

Paracetamol and antibiotics in childhood and subsequent development of wheezing/asthma: association or causation?

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Background Several studies found an association between early administration of paracetamol and antibiotics and development of wheezing. This could be due to confounding: wheeze and asthmatic symptoms in early childhood are difficult to distinguish from respiratory tract infections that are widely treated with these drugs; in case of persistence of symptoms up to school age, this could explain the observed relationship.

Methods We investigated the association between paracetamol and antibiotics use in the first year of life and wheezing phenotypes, i.e. wheezing starting in different time periods (early, persistent and late-onset) in the SIDRIA-2 study, a cross-sectional survey of 16 933 children aged 6–7 years. Directed acyclic graph (DAG) was used to depict the causal structure.

Results Paracetamol and antibiotics administration in the first year were associated with early wheezing (first 2 years of life only) [odds ratio (OR): 2.27; 95% confidence interval (95% CI): 1.98–2.62 and OR = 3.76, 95% CI: 3.31–4.27] and with persistent wheezing (first 2 years + last 12 months) (OR = 1.77, 95% CI: 1.49–2.10 and OR = 3.06, 95% CI: 2.60–3.60), whereas the association with late-onset wheezing (in the last 12 months only) was weak (OR = 1.12, 95% CI: 0.97–1.31 and OR = 1.18, 95% CI: 1.02–1.38 for paracetamol and antibiotics, respectively). DAG shows that even in the absence of a direct (causal) arrow from early drugs use to wheezing at school age, the two are associated due to confounding (through the 'infection' node).

Conclusions It is important to take into account different phenotypes in order to disentangle the association of paracetamol and antibiotics with wheezing.

Keywords Children, wheezing, phenotypes, causality, confounding factors, bias

Introduction

Asthma is one of the most frequent chronic diseases in children and adults. Long-term studies have shown that a large proportion of children with persistent asthma had started to wheeze by the age of 3 years.¹ This consideration, together with the rapid rise of asthma at the end of the 20th century, has prompted the search for environmental exposures during fetal life and early childhood that, possibly interacting with a genetically determined pathway, can cause the manifestation of the disease.

In the last few years, several studies have investigated the association between drugs widely used in childhood, such as paracetamol (the most commonly prescribed antipyretic and analgesic) and antibiotics, and asthma and wheezing in children.^{2–6} Systematic reviews and meta-analyses have confirmed the associations.^{7–10} If the associations were causal, these results would have important clinical implications and would be cause of concern.

The aim of this article is to contribute to the debate on the causal link, as opposed to confounding, between antibiotics and paracetamol use and respiratory illnesses. The issue has been recently discussed in editorials accompanying several papers and in commentaries.^{11–14} We have reanalysed data obtained in the SIDRIA (Italian Studies of Respiratory Disorders in Childhood and the Environment) phase 2 study [the Italian International Study on Asthma and Allergies in Childhood (ISAAC) initiative] on the association between paracetamol and antibiotics in the first year of life and different wheezing phenotypes.¹⁵ Our starting point is that asthma is not one single illness but a syndrome with different phenotypes.¹⁶ In previous studies, we demonstrated that taking into account specific phenotypes, based on the time of appearance and the duration of wheezing, is crucial to evaluate the role of pre–peri and post-natal determinants.^{17,18} Our present hypothesis is that the association repeatedly found between paracetamol and antibiotics administered in the first to second year of life with asthma/wheezing at the age of 6–7 years stems from neglecting that children wheezing at the age of 6–7 years include subpopulations (phenotypes) who could have experienced the drugs under study because of their disease. We also try to explore the relationship between paracetamol and antibiotics administration and wheezing by using causal diagrams [directed acyclic graphs (DAG)], a powerful tool to help answer causal queries.^{19,20}

Methods

Full details of the SIDRIA study have been reported elsewhere.²¹ Briefly, the SIDRIA study was carried out between January and May 2002 in 12 areas of Northern, Central and Southern Italy, and involved

a large sample of children of two age groups (6–7 years old and 13–14 years old).

In this article, we report data on children aged 6–7 years, for whom there is a better parental recall of events that had occurred early in life.

