Antibiotic Exposure in Infancy Can Be a factor of Increased Risk of Childhood Obesity

Kelly Johnson
*Pacific University*

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Abstract

Background: Childhood obesity is a rising epidemic worldwide. As risk factors are identified, clinicians can help prevent the rising epidemic by educating patients and family members. This review looks at the exposure of antibiotics in infancy as a potential risk factor for childhood obesity.

Methods: Exhaustive search of available medical literature was conducted in MEDLINE-Ovid, CINAHL, and Web of Science. Keywords used included antibiotic exposure, antibiotic, or antibacterial agents and infant and obesity.

Results: Forty-three articles were reviewed for relevancy, four studies were found to be relevant. Only three studies were analyzed in this systematic review, one study was excluded due to outcomes being measured less than seven years of age. All three studies showed increased risk of children being overweight after exposure to antibiotics in infancy. Two studies did further analysis on risk of childhood weight concerns in boys compared to girls. These two studies showed boys had an increased risk of childhood overweight compared to girls. The overall quality of the studies was low and further studies need to be completed looking at larger and more diverse populations with longer follow up periods.

Conclusion: Knowing that early exposure to antibiotics during infancy could be a risk factor for childhood weight concerns, including obesity, clinicians can use this information as another consideration in decreasing the amount of prescribed antibiotics in infancy and to educate parents and patients on prevention of childhood obesity.

Keywords: Antibiotic exposure, antibiotic, antibacterial agents, infant, obesity

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First Advisor
Saje Davis-Risen, PA-C, MS

Second Advisor
Annjanette Sommers, PA-C, MS

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The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Antibiotic Exposure in Infancy Can Be a factor of Increased Risk of Childhood Obesity

Kelly N. Johnson

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies

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Faculty Advisor: Saje Davis-Risen, PA-C, MS

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Kelly Johnson is a native of Colorado, where she attended the University of Denver and majored in Biologic Science with a minor in Chemistry and Psychology. After completion of her undergraduate degree, she worked for the Barbara Davis Center for Childhood Diabetes for six years before attending the Physician Assistant program at Pacific University. She enjoys spending time skiing, rafting, and playing with her chocolate lab Max. Upon finishing PA school, she hopes to return to Colorado to be a practicing PA.
Abstract

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Acknowledgements

[Redacted for privacy]
# Table of Contents

Biography............................................................................................................................. 2  
Abstract .................................................................................................................................. 3  
Acknowledgements .................................................................................................................. 4  
Table of Contents ................................................................................................................... 5  
List of Tables .......................................................................................................................... 6  
List of Figures ......................................................................................................................... 6  
List of Abbreviations ............................................................................................................. 6  
BACKGROUND ....................................................................................................................... 7  
METHODS ............................................................................................................................... 9  
RESULTS .................................................................................................................................. 9  
DISCUSSION ........................................................................................................................... 14  
CONCLUSION ......................................................................................................................... 16  
REFERENCES ........................................................................................................................ 17  
Table 1: Characteristics of Reviewed Studies ........................................................................ 19  
Table 2-3: Summary of Findings .......................................................................................... 19  
Figure 1: Summary of Findings ............................................................................................ 20
List of Tables

Table 1: Characteristics of Reviewed Studies
Table 2: Azed et al\textsuperscript{11,14}
Table 3: Ajslev et al\textsuperscript{12,15}

List of Figures

Figure 1: Trasande et al\textsuperscript{10,13}

List of Abbreviations

BMI .................................................................................................................. Body Mass Index
CI ................................................................................................................. Confidence Interval
DNBC ........................................................................................................... Danish National Birth Cohort
Antibiotic Exposure in Infancy Can Be a factor of Increased Risk of Childhood Obesity

BACKGROUND

Childhood obesity is a rising concern and can have a lasting impact on the future health of a child. According to Ogden et al,\(^1\) in 2009-2010, 16.8% of US children had a body mass index (BMI) of \(\geq\) the 95\(^{\text{th}}\) percentile according to the BMI-for-age growth charts. It is important to understand the many contributing factors that can lead to or influence obesity. Obesity can have short term and long term health, social, and economic consequences, that can have a lasting impact on one’s overall well being. Cardiovascular and metabolic complications are among the top health concerns arising from childhood obesity, along with the psychosocial implications.\(^2\) Due to these potential life-changing complications, it is important to understand the possible environmental factors that could be contributing to the increased incidence of childhood obesity.

