 37C for 80 hours.	
Outcomes	Death and GOS score at 3 months. Complications during treatment period. ICP during treatment period.	
Notes	GOS score assessed blind to treatment allocation.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	By 'sealed envelopes'.

**Clifton 2001**

Methods	Randomised controlled trial.	
Participants	Patients aged 16 to 65 with a non-penetrating head injury and a GCS score of 3 to 8 after resuscitation.	
Interventions	Hypothermia patients: cooling to 32.5-34C for 48 hours using ice, cold gastric lavage, unwarmed ventilator gases, and then temperature control pads. Rewarming at rate of up to 0.5C in 2 hours. Control: Body temperature maintained at 37C.	
Outcomes	Death and GOS score at 6 months. ICP monitored during treatment. Nine neurobehavioural and neuropsychological scales at 6 months.	
Notes	GOS score was assessed blind to treatment allocation. Outcome data missing for 7 patients, and not presented for 17 patients whose entry details were incomplete.	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	Allocation concealment unclear, but report states that "only the study biostatistician was aware of each patient's treatment group assignment". p557

**Harris 2009**

Methods	Randomised controlled trial.	
Participants	Patients over 18 years of age with a Glasgow coma scale score of $\leq 8$ , who required an ICP monitor and Foley catheter as part of routine treatment.	

**Harris 2009** (Continued)

Interventions	Hypothermia patients (n= 12): the 'Discrete Cerebral Hypothermia System cooling cap' was used to reduce cerebral temperature to a target 33 degrees Celsius for 24 hours. 'Using heating blankets, patients' core body temperatures were kept above 36 degrees Celsius to avoid systemic hypothermia' p.3. Control patients (n= 13): Patients did not receive a cooling cap, and remained at normal body temperature.	
Outcomes	Death, ICP, FIM, and GOS score at days 1, 2, 3, 4, 14, 21, 28 and 1 month (or at hospital discharge, if sooner than one month).	
Notes	Cooling was begun within 48 hours of hospital admission.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	'After informed consent was obtained, all study patients were blindly randomized in a 1:1 ratio to the treatment or control group; patients in the treatment group received the cooling cap and the controls did not. The randomization was determined by the Department of Biostatistics using computer-generated random numbers. These numbers were assigned to each patient based on their order in the study and GCS score on initial assessment (severe [5-8] vs critical [3-4]), to allow for block randomization and to provide an initial balance in severity between the 2 groups.' p.3

**Hashiguchi 2003**

Methods	Randomised controlled trial. Allocation method not stated.	
Participants	Participants age 10 years or older, with a GCS score of $\leq 8$ , 'who required continuous infusion of barbiturates to control intracranial hypertension.' p.1055	
Interventions	Hypothermia patients (n=9): intracranial temperature in the lateral ventricle was maintained at 33.5 to 34.5 degrees Celsius for 48 hours, by water circulating blankets above and below the body. Rewarming over a period of 3 days, by 1 degree Celsius each day. Control patients (n=8): intracranial temperature was maintained between 36.5 and 37.5 degrees Celsius for 5 days, by water circulating blankets above and below the body. Barbiturates were given to both groups at 6 to 8 mg/kg/h for the first 48 hours, then at 2 mg/kg/h for 3 days.	
Outcomes		
Notes		
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Not described.

**Hirayama 1994**

Methods	Randomised controlled trial. Allocation method not stated.
Participants	Patients age 18 to 81, GCS 3-7 with closed head injury. Hypothermia started within 6 hours of injury.
Interventions	Hypothermia patients: cooling to 32-33C for 48 hours using cooling blankets. Rewarming over a period of 48 hours. Control patients: Not stated.
Outcomes	Death and GOS score at 3 months. ICP during treatment period.
Notes	Blinding of outcome assessment not stated.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

**Hutchison 2008**

Methods	Randomised controlled trial.
Participants	Patients age 1-17 years, with a recent traumatic brain injury (within 8 hours) and a GCS score of $\leq 8$ .
Interventions	Hypothermia patients: cooling to 32-33C for 24 hours with surface cooling. Rewarming at a rate of 0.5C every 2 hours. Control patients: temperature was maintained at 36.5 to 37.5C.
Outcomes	Unfavourable outcome at 6 months post-injury. Pediatric Cerebral Performance Category scale at pre-injury, and at 1, 3 and 12 months post-injury.
Notes	'Overall, 20 out of the 225 patients (9%) were lost to follow-up at 6 months -- 6 out of 108 patients (6%) in the hypothermia group and 14 of 117 (12%) in the normothermia group.' p.2451

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	'...a study physician randomly assigned the patient to a treatment group with the use of a central telephone-based system that was available 24 hours a day. The randomization, prepared by an independent statistician, was blocked in groups of four (participating centers were unaware of the block size) and included two stratification variables: center and age (less than 7 years of age and 7 years of age or more).' p.2448

**Ishikura 1998**

Methods	Randomised controlled trial. Allocation by 'random sampling'.
Participants	Patients with GCS score of 3-8 with closed head injury.
Interventions	'Moderate hypothermia' without any details.
Outcomes	Thrombopoetin levels during treatment. Deaths in hypothermia arm only.
Notes	Abstract only.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	'11 patients with severe closed head injuries were divided into two groups by random sampling.' No information provided on allocation concealment.

**Jiang 2000**

Methods	Randomised controlled trial. Allocation method not clear.
Participants	Patients with mean age of 41 years, and GCS score of 3-8.
Interventions	Hypothermia patients: 'Mild hypothermia' induced using cooling blankets until ICP within 'normal range' for 24 hours. Control patients: Temperature maintained between 37-38C for 14 days.
Outcomes	Death and GOS score at 12 months. Complications.
Notes	Assessment by MD blinded to treatment allocation.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

**Marion 1997**

Methods	Randomised controlled trial. Allocation by 'sealed envelopes'.
Participants	Patients age 16 to 75, GCS score of 3-7 with closed head injury, in whom cooling could begin within 6 hours of injury.

**Marion 1997** (Continued)

Interventions	Hypothermia patients: Cooling to 32-33C for 24 hours using cooling blankets and nasogastric lavage. Rewarming over a period of 12 hours. Control patients: Active management of temperature to 37-38.5C during five day treatment period.	
Outcomes	Death and GOS score at 3, 6 and 12 months. ICP and CPP values during treatment phase. Complications for subset.	
Notes	GOS score assessment by psychiatrist blinded to treatment allocation.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	'Using a block-randomization scheme, we assigned patients with a Glasgow coma score of 3 or 4 to a treatment group separately from those with a score of 5 to 7 by choosing among equal numbers of sealed envelopes containing the group assignments.' p.540

**Meissner 2003a**

Methods	Randomised controlled trial.	
Participants	Patients with severe blunt head injury. Intervention was started within 8 hours of injury.	
Interventions	Hypothermia patients: Cooling to 32-33C for 48 hours. Control patients: Temperature maintained at 36-37C.	
Outcomes	Heart rate. Mean blood pressure. Plasma cortisol.	
Notes	Primary outcome of study was moderate hypothermia on the cardiovascular and cortisol response in severe head injury. No mortality data reported.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	Not described.

**Meissner 2003b**

Methods	Randomised controlled trial.
Participants	Patients aged 18 or older, with severe closed head injury with a GCS score of $\leq 9$ . The intervention was started within 8 hours of injury.
Interventions	Hypothermia patients: Cooling to 32-33C for 24-48 hours. Cooling was by water blankets and forced air. Control patients: Temperature maintained at 36-37C.
Outcomes	TSH TT4 FT4 TT3 FT3 RT3
Notes	This study examined thyroid hormone response in relation to therapeutic hypothermia.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

**Qiu 2007**

Methods	Randomised, controlled, double-blind trial.
Participants	Patients 18-65 years old with traumatic brain injury with a Glasgow Coma Scale score of $\leq 8$ .
Interventions	Hypothermia patients: Cooling to 33-35C for 4 days after craniotomy, using a cooling blanket and cooling head cap with circulating water at 4C. 'Natural' rewarming. Normothermia patients: cooling not used.
Outcomes	Mortality. ICP. Serum superoxide dismutase level. Glasgow Outcome Scale score at 1 year post-intervention.
Notes	

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Yes	'Allocation and randomization was concealed so that the study investigators were not aware to which group the patient would be assigned, and the allocation sequence was

Qiu 2007 (Continued)

	protected until assignment.' p.230
--	------------------------------------

**Shiozaki 1993**

Methods	Randomised controlled trial.
Participants	Patients age 10 or over, with a GCS score of $\leq 8$ with head injury, who 'required continuous infusion of barbiturates to control intracranial hypertension'. p.363
Interventions	Hypothermia patients: cooling to 33.5-34.5C using water-circulating cooling blankets for a minimum of 48 hours and until ICP was below 20 mmHg for 24 hours. Rewarming over a period of 24 hours. Control patients: No active temperature management.
Outcomes	Death and GOS score at 6 months. Pneumonia. Complications during treatment. ICP and CPP values during treatment period for hypothermic arm only.
Notes	GOS score assessed blind to treatment allocation.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

**Shiozaki 1999**

Methods	Randomised controlled trial. Allocation concealment not clear. No loss to follow up.
Participants	Patients age 10 and above with traumatic brain injury, a Glasgow coma scale score of $\leq 8$ , and 'who required continuous infusion of barbiturate medication to control intracranial hypertension.' p.185
Interventions	Hypothermia patients: cooling to 33.5-34.5C for 48 hours, using water circulating blankets. Rewarming at 1C per day. Normothermia patients: maintained at 36.5-37.5C.
Outcomes	Death and GOS score at 6 months. Complications.
Notes	Blinding of outcome assessment not stated.

