Supplemental Online Content

Leake, HB, Moseley, GL, Stanton, TR, Heathcote, LC, Pate, JW, Wewege, MA, Lee, H. Using mediation analysis to understand how treatments for paediatric pain work: A systematic review and recommendations for future research

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This supplementary material has been provided by the authors to give readers additional information about their work.

Date	Section	Original protocol	Revised protocol	Rationale
11/12/2019	Quality	Reviewers will	Reviewers will	Study published
	assessment	appraise	appraise	since date
		methodological	methodological	protocol was
		quality of studies	quality of studies	registered,
		using a critical	using a	provides a quality
		appraisal tool for	framework of	assessment tool
		mediation studies	recommendations	that is more
		developed by	adapted from Vo	relevant that the
		Mansell et al. (2013).	et al. (2020).	original.
22/04/2020	Grouping of	No description of	We will group	This decision
	studies for	grouping studies in	studies based on	reflects the
	narrative	data synthesis	duration of pain,	assumption that
	synthesis		either as acute	the mechanisms
			pain (less than 3	of treatment effect
			months duration)	may depend on
			or chronic pain	pain duration.
			(three months or	
			long duration)	
			(Merskey et al.,	
			1994).	

Supplementary Table S1 Deviations from pre-registered protocol

Supplementary Table S2. Complete search strategies for electronic databases.

MEDLINE (OvidSP)

1	mediat*.mp.
2	structural equation model?ing.mp.
3	(Baron and Kenny).mp.
4	product of coefficient.mp.
5	difference in coefficient.mp.
6	process of change.mp.
7	causal pathway.mp.
8	indirect effect.mp.
9	process variable.mp.
10	(process adj2 evaluation).mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp pain/
13	fibromyalgia/
14	juvenile idiopathic arthritis/
15	exp Complex Regional Pain Syndromes/
16	migraine disorders/
17	exp headache disorders/
18	Irritable Bowel Syndrome/
	(pain* or fibromyalgia* or crps or head?ache* or migraine* or cephalgi* or
19	stomach?ache* or tummy?ache* or abdominal?ache* or belly?ache* or "irritable
	bowel syndrome" or arthralgia or (juvenile adj2 arthrit*)).mp.
20	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp Child/
22	Adolescent/
23	Pediatrics/
24	(Child* or adolescen* or juvenil* or teen* or p?ediatric* or youth* or "young person*" or "young adult*").mp.
25	21 or 22 or 23 or 24
26	11 and 20 and 25
27	limit 26 to humans
28	limit 26 to animals
29	26 not 28
30	27 or 29

EMBASE (OvidSP)

1	mediat*.mp.
2	"structural equation model?ing".mp.
3	(Baron and Kenny).mp.
4	product of coefficient.mp.
5	difference in coefficient.mp.
6	process of change.mp.
7	causal pathway.mp.
8	indirect effect.mp.
9	process variable.mp.
10	(process adj2 evaluation).mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp pain/
13	fibromyalgia/
14	exp juvenile idiopathic arthritis/
15	exp complex regional pain syndrome/
16	exp migraine/
17	Headache/
18	irritable colon/
	(pain* or fibromyalgia* or crps or head?ache* or migraine* or cephalgi* or
19	stomach?ache* or tummy?ache* or abdominal?ache* or belly?ache* or "irritable
	bowel syndrome" or arthralgia or (juvenile adj2 arthrit*)).mp.
20	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	exp child/
22	exp adolescent/
23	pediatrics/
24	(Child* or adolescen* or juvenil* or teen* or p?ediatric* or youth* or "young
05	person [*] " or "young adult [*] ").mp.
25	21 or 22 or 23 or 24
26	11 and 20 and 25
27	limit 26 to humans
28	limit 26 to animals
29 20	26 not 28
30	27 or 29

PsycINFO (OvidSP)

5	
1	mediat*.mp.
2	structural equation model?ing.mp.
3	(Baron and Kenny).mp.
4	product of coefficient.mp.
5	difference in coefficient.mp.
6	process of change.mp.
7	causal pathway.mp.
8	indirect effect.mp.
9	process variable.mp.
10	(process adj2 evaluation).mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp pain/
13	fibromyalgia/
14	exp arthritis/
15	exp "complex regional pain syndrome (type i)"/
16	exp headache/
17	irritable bowel syndrome/
	(pain* or fibromyalgia* or crps or head?ache* or migraine* or cephalgi* or
18	stomach?ache* or tummy?ache* or abdominal?ache* or belly?ache* or "irritable
	bowel syndrome" or arthralgia or (juvenile adj2 arthrit*)).mp.
19	12 or 13 or 14 or 15 or 16 or 17 or 18
20	pediatrics/
21	(Child* or adolescen* or juvenil* or teen* or p?ediatric* or youth* or "young
	person*" or "young adult*").mp.
22	20 or 21
23	11 and 19 and 22
24	limit 23 to human
25	limit 23 to animal
26	23 not 25
27	24 or 26

Emcare (OvidSP)

1	mediat*.mp.
2	structural equation model?ing.mp.
3	(Baron and Kenny).mp.
4	product of coefficient.mp.
5	difference in coefficient.mp.
6	process of change.mp.
7	causal pathway.mp.
8	indirect effect.mp.
9	process variable.mp.
10	(process adj2 evaluation).mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp pain/
13	fibromyalgia/
14	exp juvenile rheumatoid arthritis/
15	exp complex regional pain syndrome/
16	irritable colon/
	(pain* or fibromyalgia* or crps or head?ache* or migraine* or cephalgi* or
17	stomach?ache* or tummy?ache* or abdominal?ache* or belly?ache* or "irritable
	bowel syndrome" or arthralgia or (juvenile adj2 arthrit*)).mp.
18	12 or 13 or 14 or 15 or 16 or 17
19	exp child/
20	exp adolescent/
21	pediatrics/
22	(Child* or adolescen* or juvenil* or teen* or p?ediatric* or youth* or "young person*" or "young adult*").mp.
23	19 or 20 or 21 or 22
24	11 and 18 and 23
25	limit 24 to human
26	limit 24 to animal
27	24 not 26
28	25 or 27

Cochrane Central Register of Controlled Trials (CENTRAL)

1	mediat*
2	structural equation modelling
3	structural equation modeling
4	Baron and Kenny
5	product of coefficient
6	difference in coefficient
7	process of change
8	casual pathway
9	indirect effect
10	process variable
11	process NEAR/2 evaluation
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 OR #10 OR #11
13	MeSH descriptor: [Pain] explode all trees
14	MeSH descriptor: [Fibromyalgia] explode all trees
15	MeSH descriptor: [Arthritis, Juvenile] explode all trees
16	MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
17	MeSH descriptor: [Headache Disorders] explode all trees
18	MeSH descriptor: [Irritable Bowel Syndrome] explode all trees
19	(pain* or fibromyalgia* or crps or head?ache* or migraine* or cephalgi* or
	stomach*ache* or tummy*ache* or abdominal*ache* or belly*ache* or
	"irritable bowel syndrome" or arthralgia or (juvenile NEAR/2 arthrit*))
20	#13 OR #14 OR #15 OR #16 OR #17 OR #19
21	MeSH descriptor: [Child] explode all trees
22	MeSH descriptor: [Adolescent] explode all trees
23	MeSH descriptor: [Pediatrics] explode all trees
24	(Child* or adolescen* or juvenil* or teen* or p*ediatric* or youth* or "young
	person" or "young adult")
25	#21 OR #22 OR #24
26	#12 AND #20 AND #25
	Limit to <i>Trials</i>

Supplementary Table S3. Reasons for exclusion of full text articles [*ordered alphabetically by first author*]. Full references are provided in eReferences.

