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Catherine A. Mbakwa, MSc[1,2,*], Lotte Scheres, BSc[2,*], John Penders, PhD[2,3], Monique Mommers, PhD[2], Carel Thijs, MD, PhD[2], and Ilja C. W. Arts, PhD[2,4]

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

From the [1]Top Institute Food and Nutrition, Wageningen, The Netherlands; [2]Department of Epidemiology, Maastricht University, CAPHRI School for Public Health and Primary Care; [3]Department of Medical Microbiology, Maastricht University Medical Center, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht and CAPHRI School for Public Health and Primary Care; and [4]CARIM School for Cardiovascular Diseases, and Maastricht Center for Systems Biology (MaCSBio), Maastricht, The Netherlands

*Contributed equally.

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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

not exposed to antibiotics are presented as mean ± SD for continuous variables, and numbers and percentages for categorical variables.

Generalized estimating equations (GEE) models with an autoregressive correlation structure were used to analyze the association between antibiotic use and the 7 repeated BMI z-scores, weight z-scores, height z-scores (as continuous outcomes), and overweight status over time (as a binary outcome). The age of the child at the time of weight and height measurement was included in all models as the time variable. We investigated whether the association between the main exposures and outcomes differed over time, and also, if this association differed between recruitment groups (alternative and conventional) and sex. This was done by entering a time exposure, a recruitment group-exposure, and a sex-exposure interaction term, respectively, in all models. In none of the models were these interactions statistically significant ($P > .05$). The following a priori potential confounders[33-35] were included in all adjusted (multivariable) models: recruitment group (conventional or alternative), household size, maternal education (low [primary, preparatory vocational or lower general secondary schools], middle [vocational, higher general secondary or pre-university education], high [higher vocational or academic education], or other), maternal prepregnancy weight, maternal pregnancy weight gain, smoking during pregnancy, gestational diabetes, gestational hypertension, mode and place of delivery (vaginal delivery at home, vaginal delivery in hospital, or caesarean delivery in hospital), sex, birth weight, gestational age, duration of breastfeeding, child's dietary intake (total fiber, total energy, fats and carbohydrates both as percentage of total energy), and child's physical activity.

Because of loss to follow-up and incompletely filled out questionnaires, missing values for some confounding variables occurred. To obtain an unbiased and statistically more powerful analysis,[36] we imputed these confounding variables. We used a Markov Chain Monte Carlo method for multiple imputations in SAS (SAS Institute, Cary, North Carolina) into imputed missing values: ranging from 0.004% missing values for duration of breastfeeding to 0.1% for household size. Missing values for categorical confounding variables were imputed by adding a "missing" category.

We then performed GEE analyses on the combined imputed datasets (n = 10) while averaging all parameter estimates for each variable.[37,38] Results from the combined imputed datasets were comparable with those of the original nonimputed data; hence, final results were reported from the imputed data. Data analysis was performed using statistical software packages SAS 9.3 (SAS Institute, Cary, North Carolina) and SPSS 21.0 (SPSS Inc, Chicago, Illinois). A preselected significance level of P value <.05 was considered in all analyses.

Results

From the cohort of 1171 children with information on antibiotic use, a total of 979 children were eligible for analysis (**Figure**). Participant characteristics of the current study population and the entire KOALA cohort are presented in **Table I**. In general, the KOALA cohort and the present study population were comparable, although the proportion of mothers with a high education level as well as home-born children appeared to be slightly higher, and the duration of breastfeeding appeared to be longer in the present study population. Of the 979 children, 613 (62.6%) children were exposed to at least 1 antibiotic course during follow-up (**Table II**). Of these 613 children, 127 (13%) received 4 or more courses of antibiotics over the entire follow-up period, and 64 (7%) and 102 (11.7%) were exposed to antibiotics before the age of 6 months and at 6-12 months, respectively. The majority of children, 531 (54.5%), were exposed to BS β-lactams, whereas macrolides (168; 17.2%), NS β-lactam agents (72; 7.4%), antimetabolites (37; 3.8%), and other antibiotics (24; 2.4%) were used less frequently. All children had at least 1 anthropometric measurement available during follow-up (**Table III**). At time point 1 (beginning of follow-up), anthropometric data were available for 896 of the 979 children, with 15.1% of the children being overweight. For subsequent follow-up time points, anthropometric data were available for 900, 848, 820, 757, 709, and 768 children, respectively.

When analyzing the number of courses of antibiotics to which children were exposed during the entire follow-up period, neither the crude nor adjusted models showed significant associations with BMI-, weight-, and height z-scores or overweight (**Tables II** and **IV**; **Table IV** available at www.jpeds.com).

