Supplementary Material

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

Eduardo Villamor-Martinez[1#], Monica Fumagalli[2,3#], Yaser Ibrahim Alomar[1], Sofia Passera[2], Giacomo Cavallaro[2], Fabio Mosca[2,3], Eduardo Villamor[1*]

[1]Department of Pediatrics, School for Oncology and Developmental Biology (GROW), Maastricht University Medical Center, Maastricht, Netherlands

[2]Neonatal Intensive Care Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[3]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

[#] Contributed equally to this work

*** Correspondence:**
Eduardo Villamor
e.villamor@mumc.nl

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.

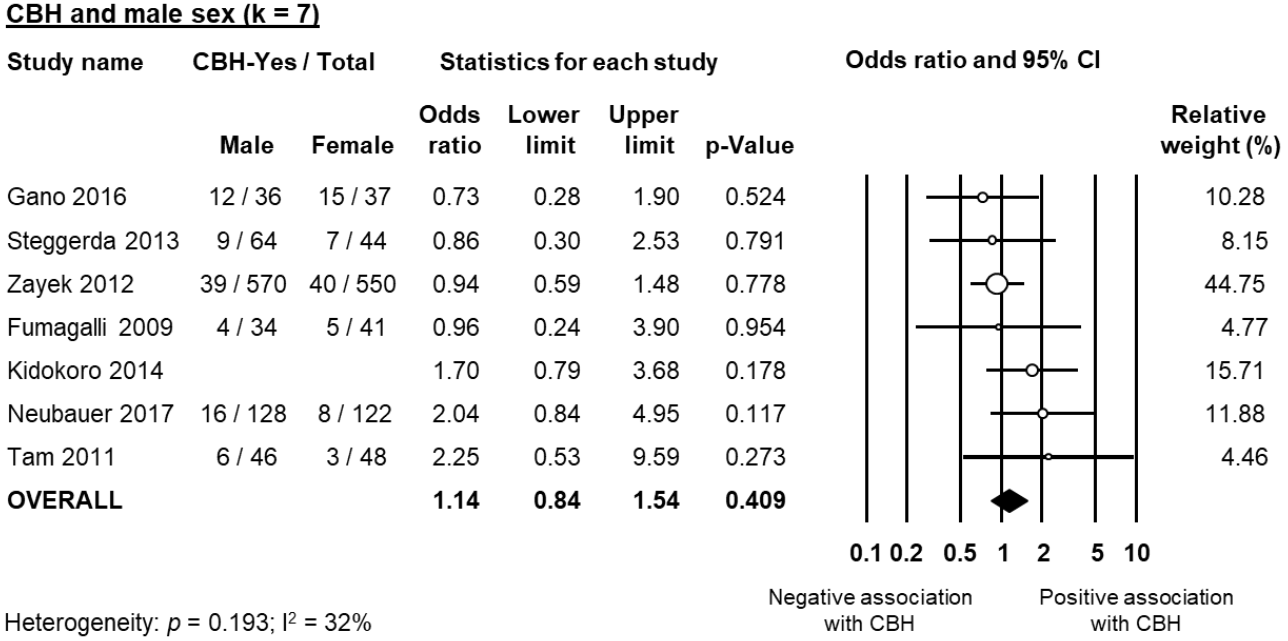
Supplementary Table 2. Details on studies that reported neurodevelopmental outcomes

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

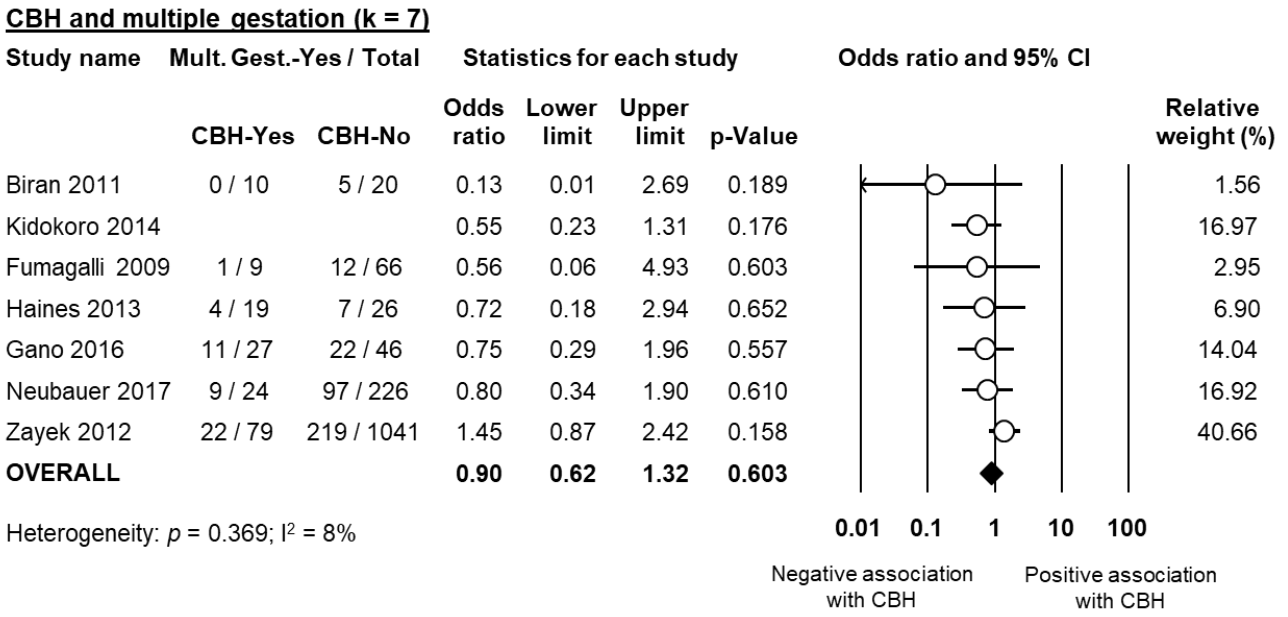
First author, year	Assessment method	Time of assessment	Impairment defined as	Summary of findings	Comments
Tam 2011	Neurological examination, WPPSI-III for developmental outcome	3-6 years (not corrected)	Not defined	Infants with CBH had increased odds (OR 5.0, 95% CI 1.1-23.1) of neurological abnormalities 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.

