




# Recurrent wheezing as a mediator between early-life exposures and childhood asthma: a mediation analysis in an Italian primary care paediatric cohort

Riccardo Boracchini <sup>1</sup>, Cristina Canova,<sup>2</sup> Stefano Bendoni,<sup>1</sup> Costanza Di Chiara <sup>3</sup>, Carlo Giaquinto,<sup>3</sup> Eugenio Baraldi,<sup>4</sup> Anna Cantarutti <sup>1</sup>

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EB and AC contributed equally.

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For numbered affiliations see end of article.

## Correspondence to

Dr Riccardo Boracchini; [riccardo.boracchini@unimib.it](mailto:riccardo.boracchini@unimib.it)

## ABSTRACT

**Introduction** Asthma represents a significant global public health concern, especially in children, due to its high prevalence and burden on the healthcare system. Early-life exposures, particularly to antibiotics and bronchiolitis, have been independently linked to an increased risk of wheezing and subsequent asthma. Despite extensive research on these risk factors, their interplay and combined impact throughout early childhood remains unclear. This study aims to clarify these relationships by investigating the mediating role of recurrent wheezing in the inception of childhood asthma.

**Methods** A retrospective birth-cohort study was conducted using data from the Italian Pediatric database, including children followed for at least 5 years. Exposure to antibiotics and bronchiolitis during the first year, episodes of wheezing between ages 1–4, and asthma diagnoses from age 5 onward were identified in outpatient records. Mediation analysis assessed the association between early-life exposures and asthma risk, with recurrent wheezing considered a potential mediator.

**Results** Among 121 255 children, 2.33% developed asthma after age 5. Our results support the hypothesis that early-life bronchiolitis and antibiotic use increase asthma risk through an indirect pathway mediated by recurrent wheezing, which accounts for the majority of the effect (up to 74%), and a direct pathway, independent of wheezing, which may reflect mechanisms such as immune dysregulation, airway remodelling or microbiome alterations. The strong mediated component underscores recurrent wheezing as a clinically relevant marker and key target for preventive strategies. Nonetheless, the presence of a residual direct effect suggests that interventions focusing exclusively on wheezing may not entirely eliminate asthma risk (up to 70%), even though they could substantially reduce it.

**Conclusions** Our findings highlight the importance of preventing bronchiolitis and wheezing to reduce asthma incidence, supporting antibiotic stewardship and respiratory syncytial virus immunisation as public health interventions.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A huge body of literature has deeply studied the key risk factors and predictors of childhood asthma. Antibiotic exposure in the first year of life has been linked to disrupted gut microbiota and increased wheezing and asthma risk, with a duration and dose-response effect. Bronchiolitis, primarily caused by respiratory syncytial virus, is a leading early-life respiratory infection associated with later wheezing and subsequent asthma. Both antibiotics and bronchiolitis independently raise wheezing risk, and these three conditions synergistically contribute to asthma development.

## WHAT THIS STUDY ADDS

⇒ To our knowledge, our study is the first to examine the early-life course epidemiology of childhood asthma by analysing the independent and joint roles of antibiotics and bronchiolitis in the development of wheezing and asthma. No study applied the mediation analysis in a large paediatric cohort using data from the outpatient clinical practice, quantifying the attributable risk of each factor and the preventable risk if recurrent wheezing is prevented.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings support prioritising early-life respiratory health as a pathway to asthma prevention. Future policies should focus on integrated strategies during infancy to improve long-term paediatric respiratory health. Furthermore, our study strongly supports the growing evidence in developing targeted antibiotic stewardship and respiratory syncytial virus immunisation campaigns. Based on our results, if nirsevimab were effective in reducing bronchiolitis in the community setting, this would be reflected in a significant reduction of asthma incidence up to 5 years in a measure of the nirsevimab impact on the population (expected around 40%) multiplied by the percentage eliminated found in this study (approximately 70%).

## INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, characterised by bronchial hyperreactivity, mucus overproduction, airway remodelling and airway narrowing.<sup>1</sup> It affects 5%–10% of the paediatric population, posing a substantial burden on disease management.<sup>2,3</sup> Growing evidence links early-life antibiotic exposure (prenatal and postnatal) to disruption of the developing gut microbiome and a 23%–52% increased risk of respiratory and allergic conditions, including wheezing and childhood asthma.<sup>4–6</sup> This risk is further influenced by factors such as antibiotic type, treatment duration and dosage. For instance, Lee *et al* found that antibiotic exposure for more than 3 days in the first year of life increases the risk of asthma.<sup>7</sup> Children exposed to antibiotics within their first 2 years of life are more likely to develop asthma by the age of 7.5, with the odds rising with the number of courses received.<sup>8</sup> Moreover, early-life antibiotic use, particularly within the first year of life, has been associated with higher odds of early, persistent and late-onset wheezing, ranging from fourfold to onefold increase, respectively.<sup>9</sup> A dose-response relationship was observed, with antibiotic exposure prevalence rising from 3.6% in children without wheezing to 10% in those with more than three episodes.<sup>10</sup>

Viral bronchiolitis is the most frequent infection of the respiratory tract and the leading cause of hospitalisation and death in infants under 1 year of age.<sup>11</sup> The most common cause is the respiratory syncytial virus (RSV), which affects over 60% of infants in the first year of life and almost all children in the first 24 months.<sup>12</sup> Hospitalised bronchiolitis is associated with subsequent asthma diagnoses in 20%–30% of cases, with a greater likelihood observed in children hospitalised for more than 3 days.<sup>13</sup> Furthermore, children with bronchiolitis, regardless of severity, have a threefold increased risk of developing wheezing and/or asthma compared with those without bronchiolitis.<sup>14</sup> A recent study has demonstrated a strong relationship between bronchiolitis and wheezing, indicating a 43% reduction in wheezing risk if bronchiolitis was absent.<sup>15</sup> Despite its viral aetiology, bronchiolitis is frequently treated with antibiotics, although this approach is generally inappropriate and unsupported by clinical guidelines. Moreover, although a recent study found that both a history of bronchiolitis and early-life antibiotic use independently raise the risk of developing paediatric asthma by approximately twofold, their combined impact is less well established. Notably, when these two factors co-occur, they appear to act synergistically, substantially increasing the likelihood of asthma-related outcomes by nearly five-fold.<sup>7</sup> Evidence suggests that this association may be driven by the inappropriate use of antibiotics to treat bronchiolitis, interfering with normal lung development in young children, thereby increasing the risk of subsequent respiratory issues, including asthma.<sup>16</sup>

Notably, children with wheezing have nearly fourfold increased risk of developing asthma by age 8.<sup>17</sup> This association is consistent with the understanding that asthma

often first presents with wheezing symptoms during the preschool years, serving as an early clinical indicator. Recurrent wheezing episodes, particularly those triggered by viral infections such as RSV and human rhinovirus (HRV), may therefore signal a higher risk of progressing to asthma. Indeed, a history of bronchiolitis, most commonly caused by RSV in the first year of life, is a well-established predictor of both recurrent wheezing and asthma development.<sup>18</sup>

Given that (1) early-life antibiotic exposure increases the risk of both wheezing and asthma, (2) bronchiolitis is associated with an increasing risk of wheezing and asthma and (3) wheezing is a significant predictor of asthma, it is clinically relevant to disentangle their individual and combined contributions to childhood asthma. This study aims to quantify the direct and indirect effects of first year of life antibiotics and bronchiolitis exposures on asthma, implementing mediation analysis to assess the role of recurrent wheezing as a potential mediator.

