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Published in:
Journal of pediatric gastroenterology and nutrition

DOI:
10.1097/MPG.0000000000002360

Published: 01/01/2019

Citation for pulished version (APA):
Kamphorst, K., Oosterloo, B. C., Vlieger, A. M., Rutten, N. B., Bunkers, C. M., Wit, E. C., & van Elburg, R. M. (2019). Antibiotic Treatment in the First Week of Life Impacts the Growth Trajectory in the First Year of Life in Term Infants. *Journal of pediatric gastroenterology and nutrition*, *69*(1), 131-136. https://doi.org/10.1097/MPG.0000000000002360

Antibiotic Treatment in the First Week of Life Impacts the Growth Trajectory in the First Year of Life in Term Infants

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ABSTRACT

Objective: Antibiotic treatment in early life appears to increase the risk for childhood overweight and obesity. So far, the association between antibiotics administrated specifically during the first week of life and growth has not been studied. Therefore, we studied the association between growth and antibiotics, given in the first week of life and antibiotic courses later in the first year of life.

Method: A prospective observational birth cohort of 436 term infants with 151 receiving broad-spectrum antibiotics for suspected neonatal infection (AB+), and 285 healthy controls (AB−) was followed during their first year. Weight, height, and additional antibiotic courses were collected monthly. A generalized-additive-mixed-effects model was used to fit the growth data. Growth curve estimation was controlled for differences in sex, gestational age, delivery mode, exclusive breast-feeding, tobacco exposure, presence of siblings, and additional antibiotic courses.

Results: Weight-for-age and length-for-age increase was lower in AB+ compared with AB− ($P < 0.0001$), resulting in a lower weight and length increase 6.26 kg (standard error [SE] 0.07 kg) and 25.4 cm (SE 0.27 cm) versus 6.47 kg (SE 0.06 kg) and 26.4 cm (SE 0.21 cm) ($P < 0.05$ and $P < 0.005$, respectively) in the first year of life. Approximately 30% of the children in both groups received additional antibiotic course(s) in their first year, whereafter additional weight gain of 76 g per course was observed ($P = 0.0285$).

Conclusions: Decreased growth was observed after antibiotics in the first week of life, whereas increased growth was observed after later antibiotic course(s) in term born infants in the first year of life. Therefore, timing of antibiotics may determine the association with growth.

Key Words: cohort, early life, environmental factors, obesity

(*JPGN* 2019;69: 131–136)

What Is Known

- Antibiotic treatment in early life increases the risk for childhood overweight and obesity.
- This risk mainly exists by exposure to antibiotics in the first 6 months of life, with a dose-response relationship.

What Is New

- The first study on the association between antibiotics in the first week of life and growth of term born infants in the first year of life showed that antibiotics in the first week of life was associated with decreased growth, whereas antibiotics later in the first year of life was associated with increased growth.
- Timing of antibiotics may determine the association with growth.

Antibiotic (AB) exposure in early life is increasingly acknowledged for its contributing role in the development of childhood obesity (1,2). The ''microbiome-induced obesity'' is one of the proposed pathophysiological mechanisms for the development of obesity (3). In mice, it has been shown that AB from birth influences the gut microbiome and metabolism with sustained effects on body composition leading to a pro-obese state (4).

A recent meta-analysis of 15 cohort studies in humans concluded that AB treatment in early life increases the risk for childhood overweight and obesity (5). The most profound increase for both overweight and obesity were found when AB exposure occurred during pregnancy and the first 6 months of life. This suggests that the effect of AB on the development of obesity is influenced by the timing of the AB treatment. In addition, exposure to more than 1 AB course increases the risk for overweight and obesity, with a dose-response relationship (5,6). Other potential factors of influence are the type and duration of AB. Broad-spectrum ABs are thought to increase the risk for obesity more than small-spectrum AB (7,6); however, data are not consistent (8,9). Furthermore, longer duration of AB is associated with a more disturbed gut microbiome (10,11), which may increase the obesity risk.

