REVIEW



What About the Little Ones? Systematic Review of Cognitive and Behavioral Outcomes Following Early TBI

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Abstract

There is increasing empirical focus on the effects of early traumatic brain injuries (TBI; i.e., before the age of six years) on child development, but this literature has never been synthetized comprehensively. This systematic review aimed to document the cognitive, academic, behavioral, socio-affective, and adaptive consequences of early TBI. Four databases (Medline, PsycNET, CINAHL, PubMed) were systematically searched from 1990 to 2019 using key terms pertaining to TBI and early childhood. Of 12, 153 articles identified in the initial search, 43 were included. Children who sustain early TBI are at-risk for a range of difficulties, which are generally worse when injury is sustained at a younger age, injury severity is moderate to severe, and injury mechanisms are non-accidental. Early childhood is a sensitive period for the emergence and development of new skills and behaviors, and brain disruption during this time is not benign. Research, clinical management, intervention, and prevention efforts should be further developed with consideration of the unique characteristics of the early childhood period.

Keywords Traumatic Brain Injury · Preschoolers · Cognition · Behavior · Systematic review

Introduction

Sustaining pediatric traumatic brain injury (TBI) can disrupt the typical development of emerging cognitive and social skills, and lead to adverse consequences and poor long-term outcomes (Anderson et al., 2005, 2009; Verger et al., 2000). During early childhood (i.e., before the age of six years), a range of cognitive and socio-affective functions undergo intense development, including attention and executive skills, as well as social cognition, emotion and behavior regulation, and adaptive functioning (Grantham-McGregor et al., 2007). Birth cohort data indicate that "early TBI", defined as an alteration in brain function caused by an external force and sustained during infancy, toddlerhood or the preschool period, is prevalent (McKinlay et al., 2008; Menon et al., 2010). As such, it is

M. H. Beauchamp miriam.beauchamp@umontreal.ca important to fully understand the consequences of early TBI on multiple functional domains. Yet, most empirical studies and reviews of TBI focus on school-aged children, adolescents, and adults rather than on the youngest, and potentially most vulnerable, developmental group.

The empirical literature focusing on the consequences of pediatric TBI in school-aged children and adolescents is exhaustive and shows a variety of consequences affecting diverse domains. Meta-analytic and systematic reviews in older pediatric age groups suggest the presence of attention, executive, and social cognition impairments (Babikian & Asarnow, 2009; Babikian et al., 2015; Rosema et al., 2012), internalizing and externalizing behavior problems (Albicini & McKinlay, 2018; Durish et al., 2018; Kennedy et al., 2017; Li & Liu, 2013), psychiatric disorders (Albicini et al., 2017; Emery et al., 2016; Keightley et al., 2014; Max et al., 1997; Narad et al., 2018), academic difficulties (Mealings et al., 2012), and poorer quality of life (Di Battista et al., 2012).

There exist a number of reviews on cognitive outcomes after pediatric TBI (Albicini et al., 2017; Albicini & McKinlay, 2018; Babikian & Asarnow, 2009; Babikian et al., 2015; Di Battista et al., 2012; Durish et al., 2018; Emery et al., 2016; Keightley et al., 2014; Lloyd et al., 2015; Lopes et al., 2013; Roberts et al., 2016; Trenchard et al.,

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2013). Some reviews focus on a subsample of TBI (e.g., mild TBI; Emery et al., 2016; Keightley et al., 2014; or nonaccidental TBI; Lopes et al., 2013), on a specific domain (e.g., social functioning; Rosema et al., 2012) or on a wide age range (e.g., 0 - 18 years old; Babikian & Asarnow, 2009; Di Battista et al., 2012; or 0 - 13 years old; Kennedy et al., 2017), but only two reviews include information on the specific effects of early TBI (Garcia et al., 2015; Wetherington & Hooper, 2006). Garcia et al. (2015) report that children who sustain TBI before the age of five years encounter difficulties such as externalizing behaviors, and attentional, language, and cognitive dysfunction (e.g., Intellectual Quotient [IQ], executive functioning). Wetherington et al. (2006) suggest the presence of developmental changes and impairments in selected cognitive abilities, motor functions, and socio-behavioral skills. However, neither review was conducted systematically, and both reviews also included children older than six years, precluding specific conclusions concerning the effects of early TBI. Moreover, the results mainly focussed on cognitive and behavioral outcomes, with limited information on socio-emotional functioning, and no coverage of adaptive functioning.

In sum, there is a growing literature concerning the effects of early TBI, but findings have not yet been presented in a synthetized and comprehensive manner. We undertook a systematic review of the literature in order to provide a broad view of the potential impact of sustaining TBI at a young age. The goal of this review was to investigate the cognitive, academic, behavioral, socio-affective, and adaptive consequences of early TBI.

Methodology

Search Strategy

A systematic review was carried out according to the PRISMA guidelines (Liberati et al., 2009). Four databases were searched: Medline (Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) from 1946 to Present), PsycNET (PSYcInfo, PSYCARTICLES, APA Books), CINAHL (Plus with Full Text) and PubMed. Two groups of key terms pertaining to TBI and the early childhood period were used with appropriate truncations: (brain injur* or head injur* or concussion* or "head trauma*" or "brain trauma*") AND (preschool* or infan* or toddler* or neonat* or pediatric* or newborn* or child*). Years searched between 1990 and 2019. The fields of search for each database were:

- PsycNET: Keywords
- Medline: Title, Keyword Heading Word, Heading Word

- CINAHL: Subject Heading (keyword search on all subject fields in the record)
- PubMed: Text Word

Eligibility Criteria

Inclusion Criteria All papers in which the main purpose of the study was to report original empirical data from early TBI (0 - 5 years; 11 months old) were retrieved according to the following criteria:

- 1) Peer-reviewed journal articles only (i.e., conference proceedings, books and book chapters were excluded).
- 2) Articles that reported empirical data from pediatric TBI (an alteration in brain function, or other evidence of brain pathology, caused by an external force; Menon et al., 2010).
- Children were < 6 years of age at the time of the injury (i.e., birth to 5 years, 11 months, 29 days).
 - a. For articles that included both children < six years and > six years and presented results by age group (e.g., preschoolers, middle school, etc.), outcomes were reported only for those who sustained early TBI, if available.
- 4) All TBI severity included (concussion or mild, moderate, and severe TBI).
- 5) Closed head injury.
- Any mechanism of TBI: accidental TBI (aTBI) or nonaccidental TBI (naTBI; for example, infantile nonaccidental trauma ["shaken baby"], inflicted TBI).
- 7) Reported outcomes known to measure at least one of the following domains: cognitive and academic outcomes (intellectual function or development, attention, executive function, memory, language, social cognition, and academic) and behavioral and socio-affective outcomes (emotion regulation and behavior, social skills and adaptive functioning).
- Studies in humans (i.e., not animal or microcellular specimens).

Exclusion Criteria Papers that contained at least one of the following elements were excluded:

- Nontraumatic mechanisms of injury, such as inflammation, infection, or autoimmunity.
- 2) Prenatal head injury or in utero head trauma.
- 3) Penetrating injury (for example, Garth et al., 1997).
- Meta-analyses, psychometric studies, rehabilitation program and intervention effectiveness studies, opinion paper, editorials, commentaries, legal cases, single case studies.
- 5) Languages other than English or French.

- 6) Outcomes:
 - Exclusively biological, physiological, neurological, genetic, sensorimotor, biomarkers, sleep, neuroimaging, occupational, global functional (e.g., Activities of Daily Living, Quality of Life), disability or morbidity outcomes.
 - b. Non-interpreted or descriptive normative data.
 - c. Postconcussive symptoms (PCS).

Manuscript Review Process

During the first stage of screening, three reviewers independently performed preliminary screening of titles and abstracts to exclude any article that did not meet the inclusion and exclusion criteria. In the second stage of screening, all remaining articles were read in full to ensure the paper met the selection criteria. Disagreements about eligibility were resolved through discussion and consensus.

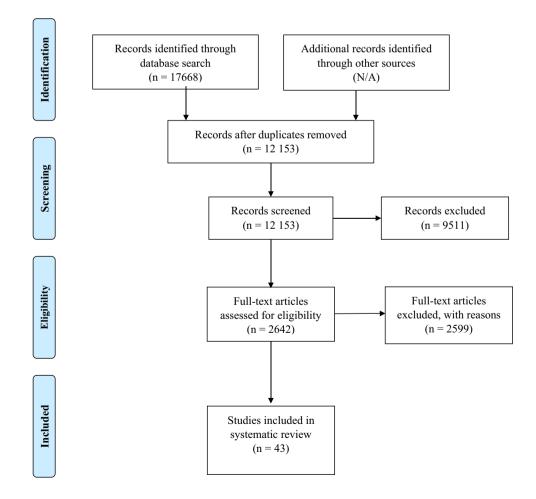
Data Collection Process

A structured database was created to extract the following predetermined information from each selected article: (a) authors and year of publication, (b) injury severity, (c) age and type of injury, (d) control group, (e) design and timing of follow-up, (f) cognitive and academic outcomes (intellectual function or development, attention, executive functioning, memory, language, social cognition and academic), and (g) behavioral and socio-affective outcomes (emotion regulation, behavior, social skills and adaptive functioning).

Risk of Bias

The quality of selected studies was independently assessed by two reviewers based on a minor adaptation of the criteria proposed by Hayden (2006). The following risks of bias were evaluated: (a) study participation (e.g., is there adequate participation in the study by eligible individuals), (b) study attrition (e.g., response rate is adequate), (c) outcomes (e.g., the method and measurement setting are the same for all study participants), (d) confounding (e.g., important potential confounders are accounted for in the study design), and (e) analysis (e.g., there is no selective reporting of results). Presence of bias was judged as "Yes", "Partly", "No" or "Unsure".

Fig. 1 PRISMA Diagram



Results

Study Selection

Details of the search results are presented in Fig. 1. The initial search identified 17,668 articles based on the keywords and search criteria used in the four databases. A total of 8967 articles were found in Ovid (Medline), 2553 in CINAHL, 2578 in PsycNET, and 3570 in PubMed. After removal of 5515 duplicates, 12, 153 were screened to evaluate whether the inclusion and exclusion criteria were met. After the first stage of screening (review of titles and abstracts), 9511 articles were excluded. After the second stage of screening (full-text review), 2599 articles were excluded. A final total of 43 articles were included in the systematic review. The majority of articles were rejected because they did not meet inclusion criteria 3 (early TBI).

Table 1 summarizes the articles that were included for systematic review as a function of participant characteristics, assessment, time since the injury. The main findings related to cognitive and academic outcomes are presented in Table 2, and behavioral and socio-affective outcomes in Table 3. For some articles, the percentage or proportion of the population with deficits in the aforementioned domains are reported (Barlow et al., 2005; Bonnier et al., 2007; Ewing-Cobbs et al., 1998, 2006; Keenan et al., 2019; Kieslich et al., 2001; Pastore et al., 2013; Prasad et al., 1999; Sonnenberg et al., 2010; Vassel-Hitier et al., 2019). Publication dates ranged from 1990 to 2019, and 11 articles were published in the last five years (2015 - 2019; Bellerose et al., 2015, 2017; D'Hondt et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja & Kolk, 2015; Keenan et al., 2018; Keenan et al., 2019; Lalonde et al., 2016; Landry-Roy et al., 2018; Vassel-Hitier et al., 2019). Abbreviations are used to reduce information burden and are defined below Table 1.

Risk of Bias

Tables 4 and 5 present the quality assessment according to five potential risks of bias (Participation, Attrition, Outcomes, Confounding and Analysis). Overall, 38 studies (88%) comprised at least one risk of potential bias. More specifically, 28 studies (65%) presented a potential risk of bias related to "study participation". In the majority of the studies (N=28, 65%), adequate participation in the study by eligible individuals was unspecified or TBI classification characteristics were vague. Twenty-seven studies (63%) had shortcomings related to "study attrition". One study (2%) had potential risks of bias related to "outcome measurement". Eight studies (19%) had shortcomings related to "confounding measurement and account", and 13 studies (30%) presented potential risk of bias regarding "analysis".

Study Characteristics

Design

Of the 43 studies identified, most studies (N=39, 91%)employed prospective designs and four studies (9%) employed a retrospective design (Bonnier et al., 2007; Kieslich et al., 2001; Papoutsis et al., 2014; Sonnenberg et al., 2010). Among the prospective studies (N=39), 19 studies (49%) were longitudinal (Coster et al., 1994; Dégeilh et al., 2018; Ewing-Cobbs et al., 1999, 2004, 2006, 2013; Gagner et al., 2018; Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2007, 2018, 2019; McKinlay et al., 2002, 2009, 2010, 2014; Prasad et al., 1999; Tonks et al., 2011; Wrightson et al., 1995), 11 studies (28%) were cross-sectional (Beers et al., 2007; Crowe et al., 2012a, b, 2013, 2014; Landry et al., 2004; Marsh & Whitehead, 2005; Pastore et al., 2013; Stipanicic et al., 2008; Walz et al., 2009; Wetherington et al., 2010), and nine studies (23%) used both longitudinal and cross-sectional designs (Barlow et al., 2005; Bellerose et al., 2015, 2017; D'Hondt et al., 2017; Ewing-Cobbs et al., 1998; Lalonde et al., 2016; Landry-Roy et al., 2018; Liu & Li, 2013; Vassel-Hitier et al., 2019).

