

Reactive hypoglycaemia in pregnancy is associated with adverse pregnancy outcomes related to glucose dysmetabolism

Muhammad Pradhiki Mahindra¹ , Michelle Jie² , Muhammad Pradhika Mapindra¹, Sara Hillman^{1,2} , Owen Vaughan¹ , Anna David^{1,2} , Dimitrios Siassakos^{1,2}

¹ University College London, London, United Kingdom

² University College London Hospital, London, United Kingdom

Introduction

- Reactive Hypoglycaemia (RH) is post-glucose-load blood sugar lower than fasting. Thresholds to define Hypo vary across studies.
- RH may be atypical diabetes

Aim: meta-analyse impact of RH on pregnancy outcomes

Methods

- Search in January 2023: Medline, Embase, Web of Science & Maternity & infant care database.
- Outcomes of interest:** large for gestational age (LGA), macrosomia, small for gestational age (SGA), Intrauterine Growth Restriction (IUGR), low birth weight (LBW), caesarean delivery, NICU admission, neonatal hypoglycaemia, polyhydramnios, 5-min APGAR score < 7, preterm delivery.
- 2 Assessors + 1 Senior investigator for Consensus as needed
- Studies included irrespective of threshold used to define hypoglycaemia
- Risk of bias assessment with *Newcastle Ottawa scale*
- Analysis with Review Manager software