Because the neonate has an almost sterile gut at birth, hypothetically, the most profound effect of AB can be expected when administered already in the first week of life. So far, the association between AB administration specifically during the first week of life and growth has not been studied. Therefore, we set up the INCA-study (INtestinal microbiota Composition after AB treatment in early life), in which we studied the association of AB treatment in the first week of life and the development of atopy,

Received December 8, 2018; accepted March 23, 2019.

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This study was registered at clinicaltrials.gov, registration number NCT02536560 (*https://www.clinicaltrials.gov/ct2/show/NCT02536560*).

This study was funded by ''Agentschap NL,'' grant number FND-06015, by Nutricia Netherlands B.V. as part of a public private partnership, and by the Christina Bader foundation (CBSIKZ).

K.K. and B.C.O. contributed equally.

The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

DOI: 10.1097/MPG.0000000000002360

microbiome development, and growth in the first year of life (12,13). In this article, we report the association between AB administered in the first week of life and growth in the first year of life and compare it with the association of AB courses administered later in the first year. In addition, the association between the duration of AB treatment and growth in the first year of life was studied, and the association with different AB types.

METHODS

Study Design

The INCA study is a prospective birth-cohort study. The study design has been published previously (12). Between August 2012 and January 2015, term born infants (≥36 weeks gestational age) were recruited from the maternity and neonatal wards of 4 teaching hospitals in the Netherlands.

AB treatment was at the pediatricians discretion, according to hospital protocol for suspected early onset neonatal infection, based on the Dutch guideline for early onset sepsis (14). In general, infants with suspicion of infection received a combination of broad-spectrum AB (gentamicin combined with either penicillin [AB^{Pen}], amoxicillin [AB^{AMX}], or amoxicillin/clavulanic acid [AB^{AMC}]). Blood cultures were taken before AB treatment was started. In case of a negative blood culture, combined with a low clinical suspicion of infection and low C-reactive protein, antibiotics were discontinued after 2 to 3 days, otherwise antibiotics were continued for 7 days.

All term born infants staying in the hospital for at least 24 hours were eligible for inclusion in either AB or control group. Exclusion criteria were severe congenital malformations; severe perinatal infection needing transfer to a neonatal intensive care unit; maternal probiotic use ≤6 weeks before delivery; and insufficient knowledge of the Dutch language. Informed consent was obtained from both parents of all participating infants. The study was approved by the regional ethical board of the St. Antonius Hospital in Nieuwegein. The trial was registered in clinical trials register as NCT02536560.

Data Collection

After inclusion, parents filled out an online questionnaire, mostly concerning the background of the family (eg, environmental factors, parental smoking habits, or presence of siblings). Moreover, parents filled out monthly questionnaires concerning last recorded weight and height at the healthy baby clinics, type of nutrition (breast-fed and/or formula fed) and additional AB treatments. Around the age of 1 year children visited the outpatient clinic of the hospital for follow-up, at which height and weight measurement was taken.

Statistical Analysis

Baseline characteristics were analyzed with the independent *t* test, one-way analysis of variance, or Chi-squared test as appropriate, for these analyses SPSS Statistics for windows, version 24.0 (Armonk, NY) was used. Because it is not standard care in all participating hospitals to determine the length after birth, a natural spline extrapolation was used to estimate the birth length in case it was missing.

In the analysis a generalized additive mixed effects model was used to fit the growth data (15). For each treatment group (AB vs no AB in the first week of life, subdivided by AB type and duration of AB administration) a flexible growth curve was estimated. Each individual was given a random intercept and each individual growth curve was modeled by a continuous autocorrelated process. By adding a random intercept in the generalized additive model, we control for birth weight. Furthermore, the growth curve estimation was controlled for by differences in sex, delivery mode, number of additional AB courses during the first year, gestational age, nutritional regime, tobacco use by the mother, whether the mother had given birth before and whether children were given probiotics. For these analyses, the package mgcv (Wood, 2006) in R version 3.3.3 (R Core Team, 2007) was used (15,16). A P value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