Comparison Groups

Thirty-four studies (79%) included a comparison group. Nine studies (21%) did not use any comparison groups, impeding the possibility of drawing brain-injury specific conclusions (Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Crowe et al., 2012a, b; Ewing-Cobbs et al., 1998; Kieslich et al., 2001; Prasad et al., 1999; Sonnenberg et al., 2010; Vassel-Hitier et al., 2019). For those that included a comparison group, seven studies (16%) included children with orthopedic injuries (Coster et al., 1994; Dégeilh et al., 2018; Keenan et al., 2018, 2019; Marsh & Whitehead, 2005; Walz et al., 2009; Wrightson et al., 1995), one study (2%) used an "other acquired brain injuries" comparison group (Pastore et al., 2013), 20 studies (47%) compared their sample to typically developing children (Bellerose et al., 2015; Crowe et al., 2012a, b, 2013, 2014; D'Hondt et al., 2017; Ewing-Cobbs et al., 1999, 2004, 2006, 2013; Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2007; Landry-Roy et al., 2018; Landry et al., 2004; Liu & Li, 2013; McKinlay, et al., 2014; Papoutsis et al., 2014; Stipanicic et al., 2008; Tonks et al., 2011; Wetherington et al., 2010), and six studies (14%) recruited both children with orthopedic injuries and typically developing children as comparison groups (Bellerose et al., 2017; Gagner et al., 2018; Lalonde et al., 2016; McKinlay et al., 2002, 2009, 2010).

Reference	Injury severity (n; % male)	Age at injury in months Range (M±SD)	Cause of injury (n; % of TBI group)	Control groups (n; % male)	Study design Post-injury timepoint in months Range (M±SD)
aTBI					
Bellerose et al. (2015)	mTBI	18-60	Falls	TDC	L (C-S), P
. ,	(51; 50.98%) mTBI	(36.00±11.19) mTBI	(49; 96.00%) Falls	(50; 34.00%) OI	Pre-injury, 6 L (C-S), P
Bellerose et al. (2017)	(72; 52.77%)	18-60 (35.57±11.59)	(67; 93.00%)	(58; 50.00%)	Pre-injury, 6 & 18
bellel use et al. (2017)		01		TDC	
	All TBI severity	18-60 (34.37±10.53) 1 mo-5.60 yrs	Falls	(83; 51.00%) OI	L, P
Coster et al. (1994) ⁺	(57; 67.00%)	(2.97±1.43) yrs	(25; 46.00%)	(17; NA)	1 & 6
	mTBI (19; 57.90%)	3wks-2 yrs; 11 mos	Falls mTBI	TDC (20; 40.00%)	C-S, P ≥ 2 yrs
	msTBI	mTBI (16.80±10.30)	(NA; 94.70%)	,	mTBI
Crowe et al. (2014)	(16; 43.80%)	msTBI	msTBI (NA; 81.30%)		NA (47.70±9.00)
		(12.30±10.60)	(INA, 01.30%)		msTBI NA (46.90±8.20)
					Ax
					3 yrs; 10 mos - 6 yrs: 00 mo old
	mTBI (20; 55.00%)	6 days - 2 yrs; 11 mos	Falls mTBI	TDC (27; 40.70%)	C-S, P ≥ 2 yrs
	msTBI	mTBI 1-35 (17.70±10.70)	(18; 90.00%)		mTBI
Crowe et al. (2012a)	(33; 53.10%)	msTBI	msTBI		29-64 (46.80±9.70)
		0-35 (21.50±12.10)	(22; 66.70%)		msTBI 24-56 (39.20±9.60)
					Ax
	mTBI	mTBI	Falls	TDC	4 yrs; 00 mo - 5 yrs; 11 mos old C-S, P
	(19; 57.90%)	(16.80±10.30)	mTBI	(20; 40.00%)	C-S, P ≥ 2 yrs
	msTBI	msTBI	(17; 89.50%)		mTBI
Crowe et al. (2013)	(16; 43.80%)	(12.30±10.60)	msTBI (12; 75.00%)		(47.70±8.90) msTBI
			(12, 75.00%)		(46.90±8.20)
					Ax
	Infant	Infant: 0-2 yrs	Falls	None	3 yrs; 10 mos - 5 yrs; 11 mos old C-S, P
	(50; NA)	mTBI	Infant	Hone	24-45
	mTBI	(1.60±0.90) yrs modTBI	(37; 74%)		(30.06±NA)
	(20; 50.00%) modTBI	(1.70±1.00) yrs	Preschool (21; 49%)		
	(23; 56.50%)	sTBI (1.90±0.70) yrs	(22) 13707		
	sTBI (7; 57.10%)				
Crowe et al. (2012b)	Preschool	Preschool: 3-6 yrs mTBI			
	(43; NA)	(5.00±1.30) yrs			
	mTBI	modTBI (4.90±1.20) yrs			
	(11; 54.40%)	sTBI			
	modTBI (19; 78.90%)	(5.10±1.10) yrs			
	sTBI				
	(13; 69.20%) mTBI	mTBI	Falls	01	L, P
	(63; 52.00%)	(35.84±11.17)	mTBI	(53; 47.00%)	Pre-injury, 6 & 18
Dégeilh et al. (2018)			(59; 94.00%)		Ax
			OI (32; 60.00%)		T0 (37.39±11.21) T1 (42.37±11.50)
	mTBI	mTPI	NA	TDC	T2 (55.22±11.09)
D'Hont et al. (2017)	(18; 72.22%)	mTBI (53.00±8.00)	NA	(15; 46.67%)	L (C-S), P 6
	mTBI (86; 53.49%)	mTBI (36.50±11.56)	Falls mTBI	OI (62; 50.00%)	L, P 6
Gagner et al. (2018)	(86; 53.49%) Uncomplicated mTBI (77; NA)	(30.30.111.30)	(78; 90.70%)	(62; 50.00%) TDC	б Ах
	Complicated mTBI (9; NA)		OI	(81; 50.61%)	(43.52±11.72)
	All TBI severity	0-5 yrs	(35; 56.45%) Falls	TDC	L, P
	(17; 58.80%)	(NA±NA)	(all sample)	(16; 37.50%)	13-16 yrs
	mTBI		(11; 64.70%)		Ax
Green et al. (2013)	(2; 11.80%)				TBI 15-18 yrs (16.50±1.00) yrs
•	modTBI (9; 52.90%)				TDC
	stBl				14-18 yrs (16.30±1.40) yrs
	(6; 35.30%)				
(aldoja et al. (2015)	mTBI (35; 46.00%)	3-65 (NA±NA)	NA	TDC (54; 59.00%)	L,P Pre-injury (3 days), 9 mos
	mTBI	18-60	Falls	01	L (c-s), P
	(47; 57.45%)	(NA±NA)	(45; 95.74%)	(27; 44.44%)	Pre-injury, 6
alonde et al. (2016)			01	TDC	Ax
			(22; 81.48%)	(56; 41.07%)	(41.65±11.49)

Table 1 Studies identified in the systematic review examining outcome after accidental TBI and non accidental TBI in early childhood: Study characteristics

Table 1 (continued)

Landry-Roy et al. (2018)	mTBI (84; 54.00%)	mTBI (36.80±11.54)	Falls (76; 91.00%)	TDC (83; 49.00%)	L (c-s), P Pre-injury (in mTBl only), 6 Ax (43.08±11.63)
Liu et al. (2013)*	mTBI (167; 57.49%)	< 6 yrs	NA Single injury (97; 14.00%) Multiple injuries (70; 10.00%)	TDC (558; 51.08%)	L (c-s), P Ax 6 yrs old
Marsh and Whitehead (2005)*	mTBI + ModTBI (19; 68.00%)	TBI 2-24 (12.11±7.73) OI 9-27 (18.50±4.80)	Falls (18; 94.70%)	OI (20; 65.00%)	C-5, P 5 yrs TBI 62-79 mos (68.79±5.38) OI 45-77 mos (61.40±9.00) Ax TBI 71-97 mos (80.89±8.18) OI 70-92 mos (79.90±7.79)
McKinlay et al. (2014)	mTBI 0-5 yrs (83; NA) Inpatient (61; NA) Outpatient (22; NA)	0-5 yrs (NA±NA)	NA	TDC (972; NA)	L,P Pre-injury (covariates), 11-20 yrs
McKinlay et al. (2002)	mTBI (101; 51.00%) Outpatient (84; NA) Inpatient (17; NA)	0-5 yrs	Falls Inpatient (NA; NA%) Outpatient (NA; NA%)	TDC and/or OI (789-807; NA%)	L,P Pre-injury (covariates) Ax 8 yrs (WISC-R) and/or 10-13 yrs (PAT & Rutter & Conners)
McKinlay et al. (2009)	mTBI (76; NA) Inpatient (19; 53.00%) Outpatient (57; 53.00%)	0-5 yrs	NA	TDC and/or OI (839; NA%)	L,P Pre-injury (covariates) Ax 14-16 yrs old
McKinlay et al. (2010)	mTBI (81; NA) Inpatient (21; 52.40%) Outpatient (60; 50.00%)	0-5 yrs	Falls Inpatient (16; 76.00%) Outpatient (NA; NA%)	TDC and/or OI (851; 49.90%)	L, P Ax 7 - 13 yrs old (yearly)
Papoutsis et al. (2014)	(3) (3) (3) (3) (3) (3) (3) (3) (3) (3)	Complicated mTBI (23.09±13.58) Uncomplicated mTBI (19.72±14.58)	NA	TDC (33; 54.54%)	R > 7 yrs Complicated mTBI (118.88±14.04) Uncomplicated mTBI (114.00±15.81) TDC (116.48±20.48)
Pastore et al. (2013)	sTBI (14; 64.30%) Brain tumour (18; 77.80%) Vascular or infectious brain lesions (23; 33.10%)	sTBI (24.79±10.69)	NA	None	C-S, P 8.40 - 16.33 (8.50±10.52) Ax sTBI (34.07±6.89)
Prasad et al. (1998)	msTBI (8; 50.00%)	13-32 (20.90±NA)	Car overhead (NA; 62.50%)	None	L, P 2 mos & 1 year
Sonnenberg et al. (2010)	msTBI (93; 61. 29%) Young msTBI (61; 63.93%) Old msTBI (32; 56.25%)	< 6 yrs (3.40±1.50) yrs Young 0-3 yrs; 11 mos (2.60±1.10) yrs Old 4-5 yrs; 11 mo (5.0±0.60) yrs	NA	None	L, R Ax msTBI 7 - 9 yrs; 11 mo (8.30±0.70) yrs
Tonks et al. (2011)*	All TBI severity (28; NA%) mTBI (21; NA%) ModTBI (2; NA%) msTBI (3, NA%) sTBI (2; NA%)	< 5 yrs old	NA	TDC (89; NA%)	C-S, P Ax 8-10 yrs old (14; NA%) (9.20±1.40) 10-16 yrs old (14; NA%) (13.10±2.17)
Walz et al. (2009)	msTBI (66; NA) modTBI (42; NA) STBI (17; NA)	3 - 5 yrs; 11 mos	NA	OI (86: NA%)	C-S, P 1
Wrightson et al. (1995)*	mTBI (78; NA%)	2.50-4.50 yrs	Falls (NA; 78.00%)	OI (86; NA%)	L, P Pre-injury, 1, 6, 12 mos & at 6.50 yrs old

Table 1 (continued)

naTBI					
	Unspecified severity	2 wks-34 mos	Whiplash shaking	None	C-S, L, P
	naTBI	(3.50±NA)	(13; 52.00%)		59 mos
	(25; 60.00%)		Impact (12; 48.00%)		C-S (13; 52.00%) L, P
					(12; 48.00%)
Barlow et al. (2005)					Ax C-S
					NA (90±50.00) L,P
					1 st Ax: NA (16.00±9.90) Last Ax:
					NA (25.30±9.10)
Ewing-Cobbs et al. (1999)	ms naTBI (28; 25.00%)	2-42 (9.28±8.59)	naTBI (28; 100%)	TDC (28; 50.00%)	L, P 1 & 3
	naTBI (40; NA%)	2-23 (NA±NA)	NA	TDC (22; 36.00%)	C-S, P NA(1.6±NA) mos
Landry et al. (2004)	msTBI (25; 28.00%)				Ax na msTBI
	modTBI (18; NA)				3-31 (10.92±8.45) TDC
	sTBI (7; NA)				3-30 (11.64±7.16)
	naTBI (11; 45.00%)	0-36 (5.09±3.23)	naTBI with or without impact	TDC (11; 45.00%)	C-S, P NA (78.90±NA)
Stipanicic et al. (2008)					Ax naTBI (87.64±25.52)
aTBI vs naTBI					(07.04123.32)
	All severity	< 3 yrs	NA	None	C-S, P
Beers et al. (2007) ⁺	naTBI (15; 47.00%)	naTBI (5.75±7.91)			6
	aTBI (15; 40.00%)	aTBI (17.22±11.33)			
	msTBI (40; 30.00%)	1 mo-6 yrs naTBI	naTBI (10; 50.00%)	None	C-S, L, P 1.30 mos
Ewing-Cobbs et al. (1998)	naTBI (20; 15.00%)	(10.60±14.87)	aTBI MVA (passenger) (9; 45.00%)		
	aTBI (20; 50.00%)	aTBI (35.55±25.35)			
aTBI vs naTBI/a	TBI & naTBI				
	All severity	0-36	naTBI (41; 64.10%)	TDC (60; 48.00%)	L, P 2 & 12 mos
	naTBI (64; 50.00%)	naTBI (8.00±7.90)	aTBI	(00, 40.0070)	Ax
Ewing-Cobbs et al. (2013)*		aTBI	Falls		naTBI
Ewilig-Cobbs et al. (2015)	aTBI (61; 59.00%)	(11.30±10.50)	(17; 26.56%)		(9.80±8.00)
					aTBI (12.60±10.30)
					TDC (11.70±8.60)
	All severity naTBI & aTBI	<2 yrs	naTBI (25; 52.00%)	TDC (31; NA)	L, P
	(48; 57.70%)	1.80 – 9.90 (4.20 median)	aTBI	, , ,	Ax naTBI
Keenan et al. (2007)+	, , ,		NA (23; 48.00%)		(3.10±NA) yrs
			(23, 48.00%)		aTBI (3.20±NA) yrs
					TDC (3.60±0.30) yrs
aTBI & naTBI		1			1
	sTBI (50; 62.00%) (40; NA)	< 3 yrs (12.50±15.00)	naTBI (29; 100%)	None	R NA (6.60±3.90 yrs)
Bonnier et al. (2007)	naTBI		aTBI MVA (passenger)		(0.0010.00 913)
	(29; NA) aTBI (11: NA)		(12; 57.14%)		
	(21; NA) msTBI (23; 52.00%)	4-71 (21.20±21.90)	naTBI (10; 47.62% 0f msTBI)	TDC (21; 47.00%)	L, P 3.80-8.30 yrs (5.70±NA)
Ewing-Cobbs et al. (2006)	naTBI		aTBI	(21,47.00%)	Ax
- • •	(10; NA) aTBI		Falls (5; 38.00%)		msTBI (89.60±26.20) TDC
	(13; NA)				(101.00±29.00)