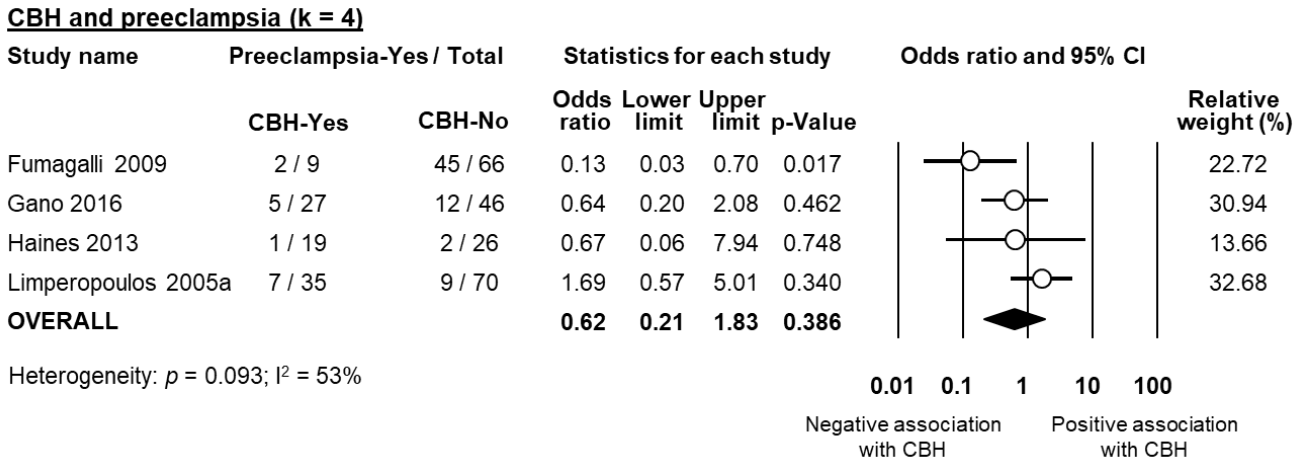
2 Supplementary Figures



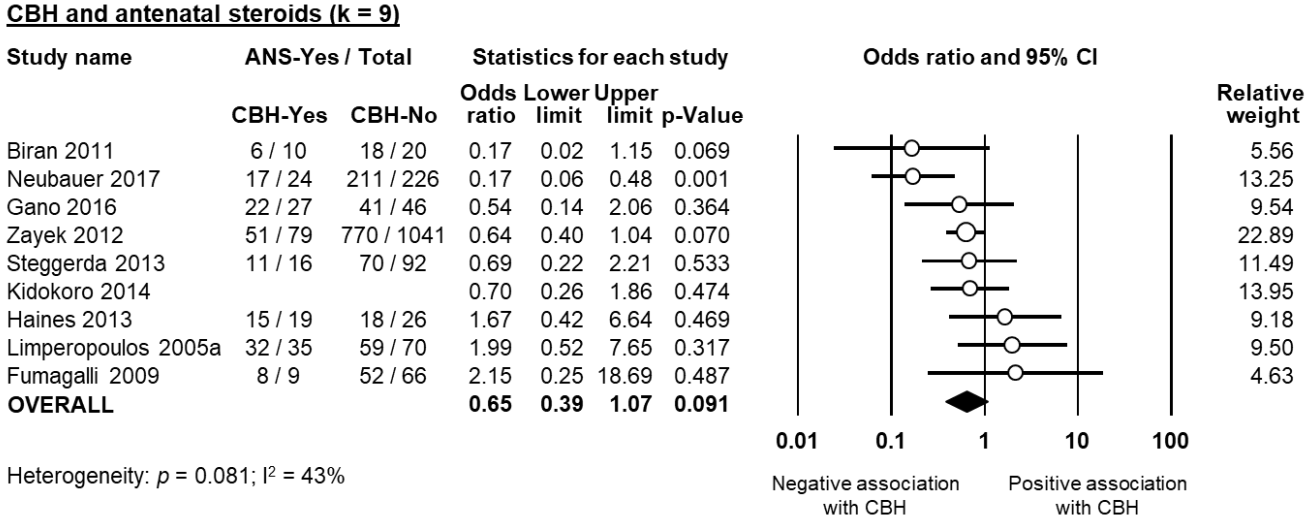
Supplementary Figure 1. Meta-analysis of cerebellar hemorrhage (CBH) and male sex. CI: confidence interval.



