

# Supplementary Material

## Cerebellar hemorrhage in preterm infants: a meta-analysis on risk factors and neurodevelopmental outcome

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## 1 Supplementary Tables

Supplementary Table 1. Quality assessment of included studies using the Newcastle Ottawa Scale.

First author, year	Selection	Comparability	Outcome/Exposure	Total	Reason for downgrade
Biran, 2011	4	1	3	8	Only matched for GA
Chau, 2012	3	0	3	6	CBH not defined, No adjustment for confounders
Duerden, 2013	3	0	3	6	CBH not defined, No adjustment for confounders
Dyet, 2006	4	0	3	7	No adjustment for confounders
Fumagalli, 2009	4	0	3	7	No adjustment for confounders
Gano, 2016	4	2	3	9	
Haines, 2013	3	2	3	8	Infants not comparable with other studies (all were autopsied)
Kidokoro, 2014	4	2	3	9	
Limperopoulos, 2005a	4	2	3	9	
Limperopoulos, 2007	4	2	3	9	
Neubauer, 2017	4	0	3	7	No adjustment for confounders
O'Shea, 2008	4	0	3	7	No adjustment for confounders
Steggerda, 2013	4	2	3	9	
Tam, 2011	4	2	3	9	
Zayek, 2012	4	2	3	9	

GA: gestational age; CBH: cerebellar hemorrhage.



Supplementary Table 2. Details on studies that reported neurodevelopmental outcomes

First author, year	Assessment method	Time of assessment	Impairment defined as	Summary of findings	Comments
Biran 2011	Neurological examination, Brunet-Lezine test for developmental quotient,	2 years (not corrected)	Developmental quotient score <70	No significant difference between groups in any element of developmental quotient (global, postural, coordination, language or sociability).	Results of neurological examination not reported.
Dyet 2006	Neurological examination, CP, Griffiths Mental Development Scales for overall DQ	18-36 months (corrected)	Developmental quotient score <70	CBH-infants had lower DQ (75 +- 24, n=5), compared with infants with normal MRI (112 +- 15, n=6). One infant with CBH had CP, compared to none in the control group.	
Kidokoro 2014	Neurological examination, CP assessment. BSID-II and BSID-III scale for MDI and PDI, CP assessment.	2 years (corrected)	BSID-II: MDI score <70, PDI score <70. BSID-III: cognition or language score <80, motor score <70	CBH was not significantly related to any adverse neurodevelopmental outcome	Two different cohorts: one cohort was evaluated with BSID-II, another cohort was evaluated with BSID-III
O'Shea 2008	Neurological examination, BSID-II scale for MDI and PDI.	2 years (corrected)	MDI score <70 PDI score <70	Children who had bilateral cerebellar hemorrhages were at highest risk of developmental delays	Results of neurological examination not reported.
Steggerda 2013	Neurological examination according to Hempel, CP assessment (GMFCS), Neurodevelopment, BSID-III	2 years (corrected)	Score 1 SD below normative mean	No relation between small CBH and mildly or severely abnormal neurodevelopment.	Study only examined small CBH

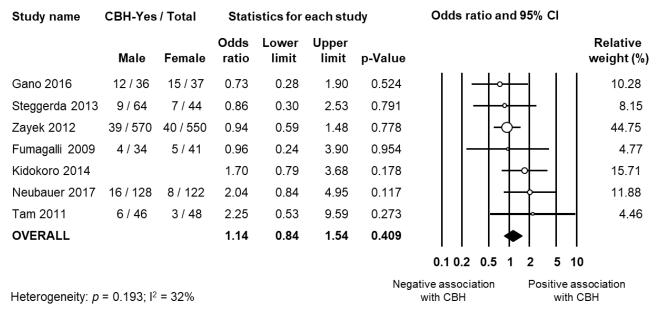
First author, year	Assessment method	Time of assessment	Impairment defined as	Summary of findings	Comments
Tam 2011	Neurological examination, WPPSI-III for developmental outcome	3-6 years (not corrected)	Not defined	Infants with CBH had increased odds (OR 5.0, 95% CI 1.1-23.1) of neurological abnormalities at ages 3-6 compared to non-CBH infants, after adjusting for GA, IVH and white matter injury. No significant differences in developmental outcome.	
Zayek 2012	CP assessment, BSID-II and BSID-III for MDI and PDI.	12-18 months (corrected)	MDI score <70, or any cognitive or language score <70. PDI score <70, or motor score <70	Infants with CBH had higher rates of mental and motor impairment, and higher cerebral palsy rates. After adjustment, CBH was still associated with mental and motor impairment, but not with cerebral palsy.	

