Impact of Fever on Outcome in Patients With Stroke and Neurologic Injury

A Comprehensive Meta-Analysis

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Background and Purpose—Many studies associate fever with poor outcome in patients with neurological injury, but this relationship is blurred by divergence in populations and outcome measures. We sought to incorporate all recent scholarship addressing fever in brain-injured patients into a comprehensive meta-analysis to evaluate disparate clinical findings.

Methods—We conducted a Medline search for articles since January 1, 1995 (in English with abstracts, in humans) and hand searches of references in bibliographies and review articles. Search terms covered stroke, neurological injury, thermoregulation, fever, and cooling. A total of 1139 citations were identified; we retained 39 studies with 67 tested hypotheses contrasting outcomes of fever/higher body temperature and normothermia/lower body temperature in patients with neurological injury covering 14 431 subjects. A separate meta-analysis was performed for each of 7 outcome measures. Significance was evaluated with Zc developed from probability values or t values. Correlational effect size, $r_{(es)}$, was calculated for each study and used to derive Cohen's d unbiased combined effect size and relative risk.

Results—Fever or higher body temperature was significantly associated with worse outcome in every measure studied. Relative risk of worse outcome with fever was: mortality, 1.5; Glasgow Outcome Scale, 1.3; Barthel Index, 1.9; modified Rankin Scale, 2.2; Canadian Stroke Scale, 1.4; intensive care length of stay, 2.8; and hospital length of stay, 3.2.

Conclusions—In the pooled analyses covering 14 431 patients with stroke and other brain injuries, fever is consistently associated with worse outcomes across multiple outcome measures. **(*Stroke*. 2008;39:000-000.)**

Key Words: fever ■ meta-analysis ■ outcome ■ stroke ■ traumatic brain injury

Fever is a common condition in patients with stroke and other brain injuries. Hyperthermia appears to correlate with poor outcome in these patients, although a direct causative link has not been established. The impact of fever on patients in a neurocritical care unit has been evaluated; after controlling for severity of illness, diagnosis, age, and complications, fever was found to be strongly associated with an increased length of intensive care unit (ICU) and hospital stay as well as a higher mortality rate and worse overall outcome.[1] These findings are consistent with the meta-analysis by Hajat and colleagues focused on stroke mortality and generalized morbidity.[2] In this study, we expand Hajat's analysis to assess the significance of the relationship between fever and outcome across the full range of neurological injury, including stroke, and its magnitude in distinct measures of clinical, functional, and economic outcome.

Excellent biological arguments exist for a direct impact of fever on neurological outcome after brain injury. On a local level, fever results in the following: (1) elevated levels of excitatory amino acids (eg, glutamate and dopamine), free radicals, lactic acid, and pyruvate[3]; (2) increased ischemic depolarizations; (3) blood–brain barrier breakdown; (4) impaired enzymatic function; and (5) reduced cytoskeletal stability. Globally, these events lead to both cerebral edema, potentially reducing cerebral perfusion pressure, and larger volumes of ischemic injury.[4,5] The inciting etiology of the brain injury appears almost immaterial when considering the aforementioned effects, because ischemic stroke,[6–8] subarachnoid hemorrhage,[9,10] intracerebral hemorrhage,[11,12] traumatic brain injury,[13] and global ischemic injury from cardiac arrest[14] have all been noted to be impacted by fever in these ways.

There is a large body of research investigating various aspects of the relationship between hyperthermia—compared with normothermia—and outcome in patients with ischemic,

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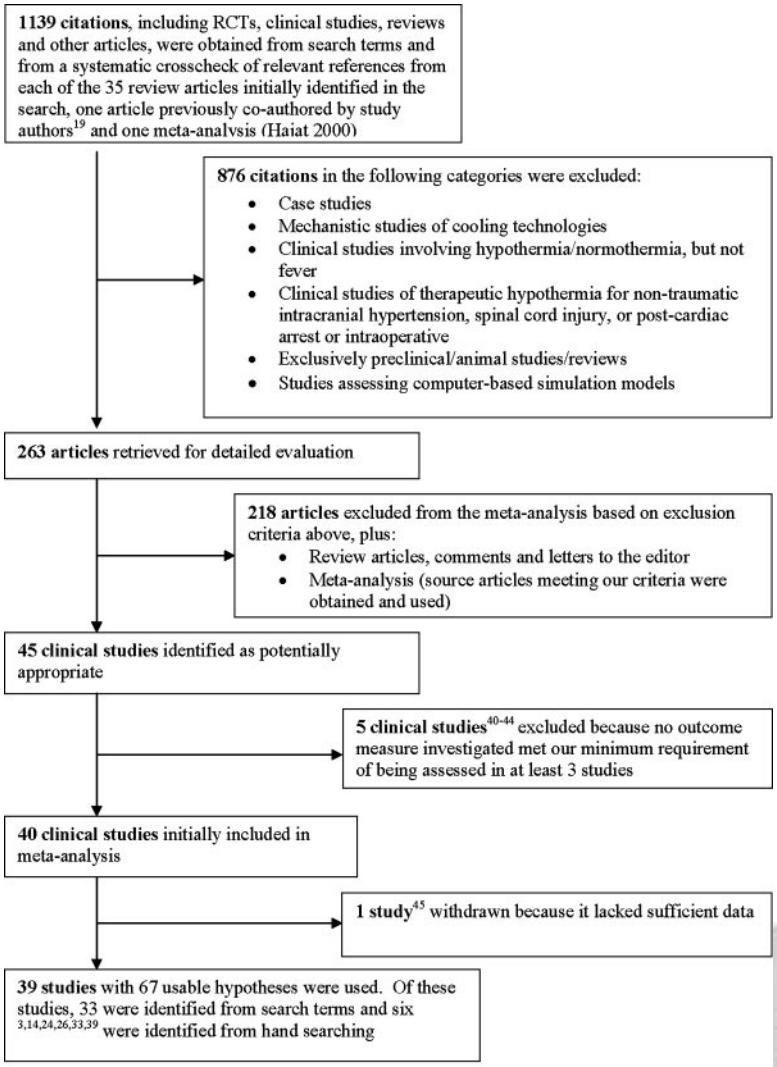

References cited in Supplemental Appendix I

Figure 1. Flow sheet.

hemorrhagic, and traumatic brain injuries. The studies are predominantly observational and retrospective, test a multitude of hypotheses, and involve a large number of intervening variables, a host of different temperatures indicative of fever, different times of onset and durations of fever, and a multiplicity of measures used to ascertain outcome. Taken singly, they provide limited and sometimes uncertain guidance. The impact of fever is significant in many studies, although some studies have found no significance. Yet despite much variance, the literature is characterized by the consistent suggestion that fever, when it is significant, contributes to problems in patients with all types of neurological injury. A meta-analysis, although it does not substitute for a randomized, controlled trial, is an approach that is well suited in this circumstance.[15] It provides a way to pull together these single studies often examining narrowly drawn aspects of this association in highly individual ways to systematically test larger questions: does fever contribute to worse outcomes across the full spectrum of brain-injured patients? Is the effect of fever significant and large enough to be clinically important in all commonly measured aspects of patient outcome?

