

PROBIOTICS SIGNIFICANTLY REDUCE MORTALITY IN PRETERM NEWBORNS WITH NECROTISING ENTEROCOLITIS: RESULTS OF LARGE NETWORK META-ANALYSIS

Saurabh (Rob) Aggarwal, BS, MS, PhD¹; Kumar S, BS¹; Topaloglu, J¹
¹Systematic Reviews and Meta-Analysis Group, NOVEL Health Strategies
Chevy Chase, MD, 20814, USA

Introduction

Several randomized control clinical trials have shown that Probiotics lower the death rates of preterm newborns with necrotising enterocolitis. However, most clinical guidelines do not currently support use of Probiotics. The objective of this study was to conduct a meta-analysis of mortality data from all available randomized control trials for Probiotics.

Methods and Materials

A systematic literature search for randomized clinical trials for use of Probiotics in preterm newborns with necrotising enterocolitis (NEC) was undertaken for the databases Pubmed, Embase, Biosis, Google Scholar and Cochrane. Data was collected for the study type, methods, country and key findings. Extracted study data included study design, patient characteristics and NEC related outcomes. A random effects meta-analysis model was developed to estimate overall odds ratios and risk ratio. A bayesian random effects network meta-analysis model with vague and informative priors was also developed.

Results

We identified 350 references and found 23 randomized trials in 7136 newborns with 408 events. The mean size of the clinical trials was approximately 300 patients. In the Probiotics and Placebo groups, there were 166 and 242 deaths, respectively. The random effects Odds Ratio for mortality for Probiotics versus Placebo was 0.69 (95% confidence interval 0.56 and 0.86; P=0.0007). The random effects risk ratio for mortality for Probiotics versus Placebo was 0.72 (95% confidence interval 0.60 and 0.88; P=0.00010).

Conclusion

This large meta-analysis shows that use of Probiotics significantly reduces the risk and odds of death in preterm newborns with necrotising enterocolitis. There is an urgent need for updating clinical guidelines based on this cumulative evidence.