In total, 608 children were included: 196 treated with AB in the first week of life (AB+) and 412 healthy controls (AB−). As 172 children were excluded from analyses due to study withdrawal or lost to follow-up (Fig. 1), final analyses were performed in 436 children (AB+ [n = 151], AB− [n = 285]). In AB+, all children were treated with gentamicin for 48 hours and in most children (145) this was combined with AB^{Pen} (n = 89), AB^{AMC} (n = 24), or AB^{AMX} (n = 32). Forty-two children were treated for 2 to 3 days (AB2), and 109 for 7 days (AB7) of which 3 had a positive blood culture (2 group B *Streptococcus* (GBS) and 1 *Streptococcus oralis*). Baseline characteristics were similar between AB− and AB+, except for higher gestational age ($P = 0.001$), birth weight ($P < 0.001$), and active maternal smoking during pregnancy in AB+ ($P = 0.009$) (Table 1). Baseline characteristics were not different between the different AB treatment groups (supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B634*).

The Model

We considered five different response variables (weight-for-age [WFA], length-for-age [LFA], weight-for-length [WFL], weight, and length). For each of the variables, the autocorrelated noise term and the random intercept were significant, suggesting a stable pattern over time within subjects but quite some variation between subjects, under the same conditions in terms of AB treatment, gestational age, and sex. No significant interaction effect between sex and AB on growth has been found, allowing for account for sex by means of an additive effect.

Antibiotics

Children in AB+ were on average 180 g heavier and 0.85 cm longer at birth, corrected for gestational age differences at birth. The mean weight increase in the first 3 months of life was 2.45 and 2.65 kg in AB+ and AB−, respectively (standard error [SE] of the difference 0.086 kg, $P = 0.0210$). The mean weight increase in the first year of life in the AB+ group (6.26 kg, SE 0.07 kg) is significantly lower ($P = 0.0179$) than in the AB− group (6.47 kg, SE 0.06 kg). Although most of the difference in absolute weight growth between the AB− and AB+ groups takes place in the first three months, the AB+ group continues to experience a continuous reduction in WFA z score throughout the first year.

The average increase in length over the first 3 months in AB+ and AB− was 10.5 cm (SE 0.27 cm) and 11.4 cm (SE 0.21 cm), respectively ($P = 0.0179$). The average length increase over the first year in AB+ and AB− was 25.4 cm (SE 0.27 cm) and 26.4 cm (SE 0.21 cm), respectively ($P = 0.0018$). Around 1 year of age, weight and length were similar in AB+ and AB− with absolute difference in weight and length of 20 g and 0.13 cm (AB+ 10.0 kg [SE 0.07 kg], 77.2 cm [SE 0.21 cm], AB− 10.1 kg [SE 0.06 kg], 77.2 cm [SE 0.19 cm]).

