

Figure 1. Study Selection Flow Diagram

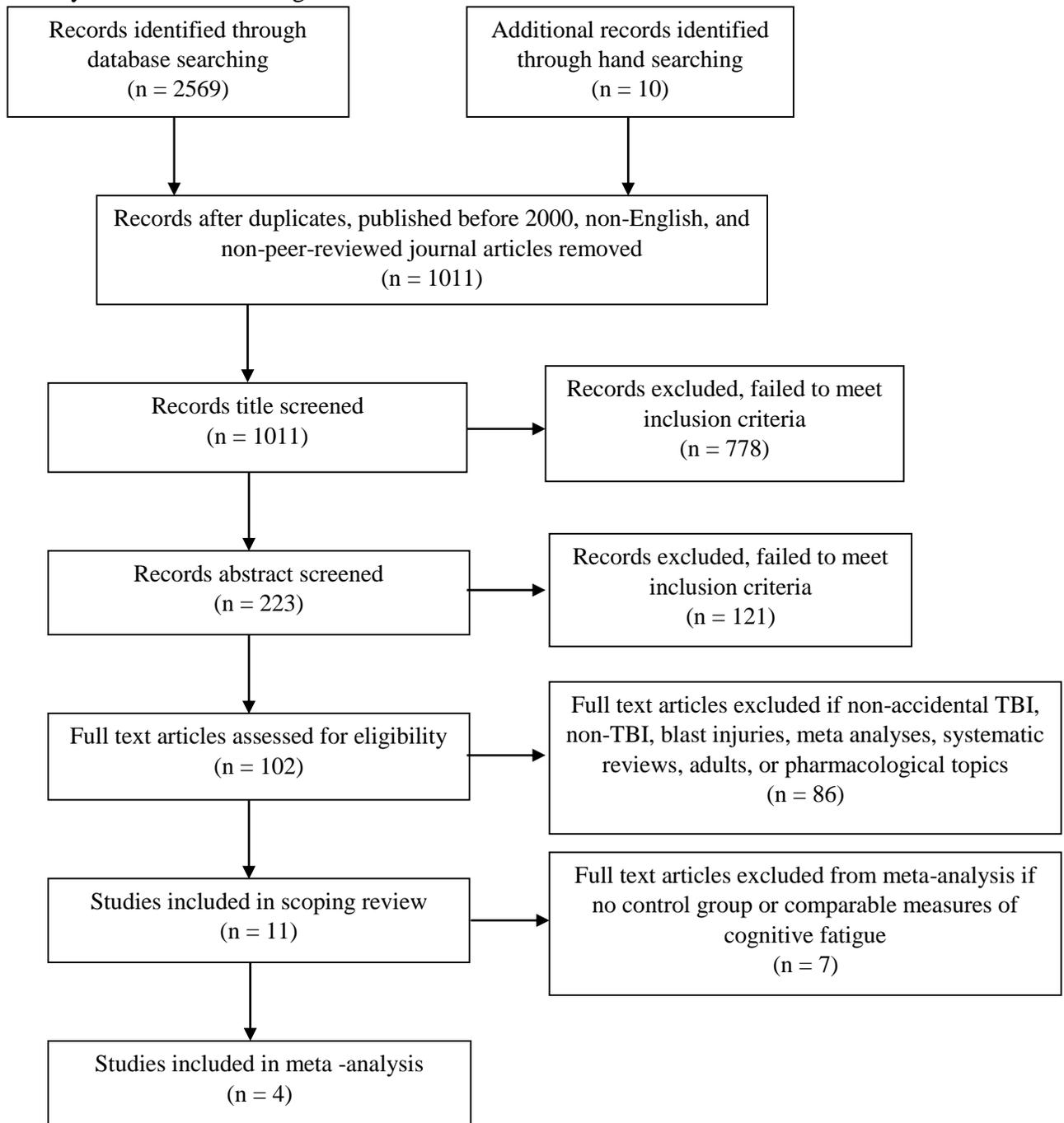
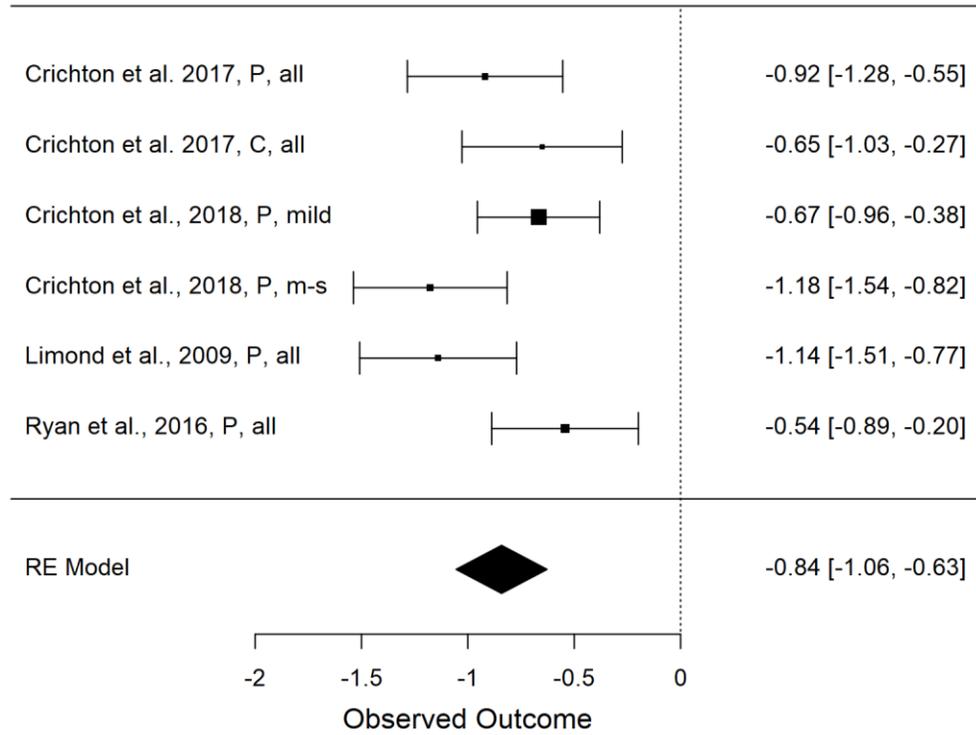
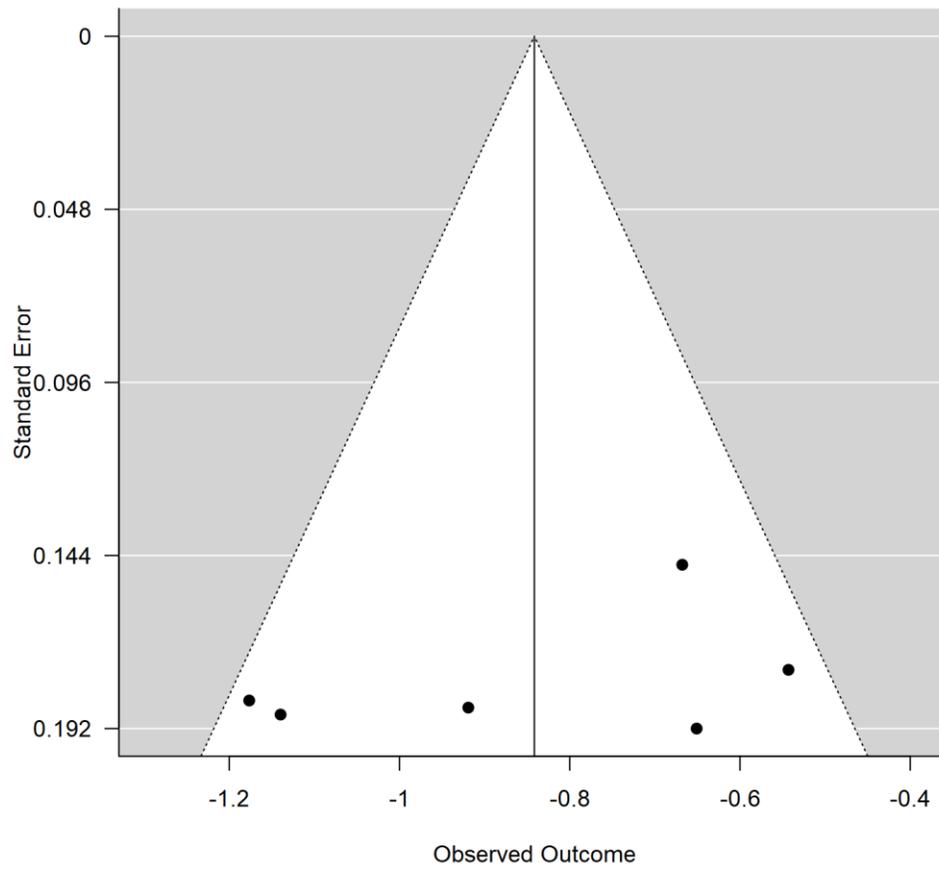


Figure 2. Forest Plot of Cognitive Fatigue Scores

P= parent report; C= child self-report; all= all severities of injuries; mild= only mild injuries; m-s= moderate-severe injuries

Figure 3. Funnel Plot of Publication Bias



1 **Title:** Cognitive fatigue in pediatric TBI: A meta analysis and scoping review

2

3 **Abstract**

4 **Objective** To review the evidence available on cognitive fatigue (i.e., increase in mental

5 exhaustion after prolonged cognitive activity) in childhood TBI, including rates, associated

6 factors and effects, and management strategies

7 **Methods** A meta analysis and scoping review of the literature were conducted following the

8 PRISMA guidelines. Terms were searched in relevant databases and through hand-searching.

9 Articles were included and excluded based on specific criteria and methods were evaluated for
10 risk of bias.

11 **Results** Of 2579 initially eligible articles, four studies with six effect sizes (due to reporting of
12 data by group in two studies) were included for a meta-analysis and 11 for a scoping review.

13 Cognitive fatigue was a common symptom in children after TBI of varying severities and times
14 post-injury. Few studies investigated factors or effects associated with cognitive fatigue,

15 although emerging evidence indicates some relations with family and injury factors and post-
16 injury functioning. Active rehabilitation was investigated by two studies and could be a safe

17 management strategy for cognitive fatigue, but additional investigation is needed on this and
18 other possible assessment and treatment approaches.

19 **Conclusions** Cognitive fatigue is a common symptom in children who experience a TBI of any

20 severity. Additional research is needed to determine the course of cognitive fatigue, elucidate the
21 relations between cognitive fatigue and secondary factors, and to build clinically-useful

22 assessment and treatment methods.

