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Thresholds for the assessment of inflicted head injury by shaking trauma in infants: a systematic review

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ABSTRACT

In order to investigate potential causal relations between the shaking of infants and injuries, biomechanical studies compare brain and skull dynamic behavior during shaking to injury thresholds. However, performing shaking tolerance research on infants, either in vivo or ex vivo, is extremely difficult, if not impossible. Therefore, infant injury thresholds are usually estimated by scaling or extrapolating adult or animal data obtained from crash tests or whiplash experiments. However, it is doubtful whether such data accurately matches the biomechanics of shaking in an infant. Hence some thresholds may be inappropriate to be used for the assessment of inflicted head injury by shaking trauma in infants.

A systematic literature review was conducted to 1) provide an overview of existing thresholds for head- and neck injuries related to violent shaking, and 2) to identify and discuss which thresholds have been used or could be used for the assessment of inflicted head injury by shaking trauma in infants.

Key findings: The majority of studies establishing or proposing injury thresholds were found to be based on loading cycle durations and loading cycle repetitions that did not resemble those occurring during shaking, or had experimental conditions that were insufficiently documented in order to evaluate the applicability of such thresholds. Injury thresholds that were applied in studies aimed at assessing whether an injury could occur under certain shaking conditions were all based on experiments that did not properly replicate the loading characteristics of shaking. Somewhat validated threshold scaling methods only exist for scaling concussive injury thresholds from adult primate to adult human. Scaling methods that have been used for scaling other injuries, or for scaling adult injury thresholds to infants were not validated. There is a clear and urgent need for new injury thresholds established by accurately replicating the loading characteristics of shaking.

1. Introduction

Retinal hemorrhage, subdural hemorrhage, diffuse axonal injury, and neck injury are symptoms often associated with violent shaking of an infant. However, the diagnosis of inflicted head injury based on the presence of such symptoms is often debated, because these symptoms can also be caused by events other than abusive shaking [1–4]. No consensus has been reached yet regarding the question if shaking alone can actually cause these symptoms [5–8].

Direct evidence or witnesses are often lacking in lawsuits regarding inflicted head injury by shaking

trauma in infants (IHI-ST) [9,10]. Instead, expert witnesses and scientific studies are currently being used as corroborative evidence [11–13]. Scientific evidence for IHI-ST may include studies that investigate brain and skull dynamic behavior during violent shaking. The obtained data are compared to injury thresholds for bulk dynamical aspects, such as rotational acceleration of the skull, in order to assess the probability of injury [7,8,14]. Such injury thresholds and head dynamics are hard to obtain directly from infants due to ethical considerations and hence are based on experiments with surrogates [15–17], mathematical models [8,18,19] or on extrapolated or scaled adult- or animal data [7,8,20].

Abbreviations: IHI-ST, InflictedHead Injury by Shaking Trauma; PRV, Protection Reference Value.

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Table 1
Database search query in general syntax.

Category	Syntax
Threshold related terms	(criteria OR criterion OR limit* OR boundar* OR threshold* OR tolerance OR ((maxim* OR peak) AND (stress OR strain OR acceleration OR velocity))) AND
Experimental conditions	((shake* OR shaking OR rotational OR whiplash AND NOT “head impact”) AND (infant OR baby OR primate OR animal OR pig OR piglet OR goat)) AND
Types of injury	(("neck injury" OR "neck trauma" OR "subdural h*ematoma" OR "diffuse axonal" OR "subdural h*emorrhage" OR "cerebral concussion" OR "retinal h*emorrhage" OR "bridging vein*") OR ((craniocerebral OR retinal OR "diffuse axonal") AND (bleeding OR trauma OR injury)))

The thresholds that are used for the assessment of IHI-ST thus originate from various experiments, not all of which resembling the specific characteristics—e.g. loading conditions and test subject properties—for the assessment of IHI-ST. To the best of the authors' knowledge, no overview is available of which injury thresholds have been *used in studies on the assessment* of IHI-ST, or which thresholds could be *considered appropriate* for the assessment of IHI-ST.

Therefore, the purpose of this study was to identify and assess thresholds that have up to now been used for the assessment of IHI-ST. A systematic literature review was conducted to address the following research questions: are the thresholds that have been used in IHI-ST assessment studies appropriate? Which thresholds—available in literature—resemble the specific characteristics of IHI-ST? A framework was proposed and applied to score the applicability of injury thresholds for the assessment of IHI-ST.

2. Methods

A systematic search for literature was conducted in the databases of Scopus, PubMed and Web of Science to retrieve relevant literature published until March 4th, 2018.

2.1. Search strategy

Studies regarding accidental falls, car crashes, and sports accidents may have constructed thresholds that are suitable for the assessment of IHI-ST. However, the loading conditions—e.g. impact of the head against an object—used in such studies often differ from the trauma mechanisms involved in IHI-ST. Another source for suitable injury thresholds are studies on material properties of tissues involved in IHI-ST. It was decided to construct a search query focused on the injuries often associated with IHI-ST—i.e. retinal hemorrhage, subdural hemorrhage, diffuse axonal injury and neck injury—and loading type—i.e. shaking or rotational loading without impact—rather than on the type of study they were established or used in. The search query is presented in Table 1.

Only literature in English or Dutch language was searched for. Duplicate records were removed after the database searches.

The reference lists of full-text articles were screened for relevant titles, and relevant citations were evaluated as well (backward snowballing). After three iterations of backward snowballing no more relevant articles were found. The articles identified in the database searches and the additional articles were put through the selection process described in section 2.2

2.2. Selection criteria

Articles were selected using the PRISMA methodology [21]; subsequently, the title, abstract and full-text were screened according to predefined selection criteria (Table 2). When there was any doubt about whether the article should be excluded, the article was put to the next step of the selection process.

2.3. Data structuring

In order to structure this systematic review, a distinction was made between 1) studies in which existing thresholds have been

Table 2
Selection criteria.

