

## SUPPLEMENTARY MATERIALS

### **Efficacy and Acceptability of Blue-Wavelength Light Therapy for Common Behavioral Symptoms After Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**

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#### **List of abbreviations:**

BWLT = Blue-wavelength light therapy  
CI = Confidence interval  
IV = Inverse variance  
LED = Light emitting diode  
SMD = Standardized mean difference  
TBI = Traumatic brain injury

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**SUPPLEMENTARY TABLES**

**S1 Table: Search Strategies and Results (April 13, 2022)**

**A. PUBMED (n = 42)**

Search number	Query	Search Details	Results
5	#1 AND #2 AND #3 AND #4	(“brain injuries”[MeSH Terms] OR (“brain”[All Fields] AND “injuries”[All Fields]) OR “brain injuries”[All Fields] OR (“brain”[All Fields] AND “injury”[All Fields]) OR “brain injury”[All Fields] OR (“craniocerebral trauma”[MeSH Terms] OR (“craniocerebral”[All Fields] AND “trauma”[All Fields]) OR “craniocerebral trauma”[All Fields] OR (“head”[All Fields] AND “injury”[All Fields]) OR “head injury”[All Fields])) AND (“phototherapy”[MeSH Terms] OR “phototherapy”[All Fields] OR (“light”[All Fields] AND “therapy”[All Fields]) OR “light therapy”[All Fields] OR (“light”[MeSH Terms] OR “light”[All Fields] OR “lighted”[All Fields] OR “lights”[All Fields] OR “lighting”[MeSH Terms] OR “lighting”[All Fields] OR “lightings”[All Fields] OR “lightness”[All Fields] OR “lightnesses”[All Fields]) AND (“therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “treatments”[All Fields] OR “therapy”[MeSH Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “treatment s”[All Fields])) OR (“phototherapy”[MeSH Terms] OR “phototherapy”[All Fields] OR “phototherapies”[All Fields])) AND (“sleep”[MeSH Terms] OR “sleep”[All Fields] OR “sleeping”[All Fields] OR “sleeps”[All Fields] OR “sleep s”[All Fields] OR (“affect”[MeSH Terms] OR “affect”[All Fields] OR “mood”[All Fields]) OR “depress*”[All Fields] OR (“fatiguability”[All Fields] OR “fatiguable”[All Fields] OR “fatigue”[MeSH Terms] OR “fatigue”[All Fields] OR “fatigued”[All Fields] OR “fatigues”[All Fields] OR “fatiguing”[All Fields] OR “fatigueability”[All Fields]) OR (“exhausted”[All Fields] OR “exhausting”[All Fields] OR “exhaustion”[All Fields] OR “exhaustions”[All Fields] OR “exhaustive”[All Fields] OR “exhaustively”[All Fields]) OR (“fatigue”[MeSH Terms] OR “fatigue”[All Fields] OR “tiredness”[All Fields]) OR (“lethargy”[MeSH Terms] OR “lethargy”[All Fields])) AND “random*”[All Fields]	42

