

Early probiotics to prevent childhood metabolic syndrome: A systematic review

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Abstract

AIM: To conduct a systematic review of studies on early probiotic supplementation to prevent childhood metabolic syndrome (MS).

METHODS: Using the Cochrane systematic review strategy we searched PubMed, EMBASE, CENTRAL, CINAHL, and the conference proceedings of the Pediatric American Society meetings and trial registries in December 2014. Randomised controlled trials (RCTs) and non RCTs of probiotic supplementation to the mother and/or infant for a minimum duration of 4 wk were selected. Of these, studies that reported on MS or its components (obesity, raised blood pressure, hyperglycemia, dyslipidemia) in children between 2-19 years were to be eligible for inclusion in the review. Risk of bias (ROB) in selected RCTs and quality assessment of non-RCT studies were to be assessed by the Cochrane ROB assessment table and New Castle Ottawa scale.

RESULTS: There were no studies on early probiotic administration for prevention of childhood MS (CMS). Follow up studies of two placebo controlled RCTs ($n = 233$) reported on the effects of early probiotics on one or more components of MS in children aged 2-19 years. Meta-analysis of those two studies could not be performed due to differences in the patient population, type of outcomes studied and the timing of their assessment. Assessment of childhood metabolic outcomes was not the primary objective of these studies. The first study that assessed the effects of prenatal and postnatal supplementation of *Lactobacillus rhamnosus GG* on body mass index till 10 years, did not report a significant benefit. In the second study, *Lactobacillus paracasei* 19 was supplemented to healthy term infants from 4-13 mo. No significant effect on body mass index, body composition or metabolic markers was detected.

CONCLUSION: Current evidence on early probiotic

administration to prevent CMS is inadequate. Gaps in knowledge need to be addressed before large RCTs can be planned.

Key words: Metabolic syndrome; Obesity; Probiotic; Infant; Perinatal; Children

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Core tip: Metabolic syndrome (MS) is a state of dysregulated glucose and lipid metabolism. The global health burden due to increasing prevalence of MS in children and adolescents, warrants urgent preventive interventions. Altered gut microbiota has been implicated in the pathogenesis of MS. The role of maternal and/or infant probiotic supplementation in improving metabolic health of the offspring is being researched. We provide a systematic review of this evidence. Gaps in the knowledge and issues regarding selection of patient population, probiotic intervention and outcomes for future trials have been discussed.

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INTRODUCTION

Metabolic syndrome (MS) is defined to include an array of risk factors that increase the chances of Cardiovascular morbidity and type 2 diabetes in an individual. The World Health Organisation (WHO) in 1998, defined MS to comprise of insulin resistance in the presence of any two of the risk factors - obesity, hypertension, high triglyceride level, reduced high-density lipoprotein cholesterol level, or micro albuminuria^[1]. Since then, various definitions for MS have been proposed. MS is increasingly being recognised in children. The diagnostic criteria for MS have been adapted for children and adolescents by the WHO, National Cholesterol Education Program, International Diabetes Federation and I Guidelines for prevention of atherosclerosis in childhood and adolescence^[1-4]. There are more than ten different clinical definitions for childhood MS (CMS)^[5]. Additionally, there are no unifying criteria that are representative of ethnically diverse groups. The age of onset of CMS is also unclear. A systematic review of 36 epidemiological studies analysing the prevalence of MS in children aged 2-19 years, reported a prevalence ranging from 1.2%-22.6% with rates up to 60% in overweight and obese children^[6]. A recent systematic review has reported a mean overall prevalence of CMS as 3.3% (range: 0%-19.2%)^[7]. The prevalence was higher in overweight [11.9% (2.8%-29.3%)] and obese [29.2%

(10%-66%)] children. It was also higher among males and older children. Higher prevalence has been reported in the Middle East and the United States compared to Europe and the Far East. The variations in the definition of MS, ethnicity, age and nutritional status of the study population may explain the wide range of prevalence reported in these studies. To our knowledge, there is no data available on the health burden of CMS. Follow up of the Framingham Heart study cohort has revealed that the combination of central obesity, hypertension and hyperglycemia led to 2.36 times increase in the incidence of cardiovascular events and three-fold increase in mortality among adults^[8]. MS results in a seven fold increase in the risk of type 2 diabetes^[9].