Materials and Methods

A Medline search for articles published since January 1, 1995, for articles (in English with abstracts, in humans) pertaining to fever in neurological patients was completed in March 2006 using the following search terms: [(head OR brain OR cerebral OR neuro OR cranial OR subdural OR epidural OR arachnoid) AND (fever OR temperature OR hyperthermia OR pyrexia) AND (tumor OR trauma OR injury OR damage OR ischemia OR hemorrhage OR tbi OR lesion OR infarct OR coma OR edema OR hematoma OR contusion OR icp OR sah OR ich OR sdh OR edh) AND (induced hypothermia OR therapeutic hypothermia OR hypothermic therapy OR thermoregulation OR thermoregulatory OR temperature control OR heat exchange OR cooling OR prognosis OR prognostic OR predictor OR predict OR outcome OR incidence)]. We included terms pertaining to hypothermia to ensure identification of all studies containing data on relevant body temperature ranges, even if a study's overt topic was not relevant to our analyses. The quality standard for inclusion was a complete clinical study published in a Medline-abstracted journal. A total of 1139 citations was identified. The reference lists in 35 systematic reviews identified among the original 1139 citations were hand-searched for additional studies of relevance to these analyses as were the bibliographies of all selected studies. Case studies, mechanistic studies of cooling technologies, reviews, comments, and studies on hypothermia in patients with cardiac arrest or lacking data on fever were eliminated. In all, 45 studies, selected

Table 1. Summary of Articles Analyzed by Nature of Neurologic Injuries Studied

						No. of Hypotheses Analyzed By Outcome Measure							
						Clinical			Economic		Functional		
Author, Year	Study Grade	Prospective	N	Mean Age	Percent Male	CSS	GOS	Mortality	ICU LOS	Hospital LOS	mRS	BI	Total
Hemorrhagic stroke													
Castellanos, 2005	2b	Yes	138	70	54%						1		1
Leira, 2004	2b	Yes	266	71	55%	1							1
Oliveira-Filho	2b	Yes	92	55	29%					1	1		2
Schwarz	4		251	64	61%		1	1					2
Suzuki	2b		82	60	66%		1	1					2
Szczudlik, 2002	2b	Yes	152	64	76%			1				1	2
Wijdicks	2b		38	58	†		1	1					2
Hemorrhagic stroke total						1	3	4		1	2	1	12
Ischemic stroke													
Castillo, 1997	2b	Yes	128	68	59%	2							2
Castillo, 1998	2b	Yes	260	70	59%	2		1				1	4
Castillo, 1999	2b	Yes	128	68	59%	2							2
Davalos, 1997	2b	Yes	128	68	59%	1							1
Fukuda, 1999	2b		138	73							1		1
Grau	2b		119	61	66%			1				2	3
Hanchaiphilboolkul	2b		332	62	63%			1					1
Rordorf	2b		63	64	49%			1					1
Szczudlik, 2003	2b	Yes	60	68	53%			1				2	3
Weimar	2b	Yes	1754	68	59%			1				1	2
Ischemic stroke total						7		6			1	6	20
All stroke (includes ischemic and hemorrhagic strokes)													
Azzimondi	2b	Yes	783	77	43%			1					1
Boyse, 2001	2b	Yes	725	75	52%						1		1
Georgilis, 1999	2b		330	73	56%						1	1	2
Jorgensen	2b	Yes	84	75	41%							1	1
Kammersgaard	2b	Yes	390	74	50%			1					1
Reith	2b	Yes	390	74	50%			1					1
Roy	4		200	61	56%			1					1
Wang	2b		509	69	57%			1					1
All stroke total								5			2	2	9
Stroke/TBI (with or without other neurological ICU patients)													
Commichau	2b	Yes	387	54	54%				1				1
Diringer	2b		4295	57	52%			1	1	1			3
Kilpatrick	2b		428						1				1
Mayer	1b	Yes	47	53	36%			1					1
Stroke/TBI with/without other neurological ICU total								2	3	1			6
TBI													
Andrews	2b	Yes	124	36	84%		2	1					3
Geffroy	2b		101	33	82%		2	1					3
Heindl*	2b	Yes	82	15	75%							1	1
Jeremitsky	2b		81	34	58%			1	1	1			3
Jiang	2b		846		79%		1	1					2
Natale	2b		117	5	67%				1				1
Qiu	1b	Yes	86	41	65%		1	1					2
Soukup	2b	Yes	58				1	1					2
Stocchetti	2b		110	34	85%				1				1
Yamamoto	2b	Yes	39	46	79%		1	1					2
TBI, general total							8	7	3	1		1	20
Grand total						8	11	24	6	3	5	10	67

Full citations are provided in Supplemental Appendix I.

*Of 127 total patients, 82 patients with TBI were evaluated; 45 hypoxic brain injuries, mostly in very young children, were excluded as noncomparable.

†Division by sex was "similar."

without regard to the specific outcome measure(s) used, were identified as potentially appropriate (citations in Supplemental Table I, available online at http://stroke.ahajournals.org). Three studies involving cooling technologies were retained because they provided comparative data on afebrile patients and patients whose body temperatures were consistent with definitions of fever used in other studies (>37.2°C, Mayer et al; ≥38C°, Qui et al; >38°C, Yamamoto et al). Our minimum requirement for pooling was a least 3 studies using the same outcome measure. Five studies were eliminated because the minimum requirement for pooling was not met, and one study was withdrawn because it lacked sufficient data to relate a single source of body temperature to outcome. Thirty-nine studies (87%) were ultimately included in our study as detailed in the flow sheet (Figure 1). Twenty-two studies (56%) were prospective. Two studies met criteria for evidence Grade 1b (individual randomized, controlled trial with a narrow confidence interval, 35 studies were Grade 2b (individual cohort study/low-quality randomized, controlled trial), and 2 studies were graded 4 (case-series/poor-quality cohort or case–control), as identified in Table 1.[16] Final selection of articles was made independently by 3 of the investigators. Data were extracted by a single investigator and reviewed independently by 2 others. All disagreements were resolved by consensus.

A separate meta-analysis was performed for each outcome measure in which our 3-study minimum was met. Only one meta-analysis contained less than 5 studies. Where a study had 2 hypotheses relevant to a given outcome measure, both were evaluated. In the

Table 2. Summary of Meta-Analysis Findings: Effect Size, Association, and RR

Outcome Measure	No. of Articles/ Hypotheses*	Total N	Zc†	Effect Size‡	RR	Fever/Higher Body Temperature Associated Significantly With
Mortality	24/24	10 460	6.31	0.46	1.5	Death
GOS	9/11	1625	3.66	0.26	1.3	Neurological deficit/death
BI	8/10	2841	4.85	0.65	1.9	More dependence
mRS	5/5	1423	−27.6	0.89	2.2	Lower functioning
CSS	5/8	910	6.09	0.35	1.4	Greater severity
ICU LOS	6/6	5418	48.48	1.66	2.8	Longer ICU stay
Hospital LOS	3/3	4468	39.55	1.53	3.2	Longer hospital stay

*Sum does not equal total articles because some articles evaluated more than one outcome measure.