4	random*	“random*”[All Fields]	1,553,012
3	sleep OR mood OR depress* OR fatigue OR exhaustion OR tiredness OR lethargy	“sleep”[MeSH Terms] OR “sleep”[All Fields] OR “sleeping”[All Fields] OR “sleeps”[All Fields] OR “sleep s”[All Fields] OR “affect”[MeSH Terms] OR “affect”[All Fields] OR “mood”[All Fields] OR “depress*”[All Fields] OR “fatiguability”[All Fields] OR “fatiguable”[All Fields] OR “fatigue”[MeSH Terms] OR “fatigue”[All Fields] OR “fatigued”[All Fields] OR “fatigues”[All Fields] OR “fatiguing”[All Fields] OR “fatigueability”[All Fields] OR “exhausted”[All Fields] OR “exhausting”[All Fields] OR “exhaustion”[All Fields] OR “exhaustions”[All Fields] OR “exhaustive”[All Fields] OR “exhaustively”[All Fields] OR “fatigue”[MeSH Terms] OR “fatigue”[All Fields] OR “tiredness”[All Fields] OR “lethargy”[MeSH Terms] OR “lethargy”[All Fields]	1,755,558
2	(light therapy) OR (light treatment) OR phototherapy	“phototherapy”[MeSH Terms] OR “phototherapy”[All Fields] OR (“light”[All Fields] AND “therapy”[All Fields]) OR “light therapy”[All Fields] OR ((“light”[MeSH Terms] OR “light”[All Fields] OR “lighted”[All Fields] OR “lights”[All Fields] OR “lighting”[MeSH Terms] OR “lighting”[All Fields] OR “lightings”[All Fields] OR “lightness”[All Fields] OR “lightnesses”[All Fields]) AND (“therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “treatments”[All Fields] OR “therapy”[MeSH Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “treatment s”[All Fields])) OR (“phototherapy”[MeSH Terms] OR “phototherapy”[All Fields] OR “phototherapies”[All Fields])	280,760
1	(brain injury) OR (head injury)	“brain injuries”[MeSH Terms] OR (“brain”[All Fields] AND “injuries”[All Fields]) OR “brain injuries”[All Fields] OR (“brain”[All Fields] AND “injury”[All Fields]) OR “brain injury”[All Fields] OR (“craniocerebral trauma”[MeSH Terms] OR (“craniocerebral”[All Fields] AND “trauma”[All Fields]) OR “craniocerebral trauma”[All Fields] OR (“head”[All Fields] AND “injury”[All Fields]) OR “head injury”[All Fields])	289,727

**B. EMBASE (n = 93)**

No. Query	Results
	93
<b>#5</b> #1 AND #2 AND #3 AND #4	2,023,880
<b>#4</b> random*	1,597,244
<b>#3</b> sleep OR mood OR depress* OR fatigue OR exhaustion OR tiredness OR lethargy	244,757
<b>#2</b> light AND therapy OR (light AND treatment) OR phototherapy	592,766
<b>#1</b> (‘brain’/exp OR brain) AND (‘injury’/exp OR injury) OR ((‘head’/exp OR head) AND (‘injury’/exp OR injury))	

**C. CINAHL (n = 13)**

#	Query	Limiters/Expanders	Last Run Via	Results
S5	S1 AND S2 AND S3 AND S4	Expanders – Apply equivalent subjects Search modes – Find all my search terms	Interface – EBSCOhost Research Databases Search Screen – Advanced Search Database – CINAHL Complete	13
S4	random*	Expanders – Apply equivalent subjects Search modes – Find all my search terms	Interface – EBSCOhost Research Databases Search Screen – Advanced Search Database – CINAHL Complete	479,581
S3	sleep OR mood OR depress* OR fatigue OR exhaustion OR tiredness OR lethargy	Expanders – Apply equivalent subjects Search modes – Find all my search terms	Interface – EBSCOhost Research Databases Search Screen – Advanced Search Database – CINAHL Complete	359,732
S2	(light therapy) OR (light treatment) OR phototherapy	Expanders – Apply equivalent subjects Search modes – Find all my search terms	Interface – EBSCOhost Research Databases Search Screen – Advanced Search Database – CINAHL Complete	23,855
S1	(brain injury) OR (head injury)	Expanders – Apply equivalent subjects Search modes – Find all my search terms	Interface – EBSCOhost Research Databases Search Screen – Advanced Search Database – CINAHL Complete	62,706

**D. COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS (n = 75)**

sleep OR mood OR (depress\*) OR (fatigue OR exhaustion OR tiredness OR lethargy ):ti,ab,kw AND (brain injury) OR (head injury):ti,ab,kw AND (light therapy) OR (light treatment) OR (phototherapy):ti,ab,kw (Word variations have been searched)

