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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary Table 1. Search strategy for MEDLINE*

1	INFANT,NEWBORN/
2	INFANT,PREMATURE/
3	(neonate* or newborn* or infant* or baby or babies).ab,ti.
4	1 or 2 or 3
5	ANALGESIA/
6	ANALGESICS/
7	CONSCIOUS SEDATION/
8	DEEP SEDATION/
9	PAIN MANAGEMENT/
10	PAIN,PROCEDURAL/
11	PAIN,POSTOPERATIVE/
12	(pain or analges* or sedat*).ab,ti.
13	("oral sucrose" or "oral dextrose" or "oral glucose").ab,ti.
14	("breast milk" or breastfeed*).ab,ti.
15	(sucking or pacifier*).ab,ti.
16	("skin to skin" or Kangaroo).ab,ti.
17	"swaddl*".ab,ti.
18	(music or singing or lullaby).ab,ti.
19	(topical and local).ab,ti.
20	(paracetamol or opioid* or ketamine or ibuprofen).ab,ti.
21	("dorsal penile nerve block*" or DPNB*)
22	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	(procedure* or procedural or intervention*).ab,ti.
24	(invasive or painful).ab,ti.
25	23 and 24
26	("heel prick*" or "heel stick*" or lancing).ab,ti.
27	(venepuncture* or venipuncture*).ab,ti.
28	"cannulation*".ab,ti.
29	"injection*".ab,ti.
30	(intramuscular or subcutaneous).ab,ti.
31	29 and 30
32	(catheterisation or catheterization).ab,ti.
33	"lumbar puncture*".ab,ti.
34	prongs.ab,ti.
35	(abscess* and drain*).ab,ti.
36	("chest drain*" and insert*).ab,ti.
37	("chest drain*" and remov*).ab,ti.
38	(clubfoot or "club foot" or talipes).ab,ti.
39	(manipulat* or casting or Ponseti).ab,ti.
40	38 and 39
41	"circumcision*".ab,ti.
42	("gastric suction*" or "nasogastric suction*").ab,ti.
43	("total parenteral " or TPN).ab,ti.
44	"central venous catheter*".ab,ti.
45	"necroti* enterocolitis".ab,ti.
46	42 or 43 or 44
47	45 and 46
48	25 or 26 or 27 or 28 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 40 or 41 or 47
49	4 and 22 and 48
50	limit 49 to animals
51	49 not 50

*Search strategies for Embase, CENTRAL and CINAHL were adapted from this strategy

Supplementary Table 2. List of comparisons included in meta-analysis

Analgesic	Comparator
<i>Heart Rate*</i>	
Breastfeeding	Placebo or no intervention
Expressed breast milk	Placebo or no intervention
Local anaesthesia	Placebo or no intervention
Music	Placebo or no intervention
Non-nutritive sucking	Placebo or no intervention
Non-nutritive sucking	Oral Sugar
Skin-to-skin	Skin-to-skin plus breastfeeding
Skin-to-skin	Placebo or no intervention
Oral Sugar	Placebo or no intervention
Swaddling	Placebo or no intervention
<i>Oxygen Saturation*</i>	
Breastfeeding	Placebo or no intervention
Expressed breast milk	Placebo or no intervention
Local anaesthesia	Placebo or no intervention
Music	Placebo or no intervention
Non-nutritive sucking	Placebo or no intervention
Non-nutritive sucking	Oral Sugar
Skin-to-skin	Placebo or no intervention
Oral Sugar	Placebo or no intervention
<i>Premature Infant Pain Profile (PIPP)*</i>	
Breastfeeding	Placebo or no intervention
Breastfeeding	Oral Sugar
Expressed breast milk	Placebo or no intervention
Expressed breast milk	Oral Sugar
Local anaesthesia	Placebo or no intervention
Non-nutritive sucking	Placebo or no intervention
Skin-to-skin	Placebo or no intervention
Skin-to-skin	Oral Sugar
Skin-to-skin	Swaddling
Oral Sugar	Placebo or no intervention
<i>Neonatal Infant Pain Scale (NIPS)*</i>	
Breastfeeding	Placebo or no intervention
Breastfeeding	Skin-to-skin
Breastfeeding	Oral Sugar
Non-nutritive sucking	Oral Sugar
Skin-to-skin	Oral Sugar
Oral Sugar	Placebo or no intervention
Swaddling	Placebo or no intervention
<i>Neonatal Facial Coding System (NFCS)*</i>	
Expressed breast milk	Placebo or no intervention
Expressed breast milk	Oral Sugar
Skin-to-skin	Placebo or no intervention
Oral Sugar	Placebo or no intervention
Local anaesthesia	Placebo or no intervention
<i>Douleur Aiguë du Nouveau-né scale (DAN)*</i>	
Expressed breast milk	Placebo or no intervention
Non-nutritive sucking	Placebo or no intervention
Non-nutritive sucking	Oral Sugar

* Outcome measure used for these comparisons

Supplementary Table 3. Study characteristics table of all 149 included studies

Study	n	Country	Methods	Procedure	Groups	Outcome measure	Age (days) at procedure (mean[SD])*
Abad 1996 ⁴²	28	Spain	RCT, PG	VP	OS, Placebo	HR, SpO ₂	6·5[3·1]
Abad 2001 ⁴⁸	47	Spain	RCT, PG	VP	OS, LA, OS+LA, Placebo	HR, SpO ₂	1·9[0·5]
Acharya 1998 ¹³⁰	19	UK	RCT, PG	VP	LA, Placebo	HR, SpO ₂ , NFCS	27·5[15·5]
Acharya 2004 ⁴⁹	39	UK	RCT, XG	VP	OS, Placebo	HR, SpO ₂ , NFCS	27·2[24·4]
Ahuja 2000 ⁵⁰	25	India	RCT, XG	IMI	OS, Placebo, No intervention	HR, SpO ₂ , NFCS	3·5
Akcam 2004 ⁵¹	34	Turkey	RCT, XG	HP	OS, Placebo	DAN	4[2·75]
Akcam 2004 ⁵²	60	Turkey	RCT, XG	HP	OS, Placebo	DAN	4·5[4·5]
Altun-Köröglü 2010 ⁵³	75	Turkey	RCT, PG	HP	OS, EBM, Placebo	NFCS	6·4
Aydin 2019 ²²	100	Turkey	RCT, PG	HP	BF, No intervention	NIPS	..
Badiee 2009 ¹³¹	72	Iran	RCT, PG	HP	PCM, Placebo	HR, SpO ₂ , PIPP	3·0[0·6]
Basnet 2010 ⁵⁴	50	Nepal	RCT, PG	VP	OS, No intervention	DAN	..
Bauer 2004 ⁵⁵	58	Germany	RCT, PG	VP	OS, Placebo	HR, PIPP	3·2[0·8]
Beken 2014 ¹³²	25	Turkey	RCT, PG	VP	OS+NNS, NNS+Placebo	NIPS	..
Bellieni 2001 ⁵⁶	17	Italy	RCT, XG	HP	OS, OS+NNS, Placebo, No intervention	PIPP	..
Bellieni 2002 ⁹²	79	Italy	RCT, PG	HP	OS, NNS, OS+NNS, No intervention	DAN	..
Bellieni 2013 ¹³³	62	Italy	RCT, XG	IMI	OS, LA	DAN	..
Bembich 2018 ³⁴	80	Italy	RCT, PG	HP	OS, BF, EBM, OS+Holding	NIPS	..
Biran 2011 ¹³⁴	76	France	RCT, PG	VP	OS+LA, OS+Placebo	PIPP, DAN	15·7[9·8]
Blass 1999 ⁵⁷	40	USA	RCT, PG	HP	OS, NNS+Placebo, NNS+OS, Placebo	HR	..
Brovedani 2007 ³⁸	146	Italy	RCT, PG	HP	OS, BF, SW	PIPP	..
Bucher 1995 ¹³⁵	16	Switzerland	RCT, XG	HP	OS, Placebo	HR, SpO ₂	..
Bueno 2012 ¹⁰⁰	88	Brazil	RCT, PG	HP	OS, EBM	PIPP	..
Butt 2000 ¹³⁶	14	Canada	RCT, XG	HP	M, No intervention	HR, SpO ₂	8·2[3·1]
Campos 1989 ¹³⁷	32	USA	RCT, PG	HP	NNS, SW	HR	..
Carbajal 1999 ⁵⁸	150	France	RCT, PG	VP	OS, NNS, OS+NNS, Placebo, No intervention	DAN	3·6[0·4]
Carbajal 2002 ⁵⁹	39	France	RCT, XG	SC	OS, OS+NNS, Placebo	DAN	26·2[6·1]
Carbajal 2003 ²³	179	France	RCT, PG	VP	OS+NNS, BF, Placebo, No intervention	NIPS, DAN	3[0·4]
Cardoso 2014 ⁹³	80	Brazil	RCT, PG	AP	OS, M, OS+M	PIPP	4
Castral 2008 ¹⁰⁴	60	Brazil	RCT, PG	HP	SS, No intervention	HR, NFCS	..
Chermont 2009 ⁹⁴	640	Brazil	RCT, PG	IMI	OS, SS, OS+SS, Placebo	PIPP, NIPS, NFCS	1·2[0·3]
Chiabi 2016 ³⁵	100	Cameroon	RCT, PG	HP	OS, BF	NIPS	2·3[0·3]
Codipietro 2008 ³⁶	101	Italy	RCT, PG	HP	OS, BF	HR, SpO ₂ , PIPP	3·4[0·5]
Collados-Gomez 2018 ¹³⁸	66	Spain	RCT, XG	VP	OS+NNS+SW, EBM+NNS+SW	PIPP	9·1[2·0]
Cong 2009 ¹⁰⁵	14	USA	RCT, XG	HP	SS, No intervention	HR	6·0[1·0]
Cong 2011 ¹⁰⁶	28	USA	RCT, XG	HP	SS (30 minutes, 80 minutes), No intervention	PIPP	5·2[0·9]
Cong 2012 ¹⁰⁷	26	USA	RCT, XG	HP	SS (15 minutes, 30 minutes), No intervention	HR	13·9[5·8]
Cook 2017 ⁹⁵	40	USA	RCT, PG	PICC	OS, Placebo	HR, SpO ₂ , PIPP	..
Corbo 2000 ¹²²	24	Italy	RCT, XG	HP	NNS, No intervention	HR	4·7[1·9]
De Bernardo 2019 ¹³⁹	66	Italy	RCT, PG	VP	OS (10%, 24%)+NNS	HR, SpO ₂ , NIPS	22·9[4·9]
De Melo 2017 ¹⁴⁰	28	Brazil	RCT, PG	AP	OS, M	NFCS	..
Deshmukh 2002 ⁶⁰	60	India	RCT, PG	VP	OS (10%, 25%), Placebo	HR, SpO ₂	7·1[1·8]
Dezhdar 2016 ⁴³	82	Iran	RCT, PG	VP	SS, SW, No intervention	HR, PIPP	..
Elserafy 2009 ⁶¹	36	Saudi Arabia	RCT, PG	VP	OS, NNS, NNS+Placebo (water), NNS+OS, Placebo (water), No intervention	HR, SpO ₂ , PIPP	..
Eriksson 1999 ⁶²	120	Sweden	RCT, PG	VP	OS, No intervention	PIPP	..
Eriksson 2004 ⁶³	43	Sweden	RCT, PG	HP	OS, Placebo	PIPP	..

Erkut 2017 ¹⁴¹	74	Turkey	RCT, PG	HP	SW, No intervention	HR, SpO ₂ , PIPP, NIPS	..
Fallah 2017 ⁴¹	120	Iran	RCT, PG	IMI	BF, SS, SW	NIPS	..
Field 1984 ¹¹⁸	96	USA	RCT, PG	HP	NNS, No intervention	HR	7·0[3·4]
Gajbhiye 2018 ²⁴	150	India	RCT, PG	IMI	OS, BF, No intervention	HR, SpO ₂ , PIPP	1·8[0·2]
Gao 2015 ¹¹⁷	76	China	RCT, PG	HP	SS, No intervention	HR	4·3[0·2]
Gao 2018 ⁶⁴	86	China	RCT, PG	HP	OS, NNS, OS+NNS, No intervention	HR, SpO ₂ , PIPP	5·1[0·2]
Gerull 2013 ¹⁴²	25	Switzerland	RCT, PG	HP	OS, SW, OS+SW	HR	..
Gharehbaghi 2007 ⁶⁵	60	Iran	RCT, PG	VP	OS, Placebo	HR	5·6[1·1]
Gibbins 2002 ¹⁴³	190	Canada	RCT, PG	HP	OS, OS+NNS, NNS+Placebo(water)	PIPP	..
Golestan 2007 ⁹⁶	60	Iran	RCT, PG	IMI	OS, Placebo, No intervention	HR	0·6[0·1]
Gormally 2001 ⁹⁷	85	Canada	RCT, PG	HP	OS, OS+Holding, Placebo (water)+Holding, No intervention	HR	2·3[0·3]
Gradin 2002 ¹⁴⁴	196	Sweden	RCT, PG	VP	OS+Placebo (cream), LA+Placebo (water)	HR, PIPP	4·3[3·3]
Gradin 2004 ⁶⁶	79	Sweden	RCT, PG	VP	OS, OS+BF, BF+Placebo, Placebo	PIPP	..
Gray 2000 ¹⁰⁸	30	USA	RCT, PG	HP	SS, No intervention	HR	..
Gray 2002 ²⁵	30	USA	RCT, PG	HP	BF, No intervention	HR	..
Gray 2012 ⁹⁸	45	USA	RCT, PG	VC	OS, NNS, No intervention	HR	..
Haouari 1995 ⁴⁴	60	United Kingdom	RCT, PG	HP	OS (12.5%, 25%, 50%), Placebo	HR	3·5[0·6]
Harrison 2003 ⁶⁷	128	Australia	RCT, PG	HP	OS, Placebo	NFCS	18·8[13·3]
Hashemi 2016 ²⁶	131	Iran	RCT, PG	IMI	BF, SW, BF+SW, No intervention	HR, SpO ₂ , NFCS	1·7[0·8]
Hatami Bavarsad 2018 ²⁷	75	Iran	RCT, PG	IMI	BF, EBM, No intervention	HR, SpO ₂ , DAN	..
Ho 2016 ¹⁴⁵	54	Hong Kong	RCT, PG	HP	SW, No intervention	HR, SpO ₂ , PIPP	9·9[7·6]
Holsti 2011 ¹⁴⁶	57	Canada	RCT, PG	HP	BF, NNS	HR	9
Hsieh 2018 ⁹⁹	20	Taiwan	RCT, XG	HP	OS, EBM, Placebo, No intervention	PIPP	..
Huang 2004 ¹⁴⁷	32	Taiwan	RCT, XG	HP	SW, No intervention	HR, SpO ₂ , PIPP	7·5[7·1]
Jain 2000 ¹⁴⁸	39	United Kingdom	RCT, PG	VP	LA, Placebo	NFCS	7·0[3·8]
Jatana 2003 ⁴⁵	125	India	RCT, PG	HP	OS, EBM, Placebo	HR, SpO ₂	..
Johnston 1997 ⁶⁸	87	Canada	RCT, PG	HP	OS, SW+Rocking, OS+SW+Rocking, Placebo (water)	HR	5·7[1·2]
Johnston 1999 ⁶⁹	47	Canada	RCT, PG	HP	OS, Placebo	PIPP	6·5[1·6]
Johnston 2003 ¹⁰⁹	74	Canada	RCT, XG	HP	SS, No intervention	HR, SpO ₂ , PIPP	..
Johnston 2008 ¹⁴⁹	61	Canada	RCT, XG	HP	SS, SW	PIPP	..
Kashaninia 2008 ¹¹⁰	100	Iran	RCT, PG	IMI	SS, No intervention	NIPS	0·08
Kaur 2003 ¹⁵⁰	60	India	RCT, PG	LP	LA, Placebo	HR, SpO ₂ , NFCS	3·4
Kristoffersen 2018 ¹⁵¹	53	Norway, South Africa	RCT, XG	VP	OS (0.2 mL, 0.5 mL)	PIPP	..
Kurdahi Badr 2017 ¹⁵²	126	Lebanon	RCT, XG	HP	M, No intervention	HR, SpO ₂ , PIPP	..
Larsson 1998 ¹⁵³	111	Sweden	RCT, PG	VP	LA, No intervention	NFCS	5·0[0·8]
Leite 2009 ²⁸	60	Brazil	RCT, PG	HP	BF, No intervention	HR, SpO ₂ , NFCS	..
Lemyre 2007 ¹⁵⁴	137	Canada	RCT, PG	VP	OS+LA+NNS+SW, OS+Placebo (cream)+NNS+SW	PIPP	6·7[2·2]
Leng 2016 ¹⁵⁵	671	China	RCT, PG	HP	OS, OS+NNS, OS+SW, OS+NNS+SW	HR, SpO ₂ , NIPP, NFCS	..
Liaw 2010 ¹¹⁹	104	Taipei, USA	RCT, PG	HP	NNS, No intervention	PIPP	6·4[2·0]
Liaw 2011 ⁷⁰	165	Taiwan	RCT, PG	IMI	OS, NNS, No intervention	HR, NFCS	2·5[0·2]
Liaw 2012 ¹²⁰	34	Taiwan	RCT, XG	HP	NNS, SW, No intervention	PIPP	7·0[5·0]
Lima 2013 ²⁹	64	Brazil	RCT, PG	VP	BF, NNS, No intervention	NIPS	..
Lima 2017 ¹⁰¹	78	Brazil	RCT, PG	IMI	OS, NNS	HR, SpO ₂ , NIPS	0·8[0·2]
Lindh 2000 ¹⁵⁶	56	Sweden	RCT, PG	VP	LA, Placebo	HR	3·4[0·4]
Liu 2010 ⁷¹	105	Taipei	RCT, PG	VP	OS, NNS, No intervention	NIPS	3·0[0·6]
Liu 2015 ¹¹¹	40	China	RCT, PG	HP	SS, No intervention	HR, SpO ₂	..

Long 2003 ¹⁵⁷	32	Northern Ireland	RCT, PG	VP	LA, Placebo	NFCS	6·9[1·2]
Ludington-Hoe 2005 ¹¹²	23	USA	RCT, XG	HP	SS, No intervention	HR, SpO ₂	22[11·4]
Marcatto 2011 ¹⁵⁸	30	Brazil	RCT, PG	PICC	OS+LA, OS+Placebo (cream), LA+Placebo (water)	HR, NIPS	..
Marin Gabriel 2013 ¹⁵⁹	127	Spain	RCT, PG	HP	OS, SS, OS+SS, BF+SS	HR, SpO ₂ , NIPS	..
Marofi 2015 ¹⁶⁰	50	Iran	RCT, PG	HP	M, No intervention	HR, SpO ₂ , PIPP	..
Mathai 2006 ⁷²	70	India	RCT, PG	HP	OS, EBM, NNS, Placebo	DAN	1·9[0·01]
Milazzo 2011 ⁷³	47	USA	RCT, PG	AP	OS, No intervention	HR, SpO ₂ , NIPS	..
Mirzarahimi 2013 ¹²¹	60	Iran	RCT, PG	HP	NNS, No intervention	HR, SpO ₂ , PIPP	..
Morrow 2010 ¹⁶¹	42	USA	RCT, PG	HP	SW, No intervention	NIPS	..
Mosayebi 2014 ¹⁶²	64	Iran	RCT, XG	HP	SS, SS+SW	PIPP	7·3[3·7]
Nimbalkar 2013 ¹¹³	47	India	RCT, XG	HP	SS, No intervention	PIPP	..
Noori Shadkam 2008 ¹⁶³	220	Iran	RCT, PG	VP	OS+Placebo (cream), LA+Placebo (water)	NIPS	4·1
Obeidat 2015 ³⁰	128	Jordan	RCT, PG	HP	BF, No intervention	PIPP	5·8[0·3]
Ogawa 2005 ⁷⁴	50	Japan	RCT, PG	VP, HP	OS, Placebo	NFCS	..
Okan 2007 ⁷⁵	93	Turkey	RCT, XG	HP	OS, Placebo	HR, SpO ₂ , NFCS	..
Okan 2010 ¹¹⁴	107	Turkey	RCT, PG	HP	SS, BF+SS, Placebo	HR, SpO ₂ , NFCS	1·4[0·1]
Olsson 2016 ¹¹⁵	10	Sweden	RCT, XG	VP	SS, No intervention	HR, SpO ₂ , PIPP	6·6[4·7]
Ors 1999 ⁷⁶	102	Turkey	RCT, PG	HP	OS, EBM, Placebo	HR	1·4[1·6]
Ou-Yang 2013 ⁷⁷	123	Taiwan	RCT, PG	HP	OS, EBM, Placebo	HR, SpO ₂ , PIPP	..
Overgaard 1999 ⁷⁸	96	Denmark	RCT, PG	HP	OS, Placebo	NIPS	..
Ozdogan 2010 ⁷⁹	142	Turkey	RCT, PG	HP	OS (single, double dose), EBM (single, double dose), Placebo (double, single dose)	NFCS	2·2[0·2]
Patel 2003 ¹⁶⁴	10	Canada	RCT, XG	HP	LA, Placebo	PIPP, NIPS	2·8[1·4]
Peng 2018 ¹⁶⁵	109	Taiwan	RCT, PG	HP	NNS+EBM, NNS+EBM+SW, No intervention	PIPP	13·1[6·6]
Ramenghi 1996 ⁴⁷	60	UK	RCT, XG	HP	OS (25%, 50%, sweetener), Placebo	HR	0·3[0·2]
Ramenghi 1996 ⁸⁰	15	United Kingdom	RCT, XG	HP	OS, Placebo	HR	8·7[6·5]
Rawal 2018 ⁸¹	63	India	RCT, PG	HP	OS, EBM, Placebo	HR, SpO ₂ , PIPP	3·1[0·7]
Rioualen 2018 ⁴⁰	102	France	RCT, PG	VP	OS, BF	NFCS	2·9[0·5]
Rogers 2006 ⁸²	33	USA	RCT, PG	BC	OS, Placebo	DAN	..
Rossi 2018 ¹⁶⁶	120	Italy	RCT, PG	IMI, HP	M (Mozarts, Beethoven, heartbeat sounds), No intervention	HR, SpO ₂ , NIPS	..
Saeidi 2011 ¹¹⁶	60	Iran	RCT, PG	IMI	SS, No intervention	SpO ₂ , NIPS	..
Sahoo 2013 ⁸³	160	India	RCT, PG	VP	OS, EBM, Placebo	HR, SpO ₂ , PIPP	3·3[0·8]
Sajedi 2006 ⁸⁴	40	Iran	RCT, PG	IMI	OS, Placebo	HR, NIPS	..
Shabani 2016 ¹⁶⁷	20	Iran	RCT, XG	AP	M, No intervention	HR, SpO ₂ , NFCS	..
Shah 2017 ¹⁶⁸	35	Australia	RCT, XG	HP	OS, M, OS+M	HR, SpO ₂ , PIPP	4·0[6·0]
Shu 2014 ¹⁶⁹	50	Taiwan	RCT, PG	HP	SW, No intervention	HR, SpO ₂ , PIPP, NIPS	1·9[1·0]
Shukla 2018 ¹⁷⁰	100	India	RCT, PG	HP	OS, SS	PIPP	14·04[11·10]
Shukla 2018 ¹⁷¹	200	India	RCT, PG	HP	EBM, SS+EBM, SS+EBM+M, M+EBM	PIPP	8·2[7·4]
Simonse 2012 ³⁹	70	Netherlands	RCT, PG	HP	OS, BF, EBM	PIPP	..
Singh 2017 ³¹	80	India	RCT, PG	HP	BF, No intervention	HR, SpO ₂	..
Skogsdal 1997 ⁴⁶	120	Sweden	RCT, PG	HP	OS, EBM, No intervention	HR, SpO ₂	5·4[4·9]
Slater 2010 ⁸⁵	44	United Kingdom	RCT, PG	HP	OS, Placebo	PIPP	3·0[2·0]
Soliman 2016 ¹⁷²	60	Egypt	RCT, PG	CPAP	LA, No intervention	PIPP	4·3[2·9]
Soltani 2018 ³⁷	161	Iran	RCT, PG	HP	OS, BF, SS, LA	NIPS	..
Stevens 1999 ¹⁷³	122	Canada	RCT, XG	HP	OS+NNS, NNS+placebo (water), No intervention	PIPP	..
Stevens 1999 ¹⁷⁴	106	Canada	RCT, XG	HP	LA, Placebo	HR, SpO ₂ , PIPP	4·1[0·6]
Stevens 2018 ¹⁷⁵	236	Canada	RCT, PG	HP	OS (0.1 mL, 0.5 mL, 1.0 mL)+NNS	PIPP	8·3

Suhrabi 2014 ⁸⁶	90	Iran	RCT, PG	IMI	OS (sucrose, glucose), No intervention	NIPS	..
Sujatha 2017 ¹⁷⁶	155	India	RCT, PG	IMI	SW, OS+SW	SpO ₂ , NIPS	..
Taddio 2008 ⁸⁷	240	Canada	RCT, PG	IMI, VP, HP	OS, Placebo	PIPP	0·04[0·01]
Taddio 2011 ¹⁷⁷	321	Canada	RCT, PG	VP	OS+LA, LA+Placebo (water), OS+Placebo (cream)	HR, SpO ₂	..
Thakkar 2016 ⁸⁸	180	India	RCT, PG	HP	OS, NNS, OS+NNS, No intervention	PIPP	..
Tutag Lehr 2015 ⁸⁹	56	USA	RCT, PG	HP	OS, Placebo	NIPS	..
Upadhyay 2004 ¹⁰²	81	India	RCT, PG	VP	EBM, Placebo	HR, SpO ₂ , NFCS	8·8[5·0]
Uyan 2005 ¹⁰³	62	Turkey	RCT, PG	HP	EBM (foremilk, hind milk), Placebo	HR	6·3[1·1]
Uzelli 2015 ⁹⁰	80	Turkey	RCT, PG	IMI	OS, No intervention	SpO ₂ , NIPS	22·3[0·7]
Yilmaz 2011 ⁹¹	120	Turkey	RCT, PG	HP	OS, EBM, NNS, No intervention	HR, NIPS	3·4[0·4]
Zargham-Boroujeni 2017 ³²	75	Iran	RCT, PG	VP	BF, No intervention	NIPS	..
Zhu 2015 ³³	250	China	RCT, PG	HP	BF, M, BF+M, No intervention	NIPS	3·3[0·3]

PG = parallel groups, XG - crossover groups, RCT = randomised controlled trials, PG = parallel groups, XG = crossover groups, VP = venepuncture, HP = heel prick, IMI = IM injection, LP = lumbar puncture, PICC = PICC line insertion, CPAP = CPAP prongs insertion, BC = bladder catheterisation, SC = subcutaneous injection, VC = vaccination, OS = oral sugar, BF = breastfeeding, EBM = expressed breast milk, NNS = non-nutritive sucking, SS = skin-to-skin, SW = swaddling, LA = topical local anaesthetic, PCM = paracetamol, M = music

*Reported where available, or where available data could be converted to a mean and standard deviation for the study population using previously described methodology.¹⁻³

1. Hozo S.P., Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;**5**,13
2. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* 2014;**14**:135
3. Bornstein M, Hedges L.V, Higgins J.P.T, Rothstein H. (2009) "Introduction to Meta-Analysis" Print ISBN:9780470057247 Copyright © 2009 John Wiley & Sons, Ltd

Supplementary Table 4: Panel’s GRADE summary of evidence table for PICO questions discussed in Results

PICO: In neonates ≤ 28 days, which of the following is superior in reducing pain during routine procedures?	Studies	Neonates	Bias	Inconsistency	Indirectness	Imprecision	Summary	Certainty†
BF versus placebo/no intervention	12	991					BF is superior to placebo/no intervention**	⊕⊕⊕⊕
BF versus OS	8	670					BF is superior to OS**	⊕⊕○○
BF versus EBM	3	136					BF is superior to EBM	⊕⊕⊕○
BF versus SS	2	160					BF is superior to SS**	⊕⊕⊕○
EBM versus placebo/no intervention	14	863					EBM is superior to placebo/no intervention **	⊕⊕⊕○
EBM versus OS	14	920					EBM is inferior to OS ≥10%.	⊕⊕⊕○
OS versus placebo/no intervention	58	3948					OS is superior to placebo/no intervention**	⊕⊕⊕⊕
OS versus NNS	11	645					OS is superior to NNS	⊕⊕○○
OS versus OS with NNS	10	837					OS is inferior to OS with NNS	⊕⊕⊕○
OS: concentration ≥24% versus <24% ¹	6*	453					OS ≥24% is superior to <24% solution	⊕⊕⊕○
OS: concentration 24-25% versus 50% ¹	3*	110					OS 24-25% may not be inferior OS 50%	⊕○○○
OS: volume ≤2 mL versus >2 mL ²	*	..					Volumes >2 mL do not increase efficacy	⊕⊕⊕○
Sucrose, glucose, dextrose, fructose versus sweeteners ³	*	..					None are clearly superior to the others	⊕⊕⊕○
SS versus placebo/no intervention	16	1054					SS is superior to placebo/no intervention**	⊕⊕⊕⊕
NNS versus placebo/no intervention	16	932					NNS is superior to placebo/no intervention **	⊕⊕⊕○
NNS versus NNS with OS	4	192					NNS is inferior to NNS with OS**	⊕⊕⊕⊕

BF: Breastfeeding; OS: Oral sugar; EBM: Expressed breastmilk; NNS: Non-nutritive sucking; SS: Skin-to-skin

Notes:

1. Oral sugar concentration: range = 5-50%, median: 25%. The concentrations directly compared varied. We grouped according to <24%, ≥24% and 50%.