†Zc is Winer's Zc for the Rankin scale and the 2 LOS measures, Stouffer's Zc for all others. For the mRS, Winer's Zc is negative because mRS scores increase as outcomes worsen, whereas the opposite occurs with the other ordinal scales.

‡Cohen's d corrected for sample size.

mortality meta-analysis, in which some studies had 3 or 4 hypotheses assessing small variations, the single hypothesis with the most distant mortality point and the least restrictive hyperthermia timing was evaluated. In all, we evaluated 67 hypotheses from 39 studies addressing the following widely used measures of clinical, functional, and economic outcome: mortality, Glasgow Outcome Scale (GOS), Barthel Index (BI), modified Rankin Scale (mRS), Canadian Stroke Scale (CSS), ICU length of stay (LOS), and hospital LOS. Sample sizes ranged from 38 to 4295, as shown in Table 1, with a total of 14 431 patients. The clinical populations of these studies overlapped. To minimize selection bias, we included studies that combined ischemic and hemorrhagic stroke and studies of neurological ICU populations that also included patients with traumatic brain injury (TBI) as well as studies examining fever in targeted stroke and TBI populations.

Statistical Analyses

Our intention to include as many studies as possible, despite great variation in individual study statistics, necessitated a flexible statistical approach. For each outcome measure, a combined test (Zc) was developed from probability values (Stouffer's approach) or t values (Winer's approach; whichever was available in the source study) and was used to determine whether there was a significant difference between the fever and nonfever groups. We calculated individual effect size $r_{(es)}$ for each study using Rosenthal's correlational approach[17] and used it to derive unbiased Cohen's d from which combined effect size was calculated for each pooled analysis. Combining effect sizes is preferable to combining probabilities from separate studies because it unambiguously adjusts for different sample sizes in the combined analysis.[18]

In addition, we derived more clinically relevant relative risk (RR) statistics for each study and for each meta-analysis. For each study, available statistics such as odds ratios, probability values, and t values were used to calculate the proportion of each group (febrile/afebrile) having a good or bad outcome, and the results were presented in a Binomial Effect-Size Display table from which relative risk for each meta-analysis was derived. Rosenthal and Rubin's Binomial Effect-Size Display approach is consistent with the dichotomized outcome reporting used in many of the studies, and it avoided excluding studies solely on the basis of statistical presentation. CIs for RR are not shown because the Binomial Effect-Size Display method for calculating RR, necessitated by the available statistics, produces a CI involving a fixed lower bound that is not directly comparable to CI around an RR calculated with more common approaches. (See Supplemental Table II, available online at http://stroke.ahajournals.org, for counter effect size provided as an alternative approach to CI around correlational effect size.) Finally, homogeneity of effect size was assessed with a χ^2 test using Cohen's d.

Description of Data Variability

Multivariate studies included a wide array of moderating or mediating variables in addition to body temperature. Studied factors included patient demographics, comorbidities, severity indicators, clinical indicators, and timing of fever onset. Covariates and results for each tested hypothesis are shown in Supplemental Table II.

As noted previously, the included articles used a range of statistical methods depending on the variables studied and on how the body temperature variable was structured. Most studies examined body temperature as a dichotomized (eg, febrile versus afebrile) or categorical (level of fever) variable, whereas some treated body temperature as a continuous variable. Thus, we refer to "fever/higher body temperature" in reporting findings across these approaches. Of studies defining fever, 13 studies used 37.5°C as the cutoff point; values from other studies ranged from 37.0 (tympanic) to 39.0°C (core), listed in Supplemental Table II.

Studies that provided sufficient detail for GOS or mRS to permit separate assessment of mortality were included in the mortality meta-analysis even if mortality was not overtly discussed in the original study. Whenever a study in the meta-analysis included a pediatric population, the meta-analysis was conducted with and without the pediatric study. In no case did inclusion of a pediatric study make a statistically significant difference in the results.

Results

Collectively, the meta-analyses presented a consistent result. In each of the 7 outcome measures evaluated, the meta-analysis indicated that fever/higher body temperature was significantly associated with worse outcome as indicated by higher mortality rates, greater disability, more dependence, worse functional outcome, greater severity, and longer stays in the hospital and ICU. The size of the effect of fever/higher body temperature on outcome in each meta-analysis ranged from moderately small (0.26 for GOS) to large (over 0.8 for mRS, ICU LOS, and hospital LOS) per Cohen's interpretation,[19] as shown in Table 2. The RR calculations for each meta-analysis (Table 2) showed results consistent with the effect size analysis. The probability of a poorer outcome among patients with hemorrhagic or ischemic stroke or traumatic brain injury who had fever/higher body temperatures ranged from 1.3 for GOS to 3.2 times greater for hospital LOS than the probability among such patients without fever or with lower body temperatures.

Figure 2 shows the meta-analyses RR results and the individual RR result for each component study grouped by outcome measure and the clinical subgroup that best catego-