Data collection was performed using the ISAAC questionnaires.²² The SIDRIA questionnaires included additional questions on topics such as individual and family characteristics, pre- and post-natal potential risk factors for wheeze and other respiratory symptoms. Questions related to paracetamol and antibiotics were: 'In the first 12 months of your child's life, did you usually give paracetamol (e.g. Tachipirina, Acetamol, Puernol, Efferalgan) for fever?', and 'In the first 12 months of your child's life, did you give antibiotics?'

The protocol was approved by Ethics Committee of the Catholic University in Rome.

Of the children enrolled in the SIDRIA study, three mutually exclusive outcomes were included in the analysis: (i) those who had at least one lower respiratory tract illness with wheezing (bronchiolitis or asthmatic bronchitis or asthma or wheezing) in the first 2 years of life, and had no wheezing in the last 12 months (transient early wheezers); (ii) those who had at least one lower respiratory tract illness with wheezing in the first 2 years of life, and had wheezing in the last 12 months (persistent wheezers); and (iii) those with no lower respiratory tract illness with wheezing in the first 2 years of life but who had wheezing in the last 12 months (late-onset wheezers). The remainders comprised those with no lower respiratory tract illness with wheezing in the first 2 years of life, no asthma up to the age of 6–7 years and no wheezing in the last 12 months (non-wheezers). Children for whom data on respiratory diseases in the first 2 years of life or on wheezing symptoms in the last 12 months were lacking were excluded from the analysis.

Data analysis

Frequencies of paracetamol and antibiotics use were computed excluding missing answers (4.3 and 7.4%, respectively). Associations between paracetamol and antibiotics use and each group of wheezing children (taking as reference group those without wheezing) were assessed by polytomous logistic regression analysis,²³ which allows three mutually exclusive outcomes to be assessed simultaneously.

In a first logistic regression analysis, odds ratios (ORs) were adjusted for age of the child, study centre, season of the questionnaire's completion and the person who completed the questionnaire. Further polytomous logistic regression analyses were conducted to investigate whether the association between antibiotics and paracetamol use and each group of wheezing children was confounded by other wheezing risk factors that had shown association with different categories of wheezing in the bivariate analysis.

The covariates included in these further polytomous logistic regression analyses were: parental history of asthma or atopy, maternal smoking in pregnancy, prematurity (<37 weeks gestation vs \geq 37 weeks), sex, maternal age at birth, parental schooling, presence of siblings, breastfeeding, day care attendance, sleeping in the same bedroom with other children in the first year of life, mould or damp in child's bedroom during her or his first year of life. The regression models were performed on the data set of children with no missing answers to any of the covariates.

Statistical analyses were performed using STATA 9 (College Station, TX, USA).

Results

Questionnaires were returned for 20016 children (response rate: 89.2%). Complete data for respiratory diseases in the first 2 years of life and for wheezing symptoms in the last 12 months were not available for 3083 children, leaving 16933 children for the present analysis. The children not included in the analysis differed from those who were included in their lower degree of parental education (university: 18.0% in those not included and 22.7% in those included; high school: 44.1% in those not included and 48.4% in those included; $P < 0.001$). Of the children studied, 9.4% (1598) were classified as having had transient early wheezing, 5.4% (910) as having had persistent wheezing and 6.0% (1011) as having had late-onset wheezing, whereas 79.2% (13414) were non-wheezers.

Table 1 shows frequencies of paracetamol and antibiotics use in the first year of life in children with transient early wheezing, persistent wheezing, late-onset wheezing and in non-wheezers; a clear gradient is seen for both paracetamol and antibiotics. In the logistic regression, the use of paracetamol and antibiotics in the first year of life was clearly associated with an increased risk of transient early wheezing and persistent wheezing, whereas the association with late-onset wheezing was weak. When the analyses were further adjusted for other potential confounders, the use of paracetamol and antibiotics was still strongly associated with both transient early (OR: 2.27; 95% CI: 1.98–2.62 for paracetamol, and OR: 3.76; 95% CI: 3.31–4.27 for antibiotics) and persistent wheezing (OR: 1.77; 95% CI: 1.49–2.10, and OR: 3.06; 95% CI: 2.60–3.60), whereas the association with late-onset wheezing was borderline (OR: 1.12; 95% CI: 0.97–1.31, and OR: 1.18; 95% CI: 1.02–1.38).