**Risk of bias**

Item	Authors' judgement	Description
------	--------------------	-------------

**Shiozaki 1999** (Continued)

Allocation concealment?	Unclear	Not described.
-------------------------	---------	----------------

**Shiozaki 2001**

Methods	Randomised controlled trial. Allocation concealment not clear. No loss to follow up.
Participants	Patients with traumatic brain injury, a Glasgow coma scale score of $\leq 8$ , and 'in whom ICP was maintained below 25mmHg by conventional therapies'. p.50
Interventions	Hypothermia patients: Cooling to 33.5-34.5C for 48 hours, using cooling blankets and gastric lavage. Rewarming at 1C per day. Normothermia patients: maintained at 36.5-37.5C.
Outcomes	Death and GOS score at 3 months. Complications.
Notes	Blinding of outcome assessment not stated.

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

**Smrcka 2005**

Methods	Randomised controlled trial - randomisation method not described. No loss to follow up described.
Participants	Patients with traumatic brain injury with a Glasgow Coma Scale score of $\leq 8$ , who were up to age 61 years of age.
Interventions	Hypothermia (n=37): surface cooling to 34C for 72 hours. Temperature measured in urinary bladder. Passive rewarming. Normothermia (n=35): cooling not used.
Outcomes	ICP CPP SvjO <sub>2</sub> (jugular bulb oxygen saturation) GOS
Notes	

**Risk of bias**

**Smrcka 2005** (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

**Yan 2001**

Methods	Randomised controlled trial. Allocation concealment not described. No loss to follow up described.
Participants	Patients with traumatic brain injury within 10 hours of injury and a Glasgow Coma Scale score of 3 to 8 on initial assessment.
Interventions	Hypothermia patients: Cooling to 32-34C for 3-5 days, using a cooling bed and, in some, ice blocks. 'Natural' rewarming. Normothermia patients: cooling not used.
Outcomes	Death, follow up period unclear. Neuroelectrophysiological measurements.
Notes	Blinding of outcome assessment not stated.

***Risk of bias***

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not described.

**Zhang 2000**

Methods	Randomised controlled trial. Allocation concealment not described. No loss to follow up mentioned.
Participants	Patients aged under 65 with traumatic brain injury and a Glasgow Coma Scale score of 3-8 on admission to hospital.
Interventions	Hypothermia patients: Cooling to 32-33C for 3-8 days. Normothermia patients: temperature not stated.
Outcomes	Death, follow up period unclear.
Notes	Blinding of outcome assessment not stated.

***Risk of bias***

Item	Authors' judgement	Description
------	--------------------	-------------

**Zhang 2000** (Continued)

Allocation concealment?	Unclear	Not described.
-------------------------	---------	----------------

**Characteristics of excluded studies** [ordered by study ID]

Bayir 2009	Report on antioxidant status of paediatric patients treated with hypothermia. These patients have already been included in this review as part of the <a href="#">Adelson 2005 HYPO1</a> and <a href="#">Adelson 2005 HYPO2</a> trial.
Chen 2001	Unclear method of randomisation. Unable to confirm method of randomisation with trial report authors.
Chouhan 2006	Patients were not cooled for a minimum of 12 consecutive hours.
Fukuoka 2004	Quasi-randomised study design.
Gal 2002	Not a randomised study.
Gentilello 1997	Randomised trial of rewarming therapy after accidental hypothermia in trauma.
Guo 2004	Not a randomised trial.
Hayashi 2002	Not a randomised study.
Hayashi 2005	Not a randomised study.
Legros 1985	Not a randomised study.
Li 2008	Unclear if randomised trial. Unable to confirm method of randomisation with trial report authors.
Liu 2005	Patients who died within 72 hours of participating in the study were not included in the analysis.
Liu 2006	Patients were not cooled for a minimum of 12 consecutive hours.
Meissner 1998	No mention of method of randomisation.
Mrlan 2006	Not a randomised study.
Nara 1997	Unable to find sufficient information on study design.
Nordby 1984	Not a randomised comparison, and hypothermia confounded with barbiturate therapy.
Qiu 2005	Unclear if randomised trial. Unable to confirm method of randomisation with trial report authors.
Qiu 2006	Not a randomised study.

(Continued)

Schulman 2005	Patients in this study were excluded if they had evidence of acute brain injury and if they had previous traumatic brain injury.
Shen 2000	Not a randomised trial.
Wang 2005	Unclear if randomised trial. Unable to confirm method of randomisation with trial report authors.
Wang 2007	Unclear if randomised trial. Unable to confirm method of randomisation with trial report authors.
Wusi 2006	Not a randomised trial.
Xia 2005	Not a randomised trial.
Yamagami 1997	Not a randomised trial; hypothermia group GCS 4-6, normothermia group GCS 8-10.
Yan 2007	Unclear if randomised trial. Unable to confirm method of randomisation with trial report authors.
Zhi 2003	Unclear if randomised trial. Unable to confirm method of randomisation with trial report authors.

### Characteristics of ongoing studies [ordered by study ID]

#### Adelson 2007

Trial name or title	Pediatric traumatic brain injury consortium: hypothermia.
Methods	Treatment, Randomized, Single Blind (outcome assessor), single group assignment, efficacy study.
Participants	TBI patients under 16 years of age, with a GCS $\leq$ 8.
Interventions	Patients in the treatment arm will be cooled to 32-33C for 48 hours and then slowly rewarmed.
Outcomes	<ul style="list-style-type: none"><li>• To determine the effect of induced moderate hypothermia (32-33C) after severe TBI in children on mortality.</li><li>• To determine the effect of hypothermia after severe TBI in children on global function and neurocognitive outcomes in the areas of intellectual ability/development, memory and learning, and behaviour.</li><li>• To determine the effect of hypothermia after severe TBI in children of different age ranges (&lt;6y and 6 to &lt;16y) on mortality and 6- and 12-month functional and neurocognitive outcomes.</li><li>• To determine the effect of hypothermia after severe TBI in children on reducing intracranial hypertension and maintaining adequate cerebral perfusion pressure (CPP).</li></ul>
Starting date	November 2007
Contact information	David Adelson +1(412)692-6347 david.adelson@chp.edu Danielle Brown +1(412)692-8794 brownds2@upmc.edu

**Adelson 2007** (Continued)

Notes	Phase III Clinical Trial. The sites participating in this trial are: Duke University, Durham, North Carolina; Johns Hopkins University, Baltimore, Maryland; Schneider Children's Hospital, New Hyde Park, New York; Penn State University College of Medicine, Hershey, Pennsylvania; University of California, Davis, Sacramento, California; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; University of Miami, Coral Gables, Florida; University of North Carolina, Chapel Hill, North Carolina; University of Pittsburgh, Pittsburgh, Pennsylvania; University of Tennessee, Memphis, Tennessee; University of Texas Southwestern, Dallas, Texas; University of Washington, Seattle, Washington.
-------	---

**Beca 2006**

Trial name or title	Pilot Study of Early and Prolonged Hypothermia in Severe Traumatic Brain Injury in Children.
Methods	International, multi-centre, randomised controlled trial, safety/efficacy study.
Participants	Children of both genders age 1 to 16. The patients must have a severe traumatic brain injury as defined by a GCS $\leq 8$ and an abnormal CT scan (intracranial haemorrhage, cerebral oedema or diffuse axonal injury) or a motor score $\leq 3$ and a normal CT scan. The patients must be mechanically ventilated.
Interventions	Patients will be randomised within 6 hours of injury. Patients will be stratified by 1) centre and 2) Glasgow Coma Score. Half the patients will be cooled to 32-33 degrees Celsius for 72 hours and then slowly rewarmed. The other patients will have their body temperature maintained at 36-37 degrees Celsius.
Outcomes	Paediatric Cerebral Performance Category (PCPC) at 6 and 12 months after injury; neuropsychological outcomes at 6 and 12 months after injury, intracranial pressure/cerebral perfusion pressure; duration of mechanical ventilation; intensive care and hospital length of stay; adverse effects.
Starting date	November 2006
Contact information	John Beca +61 649 307 4903 johnbeca@adhb.govt.nz Laura Whelan +61 649 307 4903 LCWhelan@adhb.govt.nz
Notes	The sites participating in this trial are: in Australia -- Royal Alexandra Hospital for Children, New South Wales; Sydney Children's Hospital, New South Wales; Queensland Paediatric Intensive Care Services, Queensland; Women's and Children's Hospital, South Australia; Royal Children's Hospital, Victoria; Princess Margaret Hospital, Western Australia; and in New Zealand -- Starship Children's Hospital, Auckland.

**Clifton 2002**

Trial name or title	National Acute Brain Injury Study: Hypothermia II (NABISH II).
Methods	Randomized, prospective, multi-center trial. Hypothermia for 48 hours, begun within 6 hours of severe brain injury.
Participants	Patients aged 16 to 45 years inclusive who have a closed head injury, present to the Emergency Department with a Glasgow Coma Scale score between 3-8, have a body temperature (bladder or rectal) of 35 degrees Celsius or less at admission, and an Abbreviated Injury Score (AIS) of 4 or less for the rest of the body.