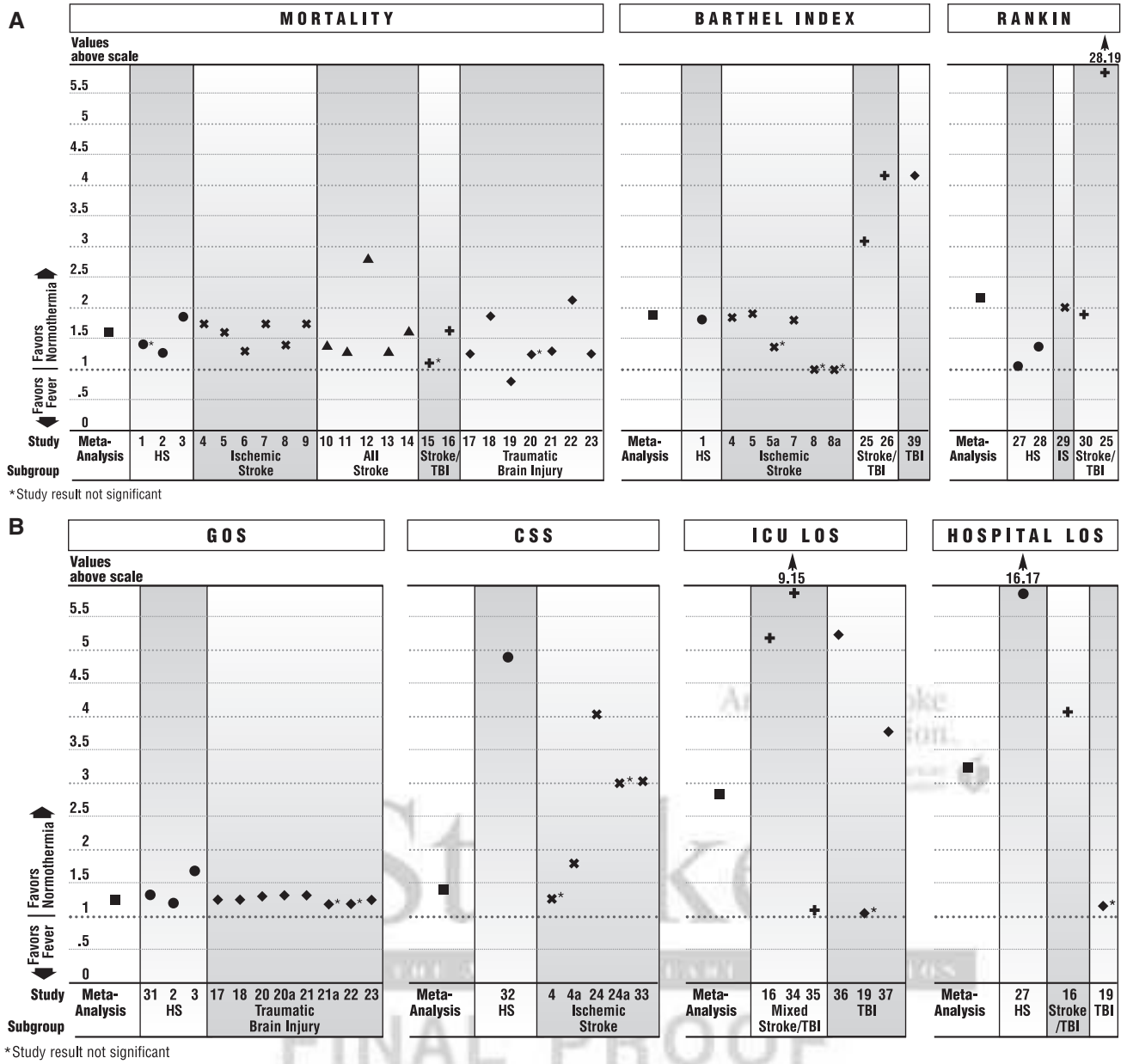

Figure 2. Relative risk of worse outcome with fever/higher body temperature.

rizes the study's population. Studies involving ischemic stroke exclusively were more consistent in their RR results than were studies also including or focusing exclusively on hemorrhagic stroke or traumatic brain injury. Mortality and GOS show the tightest clustering of individual RR around the meta-analysis results, illustrating more consistency of the relationship between fever/higher body temperature and outcomes across clinical groupings for these 2 measures compared with some of the other outcome measures. However, the overall results show that the association of fever with poorer clinical outcomes cuts across all types of neurological injury and is observed in every outcome measure analyzed.

Heterogeneity

Heterogeneity of effect size, measured using Cohen's d, was insignificant in 3 meta-analyses (mortality, GOS, and CSS) and present in 4 (ICU LOS, hospital LOS, mRS, and BI). Statistical heterogeneity is reasonably common in meta-analyses using studies with divergent structures but always warrants further examination. In these meta-analyses, there are a variety of possible contributors to heterogeneity. In the LOS analyses (ICU and hospital LOS), some studies were testing the impact of fever on LOS, whereas others used fever as the dependent variable.[20,21] Furthermore, a continuous variable such as LOS can produce larger effect sizes and therefore more potential variance than dichotomous variables or dichotomized ordinal scales. For studies examining the mRS, differences in the timing and duration of the body temperature reading(s) being assessed may have contributed to heterogeneity of effect size. In the BI meta-analysis, several studies investigated essentially the same hypothesis with different statistical methods (nonparametric tests of

ordinal [Mann–Whitney *U* or Kruskal-Wallis] or nominal [Fisher exact test] data and/or logistic regression analysis). In addition, there was variation in cut scores for good and poor outcomes across studies as well as variation in timing of outcome measurement.

Despite heterogeneity, the relationship between fever and negative outcome was statistically significant and consistent in direction in all 7 meta-analyses.

Discussion

For each measure of clinical outcome, the studies singly and collectively demonstrate a clear link between fever and worse outcome. Among 67 hypotheses in 39 studies evaluated in these meta-analyses, the relationship between fever/higher body temperature and worse outcome was confirmed as significant in 53 hypotheses, found to be statistically insignificant in 13, and significantly rejected in one, as detailed in Supplemental Table II. Independent of the origin of the neurological injury (ischemic, hemorrhagic, or traumatic), fever was associated with negative outcomes. The meta-analyses confirm that the association between fever and negative outcomes extends across all dimensions of outcome for which studies were available to analyze. Although the size of the effect varies, the range of RR indicates that fever in patients with neurological injury is a condition of clinical importance.

Relative Risk by Outcome Measure

As shown in Table 2, the largest values for RR in the meta-analyses were found in the 2 LOS analyses. Of note, several LOS studies measured fever over the entire duration of the ICU stay so that patients with a longer stay had a greater chance of fever being identified. However, several studies measuring LOS found a significant association between outcome in patients with stroke and body temperature measured on admission, suggesting that the relationship between longer LOS and fever cannot be attributed solely to treatment effect.[6,7,22–24] Although the magnitude of relative risk in ICU LOS and hospital LOS may be affected by studies with variable periods of measurement, and by the fact that LOS is a continuous variable, the direction of these findings is consistent with the other meta-analyses.

The smallest values for RR come from the GOS (RR=1.3) and CSS (RR=1.4). These results are significant but not large. However, they do suggest that fever is associated with greater neurological dysfunction with neurological injury. The higher RR levels in conjunction with mortality and functional outcome measures provide confirmation that fever in neurological injury is a clinically important condition that needs to be definitively studied.

The question of whether fever actually causes worse outcomes or whether it is largely an effect of other causative factors, known or unknown, cannot be fully addressed in this type of analysis. However, the meta-analyses and component studies do contain useful insights on this point. Across the 39 studies we analyzed, including studies involving widely defined multivariate analyses (see Supplemental Table II), findings on most covariates are consistently insignificant or mixed. No other covariate comes close to reaching the consistency of significance found with fever/higher body temperature.

