CRITICAL CARE

REVIEW

Clinical review: Brain-body temperature differences in adults with severe traumatic brain injury

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Abstract

Surrogate or 'proxy' measures of brain temperature are used in the routine management of patients with brain damage. The prevailing view is that the brain is 'hotter' than the body. The polarity and magnitude of temperature differences between brain and body, however, remains unclear after severe traumatic brain injury (TBI). The focus of this systematic review is on the adult patient admitted to intensive/neurocritical care with a diagnosis of severe TBI (Glasgow Coma Scale score of less than 8). The review considered studies that measured brain temperature and core body temperature. Articles published in English from the years 1980 to 2012 were searched in databases, CINAHL, PubMed, Scopus, Web of Science, Science Direct, Ovid SP, Mednar and ProQuest Dissertations & Theses Database. For the review, publications of randomised controlled trials, non-randomised controlled trials, before and after studies, cohort studies, case-control studies and descriptive studies were considered for inclusion. Of 2,391 records identified via the search strategies, 37 were retrieved for detailed examination (including two via hand searching). Fifteen were reviewed and assessed for methodological quality. Eleven studies were included in the systematic review providing 15 brain-core body temperature comparisons. The direction of mean brain-body temperature differences was positive (brain higher than body temperature) and negative (brain lower than body temperature). Hypothermia is associated with large brain-body temperature differences. Brain temperature cannot be predicted reliably from core body temperature. Concurrent monitoring of brain and body temperature is recommended in patients where risk of temperature-related neuronal damage is a cause for clinical concern and when deliberate induction of below-normal body temperature is instituted.

Introduction

Brain temperature monitoring has advanced since Benzinger and colleagues [1] first used the tympanum as a 'proxy' for brain temperature monitoring. It was not until 1990 that Mellergard and colleagues [2] performed the first human invasive, continuous monitoring of intracranial temperature via an intraventricular thermocouple. Since then, several types of invasive brain temperature measurement devices have been developed to investigate temperature in different parts of the human brain. The measurement of brain temperature is now more usually made in brain tissue (parenchyma), cerebral ventricle or in the subdural space using a thermistor. Patients who may benefit from continuous brain temperature monitoring include patients with severe traumatic brain injury (TBI).

For the purpose of this systematic review, severe TBI is defined as 'a brain injury incurred by a traumatic mechanism of injury with a resultant level of consciousness categorised by a Glasgow Coma Scale (GCS) score of 8 or lower' [3]. TBI affects two to three million people in the USA each year [4]. In South East Asia (Singapore) 50% of all trauma-related mortality is due to severe TBI [5].

Of the known clinical and physiological events contributing to secondary ischaemic damage in vulnerable (survivable) neurones, raised temperature (due to fever or to hyperthermia) is a potentially avoidable risk factor. The problem is that the temperature of injured tissue is seldom measured [6]. Rather, the customary assumption is that temperature, wherever it may be measured on or in the body, provides sufficient reliability and reproducibility to estimate brain temperature. During aggressive (surface or invasive) therapies directed towards induction

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of hypothermia the temperature of the 'target' organ is just a matter of guesswork. Proper and robust assessment and management of patients undergoing therapeutic temperature management warrant an objective assessment of the treatment (rate and speed of brain temperature reduction). Currently, temperature measurement of the oral cavity, skin folds (axilla, groin), tympanum, and rectum are the sites most commonly used in neurocritical care [7].

The overall aim of this systematic review was to critically appraise, synthesise and present the best available evidence that core body temperature is a reliable proxy for brain temperature in adult patients with severe TBI. Before undertaking this systematic review, library databases of the Cochrane Collaboration and of the Joanna Briggs Institute (JBI) were searched. No previous systematic reviews on the topic had been undertaken. Our objective, therefore, was to close the gap in knowledge about the reliability of assuming brain temperature values from measurements made at other body sites.

Methods

This paper is abridged and based on a detailed review published previously in the JBI Library of Systematic Reviews [8]. Ethical approval was not required to undertake the review.

Search strategy

Literature published in languages other than English were excluded from the review.

The search strategy aimed to retrieve published and unpublished studies written in the English language during the last 32 years (1980 to 2012). The justification for this publication restriction is because invasive brain temperature measurement in humans was not available before 1980. A three-step search strategy was utilized. An initial (limited) search of PubMed and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract and index terms used to describe the article. A second search using all identified keywords and index terms was undertaken for all included databases. The reference list of all identified reports and articles was then searched for additional studies. The initial keywords were categorised as three concepts (Table 1). The databases searched were: CINAHL, PubMed, Scopus, Web of Science, Science Direct, Ovid SP, Mednar, ProQuest Dissertations & Theses Database. For a full list of search terms used in this review, see [8].

Table 1. Keyword categories: development of search categories and search terms

Concepts	Keywords
Concept 1: Brain temperature	Epidural temperature
	Ventricular temperature
	Intraparenchymal temperature
	Cortical temperature
	Intraventricular temperature
	Jugular bulb temperature
	Subdural temperature
	Brain temperature
Concept 2: Core body temperature	Core temperature
	Body temperature
	Core body temperature
	Pulmonary artery temperature
	Esophageal temperature
	Oesophageal temperature
	Bladder temperature
	Tympanic temperature
	Temporal artery temperature
	Rectal temperature
Concept 3: Severe traumatic brain injury	Severe traumatic brain injury
	Traumatic brain injury
	TBI
	Brain injury
	Head injury

Inclusion criteria

Studies of male and female adult patients (in this review, aged 15 years and above) admitted to an adult ICU with the diagnosis of severe TBI (GCS ≤8) were included. Evidence of brain and body temperature monitoring during the study was a requirement for inclusion. All other conditions of acquired brain damage (for example, stroke, brain tumour, subarachnoid haemorrhage) were excluded from this review as were publications with brain temperature monitoring performed on non-human subjects.

Selection of studies

The review considered any randomised controlled trial (RCT). In the absence of RCTs, other research designs - non-randomised controlled trials, pre-test-post-test studies, cohort studies, case-control studies, and descriptive studies - were considered for inclusion.

Methods of temperature measurement

The review included studies reporting concurrent brain temperature and core body temperature measurements. The direct brain temperature monitoring methods include subdural temperature, intraventricular temperature, and tissue (parenchyma) temperature. Indirect

methods (jugular bulb temperature) for brain temperature estimation were also included [9]. Core body temperature measurement sites include tympanum, temporal artery, rectal, bladder, oesophageal and pulmonary artery sites.