**S2 Table: Excluded Trials with Reasons**

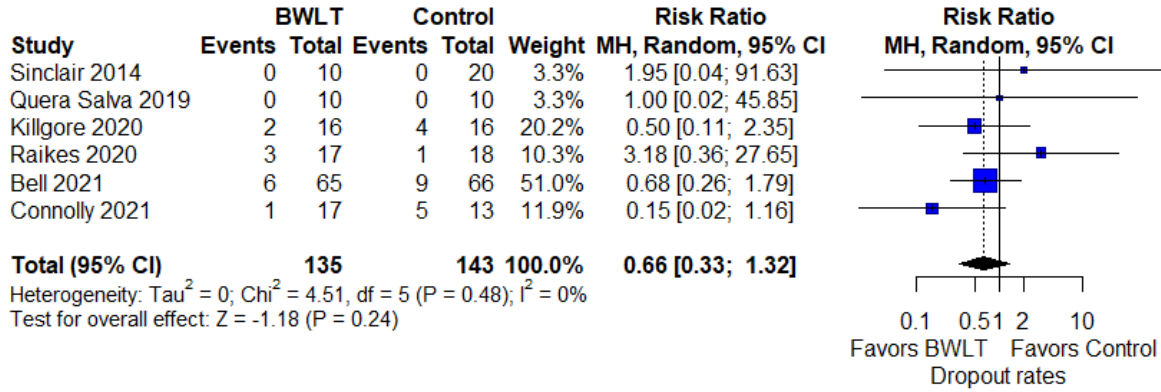
<b>Trials</b>	<b>Reason for exclusion</b>
<i>Participant mismatch</i>	
O'Brien, et al. 2017 <sup>1</sup>	13 participants with stroke and 3 participants with TBI
<i>Intervention mismatch</i>	
Bogdanova, et al. 2017 <sup>2</sup>	Transcranial LED helmets and intranasal LED applicators
NCT01725750 <sup>3</sup>	Full-spectrum bright light therapy
<i>Non-controlled trials</i>	
Elliott, et al. 2019 <sup>4</sup>	Single-arm intervention trial
<i>Trial protocols without results</i>	
NCT01175993 <sup>5</sup>	Effects of Rapid-Resisted Exercise and Bright Light Therapy on Ambulatory Adults With Traumatic Brain Injury
NCT03578003 <sup>6</sup>	Morning Bright Light to Improve Sleep Quality in Veterans
NCT03785600 <sup>7</sup>	Improving Sleep in Veterans With TBI
NCT03968874 <sup>8</sup>	Improving Sleep, Sleep-related Outcomes, and Biomarkers in Veterans

*References*

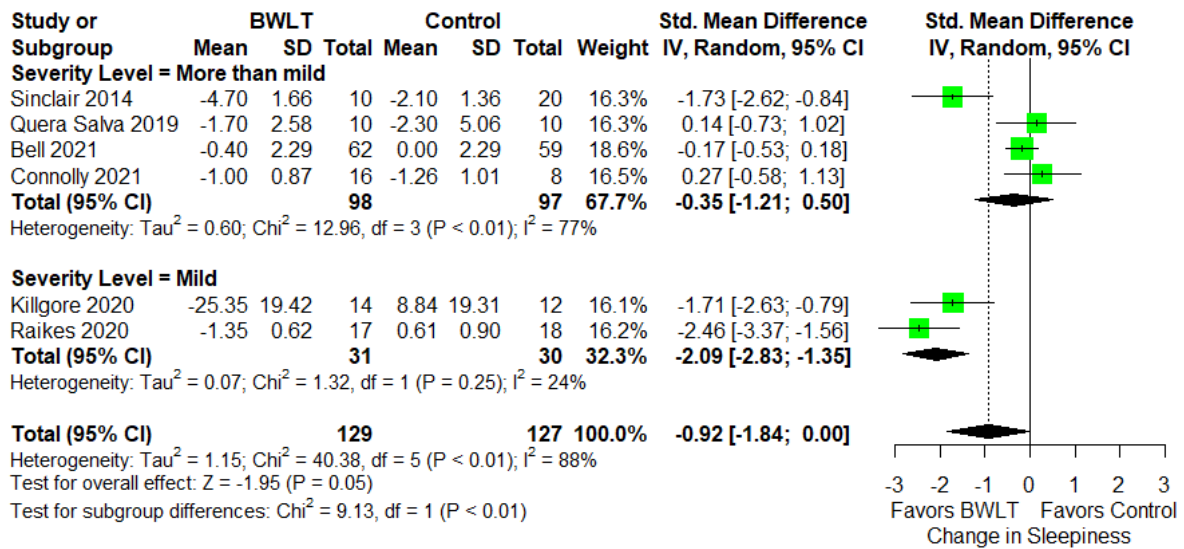
1. O'Brien, K. *et al.* Randomized trial of light therapy for cognitive function during inpatient rehabilitation for acquired brain injury. *Archives of Physical Medicine and Rehabilitation* **98**, e173–e174 (2017).
2. Bogdanova, Y. *et al.* Transcranial LED treatment for cognitive dysfunction and sleep in chronic TBI: Randomized controlled pilot trial. *Archives of Physical Medicine and Rehabilitation* **98**, e122–e123 (2017).
3. NCT01725750. Treatment of Post-Traumatic Brain Injury (Post-TBI) Fatigue With Light Therapy. <https://clinicaltrials.gov/show/NCT01725750> (2012).
4. Elliott, J. E., Balba, N. M., McBride, A. A., Thomas, S. V. & Lim, M. M. Morning bright light improves insomnia, mood, and pain in veterans with TBI and PTSD. *Sleep* **42**, A349 (2019).
5. NCT01175993. Effects of Rapid-Resisted Exercise and Bright Light Therapy on Ambulatory Adults With Traumatic Brain Injury. <https://clinicaltrials.gov/show/NCT01175993> (2010).
6. NCT03578003. Morning Bright Light to Improve Sleep Quality in Veterans. <https://clinicaltrials.gov/show/NCT03578003> (2018).
7. NCT03785600. Improving Sleep in Veterans With TBI. <https://clinicaltrials.gov/show/NCT03785600> (2018).
8. NCT03968874. Improving Sleep, Sleep-related Outcomes, and Biomarkers in Veterans. <https://clinicaltrials.gov/show/NCT03968874> (2019).