Effect Size, Timing, and Clinical Condition

Individual researchers' study designs as well as their findings reflect differences in the etiology of fever in varying types of neurological injury as well as the timing of fever measurements. In checking for possible sources of bias, we examined the distribution of the effect size of fever (irrespective of outcome measure) by the timing and/or duration of temperature measurement within these clinical groups. We found no observable trends large enough to warrant examination. We did, however, notice differences between clinical groups with regard to the timing of temperature measurement. Studies in our meta-analysis that evaluated broadly defined neurological populations with a mixture of TBI and stroke all elected to study fever throughout an ICU stay or extended time period. For the narrower clinical groups, 67% of the hypotheses in the hemorrhagic and all stroke studies evaluated results of temperatures taken on admission or within approximately the first 24 hours. For studies of ischemic stroke, 40% of the hypotheses focused on these early temperature measurements. In the TBI studies, only 20% of the studies focused on temperatures in the first 24 hours and none considered admission temperature alone. Differences in study design suggest that stroke researchers are more apt to focus on early fevers, whereas TBI researchers are interested in fever less immediately and for longer periods of time. These trends reflect the differing nature of the neurological injury; a majority of ischemic injury occurs within the first several hours, whereas in subarachnoid hemorrhage, for example, the period of brain injury that might be modified by body temperature may extend for several days. We believe that questions about when and for how long fever should be measured in various types of neurological injury is a fruitful area for future research.

Our study points to the timeliness and compelling justification for a major prospective study in neurologically injured patients to determine whether outcomes improve when fever is prevented or controlled. Findings of this meta-analysis suggest that such a study should include functional and economic outcome measures in addition to clinical ones and should be designed to yield guidance for practicing clinicians on the important questions of not only whether, but when and for how long, to maintain thermoregulation. It also remains to be seen what impact other variables of the fever may have, including fever severity, timing, and duration.

The following factors are limitations of this study: (1) there is a possible selection bias from the choice of published studies, in English; (2) 17 studies were not from prospective trials; (3) 4 of the 5 studies using the CSS were done by the same group of researchers; (4) studies used different definitions of fever and different methods of measuring temperature, introducing a potential measurement bias; (5) studies dichotomized the same outcome measure differently, but the extent to which these differences fully compensated for differences in population severity cannot be determined; (6) an insufficient number of randomized, controlled trials was available to permit pooling by study type; (7) not all studies

provided exact probability values; (8) probability values or coefficients were not always reported on insignificant results; (9) not all articles contained sufficient statistics for Stouffer's Zc, necessitating the use of a different combined measure of statistical significance for some analyses; and (10) heterogeneity of effect size was found in 4 of the 7 meta-analyses, and it was not possible to test for all root causes of heterogeneity.

Summary

In the most comprehensive analysis undertaken to date, incorporating 39 studies covering 14 431 patients with stroke and other brain injuries, fever/higher body temperature is consistently associated with worse outcome regardless of the outcome measure used. Fever was consistently associated with damaging effects, whether the neurological injury was ischemic, hemorrhagic, or traumatic in origin and whether the outcome being measured was clinical, functional, or economic. A major prospective study is clearly warranted to confirm whether aggressive efforts to prevent and control fever in neurologically injured patients will yield improvements in these outcomes.

Disclosures

S.E.F., N.L.R., M.O., and G.C.U. report financial support from Medivance, Inc under an agreement that the study be conducted independently to reduce funding bias. Accordingly, the study was designed, conducted, analyzed, interpreted, and written by investigators independent of Medivance and was not sent to agents of Medivance for prepublication review or approval.

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Table I. References for Studies Used or Considered Potentially Appropriate

Studies Used in the Meta-Analyses (in order of appearance in Figure 2)

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(*Continued*)

Table I. Continued

Studies Used in the Meta-Analyses (in order of appearance in Figure 2)

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Studies Eliminated Because None of the Investigated Outcome Measures Were Evaluated in at Least 2 Other Studies (our minimum requirement)

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Table II. Covariates, Dependent Variables, and Effect Sizes of Hypotheses Evaluated

Study*	Author, Year	DV	Temperature†	Covariates‡	Other Variables Evaluated	Population Diagnoses	Fever Definition (> or ≥, in ° C) and Measurement	Timing of Temperature Measurement	Stat¶	*r* (es)††	*r* (cn)‡‡	Fever Related to Worse Outcome
BI												
4	Castillo 1998	BI at 3 months	[a], [d]	Time interval from stroke onset of initial hypothermia, age, highest temperature, coexistent infections		Ischemic stroke	37.5, axillary	Within 24 hours of symptom onset	M	0.30	0.53	Yes
25	Georgilis, 1999	BI	[a]			Stroke (ischemic and hemorrhagic)	37.5, axillary	during hospital stay - Two consecutive days with fever	U	0.52	0.77	Yes
5	Grau	BI	[a]	Fever, age >60, diabetes, hypertension, smoking, coronary heart disease, and/or peripheral artery disease	None mentioned	Ischemic stroke	38.0, oral	Fever versus no fever within 48 hours after stroke	M	0.33	0.57	Yes
5a	Grau	BI	[a]	Severe deficit on admission, fever, age >60, diabetes, hypertension, smoking, coronary heart disease, and/or peripheral artery disease	None mentioned	Ischemic stroke	38.0, oral	Fever versus no fever within 48 hours after stroke	M	0.17	0.33	NS
39	Heindl§	BI	[a]			TBI§	38.2	Posttraumatic hyperthermia= T>38.2° C for at least 1 week; hyperthermia of infectious or other specified origin excluded	U	0.62	0.85	Yes
26	Jorgensen	BI, dichotomized	[d]	Age, body temperature on admission, neurological recovery after 1 week (SSS)	Sex, a spouse, work, home care before stroke, initial stroke severity, blood pressure, blood glucose, stroke subtype, diabetes, hypertension, atrial fibrillation, ischemic heart disease, prior stroke, other disabling disease, alcohol consumption	Severe stroke	Tympanic	On admission	M	0.62	0.85	Yes
1	Szczudlik, 2002	BI	[a]			primary intracerebral hemorrhage (PICH)	37.5, tympanic	First day of hospital stay	U	0.29	0.51	Yes
8	Szczudlik, 2003	BI at 90 days	[a]	Hyperthermia on day 2, microalbuminuria	Sex, age, neurologic deficit on admission, atrial fibrillation, urinary albumin excretion	Ischemic stroke	37.5	On second day after admission	M	0.00	0.00	NS
8a	Szczudlik, 2003	BI at 1 year	[a]	Hyperthermia on day 2, microalbuminuria	Sex, age, neurologic deficit on admission, atrial fibrillation, urinary albumin excretion	Ischemic stroke	37.5	On second day after admission	M	0.00	0.00	NS
7	Weimar	BI dichotomized, after 100 days	[a]	Neurological complications, fever, lenticulostriate arteries infarction, diabetes, prior stroke, sex, age, Rankin scale at 48–72 hours, right arm weakness, left arm weakness, National Institutes of Health Stroke Scale at admission	Body mass index, smoking, history (6 conditions), admission neurological impairments (13 separate factors), atrial fibrillation at admission or intermittent, lowering of elevated blood glucose, location of infarct (9 specific locations), TOAST classification, other medical complications‡	Stroke (ischemic), including TIA	38.0, tympanic	Within 72 hours	M	0.26	0.48	Yes

(*Continued*)