References

- Athalye-Jape, G., K. More and S. Patole (2013). "Progress in the field of necrotising enterocolitis--year 2012." *J Matern Fetal Neonatal Med* 26(7): 625-632.
- Barclay, A. R., L. M. Beattie, L. T. Weaver and D. C. Wilson (2011). "Systematic review: medical and nutritional interventions for the management of intestinal failure and its resultant complications in children." *Aliment Pharmacol Ther* 33(2): 175-184.
- Barrington, K. J. (2011). "Review: probiotics prevented necrotising enterocolitis and reduced mortality in preterm neonates." *Arch Dis Child Educ Pract Ed* 96(5): 199.
- Brok, J., O. Prydz and B. Smith (2012). "Prophylactic probiotics for preterm infants reduces mortality." *Ugeskr Laeger* 174(7): 409-412.
- Butel, M. J., A. J. Waligora-Dupriet and O. Szyll (2002). "Oligofructose and experimental model of neonatal necrotising enterocolitis." *Br J Nutr* 87 Suppl 2: S213-219.
- Caffarelli, C. and S. Bernasconi (2007). "Preventing necrotising enterocolitis with probiotics." *Lancet* 369(9573): 1578-1580.
- Chauhan, M., G. Henderson and W. McGuire (2008). "Enteral feeding for very low birth weight infants: reducing the risk of necrotising enterocolitis." *Arch Dis Child Fetal Neonatal Ed* 93(2): F162-166.
- Deshpande, G., S. Rao and S. Patole (2007). "Probiotics for prevention of necrotising enterocolitis in preterm neonates with very low birthweight: a systematic review of randomised controlled trials." *Lancet* 369(9573): 1614-1620.
- Deshpande, G., S. Rao and S. Patole (2015). "Probiotics in neonatal intensive care - back to the future." *Aust N Z J Obstet Gynaecol* 55(3): 210-217.
- Deshpande, G. C., S. C. Rao, A. D. Keil and S. K. Patole (2011). "Evidence-based guidelines for use of probiotics in preterm neonates." *BMC Med* 9: 92.
- Embleton, N. and J. E. Barrington (2013). "Probiotics reduce the risk of necrotising enterocolitis (NEC) in preterm infants." *Evid Based Med* 18(6): 219-220.
- Embleton, N. D. and R. Yates (2008). "Probiotics and other preventative strategies for necrotising enterocolitis." *Semin Fetal Neonatal Med* 13(1): 35-43.
- Fernandez-Carrasco, L. A., A. Solis-Herrera, M. Cabanillas-Ayon, R. B. Gallardo-Sarmiento, C. S. Garcia-Perez, R. Montano-Rodriguez and M. O. Echaniz-Aviles (2013). "Double-blind, randomised clinical trial to evaluate the efficacy of probiotics in preterm newborns weighing less than 1500 g in the prevention of necrotising enterocolitis." *Arch Dis Child Fetal Neonatal Ed* 98(1): F5-9.
- Garland, S. M., J. M. Tobin, M. Pirodda, S. N. Tabrizi, G. Opie, S. Donath, M. L. Tang, C. J. Morley, L. Hickey, L. Ung and S. E. Jacobs (2011). "The ProPrems trial: investigating the effects of probiotics on late onset sepsis in very preterm infants." *BMC Infect Dis* 11: 210.
- Gibbs, K., J. Lin and I. R. Holzman (2007). "Necrotising enterocolitis: the state of the science." *Indian J Pediatr* 74(1): 67-72.
- Guthmann, F., C. Kluthe and C. Buhner (2010). "Probiotics for prevention of necrotising enterocolitis: an updated meta-analysis." *Klin Padiatr* 222(5): 284-290.
- Heinritz, S. N., R. Mosenthlin and E. Weiss (2013). "Use of pigs as a potential model for research into dietary modulation of the human gut microbiota." *Nutr Res* 26(2): 191-209.
- Manzoni, P., M. Meyer, I. Stolfi, M. Rinaldi, S. Cattani, L. Pugini, M. G. Romeo, H. Messner, L. Decembrino, N. Laforgia, F. Vagnarelli, L. Memo, L. Bordignon, M. Maule, E. Gallo, M. Mostert, M. Quercia, L. Bollani, R. Pedicino, L. Renzullo, P. Betta, F. Ferrari, T. Alexander, R. Magaldi, D. Farina, F. Mosca and M. Stronati (2014). "Bovine lactoferrin supplementation for prevention of necrotizing enterocolitis in very-low-birth-weight neonates: a randomized clinical trial." *Early Hum Dev* 90 Suppl 1: S60-65.
- Millar, M., M. Wilks and K. Costeloe (2003). "Probiotics for preterm infants?" *Arch Dis Child Fetal Neonatal Ed* 88(5): F354-358.
- Modi, N. (2014). "Probiotics and Necrotizing Enterocolitis: the devil (as always) is in the detail. Commentary on N. Ofek Shlomai et al.: Probiotics for preterm neonates: what will it take to change clinical practice?" (*Neonatology* 2014;105:64-70)." *Neonatology* 105(1): 71-73.
- Rautava, S. (2007). "Potential uses of probiotics in the neonate." *Semin Fetal Neonatal Med* 12(1): 45-53.
- Samanta, M., M. Sarkar, P. Ghosh, J. Ghosh, M. Sinha and S. Chatterjee (2009). "Prophylactic probiotics for prevention of necrotizing enterocolitis in very low birth weight newborns." *J Trop Pediatr* 55(2): 128-131.
- Sanders, M. E., F. Guarner, R. Guerrant, P. R. Holt, E. M. Quigley, R. B. Sartor, P. M. Sherman and E. A. Mayer (2013). "An update on the use and investigation of probiotics in health and disease." *Gut* 62(5): 787-796.
- Schanler, R. J. (2006). "Probiotics and necrotising enterocolitis in premature infants." *Arch Dis Child Fetal Neonatal Ed* 91(6): F395-397.
- Steer, T., H. Carpenter, K. Tuohy and G. R. Gibson (2000). "Perspectives on the role of the human gut microbiota and its modulation by pro- and prebiotics." *Nutr Res Rev* 13(2): 229-254.
- Theodorakopoulou, M., E. Perros, E. J. Giamarellos-Bourboulis and G. Dimopoulos (2013). "Controversies in the management of the critically ill: the role of probiotics." *Int J Antimicrob Agents* 42 Suppl: S41-44.