Table 1 (continued)

	70			TOC	1.5
Ewing-Cobbs et al. (2004)	msTBI (44; NA) Young (18; 55.56%) Old (26; 50.00%) naTBI (NA; 41.00%) aTBI (NA; 59.00%)	NA Young: (11.20±9.40) Old: (34.20±22.20)	NA	TDC (26; 46.00%)	L, P Young: 11.30 mos Old: 26.80 mos Ax msTBl Young: 11-35 (22.55±5.26) Old: 36-85 mos (61.00±12.66) TDC TDC Young: (22.62±7.53) Old: (57.92±15.59)
Keenan et al. (2018)	naTBI & aTBI naTBI & aTBI (386; 64.00%) mTBI (144; 61.00%) cmTBI (130; 68.00%) modTBI (26; 31.00%) sTBI (86; 72.00%)	2.50-15 yrs (9.20±4.20) Age groups: 2.50-6 yrs 6-11 yrs 12-15; 11 yrs	All ages naTBI (2; 1.00%) aTBI Falls (143; 37.00%)	OI (133; 63.00%)	L, P Pre-injury, 3 & 12 mos
Keenan et al. (2019)	All severity naTBI & aTBI (123; 55.00%) mTBI (48; 54.00%) cmTBI (45; 47.00%) modTBI (7; 78.00%) sTBI (21; 67.00%)	0-30 (11.60±9.00)	n-aTBI Falls (85; 69.00%) aTBI (21; 17.00%)	Ol (45; 60.00%)	L, P Pre-injury, 3 & 12 mos
Kieslich et al. (2001)*	Severe naTBI & aTBI (318; 63.80%)	< 2 yrs (64; NA%) 2-6 yrs (38; NA%) > 6 yrs (98; NA%)	aTBI High-velocity injuries (NA; 61.40%) naTBI (NA; 6.60%)	None	R NA (8 yrs; 9 mos±NA)
Vassel-Hitier et al. (2019)	msTBI (21; 40.40%) aTBI (8; 52.50%) naTBI (13; 61.50%)	< 18 mos (0.70±0.5) mos aTBI 0.20-1.60 (0.90±0.60) yrs naTBI 0.10-1.10 (0.50±0.30) yrs	aTBI Falls (5; 62.50%) naTBI NA	None	L (C-S), P 7 yrs 3.60-9.40 (6.80±1.80) yrs
Wetherington et al. (2010)*	naTBI & aTBI (51; NA) mTBI (31; 45.16%) msTBI (20; NA)	< 2 yrs mTBI (0.49±0.57) yrs msTBI (0.81±0.62) yrs	aTBI NA (26; NA%) naTBI NA (25; NA%)	TDC (31; 64.50%)	C-S, P ≈ 3 yrs Ax mTBI (3.33±0.38) msTBI (3.25±0.27)

Sample Characteristics

Age

As per the inclusion criteria, age at injury ranged from birth to 5 years, 11 months and 29 days. When considering mean age at injury for TBI groups, 14 studies (33%) focused on infants (0 – 18 months; Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Crowe et al., 2013, 2014; Ewing-Cobbs et al., 1999, 2004, 2013; Keenan et al., 2007, 2019; Marsh & Whitehead, 2005; Stipanicic et al., 2008; Vassel-Hitier et al., 2019; Wetherington et al., 2010), 11 (26%) on toddlers (18–36 months; Bellerose et al., 2015, 2017; Coster et al., 1994; Crowe et al., 2012a, b; Dégeilh et al., 2018; Ewing-Cobbs et al., 2006; Gagner et al., 2018; Landry-Roy et al., 2018; Papoutsis et al., 2014; Pastore et al., 2013; Prasad et al., 1999), two (5%) on preschoolers (36–72 months; D'Hondt et al., 2017; Walz et al., 2009), and two (5%) combined one of these early age groups with children older than 6 years (Keenan et al., 2018; Kieslich et al., 2001). Other studies (30%) did not present mean age at injury, and instead presented age at injury as an interval from 0–15 years (Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2007, 2018; Kieslich et al., 2001; Lalonde et al., 2016; Liu & Li, 2013; McKinlay, et al., 2002, 2009, 2010, 2014; Tonks et al., 2011; Walz et al., 2009). Other studies covered more than one age group. One study (2%) examined both infants and toddlers (Landry et al., 2004). Three studies (7%) covered toddlers and preschoolers (18-72 months; Keenan et al., 2018; Kieslich et al., 2001; Lalonde et al., 2016; Wrightson et al., 1995), and 11 articles (26%) covered all three developmental groups (0-72 months; Crowe et al., 2012a, b; Ewing-Cobbs et al., 1998; Green et al., 2013; Kaldoja & Kolk, 2015; Liu & Li, 2013; McKinlay, et al., 2002, 2009, 2010, 2014; Sonnenberg et al., 2010; Tonks et al., 2011). Overall, the majority of the studies included either infants or toddlers, and few focused on preschoolers (36–60 months). In the articles that compared early childhood age groups among themselves, younger groups presented worse outcomes in comparison to older groups (Crowe et al., 2012a, b; Ewing-Cobbs et al., 2004; Keenan et al., 2018, 2019; Kieslich et al., 2001; Sonnenberg et al., 2010). Of the studies that investigated both aTBI and naTBI, some articles reported a significant difference for age at injury between the two groups, with the naTBI group being younger than the aTBI group (Ewing-Cobbs et al., 1998, 2006).

Age at Assessment (Post-injury Delay)

Follow-up periods post-injury ranged from one month to 20 years. Most studies (N = 19; 44%) documented outcomes within one year post-injury (Beers et al., 2007; Bellerose et al., 2015, 2017; Coster et al., 1994; D'Hondt et al., 2017; Dégeilh et al., 2018; Ewing-Cobbs et al., 1998, 1999, 2013; Gagner et al., 2018; Kaldoja & Kolk, 2015; Keenan et al., 2018, 2019; Lalonde et al., 2016; Landry-Roy et al., 2018; Landry et al., 2004; Prasad et al., 1999; Walz et al., 2009; Wrightson et al., 1995). Twelve studies (28%) included follow-up periods between two and five years post-injury (Barlow et al., 2005; Crowe et al., 2012a, b, 2013, 2014; Ewing-Cobbs et al., 2004, 2006; Keenan et al., 2007; Liu & Li, 2013; Marsh & Whitehead, 2005; Sonnenberg et al., 2010; Wetherington et al., 2010), and 10 studies (23%) from 6 to 10 years (Bonnier et al., 2007; Kieslich et al., 2001; McKinlay et al., 2002, 2010; Papoutsis et al., 2014; Pastore et al., 2013; Sonnenberg et al., 2010; Stipanicic et al., 2008; Tonks et al., 2011; Vassel-Hitier et al., 2019). Only two studies (5%) reported outcomes between 10 and 20 years post-injury (Green et al., 2013; McKinlay et al., 2009), and one study (2%) reported outcomes over 20 years post-injury (McKinlay et al., 2014).

Pre-injury Characteristics

Thirteen studies (30%) reported participant characteristics pre-injury (Bellerose et al., 2015, 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja & Kolk, 2015; Keenan et al., 2018, 2019; Lalonde et al., 2016; Landry-Roy et al., 2018; McKinlay, et al., 2002, 2009, 2014; Wrightson et al., 1995). Studies that assessed pre-injury behavior did so retrospectively, mainly by parental recall on questionnaires, and usually within the first two weeks after injury. Of these studies, some found differences between TBI and comparison groups. First, toddlers who sustained mTBI presented significantly more externalizing behaviors (Child Behaviour Checklist [CBCL]) compared to typically developing children (Bellerose et al., 2015; however, see also Gagner et al., 2018). Second, toddlers and preschoolers had comparable behavior (Strength and Difficulties Questionnaire [SDQ] and CBCL) to those with orthopedic injuries, regardless of mechanism and severity of injury (Keenan et al., 2018). In a third study, parent and teacher ratings of emotional regulation and behavior (Connors Rating Scale) of toddlers and preschoolers who sustained mTBI were comparable to those with orthopedic injuries (Wrightson et al., 1995). Fourth, in a group of toddlers and preschoolers who sustained either naTBI or aTBI (all severities), executive functions (Behavior Rating Inventory of Executive Function [BRIEF]) were mostly comparable to those with orthopedic injuries, except for working memory which was poorer in the uncomplicated mTBI group compared to all other groups (complicated mTBI, moderate TBI [modTBI], severe TBI [sTBI], orthopedic injuries: Keenan et al., 2018). Fifth, in a combined group of infants with naTBI or aTBI (all severities), communication (Ages & Stages Questionnaire-3 [ASQ-3]) was poorer in infants who sustained sTBI compared to infants with orthopedic injuries (Keenan et al., 2019). Sixth, in children who sustained mTBI, adaptive functions (Adaptive Behavior Assessment System [ABAS] or Vineland) were comparable to those with orthopedic injuries (Dégeilh et al., 2018; Wrightson et al., 1995) and typically developing children (Bellerose et al., 2015, 2017; Dégeilh et al., 2018), while toddlers with mTBI and TDC showed higher leisure levels compared to the orthopedic injuries group (Lalonde et al., 2016). Seventh, in children (0 - 6 years) who sustained mTBI, boys with mTBI showed more self-regulation problems (Ages and Stages Questionnaires: Social-Emotional [ASQ-S-E]) compared to girls with mTBI and typically developing boys. Girls who sustained mTBI presented more adaptive difficulties compared to typically developing girls. No difference in social difficulties, communication, compliance, and affect (ASQ-S-E) were noted between these groups during the pre-injury period (Kaldoja & Kolk, 2015). Other studies (N=3; 7%)used pre-injury characteristics only as confounding variables for main statistical analyses rather than in group comparisons (see McKinlay et al., 2002, 2009, 2014).

TBI characteristics

Type of Injury (Accidental vs Non-Accidental Injury) Twentyseven studies (63%) focused on aTBI (Albicini et al., 2017; Bellerose et al., 2015, 2017; Coster et al., 1994; Crowe et al., 2012a, b, 2013, 2014; D'Hondt et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Green et al., 2013; Kaldoja & Kolk, 2015; Lalonde et al., 2016; Landry-Roy et al., 2018; Liu & Li, 2013; Marsh & Whitehead, 2005; McKinlay, et al., 2002, 2009, 2010, 2014; Papoutsis et al., 2014; Pastore et al., 2013; Prasad et al., 1999; Sonnenberg et al., 2010; Tonks et al., 2011; Walz et al., 2009; Wetherington et al., 2007; Landry et al., 2004; Stipanicic et al., 2008), and 13 studies (30%) investigated both aTBI and naTBI (Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; EwingCobbs et al., 1998, 2004, 2006, 2013; Keenan et al., 2007, 2018, 2019; Kieslich et al., 2001; Vassel-Hitier et al., 2019; Wetherington et al., 2010). For those that investigated aTBI, 19 (44%) reported falls as the most frequent mechanism of injury.

TBI Definition

Accidental injury was usually defined as "evidence of a TBI", without further operational criteria. There was little consensus regarding the definition of TBI in papers that included specific criteria. The most commonly used definitions were "blunt trauma or acceleration or deceleration forces" and "an injury to the head with observed or reported decreased level of consciousness, amnesia, or neuropsychological abnormality or diagnosed intracranial lesion" from the Centers for Disease Control (Marr & Coronado, 2004; Keenan et al., 2018). Other authors used alternate definitions such as "crush head injury which is produced by static forces occurring when the head is stationary and pinned against a rigid structure" (Prasad et al., 1999).

Non-accidental TBI (naTBI) was typically defined through established confession of the perpetrator, or by applying an algorithm for presumptive abuse (Duhaime et al., 1992; Goldstein et al., 1993). The algorithm relies on information about the type of cranial injury, history of the injury, and associated physical findings to classify an injury as presumptive or suspicious for abuse.

TBI Severity Classification

Ten studies (23%) performed comparisons across severity groups (Crowe et al., 2014, 2013, 2012a, b; Green et al., 2013; Keenan et al., 2018, 2019; Papoutsis et al., 2014; Walz et al., 2009; Wetherington et al., 2010) and used similar severity criteria (Alexander, 1995; CDO, 2004; Keith Owen & Taylor, 2005; Marr & Coronado, 2004; Osmond et al., 2010). These typically relied on a combination of Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), duration of loss of consciousness, post-traumatic amnesia, and neuro-imaging or radiology results.