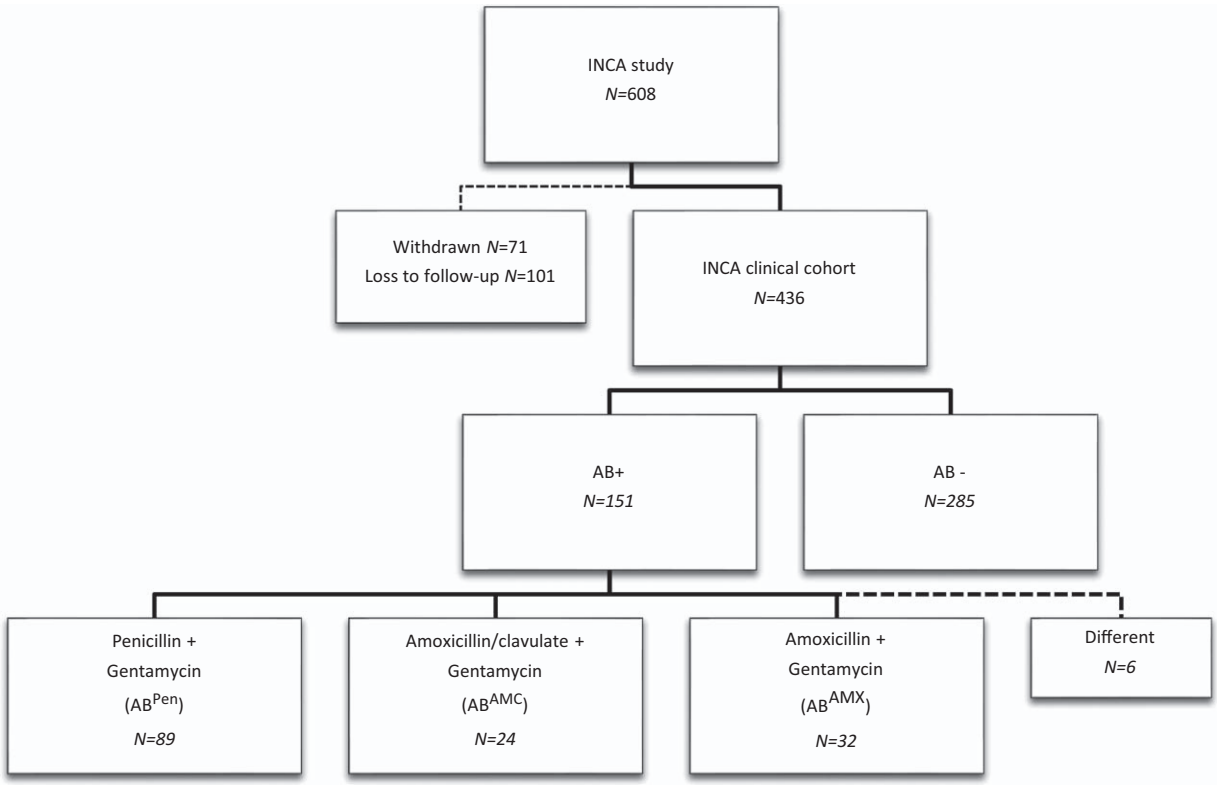

FIGURE 1. Inclusion flowchart. AB+ (antibiotic exposed); AB− (healthy controls). Dotted blocks show children excluded from (sub)analyses. Children were considered lost-to-follow up when data from <3 months were available. Children withdrawn were considered as such when parents actively withdrawn participation in the study.

At birth, WFA and LFA *z* scores were higher in AB+ than in AB− (WFA +0.314 [SE 0.074] vs −0.067 [SE 0.074], LFA +0.130 [SE 0.076] vs −0.256 [SE 0.064]), but around 1 year of age, they were lower in AB+ than AB− (WFA −0.358 [SE 0.084] vs −0.074 [SE 0.086], LFA +0.081 [SE 0.086] vs. +0.274 [SE 0.080]), respectively both $P < 0.0001$ (Fig. 2A and B). The WFA and LFA lines of AB+ and AB− cross around day 100. At birth, WFL *z* scores were lower in AB− than in AB+ (WFL AB+ −0.250 [SE 0.076] vs AB− −0.614 [SE 0.104]) but around the first birthday were similar in both groups (WFL AB+ −0.290 [SE 0.082] vs AB− −0.310 [SE 0.121]) (Fig. 2A and B).

Dose Effect Relation Additional Antibiotic

After the first week of life, in the whole INCA cohort about 30% was prescribed 1 or more AB courses before the first birthday, equally divided over the AB+ and AB− groups. Per additional course of AB in the first year of life, irrespective of AB in the first week of life, a significant mean (SE) weight gain of 76 g (34 g) was observed ($P = 0.0285$), whereas length increase 0.1 cm (0.1 cm) per course was not significant ($P = 0.532$).