Figure 1. Forest Plot for ORs (Frequentist Random Effects Model)

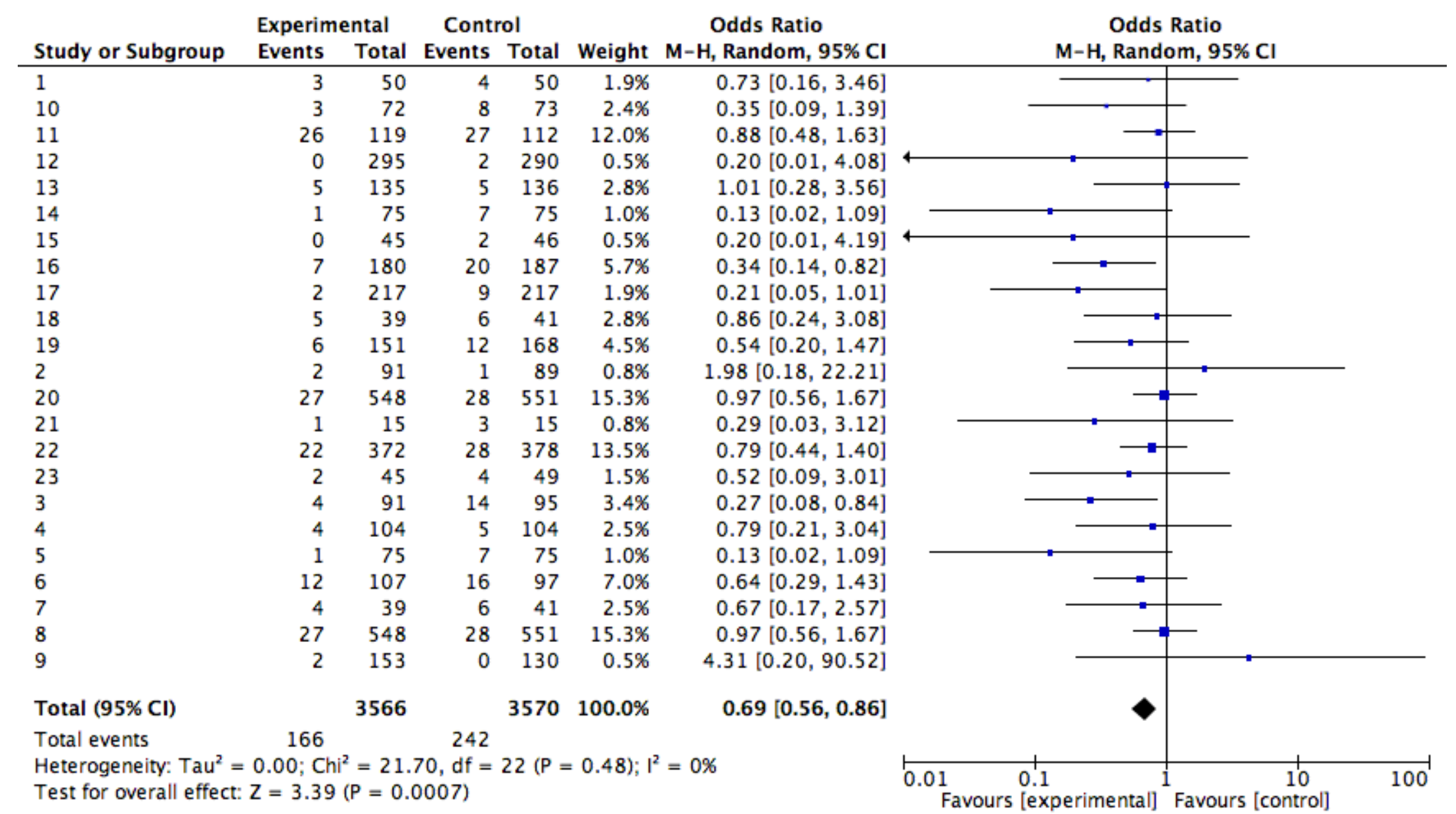


Figure 2. Forest Plot for RRs (Frequentist Random Effects Model)