23 **Keywords:** (3-5)

24 Pediatric traumatic brain injury, cognitive fatigue, fatigue

25 **Introduction**

26 Traumatic brain injury (TBI) in childhood is known to cause acute and chronic changes
27 in development and functioning.¹ Up to 60% of children with TBI experience the symptom of
28 fatigue chronically post-injury when attempting to participate in daily life.²⁻⁶ Fatigue has been
29 defined as “the awareness of a decreased capacity for physical and/or mental activity due to an
30 imbalance in the availability, utilization, and/or restoration of resources needed to perform
31 activity” (p. 46).⁷ Fatigue can be challenging to measure, particularly in individuals with TBI,
32 due to its subjective nature.^{7,8} To best understand fatigue after TBI, the influence of neuro-
33 biological and personal-contextual factors on multiple fatigue dimensions must be
34 considered.^{4,7,8}

35 The neurological and biological changes occurring chronically and acutely after a TBI are
36 often associated with decreased physical, cognitive, emotional, and sleep functioning.^{4,8}
37 Individuals with TBI than must exert increased effort to complete daily life tasks, ultimately
38 evoking fatigue more quickly and more often than individuals without TBI.⁸ When self-reporting
39 fatigue, various factors appear related to higher rates of fatigue including: higher pre-injury
40 functioning, greater mental health needs, lower resiliency, and higher academic and social
41 demands (e.g., expectations for work completion).^{4,8-10} Although the exact causes of fatigue and
42 relations amongst factors are unclear, children are at a particularly high risk for experiencing
43 fatigue after TBI due to neuro-biological and personal development and unique expectations for
44 academic and social participation.⁵

45 Fatigue is typically conceptualized as multi-dimensional including physical, emotional,
46 sleep/rest, and cognitive elements.^{7,8} One previous review paper in pediatric acquired brain
47 injury (ABI) addressed general fatigue (i.e., consideration of all fatigue dimensions).⁵ Wilkinson
48 et al. (2018) found fatigue to be prevalent following childhood ABI, affecting functional
49 participation in daily life, but failure to consider the multidimensional nature of fatigue limits the
50 understanding and management of fatigue. Based on these findings and those of other studies,
51 the consideration of cognitive fatigue appears particularly important in childhood TBI.^{10,11}

52 Post-TBI, children commonly experience deficits in cognition and executive
53 functioning.¹²⁻¹⁴ In light of these deficits, children often report feeling mentally or cognitively
54 fatigued when attempting to participate in typical academic and social activities; this is
55 sometimes referred to as feeling “mentally foggy”.^{2,15} Cognitive fatigue, as defined by Wylie &
56 Flashman,⁸ is a “transient increase in mental exhaustion resulting from prolonged periods of
57 cognitive activity” (p. 4). When experiencing cognitive fatigue, other cognitive symptoms (e.g.,
58 slower processing time) might be exacerbated, increasing the child’s frustration and decreasing
59 their motivation to participate.^{16,17} Ultimately, the child disengages academically and
60 socially.^{16,17} Although cognitive fatigue co-occurs with other fatigue dimensions, the
61 presentation and persistence of cognitive fatigue appears unique but under-investigated.^{5,10} Due
62 to the lack of discussion of cognitive fatigue in experimental studies and review papers, it
63 remains difficult for researchers and clinicians to draw conclusions about the prevalence of and
64 assessment and management strategies for cognitive fatigue after childhood TBI.

65 The primary aim of this meta-analysis and scoping review was to review the evidence
66 available in published literature on reports of cognitive fatigue after childhood (i.e., 0-18 years)
67 TBI. Secondary aims were 1) to identify factors and effects associated with cognitive fatigue,

68 and 2) to determine implications for clinical practice and future directions for practice and
69 research related to cognitive fatigue in childhood TBI. To the best of the authors' knowledge,
70 this is the first review paper focusing on cognitive fatigue in childhood TBI. Previous systematic
71 reviews in this area have not specifically analyzed cognitive fatigue in childhood TBI, rather
72 focusing on the broad multidimensional construct of fatigue post-TBI while noting the necessity
73 of separately considering different fatigue dimensions in future studies.⁴⁻⁶

74 **Methods**

75 To comprehensively assess the available literature, a meta analysis and scoping review were
76 conducted to account for studies with and without control groups. Both the meta analysis and
77 scoping review were conducted following the Preferred Reporting Items for Systematic Reviews
78 and Meta-Analyses and the extension for Scoping Reviews.^{18,19} Initially, a meta analysis was
79 intended to be conducted due to its methodological rigor. After the literature search yielded a
80 small number of peer-reviewed articles with non-injured control groups, a scoping review was
81 also included as a broad and preliminary evaluation of existing literature, including articles
82 without non-injured control groups, specifically to highlight gaps in the literature for future
83 investigation.

84 **Search Strategy & Identification**

85 In July 2019, four databases relevant to cognition and TBI were searched for peer-
86 reviewed journal articles published in the English language between 2000 and July 1, 2019.
87 Additional articles were identified by hand-searching citations of articles that met criteria and
88 from authors' knowledge of relevant publications. Table 1 provides the keywords and databases
89 used during the search. The search results were available to all reviewers via Rayyan QCRI.²⁰

90 Articles were reviewed in three stages (i.e., title screen, abstract screen, and full text screen)
91 based on the inclusion and exclusion criteria listed in Table 2.

92 **Data Extraction & Risk of Bias Assessment**

93 Articles that met criteria were available to all authors via a group folder in Google Drive.
94 Two masters students in speech-language pathology extracted preliminary data (i.e., study
95 design, participant characteristics, prevalence of cognitive fatigue, findings on related outcomes)
96 from included studies using a standardized data collection form, shared via a Google sheet with
97 all researchers. Review of and feedback on the literature search, themes, and manuscript was
98 also shared via e-mail and at three in-person meetings.

99 Risk of bias of the included articles was assessed by two masters students in speech
100 language pathology using an adapted version of guidelines proposed by Hayden et al..²¹ The
101 following domains were evaluated for risk of bias: study participation, attrition, outcome
102 measurement, confound measurement, and analysis. Each reviewer assessed each domain, rating
103 each item as “yes”, “no”, “partly”, “unsure”, or “not applicable. The ratings were summarized
104 using an adapted version of a method proposed by the Scottish Intercollegiate Guidelines
105 Network.²² Articles were classified as “high quality” (+++), “moderate quality” (++) , or “fair
106 quality” (+). No study with a retrospective design received a “high” or “moderate” classification,
107 since this is a weak study design.²²

108 **Data Analysis**

109 Studies with a control group that reported a cognitive fatigue score were included for
110 meta-analysis. Cohen’s d effect sizes and standard errors were calculated based on the data

111 available in the articles. A model of random effect sizes was used to combine effect sizes.²³
112 Statistical heterogeneity was calculated with Q and I^2 . Visual and statistical inspection (i.e., rank
113 correlation test) of publication bias was made with a funnel plot. All analyses were conducted
114 with - and the forest and funnel plots were derived from - JASP 0.9.2.0. All studies meeting
115 inclusion criteria, with or without a control group, were included for a scoping review.

116 **Results**

117 **Search Results & Data Extraction**

118 The initial search generated 2569 results, with 10 additional articles being identified from
119 hand-searching. A total of 11 articles met inclusion criteria for this study. The flow diagram of
120 study selection is depicted in Figure 1. Interrater agreement for all levels of review and data
121 extraction is presented in Table 3. All discrepancies were resolved through discussion between
122 the two reviewers/extractors and the first author.

123 **Study Characteristics**

124 A summary of the 11 included studies is presented in Table 4. Of note, one research
125 group (i.e., Crichton et al. and Ryan et al.) published four of the included articles, and, although
126 it is not explicitly stated in the studies, there is likely overlap in the samples based on study
127 timelines and locations. Average age at the time of study participation ranged from 4.8- 16.3
128 years. Sample size of TBI groups ranged from 10 to 136 participants. Four studies²⁴⁻²⁷ examined
129 mild injuries and seven studies^{3,28-33} examined multiple severities or grouped severities (e.g.,
130 mild, moderate, and severe; moderate/severe). Time post-injury ranged from two days to 2.7
131 years. Four studies measured fatigue at multiple time points, all less than seven months post-

132 injury.^{3,24,27,28} Two studies investigated the efficacy of a treatment approach,^{25,26} and all other
133 studies were descriptive.

134 **Reports of Cognitive Fatigue**

135 *Scoping Review*

136 Two types of measures were used to quantify levels of cognitive fatigue: the Pediatric
137 Quality of Life Multidimensional Fatigue Scale (PedsQL MFS)³⁴ (N= 7) or symptom rating
138 scales including item reporting for “feeling in a fog” (i.e., symptom questionnaire from ImPACT
139 test battery²⁴; Post-Concussion Symptom Scale (PCSS)²⁶; Post-Concussion Symptom Inventory
140 (PCSI)²⁷; ACE Parent Questionnaire³²) (N= 4). One study included both types of measures.²⁴
141 These measures are described in Table 5.

142 Five studies used parent report, four studies used child self-report, and two studies used
143 both parent and child self-report. The average scaled rating of cognitive fatigue on the PedsQL
144 MFS ranged from 63.7 to 83.3 for children with TBI, including the baseline ratings in the
145 treatment studies. The symptom “feeling in a fog” was endorsed by 0% to 41.4% of children
146 with TBI, and was rated between 1.0 to 1.6 on 0 to 6 severity scales (0= no symptoms, 6= most
147 severe) or in the mild-moderate range.

148 *Meta-Analysis*

149 Six measures of cognitive fatigue from four studies²⁸⁻³¹ with non-injured control groups
150 and adequate data for effect size calculations were included for meta-analysis. As two
151 manuscripts²⁸⁻²⁹ presented data based on groups (i.e., parent vs child report; mild vs moderate-
152 severe injury severity), multiple effect sizes were calculated, yielding six effect sizes from four

153 articles. Of note, all control groups were previously published controls (i.e., published normative
154 samples, published healthy sample from a study of a different clinical sample). Although Ryan et
155 al.³¹ included an experimental control group, data for this group was not reported, and an effect
156 size could not be calculated.

157 All studies used the PedsQL MFS. Five measures²⁸⁻³¹ were parent-reported and one
158 measure²⁸ was child-reported. Four measures²⁹⁻³¹ included all severities of TBI, one measure²⁸
159 included only mild TBI, and one²⁸ included moderate-severe TBI. At the time of study
160 participation, children with TBI were on average 11.22 years old (9.90-13.30 years) and 13.93
161 months post-injury (1.6-32.40 months). Studies reported average scores for children with TBI
162 between 65.70 to 77.18, and children who are typically developing between 82.40 and 90.70.
163 Meta-analysis revealed a statistically significant negative effect, $d = -.84$, 95% CI [-1.06, -0.63],
164 indicating that children with TBI had significantly lower fatigue scores (i.e., experienced higher
165 levels of cognitive fatigue) than control groups. The forest plot in Figure 2 depicts these results.
166 Heterogeneity across studies was significant, $Q_{(5)} = 11.2$, $p = 0.047$, and moderate, $I^2 = 55.67$.³⁵
167 Visual and statistical inspection of the funnel plot depicted in Figure 3 did not indicate
168 publication bias, $\tau = -0.20$, $p = 0.719$.

