

Research Media Watch:

Kamale V, Thamke R.

1. Infections during infancy – Rather than antibiotic use, as previously suspected – were associated with an increased risk of childhood obesity in *Lancet Diabetes Endocrinology* Published online November 1, 2016.

In this study, researchers reviewed 260,556 births that occurred between January 1, 1997, and March 31, 2013, at Kaiser Permanente facilities in Northern California. Kaiser Permanente's comprehensive electronic medical record, Kaiser Permanente HealthConnect®, allowed researchers to obtain data on infections and antibiotic use in infancy, and to capture heights and weights measured in these children for up to 18 years. All infant infections were included, with respiratory and ear infections accounting for the majority. The electronic medical record provided additional information that allowed Dr. Li's team to control for potential confounding factors, such as maternal smoking during pregnancy, pre-pregnancy body mass index, race/ethnicity and breastfeeding.

Children diagnosed with an infection during their first year of life who had no antibiotic use were about 25 percent more likely to become obese (defined as in the 95th percentile for body mass index of all children studied) compared to those without infections. There was a dose-response relationship, meaning that higher numbers of untreated infections were associated with a larger increased risk of obesity.

In contrast, there was no increased risk of obesity associated with antibiotic use during the first year when compared to infants with untreated infections. The type of antibiotics used (broad or narrow spectrum) did not influence the outcomes. Researchers recommend focusing efforts on

reducing infections in infancy while being careful in prescribing antibiotics.

"Antibiotics used to treat infant infections have been associated with weight gain. However, We separated the two factors and found that antibiotics do not, themselves, appear to be associated with childhood obesity," said De-Kun Li, MD, PhD, principal investigator of the study and a reproductive and perinatal epidemiologist at the Kaiser Permanente Division of Research in Oakland, California.

"Our study is one of the largest analyses of the interplay among infections, antibiotic use and childhood obesity, and adds important evidence to a small but growing body of research on how the microbiome, or gut bacteria, may be affecting children's development."

In India, more than one-fifth of children and adolescents are overweight or obese, according data available. Research has shown that energy imbalance (calories consumed versus energy expenditures) cannot account for the entire increase in obesity in childhood.

Scientists are studying numerous factors that may play a role in growth and development during early childhood, including chemicals in the environment, maternal gestational diabetes, and the metabolic programming of body weight during early childhood. Both infections and antibiotic use have been shown to influence the composition of

intestinal microorganisms; the intestinal microbiome can affect metabolic processes and the immune system, which can in turn affect metabolic processes, growth patterns and weight development.

Study Highlights

- Participants in this longitudinal birth cohort study from the Kaiser Permanente Northern California population were 260,556 infants born between January 1, 1997, and March 31, 2013.
- Antibiotic use, infection diagnosis from birth to age 1 year, and anthropometric measurements including BMI and obesity status from birth to age 18 years were determined from electronic medical records.
- Multiple BMI measurements per child (median 5 measurements) and ORs for obesity risk were assessed with standard mixed-effects logistic regression for repeated measurements.
- Compared with control infants without infection, infants with infection without antibiotic use had a 25% increased risk for childhood obesity (OR, 1.25; 95% CI, 1.20-1.29), after controlling for maternal age, race or ethnic origin, prepregnancy BMI, preterm delivery, low birth weight, maternal antibiotic use, and infection during pregnancy.
- There was a clear dose-response association between the number of infection episodes and the risk for childhood obesity (P for trend <.0001).
- Compared with infants with untreated infection, infants exposed to antibiotics did not have an increased risk for childhood obesity (OR, 1.01; 95% CI, 0.98-1.04), after controlling for underlying infection types and severity.
- Neither broad-spectrum nor narrow-spectrum antibiotic use was associated with an increased risk for childhood obesity.
- Findings were similar in a substudy of 547 same-sex twin pairs with discordant exposure status.
- On the basis of their findings, the investigators concluded that infection, not antibiotic use, during infancy was associated with an increased risk for childhood obesity, although further studies are needed for confirmation.
- They suggest that treatment of common infections with antibiotics during infancy is unlikely to be a significant contributor to childhood obesity.
- However, they note that the results do not exclude a potential effect of antibiotics on microbiome composition, and they recommend that antibiotic use always be judicious.
- These findings suggest that when used to treat infections, antibiotics do not contribute to childhood obesity, and that the benefits of treating infections are likely to outweigh the possible risk.
- To prevent childhood obesity, healthcare providers should target the infection rather than antibiotic use during infancy.
- Study limitations include lack of data on the level of compliance with prescribed antibiotics, reliance on International Classification of Diseases codes to identify infections, inability to distinguish viral from bacterial infections, and retrospective register study precluding causal inferences.
- An accompanying editorial points out an association between increased growth and antibiotic use in animals and suggests possible study limitations of selection bias or unmeasured confounding factors.