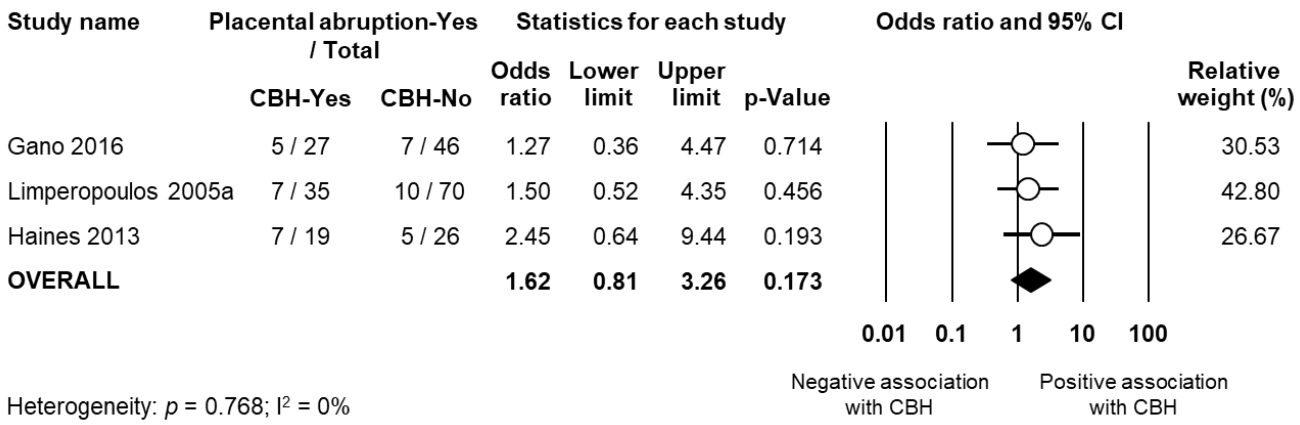
Supplementary Figure 2. Meta-analysis of cerebellar hemorrhage (CBH) and multiple gestation. CI: confidence interval.



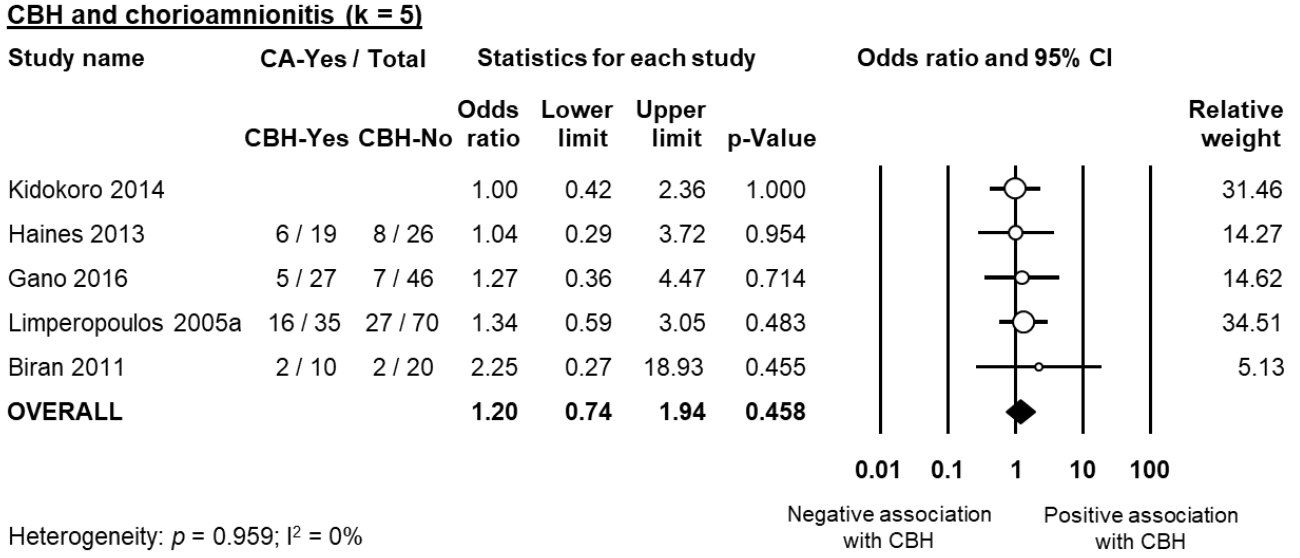
Supplementary Figure 3. Meta-analysis of cerebellar hemorrhage (CBH) and preeclampsia. CI: confidence interval.