		Criteria
Title	*Inclusion*	Title contains terms related to research on- or evaluation of biomechanics, injury mechanisms, injury criteria, pathology or pathophysiology of head- and neck injuries concerning IHI-ST. Or title contains terms concerning phenomena related to IHI-ST in an infant, animal, surrogate or mathematical model. Or title indicates potential relevance in any other way.
	Exclusion	Title is exclusively related to epidemiological research, penetrating trauma, blunt trauma/mechanical impact to the head/direct head impact, lateral/side impact, rear-end impact, drug or biochemical research, or injury diagnosis with- or evaluation of imaging techniques.
Abstract	*Inclusion*	Abstract shows that research was done regarding quantitative injury criteria, tissue properties, mechanical injury characteristics (e.g. forces, loads, stresses, strains) or kinematic injury characteristics (e.g. velocities, accelerations) related to head- and neck injuries concerning IHI-ST. Or abstract shows that a quantitative analysis or an experiment—on (the assessment or probability of) head- and neck injuries related to IHI-ST—was conducted or reviewed. Or “abstract shows that research was done using a child, animal, physical model or mathematical model to understand or explain (aspects of) IHI-ST” [22].
	Exclusion	Abstract shows that the paper is exclusively related to qualitative criteria, diagnosis, treatment or to the after effects of head- and neck injuries.
Full-text	*Inclusion*	Injury thresholds were found regarding head- and neck injuries concerning IHI-ST. Or injury thresholds were used for the assessment of IHI-ST related injuries.
	Exclusion	Axial or coronal plane angular accelerations, direct impact of or to the head and rear-impact studies—since the brain might have been injured from the blunt force impact (i.e. headrest or piston or similar objects) prior to the rotational acceleration.

applied in order to assess IHI-ST; hereafter called *assessment studies* and 2) research on or development of thresholds for injuries seen in IHI-ST; hereafter called *threshold studies*.

Five categories, each with sub-categories, were used to classify the identified thresholds according to the type of injury:

- Axonal injuries
  - Diffuse axonal injury
  - Axotomy
  - Moderate and severe traumatic brain injury
- Concussive injuries
  - Cerebral concussion
  - Mild traumatic brain injury
- Intracranial bleedings
  - Ruptured bridging veins
  - Subdural hemorrhage
  - Subdural hematoma
- Retinal injuries
  - Retinal hemorrhage
- Neck injuries
  - Structural failure
  - Functional failure

2.4. Data extraction

A pre-defined data extraction table was used to extract all relevant data from the included literature. The following data were extracted from *threshold studies*; subject type, subject's actual age, subject's representative age, subject state, test type, loading type, loading cycle repetitions, loading cycle duration, injury type, threshold type, threshold property, scaling type, scaling reference, non-infant threshold value and infant threshold value. The following data were extracted from the *assessment studies*; threshold source, references used, injury type, threshold type, threshold property, non-infant threshold value, infant threshold value and assessed infant age. In the present study, the age range for an 'infant' is defined to be from newborn up to the age of 1 year.

2.5. Threshold applicability framework

Threshold scaling methods and experimental variables are major determinants for the applicability of a threshold for IHI-ST assessment, e.g. because injury tolerance is not equal among species and depends on the loading conditions used in experiments. Hence the experimental variables found in the identified threshold studies were evaluated for their role in the assessment of IHI-ST by reviewing relevant literature. Furthermore, the original papers of any scaling methods were evaluated for applicability in IHI-ST assessment. A threshold applicability framework was proposed and applied in order to indicate to what extent the variables of threshold experiments match the conditions seen in IHI-ST and to compare the agreement to IHI-ST conditions between the thresholds for each IHI-ST injury category.