Obesity is considered the most important component of CMS. Data from the National Centre of health Statistics, United States reveal that prevalence of obesity has doubled in children and quadrupled in adolescents in the past 30 years^[10]. Increased prevalence of CMS is a direct result of the increasing trends of childhood obesity. Cost of illness studies from the United States, Australia, Germany have confirmed that health care utilisation by children with obesity, is significantly higher than their normal weight counterparts^[11]. The annual medical expenditure due to childhood obesity in the United States is approximately 14 billion United States dollar (USD) and the projected costs for the next 30 years due to currently prevailing trends of adolescent obesity would be 45 billion USD^[12,13]. Thus CMS has the potential to be a major public health concern to both the developed and developing countries^[14].

Pathogenesis of MS

Pathogenesis of MS is complex and involves insulin resistance, lipid partitioning, hepatic steatosis, free radical injury and hormonal changes (leptin, adiponectin, resistin)^[15-17].

Role of gut microbiota

Numerous reviews have indicated the role of altered gut microbiota in the pathogenesis of MS^[18-20]. Gut microbiota (*e.g.*, *bacteroides*) can mediate energy harvest from diet resulting in obesity and type 2 diabetes^[21]. Increased level of inflammatory markers (Lipopolysaccharides, Transforming growth factor- β) by gram negative bacteria in the gut can increase gut permeability and oxidant injury and thereby affect the metabolic health^[22]. The firmicutes: bacteroides ratio in the gut flora was significantly reduced in children with type 1 diabetes as compared to healthy children^[23]. Obesity and excessive weight gain during pregnancy was associated with aberrations in the maternal gut microbiota^[24]. Collado *et al*^[25] have reported lower stool bifidobacterial counts and reduced microbial diversity in infants born to obese mothers. Follow up of that cohort revealed an increased risk of obesity at seven years of age^[26]. It was suggested that early infancy gut microbial alteration could influence metabolic health of children

and adolescents. Gut microbiota is also more amenable to modulation, prior to the establishment of adult type microbiota; *i.e.*, in the first two years of life^[27]. Hence, it could be hypothesised that interventions modulating gut microbiota in early infancy can potentially reduce the risk of CMS.

Role of probiotics in prevention of MS

Probiotics are "live micro-organisms which when administered in adequate amounts confer a specific health benefit on the host". Probiotics have been shown to decrease body weight gain, adipose tissue mass, leptin and cholesterol levels. Diet induced hyperglycemia and hyperinsulinemia was controlled by probiotic supplementation. However, majority of the clinical evidence is from adult and animal studies^[28-30]. The potential of probiotics in improving metabolic outcomes in children has been studied by maternal and/or early infant supplementation. The pathways for the potential benefits are direct modulation of the infant gut flora through breast milk or placenta and regulation of risk factors such as maternal hyperglycemia and obesity^[31-34].

Given the significance of the health issue and the potential of probiotics as an intervention, we aimed to conduct a systematic review of studies reporting on probiotic supplementation to prevent CMS.

MATERIALS AND METHODS

Study selection criteria

The study selection criteria is described as follows: (1) Studies: Randomized controlled trials (RCTs) and non-RCT studies; (2) Participants: Pregnant women and/or infants that received probiotic supplementation for at least 4 wk; (3) Intervention: Probiotic supplement of any strain, dose and form with or without prebiotic oligosaccharide for a duration of at least 4 wk; (4) Control: Standard treatment but no probiotics or placebo; and (5) Outcome measures: We broadly defined our outcome measures to account for variations in age, gender and ethnicity based cut offs for individual risk factors of CMS. To be included in this review, the studies should have assessed at least one of the following four components of MS - obesity, raised blood pressure, dyslipidemia (hypertriglyceridemia or low HDL cholesterol), hyperglycemia in children between 2-19 years. The outcome equivalents for each of the components are described as follows: (1) Obesity: body mass index, waist circumference; (2) Hyperglycemia: Fasting plasma glucose, insulin levels, insulin resistance (assessed by homeostatic model assessment for insulin resistance), insulin sensitivity, fasting plasma glucose; (3) Dyslipidemia: Plasma lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, total cholesterol/HDL); and (4) Hypertension: Systolic blood pressure and /or diastolic blood pressure.

