What is the Relationship Between Antibiotic Exposure During the First Two Years of Life and Subsequent Childhood Obesity?

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Abstract

Childhood obesity is a growing pandemic with one-fifth of all children in the U.S. considered obese (Center for Disease Control and Prevention [CDC], 2018; Skinner, Ravanbakht, Skelton, Perrin, & Armstrong, 2018). This pandemic is cause for alarm because of the many medical and psychosocial complications of childhood obesity and the enormous burden on individual and public health (Daniels & Hassink, 2015; Locke et al., 2015; National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2012). Historically, known contributing factors have been genetics, diet, and exercise with the latter two being the focus of traditional interventions (CDC, 2018). Current research examines whether exposure to antibiotics during the early years of life is associated with increased risk for subsequent childhood obesity. Nola Pender's Heath Promotion Model is utilized to set a theoretical framework for this paper. A literature review of ten articles reveals that exposure to antibiotics in early childhood does increase risk for subsequent childhood obesity. The goal of this paper is to examine the relationship between antibiotic exposure during the first two years of life and subsequent childhood obesity and recommend the practice of judicious utility and prescribing of antibiotics in clinical practice.

Keywords: antibiotics, childhood, obesity

What is the Relationship Between Antibiotic Exposure During the First Two Years of Life and Subsequent Childhood Obesity?

As the prevalence of childhood obesity continues to increase in the U.S., it is crucial to explore and understand this conundrum to maximize the well-being of our children (Scott et al., 2016). Each facet makes our understanding of the causative factors of obesity more complete (Jess, 2014). While genetics, diet, and exercise are well-known and important elements of this complex problem, recent studies have focused on another element that may be contributing to the obesity pandemic, intestinal microbiota (CDC, 2018; NIDDK, 2012; Pandita et al., 2016). The growing awareness in the role of intestinal microbiota on metabolism poses new questions about mechanisms that alter this important microbial community in the gut. The purpose of this paper is to review the current literature about the relationship between antibiotic exposure during the early years of life and subsequent childhood obesity and then make an evidence-based recommendation on the judicious utility and prescribing of antibiotics in clinical practice.

Chapter 1

Background

Childhood obesity is a growing pandemic with one-fifth of all children in the U.S. considered obese (Center for Disease Control and Prevention [CDC], 2018; Fruh, 2017; Skinner, Ravanbakht, Skelton, Perrin, & Armstrong, 2018). Defined by a body mass index (BMI) equal to or greater than the 95th percentile for youth of the same age and sex, the prevalence of childhood obesity has more than tripled since the 1970’s (CDC, 2018; Fruh, 2017; National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2012). This pandemic is cause for alarm because of the many medical and psychosocial complications of childhood obesity and the enormous burden on individual and public health (CDC, 2018; Daniels &

Hassink, 2015; Locke et al., 2015, NIDDK, 2012). Many groups and experts consider this condition a public health priority, recognizing primary prevention as a critical part of a tenable solution (Daniels & Hassink, 2015; Fruh, 2017; Pandita et al., 2016).

Problem of obesity. The profuse medical and psychosocial complications of childhood obesity generate an enormous burden on individual and public health care and health care costs. Children with obesity are at increased risk of asthma, sleep apnea, bone and joint problems, type 2 diabetes, and cardiovascular disease (CVD) (CDC, 2018; Fruh, 2017; Pandita et al., 2016; Umer et al., 2017). Umer et al. (2017) note that 70% of obese children and adolescents between the ages of five and seventeen have at least one risk factor for CVD. These children are bullied and teased more than their normal weight peers and are more likely to suffer from social isolation, depression, anxiety, and low self-esteem (CDC, 2018; Fruh, 2017). Data shows that these children miss more school days compared to students of normal weight, potentially impacting their academic progress (CDC, 2018; Pandita et al., 2016).

Evidence suggests that children with obesity have as high as an 80 percent chance of having obesity as an adult, putting them at increased risk for CVD, type 2 diabetes, metabolic syndrome, and several types of cancer (CDC, 2018; Pandita et al., 2016; Scott et al., 2016; Umer et al., 2017). Umer et al. (2017) report that childhood obesity is significantly and positively associated with adult blood pressure and triglycerides, and negatively associated with HDL. This is of grave concern considering that CVD is the leading cause of global mortality and is projected to be responsible for 23.6 million deaths in 2020 (Fruh, 2017; Umer et al., 2017).

