Application of antibiotics before 3 years of age increases the risk of childhood overweight and obesity

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Abstract. Childhood obesity and antibiotics abuse have become global health problems. It is necessary to explore the correlation between application of antibiotics for children under 3 and the risk of overweight and obesity in children. In the present study, young children aged 3 (36-38 months) were investigated using a face-to-face questionnaire survey. These children were admitted to Dongying City Children's Hospital from December 2017 to May 2019, and the effective sample size was 4,258. According to the body mass index (BMI), young children were divided into two groups, including emaciation and normal group as well as overweight and obesity group. Univariate analysis was performed to identify the possible influencing factors between the two groups using chi-square test. A difference of $P<0.05$ indicated statistical significance of a certain factor between the two groups, which could be adopted as an influencing factor in Logistic regression analysis. In addition, odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were employed to quantify the correlation of antibiotic application with the risk of overweight and obesity. A total of 3,322 young children (78.0%) were included in the antibiotic group while the remaining 936 (22.0%) were enrolled in the non-antibiotic group. Logistic regression analysis revealed that antibiotic application increased the risk of overweight and obesity among the 3-year-old young children (OR, 1.44; 95% CI, 1.03-2.01). In addition, application of antibiotics for five times or higher significantly increased the risk of overweight and obesity (OR, 1.73; 95% CI, 1.07-2.80), and such risks were more significant in children who were administered antibiotics for the first time within 6 months of age (OR, 1.71; 95% CI, 1.08-2.69). The application of antibiotics in infants and young children was thus revealed to increase the risk of overweight and obesity at the age of 3 in a frequency-dependent manner.

Introduction

Antibiotics are the most frequently prescribed drugs for pediatric patients (1). Antibiotics can definitely decrease the morbidity and mortality rates of infectious diseases (2). However, they also produce certain adverse reactions, including their impacts on the colonization of intestinal microflora (2). Studies have revealed that the destruction of gut microbial composition and diversity affects the energy metabolism in the host, thereby leading to obesity (3). Such an effect has been verified in animal experiments (4,5), while research on human individuals requires further exploration. Over the last three decades, childhood obesity has rapidly increased worldwide (6). Obesity is a type of continuous body disorder, which increases the risks of chronic diseases and tumors (7). Therefore, it is important to prevent obesity at an early stage. At present, no common conclusions have been reported on the effects of antibiotics on pediatric overweight and obesity. Some studies have revealed that the use of antibiotics in the early life increases the risks of childhood overweight and obesity (8,9). Another study revealed an uncertain conclusion as to whether antibiotic use can cause childhood overweight and obesity (10). In view of the present research, since the colonization of intestinal microbes before 3 years old is susceptible to antibiotics, the time-point of 3 years old was selected. The present study aimed to explore the correlation of antibiotic use before 3 years of age with the risk of overweight and obesity.

Materials and methods

General information. In the present study, 3-year-old (36-38 months) young children were investigated using a face-to-face questionnaire survey. They were admitted to the Department of Pediatrics of Dongying City Children's Hospital from December 2017 to May 2019. The height and weight of all these young children were measured by medical staff. The exclusion criteria were as follows: Young children with a gestational age <37 weeks and birth weight <2500 g; children with diseases that may seriously affect their growth and development, including acute severe infectious diseases, genetic diseases, chronic diarrhea, asthma, nephrotic

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syndrome, congenital heart disease (CHD), and gastrointestinal deformities. Children whose mother was suffering from diseases that may affect the growth and development of young children were excluded.

Basic information of the young children. In the present study, altogether 4,682 young children aged 3 years (36-38-months old) were surveyed. There were a total of 235 questionnaires with uncertain assures, mainly in the 'application of antibiotics', accounting for 99%. Because antibiotics are prescription drugs and the management is strict, the prescription was verified. Then, there were 4 questionnaires with doubt. To reduce the influence of recall bias, these 4 questionnaires were not included. The samples that did not meet the requirements were excluded. The effective sample size was 4,258 (including 2,160 boys and 2,098 girls, with a boy:girl ratio of 1:1), with an effective rate of 90.9%. The antibiotics used, mainly include three types: Penicillins, cephalosporins and macrolides. Penicillins mainly included: Penicillin sodium, amoxicillin, ampicillin and mezlocillin sodium. Cephalosporins mainly included: Cephalexin, cephalosporin, cefixime cefaclOR, cefuroxime sodium, cefmetazole and ceftriaxone sodium. Macrolides mainly included: Azithromycin, erythromycin and roxithromycin. The main routes of administration were: Oral and intravenous drip. The dosage was the usual recommended dosage for children.