2. Volume: range= 0.05-5 mL, median=2 mL

3. Sucrose (number of studies (#) = 52), glucose (#=33), dextrose (#=8), sweetener (#=2) fructose (#=1))

* No/few direct comparative studies, therefore indirect analysis across whole data set performed.

** Quantitative analysis of any one of the outcome measures supports conclusion with 95% confidence

† The GRADE framework also allows for “Other Considerations” to determine the overall certainty in effect estimate.

	Risk of bias			Certainty of conclusion using GRADE analysis			
KEY	Not serious	Serious	Very serious	⊕⊕⊕⊕ High	⊕⊕⊕○ Moderate	⊕⊕○○ Low	⊕○○○ Very low

Supplementary Table 5. Summary of narrative synthesis findings with associated references showing superiority, equivalence or inferiority of the analgesic versus the comparator as described in the Results

PICO		Analgesic versus Comparator		
Analgesic	Comparator	Superior	Equivalence	Inferior
Breastfeeding	Placebo or no intervention	22,23,24,25,26,27,28,29,30,31,32,33
Breastfeeding	Oral sugar	24,34,35,36,37	38,39	40
Breastfeeding	Expressed breast milk	27,34	..	39
Breastfeeding	Skin-to-skin	37,41
Oral sugar \geq 24%	Oral sugar <24%	42,43,44,45,46	..	47
Oral sugar	Placebo or no intervention	24,42,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91	92,93,94,95,96,97,98,99	..
Oral sugar	Expressed breast milk	45,46,76,77,79,81,83,91,100	34,39,53,72,99	
Oral sugar	Non-nutritive sucking	91,101	61,64,70,88,92,98	58,71,72
Expressed breast milk	Placebo or no intervention	45,53,76,77,81,83,91,99,102	27,46,72,79,103	..
Skin-to-skin	Placebo or no intervention	43,94,104,105,106,107,108,109,110,111,112,113,114,115,116,	117	..
Non-nutritive sucking	Placebo or no intervention	29,56,58,61,64,70,71,72,88,91,98,118,119,120,121	122	..

Supplementary Table 6. Panel's GRADE summary of evidence table for PICO's not discussed in Results

PICO: In neonates ≤ 28 days, which of the following is superior in reducing pain during routine, acutely painful procedures?	Studies	Neonates	Bias	Inconsistency	Indirectness	Imprecision	Summary	Certainty†
BF versus swaddling	3	243	⊕	⊕	⊕	⊕	BF may not be inferior to swaddling	⊕○○○
BF versus BF with music	1	126	⊕	⊕	⊕	⊕	BF is not inferior to BF with music	⊕⊕○○
Sugar versus skin to skin	4	561	⊕	⊕	⊕	⊕	Sugar may be inferior to skin-to-skin**	⊕○○○
Sugar versus LA	7	880	⊕	⊕	⊕	⊕	Sugar is superior to LA	⊕⊕⊕⊕
Sugar versus sugar with skin-to-skin	2	387	⊕	⊕	⊕	⊕	Sugar is inferior to sugar with skin-to-skin	⊕⊕○○
Sugar versus sugar with LA	4	335	⊕	⊕	⊕	⊕	Sugar is not inferior to sugar with LA	⊕⊕⊕○
Sugar versus sugar with music	2	115	⊕	⊕	⊕	⊕	Sugar is inferior to sugar with music	⊕⊕○○
Skin-to-skin versus swaddling	3	255	⊕	⊕	⊕	⊕	Skin-to-skin is no different than swaddling**	⊕○○○
NNS versus swaddling	2	101	⊕	⊕	⊕	⊕	NNS is no different than swaddling	⊕○○○
LA versus placebo/no intervention	11	656	⊕	⊕	⊕	⊕	LA is not superior to placebo/no intervention**	⊕⊕○○
LA versus LA with sugar	3	256	⊕	⊕	⊕	⊕	LA is not inferior to LA with sugar	⊕⊕⊕○
Swaddling versus placebo/no intervention	8	410	⊕	⊕	⊕	⊕	Swaddling is not superior to placebo/no intervention	⊕⊕○○
Swaddling versus swaddling with BF or NNS	2	197	⊕	⊕	⊕	⊕	Swaddling is not inferior to swaddling with BF or NNS	⊕○○○
Music versus placebo/no intervention	6	487	⊕	⊕	⊕	⊕	Music is not superior to placebo/no intervention**	⊕⊕○○

BF = breastfeeding, LA = topical local anaesthetics, NNS = non-nutritive sucking.

** Quantitative analysis of any of the outcome measures supports conclusion with 95% confidence threshold

† The GRADE framework also allows for “Other Considerations” to determine the overall certainty in effect estimate.

	Risk of bias			Certainty of conclusion using GRADE analysis			
KEY	Not serious	Serious	Very serious	⊕⊕⊕⊕ High	⊕⊕⊕○ Moderate	⊕⊕○○ Low	⊕○○○ Very low

Supplementary Table 7. Table counting the number of the 149 studies, which studied the following procedures, analgesics and outcome measures

Procedures	n	Analgesics	n	Outcome measures	n
Heel prick	88	Oral sugar	78	Heart rate	76
Venipuncture/cannula	40	Skin-to-skin	22	Transcutaneous oxygen saturation	49
IM/SC injection	19	Breast feeding	21	Premature infant pain profile (PIPP)	57
Arteripuncture	4	Expressed breast milk	19	Neonatal facial coding system (NFCS)	22
CPAP prongs insertion	1	Non-nutritive sucking	19	Neonatal infant pain scale (NIPS)	32
Urinary catheterisation	1	Topical local anaesthesia	13	Douleur Aigue du Nouveau-ne scale (DAN)	12
Lumbar puncture	1	Swaddling	15		
..	..	Music	9		
..	..	Paracetamol	1		

Supplementary Table 8. Table of each component judged for Cochrane risk of bias for each study included in analysis

	Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall judgement of study risk of bias
Abad 1996 ⁴²								
Abad 2001 ⁴⁸								
Acharva 1998 ¹³⁰								
Acharva 2004 ⁴⁹								
Ahuja 2000 ⁵⁰								
Akcam 2004 ⁵¹								
Akcam 2004 ⁵²								
Altun-Koroglu 2010 ⁵³								
Aydin 2019 ²²								
Badiee 2009 ¹³¹								
Basnet 2010 ⁵⁴								
Bauer 2004 ⁵⁵								
Beken 2014 ¹³²								
Belliemi 2001 ⁵⁶								
Belliemi 2002 ⁹²								
Belliemi 2013 ¹³³								
Bembich 2018 ³⁴								
Biran 2011 ¹³⁴								
Blass 1999 ⁵⁷								
Brovedani 2007 ³⁸								
Bucher 1995 ¹³⁵								
Bueno 2012 ¹⁰⁰								
Butt 2000 ¹³⁶								
Campos 1989 ¹³⁷								
Carbajal 1999 ⁵⁸								
Carbajal 2002 ⁵⁹								
Carbajal 2003 ²³								
Cardoso 2014 ⁹³								
Castral 2008 ¹⁰⁴								
Chermont 2009 ⁹⁴								
Chiabi 2016 ³⁵								
Codipietro 2008 ³⁶								
Collados-Gomez 2018 ¹³⁸								
Cong 2009 ¹⁰⁵								
Cong 2011 ¹⁰⁶								
Cong 2012 ¹⁰⁷								
Cook 2017 ⁹⁵								
Corbo 2000 ¹²²								
DeBernardo 2019 ¹³⁹								
DeMelo 2017 ¹⁴⁰								
Deshmukh 2002 ⁶⁰								
Dezhdar 2016 ⁴³								
Elserafv 2009 ⁶¹								
Eriksson 1999 ⁶²								
Eriksson 2004 ⁶³								
Erkut 2017 ¹⁴¹								

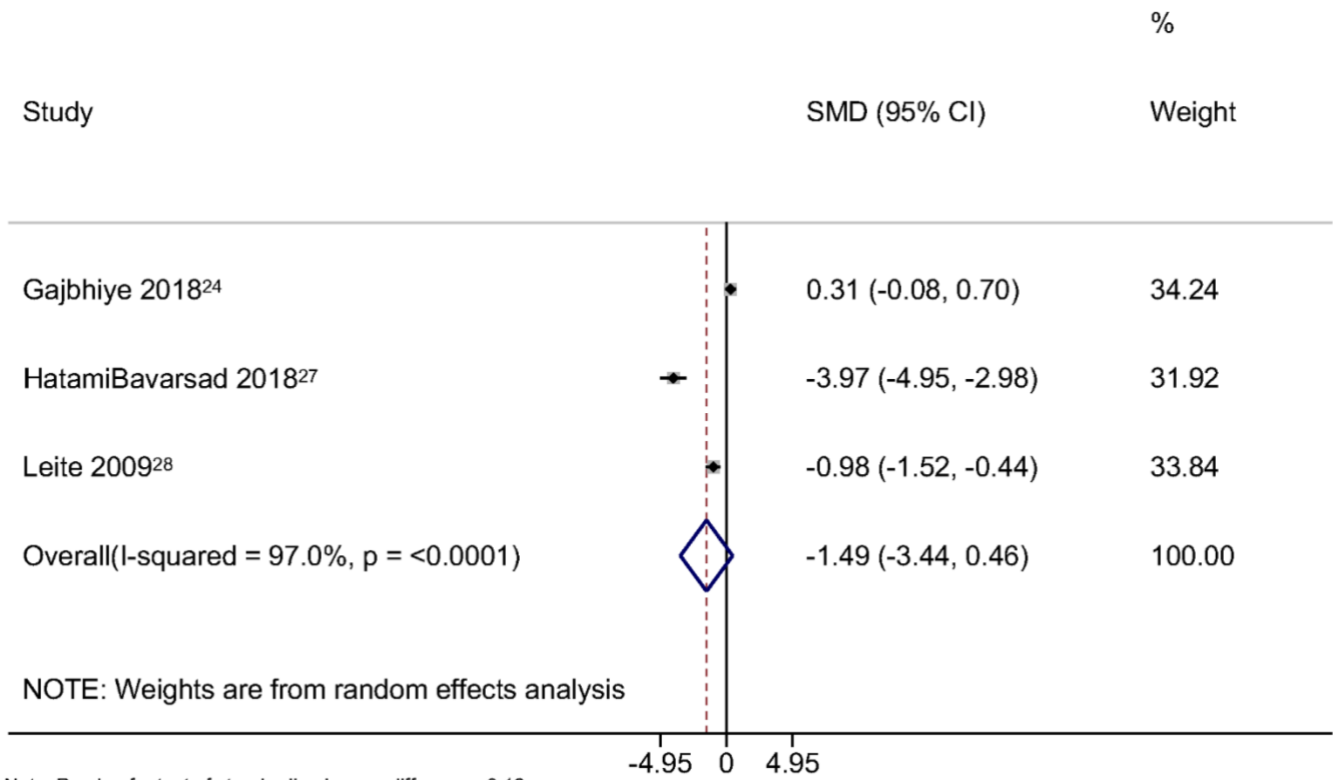
Fallah 2017 ⁴¹								
Field 1984 ¹¹⁸								
Gaibhivie 2018 ²⁴								
Gao 2015 ¹¹⁷								
Gao 2018 ⁶⁴								
Gerull 2013 ¹⁴²								
Gharehbaghi 2007 ⁶⁵								
Gibbins 2002 ¹⁴³								
Golestan 2007 ⁹⁶								
Gormally 2001 ⁹⁷								
Gradin 2002 ¹⁴⁴								
Gradin 2004 ⁶⁶								
Grav 2000 ¹⁰⁸								
Gray 2002 ²⁵								
Gray 2012 ⁹⁸								
Haouari 1995 ⁴⁴								
Harrison 2003 ⁶⁷								
Hashemi 2016 ²⁶								
HatamiBavarsad 2018 ²⁷								
Ho 2016 ¹⁴⁵								
Holsti 2011 ¹⁴⁶								
Hsieh 2018 ⁹⁹								
Huang 2004 ¹⁴⁷								
Jain 2000 ¹⁴⁸								
Jatana 2003 ⁴⁵								
Johnston 1997 ⁶⁸								
Johnston 1999 ⁶⁹								
Johnston 2003 ¹⁰⁹								
Johnston 2008 ¹⁴⁹								
Kashaninia 2008 ¹¹⁰								
Kaur 2003 ¹⁵⁰								
Kristoffersen 2018 ¹⁵¹								
KurdahiBadr 2017 ¹⁵²								
Larsson 1998 ¹⁵³								
Leite 2009 ²⁸								
Lemvre 2007 ¹⁵⁴								
Leng 2016 ¹⁵⁵								
Liaw 2010 ¹¹⁹								
Liaw 2011 ⁷⁰								
Liaw 2012 ¹²⁰								
Lima 2013 ²⁹								
Lima 2017 ¹⁰¹								
Lindh 2000 ¹⁵⁶								
Liu 2010 ⁷¹								
Liu 2015 ¹¹¹								
Long 2003 ¹⁵⁷								
Ludington-Hoe 2005 ¹¹²								
Marcatto 2011 ¹⁵⁸								
Marin Gabriel 2013 ¹⁵⁹								
Marofi 2015 ¹⁶⁰								
Mathai 2006 ⁷²								
Milazzo 2011 ⁷³								
Mirzarahimi 2013 ¹²¹								
Morrow 2010 ¹⁶¹								
Mosavebi 2014 ¹⁶²								
Nimbalkar 2013 ¹¹³								
NooriShadkam 2008 ¹⁶³								
Obeidat 2015 ³⁰								
Ogawa 2005 ⁷⁴								
Okan 2007 ⁷⁵								
Okan 2010 ¹¹⁴								
Olsson 2016 ¹¹⁵								
Örs 1999 ⁷⁶								

Ou-Yang 2013 ⁷⁷								
Overgaard 1999 ⁷⁸								
Ozdogan 2010 ⁷⁹								
Patel 2003 ¹⁶⁴								
Peng 2018 ¹⁶⁵								
Ramenghi 1996 ⁴⁷								
Ramenghi 1996 ⁸⁰								
Rawal 2018 ⁸¹								
Rioualen 2018 ⁴⁰								
Rogers 2006 ⁸²								
Rossi 2018 ¹⁶⁶								
Saeidi 2011 ¹¹⁶								
Sahoo 2013 ⁸³								
Sajedi 2006 ⁸⁴								
Shabani 2016 ¹⁶⁷								
Shah 2017 ¹⁶⁸								
Shu 2014 ¹⁶⁹								
Shukla 2018 ¹⁷⁰								
Shukla 2018 ¹⁷¹								
Simonse 2012 ³⁹								
Singh 2017 ³¹								
Skogsdal 1997 ⁴⁶								
Slater 2010 ⁸⁵								
Soliman 2016 ¹⁷²								
Soltani 2018 ³⁷								
Stevens 1999 ¹⁷³								
Stevens 1999 ¹⁷⁴								
Stevens 2018 ¹⁷⁵								
Suhrabi 2014 ⁸⁶								
Suiatha 2017 ¹⁷⁶								
Taddio 2008 ⁸⁷								
Taddio 2011 ¹⁷⁷								
Thakkar 2016 ⁸⁸								
Tutag Lehr 2015 ⁸⁹								
Upadhvay 2004 ¹⁰²								
Uyan 2005 ¹⁰³								
Uzelli 2015 ⁹⁰								
Yilmaz 2011 ⁹¹								
Zargham-Boroujeni 2017 ³²								
Zhu 2015 ¹³³								

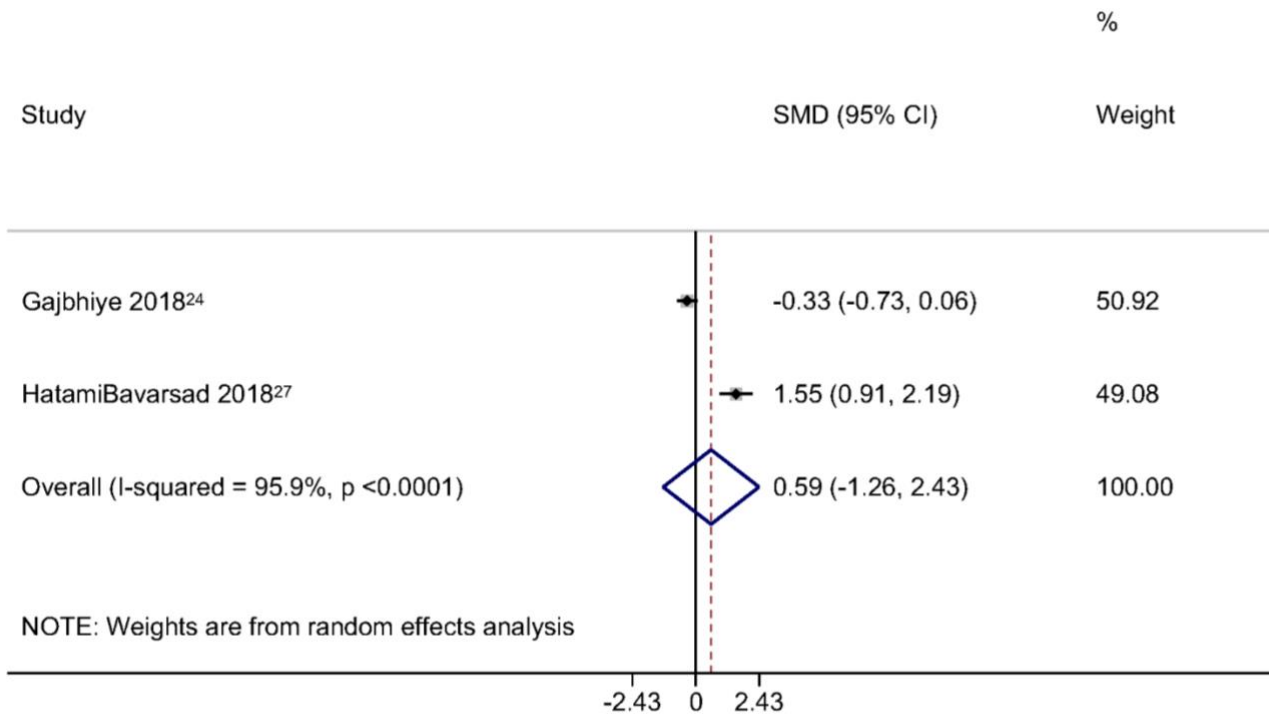
Legend for Cochrane risk of bias assessment

High	
Low	
Unclear	

Supplementary Figure 1: Standardised mean differences and their confidence intervals for the comparison of breastfeeding versus placebo or no intervention for heart rate

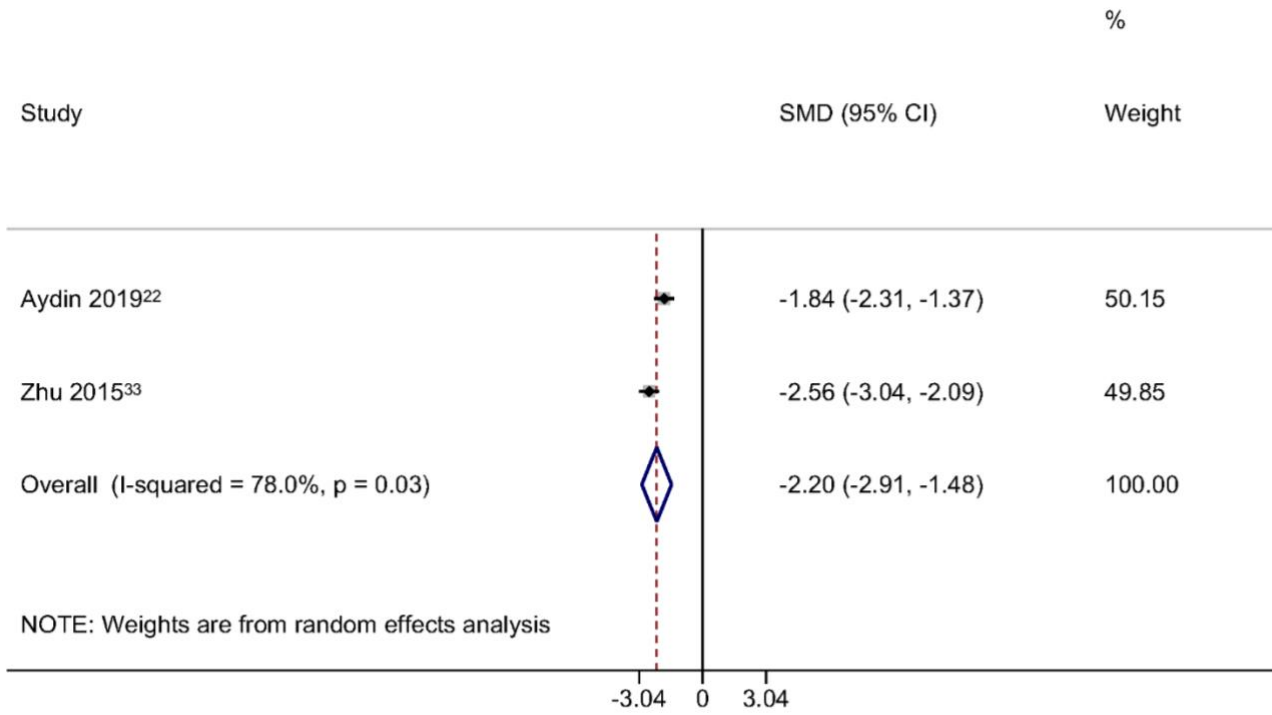


Supplementary Figure 2: Standardised mean differences and their confidence intervals for the comparison of breastfeeding versus placebo or no intervention for oxygen saturation



Note: P-value for test of standardised mean difference: 0.53
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

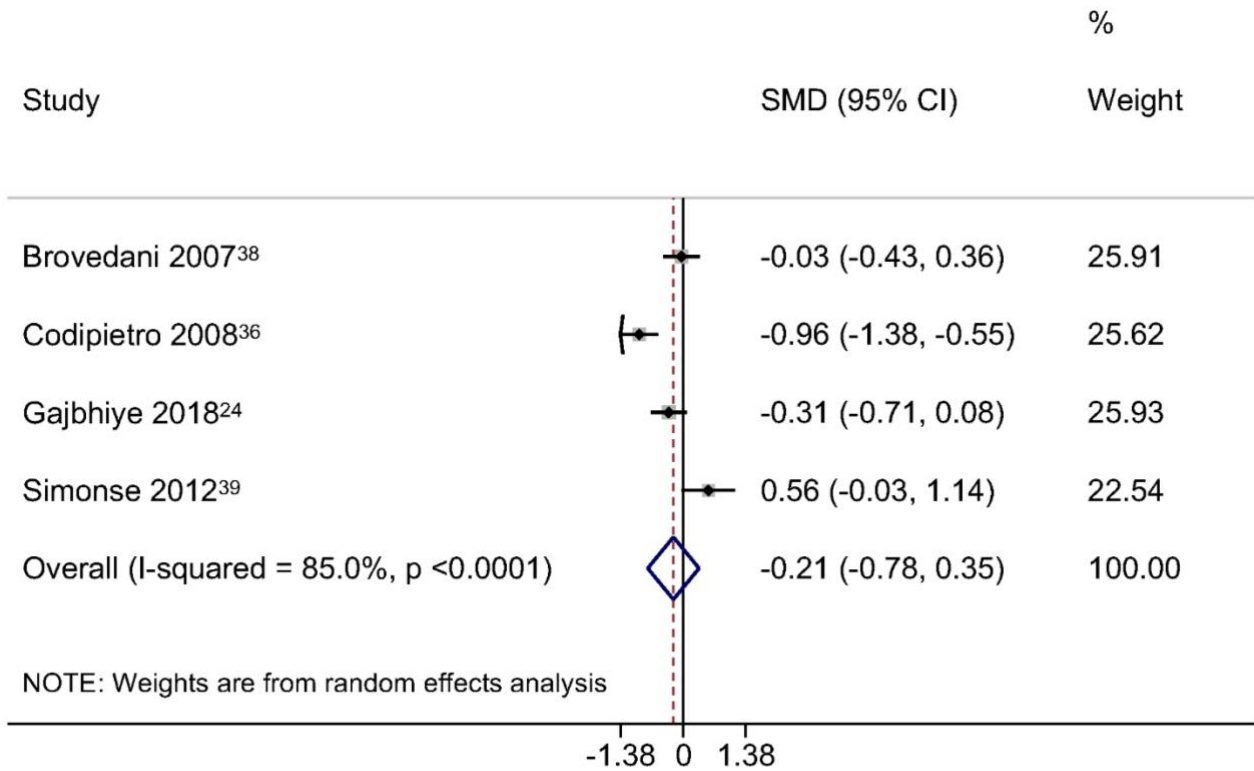
Supplementary Figure 3: Standardised mean differences and their confidence intervals for the comparison of breastfeeding versus placebo or no intervention for NIPS



Note: P-value for test of standardised mean difference: < 0.001

Abbreviations: NIPS=Neonatal Infant Pain Scale. CI=confidence interval. SMD=standardised mean difference

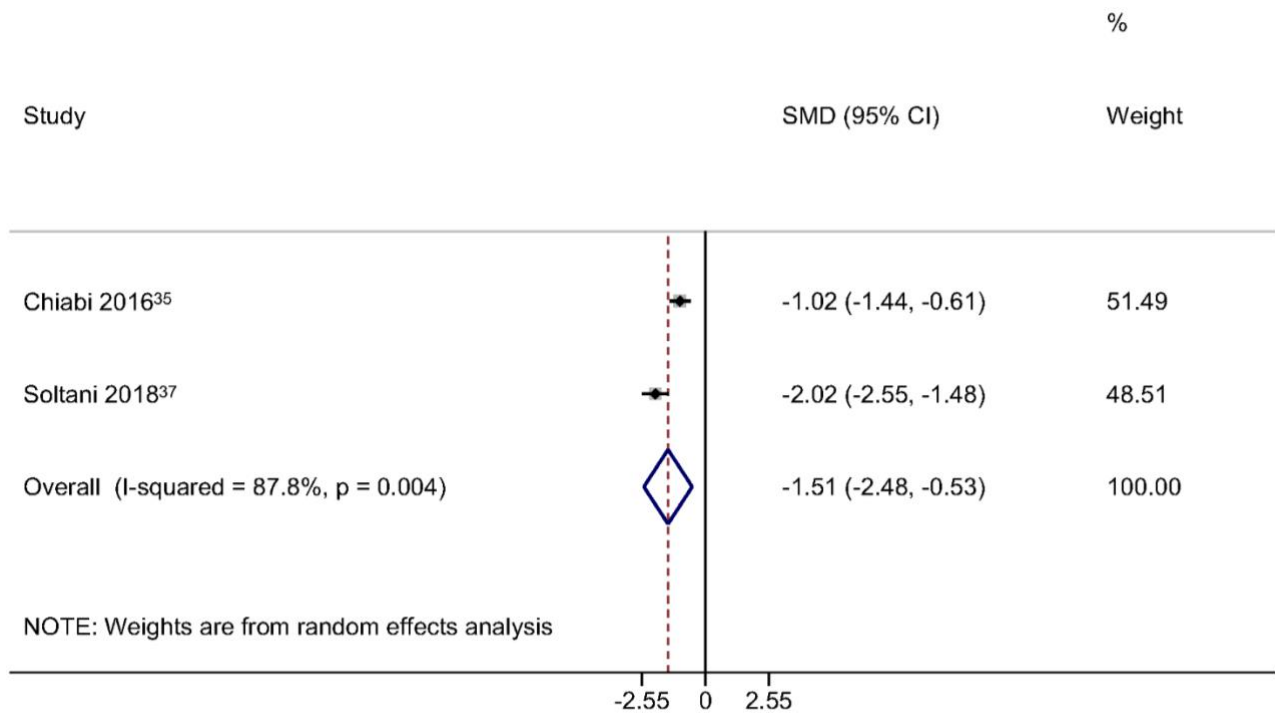
Supplementary Figure 4: Standardised mean differences and their confidence intervals for the comparison of breastfeeding versus oral sugar for PIPP



