Supplemental Online Content

Marc I, Boutin A, Pronovost E, et al. Association between enteral supplementation with high-dose docosahexaenoic acid and risk of bronchopulmonary dysplasia in preterm infants: a systematic review and meta-analysis. *JAMA Netw Open*. 2023;6(3):e233934. doi:10.1001/jamanetworkopen.2023.3934

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

eTable 1. *PubMed* search strategy and results

#	Search strategy	Results
1	"Fatty Acids, Omega-3"[Mesh:NoExp] OR "Docosahexaenoic Acids"[Mesh] OR "Fish Oils"[Mesh:NoExp] OR "Fatty Acids, Essential"[Mesh:noexp]	31,433
2	Omega 3[TIAB] OR n 3 fatty acid[TIAB] OR n 3 Oil[TIAB] OR n3 Oil[TIAB] OR Polyunsaturated Fatty Acid*[TIAB] OR polyunsaturated FA[TIAB] OR Docosahexaenoic Acid*[TIAB] OR alga* oil[TIAB] OR marine oil[TIAB] OR fish oil[TIAB] OR essential fatty acid*[TIAB] OR DHA[TIAB]	61,759
3	#1 OR #2	67,434
4	"Infant, Premature"[Mesh] OR "Infant, Low Birth Weight"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Newborn"[Mesh]	645,200
5	Premature Infant*[TIAB] OR preterm infant*[TIAB] OR low birth weight[TIAB] OR preterm birth*[TIAB] OR Premature Birth*[TIAB] OR newborn*[TIAB] OR neonate*[TIAB]	334,113
6	#4 OR #5	760,745
7	((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab] OR randomised[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab]))	5,254,468
8	(animals[MeSH] NOT humans[MeSH])	4,907,993
9	(#3 AND #6 AND #7) NOT #8	949
10	#9 AND 2021/11/02:2022/08/01[edat]	41
11	**Total PubMed results**	990

eTable 2. *Embase* search strategy and results

#	Search strategy	Results
1	'omega 3 fatty acid'/de OR 'docosahexaenoic acid'/de OR 'fish oil'/de OR 'essential fatty acid'/de	63,631
2	"Omega 3":ti,ab,kw OR "n 3 fatty acid":ti,ab,kw OR "n 3 Oil":ti,ab,kw OR "n3 Oil":ti,ab,kw OR "Polyunsaturated Fatty Acid$":ti,ab,kw OR "Polyunsaturated FA":ti,ab,kw OR "Docosahexaenoic Acid$":ti,ab,kw OR "alga* oil":ti,ab,kw OR "marine oil":ti,ab,kw OR "fish oil":ti,ab,kw OR "essential fatty acid$":ti,ab,kw OR DHA:ti,ab,kw	74,163
3	#1 OR #2	94,604
4	'prematurity'/de OR 'low birth weight'/exp OR 'very low birth weight'/exp OR 'newborn'/de	723,734
5	"Premature Infant$":ti,ab,kw OR "preterm infant$":ti,ab,kw OR "low birth weight":ti,ab,kw OR "preterm birth$":ti,ab,kw OR "Premature Birth$":ti,ab,kw OR newborn$:ti,ab,kw OR neonate$:ti,ab,kw	424,026
6	#4 OR #5	845,949
7	(("Randomized controlled trial"/de) OR ("Controlled clinical trial"/de) OR (random*:ti,ab) OR (randomization/de) OR ("intermethod comparison"/de) OR (placebo:ti,ab) OR (compare OR compared OR comparison):ti OR ((evaluated OR evaluate OR evaluating OR assessed OR assess) AND (compare OR compared OR comparing OR comparison)):ti OR (open NEAR/1 label):ti,ab OR ((double OR single OR doubly OR singly) NEAR/1 (blind OR blinded OR blindly)):ti,ab OR ("double blind procedure"/de) OR ("parallel group*":ti,ab) OR (crossover OR "cross over"):ti,ab OR ((assign* OR match OR matched OR allocation) NEAR/5 (alternate OR group* OR intervention* OR patient* OR subject* OR participant*)):ti,ab OR (assigned OR allocated):ti,ab OR (controlled NEAR/7 (study OR design OR trial)):ti,ab OR (volunteer OR volunteers):ti,ab OR ("human experiment"/de) OR (trial:ti))	3,923,157
8	((random* NEAR/1 sampl* NEAR/7 ("cross section*" or questionnaire* or survey* or database*)):ti,ab NOT ("comparative study"/de OR "controlled study"/de OR "randomi$ed controlled":ti,ab OR "randomly assigned":ti,ab) OR ("Cross-sectional study"/de NOT ("randomized controlled trial"/de OR "controlled clinical study"/de OR "controlled study"/de OR "randomi$ed controlled":ti,ab OR "control group*":ti,ab)) OR (((case NEAR/1 control*) AND random*) NOT "randomi$ed controlled"):ti,ab OR ("Systematic review" NOT (trial OR study)):ti OR (nonrandom* NOT random*):ti,ab OR ("Random field*":ti,ab) OR ("random cluster" NEAR/3 sampl*):ti,ab OR (review:ab AND review/de) NOT trial:ti OR ("we searched":ab AND (review:ti OR review/de)) OR ("update review":ab) OR (databases NEAR/4 searched):ab OR ((rat OR rats OR mouse OR mice OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset*):ti AND "animal experiment"/de) OR ("Animal experiment"/de NOT ("human experiment"/de OR human/de)))	3,751,550
9	(#3 AND #6 AND #7) NOT #8	758
10	#9 AND [02-11-2021]/sd	49
11	**Total Embase results**	807