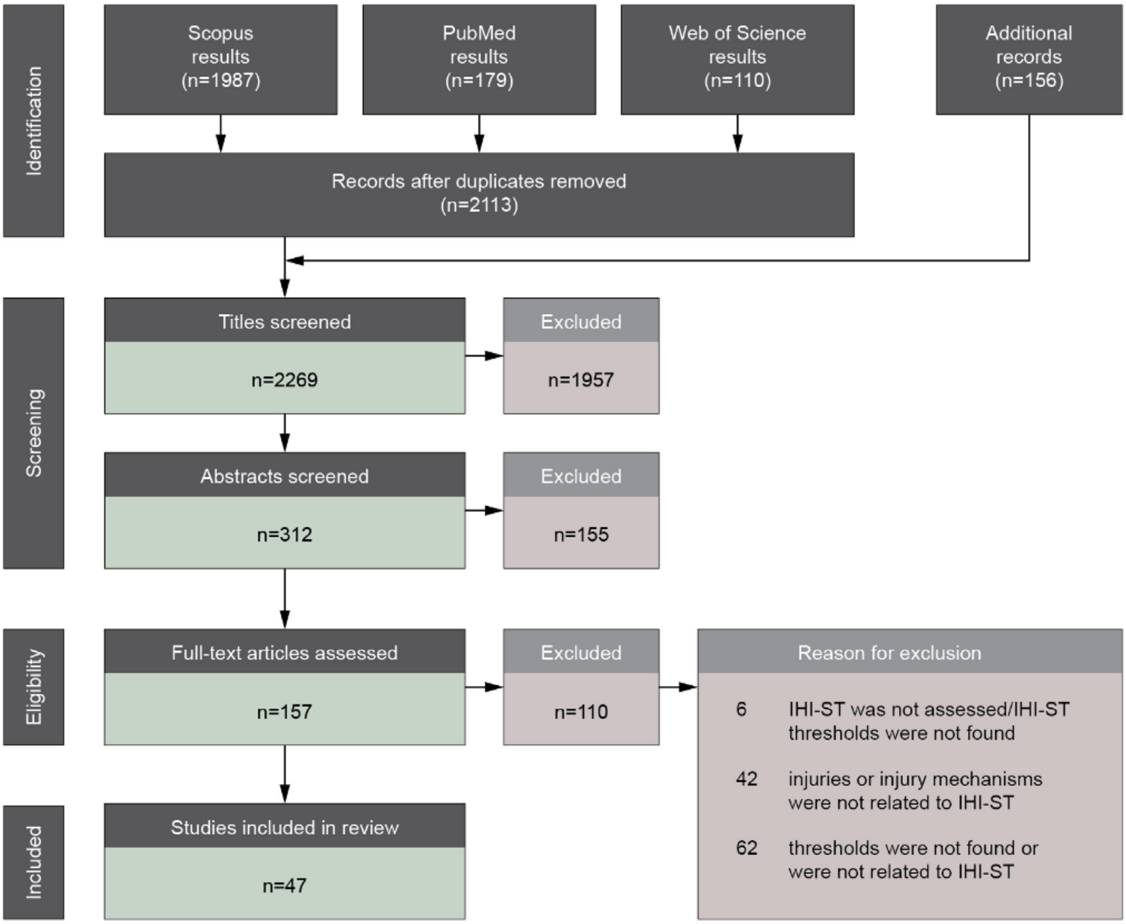

Fig. 1. PRISMA flowchart of the literature selection process.

3. Results

A total of 2269 unique records were identified, of which 47 articles were included in this systematic review. Fig. 1 shows the PRISMA flowchart of the study selection process and the reasons for exclusion of the excluded full-text articles.

3.1. Threshold experimental variables

3.1.1. Test subject properties

Interspecies variations in both anatomy and mechanical properties of tissues result in specific injury tolerance [20,23,24]. Non-human primates are the closest relatives to humans. Therefore, this group of test subjects is considered preferable over non-primate species, although still sub-optimal compared to human test subjects.

Mechanical properties of tissues affect injury tolerance because the loading response of the tissue depends directly on these mechanical properties. Stiffness and ultimate strength of the cervical spine are age-dependent [25–27], and the elastic properties of brain tissue are age-dependent as well [28–30], in both animals and humans. However, it is unclear to what extent the mechanical properties of bridging veins vary with age [20,31].

Cadaveric specimens show a different mechanical response to loading than living or fresh specimens, e.g. due to preservation methods, rigor mortis effects, preconditioning and preloading [32–34].

3.1.2. Loading conditions

Dynamics of the head during shaking are different than during impact, because the loading conditions differ. Impact is characterized by a single (often high) load with a short loading-cycle duration, whereas shaking is characterized by successive (lower) load cycles of longer cycle durations. These different loading conditions affect the response—and thus the tolerance—of the infants head to the load.

Some of the tissues inside the skull, such as brain tissue, exhibit viscoelastic behavior [35,36]. The strain and stiffness of such viscoelastic materials are loading-rate-dependent. After loading, these tissues need a certain period of time to return to the undeformed state. However, when a subsequent load is applied before the tissue could return to its initial state, this subsequent load may cause a cumulative effect on the deformation of the tissue.

Characteristic for shaking is that the consecutive rotational-loading cycles are causing a persistent high magnitude centripetal acceleration of the head [37]. This may cause an increase of both the intracranial- and arterial pressure [38], which may in turn lead to additional stresses and strains in vessel walls and surrounding tissue.

Hence stating all the above, the mechanical response of a test subject will be different in cyclic loading than in single loads, which is reflected in the injury tolerance to such motions [20,39–41]. Therefore, studies using cyclic loading ($n > 1$) in threshold experiments have a better resemblance of shaking than single load experiments and are therefore more appropriate to use for IHI-ST assessment.

Studies also have shown that the tolerance of the head to angular acceleration varies with the duration of the acceleration pulse [42,43]. The duration of a single loading-cycle for shaking was derived from shaking frequencies reported in biomechanical research and was estimated to be half the period time. The reported shaking frequencies—exerted by participants—are in the range of 2–5 Hz [14,16,17,44–46]; i.e. one loading cycle for shaking has a duration of 100–250 ms for the reported frequency range.

3.2. Threshold scaling methods applied in IHI-ST assessment studies

The threshold scaling methods from the following studies were found to be used in IHI-ST assessment studies: Ommaya et al. [47], Margulies et al. [48], Klinich et al. [49] and Thibault [28].

Ommaya et al. [47] proposed an angular acceleration scaling relation for concussion in brains with similar properties and shapes (Equation 1), based on an unpublished letter of Holbourn [50]. The scaling relation was developed for predicting the angular acceleration required to produce a concussion in the human, based on experiments with primate test subjects. However, they emphasized that the proposed scaling relation was only a “working theory, and not a factual demonstration”. Experiments were announced to validate the scaling relation on squirrel monkeys and chimpanzees.

$$\ddot{\theta}_P = \ddot{\theta}_M \left(\frac{M_M}{M_P}\right)^{2/3} \tag{1}$$

With primate and human denoted by the subscripts “*model M*” and “*prototype P*” respectively, and angular acceleration denoted by $\ddot{\theta}$.

The scaling relation of Ommaya et al. [47] (Equation 1) was eventually checked in primate experiments performed by Ommaya and Hirsch [24]. In that same study, a level of angular acceleration causing a concussion in the human was predicted using the scaling relation. This prediction was compared to a single case-history—in Ommaya and Yarnell [51]; human subject—in which cerebral concussion was not described, but “the production of a large subdural hematoma suggests a level of injury reasonably close to the threshold for cerebral concussion” [24]. Ommaya and Hirsch [24] found reasonable agreement between their prediction, and the level of angular acceleration in the—assumed concussion—case of Ommaya and Yarnell [51].

