Early Life Antibiotic Exposure and Weight Development in Children

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Objective To examine the timing, frequency, and type of antibiotic exposure during the first 10 years of life in association with (over)weight across this period in a cohort of 979 children.

Study design Within the Child, Parents and Health: Lifestyle and Genetic Constitution Birth Cohort Study, antibiotic exposure record was obtained from general practitioners. Anthropometric outcomes (age- and sex-standardized body mass index, weight and height z-scores, and overweight) were measured repeatedly at 7 time points during the first 10 years of life. Generalized estimating equations method was used for statistical analysis.

Results After adjusting for confounding factors, children exposed to one course of antibiotics compared with none in the first 6 months of life had increased weight- (adjusted generalized estimating equations estimates [adjβ] 0.24; 95% CI 0.03-0.44) and height (adjβ 0.23; 95% CI 0.0002-0.46) z-scores; exposure to ≥2 courses during the second year of life was associated with both increased weight (adjβ 0.34; 95% CI 0.07-0.60), and height z-scores (adjβ 0.29; 95% CI −0.003 to 0.59). Exposure later in life was not associated with anthropometric outcomes. Associations with weight z-scores were mainly driven by exposure to broad- (≥2 courses: adjβ 0.11; 95% CI 0.003-0.22) and narrow-spectrum β-lactams (1 course: adjβ 0.18; 95% CI 0.005-0.35) during the follow-up period. Specific antibiotic used was not associated with body mass index z-scores and overweight.

Conclusions Repeated exposure to antibiotics early in life, especially β-lactam agents, is associated with increased weight and height. If causality of obesity can be established in future studies, this further highlights the need for restrictive antibiotic use and avoidance of prescriptions when there is minimal clinical benefit. *(J Pediatr 2016;176:105-13)*.

The discovery of antibiotics in the 1940s has played an important role in the treatment of bacterial infections, leading to a substantial reduction in human morbidity and mortality.[1] Overprescription of antibiotics, however, is a threat to public health in terms of costs, increasing antibiotic resistance, and frequent side effects.[2-4] The increase in the overuse of broad-spectrum (BS) antibiotics in conditions that could be treated with narrow-spectrum (NS) agents also has been reported.[5] Despite a decreasing trend in antibiotic use among children, it is still children who continue to have the highest consumption of antibiotics. Among children, approximately 70% of antibiotics are prescribed for upper respiratory infections,[6,7] and the majority of these prescriptions are considered unnecessary.[8]

Antibiotics have been linked to both short- and long-term perturbations of the actively developing infant gut microbiota. This may have a profound impact on human health and disease throughout life, as changes in the gut microbiota during this period may disrupt metabolic and immunologic development.[9] The important metabolic role of the human gut microbiota, which includes extracting energy from otherwise indigestible dietary compounds, highlights the importance of elucidating the impact of antibiotic use on childhood weight. Several studies have shown that antimicrobial agents can alter the gastrointestinal microbial diversity and community structure,[10-12] which in turn can lead to modulation of host metabolism,[13-15] hence, resulting in an effect on body weight.[9,16]

The growth promoting effect of antibiotics was first observed in the 1950s when domesticated mammalian and avian species were routinely administered subtherapeutic doses of antibiotics to accelerate their weight gain for marketing purposes.[17-20] Previous studies in humans have shown that exposure to antibiotics

adjβ	Adjusted GEE estimates
BMI	Body mass index
BS	Broad-spectrum
FFQ	Food frequency questionnaire
GEE	Generalized estimating equations
GP	General practitioner
KOALA	Child, Parents and Health: Lifestyle and Genetic Constitution
NS	Narrow-spectrum

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Funded by TI Food and Nutrition, BBMRI-NL, a research infrastructure financed by the Dutch government (NWO 184.021.007), Netherlands Organisation for Health Research and Development (2100.0090), Netherlands Asthma Foundation (3.2.03.48 and 3.2.07.022), Netherlands Heart Foundation (2008B112), Triodos Foundation, Phoenix Foundation, Raphaël Foundation, Iona Foundation, Foundation for the Advancement of Heilpedagogiek, Royal Friesland Foods (currently FrieslandCampina), Netherlands Sugar Foundation, and the Dutch Ministry of Economic Affairs. The sponsors had no influence on the analysis and reporting of this study. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.06.015

early in life may affect weight development in children.[21-26] The differential effects of various antibiotic classes, as well as the importance of the timing of exposure on childhood weight development, remain largely unanswered.[27] Moreover, most previous studies were of cross-sectional design or, if longitudinal, did not address the transitional evolution of childhood (over)weight over an extended period of time.

The aim of the present study was to evaluate the impact of antibiotic exposure from birth until 10 years of age on height and weight development of Dutch children participating in the Child, Parents and Health: Lifestyle and Genetic Constitution (KOALA) Birth Cohort Study. The study focuses on the influence of timing of antibiotic exposure, type of antibiotics used, and the number of courses to which a child was exposed.

