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ARTICLE

Pediatrics

Early childhood infections and body mass index in adolescence

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Abstract

Background The incidence of childhood overweight and obesity is rising. It is hypothesized that infections in early childhood are associated with being overweight. This study investigated the association between the number of symptomatic infections or antibiotic prescriptions in the first 3 years of life and body mass index (BMI) in adolescence.

Subjects The current study is part of the Prevention and Incidence of Asthma and Mite Allergy population-based birth cohort study. Weight and height were measured by trained research staff at ages 12 and 16 years. The 3015 active participants at age 18 years were asked for informed consent for general practitioner (GP) data collection and 1519 gave written informed consent. Studied exposures include (1) GP-diagnosed infections, (2) antibiotic prescriptions, and (3) parent-reported infections in the first 3 years of life. Generalized estimating equation analysis was used to determine the association between each of these exposures and BMI *z*-score.

Results Exposure data and BMI measurement in adolescence were available for 622 participants. The frequencies of GP-diagnosed infections and antibiotic prescriptions were not associated with BMI *z*-score in adolescence with estimates being 0.14 (95% CI −0.09–0.37) and 0.10 (95% CI −0.14–0.34) for the highest exposure categories, respectively. Having ≥6 parent-reported infections up to age 3 years was associated with a 0.23 (95% CI 0.01–0.44) higher BMI *z*-score compared to <2 parent-reported infections.

Conclusions For all infectious disease measures an increase in BMI *z*-score for the highest childhood exposure to infectious disease was observed, although only statistically significant for parent-reported infections. These results do not show an evident link with infection severity, but suggest a possible cumulative effect of repeated symptomatic infections on overweight development.

Introduction

The proportion of children and adolescents with overweight or obesity is increasing worldwide [1, 2]. Childhood overweight (including obesity) results from an intricate interplay between key determinants including

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diet, physical activity, maternal body mass index (BMI) and gestational weight gain, socioeconomic status (SES), and genetic susceptibility [3–5]. More recently, studies have suggested that the intestinal microbiota is influential in overweight development and could explain part of the intergenerational transmission of overweight [6–9]. As such, infections or systemic antibiotics might also contribute to weight gain through perturbations of the intestinal microbiota.

The association between antibiotic use and increased weight gain was first observed in livestock, but there is also evidence for this association in humans [10]. Previous studies in children observed that antibiotic prescriptions in infancy were associated with a higher weight in childhood [11–20]. Such an association might be mediated by the altered development of the infant gut microbiota affected by the antibiotics [11–17, 19–23]. The effects of childhood systemic antibiotics on the intestinal microbiota may be especially important in the first 3 years of life when the microbiota composition is immature and relatively unstable [24]. However, recently a large birth cohort study found that early childhood infectious diseases rather than antibiotic prescriptions were associated with overweight in childhood, indicating that antibiotic prescriptions are merely a proxy for infections [25].

Studies investigating the influence of antibiotic consumption on the intestinal microbiota have shown that a higher frequency of antibiotics is associated with prolonged perturbations in the intestinal microbiota composition and increased weight [23, 26]. Similarly, the frequency of early childhood infections may be associated with a prolonged effect on gut microbiota and in turn with BMI in adolescence. Studies investigating the association between frequency of infections in early childhood and BMI in adolescence are scarce. Therefore, it is unknown to what extent early childhood infections remain associated with BMI in adolescence and in turn adulthood [25, 27].

This study investigates the association between repeated infections during early childhood and BMI in adolescence in participants of the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study. We hypothesized that a higher number of infections is associated with a higher BMI *z*-score in adolescence and that this association is stronger for more severe infections as indicated by a visit to a general practitioner (GP) or an antibiotic prescription. Three measures of early exposure to infections were therefore investigated in relation to BMI *z*-score, the number of (1) GP-diagnosed febrile infections, (2) antibiotic prescriptions (as indicators of more severe infections), and (3) parent-reported infections. We restricted the exposure period to the first 3 years of life, as these years are considered the critical developmental period of the gut microbiota [24].