Study	Reason for exclusion
Absoud et al. (2017)	Study population did not have pain at baseline
Allantaz et al. (2007)	Study design was irrelevant to this review
Allen et al. (1998)	No statistical test for mediation performed
Allison et al. (2016)	Participants not paediatric (3-18 years)
Altieri et al. (2020)	No statistical test for mediation performed
Anand et al. (2011)	Participants not paediatric (3-18 years)
Angst et al. (2012)	Participants not paediatric (3-18 years)
Atlas et al. (2014)	Participants not paediatric (3-18 years)
Baccini et al. (2017)	Participants not paediatric (3-18 years)
Baildam et al. (2013)	No statistical test for mediation performed
Barber et al. (1977)	Participants not paediatric (3-18 years)
Barlow et al. (2014)	Study design was irrelevant to this review
Beal et al. (2020)	Does not investigate the effects of an intervention
Bentley et al. (2005)	Participants not paediatric (3-18 years)
Blackwell et al. (2012)	Study design was irrelevant to this review
Bonnert et al. (2017)	Study design was irrelevant to this review
Bowers et al. (2016)	Study design was irrelevant to this review
Brennan et al. (1991)	Participants not paediatric (3-18 years)
Brown et al. (2019)	Study design was irrelevant to this review
Brown et al. (2012)	No statistical test for mediation performed
Brunner et al. (2012)	No statistical test for mediation performed
Bryskin et al. (2015)	No statistical test for mediation performed
Buenaver et al. (2012)	Study design was irrelevant to this review
Caixeta et al. (2020)	No statistical test for mediation performed
Cakar Turhan et al. (2015)	No statistical test for mediation performed
Cappucci et al. (2015)	Study design was irrelevant to this review
Castien et al. (2013)	Participants not paediatric (3-18 years)
Chan et al. (2017)	Study design was irrelevant to this review

Chou et al. (2011)	Participants not paediatric (3-18 years)
Christidis et al. (2015)	Participants not paediatric (3-18 years)
Clementi et al. (2020)	Does not compare two or more groups
Conti et al. (2020)	Participants not paediatric (3-18 years)
Corinaldesi et al. (2009)	Participants not paediatric (3-18 years)
Cunningham et al. (2020)	No statistical test for mediation performed
Dekker et al. (2016)	Study design was irrelevant to this review
DiVasta et al. (2015)	No statistical test for mediation performed
Du et al. (2018)	No statistical test for mediation performed
Dura-Ferrandis et al. (2017)	Participants not paediatric (3-18 years)
Essner (2013)	Study design was irrelevant to this review
Evans et al. (2014)	Study design was irrelevant to this review
Evans et al. (2011)	No statistical test for mediation performed
Evans et al. (2017)	Study design was irrelevant to this review
Evans et al. (2016)	Study design was irrelevant to this review
Evans et al. (2006)	Study design was irrelevant to this review
Fales et al. (2020)	No intervention
Ferrari et al. (2010)	Participants not paediatric (3-18 years)
Field et al. (2020)	No statistical test for mediation performed
Finch et al. (2009)	Participants not paediatric (3-18 years)
Fiorelli et al. (2010)	Participants not paediatric (3-18 years)
Fisher et al. (2016)	Does not compare two or more groups
Forsythe et al. (2011)	Study design was irrelevant to this review
Foxen-Craft (2017)	Study design was irrelevant to this review
Garland et al. (2012)	Participants not paediatric (3-18 years)
Gaultney (2020)	Study design was irrelevant to this review
Ghorbani et al. (2020)	Participants not paediatric (3-18 years)
Gillis (2002)	Study design was irrelevant to this review
Glenn et al. (2014)	Study design was irrelevant to this review
Gomez-Mancilla et al. (2001)	Participants not paediatric (3-18 years)

Gottschlich et al. (2011)	No statistical test for mediation performed
Grinsvall et al. (2015)	Study design was irrelevant to this review
Vos et al. (2017)	Participants not paediatric (3-18 years)
Harel et al. (2004)	No statistical test for mediation performed
Harper et al. (2012)	Study design was irrelevant to this review
Hashish et al. (1988)	Participants not paediatric (3-18 years)
He et al. (2015)	Study design was irrelevant to this review
Hechler et al. (2010)	No statistical test for mediation performed
Heeney et al. (2016a)	No statistical test for mediation performed
Heeney et al. (2018)	Study design was irrelevant to this review
Heeney et al. (2016b)	No statistical test for mediation performed
Herroeder et al. (2007)	Participants not paediatric (3-18 years)
Hildenbrand et al. (2020)	Independent variable in the mediation analysis was not
	the intervention
Hillgrove-Stuart et al. (2013)	Participants not paediatric (3-18 years)
Hilt (2009)	Study design was irrelevant to this review
Hind et al. (2017)	No statistical test for mediation performed
Hooke et al. (2018)	Does not compare two or more groups
Hoyeraal et al. (1978)	No statistical test for mediation performed
Ingelmo et al. (2007)	No statistical test for mediation performed
Janssens et al. (2014)	Does not compare two or more groups
Jones et al. (2018)	Study design was irrelevant to this review
Jonsbu et al. (2011)	Participants not paediatric (3-18 years)
Junghans-Rutelonis et al.	Independent variable in the mediation analysis was not
(2018)	the intervention
Khayat et al. (2015)	Participants not paediatric (3-18 years)
Kilkens et al. (2005)	Participants not paediatric (3-18 years)
Kobayashi et al. (2017)	Study design was irrelevant to this review
Kościelniak-Merak et al. (2020)	No statistical test for mediation performed
Lai et al. (2019)	No statistical test for mediation performed
	1

Langer et al. (2014)	Study design was irrelevant to this review
Langer et al. (2013)	Study design was irrelevant to this review
Lee et al. (2020)	No statistical test for mediation performed
Leeuw et al. (2008)	Participants not paediatric (3-18 years)
Levy et al. (2012)	Study design was irrelevant to this review
Lewis et al. (1996)	Study design was irrelevant to this review
Li et al. (2016)	Participants not paediatric (3-18 years)
Lim et al. (2019)	Study design was irrelevant to this review
Liossi et al. (2007)	Does not compare two or more groups
Lohsiriwat et al. (2004)	Participants not paediatric (3-18 years)
Love et al. (2019)	Study design was irrelevant to this review
Lowen et al. (2013)	Participants not paediatric (3-18 years)
Lu et al. (2013)	Study design was irrelevant to this review
Luciano et al. (2014)	Participants not paediatric (3-18 years)
Lustig et al. (1996)	Study design was irrelevant to this review
Maddison et al. (2006)	Participants not paediatric (3-18 years)
Malattia et al. (2020)	No statistical test for mediation performed
McGarrigle et al. (2018)	Study design was irrelevant to this review
Meier et al. (2009)	No statistical test for mediation performed
Melzack et al. (1980a)	Participants not paediatric (3-18 years)
Melzack et al. (1980b)	Participants not paediatric (3-18 years)
Miller et al. (2017)	Study design was irrelevant to this review
Milling et al. (2006)	Participants not paediatric (3-18 years)
Milling et al. (2007)	Participants not paediatric (3-18 years)
Mohammed et al. (2010)	Study design was irrelevant to this review
Moore et al. (1992)	Participants not paediatric (3-18 years)
Mulroy et al. (2011)	No statistical test for mediation performed
Neville et al. (2020)	No intervention
Nickel et al. (2012)	Participants not paediatric (3-18 years)
Niedermann et al. (2011)	Participants not paediatric (3-18 years)

Noel et al. (2015)	Does not compare two or more groups
Noel et al. (2018)	Study design was irrelevant to this review
Palermo et al. (2018)	Study design was irrelevant to this review
Palstam et al. (2016)	Participants not paediatric (3-18 years)
Pavlova et al. (2017)	Study design was irrelevant to this review
Pavlova et al. (2018)	Study design was irrelevant to this review
Pavlova et al. (2020)	Does not investigate the effects of an intervention
Peatfield et al. (1983)	Participants not paediatric (3-18 years)
Petter et al. (2014)	Independent variable in the mediation analysis was not
	the intervention
Peugh et al. (2017)	Study design was irrelevant to this review
Poppert Cordts et al. (2019)	Study design was irrelevant to this review
Posner (1999)	Study design was irrelevant to this review
Pringsheim et al. (2002)	Participants not paediatric (3-18 years)
Puzino et al. (2018)	Study design was irrelevant to this review
Quispe-Cabanillas et al. (2012)	Participants not paediatric (3-18 years)
Randall et al. (2020)	Does not compare two or more groups
Reddy et al. (2020)	No statistical test for mediation performed
Reed-Knight et al. (2018)	Study design was irrelevant to this review
Reid (2003)	Study design was irrelevant to this review
Reme et al. (2011)	Participants not paediatric (3-18 years)
Riggenbach et al. (2020)	Study design was irrelevant to this review
Robinson et al. (2013)	Study design was irrelevant to this review
Rolli Salathe et al. (2020)	Does not investigate the effects of an intervention
Ruperte et al. (2011)	No statistical test for mediation performed
Ruperto et al. (2013)	No statistical test for mediation performed
Saxe et al. (2006)	Does not compare two or more groups
Schoenen et al. (2013)	Participants not paediatric (3-18 years)
Schreiber et al. (2001)	Participants not paediatric (3-18 years)
Schurman et al. (2012)	Study design was irrelevant to this review

Shi et al. (2011)Participants not paediatric (3-18 years)Shi et al. (2015)Participants not paediatric (3-18 years)Sieberg et al. (2011)Study design was irrelevant to this reviewSimister et al. (2018)Participants not paediatric (3-18 years)Slaman et al. (2015)Participants not paediatric (3-18 years)Spinhoven et al. (2004)Participants not paediatric (3-18 years)Stratelak et al. (1996)Participants not paediatric (3-18 years)Taheri et al. (2016)Study design was irrelevant to this reviewTarnowski et al. (1987)Study design was irrelevant to this reviewter Kuile et al. (1996)Participants not paediatric (3-18 years)Thieme et al. (2015)Participants not paediatric (3-18 years)Tran et al. (2015)Participants not paediatric (3-18 years)Tran et al. (2015)Study design was irrelevant to this reviewTran (2015)Study design was irrelevant to this reviewTran (2015)Study design was irrelevant to this reviewTroullos et al. (1990)Participants not paediatric (3-18 years)Tsao et al. (2006a)Study design was irrelevant to this reviewTourner et al. (2013)No statistical test for mediation performedvan Tilburg et al. (2017)Study design was irrelevant to this reviewVanDyck et al. (1991)Participants not paediatric (3-18 years)Vari et al. (2013)No statistical test for mediation performedvan Tilburg et al. (2017)Study design was irrelevant to this reviewVari et al. (2018)Study design was irrelevant to this reviewVari et	Shah et al. (2002)	No statistical test for mediation performed
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Wand at al (2012) Dertisinante not mandiatria (2.10	Walters et al. (1999)	Study design was irrelevant to this review
Participants not paediatric (3-18 years)	Wand et al. (2013)	Participants not paediatric (3-18 years)

