Later Metabolic Risk after Nutritional Supplements in Infants Born Early or Small: An Individual Participant Data Meta-Analysis (ESSENCE IPD-MA)

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Background

Supplementing nutrition in infants born small is associated with improved early growth and cognitive outcomes, but may increase risk of later metabolic disease. Effects may also differ by sex.

Objective

To assess the sex-specific effects of macronutrient supplements in nutrition of preterm and small-for-gestational-age infants on their development and metabolism after hospital discharge.

Methodology

Study design

Individual participant data meta-analysis (IPD-MA)

Type of studies

Randomised or quasi-randomised trials.

Population

Infants born preterm or small (<2.5 kg or <10th centile).

Intervention

Supplements to increase the intake of one or more macronutrients with the primary aim of improving growth and development.

Primary outcome

Any metabolic risk (obesity, type-2 diabetes, high-density and low-density lipoproteins, triglycerides, cholesterol, fasting glucose, systolic, diastolic and mean blood pressure and body mass index).

Analysis

- One-stage analyses accounting for the clustering of participants within studies.
- Sex effects explored using subgroup analyses and interaction terms.

Results

Twenty-one trials from 12 different countries shared data with the ESSENCE IPD-MA collaboration, and 5 trials have long-term metabolic outcomes (Fig 1).

Supplementation did not alter any metabolic risk in

- childhood (3-8 years, 3 trials, n=334; aRR 1.02, 95% CI 0.77, 1.35, P=0.90),
- adolescence (9-18 years, 2 trials, n=104; aRR 0.86, 95% CI 0.64, 1.16, P=0.31), or
- at >3 years (5 trials, n=438; aRR 0.94, 95% CI 0.76, 1.17, P=0.59) (Fig 2),

and there was no significant sex interaction (Fig 3).

In childhood, children in the supplemented group had lower triglyceride concentrations (1 trial, n=207, adjusted mean difference (mmol/L) -0.12, 95% CI -0.23, -0.01, P = 0.03).

There were no differences for any other metabolic outcomes, no significant sex interaction, and no significant heterogeneity.