Subjects and methods

Study population

This study is part of the PIAMA study, a Dutch population-based birth cohort, which has been described in detail elsewhere [28, 29]. In short, pregnant women were recruited from the general population through antenatal clinics located in the north, center, and west of the Netherlands, which resulted in a baseline study population of 3963 children born in 1996 and 1997. PIAMA questionnaires were sent to parents during pregnancy, at age 3 months and thereafter annually around the birthday of the child until the age of 8 years, and at ages 11, 14, 16, and 18 years. The questionnaires included questions on occurrence of infectious diseases. Medical examinations were performed at the ages of 1, 4, 8, 12, and 16 years. Weight and height were measured at both medical examinations in adolescence. At age 18 years, all active participants were approached to consent for collection of GP data covering the full 18 years. The medical ethics committees of the participating institutes approved the study protocol.

Eligible for the present study were the 3015 participants of the 3963 PIAMA cohort members who were still active participants at age 18 years. The population for analysis consisted of participants with GP data on at least 1 of the first 3 years of life who had also a weight and height measurement at age 12 or 16 years ($N = 622$).

Data collection

At age 12 years, all active PIAMA participants ($N = 3169$ at the time) were invited for the medical examination. Weight and height were measured at the hospital or at the child's home. At age 16 years, only a subset of the cohort was invited for the medical examination ($N = 2159$) due to financial limitations, including only participants residing in the proximity of the study centers located in the north and center. Trained research staff measured weight (kg) and standing height (cm) using calibrated measuring equipment. All anthropometric variables were measured while the participants wore only underwear with accuracy at one decimal.

At age 18 years, all active PIAMA participants ($N = 3015$) were asked for informed consent for the GP data collection. GP data were collected by sending letters to the GPs including a questionnaire to obtain participant's infectious diseases diagnoses and any medication related to infections and allergies. Alternatively, GPs could request on-site data collection by the research team or send an extract of the electronic patient file to the research team. GPs provided a start and end date for the

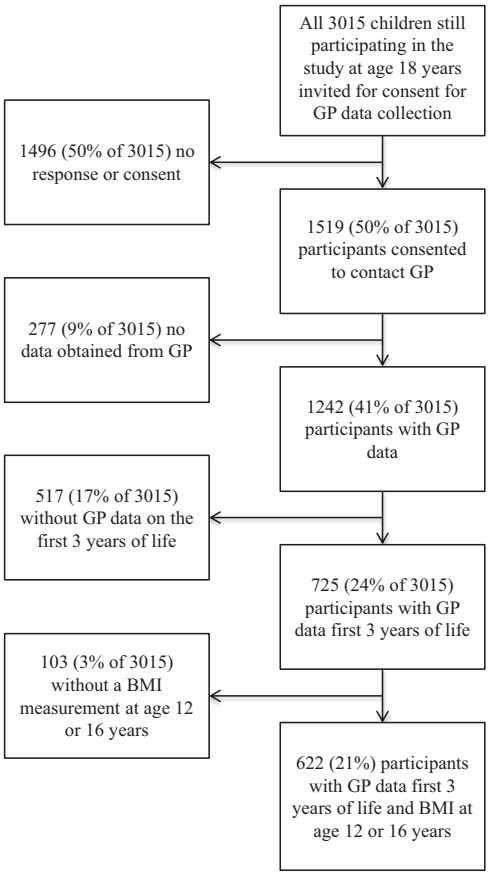

Fig. 1 Flowchart of general practitioner (GP) data collection. *BMI* body mass index.

period for which they registered the diagnoses and medication. These start and end dates were used to determine whether data for the first 3 years of life were available for the participants. Of the 3015 participants asked for informed consent for the GP data collection, 1519 (50%) participants gave written informed consent, and GP data were obtained for 1242 (41.2%) consenting participants (Fig. 1). GP data on at least 1 entire year of the first 3 years of life were available for 843 (28%) of the eligible participants.

