Administration of Antibiotics to Children Before Age 2 Years Increases Risk for Childhood Obesity

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Abstract

Background & Aims—Childhood obesity is increasing and is associated with adult obesity. Antibiotics have been used to promote weight gain in livestock for several decades. Antibiotics are commonly prescribed for children, but it is not clear how exposure to antibiotics early in life affects risk for obesity. We performed a population-based cohort study to assess the association between antibiotic exposure before age 2 years and obesity at age 4 years.

Methods—We performed a retrospective cohort study of 21,714 children in The Health Improvement Network —a population-representative dataset of more than 10 million individuals derived from electronic medical records from 1995 through 2013 in the United Kingdom. Eligible subjects were registered within 3 months of birth with complete follow-up and height and weight were recorded within 12 months of their 4th birthday. Antibiotic exposure was assessed before age 2 years, and classified based on anti-anaerobic activity. The primary outcome was obesity at age 4 years. We performed logistic regression analyses, adjusting for maternal and sibling obesity, maternal diabetes, mode of delivery, socioeconomic status, year and country of birth, and urban dwelling.

Results—In the cohort, 1306 of the children (6.4%) were obese at 4 years of age. Antibiotic exposure was associated with an increased risk of obesity at 4 years (odds ratio [OR]=1.21; 95% confidence interval [CI], 1.07–1.38). Odds ratios increased with repeated exposures: for 1–2 prescriptions, OR=1.07 (95% CI, 0.91–1.23); for 3–5 prescriptions, OR=1.41 (95% CI, 1.20–1.65); for 6 or more prescriptions, OR=1.47 (95% CI, 1.19–1.82). Antifungal agents were not associated with obesity (OR=0.81; 95% CI, 0.59–1.11).

Conclusions—Administration of 3 or more courses of antibiotics before children reach an age of 2 years is associated with an increased risk of early childhood obesity.

Antibiotics have been used to promote weight gain in the agricultural industry for decades[,]. This effect has been hypothesized to be mediated via the gut microbiome, with studies demonstrating no effect on weight gain in germ-free animals[,]. The impact of antibiotics on animal weight is greater if given earlier in life.

Childhood obesity is strongly associated with the risk of obesity and its complications in adulthood. There are limited data addressing the effect of antibiotics on human weight gain, despite clear evidence of their overuse in pediatric populations[‑]. Several studies have retrospectively examined antibiotic use by relying on parental recall to assess exposure to antibiotics. A recent UK study assessed antibiotic exposure in the first two years of life and body mass, appreciating an increased risk of obesity at 10 and 20 months, and a trend towards a sustained impact at 7 years, though this was not statistically significant after adjusting for parental obesity and tobacco use. Duration, dose, antibiotic class, and household factors such as sibling obesity were not assessed. A Danish registry examined antibiotic exposure in the first 6 months of life and demonstrated an increased risk of obesity in children of obese mothers, but noted a protective effect in children of mothers who were

not obese. Recurrent exposures could not be assessed . An international survey also found an association between parental recall of antibiotic use in the first 12 months of life and subsequent obesity.

Prior retrospective cohort studies using electronic health records have also suggested an association between antibiotics and obesity¯. However, because of the limitations of the available data, substantial uncertainty remains about the importance of the age of exposure, cumulative frequency of exposure, and spectrum of antibiotics that may influence this association. Furthermore, there is remaining uncertainty about the potential confounding effects of environmental exposures.

In this study, we examined the association between antibiotic use before 2 years of age and obesity in a large population-representative cohort in the United Kingdom with complete follow-up from birth to 48 months, allowing for complete prescription information, adjusting for multiple confounders including sibling and maternal obesity, method of delivery, year of birth, socioeconomic status, and early obesity. We also assessed whether repeated antibiotic exposures and antibiotics with broader anaerobic coverage, and therefore potentially greater impact on the microbiome, were more strongly associated with obesity.

Methods

Study design

We performed a retrospective cohort study using data collected prospectively in the scope of routine care from 1995–2013 within The Health Improvement Network (THIN). THIN data are derived from general practitioners' electronic medical records (EMR). THIN represents approximately 6% of the UK population, includes information on age, sex, socioeconomic status, medication use, and has been validated for multiple medical diagnoses¯. Height and weight data are recorded during clinical care. Mother-child pairings and siblings can be determined using a unique household code.

Study population

We identified individuals who registered with a THIN practice within 3 months of birth who had complete follow-up to 48 months. Individuals were required to have a recorded height and weight within 12 months of their fourth birthday. Height and weight must have been recorded within 1 week of each other. To ensure recording completeness, all individuals born prior to a practice's installation of the Vision electronic medical record were excluded, as were those who had died, transferred out of a practice, or did not reach their fourth birthday prior to the end of data recording. Given the potential for increased antibiotic or glucocorticoid exposures, we excluded individuals with diagnostic codes for reactive airway disease or asthma.