Table II. Continued

Study*	Author, Year	DV	Temperature†	Covariates‡	Other Variables Evaluated	Population Diagnoses	Fever Definition (> or ≥, in ° C) and Measurement	Timing of Temperature Measurement	Stat¶	r (es)††	r (cn)‡‡	Fever Related to Worse Outcome
CSS												
24	Castillo, 1997	CSS	[d]	Plasma glutamate >200 μmol/L, body temperature, plasma glycine >223 μmol/L, ultimate infarct size >10 cm^3		Ischemic stroke		On admission	M	0.20	0.38	Yes
24a	Castillo, 1997	CSS	[d]	CSF glutamate >8.2 μmol/L, body temperature, admission delay (h), CSF glycine >12.6 μmol/L, infarct size >10 cm^3		Ischemic stroke		On admission	M	0.09	0.18	NS
4	Castillo, 1998	CSS at 3 months	[a], [g]	Age, infection, highest temperature, and a "categorical" variable for time hyperthermia started (0–24 hours, 24–48 hours, and 48–72 hours), using odds ratio for highest temperature		Ischemic stroke	37.5, axillary	Within 72 hours of symptom onset	M	0.07	0.14	NS
4a	Castillo, 1998	CSS at 3 months	[a], [g]	Age, infection, highest temperature, and a "categorical" variable for time hyperthermia started (0–24 hours, 24–48 hours, and 48–72 hours), using odds ratio for 0–24 hours		Ischemic stroke	37.5, axillary	Within 24 hours of symptom onset	M	0.22	0.41	Yes
38	Castillo, 1999	Percent change in stroke severity	[a]	Age, stroke time, CSS on admission, leukocytosis, serum glucose, atrial fibrillation, temperature on admission		Ischemic stroke	37.5, axillary	On admission	M	0.28	0.50	Yes
38	Castillo, 1999	Percent change in stroke severity	[a]	Glutamate, glycine, age, stroke time, CSS on admission, leukocytosis, serum glucose, atrial fibrillation, temperature on admission		Ischemic stroke	37.5, axillary	On admission	M	0.00	0.00	NS
33	Davalos, 1997	Progressing stroke, per CSS change	[d]	Body temperature, plasma fibrinogen	Early focal hypodensity, early mass effect on CT	Ischemic stroke	Axillary	On admission	M	0.30	0.53	Yes
32	Leira, 2004	Early neurological deterioration, per CSS change	[a]	Hyperthermia, fibrinogen, neutrophil count, sex, age, time from onset to inclusion, CSS score on admission	61 clinical, biochemical, and neuroimaging variables were recorded on admission, plus 37 clinical and neuroimaging variables 48 hours after admission and were evaluated in univariate analyses; ($P<0.05$) included in regression‖	Intracerebral hemorrhage (ICH)	37.5	On admission	M	0.22	0.41	Yes
GOS												
21	Andrews	GOS at 12 months, dichotomized	[e]	Duration of hypotension, pupillary response on admission	Age, duration of pyrexia, duration of hypotension, duration of raised intracranial pressure, duration of hypertension, Injury Severity Score, postresuscitation GCS score, duration of bradycardia, duration of tachycardia	TBI	37.0	From admission through end of clinical monitoring (up to 2–3 weeks), measuring duration of pyrexia	M	0.15	0.29	Yes

(*Continued*)

Table II. Continued

Study*	Author, Year	DV	Temperature†	Covariates‡	Other Variables Evaluated	Population Diagnoses	Fever Definition (> or ≥, in ° C) and Measurement	Timing of Temperature Measurement	Stat¶	*r* (es)††	*r* (cn)‡‡	Fever Related to Worse Outcome
21a	Andrews	GOS at 12 months, dichotomized good/poor	[e]	Duration of hypotension, pupillary response on admission	Age, duration of pyrexia, duration of hypotension, duration of raised intracranial pressure, duration of hypertension, ISS, postresuscitation GCS score, duration of bradycardia, duration of tachycardia	TBI	37.0	From admission through end of clinical monitoring (up to 2–3 weeks), measuring duration of pyrexia	M	0.10	0.20	NS
20	Geffroy	GOS, good	[a]			TBI	38.5, tympanic	Within 48 hours of admission, based on maximum temperature	U	0.14	0.27	Yes
20a	Geffroy	GOS, moderate/ severe disability	[a]			TBI	38.5, tympanic	Within 48 hours of admission, Based on maximum temperature	U	0.15	0.29	Yes
18	Jiang	GOS at 1 year	[a]			TBI	Rectal	Within 72 hours postinjury, based on maximum temperature	U	0.12	0.23	Yes
17	Qiu	GOS	[a]			TBI	38.0, brain and rectal	First 3–5 days	U	0.12	0.23	Yes
31	Schwarz	GOS dichotomized	[c]	Age, sex, GCS, mean arterial pressure, blood glucose level, body temperature, location, hematoma volume, presence of ventricular hemorrhage, presence of a coagulation disorder	Location of stroke	ICH	37.5, oral/rectal	Duration of fever during first 72 hours	U	0.16	0.31	Yes
22	Soukup	GOS 3 groups	[c]			Severe head injury	37.5, brain	During ICU stay or hospital stay; unclear	U	0.10	0.20	NS
2	Suzuki	GOS	[d]			Hypertensive intracerebral hemorrhage		On admission	U	0.12	0.23	Yes
3	Wijdicks	GOS 3–12 months	[a]			Primary pontine hemorrhage	39.0, core	On admission	U	0.25	0.46	Yes
23	Yamamoto	GOS 3 groups	[a]			TBI	38.0	Shortly after admission or during surgery, for 36 hours to 7 days	U	0.12	0.23	Yes
Hospital LOS												
16	Diringer	Hospital LOS	[a], [c]	Complications, elevated body temperature, SAH	Age, sex, diagnosis, severity (APACHE)	Neurologic ICU patients	37.5, oral	During ICU stay	M	0.61	0.84	Yes
19	Jeremitsky	Hospital LOS	[a]	Hypocapnia, hypotension, acidosis, hypoxia, hyperglycemia	Hypothermia, hypercapnia, hyperthermia, seizures, coagulopathy, intercranial hypertension	TBI		Within 24 hours	M	0.06	0.12	NS
27	Oliveira-Filho	Hospital LOS	[a]			Subarachnoid hemorrhage (SAH)	38.3, tympanic	during hospital stay - Two consecutive days with fever	U	0.88	0.97	Yes
Intensive Care Unit Length of Stay												
34	Commichau	Fever	[a]	ICU LOS, depressed level of consciousness	Limb weakness, placement of a central venous, arterial or ventricular catheter; endotracheal intubation	Neurologic ICU patients	38.3, tympanic	During ICU stay	M	0.80	0.94	Yes
16	Diringer	ICU LOS	[a], [c]	Complications, elevated body temperature, SAH	Age, sex, diagnosis, severity (APACHE)	Neurologic ICU patients	37.5, oral	During ICU stay	M	0.68	0.88	Yes

(*Continued*)