Margulies et al. [48] used Holbourn’s scaling relation [47,50] for scaling diffuse axonal injury tolerance data from primates to humans, for *coronal plane rotations*, using Equations 2 and 3. In these equations angular velocity is denoted by $\dot{\theta}$. Equation 2 is the same as in Ommaya et al. [47]. The origin and validity of Equation 3 could not be traced.

$$\ddot{\theta}_P = \ddot{\theta}_M \left(\frac{M_M}{M_P}\right)^{2/3} \tag{2}$$

$$\dot{\theta}_P = \dot{\theta}_M \left(\frac{M_M}{M_P}\right)^{1/3} \tag{3}$$

Klinich et al. [49] proposed a method for scaling adult protection reference values (PRVs) to the child. However, PRVs apply specifically to crash test dummies and are usually different from injury criteria, which apply to humans [49].

An angular acceleration ratio was derived from the ratio of the brain modulus of elasticity and the ratio of brain mass between adult and child. Klinich et al. [49] emphasized that PRVs are not equal to injury criteria for humans. The scaling relation of Klinich et al. [49] was rearranged to the form of Equation 4 in order to enable comparison with other scaling methods. Variables $\mathrm{A_{child}}$ and $\mathrm{A_{adult}}$ represent the angular accelerations, $\mathrm{E_{child}}$ and $\mathrm{E_{adult}}$ represent the brain elasticities and $\mathrm{M_{child}}$ and $\mathrm{M_{adult}}$ represent the brain masses of the child and the adult respectively.

$$A_{child} = A_{adult} \cdot \frac{\mathrm{M}_{adult}}{\mathrm{M}_{child}} \cdot \frac{\mathrm{E}_{child}}{\mathrm{E}_{adult}} \tag{4}$$

Thibault [28] proposed a method for scaling angular acceleration of the adult $\ddot{\theta}_{adult}$ to the infant $\ddot{\theta}_{infant}$. The difference in brain mass M and viscoelastic properties of brain tissue G' were included in the scaling method (Equation 5). This scaling law could not be found to be validated.

$$\ddot{\theta}_{infant} = \ddot{\theta}_{adult}\left(\frac{M_{adult}}{M_{infant}}\right)^{2/3} \cdot \left(\frac{G'_{infant}}{G'_{adult}}\right) \tag{5}$$

3.3. Threshold applicability for IHI-ST assessment

Test subject type, subject state, loading cycle repetitions, loading cycle duration and scaling methods were found to be major determinants for the applicability (sections 3.1 and 3.2). Also the subject's age may affect tolerance to certain injuries. However, because the effect of age on the injury tolerance is not yet known for *every* injury category covered in the present study, it was decided for now to exclude subject age from the threshold applicability framework presented hereafter.

Using the results from sections 3.1 and 3.2 a threshold applicability framework was proposed (Table 3) in order to score thresholds for agreement with the conditions of IHI-ST in sections 3.4 and 3.5. The following applicability determinants were implemented in the framework; test subject type, subject state, loading cycle repetitions, loading cycle duration and scaling method. Each condition superior to another was rewarded one point per level of superiority in order to indicate to what extent the experimental conditions match the conditions seen in IHI-ST.

3.4. Identified threshold studies

A total of 73 threshold values related to IHI-ST were found in a total of 37 studies [7,8,18–20,23,24,26,27,31,34,42,43,47,52–73]. Most thresholds were found for neck injuries and intracranial bleedings, while thresholds for retinal injuries were scarce. An overview of the thresholds found for each injury category is presented in Fig. 2. The complete data extraction table from the included thresholds is provided as supplementary material.

An overview of the characteristics of experiments in which IHI-ST related thresholds were found is presented in Fig. 3. Some results of particular interest were:

- The majority of retinal injury and axonal injury thresholds is based on non-primate test subjects.
- The majority of all thresholds is based on a single loading cycle.
- Multiple loading cycles were only used for intracranial bleeding thresholds.
- Loading cycle duration was not reported for the majority of the thresholds and could often not be deduced from the reported data either.
- An IHI-ST related loading cycle duration was only used for intracranial bleeding thresholds.
- Most thresholds were not scaled to infant values, but were thresholds for non-infant humans or animals.

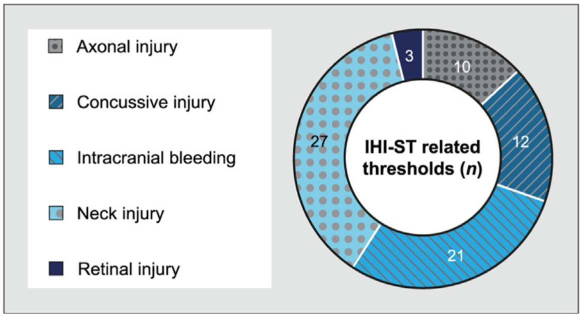

Fig. 2. Number of thresholds (n) available in literature for each injury category.

In order to visualize to what extent the experimental conditions in threshold experiments agree with the conditions in IHI-ST, all thresholds were assigned an applicability score according to the threshold applicability framework (Table 3). A normalized overview of the applicability scores that were assigned to the 73 IHI-ST related thresholds is presented in Fig. 4.

3.5. Identified assessment studies

Some of the found assessment studies used multiple thresholds for the assessment of a single injury; this was counted as a single assessment of the injury. An overview of the assessments of IHI-ST injuries is presented in Fig. 5. Intracranial bleeding was assessed most, while neck injury and retinal injury were least frequently assessed in IHI-ST studies.

A total of 14 IHI-ST assessment studies [7,8,14–16,23,46,74–80] were found. In these studies 25 unique injury thresholds were used for the 35 times that an IHI-ST injury was assessed.

In 13 out of the 35 injury assessments a threshold was used that was deemed unsuitable for IHI-ST according to the considerations stated above, because the thresholds were based on experiments in which impact to the head was part of the motion or in which rotations were not mainly in the sagittal plane. In Appendix A, an overview is provided of: the identified IHI-ST assessment studies, the thresholds that were used in these studies and their threshold applicability scores—or the reason for exclusion. The complete data extraction table from the included assessment studies is provided as supplementary material.