## MATERIALS AND METHODS

### Data source

Children were enrolled from Pedianet (<http://www.pedianet.it>), an independent network of more than 200 family paediatricians (FPs). The database collects demographic, clinical and prescription data linked with an anonymised ID from children whose parents/guardians have provided informed consent and are under the care of participating FPs. Data, generated during routine clinical practice, are stored and validated anonymously in compliance with Italian regulations at a secure data repository in Padova (Veneto region). Pedianet represents approximately 4% of the annual Italian paediatric population, which has already been described.<sup>15</sup>

### Study design and study population

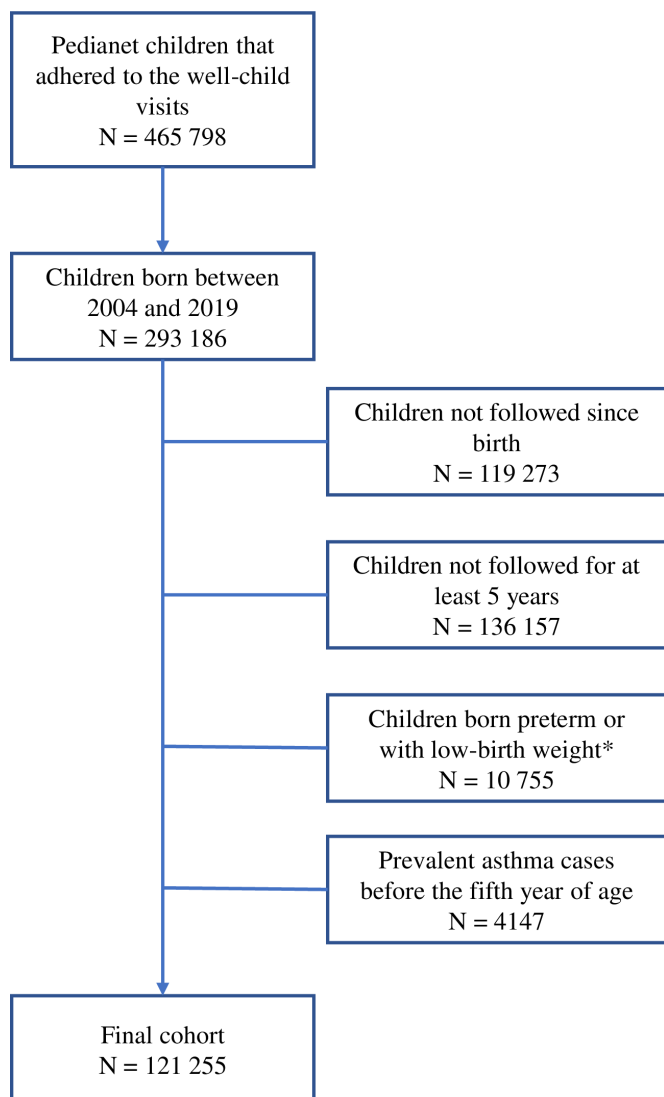
#### Study design

This retrospective, birth-cohort, observational study included children born between 2004 and 2019 and followed for at least 5 years. Children who did not adhere to the recommended child-well visits<sup>19</sup> or without continuous follow-up from birth to the fifth year of life were excluded. Children with preterm birth and/or low birth weight (LBW) were also excluded from the cohort. Prevalent asthma cases diagnosed before the fifth year of age have been excluded from the analysis (figure 1).

#### Exposures definition and assessment

Exposure to antibiotic therapy was defined as having received at least one antibiotic prescription during the first year of life. All the antibiotic therapies (Anatomical Therapeutic Chemical code J01) prescribed during this period were retrieved from FPs' electronic medical records included in the Pedianet database.