Table II. Continued

Study*	Author, Year	DV	Temperature†	Covariates‡	Other Variables Evaluated	Population Diagnoses	Fever Definition (> or ≥, in ° C) and Measurement	Timing of Temperature Measurement	Stat¶	r (es)††	r (cn)‡‡	Fever Related to Worse Outcome
19	Jeremitsky	ICU LOS	[a]	Hypocapnia, acidosis, hypoxia	Hypotension, hyperglycemia, hypothermia, hypercapnia, hyperthermia, seizures, coagulopathy, Intercranial hypertension	TBI		Within 24 hours	M	0.03	0.06	NS
35	Kilpatrick	Fever in ICU	[a]	ICU LOS, spinal disorder	Age, sex, diagnoses, infection, seizure	Neurosurgical ICU patients admitted for Neurologic diagnoses	38.5, rectal	During ICU stay	M	0.07	0.14	Yes
37	Natale	ICU LOS >3 days	[a]	Early hyperthermia, abdominal/pelvic organ injury; diffuse axonal injury, severity (GCS, trauma score), hyperglycemia, leukocytosis, hypoxia, surgery during PICU stay	Sex, extremity/pelvic fracture, thoracic organ injury, impact seizures, systolic hypotension, transfer from other hospital	TBI	38.5, oral, axillary, or rectal	Within 24 hours of admission	M	0.58	0.82	Yes
36	Stocchetti	ICU LOS	[a]	Pyrexia, severity (GCS)	None mentioned	TBI	38.0, axillary; 38.4, internal	During first week, counting no. of days with a febrile episode	M	0.71	0.89	Yes
Mortality**												
21	Andrews	Mortality at 12 months	[e]	Duration of hypotension, duration of pyrexia, and duration of hypoxemia	Age, pupillary response on admission, duration of raised intracranial pressure, duration of hypertension, Injury Severity Score, postresuscitation GCS score, duration of bradycardia, duration of tachycardia	TBI	37.0	From admission through end of clinical monitoring (up to 2–3 weeks)	M	0.16	0.31	Yes
10	Azzimondi	Mortality	[a]	Age, degree of conscious impairment, glycemia, fever	None mentioned	Stroke	37.2, axillary	Within first 7 days, based on maximum temperature	M	0.18	0.34	Yes
4	Castillo, 1998	Mortality	[a], [d]	Time interval from stroke onset of initial hyperthermia, age, highest temperature, coexistent infections		Ischemic stroke	37.5, axillary	Starting ≥48 hours	M	0.24	0.44	Yes
16	Diringer	Mortality	[a], [c]	Complications, elevated body temperature, SAH	Age, sex, diagnosis, severity (APACHE)	Neurologic ICU patients	37.5, oral	During ICU stay	M	0.22	0.41	Yes
20	Geffroy	Mortality in ICU	[a]			TBI	38.5, tympanic	Within 48 hours of admission, based on max temperature	U	0.14	0.27	NS
5	Grau	Mortality at 3 months	[a]			Ischemic stroke	38.0, oral	Fever versus no fever within 48 hours after stroke	U	0.20	0.38	Yes
9	Hanchaiphilboolkul	Mortality during hospital stay	[d]	Highest temperature in first 72 hours after admission, consciousness, ischemic heart disease	Sex, age, hypertension, diabetes, smoking, prior stroke, atrial fibrillation, subconscious or unconscious, infections	Ischemic stroke	37.5, axillary	Within 72 hours, based on maximum temperature	M	0.24	0.44	Yes
19	Jeremitsky	Mortality in hospital	[a]	Hypotension, hyperglycemia, hypothermia	Hypocapnia, acidosis, hypoxia, hypothermia, hypercapnia, hyperthermia, seizures, coagulopathy, intercranial hypertension	TBI		Within 24 hours	M	0.16	0.31	No

(*Continued*)

Table II. Continued

Study*	Author, Year	DV	Temperature†	Covariates‡	Other Variables Evaluated	Population Diagnoses	Fever Definition (> or ≥, in ° C) and Measurement	Timing of Temperature Measurement	Stat¶	*r* (es)††	*r* (cn)‡‡	Fever Related to Worse Outcome
18	Jiang	Mortality at 1 year	[a]		GCS score, age, pupillary response and size, hypoxia, hyperthermia, and high intracranial pressure	TBI	Rectal	Within 72 hours postinjury, based on maximum temperature	U	0.30	0.53	Yes
13	Kammersgaard	5-year survival rate	[d]	Blood glucose, severity, age, atrial fibrillation, hypertension	Sex, stoke subtype, ischemic heart disease, diabetes, intermittent claudication, smoking, daily intake of alcohol, prior stroke, preexisting disability	Stroke (ischemic and hemorrhagic)	37.0, tympanic	On admission	M	0.16	0.31	Yes
15	Mayer	Mortality				SAH (60%), stroke–cerebral infarction (23%), stroke–ICH (11%), TBI (4%).	37.2, Bladder	After 2 or more consecutive hours of fever after administration of acetaminophen	U	0.08	0.16	NS
17	Qiu	Mortality at 2 years	[a]			TBI	38.0, brain and rectal	First 3–5 days	U	0.17	0.27	Yes
11	Reith	Mortality	[d]	Temperature, stroke severity, previous stroke	Age, sex, severity, infections, leucocytosis, diabetes, hypertension, atrial fibrillation, ischemic heart disease, smoking, comorbidity	Stroke	37.5, tympanic	On admission	M	0.16	0.31	Yes
6	Rordorf	Mortality in ICU	[d]	Serum creatinine, WBC	Severity (APACHE)	Ischemic stroke		During ICU stay, through surgery, death or discharge	M	0.16	0.31	Yes
12	Roy	Mortality	[b]			Stroke (ischemic, N=100; hemorrhagic, N=100)	37.5, oral	On admission (to approximate within first 4–12 hours of stroke onset)	U	0.46	0.72	Yes
31	Schwarz	Mortality at 72 hours	[f]	Age, sex, GCS, mean arterial pressure, blood glucose level, body temperature, location, hematoma volume, presence of ventricular hemorrhage, presence of a coagulation disorder, presence of infection, hematoma enlargement, hem. Evacuation, duration of increased temperature, arterial hypertension	Location of stroke	Intracerebral hemorrhage	37.5, oral/rectal	Duration of fever during first 72 hours	M			Yes
22	Soukup	Mortality at 3 months	[c]			Severe head injury	37.5, brain	During ICU stay or hospital stay; unclear	U	0.36	0.61	Yes
2	Suzuki	Mortality	[d]			Hypertensive intracerebral hemorrhage		On admission	U	0.14	0.27	Yes
1	Szczudlik, 2002	Mortality	[a]	Neurological deficit on admission, age, midline shift on CT, hyperthermia on day 1, large hematoma on CT, sex		PICH	37.5, tympanic	First day of hospital stay	M	0.18	0.34	NS
8	Szczudlik, 2003	Mortality at 1 year	[a]	Hyperthermia on day 1, microalbuminuria, SSS score on admission		Ischemic stroke	37.5	Second day	M	0.18	0.34	Yes
14	Wang	Mortality at 1 year	[d]	Age >65, hyperthermia, hypothermia, swallowing difficulty, hypertension, ischemic heart disease, peripheral vascular disease, atrial fibrillation	Admission consciousness level, urinary incontinence, hemiparesis, prior stroke	Stroke (ischemic 85.9%; hemorrhagic 14.1%)	37.5, tympanic	On admission	M	0.22	0.41	Yes