Study outcome

The primary outcome was obesity at 48 months, defined using BMI z-scores calculated from the UK World Health Organization Term growth reference table using both recorded height and weight as well as age at the date they were recored. BMI can vary significantly based on

age and gender among individuals. To account for this variation, we used z-scores, which convert BMIs into numerical values that represent how many standard deviations an individual's BMI is away from the transformed age- and sex-specific population mean. Z-scores are employed in World Health Organization and Center for Disease Control growth charts. These values are particularly useful when examining extreme percentiles of the distribution, such as >99% or <1%. Obesity was defined as a BMI z-score 2.37 for males and 2.25 for females based on previously published UK population-specific cut-offs. The time point of 4 years was selected given the previously described association between obesity at this age and obesity in adulthood.

Variables of interest

Antibiotic exposure was defined as any prescription for a systemic antibiotic occurring from enrollment in the practice (no later than 3 months after birth) to 2 years of age. We assessed the impact of repeated exposures via number of antibiotic prescriptions (none, 1–2, 3–5, or >5 prescriptions). We also assessed timing of the first antibiotic prescription and timing of first exposure to antibiotics (0–6 months, 6–12 months, or 12–24 months), as prior research had demonstrated a stronger association with exposure in the first year of life. Specific classes of antibiotics were categorized as those with antianaerobic coverage (penicillins, imidazoles, lincosamides, tetracyclines) and without (cephalosporins, macrolides, sulfa-containing agents, isoniazid, rifampin, flouroquinolones, aminoglycosides). Systemic antifungal agents were assessed as a control.

We assessed those factors previously identified to be associated with obesity as potential confounders. These included calendar year, geographic region, mode of delivery, socioeconomic status, obesity as an infant, maternal diabetes, and presence of obese family members in the household. A multi-step algorithm was employed to identify mothers within the THIN database, adapted from previously published methods within the same database(see Supplemental Methods and Results). Average maternal BMI was calculated from available height and weight data from age 18 to 240 days prior to the child's birth. A multilevel variable was then generated to indicate if the mother had an average BMI greater than 30, less than 30, or if we were unable to identify a mother.

Older siblings of the individuals of interest were identified using similar techniques (see Supplemental Methods and Results). As siblings, we included male and female individuals age 18 in the same household with complete follow-up during the 4 years of follow-up of the index individual's time within THIN. BMI z-scores were calculated using the same criteria as the individuals in our primary cohort of interest. If any siblings met the criteria for obesity during the 4-year follow-up period of the individual within our cohort, they were categorized as obese. A multilevel categorical variable was then constructed, similar in structure to the maternal variable.

For each cohort member, we assessed the presence of obesity during the first year of life. To perform this analysis, we identified height and weight data within 14 days of each other within 12 months of their date of birth. Obesity was calculated for this infant data by calculating Z-Weight for length (zWFL) scores using the World Health Organization growth

chart, with obesity defined as a Z-score >2 standard deviations above the mean (zWFL>1.96).

We assessed several additional factors that may influence the risk of obesity at age 4 years. Year of birth was measured to assess the potential influence of trends in obesity over time. Postal codes were used to determine if cohort members lived in an urban versus rural environment and to compute a Townsend score for socioeconomic status. The Townsend score categorizes socioeconomic status on a 5-point scale with 5 representing "most deprived", and is derived from (1) percentage of households without access to a car, (2) percentage of households not in owner-occupied accommodations (3) percentage of households in overcrowded accommodations, and (4) the percentage of the economically active population aged 16–74 who are unemployed (See Supplemental Methods). Geographic region was categorized as Northern Ireland, Wales, Scotland, or England. Mode of delivery (caesarean or vaginal) was determined when diagnostic codes were present within 6 months after the birthdate of children of interest. In the subset of individuals who had codes for both vaginal delivery and caesarean delivery, delivery was categorized as caesarean. Maternal diabetes was assessed using diagnostic codes.

Analysis

Statistical analyses were conducted using Stata 13 (StataCorp, College Station, TX, USA). BMI z-scores were calculated using the *zanthro* package. Univariable analyses were conducted using logistic regression. We included all potential confounding covariates in a fully adjusted model, without employing a predetermined step-wise backwards elimination strategy to avoid inappropriate over-fitting or oversimplification. In a sensitivity analysis we also generated a more parsimonious model using a backwards elimination stepwise strategy to assess the impact on our results (see Supplemental Methods and Results).

Sensitivity analyses

We performed several sensitivity analyses related to antibiotic exposure. We assessed the impact of repeated antibiotic prescriptions, from 0–10 or more prescriptions, as a continuous variable in univariable and multivariable analyses. We analyzed the impact of anti-anaerobic antibiotics, given their presumed greater impact on the predominantly anaerobic gut microbiome, in univariable analyses and in a combined model stratified on whether the agents were or were not antianaerobic. We performed a sensitivity examining our classification of antibiotics with anaerobic coverage, classifying only those with definite anaerobic coverage as anaerobic, and also comparing amoxicillin, which has variable anaerobic coverage, to amoxicillin and clavulanic acid, which has more complete coverage (See Supplemental Methods). We identified households with more than one child within our cohort and assessed the impact of antibiotics among these pairs using conditional logistic regression. We repeated our primary analyses limited to those individuals with both identified mothers and siblings to assess any bias introduced by missing data on obesity among family members.