When we subsequently examined antibiotic exposure at different ages, children exposed to a single course of antibiotics in the first 6 months of life had higher weight z-scores (adjusted GEE estimates [adjβ] 0.24; 95% CI 0.03-0.44) and higher height z-scores (adjβ 0.23; 95% CI 0.0002-0.46). We found no association for exposure to a single course of antibiotics in the second 6 months of life with any of the outcomes. Possibly because of the small group sizes for exposure to ≥2 course of antibiotics in the first 6 and second 6 months of life, we did not find an association with any of the outcomes, although effect sizes were fairly comparable with the group exposed to ≥2 courses of antibiotics in the second year of life. This can be confirmed by the fact that grouping exposure in the first and second 6 months of life into exposure in the first year of life, the exposure to ≥2 courses of antibiotics was significantly associated with higher height z-scores (adjβ 0.25; 95% CI 0.04-0.46). Children exposed to ≥2 courses of antibiotics in the second year of life had higher BMI-, weight-, and height z-scores compared with children not exposed to antibiotics (**Table II**). These associations in the second year of life were significant for higher weight z-scores (adjβ 0.34; 95% CI 0.07-0.60), and borderline for BMI (adjβ 0.22; 95% CI −0.02 to 0.46) and height z-scores (adjβ 0.29; 95% CI −0.003 to 0.59). No clear associations were observed for risk of being overweight in any of the age periods (**Table IV**).

Table I. Participant characteristics of the present study population and the total KOALA Birth Cohort Study at start of the follow-up

Covariates	KOALA Birth Cohort Study (N = 3030) Mean ± SD	Study population (N = 979)* Mean ± SD	Exposed (n = 613) Mean ± SD	Unexposed (n = 366) Mean ± SD
Recruitment group, n (%)				
Conventional	2512 (81.9)	801 (81.8)	534 (87.1)	267 (73.0)
Maternal education, n (%)†				
Low	289 (9.5)	73 (7.5)	54 (8.8)	19 (5.2)
Middle	1062 (35.0)	345 (35.2)	234 (38.2)	111 (30.3)
High	1343 (44.3)	521 (53.2)	300 (48.9)	221 (60.4)
Other	108 (3.6)	30 (3.1)	18 (2.9)	12 (3.3)
Maternal smoking during pregnancy (n (%))				
Yes	200 (6.6)	49 (5.0)	28 (4.6)	11 (3.0)
Maternal prepregnancy weight (kg)	67.8 ± 13.1	68.0 ± 12.5	68.4 ± 12.6	67.4 ± 12.2
Maternal pregnancy weight gain (kg)	14.3 ± 5.1	14.0 ± 5.0	14.1 ± 5.0	13.9 ± 4.9
Gestational diabetes, n (%)				
Yes	19 (0.6)	7 (0.7)	7 (1.1)	0 (0.0)
Gestational hypertension				
Yes	118 (3.9)	48 (4.9)	31 (5.1)	17 (4.6)
Mode and place of delivery, n (%)				
Vaginally at home	1194 (39.4)	451 (46.1)	270 (44.0)	181 (49.5)
Vaginally in hospital	1149 (37.9)	395 (40.3)	253 (41.3)	142 (38.8)
Cesarean delivery at hospital	311 (10.3)	107 (10.9)	70 (11.4)	37 (10.1)
Sex, n (%)				
Male	1543 (50.9)	490 (50.1)	314 (51.2)	176 (48.1)
Birthweight (g)	3504 ± 512.4	3551.3 ± 454.7	3547 ± 456	3557 ± 453
Gestational age (wk)	39.8 ± 5.0	39.8 ± 3.0	39.8 ± 3.7	39.8 ± 1.2
Duration of breastfeeding (mo)	4.9 ± 4.6	5.4 ± 0.1	4.9 ± 4.1	6.4 ± 4.4
Dietary factors				
Total energy intake (kJ)	6173 ± 1249	6181 ± 1277	6186 ± 1245	6173 ± 1330
% energy intake from protein	14.6 ± 2.1	14.6 ± 2.0	14.6 ± 2.0	14.5 ± 2.0
% energy intake from carbohydrates	55.8 ± 5.0	55.8 ± 4.9	55.8 ± 4.9	55.7 ± 4.9
Fiber (g)	15.3 ± 4.0	15.3 ± 3.8	15.0 ± 3.7	15.7 ± 4.0
Household size	4.3 ± 0.8	4.3 ± 0.8	4.2 ± 0.7	4.4 ± 0.8
Physical activity (h/wk)	9.5 ± 4.5	9.3 ± 4.3	9.3 ± 4.4	9.1 ± 4.0

*Totals may not add up to 979 because of missing values (see number of missing values in Methods section).
†Maternal education—Low: primary school, preparatory vocational, or lower general secondary school; middle: vocational, higher general secondary, or pre-university education; high: higher vocational or academic education.