Contents and methods

Contents of the questionnaire. The contents of the survey were proposed after literature review (3-5,8-11), and the contents of the questionnaire were determined and reviewed by two experts. To be specific, the questionnaire covered four aspects: i) basic information of young children: Sex, age (months), birth weight, current height, current body weight, feeding method (within 6 months), gestational age, delivery method, history of suffocation, history of asthma and other diseases; ii) basic information of parents: Height of father, height of mother, weight of father, weight of mother before pregnancy, maternal age, and monthly family income; iii) the application of antibiotics (before 36 months of age): The age at the first application, the number of applications (treatment course), and the name of the antibiotics; and iv) whether probiotics were applied concurrently with antibiotics. One course of treatment of diseases with antibiotics was a single medication.

Survey methods. The questionnaire survey was conducted by the medical staff at Dongying City Children's Hospital among the parents of our selected young children. The height and weight of these young children were also measured. This retrospective study was approved by the Ethics Committee of Dongying City People's Hospital. The legal guardians of young children were surveyed and had signed the written informed consent to participate in the survey.

Diagnostic criteria. The medical staff measured the body weights and heights of all the enrolled young children according to the standard measurement methods in young children (11). Then, the body mass index (BMI) was calculated according to the following formula: BMI = body mass (kg)/height (m^2). According to the growth reference value and growth curve of the body mass index of Chinese children (0-18 years old) (12), the BMI was converted to the standard percentage score (BMI-P) using the SAS macro program (13). In addition, the BMI values were divided into two groups according to the threshold of sex or age P85. All respondents were classified into 2 groups, namely, children ≤P85 (emaciation and normal) and children >P85 (overweight and obesity). In adults, a BMI ≥24 kg/m^2 is diagnosed as overweight, while a BMI ≥28 kg/m^2 indicates obesity (14).

Quality control. Strict quality control was implemented, and the questionnaire survey was conducted in a face-to-face manner. All medical staff were trained and assessed before the questionnaire survey. The qualified medical staff were allowed to carry out the questionnaire survey based on a unified standard. The medical staff explained or demonstrated the questionnaire-related questions to the parents. The results were checked in a timely manner. If parents were not sure about any question, the question was marked and further verified to decrease the error. The respondents were selected in strict accordance with the inclusion and exclusion criteria, and the reproducibility survey was also conducted. Moreover, all data were input twice by professionals, followed by logical review to remove the outliers, and the consistency was as high as 100%.

Statistical analysis. The SPSS 22.0 software (IBM Corp.) was employed for data analysis. Univariate Chi-square test was performed on the risk factors that may affect the growth and development of young children or the use of antibiotics. Factors of $P<0.05$ indicated significant statistical differences between the two groups, which were used as the influencing factors for further logistic regression analysis. Moreover, odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were utilized to quantify the correlation of antibiotic use with the risk of overweight and obesity.

Results

There were 3,322 children (78.0%) in the antibiotic group and 936 (22.0%) in the non-antibiotic group, and difference in sex between the two groups was not significant ($P>0.05$). According to our results, only a markedly small proportion of young children (0.5%; 17/3,322) were treated with probiotics and antibiotics concurrently. Univariate chi-square test was carried out on the risk factors that may affect the growth and development of young children or the use of antibiotics. A difference of $P<0.05$ indicated statistical difference between the two groups, as presented in Table I. Thereafter, the factors, including delivery method, BMI of the father, BMI of the mother before pregnancy, birth weight, feeding style (within 6 months), and family income were incorporated for logistic regression analysis.

Correlation of application of antibiotics with overweight and obesity. In the present study, the detection rate of overweight and obesity in the non-antibiotic group was 4.8% (45/936), while that in the antibiotic group was 6.9% (230/3,322). In addition, the application of antibiotics was significantly and

Table I. Influencing factors possibly related to the growth and development of young children and the use of antibiotics.