We assessed interaction between the number of prescriptions and age at first prescription while avoiding collinearity by combining both age of first antibiotic prescription and number

of antibiotics over the first 2 years as a 5-level variable: No antibiotics (reference), 1–2 prescriptions with the first prescription in the first 12 months of life, 3 or greater prescriptions with the first prescription in the first 12 months of life, 1–2 prescriptions with the first prescription between 12 and 24 months of age, and 3 or greater prescriptions with the first prescription between 12 and 24 months of age (See Supplemental methods).

We performed analyses examining the effects of alternate definitions of obesity. For this sensitivity analysis, we used a BMI z-score cut-off of 3 for obesity at age 4 years. To assess the impact of categorizing obesity as a dichotomous variable, we performed linear regression to assess the impact of antibiotic exposures on BMI z-score at age 4.

To assess for possible selection bias, we examined the association of antibiotic prescriptions and recording of height and weight at age 4. To assess for the potential impact of unmeasured confounders, we determined the strength of association between an unmeasured confounder and the outcome required to explain our observed association between antibiotic exposure and obesity. We modeled our unmeasured confounder after existing data on breastfeeding, as we were unable to measure this in our dataset (See Supplemental Methods). Breastfeeding is known to be associated with both a lower risk of infection and obesity. Approximately 80% of mothers in the UK breast-feed. A recent meta-analyses demonstrated that breastfeeding is associated with a reduced risk of obesity (OR 0.78, 95% CI 0.74–0.81). Additionally, prior studies have demonstrated a protective effect of breast-feeding for respiratory tract infections, with an adjusted OR of 0.65. We also performed an analysis examining the potential confounding effect of obesity during the first 6 months of life in a cohort of individuals with recorded height and weight in that time period using z-weight-for-length scores.

This study was considered exempt by the University of Pennsylvania IRB and approved by THIN's scientific review committee.

Results

Among 533,238 children identified in THIN within 3 months of birth, 253,157 had 4 years of follow-up. 21,714 children with complete follow-up for four years met the inclusion and exclusion criteria (Figure 1); 64.1% were prescribed antibiotics prior to age 2 years. The median time from birth to cohort entry was 37 days (IQR 25–51). 1,306 (6.4%) were obese at age 4 years. Obesity at age 4 years was observed in 5.2% of children without antibiotic exposure and 6.4% of those with antibiotic exposure, with a risk difference of 1.2% (95% CI 0.1–1.9%). Baseline characteristics of obese and non-obese children are presented in Table 1.

Increasing poverty, urban dwelling, year of birth, maternal and sibling obesity, maternal diabetes, and obesity in the first year of life were associated with an increased risk of obesity at age 4 years (Table 2). The risk of obesity increased with increasing number of courses of antibiotics and with antibiotic use in the first year. After adjusting for all covariates, any antibiotic prescription (aOR 1.21, [95%CI: 1.07–1.38]) and increasing number of antibiotic prescriptions were significantly associated with obesity, specifically for those receiving 3 or

more prescriptions (1–2 prescriptions: aOR 1.07, [95% CI:0.93–1.23]; 3–5 prescriptions: aOR 1.41, [95% CI: 1.20–1.65]; >5 prescriptions: aOR 1.47, [95% CI: 1.19–1.82]). With each increase in antibiotic exposure category, there was an increased risk of obesity (p-for-trend p<0.001). Antibiotic use within the first year was also associated with increased risk: (0–6 mos: aOR, 1.33 [95% CI: 1.13–1.57], 6–12 mos: aOR, 1.27, [95% CI: 1.09–1.47]) (Table 3). After assessing for interaction between the number of prescriptions and age at first exposure, repeated exposures before age 2 had the greatest effect, regardless of whether these exposures started before or after 12 months (prior to 12 months: aOR 1.48 [95%CI 1.27–1.72]; after 12 months: aOR 1.60 [95%CI 1.22–2.10]; Table 5; See Supplemental Methods).

Anti-anaerobic antibiotics were associated with obesity in a dose-dependent manner (1–2 prescriptions: aOR, 1.09, [95% CI: 0.95–1.25]; 3–5 prescriptions: aOR, 1.45 [95% CI: 0.91–1.68]; >5 prescriptions: aOR, 1.46 [95% CI: 1.09–1.96]), while antibiotics without anti-anaerobic activity were not (Table 4). Antifungal agents were not associated with obesity (OR, 0.81, [95%CI, 0.59 – 1.11]).