Duration of Antibiotic 2 Versus 7 Days

Growth in mean (SE) weight and length increase was not different between AB2 and AB7 group in the first 3 months (2.425 kg [0.076 kg] vs 2.473 kg [0.065 kg] and 10.3 cm [0.41 cm] vs 10.7 cm [0.30 cm]), respectively, nor in the first year

TABLE 1. Baseline characteristics: AB− (healthy controls); AB+ (antibiotic exposed, total group)

	AB− N 285	AB + N 151	Mean difference	95% CI	
GA mean (SD)	39.4 (1.5)	40.0 (1.3)*	−0.5	−0.7	−0.2
Birth weight mean (SD)	3444 (537)	3681 (533)*	−237	−343	−131
Male, n (%)	152 (54)	85 (56)			
Siblings, n (%)	122 (46)	48 (35*)			
Additional AB courses					
1 Course, n (%)	50 (18)	26 (17)			
2 Courses, n (%)	28 (10)	13 (9)			
>2 Courses, n (%)	10 (4)	7 (5)			
Delivery mode					
Vaginal, n (%)	187 (66)	112 (74)			
C-section, n (%)	98 (34)	39 (26)			
Breast-feeding exclusive					
>3 mo, n (%)	104 (37)	52 (34)			
<3 mo, n (%)	116 (41)	65 (43)			
0 mo, n (%)	65 (23)	34 (23)			
Tobacco exposure					
Pregnancy active, n (%)	12 (5)	16* (12)			
Pregnancy passive, n (%)	32 (12)	23 (17)			

CI = 95% confidence interval; GA = (gestational age) in weeks; SD = (standard deviation); birth weight in grams.
*$P < 0.05$ as compared to AB−.