Intestinal microbiota. Many factors contribute to childhood obesity including genetics, metabolism, diet, physical activity, community design, sleep, and social and individual psychology (CDC, 2018; NIDDK, 2012; Pandita et al., 2016). As stores are increasingly stocked with processed and sugary foods and as physical activity becomes less accessible and enticing to many children, the growing rate of childhood obesity is not surprising. Recent scientific research has linked yet another factor contributing to obesity, intestinal microbiota (Cho et al., 2012; Finlay & Arrieta, 2016; Kalliomaki, Collado, Salminen, and Isolauri, 2008; Moreno-Indias, Cardona, Tinahones, & Queipo-Ortuno, 2014). Kalliomaki et al. (2008) report that intestinal microbiota enables hydrolysis of indigestible polysaccharides into easily absorbable monosaccharides, which are then used as energy and transported to the liver, where they are transformed into stored energy. Altering the microbiota in humans during a key maturational period is linked to the development of chronic metabolic conditions, such as obesity (Cho et al., 2012; Finlay & Arrieta, 2016; Kalliomaki et al., 2008; Moreno-Indias, Cardona, Tinahones, & Queipo-Ortuno, 2014).

The vital role of gut bacteria discovery has led scientists to call our intestinal microbiota a new organ, possibly the last human organ to be discovered by modern medicine (Finlay & Arrieta, 2016; Moreno-Indias et al., 2014). The importance of this new organ and its vulnerability, particularly early in life, warrants investigation to identify environmental factors, such as antibiotics, that are disturbing the microbial communities within us (Finlay & Arrieta, 2016). Researchers postulate that antibiotics are selecting for microbiota capable of increased metabolic activity that are more efficient at harnessing calories from food, thereby suggesting antibiotic exposure early in life disrupts the microbiota and is associated with increased risk of childhood obesity. (Bailey et al., 2014; Cho et al., 2012; Finlay & Arrieta, 2016).

Antibiotics. Antibiotics include narrow and broad-spectrum drugs that kill or inhibit the growth of bacteria (Finlay & Arrieta, 2016). Discovered in the early 1900's and becoming available to the public in 1945, antibiotics have had one of the greatest effects on improving health and longevity of any medical invention in the 20th century (Cho et al., 2012; Finlay & Arrieta, 2016; Mbakwa et al., 2016; Trasande et al., 2013). Before antibiotics, 90% of kids with bacterial pneumonia or bacterial meningitis would die, children with strep throat were put on bedrest to avoid complications of rheumatic fever, and parents of infants feared that a simple ear infection could spread to the brain (Finlay & Arrieta, 2016). Nowadays, over 150 million antibiotic prescriptions are written in the U.S. every year (CDC, 2016; Finlay & Arrieta, 2016). A study published in the Journal of the American Medical Association reported that at least 30% of antibiotics prescribed in the U.S. are not necessary (CDC, 2016). Currently, reducing the rate of inappropriate antibiotic use and prescriptions is a major initiative being led by U.S. government agencies to combat the growing problem of antibiotic-resistant bacteria (CDC, 2016; Mbakwa et al. 2016; Trasande et al., 2013).

Cho et al. (2012) note the well-known utilization of sub-therapeutic doses of antibiotics to farm animals within the agricultural industry to promote growth and weight gain by as much as 15% (Mbakwa et al., 2016; Scott et al., 2016). This practice encompasses the largest volume of usage of antibiotics in the United States and its effects are broad across vertebrate species (Cho et al., 2012; Finlay & Arrieta, 2016). Furthermore, the observed weight gain in animals subsequent to the oral administration of antibiotics is reportedly a result of altering the intestinal microbiota, changing the intra-community metabolic interactions, modifying caloric intake by enabling the usage of otherwise indigestible carbohydrates, and affecting host metabolic, hormonal and immune homeostasis (Cho et al., 2012; Kalliomaki et al., 2008; Moreno-Indias et al., 2014). The insights provided from modern agricultural practices have sparked recent research that seeks to investigate the association between antibiotic exposure in early childhood and later childhood obesity (Cho et al. 2012; Jess, 2014; Kalliomaki et al., 2008).

Theoretical framework. Pender's Health Promotion Model, created by Nola J. Pender, is a middle range integrative theory that guides a clinician's approach to promote healthy behaviors with the goal being optimal health (Butts & Rich, 2015). Pender's model views the multidimensional person interacting with their interpersonal and physical environment (Butts & Rich, 2015). This view fits well when confronting obesity because obesity is a multifactorial issue influenced by an array of personal and environmental factors (CDC, 2018; Skinner et al., 2018). It's critical to approach health promotion from a holistic perspective to confront each contributing factor of the targeted health concern. Each of the articles reviewed attempted to consider the many confounding factors related to obesity.