## SUPPLEMENTARY FIGURES

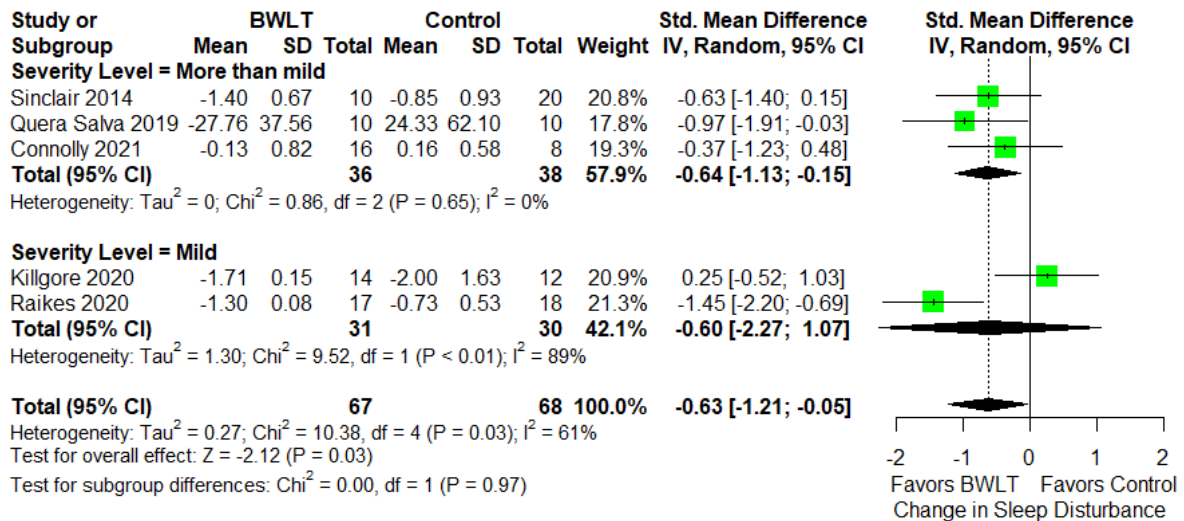
**S1 Fig.:** Forest plots comparing the dropout rates [blue-wavelength light therapy (BWLTL) vs. control interventions (amber, red, or no light therapy)].