Assessment of methodological quality

The publications selected for retrieval were assessed for methodological validity by two independent reviewers (CC and KWL) before data extraction. The JBI-MAStARI critical appraisal tool was used. However, in view of the specific review question, neither the standard nor bespoke appraisal tools available (the latter for temperature method comparison [10]) from JBI were appropriate. In this review, where measurement of temperature *per se* at two different body sites was made predominately by electronic thermometry systems, a modification of the appraisal tool of Craig and colleagues [10] was developed and approved (Figure 1) by the JBI [8]. As there were no disagreements in the assessment of methodological quality of the retrieved studies, a third, moderator, reviewer was not required.

Data extraction and data synthesis

Data were extracted from papers included in the review using a bespoke data extraction tool (Figure 2) [8]. The extraction of data included specific details of therapeutic temperature interventions, study population and methods and outcomes of significance to the review question and specific objectives. In extracting numeric data, and where mean values or confidence interval (CI) was not provided by the original study authors, CI ($\bar{x} \pm 1.96(SD/\sqrt{n})$) was calculated from raw data where available. For data synthesis, statistical pooling was not possible; therefore, findings are presented in narrative form.

Results

Search results

The literature search yielded 2,391 articles (Figure 3). Thirty-seven studies were retrieved as 'eligible'. After filtering the title and abstract, 22 were excluded following review of the full text. Of these, 15 were assessed for methodological quality. Eleven studies met the criteria for inclusion and were included in the review (Table 2).

Study characteristics

The sample size of the 11 studies included in this review ranged from 7 [11] to 58 [12], giving a total of 272 patients aged 15 years [13] to 80 years [14,15]. The publications were descriptive studies (Table 3) conducted in the USA [12,16-18], the UK [14,19], Japan [13,20], Taiwan [15], Austria [11], or People's Republic of China [21]. Patients were recruited from an adult ICU. Brain injury was described as severe TBI [11,13-15,17,19,20] or severe head injury [12,16,18,21]. At the time of brain temperature monitoring all patients in the 11 studies had a GCS of ≤8.

One study only used a prospective methodological approach in the study design to power the sample size sufficiently to identify a scale of difference between brain and body temperature [19]. The remainder were designed for observational 'convenience' or pragmatic sampling.

Seven studies were designed to investigate the difference between brain temperature and core temperature *per se* [11,14-16,18-20]. By contrast, differences between brain temperature and core temperature were not the primary objective of the remainder [12,13,17,21]. Even so, the latter studies were included because data of the temperature gradient between brain and core was reported.

Four studies investigated brain and core body temperature under standard routine care without performing any thermoregulatory interventions [14,15,18,19] (Table 2). Two performed therapeutic temperature management to a target of 'normothermia' [11,17] while in four studies therapeutic hypothermia was induced [13,16,20,21]. One study investigated temperature of patients with both induced normothermia and induced hypothermia [12]. All 11 studies provided data on brain temperature and core body temperature measurements. Temperature measurement began during the first 48 hours after injury, providing parity in the onset and temporal profile of the measurements.

Fifteen different brain-body temperature measurement comparisons were reported in the 11 studies. For comparison with brain temperature, measured in cerebral ventricle [16,17], subdural space [13] and tissue (parenchyma) [11,12,14,15,18-21], core body temperature was measured in rectum [12,13,15-19,21], bladder [11,16,20], jugular vein [13], temporal artery [14,15] and tympanic membrane [14]. Calibration of thermometers was performed in five studies only [15,16,18-20]. The remaining studies did not report any calibration procedures.

Statistical analyses

In the respective papers, descriptive statistics were used to report the mean values (with standard deviation (SD)) for brain temperature and core temperature [11,12,14, 17,18,21] separately. Seven studies report mean (SD) differences between the sites [12-15,18-20].

In seven papers [11,14-16,18-20] the study design was to show the temperature difference between brain and body. In testing for agreement of the core body temperature to perform as a measure for brain temperature, two studies only [14,15] used the statistical method proposed by Bland and Altman [22,23]. With this method the spread of differences between brain and body core sites are observed and limits of agreement indicate whether

Appraisal tool:

Reviewer: Date:

Author: Year:

Journal: Record Number:

	Yes	No	Unclear	Comments
1. Ethical approval?				
2. **Patients:** Were the patients' diagnosis Traumatic Brain Injury only?				
3. Patients: Were the patients' GCS ≤8 during recruitment?				
4. **Patients:** Were the participants more than 18 years old?				
5. **Temp:** Were comparisons of temperature performed?				
6. **Temp:** Were thermometers calibrated?				
7. **Temp:** Were all temperature measurements carried out concurrently or immediately sequentially?				
8. **Temp:** Were the test and reference standard measured independently (blind) of each other?				
9. **Temp:** Was the second reading taken before any interventions were given?				
10. **Temp:** Was there evidence of a systematic order of the temperature measurement?				
11. **Methodology:** Are the outcomes measured in a reliable way?				
12. **Methodology:** Is sample representative of patients in the population as a whole?				
13. **Methodology:** Are the patients at a similar point in the course of their condition/illness?				
14. **Methodology:** Was appropriate statistical analysis used?				

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (including reasons for excluding):

_____
_____
_____
_____
_____

Figure 1. Appraisal tool. A modification of the appraisal tool of Craig and colleagues [10] was developed and approved.

Extraction Tool

Reviewer: Date:

Author: Year:

Journal: Record Number:

Study Method:

Participants: Setting:

Population:

Sample size:

Interventions:

	Brain Temperature	Core temperature
Total number of measurements		
Measurement device		
Measurement site		
Type of thermometers		
Mean		
Standard deviation		
Range		

Differences in mean:

Differences in SD:

Range of difference:

Correlation coefficient (if applicable):

Authors Conclusions:

Comments:

Figure 2. Extraction tool. Data were extracted from papers included in the review using a bespoke data extraction tool.