**Clifton 2002** (Continued)

Interventions	The patients will be randomly allocated to either the hypothermia group or the normothermia group. A cooling suit will be used to cool the hypothermia patients down to a body temperature of 33 degrees Celsius. This temperature of 33 degrees will be maintained in the hypothermia patients for 48 hours. After 48 hours, the study nurses will gradually re-warm the hypothermia patients no faster than one degree every four hours. This takes at least 16 hours sometimes longer depending upon the stability of the patient's vital signs. The control group - normothermia will be allowed to re-warm gradually upon arrival to the hospital with no medical intervention to raise or lower the body temperature.
Outcomes	Mortality and GOS. ICP and complications. Outcomes will be measured 6 months post injury by Harvey Levin, MD at Baylor College of Medicine. The personnel conducting outcome measurements will be blinded to the patient's assigned treatment protocol (whether hypothermia or normothermia).
Starting date	4/1/02 - 6/30/08
Contact information	Guy L. Clifton, MD Chairman Neurosurgery Dept., University of Texas Medical School 6431 Fannin St., Suite 7.148 Houston, TX 77030 713-500-6135 guy.l.clifton@uth.tmc.edu Emmy R. Miller, RN, PhD, Co-investigator NABISH II Associate Professor of Neurosurgery University of Texas Medical School, Houston, TX 6431 Fannin St., Suite 7.148 Houston, TX 77030 713-500-6145 Emmy.R.Miller@uth.tmc.edu
Notes	There are other study sites participating in NABISH II. They are: University of Pittsburgh, Duke University, University of California at Los Angeles, University of California at Sacramento, University of California at San Francisco, University of Virginia at Fairfax, University of Cincinnati, University of Mississippi at Jackson. Preliminary publication and description of treatment protocol: <a href="#">Clifton 2009</a> .

**Maekawa 2002**

Trial name or title	Therapeutic Strategy for Severe Head Trauma Patients With Mild Hypothermia and Estimation of Medical Expenses in Japan.
Methods	Randomized controlled trial with parallel assignment, safety/efficacy study. Hypothermia to 32-34 degrees Celsius for 72 hours, initiated within 6 hours of injury.
Participants	Patients age 15 to 69 years, of both genders, with a closed head injury and a Glasgow Coma Scale score of 4-8.

**Maekawa 2002** (Continued)

Interventions	Patients will be randomized into two groups. The mild hypothermia group will be kept at 32-34 degrees Celsius for 72 hours, initiated within six hours of injury. Patients in the control group will have their body temperature maintained at 35.5 to 37 degrees Celsius for 72 hours. The Glasgow Outcome Scale score at six months after injury, and the total medical expenses of the two groups will be evaluated.
Outcomes	Neurological outcomes including GOS score and neuropsychological performance at 6 months after injury, total medical expenses, physiological data, and laboratory data.
Starting date	December 2002
Contact information	Yamaguchi University Hospital University Hospital Medical Information Network (UMIN, Japan) Japan Clinical Research Support Unit (J-CRSU) Tsuyoshi Maekawa, MD, PhD +81-836-22-2343 tmaekawa@yamaguchi-u.ac.jp Susumu Yamashita, MD +81-836-22-2656 sum-ygc@umin.ac.jp
Notes	Contact: Susumu Yamashita, MD

## DATA AND ANALYSES

### Comparison 1. Immediate hypothermia versus normothermia

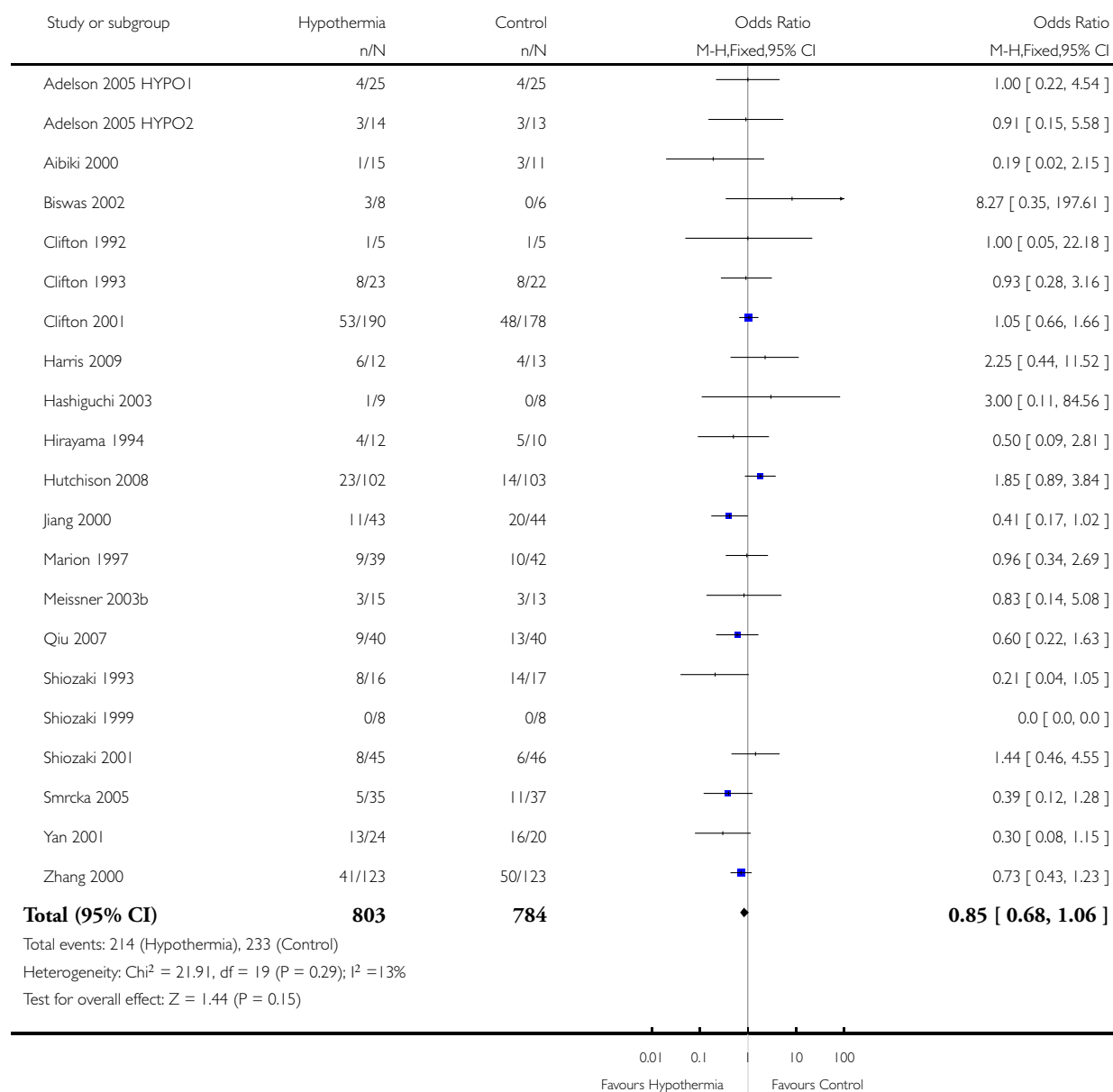
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at final follow-up	21	1587	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.68, 1.06]
2 Death at final follow-up stratified by trial quality	21	1587	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.68, 1.06]
2.1 Concealed allocation	9	891	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.82, 1.51]
2.2 Non-concealed allocation	12	696	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.44, 0.86]
3 Unfavourable outcome at final follow-up	21	1587	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.94]
4 Unfavourable outcome stratified by trial quality	21		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Concealed allocation	9	891	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.70, 1.23]
4.2 Non-concealed allocation	12	696	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.44, 0.82]
5 Unfavourable outcome stratified by treatment duration	14		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 24 hours	4	321	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.65, 1.65]
5.2 48 hours	10	683	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.70, 1.31]
6 Unfavourable outcome at various times during follow-up	15		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 3 months	6	271	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.52, 1.39]
6.2 6 months	9	839	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.57, 1.01]
6.3 12 months	4	262	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.31, 0.87]
7 Pneumonia during the treatment period	11	559	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.95, 1.91]
7.1 Concealed allocation	4	306	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.52, 1.35]
7.2 Non-concealed allocation	7	253	Odds Ratio (M-H, Fixed, 95% CI)	2.47 [1.44, 4.23]

### Analysis 1.1. Comparison 1 Immediate hypothermia versus normothermia, Outcome 1 Death at final follow-up.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 1 Death at final follow-up