Regarding the number of courses of specific types of antibiotics, we found that exposure to ≥2 courses of BS β-lactam agents over the entire follow-up period was associated with significantly increased weight z-sores (adjβ 0.11; 95% CI 0.00-0.22), and this was not the case for children exposed to only a single course of BS β-lactam agent (Table II). In addition, receipt of a single course of NS β-lactam during follow-up was associated with higher weight z-scores (adjβ 0.18; 95% CI 0.00-0.35) and a trend to higher height z-scores (adjβ 0.12; 95% CI −0.06 to 0.31), compared with children not exposed to NS β-lactams during the course of the follow-up. In contrast to these observations, exposure to ≥2 courses of NS β-lactam antibiotics was inversely associated with height z-scores (adjβ −0.49; 95% CI −0.78 to −0.19), but the number of children who had been prescribed multiple courses of NS β-lactam agents was very small (n = 7). The same was true for children exposed to ≥2 courses of antimetabolites (adjβ −0.53; 95% CI −1.01 to −0.06; n = 8). No associations were found for macrolides and other antibiotic agents (metronidazole, nitrofurantoin, gentamicin, and tetracycline) with BMI-, weight-, and height z-scores. Furthermore, no significant associations were found for any of the specific antibiotics with risk of overweight (Table IV).

Discussion

Within the context of the longitudinal KOALA study, we examined childhood exposure to antibiotics (timing, type, and number of courses) as reported by the children's GPs over an extensive follow-up period from birth up to 10 years of age. Our study demonstrates that antibiotic exposure in early childhood is associated with higher weight and height z-scores in children up to 10 years of age, independent of other determinants of growth in childhood. Exposure to a single course of antibiotics before 6 months of age and exposure to multiple courses of antibiotics between 1-2 years of age showed the most pronounced associations with height and weight z-scores. Also, β-lactam agents over the entire follow-up period were associated with increasing weight z-scores.

Several studies examined the association between parent-reported antibiotic exposures during infancy in relation to BMI or overweight in childhood.[24-26] Although these studies reported an association between antibiotic exposure and

Table II. GEE results showing associations of antibiotic exposures (number of courses, period, and type) with BMI-, weight-, and height z-scores during the first 10 years of life