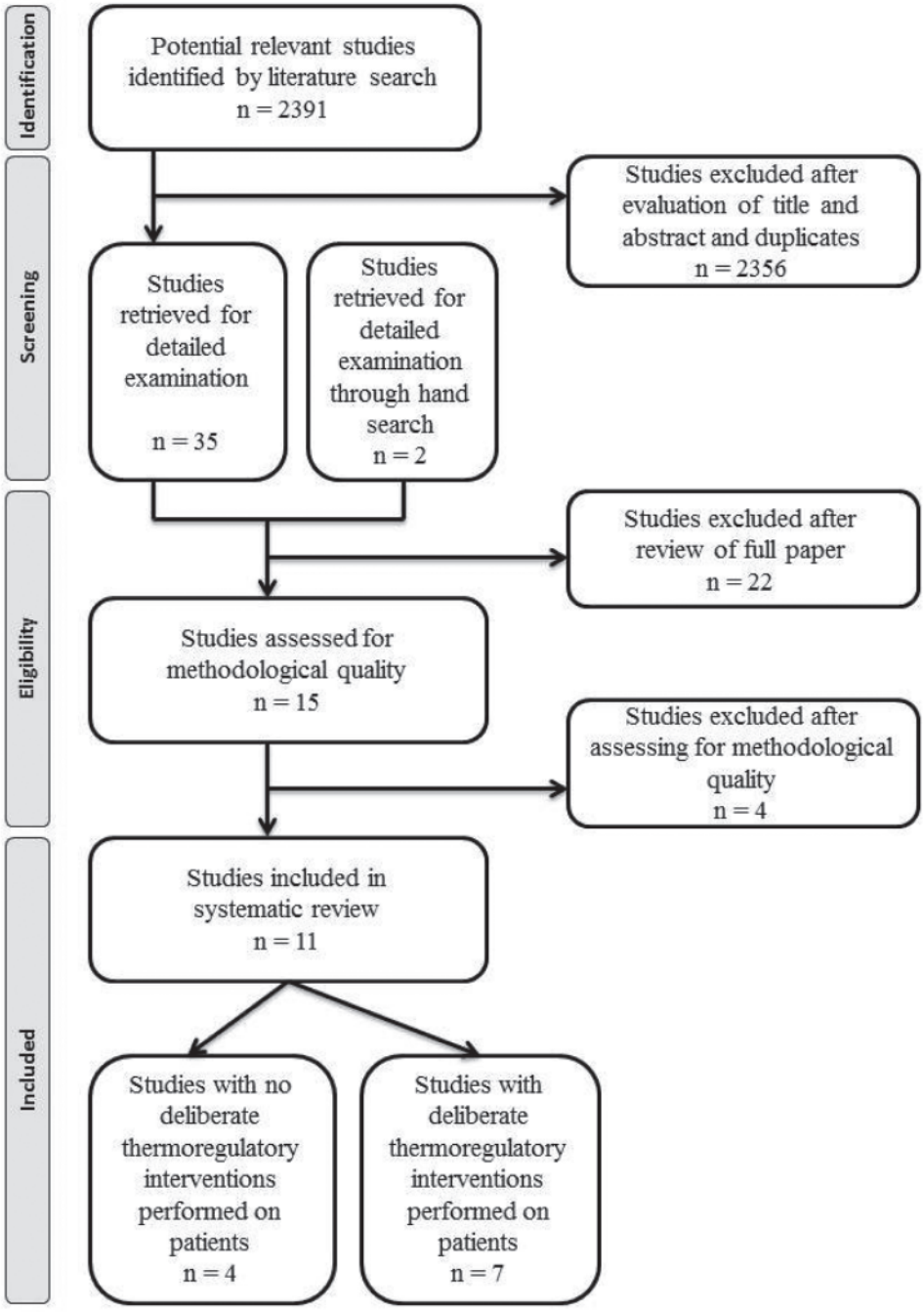

Figure 3. The selection and evaluation process for included articles for the systematic review using PRISMA (Transparent Reporting of Systematic Reviews and Meta-Analyses).

core temperature 'under-estimates' or 'over-estimates' brain temperature readings. Another study [19] calculated individual differences between brain and body (rectal) sites to produce an overall group mean with 95% CI using a random effects meta-analysis method. The remaining studies reported mean (SD) of differences only.

Four studies report temperature values incidental to a different study objective. For example, efficacy of therapeutic temperature interventions (for example, whole body cooling to induce hypothermia) [12,13,17,21] on brain and body temperature. Here, agreement between the two measurement sites was not tested; rather, mean (SD) only were reported. The results of this systematic review are presented as a narrative summary to address the review objective; whether brain temperature is higher, lower, or the same as core body temperature in patients with severe TBI.

Table 2. Differences between brain and body temperature (°C) measurement sites for studies under review

Reference	Core body temperature measurement site	Number of patients	Thermoregulatory interventions (target temperature)	Mean difference (SD) (°C)	95% confidence interval
Rumana *et al.* [18]	Rectal	30	No thermoregulatory interventions	1.1 (0.6)	(0.89 to 1.31)[a]
Zhang *et al.* [21]	Rectal	18[b]	No thermoregulatory interventions	0.8[c]	
Childs *et al.* [19]	Rectal	19	No thermoregulatory interventions	-0.04 (0.9)	(-0.13 to 0.05)
Puccio *et al.* [17]	Rectal	21	No thermoregulatory interventions	-0.4[c]	
Kirk *et al.* [14]	Tympanic membrane	20[b]	No thermoregulatory interventions	0.9 (0.7)	(0.59 to 1.21)[a]
Kirk *et al.* [14]	Temporal artery	20[b]	No thermoregulatory interventions	0.3 (0.4)	(0.12 to 0.48)[a]
Kuo *et al.* [15]	Temporal artery	28[b]	No thermoregulatory interventions	0.64 (0.60)	(0.42 to 0.86)[a]
Kuo *et al.* [15]	Rectal	28[b]	No thermoregulatory interventions	0.23 (0.45)	(0.06 to 0.40)[a]
Henker *et al.* [16]	Bladder	6[b]	Induced hypothermia therapy using hypothermia blankets, iced water lavage, and decreased ventilator circuit temperature (T_{bl}: 32.0 to 33.0°C)	1.0 (0.7)[c]	
Henker *et al.* [16]	Rectal	8[b]	Induced hypothermia therapy using hypothermia blankets, iced water lavage, and decreased ventilator circuit temperature (T_{bl}: 32.0 to 33.0°C)	0.8 (0.8)[c]	
Zhang *et al.* [21]	Rectal	18[b]	24 hours after induced hypothermia therapy using cooler blankets (T_r: 31.5 to 34.9°C)	1.1[c]	
Soukup *et al.* [12]	Rectal	58[d]	Induced hypothermia therapy (T_{br} <36.0°C)	-0.2 (0.6)	(-0.24 to -0.16)[a]
Tokutomi *et al.* [13]	Rectal	31[b]	Induced hypothermia therapy using water-circulating blankets (T_{br} = 33.0°C)	0.5 (0.3)	(0.39 to 0.61)[a]
Tokutomi *et al.* [13]	Jugular vein	31[b]	Induced hypothermia therapy using water-circulating blankets (T_{br} = 33.0°C)	0.3 (0.3)	(0.19 to 0.41)[a]
Suehiro *et al.* [20]	Bladder	11	Induced hypothermia therapy using water-cooling blankets (T_{br} = 36.0 to 37.5°C)	-0.17 (0.02)	(-0.18 to -0.16)[a]
Zhang *et al.* [21]	Rectal	18[b]	Induced normothermia using cooler blankets (T_r: 36.5 to 37.0°C)	1.4[c]	
Soukup *et al.* [12]	Rectal	58[d]	Spontaneous normothermia (T_{br}: 36.0 to 37.5°C)	0.0 (0.5)	(-0.02 to 0.02)[a]
Puccio *et al.* [17]	Rectal	21	Induced normothermia using intravascular cooling catheters (T_r: 36.0 to 36.5°C)	-0.1[c]	
Fischer *et al.* [11]	Bladder	7	Induced normothermia using intravascular cooling device (T_{bl} = 36.5°C)	0.1[c]	
Soukup *et al.* [12]	Rectal	58[d]	Spontaneous hyperthermia (T_{br} >37.5°C)	0.3 (0.5)	(0.28 to 0.32)[a]
Soukup *et al.* [12]	Rectal	58[d]	Spontaneous hypothermia (T_{br} <36.0°C)	-0.8 (1.4)	(-1.03 to -0.57)[a]