Thirty-one potential risk factors have been reported to be likely contributors to the increased incidence of childhood obesity.\(^2,3\) If scientists can understand or predict what contributes to childhood obesity, there is a chance of preventing the increased incidence. At this time, there is limited scientific data and evidence as to the exact risk factors for childhood obesity.\(^2,3\) According to the Institute of Medicine Committee on Obesity, maternal pre-pregnancy BMI, nutritional intake, physical activity, sleep duration, and screen time were identified as factors increasing childhood obesity. They noted one additional factor that is of increased interest, which is the role of the microbiome of the gut.\(^2,4\) More specifically scientists are interested at looking at antibiotic exposure and the influence antibiotics have on the gut microbiome. Antibiotics can change gut flora, theoretically contributing to increased obesity.\(^4\)
The microbiome is important in the development of humans and much of the microbiome is influenced in early infancy. While in the womb, one is considered to be in a sterile environment, but once born and out of the womb, the infant becomes exposed to numerous bacteria, which become colonized in the gut. Environmental factors such as genetics, mode of delivery, infant feeding patterns, antibiotic usage, sanitary living conditions, and long term dietary habits are all considered important contributors to how the gut is shaped and what the gut microbiome is composed of.\textsuperscript{5} Gut colonization occurs early in childhood\textsuperscript{2} and is said to be unstable until around two to three years of age. Combined with this knowledge of gut instability in infancy, looking at exposure to antibiotics during infancy, which are known to alter gut bacteria, becomes important. This alteration in gut bacteria has been studied in animals and have been shown to be linked to antibiotic exposure.\textsuperscript{5,6} Antibiotics have been given in low doses in farm animal feed to fatten them to be sold on the market. A previous study\textsuperscript{7} on animals with antibiotic exposure earlier in life, have shown a connection to increased weight gain. Gut microbiota contribute to metabolism of animals and if this gut microbiome is altered, metabolism is altered, potentially leading to increased weight.\textsuperscript{7} With the knowledge of alteration of the gut microbiome due to antibiotic use in farm animals, farmers intentionally add low dose antibiotics to their feed to increase weight. This has now been restricted and antibiotics can no longer be used in veterinary foods due to the known growth-promoting effect.\textsuperscript{7,8} This data is important as it can translate to the human gut, causing alteration of the gut microbiome, leading to increased risk of obesity after exposure to antibiotics. Can antibiotic exposure in infancy increase the risk of childhood weight concerns such as obesity, later on in life?
METHODS

An exhaustive search of the literature was performed using MEDLINE- Ovid, CINAHL, and Web of Science. Keywords used included: *antibiotic exposure, antibiotic, or antibacterial agents, and infant, and obesity*. Bibliographies of studies and other relevant articles were searched for further sources. The articles were included if they were human studies, measured outcomes after 7 years of age, or were published in the English language. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).9

RESULTS

A total of 43 articles were reviewed for relevancy. Of the articles that were reviewed, three articles fit inclusion criteria. All three studies were cohort studies.10-12 One additional study was published4, but was excluded from this systematic review due to outcomes of the study being measured less than 7 years of age. All other studies measured outcomes at 7 years of age or greater. No additional articles were found by searching the references of the included studies. See Table 1.

Trasande et al

This longitudinal cohort study10,13 looked at exposure to antibiotics during three early life time periods and body mass at five time periods. Study participants were recruited from the ALSPAC landmark longitudinal birth cohort study. In order to be included in the study, children had to be born weighing ≥ 2500g. Children were excluded if information on antibiotic exposure was missing for all three-time windows. The study cohort included 11 532 children. The groups were prognostically balanced, although the antibiotic exposure group had a larger number of children compared to the group not exposed to antibiotics.10,13
The study outcomes were directed at looking at weight-for-length Z scores, BMI Z-score, being overweight (defined as BMI 85-94th percentile for age and gender), and being obese (defined as ≥ 95th percentile for age and gender). Weight-for-length was measured at 6 weeks, 10 months, and 20 months of age. BMI was measured at 38 months and 7 years.\textsuperscript{10,13}

The study used multivariable models that included potential confounders. The study analyzed prevalence of primary outcomes and then the authors tested the relationship between exposure to antibiotics and potential confounders by using the chi-squared test for association.\textsuperscript{10}

The study results showed that antibiotic exposure less than six months of age was consistently associated with increases in body mass. When kids were exposed at less than 6 months of age, BMI scores were significantly higher and the participants were 22% more likely to be overweight than children who were never exposed. When looking at children exposed during 6-14 months of age, there was no association with increased childhood obesity; however the children who were exposed during the ages of 15-23 months had elevated BMI scores at 7 years of age. These results suggest that exposure to antibiotics at a younger age can cause obesity later in life.\textsuperscript{10} See Figure 1.