The number of parent-reported infections in the first 3 years of life, day care attendance, gestational weight gain, participant's weight, participant's height, and indoor smoke exposures were retrieved from the yearly questionnaires filled in by the parents. Information regarding education and allergies of the parents, maternal pre-pregnancy BMI, birthweight, prematurity, small for gestational age, presence of older siblings, delivery mode, and breastfeeding were retrieved from the questionnaires completed during pregnancy and at age 3 months.

Definition of exposure variables, outcome, and potential confounders

Definition of general practitioner diagnosed infections and antibiotic prescriptions

The exposure variable "number of GP-diagnosed infections" was defined as the total number of GP-diagnosed febrile infections during the first 3 years of the participant's life. Febrile infections were defined as infectious diagnoses according to the International Classification of Primary Care (ICPC) coding for which a typical disease course includes one or more days with fever, such as acute upper or lower respiratory tract infection, and urinary tract infection. These infectious diagnoses were counted irrespective of whether fever was actually reported. Appendix 1 gives a list of ICPC codes and corresponding infectious diagnoses. Similarly, the exposure variable "number of antibiotic prescriptions" was defined as the total number of systemic antibiotic prescriptions during the first 3 years of the participant's life with a maximum of one antibiotic prescription per consultation.

Definition of parent-reported infections

The exposure variable "number of parent-reported infections" was calculated using four infection-related questions from the annual questionnaires during the first 3 years of life. First, parents were asked to report the number of respiratory infections that they considered serious in their child; the question was phrased as "How often did your child have serious respiratory- and/or throat-, nose-, ear cavity infections, such as flu, infection of the throat, infection of the middle ear, sinusitis, bronchitis or pneumonia in the last 12 months?" In addition, we asked whether their child had chickenpox, physician-diagnosed measles, or whooping cough in the preceding 12 months. From these questions, an infection count variable was created for each year of life, taking the reported frequency of serious respiratory- and/or throat-, nose-, ear cavity infections and adding chickenpox, measles, and whooping cough when reported. The sum of these counts resulted in the exposure variable "number of parent-reported infections in the first 3 years of life."

Anthropometric outcome variables

BMI was calculated by dividing weight (kg) by height squared (m^2). Age- and sex-specific BMI *z*-scores were calculated using the reference data from the 1997 Dutch Growth Study [30].

Confounder definitions

Age at BMI measurement, sex, parental education, birthweight, prematurity, small for gestational age, breastfeeding, pre-pregnancy overweight, gestational weight gain, delivery mode, allergy of the mother, presence of older siblings, day care attendance, and indoor smoke exposure up to age 3 were included in all analyses as a priori potential confounders. The selection of confounders was based on previous studies [15–18, 20, 25, 31]. A binary parental education variable was used as a proxy for SES, defining high parental education as completed higher vocational or university education by one or both parents. Participants with a gestational age of <37 weeks were classified as born premature. Small for gestational age was defined as a birthweight below the tenth percentile using reference data from Dutch infants taking into account sex, gestational age, and parity [32]. Breastfeeding was categorized into no breastfeeding, ≤16 weeks of any breastfeeding, and >16 weeks of any breastfeeding. Pre-pregnancy overweight was defined as a maternal BMI of ≥25 kg/m^2 before pregnancy. Maternal gestational weight gain was categorized in inadequate, adequate, and excessive according to the Institute of Medicine 2009 guidelines and based on the pre-pregnancy BMI [33]. Delivery mode consisted of three categories, namely born at home (vaginally), born in hospital (vaginally), and born in hospital via cesarean section. Maternal allergy was considered present if a mother reported pet allergy, house dust mite allergy, or nasal allergy such as hay fever, or ever had asthma [34]. A child was defined as attending day care when he/she attended for at least half a day per week during at least 2 years in the first 3 years of life. Exposure to indoor smoke was defined as present when smoking occurred within the parental home at least once a week at ages 3 months, 1, 2, and/or 3 years.