When assessing the subgroup of individuals for whom we had identified both mothers and siblings (n=3,296), antibiotic exposure was associated with an increased risk of obesity (any exposure: OR, 1.73 [95%CI, 1.16 to 2.57]). When examining families with multiple siblings with discordant outcomes (n=361), the risk with each antibiotic prescription (aOR, 1.08 [95%CI, 0.90 to 1.30]) and with number of prescriptions (1–2: aOR, 0.72 [95%CI, 0.43 to 1.24]; 3–5: aOR, 1.20 [95%CI, 0.65 to 2.21]; >5 aOR, 1.45 [95%CI, 0.54 to 4.06]) was similar, though not statistically significant.

Sensitivity Analyses

Results in a parsimonious model retaining only covariates that were significant in univariate analyses yielded similar results to our fully adjusted model (See Supplemental Methods and Results). When examining the impact of antibiotic exposures on the BMI z-score at age 4, in our fully adjusted model, any antibiotic exposure was associated with a 0.05 point (95% CI: 0.02–0.09) increase in z-score. Each antibiotic prescription was associated with a 0.014 point (95% CI:0.01 to 0.02) increase in Z-score. When using z-score 3 as an alternate definition of obesity, 542 children were classified as obese at age 4 years. In this fully adjusted model, any antibiotic prescription was associated with an increased risk of obesity (aOR: 1.22, 95% CI: 1.01–1.48). Increasing antibiotic use was also associated with an increased risk of obesity (1–2: aOR, 1.06 [95%CI, 0.86–1.32]; 3–5: aOR, 1.47 [95%CI 1.17–1.86]; >5 aOR, 1.39 [95%CI, 1.01–1.92]).

When using a more stringent definition of antibiotics with anaerobic coverage, there were 957 individuals exposed to anaerobic antibiotics. Any exposure was associated with an increased risk of obesity at age 4, although this was not statistically significant (OR 1.21, 95%CI: 0.95–1.55). When comparing those who received no antibiotics to those who had received amoxicillin, amoxicillin and clavulanic acid, or both, the effect estimates were similar for each exposure category (amoxicillin: OR 1.18 [95% CI 1.04–1.34]; amoxicillin with clavulanic acid: OR 1.20 [95% CI 0.70–2.09]; both: OR 1.33 [95% CI 0.99–1.80]) (see Supplemental Methods and Results).

Adjusting for documented obesity within the first 6 months of life did not meaningfully alter the association between repeated antibiotic use and obesity for those who had received 3 or more prescriptions (1–2: aOR, 1.08 [95%CI, 0.93–1.23]; 3–5: aOR, 1.41[95%CI 1.21–1.65]; >5 aOR, 1.48[95%CI, 1.19–1.83).

In our analyses of unmeasured confounders and their potential impact on these results, we estimate that failure to adjust for breastfeeding only biased our results for any antibiotic exposure by approximately 2%, with an externally adjusted odds ratio of 1.22 (See Supplemental Methods). If we were to assume that the association between breast-feeding and obesity was under-estimated in the meta-analysis by Yan et al and instead use the strongest effect estimate included in that analysis (OR 0.29 (95%CI 0.08–1.05), this would result in 13% bias, with an externally adjusted OR of 1.10. When considering those with 3 or more prescriptions for antibiotics, where we observed a greater risk of obesity, the adjusted association between obesity 3 or more antibiotic exposures would be 1.27.⁻ Thus, within the plausible range of effect estimates, external adjustment for breastfeeding was not able to fully explain the association between antibiotic exposure and obesity observed in this study.

Receipt of antibiotics was not associated with recording of height and weight among all 253,137 individuals within THIN who had 4 years of follow-up (OR 1.01, [95%CI 0.98–1.04]).

Discussion

With rising rates of childhood obesity worldwide, it is important to identify modifiable contributing factors⁻. Antibiotics are prescribed during an estimated 49 million pediatric outpatient visits per year in the United States; the majority are broad-spectrum agents. Between 2006–2008, >10 million antibiotic prescriptions were written annually for children without clear indication, despite increased awareness of the societal risks of antibiotic resistance. This study identified obesity as one of a growing list of more tangible risks associated with antibiotic utilization, including dermatologic, allergic, and infectious complications, inflammatory bowel disease, and autoimmune conditions⁻. Unlike other potential risks of antibiotic use, the risk of subsequent obesity is likely easily understandable by parents. The results of this study do not imply that antibiotics should not be used when indicated, but rather highlight a reason to avoid antibiotics in the absence of well-established indications. This may be particularly important if the child has been previously treated with antibiotics as the risk of subsequent obesity was greater in those children who had received 3 or more courses of antibiotics in the first 2 years of life.

These data are supported both in the agriculture industry and in murine models. Moore and colleagues first recognized the relationship between streptomycin and weight gain in chick models in 1946. Similar results were appreciated in 1949 in experiments where chickens fed fishmeal supplemented with cobalamin derived from the bacteria *Streptomyces aureofaciens*, which also produced the antibiotic streptomycin, outgrew chickens receiving fishmeal with a liver-derived B12 supplement. Similar effects have been observed in other livestock with differing antibiotics, and the use of these agents rapidly became commonplace in the

agricultural industry. Several laboratory models have demonstrated that increases in weight induced by antibiotics are mediated via the drug's impact on the microbiome, with no effect in germ free models·. This study is one of the first to demonstrate a similar impact in a human population, while adjusting for multiple factors previously demonstrated to be associated with obesity.