Factors	Emaciation and normal [n (%)]	Overweight and obesity [n (%)]	P-value	Antibiotic group [n (%)]	Non-antibiotic group [n (%)]	P-value
Sex			NS			NS
Male	2,031 (51.0)	129 (46.9)		1,706 (51.4)	454 (48.5)	
Female	1,952 (49.0)	146 (53.1)		1,616 (48.6)	482 (51.5)	
Birth weight[a]			<0.05			NS
Normal	3,821 (95.9)	256 (93.1)		3,181 (95.8)	896 (95.7)	
High	162 (4.1)	19 (6.9)		141 (4.2)	40 (4.3)	
Number of siblings			NS			NS
0	1,873 (47.0)	127 (46.2)		1,535 (46.2)	465 (49.7)	
≥1	2,110 (53.0)	148 (53.8)		1,787 (53.8)	471 (50.3)	
Maternal age (years)			NS			NS
<30	1,633 (41.0)	112 (40.7)		1,358 (40.9)	387 (41.3)	
≥30	2,350 (59.0)	163 (59.3)		1,964 (59.1)	549 (58.7)	
Weeks of gestation			NS			NS
37-40	2,129 (53.5)	146 (53.1)		1,759 (53.0)	516 (55.1)	
≥40	1,854 (46.5)	129 (46.9)		1,563 (47.0)	420 (44.9)	
Delivery method			<0.05			NS
Smooth birth	2,463 (61.8)	147 (53.5)		2,053 (61.8)	557 (59.5)	
Cesarean section	1,520 (38.2)	128 (46.5)		1,269 (38.2)	379 (40.5)	
Feeding method			<0.05			
Breast feeding	2,350 (59.0)	156 (56.7)		1,900 (57.2)	606 (64.7)	<0.05
Mixed feeding	1,481 (37.2)	102 (37.1)		1,277 (38.4)	306 (32.7)	
Milk feeding	152 (3.8)	17 (6.2)		145 (4.4)	24 (2.6)	
Monthly family income (yuan)			NS			NS
<5,000	97 (2.4)	7 (2.5)		82 (2.5)	22 (2.4)	
5,000-10,000	1,683 (42.3)	119 (43.3)		1,406 (42.3)	396 (42.3)	
≥10,000	2,203 (55.3)	149 (54.2)		1,834 (55.2)	518 (55.3)	
Father			<0.05			
Thin and normal	2,513 (63.1)	149 (54.2)		2,068 (62.3)	594 (63.5)	NS
Overweight and obese	1,470 (36.9)	126 (45.8)		1,254 (37.7)	342 (36.5)	
Mother			<0.05			NS
Thin and normal	2,741 (68.8)	167 (60.7)		2,267 (68.2)	641 (68.5)	
Overweight and obese	1,242 (31.2)	108 (39.3)		1,055 (31.8)	295 (31.5)	
Antibiotic use			<0.05			-
No	891 (22.4)	45 (16.4)		-	936 (100)	
Yes	3,092 (77.6)	230 (83.6)		3,322 (100)	0	
Number of antibiotics applied (course)			<0.05			-
1-2	1,837 (59.4)	118 (51.3)		1,955 (58.8)	0	
3-4	922 (29.8)	81 (35.2)		1,003 (30.2)	0	
≥5	333 (10.8)	31 (13.5)		364 (11.0)	0	
Types of antibiotics used			<0.05			
Penicillins	1,793 (32.7)	133 (30.7)		1,926	0	-
Cephalosporins	2,124 (38.7)	168 (38.8)		2,292	0	
Macrolides	1,562 (28.5)	132 (30.5)		1,694	0	
Other	8 (0.1)	0		8	0	
Initial application of antibiotics (months)			<0.05			-
0-6	396 (12.8)	36 (15.6)		432 (13.0)	0	
6-12	754 (24.4)	63 (27.4)		817 (24.6)	0	
12-24	1,061 (34.3)	83 (36.1)		1,144 (34.4)	0	
24-35	881 (28.5)	48 (20.9)		929 (28.0)	0	

Table I. Continued.

Factors	Emaciation and normal [n (%)]	Overweight and obesity [n (%)]	P-value	Antibiotic group [n (%)]	Non-antibiotic group [n (%)]	P-value
Probiotic intake during antibiotic application			-			-
No	17 (0.5)	0		17 (0.5)	0	
Yes	3,075 (99.5)	230 (100)		3,305 (99.5)	0	

[a]Based on standard measurement methods in young children (11); 2,500≤ Normal <4,000 g; High ≥4,000 g. NS indicated no statistical difference between the two groups; P<0.05 indicated a statistical difference between the two groups; and '-' indicated that the P-value was not available.

Table II. Analysis of the correlation of the use of antibiotics with overweight and obesity before and after adjustment of the influencing factors.

Factors	Thin and normal [n, (%)]	Overweight and obesity [n, (%)]	OR[a]	95% CI[a]	OR[b]	95% CI[b]
Non-antibiotic group	891 (95.2)	45 (4.8)	1	1	1	1
Antibiotic group	3,092 (93.1)	230 (6.9)	1.47	(1.06-2.04)	1.44	(1.03-2.01)

[a]Univariate logistic regression analysis; [b]Multivariate logistic regression analysis on the influencing factors including delivery method, BMI of father, BMI of mother before pregnancy, birth weight, feeding history (within 6 months) and family income.

positively correlated with the detection rate of overweight and obesity. The unadjusted OR and 95% CI were 1.47 (1.06-2.04), while the adjusted OR and 95% CI were 1.44 (1.03-2.01) (Table II).