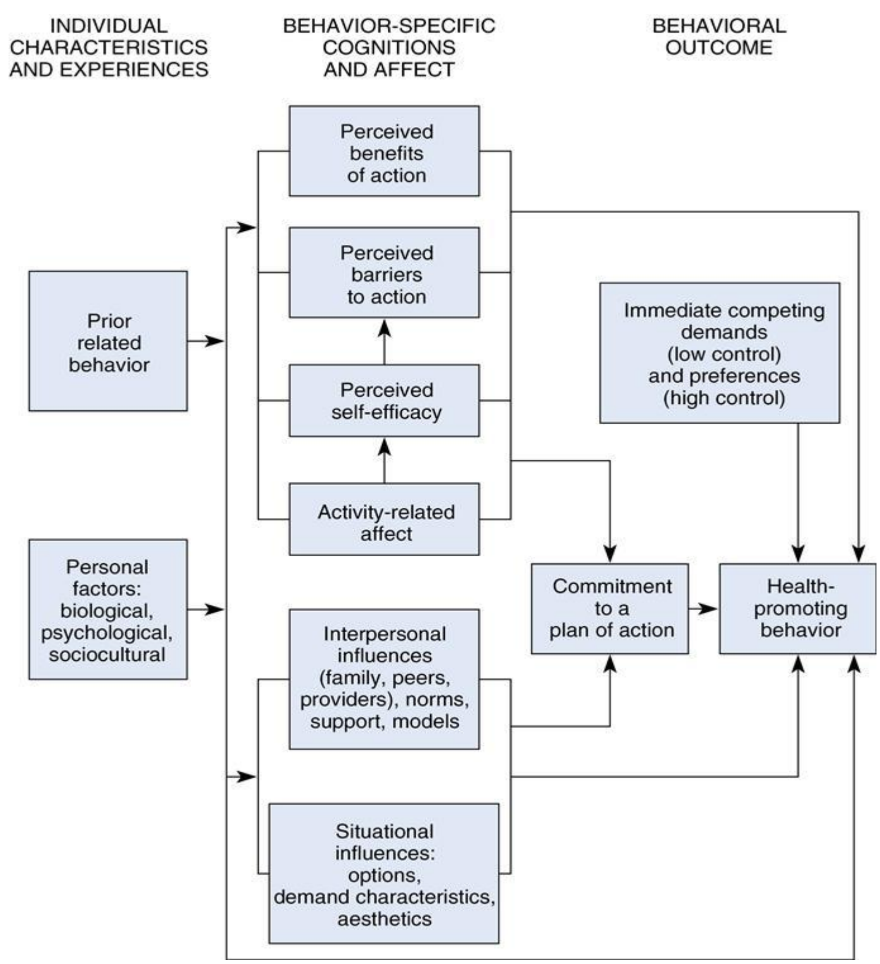

Figure 1. Pender's Health Promotion Model (Sakraida, 2017).

Chapter 2

Methods

An online literature search was completed using *PubMed@HPU* and *CINAHL* via the Hawaii Pacific University's online library with the MeSH and key terms "obesity," "childhood," "antibiotic," and "weight." The search limits included articles published within the last seven years, human subjects, and English language. PubMed returned 49 articles and CINAHL 16 articles. Many articles were duplicates among these search engines. Research articles of all levels of evidence that investigated the relationship between antibiotic exposure in early childhood and subsequent BMI were sought. Articles that focused on prenatal antibiotic exposure were excluded. Ten articles were eventually selected, reviewed, and discussed in this paper.

Chapter 3

Literature review

Ten studies have been reviewed and reveal that exposure to antibiotics in early childhood is associated with subsequent childhood obesity. Nine of these studies are level IV cohort studies and one is a level I meta-analysis. The meta-analysis, completed by Rasmussen et al. (2018), reviewed thirteen observational studies, investigating the exposure of antibiotics during the first two years of life and the risk of overweight and obesity in childhood. Rasmussen et al. (2018) concluded that two or more antibiotic exposures during the first six months of life significantly increase the risk of childhood overweight and obesity, exposure to only one antibiotic treatment and exposure after six months of life were not, and exposure to broad-spectrum antibiotics and macrolides increased the strength of association. The general outcome of this meta-analysis underscores three common themes among all the literature currently under review: 1) There is a dose-response relationship between number of antibiotic exposures and increased risk of obesity, 2) Exposure to broad-spectrum antibiotics and macrolides increased the strength of association, while narrow-spectrum antibiotics and penicillin showed much weaker associations, and 3) There is a linear trend with earlier age of exposure and associated risk of childhood obesity (Rasmussen et al., 2018).

Poulsen et al. (2017) report that among the 8,793 children studied in a retrospective cohort study in Pennsylvania, children with more than one antibiotic order in the first year of life had significantly higher BMI z-scores at age three compared to children with no orders. Poulsen et al. (2017) also found the most robust association was with macrolides, which was 35% more than cephalosporins and 77% more than penicillins.