169 **Scoping Review: Associated Factors and Effects**

170 Many studies discussed or hypothesized effects associated with cognitive fatigue, but
171 only three studies measured and ran analyses to explore the relations. Crichton et al.³ found
172 bivariate relations between cognitive fatigue and post-injury sleep, physical/motor functioning,
173 and emotional functioning. Ryan et al.³¹ observed smaller brain volumes with greater levels of
174 cognitive fatigue. Van Markus-Doornbosch et al.³³ found older age at onset (>11 yo), single

175 parent household status, greater limitations in activities and participation, and lower ratings of
176 quality of life to be associated with worse ratings of cognitive fatigue.

177 **Scoping Review: Management Strategies**

178 Although most studies discussed assessment and treatment recommendations based on
179 their findings, only two studies^{25,26} directly examined management strategies, both investigating
180 the effect of active rehabilitation on children with mild TBI and persistent symptoms. Both
181 studies implemented the same active rehabilitation program (described in detail by Gagnon et
182 al.²⁶). Active rehabilitation was defined and conceptualized as a slow return to physical activity
183 post-mild TBI that does not exacerbate symptoms.²⁶ Both studies used the PedsQL MFS to
184 measure cognitive fatigue pre- and post- treatment, with Gagnon et al.²⁶ also reporting the PCSI
185 item of “feeling mentally foggy” pre- and post-treatment. Chan et al.²⁵ did not conduct statistical
186 analyses on the pre- and post- treatment data, but, based on the data reported and analysis by the
187 authors of this paper, no significant differences were observed in cognitive fatigue from pre- to
188 post- treatment. Gagnon et al.²⁶ found significant improvement in cognitive fatigue when
189 comparing pre- and post- treatment PedsQL MFS scores. In addition, fewer participants
190 endorsed “feeling mentally foggy” post-treatment (N= 0) compared to pre-treatment (N= 2).
191 Both studies recommended the use of active rehabilitation treatment for children with mild TBI,
192 noting that the treatment approach appears safe (i.e., limited to no exacerbation of symptoms)^{25,26}
193 and potentially supports improvement of a range of common post-concussive symptoms
194 including cognitive fatigue.²⁶

195 **Risk of Bias**

196 Based on the risk of bias domains, three studies were identified as “high quality”.^{24,28,29}
197 Four studies were identified as “moderate quality”,^{25,28,31,33} and four studies were identified as
198 “fair quality”.^{26,27,30,32} Table 6 presents the risk of bias assessment results.

199 **Discussion**

200 This meta-analysis and scoping review appraised the available evidence on cognitive
201 fatigue after childhood TBI. The results from 11 studies support the main study aim, indicating
202 that children with TBI, when examined in cohorts that vary in severity, can experience cognitive
203 fatigue, even years after injury. Limited experimental evidence was available to address the
204 secondary aims of this study - factors and effects associated with cognitive fatigue and
205 management strategies. These findings suggest that cognitive fatigue is a significant symptom
206 following childhood TBI, and further research is warranted, particularly to identify effective
207 assessment and treatment approaches.

208 *Ratings of Cognitive Fatigue*

209 It is challenging to generalize findings of cognitive fatigue scores due to inconsistencies
210 in methodologies and reporting across studies. Of studies that used control groups,^{25,28–31,33} four
211 used previously published control scores (i.e., published normative samples, published healthy
212 sample from a study of a different clinical sample), all of which were included in the meta
213 analysis where demographic differences were not controlled for or not mentioned in the report.^{28–}
214 ³¹ All four studies reported that children with TBI had significantly worse levels of cognitive
215 fatigue compared to controls who were typically developing, as observed in the meta-analysis of
216 the data. Ryan et al.³¹ also included a control group specific to their study, with no significant
217 demographic differences from the TBI group, but did not find significant differences in cognitive

218 fatigue levels between groups. Unfortunately, data for the experimental control group was not
219 reported, and therefore could not be included in the meta analysis. Two studies^{25,33} control
220 groups included individuals with TBI, and were not included in the meta analysis. Chan et al.²⁵
221 utilized children with similar injuries to compare treatment effects, while Van Markus et al.³³
222 studied children with non-traumatic brain injuries and found that children with non-TBI
223 presented with worse levels of cognitive fatigue than children with TBI. Without the use of a
224 non-injured control group in which demographic and external variables can be accounted for and
225 in the absence of standardized assessments of fatigue, cognitive fatigue scores can be difficult to
226 interpret.⁶

227 All measures of cognitive fatigue were subjective, potentially biasing results. Five
228 studies^{3,28,30-32} used exclusively parent reports, and four studies²⁴⁻²⁷ used exclusively child self-
229 reports. The two studies that used both parent and child-self reports did not find a significant
230 difference between parent and child-self ratings.^{29,33} Studies on general fatigue following
231 childhood TBI suggest using both parent and child-self report forms to improve the validity of
232 the findings, while recognizing the subjective nature of experiencing fatigue. Most measures,
233 including the PedsQL MFS and post-concussion scales, are validated for both parent and child
234 report, making multiple scores from multiple reporters feasible.²⁹ To the best of the authors'
235 knowledge, objective or standardized fatigue measures have not been developed or utilized in
236 childhood TBI but are emerging for adult TBI and other populations.³⁶⁻³⁹ Pairing subjective and
237 objective measures would likely provide a more robust picture of cognitive fatigue post-
238 childhood TBI, elucidate the relationship (e.g., discrepancies) between subjective and objective
239 reports to support assessment practices, help determine clinically-significant levels and changes
240 in cognitive fatigue, and better inform management strategies.⁵

241 Because no studies included pre-injury measures of cognitive fatigue, comparisons of
242 pre- and post-injury or typical vs atypical levels were not possible. Unfortunately, all measures
243 from studies included in this review demonstrated limited utility in measuring cognitive fatigue,
244 largely due to their lack of standardized items and ability to differentiate between typical or
245 healthy fatigue levels and atypical fatigue levels.⁵ Symptom rating scales using the item related
246 to “mental fog” are less reliable and were extrapolated to represent cognitive fatigue for the
247 purpose of this review, given literature supporting the representativeness of this item.^{15,40}

248 The PedsQL MFS does include a valid and reliable sub-scale specific to cognitive
249 fatigue.³⁴ Of the studies with available comparisons between fatigue dimensions (i.e., general,
250 sleep/rest, cognitive), five studies^{3,28,30,31,33} found that cognitive fatigue was the dimension with
251 the worst ratings. Three studies^{25,26,29} found mixed results (i.e., cognitive fatigue was worse than
252 some and better than other dimensions). Interestingly, studies that found cognitive fatigue to
253 have the worst rating included younger participants (8-11 years old at injury; 8-13 years old at
254 study participation), compared to the other studies (14-18 years old at injury; 13-18 years old at
255 study participation). Consistent with a previous review on general fatigue,⁵ these findings
256 demonstrate the importance of considering fatigue dimensions separately to advance the
257 understanding of fatigue and provide tailored treatment and management strategies specific to
258 the child’s needs. Developmental stages and academic and social expectations should also be
259 considered when determining the salience of cognitive fatigue post-TBI.³³

260 With respect to age at injury, most studies examined children who experienced a TBI in
261 later childhood and early adolescence (i.e., about 8 to 18 years old). Only one study examined
262 earlier childhood TBI with an average age of injury at 4.8 years old.³² Due to a limited number of
263 studies in each age group, differences in the presentation of cognitive fatigue based on age were

264 difficult to elucidate. Studies suggested that adolescence is a particularly important time to
265 evaluate and consider fatigue, due to the natural increase of fatigue during that developmental
266 period.^{3,33} In addition, early childhood presents with the highest rates of TBI across childhood
267 with major cognitive and developmental changes shortly after injury, although Suskauer et al.³²
268 did not find notable ratings of cognitive fatigue in their sample. This could be due to adults'
269 inability to readily observe “feeling mentally foggy” in children who cannot accurately convey
270 their symptoms;³² this possibility warrants additional investigation and development of measures
271 that could accurately capture cognitive fatigue in this age group.

272 When examining cognitive fatigue levels based on severity, most studies that included
273 multiple severities did not report cognitive fatigue levels separately for severity groups, limiting
274 comparisons. Generally, children with milder injuries were over-represented compared to those
275 with moderate or severe injuries, but tended to present with lower levels of cognitive
276 fatigue.^{3,24,27,28} This trend becomes less clear when considering children with persistent
277 symptoms following a mild injury, potentially appearing more similar to moderate-severe
278 injuries.^{25,26} Future investigations should consider assessing cognitive fatigue symptoms
279 longitudinally in children with chronic mild TBI to better our understanding of the course of
280 symptoms and to inform management strategies.

281 Studies included in this review reveal multiple trajectories for the presence of cognitive
282 fatigue throughout recovery. Studies conducted in the chronic stages of recovery, about two
283 years post-injury, indicated that cognitive fatigue can persist at clinically-significant levels for all
284 severities of TBI.^{30,31,33} Changes in cognitive fatigue over time were inconsistent when examined
285 multiple times in the acute stages of recovery. One study²⁸ found that cognitive fatigue at one
286 year post-TBI was significantly worse than at six months post-TBI. Three studies,^{24,26,27}

287 including a treatment efficacy study, saw improvement within five months of injury with and
288 without intervention. One study,²⁵ a treatment efficacy study, found no change, and one study³
289 observed an increase in clinically-significant fatigue scores for individuals with mild injuries, but
290 improvement for those with moderate-severe injuries. Multiple factors could be influencing
291 levels of cognitive fatigue including: developmental stages, social and academic expectations or
292 involvement, and personal or environmental characteristics.^{3,28}

293 *Associated Factors & Effects*

294 Post-injury functioning (e.g., sleep, physical, emotional, daily participation), brain
295 volume, age at onset, parental marriage status, and quality of life appear to be associated with
296 cognitive fatigue, but the directions of these relations remain unclear.^{3,31,33} Other studies
297 hypothesized or presented additional data that could support or warrant further investigation of
298 potential relations with other factors. Children with more significant levels of cognitive fatigue
299 would likely experience greater difficulties in academics and general functioning and lower
300 quality of life.^{27,28,30} Psycho-social and mental health needs and sleep disturbances could be
301 exacerbated by and/or contribute to acute levels of cognitive fatigue.^{24,29} These hypothesized
302 relations would not be unexpected, given literature indicating the general association of these
303 factors (i.e., academic and social functioning, quality of life, psycho-social and mental health,
304 sleep) with childhood TBI.³ Although evidence is limited, given the subjective nature of fatigue,
305 personal, injury, and post-injury functioning factors are essential to the understanding of
306 cognitive fatigue and to tailor management strategies to individual needs.

