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

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eReferences

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 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 acids":ti,ab,kw OR "essential fatty acids":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	96,862
	Fatty Acid\$" OR "Polyunsaturated FA" OR "Docosahexaenoic Acid\$" OR "alga*	
	oil" OR "marine oil" OR "fish oil" OR "essential fatty acid*" OR DHA)	_
2	TS=(((premature OR preterm) NEAR/1 (Infant\$ OR birth\$)) OR "low birth weight"	331,476
	OR newborn\$ OR neonate\$)	
3	TS=(randomized OR randomised OR placebo OR randomly OR trial OR groups	7,238,171
	OR "drug therapy")	
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 Acid" 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 birth" 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 newborn OR newborns OR neonate OR newborns)	117
3	#1 OR #2	214
Ne	w 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 infant" 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

^aSearch 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)	Х	Х	Web of Science, iCite and CitationChaser	161
Protocol (20)		Х	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 interimanalysis 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	Does not exclusively include infants <29 weeks' gestation and does
2019	not report data stratified for <29 weeks' gestation
Bernabe-García et al,6	Does not exclusively include infants <29 weeks' gestation and does
2021	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
- 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	death
Makrides et al, ¹⁴ 2009	No data on BPD or death for the relevant population. Same dataset as
Manufact at 15 0040	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
Moltu et al, ¹⁶ 2014	(included in this review)
Moltu et al, " 2014	Does not exclusively include infants <29 weeks' gestation and does
Osman et al, ¹⁷ 2021	not report data stratified for <29 weeks' gestation Does not exclusively include infants <29 weeks' gestation and does
Osman et al, " 2021	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
Nigo et al, 2017	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
ou similar of all	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

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_	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Collins et al, ²⁵ 2017	•	+	+	•	+	+
Hellström et al,² 2021	6	+	+	! a	+	!
Manley et al, ³ 2011	•	+	+	+	+	+
Marc et al, ²⁷ 2020	•	+	+	•	+	+
+ !	Sama concerns					

Low; Some concerns

aRespiratory 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

	Interve	ntion	Con	trol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.1.1 Physiological BPD) based on ox	imetry ²⁸					
Collins et al,25 2017	291	592	269	613	32.4%	1.12 [0.99, 1.26]	-
Marc et al,27 2020	105	252	72	229	24.5%	1.33 [1.04, 1.69]	_
Subtotal (95% CI)		844		842	56.9%	1.18 [1.01, 1.37]	 ◆
Total events	396		341				
Heterogeneity: Tau ² = 0.0	0; Chi ² = 1.51	df = 1 (P :	$= 0.22$); $I^2 = 3$	84%			
Test for overall effect: Z =	2.12 (P = 0.0	3)					
3.1.2 BPD with no oxime	etry assessm	ent					
Hellström et al,26 2021	48	101	48	105	21.2%	1.04 [0.78, 1.39]	-
Manley et al,3 2011	50	145	70	149	21.9%	0.73 [0.55, 0.97]	-
Subtotal (95% CI)		246		254	43.1%	0.87 [0.62, 1.23]	*
Total events	98		118				
Heterogeneity: Tau ² = 0.0	04; Chi ² = 2.84	df = 1 (P :	$= 0.09$); $I^2 = 6$	65%			
Test for overall effect: Z =	0.79 (P = 0.4	3)					
Total (95% CI)		1090		1096	100.0%	1.05 [0.85, 1.29]	*
Total events	494		459				
Heterogeneity: Tau ² = 0.0	3; Chi ² = 10.3	9, df = 3 (P)	$l = 0.02$; $l^2 =$	71%		0	1 1 1 1
Test for overall effect: Z =	0.44 (P = 0.6	6)	,				0.2 0.5 1 2 5 1
Test for subgroup differen	nces: Chi² = 2.	50. df = 1 (Favou	rs [intervention] Favours [control]			