These same themes are supported by Saari, Virta, Sankilampi, Dunkel, & Saxen (2015) who conducted a population-based cohort study of 12,062 children. Saari et al. (2015) report that increased number of antibiotic exposures and the earlier in life antibiotic exposures occurred, the more significant the association between exposure and BMI z-score at two years old. Macrolides, again, stood out as the greatest offender with an odds ratio of 1.65 (95% CI 1.09 to 2.31) for boys exposed during the first six months in life (Saari et al., 2015).

A large study conducted by Scott et al. (2016) of 21,714 children observed antibiotic exposure in the first 24 months of life and BMI at four years of age. Scott et al. (2016) concluded that the risk of obesity increased with increasing number of courses of antibiotics and earlier exposure. For those children exposed to 3-5 courses of antibiotics the odds ratio for obesity at four years old was 1.41 (95% CI 1.20 to 1.65) and for those exposed to 6 or more courses, odd ratio was 1.47 (95% CI 1.19 to 1.82) (Scott et al., 2016).

A prospective cohort study conducted in Philidelphia of 65,480 children was the largest sample size among the literature reviewed (Bailey et al., 2014). Bailey et al. (2014) observed a positive association with antibiotic use with four or more doses and with earlier exposure when evaluating broad-spectrum antibiotics. This association was not present with narrow-spectrum antibiotics, including amoxicillin and penicillin (Bailey et al., 2014).

Despite the general consistency of the results of all the studies reviewed, one relatively small study of 979 children conducted by Mbakwa et al. (2016) report that the positive association between two or more courses of antibiotics and childhood weight z-scores included not only broad-spectrum antibiotics such as macrolides, but also beta lactams such as amoxicillin and cephalosporins. The latter findings are inconsistent with the results of other studies under review. The reliability of this particular study is questionable due to the small convenience sample and poor reliability of the data collection instruments. While the majority of the literature reviewed utilized electronic health records to obtain antibiotic exposure data and anthropometric data, this study utilized questionnaires completed by the providers for antibiotic exposure and questionnaires completed by the parents for anthropometric data (Mbakwa et al., 2016). The lack of reliability and validity of these data collection tools may explain the inconsistency of offending antibiotic types.

Among the ten studies reviewed, BMI was measured at various endpoints ranging from age two through age twelve. Positive associations are reported throughout all the studies, revealing that the association between antibiotic exposure and subsequent childhood obesity remained fairly consistent through late childhood. However, one study by Trasande et al. (2013) of 11,532 children examined the association of antibiotic exposure and subsequent BMI over seven years. Transande et al. (2013) report a significant association at 38 months of age but not at seven years of age. This study hints at a lack of persistence in the risk of obesity through adolescence and into adulthood and highlights a gap in the current research.

While there are numerous studies observing the relationship between antibiotic exposure in early childhood and subsequent childhood obesity, there are no long-term studies that investigate whether this observed association persists into adolescence and adulthood. While the medical and psychosocial challenges of childhood obesity are inarguable and evidence suggests that children with obesity have a high likelihood of having obesity as an adult, there is still a need for future research studies to investigate the long-term association of early childhood antibiotic exposure and subsequent adulthood obesity (CDC, 2018; Pandita et al., 2016; Scott et al., 2016; Umer et al., 2017).

In reviewing the existing literature, several strengths and weakness are noted. Samples range from low to high in potential for bias. For example, a study conducted by Ville, Heyman, Medrano, & Wojcicki (2017), consists of a cohort convenience sample of 97 Latino children in which generalizability is very low and bias is highly likely. On the contrary, a study conducted by Saari et al. (2015) studied a population-based sample of 12,062 children of Espoo, Finland, in which generalizability is still fairly low due to the lack of ethnic diversity but likelihood of bias is low. Data gathering tools also exhibited fluctuations of reliability and validity. Antibiotic exposure data and anthropometric data were gathered via electronic health records, provider questionnaires, and parental questionnaires, with the latter two tools lacking reliability and validity. When questionnaires are utilized for antibiotic exposure, reliability is low due to potential error in human recall. When questionnaires are utilized to gather anthropometric data, reliability and validity are low due to parents' lack of training in accurate measurement as well as questionable reliability of equipment used to inform height and weight.

By identifying these strength and weaknesses, future research should maximize reliability and validity by using electronic health records for data collection. In addition, future research should strive for larger population-based samples that may increase generalizability and decrease bias. Lastly, future research should consider longitudinal studies that investigate whether the association of early childhood antibiotic exposure and obesity persists into adulthood.