4. Discussion

4.1. Threshold scaling methods

Four injury threshold scaling methods were identified in the IHI-ST assessment studies. These scaling methods were originally developed only for scaling tolerance data of a specific injury, under specific loading conditions, in specific species. However, these

Table 3
Threshold applicability framework.

		Applicability score		
		2	1	0
Applicability determinant	*Subject type*	Human	Non-human primate (model)	Non-primate (model)
	Subject state	–	Living or fresh	Non-living
	Loading cycles [n]	–	Multiple	Single
	Loading duration (if n = 1) or frequency (if n > 1)	–	IHI-ST related (100–250 ms or 2–5 Hz)	Other
	Scaling method	Not scaled	Thibault [28] or Ommaya et al. [47]	Other method

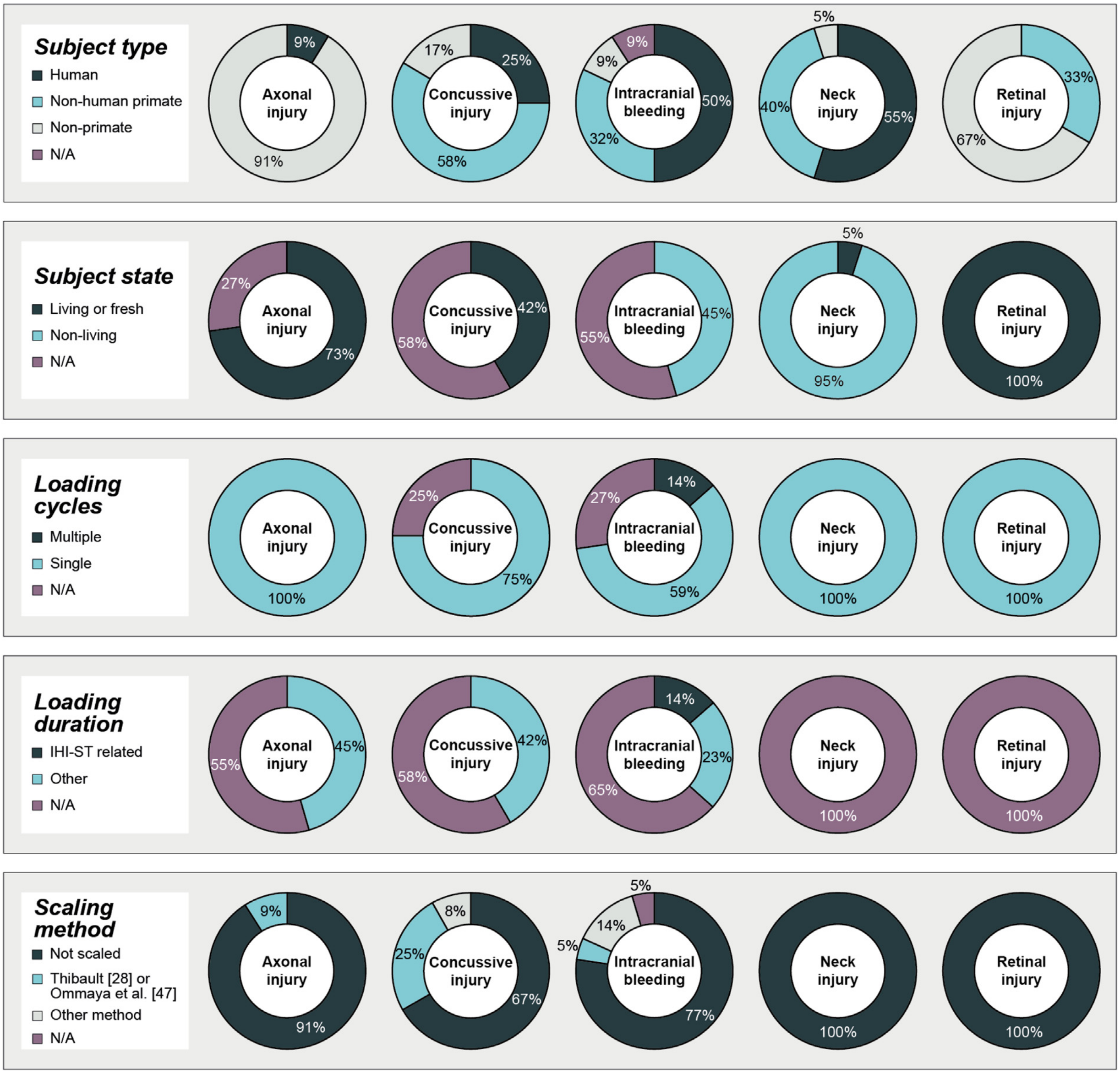

Fig. 3. Overview of the characteristics of experimental conditions in threshold studies for IHI-ST related head- and neck injuries.

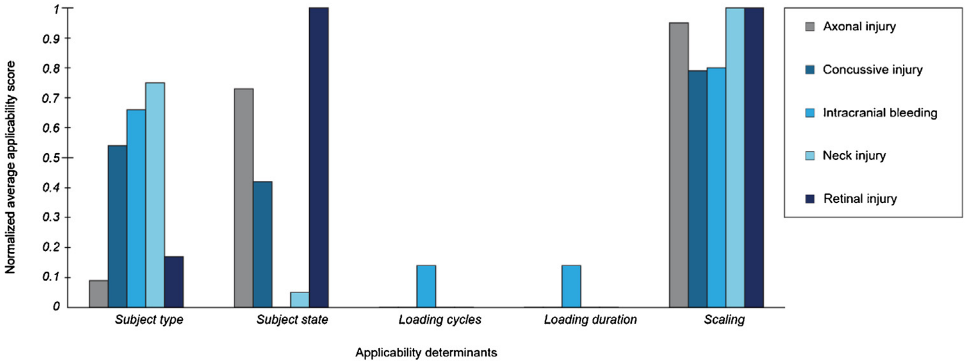

Fig. 4. Average applicability scores assigned to the 73 thresholds for IHI-ST related head- and neck injuries, per applicability determinant. The average score of each applicability determinant was divided by the maximum score possible for that determinant to obtain a normalized maximum score of 1.