Some authors did not use TBI severity classification (Wrightson et al., 1995) or used only GCS with 13–15 defined as mTBI, 8–12 as modTBI, and 3–8 as sTBI (Marsh & Whitehead, 2005). Others used a modified version of the GCS adapted from the Advanced Trauma Life Support manual (Morgan, 1997) for children younger than two years of age (Beers et al., 2007). This version modifies the verbal scale by rating the child's interactions with the environment rather than verbal skills. Other studies used further GCS adaptations (Reilly et al., 1988), taking into account language abilities in children under three years of age, for example, by replacing verbal items with questions about crying and parent-child interactions (Papoutsis et al., 2014). Ewing-Cobbs and colleagues (1999, 2004, 2013) modified the GCS motor and verbal scales to accommodate the behavior of children from birth to 35 months of age. Specifically, spontaneous movement in infants aged 0–6 months and goal-directed movements in children aged 7–35 months were considered comparable to following commands in older children. For example, "cries" and "cries to indicate need" were regarded as equivalent to the verbal scale items "confused" and "oriented".

Others research groups have since applied this modified GCS to their own work (Bonnier et al., 2007). Some studies combined TBI severity groups (e.g., modTBI and sTBI) or altered the original GCS cut-offs, for example defining moderate-severe TBI (msTBI) as a GCS of 4–13 (Pastore et al., 2013; Prasad et al., 1999). One group used the Pediatric Performance Category Scale at discharge to classify disability from mild to severe (Stipanicic et al., 2008). Finally, some authors used other measures, such as the Injury Severity Scale (ISS; Coster et al., 1994), to categorize TBI severity. In some cases, due to limited availability of valid medical diagnoses. For example, Liu and Li (2013) defined mTBI as no loss of consciousness or no hospitalization for treatment due to injury.

No firm consensus emerged regarding the use of neuroimaging findings to classify mTBI in the studies included. Likewise, definitions of concussion, uncomplicated mTBI (no visible structural brain lesions) and complicated mTBI (visible brain lesions on clinical imaging) were not uniform (Papoutsis et al., 2014).

Twenty-eight studies (65%) reported alteration of consciousness as < 24h for mTBI or modTBI and loss of consciousness as < 5, < 20, < 30, or < 60 min for mTBI (Crowe et al., 2013, Keenan et al., 2018, 2019; Liu & Li, 2013; McKinlay et al., 2010; Papoutsis et al., 2014). The same studies defined sTBI as an alteration of consciousness lasting 24 h or more, or a coma of any duration (Vassel-Hitier et al., 2019; Ewing-Cobbs et al., 1999, 2006, 2013) describe duration of impaired consciousness as the number of days during which a child was unable to follow a onestage command or engage in goal-directed movements, as indicated by the modified GCS motor scale (see above).

Few authors considered post-traumatic amnesia to define severity of injury. When reported, post-traumatic amnesia of two hours or less was associated with mTBI and more than two hours with msTBI (McKinlay, et al., 2014). Some authors included amnesia among the documented neurological signs (e.g., Bellerose et al., 2015, 2017). Finally, 16 articles (37%) reported post-concussive symptoms or neurological signs in relation to injury severity classification (e.g., Bellerose et al., 2015, 2017; Papoutsis et al., 2014).

Cognitive and academic outcome	es						
Reference	Intelligence/Development	Attention	Executive Functioning	Memory	Language	Social cognition	Academic
aTBI	1	1	L.	1	L.		
Bellerose et al. (2015)						Discrepant desires & False Beliefs <u>ToM</u> mTBI < TDC (6 mos) Discrepant desires &	
Bellerose et al. (2017)						False Beliefs ToM mTBI < TDC & OI (6 & 18 mos)	
Crowe et al. (2014)	WP951-III <u>Verbal IQ</u> msT81 (results in average range) < TDC				CELF-P Core Language Index Expressive Vocabulary/Sentence & Word structure msTBI < mTBI = TDC (results in average range) Bus Story Test Expressive language msTBI < mTBI = TDC		
Crowe et al. (2012a)	WPPSI-III <u>VIQ, PIQ, FSIQ</u> msTBI < mTBI = TDC		WPPSI-III Information processing (coding subtest) (ns)				
Crowe et al. (2013)		NEPSY-II Auditory Attention Vigilance and Selective attention (ns)	WPPSI-III Information processing (coding sublest) (ns) Seture subtest Inhibitory control (average range) msTB18, mTB1 <tdc BRIE-P Parent-rate executive function (ns)</tdc 				
Crowe et al. (2012b)	WPPSI-R/WPPSI-III/WISC-III <u>VIQ, PIQ, FSIQ</u> STBI (low average) < mTBI & modTBI (average range)		WPPSI-R/WPPSI-III/WISC-III <u>PSI</u> sTBI (low average) < mTBI & modTBI (average range)				
D'Hont et al. (2017)			Delay of Gratification			NimStim Set of Facial Expression Emotional facial expression processing mTBI < TDC	
Landry-Roy et al. (2018)			Conflict Scale Conflict Scale Conflict Scale Shape Stroop Inhibition & Cognitive flexibility mTBI = TDC (ns)				
Marsh and Whitehead (2005)*		NEPSY-II Visual Attention TBI < 01 22% TBI in impaired range	NEPSY-II Tower Planning Design fluency Cognitive flexibility Auditory Attention and Response Set Inhibition TBI = OI (ns)	NEPSY-II Memory for faces Visual memory TBI < OI 21% in TBI impaired range Memory for names, Narrative Memory, Sentence Repetition Auditive memory TBI = OI (ns)	NEPSY-II Speeded Naming, Comprehension of Instructions & Verbal fluency Language TBI = OI (ns)		WIAT Basic Reading/Maths Reasoning/Spelling TBI = OI (ns)
McKinlay et al. (2002)	WISC-R Inpatient = Outpatient = TDC/OI (ns)						PAT Inpatient = Outpatient = TDC/OI (ns)
Papoutsis et al. (2014)	8510	TEA-ch Sky Attention Visual selective attention Complicated TBI = Uncomplicated TBI = TDC (ns) Sky DT Divided attention Complicated TBI < Uncomplicated TBI = TDC	WISC-VI Coding Speed of information processing (ns) Block Design Goal setting and organization Complicated TBI = TDC (ns) Digit Span Backwards Complicated TBI = TDC (ns) BRIEF Behavioral aspects of EF BRIA MI Complicated TBI = TDC (ns)				
	BilD Development/IQ/motor functioning 2 mos Deficit range						
Prasad et al. (1998)	(63.00%) 1 yr Normal range (83.33%)						

 Table 2
 Studies identified in the systematic review examining outcome after accidental TBI and non accidental TBI in early childhood: Cognitive and academic outcomes

Table 2 (continued)

917

	u)						
			TBI = TDC				
			(ns)				
			Tower Test				
			Planning TBI = TDC				
			(ns)				
			Number-Letter Switching Cognitive flexibility				
			TBI = TDC				
			(ns) WISC-III				
			Digit Span				
			Working memory 8-10 yrs TBI = TDC				
			(ns)				
			10-16 yrs				
	Differential Ability Scales		TBI < TDC			ToM	
	(DAS)/General Conceptual					False beliefs	
	Ability (GCA) sTBI < modTBI & OI					False contents sTBI < modTBI & OI	
Walz et al. (2009)						False	
						location/Control/ToM total	
						sTBI = modTBI = OI	
			WISC	Verbal memory passage	ITPA	(ns)	Neale analysis of reading
			Coding	mTBI = OI	Visual closure (puzzles)		ability/Letter knowledge and
			Processing Speed mTBI = OI	(ns)	At 6, 12 mos post-injury & 6.50 yrs old		writing mTBI = OI
			(ns)	CMS Paired associate learning	mTBI < OI		(ns)
Wrightson et al. (1995)*				mTBI = OI (ns)	Reynell developmental language scales		
				CMS	mTBI = OI		
				Visual memory test	(ns)		
				mTBI = OI (ns)			
naTBI	•	•	•	•	•		
	BSID-II			BSID-II		1	BSID-II
	Development (8 out of 14)			Development (8 out of 14)			Development (8 out of 14)
Barlow et al. (2005)	<1st %ile			< 1 st %ile			< 1 st %ile
	(2 out of 14)			(2 out of 14)			(2 out of 14)
	1st-6th %ile BSID-II			1st-6th %ile BSID-II			1st-6th %ile BSID-II
Ewing-Cobbs et al. (1999)	Mental + physical domains			Mental + physical domains			Mental + physical domains
CMMB-CODDS et al. (1999)	1 & 3 mos			1 & 3 mos			1 & 3 mos
	na msTBI < TDC Bayley Mental Development			na msTBI < TDC Bayley Mental			na msTBI < TDC Bayley Mental Development Inc
Landry et al. (2004)	Index na msTBI < TDC			Development Index na msTBI < TDC]	na msTBI < TDC
	SB-IV	NEPSY	NEPSY	SB-IV	NEPSY	NEPSY	SB-IV
	naTBI < TDC	Auditory Attention naTBI < TDC	Digit Span Auditory Working Memory	naTBI < TDC	Auditory Attention naTBI < TDC	Digit Span	naTBI < TDC
		Visual Attention	naTBI < TDC		Visual Attention	Auditory Working	
		naTBI = TDC	Verbal Fluency		naTBI = TDC	Memory naTBI < TDC	
		(ns)	naTBI < TDC		(ns)	Verbal Fluency	
			Tower Planning			naTBI < TDC	
			naTBI < TDC			Tower	
			Statue			Planning naTBI < TDC	
			Inhibition naTBI < TDC			Statue	
Stipanicic et al. (2008)			Knock and Tap			Inhibition naTBI < TDC	
			Inhibitory control naTBI < TDC			Knock and Tap	
			WISC-III			Inhibitory control	
			Mazes			naTBI < TDC	
			Planning naTBI = TDC			WISC-III Mazes	
			(ns)			Planning	
			Halstead-Reitan Battery			naTBI = TDC (ns)	
			Progressive Figures Cognitive flexibility			Halstead-Reitan Battery	
			naTBI = TDC			Progressive Figures	
			(ns)			Cognitive flexibility naTBI = TDC	
						(ns)	
aTBI vs naTBI		1	T	1			
Beers et al. (2007)*	BSID-II/SB4 Intellectual development/ability						
	naTBI < aTBI BSID-II & SB4						
	Intellectual development/ability naTBI						
Ewing-Cobbs et al. (1998)	45.00% Deficient						
	aTBI]	
	5.00% Deficient	1	1	1	<u> </u>	+	
aTBI vs naTBI/a						Toy-centered activity	
	Mental					Initiating social	
	Developmental index Cm naTBI, moderate naTBI &					interactions aTBI < naTBI & TDC	
Ewing-Cobbs et al. (2013)*	severe naTBI <					(2 & 12 mos)	
	aTBI (12 mos)					Joint attention	
	,					sTBI < cmTBI & modTBI (2 & 12 mos)	
						,,	
	MSEL	1					
	Development Composite score			1]	
Keenan et al. (2007)*	Development Composite score TBI < TDC						
Keenan et al. (2007)*	Development_Composite score TBI < TDC < 3 SDs naTBI (40.00%)						
	Development Composite score TBI < TDC < 3 SDs						
	Development Composite score TBI < TDC < 3 SDs naTBI (40.00%) (RR: 2.60) vs aTBI (4.30%)	NEPSY	NEPSY		FEL/BEP		
aTBI & naTBI	Development Composite score TBI < TDC	NEPSY Visual selective	NEPSY Cognitive flexibility		EEL/BEP Expressive language		
Keenan et al. (2007)* aTBI & naTBI Bonnier et al. (2007)	Development Composite score TBI < TDC						

Table 2 (continued)

	(11/28) Deficient <u>Nonverbal IO</u> (8/24) Deficient <u>Development</u> (24/46) Deficient	(18/43) Deficient TEA <u>Visual RT</u> (20/25) Deficient duditor: PT	(26/35) Deficient <u>Planning</u> (14/26) Deficient WISC-III/K-ABC Auditory working memory		
		Auditory RT (24/34) Deficient	Auditory working memory (14/27) Deficient		
Ewing-Cobbs et al. (2006)	SB4 Composite score 10 ¹⁰ %ile: msTBi (48.00%) TDC (19.00%) TDC (19.00%)		SB4 Bead memory visual short- term memory msTBI = TDC (ns)	SB4 Vocabulary, pattern analysis, memory for sentences msTBI < TDC	WFHI Maths msTBI < TDC GORT-4 Comprehension, Reading & Writing msTBI < TDC Unfavorable academic outcome 48% msTBI 5% TDC
					OR = msTBI 18x > TDC
Ewing-Cobbs et al. (2004)		Stationary boxes <u>Visual scanning</u> msTBI = TDC (ns)	Delayed response <u>Visual working memory &</u> <u>Inhibitory control</u> msTBI < TDC Spatial Reversal <u>Cognitive flexibility</u> msTBI = TDC (ns)		
Keenan et al. (2018)			BRIEF/-P TBI = OI (rs, pre-injury) Inhibitory self-control & metacoantition TBI > OI (3 & 12 mos) Working memory mTBI > cmTBI & mod TBI & sTBI & OI (pre-injury) TBI > OI (3 & 12 mos)		
Keenan et al. (2019)			ASQ-3 <u>Problem solving</u> Pre-injury 33% sTBI vs 7% OI ≤ 2 nd %ile 3 & 12 mos sTBI < OI	ASQ-3 <u>Communication</u> Pre-injury 24% sTBI vs 2% OI ≤ 2 nd %ile 3& 12 mos sTBI < OI	
Kieslich et al. (2001)*	FMOS Normal Development <2 yrs: 25 (39.10%)				FMOS Intellectual and/or academical retardation < 2 yrs: 39 (61.10%) 2-6 yrs: 51 (58.00%)
Vassel-Hitler et al. (2019)	2-6 yrs 3 (38.00%) WPPS+II(WRC+V VIQ/VQ 57.10% < 80 <u>PS0/PSI</u> 76.20% < 80			Brunet-Lezine revised Scale of infant development Language/Communication 67% borderline/deficit range % of all TB with scores 5-1.SSD EVIP-A Beceptive lexicon 57% ELOLA Lexical access skills 48% •Oral comprehension strategies assessment test 0-52 Syntactic comprehension 67% TCG Syntactic expression	Ongoing aducation Mainstream school 38% Specialized institutions/classrooms 24% Receated year/adaptations 38%
Wetherington et al. (2010)*	Mullen Scales of Early Learning msTBI (low range) < mTBI (low to average) & TDC (average)			62%	

In some cases, a range of TBI severities was combined into a single TBI group (Coster et al., 1994; Tonks et al., 2011). The majority of studies reported only one severity grouping, such as mTBI (Bellerose et al., 2015, 2017) or sTBI (Bonnier et al., 2007; Pastore et al., 2013). Some articles explored the impact of TBI in multiple severity groups, typically combining participants with modTBI and sTBI (McKinlay et al., 2014).