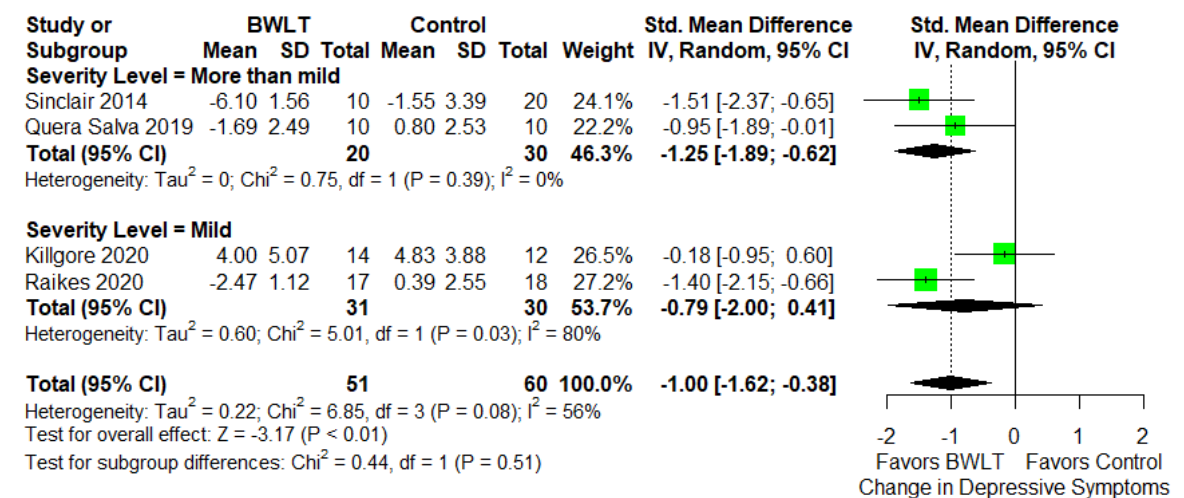
S2 Fig.: Subgroup analysis of five outcomes - based on the severity of traumatic brain injury.



A)



B)



C)



Study or Subgroup	BWL		Control		Weight	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Mean	SD		
<b>Severity Level = More than mild</b>						
Sinclair 2014	-1.30	0.38	10	-0.15	0.24	20 23.0%
Quera Salva 2019	-1.18	1.43	10	0.29	1.17	10 24.8%
Bell 2021	-10.20	15.70	62	-8.10	15.70	59 27.1%
Connolly 2021	-0.71	0.55	16	-0.12	0.59	8 25.1%
<b>Total (95% CI)</b>			<b>98</b>			<b>97 100.0%</b>

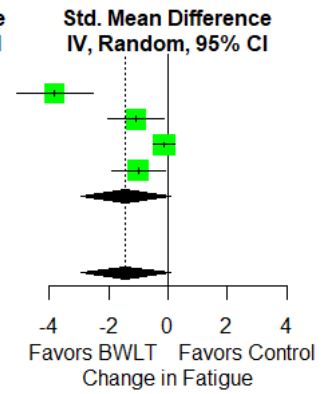
Heterogeneity:  $\tau^2 = 2.16$ ;  $\chi^2 = 32.46$ ,  $df = 3$  ( $P < 0.01$ );  $I^2 = 91\%$

**Total (95% CI)** 98 97 100.0% -1.44 [-2.95; 0.08]

Heterogeneity:  $\tau^2 = 2.16$ ;  $\chi^2 = 32.46$ ,  $df = 3$  ( $P < 0.01$ );  $I^2 = 91\%$

Test for overall effect:  $Z = -1.86$  ( $P = 0.06$ )

Test for subgroup differences:  $\chi^2 = 0.00$ ,  $df = 0$  ( $P = NA$ )



D)