Statistical analysis

The exposure variables, the number of GP-diagnosed infections, antibiotic prescriptions, and parent-reported infections were each categorized into four categories based on quartiles in order to limit the influence of outliers and to allow for a non-linear association.

The associations between each of these exposure variables and measured BMI *z*-score as a continuous outcome variable were investigated using separate models for each exposure variable. As BMI had been measured during the medical examinations at both ages 12 and 16 years two measurements were available for some participants. Therefore, generalized estimating equation analysis with an exchangeable working correlation structure and an identity link function was used to take into account the correlation between repeated observations within participants. All a priori defined potential confounders were added to the models. In addition, two sensitivity analyses were performed. First, to investigate whether the associations present in early adolescence were also present during the entire childhood, we assessed the association between BMI *z*-score at any available age between 3 and 18 years, medical examination, and questionnaire data combined, with each of the three exposure variables. Second, as previous studies have shown that the associations are dependent on exposure period and there are suggestions that the first year of life may be an even more relevant defining period, we restricted the exposure period of interest to the first year of life for each of the infection measures and assessed the association between BMI *z*-scores in adolescence and the number infections in the first year of life [17, 20, 35]. *P* values were not adjusted for multiple comparisons.

To prevent bias in the parameter estimates, missing values for confounders and number of infections were imputed for participants with GP data available for at least 1 of the first 3 years of life and at least one BMI measurement at age 12 or 16. The imputation model included all confounders, outcome, and predictors of parent-reported and childhood infections, namely maternal smoking during pregnancy and paternal allergy. We imputed missing values using Multivariate Imputation by Chained Equations resulting in ten imputed datasets. Data were imputed using the Random Forest method.

Analyses were performed using SPSS version 24.0.0.1 (IBM Corp., Armonk, New York) and RStudio version 1.0.143 (R version 3.5.1, Boston, Massachusetts). The confidence intervals around the incidence rates were calculated using OpenEpi (Open Source Epidemiologic Statistics for Public Health, version 3.01) [36].

Results

For 622 participants, GP data for at least 1 of the first 3 years of life and at least one BMI measurement at age 12 or 16 years were available. These participants were included in the current analysis. For 339 (54.5%) participants, BMI measurements at both ages 12 and 16 years were available.

The characteristics of the population for analysis are shown in Table 1; participant characteristics of the eligible population and of the total PIAMA study population can be found in Appendix 2. Some differences between the population for analysis and the total PIAMA study population were observed, for instance compared to the population for analysis the total PIAMA study population had a higher percentage of children with low parental education, ≤16 weeks of breastfeeding, and overweight mothers. The mean BMI at age 12 was 18.6 kg/m^2 (BMI *z*-score 0.08). At age 16 years, the mean BMI was 20.8 kg/m^2 (BMI *z*-score

Table 1 Characteristics of study population with GP data on at least 1 of the first 3 years of life and a BMI measurement at age 12 and/or 16 years.

	Study population before MI		Study population after MI, $N = 622$
	%	N	%
Complete parent-reported data on the first 3 years of life	94.4	587	100
Complete GP data on the first 3 years of life	86.2	536	100
Sex		622	
Male	48.7		48.7
Female	51.3		51.3
Overweight mother before pregnancy		588	
No	83.3		82.2
Yes	16.7		17.8
Gestational weight gain		576	
Inadequate	32.1		31.4
Adequate	43.6		43.2
Excessive	24.3		25.4
Delivery		621	
Born at home	48.1		48.2
Born in hospital (vaginally)	43.3		43.3
Born in hospital by caesarian section	8.5		8.6
Small for gestational age		616	
No	92.5		92.2
Yes	7.5		7.8
Preterm		622	
No	96.0		96.0
Yes	4.0		4.0
Parental education		617	
Low	41.2		41.5
High	58.8		58.5
Exposure to smoking indoors first 3 years of life		618	
No	71.0		71.2
Yes	29.0		28.8
Older sibling(s)		622	
No	50.2		50.2
Yes	49.8		49.8
Day care attendance		619	
No	66.6		66.7
Yes	33.4		33.3
Breastfeeding		622	
No breastfeeding	14.0		14.0
≤16 weeks of breastfeeding	44.4		44.4
>16 weeks of breastfeeding	41.6		41.6