Methodology

Sample Size

et al., 2013; Marsh & Whitehead, 2005; Pastore et al., 2013; Prasad et al., 1999; Stipanicic et al., 2008) to more substantial sample sizes of 100 participants or more (e.g., Ewing-Cobbs et al., 2013; Keenan et al., 2018, 2019; Kieslich et al., 2001; Liu & Li, 2013; McKinlay et al., 2002).

Measures and Assessment Tools

When reporting cognitive or academic outcomes, nine (21%) studies used direct assessment methods exclusively (Bonnier et al., 2007; Crowe et al., 2014, 2012a, b; Ewing-Cobbs et al., 1998, 2004; Landry-Roy et al., 2018; Papoutsis et al., 2014; Stipanicic et al., 2008; Walz et al., 2009). When reporting behavioral and socio-affective outcomes, 12 (28%) studies used indirect methods such as questionnaires com-

 Table 3
 Studies identified in the systematic review examining outcome after accidental TBI and non accidental TBI in early childhood: socioaffective, behavioral and adaptive outcomes

Socio-affective, behavioral and ada	aptive outcomes		
Reference	Emotion regulation & behavior	Social skills	Adaptive Functioning
aTBI	·		
Bellerose et al. (2015)	CBCL Externalizing scale mTBI > TDC (pre-injury & 6 mos)		ABAS-II Social & GAC mT81 = TDC (ns; pre-injury & 6 mos) ABAS-II
Bellerose et al. (2017)			Social & GAC mTBI = TDC (ns; pre-injury, 6 & 18 mos)
Coster et al. (1994)*	CBCL Total problems (ns)		PEDI Functional Skills & Caregiver Assistance \uparrow Self-Care & Social Function Assistance post-injury TBI > OI (1 & 6 mos)
Crowe et al. (2012a)	CBCL (ns)	SSRS (ns)	
Dégeilh et al. (2018)			ABAS-II Practical & conceptual mTB1 = 0 (rs; pre-injury, 6 & 18 mos) Social mTB1 = 01 (rs; pre-injury) mTB1 < 01 (6 & 18 mos)
Gagner et al. (2018)	CBCL Externalizing scale mTBI > OI (pre-injury) Internalizing externalizing scale mTBI > OI & TDC (6 mos)		
Green et al. (2013)			SPRS-C Total score TBI = TDC (ns) <u>School/Leisure</u> sTBI < TDC
Kaldoja et al. (2015)	ASQ:5-E Self-regulation & autonomy difficulties Pre-injury mTBI Boys > mTBI Girls (self-regulation only) mTBI Boys > TD Boys Post-injury Self-regulation mTBI Boys > mTBI Girls mTBI Boys > TD Boys <u>Compliance & Affect</u>	ASQ:S-E Social difficulties Pre-injury (ns) Post-injury mTBI boys > TD Boys <u>Communication</u> (ns)	ASQ:S-E <u>Adaptive difficulties</u> Pre-injury mTBI Girls > TDC Girls Post-injury (ns)
Lalonde et al. (2016)	(ns)	MRO (Observational measure) Parent-child interaction quality mTBI < TDC	ABAS-II Leisure subscale TDC & mTBI > OI (pre-injury) Other subscales mTBI = OI = TDC (ns; pre-injury)
Liu et al. (2013)*	CBCL Withdrawn behavior Single injury & Multiple > TDC		
Marsh and Whitehead (2005)*	CBCL (parents + teacher) Total competence, Internalizing + Externalizing + Total problems TBI = OI (ns)		
McKinlay et al. (2014)	Self-Report Delinquency Inventory & Interview Sx drug dependence DSM-IV criteria Inpatient > Outpatient = TDC Property offenses Inpatient > Outpatient = TDC <u>Violent offenses</u> Inpatient = Outpatient > TDC		
McKinlay et al. (2002)	Rutter & Conners <u>Conduct & Hyperactivity/Inattention problems</u> Inpatient > Outpatient + TDC/OI		
McKinlay et al. (2009)	SERD & RBPC & DISC & RAPI Conduct & ODD/Attention deficit/Hyperactivity/ Substance abuse/Mood disorder Inpatient > Outpatient + TDC/OI DISC Anxiety disorder Inpatient = Outpatient = TDC/OI		

Table 3 (continued)

McKinlay et al. (2010)	Rutter & Conners <u>ADHD & Conduct & Hyperactivity/Inattention problems</u> Inpatient > Outpatient + TDC/OI		
Pastore et al. (2013)	CBCL Frequency of problems Externalizing (50.00%) Destructive (42.90%) Aggressive (35.70%) Internalizing (77.80%) Anxious/Depressed (55.50%) Somatic (55.50%)		VABS Daily living skills sTBI & Brain tumour > Vascular/infectious brain lesions
Prasad et al. (1998)			VABS <u>Composite score</u> 2 mos & 1 year 2 Average range (83.35%)
Sonnenberg et al. (2010)		MPAI-P Social function Normal (20%) Mild (41%) Moderate (23%) Severe impairment (16%) Mild impairment Old (72%) > Young (55%) Severe impairment Young (44%) > Old (28%) Social and cognitive skills Young < Old	
Tonks et al. (2011)+	SDQ Socio-emotional difficulties TBI > TDC		
Wrightson et al. (1995)*	Concors parent mTBI = 01 (ns; pre-injury, 1, 6, 12 mos) Concors teacher mTBI = 01 (ns; 6, 50 yrs old)		Vineland social maturity scale mTBI = Oi (ns, pre-injury, 1, 6, 12 mos)
naTBI			
Barlow et al. (2005)	BBRS <u>Orientation & Engagement impairment</u> (1 & 3 mos) <u>Attention/arousal</u> (1 mo) <u>Emotion regulation</u> (3 mos) na msTBI > TDC		
Ewing-Cobbs et al. (1999)	Toy-centered activity Positive affect/Compliance na msTBI < TDC Negative affect na msTBI = TDC (ns)	Toy-centered activity Social interactions na msTBI < TDC Communicating/Complexity of independent toy play na msTBI = TDC (ns)	
Stipanicic et al. (2008)			VABS <u>Composite score</u> naTBI < aTBI
aTBI vs naTBI			
Beers et al. (2007)*			VABS <u>Socialization</u> STBI < cmTBI & mod TBI (12 mos) <u>Communication</u> naTBI < aTBI (severe aTBI < cm aTBI & moderate aTBI) (12 mos)
Ewing-Cobbs et al. (1998)			(12 mos) SIB-R <u>Adaptive behavior</u> TBI (average) < TDC ≥ 3 SDs n-aTBI (RR: 1.60) vs aTBI
aTBI & naTBI			
Bonnier et al. (2007)	ASQ-3 <u>Socio-emotional</u> 3& 12 mos sTBI < OI	ASQ-3 Personal-social 3& 12 mos sTBI < OI	
Ewing-Cobbs et al. (2004)		Brunet-Lezine revised Scale of infant development Sociability 78% borderline/deficit range	Brunet-Lezine revised Scale of infant development <u>Autonomy</u> 78% borderline/deficit range
Keenan et al. (2018)	CBCL Withdrawal behavior msTB1 > mTB1 & TDC Other behaviors/problems msTB1 = mTB1 = TDC (ns)		
Keenan et al. (2019)	(is) CBCL Externalizing scale mTBI > TDC (pre-injury & 6 mos)		ABAS-II <u>Social & GAC</u> mTBI = TDC (ns; pre-injury & 6 mos)
Kieslich et al. (2001)*			ABA5-IIAC Social & GAC mTBI = TDC (ns; pre-injury, 6 & 18 mos)
Vassel-Hitier et al. (2019)	CBCL Total problems (ns)		PEDI Functional Skills & Caregiver Assistance \uparrow Self-Care & Social Function Assistance post-injury TBI > OI (1 & 6 & mos)

Author, Year	Participation	Attrition	Outcomes	Confounding	Analysis
Bellerose et al., 2015	Partly	Partly	No	No	No
Bellerose et al., 2017	No	Partly	No	No	No
Coster et al., 1994	Partly	Partly	No	Partly	Partly
Crowe et al., 2014	Partly	Partly	No	No	No
Crowe et al., 2012a	Partly	Partly	No	No	No
Crowe et al., 2013	No	No	No	No	No
Crowe et al., 2012b	No	N/A	No	No	No
Dégeilh et al., 2018	No	Partly	No	No	No
D'Hondt et al., 2017	Partly	N/A	No	No	No
Gagner et al., 2018	No	Partly	No	No	No
Green et al., 2013	Partly	Yes	No	Partly	Partly
Kaldoja et al., 2015	Partly	Yes	Yes	No	No
Lalonde et al., 2016	No	Yes	No	No	No
Landry-Roy et al., 2018	No	Partly	No	No	No
Liu et al., 2013	No	N/A	No	Partly	No
Marsh and Whitehead 2005	Partly	N/A	No	No	No
McKinlay et al., 2014	Partly	Yes	No	No	No
McKinlay et al., 2002	No	Yes	No	No	No
McKinlay et al., 2010	Partly	Yes	No	No	No
McKinlay et al., 2009	Partly	Partly	No	No	No
Papoutsis et al., 2014	No	N/A	No	No	No
Pastore et al., 2013	Partly	N/A	No	Partly	No
Prasad et al., 1999	Partly	Yes	No	Yes	Partly
Sonnenberg et al., 2010	Partly	Yes	No	Partly	No
Tonks et al., 2011	Yes	N/A	No	Yes	Partly
Walz et al., 2009	Partly	N/A	No	No	No
Wrightson et al 1995	Partly	Yes	No	No	No

N/A: non applicable

Table 5 Risk of bias for studies reporting outcomes following non-accidental and accidental TBI

Author, Year	Participation	Attrition	Outcomes	Confounding	Analysis
Barlow et al., 2005	No	Partly	No	Partly	Partly
Beers et al., 2007	Partly	N/A	No	No	Partly
Bonnier et al., 2007	Partly	N/A	No	No	Partly
Ewing-Cobbs et al., 1998	No	Yes	No	No	Partly
Ewing-Cobbs et al., 1999	Partly	Yes	No	No	No
Ewing-Cobbs et al., 2006	Partly	Partly	No	No	No
Ewing-Cobbs et al., 2004	Partly	N/A	No	No	No
Ewing-Cobbs et al., 2013	Partly	Yes	No	No	No
Keenan et al., 2018	Partly	Yes	No	No	No
Keenan et al., 2007	No	Yes	No	No	Partly
Keenan et al., 2019	Partly	Yes	No	No	No
Kieslich et al., 2001	Partly	N/A	No	Yes	Partly
Landry et al., 2004	No	N/A	No	No	No
Stipanicic et al., 2008	Partly	N/A	No	No	Partly
Vassel-Hitier et al., 2019	No	Yes	No	Partly	Partly

N/A

Partly

N/A: non applicable

Wetherington et al., 2010

pleted by primary caregivers, teachers (Coster et al., 1994; Gagner et al., 2018; Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2018, 2019; Liu & Li, 2013; McKinlay et al., 2009, 2010, 2014; Pastore et al., 2013), or physicians (Sonnenberg et al., 2010). The majority of studies combined both direct and indirect assessment methods to describe either cognitive or behavioral outcomes and socioaffective outcomes (N=15; 35%; Barlow et al., 2005; Beers et al., 2007; Bellerose et al., 2015, 2017; Crowe et al., 2012a, b, 2013; Dégeilh et al., 2018; Ewing-Cobbs et al., 1999; Keenan et al., 2007; Marsh & Whitehead, 2005; McKinlay et al., 2002; Prasad et al., 1999; Tonks et al., 2011; Wetherington et al., 2010; Wrightson et al., 1995). Two studies (5%; D'Hondt et al., 2017; Ewing-Cobbs et al., 2013) used direct observational measures exclusively, and two (5%) other studies used a combination of indirect assessment (e.g., questionnaires) and observational methods to measure behavioral and socio-affective consequences (5%; Albicini et al., 2017; Lalonde et al., 2016; Landry et al., 2004). Finally, three articles used a combination of direct assessment with school outcomes (7%; Ewing-Cobbs et al., 2006; Kieslich et al., 2001; Vassel-Hitier et al., 2019).

Study Outcomes

In Tables 2 and 3, results of group comparisons are reported where possible (e.g., typically developing children vs. TBI vs. orthopedic injuries). Otherwise, percentages (Barlow et al., 2005; Marsh & Whitehead, 2005; Pastore et al., 2013; Prasad et al., 1999; Sonnenberg et al., 2010; Vassel-Hitier et al., 2019), proportions (Bonnier et al., 2007), frequencies (Kieslich et al., 2001), and odds-ratios were documented (Ewing-Cobbs et al., 2006; Keenan et al., 2007). Of the 43 articles included in the review, 16 (37%) focused on cognitive or academic outcomes, 11 (26%) on behavioral and socio-affective outcomes, and 16 (37%) investigated both domains.

No

No

No

To structure the presentation of study outcomes by domain, mechanism, injury severity, and age at injury, each of the following sections are divided according to the three types of injuries (aTBI, naTBI, or both aTBI and naTBI). For each type of injury, outcomes are then separated according to injury severity (mild, moderate, severe), and in each of these subcategories, study findings are presented according to age at injury (infants, toddlers, preschoolers).