307 *Management Strategies*

308 Suggestions for assessment of cognitive fatigue in childhood TBI included: regular and
309 systematic screenings for symptoms into the chronic stages of recovery to track progress and
310 ongoing needs;^{24,27,29,30} multidimensional fatigue assessments with multiple reporters;^{3,28,29,33}
311 structural imaging of biomarkers to identify and predict cognitive fatigue;⁴¹ and self-report
312 assessments specific to the child's developmental stage (e.g., including more concrete language
313 regarding cognitive fatigue for younger children).³² From the two studies that evaluated
314 treatment efficacy, active physical rehabilitation did not appear to exacerbate general post-
315 concussion or fatigue symptoms following childhood TBI and could improve cognitive fatigue,
316 but additional investigation is needed.^{25,26} Many additional management strategies were
317 suggested in the included articles but did not include empirical evidence. Recommendations for
318 interventions included: treat both the cognitive fatigue symptoms and areas of functioning
319 associated with greater fatigue (e.g., physical skills);³ support functional improvements for
320 participation and quality of life through cognitive rehabilitation, behavior management, and
321 academic supports;^{27,29,30,33} and consider external demands based on age when designing
322 supports and implementing services.³² One study³⁰ reported that children who experienced
323 cognitive fatigue did not receive specialty supports at school, reinforcing the potential broader
324 impact of unmet need in children with TBI.^{42,43} Evidence-based management strategies for
325 cognitive fatigue after childhood TBI are limited and need additional attention to support
326 positive outcomes.

327 **Future Directions**

328 Future research in cognitive fatigue after childhood TBI should utilize more robust
329 methodologies such as pairing objective and subjective measures of cognitive fatigue, measuring
330 cognitive fatigue at multiple time points, and controlling for confounding factors. Additional

331 attention is needed on younger children with TBI including monitoring symptoms into later
332 childhood and adolescence. Research in the neuro-biological mechanisms underlying cognitive
333 fatigue and changes in fatigue with overall development could provide valuable information to
334 inform management. Translational research investigating the feasibility and efficacy of
335 assessment and treatment methods is essential to support long-term outcomes for children with
336 TBI. Establishing a program, such as TBI Model Systems, for children could support
337 longitudinal and clinical research to better inform management of cognitive fatigue after TBI.

338 **Limitations**

339 Although our literature search reached the point of duplication, some relevant studies
340 might have been missed. Overall, limited evidence was available on cognitive fatigue after
341 childhood TBI. Of the available research, few studies used control groups; therefore results of
342 the meta-analysis should be interpreted with caution. In addition, multiple studies published by
343 the same research group likely included overlapping samples, potentially decreasing the efficacy
344 of the meta analysis due to correlation amongst samples. Comparisons across studies were
345 difficult due to differences in methodology (e.g., time since injury, severity of injury, measures
346 of course of fatigue, parent vs child-self report), limiting the generalizability of results. Despite
347 these limitations, results of this study provide a comprehensive summary of the available
348 evidence on cognitive fatigue after childhood TBI and highlight areas in need of further
349 investigation.

350 **Conclusions & Clinical Implications**

351 Specific consideration of cognitive fatigue is necessary for effective assessment and
352 treatment after childhood TBI. Additional investigation is needed to better inform clinical

353 services. Based on the current literature, children with any severity of TBI should be
 354 continuously assessed for cognitive fatigue through the chronic stages of recovery, with special
 355 focus on children with associated factors including lower general post-injury functioning and
 356 lower quality of life. Treatment approaches should include direct management of cognitive
 357 fatigue and reduction of the secondary effects, such as academic and social engagement, to
 358 improve long-term quality of life in children with TBI.

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Table 1. Search Terms and Databases	
Search Terms (searched in each database)	<p>Cogn* and fatigue and child* and brain injury</p> <p>Cogn* and fatigue and pediatric and brain injury</p> <p>Cogn* and fatigue and child* and acquired brain injury</p> <p>Cogn* and fatigue and pediatric and acquired brain injury</p> <p>Cogn* and fatigue and child* and traumatic brain injury</p> <p>Cogn* and fatigue and pediatric and traumatic brain injury</p> <p>Mental and fatigue and child* and brain injury</p> <p>Mental and fatigue and pediatric and brain injury</p> <p>Mental and fatigue and child* and acquired brain injury</p> <p>Mental and fatigue and pediatric and acquired brain injury</p> <p>Mental and fatigue and child* and traumatic brain injury</p> <p>Mental and fatigue and pediatric and traumatic brain injury</p>
Databases	Pubmed, PSYCINFO, ERIC, ScienceDirect

Table 2. Inclusion and Exclusion Criteria	
Inclusion Criteria	Fatigue with some mention of cognitive and/or mental fatigue; child/pediatric/adolescents; brain injury
Exclusion Criteria	non-ABI; Non-accidental ABI or child abuse; blast injuries; meta analyses, systematic reviews, or non-peer reviewed papers; adults

Table 3. Interrater Agreement for Study Selection, Data Extraction, & Risk of Bias	
Review	Agreement Prior to Resolution (proportion of items review)
Title Screen	90.5% (915/1011)
Abstract Screen	84.98% (191/223)
Full Text Screen	94.2%

	(96/102)
Data Extraction	98.8% (543/550)
Risk of Bias Assessment	96.4% (53/55)

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Table 4. Summary of Included Summaries					
Study (Author, Year Location)	Level of Evidence Study Design no studies using published controls received a rating higher than a III	TBI Group Characteristics (N severity; % male; Age at study participation (AS) (M (SD)); Time post injury (TPI) (M (SD))	Control Group Characteristics (N type; Age at survey (AS) (M (SD))	Reporter; Measure	Results for Cognitive Fatigue
Blinman, 2009 Pennsylvania, USA	III Prospective cohort without controls	63 mild; 69.8% male; AS: 14.1 (SD not reported) yrs; TPI: 2 days and 2-3 wks	n/a	Self-report; Symptom questionnaire of the ImPACT neurocognitive test battery (item: “feeling mentally foggy”) rated 0=no symptoms to 6= severe	41.4% (2.7 average rating) reported “feeling mentally foggy” at initial visit; 19.1% (1.6 average rating) reported at follow-up visits
Chan, 2018 British Columbia, Vancouver, Canada	I Single-site, parallel, open-label, randomized control	10 mild, PCS; 40% male; AS: 15.9 (1.66) yrs; TPI: 132 (52.0) days for initial assessment and post-treatment	9 mild, PCS; AS: 15.1 (1.42) yrs	Self-report; PedsQL MFS	Children who participated in a closely monitored, active rehabilitation treatment program did not experience more adverse effects than those receiving treatment as usual. No significant changes were observed between physical activity, symptom exacerbation, and clinical outcomes. Chan et al. did not perform statistical analysis of fatigue data, due to its exploratory nature in this study. The authors of this meta analysis conducted paired sample t- tests to compare pre- and post-treatment fatigue scores. No significant differences were found in the cognitive fatigue ratings for the active rehabilitation group. <i>Management Strategies:</i> Active rehabilitation, when closely monitored, could be beneficial for adolescents with persistent symptoms, such as cognitive fatigue, post-TBI.

Crichton, 2017 Melbourne, Australia	III Prospective with published controls	27 mild, 5 mod, 3 severe; 34 parent proxies; % male not reported; AS: not reported (age at injury: 13.3 (2.4) yrs (mild), 13.2 (2.6) yrs (mod/severe)); TPI: 7.3 (1.6) wks	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample ¹ and demographic differences could not be controlled	Self-report and parent-report; PedsQL MFS	Children and parents reported significantly greater levels of cognitive fatigue for the TBI group than the control sample.
Crichton, 2018a Australia and Canada	III Longitudinal prospective with published controls	59 mild, 36 mod/severe; 77% male; AS: not reported (age at injury: 9.9 (5.0) yrs); TPI: 6 and 12 mos	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample ¹ and demographic differences could not be controlled	Parent-report; PedsQL MFS	Cognitive fatigue was significantly worse for children with moderate-severe TBI than mild TBI. Cognitive fatigue worsened significantly from 6 months to 12 months post-injury.
Crichton, 2018b Australia and Canada	III Prospective, non-randomized cohort without controls	52 mild, 27 mod/severe; 82.69% male (mild), 85.19% (male mod/severe); AS: 11.73 (4.42) yrs (mild), 9.72 (5.17) yrs (mod/severe); TPI: 6 and 12 months	n/a	Parent-report; PedsQL MFS	At 6 and 12 months post-TBI, 10% and 17%, of children with mild TBI and 27% and 19% of children with mod-severe TBI were rated in the clinical range for total fatigue, respectively (cognitive fatigue levels were not individually reported). Cognitive fatigue was the dimension with the worst ratings compared to sleep/rest and general fatigue. <i>Associated Effects:</i> General post-injury physical functioning significantly predicted cognitive fatigue 12 mos post-TBI (child factors and injury severity did not). Relationships with pre and post injury functioning might be bi-directional.
Gagnon, 2016 Montreal, Canada	III Clinical series without controls	10 sport-related concussion (slow to recover); 70% male; AS: 14-18 yrs; TPI: 7.9 wks for initial assessment and post-6 week treatment	n/a	Self-report; PedsQL MFS and PCSS (item: “feeling mentally foggy”)	Cognitive fatigue and all fatigue measures improved significantly post-treatment in an active rehabilitation program. “Feeling mentally foggy” was endorsed by 2 participants pre-treatment and no participants post-treatment. <i>Management Strategies:</i> Low-levels of active rehabilitation might be beneficial for children who are slow-to-recover from concussion. Active rehabilitation appears to support improvement

					across different symptoms, particularly fatigue dimensions.
Limond, 2009 United Kingdom	III Retrospective, cross-sectional study compared to published normative data	47 mild, moderate, and severe (hospitalized for at least 48 hrs); % male not reported; AS: 10.5 (3.6) yrs; TPI: 2.7 (1.2) yrs	105 healthy; 68.6% male; AS: 13.70 (9.47) yrs parent report: 157 healthy; 62.4% male; AS: 11.63 (8.59) years *controls are from a published normative sample ² and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI were reported to have significantly greater levels of fatigue for all injury severities compared to the control sample. Cognitive fatigue was the dimension with the worst rating compared to sleep/rest and general fatigue. Less than half (47%) of children with TBI had ratings of “normal” levels of cognitive fatigue, while 15% were considered “borderline” and 38% were considered “abnormal”, based on cut-off scores.
Macartney, 2018 Ontario, Canada	III Retrospective chart review without controls	136 mild; 45.6% male; AS: 15.4 (median); TPI: 5.4 (3-10.8) days for initial assessment then 28 days, 56 days, and 84 days *participants were discharged when symptoms returned to baseline therefore not all participants required assessment at all time points	n/a	Self-report; PCSI (item: “feeling in a fog”) rated 0 to 6 (higher scores= more severe)	The median rating of “feeling in a fog” was 2.9 (1.0-5.8); 1.4 (0.1-5.2); 1.0 (0.4-5.0), at 28; 56; and 84 days, respectively.
Ryan, 2016 Melbourne, Australia	III Prospective, non-randomized cohort with experimental controls and published controls	67 mild, 24 moderate, 12 severe; 67.96% male; AS: 10.54 (2.39) yrs (mild), 10.37 (2.58) yrs (moderate), 10.41 (3.10) yrs (severe); TPI: 24 months	Experimental: 34 healthy; 21% male; AS: 10.41 (2.76) *no demographic differences between groups Published: 157 healthy; 47.1% male; AS: 13.68 (2.17) yrs *controls are from a published normative sample ³ and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI had significantly greater levels of cognitive fatigue compared to the published control sample, but, when compared with experimental controls, no differences were observed. <i>Associated Effects:</i> Cognitive fatigue was significantly associated with smaller brain volumes. This finding could indicate disruptions of neural pathways cause an imbalance in effort-reward experiences which is subjectively reported as cognitive fatigue.