Correlation of the time of antibiotics applications with overweight and obesity. The detection rate of overweight and obesity was 6.0% (118/1,955) among young children treated with antibiotics for 1-2 times, 8.1% (81/1,003) in those treated with antibiotics for 3-4 times, and 8.5% (31/364) in those treated with antibiotics for 5 times or more.

The frequency of antibiotic application was correlated with the risk of overweight and obesity. Typically, in the aforementioned three subgroups of young children, the unadjusted ORs and 95% CIs were 1.25 (0.88-1.78), 1.68 (1.15-2.44) and 1.77 (1.11-2.83), respectively. The adjusted ORs and 95% CIs were 1.23 (0.86-1.76), 1.65 (1.12-2.41) and 1.73 (1.07-2.80), respectively. In addition, it is suggested in the present study that, the risk of overweight and obesity at the age of 3 years increased for infants who were treated with antibiotics 3 times or more. Moreover, more application times suggested a higher risk (Table III).

Correlation of the age of first application of antibiotics with overweight and obesity. The detection rate of overweight and obesity was 8.3% (36/432) among young children who were first treated with antibiotics at 0-6 months of age, 7.7% (63/817) in those first treated with antibiotics at 6-12 months of age, 7.3% (83/1,144) in those first treated with antibiotics at 12-24 months of age, and 5.2% (48/929) in those first treated with antibiotics at 24-35 months of age. Moreover, a younger age at first antibiotic application resulted in a greater correlation with overweight and obesity. In addition, for young children in the aforementioned subgroups, the unadjusted ORs and 95% CIs were 1.73 (1.11-2.71), 1.60 (1.09-2.37), 1.51 (1.04-2.19) and 1.07 (0.70-1.63), respectively. The adjusted ORs and 95% CIs were 1.71 (1.08-2.69), 1.57 (1.06-2.34), 1.47 (1.01-2.15) and 1.02 (0.65-1.58), respectively. It was revealed in this study that first antibiotic application within 24 months of age increased the risk of obesity and overweight at the age of 3 years in young children, and earlier first antibiotic application in infants resulted in greater risk (Table IV).

Discussion

Childhood obesity is jointly affected by both adjustable factors (social and environmental factors) and fixed factors (genetic factors). As the global incidence of childhood obesity continuously rises, it is important to determine the adjustable factors (15). The present study revealed that overweight and obesity were significantly and positively correlated with application of antibiotics, which was consistent with the results of most studies (8,9,16,17).

In addition, it was revealed in the present study that the application of antibiotics for 3 times or more at the age of 3 years, increased the risk of overweight and obesity, and a greater application time resulted in a higher risk. At present, antibiotics have been widely utilized in infants and young children, and numerous experts have appealed to the restriction of antibiotic use (18), yet unreasonable applications remain (19). The cumulative application of antibiotics increases the risk of overweight and obesity among young children, which cautions that the indications for the use of antibiotics, should strictly be followed, thus avoiding the risk of overweight and obesity in young children.

Table III. Analysis of the correlation of antibiotic application time with the risk of overweight and obesity in young children before and after adjustment of the influencing factors.

Frequency (course)	N (%)	Overweight and obesity [n (%)]	OR[a]	95% CI[a]	OR[b]	95% CI[b]
0	936 (100)	45 (4.8)	1	1	1	1
1-2	1,955 (58.8)	118 (6.0)	1.25	(0.88-1.78)	1.23	(0.86-1.76)
3-4	1,003 (30.2)	81 (8.1)	1.68	(1.15-2.44)	1.65	(1.12-2.41)
≥5	364 (11.0)	31 (8.5)	1.77	(1.11-2.83)	1.73	(1.07-2.80)

[a]Univariate logistic regression analysis; [b]Multivariate logistic regression analysis on the influencing factors, including delivery method, BMI of father, BMI of mother before pregnancy, birth weight, feeding history (within 6 months) and family income.

Table IV. Analysis of the correlation of the first antibiotic application time with the risk of overweight and obesity in young children before and after adjustment of the influencing factors.