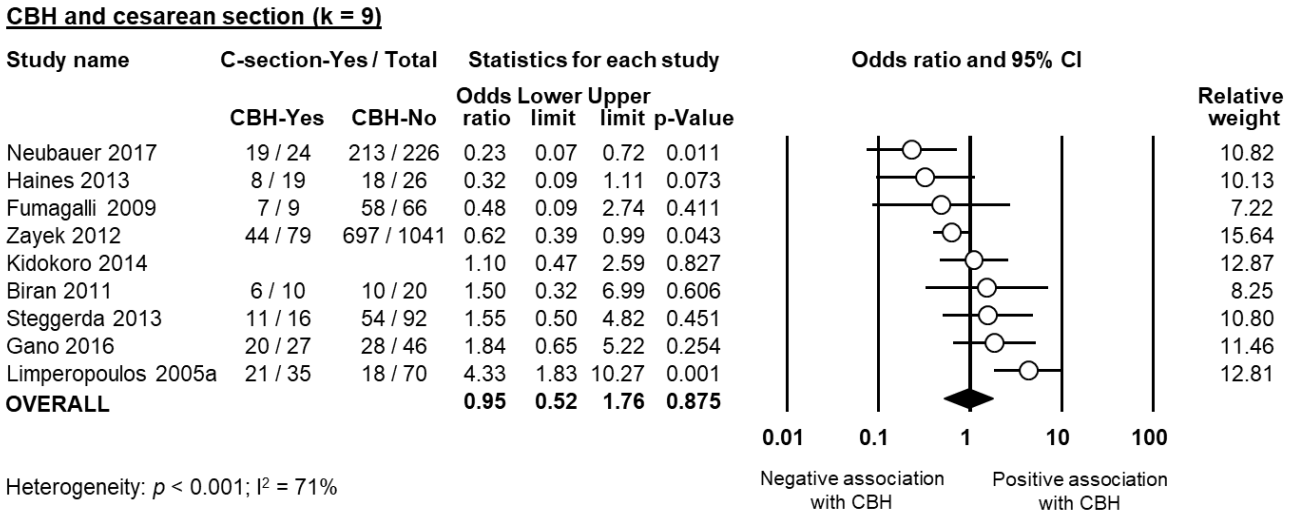
Supplementary Figure 4. Meta-analysis of cerebellar hemorrhage (CBH) and antenatal steroids. CI: confidence interval.



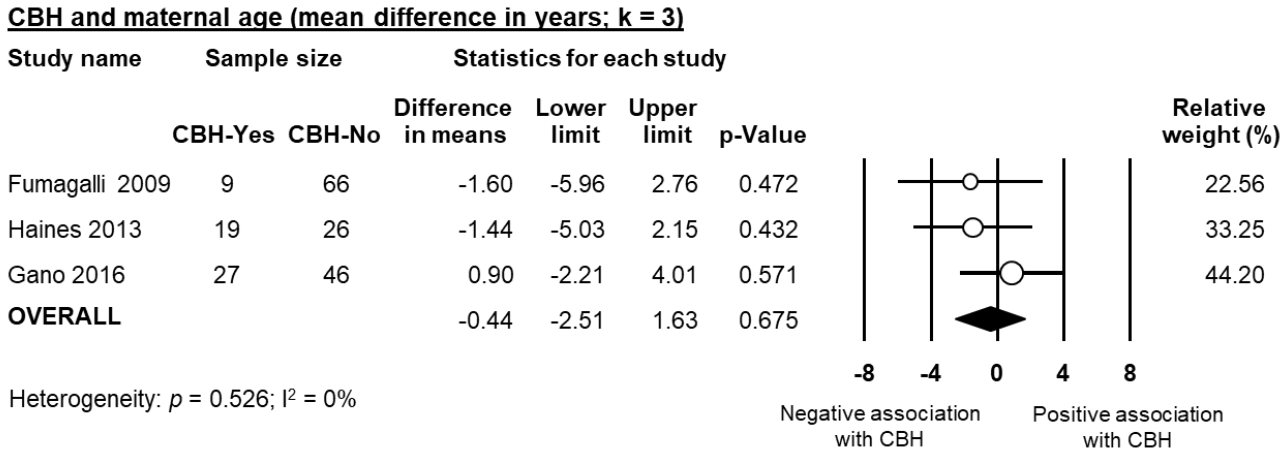
Supplementary Figure 5. Meta-analysis of cerebellar hemorrhage (CBH) and placental abruption. CI: confidence interval.