Cognitive or Academic Outcomes

Intelligence or Global Development

Twenty articles (46%) reported IQ or global developmental outcomes.

aTBI

mTBI. Children (0-6 years) who sustained mTBI presented IQ or global developmental functioning comparable to that of orthopedic injury groups and typically developing groups up to 10 years post-injury (Crowe et al., 2012a, b, 2013; McKinlay et al., 2002; Papoutsis et al., 2014; Wetherington et al., 2010; Wrightson et al., 1995).

msTBI. Children (0-6 years) who sustained msTBI had poorer IQ or global developmental functioning up to three years (verbal IQ; Crowe et al., 2014; Global: Wetherington et al., 2010) and four years (verbal and non-verbal IQ; Crowe et al., 2012a, b) post-injury, compared to typically developing children, and up to one month post-injury when compared to orthopedic injury groups (Walz et al., 2009).

naTBI

Infants and toddlers who sustained naTBI had impaired (Barlow et al., 2005) or poorer developmental and intellectual functioning compared to those who sustained aTBI (Beers et al., 2007; Ewing-Cobbs et al., 1998) and typically developing children (Ewing-Cobbs et al., 1999, 2006; Landry et al., 2004; Stipanicic et al., 2008) up to two years post-injury.

aTBI vs naTBI

Toddlers with naTBI had poorer developmental outcomes (<3 SDs) compared to those with aTBI up to one year post-injury (Keenan et al., 2007).

aTBI & naTBI

In a combined group of infants who sustained severe aTBI or naTBI, global development, as well as verbal and nonverbal IQ, were impaired up to 6.60 years post-injury (Bonnier et al., 2007). Similarly, in another study, verbal IQ was impaired up to 6.80 years post-injury (Vassel-Hitier et al., 2019). Finally, more than half of children (0–6 years) with moderate-severe naTBI or aTBI showed intellectual or academic delays up to 8.75 years postinjury (Kieslich et al., 2001).

Attention

Five studies (12%) reported on attention.

aTBI

mTBI and modTBI. In infants who sustained mTBI, auditory vigilance and selective attention were comparable to typically developing children up to 3.91 years post-injury (Crowe et al., 2013). In infants who sustained either complicated or uncomplicated mTBI, visual selective attention was comparable to typically developing children up to seven years post-injury (Papoutsis et al., 2014).

In a combined group of infants who sustained mTBI or modTBI, visual attention was poorer compared to orthopedic injury up to 6.60 years post-injury (Marsh & Whitehead, 2005). In toddlers who sustained complicated mTBI, divided attention was poorer than in those with uncomplicated TBI or typically developing children up to seven years post-injury (Papoutsis et al., 2014). *msTBI*. In infants who sustained msTBI, auditory vigilance and selective attention were comparable to typically developing children up to 3.91 years post-injury (Crowe et al., 2013).

naTBI

In infants who sustained naTBI, auditory attention was poorer, while visual attention was comparable to typically developing children up to 78 months post-injury (Stipanicic et al., 2008).

aTBI & naTBI

In a group of infants who sustained moderate-severe naTBI or aTBI, visual scanning was comparable to typically developing children up to one year post-injury (Ewing-Cobbs et al., 2004). In a combined group of infants who sustained severe aTBI or naTBI, visual and auditory reaction times and selective attention were impaired up to 6.60 years postinjury (Bonnier et al., 2007).

Executive Functioning

Fourteen studies (33%) reported on executive functioning.

aTBI

mTBI. In infants who sustained mTBI, inhibition was poorer while parent-rated executive functions were comparable to typically developing children up to 3.91 years post-injury (Crowe et al., 2013). In a combined group of infants who sustained either mTBI or modTBI, inhibition, planning, and cognitive flexibility were comparable to orthopedic injury up to five years post-injury (Marsh & Whitehead, 2005). In toddlers with uncomplicated or complicated mTBI, information processing, auditory working memory, goal setting, organization, and parent-rated executive functions were comparable to typically developing children up to seven years post-injury (Papoutsis et al., 2014). Also, in toddlers and preschoolers who sustained mTBI, inhibition and cognitive flexibility were comparable to typically developing children up to six months post-injury (Landry-Roy et al., 2018). Finally, in toddlers and preschoolers who sustained mTBI, information processing was comparable to orthopedic injury up to 12 months post-injury (Wrightson et al., 1995). msTBI. In infants who sustained msTBI, inhibition was poorer while parent-rated executive functions were comparable to typically developing children up to 3.91 years postinjury (Crowe et al., 2013). In infants who sustained sTBI, information processing was poorer compared to infants who sustained mTBI or modTBI up to 2.50 years post-injury (Crowe et al., 2012a, b).

In a study of children 0–6 years, regardless of TBI severity, verbal fluency, flexibility, and planning were comparable to typically developing children up to 10 years post-injury (Tonks et al., 2011). However, in the same cohort, children assessed at 10–16 years presented poorer working memory compared to typically developing children, while those tested at 8–10 years showed comparable results (Tonks et al., 2011). Moreover, regardless of severity, information processing was comparable to typically developing children up to 3.91 years post-injury (Crowe et al., 2013, 2012a, b).

naTBI

In infants who sustained naTBI, auditory working memory, verbal fluency, planning (tower), motor and cognitive inhibition were poorer, while planning (mazes) and cognitive flexibility were comparable to typically developing children up to 78.90 months post-injury (Stipanicic et al., 2008).

aTBI & naTBI

In a combined group of infants with moderate to severe naTBI or aTBI, visual working memory and inhibition were poorer while cognitive flexibility was comparable to typically developing children up to one year post-injury (Ewing-Cobbs et al., 2004). In a combined group of infants who sustained severe aTBI or naTBI, auditory working memory, inhibition, cognitive flexibility, and planning were impaired compared to normative data up to 6.60 years post-injury (Bonnier et al., 2007). Also, in infants who sustained severe naTBI and aTBI, problem solving was impaired compared to orthopedic injury groups one year post-injury (Keenan et al., 2019). In a combined group of toddlers with either moderate-severe naTBI or aTBI, visual working memory was comparable to typically developing children up to 5.70 years post-injury (Ewing-Cobbs et al., 2006).

In a group of toddlers and preschoolers with all severity types of naTBI or aTBI, inhibition, metacognition (all severities) and working memory (complicated mTBI and modTBI only) were poorer compared to orthopedic injury at three and 12 months post-injury (Keenan et al., 2018).

Memory

Three articles (7%) reported on memory processes.

aTBI

mTBI and modTBI. In infants who sustained mTBI or mod-TBI, visual memory was poorer and auditory-verbal memory was comparable to orthopedic injury groups up to five year post-injury (Marsh & Whitehead, 2005). In toddlers and preschoolers with mTBI, visual and auditory-verbal memory were comparable to orthopedic injury groups after one month, and up to 6.50 years post-injury (Wrightson et al., 1995).

naTBI

In infants who sustained naTBI, verbal and visual memory were comparable to typically developing children up to 78.90 months post-injury (Stipanicic et al., 2008).

Language

Nine articles (21%) reported on language outcomes.

aTBI

mTBI and modTBI. In toddlers and preschoolers who sustained mTBI, global developmental language scales were comparable to orthopedic injury up to 12 months post-injury (Wrightson et al., 1995). In a combined group of infants who sustained either mTBI or modTBI, language skills such as speeded naming, comprehension of instructions, and verbal fluency were comparable to orthopedic injury up to five years post-injury (Marsh & Whitehead, 2005).

msTBI. In infants who sustained moderate to severe aTBI, language skills, such as expressive vocabulary, sentence and word structure, were poorer compared to mTBI and typically developing children up to 47 months post-injury (Crowe et al., 2014).

naTBI

In infants who sustained naTBI, abnormalities in speech and language skills were reported compared to normative data up to 90 months post-injury (Barlow et al., 2005). Poorer receptive language was noted compared to typically developing children up to 78.90 months post-injury (Stipanicic et al., 2008).

aTBI & naTBI

In a combined group of infants who sustained severe aTBI or naTBI, expressive and receptive language, as well as written language skills (i.e., receptive and expressive lexicon, lexical organization, sentence comprehension, syntactic expression and communication) were impaired compared to normative data up to 6.80 years post-injury (Bonnier et al., 2007; Vassel-Hitier et al., 2019). In a group of tod-dlers who sustained moderate-severe aTBI or naTBI, language (vocabulary, pattern analysis, and memory for sentences) was poorer compared to typically developing children up to 5.70 years post-injury (Ewing-Cobbs et al., 2006).

Social Cognition

Six articles (14%) reported social cognitive outcomes.

aTBI

mTBI. In toddlers who sustained mTBI, theory of mind was poorer compared to typically developing children and orthopedic injury groups, six and 18 months post-injury (Bellerose et al., 2015, 2017). In a subgroup of the same cohort, emotional facial expression processing (measured using event-related potentials) was impaired compared to typically developing children six months post-injury (D'Hondt et al., 2017). *msTBI*. In preschoolers (3–6 years) who sustained severe aTBI, false content belief was poorer, while false location belief and global theory of mind skills (i.e. sum of appearance-reality tasks, false content or location tasks, and control tasks) were comparable to modTBI and orthorpedic injury up to one month post-injury (Walz et al., 2009).

aTBI vs naTBI

In infants who sustained aTBI, regardless of severity, initiating social interactions was poorer compared to naTBI and typically developing children two months post-injury. These difficulties resolved one year post-injury (Ewing-Cobbs et al., 2013).

aTBI & naTBI

In infants who sustained aTBI or naTBI, joint attention was poorer in sTBI compared to complicated mTBI and modTBI up to one year post-injury (Ewing-Cobbs et al., 2013).

Academic Achievement

Five articles reported on academic outcomes (12%).

aTBI

mTBI and modTBI. In a combined group of children (0–6 years) who sustained either mTBI or modTBI, academic abilities (e.g., mathematic reasoning and written language including letter knowledge, spelling, reading, and writing) were comparable to orthopedic injury groups up to 79 months post-injury (Marsh & Whitehead, 2005; McKinlay et al., 2002; Wrightson et al., 1995).

aTBI & naTBI

In infants who sustained either moderate to severe aTBI or naTBI, 38% were reported to be attending mainstream school with adaptations or to have repeated a school year,

and 24% were attending specialized classrooms up to 6.80 years post-injury (Vassel-Hitier et al., 2019).

Toddlers who sustained moderate to severe aTBI or naTBI presented poorer mathematics, comprehension, reading, and writing abilities, and showed more unfavorable academic outcomes compared to typically developing children up to 5.70 year post-injury (Ewing-Cobbs et al., 2006).

More than half of children (0–6 years) who sustained moderate to severe naTBI or aTBI showed global intellectual or academic delays (e.g., repeating a school year) up to 8.75 years post-injury (Kieslich et al., 2001).

Behavior and Socio-affective Skills

Twenty-eight articles (65%) reported behavioral or socioaffective outcomes, with 19 studies (44%) documenting emotion regulation and behavior, six studies (14%) documenting social behavior, and 14 studies (33%) documenting adaptive skills.

Emotional Regulation and Behavior

aTBI

mTBI and modTBI. In a combined group of infants who sustained either mTBI or modTBI, externalizing and internalizing behaviors were comparable to orthopedic injury groups up to five years post-injury (Marsh & Whitehead, 2005). In toddlers who sustained mTBI, more externalizing behaviors were observed compared to typically developing children (Bellerose et al., 2015; Gagner et al., 2018) and orthopedic injury groups (Gagner et al., 2018) six months post-injury. More internalizing behaviors were also observed in toddlers who sustained mTBI compared to both orthopedic injury groups and typically developing children six months post-injury (Gagner et al., 2018). Parent and teacher ratings of emotional regulation and behavior of toddlers and preschoolers who sustained mTBI were comparable to those of orthopedic injury groups up to 6.50 years post-injury (Wrightson et al., 1995). Moreover, internalizing and externalizing behaviors were also observed in children with mTBI compared to typically developing children when investigated at six years of age (Liu & Li, 2013).

In children (0–6 years) who sustained mTBI, more ADHD-type behaviors as well as conduct and hyperactivity or inattention problems were observed in inpatient (i.e., all children admitted to hospital for less than two days) compared to outpatient (i.e., all children seen by a general practitioner or at an emergency department and sent home), orthopedic injury groups, and typically developing children when children were assessed at seven years (McKinlay et al., 2010), and up to 16 years of age (McKinlay et al., 2002, 2009). Moreover, more substance abuse and mood disorders

were noted in inpatients compared to outpatients, orthopedic injury groups, and typically developing children, while comparable levels of anxiety disorders were observed in the same groups when children were assessed between 14 and 16 years of age (McKinlay et al., 2009). Finally, more violent offenses in inpatients and outpatients were noted compared to typically developing children. More property offenses were noted in inpatients compared to outpatients and typically developing children, and greater drug dependence was observed in inpatients compared to typically developing children when children were assessed 11 to 20 years post-injury (McKinlay et al., 2014).

In children (0–6 years) who sustained mTBI, boys with mTBI showed more self-regulation problems compared to girls with mTBI and typically developing boys at nine months post-injury. Boys who sustained mTBI also presented poorer autonomy compared to typically developing boys and girls with mTBI, nine months post-injury. Finally, no compliance or affective difficulties were found in these groups for the same post-injury period (Kaldoja & Kolk, 2015).

msTBI. In toddlers with severe aTBI, internalizing and externalizing problems were present with reported increases in behaviors such as aggression, destructive behaviors, anxiety, depression, and somatic complaints up to 8.50 years post-injury (Pastore et al., 2013).