Suskauer, 2018 Maryland, USA	III Retrospective medical record review	28 mild/moderate/severe; 50% male; AS: not reported (age at injury: 4.8 yrs); TPI: 38 days	n/a	Parent-report; ACE Parent Questionnaire (item: “feeling mentally foggy”) classified as “ever experienced post-TBI” or “currently experiencing post-TBI”	No parents (0%) reported their child ever or was currently experiencing “feeling mentally foggy”.
van Markus-Doornbosch, 2016 Netherlands	III Prospective review and follow-up study without controls	58 mild, 11 moderate/severe; 46% male; AS: not reported (age at injury: 11 (6) yrs (median, IQR)); TPI: 24-30 mos	19 non-traumatic BI (NTBI); 11% male; AS: 14 (7); TPI: 24-30 mos	Parent-report and self-report; PedsQL MFS	Children with NTBI were parent- and self-reported to have significantly greater levels of cognitive fatigue compared to children with TBI. No significant difference was observed between parent and child self-report for cognitive fatigue. <i>Associated Effects:</i> Greater levels of cognitive fatigue was significantly associated with older age at onset (>11 yo); single parent household; greater limitations in activities and participation; and lower quality of life.

Table 5. Measures used to quantify levels of cognitive fatigue	
Measure	Description
PedsQL Multidimensional Fatigue Scale (PedsQL MFS) ³⁴	<ul style="list-style-type: none"> - parent and child self-report forms for ages 2-18 years old - 3 subscales (i.e., general fatigue, sleep, cognitive fatigue) are rated on a Likert scale (0= never a problem to 4= almost always a problem over the past month). Items are then reverse scored and transformed to a 0- to 100-point scale, such that higher scores indicate less fatigue.^a - shown good internal consistency reliability, test-retest reliability, and inter-observer reliability³⁴
Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) ⁴⁴	<ul style="list-style-type: none"> - FDA endorsed online tool for baseline and post-injury testing for ages 12-59 years old - assesses visual and verbal memory, reaction time, and processing speed through 8 tasks and includes a series of symptom-related questions rated on a 7-point Likert scale (0= no symptom, 6= severe symptom) - validity and reliability are unclear and highly dependent on time administered post-injury, area assessed, and other factors^{45,46}
Post-Concussion Symptom Scale (PCSS) ⁴⁷	<ul style="list-style-type: none"> - self-report for individuals over 11 years old - 22-items of symptom-related questions rated from 0 (not endorsed) to 6 (severe) - shown good test-retest reliability and internal consistency reliability and reliable to detect change over time⁴⁸
Post-Concussion Symptom Inventory (PCSI) ⁴⁹	<ul style="list-style-type: none"> - parent and child self-report for ages 5-18 years old - 27-items of symptom-related questions rated from 0-6 with higher scores representing more severe symptoms - shown good internal consistency⁵⁰
Acute Concussion Evaluation (ACE) ⁵¹	<ul style="list-style-type: none"> - parent and child self-report for ages 4 years old-adult - shown good internal consistency reliability, content validity, predictive validity, convergent/divergent validity, and construct validity⁵²
^a Chan et al. ²⁵ did not appear to calculate the scaled score in reporting results	

Table 6. Risk of Bias Summary						
Author, Year	Study Participation	Attrition	Outcome Measurement	Confound Measurement	Analysis	Assessment Summary
Blinman et al., 2009	no	partly	no	no	no	+++
Chan et al., 2018	no	no	partly	partly	no	++
Crichton et al., 2017	no	no	partly	no	no	+++
Crichton, Anderson, et al., 2018	no	no	no	no	no	+++
Crichton, Oakley, et al., 2018	partly	no	partly	no	no	++
Gagnon et al., 2015	no	no	partly	yes	partly	+
Limond et al., 2009	no	no	partly	no	no	+
Macartney et al., 2018	no	no	partly	no	no	+
Ryan et al., 2016	no	no	yes	no	no	++
Suskauer et al., 2017	no	no	partly	partly	no	+
van Markus-Doornbosch et al., 2016	no	partly	partly	no	no	++

Note: no= no to little potential bias; partly= some bias; yes= likely bias

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10 Jessica Salley Riccardi has no conflicts of interest and no financial or nonfinancial relationships
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15

16

17 **Abstract**

18 **Objective** To review the evidence available on cognitive fatigue (i.e., increase in mental
19 exhaustion after prolonged cognitive activity) in childhood TBI, including rates, associated
20 factors and effects, and management strategies

21 **Methods** A meta analysis and scoping review of the literature were conducted following the
22 PRISMA guidelines. Terms were searched in relevant databases and through hand-searching.
23 Articles were included and excluded based on specific criteria and methods were evaluated for
24 risk of bias.

25 **Results** Of 2579 initially eligible articles, four studies with six effect sizes (due to reporting of
26 data by group in two studies) were included for a meta-analysis and 11 for a scoping review.
27 Cognitive fatigue was a common symptom in children after TBI of varying severities and times
28 post-injury. Few studies investigated factors or effects associated with cognitive fatigue,
29 although emerging evidence indicates some relations with family and injury factors and post-
30 injury functioning. Active rehabilitation was investigated by two studies and could be a safe
31 management strategy for cognitive fatigue, but additional investigation is needed on this and
32 other possible assessment and treatment approaches.

33 **Conclusions** Cognitive fatigue is a common symptom in children who experience a TBI of any
34 severity. Additional research is needed to determine the course of cognitive fatigue, elucidate the
35 relations between cognitive fatigue and secondary factors, and to build clinically-useful
36 assessment and treatment methods.

37 **Keywords:** (3-5)

38 Pediatric traumatic brain injury, cognitive fatigue, fatigue

39 **Introduction**

40 Traumatic brain injury (TBI) in childhood is known to cause acute and chronic changes
41 in development and functioning.¹ Up to 60% of children with TBI experience the symptom of
42 fatigue chronically post-injury when attempting to participate in daily life.²⁻⁶ Fatigue has been
43 defined as “the awareness of a decreased capacity for physical and/or mental activity due to an
44 imbalance in the availability, utilization, and/or restoration of resources needed to perform
45 activity” (p. 46).⁷ Fatigue can be challenging to measure, particularly in individuals with TBI,
46 due to its subjective nature.^{7,8} To best understand fatigue after TBI, the influence of neuro-
47 biological and personal-contextual factors on multiple fatigue dimensions must be
48 considered.^{4,7,8}

49 The neurological and biological changes occurring chronically and acutely after a TBI are
50 often associated with decreased physical, cognitive, emotional, and sleep functioning.^{4,8}
51 Individuals with TBI than must exert increased effort to complete daily life tasks, ultimately
52 evoking fatigue more quickly and more often than individuals without TBI.⁸ When self-reporting
53 fatigue, various factors appear related to higher rates of fatigue including: higher pre-injury
54 functioning, greater mental health needs, lower resiliency, and higher academic and social
55 demands (e.g., expectations for work completion).^{4,8-10} Although the exact causes of fatigue and
56 relations amongst factors are unclear, children are at a particularly high risk for experiencing
57 fatigue after TBI due to neuro-biological and personal development and unique expectations for
58 academic and social participation.⁵

59 Fatigue is typically conceptualized as multi-dimensional including physical, emotional,
60 sleep/rest, and cognitive elements.^{7,8} One previous review paper in pediatric acquired brain
61 injury (ABI) addressed general fatigue (i.e., consideration of all fatigue dimensions).⁵ Wilkinson
62 et al. (2018) found fatigue to be prevalent following childhood ABI, affecting functional
63 participation in daily life, but failure to consider the multidimensional nature of fatigue limits the
64 understanding and management of fatigue. Based on these findings and those of other studies,
65 the consideration of cognitive fatigue appears particularly important in childhood TBI.^{10,11}

66 Post-TBI, children commonly experience deficits in cognition and executive
67 functioning.¹²⁻¹⁴ In light of these deficits, children often report feeling mentally or cognitively
68 fatigued when attempting to participate in typical academic and social activities; this is
69 sometimes referred to as feeling “mentally foggy”.^{2,15} Cognitive fatigue, as defined by Wylie &
70 Flashman,⁸ is a “transient increase in mental exhaustion resulting from prolonged periods of
71 cognitive activity” (p. 4). When experiencing cognitive fatigue, other cognitive symptoms (e.g.,
72 slower processing time) might be exacerbated, increasing the child’s frustration and decreasing
73 their motivation to participate.^{16,17} Ultimately, the child disengages academically and
74 socially.^{16,17} Although cognitive fatigue co-occurs with other fatigue dimensions, the
75 presentation and persistence of cognitive fatigue appears unique but under-investigated.^{5,10} Due
76 to the lack of discussion of cognitive fatigue in experimental studies and review papers, it
77 remains difficult for researchers and clinicians to draw conclusions about the prevalence of and
78 assessment and management strategies for cognitive fatigue after childhood TBI.

79 The primary aim of this meta-analysis and scoping review was to review the evidence
80 available in published literature on reports of cognitive fatigue after childhood (i.e., 0-18 years)
81 TBI. Secondary aims were 1) to identify factors and effects associated with cognitive fatigue,

82 and 2) to determine implications for clinical practice and future directions for practice and
83 research related to cognitive fatigue in childhood TBI. To the best of the authors' knowledge,
84 this is the first review paper focusing on cognitive fatigue in childhood TBI. Previous systematic
85 reviews in this area have not specifically analyzed cognitive fatigue in childhood TBI, rather
86 focusing on the broad multidimensional construct of fatigue post-TBI while noting the necessity
87 of separately considering different fatigue dimensions in future studies.⁴⁻⁶

88 **Methods**

89 To comprehensively assess the available literature, a meta analysis and scoping review were
90 conducted to account for studies with and without control groups. Both the meta analysis and
91 scoping review were conducted following the Preferred Reporting Items for Systematic Reviews
92 and Meta-Analyses and the extension for Scoping Reviews.^{18,19} Initially, a meta analysis was
93 intended to be conducted due to its methodological rigor. After the literature search yielded a
94 small number of peer-reviewed articles with non-injured control groups, a scoping review was
95 also included as a broad and preliminary evaluation of existing literature, including articles
96 without non-injured control groups, specifically to highlight gaps in the literature for future
97 investigation.

98 **Search Strategy & Identification**

99 In July 2019, four databases relevant to cognition and TBI were searched for peer-
100 reviewed journal articles published in the English language between 2000 and July 1, 2019.
101 Additional articles were identified by hand-searching citations of articles that met criteria and
102 from authors' knowledge of relevant publications. Table 1 provides the keywords and databases
103 used during the search. The search results were available to all reviewers via Rayyan QCRI.²⁰

104 Articles were reviewed in three stages (i.e., title screen, abstract screen, and full text screen)
105 based on the inclusion and exclusion criteria listed in Table 2.