Note: P-value for test of standardised mean difference: 0.46

Abbreviations: CI=confidence interval. SMD=standardised mean difference. PIPP=Premature Infant Pain Profile

Supplementary Figure 5: Standardised mean differences and their confidence intervals for the comparison of breastfeeding versus oral sugar for NIPS



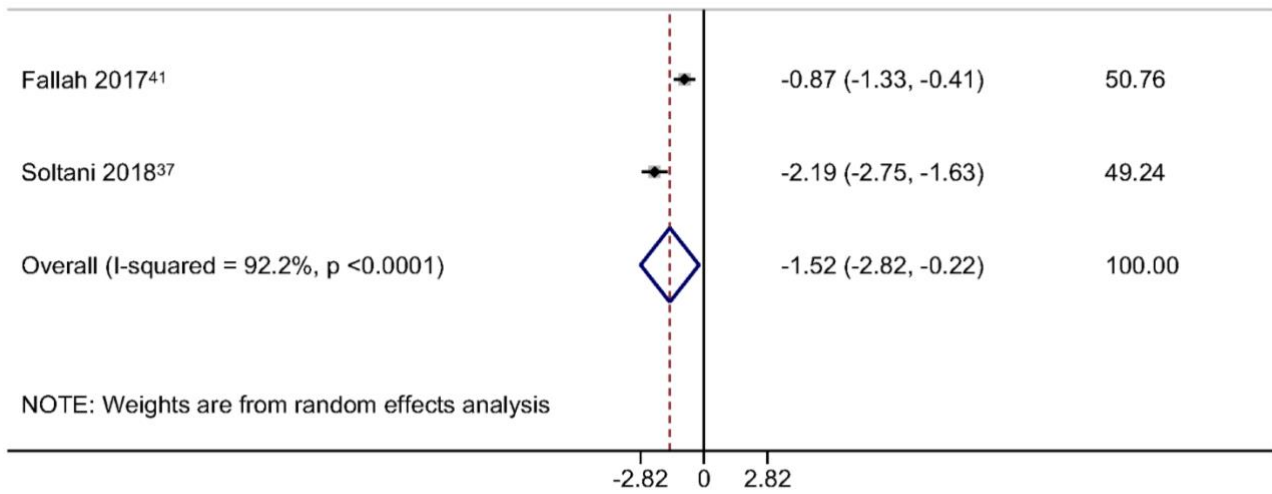
Note: P-value for test of standardised mean difference: 0.002

Abbreviations: CI=confidence interval, SMD=standardised mean difference, NIPS=Neonatal Infant Pain Scale

Supplementary Figure 6: Standardised mean differences and their confidence intervals for the comparison of breastfeeding versus skin-to-skin for NIPS

%

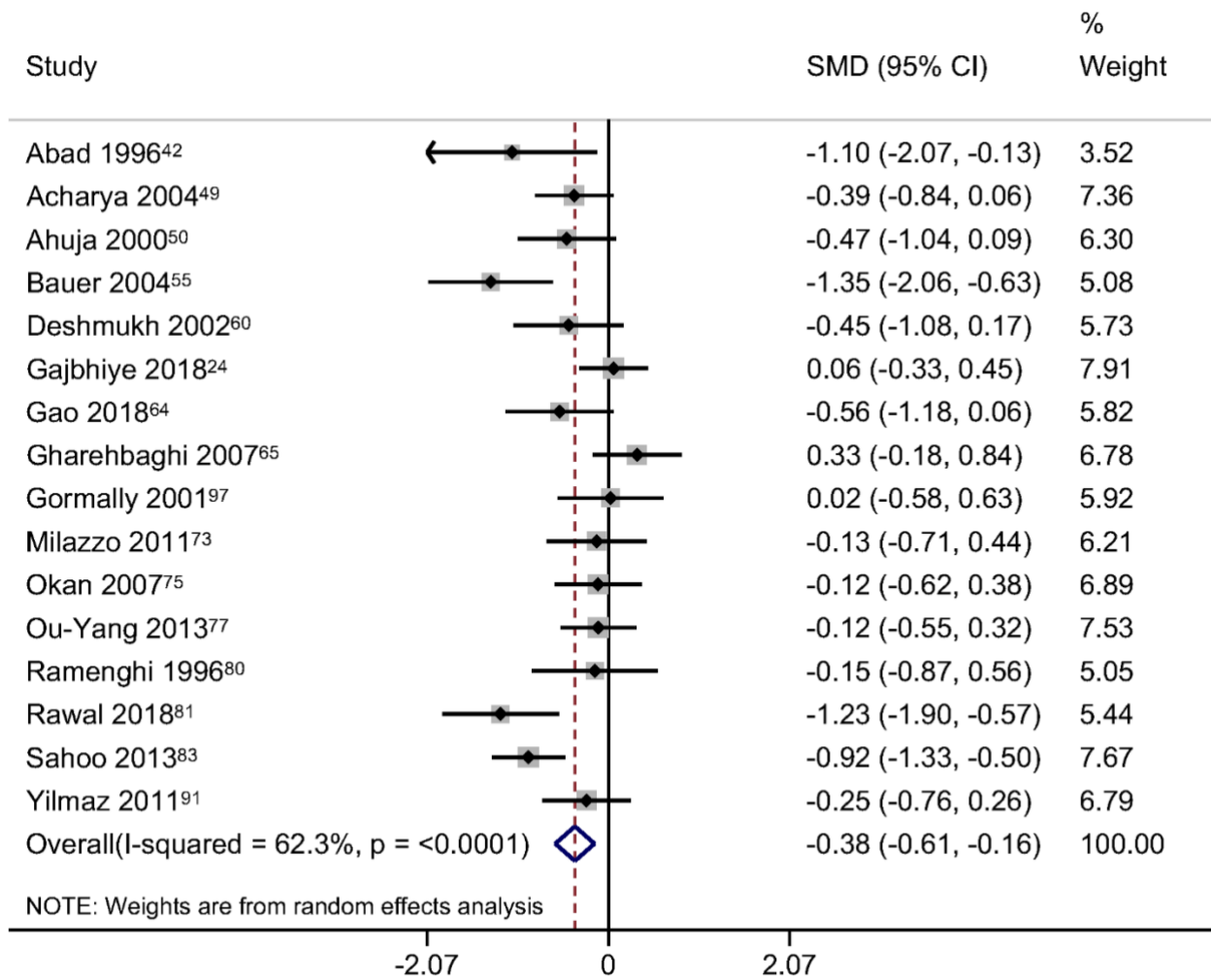
Study SMD (95% CI) Weight



Note: P-value for test of standardised mean difference: 0.02

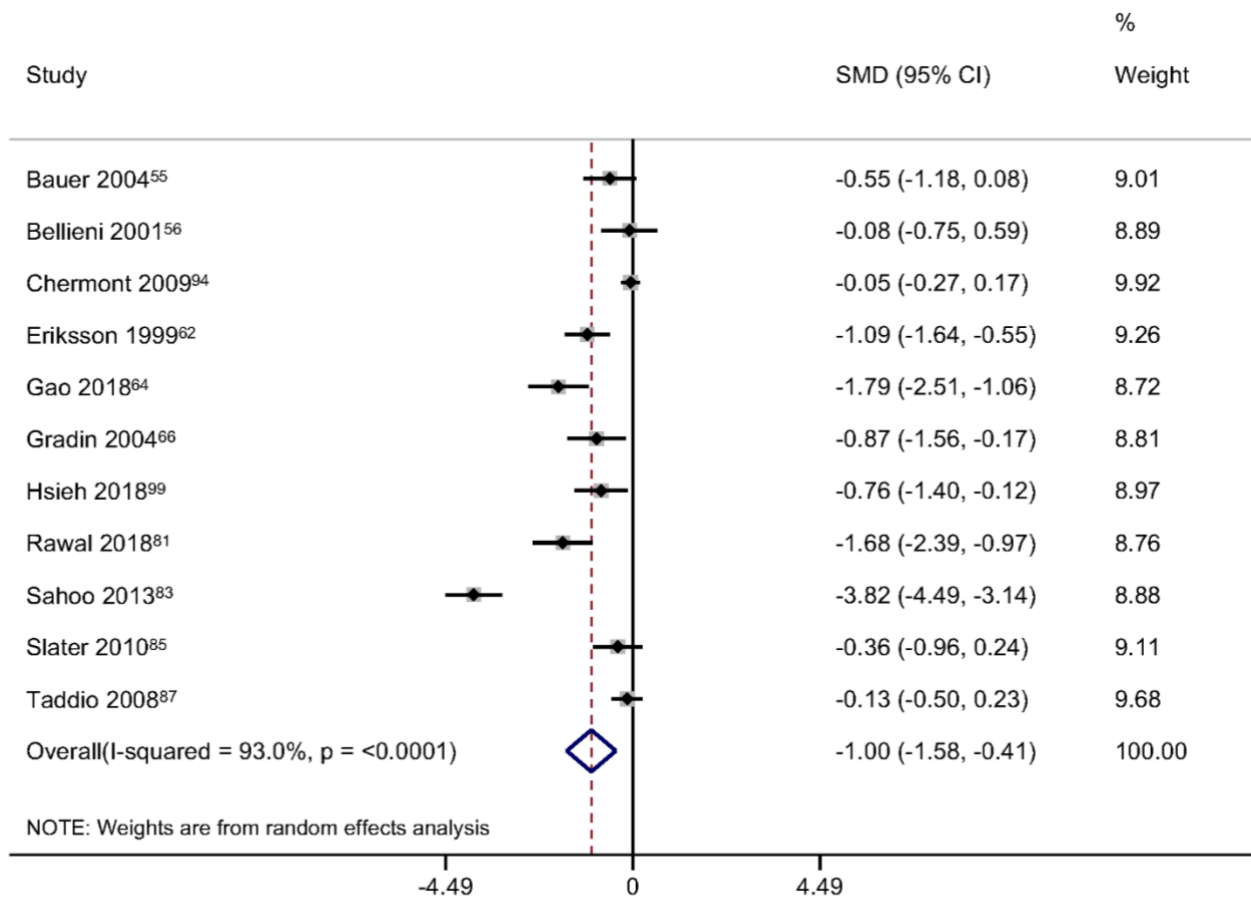
Abbreviations: CI=confidence interval. SMD=standardised mean difference. NIPS=Neonatal Infant Pain Scale

Supplementary Figure 7. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for heart rate



Note: P-value for test of standardised mean difference: 0.001
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

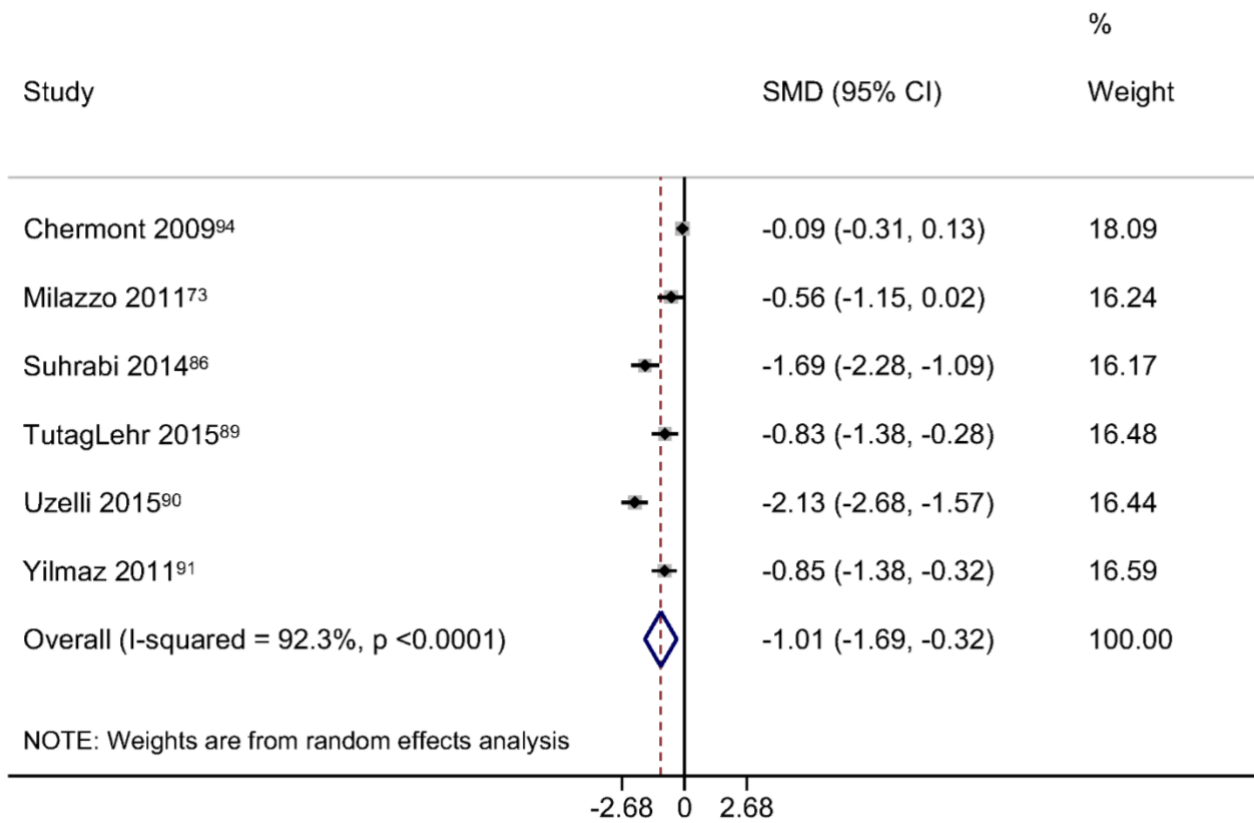
Supplementary Figure 8. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for PIPP



Note: P-value for test of standardised mean difference: 0.001

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

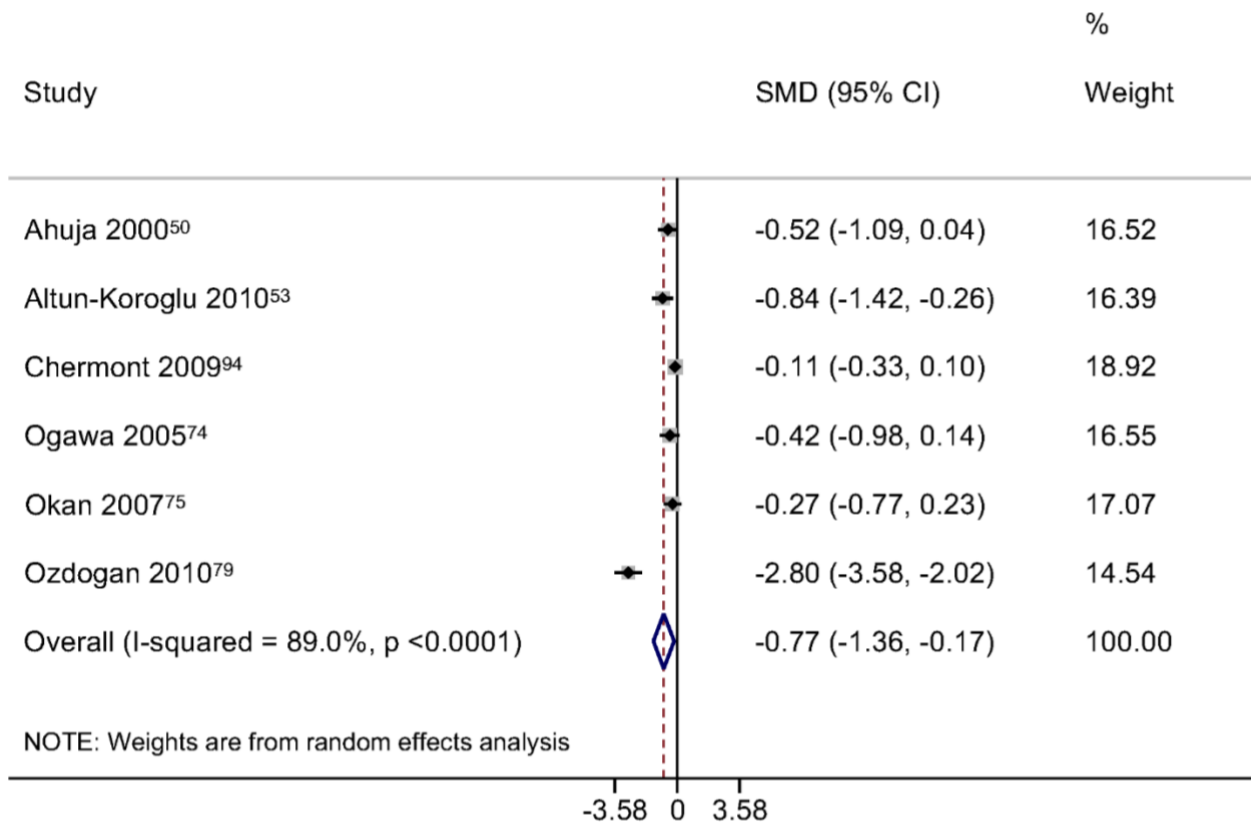
Supplementary Figure 9. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for NIPS



Note: P-value for test of standardised mean difference: 0.004

Abbreviations: CI=confidence interval, SMD=standardised mean difference, NIPS=Neonatal Infant Pain Scale

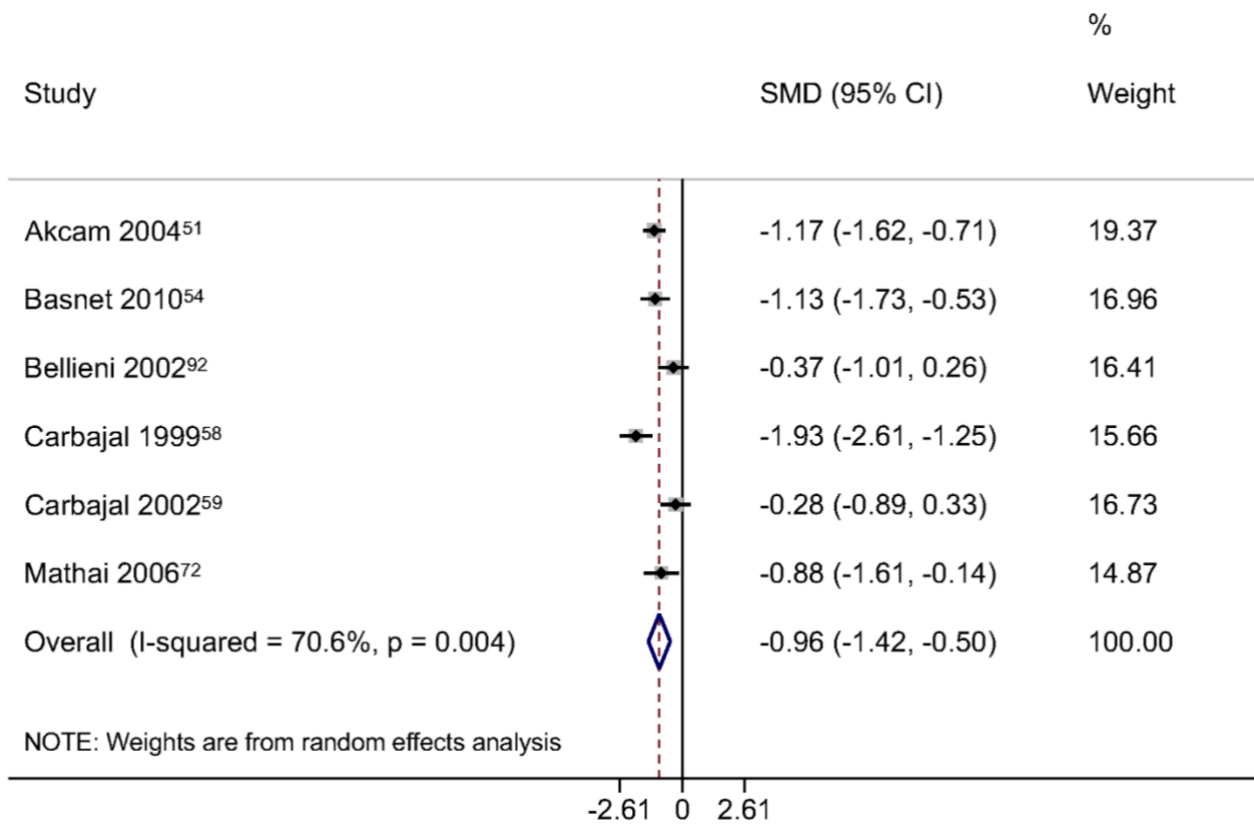
Supplementary Figure 10. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for NFCS



Note: P-value for test of standardised mean difference: 0.01

Abbreviations: CI=confidence interval, SMD=standardised mean difference, NCFS= Neonatal Facial Coding System

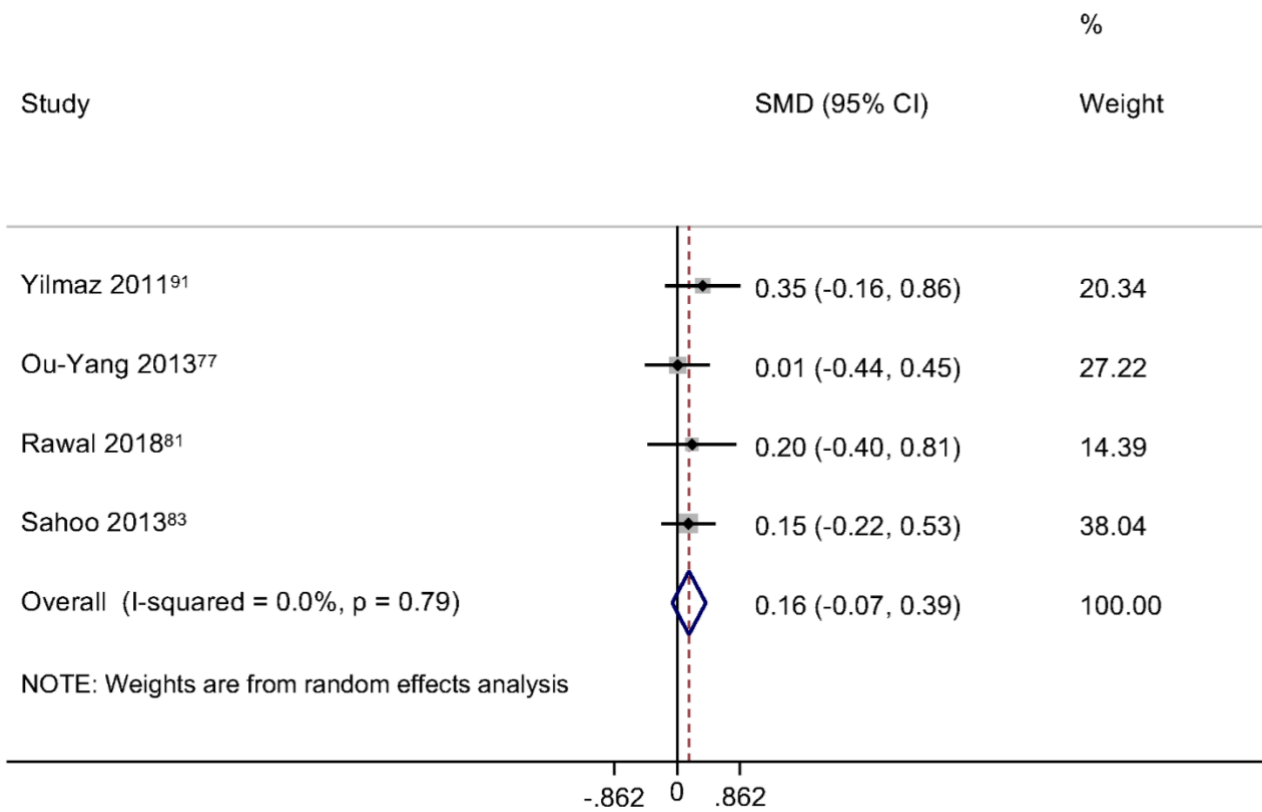
Supplementary Figure 11. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for DAN



Note: P-value for test of standardised mean difference: p < 0.001

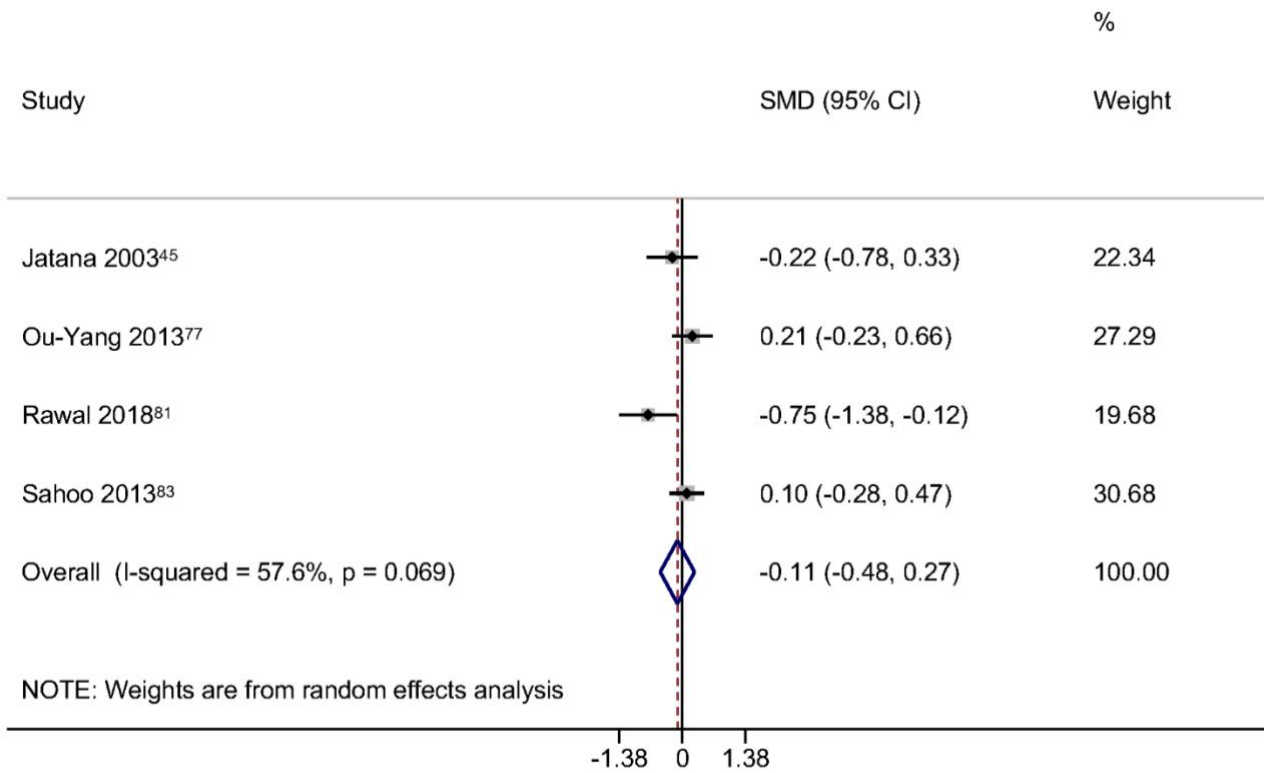
Abbreviations: CI=confidence interval, SMD=standardised mean difference, DAN= Douleur Aigue du Nouveau-né

Supplementary Figure 12. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk versus oral sugar for heart rate



Note: P-value for test of standardised mean difference: 0.17
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