Chapter 4

Conclusion

Despite intense clinical and public health focus on obesity in the U.S., obesity prevalence remains high with minimal evidence that current efforts are counteracting the complex personal and environmental forces that contribute to excess weight gain in children (Skinner et al., 2018). Since children with obesity have as high as an 80 percent chance of having obesity as an adult, the increased risk for CVD, type 2 diabetes, metabolic syndrome, bone and joint problems, psychosocial problems, and certain cancers are sustained from childhood through adulthood (CDC, 2018; Umer et al., 2017).

With the crusade against childhood obesity still in its infancy, exploring and understanding the complex mechanisms contributing to our growing obesity problem may offer a new resort in the fight against it (Kalliomaki et al., 2008). Pender's Health Promotion Model supports this multidimensional approach and underscores that optimal health is attained by addressing each contributing factor. Research is now providing evidence that altering the human microbiome by ingesting antibiotics during early childhood is linked to the development of obesity. The overall quality of evidence is very good, with most studies having good reliability and validity. The consensus of the evidence indicates that the relationship between antibiotic exposure in early childhood and subsequent obesity is strongest with repeated exposures, earlier age of exposure, and exposure to broad-spectrum antibiotics and macrolides.

This evidence strongly supports the recommendation that clinicians practice judicious prescribing of antibiotics to cases where efficacy is well demonstrated and highlights the need for improved antibiotic stewardship programs (Azad et al., 2014; Bailey et al., 2014; Saari et al., 2015). The significance of the effects of antibiotics in the development of obesity should be weighed against the beneficial effects of clinically indicated treatment (Jess, 2014; Scott et al., 2016). Clinicians should not restrain antibiotic prescriptions to children when clinically indicated, however the evidence supports careful consideration (Rasmussen et al., 2018). Furthermore, this evidence presents a unique opportunity to address a potentially modifiable risk factor for childhood obesity, providing more ammunition to confront this formidable challenge.

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Appendix

Literature Matrix

Authors, date, title of study, journal name	Level of Evidence	Article question or purpose	Design	Sample	Data collection instruments	Results/Findings	Limitations	Applicability
Ajslev, T.A., Andersen, C.S., Gamborg, M., Sorensen, T.I.A, & Jess, T. (2011). Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. *International Journal of Obesity*	Level IV	Investigated whether delivery mode, maternal pre-pregnancy BMI, and antibiotic exposure during the first six months of life influences a child's risk of becoming overweight at seven years of age.	Longitudinal, prospective cohort study	28,354 mother-child dyads. Convenience sample populated from 40,640 mother-child dyads who participated in the Danish National Birth Cohort (established in 1997 to 2002; included 30% of the Danish pregnant population) Inclusion: term, singleton babies whose mothers agreed. Exclusion: mothers with diabetes or preeclampsia, children with missing or unrealistic height or weight measurements.	Anthropometric data gathered via parental questionnaire by internet or paper format (measurements done by parents or parents utilized measurements taken during primary care visits). Antibiotic exposure data was gathered by telephone interview of mothers during pregnancy and when children were six months old	Exposure to antibiotics during the first six months of life did increase the risk of childhood obesity in children of normal-weight mothers (adjusted odds ratio 1.54, 95% confidence interval 1.09-2.17). In contrast, a protective effect was observed for infants exposed to antibiotics during the first six months of life of overweight mothers compared with children unexposed to antibiotics of overweight mothers.	Many dyads were lost to follow-up, consequently leaving questions for selection bias. Questionable reliability of the parents' measuring and recall.	Reinforces that the risk of childhood obesity is strongly associated with maternal pre-pregnancy BMI and exposure to antibiotics during early childhood could modify the microbial diversity in a positive or negative direction, modifying the subsequent risk of childhood obesity.
Azad, M.B., Bridgman, S.L., Becker, A.B., & Kozyrskyj, A.L. (2014). Infant antibiotic exposure and the development of childhood overweight and central adiposity. *International Journal of Obesity*	Level IV	Investigate the association between early-life antibiotic exposure and subsequent risk of becoming overweight and developing central adiposity.	Nested case-control linked to birth cohort data (secondary analysis of a 1995 longitudinal birth cohort case-control study)	616 children with available prescription records and anthropometric data from a convenience sample created by mailing a 1-page survey to all households in Manitoba, Canada of children born in 1995 who were still living in the province at 7 years old. 3598 returned surveys; nested case-control sample was populated to include 723 children whose parents agreed to participate.	Provincial health-care database prescription records. Anthropometric data was collected in a clinical setting. Standardized survey completed by parents and children to develop covariates.	At age 9, 32.9% of exposed children had become overweight, compared with 20.8% of unexposed children (P=0.003). At age 12, 32.4% of exposed children had become overweight, compared to 18.2% of unexposed children (P=0.01). Upon stratification for gender, results were significant among boys revealing a five-fold increased risk of becoming overweight for boys exposed to antibiotics during their first year of life, compared with unexposed boys, but there was no association for girls	Convenience sample at risk for bias, due to subject's parents volunteering via a survey and a reported 30% mortality rate. Relatively small sample size	Provides evidence for a relationship between antibiotics exposure during first year of life and consequential obesity, especially among boys.