	Mean	SE (*N*)	Mean	SE
Birthweight, g	3514	21.3 (621)	3514	21.3
BMI at age 12 years (medical examination), kg/m^2	18.6	0.12 (580)	NA	NA
BMI at age 16 years (medical examination), kg/m^2	20.8	0.14 (381)	NA	NA

BMI body mass index, *GP* general practitioner, *MI* multiple imputation, *NA* not applicable (was not imputed).

Table 2 Prevalence of different measures of childhood infections in the first 3 years of life, before and after multiple imputation.

	Before MI		After MI ($N = 622$)
	%	N	%
GP-diagnosed infections per participant		536	
0–1 infection	38.4		39.1
2 infections	14.0		14.5
3–5 infections	27.2		27.2
≥6 infections	20.3		19.2
Antibiotic prescriptions per participant		536	
0 prescriptions	46.8		47.3
1 prescription	22.9		23.5
2 prescriptions	14.7		14.7
≥3 prescriptions	15.5		14.5
Parent-reported infections per participant		587	
<2 infections	32.5		31.5
2–3 infections	21.3		21.1
4-<6 infections	25.2		25.1
≥6 infections	21.0		22.3

MI multiple imputation, *GP* general practitioner.

0.02). After multiple imputation, the incidence of GP-diagnosed infections in the first 3 years of life was 1.08 per child year (95% CI 1.04–1.13) and 1.34 per child year (95% CI 1.29–1.40) for parent-reported infections. Multiple imputation did not meaningfully change the distribution of the characteristics of the study population and the exposure variables (Tables 1 and 2).

Table 3 presents the mean difference in BMI *z*-score between exposed and unexposed children for all three infection measures. Overall, the BMI *z*-scores were higher for children with a higher number of infections or antibiotic prescriptions, but only for parent-reported infections this association reached statistical significance. Having at least six parent-reported infections in the first 3 years of life was associated with a 0.23 (95% CI 0.01–0.44) higher BMI *z*-score in adolescence. The first sensitivity analysis showed similar effect estimates for BMI *z*-score at all available ages. In agreement with the primary analysis, the association between having at least six parent-reported infections and BMI *z*-score at all available ages was statistically significant in this sensitivity analysis (mean increase: 0.16 BMI *z*-score (Appendix 3)). The second sensitivity analysis showed that the observed association was already present when investigating the number of parent-reported infections in the first year of life only and a similar effect estimate was observed (Appendix 4). The results of all the anthropometric

Table 3 Difference in BMI *z*-score at age 12 and/or 16 years between exposed and reference group after multiple imputation. BMI data from the medical examinations were used.

Determinant	Δ BMI *z*-score (95% CI)	
	Crude[a]	Adjusted[b]
GP-diagnosed infections		
0–1 infection	Ref.	Ref.
2 infections	−0.03 (−0.29–0.23)	−0.02 (−0.26–0.23)
3–5 infections	0.12 (−0.09–0.33)	0.15 (−0.05–0.35)
≥6 infections	0.20 (−0.03–0.44)	0.14 (−0.09–0.37)
Antibiotic prescriptions		
0 prescriptions	Ref.	Ref.
1 prescription	−0.08 (−0.30–0.14)	−0.09 (−0.31–0.12)
2 prescription	0.02 (−0.22–0.26)	0.03 (−0.21–0.26)
≥3 prescriptions	0.15 (−0.11–0.41)	0.10 (−0.14–0.34)
Parent-reported infections		
<2 infections	Ref.	Ref.
2–3 infections	0.11 (−0.12–0.34)	0.12 (−0.09–0.33)
4-<6 infections	0.12 (−0.09–0.34)	0.10 (−0.11–0.30)
≥6 infections	0.26 (0.03–0.49)*	0.23 (0.01–0.44)*

BMI body mass index, *GP* general practitioner.