Fig 1. Study selection

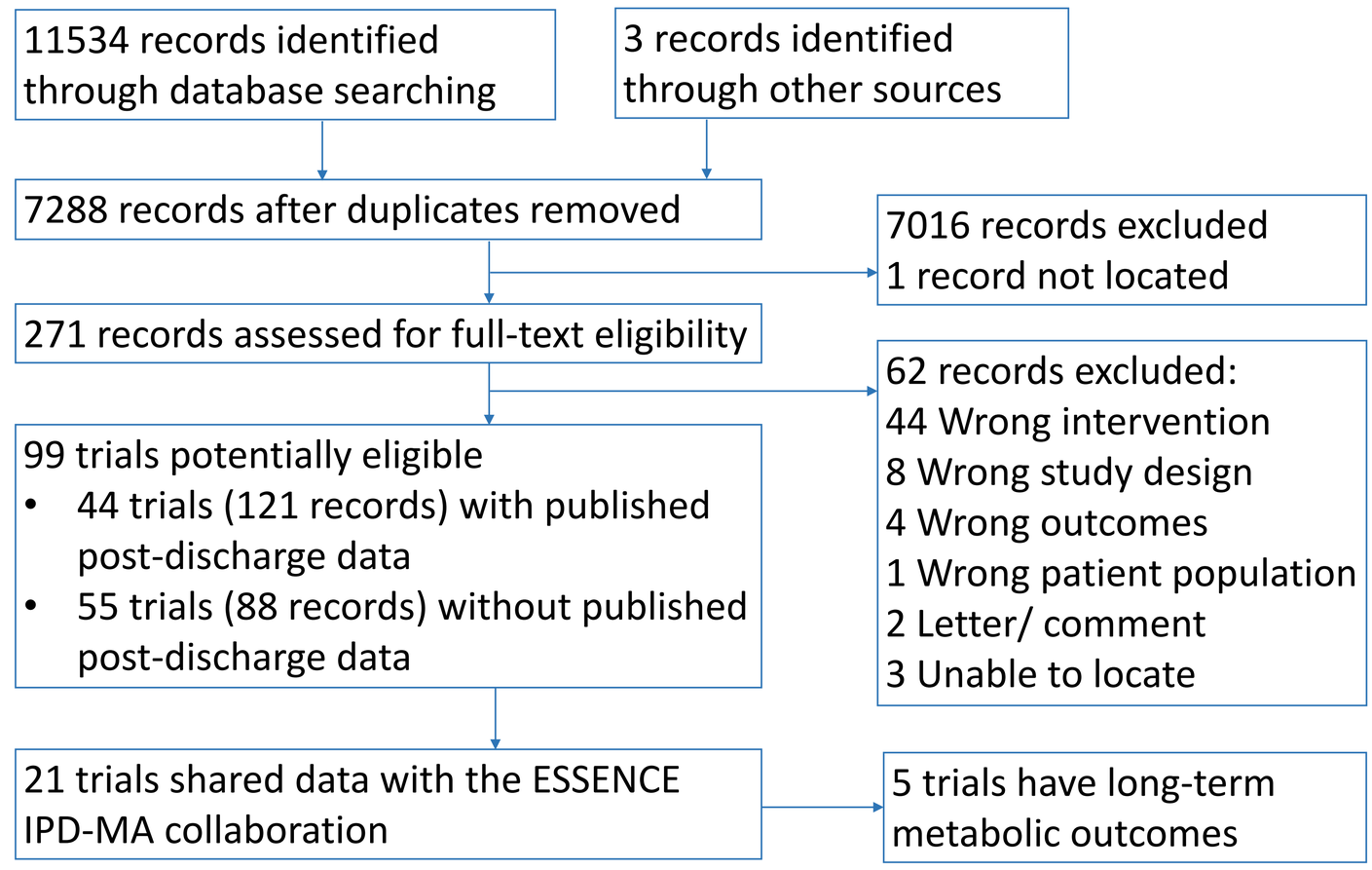
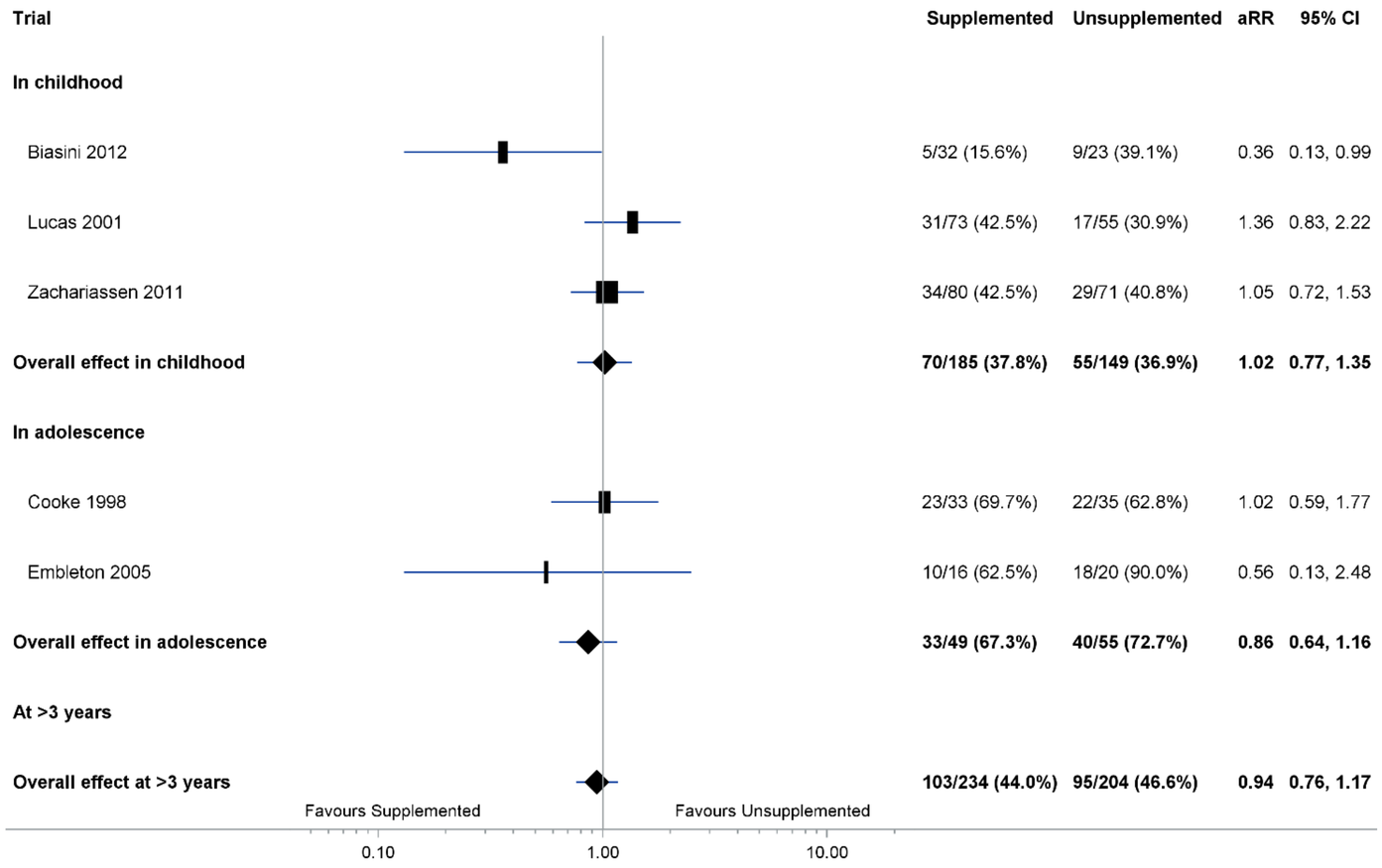
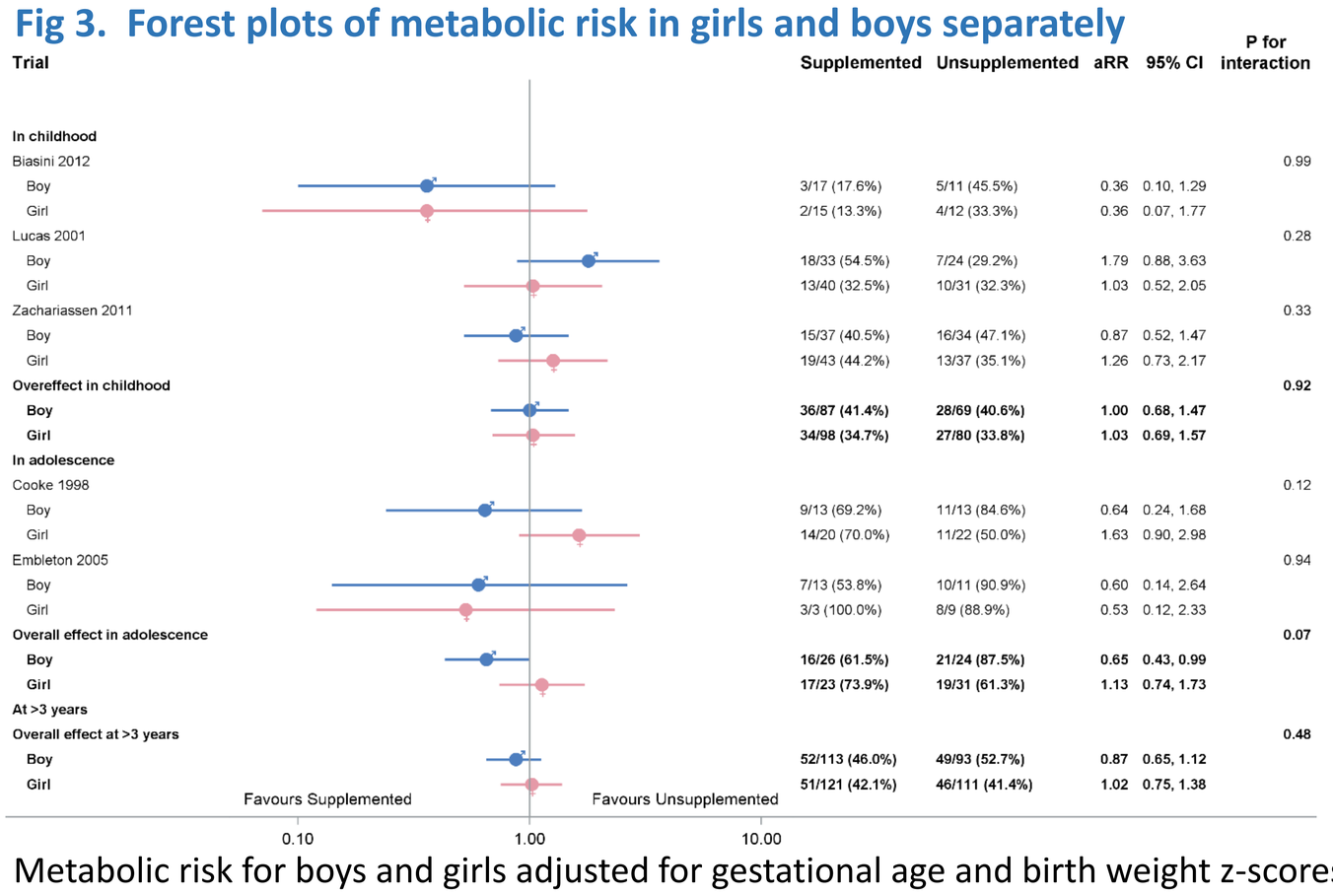


Fig 2. Forest plots of metabolic risk at different ages



Metabolic risk in childhood, in adolescence or at >3 years adjusting for sex, gestational age and birth weight z-scores. P-value for heterogeneity in childhood = 0.23, in adolescence = 0.15, at >3 years = 0.07.

Fig 3. Forest plots of metabolic risk in girls and boys separately



Metabolic risk for boys and girls adjusted for gestational age and birth weight z-scores.

Conclusions

Contrary to observational studies, IPD of randomised trials shows early macronutrient supplementation for infants born small does not increase later metabolic risk.