In toddlers with aTBI, regardless of TBI severity, behavior was comparable to that of toddlers with orthopedic injuries up to six months post-injury (Coster et al., 1994), and to typically developing children up to 3.90 years postinjury (Crowe et al., 2012a, b). Finally, children (0–6 years; regardless of severity) presented more socio-emotional difficulties compared to typically developing children when assessed at 8 to 10 years and 10 to 16 years of age (Tonks et al., 2011).

naTBI

Regardless of injury severity, infants who sustained naTBI displayed behavior problems up to 90 months post-injury (Barlow et al., 2005). Moreover, in infants who sustained moderate to severe naTBI, emotion regulation, as well as others indices such as attention arousal (one month post-injury only) and orientation and engagement (measured by the Bayley Behavior Rating Scale, Bailey, 1969) were impaired compared to typically developing children up to three months post injury (Ewing-Cobbs et al., 1999).

aTBI & naTBI

In a combined group of infants who sustained moderate to severe aTBI or naTBI, more internalizing behaviors (e.g., withdrawal) were noted while externalizing behaviors were comparable to mTBI and typically developing children up to three years post-injury (Wetherington et al., 2010).

In a combined group of infants and toddlers who sustained moderate to severe naTBI, levels of positive affect and compliance were poorer, while negative affect was comparable to typically developing children up to one year postinjury (Landry et al., 2004).

Infants and toddlers with severe aTBI or naTBI presented more socio-emotional difficulties (e.g., self-regulation, affect, communication) compared to typically developing children up to one year post-injury (Keenan et al., 2019). In toddlers and preschoolers, regardless of mechanisms of injury, more behavioral difficulties were found in sTBI compared to orthopedic injury groups at three months and up to 12 months post-injury (Keenan et al., 2018). Moreover, in the same groups, regardless of mechanism and severity of injury, most behaviors were comparable except affective, anxious behaviors and ADHD-type behaviors were more elevated in TBI groups compared to at three months and up to 12 months post-injury (Keenan et al., 2018).

Social Skills

Six articles reported social skills outcomes (14%).

aTBI

mTBI. Toddlers who sustained mTBI presented poorer parent–child interaction quality compared to typically developing children, and similar quality of parent–child dysfunctional interaction compared to orthopedic injury groups and typically developing children six months post-injury (Lalonde et al., 2016). In children (0–6 years) who sustained mTBI, more social difficulties were reported for boys with mTBI compared to typically developing boys, while no communication difficulties were noted in these groups up to nine months (Kaldoja & Kolk, 2015). Lastly, in a combined group of infants and toddlers who sustained aTBI, regardless of severity, social skills were comparable to typically developing children up to 3.90 years post-injury (Crowe et al., 2012a, b).

msTBI. In children (0–6 years) who sustained msTBI, 20% had normal social function, 41% had mild impairment, 23% had moderate impairment, and 16% had severe impairment (Sonnenberg et al., 2010). In the same cohort, children who sustained injury at 2.6 years had poorer social outcomes compared to those who sustained injury at 5.0 years of age.

naTBI

In infants and toddlers who sustained moderate to severe naTBI, social interactions (gaze) were poorer while communicating (gestures and words) and complexity of toy play was comparable to typically developing children up to one year post-injury (Landry et al., 2004). In infants with severe naTBI, personal-social skills were poorer comparable to orthopedic injury two months and up to one year postinjury (Keenan et al., 2019).

aTBI & naTBI

In a combined group of infants who sustained severe aTBI or naTBI, sociability and autonomy were found to be impaired up to 6.80 years post-injury (Vassel-Hitier et al., 2019). Also, in a combined group of infants and toddlers who sustained sTBI, more difficulties in personal-social behaviors were observed compared to typically developing children up to one year post-injury (Keenan et al., 2019).

Adaptive Functioning

Fourteen articles (33%) reported adaptive behavior outcomes.

aTBI

mTBI. In toddlers who sustained mTBI, conceptual and practical adaptation, as well as global adaptive functioning, were comparable to typically developing children and orthopedic injury groups up to 18 months post-injury (Bellerose et al., 2015, 2017). However, social adaptation was poorer compared to orthopedic injury groups six to 18 months post-injury (Dégeilh et al., 2018). In a combined group of toddlers and preschoolers who sustained mTBI, global adaptive functioning was comparable to orthopedic injury groups one month and up to 12 months post-injury (Wrightson et al., 1995).

msTBI. In toddlers who sustained severe aTBI, daily living skills were poorer compared to toddlers with other acquired brain injuries up to 8.50 years post-injury (Pastore et al., 2013). In toddlers who sustained msTBI, global adaptive functioning was in the average range for most children (83.33%) compared to normative data, two months and up to one year post-injury (Prasad et al., 1999).

In children (0–6 years), regardless of injury severity, need for self-care and social functioning assistance were greater in children who sustained TBI compared to orthopedic injuries one month and up to six months post-injury (Coster et al., 1994). Similarly, in children (0–6 years), regardless of injury severity, global adaptive functioning was comparable to typically developing children, and school or leisure participation and daily living skills were poorer compared to typically developing children 13 to 16 years post-injury (Green et al., 2013).

naTBI

Regardless of severity, infants who sustained naTBI presented moderately lower levels of socialization adaptation, communication, and daily living skills compared to normative data up to 90 months post-injury (Barlow et al., 2005).

aTBI vs naTBI

Infants who sustained naTBI showed poorer global adaptive functioning compared to those who sustained aTBI up to six months post-injury (Beers et al., 2007), as well as compared to typically developing children and normative data (Keenan et al., 2007). Infants with naTBI were at greater risk (Risk Ratio: 1.6) for poor adaptive functioning compared to aTBI (Keenan et al., 2007).

aTBI & naTBI

In a combined group of infants and toddlers, adaptive communication was significantly poorer following naTBI compared to aTBI, and was poorer in children with severe injuries compared to those with complicated mild or moderate injuries. Social adaptation was poorer in children with severe injuries compared to those with complicated to mild or moderate injuries, but did not vary by external cause of injury (i.e., aTBI or naTBI; Ewing-Cobbs et al., 2013).

Discussion

This systematic review aimed to document the cognitive, academic, behavioral, socio-affective, and adaptive consequences of early TBI sustained before six years of age, as well as to summarize the state of research in this field and identify limitations and gaps to be addressed in future work. Considering the unique characteristics of this developmental group and associated methodological challenges, we consider limitations of the work to date throughout the discussion, and propose corresponding recommendations and avenues for innovation and action, summarized in Table 6.

Summary of Outcomes

Based on the review, evidence for detrimental consequences of early TBI on intelligence and global development, attention, language, executive functions, and academic achievement is fairly consistent. Deficits in IQ (Barlow et al., 2005; Beers et al., 2007; Bonnier et al., 2007; Crowe et al., 2012a, b, 2014; Ewing-Cobbs et al., 1998, 1999, 2006, 2013; Keenan et al., 2007; Kieslich et al., 2001; Landry et al., 2004; Prasad et al., 1999; Stipanicic et al., 2008; Vassel-Hitier et al., 2019; Walz et al., 2009; Wetherington et al., 2010), attention (Achenbach & Edelbrock, 1983; Bonnier et al., 2007; Marsh & Whitehead, 2005; Papoutsis et al., 2014; Stipanicic et al., 2008), executive functioning (Bonnier et al., 2007; Crowe et al., 2012a, b, 2013; Ewing-Cobbs et al., 2004; Keenan et al., 2018; Keenan et al., 2019; Stipanicic et al., 2008; Tonks et al., 2011), language (Barlow et al., 2005; Bonnier et al., 2007; Crowe et al., 2014; Ewing-Cobbs et al., 2006; Keenan et al., 2019; Stipanicic et al., 2008; Vassel-Hitier et al., 2019; Wrightson et al., 1995), social cognition (Bellerose et al., 2015, 2017; D'Hondt et al., 2017; Ewing-Cobbs et al., 2013; Landry et al., 2004; Walz et al., 2009), and academic achievement (Ewing-Cobbs et al., 2006; Vassel-Hitier et al., 2019) are documented in the literature, but vary as a function of injury characteristics such as severity, mechanism, and age at injury.

These findings are congruent with a previous review by Garcia et al. (2015) that concluded that children who sustain early TBI encounter cognitive difficulties including intellectual, attention, language, and executive dysfunction. However, in their respective reviews, Garcia et al. (2015) and Wetherington and Hooper (2006) included children older than six years, ruling out the possibility of drawing any specific conclusions concerning the unique effects of early TBI. The findings of the current review clarify that difficulties in these domains are not solely driven by the results of older children.

A novelty of the current review is the inclusion of additional functional domains such as socio-affective and adaptive functioning following early TBI. Evidence for difficulties in these domains is less unanimous, and conclusions tend to vary across studies. For example, social skills are consistently reported as being affected by early TBI (Achenbach et Edelbrock, 1983; Ewing-Cobbs et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2019; Lalonde et al., 2016; Sonnenberg et al., 2010), whereas the findings are variable for emotion regulation and behavior (Barlow et al., 2005; Bellerose et al., 2015; Ewing-Cobbs et al., 1999; Gagner et al., 2018; Kaldoja & Kolk, 2015; Keenan et al., 2018, 2019; Landry et al., 2004; Liu & Li, 2013; McKinlay et al., 2002, 2009, 2010, 2014; Pastore et al., 2013; Tonks et al., 2011; Wetherington et al., 2010), as well as for adaptive functioning (Barlow et al., 2005; Beers et al., 2007; Coster et al., 1994; Dégeilh et al., 2018; Ewing-Cobbs et al., 2013; Green et al., 2013; Kaldoja & Kolk, 2015; Keenan et al., 2007; Lalonde et al., 2016; Pastore et al., 2013). In addition to discrepancies among the studies of early TBI, some of the conclusions drawn are inconsistent with studies in school-aged children and adolescents, which, in general, do not identify negative socio-behavioral outcomes in the long-term after mTBI. These inconsistencies are likely to be in part methodological, due, for example, to the multiple different types of measures used to document behavior, or to issues of timing of the injury and assessment. For example, those that found problems after early mTBI assessed behavior within 12 months of mTBI (Bellerose et al., 2015; Gagner et al., 2018; Liu et al., 2013), whereas those that did not identify difficulties assessed behavior in the longer term (\geq 2 years; Crowe et al., 2012a, b; \approx 3 years; Wetherington et al., 2010; 5 years; Marsh et al., 2005).

Overall, there is published evidence that children who sustain early TBI exhibit altered functioning in a range of domains including cognitive functioning and academic achievement, along with socio-affective, behavioral, and adaptive functioning. The significance of these problems appears to be modulated by a number of factors such that outcomes are generally reported as being worse in the following four situations: 1) TBI occurs at a younger age, 2) injury severity is moderate-severe, 3) mechanism of injury is non-accidental, 4) the comparison group is typically developing children (rather than orthopedic injuries, for example).

1) Younger age at injury

There is ongoing debate regarding whether brain injury at a younger age incurs better or worse outcome as a function of brain plasticity or vulnerability. On one hand, there is evidence that sustaining brain injury at a younger age is less detrimental than at older ages, because of the increased structural and functional plasticity that is present earlier in the developmental course (Anderson et al., 2005; Aram & Ekelman, 1986; Dennis, 1980). Taken in the context of pediatric mTBI research, there is consistent evidence in school-aged children (5-18 years) that younger age at injury results in fewer postconcussive symptoms, and overall better outcomes than older age (i.e., adolescence) at injury (Anderson & Moore, 1995; Zemek et al., 2013). However, this effect appears to be reversed in the early childhood period, such as illustrated in the studies included in this review that show that injury at a younger age results in poorer outcomes than when sustained at an older age (all TBI severities; e.g., Crowe et al., 2012a, b; Ewing-Cobbs et al., 2004; Keenan et al., 2018, 2019; Sonnenberg et al., 2010). The brains of infants and toddlers may be particularly vulnerable to insult because of rapid brain maturation occurring during those years and sensitive periods for the development of cognitive and social functions (Alexander, 1995; Anderson et al., 2009; Grantham-McGregor et al., 2007; Kieslich et al., 2001; Kolb et al., 2000; Kriel et al., 1989; Thompson & Nelson, 2001).

TBI sustained at a younger age and during a sensitive period may impair the development of functions such as language, or alter the emergence of associated cognitive, socio-affective, and behavioral functions (Bonnier et al., 2007; Crowe et al., 2014; Vassel-Hitier et al., 2019). As a whole, the review results suggest that TBI sustained during early development is not benign and cannot solely be interpreted in accordance with compensatory brain plasticity mechanisms, and that even milder injuries may temporarily or persistently impede functioning in various domains (Anderson et al., 2005; Bellerose et al., 2015; Bellerose et al., 2017; Crowe et al., 2013; D'Hondt et al., 2017; Dégeilh et al., 2018; Gagner et al., 2018; Kaldoja & Kolk, 2015; Keenan et al., 2018; Lalonde et al., 2016; Liu et Li, 2013; McKinlay et al., 2002, 2009, 2010, 2014; Papoutsis et al., 2014; Schneider, 1979).

2) TBI severity

As documented in school-aged children, adolescents, and adults, msTBI sustained early in development leads to worse outcomes than milder injuries (Anderson & Catroppa, 2005; Anderson et al., 2005). Babikian and Asarnow (2009) present a "double hazard" injury model, suggesting that children with younger age at injury and more severe TBI have a reduced rate of normal developmental progress (Anderson et al., 2005; Kriel et al., 1989). In the present review, IQ, attention, executive functioning, language, social cognition, academic achievement, socio-affective, adaptive functioning, and social behavior (regardless of age at injury) were generally poorer in children who sustained msTBI compared to mTBI and comparison groups (i.e., orthopedic injuries and typically developing children; Crowe et al., 2014, 2012a, b; Ewing-Cobbs et al., 1999, 2004, 2006, 2013; Green et al., 2013; Keenan et al., 2018, 2019; Landry et al., 2004; Pastore et al., 2013; Walz et al., 2009; Wetherington et al., 2010).