[a]Mean difference, standard deviation (SD), and 95% confidence interval; data calculated by reviewers using 'raw' data values provided in the respective publications. [b]Multiple recruitment categories. [c]Unable to calculate SD and/or 95% CI due to insufficient 'raw' data in publication. [d]Authors did not specify patients in each group. T_{bl}, bladder temperature; T_{br}, brain temperature; T_r, rectal temperature.

Table 3. Studies included in the review

Reference	Study design, setting, country	Population and sample size	Age range (years) and GCS score	Brain device and method	Core device and method	Calibration	Deliberate thermoregulatory interventions	Results (°C)
Henker *et al.* (1998) [16]	Descriptive comparison ICU USA	Severe head injury n = 8	Age: 18-58 GCS: 4-7	Site: right lateral ventricle Device: type T thermocouple (model no. 12983 Ventricular Catheter with Thermocouple; Radionics, Burlington, MA, USA)	Site 1: rectum Device: Hewlett-Packard Model 21090A probe (Hewlett-Packard Company, Androver, MA, USA) Site 2: bladder Device: bladder catheter (Bardex Lubricath, model 909116; CR Bard, Inc., Convington, GA, USA)	Yes	Random assignment to groups Hypothermia ('target' 32°C for 48 h, n = 5) Normothermia group (n = 3)	• Mean (SD) of T_{br} - T_r: 0.8 (0.8) °C • Mean (SD) of T_{br} - T_{bl}: 1.0 (0.7) °C Brain temperature is higher than rectal and higher than bladder temperature Not possible to determine which patients reached the hypothermia 'target'
Rumana *et al.* (1998) [18]	Descriptive study ICU USA	Severe head injury n = 30	Mean (SD) age: 30.7 (13.0) GCS: ≤8 (n = 25); >8 (n = 5)	Site: intraparenchyma Device: Licox, Kiel-Mielkendorf, Germany	Site: rectum Device: 10-Fr thermistor probe (400 series, Sheridan Catheter Corporation, Argyle, NY, USA)	Yes	No	• Mean (SD) of T_{br} - T_r: 1.1 (0.6) °C Brain temperature is higher than rectal temperature
Zhang *et al.* (2002) [21]	Descriptive study Unclear China	Severe head injury n = 18	Age: 20-73 GCS: ≤8	Site: frontal white matter Device: flexible Clark-type microcatheter (Licox-II system, GSM Co. Ltd, Germany)	Site: rectum Device: not reported	Unclear	Mild hypothermia on all patients	• Mean of T_{br} - T_r at 0 hours after cooling: 0.8°C • Mean of T_{br} - T_r at 24 hours after cooling: 1.1°C • Mean of T_{br} - T_r at 72 hours after cooling: 1.4°C Brain temperature is consistently higher at 0, 24 and 72 hours after cooling
Soukup *et al.* (2002) [12]	Descriptive study ICU USA	Severe head injury n = 58	Age: ≥16 GCS: ≤8	Site: parenchyma Device: Paratrend 7, Diametrics Medical Inc., Roseville, MN, USA	Site: rectum Device: Hewlett Packard	Unclear	Mild hypothermia (n = 33); Control (n = 25)	• Mean (SD) of T_{br} - T_r in the normothermic group: 0.0 (0.5) °C • Mean (SD) of T_{br} - T_r in the hyperthermic group: 0.3 (0.5) °C • Mean (SD) of T_{br} - T_r in the therapeutic 'cooled' group: -0.2 (0.6) °C • Mean (SD) of T_{br} - T_r of spontaneous hypothermia group: -0.8 (1.4) °C Brain temperature is higher than rectal temperature at normothermia and hyperthermia conditions, but lower during therapeutic cooling and spontaneous hypothermia
Tokutomi *et al.* (2003) [13]	Descriptive study ICU Japan	Severe brain injury n = 31	Age: 15-69 GCS: 3-5	Site: subdural Device: Camino Direct Pressure monitor (Camino Laboratories, San Diego, CA, USA)	Site: rectum Device: Bi-Temp (RSP, Boston, MA, USA) Site 2: Jugular vein Device: fibreoptic catheter (manufacturer type not stated)	Unclear	Hypothermia therapy on all patients	• Mean (SD) of T_{br} - T_r: 0.5 (0.3) °C • Mean (SD) of T_{br} - T_{jv}: 0.3(0.3) °C Brain temperature is higher than both rectal and jugular vein temperature
Childs *et al.* (2005) [19]	Descriptive study ICU UK	Severe TBI n = 19	Age: 19-70 GCS: 3-13	Site: brain parenchyma Device: Camino 110-4BBT, 4 Fr, fibre-optic, transducer tipped sensor (Integra Neurosciences, Andover, UK)	Site: rectum Device: Mon-a-therm 400 series, 9 Fr, thermistor (Mallinckrodt Medical, Tyco Healthcare, Gosport, UK)	Yes	No	• Mean (SD) of T_{br} - T_r: -0.04 (0.9) °C No evidence of systematic difference between brain and core temperature. Brain temperature is lower than rectal temperature