106 **Data Extraction & Risk of Bias Assessment**

107 Articles that met criteria were available to all authors via a group folder in Google Drive.
108 Two masters students in speech-language pathology extracted preliminary data (i.e., study
109 design, participant characteristics, prevalence of cognitive fatigue, findings on related outcomes)
110 from included studies using a standardized data collection form, shared via a Google sheet with
111 all researchers. Review of and feedback on the literature search, themes, and manuscript was
112 also shared via e-mail and at three in-person meetings.

113 Risk of bias of the included articles was assessed by two masters students in speech
114 language pathology using an adapted version of guidelines proposed by Hayden et al..²¹ The
115 following domains were evaluated for risk of bias: study participation, attrition, outcome
116 measurement, confound measurement, and analysis. Each reviewer assessed each domain, rating
117 each item as “yes”, “no”, “partly”, “unsure”, or “not applicable. The ratings were summarized
118 using an adapted version of a method proposed by the Scottish Intercollegiate Guidelines
119 Network.²² Articles were classified as “high quality” (+++), “moderate quality” (++) , or “fair
120 quality” (+). No study with a retrospective design received a “high” or “moderate” classification,
121 since this is a weak study design.²²

122 **Data Analysis**

123 Studies with a control group that reported a cognitive fatigue score were included for
124 meta-analysis. Cohen’s d effect sizes and standard errors were calculated based on the data

125 available in the articles. A model of random effect sizes was used to combine effect sizes.²³
126 Statistical heterogeneity was calculated with Q and I^2 . Visual and statistical inspection (i.e., rank
127 correlation test) of publication bias was made with a funnel plot. All analyses were conducted
128 with - and the forest and funnel plots were derived from - JASP 0.9.2.0. All studies meeting
129 inclusion criteria, with or without a control group, were included for a scoping review.

130 **Results**

131 **Search Results & Data Extraction**

132 The initial search generated 2569 results, with 10 additional articles being identified from
133 hand-searching. A total of 11 articles met inclusion criteria for this study. The flow diagram of
134 study selection is depicted in Figure 1. Interrater agreement for all levels of review and data
135 extraction is presented in Table 3. All discrepancies were resolved through discussion between
136 the two reviewers/extractors and the first author.

137 **Study Characteristics**

138 A summary of the 11 included studies is presented in Table 4. Of note, one research
139 group (i.e., Crichton et al. and Ryan et al.) published four of the included articles, and, although
140 it is not explicitly stated in the studies, there is likely overlap in the samples based on study
141 timelines and locations. Average age at the time of study participation ranged from 4.8- 16.3
142 years. Sample size of TBI groups ranged from 10 to 136 participants. Four studies²⁴⁻²⁷ examined
143 mild injuries and seven studies^{3,28-33} examined multiple severities or grouped severities (e.g.,
144 mild, moderate, and severe; moderate/severe). Time post-injury ranged from two days to 2.7
145 years. Four studies measured fatigue at multiple time points, all less than seven months post-

146 injury.^{3,24,27,28} Two studies investigated the efficacy of a treatment approach,^{25,26} and all other
147 studies were descriptive.

148 **Reports of Cognitive Fatigue**

149 *Scoping Review*

150 Two types of measures were used to quantify levels of cognitive fatigue: the Pediatric
151 Quality of Life Multidimensional Fatigue Scale (PedsQL MFS)³⁴ (N= 7) or symptom rating
152 scales including item reporting for “feeling in a fog” (i.e., symptom questionnaire from ImPACT
153 test battery²⁴; Post-Concussion Symptom Scale (PCSS)²⁶; Post-Concussion Symptom Inventory
154 (PCSI)²⁷; ACE Parent Questionnaire³²) (N= 4). One study included both types of measures.²⁴
155 These measures are described in Table 5.

156 Five studies used parent report, four studies used child self-report, and two studies used
157 both parent and child self-report. The average scaled rating of cognitive fatigue on the PedsQL
158 MFS ranged from 63.7 to 83.3 for children with TBI, including the baseline ratings in the
159 treatment studies. The symptom “feeling in a fog” was endorsed by 0% to 41.4% of children
160 with TBI, and was rated between 1.0 to 1.6 on 0 to 6 severity scales (0= no symptoms, 6= most
161 severe) or in the mild-moderate range.

162 *Meta-Analysis*

163 Six measures of cognitive fatigue from four studies²⁸⁻³¹ with non-injured control groups
164 and adequate data for effect size calculations were included for meta-analysis. As two
165 manuscripts²⁸⁻²⁹ presented data based on groups (i.e., parent vs child report; mild vs moderate-
166 severe injury severity), multiple effect sizes were calculated, yielding six effect sizes from four

167 articles. Of note, all control groups were previously published controls (i.e., published normative
168 samples, published healthy sample from a study of a different clinical sample). Although Ryan et
169 al.³¹ included an experimental control group, data for this group was not reported, and an effect
170 size could not be calculated.

171 All studies used the PedsQL MFS. Five measures²⁸⁻³¹ were parent-reported and one
172 measure²⁸ was child-reported. Four measures²⁹⁻³¹ included all severities of TBI, one measure²⁸
173 included only mild TBI, and one²⁸ included moderate-severe TBI. At the time of study
174 participation, children with TBI were on average 11.22 years old (9.90-13.30 years) and 13.93
175 months post-injury (1.6-32.40 months). Studies reported average scores for children with TBI
176 between 65.70 to 77.18, and children who are typically developing between 82.40 and 90.70.
177 Meta-analysis revealed a statistically significant negative effect, $d = -.84$, 95% CI [-1.06, -0.63],
178 indicating that children with TBI had significantly lower fatigue scores (i.e., experienced higher
179 levels of cognitive fatigue) than control groups. The forest plot in Figure 2 depicts these results.
180 Heterogeneity across studies was significant, $Q_{(5)} = 11.2$, $p = 0.047$, and moderate, $I^2 = 55.67$.³⁵
181 Visual and statistical inspection of the funnel plot depicted in Figure 3 did not indicate
182 publication bias, $\tau = -0.20$, $p = 0.719$.

183 **Scoping Review: Associated Factors and Effects**

184 Many studies discussed or hypothesized effects associated with cognitive fatigue, but
185 only three studies measured and ran analyses to explore the relations. Crichton et al.³ found
186 bivariate relations between cognitive fatigue and post-injury sleep, physical/motor functioning,
187 and emotional functioning. Ryan et al.³¹ observed smaller brain volumes with greater levels of
188 cognitive fatigue. Van Markus-Doornbosch et al.³³ found older age at onset (>11 yo), single

189 parent household status, greater limitations in activities and participation, and lower ratings of
190 quality of life to be associated with worse ratings of cognitive fatigue.

191 **Scoping Review: Management Strategies**

192 Although most studies discussed assessment and treatment recommendations based on
193 their findings, only two studies^{25,26} directly examined management strategies, both investigating
194 the effect of active rehabilitation on children with mild TBI and persistent symptoms. Both
195 studies implemented the same active rehabilitation program (described in detail by Gagnon et
196 al.²⁶). Active rehabilitation was defined and conceptualized as a slow return to physical activity
197 post-mild TBI that does not exacerbate symptoms.²⁶ Both studies used the PedsQL MFS to
198 measure cognitive fatigue pre- and post- treatment, with Gagnon et al.²⁶ also reporting the PCSI
199 item of “feeling mentally foggy” pre- and post-treatment. Chan et al.²⁵ did not conduct statistical
200 analyses on the pre- and post- treatment data, but, based on the data reported and analysis by the
201 authors of this paper, no significant differences were observed in cognitive fatigue from pre- to
202 post- treatment. Gagnon et al.²⁶ found significant improvement in cognitive fatigue when
203 comparing pre- and post- treatment PedsQL MFS scores. In addition, fewer participants
204 endorsed “feeling mentally foggy” post-treatment (N= 0) compared to pre-treatment (N= 2).
205 Both studies recommended the use of active rehabilitation treatment for children with mild TBI,
206 noting that the treatment approach appears safe (i.e., limited to no exacerbation of symptoms)^{25,26}
207 and potentially supports improvement of a range of common post-concussive symptoms
208 including cognitive fatigue.²⁶

209 **Risk of Bias**

210 Based on the risk of bias domains, three studies were identified as “high quality”.^{24,28,29}
211 Four studies were identified as “moderate quality”,^{25,28,31,33} and four studies were identified as
212 “fair quality”.^{26,27,30,32} Table 6 presents the risk of bias assessment results.

213 **Discussion**

214 This meta-analysis and scoping review appraised the available evidence on cognitive
215 fatigue after childhood TBI. The results from 11 studies support the main study aim, indicating
216 that children with TBI, when examined in cohorts that vary in severity, can experience cognitive
217 fatigue, even years after injury. Limited experimental evidence was available to address the
218 secondary aims of this study - factors and effects associated with cognitive fatigue and
219 management strategies. These findings suggest that cognitive fatigue is a significant symptom
220 following childhood TBI, and further research is warranted, particularly to identify effective
221 assessment and treatment approaches.

222 *Ratings of Cognitive Fatigue*

223 It is challenging to generalize findings of cognitive fatigue scores due to inconsistencies
224 in methodologies and reporting across studies. Of studies that used control groups,^{25,28–31,33} four
225 used previously published control scores (i.e., published normative samples, published healthy
226 sample from a study of a different clinical sample), all of which were included in the meta
227 analysis where demographic differences were not controlled for or not mentioned in the report.^{28–}
228 ³¹ All four studies reported that children with TBI had significantly worse levels of cognitive
229 fatigue compared to controls who were typically developing, as observed in the meta-analysis of
230 the data. Ryan et al.³¹ also included a control group specific to their study, with no significant
231 demographic differences from the TBI group, but did not find significant differences in cognitive

232 fatigue levels between groups. Unfortunately, data for the experimental control group was not
233 reported, and therefore could not be included in the meta analysis. Two studies^{25,33} control
234 groups included individuals with TBI, and were not included in the meta analysis. Chan et al.²⁵
235 utilized children with similar injuries to compare treatment effects, while Van Markus et al.³³
236 studied children with non-traumatic brain injuries and found that children with non-TBI
237 presented with worse levels of cognitive fatigue than children with TBI. Without the use of a
238 non-injured control group in which demographic and external variables can be accounted for and
239 in the absence of standardized assessments of fatigue, cognitive fatigue scores can be difficult to
240 interpret.⁶