Exposure to bronchiolitis was defined as having at least one documented episode of bronchiolitis in the first year of life. Bronchiolitis cases were identified based on medical diagnosis recorded in outpatient primary care



**Figure 1** Flow chart of the cohort under study. \*When birth weight data were unavailable, but a weight measurement within the first 2 months of life was recorded, the LBW status was imputed using an estimation model. This model predicted LBW based on the first available measurement, accounting for the time elapsed since birth, the infant sex and the date of the recorded measurement. The model performance was evaluated through discrimination (area under the receiver operating characteristic curve=0.97) and calibration (Hosmer-Lemeshow  $p < 0.0001$ ), demonstrating excellent predictive accuracy. LBW, low birth weight.

using International Classification of Diseases, 9th revision - Clinical Modification (ICD-9-CM) codes (466.0, 466.1, 466.11), or through free text in medical charts, following a previously validated approach developed by our research group.<sup>20</sup>

To assess the combined effect of antibiotic exposure and bronchiolitis, we defined a four-level categorical variable:

- ▶ Reference level: no antibiotics exposure and no bronchiolitis.
- ▶ Level 1: only antibiotic exposure.
- ▶ Level 2: only bronchiolitis.

- ▶ Level 3: both antibiotic exposure and bronchiolitis.

### Mediator definition

A wheezing episode was defined as any medical diagnosis of wheezing recorded in the outpatient primary care visits identified either with ICD-9-CM codes (519.11, 786.07), or through free text in medical charts, as previously reported by our research group.<sup>15</sup> Only episodes occurring between the second and fourth years of life were considered. Recurrent wheezing was defined as two episodes occurring within a 1-year period and was treated as the mediator of interest.<sup>21</sup>

### Outcome definition

The primary outcome was the incident medical diagnosis of asthma after the age of five, according to guidelines,<sup>3</sup> defined as any paediatrician-diagnosed recorded with ICD-9-CM code 493.\*, or through free text in medical charts, as previously reported by our research group.<sup>22</sup> The date of asthma onset was defined as the first diagnosis recorded after the fifth birthday.

All cases identified via free-text search were then individually reviewed to ensure correct classification.

### Covariates

Covariates of interest were identified from electronic medical records reported in Pedianet. They included sex (male or female), familiarity of atopy or asthma (yes or no), the presence of eczema or atopic dermatitis in the first year of life (yes or no),<sup>5</sup> and the area deprivation index as a proxy of socioeconomic status.<sup>23</sup>

### Patient and public involvement

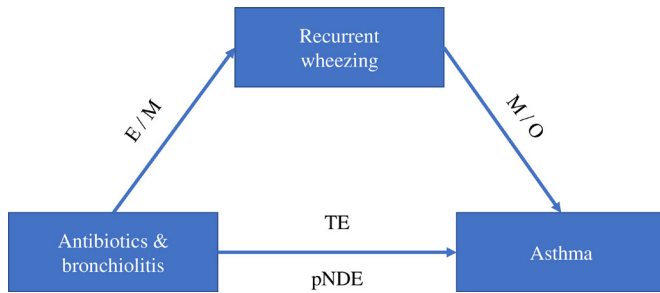
Given the retrospective observational nature of the study, patient and public have not been involved in the design, conduct, reporting or dissemination plans of our research.

### Statistical methods

The sociodemographic and clinical characteristics of the enrolled children were summarised using frequencies and percentages, stratified by the presence or absence of wheezing and/or asthma.

Mediation analysis was conducted to decompose the total effect of early-life exposures on asthma into direct and indirect effects, with recurrent wheezing serving as the mediator. Specifically, Cox regression was used to model the time-to-asthma outcome, yielding HRs and 95% CI. Logistic regression was applied to model the binary mediator (recurring wheezing), providing ORs and 95% CIs.<sup>15 24</sup> This approach allowed us to estimate the direct effect of antibiotic and bronchiolitis exposures on asthma, while accounting for the mediating role of recurrent wheezing (figure 2).