Continued overleaf

Table 3. Continued

Reference	Study design, setting, country	Population and sample size	Age range (years) and GCS score	Brain device and method	Core device and method	Calibration	Deliberate thermoregulatory interventions	Results (°C)
Kirk *et al.* (2009) [14]	Descriptive study ICU UK	Severe TBI n = 20	Age: 17-76 GCS: ≤8	Site: intraparenchyma Device: Neurovent-PTemp™, Raumedic AG, Münchberg, Germany	Site 1: tympanic membrane Device: Core-Check thermometer (model 2090 IVAC Corporation, San Diego, California, USA) Site 2: temporal artery, Device: model TAT5000, Exergen, Watertown, MA, USA	Unclear	No	• Mean (SD) of T_{br} - T_{tm}: 0.9 (0.7) °C • Mean (SD) of T_{br} - T_{ta}: 0.3 (0.4) °C Brain temperature is higher than both tympanic membrane and temporal artery temperature Temporal artery temperature is closer to brain than tympanic membrane temperature is
Puccio *et al.* (2009) [17]	Descriptive study Neurotrauma ICU USA	Severe TBI n = 42	Mean (SD) Age: 36.4 (14.8) GCS: 3-8	Site: intraventricular Device: Licox® (Integra LifeSciences Corp., Plainsboro, NJ, USA)	Site: rectum Device: not reported	Unclear	Induced normothermia (n = 21) Control (n = 21)	• Mean of T_{br} - T_r in the control group: -0.4°C • Mean of T_{br} - T_r in the induced normothermic group: -0.1°C Brain temperature is lower than rectal temperature in both groups of patients
Kuo *et al.* (2011) [15]	Descriptive study ICU Taiwan	TBI n = 28	Age: 16-80 GCS: 6 (median)	Site: intraparenchyma Device: 110-4BT, Pressure-Temperature Monitoring Kit (Integra Camino, San Diego, CA, USA)	Site 1: rectum Device: Medi-Therm II Hyper-Hypothermia Machine (Gaymar Industries, Orchard Park, NY, USA) Site 2: temporal artery Device: Temporal Scanner™ TAT-5000 (EXERGEN, Boston, MA, USA)	Yes	No	• Mean (SD) of T_{br} - T_r: 0.23 (0.45) °C • Mean (SD) of T_{br} - T_{ta}: 0.64 (0.60) °C Brain temperature is higher than both rectal temperature and temporal artery temperature
Suehiro *et al.* (2011) [20]	Descriptive study Did not specify Japan	Severe TBI n = 11	Age: 15-73 GCS: ≤8	Site: intraparenchyma Device: Camino Laboratories, San Diego, California, USA	Site: bladder Device: thermocouple (Terumo, Tokyo, Japan)	Yes	Mild hypothermia on all patients	• Mean (SD) of T_{br} - T_{bl}: -0.17 (0.02) °C Brain temperature is lower than bladder temperature
Fischer *et al.* (2011) [11]	Descriptive study Neuro-ICU Austria	Severe TBI n = 7	Age: 21-69 GCS: 3-8	Site: intraparenchyma Device: Neurovent-Temp-P (Raumedic AG, Muenchberg, Germany)	Site: bladder Device: Kendall Curity, Mansfield, Massachusetts, USA	Unclear	Induced normothermia (36.5°) on all patients	• Mean of T_{br} - T_{bl}: 0.1°C Brain temperature is higher than bladder temperature during induced normothermia

TBI, traumatic brain injury; T_{bl}, brain temperature; T_r, rectal temperature; T_{bl}, bladder temperature; T_{tm}, tympanic membrane temperature; T_{ta}, temporal artery temperature; T_{jv}, jugular vein temperature.

Brain temperature versus rectal temperature

Eight of eleven studies investigated the difference between brain temperature and rectal temperature [12,13,15-19,21]. Patients were studied under standard care, that is, they did not receive therapeutic temperature management in three studies [15,18,19]. For the remainder, therapeutic temperature management to a target of normothermia [17] or mild hypothermia [13,21] was used for all study patients or for selected patients within the study cohort [12,16].

Data are expressed as mean (SD). The mean difference (SD) between sites is standardised throughout the review as mean brain temperature minus mean core body temperature. A positive mean difference (MD) indicates brain temperature higher than body core temperature whereas a negative MD indicates that brain is lower than body core temperature. Data are also shown as mean (95% CI) where values are either given by the study author [19] or calculated by the reviewer (KWL) from data available.

Standard routine management

Childs and colleagues [19] compared the difference between brain parenchyma temperature with rectal temperature in 19 patients. They report a MD (SD) of -0.04°C (0.9°C) and a 95% CI of -0.13 to 0.05 between the two sites. There was no evidence of a systematic difference between brain and core body temperature. By contrast, Rumana and colleagues [18], measuring temperature at the same sites, report a temperature MD (brain parenchyma-rectum) of 1.1°C (SD 0.6°C). The 95% CI was calculated by review author KWL to be 0.89 to 1.31. This showed that mean brain temperature was more than 1°C higher than mean rectal temperature.

For studies where induction of normothermia was the therapeutic temperature management intervention, Puccio and colleagues [17] compared temperature measured in rectum and cerebral ventricle in two groups of patients. In one group (n = 21) rectal temperature was maintained at 36.5°C for three days while the other group received standard care (control, n = 21). Mean (SD) brain temperature was 36.6°C (0.9°C) and 37.4°C (1.4°C) for normothermia and control groups, respectively. For rectal temperature, mean temperature (SD) was 36.5°C (0.6°C) and 37.0°C (0.9°C). The authors did not report MD (SD) between the two sites. From the data available, author (KWL) calculated temperature MD (brain minus rectum). For both the induced normothermia and control group, the MD was slightly negative but clinically insignificant at -0.1°C under conditions of normothermia. For the control group, mean brain temperature was slightly (0.4°C) higher than mean rectal temperature. The CI of this study could not be calculated from data provided in the publication.

Hypothermia therapy

Tokutomi and colleagues [13] and Zhang and colleagues [21] examined the differences between brain temperature and rectal temperature in their studies, which explored the effect of mild hypothermia on brain temperature and other physiological parameters (brain tissue partial pressure of oxygen, intracranial pressure, systemic and intracranial haemodynamics, metabolism). For the former study [13], 31 patients were 'cooled' to 33°C followed by slow re-warming after 48 to 72 hours of hypothermia. Mean brain (subdural) temperature was consistently higher than mean rectal temperature: MD 0.5°C (0.3°C), 95% CI 0.39 to 0.61.

For the 18 patients recruited by Zhang and colleagues [21] blankets were used to lower body temperature (Meditherm-Gaymar, USA) to a target (rectal) of 31.5°C to 34.9°C for between 1 and 7 days (average 58 hours). The MD (SD) of brain temperature at 0 hours, 24 hours and 72 hours after therapeutic hypothermia was 38.5°C (1.5°C), 33.6°C (1.5°C) and 34.5°C (1.8°C), respectively, and the mean (SD) of rectal temperature for the same interval after hypothermia (0 hours, 24 hours, 72 hours) was 37.7°C (1.7°C), 32.5°C (1.2°C) and 33.1°C (1.5°C), respectively. No data regarding the MD between the two sites were provided by the authors but, from the data available, MD of brain minus rectum (calculated by KWL) at 0 hours, 24 hours, and 72 hours was 0.8°C, 1.1°C, and 1.4°C, respectively. The CI could not be calculated from data available. In this study mean brain temperature was consistently higher than mean rectal temperature at all three of the therapeutic hypothermia treatment time-points.