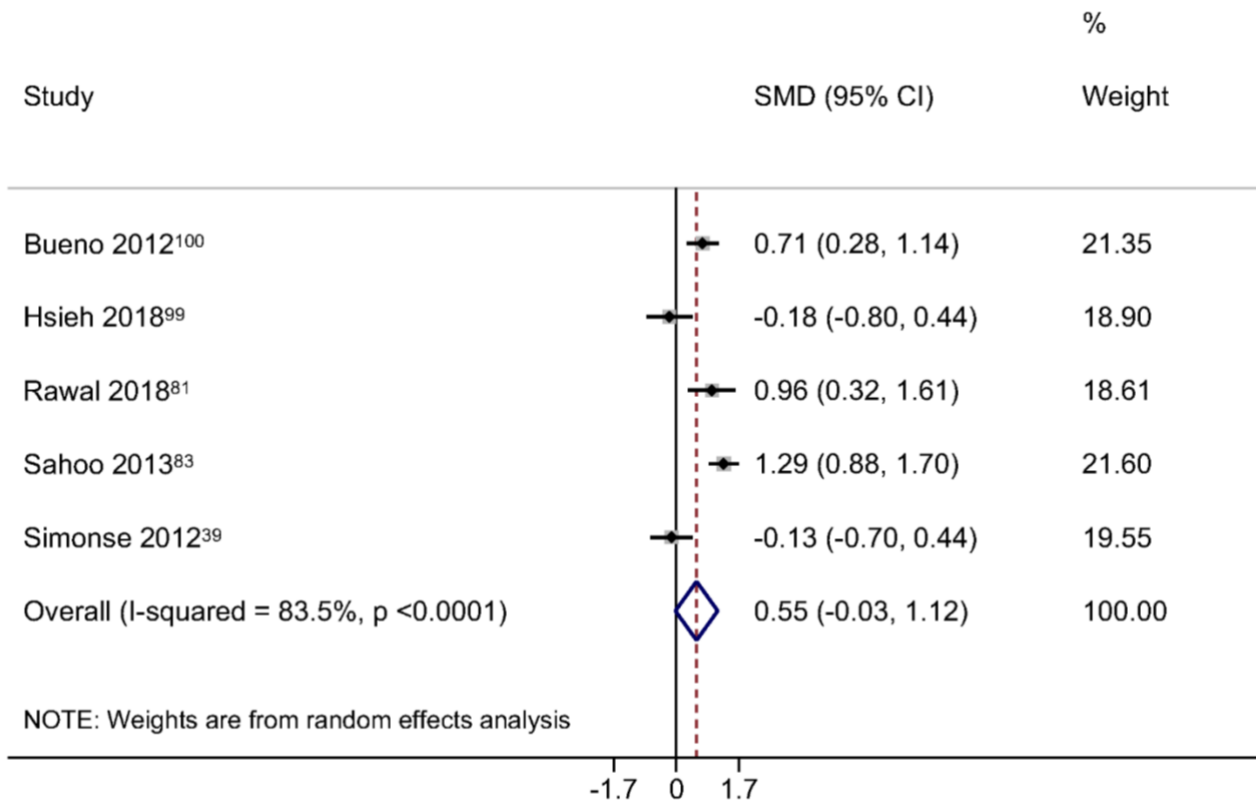
Supplementary Figure 13. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk vs oral sugar for oxygen saturation



Note: P-value for test of standardised mean difference: 0.57

Abbreviations: CI=confidence interval, SMD=standardised mean difference

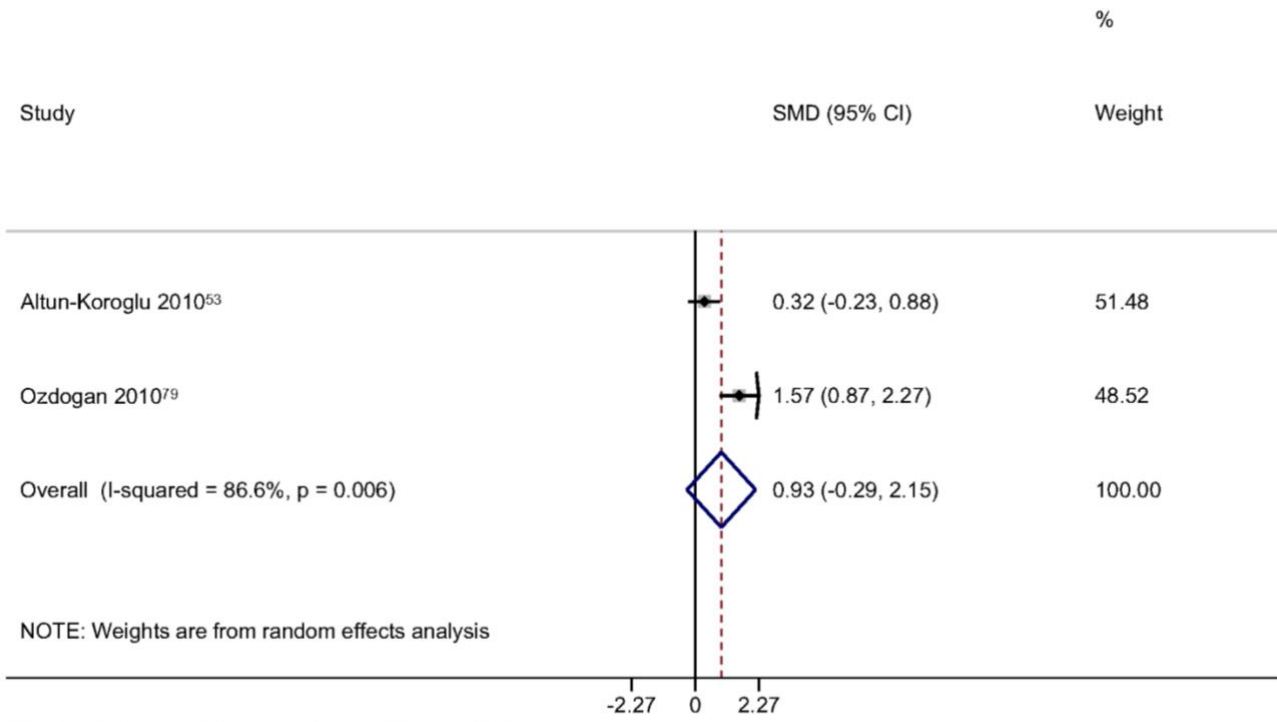
Supplementary Figure 14. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk versus oral sugar for PIPP



Note: P-value for test of standardised mean difference: 0.061

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

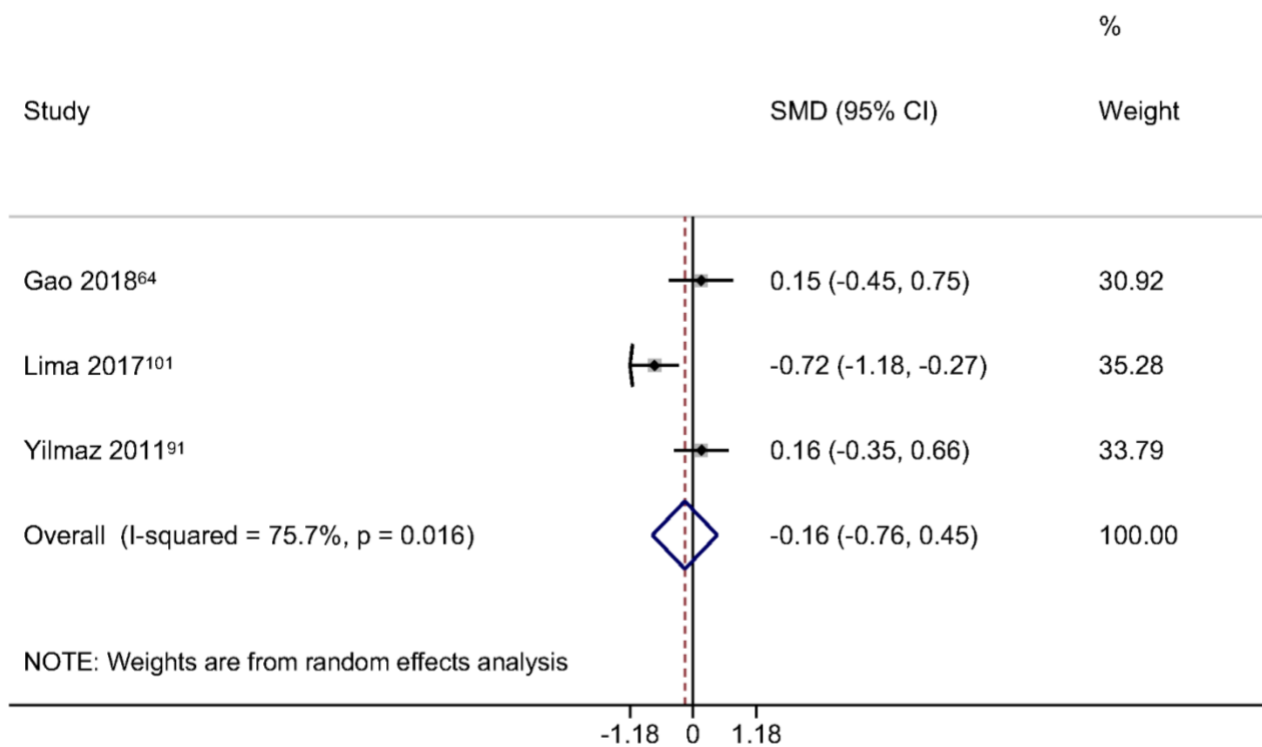
Supplementary Figure 15. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk versus oral sugar for NFCS



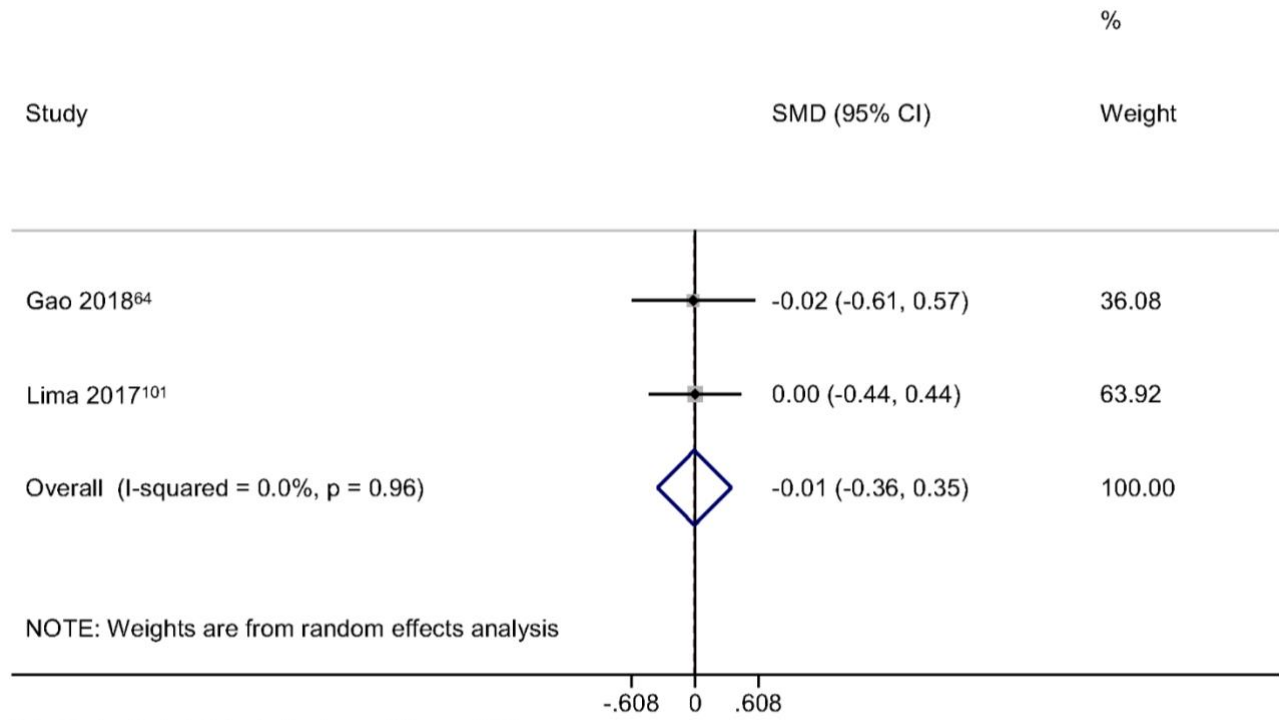
Note: P-value for test of standardised mean difference: 0.14

Abbreviations: CI=confidence interval, SMD=standardised mean difference, NCFS= Neonatal Facial Coding System

Supplementary Figure 16. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking versus oral sugar for heart rate



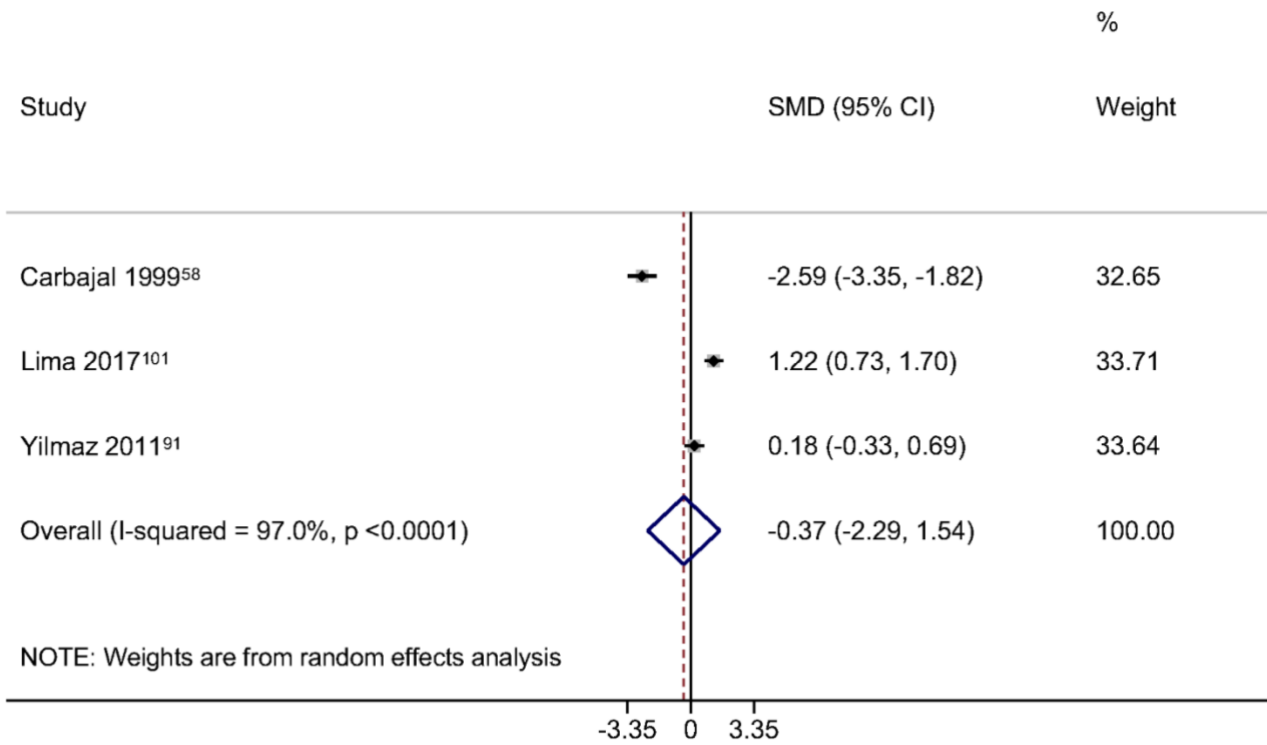
Supplementary Figure 17. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking vs oral sugar for oxygen saturation



Note: P-value for test of standardised mean difference: 0.97

Abbreviations: CI=confidence interval, SMD=standardised mean difference

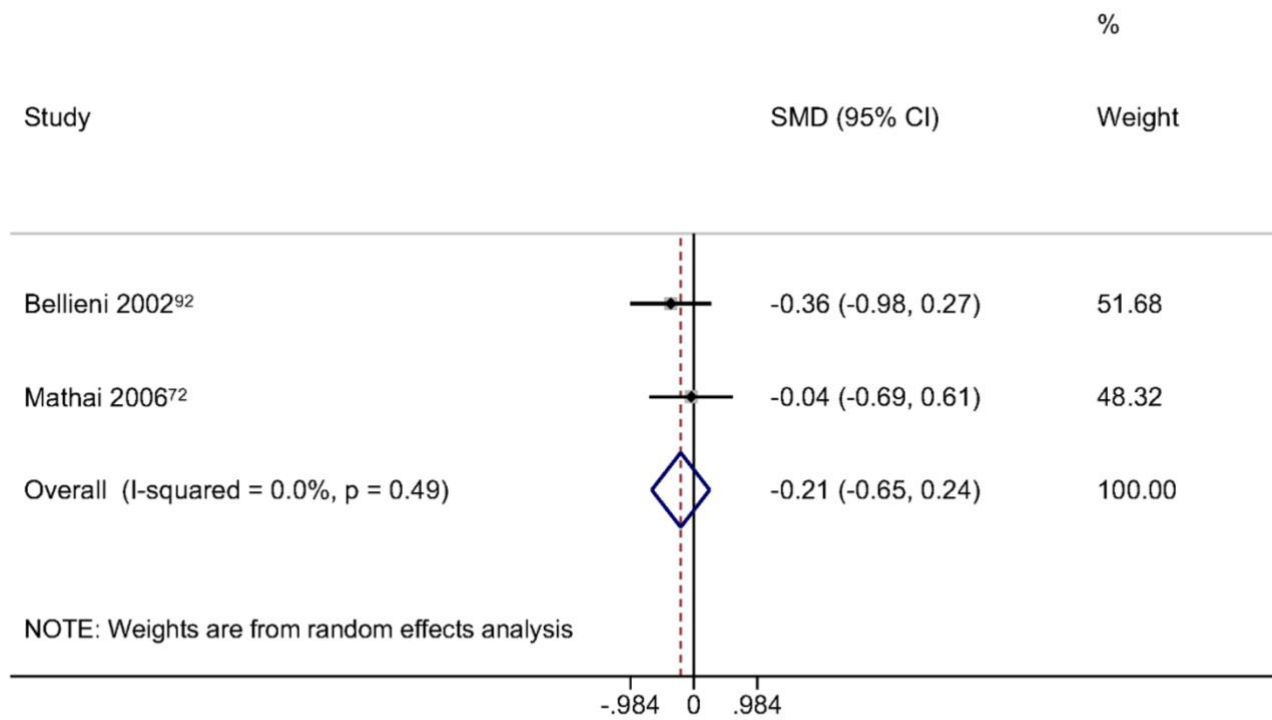
Supplementary Figure 18. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking versus oral sugar for NIPS



Note: P-value for test of standardised mean difference: 0.70

Abbreviations: CI=confidence interval, SMD=standardised mean difference, NIPS=Neonatal Infant Pain Scale

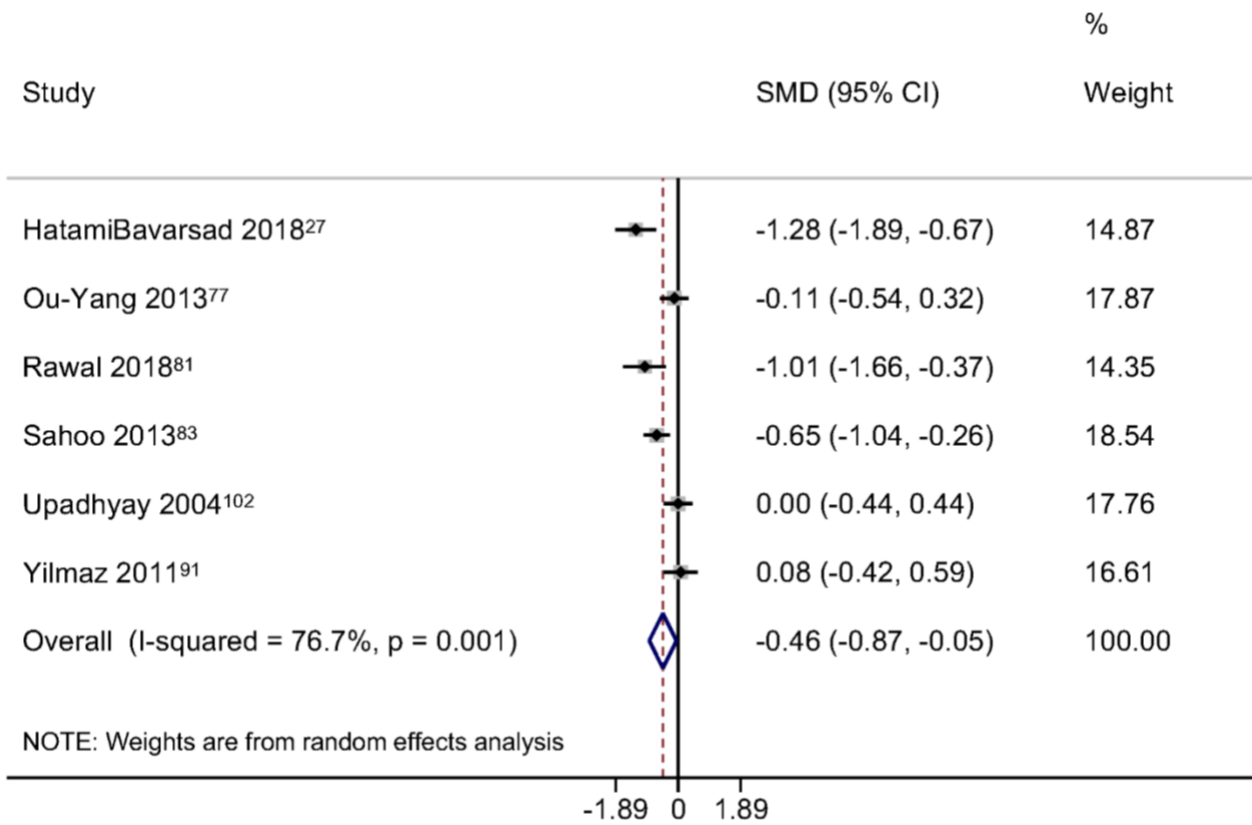
Supplementary Figure 19. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking versus oral sugar for DAN



Note: P-value for test of standardised mean difference: 0.37

Abbreviations: CI=confidence interval, SMD=standardised mean difference, DAN= Douleur Aigue du Nouveau-né

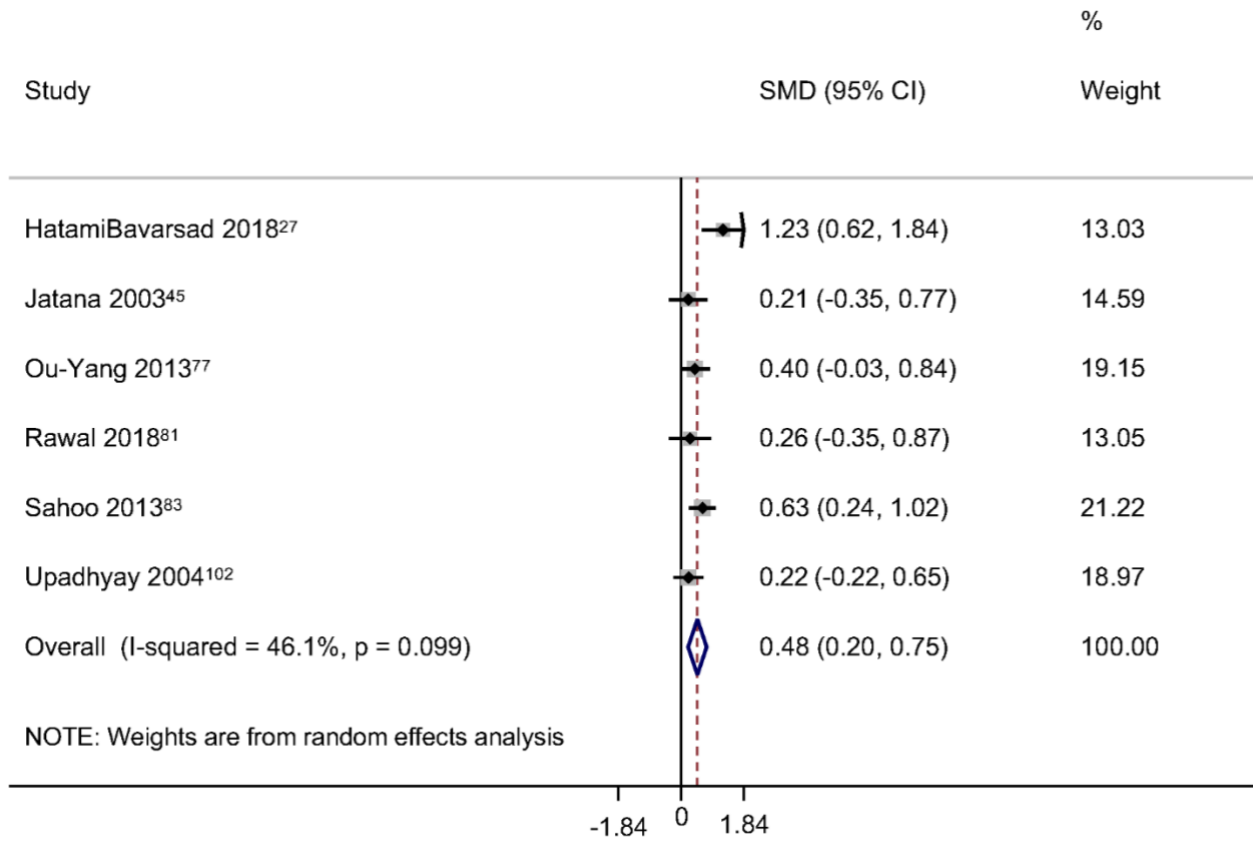
Supplementary Figure 20. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk versus placebo or no intervention for heart rate



Note: P-value for test of standardised mean difference: 0.028

Abbreviations: CI=confidence interval, SMD=standardised mean difference

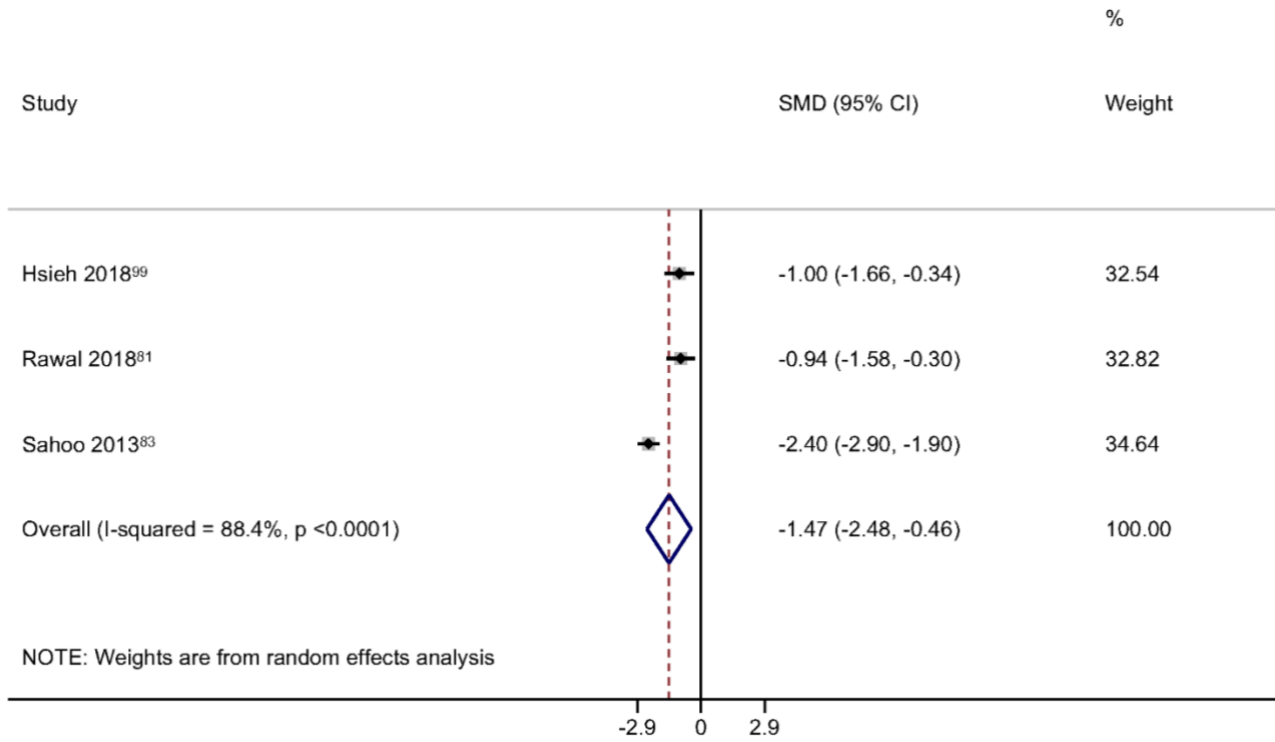
Supplementary Figure 21. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk vs placebo or no intervention for oxygen saturation