Wong et al. (2015)	Participants not paediatric (3-18 years)
Yang et al. (2017)	Participants not paediatric (3-18 years)
Yang et al. (2020)	Language: not reported in English, Portuguese, Spanish or German
Zeidan et al. (2016)	Participants not paediatric (3-18 years)
Ziadni et al. (2020)	Study design was irrelevant to this review
Zinman et al. (2005)	Participants not paediatric (3-18 years)

Study	Intervention vs Comparator	Path <i>a</i> (I→M)	Mediator	Path b (M \rightarrow O)	Outcome (Parent-Reported)	Indirect Effect
Lalouni et	Exposure-based internet-CBT vs	NR	GI-specific avoidance behaviour	NR	GI symptoms	+
al. (2020)	treatment as usual	NR	GI-specific anxiety	NR	GI symptoms	+
		+	Perceived pain threat	+	GI symptom severity at 3 months	_
		+	Perceived pain threat	+	GI symptom severity at 6 months	_
		+	Perceived pain threat	+	GI symptom severity at 12 months	+
		+	Perceived pain threat	+	Pain intensity at 3 months	+
		+	Perceived pain threat	+	Pain intensity at 6 months	+
		+	Perceived pain threat	_	Pain intensity at 12 months	+
		+	Solicitousness	_	GI symptom severity at 3 months	_
		+	Solicitousness	_	GI symptom severity at 6 months	_
Levy et	CL CDT and a data of an	+	Solicitousness	_	GI symptom severity at 12 months	_
al. (2014)	SLCBT vs education	+	Solicitousness	_	Pain intensity at 3 months	_
		+	Solicitousness	_	Pain intensity at 6 months	_
		+	Solicitousness	_	Pain intensity at 12 months	_
		+	Pain catastrophizing	_	GI symptom severity at 3 months	_
		+	Pain catastrophizing	_	GI symptom severity at 6 months	_
		+	Pain catastrophizing	_	GI symptom severity at 12 months	_
		+	Pain catastrophizing	_	Pain intensity at 3 months	_
		+	Pain catastrophizing	+	Pain intensity at 6 months	_
		+	Pain catastrophizing	_	Pain intensity at 12 months	_

Supplementary Table S4. Summary of mediation analyses using parent-reported outcomes.

Statistical significance is defined as 95% confidence intervals that do not contain zero. (+): statistically significant association; (–): statistically non-significant association; CBT, Cognitive Behavioral Therapy; I, Intervention; GI, Gastro-Intestinal; M, Mediator; O, Outcome; SLCBT, Social-Learning Cognitive Behavioral Therapy.

Supplementary	Table S5. Results	of mediation	analyses u	sing parent-	reported outcome	5.
			-			

Study	Intervention vs Comparator → Mediator (Measure) → Outcome (Measure) Parent-Reported	Path a Point Estimate (Error)	Path b Point Estimate (Error)	Direct Effect (c') Point Estimate (Error)	Indirect Effect (ab) Point Estimate (Error)	Total effect (c) Point Estimate (Error)	Proportion Mediated
Lalouni	Exposure-based internet-CBT vs treatment as usual → GI-avoidance (BRQ-C) → Health-related quality of life (PedQL-GI)	-1.99 (error NR)	-0.72 (error NR)	0.36 (error NR)	1.43 (95% CI=0.42, 3.23)	1.71 (error NR)	79.8%
et al. (2021)	Exposure-based internet-CBT vs treatment as usual → GI-anxiety (VSI- C)→ Health-related quality of life (PedQL-GI)	-1.39 (error NR)	-1.13 (error NR)	0.43 (error NR)	1.58 (95% CI=0.43, 3.62)	1.71 (error NR)	78.6%
	SLCBT vs education \rightarrow Parent threat (PBQ) \rightarrow GI symptom severity (CSI) <i>at</i> 3 months		0.32 (SE=0.09; 95% CI=0.14, 0.50)	0.01 (SE=0.06; 95% CI= -0.11, 0.13)	-0.06 (SE=0.02; 95% CI=- 0.09, 0.02)	NR	NR
	SLCBT vs education \rightarrow Parent threat (PBQ) \rightarrow GI symptom severity (CSI) <i>at</i> 6 months	95% CI=-0.24, -	95% CI=0.16,	-0.01 (SE=0.05; 95% CI=-0.11, 0.09)	-0.05 (SE=0.02; 95% CI=- 0.08, 0.02)	NR	NR
	SLCBT vs education \rightarrow Parent threat (PBQ) \rightarrow GI symptom severity (CSI) <i>at</i> 12 months	-0.17 (SE=0.03; 95% CI=-0.23, - 0.11)	0.33 (SE=0.09; 95% CI=0.15, 0.51)	-0.001 (SE=0.06; 95% CI=-0.12, 0.12	-0.06 (SE=0.02; 95% CI=- 0.09, -0.02)	NR	NR
Levy et	SLCBT vs education \rightarrow Parent threat (PBQ) \rightarrow Pain intensity (FPS-R) at 3 months	-0.18 (SE=0.03; 95% CI=-0.24, - 0.12)		-0.02 (SE=0.19; 95% CI=-0.39, 0.35)	-0.23 (SE=0.06; 95% CI=- 0.35, -0.11)	NR	NR
al. (2014)	SLCBT vs education \rightarrow Parent threat (PBQ) \rightarrow Pain intensity (FPS-R) <i>at 6</i> <i>months</i>	-0.18 (SE=0.03; 95% CI=-0.24, - 0.12)		-0.15 (SE=0.20; 95% CI=-0.54, 0.24)	-0.16 (SE=0.06; 95% CI=- 0.27, -0.04)	NR	NR
	SLCBT vs education \rightarrow Parent threat (PBQ) \rightarrow Pain intensity (FPS-R) <i>at 12</i> <i>months</i>	-0.18 (SE=0.03; 95% CI=-0.24, - 0.12)		0.24 (SE=0.18; 95% CI=-0.11, 0.59)	-0.16 (SE=0.05; 95% CI=- 0.26, -0.06)	NR	NR
	SLCBT vs education \rightarrow Parent solicitousness (ARCS) \rightarrow GI symptom severity (CSI) at 3 months	-0.21 (SE=0.03; 95% CI=-0.27, - 0.15)		0.01 (SE=0.06; 95% CI=-0.11, 0.13)	-0.02 (SE=0.02; 95% CI=- 0.06, 0.02)	NR	NR
	SLCBT vs education \rightarrow Parent solicitousness (ARCS) \rightarrow GI symptom severity (CSI) at 6 months		•	-0.01 (SE=0.05; 95% CI=-0.11, 0.09)	-0.0004 (SE=0.02; 95% CI=-0.04, 0.04)	NR	NR