		BMI z-score			Weight z-score			Height z-score		
		Unadjustedβ (95% CI)*	adjβ† (95% CI)	*P* value‡	Unadjustedβ (95% CI)	adjβ (95% CI)*	*P* value	Unadjustedβ (95% CI)	adjβ (95% CI)	*P* value
No. of courses during follow-up	n									
None	366	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	259	0.06 (−0.07 to 0.18)	0.03 (−0.11 to 0.18)	.655	0.03 (−0.10 to 0.16)	−0.03 (−0.15 to 0.09)	.635	−0.05 (−0.19 to 0.09)	−0.09 (−0.21 to 0.04)	.185
2-3	221	0.12 (−0.01 to 0.25)	0.07 (−0.05 to 0.19)	.263	0.09 (−0.05 to 0.22)	0.04 (−0.07 to 0.16)	.477	−0.02 (−0.16 to 0.13)	−0.02 (−0.16 to 0.11)	.713
≥4	127	0.05 (−0.10 to 0.21)	0.01 (−0.11 to 0.13)	.839	0.11 (−0.05 to 0.27)	0.11 (−0.04 to 0.25)	.153	0.09 (−0.08 to 0.26)	0.11 (−0.05 to 0.28)	.173
No. of courses of antibiotics by period										
First 6 mo of life (0-6)										
None	910	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	54	0.10 (−0.12 to 0.31)	0.14 (−0.05 to 0.33)	.152	0.18 (−0.06 to 0.41)	0.24 (0.03 to 0.44)	.025	0.17 (−0.08 to 0.41)	0.23 (0.0002 to 0.46)	.0498
≥2	10	0.39 (−0.10 to 0.88)	0.23 (−0.21 to 0.66)	.304	0.43 (−0.08 to 0.93)	0.09 (−0.15 to 0.57)	.253	0.25 (−0.15 to 0.64)	0.09 (−0.26 to 0.44)	.604
Second 6 mo of life (6-12)										
None	824	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	86	0.05 (−0.13 to 0.24)	0.03 (−0.13 to 0.20)	.687	0.02 (−0.15 to 0.19)	0.04 (−0.10 to 0.19)	.605	0.04 (−0.11 to 0.19)	0.04 (−0.10 to 0.19)	.945
≥2	16	0.17 (−0.67 to 0.44)	0.14 (−0.65 to 0.37)	.593	0.04 (−0.38 to 0.45)	0.04 (−0.34 to 0.53)	.675	0.18 (−0.18 to 0.54)	0.25 (−0.09 to 0.60)	.153
Second year of life (1-2 y)										
None	804	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	140	−0.02 (−0.15 to 0.12)	0.01 (−0.12 to 0.13)	.938	0.02 (−0.11 to 0.16)	0.05 (−0.07 to 0.17)	.424	0.04 (−0.12 to 0.20)	0.06 (−0.09 to 0.21)	.422
≥2	30	0.25 (−0.02 to 0.52)	0.22 (−0.02 to 0.46)	.069	0.36 (0.04 to 0.68)	0.34 (0.07 to 0.60)	.012	0.30 (−0.03 to 0.63)	0.29 (−0.003 to 0.59)	.052
Above second year of life (>2 y)										
None	438	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	266	0.04 (−0.08 to 0.16)	0.003 (−0.11 to 0.12)	.954	0.05 (−0.08 to 0.17)	0.01 (−0.10 to 0.12)	.858	0.001 (−0.13 to 0.13)	−0.01 (−0.14 to 0.11)	.816
≥2	260	0.07 (−0.05 to 0.18)	0.03 (−0.08 to 0.14)	.596	0.06 (−0.06 to 0.19)	0.04 (−0.06 to 0.15)	.432	−0.002 (−0.13 to 0.13)	0.02 (−0.10 to 0.14)	.767
No. of courses by type of antibiotics										
BS β-lactams§										
None	442	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	269	−0.03 (−0.15 to 0.09)	−0.05 (−0.16 to 0.06)	.413	−0.03 (−0.16 to 0.09)	−0.04 (−0.16 to 0.07)	.439	−0.04 (−0.18 to 0.09)	−0.03 (−0.16 to 0.09)	.589
≥2	262	0.10 (−0.02 to 0.21)	0.07 (−0.04 to 0.19)	.187	0.12 (−0.004 to 0.24)	0.11 (0.003 to 0.22)	.044	0.05 (−0.08 to 0.18)	0.08 (−0.05 to 0.20)	.223
NS β-lactams§										
None	902	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	65	0.11 (−0.08 to 0.29)	0.08 (−0.10 to 0.26)	.370	0.19 (0.0003 to 0.38)	0.18 (0.005 to 0.35)	.044	0.17 (−0.04 to 0.37)	0.12 (−0.06 to 0.31)	.063
≥2	7	0.10 (−0.25 to 0.45)	0.16 (−0.18 to 0.49)	.359	−0.29 (−0.69 to 0.11)	−0.17 (−0.49 to 0.15)	.292	−0.63 (−1.02 to −0.24)	−0.49 (−0.78 to −0.19)	.001
Macrolide§										
None	806	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	116	0.14 (−0.01 to 0.28)	0.09 (−0.05 to 0.23)	.189	0.15 (−0.01 to 0.30)	0.09 (−0.04 to 0.22)	.193	0.08 (−0.09 to 0.26)	0.05 (−0.12 to 0.21)	.567
≥2	52	−0.06 (−0.28 to 0.16)	−0.07 (−0.28 to 0.14)	.511	0.002 (−0.23 to 0.23)	−0.01 (−0.21 to 0.19)	.906	0.03 (−0.19 to 0.25)	0.03 (−0.16 to 0.22)	.745
Antimetabolite§										
None	937	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	29	−0.08 (−0.36 to 0.20)	−0.05 (−0.30 to 0.19)	.670	−0.01 (−0.36 to 0.35)	0.04 (−0.25 to 0.33)	.250	0.11 (−0.25 to 0.47)	0.17 (−0.15 to 0.49)	.307
≥2	8	−0.11 (−0.58 to 0.36)	−0.02 (−0.41 to 0.37)	.912	−0.47 (−1.05 to 0.12)	−0.30 (−0.81 to 0.21)	.794	−0.71 (−1.19 to −0.24)	−0.53 (−1.01 to −0.06)	.029
Others§										
None	950	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	
1	15	0.20 (−0.21 to 0.61)	0.13 (−0.29 to 0.56)	.539	0.18 (−0.29 to 0.66)	0.11 (−0.34 to 0.56)	.629	0.04 (−0.45 to 0.54)	−0.01 (−0.46 to 0.45)	.980
≥2	9	−0.11 (−0.49 to 0.27)	−0.16 (−0.51 to 0.19)	.369	−0.13 (−0.54 to 0.29)	−0.19 (−0.58 to 0.19)	.324	−0.11 (−0.50 to 0.28)	−0.17 (−0.55 to 0.21)	.374

*β: Regression coefficients (with 95% CI) from linear regression using GEE with an autoregressive correlation structure, and age of weight/height measurement as the time variable.

†Adjusted for recruitment group (conventional or alternative lifestyle), household size, maternal level of education (low, middle, high, and others), maternal prepregnancy weight, maternal pregnancy weight gain, smoking during pregnancy (yes/no), gestational diabetes, gestational hypertension, place and mode of delivery, sex, birthweight, gestational age, duration of breastfeeding, dietary intake (total fiber, total energy, fats and carbohydrates both as percentage of total energy), child's physical activity, and child's ages during anthropometric measurements.

‡Column represents *P* values for the adjusted analysis.

§BS β-lactams (amoxicillin, cephalosporin), NS β-lactams (flucloxacillin, pheneticillin, phenoxymethylpenicillin), macrolides (erythromycin, clarithromycin, azithromycin), antimetabolites (co-trimoxazole, trimethoprim), and others (nitrofurantoin, metronidazole, gentamicin, and tetracycline).