Strengths of the study are the large sample size, near complete capture of lifetime antibiotic exposure, and adjustment for multiple factors including both maternal and sibling obesity, maternal diabetes, obesity in the first year of life, mode of birth, and socioeconomic status. This design allowed us to disentangle the effects of age at first exposure to antibiotics and the number of courses, identifying repeated antibiotic exposure as the pivotal factor linking antibiotic exposure to childhood obesity. This supports the hypothesis that antibiotics may progressively alter the composition and function of the gut microbiome, thereby predisposing children to obesity as is seen in livestock and animal models.

There are several potential limitations of this research. We did not measure the indication for antibiotic use. However, recent data suggest no causal association between common antibiotic indications and obesity. Children who receive multiple antibiotic prescriptions may differ from those with none or few in ways that relate to future risks of obesity. However, one would expect that in those children with more serious or repeated infections between ages 0 and 2, poor weight gain would be more common than excessive weight gain, thereby biasing our results towards the null. Employing an outpatient medical record, we were unable to capture inpatient medication administration. However, this represents a small minority of prescriptions and would also likely bias the results toward the null. Thus, our design may have slightly underestimated the association of antibiotic exposure and subsequent childhood obesity.

As with any retrospective study, it is possible that selection bias could influence our results. While growing children in the UK have routine measurements of their height and weight, these measurements are typically recorded via a paper record known as the Personal Child Health Record as opposed to in the EMR. Inclusion in the EMR, and subsequently THIN, is at the discretion of the treating physician. Therefore, it is possible that selective recording of this information could influence our findings. However, when examining overall obesity rates in the United Kingdom, observed rates within THIN were only slightly lower than those previously published for the UK, and demonstrated similar temporal trends within our cohort (data not shown). For selection bias to have influenced the results of this study, recording of height and weight data would have to be associated with both obesity and receipt of antibiotics. As we observed no association between receipt of antibiotics and recording of height and weight in the overall cohort, selection bias is unlikely to explain the observed associations.

Despite adjusting for many potential confounders associated with obesity, there are a few potential confounders that we were not able to adjust for, including breast feeding, physical activity, and sleep″. However, it is unlikely that these factors fully explain the association between obesity and antibiotic exposure appreciated within our data given the results of the analyses of unmeasured confounders. The sensitivity analysis using external adjustment

demonstrated that our estimate was robust to unmeasured confounders, even if they were strongly protective against future obesity. Furthermore, recent survey data demonstrate that mode of feeding does not usually differ within households, and we appreciated similar effects of repeated antibiotic exposure among sibling pairs discordant for obesity. Although we were able to identify family members in order to adjust for environmental and genetic confounders, we were underpowered to perform a similar analysis examining only multiple births (i.e. twins or triplets), as obesity status and antibiotic exposure were nearly identical between these individuals. We also excluded children with asthma or reactive airway disease from our analyses, given the known association between these conditions and obesity and the potential for confounding due to glucocorticoid exposure.. Therefore, one should use caution when interpreting the impact of our results in these populations. Further research is required to assess the durability of this response later into adolescence and young adulthood as well as later onset obesity.

Lastly, it is possible that our analyses examining antibiotic spectrum coverage could be underpowered and subject to misclassification bias. We appreciated an association between obesity and anti-anaerobic agents, with a dose-dependent response. As the majority of antibiotics prescribed were anti-anaerobic in our primary analyses, it is possible that the lack of association with the use of antibiotics without anti-anaerobic coverage was due in part to smaller numbers. In our sensitivity analysis, amoxicillin, an agent with minimal anti-anaerobic activity was significantly associated with obesity with an odds ratio comparable to that for amoxicillin with clavulanic acid. While our analysis of amoxicillin with clavulanic acid did not reach statistical significance, this may be due to limited numbers of individuals with this exposure in comparison to amoxicillin alone (see Supplemental Methods and results). As such, repeated courses of antibiotic exposure may be a more important risk factor than spectrum of activity. Further research is required to determine if specific classes of antibiotics are more strongly associated with subsequent obesity.