B "BPD or death" at 36 weeks' PMA^a

	Interve	ntion	Con	trol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.2.1 Physiological BPI	D based on ox	imetry ²⁸					
Collins et al,25 2017	330	631	298	642	34.4%	1.13 [1.01, 1.26]	•
Marc et al,27 2020	121	268	98	255	24.2%	1.17 [0.96, 1.44]	 -
Subtotal (95% CI)		899		897	58.7%	1.14 [1.03, 1.25]	♦
Total events	451		396				
Heterogeneity: Tau ² = 0.0	00; Chi ² = 0.12	df = 1 (P =	$= 0.72$; $I^2 = 0$)%			
Test for overall effect: Z =	= 2.58 (P = 0.0	10)					
3.2.2 BPD with no oxim	etry assessm	ent					
Hellström et al,26 2021	64	101	61	106	22.6%	1.10 [0.88, 1.37]	 -
Manley et al,3 2011	55	147	73	149	18.7%	0.76 [0.59, 1.00]	-
Subtotal (95% CI)		248		255	41.3%	0.92 [0.64, 1.33]	•
Total events	119		134				
Heterogeneity: Tau ² = 0.0	05; Chi ² = 4.47	df = 1 (P =	$= 0.03$); $I^2 = 7$	78%			
Test for overall effect: Z =	= 0.43 (P = 0.6	7)					
Total (95% CI)		1147		1152	100.0%	1.05 [0.90, 1.23]	•
Total events	570		530				
Heterogeneity: Tau ² = 0.0	01: Chi ² = 7.76	df = 3 (P =	0.05); $I^2 = 6$	1%		⊢	+ + + + + + + + + + + + + + + + + + + +
Test for overall effect: Z =			,,,				0.2 0.5 1 2 5 1
Test for subgroup differen			P = 0.28), I ² :	= 14.2%		Favou	rs [intervention] Favours [control]

C Death up to 36 weeks' PMAa

•								
	Interve	ntion	Con	trol		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	_
Collins et al,25 2017	39	631	29	642	35.8%	1.37 [0.86, 2.18]	+-	
Hellström et al,26 2021	16	101	13	106	25.7%	1.29 [0.65, 2.55]		
Manley et al,3 2011	5	145	3	149	9.3%	1.71 [0.42, 7.04]	-	ii.
Marc et al,27 2020	16	268	26	255	29.2%	0.59 [0.32, 1.07]	-	
Total (95% CI)		1145		1152	100.0%	1.07 [0.67, 1.72]	•	
Total events	76		71					
Heterogeneity: Tau2 = 0.1	0; Chi ² = 5.68	, df = 3 (P =	$= 0.13$); $I^2 = 4$	7%		<u> </u>	1 1 1	
Test for overall effect: Z =	= 0.30 (P = 0.7)	7)				0.1	0.2 0.5 1 2 5	10
	,	,				Favoi	urs [intervention] Favours [control]	į.

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

	Interve	ntion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Collins et al,25 2017	267	592	244	612	66.8%	1.13 [0.99, 1.29]	
Hellström et al,26 2021	48	101	48	106	13.5%	1.05 [0.78, 1.41]	+
Marc et al,27 2020	104	252	71	229	19.7%	1.33 [1.04, 1.70]	-
Total (95% CI)		945		947	100.0%	1.16 [1.04, 1.29]	♦
Total events	419		363				
Heterogeneity: Tau ² = 0.0	0; Chi ² = 1.82	, df = 2 (P =	= 0.40); I ² = 0%	,			0.2 0.5 1 2 5 10
Test for overall effect: Z =	2.64 (P = 0.0	08)					0.2 0.5 1 2 5 10 urs [intervention] Favours [control]

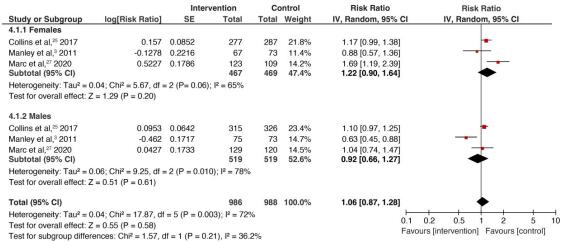
E Severe BPD at 36 weeks' PMAb

	Interve	ntion	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Collins et al,25 2017	202	592	194	612	64.5%	1.08 [0.92, 1.26]	=
Hellström et al,26 2021	22	101	21	106	8.3%	1.10 [0.65, 1.87]	
Marc et al,27 2020	88	252	58	229	27.2%	1.38 [1.04, 1.82]	-
Total (95% CI)		945		947	100.0%	1.15 [0.99, 1.35]	•
Total events	312		273				
Heterogeneity: Tau ² = 0.0	0; Chi ² = 2.29	, df = 2 (P=	= 0.32); I ² = 13	<u> </u>	 		
Test for overall effect: Z =	1.79 (P = 0.0	7)				***	0.2 0.5 1 2 5 10
	(Favou	irs [intervention] Favours [control]