eTable 3. *Cochrane Library* search strategy and results

#	Search strategy	Results
1	[mh ^"Fatty Acids, Omega-3"] OR [mh "Docosahexaenoic Acids"] OR [mh "Fish Oils"] OR [mh ^"Fatty Acids, Essential"]	3,747
2	"Omega 3":ti,ab,kw OR "n 3 fatty acid":ti,ab,kw OR "n 3 Oil":ti,ab,kw OR "n3 Oil":ti,ab,kw OR "Polyunsaturated Fatty Acid":ti,ab,kw OR "Polyunsaturated Fatty Acids":ti,ab,kw OR "Polyunsaturated FA":ti,ab,kw OR "Docosahexaenoic Acid":ti,ab,kw OR "Docosahexaenoic Acids":ti,ab,kw OR (alga* near/1 oil):ti,ab,kw OR "marine oil":ti,ab,kw OR "fish oil":ti,ab,kw OR "essential fatty acid":ti,ab,kw OR "essential fatty acids":ti,ab,kw OR DHA:ti,ab,kw	10,907
3	#1 OR #2	11,154
4	[mh "Infant, Premature"] OR [mh "Infant, Low Birth Weight"] OR [mh "Premature Birth"] OR [mh "Infant, Newborn"]	18,086
5	((premature OR preterm) NEAR/1 (Infant* OR birth*)):ti,ab,kw OR "low birth weight":ti,ab,kw OR newborn*:ti,ab,kw OR neonate*:ti,ab,kw	39,945
6	#4 OR #5	39,958
7	#3 AND #6	810
8	Trials results only	798
9	Date added to CENTRAL trials database limit 02/11/2021 to 01/08/2022	43
10	**Total Cochrane Library results**	841

eTable 4. *Web of Science* search strategy and results

#	Search strategy	Results
1	TS=("Omega 3" OR "n 3 fatty acid" OR "n 3 Oil" OR "n3 Oil" OR "Polyunsaturated Fatty Acid$" OR "Polyunsaturated FA" OR "Docosahexaenoic Acid$" OR "alga* oil" OR "marine oil" OR "fish oil" OR "essential fatty acid*" OR DHA)	96,862
2	TS=(((premature OR preterm) NEAR/1 (Infant$ OR birth$)) OR "low birth weight" OR newborn$ OR neonate$)	331,476
3	TS=(randomized OR randomised OR placebo OR randomly OR trial OR groups OR "drug therapy")	7,238,171
4	#1 AND #2 AND #3	1,219
5	Publication date database limit 2021-11-02 to 2022-08-01	46
6	**Total Web of Science results**	1265

eTable 5. *MedRXiv* search strategy and results

#	Search strategy	Results
1	("omega 3" OR "n 3 fatty acid" OR "n 3 Oil" OR "n3 Oil" OR "polyunsaturated Fatty Acid" OR "polyunsaturated Fatty Acids" OR "polyunsaturated FA" OR "docosahexaenoic Acid" OR "docosahexaenoic Acids" OR "alga oil" OR "marine oil" OR "fish oil" OR "essential fatty acid" OR "essential fatty acids" OR DHA) AND ("Premature Infant" OR "Premature Infants" OR "preterm infant" OR "preterm infants" OR "low birth weight" OR "preterm birth" OR "preterm births" OR "premature Birth" OR "Premature Birth" OR newborn OR newborns OR neonate OR newborns)	0
2	Publication date database limit 2021-11-02 to 2022-08-01	0
3	**Total MedRxiv results**	0

eTable 6. *Clinicaltrials.gov* search strategy and results

#	Search strategy[a]	Results
1	("omega 3" OR "n 3 fatty acid" OR "n 3 Oil" OR "n3 Oil" OR "polyunsaturated Fatty Acid" OR "polyunsaturated Fatty Acids" OR "polyunsaturated FA" OR "docosahexaenoic Acid") AND ("Premature Infant" OR "Premature Infants" OR "preterm infant" OR "preterm infants" OR "low birth weight" OR "preterm birth" OR "preterm births" OR "premature Birth" OR "Premature Birth" OR newborn OR newborns OR neonate OR newborns)	97
2	("docosahexaenoic Acids" OR "alga oil" OR "marine oil" OR "fish oil" OR "essential fatty acid" OR "essential fatty acids" OR DHA) AND ("Premature Infant" OR "Premature Infants" OR "preterm infant" OR "preterm infants" OR "low birth weight" OR "preterm birth" OR "preterm births" OR "premature Birth" OR "Premature Birth" OR newborn OR newborns OR neonate OR newborns)	117
3	#1 OR #2	214
New search on 2022-08-01		
1	("omega 3" OR "n 3 fatty acid" OR "n 3 Oil" OR "n3 Oil" OR "polyunsaturated Fatty Acid" OR "polyunsaturated Fatty Acids" OR "polyunsaturated FA" OR "docosahexaenoic Acid") AND ("Premature Infant" OR "Premature Infants" OR "preterm infant" OR "preterm infants" OR "low birth weight" OR "preterm birth" OR "preterm births" OR "premature Birth" OR "Premature Birth" OR newborn OR newborns OR neonate OR newborns)	105
2	("docosahexaenoic Acids" OR "alga oil" OR "marine oil" OR "fish oil" OR "essential fatty acid" OR "essential fatty acids" OR DHA) AND ("Premature Infant" OR "Premature Infants" OR "preterm infant" OR "preterm infants" OR "low birth weight" OR "preterm birth" OR "preterm births" OR "premature Birth" OR "Premature Birth" OR newborn OR newborns OR neonate OR newborns)	127
3	#1 OR #2	232

[a]Search was executed in the “Intervention/treatment” and “Other terms” fields.

eTable 7. Citation searching details and results

Seminal papers	Backward citations	Forward citations	Tool/method use	Results
Reviews known by the research team (28)	X		Web of Science	765
Included studies (4)	X	X	Web of Science, iCite and CitationChaser	161
Protocol (20)		X	Web of Science, iCite	61
Total citation searching results				987