In the mediation analysis, children without recurrent wheezing were used as the reference group compared with those with recurrent wheezing. The analysis was implemented in R using the *regmedint* package, based on



**Figure 2** Conceptual diagram of the mediation model. TE is the relationship between the exposure and the outcome, while pNDE represents this relationship when controlling by the effect of the mediator. The indirect effect (tNIE) is equal to E/M out of M/O. E/M, relationship between exposure and mediator; M/O, relationship between mediator and outcome; pNDE, pure natural direct effect; TE, total effect; tNIE, total natural indirect effect.

the methodological framework proposed by Valeri and VanderWeele.<sup>25 26</sup>

Sensitivity and stratified analyses have been performed (online supplemental eMethods). We followed the STrengthening the Reporting of OBServational studies in Epidemiology guidelines. All statistical analyses were performed using SAS software, V.9.4 (SAS Institute) and R Statistical Software V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Cohort description

Among the 121 255 children included in the cohort, 2830 (2.33%) were diagnosed with asthma after age 5, reaching 5.56% (6977/125 402) when considering prevalent cases (table 1, figure 1). Overall, 62 563 (52%) were male, and socioeconomic deprivation was evenly distributed across the cohort. A total of 674 children (0.56%) had a familiarity of atopy or asthma, while 12 578 (10%) were diagnosed with eczema or atopic dermatitis during their first year of life (table 1). Antibiotic use was widespread, with nearly half of the children receiving at least one prescription during their first year of life. The most prescribed antibiotic was amoxicillin, both alone and with clavulanic acid, accounting for approximately 60% of all antibiotic prescriptions (online supplemental eTable 1). Bronchiolitis was a commonly diagnosed condition, affecting 8726 children (7%), and 5995 (5%) experienced both bronchiolitis and antibiotic exposure during the first year of life.

Wheezing affected 21% of our paediatric population, with 4738 out of 25 803 (18%) wheezing children classified as having recurrent wheezing. Across the spectrum from no wheezing to wheezing and recurrent wheezing, an increasing trend was observed in several characteristics: male sex (50%, 56% and 60%), familiarity of atopy or asthma (0.51%, 0.70% and 0.76%), eczema or atopic dermatitis (9%, 14% and 16%), antibiotic use (44%, 53%

and 60%) and bronchiolitis diagnoses (6%, 12% and 17%).

A similar pattern was observed across exposure levels: the proportion of unexposed children (ie, those with no antibiotics and no bronchiolitis) decreased from those with isolated wheezing to those with recurrent wheezing (54%, 43% and 35%). In contrast, high exposure levels (i.e., both antibiotics and bronchiolitis) were positively associated with more frequent wheezing episodes (4%, 8% and 12%).

Children with asthma (2.33% of the cohort) differed from asthma-free children in several characteristics: they were more frequently male (64% vs 51%), had a higher prevalence of family history of atopy or asthma (0.78% vs 0.55%), were more frequently diagnosed with eczema or atopic dermatitis (17% vs 10%), had higher antibiotic use (52% vs 46%) and experienced more bronchiolitis (10% vs 7%) (table 1).

### Mediation analysis

Figure 3 illustrates the mediation effects of recurrent wheezing on the association between exposure to antibiotics and/or bronchiolitis and the development of asthma. The total effect of these exposures on asthma risk ranged from a 24% increase (HR 1.24, 95% CI 1.13 to 1.36) for antibiotic use alone to a 51% increase (HR 1.51, 95% CI 1.15 to 1.99) for the exposure to bronchiolitis and to 48% (HR 1.48, 95% CI 1.23 to 1.79) for the combined exposure.

The indirect effect mediated by recurrent wheezing varied by exposure type: it accounted for 6% (OR 1.06, 95% CI 1.05 to 1.17) of the asthma risk in children exposed only to antibiotics, 28% (OR 1.28, 95% CI 1.12 to 1.45) in those exposed only to bronchiolitis, and 32% (OR 1.32, 95% CI 1.20 to 1.45) in those with both exposures.

The direct effects (i.e., independent of wheezing) also showed an increased risk of asthma: 17% (HR 1.17, 95% CI 1.07 to 1.28) for antibiotics exposure only, 19% (HR 1.19, 95% CI 0.86 to 1.63) for bronchiolitis alone and 13% (1.13, 95% CI 0.90 to 1.41) for combined exposures.