In summary, we have demonstrated that exposure to antibiotics in the first two years of life is associated with an approximately 1.2% absolute and 25% relative increase in the risk of early childhood obesity. This relationship is strongest when considering repeat exposures, particularly with 3 or more courses. While early antibiotic use has been associated with a number of rare long-term health consequences, these data link antibiotics to one of the most important and growing public health problems worldwide.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

aOR	Adjusted odds ratio
BMI	Body Mass Index
CI	Confidence Interval
EMR	Electronic Medical Record
OR	Odds ratio
THIN	The Health Improvement Network
UK	United Kingdom
zWFL	z-Weight for Length score

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26,867 children entering cohort within 3 months of birth with recorded height and weight within 6 months of 4th birthday

5,153 children excluded due to reactive airway disease or asthma

21, 714 children in final cohort

1,306 obese children at age 4
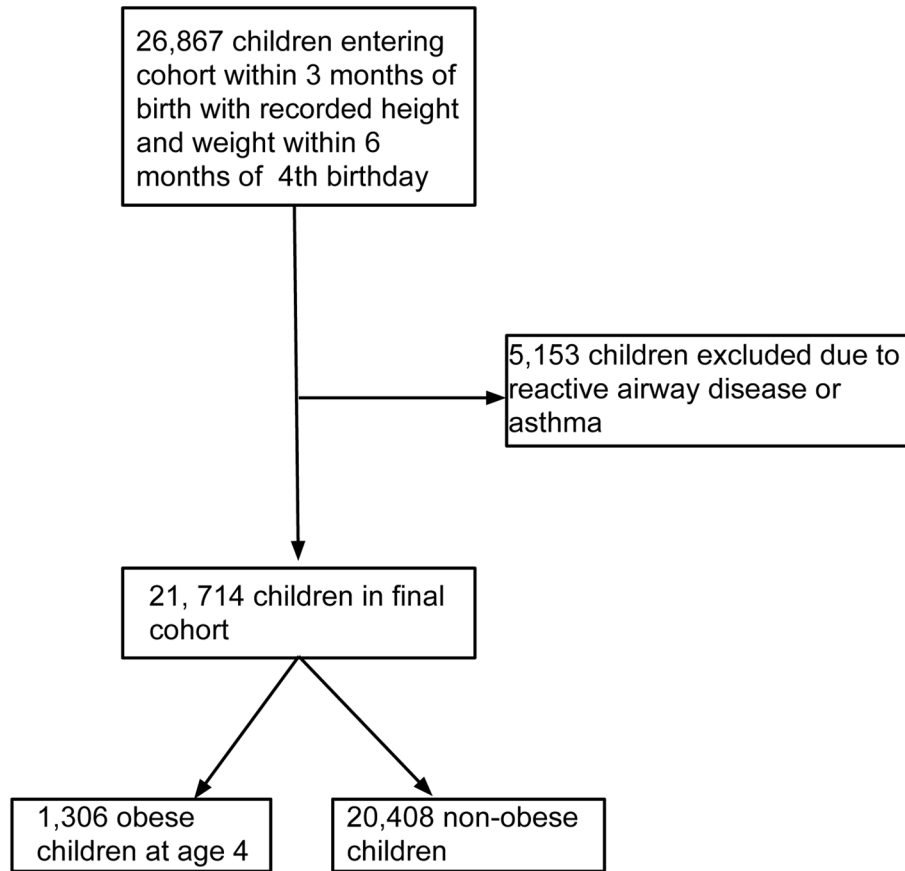
20,408 non-obese children

Figure 1.
CONSORT Diagram: CONSORT diagram of children included in the study, demonstrating those with complete follow up and height and weight data that were then excluded based on exclusion criteria.

Table 1

Characteristics of children within the cohort, stratified by the presence of obesity at 48 months

Characteristics	Non-Obese (N=20,408)	Obese (N=1,306)
Born before 2000, No. (%)	4,264 (20.9%)	219 (16.8%)
Born after 2000, No. (%)	16,144 (79.1%)	1,087 (83.2%)
Sex		
Male, No. (%)	10,421 (51.1%)	673 (51.5%)
Female, No. (%)	9,987 (48.9%)	633 (48.5%)
Area of Residence		
Non-Urban environment, No. (%)	3,360 (16.5%)	193 (14.8%)
Urban environment, No. (%)	12,319 (60.4%)	847 (64.9%)
Residence data missing, No. (%)	4,729 (23.2%)	266 (20.4%)
Townsend Score[a]		
1, No. (%)	4,255 (20.9%)	221 (16.9%)
2, No. (%)	4,024 (19.7%)	227 (17.4%)
3, No. (%)	4,013 (19.6%)	239 (18.3%)
4, No. (%)	4105 (20.1%)	296 (22.7%)
5, No. (%)	3,172 (15.5%)	275 (21.1%)
Missing data, No. (%)	839 (4.1%)	48 (3.7%)
Mother identified, No. (%)	11,715 (57.4%)	712 (54.5%)
Mother with documented obesity, No. (%)	1,308 (6.4%)	155 (11.9%)
Mother without documented obesity, No. (%)	10,407 (51.0%)	557 (42.7%)
Mother with diabetes, No, (%)	92 (0.5%)	11 (0.8%)
Sibling identified, No. (%)	4,779 (23.4%)	1,049 (19.7%)
Sibling with documented obesity, No. (%)	325 (1.6%)	49 (3.8%)
Sibling without documented obesity, No. (%)	4,454 (21.8%)	208 (15.9%)
Mode of delivery identified, No. (%)	5,403 (26.5%)	336 (25.7%)
Caesarean delivery, No. (%)	946 (4.6%)	75 (5.7%)
Vaginal delivery, No (%)	4,457 (21.8%)	261 (20.0%)
Antibiotic unexposed, No. (%)	6,489 (31.8%)	355 (27.2%)
Antibiotic exposed, No. (%)	13,919 (68.2%)	951 (72.8%)
1–2 prescriptions, No. (%)	8269 (40.5%)	492 (37.7%)
3–5 prescriptions, No. (%)	4149 (20.3%)	332 (25.4%)
>5 prescriptions, No. (%)	1501 (7.4%)	127 (9.7%)
Exposure by antibiotic class		
Penicillins	13,244 (64.9%)	909 (69.6%)
Cephalosporin	992 (4.9%)	78 (6.0%)
Macrolides	3,115 (15.3%)	234 (17.9%)
Imidazoles	44 (0.2%)	2 (0.2%)