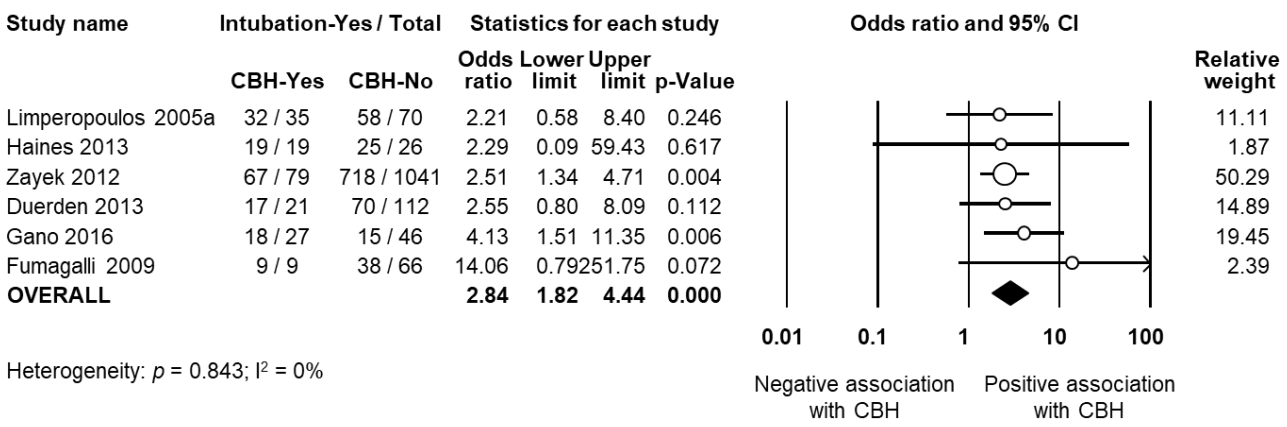
Supplementary Figure 6. Meta-analysis of cerebellar hemorrhage (CBH) and chorioamnionitis. CI: confidence interval.



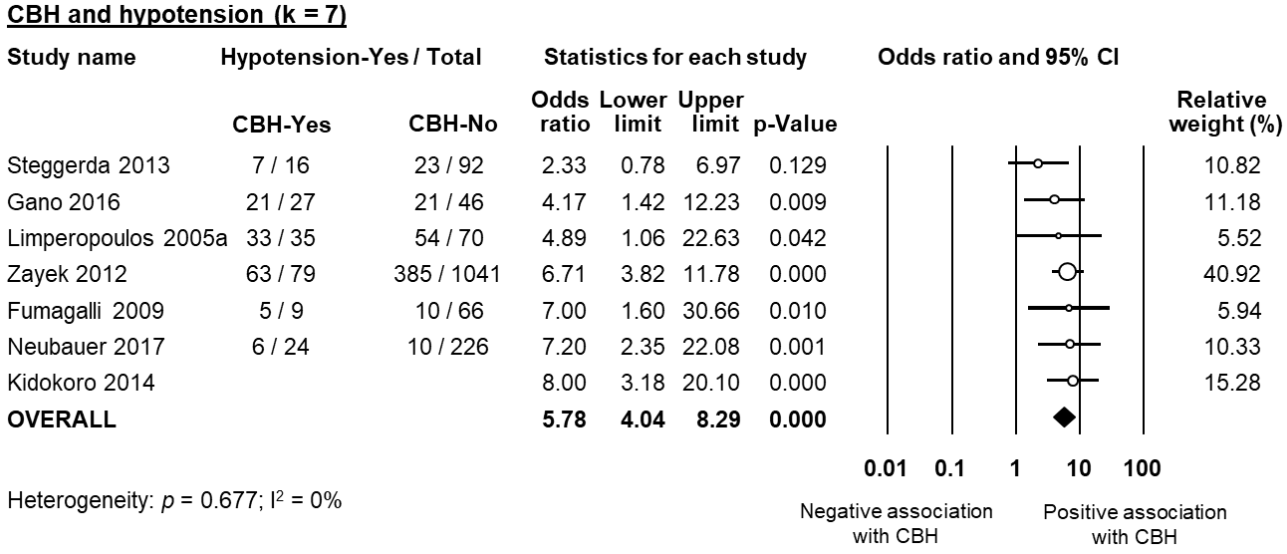
Supplementary Figure 7. Meta-analysis of cerebellar hemorrhage (CBH) and cesarean section. CI: confidence interval.



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



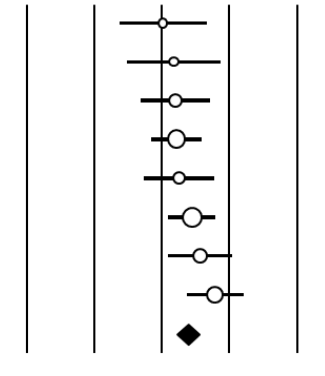
Supplementary Figure 9. Meta-analysis of cerebellar hemorrhage (CBH) and intubation. CI: confidence interval.