The researchers identified the limitations to this study to include social, behavioral, and biological factors. Parental BMI, maternal smoking, socioeconomic class, sedentary behavior, and sleep patterns could all be confounders to the data. However, the ALSPAC study controlled for many of the confounders by using multivariate analysis. Another important limitation to consider is the study only included children born ≥ 2500g. The authors state that the cohort could have included children with normal birth weight, but may have had underlying substantial illnesses that could have factored into increased obesity.\textsuperscript{10,13}
Azed et al

This study\textsuperscript{11,14} was a nested case-control study that measured total adiposity at ages 9 and 12 years of age and central adiposity at age 12. This study originated from the SAGE longitudinal birth cohort study. Surveys were mailed to all Manitoba children born in 1995 and who still were residing in Manitoba at age 7 years. There were 3598 surveys that were returned and the nested case-control study was developed with 723 children. Children were included in the study if they had prescription records and anthropometric data. There were 107 children who were excluded from the study due to prescription records being unavailable.\textsuperscript{11,14}

Study outcomes evaluated total adiposity at age 9 and 12 years of age based on BMI measurements and central adiposity measured at age 12 based on waist circumference, with the primary exposure of any antibiotic exposure in the first year of life. Azad et al defined a child being overweight if the BMI was > the 85\textsuperscript{th} percentile and high central adiposity was defined as waist circumference > the 75\textsuperscript{th} percentile. Both BMI and high central adiposity measurements were according to the published age and sex-standardized reference charts by US Centres for Disease Control.\textsuperscript{11,14}

This study used multiple logistic regression analysis to determine the likelihood of being overweight or of having high central adiposity according to antibiotic exposure during the first year of life. The authors corrected for potential confounders with their analysis. The study had case and control groups that were prognostically balanced, although the control group was larger than the case group. There were 185 children who were lost to follow up at age 12.\textsuperscript{11}

The study results indicated that of the 616 children included in the study, 71.1\% of them received antibiotics before their first birthday. At age 9, prevalence of overweight children was 29.4\% and 28.1\% at age 12. High central adiposity was 33.9\% at age 12. When looking at
antibiotic exposure and the outcomes of being overweight and having central adiposity without correcting for potential confounders, children exposed to antibiotics were more likely to be overweight at age 9 compared to children who had not been exposed to antibiotics (P = 0.003). Similar results were shown for being overweight (P = 0.002) and having high central adiposity (P = 0.01) at age 12 between children exposed to antibiotics compared to children not exposed to antibiotics. After adjusting for potential covariates and known obesity risk factors, infant antibiotic exposure remained independently associated with childhood weight concerns and high central adiposity. Further analysis identified that boys who were exposed to antibiotics in infancy had a five fold increased risk of being overweight at age 12 compared to girls where there was no association.11

Limitations to this study were identified as the small sample size compared to previous studies and the 30% loss to follow up at age 12. Another limitation to this study was they were unable to account for antibiotic exposure administered in the hospital setting, as this information was not part of the database.11 See Table 2.

Ajslev et al

This study12,15 was a longitudinal prospective study from the Danish National Birth Cohort (DNBC) that studied 28 354 mother-child dyads. The DNBC was established in 1997-2002 and studied the Danish population that was pregnant during this time. There was a 7-year follow up period where parents were asked to fill out a questionnaire. Inclusion requirements for this study were live born, term delivered singleton births, and mothers who participated in interview 1 and in the 7-year follow up. Exclusion criteria included mothers with diabetes, if mothers developed gestational diabetes or pre-eclampsia during pregnancy. Siblings were excluded, meaning that mothers with their second or more pregnancies were excluded. Children
were excluded if they had missing, unrealistic, or different-date time measurements of height and weight at the 7-year follow-up. Also the study excluded children with an age of less than 5 or greater than 9 at the 7-year follow-up.\textsuperscript{12,15}