While it is clear that early msTBI is associated with detrimental consequences, conclusions on the impact of early mTBI are more blurred. Drawing unequivocal conclusions is hampered by problems in identifying and describing early mTBI. For example, some studies of accidental mTBI relied on ambiguous definitions or criteria (e.g., Liu et al., 2013; Wrightson et al., 1995). In these cases, the broad term "head injury" was used in the definition (e.g., diagnosis of a head injury at a hospital emergency department, not severe enough to require admission for observation; Wrightson et al., 1995), and no other objective criteria were considered for inclusion. For these studies, it is not clear whether absence of findings in some areas of functioning (speed of information processing, memory, language, academic achievement, behavior, adaptive skills) is attributable to the inclusion of superficial head injuries not involving the brain in the sample. Conversely, it may be that significant group differences in the areas of visual closure (Wrightson et al., 1995) and withdrawal (Liu et al., 2013), are explained by the inclusion of more severe injuries (e.g., mild complex TBI). The lack of group differences in these two studies could suggest relatively minor or isolated problems after early mTBI.

Yet, other studies using more definitive inclusion criteria do report certain difficulties (e.g., inhibition, social cognition, social interactions, behavior). Drawing clear and digestible conclusions regarding early accidental mTBI outcomes is challenging. The limited number of studies, ambiguity in definitions and criteria, and lack of harmonisation across domains and measures studied, all cloud the interpretation of existing work. Special interest groups or expert panels may be useful for developing criteria specific to the early childhood period and establishing what domains constitute priority areas of investigation. Interpretations of the nature and severity of outcomes are confounded by age, mechanism, and severity. While modest sample sizes and multiple levels of analysis often limit the possibility of creating subgroups for comparison, providing descriptive data and fine-grained information (e.g., mechanism, age, sex, gender) may facilitate meta-analyses that could clarify the interpretations and conclusions drawn from early mTBI studies.

3) TBI mechanism (accidental vs non-accidental)

The majority of studies that have compared the outcomes of children with early naTBI to those with accidental injuries find poorer outcomes in the former group (Beers et al., 2007; Ewing-Cobbs et al., 1998, 1999; Keenan et al., 2007). These children also exemplify the double hazard model put forth by Babikian et al. (2015), given that children who sustain naTBI are typically younger than two years old and that naTBI often results in moderate to severe injuries. In addition, naTBI may occur in family and socio-demographic contexts associated with greater risk for poor outcome (Chevignard & Lind, 2014; Liley et al., 2012; Lind et al., 2016). Household falls typical of accidental early TBI (Haarbauer-Krupa et al., 2018; Kaushik et al., 2015; Loder, 2008) usually involve low velocity translational forces, whereas naTBI often involves a combination of acceleration or deceleration forces and rotational or shearing injury due to shaking (Ewing-Cobbs et al., 2000). While it is still debated whether sudden shaking is more likely to result in intracranial injury characteristic of more severe TBI, pathophysiological differences seem to exist and contribute to the variability of outcomes observed following early TBI (Cory & Jones, 2003). Further explanation for the differences observed in outcomes between aTBI and naTBI could be the presence of repetitive episodes of injury overtime in the latter (Adamsbaum et al., 2010). An important skew should be noted in contrasting the outcomes of early aTBI and naTBI: aTBI samples tend to mostly consist of mild injuries, whereas naTBI samples are more likely to be moderate to severe in nature. It is therefore possible that the conclusions drawn from this literature reflect a greater overall prevalence of mild aTBI compared to moderate to severe naTBI, confusing

the question of whether accidental and non-accidental mechanisms are comparable in outcome.

4) Comparison groups

Most studies identified in the present review included a comparison group. Those that compared children with early TBI to typically developing children were more likely to find significantly elevated rates of problems than studies that compared children with mTBI to children with orthopedic injuries. Both typically developing children and children with orthopedic injuries present advantages and disadvantages in TBI research. Comparisons using uninjured children recruited from the community allow conclusions to be drawn regarding the expected trajectory of learning and development, and to identify areas in which children with TBI may fall short of their peers. Orthopedic injury groups account for potential pre-existing differences between children who may be more prone to injury, in addition to controlling for common factors associated with traumatic injuries such as pain, fatigue, and stress. A study by our group found that young children with orthopedic injuries and typically developing children are comparable on a broad range of pre-injury and post-injury characteristics, including demographic variables, developmental and medical history, behavioral and adaptive profiles (Beauchamp et al., 2017). Children with orthopedic injuries and typically developing children were also found to be comparable on measures of adaptive functioning, behavior, family functioning, post-concussive symptoms, and cognition (Beauchamp et al., 2017). It was cautiously concluded that there is no clear advantage in recruiting orthopedic injury groups. However, there may be other domains in which the groups differ that were not documented in that study. The decision to use either orthopedic injury or typically developing comparison groups when investigating early TBI should be considered with respect to the aims of the study and the primary outcomes of interest.

Additional Challenges Identified in the Systematic Review

The results of the review highlight the use of robust methodology in several instances (e.g., prospective and longitudinal study designs), but also point to methodological and clinical challenges associated with conducting research in infants, toddlers, and preschoolers with TBI. Some of these have already been discussed in the preceding sections (e.g., definition and diagnosis, terminology, sample composition). In addition, the review highlights limitations regarding developmental groups, in that age groups may be created across developmental periods (infancy, toddlerhood, preschool) further complicating terminology and comparisons. Study design challenges are also observed with few longitudinal designs and long-term outcomes measured. Measurement issues are present in the form of poor harmonisation across studies, precluding direct comparisons across the literature. While the breadth of outcome domains studied is a strength of the early TBI literature, conversely almost no information is available regarding post-concussive symptoms, a vital indicator of outcome and recovery, especially after mTBI. Assessment limitations include frequent reliance on third party questionnaires, with limited direct measurement and lack of performance validity measurement in any of the studies reviewed.

Threats to performance validity are a reality across age groups, but may be especially important to understand in young children. School-age children may feign or exaggerate symptoms (Kirkwood, 2015), an effect that can be captured using stand-alone or embedded tools such as the Test of Memory Malingering (Tombaugh, 1996) as of five years (for a systematic review and meta-analysis, see Clark et al., 2020). No such tools are available of infants and toddlers, and it is not as clear what incentive or capacity they have to intentionally feign symptoms or problems in the context of TBI, although it is plausible that a young child may implicitly discover a benefit of over-reporting symptoms or problems. For example, a child might realize that they are getting more attention from their parents, or that they can stay home from daycare if they report or exhibit signs that they are unwell. Finally, collaboration or participation issues can affect the validity and quality of the data collected (e.g., refusal to complete a task, fatigue, oppositional behavior, tantrums, parental separation anxiety). Going forward, these issues should be more clearly or quantitatively reported to aid in understanding the true nature of early TBI consequences.

Considering these limitations and challenges is useful in interpreting the findings of individual studies and drawing cautious conclusions regarding the effects of early TBI, while also providing opportunities for future research, recommendations to move the field forward, and translation of empirical findings to clinical practice. Table 6 summarizes these points as a way to provide preliminary reflections and building blocks for mobilizing the efforts of those interested in the topic of early TBI and the development of more concrete and concerted initiatives. The suggestions should be considered alongside the usual recommendations for conducting valid and bias-free research.

Strengths and Limitations of the Review

This review of early TBI was conducted systematically, presents a broad range of post-injury outcomes, includes both studies of naTBI and aTBI, and focuses specifically on injuries under the age of six years. Despite these strengths, a number of limitations should be considered. First, although focussing on injuries before the age of six years facilitates

	Current limitations	Challenges	Recommendations	Possible avenues-actions
Definition & Diagnosis	No definition for diagnosing early mTBI and no consensus on the list of commonly accepted inclusion criteria	Children 5 years and under may not exhibit the same signs and symptoms of TBI as older children, adolescents or adults	Develop a consensus to establish a common definition and diagnostic criteria	Organize consensus working groups, special interest groups, and panels of experts
Terminology	Numerous terms are used within the literature across age groups	Early childhood TBI includes several developmental subgroups	Ensure that terms are clearly operation- alized and defined	Define early childhood TBI (or early TBI) as sustained in children 5 years and under Use developmental labels such as infants, toddlers and preschoolers to help char- acterize are subgroups
	Variability in the terms used to describe mechanisms	Terms related to mechanism have evolved over time	Ensure most current terms are used	Report breakdown of mechanisms and causes in study results
Sample composition	Interpretations regarding the nature and severity of outcomes are often confounded by age, mechanism, and severity	Modest sample sizes and multiple levels of analysis limit the possibility of creating subgroups for comparison	Report groups according to mechanism, age, sex and gender	Provide descriptive data and fine-grained information to allow for future meta- analyses when sample sizes are too small to reliably compare subgroups
	Not all studies use comparison groups	Putative differences between com- parison and TBI groups are difficult to ascertain given short pre-morbid history and lack of knowledge on emergent conditions	Include at least one comparison group	Continue to document potential differ- ences between typically developing and orthopedically injured children
Design	Few longitudinal designs and long-term outcomes seldom measured	Young children develop extremely rapidly and constructs and tasks appropriate at one age may not be a few months or years later	Continue to encourage longitudinal approaches to better characterize the full scope of consequences across the lifespan	Use developmentally appropriate constructs and tests at each age, and incorporate some core constructs or measures that can be tracked over time and across developmental groups, allowing trajectory analyses
Assessment	Some domains (e.g., behavioral, social) almost exclusively based on third party questionnaires with limited or no direct measurement	Fewer standardized measures in early childhood (relative to older children)	Reduce bias by including a mix of questionnaires, observational coding and direct measurement	Consider developmentally appropriate and valid experimental paradigms to document cognitive, social and behav- ioral outcomes alongside commonly used standardized measures
	No reports of performance validity	Threats to effort and validity due to cooperation and participant challenges at young ages	Document behavior and reasons for reduced participation throughout direct assessment	Include stand-alone and/or embedded measures of validity to all assessment batteries for children ages 5+ Use detailed missing data codes and/ or score behavior using observational measures during assessment
		Few or no measure of validity for chil- dren 4 years and younger	Develop standardized measures of validity for this age group	Consider validating effort performance tests in children under 5 years
Measures	Numerous different measures used across studies precluding direct com- parisons across the literature	Few detailed guidelines exist regarding potential common data elements for early TBI	Continue to develop common data ele- ments based on empirical findings in early TBI	Consider experimental tasks that have demonstrated validity as potential measurement tools

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	Current limitations	Challenges	Recommendations	Possible avenues-actions
Outcome Domains	Broad range of outcomes studied, but almost no information regarding post- concussive symptoms	Infants and toddlers have limited verbal Limit downward extension of existing abilities to report abstract symptoms measures and instead use develop- typical of post-concussive symptoms mentally appropriate approaches	Limit downward extension of existing measures and instead use develop- mentally appropriate approaches	Rely on observational approaches in addition to third party reports for collecting data on post-concussive symptoms in children with limited verbal skills

Table 6 (continued)

conclusions regarding the specific effect of TBI during early childhood, several articles were excluded from the review because of this criterion. Some excluded studies covered overlapping age or developmental groups, often including toddlers and preschoolers alongside school-age children (e.g., participants aged two to nine years). While including these studies would have negated the objective of presenting findings for the youngest portion of the population, it might have provided an opportunity to compare timing of injuries between "early" and "late" childhood.

Second, the effect of multiple TBIs was not documented. Only two articles were identified that included multiple injuries. One was included in the review because it presented outcomes in the single TBI group separately (Liu et Li, 2013). The other was not included in the results tables because it was not possible to dissociate the effects of single versus multiple injuries (Bijur et al., 1996).

Third, article selection criteria did not include motor functioning, nor did it cover broad areas of global functioning such as quality of life, or intervention studies that may have reported cognitive or behavioral outcome at pre-test or admission, for example. There is also a gray area as to what studies and measures can be considered to target "adaptive functioning". For inclusion we used a socio-behavioral perspective of this construct (Bellini, 2003). Notably, there is a rich literature on functional disability, a construct that often overlaps with adaptive abilities, in the context of TBI rehabilitation programs that have used measures such as the Functional Independence Measure for children (Msall et al., 1994). These studies were identified in the first stage of the review and met the criteria for the outcome of interest, but all were ultimately excluded for other reasons, mostly due to age at injury (>6 years old) or injury groups not exclusive to TBI.

Fourth, effects of early TBI on post-concessive symptoms were not reported despite their central importance in mTBI or concussion research. There are few published studies that report post-concessive symptoms, likely because no validated measures of post-concessive symptoms exist under the age of five years, and few studies have tracked the effects of early TBI acutely. Current reports of post-concessive symptoms in young children consist of downward adaptation of existing school-aged children questionnaires or chart reviews of symptoms reported (Bellerose et al., 2017; Gagner et al., 2018; McKinlay et al., 2014; Suskauer et al., 2018). Efforts are currently underway to validate a developmentallyappropriate measure of post-concessive symptoms in young children (Dupont et al., 2021). Finally, it is worth noting that the review conclusions are subject to inherent publication biases and that the absence of results in any one domain may simply be the reflection of non-significant (and therefore unpublished) findings.

Conclusions

This review provides a comprehensive summary of the consequences of TBI sustained before the age of six years. While it is complex to distill clear conclusions due to the methodological challenges and developmental characteristics of this group, the review highlights that children who sustain TBI during early childhood, a sensitive period for the development of cognitive and social skills and associated behaviors, may show difficulties in a range of outcomes, and these are sometimes apparent even after mTBI. Though it is likely that the majority of children with mTBI will recover entirely, some studies report social and behavioral issues in the longer term. It is critical that research, diagnosis, assessment, clinical management, as well as prevention efforts, and consensus definitions be further developed based on this empirical literature, and in a manner that is specific to the unique characteristics of early childhood.

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Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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