We followed the standard Cochrane methodology and the preferred reporting items for systematic reviews

and meta-analysis, for conducting and reporting RCTs in this systematic review^[35]. We followed the Meta-analysis of observational studies in epidemiology guidelines for conducting and reporting outcomes of non-RCTs in this systematic review^[36].

Literature search

We searched the Cochrane central register of controlled trials (CENTRAL) (<http://www.cochrane.org/cochrane/hbook.htm>), MEDLINE *via* PubMed (<http://www.ncbi.nlm.nih.gov/Pubmed>), EMBASE (<http://www.embase.com>) and annual conference proceedings of the Pediatric Academic Societies (www.pas-meeting.org/) in December 2014. PubMed was searched using two search strategies: (1) Studies of probiotics related to the components of MS using the Medical Subject Heading keywords "insulin resistance" or "insulin sensitivity" or "hyperglycemia" or "type 2 diabetes mellitus" or "obesity" or "overweight" or "adipose tissue" or "dyslipidemia" or "body composition" or "bodyweights and measures" or "hypertension" or "blood pressure" and "probiotics"; and (2) Studies of probiotic supplementation in pregnant women and infants using the MeSH keywords "infant" or "infant, newborn" or "pregnancy" and "probiotics".

For both searches, the MeSH word "probiotics" was replaced by *Lactobacillus*, *Bifidobacterium* and *Saccharomyces* and citations were retrieved. We combined both the search strategies to retrieve studies of probiotics in pregnant women and infants that assessed one or more components of MS as defined for this review. The results of the database search are shown in a flow diagram (Figure 1).

No restrictions were applied on study design or language. Animal studies and studies involving patients > 19 years were excluded. References of the obtained studies were also reviewed to identify additional studies. The international trial registry (www.clinicaltrials.gov) and Australian Clinical Trials Registry (www.anzctr.org.au) were checked for ongoing/registered trials in this area.

Data collection and analysis

Selection of studies: Balasubramanian H and Patole S independently assessed for inclusion all the potential studies identified as a result of the search strategy. Any disagreements about study selection were resolved by discussion.

Data extraction and management: Both the authors independently completed a pre specified data extraction form for all included studies. Any disagreements in the extracted data were resolved through discussion.

Assessment of risk of bias in included studies: Risk of bias (ROB) in selected RCTs and quality assessment of non-RCT studies were assessed by the Cochrane ROB assessment table and the New Castle Ottawa scale^[37,38]. Both the authors separately assessed each

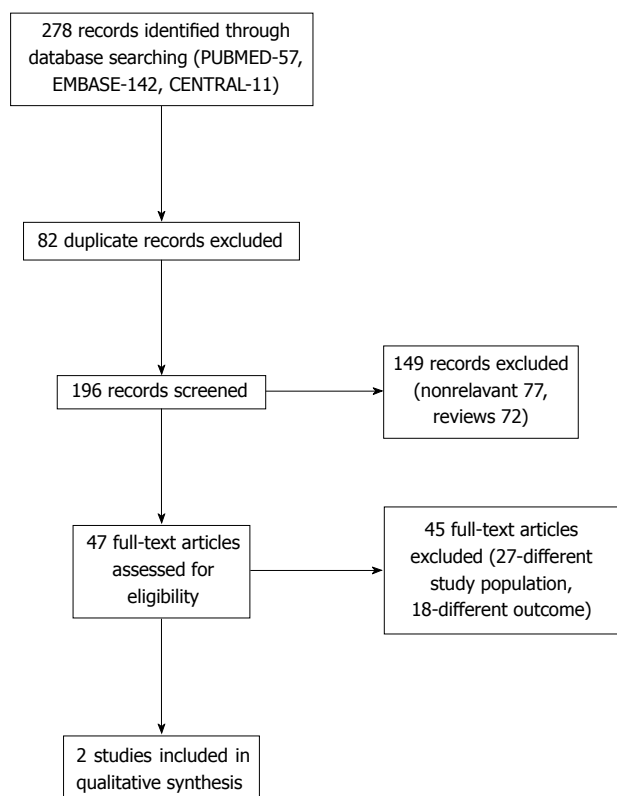


Figure 1 Flow diagram of study selection process.

study. Additional information from the trial authors was requested to clarify methodology as necessary. Any disagreement was resolved by discussion.