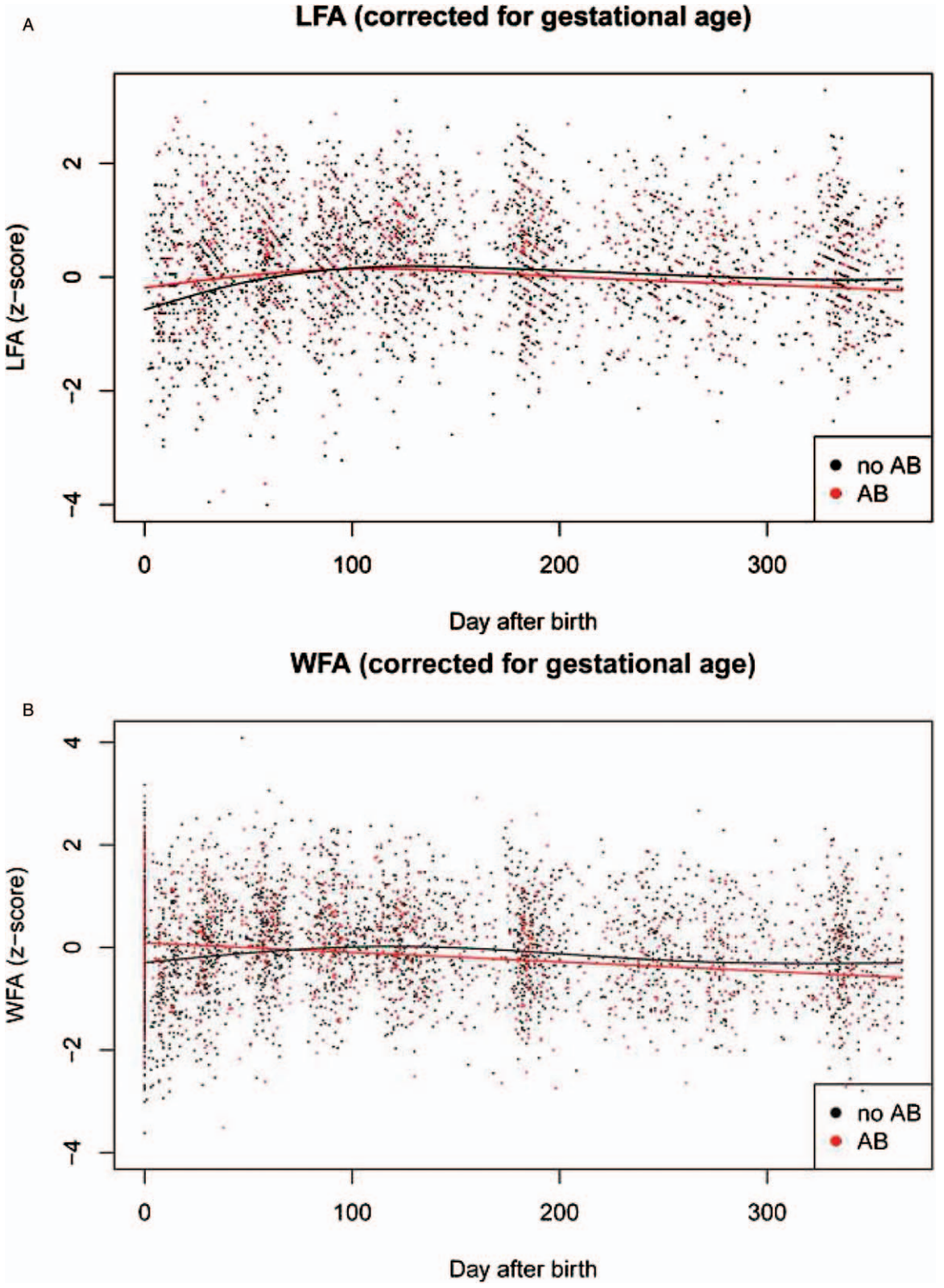

FIGURE 2. A, B, Graphs of the generalized additive mixed effects model analyses with the growth curves of the cohort. Weight-for-age (WFA) and length-for-age (LFA) development over the first year of life, respectively. AB (treated with antibiotics), no AB (healthy controls).

of life (6.234 kg [0.086 kg] vs 6.262 kg [0.071 kg] and 25.7 cm [0.41 cm] vs 25.2 cm [0.30 cm]), respectively.

Type of Antibiotics

The only significant differences were observed between AB^{AMX} and AB^{AMC} and between AB^{AMX} and AB^{Pen}. AB^{AMX} administered in the first week of life showed a smaller weight increase of on average 409 gram (SE 0.130 kg) than AB^{AMC} ($P = 0.001$) in the first year of life. AB^{AMX} administered in the first week showed a smaller length increases of on average 1.8 cm (SE 0.53 cm) than AB^{Pen} in the first 3 months of life and 1.3 cm (SE 0.51 cm) in the first year of life ($P = 0.0006$ and $P = 0.0101$, respectively).

DISCUSSION

This is the first study examining the association between AB administered in the first week of life and the growth trajectory in the first year of life. A decreased growth was observed after AB in the first week of life compared to the AB−, whereas, after each additional AB− course later in the first year of life a significant additional weight gain of 76 g was observed, irrespective of AB in the first week of life.

Our results are partly in contrast to previously published systematic reviews, showing an increased risk for childhood obesity after AB treatment in the first 2 years of life (5,6). When these studies are evaluated in detail, it appears that especially AB exposure in the first 6 months of life contribute to this increased risk of overweight or obesity at 2 (9,17) or 7 (18,19) years of age. However, none of these previously published studies evaluated the association between AB and growth specifically in the neonatal period. After the first week of life, in line with existing literature, we showed an additional weight gain of 76 g after every additional AB course in the first year of life (5,6).

Several explanations are possible for the different association between weight gain and AB given in the first week of life versus AB later in life. First, it is known that the microbiome rapidly changes in the first weeks of life (20). Therefore, the developmental stage of the microbiome at the moment of AB treatment may be an important factor in the pathophysiological mechanism of AB-induced obesity. Second, the route of AB administration may have different effects on the gut microbiome and thus different associations with weight gain (21–23). In our study, ABs were administrated intravenously in the first week of life, whereas AB treatments later in the first year were mostly prescribed orally. It has been shown previously that a combination of oral and intravenously AB administration can have a larger detrimental effect on the gut-microbiome than purely intravenously administration (22). Therefore, it is possible that the different associations on growth, as found in our study between AB in the first week versus AB later in the first year, may not (only) have been a time-dependent factor, but influenced by the route of administration. Future studies in neonates must investigate the difference between oral and intravenously administration (or a combination of the two) on growth and the microbiome development.