(*Continued*)

Table II. Continued

Study*	Author, Year	DV	Temperature†	Covariates‡	Other Variables Evaluated	Population Diagnoses	Fever Definition (> or ≥, in ° C) and Measurement	Timing of Temperature Measurement	Stat¶	*r* (es)††	*r* (cn)‡‡	Fever Related to Worse Outcome
7	Weimar	Mortality	[a]	Fever, age, National Institutes of Health Stroke Scale at admission	41 variables were evaluated	Stroke (ischemic)	38.0, tympanic	Within 72 hours	M	0.24	0.44	Yes
3	Wijdicks	Mortality	[a]			Primary pontine hemorrhage	39.0, core	On admission	U	0.28	0.50	Yes
23	Yamamoto	Mortality	[a]			TBI	38.0	shortly after admission or during surgery, for 36 hours to 7 days	U	0.14	0.27	Yes
mRS												
30	Boysen, 2001	mRS at 3 months	[g]			Stroke (ischemic stroke, n=584; ICH; n=141)	Tympanic	Temperature at admission	U	0.31	0.55	Yes
28	Castellanos, 2005	Rankin 3 mos 2 groups	[d]			Stroke (hemorrhagic: supratentorial intracerebral hemorrhage)		On admission	U	0.18	0.35	Yes
29	Fukuda, 1999	Rankin 3 months 2 groups	[d]	Age, infarct size, maximum body temperature in 7 days, prestroke mRS, admission mRS	Prior cerebrovascular accident, atrial fibrillation, hemorrhagic transformation, infection, hypothalamic lesion	Stroke (cerebral infarction only)	Axillary	Maximum temperature in first 7 days after stroke onset	M	0.33	0.58	Yes
25	Georgilis, 1999	mRS	[a]			Stroke (ischemic and hemorrhagic)	37.5, axillary	during hospital stay - Two consecutive days with more than Two occasions of fever	U	0.93	0.98	Yes
27	Oliveira-Filho	mRS on discharge, 2 groups	[a]	Intubation, Fisher group 3 versus others; no. of days febrile, age	Adverse Hunt-Hess grade, GCS on admission, VSP, symptomatic VSP, papaverine or angioplasty treatment, infection, surgical clipping, endovascular coiling	SAH	38.3, tympanic	during hospital stay—2 consecutive days with fever	M	0.08	0.17	Yes

*Study numbers refer to Supplemental Appendix I; the no. and letter correspond to Figure 2.

†Nature of the body temperature variable: [a] dichotomized; [b] 3 groups; [c] 4 groups; [d] continuous variable; [e] duration, continuous variable; [f] duration, 3 groups; [g] continuous, grouped by hours from stroke onset to admission; [h] fever burden, continuous.

‡More specifically: body mass index, smoking, prior myocardial infarction, prior ischemic heart disease, prior cardiac dysrhythmia, prior peripheral arterial disease, hypertension, prior aspirin, admission neurological impairments (level of consciousness, questions, commands, best gaze, visual, facial palsy, motor left leg, motor right leg, limb ataxia, sensory, best language, dysarthria, extinction, and inattention), atrial fibrillation at admission, lowering of elevated blood glucose, location of infarct (9 specific locations), TOAST classification, intermittent atrial fibrillation, other medical complications.

§Of 127 total patients, 82 patients with TBI were evaluated; 45 hypoxic brain injuries, mostly in very young children, were excluded as noncomparable.

||Variables analyzed on admission: age, sex, time of onset, time delay to study inclusion, arterial hypertension, alcohol use, liver disease, renal failure, tobacco use, diabetes mellitus, antiplatelet drug use, cytostatic drug use, illicit drug use, hematologic disease, TIA/cerebral infarction, cognitive deterioration, preceding infection within 15 days, inflammatory disease within 30 days, coma, vomiting, seizures, body temperature, systolic blood pressure, diastolic blood pressure, headache, headache location, headache characteristics, CSS, ICH location, ventricular bleeding, mass effect, perihematoma hypodensity, ICH volume, total volume, edema volume, leukoacidosis, cerebral atrophy, lacunar infarction, old lesion on CT scan, hematocrit, hemoglobin level, leukocyte count, neutrophil count, fibrinogen level, prothrombin time, coagulation time, C-reactive protein, erythrocyte sedimentation rate, serum glucose levels, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum glutamic–oxaloacetic transaminase, serum glutamic–pyruvic transamylase, glutamyl transpeptidase, alkaline phosphatase level, CPK level, intracranial pressure, use of osmotic agents. Variables analyzed at 48 hours: body temperature, systolic blood pressure, highest and lowest levels, diastolic blood pressure, highest and lowest levels, headache, headache location, headache characteristics, dysphagia, cardiac arrhythmia, cardiac arrest, arterial hypotension, myocardial infarction, cardiac failure, thrombophlebitis, pulmonary embolism, pneumonia, bronchial secretions, gastric ulceration, gastrointestinal bleed, allergic reactions, urinary tract infection, sepsis, decubitus ulcer, SIADH, hyperglycemia, seizures, cerebral infarction, CSS, ventricular bleeding, mass effect, perihematoma hypodensity, ICH volume, total volume, edema volume, intracranial hypertension, use of osmotic agents.

¶"M" designates multivariate; "U" designates univariate, pertaining to the statistic from which the effect size was calculated. Among studies that presented both multivariate and univariate results, we selected multivariate results whenever sufficient statistics were presented and the dependent variable was appropriate.

**Studies that provided sufficient detail in GOS results to permit separate assessment of mortality were included in the mortality analysis even if mortality was not overtly discussed in the original study. Studies using mRS were similarly reviewed, but none met the criterion.

††*r* (es) is the correlational effect size.

‡‡*r* (cn) is the counter-null effect size, which forms the upper bound of an interval around *r*(es), for which the fixed lower bound is defined as zero.

DV indicates dependent variable; BI, Barthel Index; TOAST, Trial of Org 10172 in Acute Stroke Treatment; CSF, cerebrospinal fluid; CSS, Canadian Stroke Scale; TBI, traumatic brain injury; GCS, Glasgow Coma Score; ISS, International Stroke Society; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SAH, subarachnoid hemorrhage; LOS, length of stay; mRS, modified Rankin Scale; WBC, white blood cell; SSS, Scandinavian Stroke Scale; VSP, vasospasm.