Characteristics	Non-Obese (N=20,408)	Obese (N=1,306)
Isoniazid/Rifampin	17 (0.1%)	4 (0.3%)
Tetracyclines	1(0.0%)	0 (0.0%)
Flouroquinolones	24 (0.1%)	1 (0.1%)
Aminoglycosides	4 (0.02%)	0 (0.0%)
Sulfa-based	769 (3.8%)	63 (4.8%)

[a]Townsend score from least impoverished (1) to greatest level of poverty (5)

Table 2

Univariable and multivariable models assessing the association of antibiotic exposure and all covariates of interest with the risk of obesity at age 4 years

Exposure	Exposed and obese		Univariable Analysis	Most fully adjusted model assessing number of prescriptions
	Number exposed	Number obese (% of exposed)	OR, (95% CI)	OR, (95% CI)
Number of antibiotic prescriptions:	6,844	355 (5.2%)	1.00	1.00
0 (ref)				
1–2	8,761	492 (5.6%)	1.09 (0.95–1.25)	1.07 (0.93–1.23)
3–5	4,481	332 (7.4%)	1.46 (1.25–1.71)	1.41 (1.20–1.65)
>5	1,628	127 (7.8%)	1.55 (1.25–1.91)	1.47 (1.19–1.82)
Maternal Obesity	10,964	557 (5.1%)	1.00	1.00
Non-obese mother identified (ref)				
No mother identified	9,287	594 (6.4%)	1.27 (1.13–1.44)	1.25 (1.08–1.43)
Obese mother identified	1,463	155 (10.6%)	2.21 (1.84–2.67)	1.97 (1.62–2.38)
Maternal Diabetes	12,324	701 (5.7%)	1.00	1.00
Not diabetic (ref)				
Diabetic mother	103	11 (10.3%)	1.98 (1.06–3.72)	1.51 (0.79–2.90)
Sibling obesity	4,662	208 (4.5%)	1.00	1.00
Siblings identified without obesity (ref)				
No Sibling identified	16,678	1,049 (6.3%)	1.44 (1.23–1.67)	1.42 (1.23–1.68)
Obese sibling identified	374	49 (13.1%)	3.23 (2.32–4.50)	2.64 (1.88–3.70)
Country	16,231	981 (6.0%)	1.00	1.00
England (ref)				
N. Ireland	896	48 (5.4%)	0.88 (0.65–1.19)	2.08 (1.07–4.11)
Scotland	3,401	188 (5.5%)	0.91 (0.77–1.07)	2.18 (1.17–4.03)
Wales	1,186	89 (7.5%)	1.26 (1.01–1.58)	1.09 (0.86–1.37)
Townsend Score	4,476	221 (4.9%)	1.00	1.00
1 (ref)				
2	4,251	227 (5.3%)	1.08 (0.90–1.31)	1.07 (0.88–1.29)
3	4,252	239 (5.6%)	1.15 (0.95–1.38)	1.10 (0.91–1.33)
4	4,401	296 (6.7%)	1.39 (1.16–1.66)	1.30 (1.15–1.63)
5	3,447	275 (8.0%)	1.67 (1.39–2.00)	1.52 (1.26–1.84)
Missing	887	48 (5.4%)	1.10 (0.80–1.52)	2.19 (1.30–3.71)
Urban environment	3,553	193 (5.4%)	1.00	1.00
Non-urban environment (ref)				
Urban environment	13,166	847 (6.4%)	1.20 (1.02–1.41)	1.06 (0.90–1.25)
Missing t	4,995	266 (5.3%)	0.98 (0.81–1.18)	0.39 (0.21–0.76)
Gender	11,094	673 (6.1%)	1.00	1.00