Another important difference between AB in the first week of life and AB later in the first year of life is the type and combination of AB. In our study, in the first week of life all children were treated with gentamicin for 2 days and a β-lactam AB for 2 to 7 days depending on the local hospital protocol. After the first week of life, children were treated with a single AB (mostly amoxicillin). The metabolomic function of the gut (and thus its effect on growth) is strongly affected by bacterial composition, which in turn has been shown to be affected by the type of AB (24). The combination of 2 ABs (eg, gentamicin and ampicillin) has been shown to have a larger detrimental effect on the gut-microbiome than each AB separately (24). Previous clinical studies evaluated treatment with either a single broad- or small-spectrum (β-lactam) AB, macrolide, or antimetabolite agents, but found no consistent results in the effect on growth of children (8,9,25). In our study we also found differences between the types of AB given in the first week, with AB^{AMX} showed the lowest weight gain. Fecal samples, collected within the INCA study, may provide more insight in differences in the microbiome development between the AB types. Moreover, future studies will be needed to study the effects of different types of AB in the neonatal period on the developing microbiome and on growth.

Given the findings in this study, it is possible that AB in the first week of life is associated with a decreased growth rate instead of an increased growth rate as found after AB exposure later during the first year of life. Although the absolute differences in growth are small, small impairments in growth patterns in early life may affect later growth and health, such as shorter adult height, lower attained schooling, reduced adult income, and several chronic diseases such as cardiovascular disorders and diabetes (26). Longer follow-up of the INCA cohort is therefore important, to evaluate the long-term consequences of AB in the first week of life, and additional AB courses during the first year of life, because already it has been shown that rapid growth in early life is associated with an increased risk for obesity later in childhood and adolescence (27).

The prospective design of the INCA study with healthy term born infants as a control group is an important strength of this study. Data on growth were collected on 10 time points in the first year of life. These measurements were mostly done by the healthy baby clinic, which parents visit regularly in the first year of life, resulting in standardized measurements by health care professionals. Furthermore, since data regarding additional AB courses were collected every month, there was a low chance on recall bias.

A limitation of this study is the fact that type and route of administration of AB given later in life was not similar to AB given in the first week of life, which prevents solid conclusions on the associations between growth and AB given in the first week versus AB later during the first year of life. Moreover, we did not have data on several confounders, associated with growth in early life, such as the age of solid food introduction, antibiotic exposure during pregnancy or maternal prepregnancy weight and gestational weight gain. For future research, we recommend considering these factors as well.

CONCLUSIONS

In the INCA-cohort, we have shown less growth in infants who were treated with AB in their first week of life compared to healthy controls. In contrast, additional weight gain was observed after each additional course of AB later in the first year of life. Follow-up of the INCA cohort is necessary to show whether these differences in growth trajectories will continue after the first year of life and whether this will result in a different prevalence's of overweight and obesity later in childhood.

REFERENCES

1. Turta O, Rautava S. Antibiotics, obesity and the link to microbes—what are we doing to our children? *BMC Med* 2016;14:57.
2. Woo Baidal JA, Locks LM, Cheng ER, et al. Risk factors for childhood obesity in the first 1,000 days: a systematic review. *Am J Prev Med* 2016;50:761–79.
3. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci USA* 2004;101:15718–23.