BSID-II: Bayley Scales of Infant Development, Second Edition; MDI: Mental Development Index; PDI: Psychomotor Developmental Index; CBH: cerebellar hemorrhage; WPPSI-III: Wechsler Preschool Primary Scale of Intelligence; CP: Cerebral Palsy; GMFCS: Gross Motor Function Classification System; IVH: intraventricular hemorrhage; DQ: developmental quotient.

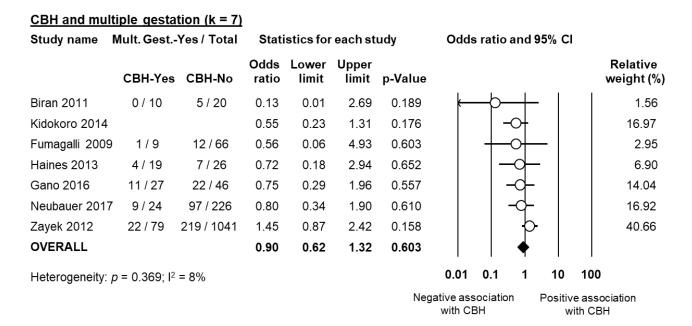


### 2 Supplementary Figures

### CBH and male sex (k = 7)



**Supplementary Figure 1.** Meta-analysis of cerebellar hemorrhage (CBH) and male sex. CI: confidence interval.



**Supplementary Figure 2.** Meta-analysis of cerebellar hemorrhage (CBH) and multiple gestation. CI: confidence interval.

### CBH and preeclampsia (k = 4) Study name Preeclampsia-Yes / Total Statistics for each study Odds ratio and 95% Cl Odds Lower Upper Relative CBH-No **CBH-Yes** ratio limit limit p-Value weight (%) Fumagalli 2009 2/9 45 / 66 0.03 0.70 0.017 22.72 0.13 Gano 2016 5/27 12/46 0.64 0.20 2.08 0.462 30.94 Haines 2013 1/19 2/26 0.67 0.06 7.94 0.748 13.66 Limperopoulos 2005a 7/35 9/70 1.69 0.57 5.01 0.340 32.68 **OVERALL** 0.62 0.21 1.83 0.386 Heterogeneity: p = 0.093; $I^2 = 53\%$ 0.01 0.1 1 10 100 Negative association Positive association with CBH with CBH