SLCBT vs education \rightarrow Parent	-0.21 (0.03; 95%	0.14 (SE=0.11;	-0.001 (SE=0.06;	-0.03 (SE=0.02; 95% CI=-		
solicitousness (ARCS) \rightarrow GI symptom	CI=-0.27, -0.15)		, , , , , , , , , , , , , , , , , , , ,	0.08, 0.02)	NR	NR
severity (CSI) at 12 months	. ,	0.36)	0.12)	, ,		
SLCBT vs education \rightarrow Parent	-0.21 (SE=0.03;	· · ·	-0.02 (SE=0.19;	-0.07 (SE=0.07; 95% CI=-		
solicitousness (ARCS) \rightarrow Pain	95% CI=-0.27, -	95% CI=-0.29,	95% CI=-0.39,	0.20, 0.06)	NR	NR
intensity (FPS-R) at 3 months	0.15)	0.97)	0.35)	0.20, 0.00)		
SLCBT vs education \rightarrow Parent	-0.21 (SE=0.03;	-0.27 (SE=0.34;	-0.15 (SE=0.20;	0.06 (SE=0.07; 95% CI=-		
solicitousness (ARCS) \rightarrow Pain	95% CI=-0.27, -	95% CI=-0.94,	95% CI=-0.54,	0.08, 0.20)	NR	NR
intensity (FPS-R) at 6 months	0.15)	0.40)	0.24)	0.08, 0.20)		
SLCBT vs education \rightarrow Parent	-0.20 (SE=0.03;	0.32 (SE=0.30;	0.24 (SE=0.18;			
solicitousness (ARCS) \rightarrow Pain	95% CI=-0.26, -	95% CI=-0.27,	95% CI=-0.11,	-0.06 (SE=0.06; 95% CI=-	NR	NR
intensity (FPS-R) at 12 months	0.14)	0.91)	0.59)	0.18, 0.06)		
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.08 (SE=0.07;	0.01 (SE=0.06;	0.01 (CE. 0.01.050/ CI		
catastrophizing (PRI) \rightarrow GI symptom	95% CI=-0.22, -	95% CI=-0.06,	95% CI= -0.11,	-0.01 (SE=0.01; 95% CI=-	NR	NR
severity (CSI) at 3 months	0.02)	0.22)	0.13)	0.03, 0.01)		
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	-0.01 (SE=0.06;	-0.01 (SE=0.05;	0.001 (CE. 0.01.0E0/ CI		
catastrophizing (PRI) \rightarrow GI symptom	95% CI=-0.22, -	95% CI=-0.13,	95% CI=-0.11,	0.001 (SE=0.01; 95% CI=-	NR	NR
severity (CSI) at 6 months	0.02)	0.11)	0.09)	0.01, 0.02)		
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.03 (SE=0.07;	-0.001 (SE=0.06;	0.004 (CE. 0.01.050)		
catastrophizing (PRI) \rightarrow GI symptom	95% CI=-0.22, -	95% CI=-0.11,	95% CI=-0.12,	-0.004 (SE=0.01; 95%	NR	NR
severity (CSI) at 12 months	0.02)	0.17)	0.12)	CI=-0.02, 0.01)		
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.37 (SE=0.21;	-0.02 (SE=0.19;	0.04/05 0.02 050/ 07		
catastrophizing (PRI) \rightarrow Pain intensity	95% CI=-0.22, -	95% CI=-0.04,	95% CI=-0.39,	-0.04 (SE=0.03; 95% CI=-	NR	NR
(FPS-R) at 3 months	0.02)	0.78)	0.35)	0.11, 0.02)		
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.03 (SE=0.22;	-0.15 (SE=0.20;	0.0004 (CE. 0.02, 050)		
catastrophizing (PRI) \rightarrow Pain intensity	95% CI=-0.22, -	95% CI=-0.40,	95% CI=-0.54,	-0.0004 (SE=0.03, 95%	NR	NR
(FPS-R) at 6 months	0.02)	0.46)	0.24)	CI=-0.06, 0.05)		
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.25 (SE=0.20;	0.24 (SE=0.18;			
catastrophizing (PRI) \rightarrow Pain intensity	95% CI=-0.22, -	95% CI=-0.14,	95% CI=-0.11,	-0.03 (SE=0.03; 95% CI=-	NR	NR
(FPS-R) at 12 months	0.02)	0.64)	0.59)	0.08, 0.02)		

1. PLANNING	Olbrecht et al.	Bonnert et al.	Lalouni et al.	Levy et al. (2014)	Kashikar-Zuck et	Wicksell et al.
	(2018)	(2018)	(2020)		al. (2013)	(2011)
1.1 Was the mediation analyses planned a priori in the trial protocol?	No	Yes (NCT02306369)	Yes (NCT02873078)	No	No	No
1.2 Was the choice of mediators based on clinical rationale underlying the mechanisms through which the treatment affects the outcome, or based on independent data?	Yes, based on clinical rationale.	Yes, based on clinical rationale and independent data.				
1.3 ^a Was there a plan to collect pre- and post-randomization confounders of the mediator- mediator and mediator-outcome relationships? Could the authors foresee if any of these confounders were treatment- induced (e.g. collected after the onset of treatment, and therefore possibly affected by treatment)?	Yes, there was a plan to collect data on variables used to calculate propensity scores, to use for all linear models, thus adjusting for exposure-mediator, mediator-outcome and exposure- outcome relationships. No discussion of potential that confounders were treatment-induced.	No	No	No	No	No
1.4 Were the mediators measured prior to the outcome, and	Yes, the mediators were measured prior	Yes, the mediators were measured prior	Yes, the mediators were measured prior	Yes, the mediators were measured prior	Yes, the mediators were measured prior	Yes, the mediators were measured prior
preferably repeatedly, to assure	to the outcome.	to the outcome.	to the outcome.	to the outcome.	to the outcome.	to the outcome.

Supplementary	Table S6. Justifications	of study quality assessme	ent.

the causal interpretation of the findings?	No, the mediator was not measured at	Yes, the mediators were measured at	Yes, the mediators were measured at	No, the mediator was not measured at	No, the mediator was not measured at	No, the mediator was not measured at
	repeated time points	repeated time points	repeated time points	repeated time points	repeated time points.	multiple time points.
1.5 Was a causal diagram reported, underlying the causal relationship of the treatment, mediator(s) and outcome?	Yes	Yes	Yes	Yes	No	No
1.6 Was the sample size for the mediation analysis estimated?	No	No	No	No	No	No
1.7 Was the conduct of a mediation analysis dependent on	Unsure	Unsure	Unsure	Unsure	Unsure	Unsure
whether a statistically significant intention-to-treat treatment effect was found?	There was a difference in outcome between groups, but it is not clear this was known prior to the analysis (primary data), and there is no mention that the analysis was <i>dependent</i> on a treatment effect being present.	It is stated that a treatment effect in the primary RCT was found. It is not stated that mediation analysis was <i>dependent</i> on treatment effect.	It is stated that a treatment effect in the primary RCT was found. It is not stated that mediation analysis was <i>dependent</i> on treatment effect. Mediation analysis was pre-planned in the trial protocol with no stipulation of the necessity of a treatment effect to proceed with mediation analysis.	It is not explicitly stated that mediation analysis was <i>dependent</i> on treatment effect. However, it is stated that in the primary RCT that a significant treatment effect is present, and an analysis is conducted demonstrating that the putative mediators all had a moderate-large effect size change from baseline to post-treatment compared between	It is not explicitly stated that conduct of mediation was <i>dependent</i> on treatment effect, however outcomes (depression, disability) were chosen for mediation analysis because these were significant in the primary RCT, and others (e.g., pain intensity) were not.	It is stated that a treatment effect was found. It is not stated that the conduct of the mediation was <i>dependent</i> on a treatment effect being present.

2.1 Was multiple imputation (or other valid approaches) used to	Missing data handled using list-	Missing data was assumed missing at	Missing data was handled using full	Missing data was handled using full	No missing data.	No imputation was used.
handle missing data? If a complete-case analysis was used, did they adjust for baseline covariates that were differentially distributed between responders and non-responders? Was a	wise deletion Yes, a complete-case analysis was conducted. Yes, there was	random and handled using full information maximum likelihood.	information maximum likelihood. No, a complete-case analysis was not	information maximum likelihood. No, a complete-case analysis was not	Yes, a complete-case analysis was conducted. No adjustment for baseline covariates as no significant	Unclear if a complete-case analysis was conducted. No reporting of
sensitivity analysis conducted to assess the impact of different approaches on the findings?	adjustment for baseline covariates using propensity scores.	No, a complete-case analysis was not used.	used. No sensitivity analysis.	used. No sensitivity analysis.	differences between groups for measured variables.	adjusting for baseline covariates. No sensitivity
	No sensitivity analysis.	No sensitivity analysis.			n/a – sensitivity analysis.	analysis.
2.2 Does the study report separate analyses for separate mediators?	n/a – one mediator tested	Yes	Yes	Yes	Yes	Yes
2.3 Does the study use an appropriate framework for analysis?	Yes, product of coefficient approach justified assuming both models for the outcome and mediator are linear with no interaction.	Yes, product of coefficient approach justified assuming both models for the outcome and mediator are linear with no interaction.	Yes, product of coefficient approach justified assuming both models for the outcome and mediator are linear with no interaction.	Yes, structural equation modelling approach justified assuming both models for the outcome and mediator are linear with no interaction.	Yes, product of coefficient approach justified assuming both models for the outcome and mediator are linear with no interaction.	Yes, product of coefficient approach justified assuming both models for the outcome and mediator are linear with no interaction.
2.4 Does the study assess potential interaction(s) between treatment and confounding factors, treatment and mediator,	No assessment of potential interaction(s)	No assessment of potential interaction(s).	Yes, the study assesses potential interactions between the treatment and	No assessment of potential interaction(s)	No assessment of potential interaction(s)	No assessment of potential interaction(s)
mediator and mediator in the mediator and outcome models? Does the study evaluate the goodness-of-fit of each model?	No goodness-of-fit model.	No goodness-of-fit model.	mediator. No goodness-of-fit model.	No goodness-of-fit model.	No goodness-of-fit model.	No goodness-of-fit model.