Notably, recurrent wheezing mediated approximately one-third of the asthma risk associated with antibiotic use, and a larger proportion, 64% and 74%, when bronchiolitis was the primary or combined exposure, respectively. The proportion eliminated, reflecting the hypothetical reduction in asthma risk if recurrent wheezing were prevented, suggests that 6%–70% of the exposure-related asthma risk could potentially be avoided.

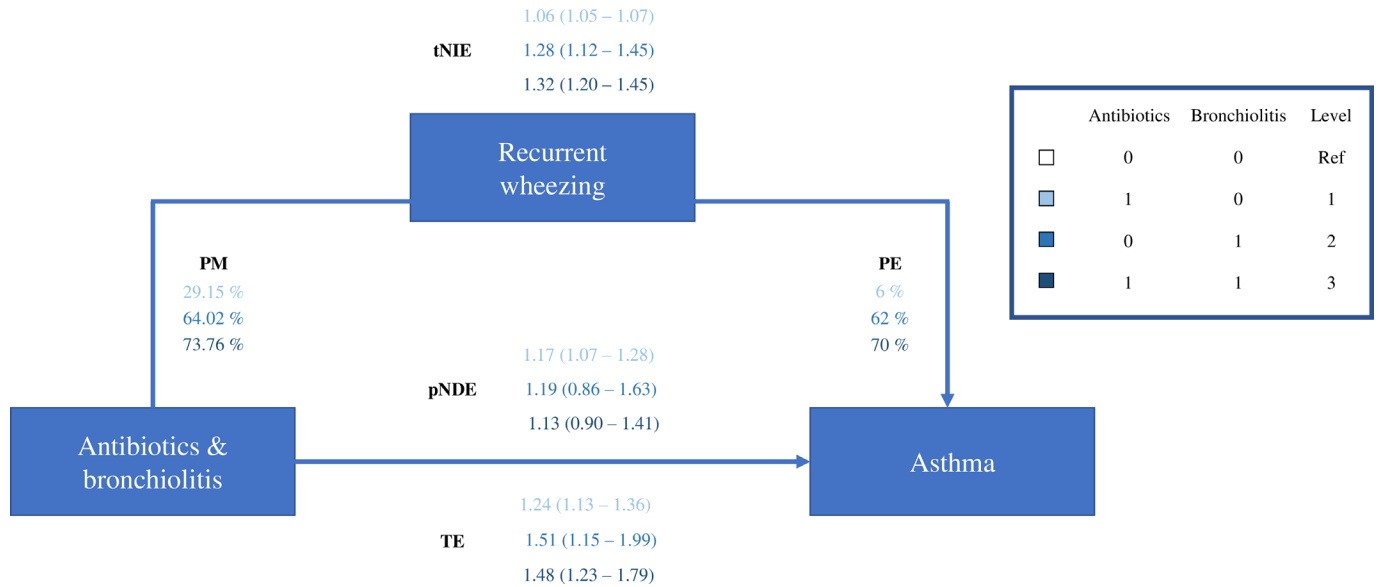
### Sensitivity and stratified analysis

The results of the stratified analyses are summarised in figure 4. The observed increased risk in wheezing-free children, but not in those with wheezing, highlights the significant role of wheezing, not just recurrent wheezing, in mediating the effect of antibiotics and bronchiolitis exposure on asthma risk.