Discussion

The natural history of wheezing has been elucidated in the last several years, and different phenotypes have been described.¹ In this study, we investigated, by reanalysing SIDRIA data, the association between

paracetamol and antibiotics use in the first year of life and three wheezing phenotypes, defined using the original criteria of Martinez and coworkers,²⁴ as transient early wheezing, persistent wheezing and late-onset wheezing, and found a different association with different phenotypes. We showed that paracetamol (and antibiotics) were strongly associated with two of the phenotypes (early and persistent wheezing), whereas the association with late-onset wheezing was weak. In our study, about half of the children wheezing at the age of 6–7 years were persistent wheezers, and when we considered together persistent and late-onset wheezers, we also found in multivariate logistic regression analysis a positive association both for paracetamol (OR: 1.27; 95% CI: 1.13–1.42), and antibiotics (OR: 1.57; 95% CI: 1.40–1.75) (data not shown). Taking into account different phenotypes would be, therefore, important in order to disentangle the role of different potential risk factors (in the present study: paracetamol and antibiotics) on wheezing.

It is well known that wheeze, especially in the first years of life, is chiefly triggered in susceptible individuals by viral infections,^{25,26} for which paracetamol (owing to accompanying fever) and antibiotics (owing to a difficult differential diagnosis with bacterial infections) are often prescribed.²⁷ Thus, the association we found between paracetamol and antibiotics and wheeze in the first to second year could possibly be explained by confounding. Some infants who wheeze early, mainly those with an atopic/asthmatic predisposition, continue to wheeze up to school age (persistent wheezers). The analysis of wheezers at the age of 6–7 years, without taking into account the different phenotypes, will include both children who did and those who did not wheeze at the age of 1–2 years, with a possibly confounded association between paracetamol/antibiotics and wheezing.

In Figure 1, the DAG summarizes possible relationships between the variables, taking into account what is known on this topic. The (confounded) association between paracetamol/antibiotics and wheeze in the first 2 years of life (persistent wheezing) through infection and fever is shown in the DAG by the arrows from 'viral infection/fever' to 'wheezing P', and to 'paracetamol/antibiotics'. According to causal theory, we need not postulate a direct arrow (representing a causal effect) from paracetamol/antibiotics in the first year to outcomes at the age of 6–7 years, to explain an association, if there are 'open' paths between paracetamol/antibiotics and outcome. In other words, if there are non-causal (biasing) paths open, a non-null association will be found independently of the true effect of paracetamol/antibiotics.

The DAG shows that such paths exist: [backdoor path 'paracetamol/antibiotics-infection-wheezing' at school age]. To block this path and to obtain unconfounded estimates of the association between paracetamol/antibiotics and wheeze at school age (if

Table 1 Associations of paracetamol and antibiotics use in the first year of life with wheezing in young children

	Transient early wheezing (n = 1598)	Persistent wheezing (n = 910)	Late-onset wheezing (n = 1011)	Non-wheezers (n = 13 414)
Paracetamol use in the first year of life				
Frequency (%)	79.4	76.0	64.4	60.0
OR (95% CI) ^a	2.53 (2.22–2.89)	2.05 (1.74–2.41)	1.18 (1.03–1.36)	1.0
OR (95% CI) ^b	2.27 (1.98–2.62)	1.77 (1.49–2.10)	1.12 (0.97–1.31)	1.0
Antibiotics use in the first year of life				
Frequency (%)	69.7	65.5	40.8	35.4
OR (95% CI) ^a	4.20 (3.73–4.73)	3.43 (2.95–3.99)	1.23 (1.07–1.41)	1.0
OR (95% CI) ^b	3.76 (3.31–4.27)	3.06 (2.60–3.60)	1.18 (1.02–1.38)	1.0

^aThe ORs have been adjusted in the polytomous logistic regression model for age of the child, study centre, season of the questionnaire's completion and the person who completed the questionnaire. Children with complete covariate data: 15 845 for paracetamol and 15 325 for antibiotics.