2.5ª Does the study adjust for mediator-mediator and mediator- outcome confounders?	Mediator-mediator confounders – n/a Yes, adjusts for both exposure-mediator and mediator- outcome confounders. The study adjusts for baseline covariates by using propensity scores in all analyses.	No adjustment for mediator-mediator confounders Yes, adjusted for mediator-outcome confounders by adjusting for reciprocal mediators in the multiple mediator model.	No adjustment for mediator-mediator or mediator-outcome confounders.	No adjustment for mediator-mediator confounders Yes, adjusted for mediator-outcome confounders by adjusting for reciprocal mediators in the multiple mediator model.	No adjustment for mediator-mediator or mediator-outcome confounders.	No adjustment for mediator-mediator or mediator-outcome confounders.
2.6 Does the study perform sensitivity analysis to assess sensitivity of the results to (1) the assumption of no measured mediator-mediator or mediator- outcome confounders, (2) potential measurement errors of the mediators?	No sensitivity analyses	No sensitivity analyses	No sensitivity analyses	No sensitivity analyses	No sensitivity analyses	No sensitivity analyses
2.7 Does the study use apt strategies when some of the mediator-mediator or mediator- outcome confounders are potentially affected by the treatment (e.g., by considering confounders as mediators themselves)?	No	No	No	No	No	No
3. REPORTING						
3.1 Does the study report the approaches used for mediation and provide a causal diagram that underlies the analysis?	Yes, the approach for mediation is described, and a causal diagram is provided.	Yes, the approach for mediation is described, and a causal diagram is provided.	Yes, the approach for mediation is described, and a causal diagram is provided.	Yes, the approach for mediation is described, and a causal diagram is provided.	Yes, the approach for mediation is described. No, a causal diagram is not provided.	Yes, the approach for mediation is described. No, a causal diagram is not provided.

3.2 Does the study report the sample size calculation, the actual sample size of the mediation analysis and how the missing	No sample size calculation provided.	No sample size calculation provided.	No sample size calculation provided.	No sample size calculation provided.	No sample size calculation provided.	No sample size calculation provided.
data is handled?	Yes, actual sample size is described.	Yes, actual sample size is described.	Yes, actual sample size is described.	Yes, actual sample size is described.	Yes, described actual sample size.	Yes, described actual sample size.
	Yes, description of how missing data were handled.	Yes, description of how missing data were handled.	Yes, description of how missing data were handled.	Yes, description of how missing data were handled.	n/a – no missing data.	No description of how missing data were handled.
3.3 Does the study report all confounders considered and adjusted for in the analysis?	Yes, all baseline covariates considered and adjusted for via propensity scores are reported.	No confounders were considered or adjusted for.	No confounders were considered or adjusted for.	Yes, baseline values of the mediator and outcome variables that were considered and adjusted for in the analysis as covariates are reported.	No confounders were considered or adjusted for.	No confounders were considered or adjusted for.
3.4 Does the study report the model building procedure and the final form of all models used in the analysis? Do they report the goodness-of-fit of these models?	No, model building procedures and final form of all models in the analysis are not described. No goodness-of-fit	No, model building procedures and final form of all models in the analysis are not described. No goodness-of-fit	No, model building procedures and final form of all models in the analysis are not described. No goodness-of-fit	No, model building procedures and final form of all models in the analysis are not described. No goodness-of-fit	No, model building procedures and final form of all models in the analysis are not described. No goodness-of-fit	No, model building procedures and final form of all models in the analysis are not described. No goodness-of-fit
3.5 Does the study report the point estimates and the confidence intervals (CIs) of the different direct, indirect and total treatment effects?	metric is provided. Reported: point estimates of the direct and total effect. Not reported: point	metric is provided. Reported: point estimates and CIs of the indirect and direct effect. Not reported: point	metric is provided. Reported: point estimates and CIs of the indirect effect. Not reported: point estimates and CIs of	metric is provided. Reported: point estimates and CIs of the indirect and direct effect. Not reported: point	metric is provided. Reported: point estimates and CIs of the indirect effect. Not reported: point estimate and CIs of	metric is provided. Reported: point estimates for the direct, indirect and total effects and CIs of the indirect effect.
	estimates of the indirect effect, and CIs of direct, indirect or total effect.	estimates and CIs of the total effect.	the direct or total effect.	estimates and CIs of the total effect.	the direct and total effects.	Not reported: CIs of the direct and total effects.

3.6 Does the study report the methods and results of all sensitivity and other additional analyses (in the main paper or appendices)?	N/a - no sensitivity or other analyses are conducted.	Yes, the study reports methods and results of additional analyses (time- lagged analysis). n/a for sensitivity analysis as none conducted.	N/a - no sensitivity or other analyses are conducted.	N/a - no sensitivity or other analyses are conducted.	N/a - no sensitivity or other analyses are conducted.	Yes, the study reports methods and results of additional analyses. n/a for sensitivity analysis as none conducted.
3.7 Does the study discuss the validity of all causal assumptions underlying the analysis (in the main paper or appendices)?	No - Does not discuss assumption of temporal ordering. Yes - Acknowledges the plausibility of bias due to unmeasured confounders. But, does not justify all measured confounders are adequate to fully adjust for confounding. Also does not follow with a sensitivity analysis to test the plausibility of the assumption.	Yes - Acknowledges the requirement for temporal ordering and conducts a time- lagged analyses to justify the validity of the assumption of temporal ordering No - Does not acknowledge or justify the plausibility of the assumption of no unmeasured confounding. Does not follow with a sensitivity analysis to test the plausibility of the assumption.	Yes - Acknowledges the limitation that temporal order between mediator and outcome was not established. Does not conduct analyses to justify the validity of the assumption of temporal ordering. Yes - Acknowledges the limitation that confounders were not measured or assessed. Does not conduct a sensitivity analysis to test the plausibility of the assumption of no unmeasured confounders.	Yes - Acknowledges the requirement for temporal ordering and conducts a time- lagged mediation model to justify the validity of the assumption of temporal ordering No - Does not acknowledge or justify the plausibility of the assumption of no unmeasured confounding. Does not follow with a sensitivity analysis to test the plausibility of the assumption.	Yes - Acknowledges the requirement for temporal ordering. Does not conduct analyses to justify the validity of the assumption of temporal ordering. No - Does not acknowledge or justify the plausibility of the assumption of no unmeasured confounding. Does not follow with a sensitivity analysis to test the plausibility of the assumption.	Yes - Acknowledges the requirement for temporal ordering and conducts hierarchical regression analyses to justify the validity of the assumption of temporal ordering. No - Does not acknowledge or justify the plausibility of the assumption of no unmeasured confounding. Does not follow with a sensitivity analysis to test the plausibility of the assumption.

^aAt item 1.3 and 2.5, for observational study designs we also considered adjustment for intervention-mediator and intervention-outcome confounders.

Supplementary Table S7. Findings of mediation analyses of included studies (with child-reported outcomes).

Study	Intervention vs Comparator \rightarrow Mediator (Measure) \rightarrow Outcome (Measure) <i>Child-Reported</i>	Path a Point Estimate (Error)	Path b Point Estimate (Error)	Direct effect (c') Point Estimate (Error)	Indirect Effect (ab) Point Estimate (error)	Total Effect (c) Point Estimate (Error)	Proportion Mediated
Olbrec	Intravenous acetaminophen vs no	-0.575 (SE=0.133;	0.539	-0.077 (SE=0.262;	-0.31 (Sobel's test	-0.361	78.72%
ht et al.	intravenous acetaminophen \rightarrow Morphine	95% CI=-0.84, -	(SE=0.178; 95%	95% CI=-0.59,	p=0.013)	(SE=0.253;	
(2018)	consumption \rightarrow Hospital length of stay	0.31; p<0.0001)	CI=0.19, 0.89;	<mark>0.44;</mark> p=0.770)		95% CI=-0.86,	
			p<0.0032)			0.13; p=0.157)	
Bonner	Exposure-based internet-CBT vs waitlist	-1.08 (SE=0.39;	0.34 (SE=0.02;	-0.17 (SE=0.19;	-0.37 (95% CI= -0.62, -	NR	67.3%
t et al.	\rightarrow Avoidance behavior (IBS-BRQ) \rightarrow GI	95% CI=-1.84, -	95% CI=0.30,	95% CI=-0.54,	0.09)		
(2018)	symptoms (GSRS-IBS)	0.32; p=0.0060	0.38; p<0.001)	0.20; p=0.373)			
	Exposure-based internet-CBT vs waitlist \rightarrow	0.004 (SE=0.11;	0.41 (SE=0.06,	-0.55 (SE=0.21;	0.002 (95% CI = -0.08,	NR	0.3%
	Perceived stress (PSS-10) \rightarrow GI symptoms	95% CI=-0.21,	95% CI=0.29,	95% CI=-0.96, -	0.09)		
	(GSRS-IBS)	0.22; p=0.972)	0.53; p<0.001)	0.14, p=0.009)			
Lalouni	Exposure-based internet-CBT vs treatment	-2.14 (SE=0.71;	-0.81 (SE=0.24;	NR	1.73 (95% CI=0.48, 3.64)	NR	NR
et al.	as usual \rightarrow GI-avoidance (BRQ-C) \rightarrow	95% CI=-3.54, -	95% CI=-1.27, -		1		
(2021)	Health-related quality of life (PedQL-GI)	0.75; p=0.003)	0.35; p=0.001)				
()	Exposure-based internet-CBT vs treatment	-1.38 (SE=0.33;	-1.62 (SE=0.33;	NR	2.23 (95% CI=0.66, 4.37)	NR	NR
	as usual \rightarrow GI-anxiety (VSI-C) \rightarrow Health-	95% CI=-2.03, -	95% CI=-2.27, -				
	related quality of life (PedQL-GI)	0.73; p=0.012)	0.97; p<0.001)				
Levy et	SLCBT vs education \rightarrow Parent threat	-0.17 (SE=0.03;	0.06 (SE=0.07;	0.02 (SE=0.05;	-0.01 (SE=0.01; 95% CI=-	NR	NR
al.	(PBQ) \rightarrow GI symptom severity (CSI) <i>at</i> 3	95% CI=-0.23, -	95% CI=-0.08,	95% CI= -0.08,	0.03, 0.01)		
(2014)	months	0.11)	0.20)	0.12)			
	SLCBT vs education \rightarrow Parent threat	-0.18 (SE=0.03;	0.13 (SE=0.07;	-0.003 (SE=0.05;	-0.02 (SE=0.01; 95% CI=-	NR	NR
	(PBQ) \rightarrow GI symptom severity (CSI) at 6	95% CI=-0.24, -	95% CI=-0.01,	95% CI=-0.10,	0.05, 0.002)		
	months	0.12)	0.27)	0.10)			
	SLCBT vs education \rightarrow Parent threat	-0.18 (SE=0.03;	0.05 (SE=0.09;	-0.11 (SE=0.06;	-0.01 (SE=0.02; 95% CI=-	NR	NR
	(PBQ) \rightarrow GI symptom severity (CSI) at 12	95% CI=-0.24, -	95% CI=-0.13,	95% CI=-0.23,	0.04, 0.02)		
	months	0.12)	0.23)	0.01			