Study or Subgroup	BWL		Control		Weight	Risk Ratio MH, Random, 95% CI
	Events	Total	Events	Total		
<b>Severity Level = More than mild</b>						
Sinclair 2014	0	10	0	20	3.3%	1.95 [0.04; 91.63]
Quera Salva 2019	0	10	0	10	3.3%	1.00 [0.02; 45.85]
Bell 2021	6	65	9	66	51.0%	0.68 [0.26; 1.79]
Connolly 2021	1	17	5	13	11.9%	0.15 [0.02; 1.16]
<b>Total (95% CI)</b>	<b>102</b>		<b>109</b>	<b>69.5%</b>		<b>0.56 [0.24; 1.30]</b>

Heterogeneity:  $\tau^2 = 0$ ;  $\chi^2 = 2.22$ ,  $df = 3$  ( $P = 0.53$ );  $I^2 = 0\%$

**Severity Level = Mild**

Killgore 2020 2 16 4 16 20.2% 0.50 [0.11; 2.35]

Raikes 2020 3 17 1 18 10.3% 3.18 [0.36; 27.65]

**Total (95% CI)** 33 34 30.5% 1.07 [0.18; 6.39]

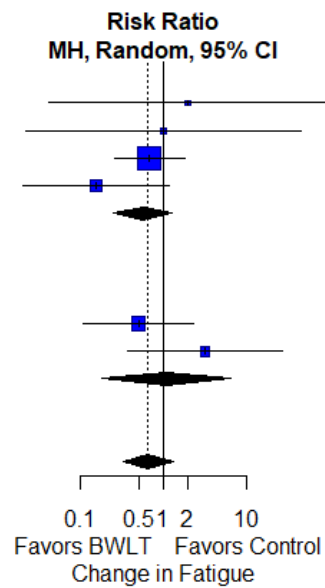
Heterogeneity:  $\tau^2 = 0.79$ ;  $\chi^2 = 1.85$ ,  $df = 1$  ( $P = 0.17$ );  $I^2 = 46\%$

**Total (95% CI)** 135 143 100.0% 0.66 [0.33; 1.32]

Heterogeneity:  $\tau^2 = 0$ ;  $\chi^2 = 4.51$ ,  $df = 5$  ( $P = 0.48$ );  $I^2 = 0\%$

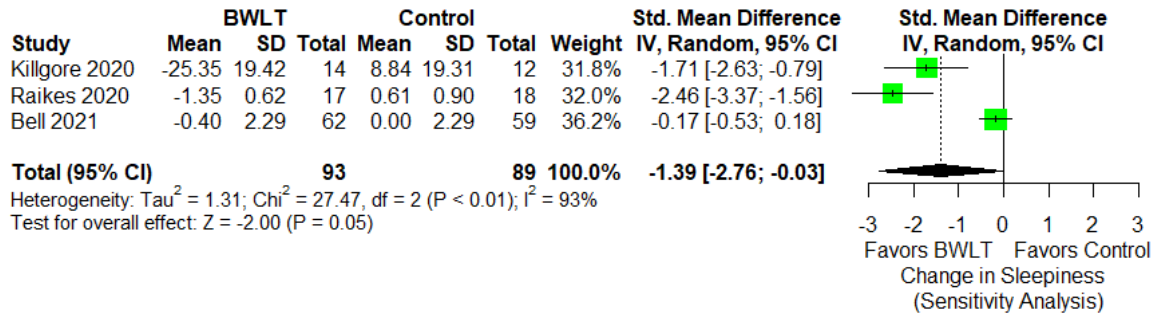
Test for overall effect:  $Z = -1.18$  ( $P = 0.24$ )

Test for subgroup differences:  $\chi^2 = 0.41$ ,  $df = 1$  ( $P = 0.52$ )

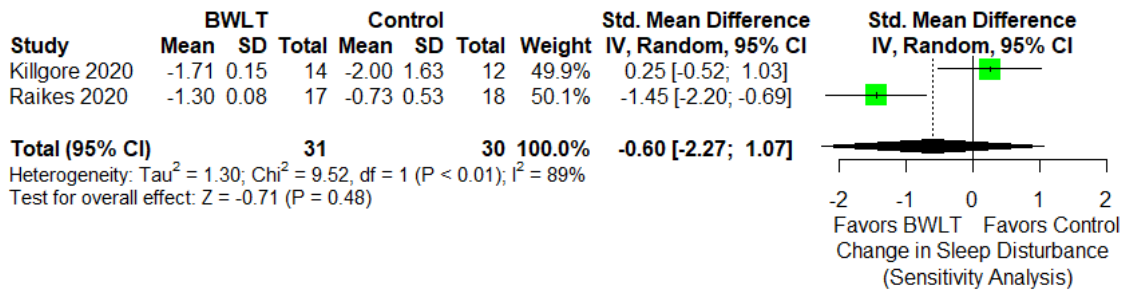


E)