**Supplementary Figure 3.** Meta-analysis of cerebellar hemorrhage (CBH) and preeclampsia. CI: confidence interval.

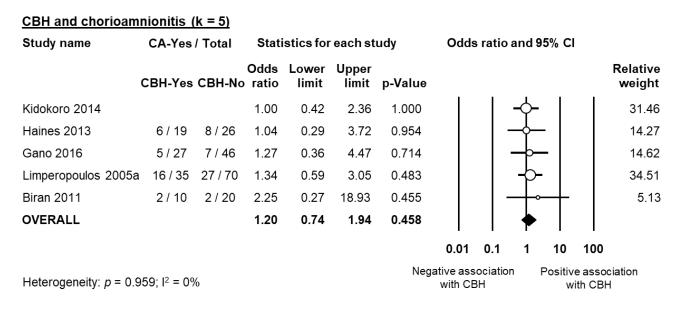
### CBH and antenatal steroids (k = 9) ANS-Yes / Total Odds ratio and 95% CI Study name Statistics for each study Odds Lower Upper Relative CBH-Yes CBH-No ratio limit limit p-Value weight 6/10 5.56 Biran 2011 18/20 0.17 0.02 1.15 0.069 Neubauer 2017 17/24 211/226 0.17 0.06 0.48 0.001 13.25 Gano 2016 22/27 41/46 0.54 0.14 2.06 0.364 9.54 Zayek 2012 51/79 770 / 1041 0.64 0.40 1.04 0.070 22.89 Steggerda 2013 11/16 70/92 0.69 0.22 2.21 0.533 11.49 Kidokoro 2014 0.70 0.26 1.86 0.474 13.95 Haines 2013 15/19 18/26 1.67 0.42 6.64 0.469 9.18 Limperopoulos 2005a 32/35 59/70 1.99 0.52 7.65 0.317 9.50 Fumagalli 2009 8/9 52/66 2.15 0.25 18.69 0.487 4.63 **OVERALL** 0.65 0.39 1.07 0.091 0.01 0.1 10 100 1 Heterogeneity: *p* = 0.081; I<sup>2</sup> = 43% Negative association Positive association with CBH with CBH

**Supplementary Figure 4.** Meta-analysis of cerebellar hemorrhage (CBH) and antenatal steroids. CI: confidence interval.

### CBH and placental abruption (k = 3)

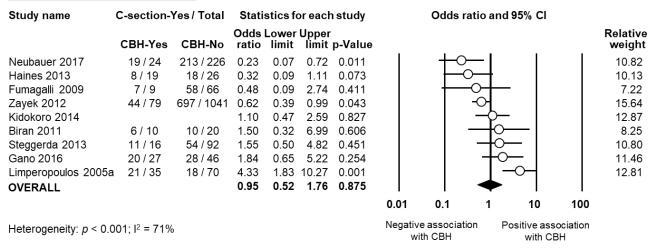
Study name Placental abr		•	Statistics for each study				Odds ratio and 95% Cl	
	/ Tot CBH-Yes	al CBH-No	Odds ratio	Lower limit	Upper limit	p-Value		Relative weight (%)
Gano 2016	5/27	7 / 46	1.27	0.36	4.47	0.714	- <del> </del>	30.53
Limperopoulos 20	05a 7/35	10 / 70	1.50	0.52	4.35	0.456		42.80
Haines 2013	7 / 19	5 / 26	2.45	0.64	9.44	0.193		26.67
OVERALL			1.62	0.81	3.26	0.173		
							0.01 0.1 1 10 10	00
Heterogeneity: <i>p</i> = 0.768; l <sup>2</sup> = 0%						-	ive association Positive ass with CBH with C	

**Supplementary Figure 5.** Meta-analysis of cerebellar hemorrhage (CBH) and placental abruption. CI: confidence interval.



**Supplementary Figure 6.** Meta-analysis of cerebellar hemorrhage (CBH) and chorioamnionitis. CI: confidence interval.

### CBH and cesarean section (k = 9)



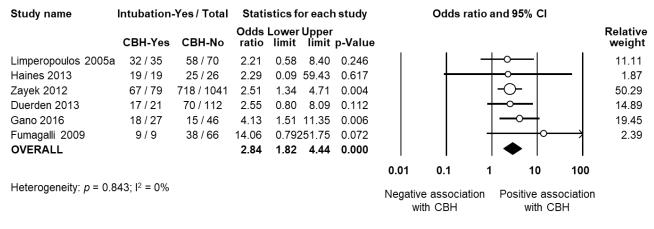
**Supplementary Figure 7.** Meta-analysis of cerebellar hemorrhage (CBH) and cesarean section. CI: confidence interval.