Study outcome looked at children being overweight at 7 years of age after exposure to antibiotic in infancy (<6 months). This study defined children being overweight by BMI cutoff scores by the International Obesity Task Force’s age and sex specific BMI. The study analysis took into consideration multiple covariates including maternal age, socioeconomic status, maternal pre-pregnancy height and weight, parity, and smoking status. Analysis originally only looked at primary exposures, and then analyzed data with covariates and exposures. Analysis was done with multiple logistic regressions and compared to the reference group. Each analysis was done with the entire cohort and then was split into males and females.\textsuperscript{12,15}

The study suggested that the prevalence in 7-year old girls was 10.9\% for overweight and 1.6\% for obesity. In 7-year old boys prevalence of overweight was 8.3\% and 1.1\% for obesity. When looking at exposure to antibiotics in infancy and not adjusting for covariates, the OR indicated an association for children being overweight (OR 1.20, 95\% CI 1.02-1.40). When the study adjusted for covariates, the association was not present (OR 1.04, 95\% CI 0.79-1.37).\textsuperscript{12,15} The study further analyzed gender specific relationships between exposure to antibiotics in infancy and children being overweight. Ajslev et al found that antibiotic exposure during infancy had an increased risk for both boys (OR 1.33, 95\% CI 0.99-1.79) and girls (OR 1.37, 95\% CI 1.01-1.87) when unadjusted for covariates. When the study adjusted for covariates, the relationship only persisted in boys (OR 1.75, 95\% CI 1.18-2.60).\textsuperscript{12,15} See Table 3.

Limitations to this study include families being lost to follow up, which could potentially contribute to the number of overweight children that are represented in this cohort. The study
states that there may be selection bias present. Another limitation includes self-measurement of
the children’s weight and height and some data that was provided was from different dates.
Although children with different date measurements were excluded from the study, this limited
the overall number of subjects making this a smaller cohort.12,15

DISCUSSION

This systematic review was able to identify three published articles10-12 that addressed the
question of whether exposure to antibiotics in infancy can contribute to childhood obesity. These
three articles10-12 looked at the primary outcome of overweight with a BMI > the 85th percentile.
All three of these papers evaluated being overweight after age 7. Each study identified that
exposure to antibiotics in infancy had an increased risk for overweight children although the
association seemed stronger for male participants. Each study was evaluated using the GRADE
method and can be seen in Table 1.

Another article published by Bailey et al4 in 2014 looked at BMI at visits between 24-59
months of age after exposure to antibiotics in infancy. This study was not included in the
systematic review due to the primary outcome being evaluated at such young ages. The results of
the study show that exposure to broad-spectrum antibiotics during infancy is a risk factor for
childhood obesity. The results of this study are consistent with the three other studies.

The Azad et al11 study further analyzed the antibiotic exposure by type of antibiotic,
whether it was broad spectrum antibiotic use verse narrow spectrum antibiotic use. Narrow
spectrum antibiotics were defined as penicillin, cloxacillin, cephalxin, cefadroxil, and
erythromycin.11 All other antibiotics were classified as broad-spectrum antibiotics. Of the 616
children, 354 were exposed to broad-spectrum antibiotics during infancy. The study had
difficulty finding differences with weight status according to antibiotic spectrum due to such a
small number of children receiving narrow spectrum antibiotics.\textsuperscript{11} When the study analyzed exposure to broad-spectrum antibiotics and risk of being overweight at age 12 alone, the results showed an OR 2.48, 95% CI 1.31-4.68.\textsuperscript{11} This information can be used to educate clinicians and parents that antibiotics are not prescribed without harm and it is important to understand the potential risk associated with prescribing antibiotics.

There has not been an identified mechanism that answers all of the questions related to gut alteration by antibiotics, but there have been studies that have shown that the makeup of gut microbiota differs between obese and non-obese individuals.\textsuperscript{11} With this information and the evidence of the three studies evaluated in this systematic review, early life antibiotic exposure could be a risk factor for childhood obesity.

Based on this research clinicians need to teach parents that antibiotics are not always the correct answer. If clinicians do provide antibiotics it is important to teach parents about healthy gut bacteria. Also, it may be important to provide patients with probiotics while on a course of antibiotics to help promote healthy gut bacteria. Some of these simple tasks could be important steps to help reduce the increased risk of childhood obesity caused by antibiotic exposure during infancy.