Clinical Implications

- Infection, not antibiotic use, during infancy was associated with an increased risk for childhood

obesity, based on a longitudinal birth cohort study.

- The investigators suggest that to prevent childhood obesity, healthcare providers should be targeting infection rather than antibiotic use during infancy.

Implications for the Healthcare Team:
Although the benefits of treating infections are likely to outweigh the possible risks, antibiotic use should always be judicious.

2. Efficacy and Safety of *Saccharomyces boulardii* in Acute Rotavirus Diarrhea: Double Blind Randomized Controlled Trial from a Developing Country

Susrut Das, Pradeep Kumar Gupta, Rashmi Ranjan Das *J Trop Pediatr* (2016) doi: 10.1093/tropej/fmw032 First published online: June 9, 2016

Objective:

To study the efficacy and safety of *Saccharomyces boulardii* (SB) in acute childhood rotavirus diarrhea. Methods: Children (3 months to 5 years) with WHO-defined acute watery diarrhea and stool rotavirus positive ($n = 60$) were randomized into intervention ($n = 30$) and control ($n = 30$) groups. The intervention group received SB (500 mg/day) for 5 days.

Results:

The median duration (hours) of diarrhea was significantly shorter in the intervention group (60 vs. 89; 95% CI: -41.2 to -16.8). A significantly shorter duration of hospitalization (74 vs. 91; 95% CI: -33.46 to -0.54) was also seen in the intervention group, but no significant difference was seen for fever and vomiting. There was also no difference between the two groups in the proportion of children requiring parenteral rehydration and persistence of diarrhea lasting beyond day 7. There was no report of any adverse events.

Conclusions:

The present trial showed that SB is effective and safe in acute rotavirus diarrhea.

Clinical implications-

Two RCTs using *S. boulardii* showed that this probiotic may be effective in treating acute adult diarrhea due to a variety of causes and can significantly lower diarrhea severity score compared with controls [Hochter et al. 1990; Mansour-Ghanaei et al. 2003]. Unfortunately, since the number of trials in this area is small and the etiologies were different in the two trials, only limited conclusions can be reached.

A recent RCT conducted in 100 hospitalized children showed that *S. boulardii* treatment for 5 days significantly reduces the mean duration of acute diarrhea and frequency of stools, and normalizes stool consistency [Htwe et al. 2008]. One RCT regarding the efficacy of *S. boulardii* for the prevention of acute diarrhea involved 100 children with acute watery diarrhea and reported a significant difference in the incidence of diarrheal episodes in the group receiving *S. boulardii* compared with the control group during 2 months follow up [Biloo et al. 2006].

A meta-analysis based on 5 RCTs (619 participants) [Biloo et al. 2006; Kurugol and Koturoglu, 2005; Villarruel et al. 2007] indicated that *S. boulardii* significantly reduces the duration

of acute childhood diarrhea and the risk of prolonged diarrhea compared with control [Szajewska et al. 2007]. A meta-analysis of seven RCTs (944 participants) showed a reduction in the duration of acute childhood diarrhea by approximately 1 day in those treated with *S. boulardii* compared with placebo [Szajewska and Skorka, 2009]. The absence of blinding as well as

other factors such as ambulatory care may explain why *S. boulardii* had no effect in a European RCT [Canani et al. 2007]. In summary, the findings from RCTs and guidelines from professional pediatric societies indicate that *S. boulardii* may be an effective adjunct therapy in managing acute gastroenteritis in children [Guarino et al. 2008].

3. Clinical Trial of Erythropoietin in Young Children With Cerebral Palsy

Kye Hee Cho, MD, Kyunghoon Min, MD, Seung Hoon Lee, MD, SunHee Lee, BN, SeongSoo A. An, PhD, MinYoung Kim, MD, PhD. *Journal of Child Neurology* First Published May 27, 2016

Abstract:

This study was conducted to assess the safety and efficacy of recombinant human erythropoietin in young children with cerebral palsy aged between 6 months and 3 years. All participants received subcutaneous recombinant human erythropoietin and 8 weeks of rehabilitation therapy. Adverse events, changes of vital signs, and hematologic tests were monitored up to 8 weeks postinjection. Functional measures of development at 4 and 8 weeks postinjection were compared with baseline values, and improvements were compared with those of an age-matched historical control group. Nine participants completed the trial from June 2012 to February 2015. No adverse events were related to recombinant human erythropoietin. Erythropoiesis was noted, although within normal range. Functional improvements were observed in all participants ($P < .05$) and increases in motor function were higher in recombinant human erythropoietin group than the control group. Accordingly, recombinant human erythropoietin administration was safe without any significant adverse events and improved the functional outcomes in young children with cerebral palsy.