RESULTS

Initial broad search yielded 278 citations. We could not find any study on the effects of probiotic administration on CMS. However, we retrieved two RCTs ($n = 233$) reporting on the effects of early probiotics on one or more components of MS in children aged 2-19 years^[39,40] (Figure 1). Meta-analysis of these 2 studies could not be performed due to differences in the patient population, type of outcomes and the timing of their assessment. Hence we decided to conduct a narrative synthesis.

Luoto 2010

This was a follow up study of a double blinded RCT involving 159 mothers with family history of atopic eczema, allergic rhinitis or asthma. They were randomized to receive probiotics ($n = 77$) or placebo ($n = 82$). The intervention group received 1×10^{10} cfu/d of *Lactobacillus rhamnosus* GG for 4 wk before expected delivery and extending for 6 mo postnatally to the mother/infant.

Frequency of atopic eczema in their children till 2 years of age was the primary end point of the study. The BMI and frequency of overweight and obesity was assessed in 113 children (Probiotic: 59, Placebo: 54) at

2, 4, 7, and 10 years of age. Obesity and overweight was assessed in both groups using the international obesity task force criteria. There was no significant difference in the adjusted mean BMI at any age between the 2 groups. Among the children that were overweight at 10 years, (Probiotic: 13, Placebo: 12), there was tendency towards lower mean BMI at 4 years in the probiotic group ($P = 0.063$, Analysis of variance for repeated measures).

Videhult 2014

This was the follow up study of a RCT involving 179 vaginally delivered term infants with birth weight > 2500 g. These infants were fed cereals with or without probiotic (*Lactobacillus paracasei* ssp F19 - 1×10^8 CFU) between 4-13 mo. The outcomes of interest were the number of days with infections and antibiotic prescriptions before and after the second and third doses (5.5 and 12 mo) of DTaP vaccine. A total of 120/179 children were assessed at 8-9 years for the following outcomes-BMI Z score, sagittal abdominal diameter, body composition (fat free mass, fat mass index, truncal fat %, android or gynoid fat %), plasma lipids, insulin, glucose and transaminases. No significant differences in body composition, growth and metabolic markers were noted in the two groups at 8-9 years of age.

Results of the ROB assessment are reported in Table 1.

DISCUSSION

Our systematic review identified two RCTs ($n = 233$) studying the effects of early probiotic supplementation on metabolic health in children. Meta-analysis of these 2 studies could not be performed due to differences in the patient population, type of outcomes studied and the timing of their assessment. The current evidence on the administration of probiotics to the mother or infant to prevent CMS is thus inadequate.

To our knowledge this is the first systematic review assessing the role of early probiotic supplementation in the prevention of CMS. Small number and sample size of the included studies was the main limitation of this systematic review. Included studies were not designed to study metabolic outcomes in children and had follow up losses of up to 30%. Considering the global burden of CMS and the metabolic benefits of probiotics in adults and animal models it is important to assess this intervention in large RCTs. Few issues need to be discussed with regards to the patient population, probiotic intervention and outcome assessment in such trials.

Selection of the infant population for such trials is crucial as the current evidence on benefits of probiotics with regards to CMS related outcomes is based on healthy term infants. Preterm infants and those with intrauterine growth restriction are at high risk for MS due to catch up growth and reduction in insulin sensi-