Table III. Anthropometric measures of the study population (N = 979) at the 7 different follow-up time points

	Time point 1 (2001)	Time point 2 (2002)	Time point 3 (2006)	Time point 4 (2007)	Time point 5 (2008)	Time point 6 (2009)	Time point 7 (2010)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Children with anthropometric data, n (%)	896 (91.5)	900 (91.9)	848 (86.6)	820 (83.8)	757 (77.3)	709 (72.4)	768 (78.4)
Age (y)	0.9 ± 0.1	1.8 ± 0.3	4.7 ± 0.3	6.2 ± 0.5	6.8 ± 0.5	7.8 ± 0.5	8.8 ± 0.5
Overweight, n (%)							
Yes	135 (15.1)	129 (14.3)	63 (7.4)	48 (5.9)	42 (5.5)	48 (6.8)	69 (9.0)
No	761 (84.9)	771 (85.7)	785 (72.6)	772 (94.1)	715 (94.5)	661 (93.2)	699 (91.0)
BMI z-score	0.05 ± 1.02	−0.07 ± 1.04	−0.28 ± 1.02	0.31 ± 0.95	0.33 ± 0.94	−0.30 ± 0.96	−0.25 ± 0.97
Weight z-score	−0.02 ± 0.90	−0.05 ± 0.94	−0.25 ± 0.96	−0.23 ± 0.95	−0.30 ± 0.94	−0.28 ± 0.95	−0.21 ± 0.93
Height z-score	−0.02 ± 1.00	−0.02 ± 1.03	−0.10 ± 1.03	−0.05 ± 0.96	−0.10 ± 0.95	−0.09 ± 0.94	−0.07 ± 0.92

increased weight, these associations were sometimes found only in subgroups. Murphy et al[25] found an association between antibiotic exposure and increased weight in boys but not in girls, and Asjlev et al[26] found this association apparent only in children from normal weight mothers. An important limitation of studies using parent-reported antibiotic exposure is their inability to distinguish between different types of antibiotics or to examine the effect of the number of antibiotic courses to which children were exposed.

Two large GP and prescription registry-based cohort studies examined the association between antibiotic exposure within the first 2 years of life and BMI in early childhood.[21,23] These studies took into account the timing, number of prescriptions, and the type of antibiotics but were not able to control for confounding factors, such as habitual diet or physical activity. Both studies showed that antibiotic exposure was associated with increased (over)weight, which appeared to be most pronounced for exposure to macrolides[21] and BS antibiotics,[23] respectively.

Azad et al[22] investigated antibiotic exposure in the first year of life, as retrieved from prescription records, in association with overweight and adiposity at the ages of 9 and 12 years within the context of the Canadian Study of Asthma, Genes and the Environment. Infants receiving antibiotics in the first year of life were more likely to develop overweight and have higher central adiposity in later childhood compared with unexposed infants. These associations only remained statistically significant in boys but not in girls.[22] Several previous studies indicated the existence of sex differences in the association between antibiotic exposure and anthropometric outcomes.[21,22,25] In our study, we did not find a statistically significant interaction between antibiotic exposure and sex in association with these anthropometric outcomes.

In contrast to previous studies, we were able to account for antibiotic exposure over a long period of time (up to 10 years of age). We, however, found that exposure to antibiotics in the first 2 years of life, but not exposure over the entire follow-up period was associated with weight-related outcomes. A single course of antibiotics in the first 6 months of life was significantly associated with increased weight- and height z-scores. This is consistent with the results of Trasande et al, who found that antibiotic exposure in the first 6 months of life (but not exposure from 6 to 14 months of age) was consistently associated with increased body mass at 10, 20, and 38 months of age, respectively, and with overweight at 38 months of age.[24] We also found that multiple courses of antibiotics during the second year of life was associated with increased weight- and height z-scores. This could indicate that repeated antibiotic-induced microbial perturbations are required to demonstrate an effect on weight development at the age when the microbiome starts to become more resilient.

Our findings support the hypothesis that the time window in which antibiotics can influence weight development appears to be within the first 2 years of life. In a mouse model to mimic pediatric antibiotic use, therapeutic antibiotic

administration accelerated total mass growth and progressively changed the microbiome composition and function, depending on the number of courses and type of antibiotic.[39]

Consistent with the findings of Bailey et al,[23] in which antibiotic exposure was also assessed using medical records obtained from GPs, we found that exposure to β-lactam agents, especially repeated exposure to BS β-lactam agents, is associated with increased weight z-scores. This association was also seen for exposure to a single course of a NS β-lactam agent but not for repeated exposure to NS β-lactam agents. However, there were only a few children (n = 7) who were repeatedly exposed to NS β-lactam agents, hence, statistical power to detect associations with regards to weight z-scores was limited.