Note: P-value for test of standardised mean difference: <0.001

Abbreviations: CI=confidence interval, SMD=standardised mean difference

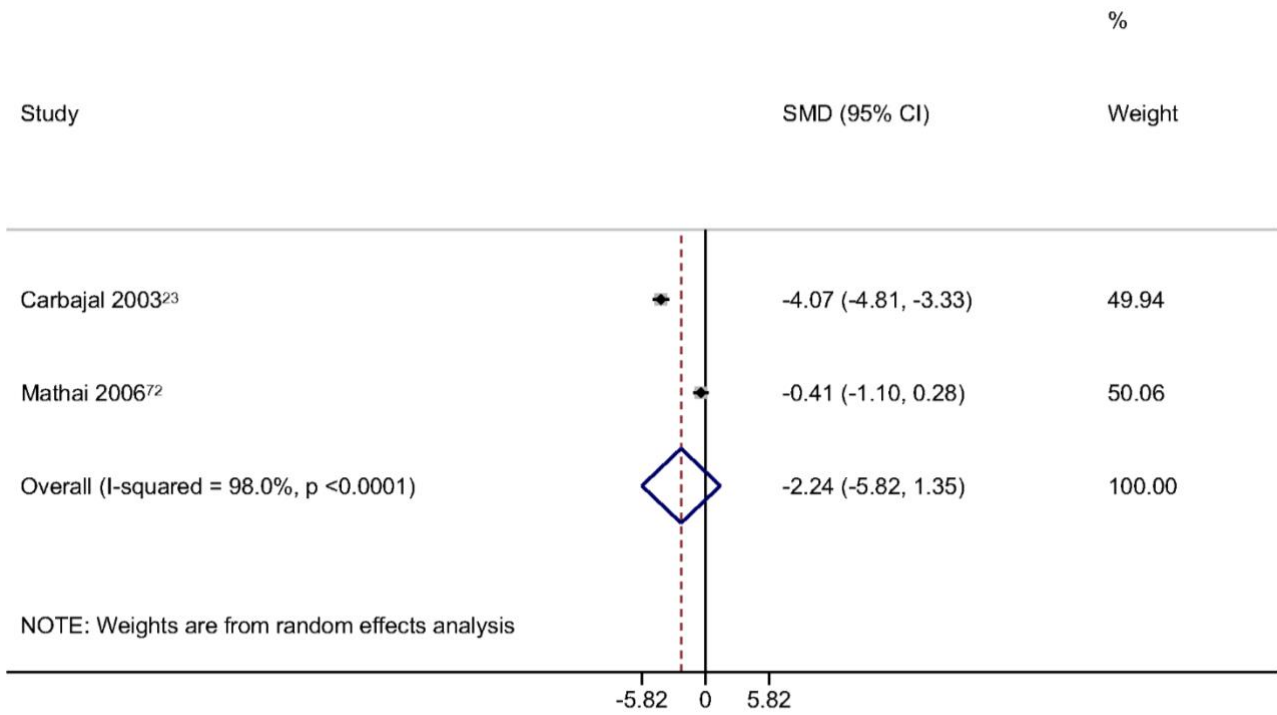
Supplementary Figure 22. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk versus placebo or no intervention for PIPP



Note: P-value for test of standardised mean difference: 0.004

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

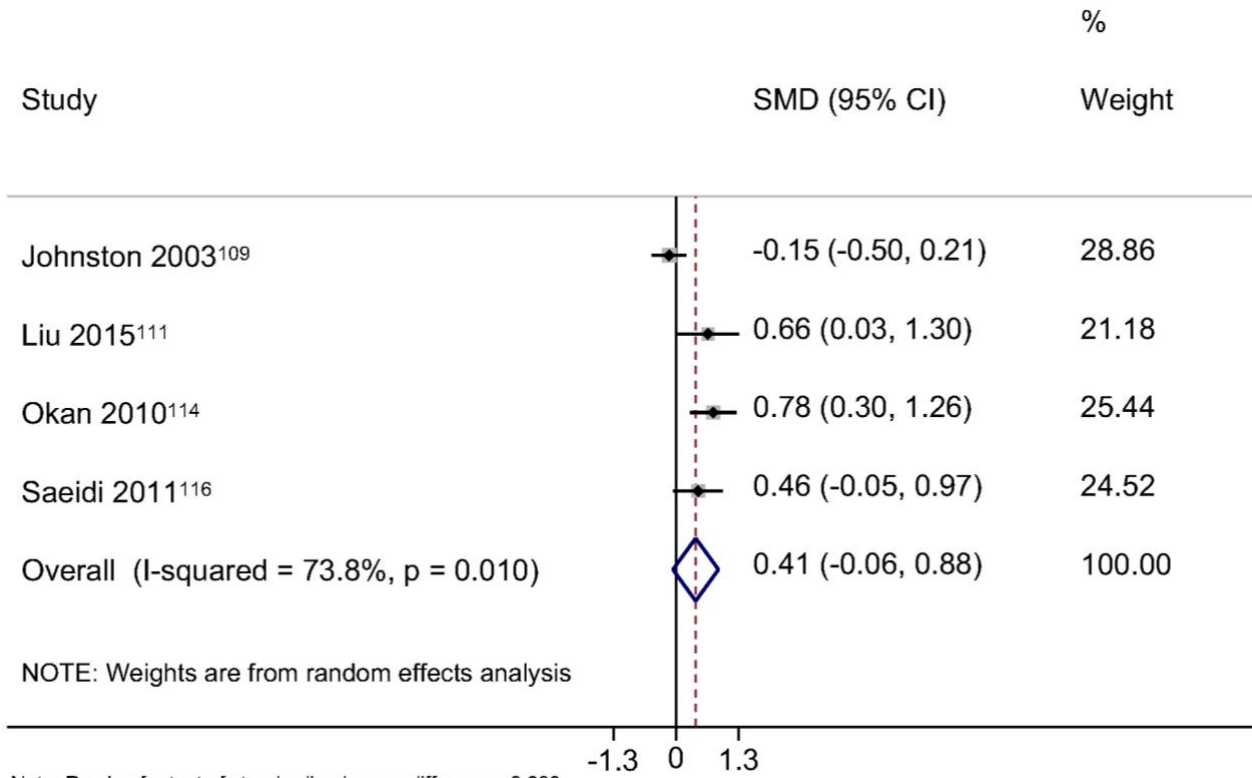
Supplementary Figure 23. Standardised mean differences and their confidence intervals for the comparison of expressed breast milk versus placebo or no intervention for DAN



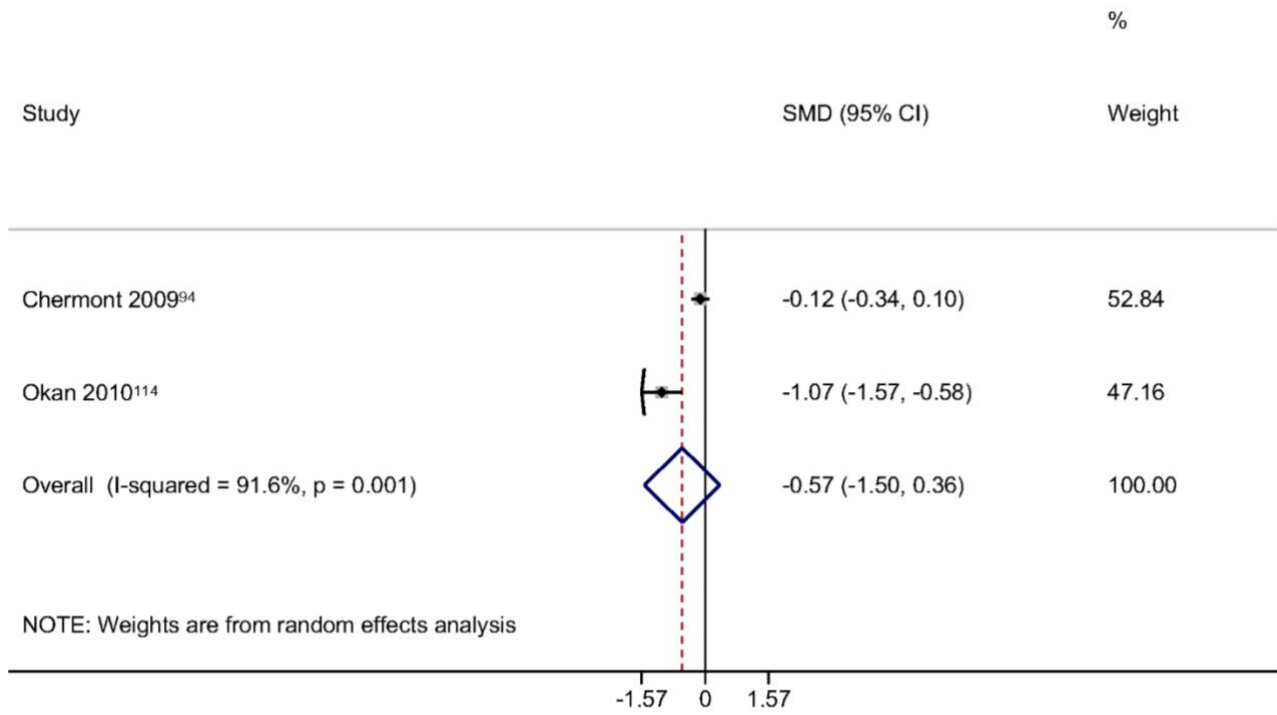
Note: P-value for test of standardised mean difference: 0.21

Abbreviations: CI=confidence interval, SMD=standardised mean difference, DAN= Douleur Aigue du Nouveau-né

Supplementary Figure 24. Standardised mean differences and their confidence intervals for the comparison of skin-to-skin versus placebo or no intervention for oxygen saturation



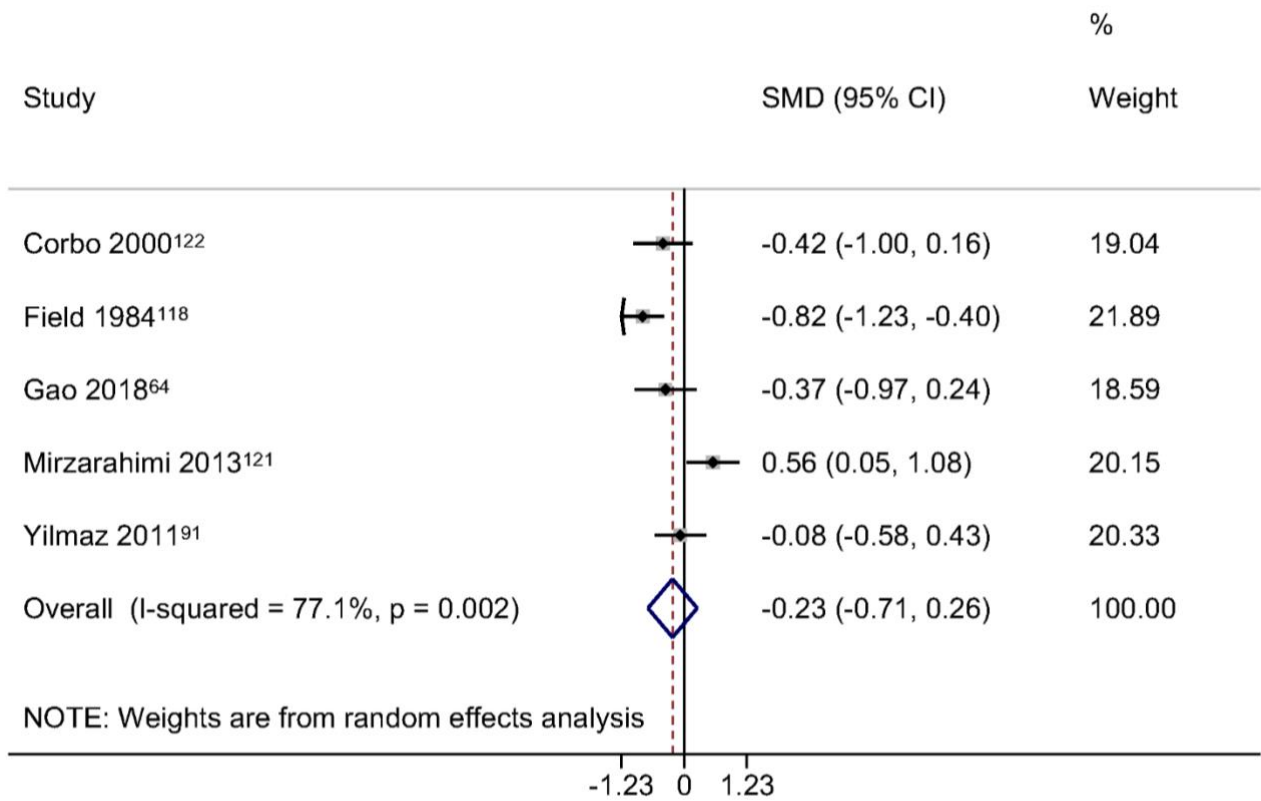
Supplementary Figure 25. Standardised mean differences and their confidence intervals for the comparison of skin-to-skin versus placebo or no intervention for NFCS



Note: P-value for test of standardised mean difference: 0.23

Abbreviations: CI=confidence interval, SMD=standardised mean difference, NFCS= Neonatal Facial Coding System

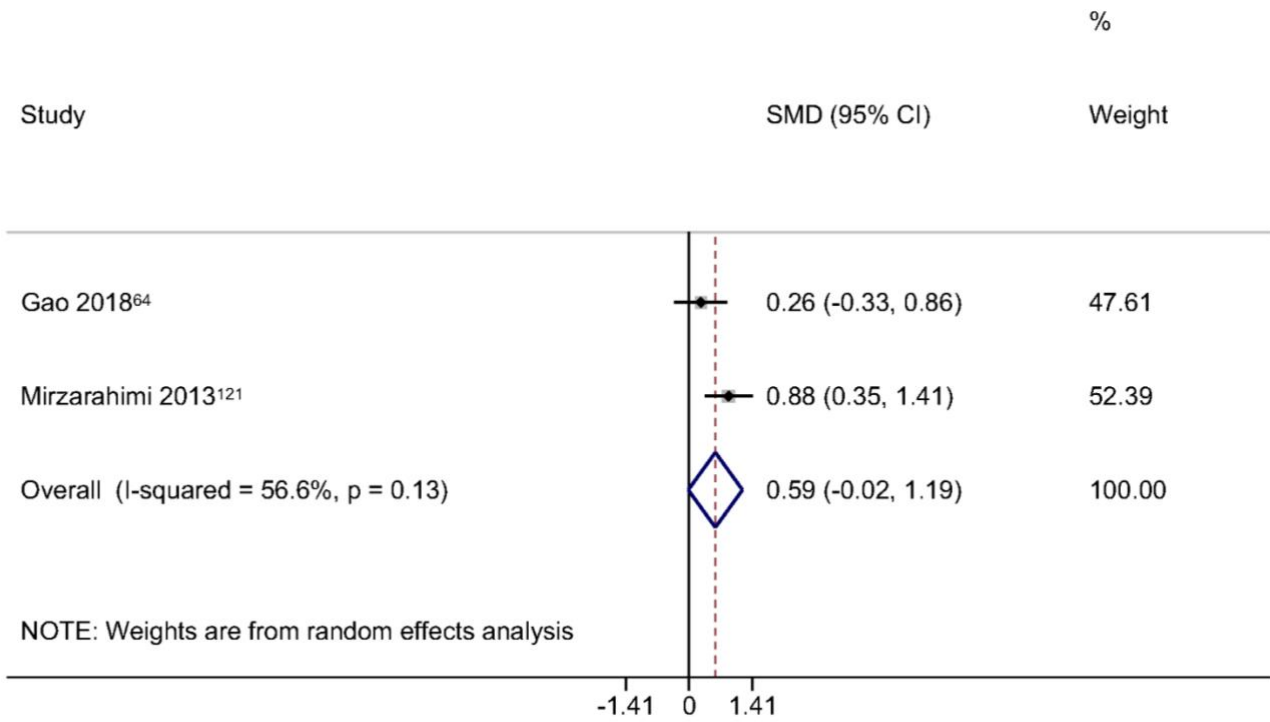
Supplementary Figure 26. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking versus placebo or no intervention for heart rate



Note: P-value for test of standardised mean difference: 0.35

Abbreviations: CI=confidence interval, SMD=standardised mean difference

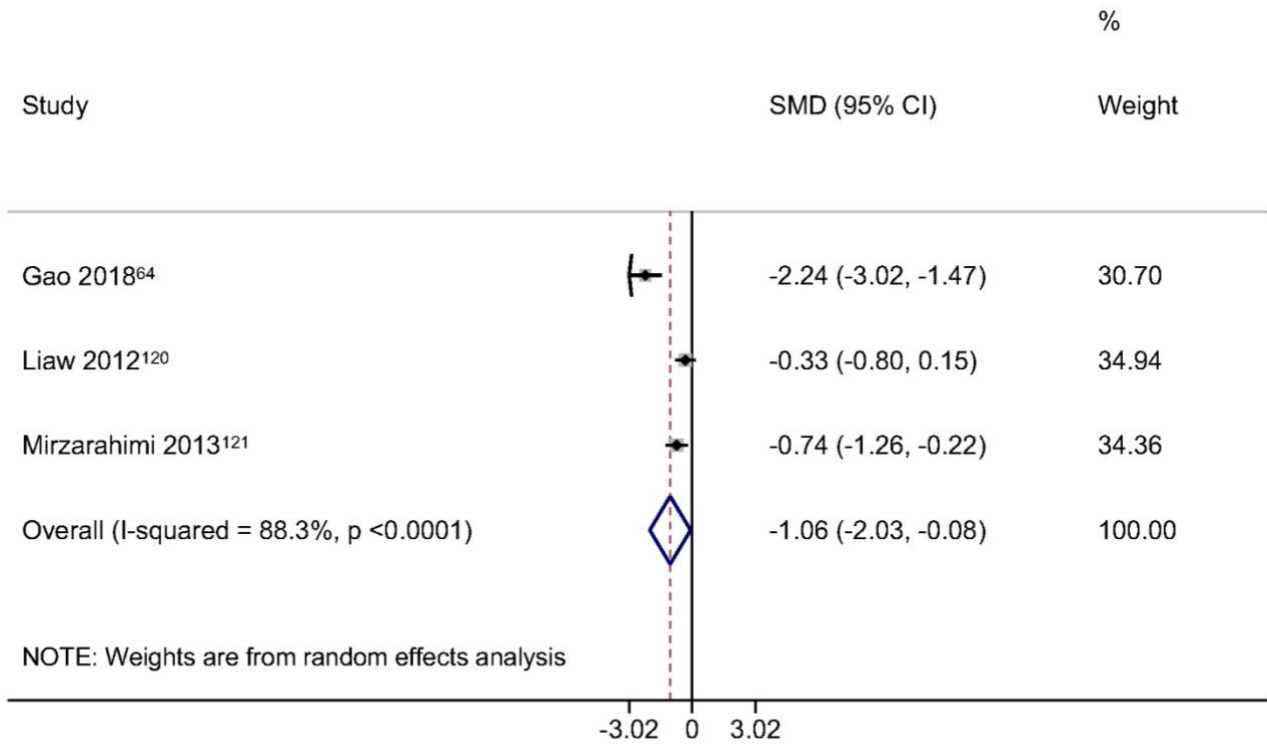
Supplementary Figure 27. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking versus placebo or no intervention for oxygen saturation



Note: P-value for test of standardised mean difference: 0.057

Abbreviations: CI=confidence interval, SMD=standardised mean difference

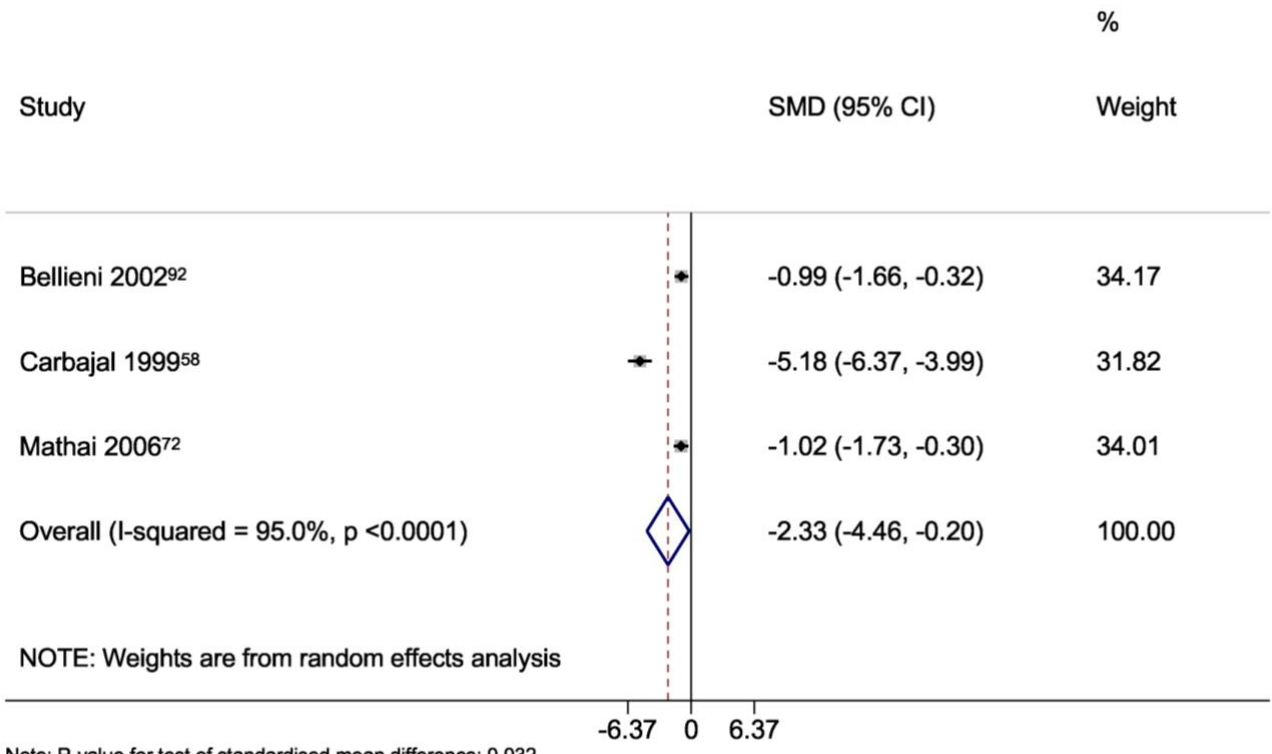
Supplementary Figure 28. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking versus placebo or no intervention for PIPP



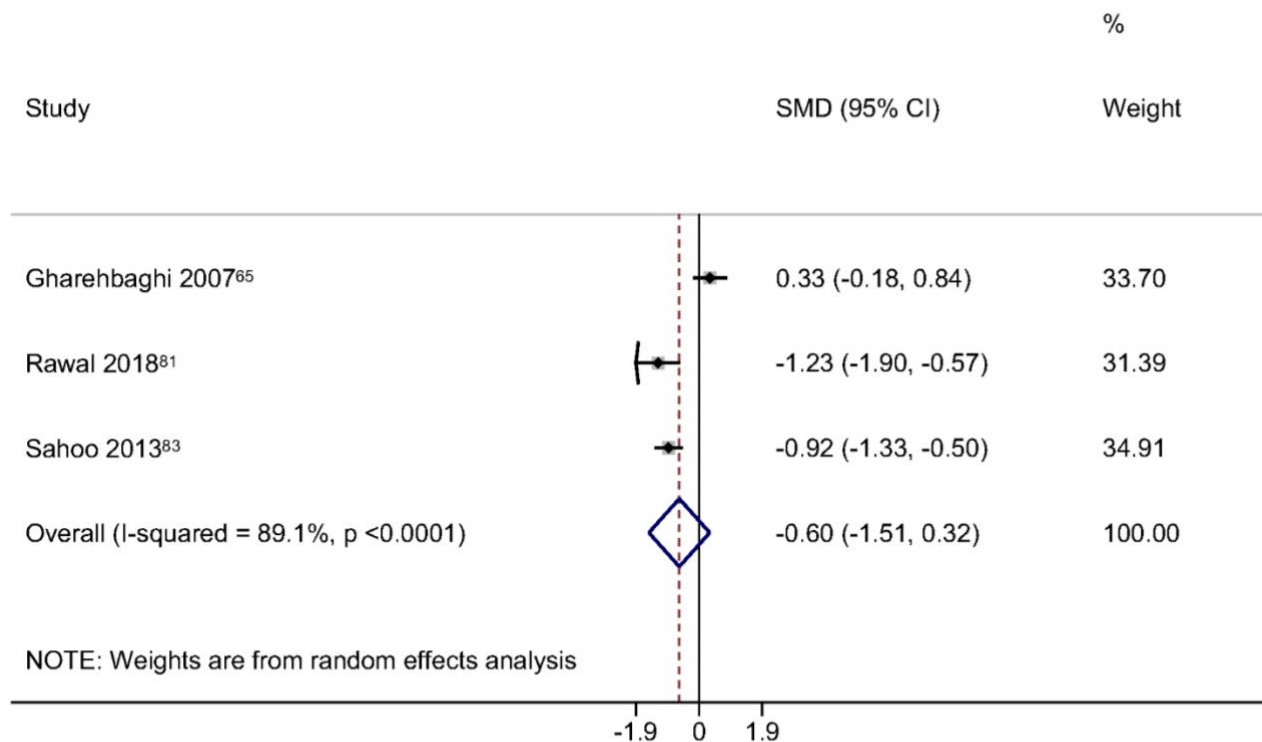
Note: P-value for test of standardised mean difference: 0.034

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

Supplementary Figure 29. Standardised mean differences and their confidence intervals for the comparison of non-nutritive sucking versus placebo or no intervention for DAN



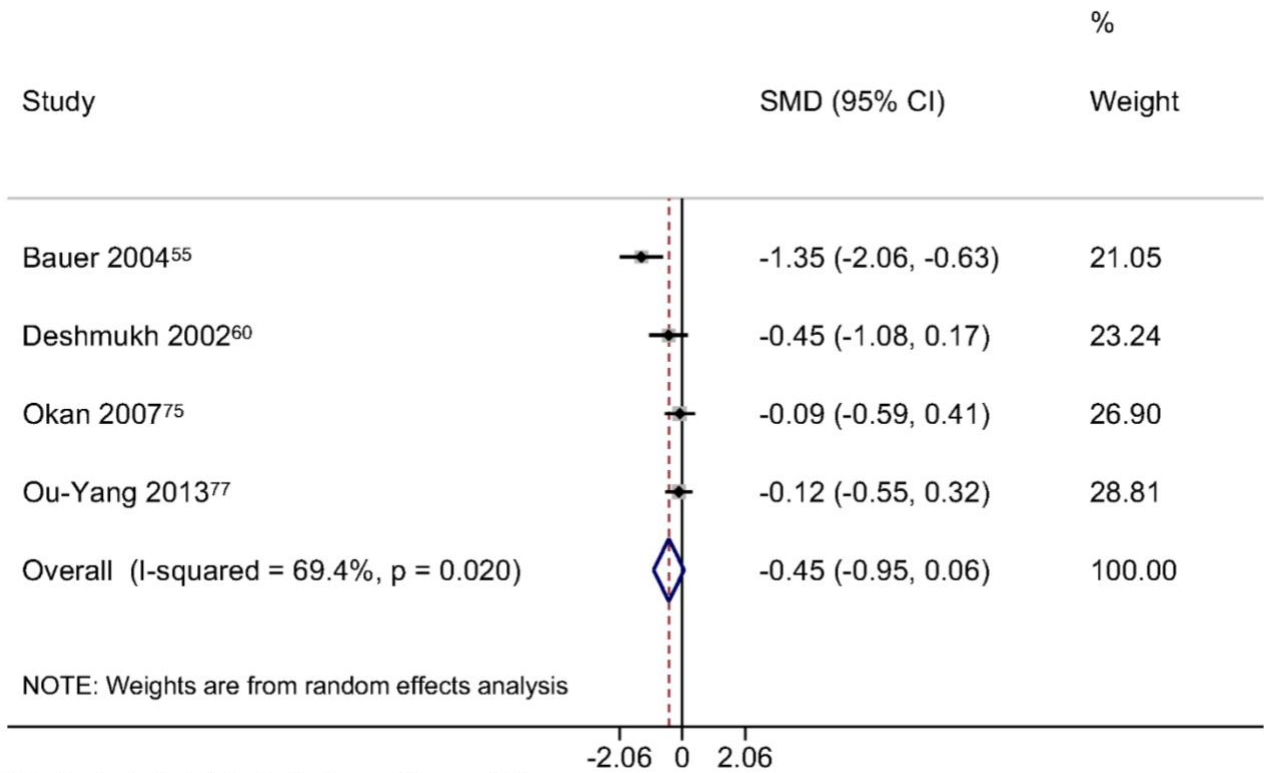
Supplementary Figure 30. Standardised mean differences and their confidence intervals for the comparison of oral dextrose versus placebo or no intervention for heart rate