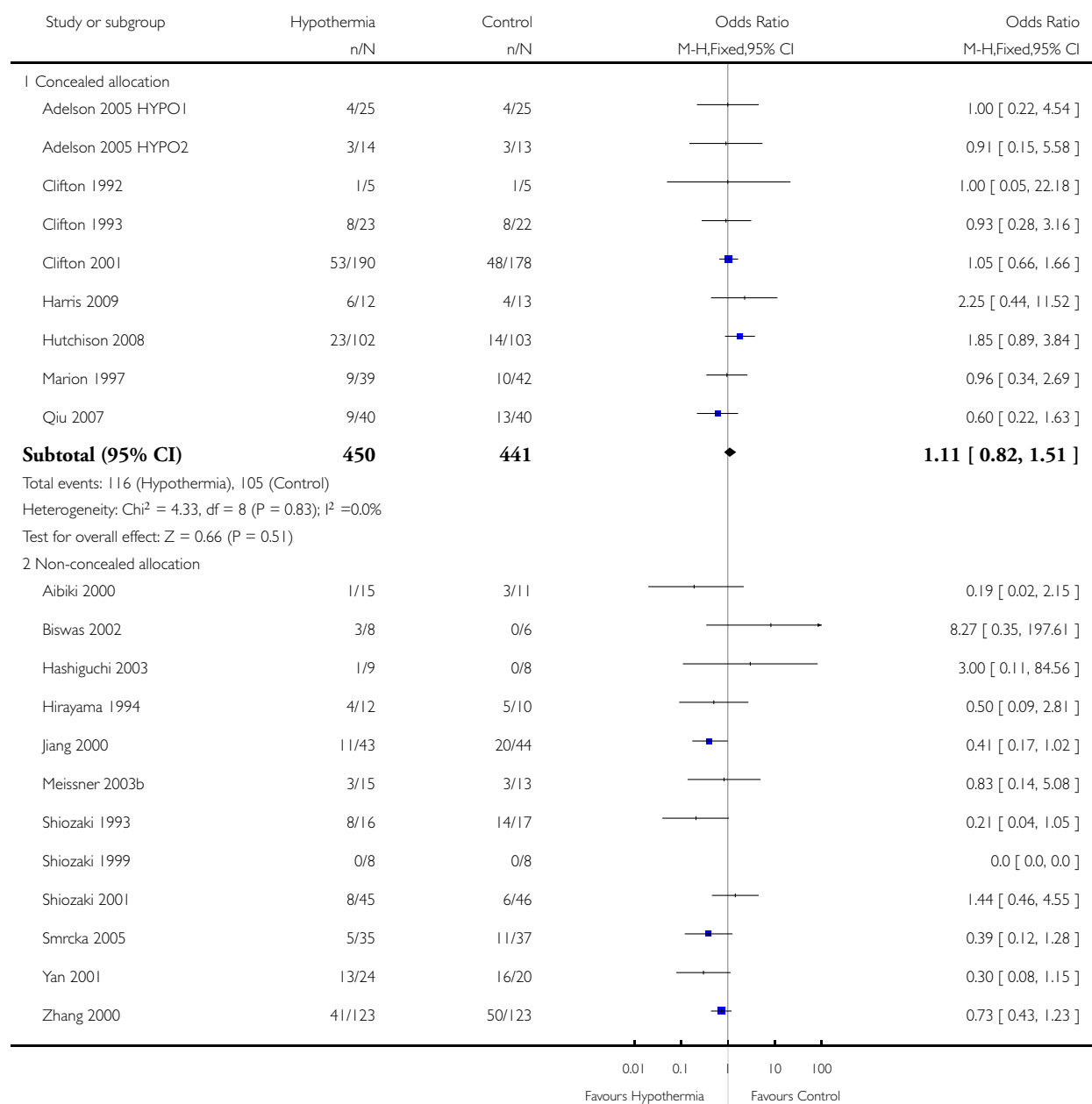


## Analysis 1.2. Comparison 1 Immediate hypothermia versus normothermia, Outcome 2 Death at final follow-up stratified by trial quality.

Review: Hypothermia for traumatic head injury

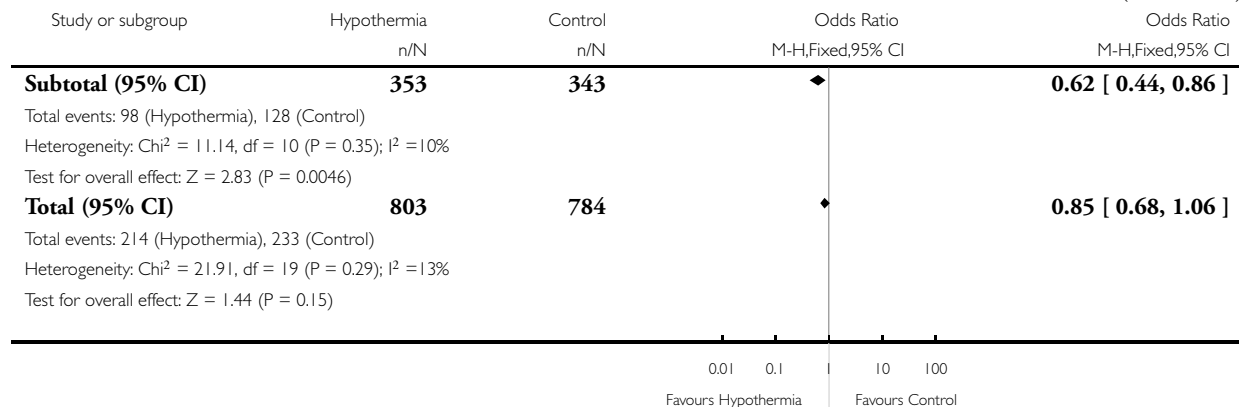
Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 2 Death at final follow-up stratified by trial quality



(Continued . . .)

(... Continued)

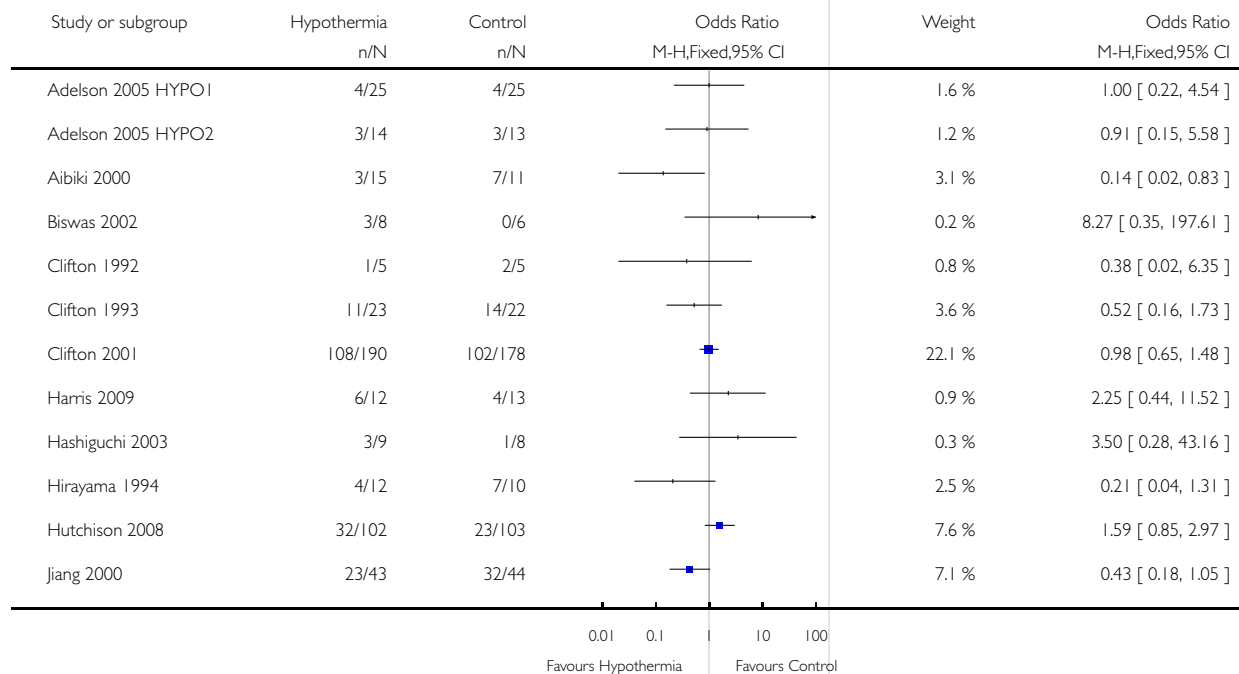


### Analysis 1.3. Comparison 1 Immediate hypothermia versus normothermia, Outcome 3 Unfavourable outcome at final follow-up.

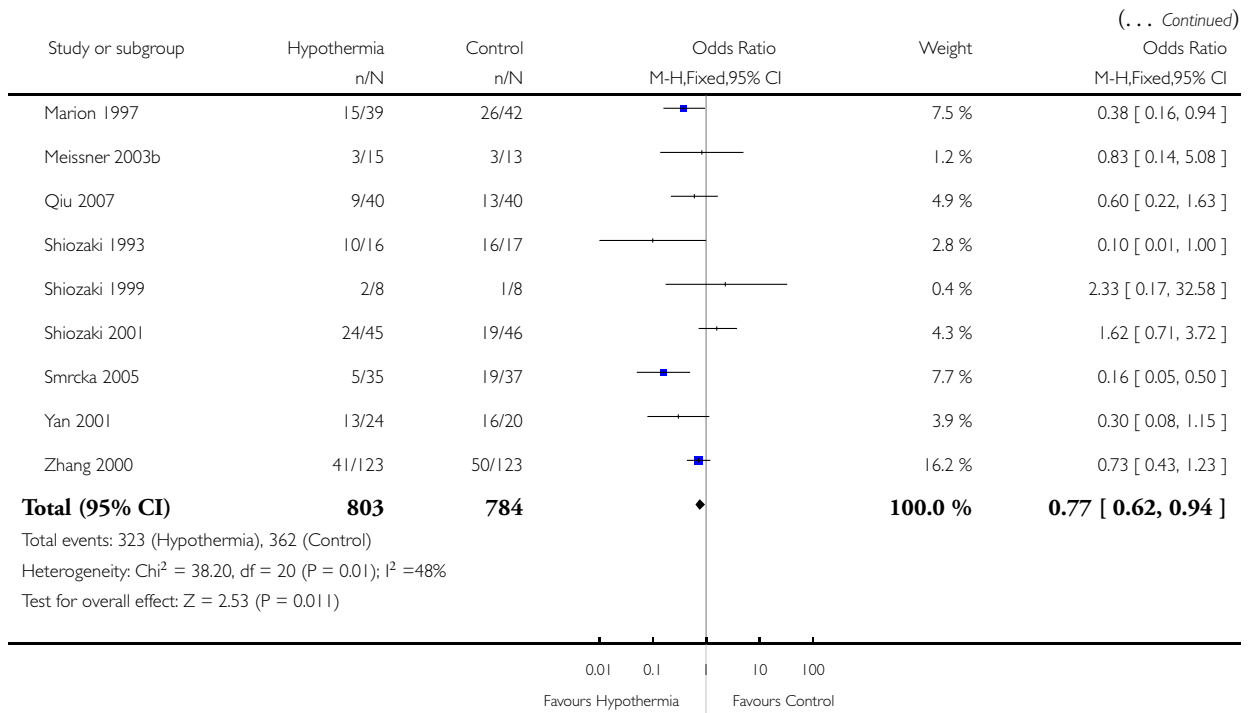
Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 3 Unfavourable outcome at final follow-up



(Continued ...)