**Table 1** Sociodemographic and clinical characteristics of children included in the cohort, overall and stratified by wheezing and asthma conditions

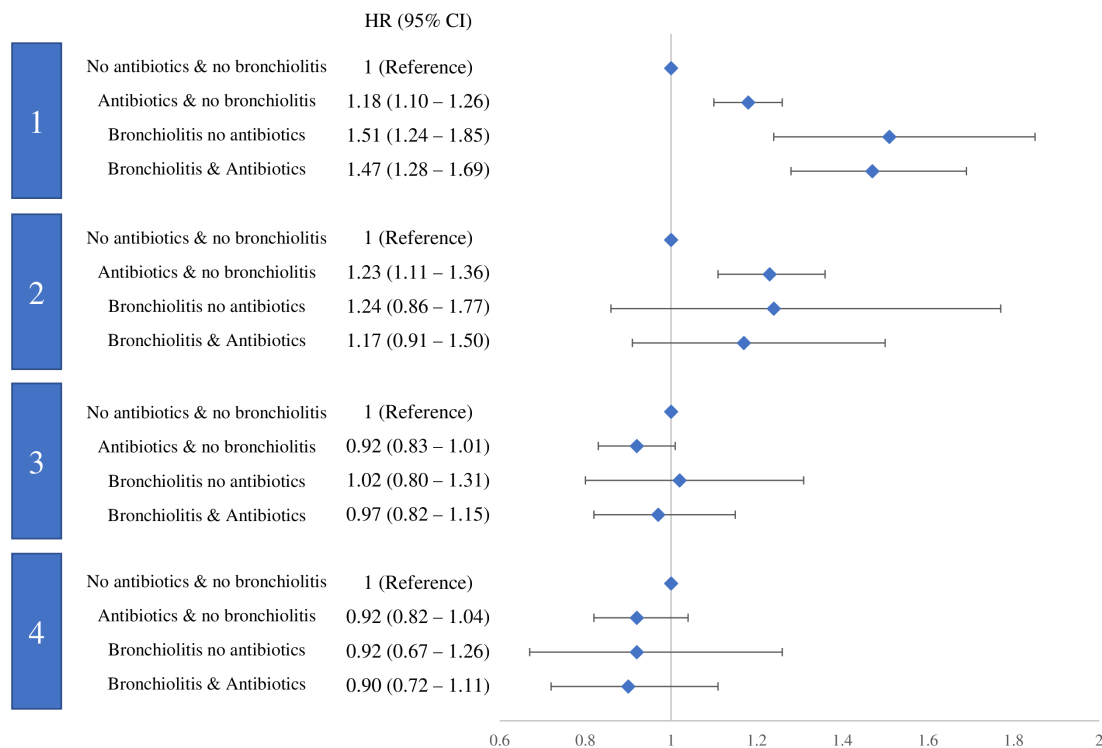
Children's characteristics	Overall		Healthy		Wheezing		Recurrent		No wheezing		Wheezing		No asthma		Asthma	
	N=121 255	N=95 452	N=21 065	N=4738	N=95 452	N=21 065	N=4738	N=4738	N=95 452	N=21 065	N=25 803	N=18 425	N=18 425	N=2830		
Sex, N (%)																
Female	58 692 (48.40)	47 566 (49.83)	9223 (43.78)	1903 (40.16)	47 566 (49.83)	9223 (43.78)	1903 (40.16)	47 566 (49.83)	47 566 (49.83)	9223 (43.78)	11 126 (43.12)	57 659 (48.69)	1033 (36.50)			
Male	62 563 (51.60)	47 886 (50.17)	11 842 (56.22)	2835 (59.84)	47 886 (50.17)	11 842 (56.22)	2835 (59.84)	47 886 (50.17)	47 886 (50.17)	14 677 (56.88)	60 766 (51.31)	1797 (63.50)				
Deprivation Index, N (%)																
1	19 902 (16.41)	15 649 (16.39)	3493 (16.58)	760 (16.04)	15 649 (16.39)	3493 (16.58)	760 (16.04)	15 649 (16.39)	15 649 (16.39)	4253 (16.48)	19 428 (16.41)	474 (16.75)				
2	21 177 (17.46)	16 739 (17.54)	3629 (17.23)	809 (17.07)	16 739 (17.54)	3629 (17.23)	809 (17.07)	16 739 (17.54)	16 739 (17.54)	4438 (17.20)	20 699 (17.48)	478 (16.89)				
3	21 500 (17.73)	16 908 (17.71)	3739 (17.75)	853 (18.00)	16 908 (17.71)	3739 (17.75)	853 (18.00)	16 908 (17.71)	16 908 (17.71)	4592 (17.80)	20 920 (17.67)	580 (20.49)				
4	20 081 (16.56)	15 722 (16.47)	3567 (16.93)	792 (16.72)	15 722 (16.47)	3567 (16.93)	792 (16.72)	15 722 (16.47)	15 722 (16.47)	4359 (16.89)	19 589 (16.54)	492 (17.39)				
5	18 376 (15.15)	14 269 (14.95)	3311 (15.72)	796 (16.80)	14 269 (14.95)	3311 (15.72)	796 (16.80)	14 269 (14.95)	14 269 (14.95)	4107 (15.92)	17 978 (15.18)	398 (14.06)				