eTable 8. Status of protocols for citation searching

Registration number	Title of the trial	Recruitment status
ACTRN12612000503820	In preterm infants born at <29 weeks gestation is an emulsion containing a higher amount of docosahexaenoic acid (DHA) more effective than an emulsion with no additional DHA in reducing the incidence of bronchopulmonary dysplasia at 36 weeks post menstrual age?	Completed
ACTRN12617001078347	Double-blind RCT of fish oil supplementation in pregnancy and lactation to improve metabolic health in the children of mothers with overweight or obesity	Active, not recruiting
N/A	Effect of alpha-linolenic acid intake and postmenstrual age on arachidonic and docosahexaenoic acid biosynthesis in preterm infants	N/A
NCT00226187	A Randomized Clinical Trial on Supplementation of DHA and AA to Preterm Infants	Completed
NCT00872664	Skin and Serum Carotenoids in Preterm Infants Fed on a Formula Supplemented With Carotenoids	Completed
NCT01103219	Nutrition, Growth and Development Among Very Preterm Infants	Terminated (a planned interim-analysis revealed increased number of infections in the intervention arm)
NCT01306838	Early Provision of Enteral Microlipid and Fish Oil to Infants With Enterostomy	Completed
NCT01732874	DHA Supplementation for Lactating Mothers	Completed
NCT01940640	Effect of Mother DHA Supplementation on Premature Newborn	Completed
NCT01955044	PUFA Supplementation in Premature Infants	Completed
NCT02371460	Maternal Omega-3 Supplementation to Reduce Bronchopulmonary Dysplasia	Active, not recruiting
NCT03192839	Early DHA Supplementation in Very Low Birth Weight Infants	Completed
NCT03201588	Multi-Center Study to Determine the Role of Fatty Acids in Serum in Preventing Retinopathy of Prematurity (MDM)	Completed
NCT03555019	Nutrition Therapy in the Immature Infant (ImNuT)	Active, not recruiting
NCT03700957	The Impact of Docosahexaenoic Acid on the Prevention of Necrotizing Enterocolitis in Preterm Neonates	Unknown
NCT03739463	Pro-omega-3, Reduction of Inflammation and Modulation of Prematurity	Unknown
NCT04746885	Effect of DHA on Proinflammatory Cytokines Including Platelets Activating Factor (PAF) in Preterm Neonates	Completed
ISRCTN59878178	Exploratory randomised double-blind controlled trial of breast milk fortifier with and without long chain polyunsaturated fatty acid (LCPUFA) supplementation on body composition in preterm infants	No longer recruiting

eTable 9. Reasons for exclusion at full-text assessment

Study	Reason for exclusion
AbouElFadl et al,[1] 2021	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Atwell et al,[2] 2013	No data on BPD or death for the relevant population. Same dataset as Manley et al,[3] 2011 (included in this review)
Baack et al,[4] 2016	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Bernabe-García et al,[5] 2019	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Bernabe-García et al,[6] 2021	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Carlson et al,[7] 1996	Intervention evaluates low doses of DHA
Carlson et al,[8] 1998	Intervention evaluates low doses of DHA
Clandinin et al,[9] 1997	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation, no data on BPD or death
Clandinin et al,[10] 2005	Intervention evaluates low doses of DHA
Fewtrell et al,[11] 2002	Intervention evaluates low doses of DHA
Frost et al,[12] 2021	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Khalesi et al,[13] 2018	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation, no data on BPD or death
Makrides et al,[14] 2009	No data on BPD or death for the relevant population. Same dataset as Manley et al,[3] 2011 (included in this review)
Manley et al,[15] 2010	Conference abstract and same dataset as Manley et al,[3] 2011 (included in this review)
Moltu et al,[16] 2014	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Osman et al,[17] 2021	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Picaud et al,[18] 2022	Conference abstract
Rigo et al,[19] 2017	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation
Valentine et al,[20] 2019	No clinical outcome
Vanderhoof et al,[21] 2000	Intervention evaluates low doses of DHA
Strømmen et al,[22] 2016	Not an RCT and same dataset as Moltu et al,[16] 2014 (excluded)
Strømmen et al,[23] 2017	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation Same dataset as Moltu et al,[16] 2014 (excluded)
Westerberg et al,[24] 2011	Does not exclusively include infants <29 weeks' gestation and does not report data stratified for <29 weeks' gestation, no data on BPD or death

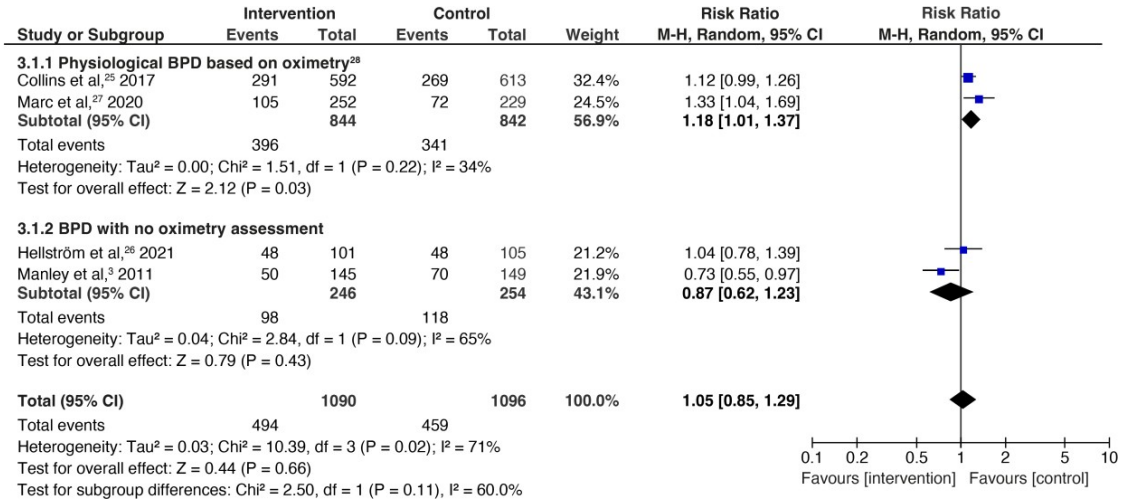
BPD: Bronchopulmonary dysplasia; DHA: Docosahexaenoic acid; RCT: Randomized Controlled Trial.