**P* value below 0.05.

[a]Crude model adjusted for age.

[b]Adjusted model included gestational weight gain, breastfeeding, age (days), birthweight, maternal overweight before pregnancy, parental education, sex, delivery mode, preterm, smoke exposure, small for gestational age, allergy of mother, siblings, and day care attendance.

measurements of the study population are presented in Appendix 5.

Discussion

We observed that at least six parent-reported infections in the first 3 years of life were associated with a higher BMI *z*-score in adolescence. No significant association was observed between the number of GP-diagnosed infections or antibiotic prescriptions and BMI *z*-score.

We hypothesized that a higher frequency of more severe infections, as reflected by GP diagnoses, and antibiotic prescriptions in early childhood would be associated with a higher BMI *z*-score in adolescence. This hypothesis was not supported by the results of our study, although the direction of the observed associations, i.e., a higher number of infections being associated with a higher BMI *z*-score, was consistent across all infection exposure measures. An association between antibiotic prescriptions in early childhood and a higher BMI in childhood has been consistently reported in the literature [11–13, 15–17, 19, 22, 31]. However, recently it has been questioned whether antibiotics indeed mediate this association or that antibiotic use serves as an indicator of the presence of (severe) infections. The large electronic medical record study of Li et al. [25] reported that infections, but not the antibiotics prescribed for the infections, were associated with childhood obesity. The results of the current study are in line with this finding. Importantly, antibiotic prescription rates are relatively low in the Netherlands. In the current study, 75% of the participants had no antibiotic prescription in the first year of life while this ranged from 17 to 78% in other studies [12, 13, 16, 25, 37, 38]. Most of the previous studies only found an association between antibiotics and weight gain when the number of prescriptions was more than one [18, 22, 23, 26, 39]. The restrictive use of antibiotics in the Netherlands therefore provides an alternative explanation for the absence of a statistically significant association between antibiotic prescriptions and BMI *z*-score in our study [18, 22, 23, 26, 37–39].

The mechanism proposed for the potential link between infections and increased weight gain is related to the microbiota, as previous studies have reported an association between respiratory infections and changes in gut microbiota in mice [40, 41]. The number of parent-reported infections of the current study consisted mainly of serious respiratory infections, as the question posed to the parents was "How often did your child have serious respiratory- and/or throat-, nose-, ear infections, such as flu, infection of the throat, infection of the middle ear, sinusitis, bronchitis or pneumonia in the last 12 months?" In addition, the number of parent-reported cases of whooping cough, chickenpox, and measles was small; therefore, the contribution of respiratory infections to the final count of parent-reported infections was most important (~80%). Together with previous research, this suggests that the frequency of serious respiratory infections might be associated with a higher BMI in adolescence. Surprisingly, in the current study, GP-diagnosed infections were not statistically significantly associated with a long-term effect on BMI. Parent-reported infections might be a better reflection of total infectious disease burden in comparison with GP-diagnosed infections, since parent-reported infections include infections of mild to high severity, while GP-diagnosed infections will in general include more severe infections. Besides the severity of the infection, the number of GP-diagnosed infections is also influenced by health-seeking behavior that might result in differences in the number of GP-diagnosed infections between children irrespective of the actual infectious disease burden, as the percentage of parents seeking healthcare when there child has an infection is low in the Netherlands compared to other countries these differences might be considerable in this study [42, 43]. Only a relatively high number of parent-reported infections was associated with a higher BMI *z*-score in the current study, which is in line with antibiotic

studies showing that repeated courses are associated with a higher weight or BMI [13, 17–19, 22, 23, 26]. We are not aware of potential confounders that may explain the association between parent-reported infections and BMI *z*-score in adolescence that are not related to GP-diagnosed infections or antibiotic prescriptions.