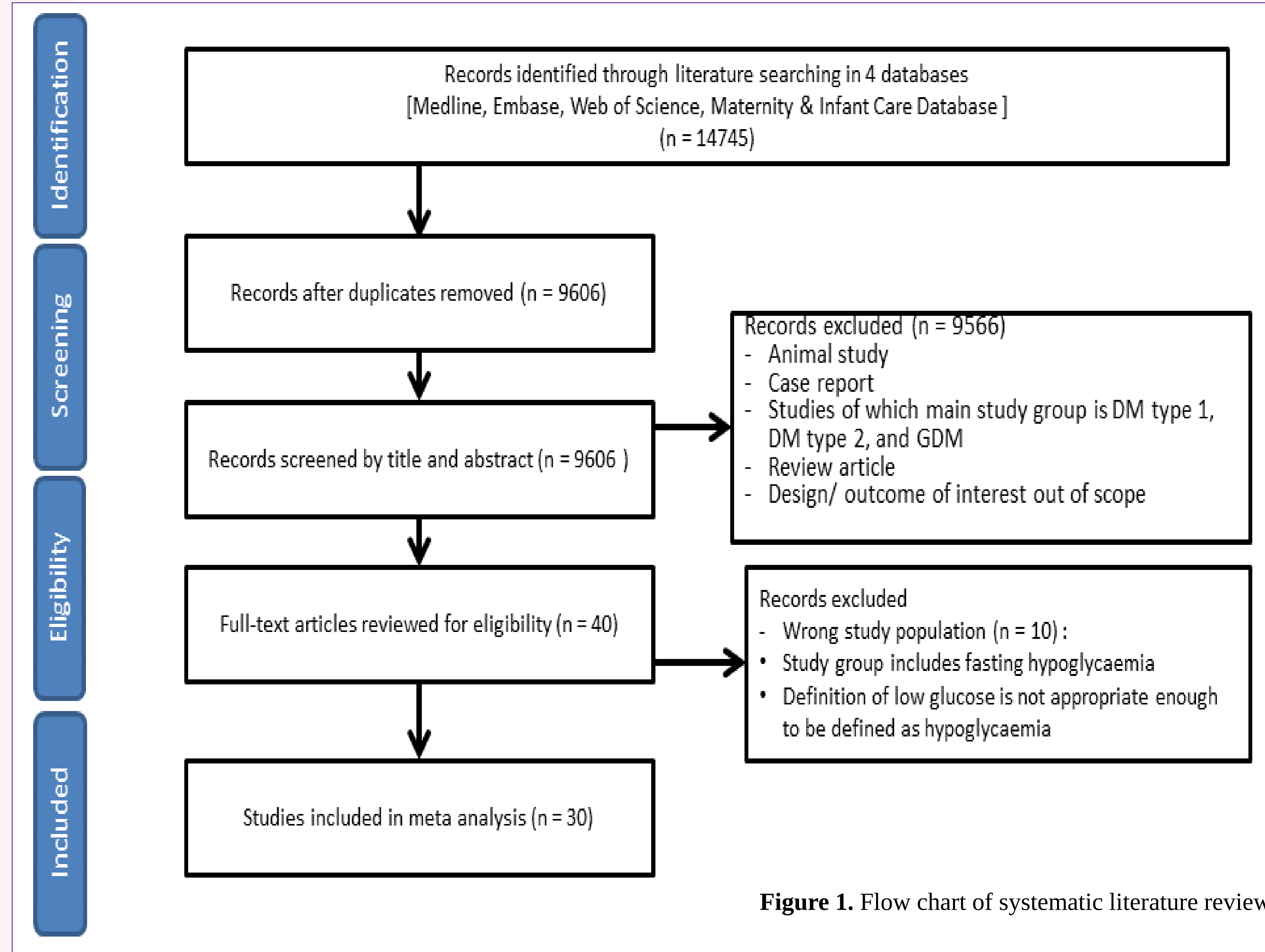


Figure 1. Flow chart of systematic literature review

Results

- 30 Studies meta-analyzed
- 75,453 participants, including 14,607 with RH
- RH associated with ↑ risk of **SGA, LBW & NICU admission** compared to euglycemic; but not LGA / polyhydramnios in the existing literature
- Evidence from single study in Bristol & London that RH with more inclusive threshold significantly ↑ risk of most GDM-related outcomes including **macrosomia & polyhydramnios**

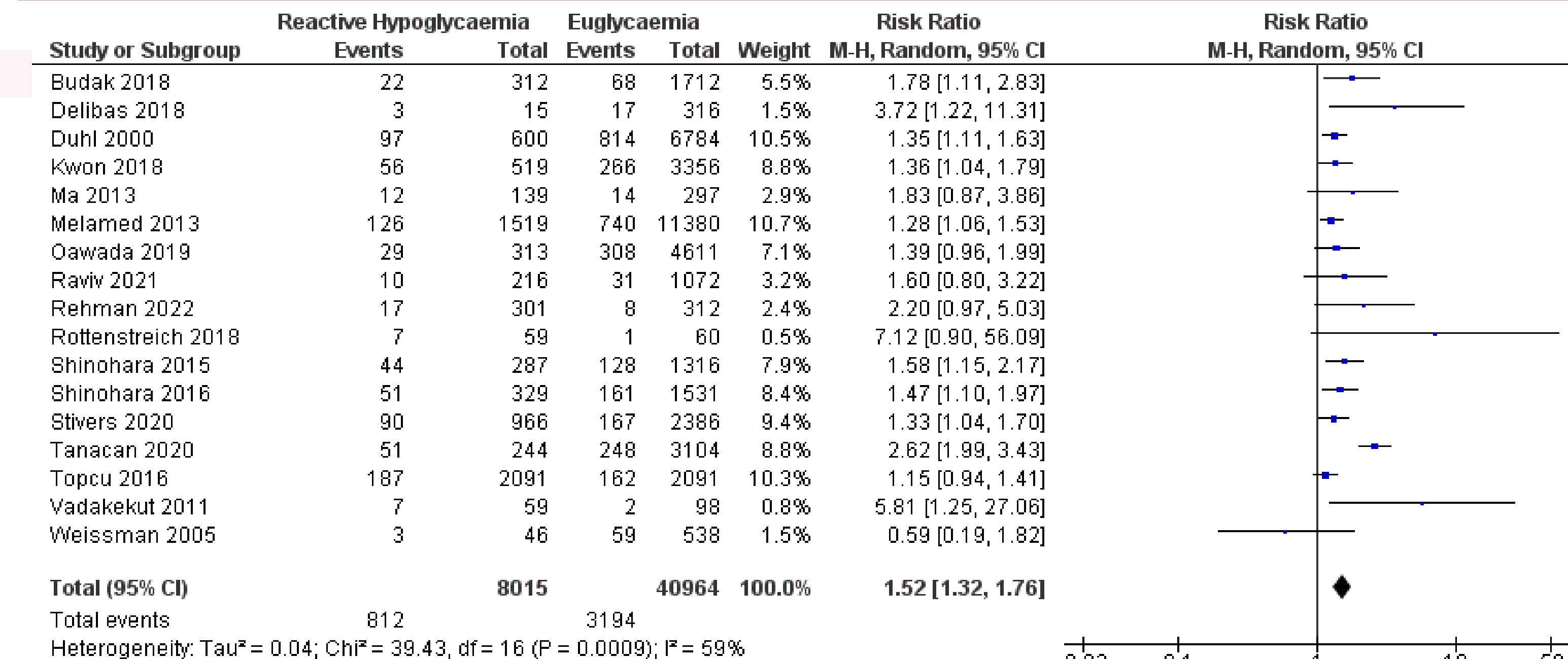


Figure 2. The forest plot shows the pooled effect of estimate (RR) of SGA when the RH group compared with euglycemic values