^bThe ORs have been adjusted in the polytomous logistic regression model for age of the child, study centre, parental schooling, season of the questionnaire's completion, the person who completed the questionnaire, parental history of asthma or atopy, maternal smoking in pregnancy, sex, prematurity, maternal age at birth, breastfeeding, siblings, day care, sleep in the same bedroom with other children, mould or damp in child's bedroom. Children with complete covariate data: 14 087 for paracetamol and 13 613 for antibiotics.

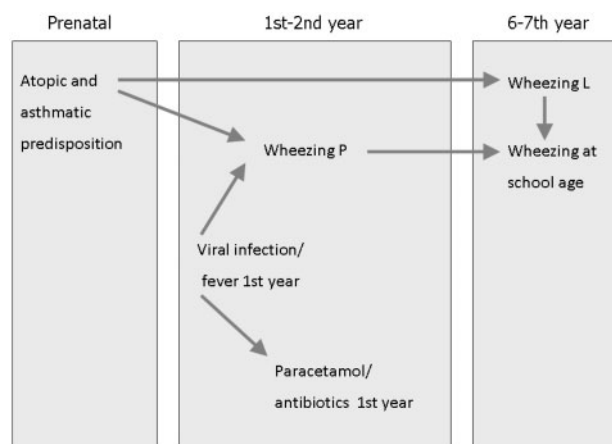


Figure 1 Relationship between paracetamol and antibiotics use in the first year of life and different wheezing phenotypes. Wheezing P: persistent wheezing; Wheezing L: late-onset wheezing

any), we should condition on (stratify for or adjust for) infection.^{19,20} Interestingly, in two longitudinal studies in which also indication for paracetamol²⁸ and antibiotics use⁵ was documented, when the effect of early respiratory infection was taken into account, the association found in univariate analysis between drugs use and subsequent wheezing became non-significant, or marginally significant. In another study²⁹ on a small cohort of infants, with parents keeping diaries in which they recorded all illnesses in the child and drugs prescription, children with respiratory infections and wheeze had used antibiotics twice as often as compared with children without wheeze. Antibiotic use was associated with later asthma, but this association was greatly reduced after propensity score adjustment (indication for

antibiotic use). It is, however, important to underline that also in longitudinal studies information about the indication for antibiotics/paracetamol prescription or details on infectious episodes at the time of exposure are not easy to collect, and adequate adjustment could not be feasible.¹³

Another way to estimate the association between paracetamol/antibiotics and wheezing at school age is to focus on 'late-onset wheezers', i.e. children who do not wheeze at 1–2 years. In our data, paracetamol administered in the first year of life was not associated with late-onset wheezing, whereas antibiotics had a weak association that could possibly be due to misclassification (inclusion in late-onset wheezers of a number of children who had milder symptoms in the first 2 years of life, and whose true status is that of persistent wheezers).

Based on these data, we cannot completely dismiss that paracetamol and antibiotics can have an effect on wheezing at school age, and we fully agree that in consideration of the importance of the matter and of the widespread use of these drugs in infants, prospective *ad hoc* trials should be warranted¹⁴ and in the meantime use of these drugs, which is often not justified, should be minimized. On the other hand, DAG suggests that even in absence of such an effect, an association will be found. The fact that very different classes of drugs have a similar pattern of association also speaks against the specificity of action (one of the classical Hill's criteria for causation³⁰), whereas can be well explained by confounding.

In conclusion, our results are consistent with a different association between paracetamol and antibiotics and different wheezing phenotypes. When different phenotypes are not taken into account,

children wheezing at school age are significantly more likely to have been treated with paracetamol and antibiotics in the first year of life. DAG helped to clarify that such an association might be, fully or in part, due to confounding. As observational studies are more prone than interventional studies to difficulties in inferring causation from results, epidemiologists should pay attention to the aspect of association vs causation. If research has to modify reality and contribute to change risk factors, it is of paramount importance that it concentrates on causal pathways, trying to tell them apart from associational paths.³¹

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Conflict of interest: None declared.

KEY MESSAGES

- Among children who wheeze at school age, 'persistent wheezers' have a stronger association than 'late-onset wheezers' with paracetamol/antibiotics administered early in life.
- The DAG indicates that the association with wheezing at school age can occur independently of the causal effect of the drugs.
- These results contribute to the debate on the causal link, as opposed to confounding, between antibiotics and paracetamol use and respiratory illnesses in childhood.

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