SLCBT vs education \rightarrow Parent threat	-0.18 (SE=0.03;	0.59 (SE=0.19;	0.03 (SE=0.13;	-0.11 (SE=0.04; 95% CI=-	NR	NR
(PBQ) \rightarrow Pain intensity (FPS-R) at 3 months	95% CI=-0.24, -	95% CI=0.22,	95% CI=-0.22,	0.18, -0.03)		
	0.12)	0.96)	0.28)			
SLCBT vs education \rightarrow Parent threat	-0.18 (SE=0.03;	0.37 (SE=0.17;	0.06 (SE=0.12;	-0.07 (SE=0.03; 95% CI=-	NR	NR
$(PBQ) \rightarrow Pain intensity (FPS-R) at 6 months$	95% CI=-0.24, -	95% CI=0.04,	95% CI=-0.18,	0.13, -0.003)		
	0.12)	0.70)	0.30)			
SLCBT vs education \rightarrow Parent threat	-0.17 (SE=0.03;	0.28 (SE=0.19;	0.09 (SE=0.13;	-0.05 (SE=0.03; 95% CI=-	NR	NR
(PBQ) \rightarrow Pain intensity (FPS-R) at 12	95% CI=-0.23, -	95% CI=-0.09,	95% CI=-0.16,	0.11, 0.02)		
months	0.11)	0.65)	0.34)			
SLCBT vs education \rightarrow Parent	-0.21 (SE=0.03;	-0.01 (SE=0.08;	0.02 (SE=0.05;	0.002 (SE=0.02; 95% CI=-	NR	NR
solicitousness (ARCS) \rightarrow GI symptom	95% CI=-0.27, -	95% CI=-0.17,	95% CI=-0.08,	0.03, 0.03)		
severity (CSI) at 3 months	0.15)	0.15)	0.12)			
SLCBT vs education \rightarrow Parent	-0.21 (SE=0.03;	-0.08 (SE=0.08;	-0.003 (SE=0.05;	0.02 (SE=0.02; 95% CI=-	NR	NR
solicitousness (ARCS) \rightarrow GI symptom	95% CI=-0.27, -	95% CI=-0.24,	95% CI=-0.10,	0.02, 0.05)		
severity (CSI) at 6 months	0.15)	0.08)	0.10)			
SLCBT vs education \rightarrow Parent	-0.21 (0.03; 95%	-0.08 (SE=0.10;	-0.11 (SE=0.06;	0.02 (SE=0.02; 95% CI=-	NR	NR
solicitousness (ARCS) \rightarrow GI symptom	CI=-0.27, -0.15)	95% CI=-0.28,	95% CI=-0.23,	0.02, 0.06)		
severity (CSI) at 12 months		0.12)	0.01)			
SLCBT vs education \rightarrow Parent	-0.21 (SE=0.03;	-0.16 (SE=0.23;	0.03 (SE=0.13;	0.03 (SE=0.05; 95% CI=-	NR	NR
solicitousness (ARCS) \rightarrow Pain intensity	95% CI=-0.27, -	95% CI=-0.61,	95% CI=-0.22,	0.06, 0.13)		
(FPS-R) at 3 months	0.15)	0.29)	0.28)			
SLCBT vs education \rightarrow Parent	-0.21 (SE=0.03;	-0.37 (SE=0.20;	0.06 (SE=0.12;	0.08 (SE=0.04; 95% CI=-	NR	NR
solicitousness (ARCS) \rightarrow Pain intensity	95% CI=-0.27, -	95% CI=-0.76,	95% CI=-0.18,	0.01, 0.16)		
(FPS-R) at 6 months	0.15)	0.02)	0.30)			
SLCBT vs education \rightarrow Parent	-0.21 (SE=0.03;	-0.10 (SE=0.23;	0.09 (SE=0.13;	0.02 (SE=0.05; 95% CI=-	NR	NR
solicitousness (ARCS) \rightarrow Pain intensity	95% CI=-0.27, -	95% CI=-0.55,	95% CI=-0.16,	0.07, 0.12)		
(FPS-R) at 12 months	0.15)	0.35)	0.34)			
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.14 (SE=0.05;	0.02 (SE=0.05;	-0.02 (SE=0.01; 95% CI=-	NR	NR
catastrophizing (PRI) \rightarrow GI symptom	95% CI=-0.22, -	95% CI=0.04,	95% CI= -0.08,	0.03, -0.001)		
severity (CSI) at 3 months	0.02)	0.24)	0.12)			
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.18 (SE=0.05;	-0.003 (SE=0.05;	-0.02 (SE=0.01; 95% CI=-	NR	NR
catastrophizing (PRI) \rightarrow GI symptom	95% CI=-0.22, -	95% CI=0.08,	95% CI=-0.10,	0.04, 0.0004)		
severity (CSI) at 6 months	0.02)	0.28)	0.10)			
SLCBT vs education \rightarrow Child	-0.12 (SE=0.05;	0.12 (SE=0.07;	-0.11 (SE=0.06;	-0.01 (SE=0.01; 95% CI=-	NR	NR
catastrophizing (PRI) \rightarrow GI symptom	95% CI=-0.22, -	95% CI=-0.02,	95% CI=-0.23,	0.03, 0.06)		
severity (CSI) at 12 months	0.02)	0.26)	0.01)	· ·		