Comments:

Medications that can lessen the tightness of muscles may be used to improve functional abilities, treat pain and manage complications related to spasticity or other cerebral palsy symptoms.

It's important to talk about drug treatment risks with your doctor and discuss whether medical treatment is appropriate for your child's needs. Medication selection depends on whether the problem affects only certain muscles (isolated) or the whole body (generalized). Drug treatments may include the following:

- Isolated spasticity. When spasticity is isolated to one muscle group, your doctor may recommend onabotulinumtoxinA (Botox) injections directly into the muscle, nerve or both. Botox injections may help to improve drooling. Your child will need injections about every three months.

Side effects may include pain, mild flu-like symptoms, bruising or severe weakness. Other more-serious side effects include difficulty breathing and swallowing.

- Generalized spasticity. If the whole body is affected, oral muscle relaxants may relax stiff, contracted muscles. These drugs include diazepam (Valium), dantrolene (Dantrium) and baclofen (Gablofen).

Diazepam carries some dependency risk, so it's not recommended for long-term use. Its side effects include drowsiness, weakness and drooling.

Dantrolene side effects include sleepiness, weakness, nausea and diarrhea.

Baclofen side effects include sleepiness, confusion and nausea. Note that baclofen may also be pumped directly into the spinal cord with a tube. The pump is surgically implanted under the skin of the abdomen.

Your child also may be prescribed medications to reduce drooling. Medications such as trihexyphenidyl, scopolamine or glycopyrrolate (Robinul, Robinul Forte) may be helpful, as can Botox injection into the salivary glands.

4. Effects of calcium supplementation on body weight: a meta-analysis

Ping Li, Chaonan Fan, Yuanyuan Lu, and Kemin Qi in *American Journal of Clinical Nutrition*, October 2016

Abstract

Background: Whether calcium supplementation can reduce body weight and prevent obesity remains unclear because of inconsistent reports.

Objective: We performed a meta-analysis to investigate the correlations between calcium supplementation and changes in body weight on the basis of age, sex, body mass index (BMI) of the subjects, and length of calcium intervention.

Design: PubMed, EMBASE, Web of Knowledge, and China National Knowledge Infrastructure databases were systematically searched to select relevant studies that were published from January 1994 to March 2016. Both randomized controlled trials and longitudinal studies of calcium supplementation were included, and random- or fixed-effects models in a software program were used for the data analysis.

Results:

Thirty-three studies involving a total of 4733 participants were included in this meta-analysis.

No significant differences in weight changes were shown between calcium intervention and control groups (mean: -0.01 kg; 95% CI $-0.02, 0.00$ kg; $P = 0.12$). However, negative correlations between calcium supplementation and weight changes were shown in children and adolescents (mean: -0.26 kg; 95% CI: $-0.41, -0.11$ kg; $P < 0.001$) and in adult men and either premenopausal or old (>60 y of age) women (mean: -0.91 kg; 95% CI: $-1.38, -0.44$ kg; $P < 0.001$) but not in postmenopausal women (mean: -0.14 kg; 95% CI: $-0.54, 0.26$ kg; $P = 0.50$). When BMI was considered, a negative correlation between calcium supplementation and weight changes was observed in subjects with normal BMI (mean: -0.53 kg; 95% CI: $-0.89, -0.16$ kg; $P = 0.005$) but not in overweight or obese subjects (mean: -0.35 kg; 95% CI: $-0.81, 0.11$ kg; $P = 0.14$). Compared with the control groups, no differences in weight changes were shown in the calcium-intervention groups when the lengths of calcium interventions were <6 mo (mean: -0.09 kg; 95% CI: $-0.45, 0.26$ kg; $P = 0.60$) or ≥ 6 mo (mean: -0.01 kg; 95% CI: $-0.02, 0.01$ kg; $P = 0.46$).

Conclusion:

Increasing calcium intake through calcium supplements can reduce body weight in subjects who have a normal BMI or in children and adolescents, adult men, or premenopausal women.

Risk of calcium supplements: Calcium supplements aren't for everyone. For instance, if you have a health condition that causes excess calcium in your bloodstream (hypercalcemia), you should avoid calcium supplements.

It's not definitive, but there may be a link between calcium supplements and heart disease. The evidence is mixed and more research is needed

before doctors know the effect calcium supplements may have on heart attack risk.

A similar controversy surrounds calcium and prostate cancer. Some studies have shown that high calcium intake from dairy products and supplements may increase risk, whereas another more recent study showed no increased risk of prostate cancer associated with total calcium, dietary calcium or supplemental calcium intakes.

Until more is known about these possible risks, it's important to be careful to avoid excessive amounts of calcium. As with any health issue, it's important to talk to your doctor to determine what's right for you.

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