BPD: Bronchopulmonary dysplasia; CI: Confidence interval; M-H: Mantel-Haenszel; PMA: Postmenstrual age.
^aDeath up to 36 weeks' PMA except in Hellström et al, ²⁶ 2021 where death was up to 40 weeks' PMA.
^bClassified according to criteria from the National Institute of Child Health and Human Development²⁹ 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' PMAa



B "BPD or death" at 36 weeks' PMA^a

		Inter	rvention	Co	ontrol	Risk Ratio	Risk Ratio	
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% C	CI .
4.2.1 Females	P. 198							
Collins et al,25 2017	0.1398	0.0868	293	300	21.5%	1.15 [0.97, 1.36]	-	
Manley et al,3 2011	-0.0943	0.2125	70	75	10.9%	0.91 [0.60, 1.38]		
Marc et al,27 2020	0.4256	0.1533	133	118	15.2%	1.53 [1.13, 2.07]		
Subtotal (95% CI)			496	493	47.6%	1.20 [0.94, 1.52]	•	
Heterogeneity: Tau2 = 0	0.03; Chi ² = 4.44, df =	= 2 (P= 0.11); $I^2 = 55\%$					
Test for overall effect: Z	Z = 1.44 (P = 0.15)							
4.2.2 Males								
Collins et al,25 2017	0.0862	0.0701	338	342	23.1%	1.09 [0.95, 1.25]	•	
Manley et al,3 2011	-0.4155	0.1732	77	74	13.6%	0.66 [0.47, 0.93]		
Marc et al,27 2020	-0.0945	0.1475	135	137	15.7%	0.91 [0.68, 1.21]	-	
Subtotal (95% CI)			550	553	52.4%	0.90 [0.68, 1.19]	•	
Heterogeneity: Tau ² = 0	0.05; Chi ² = 7.68, df =	= 2 (P = 0.02	(2) ; $I^2 = 74\%$					
Test for overall effect: Z	Z = 0.75 (P = 0.45)							
Total (95% CI)			1046	1046	100.0%	1.03 [0.86, 1.24]	•	
Heterogeneity: Tau ² = 0	0.03; Chi ² = 15.78, df	= 5 (P = 0.0	$(008); I^2 = 689$	6			+ + + + +	
Test for overall effect: Z	I = 0.36 (P = 0.72)		074				0.2 0.5 1 2	5
Test for subgroup differ	ences: Chi² = 2.28, 0	df = 1 (P = 0	.13), I ² = 56.	1%		Favour	rs [intervention] Favours	[control]

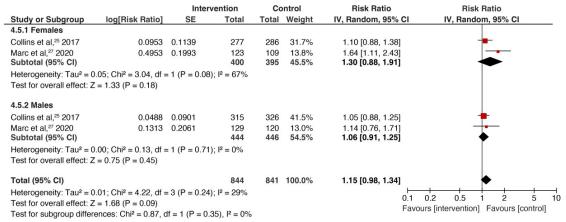
C Death up to 36 weeks' PMA

			vention		ntrol	Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.3.1 Females							***
Collins et al,25 2017	0.1823	0.3798	293	300	23.1%	1.20 [0.57, 2.53]	-
Manley et al,3 2011	0.4745	0.8976	70	75	6.2%	1.61 [0.28, 9.33]	•
Marc et al,27 2020	-0.0143	0.4417	133	118	19.1%	0.99 [0.41, 2.34]	
Subtotal (95% CI)			496	493	48.5%	1.14 [0.67, 1.96]	•
Heterogeneity: Tau ² = 0.	.00; Chi ² = 0.27, df =	= 2 (P = 0.87)	7); $I^2 = 0\%$				
Test for overall effect: Z	= 0.49 (P = 0.63)						
4.3.2 Males							
Collins et al,25 2017	0.3646	0.2999	338	342	29.8%	1.44 [0.80, 2.59]	+-
Manley et al,3 2011	0.6534	1.2139	77	74	3.6%	1.92 [0.18, 20.75]	-
Marc et al,27 2020	-1.0267	0.4591	135	137	18.2%	0.36 [0.15, 0.88]	-
Subtotal (95% CI)			550	553	51.5%	0.88 [0.29, 2.67]	
Heterogeneity: Tau ² = 0.	.62; Chi ² = 6.76, df =	= 2 (P = 0.03)	B); I ² = 70%				
Test for overall effect: Z	= 0.23 (P = 0.82)						
Total (95% CI)			1046	1046	100.0%	1.01 [0.64, 1.61]	*
Heterogeneity: Tau ² = 0.	.10; Chi ² = 7.21, df =	= 5 (P = 0.21); I ² = 31%				
Test for overall effect: Z		,	**			0.01	0.1 1 10 10
Test for subgroup differe	, ,	df = 1 (P = 0)	.67), I ² = 0%			Favo	urs [intervention] Favours [control]