Appendix

Literature Matrix

Bailey, L.C., Forrest, C.B., Zhang, P., Richards, T.M., Livshits, A., & DeRusso, P.A. (2014). Association of antibiotics in infancy with early childhood obesity. *Journal of American Medical Association Pediatrics*	Level IV	Assess the impact of antibiotics prescribed in infancy on obesity in early childhood.	Longitudinal, prospective cohort study	65,480 children Convenience sample spanning a network of primary care practices affiliated with the Children's Hospital of Philadelphia from 2001 to 2013 Inclusion: children with at least one primary care visit at zero to 11 months and 12 to 24 months of age as well as at least one additional visit between 24 and 59 months Exclusion: prematurity or low birth weight at any time during the first year of life	Electronic Health Records (EHRs) Outpatient prescriptions and patient-reported medications recorded at all primary care visits; potential threats to reliability due to parents' recall accuracy	Increased risk of obesity with antibiotic use with four or more doses and with earlier exposure when evaluating broad-spectrum antibiotics. This association was not observed with narrow-spectrum antibiotics	Convenience sample may be bias. Reliability questionable due to accuracy of parent's recall and the inability to capture medications prescribed at out-of-network visits.	Shows that narrow-spectrum vs broad-spectrum antibiotic selection is potentially a modifiable risk factor for childhood obesity.
Mbakwa, C.A., Scheres, L., Penders, J., Mommers, M., Thijs, C., & Arts, I.C. (2016). Early life antibiotic exposure and weight development in children. *The Journal of Pediatrics*	Level IV	Evaluate the impact of antibiotic exposure from birth until 10 years of age on height and weight of Dutch children, focusing on timing, type, and frequency of antibiotic exposure.	Longitudinal, prospective cohort study	979 children Convenience sample from children of mothers originally recruited for the KOALA Birth Cohort study in the Netherlands Inclusion: Children whose GP provided information on medication prescribed. Exclusion: children born <37 weeks gestation, twins, with congenital abnormalities, and without detailed information on antibiotic use	Questionnaires filled out by GP for antibiotic information Questionnaire filled out by parents for anthropometric data; threat to reliability due to parent's lack of training, inconsistent measuring tools, and potential to falsify data EHR for obstetric data	Exposure to a single course of antibiotics in the first 6 months of life had higher weight and height z-scores. Exposure to 2 or more courses of broad-spectrum beta lactam antibiotics was significantly associated with higher weight z-scores but was not the case if exposure was only a single course.	Convenience sample may be bias and sample size is small. Sample consists of 100% Caucasian children so data is not generalizable to other ethnic groups. Reliability questionable due potential threats related to parent's measurement accuracy and tool reliability (scales, measuring tapes).	Supports previous evidence that repeated childhood exposure to antibiotics, especially broad-spectrum beta lactam agents, increases the risk of subsequent increased weight gain in children.
Poulsen, M.N., Pollack, J., Baily-Davis, L., Hirsch, A.G., Glass, T.A., Schwartz, B.S. (2017). Associations of prenatal and childhood	Level IV	Determine whether prenatal and childhood antibiotic use are independently associated with BMI at	Retrospective cohort study	8793 mothers and singleton children delivered at Geisinger Clinic in Pennsylvania,	EHR for antibiotic orders/exposure and BMI at 3 years old	Prenatal antibiotic exposure revealed no association with BMI z-scores. Children with 2 or more antibiotic orders in the first year of life had significantly	Convenience sample potentially bias and represents the general population	Provides evidence that there is a strong association between cumulative