Only one recent study investigated the association of antibiotic exposure with height.[21] Consistent with our findings, they reported an increase in height in children exposed to antibiotics (especially penicillins) in the first 2 years of life compared with unexposed children. In addition, we found that repeated exposure to both NS β-lactam agents and antimetabolite antibiotics was associated with decreased height z-scores. However, because only a few children were prescribed multiple courses of these antibiotics (n = 7 and n = 8, respectively), these findings should be validated. Furthermore, little is known regarding the associations of β-lactam antibiotics and antimetabolites with anthropometric outcomes, hence, further studies are required.

Although the underlying mechanisms by which antibiotics mediate growth promotion is not completely understood, it is generally accepted that antibiotic-induced perturbations of the gut microbiota contribute to growth-promoting effects.[15] A study in germ-free mice receiving microbiota transplants of murine donors receiving low-dose antibiotics showed an increase in fat mass, whereas this was not observed in germ-free mice receiving fecal transplants from donors without antibiotic exposure.[9] This transferability of the growth promotion phenotype indicates that, instead of the antibiotics themselves, the antibiotic-induced microbial perturbations play a causal role. In addition, some studies also showed that the effects on both growth promotion and the ability to convert food calories into body mass was greater for animals exposed to antibiotics earlier in life compared with those exposed in later life.[19,40] This might explain why antibiotic exposure during early life has more pronounced effects on weight development than exposure in later childhood because the infant microbiota is more susceptible to antibiotic-induced perturbations compared with the more resilient adult-like microbiota that is established around 2-3 years of age.[40-42]

A major strength of our study is that multiple questionnaires were sent over the years, which led to comprehensive data on background information enabling the adjustment for many determinants of growth development in infancy. In addition, we had 7 occasions of outcome measurements over a time period of 10 years, which were modeled together taking into account the correlations between the repeated outcome measures within each subject. Moreover, reliable data on antibiotic exposure (including timing, type, and number of courses) of the children also were available over the entire follow-up period as retrieved from GP records.

Our study has several limitations. As a consequence of the detailed and longitudinal characterization of the participating children, the sample size is not as large as several previous studies in which information on antibiotic exposure was obtained during the first[25,26] and the second[21,23,24] years of life. We did not have information on antibiotics that could have been prescribed in the hospital and whether the oral antibiotics prescribed were actually taken by the children. In The Netherlands, as in most other developed countries, most antibiotics for childhood infections, including infections of the respiratory tract, urinary tract, and skin, are prescribed in primary care.[43] As such, underestimation of antibiotic exposure is limited. Another potential limitation is the potential bias introduced by the fact that weight and height measurements were parent reported. Even though the procedure of measuring weight and height was explained in detail to the participating parents, parents may tend to overreport body weight in children with a low BMI and underreport weight in children with a high BMI, hence, lower prevalence of overweight.[44] An underestimation of overweight with parent-reported data compared with data collected during home visits was reported by a validation study of the KOALA Birth Cohort Study.[45] This may have resulted in an underestimation of the true associations as we saw weak associations with BMI z-scores and none with overweight. This lack of associations between antibiotic use and overweight might be due to the low prevalence of overweight children in our study population and, consequently, the limited statistical power. To control for dietary factors, dietary information was collected only once at 5 years of age using a FFQ. Yet, FFQs are specifically designed to reflect a long-term dietary pattern and give a good estimate of habitual dietary intake. Moreover, previous studies have shown a relatively stable dietary pattern during childhood.[46] Lastly, our study population consisted entirely of Dutch Caucasian children, hence results might not be generalizable to children with other ethnic or racial backgrounds.

We did not take the indication for which antibiotics were prescribed into account and, therefore, confounding-by-indication cannot be completely ruled out.[47] Confounding-by-indication occurs when the indication for which the antibiotics are prescribed, instead of the antibiotics, are causally related to weight development. However, this is unlikely to explain our results, as multiple infectious episodes in early infancy are more likely associated with decreased rather than increased weight.[48]

In conclusion, our study among Dutch Caucasian children supports previous evidence that repeated childhood exposure (in terms of number of courses) to antibiotics, especially BS β-lactam agents, leads to perturbations of the gut microbiota and subsequent weight development in children. Our findings suggest that exposure below 2 years of age is a critical time in which antibiotics influence the gut microbiota and, thus, metabolism as we saw that antibiotic exposure above

2 years of age had little effect on growth development over time. Given the high antibiotic prescription rates in early childhood and the growing pandemic of overweight and obesity in children in western countries, further research is needed to identify long-term implications in adulthood, and to determine the exact mechanisms of this association. ■

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Reprint requests: Catherine A. Mbakwa, MSc, Department of Epidemiology, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands. E-mail: catherine.akwimbakwa@maastrichtuniversity.nl

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50 Years Ago in *The Journal of Pediatrics*

Brain Scanning in Childhood

Mealey J. J Pediatr 1966;69:399-405

Are there times we just "get it wrong"? Fifty years ago in *The Journal*, Mealey reported the results of radioisotope brain scanning, most often with chlormerodrin mercury (Hg^{203}), from 50 children. Although the authors reported excellent specificity, with zero false positive results to detect tumors and a handful of other focal brain lesions, the sensitivity of the technique was poor. Five of 7 supratentorial tumors were detected and confirmed by surgical biopsy, but in the posterior fossa only 2 of 10 tumors were detected by scanning. Two other non-neoplastic intracranial lesions were identified: an epidural hematoma and a subdural empyema.