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

		Inte	rvention	Co	ontrol	Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.4.1 Females							
Collins et al,25 2017	0.1653	0.1072	277	287	30.6%	1.18 [0.96, 1.46]	-
Marc et al,27 2020	0.5056	0.1794	123	109	15.0%	1.66 [1.17, 2.36]	-
Subtotal (95% CI)			400	396	45.6%	1.36 [0.98, 1.88]	•
Heterogeneity: Tau ² = 0.	.04; Chi ² = 2.65, df =	1 (P = 0.10	0); $I^2 = 62\%$				
Test for overall effect: Z	= 1.82 (P = 0.07)						
4.4.2 Males							
Collins et al,25 2017	0.0954	0.0856	315	326	38.8%	1.10 [0.93, 1.30]	-
Marc et al,27 2020	0.0674	0.1751	129	120	15.6%	1.07 [0.76, 1.51]	-
Subtotal (95% CI)			444	446	54.4%	1.09 [0.94, 1.27]	*
Heterogeneity: Tau ² = 0.	.00; Chi ² = 0.02, df =	1 (P = 0.8	9); $I^2 = 0\%$				
Test for overall effect: Z	= 1.17 (P = 0.24)						
Total (95% CI)			844	842	100.0%	1.19 [1.02, 1.39]	•
Heterogeneity: Tau ² = 0.	.01; Chi ² = 4.56, df =	3 (P = 0.2	1); I ² = 34%				
Test for overall effect: Z	= 2.23 (P = 0.03)	10	5.0			0.1	0.2 0.5 1 2 5 10
Test for subgroup differen	ences: Chi² = 1.36, c	If = 1 (P = 0)	.24), I ² = 26.6	6%		Fav	rours [intervention] Favours [control]

E Severe BPD at 36 weeks' PMAb

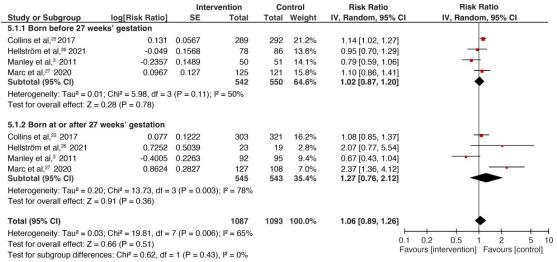


BPD: Bronchopulmonary dysplasia; CI: Confidence interval; IV: Inverse variance; PMA: Postmenstrual age; SE: Standard

^aPhysiological BPD based on oximetry²⁸ except in Manley et al,³ 2011 where BPD was with no oximetry assessment. ^bClassified 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' PMAa



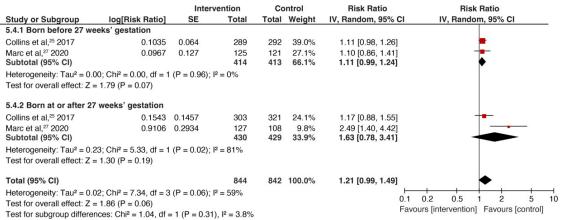
B "BPD or death" at 36 weeks' PMA^{a, b}