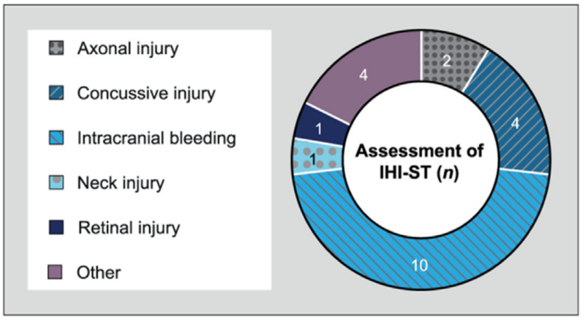

Fig. 5. Number of times (n) that each IHI-ST injury was assessed in literature. The category 'other' was appointed when a study used more general definitions such as 'head injury' or 'neck injury'.

scaling methods have been used by several studies far beyond their originally intended purpose.

The scaling relation of Ommaya et al. [47] was proposed for scaling concussion thresholds between brains with similar properties and shapes but was merely a "working theory, and not a factual demonstration" [47]. Later Ommaya and Hirsch [24] found a good agreement between experimental concussion data from three primate species—rhesus monkey, squirrel monkey and chimpanzee—and the predictions from the scaling method of Ommaya et al. [47]. Furthermore, a reasonable agreement was found between their prediction of a concussion threshold for the human and a single case-history in Ommaya and Yarnell [51]. However, the viscoelastic properties of human brain tissue were found to be age-dependent [30]. Thibault [28] and Thibault and Margulies [29] found that adult and infant porcine brain properties are not similar and that the age-dependent material properties of brain tissue "affect the mechanical response of the brain to inertial loading" [29]. Thus if the same relation between material properties and the mechanical response of the brain holds for human brain tissue, then the threshold scaling method proposed by Ommaya et al. [47] cannot be used directly for scaling human adult thresholds to the infant.

Margulies et al. [48] used the method of Ommaya et al. [47] and Holbourn [50] for scaling diffuse axonal injury angular acceleration and angular velocity thresholds for coronal plane head rotations, in order to predict injury thresholds for humans based on primate experiments. Although Margulies et al. [48] reported that the results were in agreement with other physical model studies, the experiments only included head rotations in the coronal plane, while injury tolerance is specific to the plane of rotation, and tolerance for axonal injury is significantly higher for angular accelerations of the head in the coronal plane than in the sagittal plane [81,82]. Rotations of the head in IHI-ST are mainly in the sagittal plane and it is not known whether the scaling relation holds for both coronal and sagittal plane head rotations.

The scaling relation of Klinich et al. [49] was developed for scaling adult PRVs for dummies to the infant, it was not developed for scaling injury thresholds for humans. PRVs apply specifically to crash test dummies and are usually different from injury criteria that apply to humans [49]. It is not known if the scaling relation for dummies also holds for scaling human concussion tolerance data between adult and infant.

Thibault [28] used the scaling relation of Ommaya et al. [47]—originally intended for scaling concussion thresholds between primate species and human—and incorporated the different material properties of adult and infant brain in order to scale concussion tolerance data from the adult to the infant. Thibault [28] assumed that the scaling method of Ommaya et al. [47] was also valid for scaling between adult and infant if it would be accounted for that the material properties of the adult and infant brain are not equal—because Ommaya et al. [47] assumed equal brain properties. The improved scaling relation of Thibault [28] is the most comprehensive one compared to the other scaling methods discussed in this section.

4.2. Validation of threshold scaling methods

The scaling relation of Ommaya et al. [47] for concussion thresholds was validated in primate experiments and reasonable agreement was found for scaling primate concussion tolerance data to the human adult. Therefore, this scaling relation can be used only for scaling concussion thresholds between primate species, or for scaling between primate and human—not for scaling thresholds from adult to infant.

Validation of scaling methods between animals does not justify the use of these scaling methods for scaling animal injury thresholds to the human adult or to the infant, which would require further validation. However, experimental data from fresh or cadaveric pediatric specimens are hard to obtain. In addition to ethical considerations, there is only limited availability of pediatric cadaveric specimens. Adult to infant scaling methods can currently hardly be validated with the use of finite element models for the same reasons. Hence it remains unclear if existing methods for scaling between adults and infants are appropriate.

Because adult and infant brain material properties are not the same—adult brain is found to be 3-4 times stiffer than the brain of a 5 months old infant [30]—it must be emphasized that the difference in mechanical properties between adult and infant brain tissue must not be neglected when scaling injury thresholds. After all, the loading response of the brain directly depends on its material properties. Validated scaling methods that incorporate the different material properties of adult and infant brains thus would be most useful for IHI-ST assessment.

4.3. Threshold studies

The identified thresholds for the head- and neck injuries related to IHI-ST were evaluated for their agreement with the rather specific conditions of IHI-ST. The identified injury threshold experiments were only occasionally focused specifically on IHI-ST, more often the thresholds were developed in studies with a focus on whiplash experiments or on tissue strength properties. This may also be a reason for the over-representation of neck injury- and bridging vein rupture thresholds, compared to the only few retinal injury thresholds.

The experimental variables that were used in these studies differ a lot from the conditions that are required for a good agreement with IHI-ST conditions. Furthermore, experimental variables that are important for evaluating the agreement with IHI-ST conditions were often not reported in the threshold studies, most likely because they were simply not relevant for the kind of application those studies were intended for. This is reflected by the fact that the majority of the identified thresholds is based on a single loading cycle and the loading cycle duration was shorter than in IHI-ST—or was not reported at all.