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

CBH and PDA (k = 8)

Study name	PDA-Yes / Total		Statistics for each study				Odds ratio and 95% CI
	CBH-Yes	CBH-No	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Fumagalli 2009	6 / 9	43 / 66	1.07	0.24	4.68	0.929	6.40
Biran 2011	4 / 10	6 / 20	1.56	0.32	7.60	0.585	5.54
Steggerda 2013	5 / 16	20 / 92	1.64	0.51	5.26	0.408	10.23
Neubauer 2017	11 / 24	75 / 226	1.70	0.73	3.98	0.219	19.33
Haines 2013	11 / 19	11 / 26	1.88	0.57	6.21	0.304	9.72
Kidokoro 2014			2.90	1.30	6.48	0.010	21.53
Gano 2016	12 / 27	8 / 46	3.80	1.30	11.14	0.015	12.05
Limperopoulos 2005a	28 / 35	27 / 70	6.37	2.44	16.60	0.000	15.20
OVERALL			**2.48**	**1.68**	**3.67**	**0.000**	

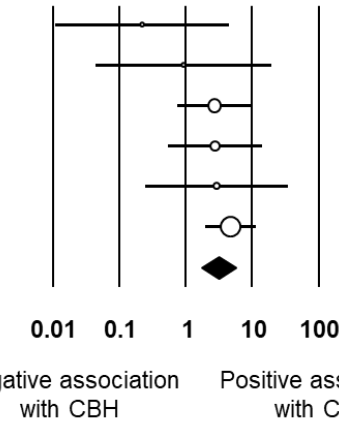


Heterogeneity: $p = 0.379$; $I^2 = 7\%$

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

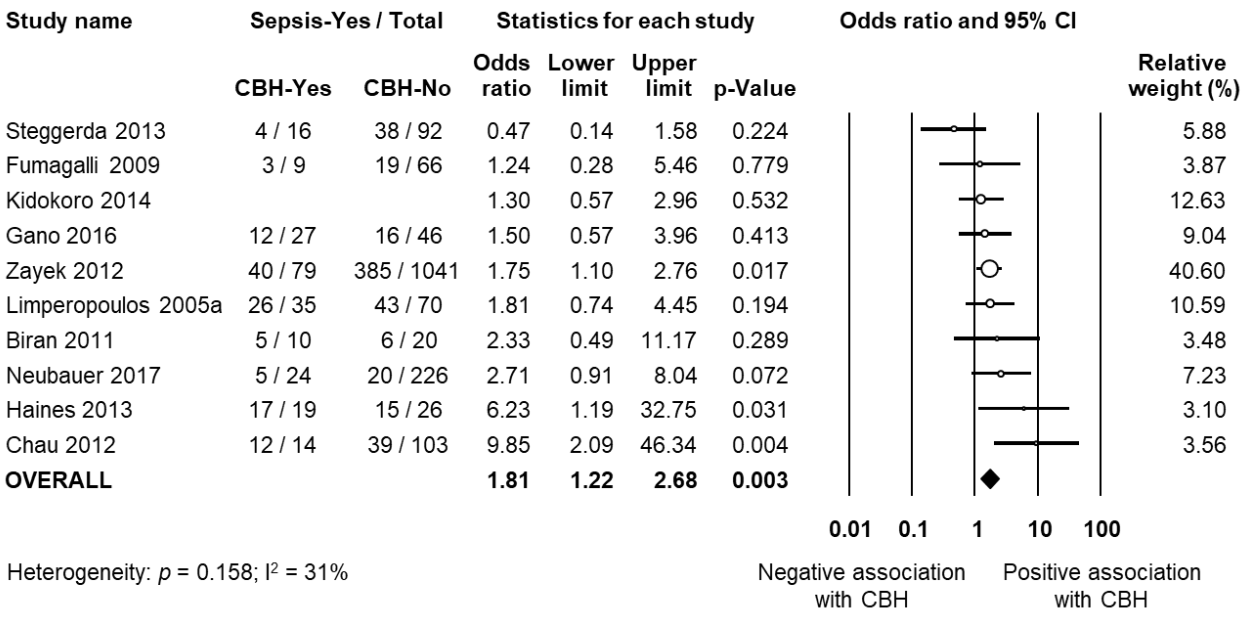
CBH and NEC (k = 6)

Study name	NEC-Yes / Total		Statistics for each study				Odds ratio and 95% CI
	CBH-Yes	CBH-No	Odds ratio	Lower limit	Upper 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**	