eFigure 1. Risk of bias assessment of included trials

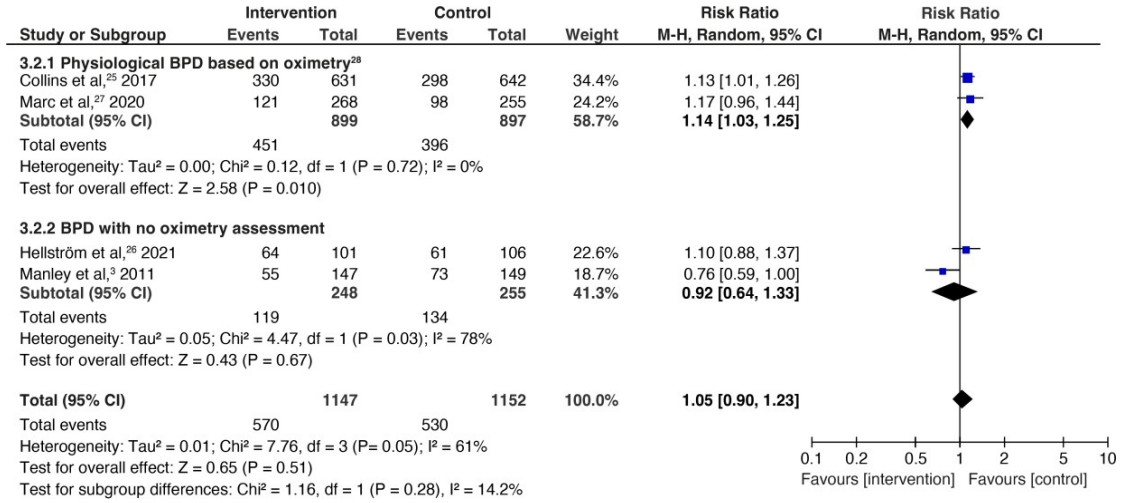
[a]Respiratory care management and consequently the assessment of BPD may have been influenced by the knowledge of the group due to the lack of placebo administration in the control group.

eFigure 2. Meta-analysis pooling risk ratio from reported frequencies on BPD outcomes

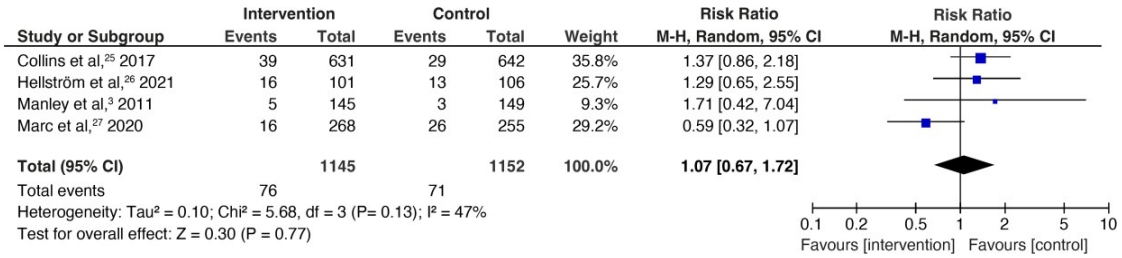
A BPD at 36 weeks' PMA



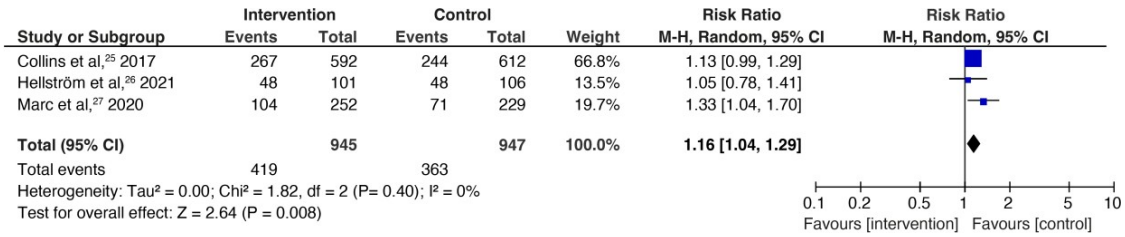
B "BPD or death" at 36 weeks' PMA[a]



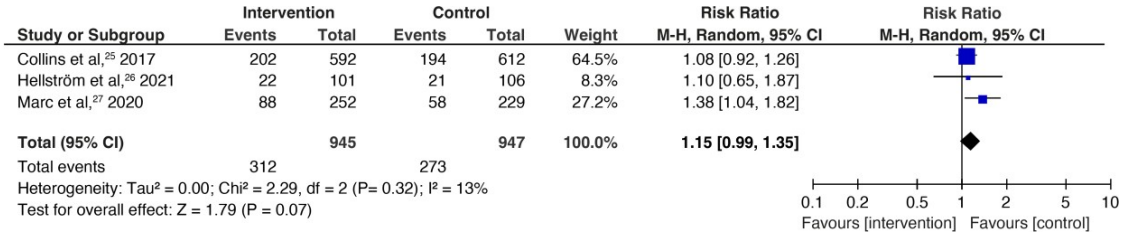
C Death up to 36 weeks' PMA[a]



D Moderate-to-severe BPD at 36 weeks' PMA[b]



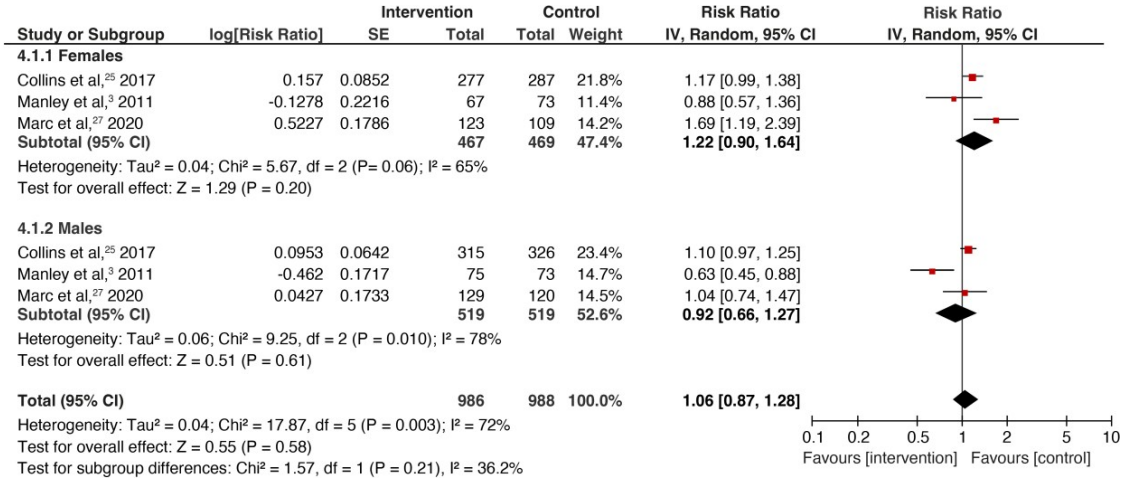
E Severe BPD at 36 weeks' PMA[b]