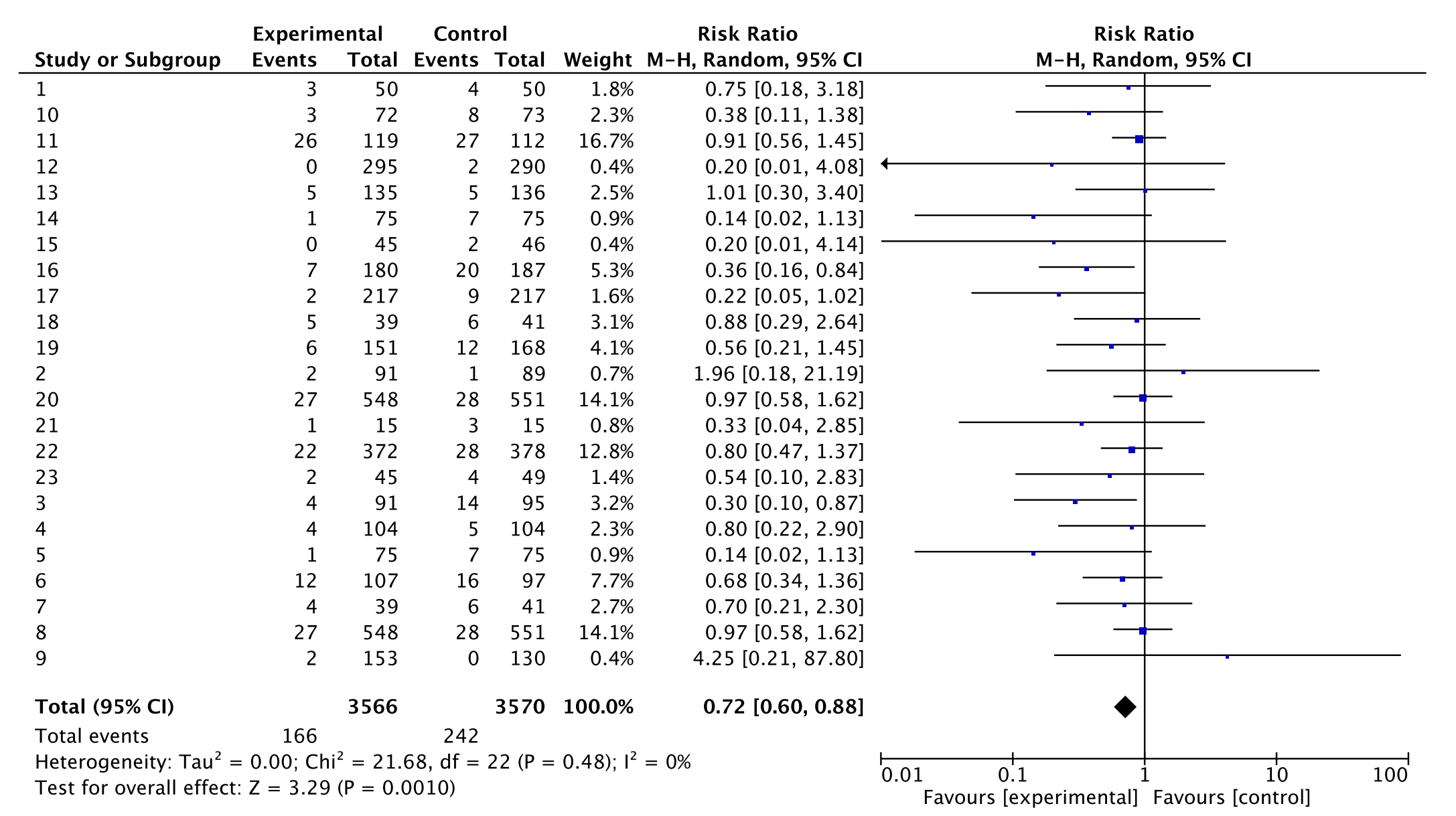


Table 1. Bayesian Random Effects Model Results

node	mean	sd	MC error	2.50%	median	97.50%	start	sample
OR[1,2]	0.6146	0.08925	0.001904	0.4428	0.6125	0.7952	10001	30000
SUCRA[1]	2.67E-04	0.01633	9.35E-05	0	0	0	10001	30000
SUCRA[2]	0.9997	0.01633	9.35E-05	1	1	1	10001	30000
best[1]	2.67E-04	0.01633	9.35E-05	0	0	0	10001	30000
best[2]	0.9997	0.01633	9.35E-05	1	1	1	10001	30000
prob[1,1]	2.67E-04	0.01633	9.35E-05	0	0	0	10001	30000
prob[1,2]	0.9997	0.01633	9.35E-05	1	1	1	10001	30000
prob[2,1]	0.9997	0.01633	9.35E-05	1	1	1	10001	30000
prob[2,2]	2.67E-04	0.01633	9.35E-05	0	0	0	10001	30000
resdev[1]	1.217	1.464	0.01022	0.02113	0.7014	5.392	10001	30000
resdev[2]	1.711	1.587	0.01213	0.07958	1.252	6.029	10001	30000
resdev[3]	1.975	1.827	0.0178	0.06759	1.477	6.766	10001	30000
resdev[4]	2.942	1.597	0.01104	1.114	2.488	7.368	10001	30000
resdev[5]	1.636	1.578	0.01159	0.07584	1.157	5.888	10001	30000
resdev[6]	3.332	1.867	0.0236	0.5174	3.093	7.863	10001	30000
resdev[7]	2.938	1.62	0.01087	1.109	2.473	7.399	10001	30000
resdev[8]	2.366	1.861	0.02381	0.09613	1.988	7.101	10001	30000
resdev[9]	2.723	1.822	0.02197	0.2185	2.43	7.354	10001	30000
resdev[10]	1.388	1.507	0.01036	0.0421	0.8875	5.572	10001	30000
resdev[11]	1.364	1.537	0.01037	0.0308	0.8497	5.682	10001	30000