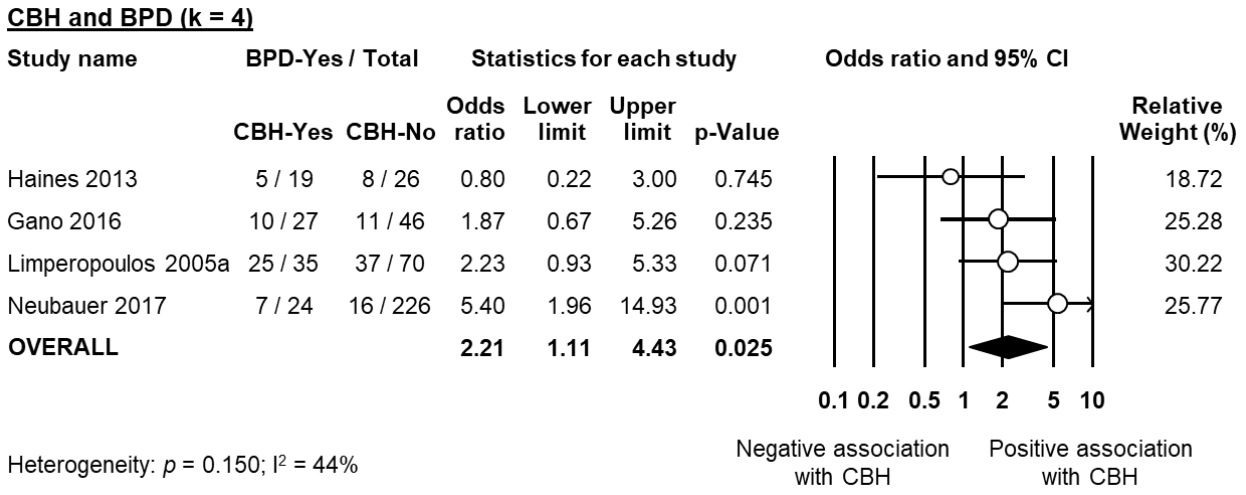


Heterogeneity: $p = 0.469$; $I^2 = 0\%$

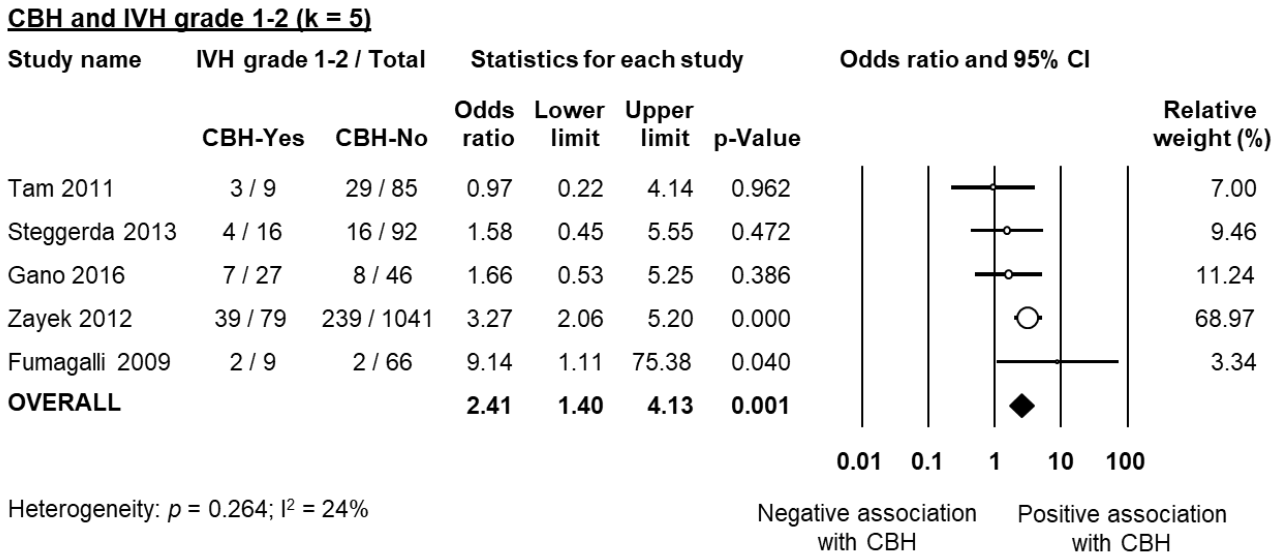
Supplementary Figure 12. Meta-analysis of cerebellar hemorrhage (CBH) and necrotizing enterocolitis (NEC). CI: confidence interval.



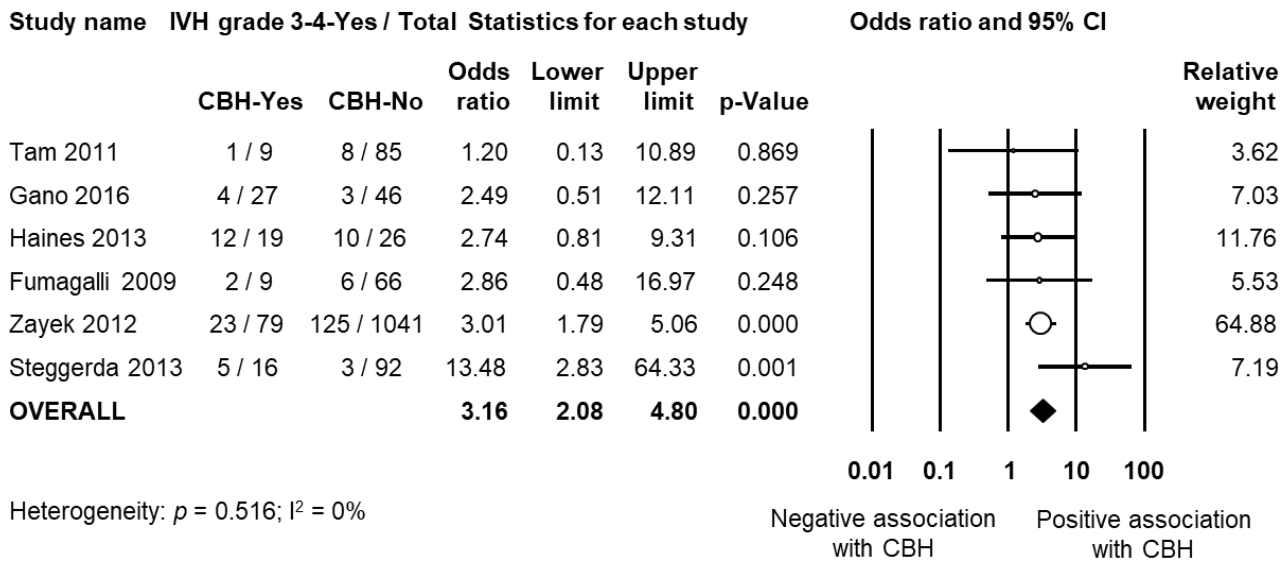
Supplementary Figure 13. Meta-analysis of cerebellar hemorrhage (CBH) and sepsis. CI: confidence interval.