Table 1 Assessment of risk of bias in the included studies

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Luoto <i>et al</i> ^[40]	Low	Low	Low	Low	High	Low	Low
Videhult <i>et al</i> ^[39]	Low	Low	Low	Low	High	Low	Low

tivity^[41,42]. Infants of diabetic mothers are also at higher risk of MS^[43]. Factors that put these infants at high risk of early infancy gut microbial aberrations include increased risk of caesarean delivery, prolonged hospital stay, decreased maternal contact, perinatal and/or postnatal antibiotic exposure, delayed enteral feeding, need for tube feeds, formula feeding and suboptimal nutrition^[44]. Hence research should focus on these high risk infant groups, and maternal population, especially obese and diabetic mothers. Comprehensive assessment of gut flora and immunological profile would also be essential as they relate to the mechanisms/pathways of benefit of probiotic supplementation. Considering that the effects of probiotics are strain specific and host specific, selection of probiotics is an important issue. A comparative meta-analysis by Million *et al*^[45] has shown that *Lactobacillus acidophilus* administration resulted in significant weight gain in humans and in animals and *Lactobacillus gasseri* was associated with weight loss both in obese humans and in animals. The same authors have also reported that obesity-associated gut microbiota is rich in *Lactobacillus reuteri* and depleted in *Bifidobacterium animalis* and *Methanobrevibacter smithii*^[46]. Assessment of the effects of probiotics on body composition is helpful considering the nutritional benefits of probiotics^[47,48]. Assessment of optimal timing and duration of intervention are also important issues in the RCTs of early probiotic supplementation for preventing CMS. Rinne *et al*^[49] have demonstrated that probiotic administration during the last 6 mo of pregnancy and first 6 mo postpartum did not influence long term (2 years) composition of the infant gut flora. Perinatal metabolic programming and immune mediated effects on the infant gut flora by the administration of probiotic could explain the pathway of benefit^[50]. Controlling for confounders (e.g., dietary and lifestyle changes), assuring compliance during the prolonged period of supplementation, and monitoring for complications will be necessary^[51-53]. Currently there are no universally accepted criteria for defining CMS or its components^[54]. Selection of primary outcomes representative of some or all components of MS would be essential. Since the minimum age cut off described for CMS is unclear, standardisation of surrogate end points will be essential. Currently there are no studies showing a causal relation between MS and gut microbiota. Moreover, the risk factors for MS differ with age. Prematurity, low and high birth weight, rapid catch up growth, maternal undernutrition, maternal obesity and diabetes are potential risk factors for the components of CMS. This highlights the necessity to

test early interventions (perinatal, early postnatal) for preventing CMS.

In summary, current evidence is insufficient to assess the effects of probiotics in reducing the risk of MS in children and adolescents. Considering the global health burden of CMS and the potential role of a low cost intervention such as probiotic supplementation, clinical and epidemiological studies are urgently required in this field. Better understanding of the pathogenesis and population specific cut offs of the various components of CMS is required before high quality randomised trials can be undertaken to address this important issue.

COMMENTS

Background

Metabolic syndrome (MS) in children and adolescents is defined to include central obesity, hyperglycemia, high blood pressure and dyslipidemia. Probiotics have shown to reduce adipose tissue, glucose and triglyceride levels in animal models, but evidence in children and adolescents is insufficient.

Research frontiers

Observational studies have shown that altered gut flora in infancy is associated with obesity in childhood. Altered gut flora has also been noted in children with type 1 diabetes. Whether modulation of gut flora in early infancy by probiotic supplementation would decrease the risk of childhood obesity and glucose intolerance is unclear.

Innovations and breakthroughs

Evidence from a clinical trial suggests that perinatal probiotic interventions may decrease the risk of gestational diabetes and central obesity. A prospective study of perinatal probiotic supplementation in early infancy has shown to reduce the risk of excessive weight gain in obese children. However, data on childhood metabolic outcomes is limited. Currently there is insufficient evidence to support the role of early probiotics in childhood MS (CMS).

Applications

To date, there is no systematic review on early interventions to prevent CMS. Given the magnitude of the problem, they analysed the potential role of probiotic exposure in early life for prevention of CMS or its components. The cause - effect relationship of altered gut flora vs CMS needs to be studied. High quality RCTs analysing all components of CMS are required.

Peer-review

Definitely this is an interesting topic and is properly argued by the authors. Unfortunately they could not present a meta-analysis because of the data available in the literature. However, it is important to publish this work to emphasize the urgent need for this kind of research.

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