241 All measures of cognitive fatigue were subjective, potentially biasing results. Five
242 studies^{3,28,30-32} used exclusively parent reports, and four studies²⁴⁻²⁷ used exclusively child self-
243 reports. The two studies that used both parent and child-self reports did not find a significant
244 difference between parent and child-self ratings.^{29,33} Studies on general fatigue following
245 childhood TBI suggest using both parent and child-self report forms to improve the validity of
246 the findings, while recognizing the subjective nature of experiencing fatigue. Most measures,
247 including the PedsQL MFS and post-concussion scales, are validated for both parent and child
248 report, making multiple scores from multiple reporters feasible.²⁹ To the best of the authors'
249 knowledge, objective or standardized fatigue measures have not been developed or utilized in
250 childhood TBI but are emerging for adult TBI and other populations.³⁶⁻³⁹ Pairing subjective and
251 objective measures would likely provide a more robust picture of cognitive fatigue post-
252 childhood TBI, elucidate the relationship (e.g., discrepancies) between subjective and objective
253 reports to support assessment practices, help determine clinically-significant levels and changes
254 in cognitive fatigue, and better inform management strategies.⁵

255 Because no studies included pre-injury measures of cognitive fatigue, comparisons of
256 pre- and post-injury or typical vs atypical levels were not possible. Unfortunately, all measures
257 from studies included in this review demonstrated limited utility in measuring cognitive fatigue,
258 largely due to their lack of standardized items and ability to differentiate between typical or
259 healthy fatigue levels and atypical fatigue levels.⁵ Symptom rating scales using the item related
260 to “mental fog” are less reliable and were extrapolated to represent cognitive fatigue for the
261 purpose of this review, given literature supporting the representativeness of this item.^{15,40}

262 The PedsQL MFS does include a valid and reliable sub-scale specific to cognitive
263 fatigue.³⁴ Of the studies with available comparisons between fatigue dimensions (i.e., general,
264 sleep/rest, cognitive), five studies^{3,28,30,31,33} found that cognitive fatigue was the dimension with
265 the worst ratings. Three studies^{25,26,29} found mixed results (i.e., cognitive fatigue was worse than
266 some and better than other dimensions). Interestingly, studies that found cognitive fatigue to
267 have the worst rating included younger participants (8-11 years old at injury; 8-13 years old at
268 study participation), compared to the other studies (14-18 years old at injury; 13-18 years old at
269 study participation). Consistent with a previous review on general fatigue,⁵ these findings
270 demonstrate the importance of considering fatigue dimensions separately to advance the
271 understanding of fatigue and provide tailored treatment and management strategies specific to
272 the child’s needs. Developmental stages and academic and social expectations should also be
273 considered when determining the salience of cognitive fatigue post-TBI.³³

274 With respect to age at injury, most studies examined children who experienced a TBI in
275 later childhood and early adolescence (i.e., about 8 to 18 years old). Only one study examined
276 earlier childhood TBI with an average age of injury at 4.8 years old.³² Due to a limited number of
277 studies in each age group, differences in the presentation of cognitive fatigue based on age were

278 difficult to elucidate. Studies suggested that adolescence is a particularly important time to
279 evaluate and consider fatigue, due to the natural increase of fatigue during that developmental
280 period.^{3,33} In addition, early childhood presents with the highest rates of TBI across childhood
281 with major cognitive and developmental changes shortly after injury, although Suskauer et al.³²
282 did not find notable ratings of cognitive fatigue in their sample. This could be due to adults'
283 inability to readily observe “feeling mentally foggy” in children who cannot accurately convey
284 their symptoms;³² this possibility warrants additional investigation and development of measures
285 that could accurately capture cognitive fatigue in this age group.

286 When examining cognitive fatigue levels based on severity, most studies that included
287 multiple severities did not report cognitive fatigue levels separately for severity groups, limiting
288 comparisons. Generally, children with milder injuries were over-represented compared to those
289 with moderate or severe injuries, but tended to present with lower levels of cognitive
290 fatigue.^{3,24,27,28} This trend becomes less clear when considering children with persistent
291 symptoms following a mild injury, potentially appearing more similar to moderate-severe
292 injuries.^{25,26} Future investigations should consider assessing cognitive fatigue symptoms
293 longitudinally in children with chronic mild TBI to better our understanding of the course of
294 symptoms and to inform management strategies.

295 Studies included in this review reveal multiple trajectories for the presence of cognitive
296 fatigue throughout recovery. Studies conducted in the chronic stages of recovery, about two
297 years post-injury, indicated that cognitive fatigue can persist at clinically-significant levels for all
298 severities of TBI.^{30,31,33} Changes in cognitive fatigue over time were inconsistent when examined
299 multiple times in the acute stages of recovery. One study²⁸ found that cognitive fatigue at one
300 year post-TBI was significantly worse than at six months post-TBI. Three studies,^{24,26,27}

301 including a treatment efficacy study, saw improvement within five months of injury with and
302 without intervention. One study,²⁵ a treatment efficacy study, found no change, and one study³
303 observed an increase in clinically-significant fatigue scores for individuals with mild injuries, but
304 improvement for those with moderate-severe injuries. Multiple factors could be influencing
305 levels of cognitive fatigue including: developmental stages, social and academic expectations or
306 involvement, and personal or environmental characteristics.^{3,28}

307 *Associated Factors & Effects*

308 Post-injury functioning (e.g., sleep, physical, emotional, daily participation), brain
309 volume, age at onset, parental marriage status, and quality of life appear to be associated with
310 cognitive fatigue, but the directions of these relations remain unclear.^{3,31,33} Other studies
311 hypothesized or presented additional data that could support or warrant further investigation of
312 potential relations with other factors. Children with more significant levels of cognitive fatigue
313 would likely experience greater difficulties in academics and general functioning and lower
314 quality of life.^{27,28,30} Psycho-social and mental health needs and sleep disturbances could be
315 exacerbated by and/or contribute to acute levels of cognitive fatigue.^{24,29} These hypothesized
316 relations would not be unexpected, given literature indicating the general association of these
317 factors (i.e., academic and social functioning, quality of life, psycho-social and mental health,
318 sleep) with childhood TBI.³ Although evidence is limited, given the subjective nature of fatigue,
319 personal, injury, and post-injury functioning factors are essential to the understanding of
320 cognitive fatigue and to tailor management strategies to individual needs.

321 *Management Strategies*

322 Suggestions for assessment of cognitive fatigue in childhood TBI included: regular and
323 systematic screenings for symptoms into the chronic stages of recovery to track progress and
324 ongoing needs;^{24,27,29,30} multidimensional fatigue assessments with multiple reporters;^{3,28,29,33}
325 structural imaging of biomarkers to identify and predict cognitive fatigue;⁴¹ and self-report
326 assessments specific to the child's developmental stage (e.g., including more concrete language
327 regarding cognitive fatigue for younger children).³² From the two studies that evaluated
328 treatment efficacy, active physical rehabilitation did not appear to exacerbate general post-
329 concussion or fatigue symptoms following childhood TBI and could improve cognitive fatigue,
330 but additional investigation is needed.^{25,26} Many additional management strategies were
331 suggested in the included articles but did not include empirical evidence. Recommendations for
332 interventions included: treat both the cognitive fatigue symptoms and areas of functioning
333 associated with greater fatigue (e.g., physical skills);³ support functional improvements for
334 participation and quality of life through cognitive rehabilitation, behavior management, and
335 academic supports;^{27,29,30,33} and consider external demands based on age when designing
336 supports and implementing services.³² One study³⁰ reported that children who experienced
337 cognitive fatigue did not receive specialty supports at school, reinforcing the potential broader
338 impact of unmet need in children with TBI.^{42,43} Evidence-based management strategies for
339 cognitive fatigue after childhood TBI are limited and need additional attention to support
340 positive outcomes.

341 **Future Directions**

342 Future research in cognitive fatigue after childhood TBI should utilize more robust
343 methodologies such as pairing objective and subjective measures of cognitive fatigue, measuring
344 cognitive fatigue at multiple time points, and controlling for confounding factors. Additional

345 attention is needed on younger children with TBI including monitoring symptoms into later
346 childhood and adolescence. Research in the neuro-biological mechanisms underlying cognitive
347 fatigue and changes in fatigue with overall development could provide valuable information to
348 inform management. Translational research investigating the feasibility and efficacy of
349 assessment and treatment methods is essential to support long-term outcomes for children with
350 TBI. Establishing a program, such as TBI Model Systems, for children could support
351 longitudinal and clinical research to better inform management of cognitive fatigue after TBI.

352 **Limitations**

353 Although our literature search reached the point of duplication, some relevant studies
354 might have been missed. Overall, limited evidence was available on cognitive fatigue after
355 childhood TBI. Of the available research, few studies used control groups; therefore results of
356 the meta-analysis should be interpreted with caution. In addition, multiple studies published by
357 the same research group likely included overlapping samples, potentially decreasing the efficacy
358 of the meta analysis due to correlation amongst samples. Comparisons across studies were
359 difficult due to differences in methodology (e.g., time since injury, severity of injury, measures
360 of course of fatigue, parent vs child-self report), limiting the generalizability of results. Despite
361 these limitations, results of this study provide a comprehensive summary of the available
362 evidence on cognitive fatigue after childhood TBI and highlight areas in need of further
363 investigation.

364 **Conclusions & Clinical Implications**

365 Specific consideration of cognitive fatigue is necessary for effective assessment and
366 treatment after childhood TBI. Additional investigation is needed to better inform clinical

367 services. Based on the current literature, children with any severity of TBI should be
 368 continuously assessed for cognitive fatigue through the chronic stages of recovery, with special
 369 focus on children with associated factors including lower general post-injury functioning and
 370 lower quality of life. Treatment approaches should include direct management of cognitive
 371 fatigue and reduction of the secondary effects, such as academic and social engagement, to
 372 improve long-term quality of life in children with TBI.