	SLCBT vs education \rightarrow Child catastrophizing (PRI) \rightarrow Pain intensity	-0.12 (SE=0.05; 95% CI=-0.22,	0.24 (SE=0.15; 95% CI=-0.05,	0.03 (SE=0.13; 95% CI=-0.22,	-0.03 (SE=0.02; 95% CI=- 0.07, 0.01)	NR	NR
	(FPS-R) at 3 months SLCBT vs education \rightarrow Child catastrophizing (PRI) \rightarrow Pain intensity (FPS-R) at 6 months	0.02) -0.12 (SE=0.05; 95% CI=-0.22, 0.02)	0.53) 0.26 (SE=0.13; 95% CI=0.005, 0.52)	0.28) 0.06 (SE=0.12; 95% CI=-0.18, 0.30)	-0.03 (SE=0.02, 95% CI=- 0.07, 0.009)	NR	NR
	SLCBT vs education \rightarrow Child catastrophizing (PRI) \rightarrow Pain intensity (FPS-R) <i>at 12 months</i>	-0.12 (SE=0.05; 95% CI=-0.22, 0.02)	0.16 (SE=0.15; 95% CI=-0.13, 0.45)	0.09 (SE=0.13; 95% CI=-0.16, 0.34)	-0.02 (SE=0.02; 95% CI=- 0.06, 0.02)	NR	NR
Kashik ar-Zuck et al.	CBT vs fibromyalgia education \rightarrow Pain coping (PCQ) \rightarrow Functional disability (FDI) at 6 months	NR	NR	NR	-0.004 (95% CI = -0.06, 0.06)	NR	NR
(2013)	CBT vs fibromyalgia education \rightarrow Pain coping (PCQ) \rightarrow Depression (CDI) <i>at 6</i> <i>months</i>	NR	NR	NR	-0.12 (95% CI = -0.82, 0.46)	NR	NR
	CBT vs fibromyalgia education \rightarrow Catastrophizing (PCQ) \rightarrow Functional disability (FDI) <i>at 6 months</i>	NR	NR	NR	0.02 (95% CI = -0.04, 0.09)	NR	NR
	CBT vs fibromyalgia education \rightarrow Catastrophizing (PCQ) \rightarrow Depression (CDI) <i>at 6 months</i>	NR	NR	NR	-0.32 (95% CI = -1.43, 0.19)	NR	NR
	CBT vs fibromyalgia education \rightarrow Coping efficacy (PCQ) \rightarrow Functional disability (FDI) <i>at 6 months</i>	NR	NR	NR	-0.04 (95% CI = -0.10, 0.03)	NR	NR
	CBT vs fibromyalgia education \rightarrow Coping efficacy (PCQ) \rightarrow Depression (CDI) <i>at 6 months</i>	NR	NR	NR	-0.24 (95% CI = -1.15, 0.38)	NR	NR
Wicksel l et al. (2011)	ACT vs MDT + amitriptyline \rightarrow Pain impairment beliefs (PAIRS) \rightarrow Pain interference (PII) at 3.5 months	16.18 (SE=5.92; 95% CI=4.58, 27.78; p=0.0121)	0.05 (SE=0.04; 95% CI=-0.03, 0.13; p=0.2607	-0.21 (SE=1.42, 95% CI=-2.99, 2.57; p=0.8847)	0.83 (SE=0.74; 90% CI=0.00, 2.40; 95% CI=- 0.62, 2.28; p=0.2669)	0.62 (SE=1.23; 95% CI=-1.79, 3.03; p=0.6218)	NR
	ACT vs MDT + amitriptyline \rightarrow Pain impairment beliefs (PAIRS) \rightarrow Pain interference (PII) at 7 months	13.83 (SE=4.86; 95% CI=4.30, 23.36; p=0.0103)	0.08 (SE=0.07; 95% CI=-0.06, 0.22; p=0.2148)	0.40 (SE=1.66; 95% CI=-2.85, 3.65; p=0.8115)	1.16 (SE=0.95; 90% CI=- 0.41, 3.18; 95% CI=-0.70, 3.02; p=0.2188)	1.57 (SE=1.41; 95% CI=-1.19, 4.33; p=0.2807)	NR
	ACT vs MDT + amitriptyline \rightarrow Pain impairment beliefs (PAIRS) \rightarrow Depression (CES-DC) at 3.5 months	16.02 (SE=5.69; 95% CI=4.87, 27.17; p=0.0099)	0.43 (SE=0.019; 95% CI=0.39, 0.47; p=0.0358)	-0.31 (SE=6.09; 95% CI=-12.25, 11.63; p=0.9597)	6.89 (SE=3.80; 95% CI=1.75, 14.59; p=0.0699)	6.58 (SE=5.69; 95% CI=-4.57,	NR

					17.73; p=0.2595)	
ACT vs MDT + amitriptyline \rightarrow Pain	17.64 (SE=5.43;	0.66 (SE=0.33;	-4.36 (SE=9.48;	11.56 (SE=6.52; 95%	7.20 (SE=8.05;	N
impairment beliefs (PAIRS) \rightarrow Depression	95% CI=7.00,	95% CI=0.01,	95% CI=-22.94,	CI=2.46, 26.55; p=0.0763)	95% CI=-8.58,	
(CES-DC) at 7 months	28.28; p=0.0047)	1.31; p=0.0662)	14.22; p=0.6520)		22.98;	
					p=0.3835)	
ACT vs MDT + amitriptyline \rightarrow Pain	1.80 (SE=0.88;	0.61 (SE=0.31;	0.03 (SE=1.32;	1.10 (SE=0.74; 95%	1.12 (SE=1.29;	N
reactivity (PRS) \rightarrow Pain interference (PII)	95% CI=0.08,	95% CI=0.01,	95% CI=-2.56,	CI=0.08, 3.01; p=0.1384)	95% CI=-1.41,	
at 3.5 months	3.52; p=0.0535)	1.22; p=0.0617)	2.62; p=0.9846)	- · ·	3.65; p=0.3941)	
ACT vs MDT + amitriptyline \rightarrow Pain	1.74 (SE=0.87;	0.97 (SE=0.32;	0.29 (SE=1.31;	1.69 (SE=0.98; 95%	1.98 (SE=1.43;	Ν
reactivity (PRS) \rightarrow Pain interference (PII)	95% CI=0.03,	95% CI=0.34,	95% CI=-2.28,	CI=0.17, 4.32; p=0.844)	95% CI=-0.82,	
at 7 months	3.45; p=0.0617)	1.60; p=0.0075)	2.86; p=0.8281)	· · · ·	4.78; p=0.1836)	
ACT vs MDT + amitriptyline \rightarrow Pain	1.98 (SE=0.87;	2.75 (SE=1.33;	4.52 (SE=5.89;	5.43 (SE=3.41; 95%	9.95 (SE=5.66;	Ν
reactivity (PRS) \rightarrow Depression (CES-DC)	95% CI=0.27,	95% CI=0.14,	95% CI=-7.02,	CI=0.01, 14.77; p=0.1119)	95% CI=-1.14,	
at 3.5 months	3.69; p=0.0329)	5.36; p=0.0519)	16.06; p=0.4510)	_	21.04; p=0.935)	
ACT vs MDT + amitriptyline \rightarrow Pain	1.45 (SE=0.92;	4.16 (SE=2.03;	4.26 (SE=8.02;	6.05 (SE=4.63; 90%	10.31	Ν
reactivity (PRS) \rightarrow Depression (CES-DC)	95% CI=-0.35,	95% CI=0.18,	95% CI=-11.46,	CI=3.52, 31.96; 95% CI=-	(SE=8.17; 95%	
at 7 months	3.25; p=0.1330)	8.14; p=0.0582)	19.98; p=0.6028)	3.02, 15.12; p=0.1912)	CI=-5.70,	
	_	_	_	_	26.32;	
					p=0.2248)	
ACT vs MDT + amitriptyline \rightarrow Self-	-23.31 (SE=12.70;	-0.02 (SE=0.02;	0.08 (SE=1.40;	0.48 (SE=0.55; 90% CI=-	0.52 (SE=1.30;	Ν
efficacy (SES) \rightarrow Pain interference (PII) at	95% CI=-48.20,	95% CI=-0.06,	95% CI=-2.66,	0.35, 1.79; 95% CI=-0.60,	95% CI=-2.03,	
3.5 months	1.58; p=0.0806)	0.02; p=0.4008)	2.82; p=0.9572)	1.56; p=0.4168)	3.07; p=0.6896)	
ACT vs MDT + amitriptyline \rightarrow Self-	-25.98 (SE=14.89;	-0.02 (SE=0.02;	0.99 (SE=1.63;	0.47 (SE=0.64; 90% CI=-	1.45 (SE=1.49;	Ν
efficacy (SES) \rightarrow Pain interference (PII) <i>at</i>	95% CI=-55.16,	95% CI=-0.06,	95% CI=-2.20,	0.27, 2.32; 95% CI=-0.78,	95% CI=-1.47,	
7 months	3.20; p=0.0981)	0.02; p=0.4566)	4.18; p=0.5524)	1.72; p=0.4626)	4.37; p=0.3400)	
ACT vs MDT + amitriptyline \rightarrow Self-	-23.92 (SE=12.23;	-0.04 (SE=0.11;	5.35 (SE=6.60;	1.01 (SE=2.48; 90% CI -	6.36 (SE=5.97;	N
efficacy (SES) \rightarrow Depression (CES-DC) <i>at</i>	95% CI=-47.89,	95% CI=-0.26,	95% CI=-7.56,	3.28, 7.42; 95% CI=-3.85,	95% CI=-5.34,	
3.5 months	<mark>0.06;</mark> p=0.0634)	0.18; p=0.6946)	18.29; p=0.4264)	5.87; p=0.6834)	18.06;	
					p=0.2983)	
ACT vs MDT + amitriptyline \rightarrow Self-	-21.03 (SE=15.24;	0.02 (SE=0.15;	7.35 (SE=9.43;	-0.33 (SE=2.90; 90% CI=-	7.03 (SE=8.64;	Ν
efficacy (SES) \rightarrow Depression (CES-DC) at 7	95% CI=-50.90,	95% CI=-0.27,	95% CI=-11.13,	10.22, 3.09; 95% CI=-6.01,	95% CI=-9.90,	
months	<mark>8.84;</mark> p=0.1865)	0.31; p=0.9168)	25.83; p=0.4477)	5.35; p=0.9102)	23.96;	
					p=0.4278)	