Methods

The KOALA Birth Cohort Study is an ongoing cohort study in The Netherlands, described in detail elsewhere.[28] Briefly, from October 2000 until December 2002, a total of 3030 pregnant women were recruited at 34 weeks of gestation. Pregnant women with a conventional lifestyle (n = 2512) were recruited from an ongoing prospective cohort study on pregnancy-related pelvic girdle pain in The Netherlands.[29] A second group of pregnant women (n = 518) with alternative lifestyles with regards to dietary habits (organic food choice), child rearing practices, vaccination schemes, and/or use of antibiotics was recruited through alternative channels, organic food shops, Steiner schools, magazines, and anthroposophic doctors and midwives. Over time, data were collected using questionnaires, during home visits, and by clinical/laboratory examinations. The study was approved by the Medical Ethics Committee of the Maastricht University Medical Center, The Netherlands.

A subgroup of 1793 parents (of 2313 approached) gave informed consent to obtain information regarding their child's medication use from general practitioner (GP) records. In 2014, a postal questionnaire was sent to GPs to retrieve this information. Finally, 529 of the 744 contacted GPs provided information on medication used for a total of 1171 children. After excluding premature children (<37 weeks of gestation, n = 28), twins (n = 16), children with congenital abnormalities related to growth (eg, Down syndrome, cystic fibrosis, Turner syndrome, and tetralogy of Fallot, n = 12), as well as children without detailed information on antibiotic use (n = 136), a total sample size of 979 children was eligible for further analysis (**Figure**; available at www.jpeds.com). All children in this study were Caucasian.

Antibiotic Use

The questionnaires sent to GPs and others referred to exposure of the child to oral antibiotics over the child's lifetime (ie, "Did the child ever use antibiotics" and "If yes, could you give the generic drug name and date of each prescription."). In addition, GPs were asked to attach the entire medication history (including generic drug name and date of prescription) of the child from birth onward. Both sources of information were used to determine the antibiotic use for each child. We did not collect information on antibiotics administered in hospitals.

The number of courses of antibiotics prescribed to children in the first 10 years of life was analyzed as a categorical variable (none, 1, 2-3, and ≥4 courses). Separate variables were subsequently created to examine antibiotic exposure at different ages: 0-6 months, 6-12 months, 1-2 years, and >2 years, and to examine the effects of different types of antibiotics prescribed (ie, BS β-lactam agents [amoxicillin, cephalosporin], NS β-lactams [flucloxacillin, pheneticillin, phenoxymethylpenicillin], macrolides [erythromycin, clarithromycin, azithromycin], antimetabolites [co-trimoxazole, trimethoprim], and others [nitrofurantoin, metronidazole, gentamicin, and tetracycline]). Within these variables, the number of antibiotic courses (none, 1, and ≥2 courses) was compared with anthropometric outcomes.

Data Collection and Longitudinal Outcome Measures

Pregnant women received questionnaires at 14 and 34 weeks of gestation, collecting data on prepregnancy weight, weight gain during pregnancy, maternal education, and family size. Data from obstetric reports and questionnaires completed by the mothers were obtained 2 weeks after childbirth, with data on gestational age, birth weight, sex, mode and place of delivery, smoking during pregnancy, and gestational hypertension or diabetes. At the children's age (mean ± SD) 5 ± 0.6 years, food frequency questionnaires (FFQs) were filled out by the parents to report the dietary habits and physical activity of their children. The FFQ was developed and validated with the doubly labeled water method to measure energy intake at 4-6 years of age.[30]

Information on the child's weight, height, and age at the time of measurement was collected via self-administered questionnaires at 7 different time points. At the first 2 follow-up time points, when the children had attained the age (mean ± SD) of 0.9 ± 0.1 and 1.8 ± 0.3 years, parents were asked to report the most recent height and weight measurements including age at measurement (in months) at the Baby Welfare clinics. At the other 5 follow-up points, questionnaires were sent to the parents in which they were asked to measure and report the child's height (cm) and weight (kg, specified to 1 decimal) without clothes or shoes at ages (mean ± SD) of 4.7 ± 0.3, 6.2 ± 0.5, 6.8 ± 0.5, 7.8 ± 0.5, and 8.8 ± 0.5 years, respectively. Body mass index (BMI = weight/height^2 in kg/m^2) and height and weight measurements were standardized by recoding them into age- and sex-specific z-scores using the Dutch Growth Study[31] as a reference population. BMI z-scores were used as continuous outcomes, as well as dichotomized into "not overweight" vs "overweight," based upon a cut-off z-score ≥1.04 (BMI z-score agreeing with the 85th percentile) standardized for age and sex.[32]

Statistical Analyses

Summary statistics of exposure variables and characteristics of the study population for children who were exposed and