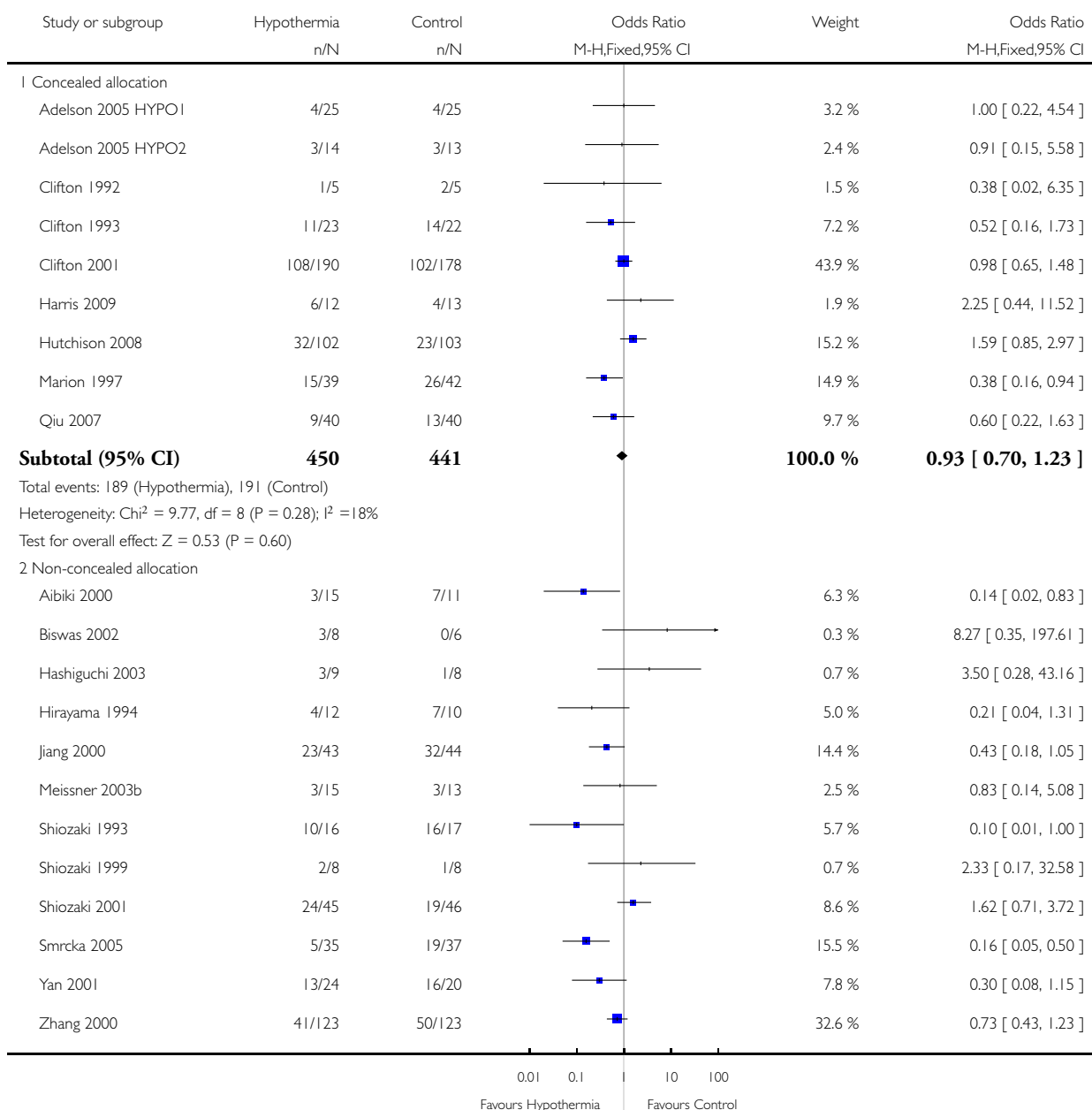


### Analysis 1.4. Comparison 1 Immediate hypothermia versus normothermia, Outcome 4 Unfavourable outcome stratified by trial quality.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 4 Unfavourable outcome stratified by trial quality



(Continued . . .)

(... Continued)

Study or subgroup	Hypothermia n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
<b>Subtotal (95% CI)</b>	<b>353</b>	<b>343</b>	<b>◆</b>	<b>100.0 %</b>	<b>0.60 [ 0.44, 0.82 ]</b>
Total events: 134 (Hypothermia), 171 (Control)					
Heterogeneity: Chi <sup>2</sup> = 24.64, df = 11 (P = 0.01); I <sup>2</sup> = 55%					
Test for overall effect: Z = 3.19 (P = 0.0014)					

0.01 0.1 10 100  
Favours Hypothermia Favours Control

### Analysis 1.5. Comparison 1 Immediate hypothermia versus normothermia, Outcome 5 Unfavourable outcome stratified by treatment duration.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

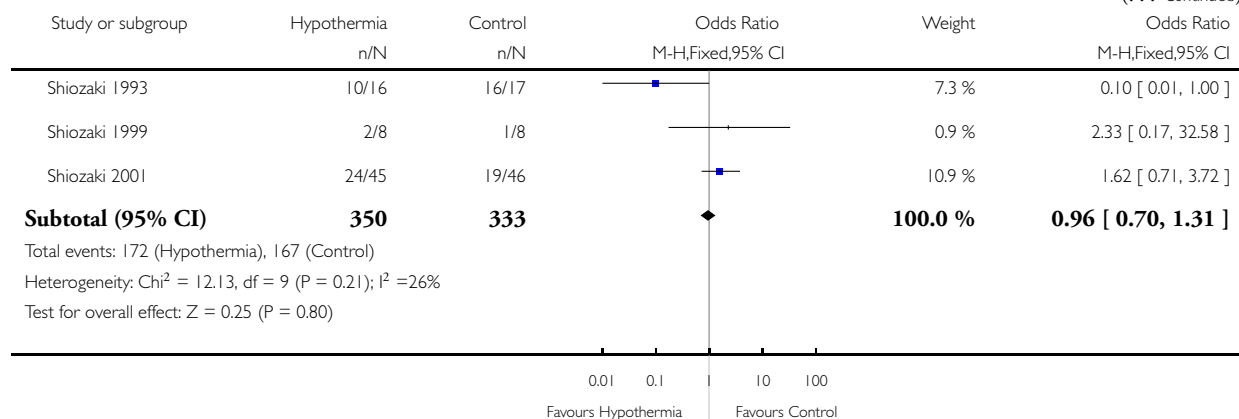
Outcome: 5 Unfavourable outcome stratified by treatment duration

Study or subgroup	Hypothermia n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
<b>1 24 hours</b>					
Clifton 1992	1/5	2/5	0.38 [ 0.02, 6.35 ]	4.6 %	0.38 [ 0.02, 6.35 ]
Harris 2009	6/12	4/13	2.25 [ 0.44, 11.52 ]	5.5 %	2.25 [ 0.44, 11.52 ]
Hutchison 2008	32/102	23/103	1.59 [ 0.85, 2.97 ]	45.4 %	1.59 [ 0.85, 2.97 ]
Marion 1997	15/39	26/42	0.38 [ 0.16, 0.94 ]	44.5 %	0.38 [ 0.16, 0.94 ]
<b>Subtotal (95% CI)</b>	<b>158</b>	<b>163</b>	<b>◆</b>	<b>100.0 %</b>	<b>1.03 [ 0.65, 1.65 ]</b>
Total events: 54 (Hypothermia), 55 (Control)					
Heterogeneity: Chi <sup>2</sup> = 7.86, df = 3 (P = 0.05); I <sup>2</sup> = 62%					
Test for overall effect: Z = 0.14 (P = 0.89)					
<b>2 48 hours</b>					
Adelson 2005 HYPO1	4/25	4/25	1.00 [ 0.22, 4.54 ]	4.2 %	1.00 [ 0.22, 4.54 ]
Adelson 2005 HYPO2	3/14	3/13	0.91 [ 0.15, 5.58 ]	3.0 %	0.91 [ 0.15, 5.58 ]
Biswas 2002	3/8	0/6	8.27 [ 0.35, 197.61 ]	0.4 %	8.27 [ 0.35, 197.61 ]
Clifton 1993	11/23	14/22	0.52 [ 0.16, 1.73 ]	9.3 %	0.52 [ 0.16, 1.73 ]
Clifton 2001	108/190	102/178	0.98 [ 0.65, 1.48 ]	56.7 %	0.98 [ 0.65, 1.48 ]
Hashiguchi 2003	3/9	1/8	3.50 [ 0.28, 43.16 ]	0.9 %	3.50 [ 0.28, 43.16 ]
Hirayama 1994	4/12	7/10	0.21 [ 0.04, 1.31 ]	6.3 %	0.21 [ 0.04, 1.31 ]

0.01 0.1 10 100  
Favours Hypothermia Favours Control

(Continued ...)