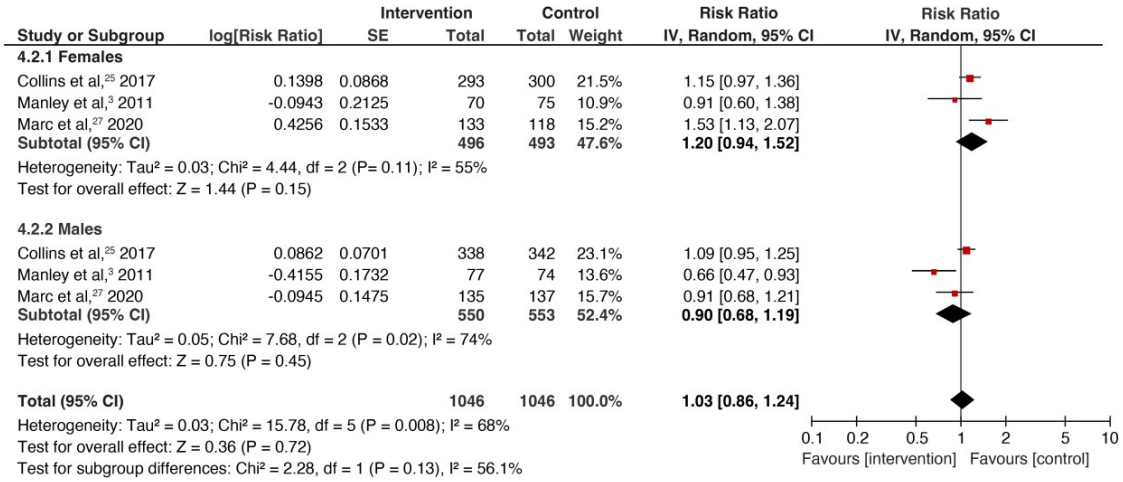
BPD: Bronchopulmonary dysplasia; CI: Confidence interval; M-H: Mantel-Haenszel; PMA: Postmenstrual age.
[a]Death up to 36 weeks' PMA except in Hellström et al,[26] 2021 where death was up to 40 weeks' PMA.
[b]Classified according to criteria from the National Institute of Child Health and Human Development[29] in Collins et al,[25] 2017 and Marc et al,[27] 2020. Definition not specified in Hellström et al,[26] 2021.

eFigure 3. Meta-analysis results on BPD outcome stratified by sex

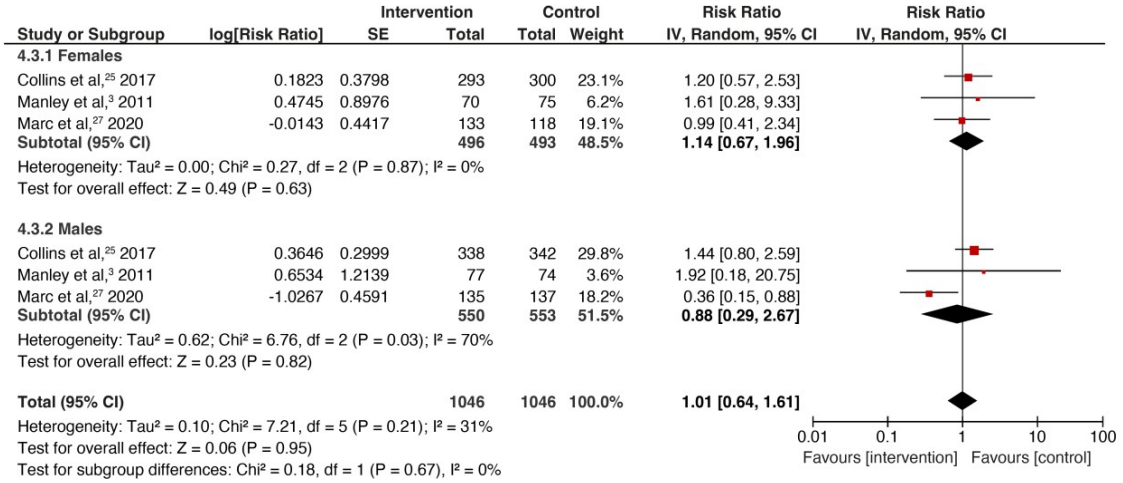
A BPD at 36 weeks' PMA[a]



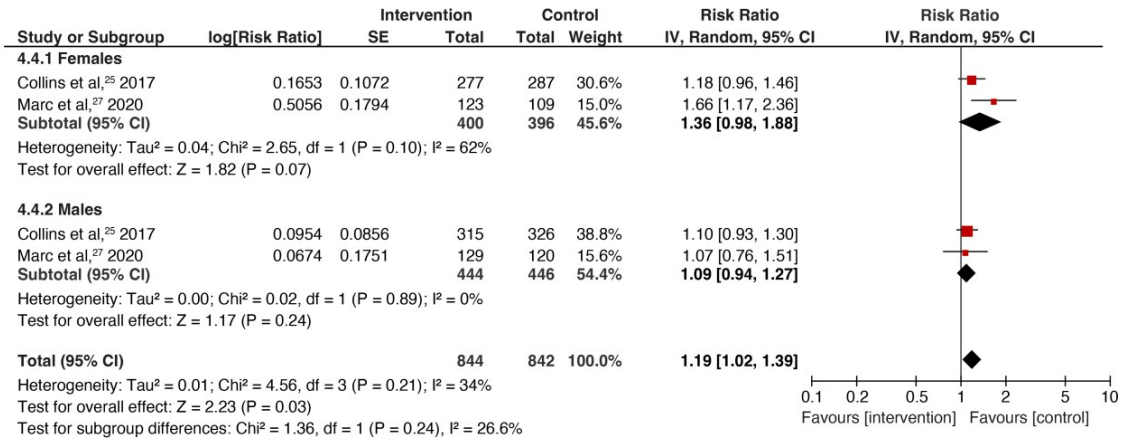
B "BPD or death" at 36 weeks' PMA[a]