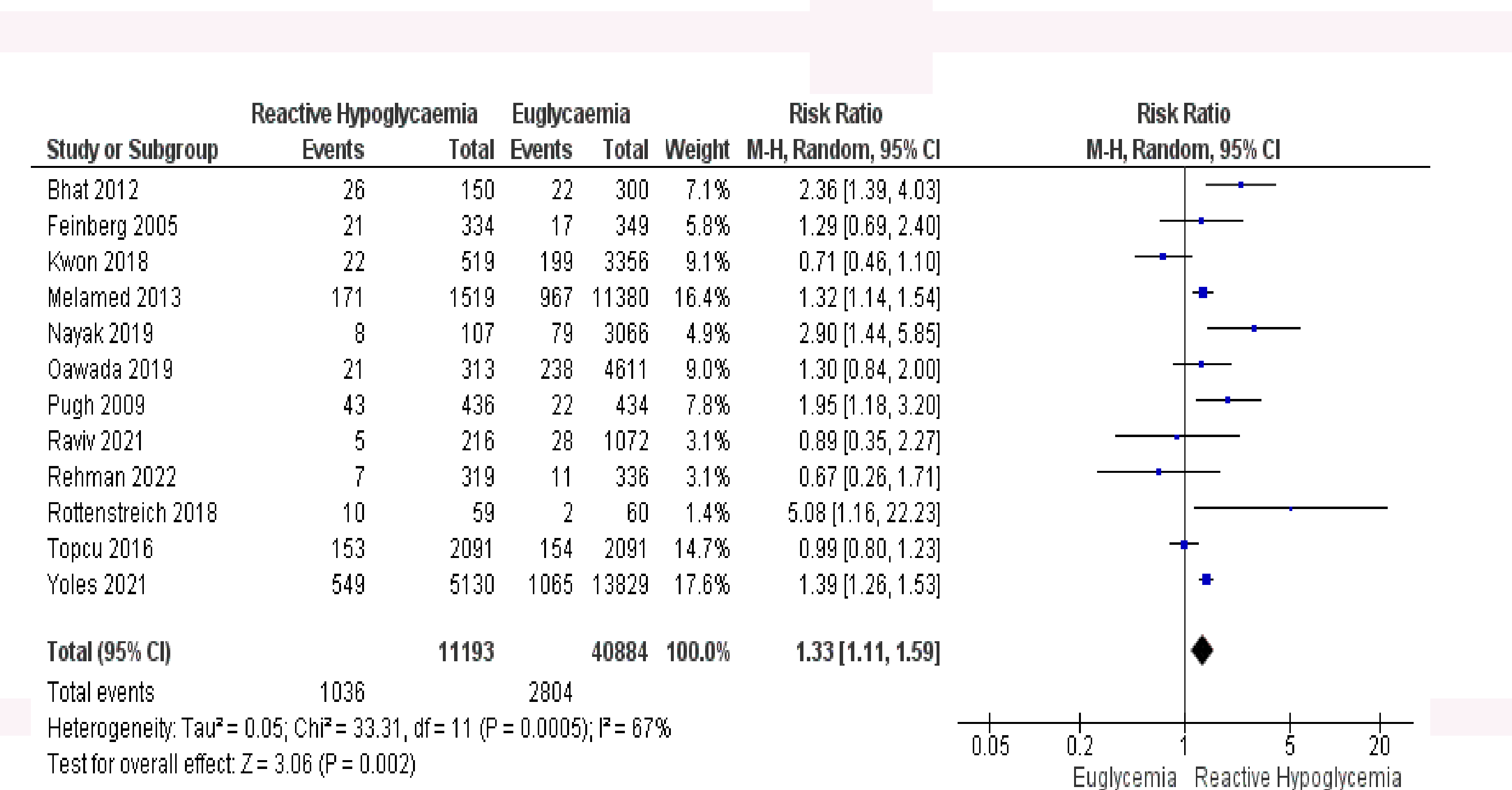


Figure 3. The forest plot shows the pooled effect of estimate (RR) of LBW when the RH group compared with euglycemic values