Furthermore, the majority of thresholds for neck injuries and retinal injuries—and a fewer number for axonal injuries—proposed an ultimate or structural failure value, while functional failure might occur already at lower levels. Such thresholds might still be useful for the assessment of IHI-ST, although it must be taken into account that these thresholds represent a rather liberal threshold, which in turn may cause an overestimated tolerance to shaking.

Most of the identified thresholds were applicable only for adult injury assessment. The few thresholds that were found for infants were almost always scaled from animal tolerance data while it remains unclear if these scaling methods are valid.

4.4. Assessment studies

Retinal hemorrhage, subdural hemorrhage, diffuse axonal injury and neck injury all are symptoms that are often associated with violent shaking of an infant. However, the distribution of the assessment of each injury category was found to be far from balanced. The majority of the IHI-ST assessment studies assessed concussive injury and intracranial bleeding, while only a few studies assessed axonal injury, neck injury or retinal bleeding. This may be explained by the fact that the thresholds existing for axonal- and retinal injury were all based on animal data, and no scaling methods exist for scaling thresholds for these injuries. The thresholds that were identified for neck injury and retinal injury all describe an ultimate failure threshold; e.g. neck distraction force or retinal detachment force. This could explain the lack of assessment of such injuries because the injuries following from shaking trauma are less extreme.

In several studies thresholds were used for the assessment of IHI-ST that were excluded from the present study. In these threshold experiments impact of the head or to the head was part of the motion or motions were not mainly in the sagittal plane, while injury tolerance under these conditions is not the same as in IHI-ST. Although linear acceleration of the brain due to direct impact of the head or to the head has the potential of causing similar injuries—e.g. concussion—as angular acceleration, the tolerance to linear acceleration is higher than to angular acceleration [24,83]. Adoption of such thresholds in IHI-ST assessment studies may result in an overestimated tolerance to shaking.

Thresholds that were used in IHI-ST assessment studies were often based on a single loading cycle with a loading duration that was not related to IHI-ST—or was not reported at all. It was already emphasized that injury tolerance and the mechanical response of the brain are dependent on the loading duration and loading cycle repetitions.

The majority of the infant injury thresholds that were used in IHI-ST assessment studies was scaled from adult or animal data. In some cases, it was not reported which scaling methods were applied, or scaling methods were used outside the originally intended purpose. Although for most studies scaling methods were used—either directly or indirectly—that were in good agreement with the intended purpose of the scaling method, the validity of these scaling methods is still not known.

4.5. Limitations

The applicability scores that were assigned in section 3.3 merely indicate a level of superiority *within* that specific applicability determinant. By no means, is the presented qualitative applicability score meant to be used as a definitive grade. Additional weighting for experimental conditions within each applicability determinant and amongst the other applicability determinants would first be required.

Whenever certain information on experimental variables was not reported in a threshold- or assessment study, the assigned applicability score was 0 because the applicability of such a threshold for the assessment of IHI-ST could not be appraised. This does not refer to the quality of the study concerned.

The purpose of the present study was to identify and discuss which thresholds have been used for the assessment of IHI-ST; not to identify all injury threshold scaling methods that exist in general. Therefore, methods for scaling injury thresholds were identified only if they have ever been used within the included threshold- or assessment studies. Hence, it could be that some scaling methods that would be suitable for scaling injury thresholds were not identified in the current study.

4.6. Future research

It is suggested that future research investigates the effect of each individual applicability determinant on the applicability of the threshold for IHI-ST assessment, in order to quantify the consequences of the disagreement that was found between the conditions in currently available injury thresholds and the rather specific conditions of IHI-ST. Furthermore, future research should be directed towards the selection or development of injury thresholds specifically for the conditions as seen in IHI-ST and on validation of the methods for scaling animal or human adult injury tolerance data to infants.

5. Conclusion

An applicability framework was proposed and applied in order to examine to what extent the variables of head- and neck injury threshold experiments match the conditions seen in IHI-ST. As hardly any existing thresholds linking bulk dynamics to injury are based on actual infant data or on tests with dynamics similar to shaking, the identified thresholds for the head- and neck injuries related to IHI-ST, as well as the thresholds applied in IHI-ST assessment studies, generally do not match the conditions of IHI-ST.

Validated scaling methods were only found for scaling concussive injury thresholds from primate to human. Scaling methods that were used for scaling other injuries, or for scaling adult injury thresholds to the infant could not be found to be validated. Therefore it is suggested to not use these thresholds for IHI-ST assessment.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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CRediT authorship contribution statement

Luuk A.H. Schiks: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft. **Jenny Dankelman:** Conceptualization, Resources, Writing - review & editing. **Arjo J. Loeve:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Appendix A. IHI-ST assessment studies

See Table A1

Table A1
Characteristics of the thresholds used in IHI-ST assessment studies. The maximum score of each applicability determinant was normalized to a maximum score of 1.