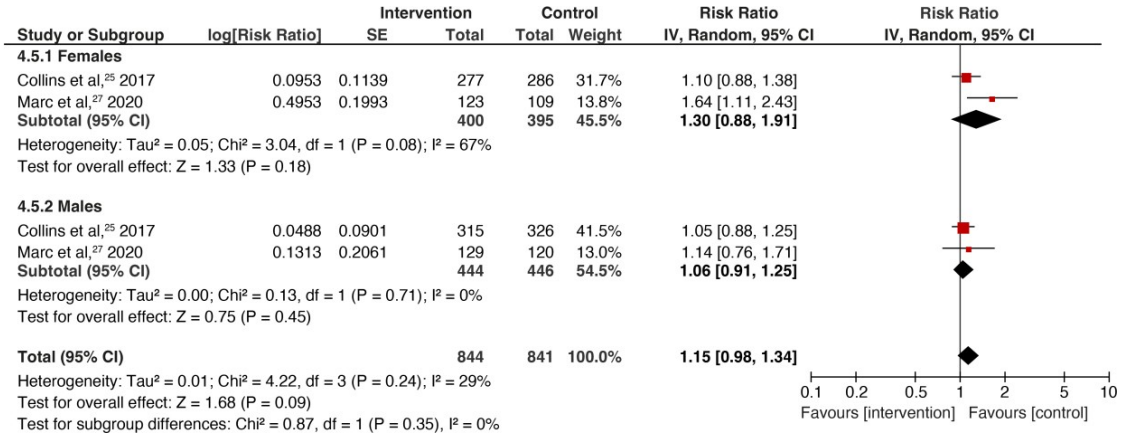
C Death up to 36 weeks' PMA



D Moderate-to-severe BPD at 36 weeks' PMA[b]



E Severe BPD at 36 weeks' PMA[b]



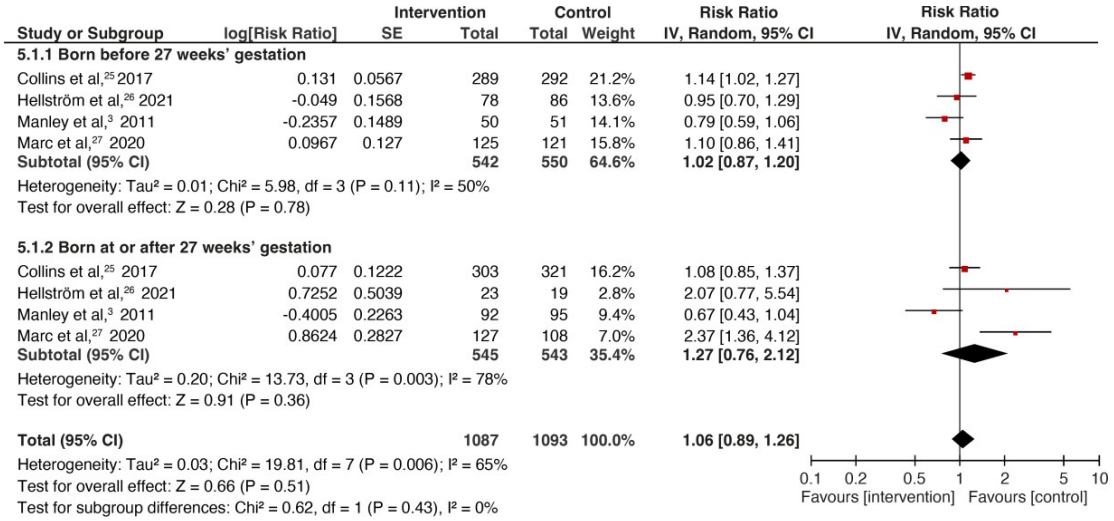
BPD: Bronchopulmonary dysplasia; CI: Confidence interval; IV: Inverse variance; PMA: Postmenstrual age; SE: Standard error.

[a]Physiological BPD based on oximetry[28] except in Manley et al,[3] 2011 where BPD was with no oximetry assessment.

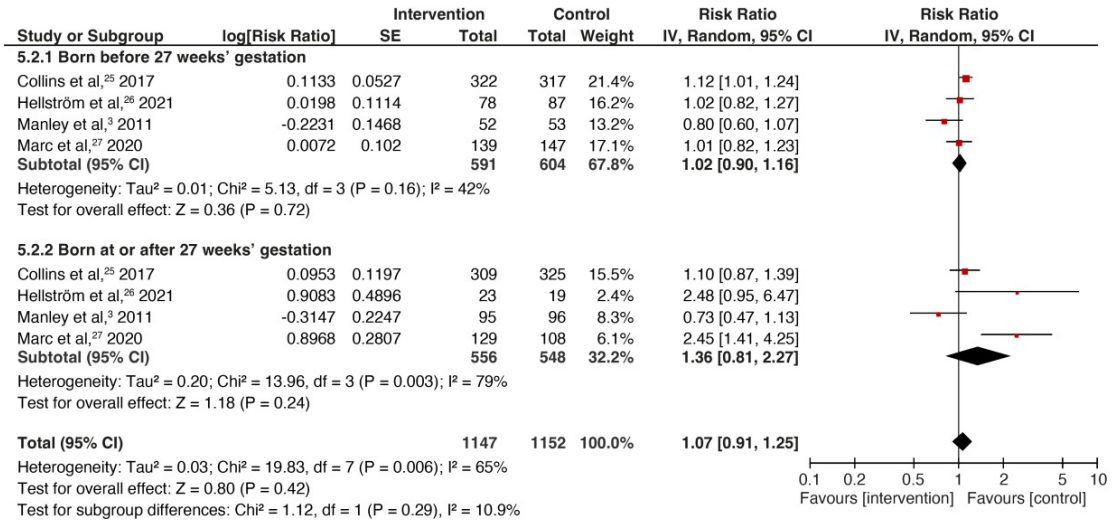
[b]Classified according to criteria from the National Institute of Child Health and Human Development.[29]