Note: P-value for test of standardised mean difference: 0.20

Abbreviations: CI=confidence interval, SMD=standardised mean difference

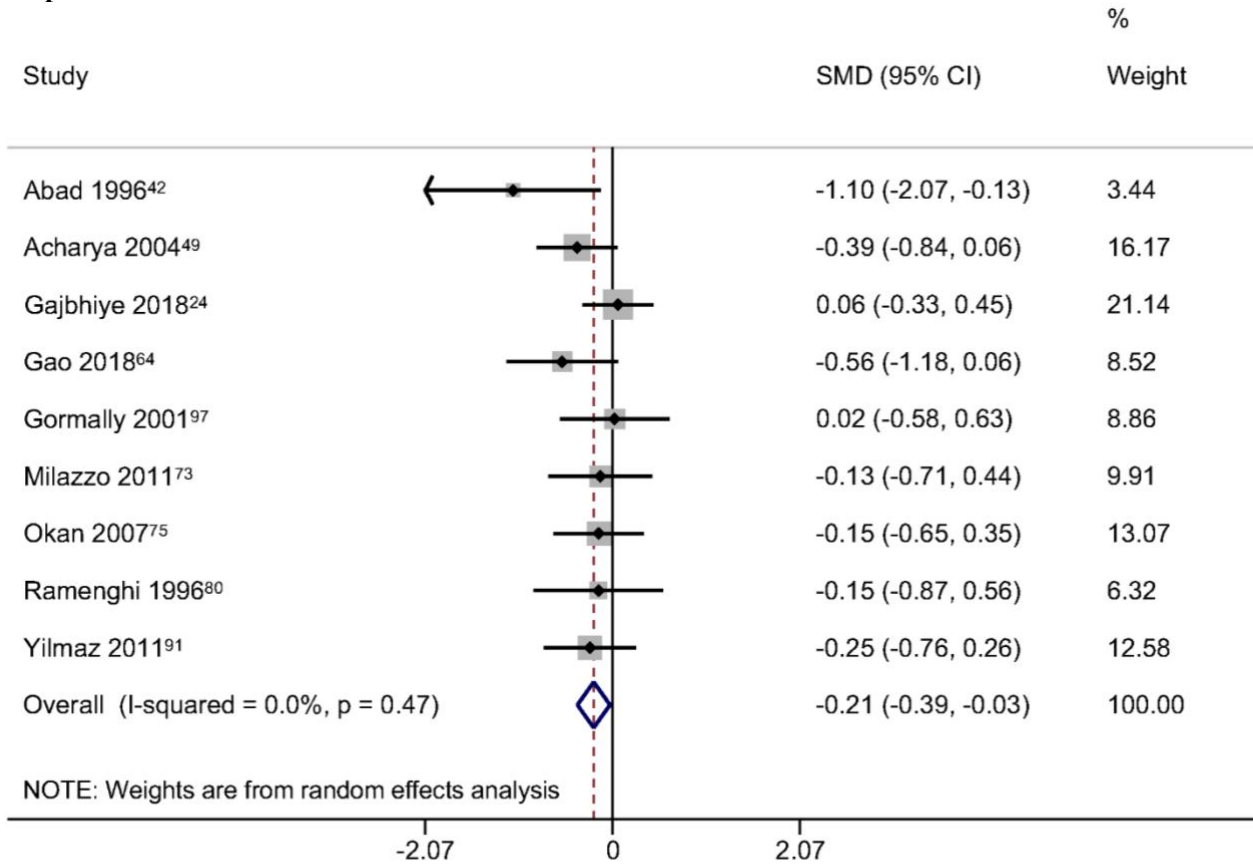
Supplementary Figure 31. Standardised mean differences and their confidence intervals for the comparison of oral glucose versus placebo or no intervention for heart rate



Note: P-value for test of standardised mean difference: 0.08

Abbreviations: CI=confidence interval, SMD=standardised mean difference

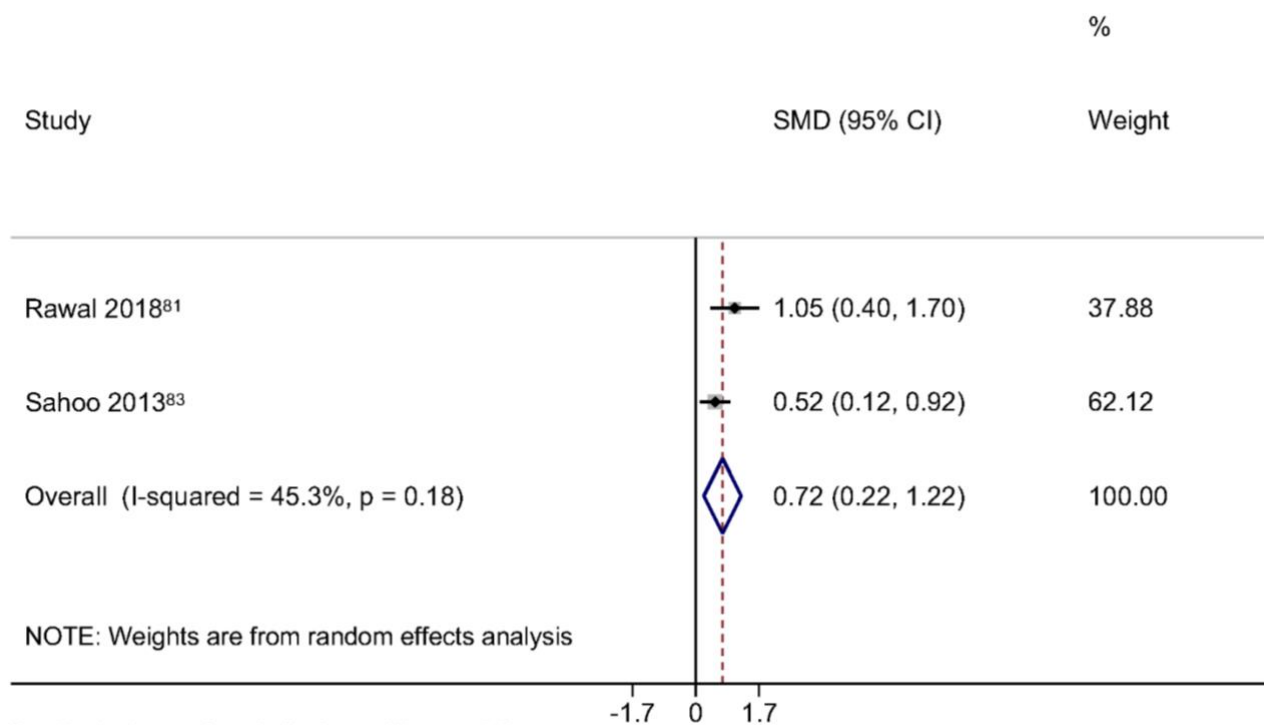
Supplementary Figure 32. Standardised mean differences and their confidence intervals for the comparison of oral sucrose versus placebo or no intervention for heart rate



NOTE: Weights are from random effects analysis

Note: P-value for test of standardised mean difference: 0.023
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

Supplementary Figure 33. Standardised mean differences and their confidence intervals for the comparison of oral dextrose versus placebo or no intervention for oxygen saturation

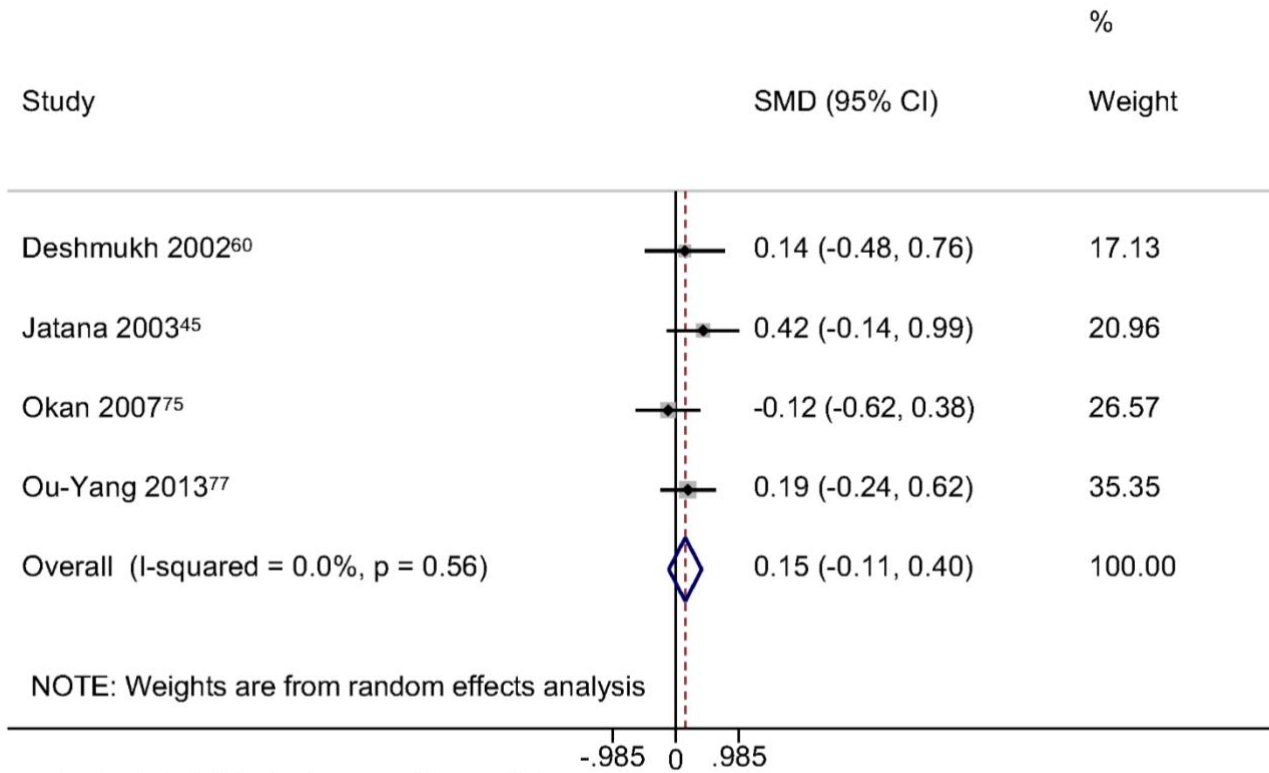


NOTE: Weights are from random effects analysis

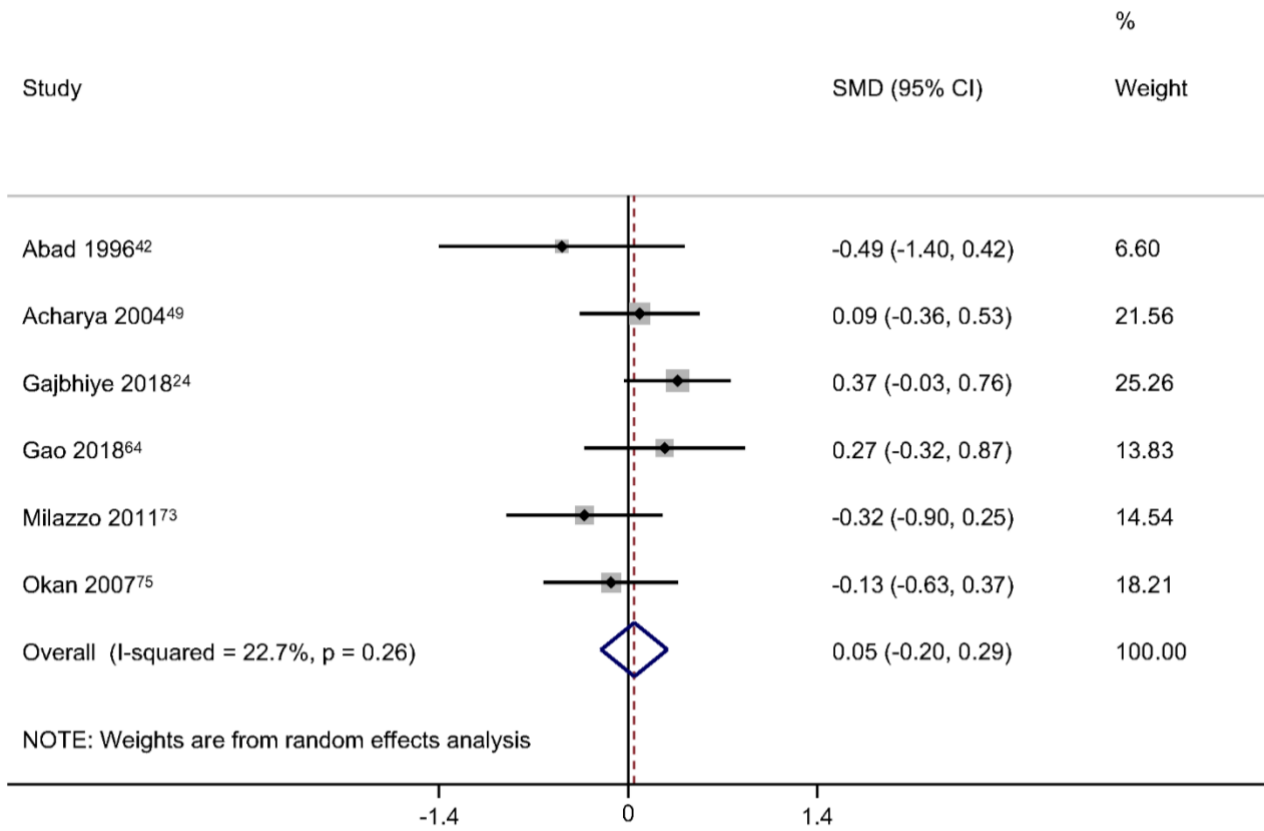
Note: P-value for test of standardised mean difference: 0.01

Abbreviations: CI=confidence interval, SMD=standardised mean difference

Supplementary Figure 34. Standardised mean differences and their confidence intervals for the comparison of oral glucose versus placebo or no intervention for oxygen saturation



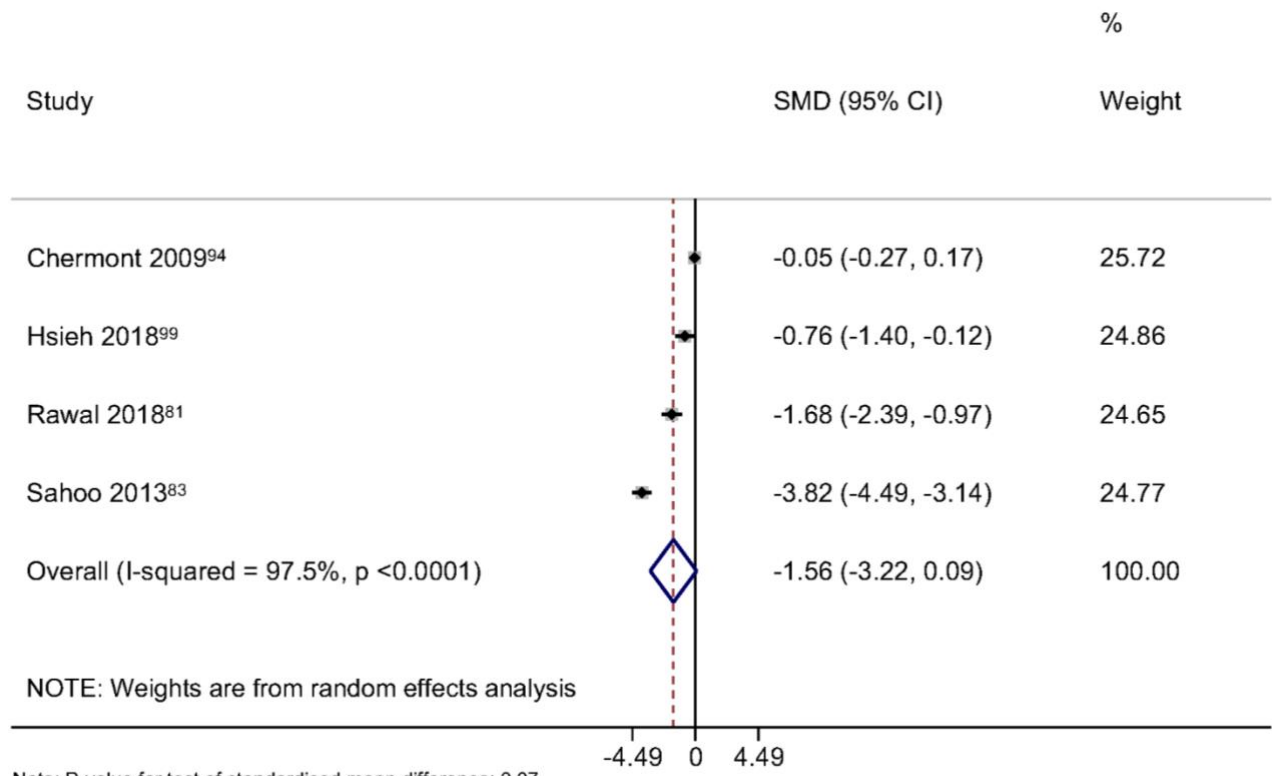
Supplementary Figure 35. Standardised mean differences and their confidence intervals for the comparison of oral sucrose versus placebo or no intervention for oxygen saturation



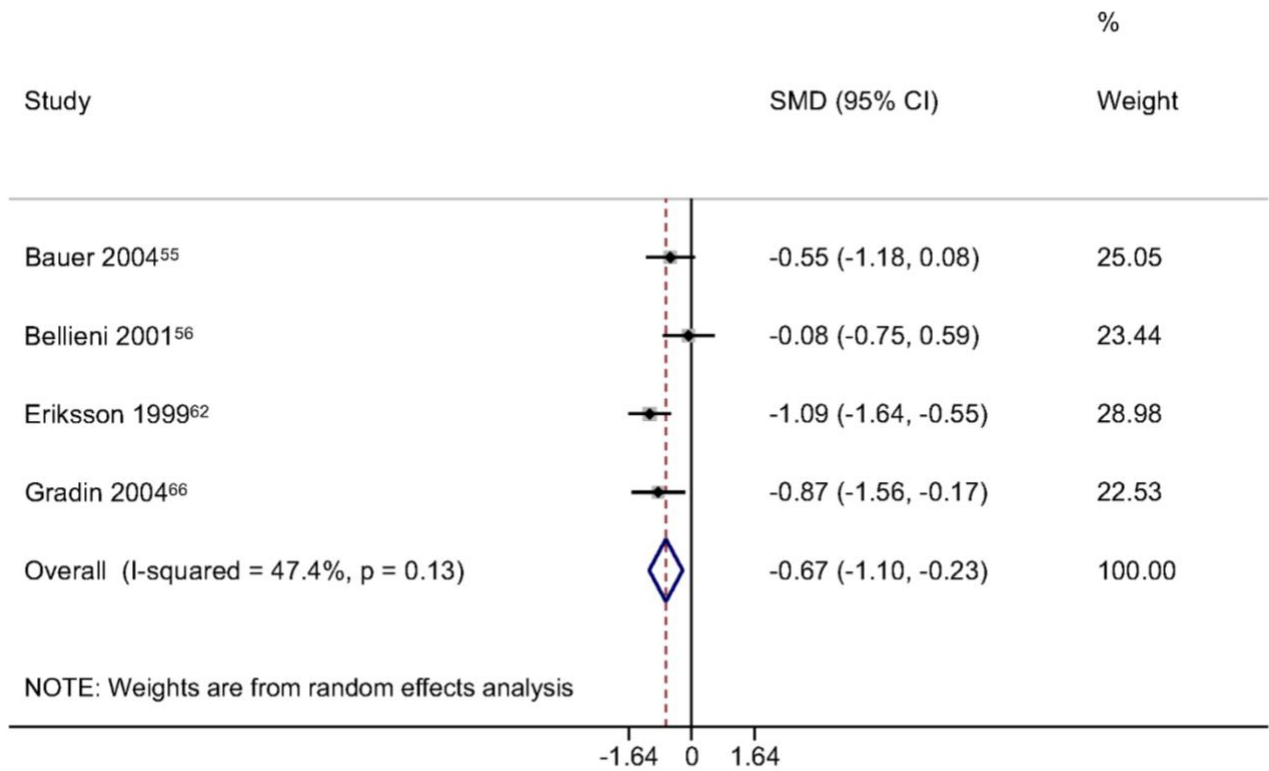
Note: P-value for test of standardised mean difference: 0.71

Abbreviations: CI=confidence interval, SMD=standardised mean difference

Supplementary Figure 36. Standardised mean differences and their confidence intervals for the comparison of oral dextrose versus placebo or no intervention for PIPP



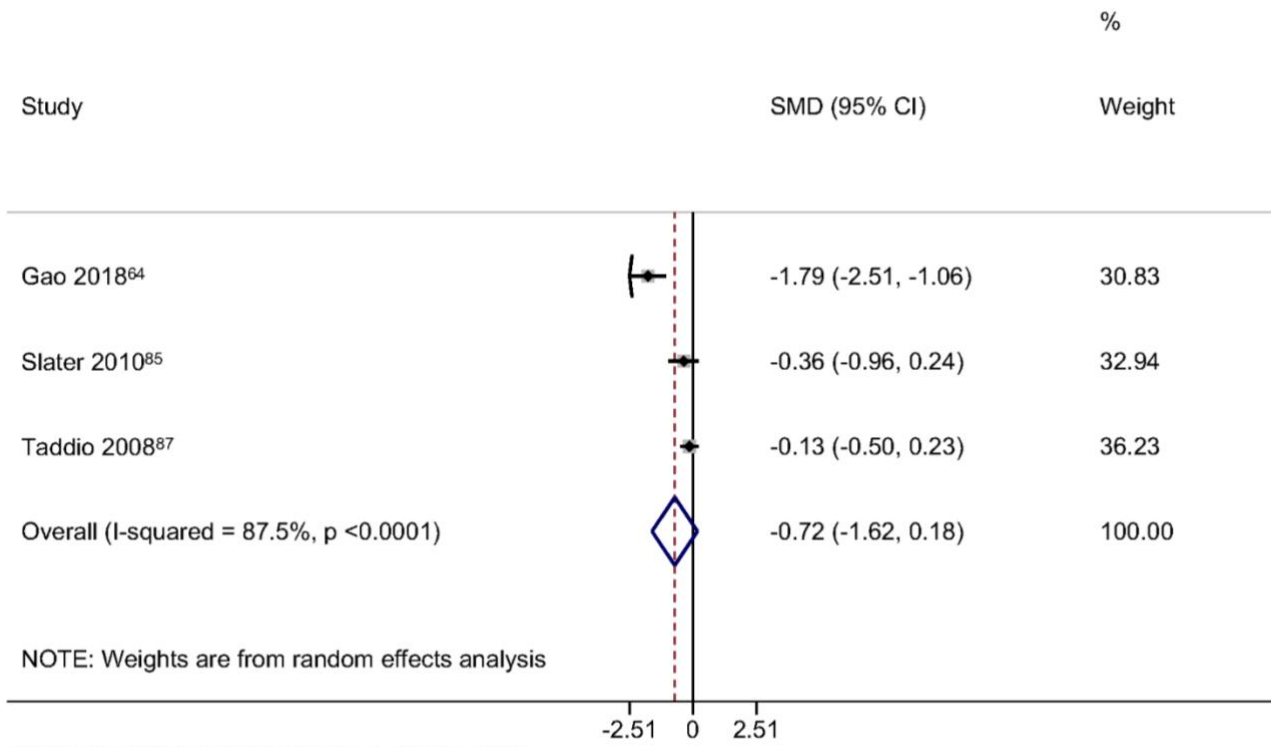
Supplementary Figure 37. Standardised mean differences and their confidence intervals for the comparison of oral glucose versus placebo or no intervention for PIPP



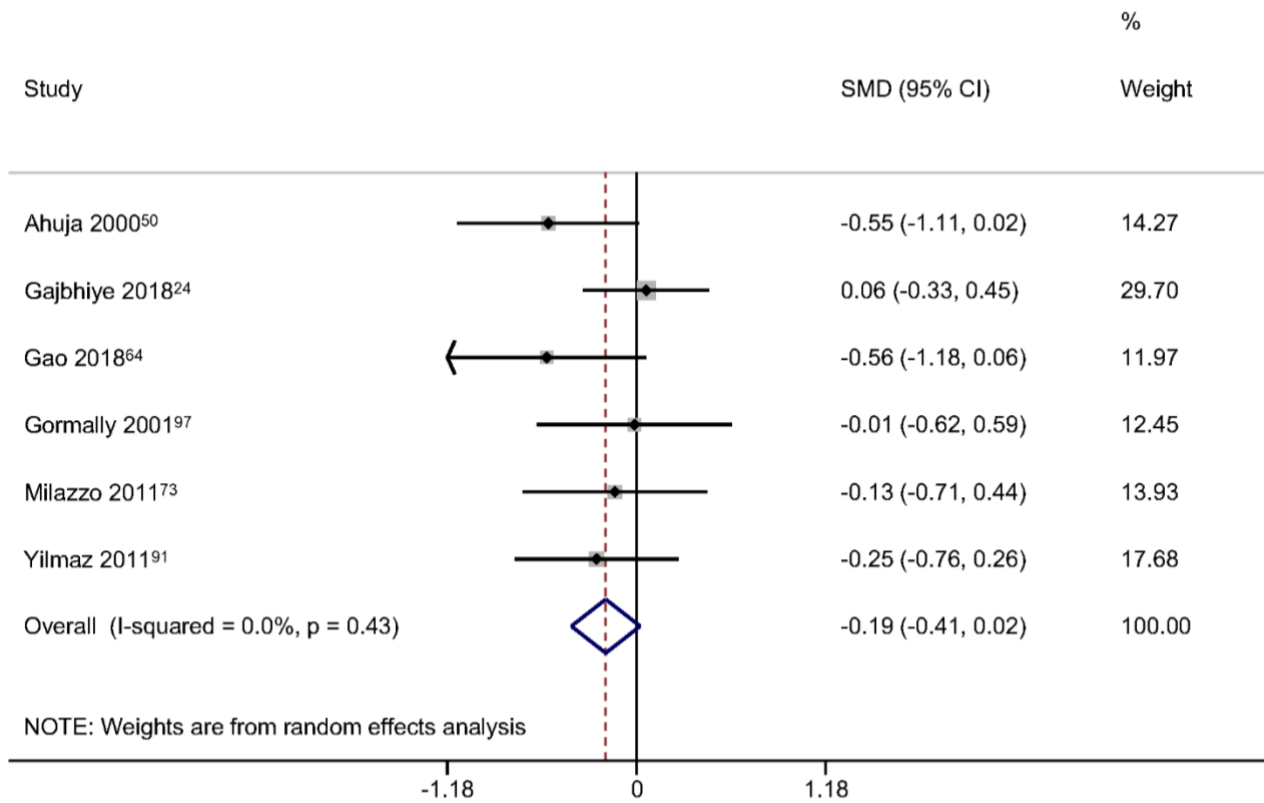
Note: P-value for test of standardised mean difference: 0.003