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Table 1. Search Terms and Databases	
Search Terms (searched in each database)	<p>Cogn* and fatigue and child* and brain injury</p> <p>Cogn* and fatigue and pediatric and brain injury</p> <p>Cogn* and fatigue and child* and acquired brain injury</p> <p>Cogn* and fatigue and pediatric and acquired brain injury</p> <p>Cogn* and fatigue and child* and traumatic brain injury</p> <p>Cogn* and fatigue and pediatric and traumatic brain injury</p> <p>Mental and fatigue and child* and brain injury</p> <p>Mental and fatigue and pediatric and brain injury</p> <p>Mental and fatigue and child* and acquired brain injury</p> <p>Mental and fatigue and pediatric and acquired brain injury</p> <p>Mental and fatigue and child* and traumatic brain injury</p> <p>Mental and fatigue and pediatric and traumatic brain injury</p>
Databases	Pubmed, PSYCINFO, ERIC, ScienceDirect

Table 2. Inclusion and Exclusion Criteria	
Inclusion Criteria	Fatigue with some mention of cognitive and/or mental fatigue; child/pediatric/adolescents; brain injury
Exclusion Criteria	non-ABI; Non-accidental ABI or child abuse; blast injuries; meta analyses, systematic reviews, or non-peer reviewed papers; adults

Table 3. Interrater Agreement for Study Selection, Data Extraction, & Risk of Bias	
Review	Agreement Prior to Resolution (proportion of items review)
Title Screen	90.5% (915/1011)
Abstract Screen	84.98% (191/223)
Full Text Screen	94.2%

	(96/102)
Data Extraction	98.8% (543/550)
Risk of Bias Assessment	96.4% (53/55)

Table 4. Summary of Included Summaries					
Study (Author, Year Location)	Level of Evidence Study Design no studies using published controls received a rating higher than a III	TBI Group Characteristics (N severity; % male; Age at study participation (AS) (M (SD)); Time post injury (TPI) (M (SD))	Control Group Characteristics (N type; Age at survey (AS) (M (SD))	Reporter; Measure	Results for Cognitive Fatigue
Blinman, 2009 Pennsylvania, USA	III Prospective cohort without controls	63 mild; 69.8% male; AS: 14.1 (SD not reported) yrs; TPI: 2 days and 2-3 wks	n/a	Self-report; Symptom questionnaire of the ImPACT neurocognitive test battery (item: “feeling mentally foggy”) rated 0=no symptoms to 6= severe	41.4% (2.7 average rating) reported “feeling mentally foggy” at initial visit; 19.1% (1.6 average rating) reported at follow-up visits
Chan, 2018 British Columbia, Vancouver, Canada	I Single-site, parallel, open-label, randomized control	10 mild, PCS; 40% male; AS: 15.9 (1.66) yrs; TPI: 132 (52.0) days for initial assessment and post-treatment	9 mild, PCS; AS: 15.1 (1.42) yrs	Self-report; PedsQL MFS	Children who participated in a closely monitored, active rehabilitation treatment program did not experience more adverse effects than those receiving treatment as usual. No significant changes were observed between physical activity, symptom exacerbation, and clinical outcomes. Chan et al. did not perform statistical analysis of fatigue data, due to its exploratory nature in this study. The authors of this meta analysis conducted paired sample t- tests to compare pre- and post-treatment fatigue scores. No significant differences were found in the cognitive fatigue ratings for the active rehabilitation group. <i>Management Strategies:</i> Active rehabilitation, when closely monitored, could be beneficial for adolescents with persistent symptoms, such as cognitive fatigue, post-TBI.

Crichton, 2017 Melbourne, Australia	III Prospective with published controls	27 mild, 5 mod, 3 severe; 34 parent proxies; % male not reported; AS: not reported (age at injury: 13.3 (2.4) yrs (mild), 13.2 (2.6) yrs (mod/severe)); TPI: 7.3 (1.6) wks	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample ¹ and demographic differences could not be controlled	Self-report and parent-report; PedsQL MFS	Children and parents reported significantly greater levels of cognitive fatigue for the TBI group than the control sample.
Crichton, 2018a Australia and Canada	III Longitudinal prospective with published controls	59 mild, 36 mod/severe; 77% male; AS: not reported (age at injury: 9.9 (5.0) yrs); TPI: 6 and 12 mos	209, healthy; 259 parent proxies; 55.2% male; AS: 12.2 (4.0) yrs *controls are from a published healthy sample from a study of a different clinical sample ¹ and demographic differences could not be controlled	Parent-report; PedsQL MFS	Cognitive fatigue was significantly worse for children with moderate-severe TBI than mild TBI. Cognitive fatigue worsened significantly from 6 months to 12 months post-injury.
Crichton, 2018b Australia and Canada	III Prospective, non-randomized cohort without controls	52 mild, 27 mod/severe; 82.69% male (mild), 85.19% (male mod/severe); AS: 11.73 (4.42) yrs (mild), 9.72 (5.17) yrs (mod/severe); TPI: 6 and 12 months	n/a	Parent-report; PedsQL MFS	At 6 and 12 months post-TBI, 10% and 17%, of children with mild TBI and 27% and 19% of children with mod-severe TBI were rated in the clinical range for total fatigue, respectively (cognitive fatigue levels were not individually reported). Cognitive fatigue was the dimension with the worst ratings compared to sleep/rest and general fatigue. <i>Associated Effects:</i> General post-injury physical functioning significantly predicted cognitive fatigue 12 mos post-TBI (child factors and injury severity did not). Relationships with pre and post injury functioning might be bi-directional.
Gagnon, 2016 Montreal, Canada	III Clinical series without controls	10 sport-related concussion (slow to recover); 70% male; AS: 14-18 yrs; TPI: 7.9 wks for initial assessment and post-6 week treatment	n/a	Self-report; PedsQL MFS and PCSS (item: “feeling mentally foggy”)	Cognitive fatigue and all fatigue measures improved significantly post-treatment in an active rehabilitation program. “Feeling mentally foggy” was endorsed by 2 participants pre-treatment and no participants post-treatment. <i>Management Strategies:</i> Low-levels of active rehabilitation might be beneficial for children who are slow-to-recover from concussion. Active rehabilitation appears to support improvement

					across different symptoms, particularly fatigue dimensions.
Limond, 2009 United Kingdom	III Retrospective, cross-sectional study compared to published normative data	47 mild, moderate, and severe (hospitalized for at least 48 hrs); % male not reported; AS: 10.5 (3.6) yrs; TPI: 2.7 (1.2) yrs	105 healthy; 68.6% male; AS: 13.70 (9.47) yrs parent report: 157 healthy; 62.4% male; AS: 11.63 (8.59) years *controls are from a published normative sample ² and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI were reported to have significantly greater levels of fatigue for all injury severities compared to the control sample. Cognitive fatigue was the dimension with the worst rating compared to sleep/rest and general fatigue. Less than half (47%) of children with TBI had ratings of “normal” levels of cognitive fatigue, while 15% were considered “borderline” and 38% were considered “abnormal”, based on cut-off scores.
Macartney, 2018 Ontario, Canada	III Retrospective chart review without controls	136 mild; 45.6% male; AS: 15.4 (median); TPI: 5.4 (3-10.8) days for initial assessment then 28 days, 56 days, and 84 days *participants were discharged when symptoms returned to baseline therefore not all participants required assessment at all time points	n/a	Self-report; PCSI (item: “feeling in a fog”) rated 0 to 6 (higher scores= more severe)	The median rating of “feeling in a fog” was 2.9 (1.0-5.8); 1.4 (0.1-5.2); 1.0 (0.4-5.0), at 28; 56; and 84 days, respectively.
Ryan, 2016 Melbourne, Australia	III Prospective, non-randomized cohort with experimental controls and published controls	67 mild, 24 moderate, 12 severe; 67.96% male; AS: 10.54 (2.39) yrs (mild), 10.37 (2.58) yrs (moderate), 10.41 (3.10) yrs (severe); TPI: 24 months	Experimental: 34 healthy; 21% male; AS: 10.41 (2.76) *no demographic differences between groups Published: 157 healthy; 47.1% male; AS: 13.68 (2.17) yrs *controls are from a published normative sample ³ and demographic differences were not discussed	Parent-report; PedsQL MFS	Children with TBI had significantly greater levels of cognitive fatigue compared to the published control sample, but, when compared with experimental controls, no differences were observed. <i>Associated Effects:</i> Cognitive fatigue was significantly associated with smaller brain volumes. This finding could indicate disruptions of neural pathways cause an imbalance in effort-reward experiences which is subjectively reported as cognitive fatigue.

Suskauer, 2018 Maryland, USA	III Retrospective medical record review	28 mild/moderate/severe; 50% male; AS: not reported (age at injury: 4.8 yrs); TPI: 38 days	n/a	Parent-report; ACE Parent Questionnaire (item: “feeling mentally foggy”) classified as “ever experienced post-TBI” or “currently experiencing post-TBI”	No parents (0%) reported their child ever or was currently experiencing “feeling mentally foggy”.
van Markus-Doornbosch, 2016 Netherlands	III Prospective review and follow-up study without controls	58 mild, 11 moderate/severe; 46% male; AS: not reported (age at injury: 11 (6) yrs (median, IQR)); TPI: 24-30 mos	19 non-traumatic BI (NTBI); 11% male; AS: 14 (7); TPI: 24-30 mos	Parent-report and self-report; PedsQL MFS	Children with NTBI were parent- and self-reported to have significantly greater levels of cognitive fatigue compared to children with TBI. No significant difference was observed between parent and child self-report for cognitive fatigue. <i>Associated Effects:</i> Greater levels of cognitive fatigue was significantly associated with older age at onset (>11 yo); single parent household; greater limitations in activities and participation; and lower quality of life.

Table 5. Measures used to quantify levels of cognitive fatigue	
Measure	Description
PedsQL Multidimensional Fatigue Scale (PedsQL MFS) ³⁴	<ul style="list-style-type: none"> - parent and child self-report forms for ages 2-18 years old - 3 subscales (i.e., general fatigue, sleep, cognitive fatigue) are rated on a Likert scale (0= never a problem to 4= almost always a problem over the past month). Items are then reverse scored and transformed to a 0- to 100-point scale, such that higher scores indicate less fatigue.^a - shown good internal consistency reliability, test-retest reliability, and inter-observer reliability³⁴
Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) ⁴⁴	<ul style="list-style-type: none"> - FDA endorsed online tool for baseline and post-injury testing for ages 12-59 years old - assesses visual and verbal memory, reaction time, and processing speed through 8 tasks and includes a series of symptom-related questions rated on a 7-point Likert scale (0= no symptom, 6= severe symptom) - validity and reliability are unclear and highly dependent on time administered post-injury, area assessed, and other factors^{45,46}
Post-Concussion Symptom Scale (PCSS) ⁴⁷	<ul style="list-style-type: none"> - self-report for individuals over 11 years old - 22-items of symptom-related questions rated from 0 (not endorsed) to 6 (severe) - shown good test-retest reliability and internal consistency reliability and reliable to detect change over time⁴⁸
Post-Concussion Symptom Inventory (PCSI) ⁴⁹	<ul style="list-style-type: none"> - parent and child self-report for ages 5-18 years old - 27-items of symptom-related questions rated from 0-6 with higher scores representing more severe symptoms - shown good internal consistency⁵⁰
Acute Concussion Evaluation (ACE) ⁵¹	<ul style="list-style-type: none"> - parent and child self-report for ages 4 years old-adult - shown good internal consistency reliability, content validity, predictive validity, convergent/divergent validity, and construct validity⁵²
^a Chan et al. ²⁵ did not appear to calculate the scaled score in reporting results	

Table 6. Risk of Bias Summary						
Author, Year	Study Participation	Attrition	Outcome Measurement	Confound Measurement	Analysis	Assessment Summary
Blinman et al., 2009	no	party	no	no	no	+++
Chan et al., 2018	no	no	partly	partly	no	++
Crichton et al., 2017	no	no	partly	no	no	+++
Crichton, Anderson, et al., 2018	no	no	no	no	no	+++
Crichton, Oakley, et al., 2018	partly	no	partly	no	no	++
Gagnon et al., 2015	no	no	partly	yes	partly	+
Limond et al., 2009	no	no	partly	no	no	+
Macartney et al., 2018	no	no	partly	no	no	+
Ryan et al., 2016	no	no	yes	no	no	++
Suskauer et al., 2017	no	no	partly	partly	no	+
van Markus-Doornbosch et al., 2016	no	partly	partly	no	no	++

Note: no= no to little potential bias; partly= some bias; yes= likely bias