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



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



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

3 References

Biran, V., Bodiou, A.-M., Zana, E., Gaudin, A., Farnoux, C., Hovhannisyan, S., Alison, M., Elmaleh, M., Oury, J.-F., and Maury, L. (2011). Lésions acquises du cervelet chez le grand prématuré: prévalence, facteurs de risque et conséquences fonctionnelles. Arch Pediatr 18, 261-266.

Chau, V., Brant, R., Poskitt, K.J., Tam, E.W., Synnes, A., and Miller, S.P. (2012). Postnatal infection is associated with widespread abnormalities of brain development in premature newborns. Pediatr Res 71, 274.

Duerden, E.G., Brown-Lum, M., Chau, V., Poskitt, K.J., Grunau, R.E., Synnes, A., and Miller, S.P. (2013). Resuscitation intensity at birth is associated with changes in brain metabolic development in preterm neonates. Neuroradiology 55, 47-54.

Dyet, L.E., Kennea, N., Counsell, S.J., Maalouf, E.F., Ajayi-Obe, M., Duggan, P.J., Harrison, M., Allsop, J.M., Hajnal, J., and Herlihy, A.H. (2006). Natural history of brain lesions in extremely preterm infants studied with serial magnetic resonance imaging from birth and neurodevelopmental assessment. Pediatrics 118, 536-548.

Fumagalli, M., Ramenghi, L.A., Righini, A., Groppo, M., Bassi, L., De Carli, A., Parazzini, C., Triulzi, F., and Mosca, F. (2009). Cerebellar haemorrhages and pons development in extremely low birth weight infants. Front Biosci 1, 537-541.

Gano, D., Ho, M.-L., Partridge, J.C., Glass, H.C., Xu, D., Barkovich, A.J., and Ferriero, D.M. (2016). Antenatal exposure to magnesium sulfate is associated with reduced cerebellar hemorrhage in preterm newborns. J Pediatr 178, 68-74.

Haines, K.M., Wang, W., and Pierson, C.R. (2013). Cerebellar hemorrhagic injury in premature infants occurs during a vulnerable developmental period and is associated with wider neuropathology. Acta Neuropathol Commun 1, 69.

Kidokoro, H., Anderson, P.J., Doyle, L.W., Woodward, L.J., Neil, J.J., and Inder, T.E. (2014). Brain injury and altered brain growth in preterm infants: predictors and prognosis. Pediatrics, peds. 2013-2336.

Limperopoulos, C., Bassan, H., Gauvreau, K., Robertson, R.L., Sullivan, N.R., Benson, C.B., Avery, L., Stewart, J., Soul, J.S., and Ringer, S.A. (2007). Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics 120, 584-593.

Limperopoulos, C., Benson, C.B., Bassan, H., Disalvo, D.N., Kinnamon, D.D., Moore, M., Ringer, S.A., Volpe, J.J., and Du Plessis, A.J. (2005). Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. Pediatrics 116, 717-724.

Neubauer, V., Djurdjevic, T., Griesmaier, E., Biermayr, M., Gizewski, E.R., and Kiechl-Kohlendorfer, U. (2017). Routine magnetic resonance imaging at term-equivalent age detects brain injury in 25% of a contemporary cohort of very preterm infants. PloS one 12, e0169442.

O'shea, T.M., Kuban, K.C., Allred, E.N., Paneth, N., Pagano, M., Dammann, O., Bostic, L., Brooklier, K., Butler, S., and Goldstein, D.J. (2008). Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. Pediatrics 122, e662.

Steggerda, S.J., De Bruïne, F.T., Van Den Berg-Huysmans, A.A., Rijken, M., Leijser, L.M., Walther, F.J., and Van Wezel-Meijler, G. (2013). Small cerebellar hemorrhage in preterm infants: perinatal and postnatal factors and outcome. Cerebellum 12, 794-801.

Tam, E.W., Rosenbluth, G., Rogers, E.E., Ferriero, D.M., Glidden, D., Goldstein, R.B., Glass, H.C., Piecuch, R.E., and Barkovich, A.J. (2011). Cerebellar hemorrhage on magnetic resonance imaging in preterm newborns associated with abnormal neurologic outcome. J Pediatr 158, 245-250.

Zayek, M., Benjamin, J., Maertens, P., Trimm, R., Lal, C., and Eyal, F. (2012). Cerebellar hemorrhage: a major morbidity in extremely preterm infants. J Perinatol 32, 699.