Hypothermia therapy on selected patients

Soukup and colleagues [12] used induction of mild hypothermia (<36°C) in 25 of 33 patients. Brain-rectum MD (SD) was reported according to four different clinical situations: a normothermia group (brain temperature between 36.0°C and 37.5°C); a hyperthermia group (brain temperature >37.5°C); a therapeutic cooling group (brain temperature <36.0°C in response to therapy); and a spontaneous hypothermia group (brain temperature <36°C without any active cooling or management strategy for the low temperature). In the normothermia group, MD (SD) between the two sites was 0.0°C (0.5°C), 95% CI -0.02 to 0.02 (calculated by KWL). In the hyperthermia group MD (SD) between the sites was 0.3°C (0.5°C), 95% CI (calculated) 0.28 to 0.32. In the therapeutic cooling group, MD (SD) was -0.2°C (0.6°C), 95% CI (calculated) -0.24 to -0.16. The greatest differences in temperature (brain-rectum) was in the spontaneous hypothermia group; MD (SD) -0.8°C (1.4°C), 95% CI (calculated by KWL) -1.03 to -0.57. Results show that at temperatures below 36°C (either spontaneously or due to deliberate cooling) brain temperature is lower than core body temperature. In the study by Henker and colleagues [16],

patients were recruited as a part of a study of therapeutic hypothermia (target temperature 32 to 33ºC). Five patients were randomly assigned to the hypothermia treatment group and three to the normothermia group. It is not possible from the data to identify those who received the different temperature management strategies but the range of MD (SD) between brain and rectal temperature for individual patients was 0.1 to 2.7°C.

Brain temperature versus jugular vein temperature

Only one study [13] focused on the differences between brain (cerebral) temperature and jugular vein temperature measured at the jugular bulb. Tokutomi and colleagues [13] studied 31 patients who were cooled to 33°C and then slowly re-warmed after 48 to 72 hours of hypothermia. They reported a MD of 0.3°C and a SD of 0.3°C between these two sites of measurement. The calculated 95% CI of this study ranged from 0.19 to 0.41.

Brain temperature versus bladder temperature

Henker and colleagues [16] measured brain temperature (ventricle) and bladder temperature simultaneously in eight patients. The MD between brain temperature and bladder temperature based on temperature values across three ranges (≤36°C, >36 to ≤38°C, >38°C) ranged from 0.1°C to 2.7°C. A MD (SD) of 1.0°C (0.7°C) was calculated by KWL from the data provided. In this study determination of patients undergoing hypothermia to target temperature was not possible from the data provided.

Fischer and colleagues [11] maintained the brain temperature of seven patients at 36.5°C as a form of prophylactic normothermia. The mean (SD) of brain temperature was 36.4°C (0.5°C) while the mean (SD) of bladder temperature was 36.3°C (0.4°C). The MD between the two sites was 0.1°C. The SD of differences between the two sites was not reported. Suehiro and colleagues [20] on the other hand cooled their patients and kept the brain temperature at 33°C to 35°C for at least three days. The MD (SD) between brain temperature and bladder temperature was reported to be -0.17°C (0.02°C).

Brain temperature versus tympanic membrane temperature

Kirk and colleagues [14] compared brain parenchyma temperature and tympanic membrane temperature in 20 patients with severe TBI. Mean (SD) of brain temperature and tympanic membrane was 37.8°C (0.7°C) and 36.9°C (0.8°C), respectively. A MD and SD of 0.9°C (0.7°C) was reported between the two measurement sites. The 95% CI of this study ranged from 0.59 to 1.21, as calculated by KWL.

Brain temperature versus temporal artery temperature

In the same paper, Kirk and colleagues [14] also investigated the difference between brain and temporal artery temperature. Mean (SD) temporal artery temperature was 37.5°C (0.5°C). MD (SD) between brain parenchyma temperature and temporal artery temperature was 0.3°C (0.4°C) with 95% CI of 0.12 to 0.48, as calculated by KWL. In addition to comparing brain temperature with rectal temperature under standard conditions (MD between the two temperature measurement sites of 0.23°C, SD 0.45°C), Kuo and colleagues [16] also compared brain and temporal artery temperature. The authors report a MD of 0.64°C and a SD of 0.60°C. Temporal artery temperature may lead to underestimation of brain temperature.

Discussion

Problems in the interpretation of results are evident because there is, as yet, no consensus of what value constitutes a clinically relevant difference between brain and body temperature [24]. From a pragmatic viewpoint, it would be fair to assume that measurement differences that exceed the manufacturer's stated accuracy for the thermistor (typically ±0.2°C) would be the smallest difference that could be expected. However, and assuming all sensors have a manufacturer's stated accuracy of this order, and taking into consideration 'real' measurement differences, a value of 0.2°C might be the minimum difference that one could propose as a clinically significant measurement difference between brain and core body sites. Implicit in such an assumption, however, is the need to be certain that measurements at both brain and core sites are 'true'. For example, whilst sensors inserted into the brain are less likely to be dislodged, it is appreciated clinically that core body measurements can be unreliable; rectal thermometry being a good example. In the event that the thermistor slips from its optimum position 10 cm into the rectum, readings will be influenced greatly by 'external' factors. This type of measurement error, although common, is frequently overlooked, and would lead to an underestimation of brain temperature; not due to tissue temperature differences *per se* but rather to erroneous core body temperature readings and poor measurement practice.

There remains no consensus on the reliability of 'core' body temperature as a surrogate measure of the temperature of healthy or injured human brain despite concerns being raised and efforts made to tackle the issue [24]. Neurocritical care research represents a field of active and lively scientific and clinical investigation with respect to altered thermal homeostatic and physiological derangements after severe TBI. This is particularly relevant to the ongoing debate as to the benefits, or otherwise, of therapeutic temperature management (for example, moderate hypothermia of 33 to 34°C). Whilst temperature at one or more sites may be reported as a secondary finding, prospective studies to determine the 'true' difference in temperature 'inside' versus 'outside'

the head are clearly inconclusive. As a result, the clinician must inevitably base decisions on common assumption rather than robust evidence for practice. This is not ideal in the setting of neurocritical care since a rise in the temperature of injured neurones is considered to carry a higher risk for accelerated secondary brain damage. Of interest to this current systematic review is the observation that the largest average temperature differences occur under conditions of hypothermia, irrespective of the measurement sites used for temperature monitoring.