Exposure	Exposed and obese		Univariable Analysis	Most fully adjusted model assessing number of prescriptions
	Number exposed	Number obese (% of exposed)	OR, (95% CI)	OR, (95% CI)
Male (ref)				
Female	10,620	633 (6.0%)	0.98 (0.88–1.10)	1.03 (0.92–1.15)
Year of birth	---	---	1.04 (1.02–1.06)	1.03 (1.02–1.05)
Obesity in first year	8,928	471 (5.3%)	1.00	1.00
Non-Obese in first year (ref)				
Obese in first year	617	93 (15.1%)	3.19 (2.51–4.05)	3.13 (2.46–4.00)
Missing	12,169	742 (6.1%)	1.17 (1.04–1.32)	1.14 (1.00–1.29)
Method of delivery	4,718	261 (5.5%)	1.00	1.00
Vaginal Delivery (ref)				
Caesarian section	946	75 (7.4%)	1.35 (1.04–1.77)	1.20 (0.92–1.15)
Missing	15,005	970 (6.1%)	1.10 (0.96–1.27)	0.97 (0.82–1.14)

Table 3

Univariable and fully adjusted models assessing association between number of antibiotic prescriptions, time of first prescription, and obesity

Exposure	Number exposed	Number obese (% of exposed)	Univariable Analysis	Adjusted model assessing number of prescriptions	Adjusted model assessing age at first prescribed antibiotic
			OR, (95% CI)	OR, (95% CI)	OR, (95% CI)
Number of antibiotic prescriptions:	6,844	355 (5.2%)	1.00	1.00	--
0 (ref)					
1–2	8,761	492 (5.6%)	1.09 (0.95–1.25)	1.07 (0.93–1.23)	--
3–5	4,481	332 (7.4%)	1.46 (1.25–1.71)	1.41 (1.20–1.65)	--
>5	1,628	127 (7.8%)	1.55 (1.25–1.91)	1.47 (1.19–1.82)	--
Age at first prescription:	6,489	355 (5.2%)	1.00	--	1.00
None(ref)					
0–6 months	3,837	267 (7.0%)	1.37 (1.16–1.61)	--	1.33 (1.13–1.57)
6–12 months	5,851	390 (6.7%)	1.31 (1.13–1.51)	--	1.27 (1.09–1.47)
12–24 months	5,182	294 (5.7%)	1.10 (0.94–1.29)	--	1.07 (0.91–1.26)

Table 4

Impact of anti-anaerobic activity on association with obesity

Antibiotic Spectrum	1 or more prescriptions (Unadjusted)		1 or more prescriptions (Adjusted analysis)		Effect per number of prescriptions (adjusted OR, (95% CI)				
	No./Total (%)	(OR, 95%CI)	No./Total (%)	(OR, 95% CI)	0	1–2	3–5	>5
No antibiotic exposure	355/6,489 (5.5%)	1.00	345/6,245 (5.5)	1.00	1.00	1.00	1.00	1.00
Any antibiotic exposure	951/13,919 (6.8%)	1.24 (1.10–1.42)	931/13,324 (6.9%)	1.24 (1.09–1.41)	1.00	1.07 (0.93–1.24)	1.48 (1.27–1.74)	1.52 (1.23–1.89)
Antibiotics with anaerobic coverage	909/13,257 (6.9%)	1.24 (1.09–1.39)	872/12,683 (6.9%)	1.23 (1.08–1.39)	1.00	1.09 (0.95–1.25)	1.45 (0.91–1.68)	1.46 (1.09–1.96)
Antibiotics without anaerobic coverage	316/4,248 (7.4%)	1.21 (1.07–1.38)	303/4,059 (7.5%)	1.21 (1.06–1.38)	1.00	1.09 (0.93–1.27)	1.24 (0.91–1.68)	1.00 (0.63–1.60)

Impact of any antibiotic exposure and antibiotic exposure when stratified by anaerobic coverage. Exposure was assessed as any exposure, a continuous exposure with increasing antibiotic prescriptions, and as a categorical variable.

[a]Multivariable models included year of birth, maternal and sibling obesity, maternal diabetes, mode of delivery, country of origin, urban environment, and Townsend score.

Table 5

Multivariable model assessing interaction variable of time of first antibiotic and number of antibiotic prescriptions with obesity

Exposure	Multivariable Analysis	
	No./Total(%)	OR, (95%CI)
No antibiotic exposures	345/6590 (5.2)	1.00
1–2 prescriptions with first exposure between 0–12 months	259/4279 (6.1)	1.18 (0.995–1.39)
3 or more prescriptions with first exposure between 0–12 months	377/4989 (7.6)	1.48 (1.27–1.72)
1–2 prescriptions with first exposure between 12–24 months	210/4141 (5.1)	0.96 (0.81–1.15)
3 or more prescriptions with first exposure between 12–24 months	67/828 (8.1)	1.60 (1.22–2.10)

Multivariable model assessing the association of obesity at age 4 with time of first antibiotic exposure and number of exposures as a combined single interaction variable, adjusted for Townsend quintile (poverty scale), sibling and maternal obesity, and birth before or after 2000. In this model, there is a strong association between exposure to 3 or more antibiotics, regardless of first exposure before or after 12 months of age.