(... Continued)

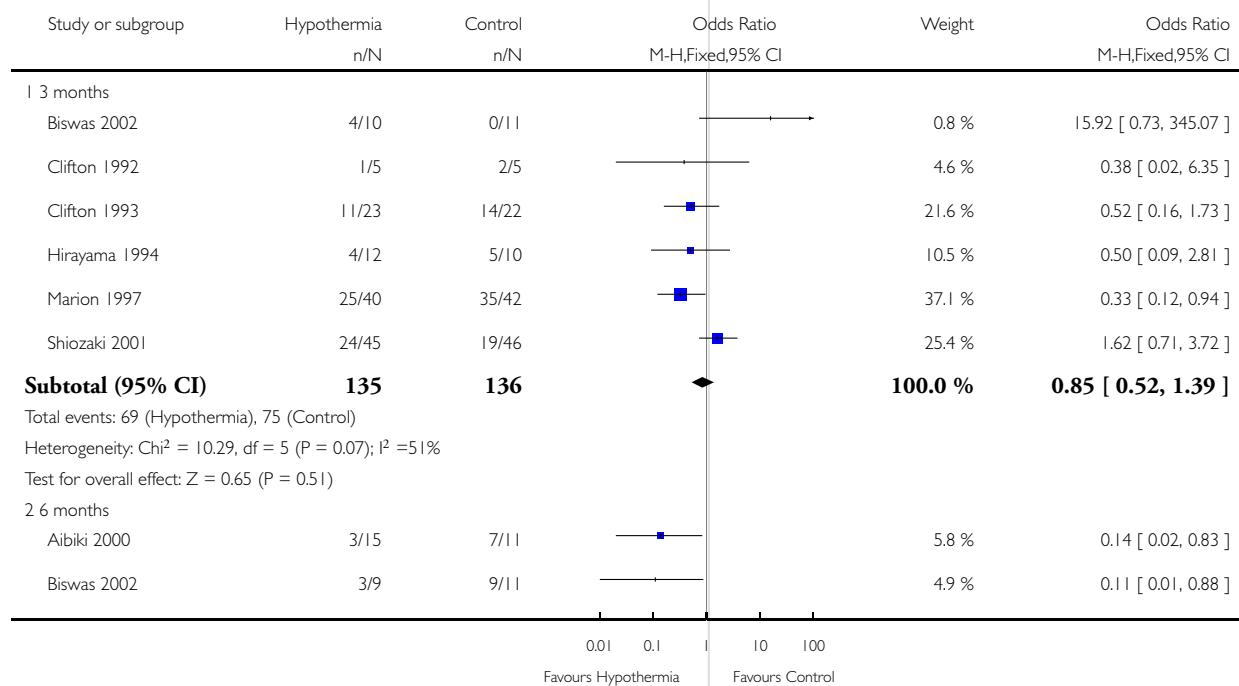


### Analysis 1.6. Comparison 1 Immediate hypothermia versus normothermia, Outcome 6 Unfavourable outcome at various times during follow-up.

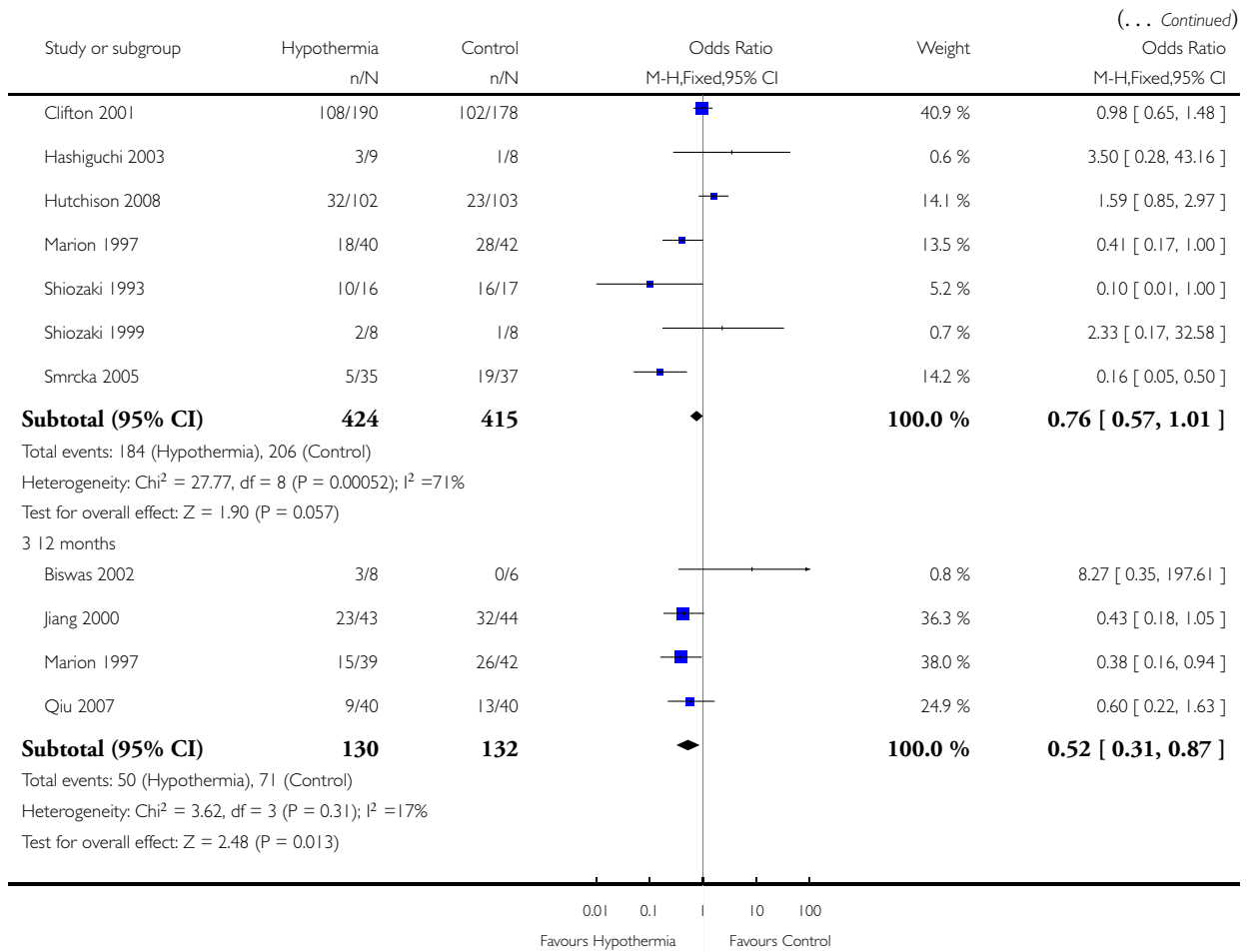
Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 6 Unfavourable outcome at various times during follow-up



(Continued ...)

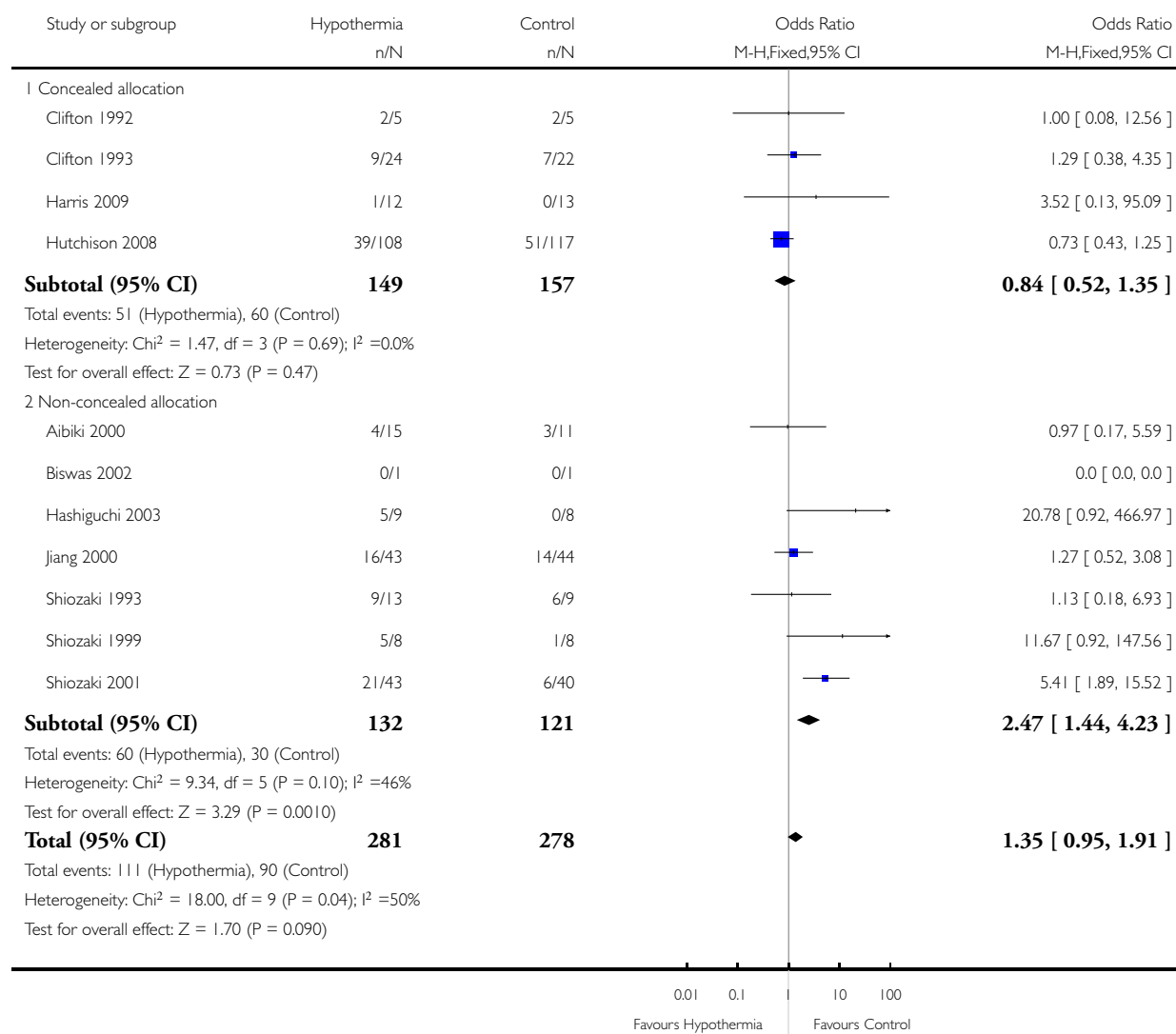


### Analysis 1.7. Comparison 1 Immediate hypothermia versus normothermia, Outcome 7 Pneumonia during the treatment period.