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

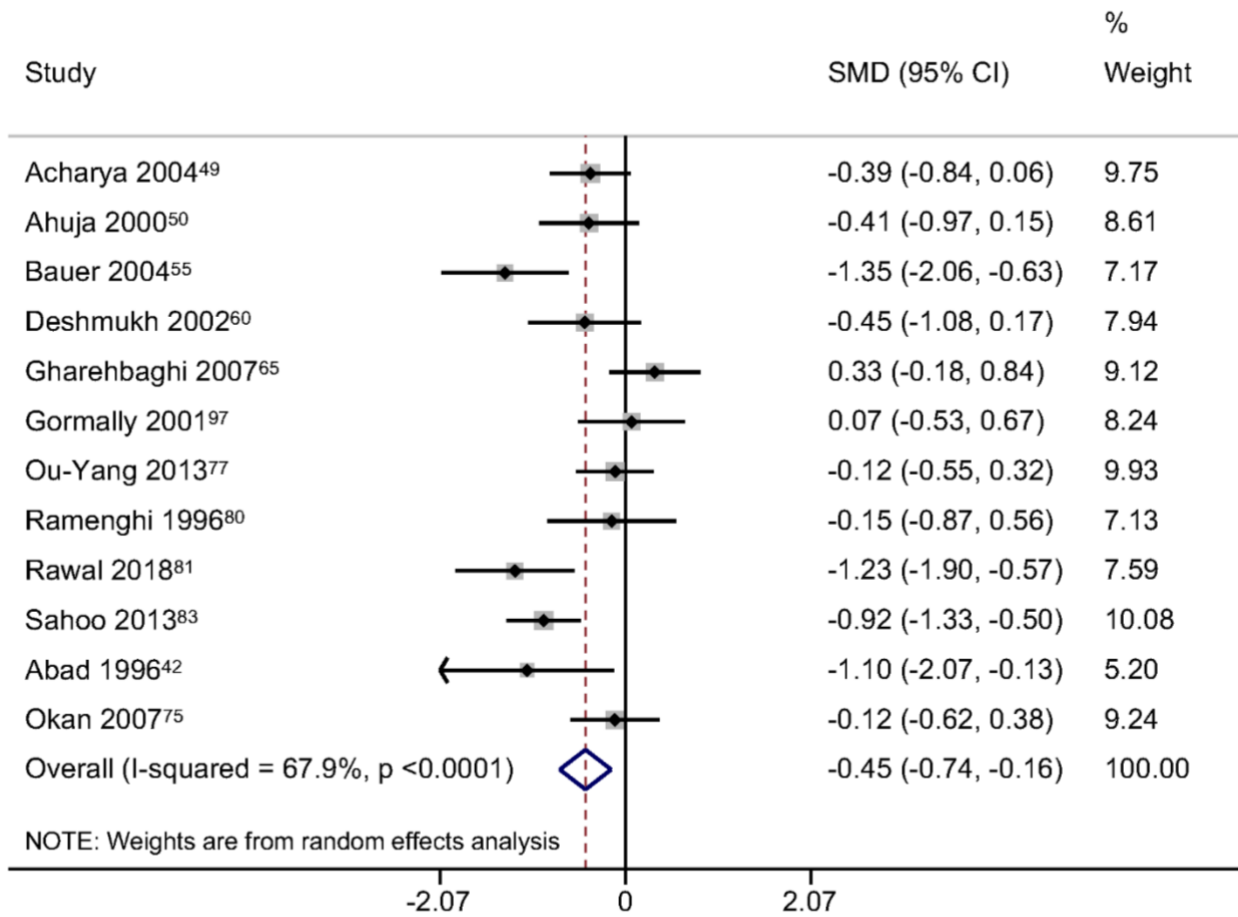
Supplementary Figure 38. Standardised mean differences and their confidence intervals for the comparison of oral sucrose versus placebo or no intervention for PIPP



Supplementary Figure 39. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus no intervention only for heart rate

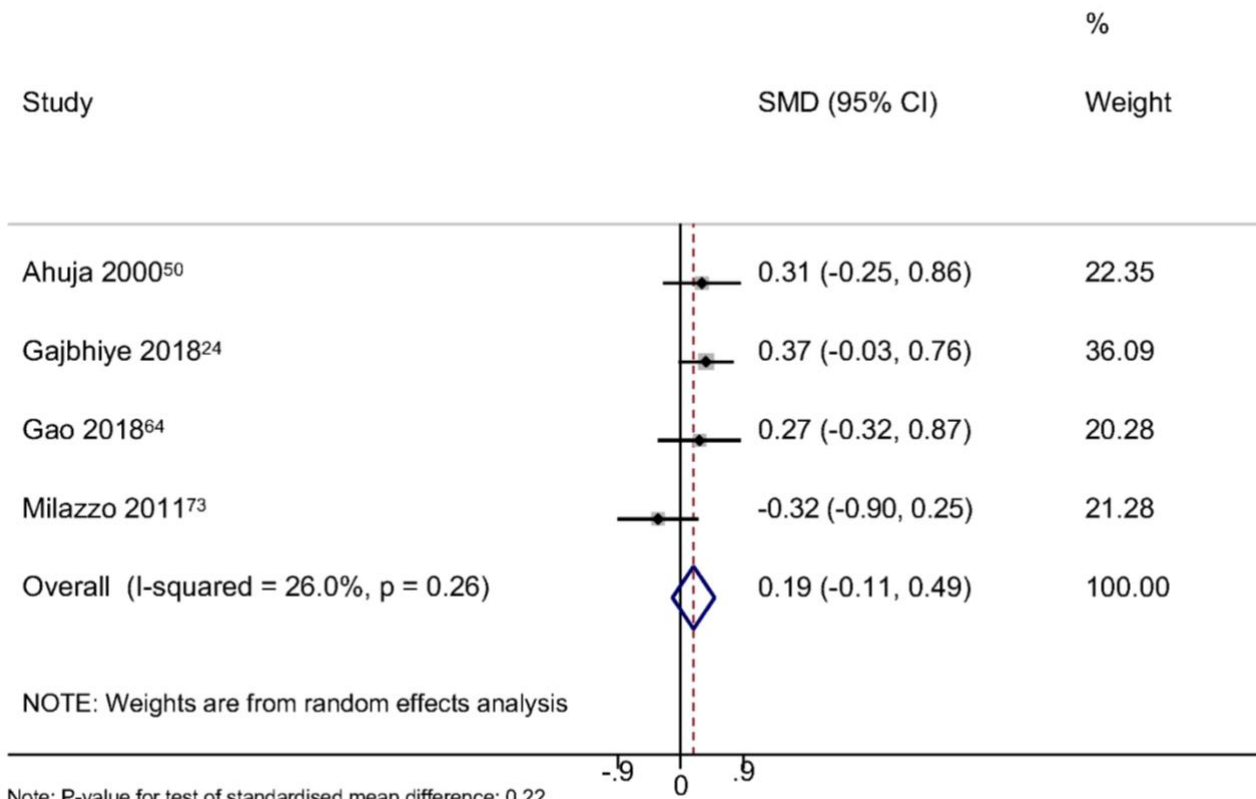


Supplementary Figure 40. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo only for heart rate

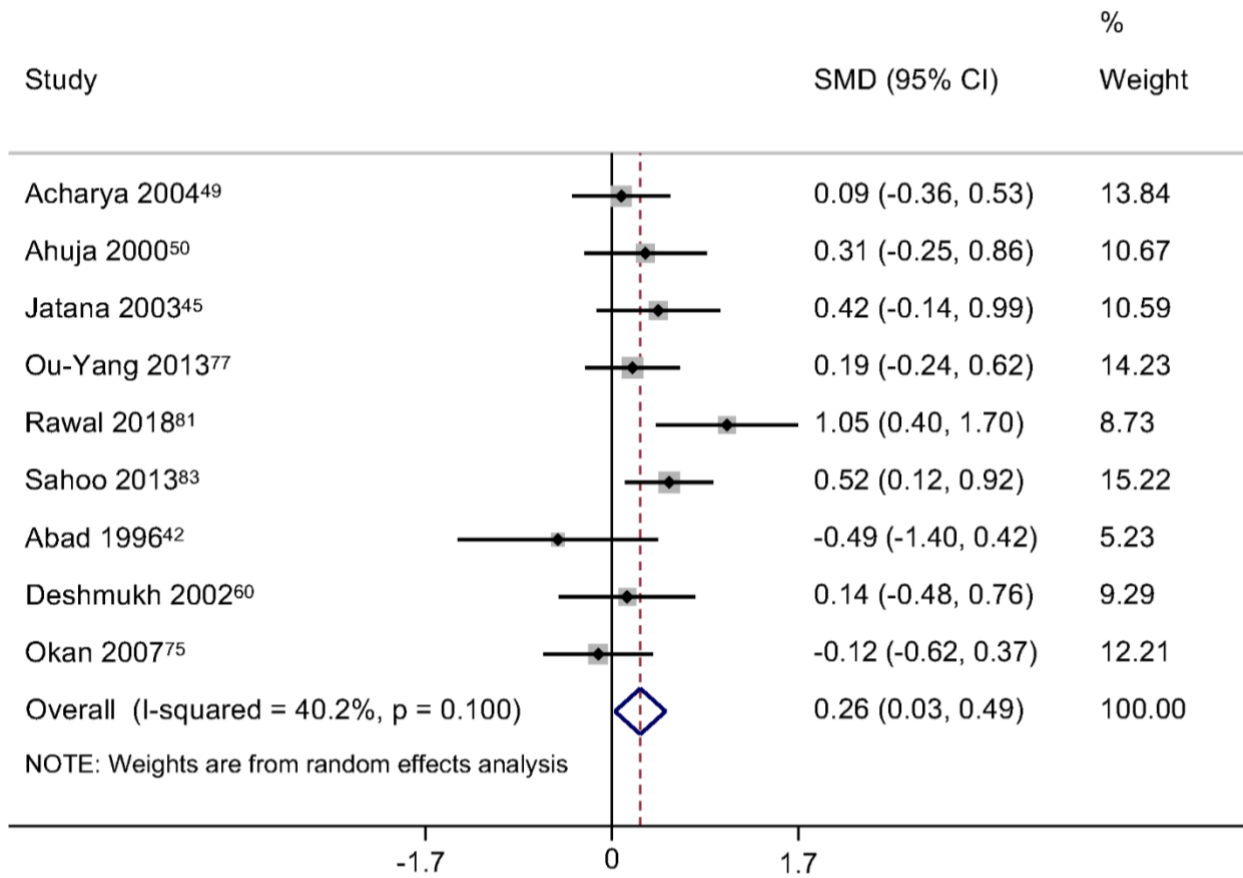


Note: P-value for test of standardised mean difference: 0.002
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

Supplementary Figure 41. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus no intervention only for oxygen saturation

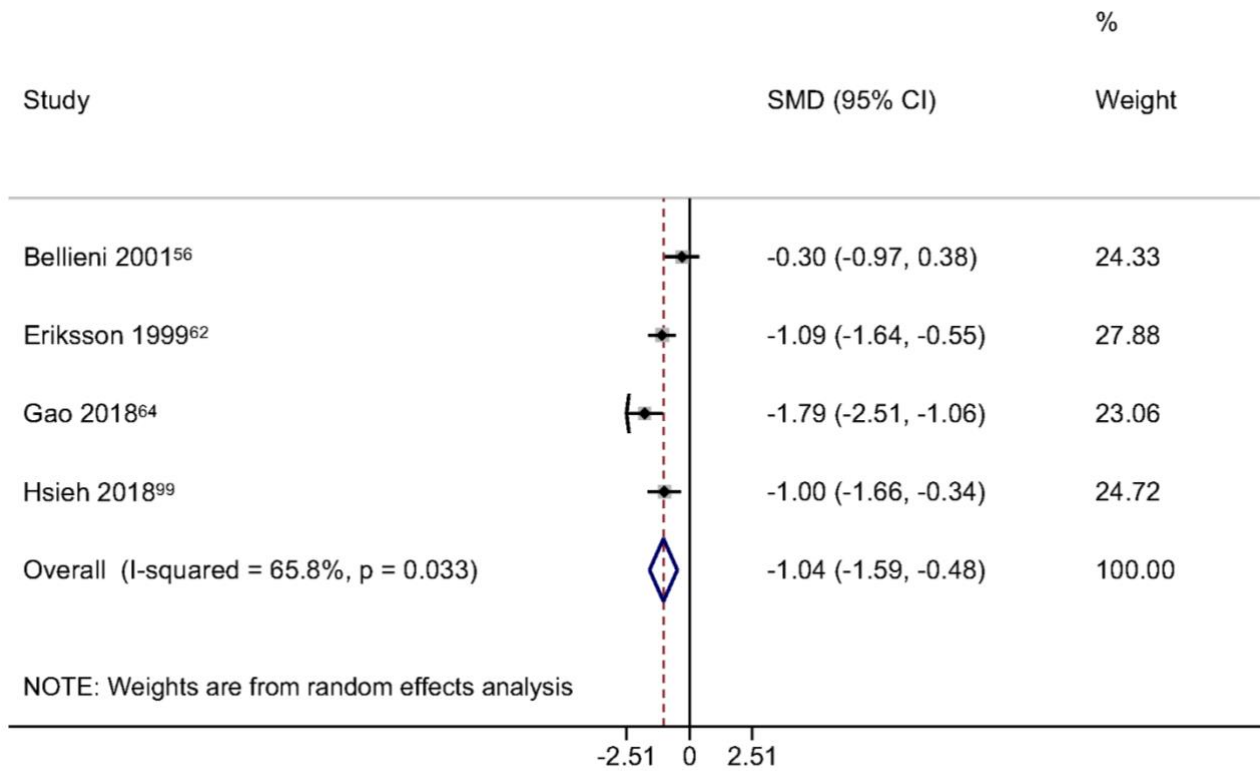


Supplementary Figure 42. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo only for oxygen saturation

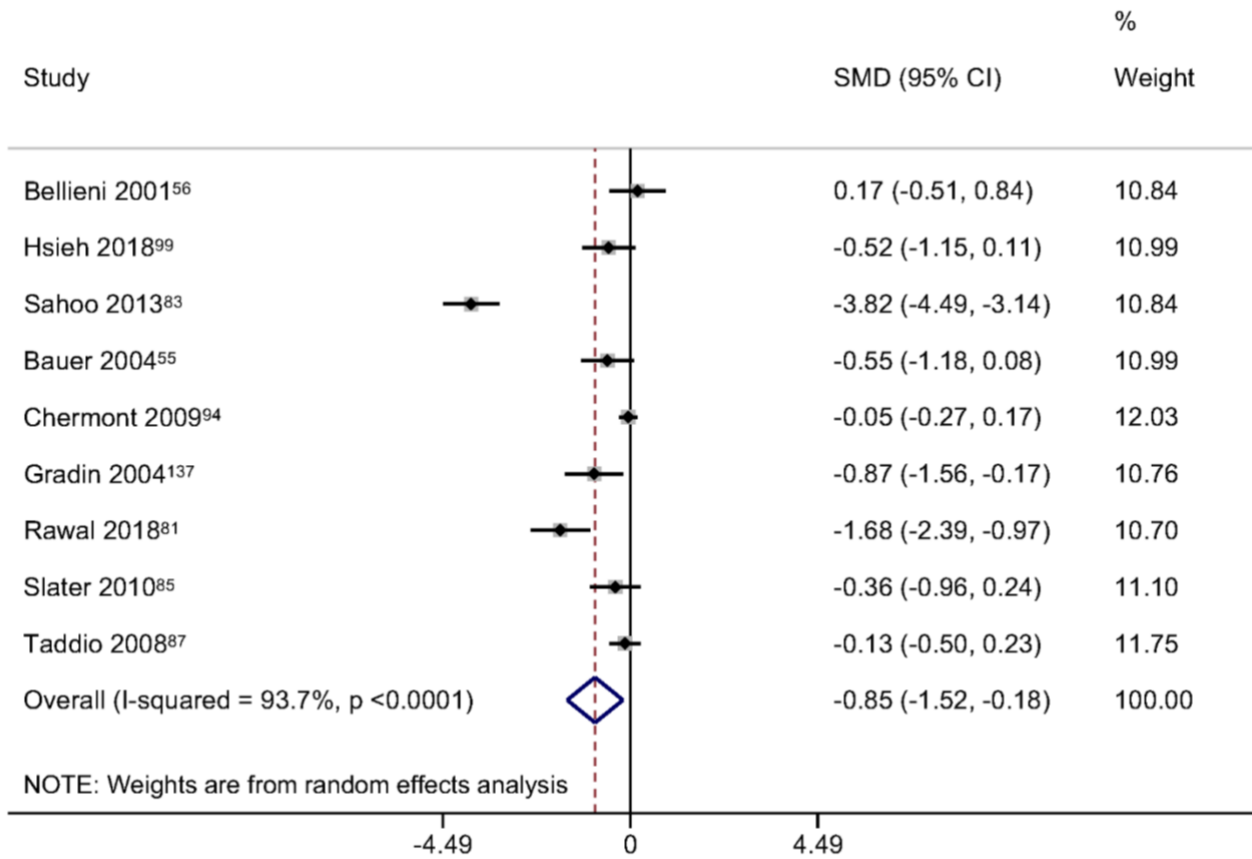


Note: P-value for test of standardised mean difference: 0.027
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

Supplementary Figure 43. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus no intervention only for PIPP



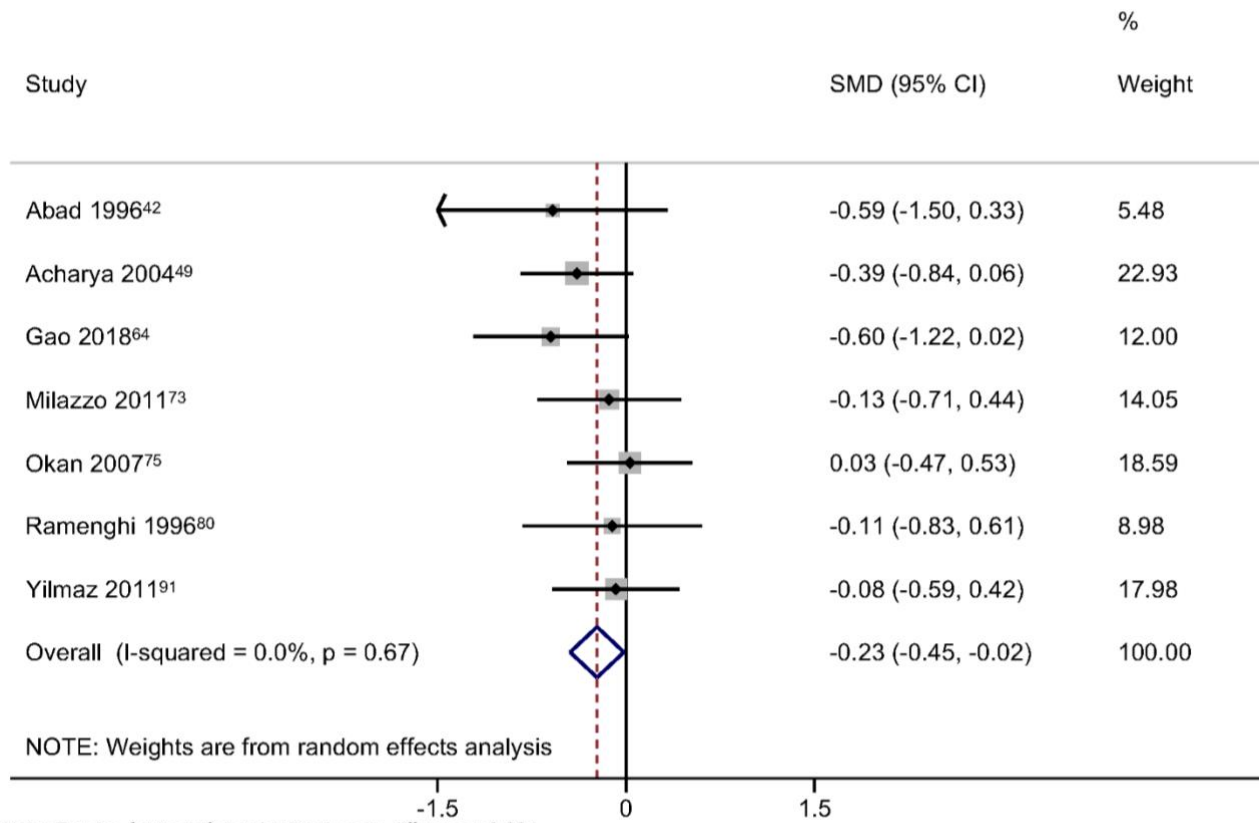
Supplementary Figure 44. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo only for PIPP



Note: P-value for test of standardised mean difference: 0.001

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

Supplementary Figure 45. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention with heart rate measured ≤ 1 minute after procedure commencement

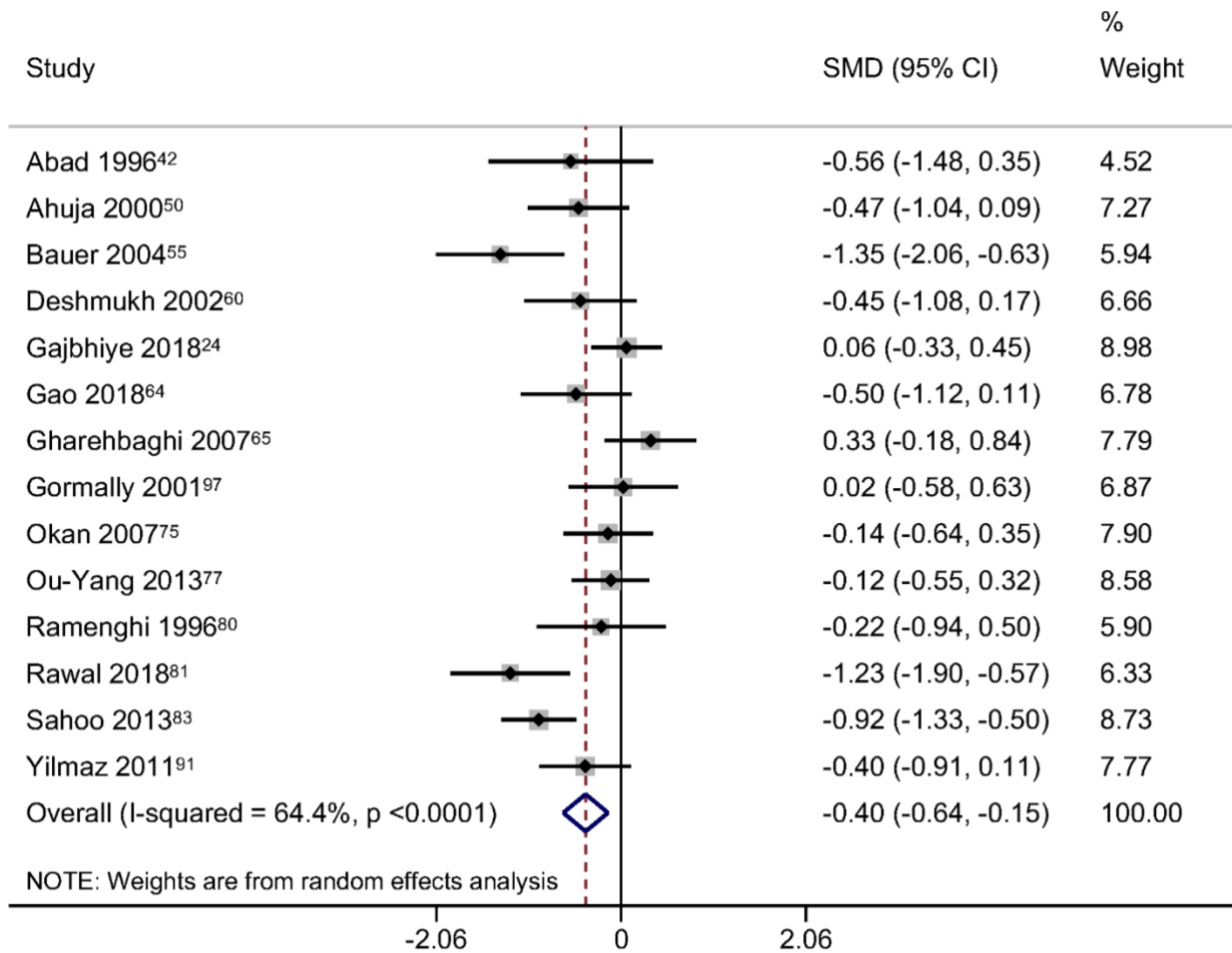


NOTE: Weights are from random effects analysis

Note: P-value for test of standardised mean difference: 0.034

Abbreviations: CI=confidence interval, SMD=standardised mean difference

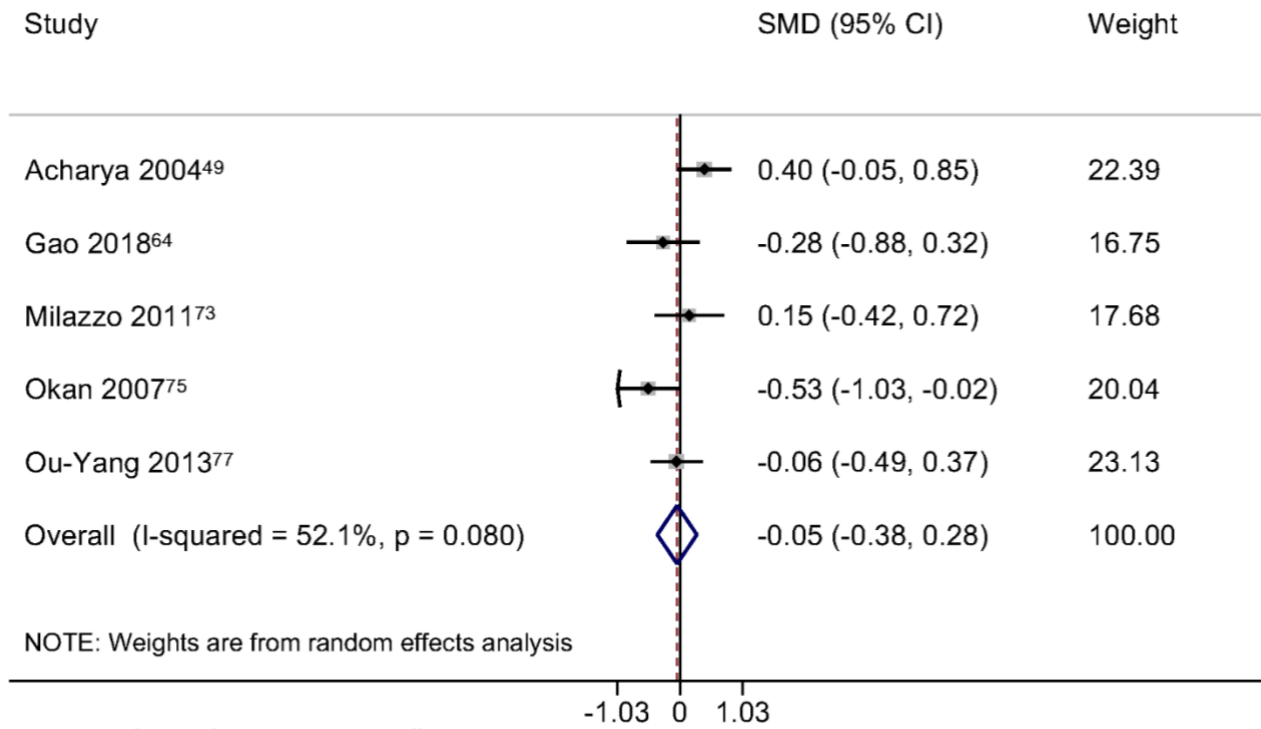
Supplementary Figure 46. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention with heart rate measured >1 minute after procedure commencement



Note: P-value for test of standardised mean difference: 0.002
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

Supplementary Figure 47. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention with oxygen saturation measured ≤ 1 minute after procedure commencement