		Inte	rvention	Co	ntrol	Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.2.1 Born before 27 we	eks' gestation						
Collins et al,25 2017	0.1133	0.0527	322	317	21.4%	1.12 [1.01, 1.24]	-
Hellström et al,26 2021	0.0198	0.1114	78	87	16.2%	1.02 [0.82, 1.27]	+
Manley et al,3 2011	-0.2231	0.1468	52	53	13.2%	0.80 [0.60, 1.07]	
Marc et al,27 2020	0.0072	0.102	139	147	17.1%	1.01 [0.82, 1.23]	+
Subtotal (95% CI)			591	604	67.8%	1.02 [0.90, 1.16]	•
Heterogeneity: Tau ² = 0.0	1; Chi ² = 5.13, df = 3	B(P = 0.16)	$I^2 = 42\%$				
Test for overall effect: Z =	: 0.36 (P = 0.72)						
5.2.2 Born at or after 27	weeks' gestation						
Collins et al,25 2017	0.0953	0.1197	309	325	15.5%	1.10 [0.87, 1.39]	 -
Hellström et al,26 2021	0.9083	0.4896	23	19	2.4%	2.48 [0.95, 6.47]	•
Manley et al,3 2011	-0.3147	0.2247	95	96	8.3%	0.73 [0.47, 1.13]	
Marc et al,27 2020	0.8968	0.2807	129	108	6.1%	2.45 [1.41, 4.25]	
Subtotal (95% CI)			556	548	32.2%	1.36 [0.81, 2.27]	
Heterogeneity: $Tau^2 = 0.2$	20; Chi ² = 13.96, df =	3 (P = 0.00)	03); I ² = 79%				
Test for overall effect: Z =	: 1.18 (P = 0.24)						
Total (95% CI)			1147	1152	100.0%	1.07 [0.91, 1.25]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: $Tau^2 = 0.0$		7 (P = 0.00)	(6) ; $I^2 = 65\%$			0.1	0.2 0.5 1 2 5 10
Test for overall effect: Z =	,						ours [intervention] Favours [control]
Test for subgroup differer	nces: $Chi^2 = 1.12$, df	= 1 (P = 0.2)	$(9), I^2 = 10.9\%$			r av	reare [

C Death up to 36 weeks' PMAb

		Inte	rvention	Co	ontrol	Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.3.1 Born before 27 we	eks' gestation						
Collins et al,25 2017	0.2624	0.2541	322	317	36.3%	1.30 [0.79, 2.14]	
Hellström et al,26 2021	0.1833	0.3522	78	87	21.5%	1.20 [0.60, 2.40]	-
Manley et al,3 2011	0.019	0.9808	52	53	3.2%	1.02 [0.15, 6.97]	
Marc et al,27 2020	-0.5631	0.3097	139	147	26.7%	0.57 [0.31, 1.04]	
Subtotal (95% CI)			591	604	87.7%	0.98 [0.63, 1.52]	•
Heterogeneity: Tau ² = 0.0	07; Chi ² = 4.64, df = 3	P = 0.20	$I^2 = 35\%$				
Test for overall effect: Z =	= 0.11 (P = 0.91)						
5.3.2 Born at or after 27	weeks' gestation						
Collins et al,25 2017	0.4511	0.6376	309	325	7.3%	1.57 [0.45, 5.48]	
Hellström et al,26 2021	1.4271	1.5193	23	19	1.3%	4.17 [0.21, 81.85]	· · · · · · · · · · · · · · · · · · ·
Manley et al,3 2011	1.1091	1.1456	95	96	2.4%	3.03 [0.32, 28.63]	- •
Marc et al,27 2020	1.4333	1.5437	129	108	1.3%	4.19 [0.20, 86.39]	
Subtotal (95% CI)			556	548	12.3%	2.18 [0.83, 5.75]	
Heterogeneity: Tau ² = 0.0	00; Chi ² = 0.71, df = 3	P = 0.87	$I^2 = 0\%$				
Test for overall effect: Z =	= 1.57 (P = 0.12)						
Total (95% CI)			1147	1152	100.0%	1.09 [0.77, 1.54]	*
Heterogeneity: Tau ² = 0.0	02; $Chi^2 = 7.62$, $df = 7$	(P= 0.37);	$I^2 = 8\%$			0.01	
Test for overall effect: Z =	= 0.46 (P = 0.64)					0.01	0.1 1 10 100 urs [intervention] Favours [control]
Test for subgroup differen	nces: Chi2 = 2.18, df :	= 1 (P = 0.1	4), I ² = 54.1%			Favol	instillervention Favours [control]