Average core body temperature ranges from 1.4°C above brain temperature to almost 1.0°C below brain temperature. Some healthy scepticism is warranted here with respect to measurement error. Whilst the techniques for insertion of single, dual or multiple sensor placement are typically robust (via a fixed skull bolt), this is not the case for sensors placed on or within the body. For example, rectal temperature measurement has the potential to be a very good surrogate for brain temperature as shown by Childs and colleagues [19] but if the thermistor slips from the insertion site, measurements will be unreliable. Bowel movements, position, turning and personal care are all factors that could cause the sensor to 'fall out'. Clinical experience tells us that physiological range rectal temperatures are common even with the sensor lying under (rather than inside) the patient's body. Under such circumstances, sensor displacement would lead to a temperature reading artefact and a false increase in brain temperature compared to body temperature. For other core body sites, reliability of measurement has been called into question, especially with regard to tympanic thermometry [14] and especially if local regions are 'contaminated' by the effects of skin (or internal, such as bladder) cooling.

In the present series, two studies [18,19] adopted similar study designs in a group of patients with severe TBI. Measurements of brain parenchyma and core body (rectal) temperature were made under standard routine care without any deliberate thermoregulatory interventions. The results reported on brain-body temperature differences are polar and, at first sight, without any obvious explanation. Childs and colleagues [19] showed that there was no systematic difference between brain parenchyma and rectal temperature, whilst Rumana and colleagues [18] found a mean difference of 1.1°C. Adding some weight to the observation, at least for the reliability of rectal temperature, is the evidence that rectal temperature readings were comparable to 'gold' standard measurements of core temperature measured in blood, albeit venous (jugular vein). As a consequence, results show that rectal temperature is at least as reliable as blood temperature. Moreover, results from Rumana and colleagues [18] suggest that jugular vein temperature reflects body rather than brain temperature.

There are a number of factors that might be postulated to account for the difference in results between the studies by Childs and colleagues [19] and Rumana and colleagues [18]. Despite recruiting patients of the same diagnosis (severe TBI) with GCS score ≤8, both studies measured brain temperature and core temperature under 'standard care'. However, 'standard care' can differ across institutions, and country practice may vary considerably. Early versus late surgery, and pharmacological and non-pharmacological interventions for high or low temperature are two examples of the variations that might exist in each institution's 'standard care'. In addition, certain pharmacological treatments, such as administration of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), can have a major impact on thermoregulation. Complete reporting of standard care and/or full interventions is not common practice, principally due to limitations in manuscript word count. Institutional variations can occur but, broadly, neurocritical management practices are similar and follow Brain Trauma Foundation Guidelines [25].

The same issues are evident where therapeutic temperature interventions have been used. Here, the discrepancy between the two temperature measurement sites is larger but it is not clear whether this is due to effects of the intervention *per se* or differences elsewhere, such as the severity and nature of the injury or subtle differences in the clinical management of the patient. Whatever the reason for the somewhat larger difference reported between the temperature sites under hypothermic conditions, the results of this systematic review suggest that when brain temperature falls below 36.0°C, either by deliberate body cooling or spontaneously as a consequence of the injury, the dissociation between brain-body temperature widens by as much as 1.5°C in either direction. Therefore, extra caution should be exercised when therapeutic temperature interventions are ongoing because using core body temperature as a surrogate or 'proxy' for brain temperature may become less reliable compared to normothermic conditions.

The results from this systematic review differ from the literature review of Mcilvoy [26], who concluded that brain temperature is predominantly higher than body temperature. Here, the main difference is the patient population. Mcilvoy [26] included patients with various neurological injuries (stroke, tumour, hydrocephalus, TBI) while the current systematic review focuses only on patients with severe TBI. It is well recognised that the pathophysiology of various neurological injuries such as stroke, brain trauma and intracerebral haemorrhage differ and this may explain why there is a lack of agreement between previous reviews and the current review, particularly as the two papers [17,19] showing brain temperature lower than body temperature were

published after the review of Mcilvoy [26] was published.

Limitations

This systematic review sourced publications in English only. Non-English publications with relevant information may have been missed. To aid synthesis of information, it was necessary to develop an appraisal tool specifically for the purpose of this review. An appraisal tool for method comparison studies used in a previously published systematic review was modified for use in investigating the temperature differences between brain and body sites. This modified critical appraisal tool has not been subjected to peer review or tested for validity under the conditions of the current review.

As noted in the discussion, seven studies only of the included publications specifically set out to determine the agreement between brain and body temperature. Temperature calibration formed a component of the methodological investigation, but only five studies clearly indicated calibration was done for their thermometer before commencing data collection. For the remainder of the studies it is not clear if thermometers were calibrated or if measurement reliability was checked. Similarly, these studies did not report sufficient statistical information, showing no more than the mean values with standard deviation of the differences. Relevant statistical analyses were not done to test statistical agreement between the two measurement sites. With the exception of one study that was powered to show a difference between the two measurement sites, the remaining studies adopted convenience sampling; sample sizes were small only. Therefore, generalisation of the results should be viewed with caution.

Brain temperature was measured at one of three sites (parenchyma, ventricle, and subdural space) in this systematic review. It has been noted that brain temperature may vary across different sites of the brain [27,28]. Whilst the evidence is sparse, comparisons between different brain sites compared to different core body sites is a further source of inconsistency in measurement. Temperature measured at the tip of the thermistor *in situ* and irrespective of brain site has been regarded as 'brain' temperature for the purposes of this systematic review but issues regarding the site of measurement and differences in temperature values at damaged versus undamaged sites could have a bearing on the brain temperature reading. As shown using magnetic resonance spectroscopic techniques for absolute temperature measurement [29] in experimental (non-human primate) stroke, highest values were observed in the ischaemic penumbra, values higher than in the contralateral (unaffected) region and ischaemic core [30]. Such findings suggest a potential explanation for the variations between study groups, possibly on the basis of evolution of the primary injury to infarction. As too is the possibility of the role of haem products due to haemorrhage when traumatic subarachnoid haemorrhage may co-exist with tissue injury, so exacerbating inflammation (and local heat production) in the brain [31].

Conclusion

The results of this systematic review show that core body temperature (measured at various sites of the body) is not a reliable 'proxy' for brain temperature in patients with severe TBI. Hence, the use of body temperature to predict brain temperature is not advisable in the clinical setting. Direct brain measurement is still the best way to monitor brain temperature in patients with severe traumatic brain injury.