Through the "retrospectroscope," some of the claims made seem odd today: "Brain scanning has now gained broad clinical acceptance and is widely used as a neurodiagnostic test" and "Radioactive mercury compounds …are the agents most commonly employed. This procedure is safe…"

We appreciate today the grave toxicity of mercury. We can understand in hindsight how this type of brain scanning appeared promising compared with other methods available at that time, mainly pneumoencephalography. But, by the late 1970s and 1980s, computed tomography and magnetic resonance imaging, respectively, would supplant all these techniques. Brain scanning with other radioisotopes still has a role today distinguishing metabolically active tumors from necrotic lesions, but this application is limited.

Although the authors concluded, "This test will undoubtedly be done more often in this age group as agents with lower, less objectionable radiation doses such as chlormerodrin Hg^{197} are used more routinely," we should recognize this was just incorrect. Yes, even in recent times the field of pediatrics has taken paths that were toxic and without efficacy. We should remember this lesson whenever frustrated today with diagnoses that remain difficult to make or conditions that are refractory to treatment. *Primum non nocere.*

Paul Graham Fisher, MD
Departments of Neurology
Pediatrics, and Human Biology
Stanford University
Lucile Packard Children's Hospital
Palo Alto, California

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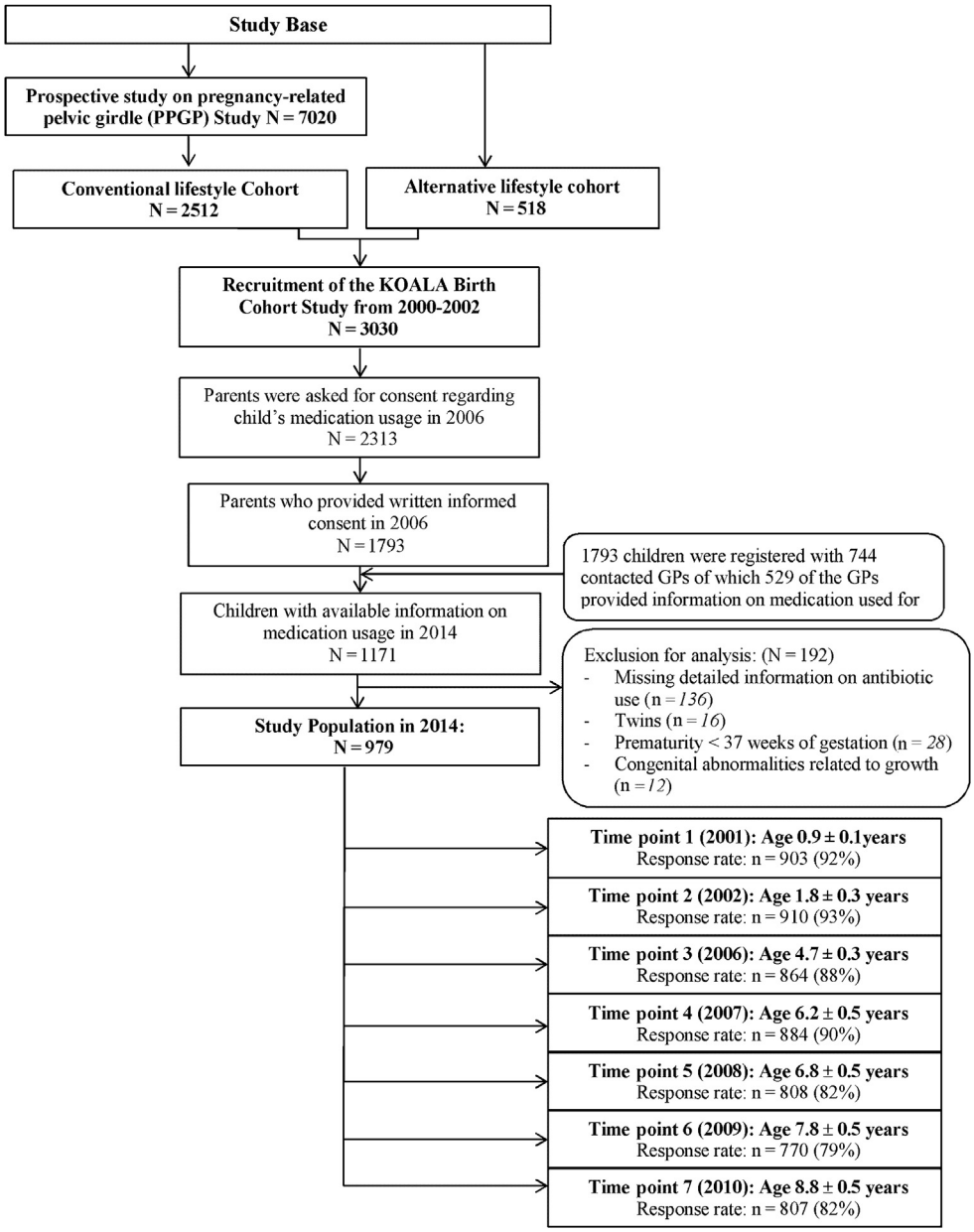