Review: Hypothermia for traumatic head injury

Comparison: 1 Immediate hypothermia versus normothermia

Outcome: 7 Pneumonia during the treatment period



## APPENDICES

### Appendix I. Latest search strategy

#### Injuries Group's Specialised Register (searched 12 January 2009)

((injur\* or trauma\* or lesion\* or damage\* or wound\* or oedema\* or edema\* or fracture\* or contusion\* or concus\* or commotion\* or pressur\*) and (head or crani\* or capitis or brain\* or forebrain\* or skull\* or hemisphere or intracran\* or orbit\*)) and (hypotherm\* or normotherm\* or cool\* or cold\* or temperature\* or cryother\* or cryogen\* or cryotreat\*)

#### CENTRAL (*The Cochrane Library 2009, Issue 1*)

- #1MeSH descriptor Craniocerebral Trauma explode all trees
- #2MeSH descriptor Cerebrovascular Trauma explode all trees
- #3MeSH descriptor Brain Edema explode all trees
- #4(brain or cerebral or intracranial) near3 (oedema or edema or swell\*)
- #5MeSH descriptor Glasgow Coma Scale explode all trees
- #6MeSH descriptor Glasgow Outcome Scale explode all trees
- #7MeSH descriptor Unconsciousness explode all trees
- #8glasgow near3 (coma or outcome) near3 (score or scale)
- #9(Unconscious\* or coma\* or concuss\* or 'persistent vegetative state') near 3 (injur\* or trauma\* or damag\* or wound\* or fracture\*)
- #10"Rancho Los Amigos Scale"
- #11(head or crani\* or cerebr\* or capitis or brain\* or forebrain\* or skull\* or hemispher\* or intra-cran\* or inter-cran\*) near3 (injur\* or trauma\* or damag\* or wound\* or fracture\* or contusion\*)
- #12Diffuse near3 axonal near3 injur\*
- #13(head or crani\* or cerebr\* or brain\* or intra-cran\* or inter-cran\*) near3 (haematoma\* or hematoma\* or haemorrhag\* or hemorrhag\* or bleed\* or pressure)
- #14(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
- #15MeSH descriptor Hypothermia, Induced explode all trees
- #16MeSH descriptor Cryotherapy explode all trees
- #17MeSH descriptor Body Temperature explode all trees
- #18hypotherm\* or normotherm\* or cool\* or cold\* or temperature\* or cryother\* or cryogen\* or cryotreat\*
- #19(#15 OR #16 OR #17 OR #18)
- #20(#14 AND #19)
- #21neonat\*
- #22(#20 AND NOT #21)

#### MEDLINE STRATEGY (1966 to March week 4, 2009)

- 1.exp Craniocerebral Trauma/
- 2.exp Brain Edema/
- 3.exp Glasgow Coma Scale/
- 4.exp Glasgow Outcome Scale/
- 5.exp Unconsciousness/
- 6.exp Cerebrovascular Trauma/
- 7.((head or crani\$ or cerebr\$ or capitis or brain\$ or forebrain\$ or skull\$ or hemispher\$ or intra-cran\$ or inter-cran\$) adj3 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$ or contusion\$)).ab,ti.
- 8.((head or crani\$ or cerebr\$ or brain\$ or intra-cran\$ or inter-cran\$) adj3 (haematoma\$ or hematoma\$ or haemorrhag\$ or hemorrhag\$ or bleed\$ or pressure)).ti,ab.
- 9.(Glasgow adj3 (coma or outcome) adj3 (scale\$ or score\$)).ab,ti.
- 10."rancho los amigos scale".ti,ab.
- 11.("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
- 12.((brain or cerebral or intracranial) adj3 (oedema or edema or swell\$)).ab,ti.
- 13.((unconscious\$ or coma\$ or concuss\$ or 'persistent vegetative state') adj3 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$)).ti,ab.
- 14.or/1-13

15.(randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial\$.tw,hw.  
 16.clinical trial.pt.  
 17.randomized controlled trial.pt.  
 18.15 or 16 or 17  
 19.exp models, animal/  
 20.exp Animals/  
 21.exp Animal Experimentation/  
 22.exp Disease Models, Animal/  
 23.exp Animals, Laboratory/  
 24.or/19-23  
 25.Humans/  
 26.24 not 25  
 27.18 not 26  
 28.14 and 27  
 29.exp Hypothermia, Induced/  
 30.exp Cryotherapy/  
 31.exp Body Temperature/  
 32.(hypotherm\* or normotherm\* or cool\* or cold\* or temperature\* or cryother\* or cryogen\* or cryotreat\*).ab,ti.  
 33.or/29-32  
 34.neonat\*.ab,ti.  
 35.33 not 34  
 36.28 and 35

**PUBMED Searched 6 April 2009 (last 90 days)**

#1Cranocerebral Trauma [mh] OR Brain Edema [mh] OR Glasgow Coma Scale [mh] OR Glasgow Outcome Scale [mh] OR Unconsciousness [mh] OR Cerebrovascular Trauma [mh] OR ((head or cranial or cerebral or brain\* or intra-cranial or inter-cranial) AND (haematoma\* or hematoma\* or haemorrhag\* or hemorrhage\* or bleed\* or pressure)) OR (Glasgow AND scale) OR (“diffuse axonal injury” OR “diffuse axonal injuries”) or (“persistent vegetative state”) OR ((unconscious\* OR coma\* OR concuss\*) AND (injury\* OR injuries OR trauma OR damage OR damaged OR wound\* OR fracture\* OR contusion\* OR haematoma\* OR hematoma\* OR haemorrhag\* OR hemorrhag\* OR bleed\* OR pressure))  
 #2(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh]) NOT ((models, animal[mh] OR Animals[mh] OR Animal Experimentation[mh] OR Disease Models, Animal[mh] OR Animals, Laboratory[mh]) NOT (Humans[mh]))  
 #31 and 2  
 #4(“Hypothermia, Induced”[Mesh] OR “Cryotherapy”[Mesh]) OR “Body Temperature”[Mesh]  
 #5hypotherm\* or normotherm\* or cool\* or cold\* or temperature\* or cryother\* or cryogen\* or cryotreat\* Field: Title/Abstract  
 #64 or 5  
 #7Neonat\* Field: Title/Abstract  
 #86 not 7  
 #93 and 8

**EMBASE 1980 to (week 14) March 2009**

1.exp Brain Injury/  
 2.exp Brain Edema/  
 3.exp Glasgow Coma Scale/  
 4.exp Glasgow Outcome Scale/  
 5.exp Rancho Los Amigos Scale/  
 6.exp Unconsciousness/  
 7.((brain or cerebral or intracranial) adj3 (oedema or edema or swell\$)).ab,ti.  
 8.((head or crani\$ or cerebr\$ or capitis or brain\$ or forebrain\$ or skull\$ or hemispher\$ or intra-cran\$ or inter-cran\$) adj3 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$ or contusion\$)).ab,ti.  
 9.(Glasgow adj3 (coma or outcome) adj3 (scale\$ or score\$)).ab,ti.

10. Rancho Los Amigos Scale.ab,ti.
- 11.((unconscious\$ or coma\$ or concuss\$ or 'persistent vegetative state') adj3 (injur\$ or trauma\$ or damag\$ or wound\$ or fracture\$)).ti,ab.
12. Diffuse axonal injur\$.ab,ti.
- 13.((head or crani\$ or cerebr\$ or brain\$ or intra-cran\$ or inter-cran\$) adj3 (haematoma\$ or hematoma\$ or haemorrhag\$ or hemorrhag\$ or bleed\$ or pressure)).ab,ti.
- 14.or/1-13
- 15.exp animal model/
16. Animal Experiment/
- 17.exp ANIMAL/
- 18.exp Experimental Animal/
- 19.15 or 16 or 17 or 18
20. Human/
- 21.19 not 20
- 22.(randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial\$).tw,hw.
- 23.exp clinical trial/
- 24.22 or 23
- 25.24 not 21
- 26.14 and 25
- 27.exp INDUCED HYPOTHERMIA/
- 28.exp PROFOUND INDUCED HYPOTHERMIA/
- 29.exp CRYOTHERAPY/
- 30.exp Body Temperature/
- 31.(hypotherm\* or normotherm\* or cool\* or cold\* or temperature\* or cryother\* or cryogen\* or cryotreat\*).ab,ti.
- 32.27 or 28 or 29 or 30 or 31
- 33.neonat\*.ab,ti.
- 34.32 not 33
- 35.26 and 34

**Controlled Trials metaRegister of trials (mRCT) <http://www.controlled-trials.com/mrct/> (Searched 12 January 2009)**

((injur\* or trauma\* or damage\*) and (head or crani\* or brain\* or forebrain\* or intracran\*)) and (hypotherm\* or normotherm\* or cool\* or cold\* or temperature\* or cryother\*)

**ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 to April 2009 and Conference Proceedings Citation Index- Science (CPCI-S) 1990 to 7 April 2009.**

- 1.Topic=((injur\* or trauma\* or lesion\* or damage\* or wound\* or oedema\* or edema\* or fracture\* or contusion\* or concus\* or commotion\* or pressur\*) AND (head or crani\* or capitis or brain\* or forebrain\* or skull\* or hemisphere or intracran\* or orbit\*)) AND Topic=(hypotherm\* or normotherm\* or cool\* or cold\* or temperature\* or cryother\* or cryogen\* or cryotreat\*) NOT Topic=(neonat\*)
- 2.Topic=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR controlled trial OR clinical trial) NOT Topic=(animal model\* OR Animals OR Animal Experiment\* OR Laboratory animals\* or animal disease model\*)
- 3.1 and 2

**ZETOC (searched 12 January 2009)**

Hypotherm\* head injur\* trial\*  
 Hypotherm\* head injur\* random\*  
 Hypotherm\* head injur\* control\*

Hypotherm\* brain injur\* trial\*  
 Hypotherm\* brain injur\* random\*  
 Hypotherm\* brain injur\* control\*

Hypotherm\* head trauma\* trial\*  
Hypotherm\* head trauma\* random\*  
Hypotherm\* head trauma\* control\*

Hypotherm\* brain trauma\* trial\*  
Hypotherm\* brain trauma\* random\*  
Hypotherm\* brain trauma\* control\*

## Appendix 2. Original search strategy

For the initial version of the review the following search was done:

The Specialist Trials Register for the Injuries Group was searched in May 1998 for any relevant randomised trials relating to temperature control using the search terms: hypotherm\* OR normotherm\* OR cool\* OR cold\* OR temperature.

The search strategy for the register is primarily an electronic search of both MEDLINE and CENTRAL, supplemented by various hand-searching activities listed in the Group details. This was supplemented by a comprehensive EMBASE search, also performed in May 1998 as follows, to identify all potential RCTs involving human head injury and temperature control from 1980 onwards :

001 exp head injury/  
002 pneumocephalus/  
003 cerebrospinal fluid/  
004 otorrhea/  
005 exp skull fracture/  
006 exp spine fracture/  
007 Cerebrospinal Fluid Rhinorrhea/  
008 exp asphyxia/  
009 exp spine injury/  
010 helmet/  
011 brain protection/  
012 brain edema/  
013 exp brain hemorrhage/  
014 brain hypoxia/  
015 coma/  
016 persistent vegetative state/  
017 Traumatic Epilepsy/  
018 or/1-17  
019 (head or brain or cerebr\$ or skull or crani\$ or spin\$).tw.  
020 (wound\$ or injur\$ or trauma\$ or oedema\$ or edema\$).tw.  
021 damage\$.tw.  
022 20 or 21  
023 19 and 22  
024 18 or 23  
025 human/  
026 "888".tg.  
027 25 or 26  
028 Nonhuman/  
029 "777".tg.  
030 28 or 29  
031 27 and 30  
032 30 not 31  
033 clinical trial/  
034 Multicenter Study/  
035 phase 2 clinical trial/

036 phase 3 clinical trial/  
 037 Phase 4 Clinical Trial/  
 038 Randomized Controlled Trial/  
 039 controlled study/  
 040 meta analysis/  
 041 crossover procedure/  
 042 double blind procedure/  
 043 Single Blind Procedure/  
 044 randomization/  
 045 Major Clinical Study/  
 046 placebo/  
 047 drug comparison/  
 048 clinical study/  
 049 "0197".tg.  
 050 "0150".tg.  
 051 "03738".dc.  
 052 (clin\$ adj25 trial\$).tw.  
 053 ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj25 (blind\$ or mask\$)).tw.  
 054 placebo\$.tw.  
 055 random\$.tw.  
 056 control\$.tw.  
 057 or/33-56  
 058 24 not 32  
 059 Induced Hypothermia/  
 060 Profound Induced Hypothermia/  
 061 exp temperature/  
 062 exp low temperature procedures/  
 063 cold/  
 064 cold air/  
 065 cold exposure/  
 066 (hypotherm\$ or normotherm\$ or cool\$ or cold\$ or temperature\$).tw.  
 067 or/59-66  
 068 58 and 67  
 069 68 and 57

The searches were supplemented by further handsearching of conference proceedings and abstracts as follows:

- International Conference on Recent Advances in Neurotraumatology, Italy 1996
- 2nd International Neurotrauma Symposium, Glasgow 1993
- 3rd International Neurotrauma Symposium, Toronto 1995
- 4th International Neurotrauma Symposium, Seoul 1997
- 27th Meeting of the Society for Critical Care Medicine, USA 1998
- 10th International Symposium on Intracranial Pressure, USA 1997

## WHAT'S NEW

Last assessed as up-to-date: 6 April 2009.

8 July 2009	New search has been performed	The review has been updated with data from one new trial (Harris 2009). The results have been amended accordingly. The conclusions remain the same.
-------------	-------------------------------	---

## HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 2, 1999

7 April 2009	New search has been performed	<p>The search has been updated to 7 April 2009. Two new trials have been identified as meeting the inclusion criteria, but the publications are not yet available (Bayir 2009, Harris 2009). Data from these trials will be included in the next update of this review.</p> <p>Other sections of the review have also been amended:</p> <ul style="list-style-type: none"><li>- The Background section has been updated.</li><li>- The last version of this review was updated to January 2009, with ten trials in 'Studies awaiting classification' pending confirmation of randomisation. The review authors have been unable to confirm these trials are randomised controlled trials, and they have been excluded.</li><li>- With this update, and to ensure consistency across included trials, all included trials have been re-assessed against the inclusion criteria. One trial that was included in previous versions of the review has now been excluded (Meissner 1998) as there is no mention of randomisation.</li><li>- The results have been amended accordingly; the conclusions of the review remain the same.</li><li>- The details of two ongoing trials have been included (Beca 2006, Maekawa 2002).</li></ul>
26 January 2009	New citation required and conclusions have changed	<p>Review updated; search updated to 12 January 2009. Data from one new study is included (Hutchinson 2008). The results of the review have been amended accordingly.</p> <p>One further study was excluded (Gal 2002).</p>
31 October 2008	New citation required and conclusions have changed	<p>Eight new trials are included in this update. The results of the review have been amended accordingly.</p> <p>One trial currently in 'studies awaiting assessment' (</p>

(Continued)

		<p>Hutchison 2008a) was identified after the search was completed for this update. Data from this trial will be included in the review for Issue 2, 2009.</p> <p>The title has been changed from 'Therapeutic hypothermia for head injury' to 'Hypothermia for traumatic head injury'.</p> <p>The authors of the review have changed.</p>
9 July 2008	Amended	<p>The version of this review published in July 2008 mistakenly included three additional trials in the table of included studies and references sections.</p> <p>Data from these three studies were not included in the review. The text of the review is the same as the 28 July 2004 update.</p>
14 May 2008	Amended	<p>Converted to new review format.</p>
28 July 2004	New search has been performed	<p>Substantive amendment. New studies found and included or excluded.</p> <p>Two more trials have been included, and one added to the awaiting assessment list as we have not been able to obtain a copy of the trial.</p> <p>Conclusions have been reviewed and compared to those found in a review of the topic in JAMA.</p>
12 November 2001	New search has been performed	<p>Four studies were included, which were published since the original version of this review.</p> <p>Quantitative synthesis of the incidence of pulmonary infections was conducted in the 2001 update.</p>

## CONTRIBUTIONS OF AUTHORS

David Signorini wrote the protocol, performed the searches and reviewed the titles and abstracts, extracted the data, performed the analyses and wrote the draft of the review. Phil Alderson (PA) reviewed the manuscripts of potential trials, extracted the data and edited the draft review.

For the 2001 update, the Injuries Group performed the search and screened studies. PA and Chirag Gadkary assessed eligibility, extracted data, performed the analysis and redrafted the text.

For the 2004 update, the Injuries Group performed the search and screened studies. PA and the Injuries Group extracted data, and PA performed the analysis and rewrote the text.

For the 2008 update, the search was carried out by Karen Blackhall of the Cochrane Injuries Group. ES and IR assessed trial eligibility and applied the selection criteria. ES extracted data, and IR checked for accuracy. ES updated the text of the review. IR and ES performed the analysis and edited the manuscript. PA checked the final manuscript of the update.

Karen Blackhall performed the search for the January 2009 update. ES and IR assessed trial eligibility and applied the selection criteria. ES extracted the data, and IR checked the extracted data for accuracy. ES updated the text of the review. IR and ES performed the analysis and edited the manuscript. PA checked the final manuscript of the update.

In April 2009, Karen Blackhall updated the search for trials. ES and IR assessed trial eligibility and applied the selection criteria. ES and IR re-assessed all previously included trials against the inclusion criteria. All authors agreed that the Meissner 1998 study should be excluded. ES updated the text of the review. IR and PA checked the final manuscript of the update.

Emma Sydenham included data from the Harris 2009 trial for the July 2009 update. IR and PA checked the extracted data. All authors approved the manuscript for publication.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- DFS was supported by MRC project grant G9604637, UK.
- NHS R&D Programme, UK.

### External sources

- CG was supported by the Doris Duke Research Fellowship, USA.

## **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

The 2008 update of this review evaluated study quality by allocation concealment only. The incidence of pneumonia was also stratified by study quality.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

\*Hypothermia, Induced [adverse effects; mortality]; Craniocerebral Trauma [mortality; \*therapy]; Randomized Controlled Trials as Topic

### **MeSH check words**

Humans