					Normalized applicability score/reason for exclusion				
Author(s)	Source*	References	Id. **	Injury	Type	State	Cycles	Duration	Scaling
Bandak [84]	EXT	Nuckley et al. [85], Ching et al. [86]	49	Major structural failure of the cervical spine	0.50	0.00	0.00	0.00	0.00
	EXT	Mayer et al. [87]	-	Major structural failure of the cervical spine	Excluded from the present study because no thresholds were found in Mayer et al. [87].				
	EXT	Duncan [88]	62	Major structural failure of the cervical spine	1.00	1.00	0.00	0.00	1.00
Cory and Jones [89]	EXT	Duhaime et al. [90]	27	Subdural hematoma	0.50	0.00	0.00	0.00	0.00
	EXT	Duhaime et al. [90] 1 mo	-	Concussion	Excluded from the present study because Duhaime et al. [90] used thresholds from Thibault and Gennarelli [91] which was excluded from the present study because rotations were not mainly in the sagittal plane.				
	INT	Non-infant threshold: unknown source. Scaling: Thibault and Margulies [92]	25	Subdural hematoma	0.00	0.00	0.00	0.00	0.50
	INT	Non-infant threshold: unknown source. Scaling: Thibault and Margulies [92]	13	Concussion	0.00	0.00	0.00	0.00	0.50
	INT	Non-infant threshold: Ommaya [93], Scaling: Klinich et al. [94]	14	50% risk of concussion	0.00	0.00	0.00	0.00	0.00
	EXT	Sturtz [95]	-	Head injury	Excluded from the present study because Head and neck injury values were for direct frontal and dorsal impact loading.				
Couper and Albermani [96]	EXT	Lee and Haut [97]	30	Subdural hematoma; bridging vein rupture	1.00	0.00	0.00	0.00	1.00
	EXT	Morrison et al. [98]	6	Axonal injury	0.00	1.00	0.00	0.00	1.00
Duhaime et al. [90]	INT	Non-infant threshold: Thibault and Gennarelli [91], Scaling: unknown	-	Concussion	Excluded from the present study because in Thibault and Gennarelli [91] rotations were not mainly in the sagittal plane.				
	INT	N/A	27	Subdural hematoma	0.50	0.00	0.00	0.00	0.00
	INT	Non-infant threshold: Thibault and Gennarelli [91], Scaling: unknown	-	Diffuse axonal injury	Excluded from the present study because in Thibault and Gennarelli [91] rotations were not mainly in the sagittal plane.				
Hans et al. [99]	EXT	Kita and Marmor [100]	88	Retinal hemorrhage	0.50	1.00	0.00	0.00	1.00
Koizumi et al. [101]	EXT	Lee and Haut [97]	30	Acute subdural hematoma; bridging vein rupture	1.00	0.00	0.00	0.00	1.00
Koizumi et al. [102]	EXT	Lee and Haut [97]	30	Acute subdural hematoma; bridging vein rupture	1.00	0.00	0.00	0.00	1.00
Lintern et al. [103]	INT	Newborn infant threshold: Duhaime et al. [90], Scaling: Margulies et al. [104]	-	Concussion	Excluded from the present study because Duhaime et al. [90] used thresholds from Thibault and Gennarelli [91] which was excluded from the present study because rotations were not mainly in the sagittal plane.				
	INT	4.5mo infant threshold: Duhaime et al. [90], Scaling: Margulies et al. [104]	-	Concussion	Excluded from the present study because Duhaime et al. [90] used thresholds from Thibault and Gennarelli [91] which was excluded from the present study because rotations were not mainly in the sagittal plane.				
	INT	1y infant threshold: Duhaime et al. [90], Scaling: Margulies et al. [104]	-	Concussion	Excluded from the present study because Duhaime et al. [90] used thresholds from Thibault and Gennarelli [91] which was excluded from the present study because rotations were not mainly in the sagittal plane.				
	INT	Newborn infant threshold: Duhaime et al. [90], Scaling: Margulies et al. [104]	32	Subdural hemorrhage	0.50	0.00	0.00	0.00	0.00
	INT	4.5mo infant threshold: Duhaime et al. [90], Scaling: Margulies et al. [104]	33	Subdural hemorrhage	0.50	0.00	0.00	0.00	0.00
	INT	1y infant threshold: Duhaime et al. [90], Scaling: Margulies et al. [104]	34	Subdural hemorrhage	0.50	0.00	0.00	0.00	0.00
Lloyd et al. [105]	EXT	Depreitere et al. [106]	-	Subdural hematoma	Excluded from the present study because in the experiment of Depreitere et al. [106] impact to the head was part of the motion.				
	EXT	Van Ee et al. [107], Melvin [108]	-	Severe head injury	Excluded from the present study because in the experiment of Melvin				

Table A1 (*Continued*)

Author(s)	Source*	References	Id.**	Injury	Normalized applicability score/reason for exclusion				
					Type	State	Cycles	Duration	Scaling
					[108] impact to the head was part of the motion.				
Morison [109]	INT	N/A	41	Bridging vein rupture	1.00	0.00	0.00	0.00	1.00
Ponce and Ponce [110]	EXT	Meyer et al. [111]	-	50% probability of neck and brain injury	Excluded from the present study because in the experiment of Meyer et al. [111] impact to the head was part of the motion.				
	EXT	Meyer et al. [111]	-	100% probability of neck and brain injury	Excluded from the present study because in the experiment of Meyer et al. [111] impact to the head was part of the motion.				
Prange et al. [112]	EXT	Pincemaille et al. [113]	-	Head injury	Excluded from the present study because in the experiment of Pincemaille et al. [113] impact to the head was part of the motion.				
Roth et al. [114]	EXT	Lee and Haut [97]	30	Subdural hematoma; bridging vein rupture	1.00	0.00	0.00	0.00	1.00
Wolfson et al. [115]	EXT	Duhaime et al. [90]	-	Concussion	Excluded from the present study because Duhaime et al. [90] used thresholds from Thibault and Gennarelli [91] which was excluded from the present study because rotations were not mainly in the sagittal plane.				
	EXT	Duhaime et al. [90]	27	Subdural hematoma	0.50	0.00	0.00	0.00	0.00
	EXT	Cory and Jones [89]	25	Subdural hematoma	0.00	0.00	0.00	0.00	0.50
	EXT	Cory and Jones [89]	13	Concussion	0.00	0.00	0.00	0.00	0.50
	EXT	Cory and Jones [89]	14	50% risk of concussion	0.00	0.00	0.00	0.00	0.00
Average normalized applicability score:					**0.48**	**0.14**	**0.00**	**0.00**	**0.48**

[*] Abbreviations: INT, established in reported study; EXT, obtained from external study.

[**] For the thresholds that were included in the present study, the threshold Id. in this table corresponds with the threshold Id. in the supplementary material.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.forsciint.2019.110060.

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