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antibiotic use with child body mass index at age three years. *Obesity*		age 3 years; also compared age of usage, class of antibiotics, and administration route.		USA, between 2006 – 2012. Inclusion: child had an age 3 BMI measurement documented in EHR Exclusion: children with serious birth defects, birth weight < 500 grams, gestational age < 22 weeks, mother <18 years old or with missing data on pre-gravid BMI		higher BMI z-scores at age 3 compared to children with no orders. There was a significant trend of increasing BMIz with increasing use. The most robust association was for macrolides, which was 35% more than cephalosporins and 77% more than penicillins.	in central and northeastern Pennsylvania, vast majority being Caucasian, limiting generalizability. Lacked information on whether the patients took antibiotics as ordered.	lifetime antibiotic orders and increased child BMI. Reinforces the judicious use of antibiotics to include: avoiding broad-spectrum when feasible, limiting repeated exposures, and eliminating antibiotic use in cases that lack efficacy.
Rasmussen, S.H., Shrestha, S., Bjerregaard, L.G., Angquist, L.H., Baker, J.L., Jess, T., & Allin, K.H. (2018). Antibiotic exposure in early life and childhood overweight and obesity: A systematic review and meta-analysis. *Diabetes, Obesity, & Metabolism*	Level I	Conduct a systematic review, quality assessment, and meta-analysis of observational studies examining the association between antibiotics exposure during the first 2 years of life and the risk of overweight and obesity in childhood.	Systematic review & Meta-analysis	13 observational studies for the qualitative synthesis, 8 of which were eligible for quantitative synthesis, published between 2011 and 2017. 12 were cohort studies and 1 was a nested case-control study. 527,504 children in total. Inclusion: studies that investigated children who were exposed to antibiotics before 24 months of age and had their body weight and height measured after 24 months old until 12 years old. Exclusion: studies of children with chronic disease or malnutrition, animal studies, reviews and meta-analyses. For quantitative meta-analysis, studies considered high risk for bias or had	A systematic literature search with no language restrictions from inception until mid-March 2017 in Pubmed, Embase, Cochrane Library, and SCOPUS. Titles were independently screened by two authors; any disagreement regarding eligibility was resolved by consensus among all authors. Risk of bias was assessed using Risk of Bias Assessment tool for Nonrandomized Studies and the Newcastle-Ottawa Scale.	Exposure to antibiotics in infancy was associated with an increased odds ratio of childhood overweight and obesity (OR 1.11, 95% CI 1.02-1.20). Exposure to one treatment only and exposure between 6 and 24 months were not associated with increased risk. However, > 1 exposure OR = 1.24 (CI 1.09 - 1.43) and exposure within first 6 months OR = 1.20 (CI 1.04 – 1.37), indicating a significant association. Overall, exposure to broad-spectrum antibiotics and macrolides increased the strength of association between antibiotic exposure and childhood overweight and obesity, whereas exposure to narrow-spectrum antibiotics and penicillin showed weaker associations.	Definition of overweight/ obesity and time point for outcome measurement varied across studies. Several studies adjusted for confounders inadequately.	Findings suggests that prescription of multiple antibiotic treatments within the first 6 months of life should be carefully considered. But providers should not restrain from prescribing antibiotics to infants when clinically necessary.

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				incomplete data were excluded.				
Saari, A., Virta, L.J., Sankilampi, U., Dunkel, L., & Saxen, H. (2015). Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. *Pediatrics*	Level IV	Evaluate the impact of antibiotic exposure during infancy on height and weight of healthy Finnish children. Also assessed were potential differences in antibiotic types and the impact of early versus late, as well as single versus multiple exposures.	Population-based, prospective cohort study	6114 boys and 5948 girls population-based study Inclusion: all children born between January 1, 2003 and April 30, 2007, who attended child welfare clinics in the city of Espoo, Finland who had more than one primary care visit after age 24 months old. 94.4% Finnish in origin Exclusion: subjects with congenital syndromes, preterm birth before 37 weeks gestation, lack of birth data, diagnosed postnatal growth disorders, and regular medication ingestion possibly affecting growth	EHRs and Drug Prescription Register. Control for internal validity: used scatter plots and either corrected or excluded the erroneous data	Boys who received antibiotics during the first 24 months of life were on average heavier and slightly taller when measured at 2 years old than boys who were unexposed to antibiotics. The younger the boy at first antibiotic exposure, the greater the adjusted difference between zBMI scores at age 2 years old. Girls, overall, a similar tendency was seen but the only significant differences were in girls who had been exposed to antibiotics at 12 to 17 months old. There was a linear trend in the number of antibiotic exposures and zBMI scores. The adjusted OR of being overweight at 2 years of age was 1.34 (95% CI 1.06 to 1.66) in boys and 1.16 (0.87 to 1.56) in girls when the first antibiotic exposure occurred before 6 months of age. The adjusted OR for boys who were exposed to macrolides younger than 6 months old was 1.65 (95% CI 1.09 to 2.31)	Poor generalizability to other populations/ races.	Highlights the importance of judicious use of antibiotics during infancy, favoring narrow-spectrum antibiotics and avoiding repeated exposure when possible.
Scott, F.I., Horton, D.B., Mamtani, R., Haynes, K., Goldberg, D.S., Lee, D. Y., & Lewis, J.D. (2016). Administration of antibiotics to children before age 2 years increases risk for childhood obesity. *Gastroenterology*	Level IV	Assess the association between antibiotic exposure before age 2 years and obesity at age 4 years and whether repeated exposures and broader anaerobic antibiotics have a greater association.	Retrospective population-based cohort study.	21,714 children Population-based Derived from 533,238 children within The Health Improvement Network (THIN: population-representative dataset from 1995 to 2013 in the United Kingdom). Inclusion: registered with a THIN practice within 3 months of birth who had	EHRs of data that was collected prospectively in the scope of routine care by general practitioners. Data has been validated in the past for various medical diagnoses.	The risk of obesity increased with increasing number of courses of antibiotics and with earlier exposure to antibiotics. For those exposed to 3-5 courses of antibiotics, adjusted odds ratio for obesity at 4 years = 1.41 (95% CI 1.20 to 1.65); more than 5 courses, adjusted odds ratio = 1.47 (95% CI 1.19 to 1.82).	Cannot generalize to children with asthma or reactive airway disease since this population was excluded. Did not adjust for the confounders: breastfeeding, physical activity, and sleep. THIN represents 6% of UK population but no mention of	Demonstrated that exposure to antibiotics in the first 2 years of life is associated with an approximately 25% relative increase risk in childhood obesity, underscoring the importance of avoiding antibiotics in the absence of well-