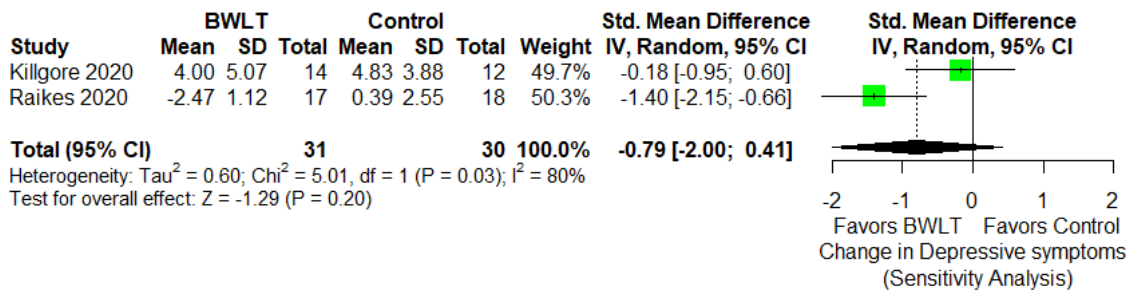
**S3 Fig.:** Sensitivity analysis of five outcomes – excluding three trials with a high-risk of bias.



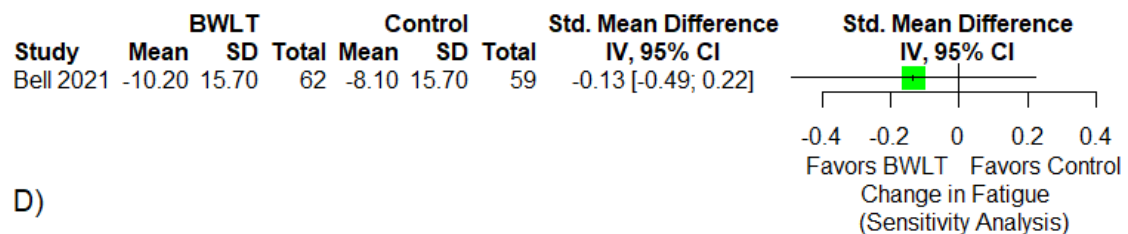
A)



B)



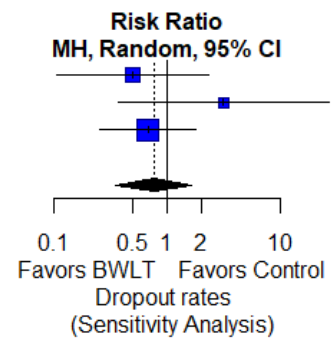
C)



D)

Study	BWL		Control		Weight	Risk Ratio
	Events	Total	Events	Total		MH, Random, 95% CI
Killgore 2020	2	16	4	16	24.7%	0.50 [0.11; 2.35]
Raikes 2020	3	17	1	18	12.7%	3.18 [0.36; 27.65]
Bell 2021	6	65	9	66	62.6%	0.68 [0.26; 1.79]
<b>Total (95% CI)</b>		<b>98</b>		<b>100</b>	<b>100.0%</b>	<b>0.76 [0.35; 1.65]</b>

Heterogeneity:  $\tau^2 < 0.01$ ;  $\text{Chi}^2 = 2.01$ ,  $\text{df} = 2$  ( $P = 0.37$ );  $I^2 = 1\%$   
 Test for overall effect:  $Z = -0.68$  ( $P = 0.49$ )



E)

**S4 Fig.:** Funnel plot showing the treatment-effect estimates of dropout rates.