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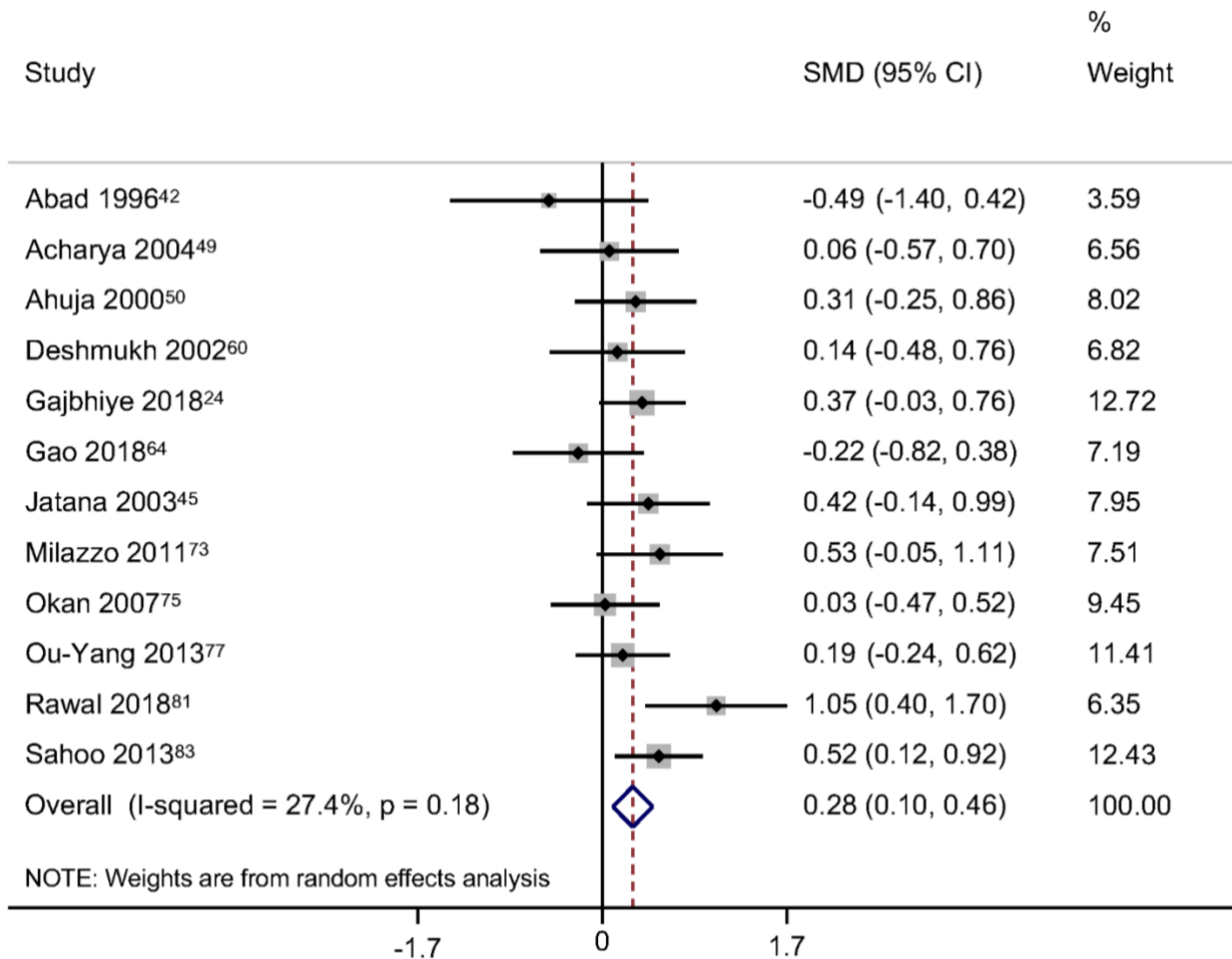


NOTE: Weights are from random effects analysis

Note: P-value for test of standardised mean difference: 0.77

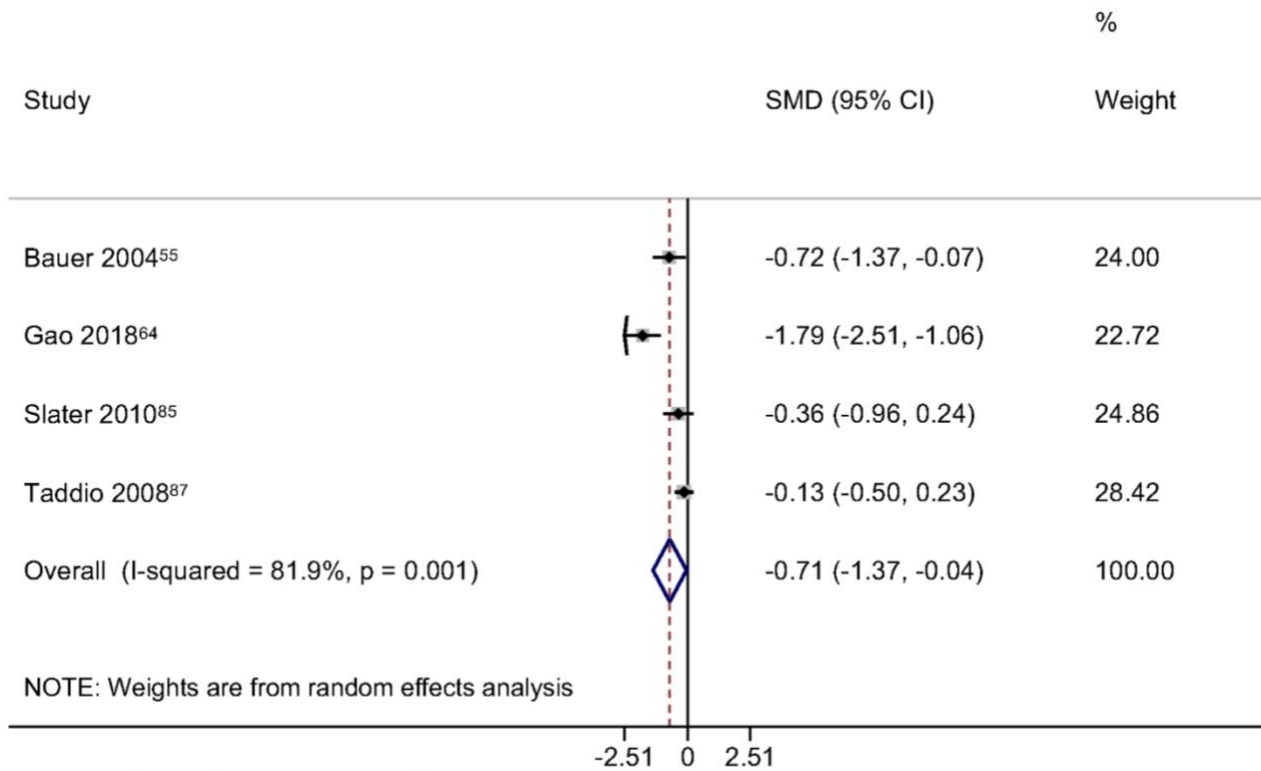
Abbreviations: CI=confidence interval, SMD=standardised mean difference

Supplementary Figure 48. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention with oxygen saturation measured >1 minute after procedure commencement



Note: P-value for test of standardised mean difference: 0.003
 Abbreviations: CI=confidence interval, SMD=standardised mean difference

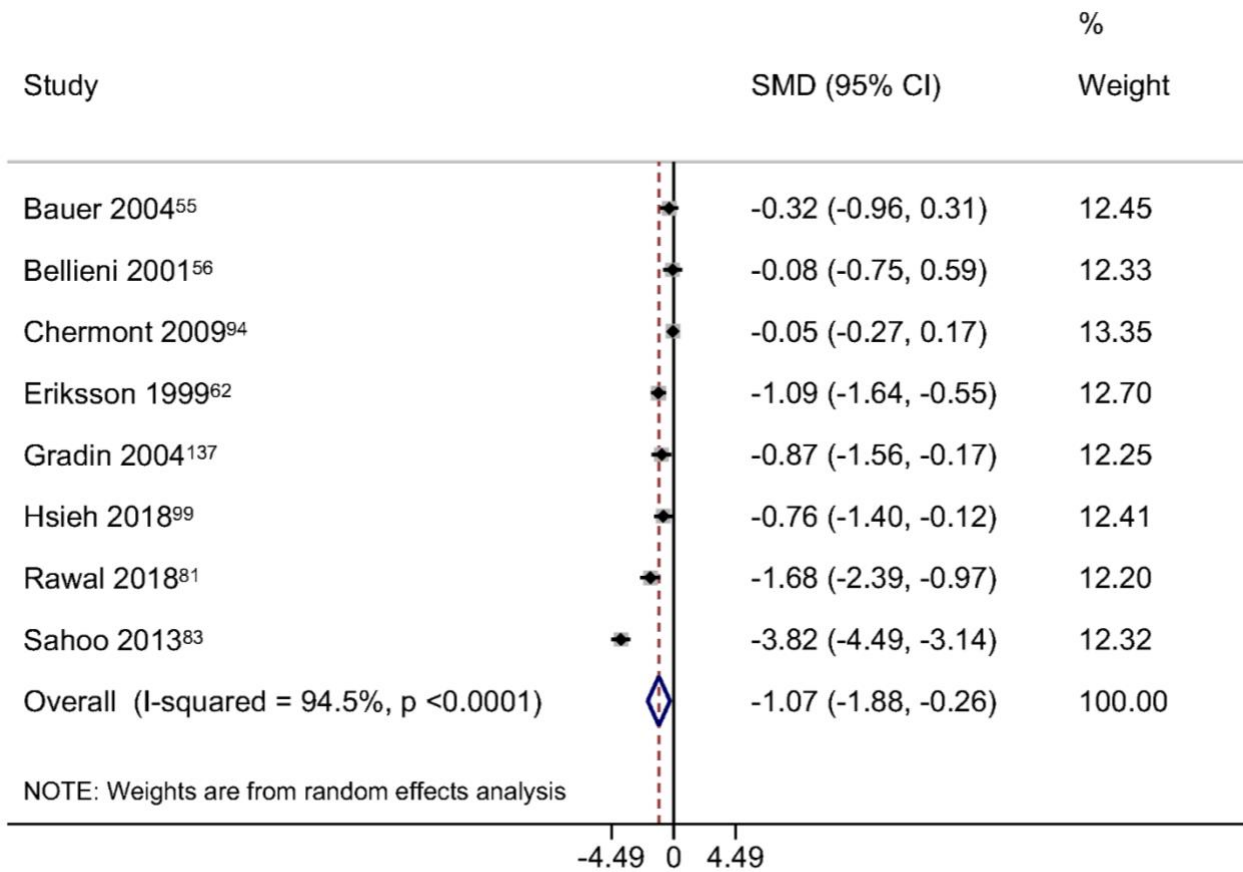
Supplementary Figure 49. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention with PIPP measured ≤ 1 minute after procedure commencement



Note: P-value for test of standardised mean difference: 0.038

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

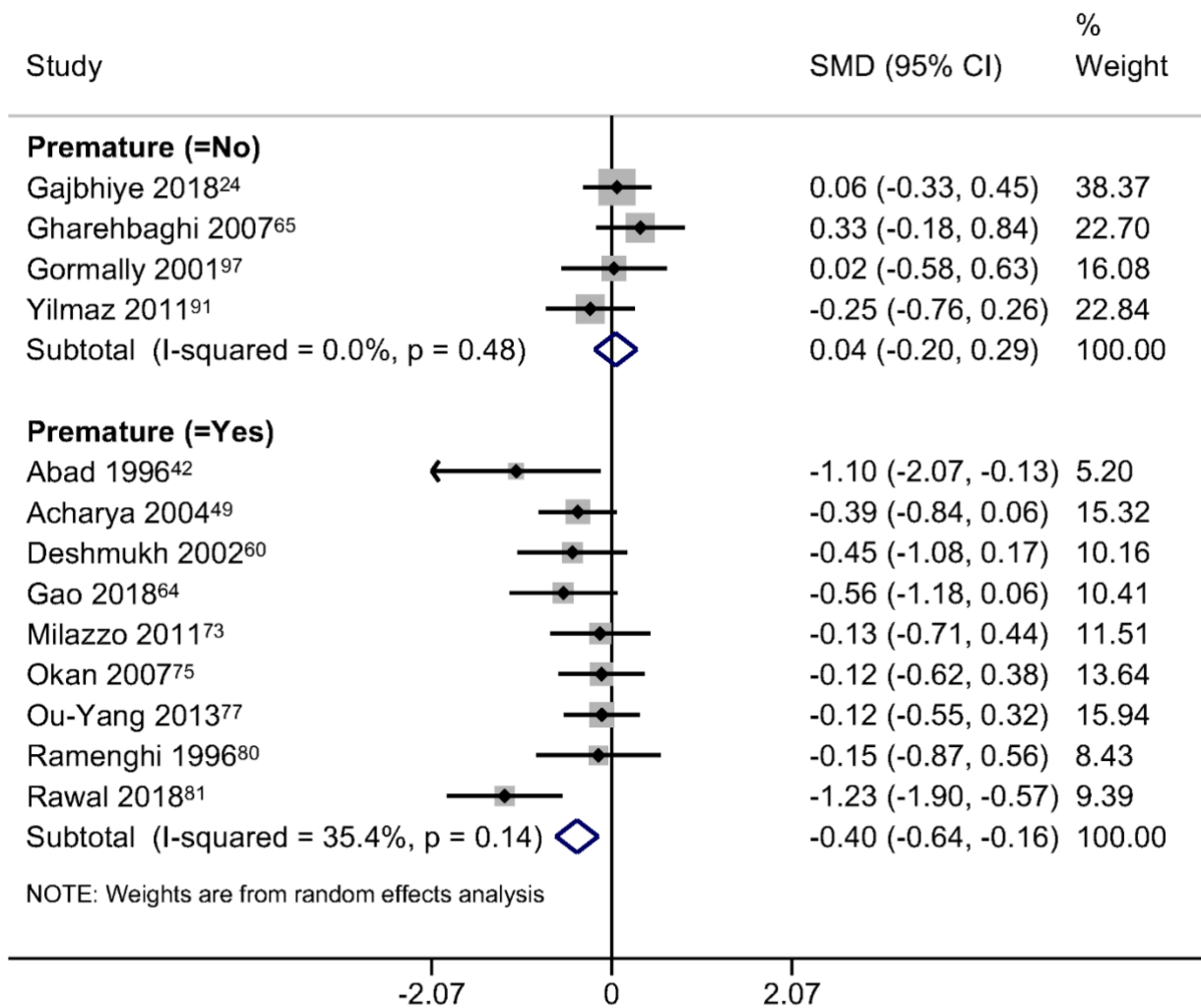
Supplementary Figure 50. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention with PIPP measured >1 minute after procedure commencement



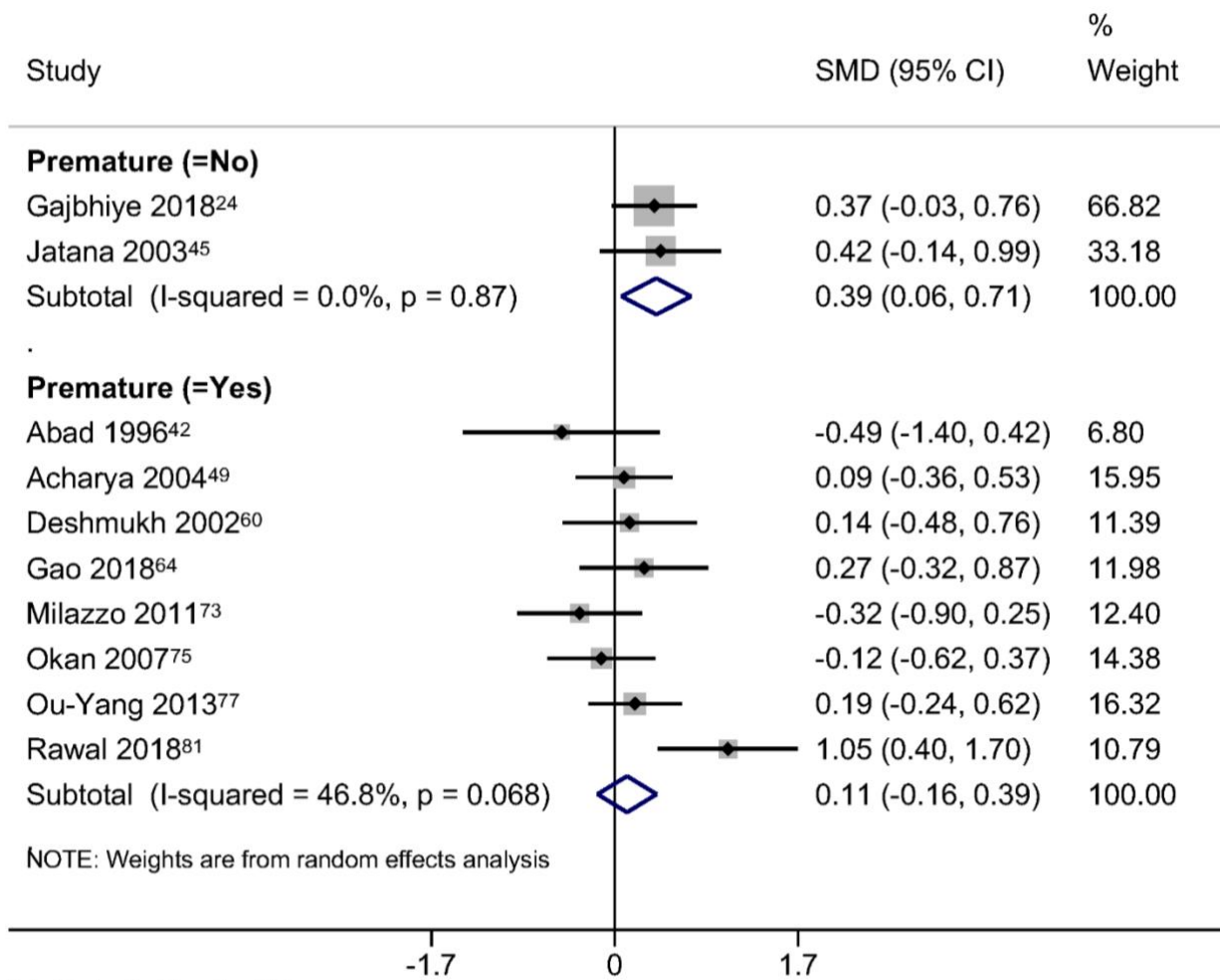
Note: P-value for test of standardised mean difference: 0.010

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

Supplementary Figure 51. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for heart rate by prematurity status



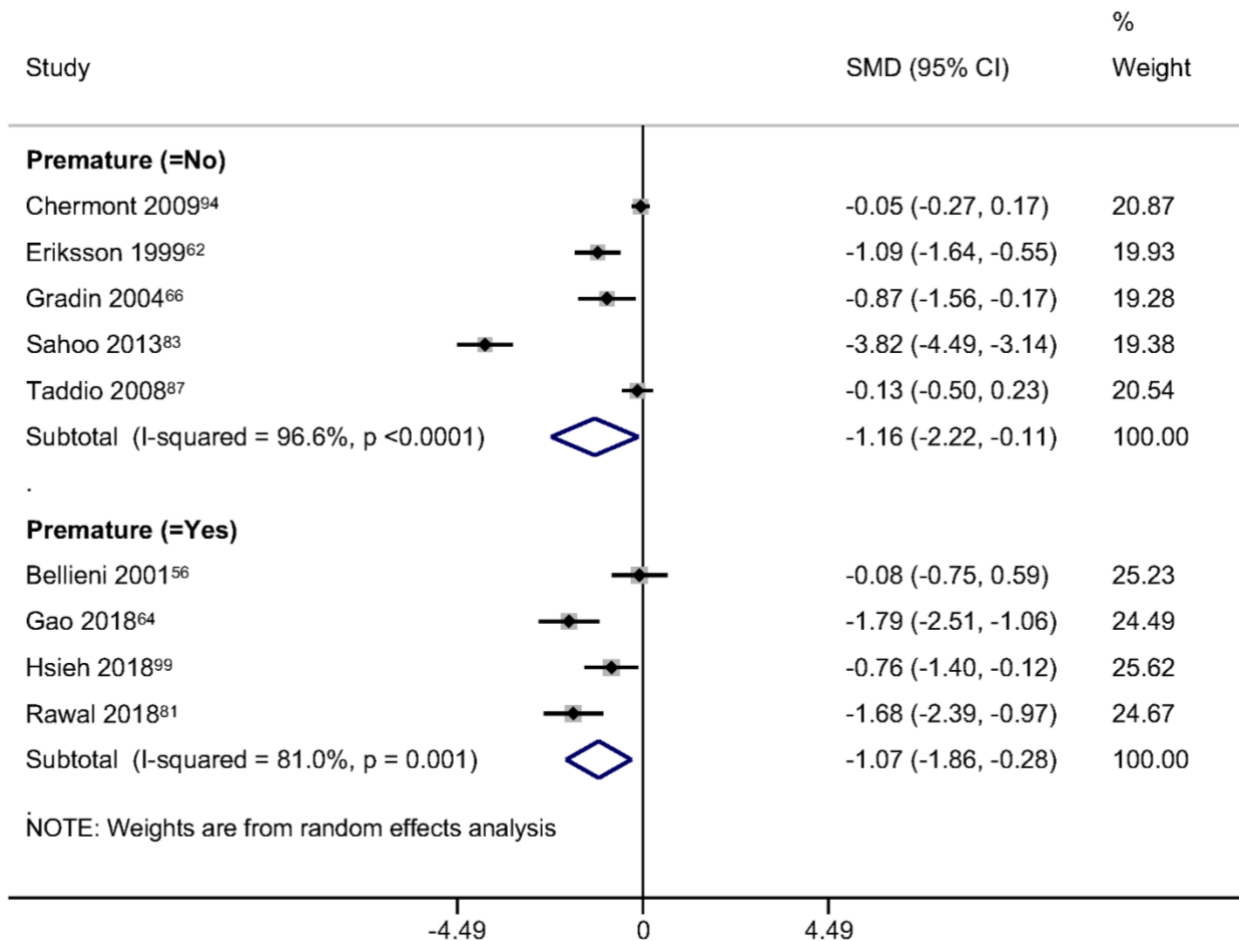
Supplementary Figure 52. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for oxygen saturation by prematurity status



Note: P-value for interaction: 0.65

Abbreviations: CI=confidence interval, SMD=standardised mean difference

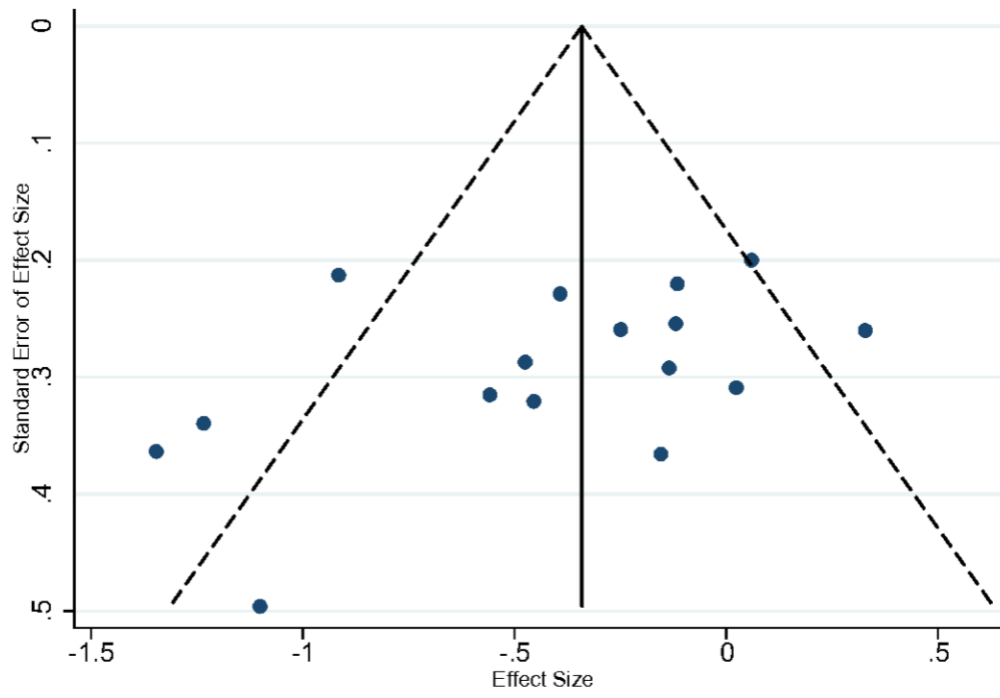
Supplementary Figure 53. Standardised mean differences and their confidence intervals for the comparison of oral sugar versus placebo or no intervention for PIPP by prematurity status



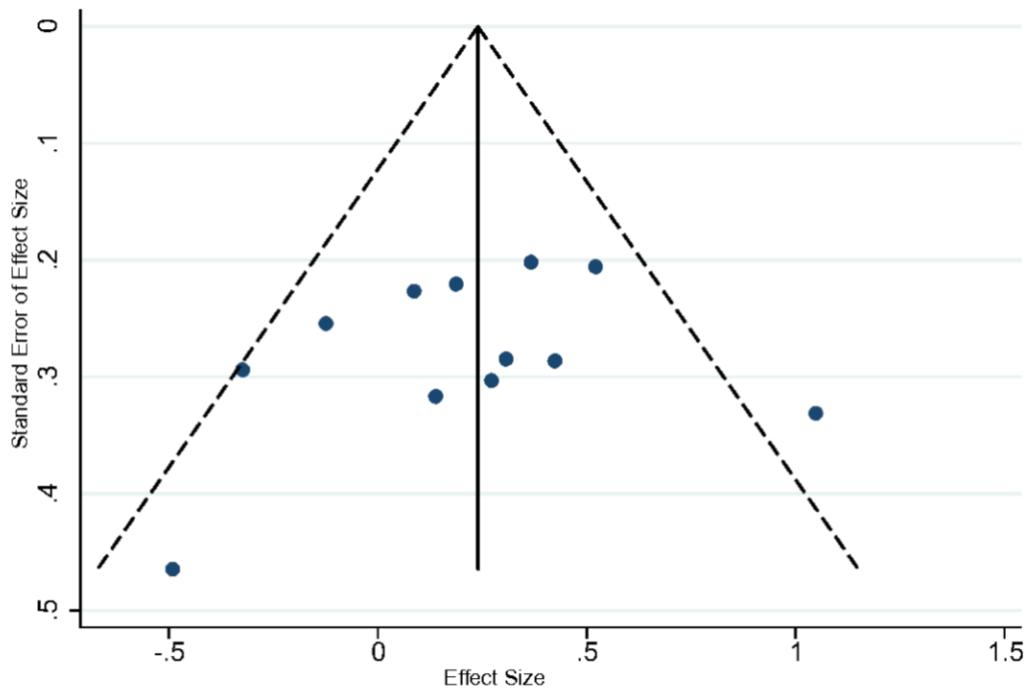
Note: P-value for interaction: 0.48

Abbreviations: CI=confidence interval, SMD=standardised mean difference, PIPP=Premature Infant Pain Profile

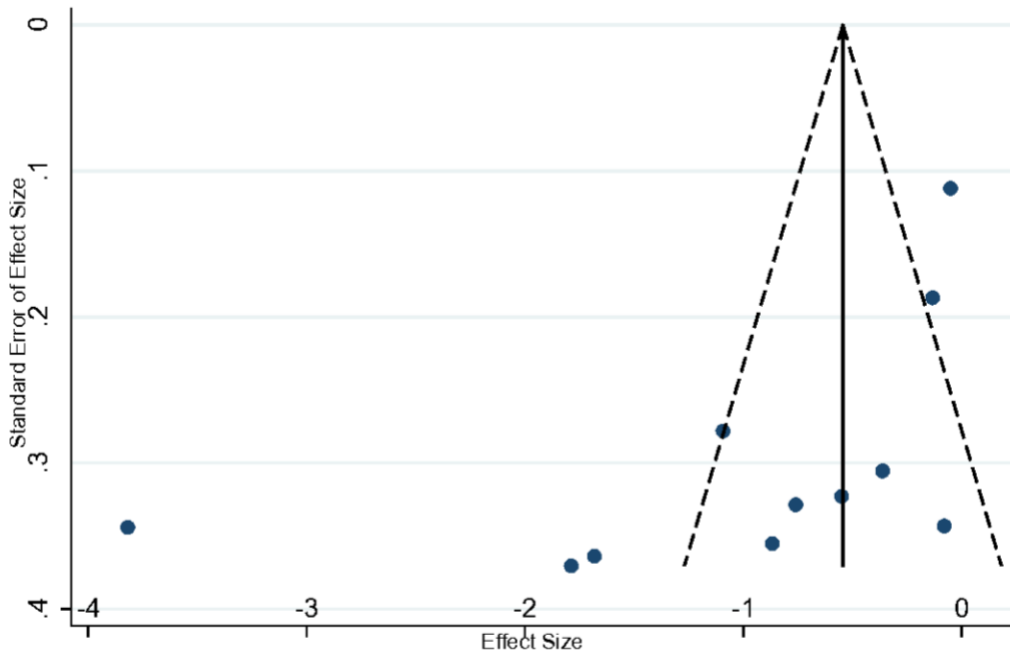
Supplementary Figure 54. Funnel plot (with pseudo 95% confidence limits) of studies for oral sugar versus placebo or no intervention using heart rate^{24, 42, 49, 50, 55, 60, 64, 65, 73, 75, 77, 80, 81, 83, 91, 97}



Supplementary Figure 55. Funnel plot (with pseudo 95% confidence limits) of studies for oral sugar versus placebo or no intervention using oxygen saturation^{24, 42, 49, 50, 60, 64, 45, 73, 75, 77, 81, 83}



Supplementary Figure 56. Funnel plot (with pseudo 95% confidence limits) of studies for oral sugar versus placebo or no intervention using Premature Infant Pain Profile (PIPP)^{55, 56, 62, 64, 66, 81, 83, 85, 87, 94, 99}



Further reading panel of references for PICO questions deprioritised by the Neonatal Pain Guideline Group

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