4. Cox LM, Yamanishi S, Sohn J, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* 2014;158:705–21.
5. Shao X, Ding X, Wang B, et al. Antibiotic exposure in early life increases risk of childhood obesity: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2017;8:170.
6. Rasmussen SH, Shrestha S, Bjerregaard LG, et al. Antibiotic exposure in early life and childhood overweight and obesity: a systematic review and meta-analysis. *Diabetes Obes Metab* 2018;20:1508–14.
7. Bailey LC, Forrest CB, Zhang P, et al. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr* 2014;168:1063–9.
8. Gerber JS, Bryan M, Ross RK, et al. Antibiotic exposure during the first 6 months of life and weight gain during childhood. *JAMA* 2016;315: 1258–65.
9. Mbakwa CA, Scheres L, Penders J, et al. Early life antibiotic exposure and weight development in children. *J Pediatr* 2016;176:105.e2–13.e2.
10. Zwittink RD, Van Zoeren-Grobben D, Martin R, et al. Metaproteomics reveals functional differences in intestinal microbiota development of preterm infants. *Mol Cell Proteomics* 2017;16:1610–20.
11. Fouhy F, Guinane CM, Hussey S, et al. High-throughput sequencing reveals the incomplete, short-term recovery of infant gut microbiota following parenteral antibiotic treatment with ampicillin and gentamicin. *Antimicrob Agents Chemother* 2012;56:5811–20.
12. Rutten NB, Rijkers GT, Meijssen CB, et al. Intestinal microbiota composition after antibiotic treatment in early life: the INCA study. *BMC Pediatr* 2015;15:204.
13. Oosterloo BC, Van Elburg RM, Rutten NB, et al. Wheezing and infantile colic are associated with neonatal antibiotic treatment. *Pediatr Allergy Immunol* 2018;29:151–8.
14. Guideline; Perinatal group B-streptococcal (GBS) Disease: Dutch Society for Obstetrics and Gyneacology (NVOG); 2008. Available at: https://www.nvk.nl/Kwaliteit/Richtlijnen-overzicht/Details/articleType/ArticleView/articleId/694/Preventie-en-behandeling-van-early-onset-neonatale-infecties#tab15.
15. Wood SN. Generalized Additive Models: An Introduction With R: United Kingdom: Chapman and Hall/CRC; 2006.
16. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2017. Available online at https://www.R-project.org/.
17. Ville AP, Heyman MB, Medrano R, et al. Early antibiotic exposure and risk of childhood obesity in Latinos. *Child Obes* 2017;13:231–5.
18. Ajslev TA, Andersen CS, Gamborg M, et al. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, prepregnancy weight and early administration of antibiotics. *Int J Obes (Lond)* 2011;35:522–9.
19. Trasande L, Blustein J, Liu M, et al. Infant antibiotic exposures and early-life body mass. *Int J Obes (Lond)* 2013;37:16–23.
20. Timmerman HM, Rutten N, Boekhorst J, et al. Intestinal colonisation patterns in breastfed and formula-fed infants during the first 12 weeks of life reveal sequential microbiota signatures. *Sci Rep* 2017;7:8327.
21. Zaura E, Brandt BW, Teixeira de Mattos MJ, et al. Same exposure but two radically different responses to antibiotics: resilience of the salivary microbiome versus long-term microbial shifts in feces. *MBio* 2015;6:e01693–1715.
22. Arat S, Spivak A, Van Horn S, et al. Microbiome changes in healthy volunteers treated with GSK1322322, a novel antibiotic targeting bacterial peptide deformylase. *Antimicrob Agents Chemother* 2015;59:1182–92.
23. Arboleya S, Sanchez B, Milani C, et al. Intestinal microbiota development in preterm neonates and effect of perinatal antibiotics. *J Pediatr* 2015;166:538–44.
24. Ferrer M, Mendez-Garcia C, Rojo D, et al. Antibiotic use and microbiome function. *Biochem Pharmacol* 2017;134:114–26.
25. Saari A, Virta LJ, Sankilampi U, et al. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. *Pediatrics* 2015;135:617–26.
26. De Onis M. Child growth and development. In: de Pee S, Taren D, Bloem MW, eds. *Nutrition and Health in a Developing World.* Cham: Springer International Publishing; 2017:119–41.
27. Andrea SB, Hooker ER, Messer LC, et al. Does the association between early life growth and later obesity differ by race/ethnicity or socioeconomic status? A systematic review. *Ann Epidemiol* 2017;27:583.e5–92.e5.