eFigure 4. Meta-analysis results on BPD outcome stratified by gestational age

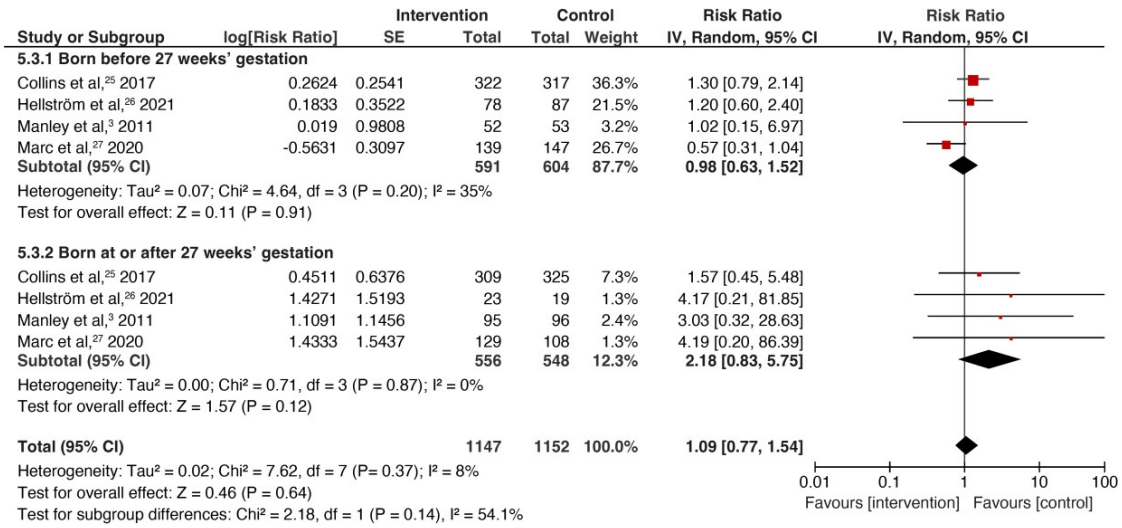
A BPD at 36 weeks' PMA[a]



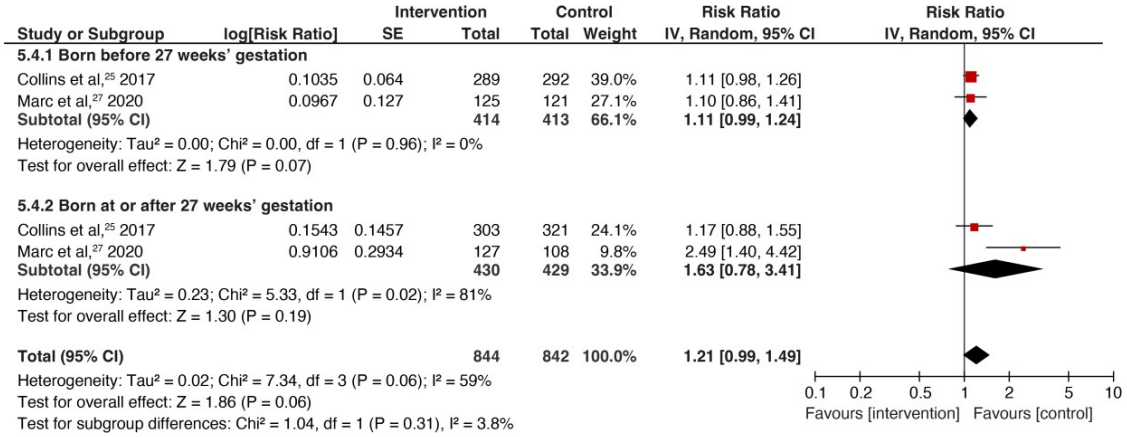
B "BPD or death" at 36 weeks' PMA[a, b]



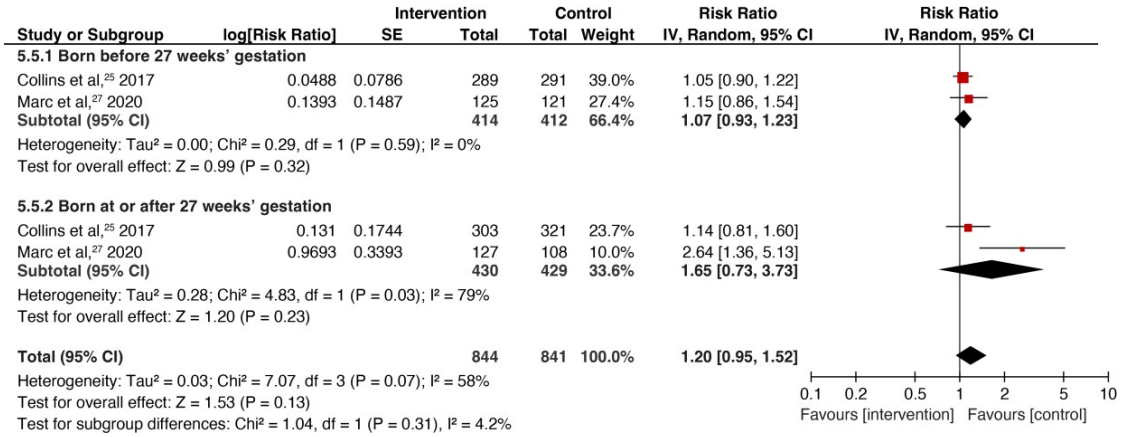
C Death up to 36 weeks' PMA[b]



D Moderate-to-severe BPD at 36 weeks' PMA[c]



E Severe BPD at 36 weeks' PMA[c]



BPD: Bronchopulmonary dysplasia; CI: Confidence interval; IV: Inverse variance; PMA: Postmenstrual age; SE: Standard error.