Figure. Flow chart illustrating how the present study population of 979 children was obtained.

Table IV. GEE results showing associations of antibiotic exposures (number of courses, type, and period) with the risk of being overweight during the first 10 years of life

		Overweight			
		Unadjusted OR (95% CI)*	*P* value	aOR (95% CI)†	*P* value‡
Number of courses during follow-up	n				
None	366	1 (Reference)		1 (Reference)	
1	259	1.22 (0.85-1.75)	.275	1.09 (0.76-1.57)	.640
2-3	221	1.26 (0.88-1.80)	.209	1.13 (0.79-1.63)	.506
≥4	127	1.13 (0.72-1.79)	.598	1.03 (0.66-1.60)	.891
No. of courses of antibiotics by age period					
First 6 mo of life					
None	910	1 (Reference)		1 (Reference)	
1	54	1.23 (0.79-1.91)	.252	1.21 (0.78-1.87)	.396
≥2	10	1.13 (0.39-3.29)	.843	1.19 (0.38-3.74)	.762
6-12 mo of life					
None	872	1 (Reference)		1 (Reference)	
1	86	1.34 (0.81-2.20)	.361	1.40 (0.81-2.42)	.223
≥2	16	1.15 (0.29-4.54)	.821	0.83 (0.26-2.67)	.754
Second year of life (1-2 y)					
None	804	1 (Reference)		1 (Reference)	
1	140	0.88 (0.58-1.33)	.536	0.96 (0.63-1.46)	.859
≥2	30	1.25 (0.66-2.37)	.488	1.14 (0.61-2.13)	.676
Above second year of life (>2 y)					
None	438	1 (Reference)		1 (Reference)	
1	266	1.33 (0.95-1.85)	.092	1.21 (0.87-1.70)	.263
≥2	260	1.14 (0.81-1.60)	.464	1.02 (0.73-1.43)	.890
No. of courses by type of antibiotic					
No. of observations = 5661					
BS β-lactams§					
None	437	1 (Reference)		1 (Reference)	
1	269	1.02 (0.73-1.44)	.892	0.95 (0.68-1.34)	.790
≥2	262	1.28 (0.92-1.78)	.148	1.20 (0.86-1.67)	.278
NS β-lactams§					
None	902	1 (Reference)		1 (Reference)	
1	65	1.03 (0.59-1.79)	.918	1.00 (0.57-1.76)	.986
≥2	7	0.32 (0.05-2.14)	.240	0.41 (0.06-2.63)	.347
Macrolide§					
None	806	1 (Reference)		1 (Reference)	
1	116	1.39 (0.97-2.00)	.073	1.29 (0.89-1.86)	.178
≥2	52	0.74 (0.42-1.32)	.309	0.64 (0.35-1.16)	.140
Antimetabolites§					
None	937	1 (Reference)		1 (Reference)	
1	29	0.82 (0.33-2.05)	.674	0.83 (0.33-2.11)	.699
≥2	8	0.69 (0.19-2.51)	.569	0.67 (0.19-2.31)	.524
Others§					
None		1 (Reference)		1 (Reference)	
1	15	1.65 (0.55-5.02)	.374	1.62 (0.52-5.06)	.407
≥2	9	0.57 (0.20-1.68)	.310	0.50 (0.21-1.20)	.119

*$OR = e^{crude(\beta)}$ or $e^{adjusted(\beta)}$.

†Adjusted for; recruitment group (conventional or alternative lifestyle), household size, maternal level of education (low, middle, high, and others), maternal prepregnancy weight, maternal pregnancy weight gain, smoking during pregnancy (yes/no), gestational diabetes, gestational hypertension, place and mode of delivery, sex, birthweight, gestational age, duration of breastfeeding, dietary intake (total fiber, total energy, fats and carbohydrates both as percentage of total energy), child's physical activity, and child's ages during anthropometric measurements.

‡Column represents *P* values for the adjusted analysis.

§BS β-lactams (amoxicillin, cephalosporin), NS β-lactams (flucloxacillin, pheneticillin, phenoxymethylpenicillin), macrolides (erythromycin, clarithromycin, azithromycin), antimetabolites (co-trimoxazole, trimethoprim), and others (nitrofurantoin, metronidazole, gentamicin, and tetracycline).