Application time (months)	N (%)	Overweight and obesity [n (%)]	OR[a]	95% CI[a]	OR[b]	95% CI[b]
0	936 (100)	45 (4.8)	1	1	1	1
0-6	432 (13.0)	36 (8.3)	1.73	(1.11-2.71)	1.71	(1.08-2.69)
6-12	817 (24.6)	63 (7.7)	1.60	(1.09-2.37)	1.57	(1.06-2.34)
12-24	1,144 (34.4)	83 (7.3)	1.51	(1.04-2.19)	1.47	(1.01-2.15)
24-35	929 (28.0)	48 (5.2)	1.07	(0.70-1.63)	1.02	(0.65-1.58)

[a]Univariate logistic regression analysis; [b]Multivariate logistic regression analysis on the influencing factors, including delivery method, BMI of father, BMI of mother before pregnancy, birth weight, feeding history (within 6 months) and family income.

Early life is a critical period for the colonization of intestinal microbiota (20). The gut microbiota from colonization to maturity is susceptible to antibiotics (21). As revealed in animal studies, the application of antibiotics in early life can more effectively promote the gain of body mass than that in the later period (22). This study also discovered that the first application of antibiotics within 24 months of age increased the risk of obesity and overweight at the age of 3 years, and first application of antibiotics at a younger age led to a higher risk. With regard to the possible causes, animal experiments have indicated that antibiotics can regulate the metabolism in the host (23,24). In mouse experiments, mice treated with antibiotics alone for 4 weeks after birth had increased fat content from the 20th week, accompanied with obesity. After applying antibiotics in mice, the microorganisms of segmented filamentous bacteria, *Lactobacillus* and *Mycoplasma* in the intestinal tracts decrease, which play an important role in regulating the host metabolism (24).

At present, existing studies have revealed that certain types of intestinal microorganisms can affect the body mass (25), and the use of probiotics greatly improves the balance of intestinal microbiota (26,27). As suggested in some studies, *Lactobacillus* and *Bifidobacterium* decrease the risk of obesity (28,29). Moreover, mouse experiments have reported that, treatments with lactic acid bacteria, *Bifidobacteria*, *Lactobacillus rhamnosus* and other probiotics in food-borne obese mice can produce changes in the gut microbial compositions, thereby decreasing the risk of overweight and obesity (30,31). Currently, the number of probiotics available is markedly limited compared with the complex and diverse microbiome in infants and young children. However, according to existing investigations (26,27), probiotics may be beneficial for regulating the gut microbial disturbance after application of antibiotics. In any case, more studies are warranted to confirm the specific effects of application of probiotics on the metabolism in the host. Unfortunately, the present study found that, considerably few infants and young children were treated with probiotics and antibiotics concurrently (0.5%, 17/3322). Therefore, analysis on probiotics was not conducted in the present study. In this regard, further prospective studies on probiotics are required to provide better clinical guidance.

The present study has several limitations. The indications of antibiotics for infants and young children were not investigated. However, a recent study has revealed that there is no causal relationship between the indications of common antibiotics and overweight and obesity (4). The antibiotics used in the present study are all common antibiotics. No definite evidence has been found that overweight and obesity in infants increase bacterial infections in infants and young children.

Although numerous confounding factors related to overweight and obesity have been adjusted in the present study, there may still be some potential confounding factors that cannot be adjusted, including activity level, energy intake, diet structure, feeding speed, and sleep time. However, due to the investigation of infants and young children who regularly visit the Children's Health Department of our hospital (Dongying

People's Hospital, Dongying, China) for physical examinations, the health care doctor has promptly corrected some problems affecting growth and development. They are infants of the same living area, therefore, it is surmised that the impact of potential confounding factors is limited. These factors are unlikely to fully explain the association between overweight, obesity and antibiotic use.

Different types of antibiotics may have different effects on overweight and obesity. Unfortunately, the sample size of only one type of antibiotics before the age of 3 in this study is limited, thus further analysis by antibiotic category could not be performed. This does not affect the study, but will be the next direction of exploration, providing a better scientific basis for future clinical guidance.

Although the present study did not include infants or infants whose mothers had diseases that affect their growth and are exposed to glucocorticoids, the confounding factors affecting overweight and obesity were also adjusted. Findings in the present study significantly indicated that the application of antibiotics in early life increased the risk of overweight and obesity, although this was not a multi-center study. Notably, the present results provide a novel perspective for the prevention of childhood obesity, and offer scientific evidence for the rational use of antibiotics among infants and young children.

In conclusion, application of antibiotics in infants was revealed to increase the risk of overweight and obesity at the age of 3 years, and a higher antibiotic application time resulted in an increased risk of overweight and obesity.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JT designed the study and drafted the manuscript. HL and HG were responsible for the collection and analysis of the experimental data. WH, HD and TC determined and reviewed the contents of the questionnaire, and conducted the questionnaire survey.. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Dongying People's Hospital, China. Signed written informed consents were obtained from the guardians of the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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