The 0.23 higher BMI *z*-score observed in this study is higher than the effect estimates of other early life risk factors associated with childhood overweight, such as caesarean delivery and childcare [44, 45]. A reduction of 0.25 BMI *z*-score has been associated with clinically relevant reductions in cardiovascular risk factors in overweight children, indicating the potential public health relevance of the reported association between frequent infections and BMI *z*-score [46, 47]. The percentage of children with at least six parent-reported infections in the first 3 years of life was approximately 20%. This implicates a substantial attributable effect of frequent childhood infections on the weight distribution and overweight prevalence in the general adolescent population.

Some limitations should be kept in mind when interpreting the results. As our data on antibiotic exposure were based on GP prescriptions, we do not know the degree of adherence by the participants. Non-adherence would have resulted in misclassification, as participants who got an antibiotic prescription but did not take the medication would have been classified as "exposed" in the current study. Misclassification would have resulted in a dilution of the observed effects for number of antibiotic prescriptions. However, most of the previous studies investigating the association between antibiotics and weight gain also used prescription data; therefore, it is unlikely that non-adherence could explain the observed association [12, 13, 17–19, 22, 25]. In addition, it was not possible to investigate the association between GP-diagnosed infections for which no antibiotic was prescribed and BMI *z*-score since the antibiotics were not necessarily prescribed on the same day as the GP consultation for the infection. However, the prescription rate was low in this study making it unlikely that our results would have been substantially different when we would have been able to exclude GP-diagnosed infections with an antibiotic prescription. The current study was conducted in a high-income country with a relatively low infectious disease burden and high coverage of childhood vaccinations. Our findings may not be generalizable to low- and middle-income countries where the infectious disease burden is different and substantially higher [48]. In addition, the different measures of infectious disease exposure in early childhood may be subject to misclassification, most likely non-differential. Non-differential misclassification could lead to an underestimation of the investigated associations. In the Netherlands, all inhabitants are registered at a general practice and referral from a GP is needed before an inhabitant can visit the hospital. Therefore, the number of GP-diagnosed infections and antibiotic prescriptions are less likely to be subject to non-differential misclassification. Parent-reported infections are more likely to be subject to misclassification due to the variation between parents. The current study took place in 16% of the total PIAMA study population. Given the vast amount of longitudinal information on the 3341 participants who were not included in the current analysis, we were able to make a detailed comparison between participants in the study population and in the total PIAMA study population. The differences in relevant participant characteristics were related to SES, with a higher percentage of highly educated parents, more breastfeeding, and less overweight mothers in the study population (Table 1 and Appendix 2). However, we consider it unlikely that the associations observed in the current study would be different from those in the entire PIAMA study population ($N = 3963$) as the associations were similar for participants with different SES.

The PIAMA birth cohort study includes extensive information about childhood development up to 18 years of age from repeated parental questionnaires, medical examinations performed by trained research staff, and GP data on both diagnoses and antibiotic prescriptions. This combination provided the opportunity to adjust for relevant confounders, to limit potential selection and information bias. These are important strengths of the current study. Many of the studies investigating antibiotic prescriptions and weight were subject to either one or more of these biases [11–16, 18, 20, 22, 23, 31, 49].

In conclusion, in this prospective birth cohort with 18 years of follow-up, a high frequency of parent-reported infections was associated with BMI *z*-score in adolescence, while we did not observe an association between frequency of GP-diagnosed infections and antibiotic prescriptions and BMI *z*-score. This provides further evidence of an association between the total burden of childhood infections and BMI in adolescence.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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