resdev[12]	1.988	1.608	0.01083	0.2916	1.496	6.351	10001	30000
resdev[13]	2.37	2.009	0.02801	0.0819	1.891	7.48	10001	30000
resdev[14]	1.496	1.517	0.009425	0.09177	1.002	5.73	10001	30000
resdev[15]	1.735	1.721	0.01559	0.0507	1.228	6.455	10001	30000
resdev[16]	1.196	1.489	0.009747	0.02111	0.6601	5.369	10001	30000
resdev[17]	2.698	1.898	0.02653	0.1566	2.386	7.382	10001	30000
resdev[18]	1.307	1.509	0.00992	0.03062	0.7962	5.516	10001	30000
resdev[19]	3.352	1.875	0.02448	0.517	3.114	8.021	10001	30000
resdev[20]	1.394	1.572	0.01325	0.02693	0.8694	5.758	10001	30000
resdev[21]	1.227	1.485	0.01015	0.01978	0.7102	5.442	10001	30000
resdev[22]	2.374	2.005	0.02863	0.08084	1.887	7.42	10001	30000
resdev[23]	4.348	1.701	0.01226	2.079	3.949	8.858	10001	30000
rk[1]	2	0.01633	9.35E-05	2	2	2	10001	30000
rk[2]	1	0.01633	9.35E-05	1	1	1	10001	30000
sd	0.3043	0.1865	0.00619	0.02521	0.2835	0.7278	10001	30000
totresdev	49.08	8.411	0.116	33.71	48.67	66.58	10001	30000

Contact

Saurabh (Rob) Aggarwal, BS, MS, PhD
Principal & Co-Founder
NOVEL Health Strategies
sa2@novelhealthstrategies.com
www.novelhealthstrategies.com
202-618-9365



Awarded Two Platinum and One Bronze Medal by AMCP

This study was sponsored by NOVEL to support evidence development for natural products