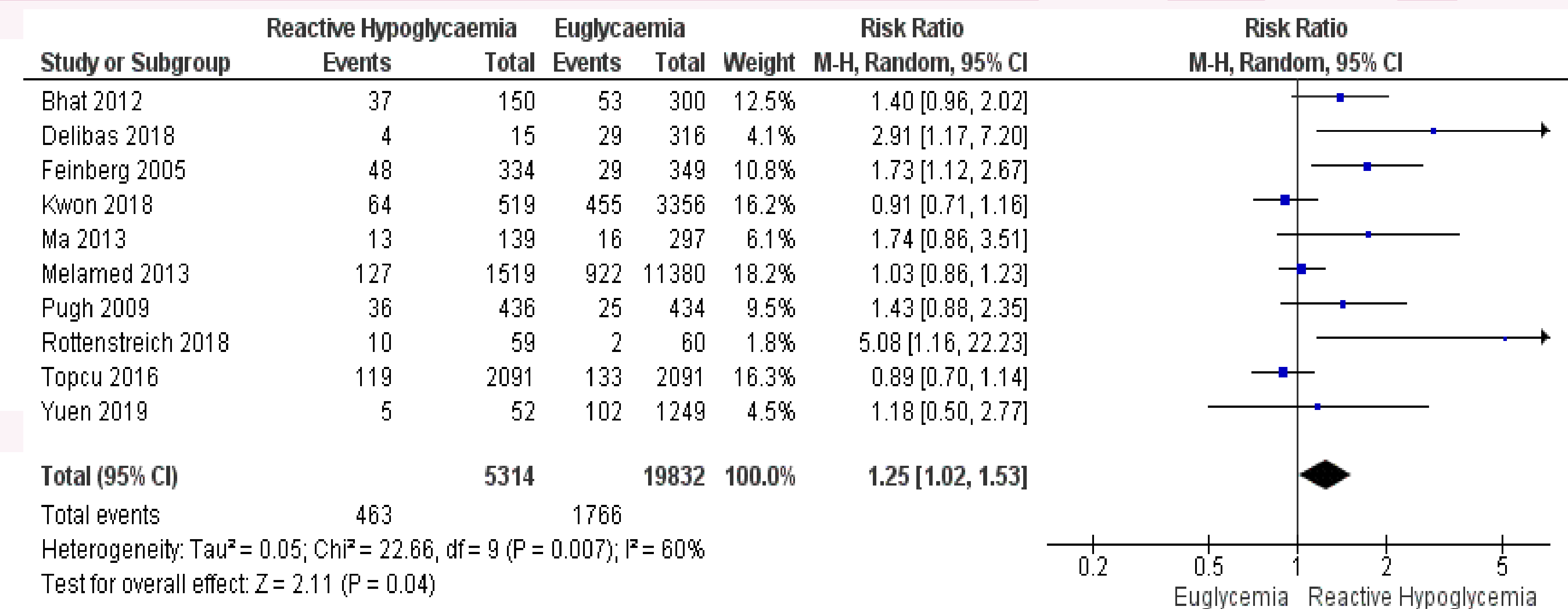


Figure 4. The forest plot shows the pooled effect of estimate (RR) of NICU admission when the RH group compared with euglycemic values

Further discussion

- Transplacental glucose and amino acid transport may take part in intrauterine growth
- No studies address **placental nutrient transport function & histology** in pregnancies with Reactive Hypoglycemia (RH)

Conclusions

- Women with RH are at risk for **adverse fetal-neonatal outcomes**: growth restriction, smaller offspring, and NICU admission
- Prospective study** needed to determine if **more inclusive threshold** confirms link with diabetes-related outcomes, with mechanistic evidence to support **causality**

Reference:

- Mitra et al. Am J Perinatol. 2021 Jul 1;39(8):841-7.
- Boyd et al. New England Journal of Medicine. 2008;365:687-96.
- HAPO Study Cooperative Research Group. International Journal of Gynecology and Obstetrics. 2002;78:69-77.
- Stroup et al. Meta-analysis of Observational Studies. 2022;
- Shamseer et al. BMJ (Online) [Internet]. 2015;349(January):1-25.
- Wells et al. https://www.ohm.ca/hypoglycemia/clinical_guidelines/ohm-ohf.asp
- Rottenstreich A, Elazary R, Ezra Y, Kleinstern G, Beglaibter N, Elchalal U. Surgery for Obesity and Related Diseases. 2018 Mar 1;14(3):347-53.
- Rehman S, Kazi S, Kindinger L, Wallis N, Whitten M, Siassakos D. In: HOT TOPICS (EMERGING RESEARCH/ ISSUES) IN OBSTETRICS. 2022. p. 72-3.
- Yuen L, Bontempo S, Wong VW, Russell H. Diabetes Res Clin Pract. 2019 Jan 1;147:111-7.
- Nayak AU, Vijay AMA, Indusekar R, Kalidindi S, Karreddy VM, Varadhan L. World J Diabetes. 2019 May 15;10(5):304-10.
- Delibas JB, Tanriverdi S, Calanak B, Ginekol Pol. 2018;89(1):25-9.
- Raviv S, Wilkof-Sagev R, Yosef-Sagev E, Naeh A, Yosef Y, Hallak M, et al. International Journal of Gynecology and Obstetrics. 2021;1(June):1-7.
- Reicher L, Lavie A, Attali E, Fouks Y, Feinmesser L, Landesberg I, et al. 2021;
- Vadakekut ES, McCoy SJB, Payto ME. Journal of the American Osteopathic Association. 2011;111(3):148-52.
- Weissman A, Soli I, Zloczower M, Jakobi P. Obstetrics and Gynecology. 2005 Jun;105(6):1424-8.
- Calfee EF, Ruse OA, Boffill JA, Ross EL, Morrison JC. Current Concepts [Internet]. Vol. 19. Journal of Perinatology. 1999.
- Feinberg JH, Magann EE, Morrison JC, Holman JR, Polizzotto MJ. Journal of Perinatology. 2005;25(8):509-13.
- Pugh SK, Doherty DA, Magann EF, Chauhan SP, Hill JB, Morrison JC. Reprod Health. 2009;6(1):1-7.
- Stivers SL, Thomas M, Devaiah G, Lambers D. 2022.
- Topcu HO, Iskender CT, Gelen S, Oskovi A, Uygun D, Erkaya S. J Perinat Med. 2016 May 1;44(4):369-76.
- Bhat RG, Bhagya K V, Kumar P. International Journal of Infertility and Fetal Medicine. 2012;3(1):22-5.
- Budak MS, Aray E. Gineköl Pol. 2018;89(7):370-4.
- Duhl AJ, Ural SH, Witer FR. Journal of Perinatology [Internet]. 2000;5:288-90.
- Kwon H, Lee J, Lee BW, Kwon JY, Kim YH. J Womens Health. 2018;27(6):801-7.
- Kwon HY, Park HS, Shin AS, Kim YH, Park YW. Vol. 43. Journal of Perinatal Medicine. 2015.
- Ma KK, Mele L, London MB, Spang CY, Ramin SM, Casey B, et al. Am J Perinatol. 2013;30(9):715-21.
- Melamed N, Hersch L, Peled Y, Hod M, Winitzner A, Yagov Y. Journal of Maternal-Fetal and Neonatal Medicine. 2013;26(11):1107-11.
- Oawada N, Aoki S, Sakamaki K, Obata S, Seki K, Hirahara F. Journal of Maternal-Fetal and Neonatal Medicine. 2019;32(1):58-61.
- Shinohara S, Hirai M, Hirata S, Suzuki K. Journal of Obstetrics and Gynaecology Research. 2015;41(11):1752-6.
- Shinohara S, Uchida Y, Hirai M, Hirata S, Suzuki K. BMJ Open [Internet]. 2016;6:13749.
- Tanacan A, Mert Eyyoglu, Fadiloglu, Erdem, Hatice, Zengin Y, Karasoglu, Ergun, et al. neonates. J Diabetes. 2020;12:792-7.
- Yoles I, Vaishach E, Wainstock T, Barak O, Schiller T. 33rd Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research. 2021.
- Venareddy K, Burgess T, Minkoff H. Am J Obstet Gynecol. 2009;201(6):S51.
- Lurie S, Levy R, Weiss R, Boulton G, Hagay ZJ. J Obstet Gynaecol (Lahore). 1998;18(5):451-4.
- Ong KK, Diderholm B, Salzano G, Wingate D, Hughes IA, MacDougall J, et al. Diabetes Care. 2008;31(11):2193-7.
- Mitra M, Sanchez-Ramos L, Roekner JT, Bennett S, Kovacs A, Kaminz AM. Am J Perinatol. 2021 Jul 1;39(8):841-7.
- Bienstock JL, Hulcroft CJ, Althaus J. Ultrasound in Obstetrics and Gynecology. 2006;31(5):517-9.