Abbreviations

CI, confidence interval; GCS, Glasgow Coma Score; JBI, Joanna Briggs Institute; MD, mean difference; RCT, randomised controlled trial; SD, standard deviation; TBI, traumatic brain injury.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

CC conceived of the review topic, participated in the evaluation, data extraction and synthesis and drafted the manuscript and wrote the final draft. KWL undertook the searching, participated in the evaluation, data extraction and synthesis and co-drafted the manuscript. Both authors read and approved the final manuscript.

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Appraisal tool:

Reviewer: Date:

Author: Year:

Journal: Record Number:

	Yes	No	Unclear	Comments
1. Ethical approval?				
2. **Patients:** Were the patients' diagnosis Traumatic Brain Injury only?				
3. Patients: Were the patients' GCS ≤8 during recruitment?				
4. **Patients:** Were the participants more than 18 years old?				
5. **Temp:** Were comparisons of temperature performed?				
6. **Temp:** Were thermometers calibrated?				
7. **Temp:** Were all temperature measurements carried out concurrently or immediately sequentially?				
8. **Temp:** Were the test and reference standard measured independently (blind) of each other?				
9. **Temp:** Was the second reading taken before any interventions were given?				
10. **Temp:** Was there evidence of a systematic order of the temperature measurement?				
11. **Methodology:** Are the outcomes measured in a reliable way?				
12. **Methodology:** Is sample representative of patients in the population as a whole?				
13. **Methodology:** Are the patients at a similar point in the course of their condition/illness?				
14. **Methodology:** Was appropriate statistical analysis used?				

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (including reasons for excluding):

_____

_____

_____

_____

Figure 1

Extraction Tool

Reviewer: Date:

Author: Year:

Journal: Record Number:

Study Method:

Participants: Setting:

Population:

Sample size:

Interventions:

	Brain Temperature	Core temperature
Total number of measurements		
Measurement device		
Measurement site		
Type of thermometers		
Mean		
Standard deviation		
Range		

Differences in mean:

Differences in SD:

Range of difference:

Correlation coefficient (if applicable):

Authors Conclusions:

Comments:

Figure 2

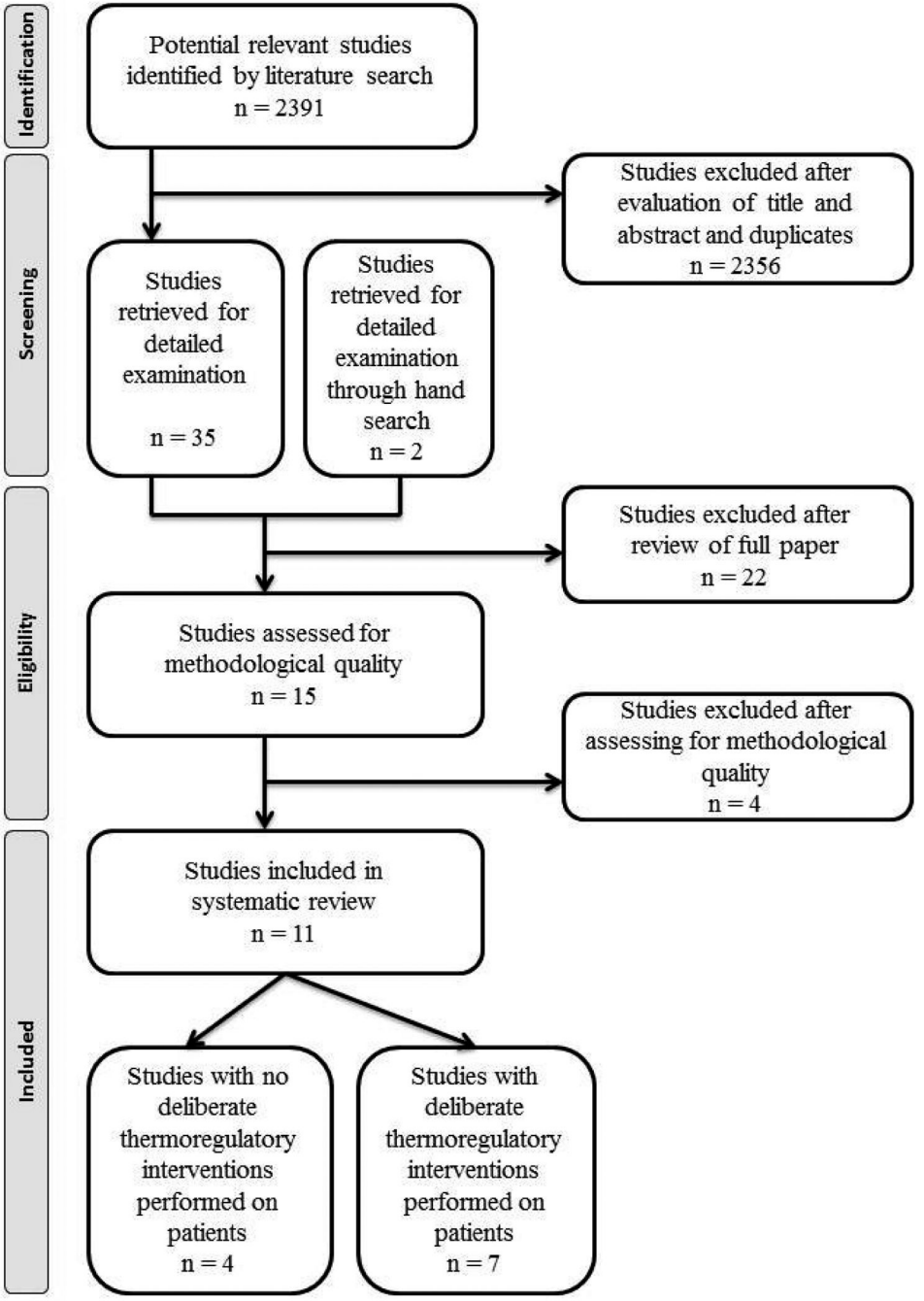
Identification
Potential relevant studies identified by literature search n = 2391
Screening
Studies excluded after evaluation of title and abstract and duplicates n = 2356
Studies retrieved for detailed examination n = 35
Studies retrieved for detailed examination through hand search n = 2
Eligibility
Studies excluded after review of full paper n = 22
Studies assessed for methodological quality n = 15
Studies excluded after assessing for methodological quality n = 4
Included
Studies included in systematic review n = 11
Studies with no deliberate thermoregulatory interventions performed on patients n = 4
Studies with deliberate thermoregulatory interventions performed on patients n = 7

Figure 3