However, these studies are not without limitations. Some limitations include cohort size, loss to follow up, blinding, recall bias, attrition bias and selection bias (see Table 1). The Trasande et al\textsuperscript{10} study measured exposure to antibiotics by parental recall, which could cause bias towards study results as parental recall is imprecise. Azad et al\textsuperscript{11} had a large loss to follow up of 30\%, which is a huge limitation to their study. Along with the large loss to follow up, this study had a much smaller cohort compared to the other two studies. Although these studies
adjusted for the published risk factors, there could be other confounders that have not been accounted for in these analyses.

Although this research has proven that early antibiotic exposure may carry an increased risk for development of childhood obesity, further studies need to be performed. These three studies have very low quality of evidence; further observational data with more control over the confounders would be useful.

**CONCLUSION**

These studies have shown a possible increased risk for development of childhood obesity, however more studies need to be done to have more reliable data, as the current data has low quality. Although the studies showed increased risk of childhood obesity, there are many factors that can contribute to this risk. Future studies need to evaluate children for multiple years after exposure. With improved study results, clinicians could use the data with more applicability to help prevent childhood obesity.
REFERENCES


Table 1. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overweight (BMI &gt;85&lt;sup&gt;th&lt;/sup&gt; percentile)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very Low</td>
</tr>
<tr>
<td>Trasande et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Observational</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>No</td>
<td>Very Low</td>
</tr>
<tr>
<td>Azed et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Observational</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Not serious</td>
<td>No</td>
<td>Very Low</td>
</tr>
<tr>
<td>Ajslev et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Observational</td>
<td>Very serious&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not Serious</td>
<td>Not serious</td>
<td>No</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>High Central Adiposity (Waist circumference &gt;75&lt;sup&gt;th&lt;/sup&gt; percentile)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Azed et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Observational</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious</td>
<td>Not serious</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Obese (BMI &gt;95&lt;sup&gt;th&lt;/sup&gt; percentile)</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Trasande et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Observational</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>No</td>
<td>Low</td>
</tr>
</tbody>
</table>

<sup>a</sup>The three studies evaluated overweight BMI at three different time periods. Two studies evaluated BMI at age 7 and one study evaluated BMI at age 9 and 12

<sup>b</sup>Trasande et al study had parental recall for exposure

<sup>c</sup>Azed et al study had 30% loss of follow up at 12 years of age

<sup>d</sup>Small sample size

<sup>e</sup>The Ajslev et al study (observational) contained a high risk for selection bias because of high loss to follow up and women being selected from highest pre-pregnancy BMI group

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Table 2. Azed et al<sup>11</sup>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Children OR (95% CI)</th>
<th>Girls OR (95% CI)</th>
<th>Boys OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight 9 years old</td>
<td>1.87 (1.23-2.52)</td>
<td>1.76 (0.96-3.23)</td>
<td>1.91 (1.08-3.38)</td>
</tr>
<tr>
<td>Overweight 12 years old</td>
<td>2.16 (1.31-3.58)</td>
<td>1.35 (0.66-2.78)</td>
<td>3.16 (1.51-6.60)</td>
</tr>
<tr>
<td>High Central Adiposity 12 years old</td>
<td>1.80 (1.14-2.85)</td>
<td>1.57 (0.79-3.11)</td>
<td>1.93 (1.03-3.61)</td>
</tr>
</tbody>
</table>

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Table 3. Ajslev et al<sup>12</sup>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted for Covariates OR (95% CI)</th>
<th>Adjusted for Covariates OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight 7 years old</td>
<td>1.20 (1.02-1.40)</td>
<td>1.04 (0.79-1.37)</td>
</tr>
<tr>
<td>Boys: Overweight 7 years old</td>
<td>1.33 (0.99-1.79)</td>
<td>1.75 (1.18-2.60)</td>
</tr>
<tr>
<td>Girls: Overweight 7 years old</td>
<td>1.37 (1.01-1.87)</td>
<td>1.09 (0.66-1.79)</td>
</tr>
</tbody>
</table>
Figure 1. Trasande et al\textsuperscript{10}

*Figure 1 is from Trasande et al\textsuperscript{10} and is being used in this review with permission from the author