### Study name Sample size Statistics for each study Difference Lower Upper Relative CBH-Yes CBH-No in means limit p-Value weight (%) limit Fumagalli 2009 9 66 -1.60 -5.96 2.76 0.472 22.56 -5.03 Haines 2013 19 26 -1.44 2.15 0.432 33.25 Gano 2016 27 46 0.90 4.01 0.571 44.20 -2.21 OVERALL -0.44 -2.51 1.63 0.675 8 -8 -4 ٥ 4 Heterogeneity: p = 0.526; $I^2 = 0\%$ Negative association Positive association with CBH with CBH

Supplementary Figure 8. Meta-analysis of cerebellar hemorrhage (CBH) and maternal age.

## CBH and maternal age (mean difference in years; k = 3)

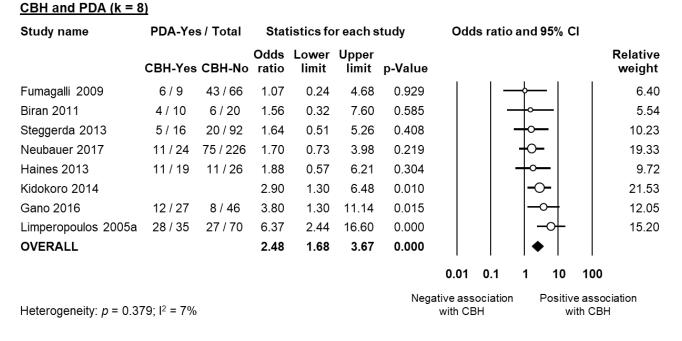
### CBH and intubation (k = 6)



**Supplementary Figure 9.** Meta-analysis of cerebellar hemorrhage (CBH) and intubation. CI: confidence interval.

### CBH and hypotension (k = 7) Hypotension-Yes / Total Odds ratio and 95% Cl Study name Statistics for each study Odds Lower Upper Relative CBH-No ratio limit limit p-Value weight (%) **CBH-Yes** Steggerda 2013 7/16 23/92 2.33 0.78 6.97 0.129 10.82 Gano 2016 21/46 0.009 11.18 21/27 4.17 1.42 12.23 Limperopoulos 2005a 33/35 54/70 4.89 1.06 22.63 0.042 5.52 Zayek 2012 40.92 63/79 385 / 1041 6.71 3.82 11.78 0.000 Fumagalli 2009 5/9 10/66 7.00 1.60 30.66 0.010 5.94 Neubauer 2017 6/24 10/226 7.20 2.35 22.08 0.001 10.33 Kidokoro 2014 8.00 3.18 20.10 0.000 15.28 OVERALL 5.78 4.04 8.29 0.000 0.01 0.1 1 10 100 Heterogeneity: p = 0.677; $I^2 = 0\%$ Negative association Positive association with CBH with CBH

**Supplementary Figure 10.** Meta-analysis of cerebellar hemorrhage (CBH) and hypotension. CI: confidence interval.



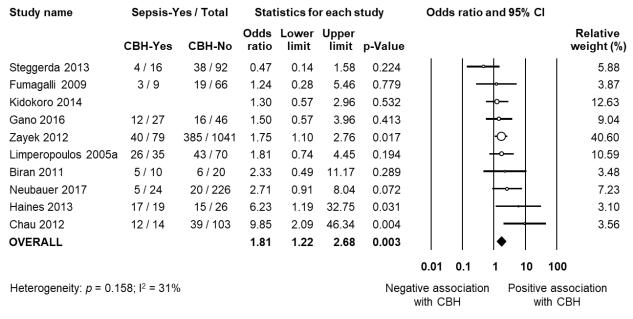
**Supplementary Figure 11.** Meta-analysis of cerebellar hemorrhage (CBH) and patent ductus arteriosus (PDA). CI: confidence interval.