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



E Severe BPD at 36 weeks' PMAc

		Inter	vention	Co	ontrol	Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.5.1 Born before 27 we	eks' gestation				200	70	
Collins et al,25 2017	0.0488	0.0786	289	291	39.0%	1.05 [0.90, 1.22]	+
Marc et al,27 2020	0.1393	0.1487	125	121	27.4%	1.15 [0.86, 1.54]	
Subtotal (95% CI)			414	412	66.4%	1.07 [0.93, 1.23]	*
Heterogeneity: Tau ² = 0.0	00; $Chi^2 = 0.29$, $df = 1$	(P = 0.59);	$I^2 = 0\%$				
Test for overall effect: Z =	0.99 (P = 0.32)						
5.5.2 Born at or after 27	weeks' gestation						
Collins et al,25 2017	0.131	0.1744	303	321	23.7%	1.14 [0.81, 1.60]	-
Marc et al,27 2020	0.9693	0.3393	127	108	10.0%	2.64 [1.36, 5.13]	
Subtotal (95% CI)			430	429	33.6%	1.65 [0.73, 3.73]	
Heterogeneity: Tau ² = 0.2	28; Chi ² = 4.83, df = 1	(P = 0.03);	$I^2 = 79\%$				
Test for overall effect: Z =	= 1.20 (P = 0.23)						
T (050/ O1)					100.00/	4 00 10 05 4 501	_
Total (95% CI)			844	841	100.0%	1.20 [0.95, 1.52]	
Heterogeneity: Tau ² = 0.0	03; Chi ² = 7.07, df = 3	8 (P = 0.07);	$I^2 = 58\%$			0.1	0.2 0.5 1 2 5 10
Test for overall effect: Z =	= 1.53 (P = 0.13)						- 19 - 19 - 19 - 19 - 19 - 19 - 19 - 19
Test for subgroup differer	nces: Chi2 = 1.04, df	= 1 (P = 0.31)), $I^2 = 4.2\%$			Favou	rs [intervention] Favours [control]

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

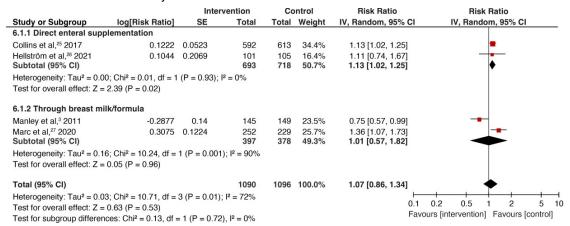
^aPhysiological BPD based on oximetry²⁸ except in Hellström et al,²⁶ 2021 and Manley et al,³ 2011 where BPD was with no oximetry assessment.

^bDeath up to 36 weeks' PMA except in Hellström et al, ²⁶ 2021 where death was up to 40 weeks' PMA.

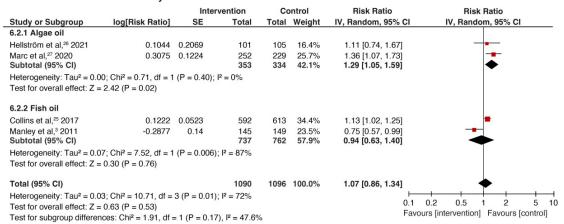
[°]Classified according to criteria from the National Institute of Child Health and Human Development.²⁹

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

		Inter	vention	Co	ntrol	Risk Ratio	Risk Ratio
Study or Subgroup	log[Risk Ratio]	SE	Total	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
6.3.1 DHA alone	1000						
Collins et al,25 2017	0.1222	0.0523	592	613	34.4%	1.13 [1.02, 1.25]	-
Manley et al,3 2011	-0.2877	0.14	145	149	23.5%	0.75 [0.57, 0.99]	-
Marc et al,27 2020 Subtotal (95% CI)	0.3075	0.1224	252 989	229 991	25.7% 83.6 %	1.36 [1.07, 1.73] 1.06 [0.81, 1.39]	•
Heterogeneity: Tau ² = 0.05	5; Chi ² = 10.71, df =	2 (P = 0.005)	5); $I^2 = 81\%$				
Test for overall effect: Z =	0.44 (P = 0.66)						
6.3.2 DHA + AA							
Hellström et al,26 2021	0.1044	0.2069	101	105	16.4%	1.11 [0.74, 1.67]	-
Subtotal (95% CI)			101	105	16.4%	1.11 [0.74, 1.67]	•
Heterogeneity: Not applica	able						
Test for overall effect: Z =	0.50 (P = 0.61)						
Total (95% CI)			1090	1096	100.0%	1.07 [0.86, 1.34]	*
Heterogeneity: Tau ² = 0.03	3; Chi ² = 10.71, df =	3(P = 0.01)	$ ^2 = 72\%$			96 0 90	
Test for overall effect: Z =	0.63 (P = 0.53)		200//200				0.1 0.2 0.5 1 2 5 10
Test for subgroup differen	ces: Chi2 = 0.03, df :	= 1 (P = 0.86)	$3), I^2 = 0\%$			F	Favours [intervention] Favours [control]

AA: Arachidonic acid; BPD: Bronchopulmonary dysplasia; CI: Confidence interval; DHA: Docosahexaenoic acid; IV: Inverse variance; PMA: Postmenstrual age; SE: Standard error.

^aPhysiological BPD based on oximetry²⁸ except in Hellström et al,²⁶ 2021 and Manley et al,³ 2011 where BPD was with no oximetry assessment.

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