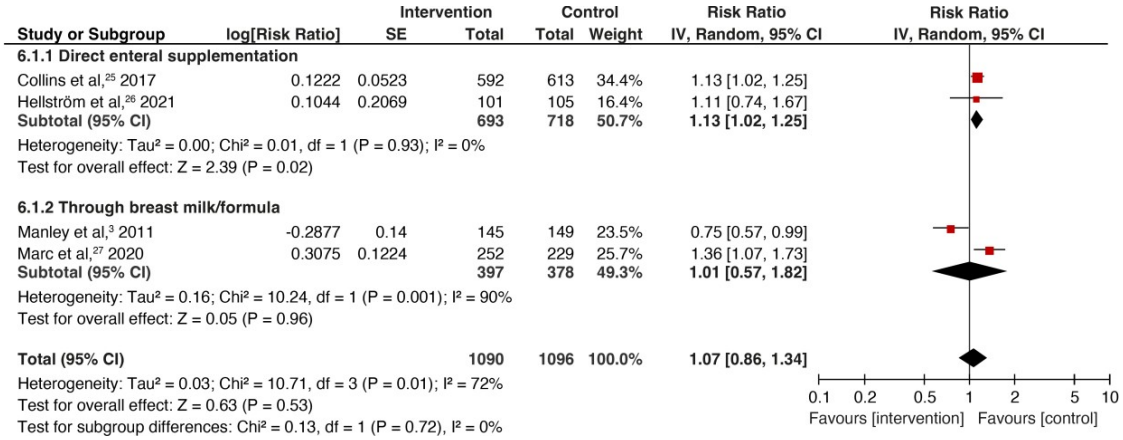
[a]Physiological BPD based on oximetry[28] except in Hellström et al,[26] 2021 and Manley et al,[3] 2011 where BPD was with no oximetry assessment.

[b]Death up to 36 weeks' PMA except in Hellström et al,[26] 2021 where death was up to 40 weeks' PMA.

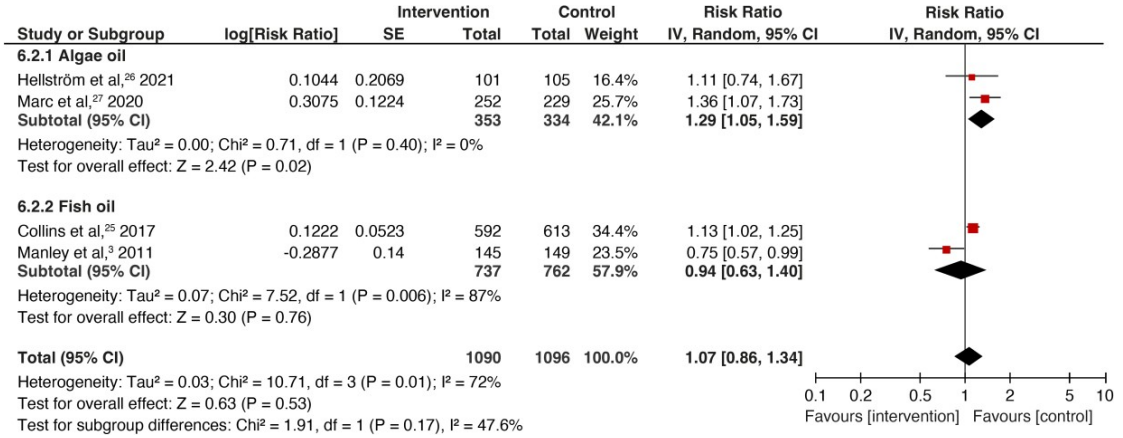
[c]Classified according to criteria from the National Institute of Child Health and Human Development.[29]

eFigure 5. Meta-analysis results on BPD outcome stratified by mode of administration, source of DHA and type of supplementation

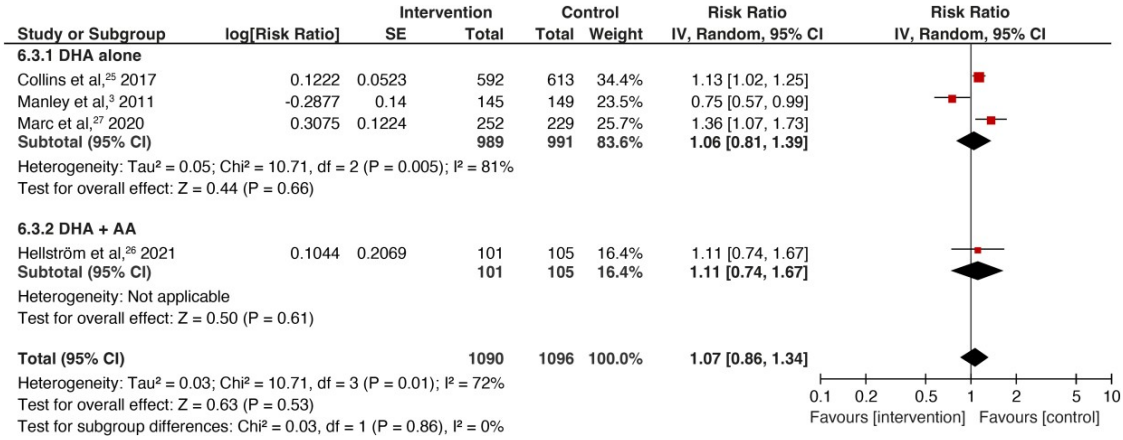
A BPD at 36 weeks' PMA by mode of administration[a]



B BPD at 36 weeks' PMA by source of DHA[a]



C BPD at 36 weeks' PMA by type of supplementation[a]



AA: Arachidonic acid; BPD: Bronchopulmonary dysplasia; CI: Confidence interval; DHA: Docosahexaenoic acid; IV: Inverse variance; PMA: Postmenstrual age; SE: Standard error.
[a]Physiological BPD based on oximetry[28] except in Hellström et al,[26] 2021 and Manley et al,[3] 2011 where BPD was with no oximetry assessment.

eReferences

1. Abou El Fadl DK, Ahmed MA, Aly YA, Darweesh EAG, Sabri NA. Impact of Docosahexaenoic acid supplementation on proinflammatory cytokines release and the development of Necrotizing enterocolitis in preterm Neonates: A randomized controlled study: Impact of Docosahexaenoic acid supplementation on proinflammatory cytokines. *Saudi Pharmaceutical Journal.* 2021.
2. Atwell K, Collins CT, Sullivan TR, et al. Respiratory hospitalisation of infants supplemented with docosahexaenoic acid as preterm neonates. *J Paediatr Child Health.* 2013;49(1):E17-22.
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