### CBH and NEC (k = 6)

Study name	NEC-Yes / Total		Stat	istics fo	or each s	study	Odds ratio and 95% Cl	
	CBH-Yes	CBH-No		Lower limit		p-Value		Relative weight
Gano 2016	0 / 27	3 / 46	0.23	0.01	4.55	0.331		4.11
Fumagalli 2009	0/9	3 / 66	0.95	0.05	19.97	0.976		4.00
Kidokoro 2014			2.80	0.79	9.96	0.112		22.99
Neubauer 2017	2/24	7 / 226	2.84	0.56	14.54	0.209	+	13.91
Steggerda 2013	1 / 16	2 / 92	3.00	0.26	35.18	0.382		6.11
Limperopoulos 2005a	22 / 35	18 / 70	4.89	2.05	11.67	0.000		48.88
OVERALL			3.20	1.74	5.87	0.000		
Heterogeneity: <i>p</i> = 0.46	9; I <sup>2</sup> = 0%					-	0.01 0.1 1 10 10 tive association Positive as with CBH with 0	sociation

**Supplementary Figure 12.** Meta-analysis of cerebellar hemorrhage (CBH) and necrotizing enterocolitis (NEC). CI: confidence interval.

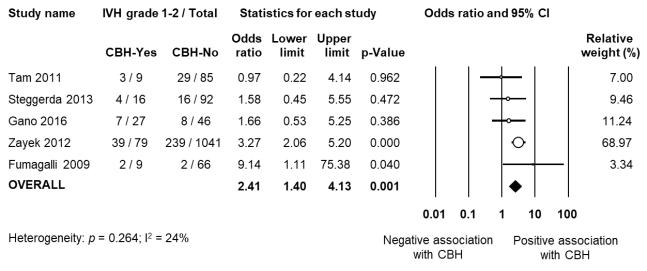
### CBH and sepsis (k = 10)



**Supplementary Figure 13.** Meta-analysis of cerebellar hemorrhage (CBH) and sepsis. CI: confidence interval.

<u>CBH and BPD (k = 4)</u>										
Study name	BPD-Yes / Total		Stat	tistics fo	or each s	study	Odds ratio and 95% Cl			
	CBH-Yes	CBH-No		Lower limit		p-Value		Relative Weight (%)		
Haines 2013	5/19	8 / 26	0.80	0.22	3.00	0.745		18.72		
Gano 2016	10 / 27	11 / 46	1.87	0.67	5.26	0.235		25.28		
Limperopoulos 2005a	a 25/35	37 / 70	2.23	0.93	5.33	0.071		30.22		
Neubauer 2017	7 / 24	16 / 226	5.40	1.96	14.93	0.001		25.77		
OVERALL			2.21	1.11	4.43	0.025				
							0.1 0.2 0.5 1 2 5 10	D		
Heterogeneity: <i>p</i> = 0.150; I <sup>2</sup> = 44%							tive association Positive as with CBH with C			

**Supplementary Figure 14.** Meta-analysis of cerebellar hemorrhage (CBH) and bronchopulmonary dysplasia (BPD). CI: confidence interval.



### CBH and IVH grade 1-2 (k = 5)

**Supplementary Figure 15.** Meta-analysis of cerebellar hemorrhage (CBH) and intraventricular hemorrhage (IVH) grade 1-2. CI: confidence interval.

### CBH and IVH grade 3-4 (k = 6)

Study name IVH grade 3-4-Yes / Total Statistics for each study Odds ratio and 95% CI Odds Lower Upper Relative CBH-Yes CBH-No ratio limit limit p-Value weight Tam 2011 1/98 / 85 1.20 10.89 0.869 0.13 3.62 Gano 2016 4/27 3/46 2.49 0.51 12.11 0.257 7.03 Haines 2013 12/19 10/26 2.74 0.81 0.106 11.76 9.31 Fumagalli 2009 2/9 6/66 2.86 16.97 0.248 5.53 0.48 Zayek 2012 23/79 125/1041 3.01 0.000 Ò 64.88 1.79 5.06 Steggerda 2013 5/16 3/92 13.48 2.83 64.33 0.001 7.19 OVERALL 3.16 2.08 4.80 0.000 0.01 0.1 1 10 100 Heterogeneity: p = 0.516;  $I^2 = 0\%$ Negative association Positive association with CBH with CBH

**Supplementary Figure 16.** Meta-analysis of cerebellar hemorrhage (CBH) and intraventricular hemorrhage (IVH) grade 3-4. CI: confidence interval.

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