ACT vs MDT + amitriptyline \rightarrow	3.84 (SE=3.03;	0.07 (SE=0.09;	0.36 (SE=1.29;	0.26 (SE=0.38; 90% CI=-	0.62 (SE=1.23;	NR
Kinesiophobia (TSK) \rightarrow Pain interference	95% CI=-2.10,	95% CI=-0.11,	95% CI=-2.17,	0.17; 95% CI=-0.48, 1.00;	95% CI=-1.79,	
(PII) at 3.5 months	9.78; p=0.2172)	0.25; p=0.4513)	2.89; p=0.7839)	1.43, p=0.4945)	3.03; p=0.6218)	
ACT vs MDT + amitriptyline \rightarrow	3.78 (SE=2.92;	0.19 (SE=0.10;	0.85 (SE=1.39;	0.71 (SE=0.66; 90% CI=-	1.57 (SE=1.41;	NR
Kinesiophobia (TSK) \rightarrow Pain interference	95% CI=-1.94,	95% CI=-0.01,	95% CI=-1.87,	0.15, 2.62; 95% CI=-0.58,	95% CI=-1.19,	
(PII) at 7 months	9.50; p=0.2119)	0.39; p=0.0879)	3.57; p=0.55)	2.00; p=0.2768)	4.33; p=0.2807)	
ACT vs MDT + amitriptyline \rightarrow	4.00 (SE=2.92;	0.36 (SE=0.41;	5.14 (SE=5.95;	1.44 (SE=1.87; 90% CI=-	6.58 (SE=5.69;	NR
Kinesiophobia (TSK) \rightarrow Depression (CES-	95% CI=-1.72,	95% CI=-0.44,	95% CI=-6.52,	0.85, 7.76; 95% CI=-2.23,	95% CI=-4.57,	
DC) at 3.5 months	9.72; p=0.1836)	1.16; p=0.3895)	16.80; p=0.3965)	5.11; p=0.4430)	17.73;	
	- · ·	-	-		p=0.2595)	
ACT vs MDT + amitriptyline \rightarrow	4.33 (SE=3.47;	0.59 (SE=0.56;	4.64 (SE=8.39;	2.57 (SE=3.04; 90% CI=-	7.20 (SE=8.05;	NR
Kinesiophobia (TSK) \rightarrow Depression (CES-	95% CI=-2.47,	95% CI=-0.51,	95% CI=-11.80,	1.29, 16.77; 95% CI=-3.39,	95% CI=-8.58,	
DC) at 7 months	11.13; p=0.2285)	1.68; p=0.3065)	21.08; p=0.5880)	8.53; p=0.3984)	22.98;	
					p=0.3835)	
ACT vs MDT + amitriptyline \rightarrow	-1.39 (SE=1.89;	0.08 (SE=0.15;	1.10 (SE=1.28;	-0.11 (SE=0.24; 90% CI=-	0.99 (SE=1.25;	NR
Catastrophizing (PCQ) \rightarrow Pain	95% CI=-5.09,	95% CI=-0.21,	95% CI=-1.41,	1.04, 0.09; 95% CI=-0.58,	95% CI=-1.46,	
interference (PII) at 3.5 months	2.31; p=0.4710)	0.37; p=0.5956)	3.61; p=0.4000)	0.36; p=0.6513)	3.44; p=0.4337)	
ACT vs MDT + amitriptyline \rightarrow	-2.28 (SE=1.94;	-0.03 (SE=0.18;	1.92 (SE=1.53;	0.06 (SE=0.39; 90% CI=-	1.98 (SE=1.43;	NR
Catastrophizing (PCQ) \rightarrow Pain	95% CI=-6.08,	95% CI=-0.38,	95% CI=-1.08,	0.47, 0.74; 95% CI=-0.70,	95% CI=-0.82,	
interference (PII) at 7 months	1.52; p=0.2554)	0.32; p=0.8843)	4.92; p=0.2259)	0.82; p=0.88)	4.78; p=0.1836)	
ACT vs MDT + amitriptyline \rightarrow	-0.84 (SE=1.94;	0.51 (SE=0.63;	9.09 (SE=5.73;	-0.43 (SE=1.08; 90% CI=-	8.66 (SE=5.66;	NR
Catastrophizing (PCQ) \rightarrow Depression	95% CI=-4.64,	95% CI=-0.72,	95% CI=-2.14,	4.73, 0.90; 95% CI=-2.55,	95% CI=-2.43,	
(CES-DC) at 3.5 months	2.96; p=0.6678)	1.74; p=0.4295)	20.32; p=0.1274)	1.69; p=0.6940)	19.75;	
					p=0.1399)	
ACT vs MDT + amitriptyline \rightarrow	-2.22 (SE=1.98;	0.25 (SE=1.06;	10.86 (SE=8.74;	-0.55 (SE=2.26; 90% CI=-	10.31	NR
Catastrophizing (PCQ) \rightarrow Depression	95% CI=-6.10,	95% CI=-1.83,	95% CI=-6.27,	11.14, 0.44; 95% CI=-4.98,	(SE=8.17; 95%	
(CES-DC) at 7 months	1.66; p=0.2795)	2.33; p=0.8179)	27.99; p=0.2331)	3.88; p=0.8074)	CI=-5.70,	
					26.32;	
					p=0.2248)	
ACT vs MDT + amitriptyline \rightarrow Pain	1.41 (SE=1.05;	0.42 (SE=0.24;	0.02 (SE=1.23;	0.60 (SE=0.54; 90% CI=-	0.62 (SE=1.23;	NR
intensity (VAS) \rightarrow Pain interference (PII)	95% CI=-0.65,	95% CI=-0.05,	95% CI=-2.39,	0.02, 2.18; 95% CI=-0.46,	95% CI=-1.79,	
at 3.5 months	3.47; p=0.1920)	0.89; p=0.0921)	2.43; p=0.9869)	1.66; p= 0.2697)	3.03; p=0.6218)	
ACT vs MDT + amitriptyline \rightarrow Pain	1.64 (SE=1.11;	0.32 (SE=0.29;	1.04 (SE=1.48;	0.52 (SE=0.57; 90% CI=-	1.57 (SE=1.41;	NR
intensity (VAS) \rightarrow Pain interference (PII)	95% CI=-0.54,	95% CI=-0.25,	95% CI=-1.86,	0.04, 2.35; 95% CI=-0.60,	95% CI=-1.19,	
at 7 months	3.82; p=0.1564)	0.89; p=0.2845)	3.94; p=0.4905)	1.64; p=0.3564)	4.33; p=0.2807)	

ACT	Γ vs MDT + amitriptyline \rightarrow Pain	1.30 (SE=1.02;	0.60 (SE=1.18;	5.80 (SE=5.98;	0.78 (SE=1.59; 90% CI=-	6.58 (SE=5.69;	NR
inten	nsity (VAS) \rightarrow Depression (CES-DC) at	95% CI=-0.70,	95% CI=-1.71,	95% CI=-5.92,	1.33, 6.08; <mark>95% CI= -2.34</mark> ,	95% CI=-4.57,	
3.5 m	nonths	3.30; p=0.2162)	<mark>2.91;</mark> p=0.6149)	17.52, p=0.3432)	<mark>3.90;</mark> p=0.6220)	17.73;	
		-	-	-	-	p=0.2595)	
ACT	Γ vs MDT + amitriptyline \rightarrow Pain	1.63 (SE=1.20;	-0.13 (SE=1.67;	7.42 (SE=8.74,	-0.22 (SE=2.58; 90% CI=-	7.20 (SE=8.05;	NR
inten	nsity (VAS) \rightarrow Depression (CES-DC) <i>at</i>	95% CI=-0.72,	95% CI=-3.40,	95% CI=-9.71,	12.16, 0.33; <mark>95% CI=-5.28,</mark>	95% CI=-8.58,	
7 mor	onths	3.98; p=0.1926)	<mark>3.14;</mark> p=0.9379)	24.55; p=0.4082)	4.84; p=0.9332)	22.98;	
						p=0.3835)	

If 95% confidence intervals not stated in original study, or only 90% confidence interval provided, then they were calculated using the standard error (indicated in red). Abbreviations: ACT, Acceptance and Commitment Therapy; ARCS, Adult Responses to Children's Symptoms; CBT, Cognitive Behavioral Therapy; CDI, Children's Depression Inventory; CES-DC, Centre for Epidemiological Studies Depression Scale for Children; CI, Confidence Interval; CSI, Children's Somatization Inventory; FDI, Functional Disability Inventory; FPS-R, Faces Pain Scale – Revised; GSRS-IBS, Gastrointestinal Symptom Rating Scale – Irritable Bowel Syndrome; IBS-BRQ, IBS-specific Behavioural Response Questionnaire; MDT, Multidisciplinary Treatment; NR, Not Reported; PBQ, PAIRS, Pain and Impairment Relationship Scale; PBQ, Pain Beliefs Questionnaire; PCQ, Pain Coping Questionnaire; PII, Pain Interference Index; PRI, Pain Response Inventory; PRS, Pain Reactivity Scale; PSS-10, Perceived Stress Scale – 10; SES, Self-Efficacy Scale; SE, Standard error; SLCBT, Social Learning and Cognitive Behavioral Treatment; TSK, Tampa Scale of Kinesiophobia; VAS, Visual Analogue Scale

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