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				complete follow-up to 48 months and had height and weight recorded within 12 months of 4th birthday. Exclusion: Children born before practice's use of EHR and those with diagnostic codes for asthma or reactive airway disease.			ethnic demographics therefore limiting generalizability to other populations with different ethnic diversities.	established indications.
Trasande, L., Blustein, J., Liu, M., Corwin, E., Cox, L.M., & Blaser, M.J. (2013). Infant antibiotic exposures and early-life body mass. *International Journal of Obesity*	Level IV	Examine the association of antibiotic exposures during the first 24 months of life and the development of body mass over the first seven years of life.	Secondary analysis of a longitudinal, prospective birth cohort study.	11,532 children Population-based 85% of all pregnant woman residing in Avon, UK with expected delivery dates from April 1, 1991 to December 31, 1992 were recruited Exclusion: birth weight less than 2500 grams and subjects who had missing information regarding antibiotic exposure.	3 postal parent questionnaires elicited at 6 months, 15 months, and 24 months of age asking parents whether antibiotics were given to the child in the prior 6 months. Anthropometric measures obtained from medical records.	Antibiotic exposure at less than six months of age was consistently associated with increased BMI at 38 months of age but not at seven years of age. Upon stratification by maternal BMI, at 38 months, children of normal weight mothers exposed to antibiotics at less than six months of age was associated with a 29.4% increase risk of becoming overweight (P=0.032), with no increased risk for children of overweight or obese mothers.	Population-based sample may be bias as the article reports that the study population was slightly more affluent than the general UK population, limiting generalizability. Questionable reliability related to parental recall.	Reinforces concerns that early antibiotic exposure may cause increase in body mass, pointing to the period from birth to 6 months as a critical window of vulnerability.
Ville, A.P., Heyman, M.B., Medrano, R., & Wojcicki, J.M. (2017). Early antibiotic exposure and risk of childhood obesity in Latinos. *Childhood Obesity*	Level IV	To test the hypothesis that antibiotic exposure in the first year of life leads to development of obesity by 2 years old.	Prospective, longitudinal cohort study.	97 children given birth to by self-identified Latina women who were recruited before delivery at the prenatal clinics at San Francisco General Hospital in 2012 and 2013. Sample described as high-risk, low-income, urban Latino. Besides self-identification as Latino, no inclusion or exclusion criteria mentioned.	Type and frequency of dietary intake and antibiotics collected via questionnaires of maternal self-report. Birth mode via medical record. Anthropo-metrics collected by digital scales and measuring boards.	Antibiotic exposure during the first 6 months of life independently predicted obesity at 2 years of age, adjusting for maternal BMI, weight for length z score at birth, breastfeeding, rapid infant weight gain, and infant sex, odds ratio = 6.15 (95% CI 1.03-36.70). There was no correlation of obesity at 2 years old with infant sex, delivery mode, feeding variables, dietary intake, maternal age, pre-pregnancy maternal BMI, or exposure to maternal smoking.	Small sample limited to low-income, urban, Latino population; cannot be generalized. Reliability questionable due to maternal recall accuracy. No mention of who collected anthropometric data or standardized training to control for interrater reliability.	Supports recent calls for continued improvement in antibiotic stewardship interventions for appropriate antibiotic exposure, especially during the first 6 months.