6	20 219 (16.67)	16 165 (16.94)	3326 (15.79)	728 (15.37)	16 165 (16.94)	3326 (15.79)	728 (15.37)	16 165 (16.94)	16 165 (16.94)	4054 (15.71)	19 811 (16.73)	408 (14.42)				
History of atopy or asthma, N (%)																
No	120 581 (99.44)	94 961 (99.49)	20 918 (99.30)	4702 (99.24)	94 961 (99.49)	20 918 (99.30)	4702 (99.24)	94 961 (99.49)	94 961 (99.49)	25 620 (99.29)	117 773 (99.45)	2808 (99.22)				
Yes	674 (0.56)	491 (0.51)	147 (0.70)	36 (0.76)	491 (0.51)	147 (0.70)	36 (0.76)	491 (0.51)	491 (0.51)	183 (0.71)	652 (0.55)	22 (0.78)				
Eczema/atopic dermatitis, N (%)																
No	108 677 (89.63)	86 508 (90.63)	18 182 (86.31)	3987 (84.15)	86 508 (90.63)	18 182 (86.31)	3987 (84.15)	86 508 (90.63)	86 508 (90.63)	22 169 (85.92)	106 316 (89.77)	2361 (83.43)				
Yes	12 578 (10.37)	8944 (9.37)	2883 (13.69)	751 (15.85)	8944 (9.37)	2883 (13.69)	751 (15.85)	8944 (9.37)	8944 (9.37)	3634 (14.08)	12 109 (10.23)	469 (16.57)				
Antibiotics, N (%)																
No	65 351 (53.90)	53 582 (56.14)	9878 (46.89)	1891 (39.91)	53 582 (56.14)	9878 (46.89)	1891 (39.91)	53 582 (56.14)	53 582 (56.14)	11 769 (45.61)	63 994 (54.04)	1357 (47.95)				
Yes	55 904 (46.10)	41 870 (43.86)	11 187 (53.11)	2847 (60.09)	41 870 (43.86)	11 187 (53.11)	2847 (60.09)	41 870 (43.86)	41 870 (43.86)	14 034 (54.39)	54 431 (45.96)	1473 (52.05)				
Bronchiolitis, N (%)																
No	112 529 (92.80)	90 048 (94.34)	18 541 (88.02)	3940 (83.16)	90 048 (94.34)	18 541 (88.02)	3940 (83.16)	90 048 (94.34)	90 048 (94.34)	22 481 (87.13)	109 977 (92.87)	2552 (90.18)				
Yes	8726 (7.20)	5404 (5.66)	2524 (11.98)	798 (16.84)	5404 (5.66)	2524 (11.98)	798 (16.84)	5404 (5.66)	5404 (5.66)	3322 (12.87)	8448 (7.13)	278 (9.82)				
Exposure, N (%)																
No antibiotics no bronchiolitis	62 620 (51.64)	51 836 (54.31)	9119 (43.29)	1665 (35.14)	51 836 (54.31)	9119 (43.29)	1665 (35.14)	51 836 (54.31)	51 836 (54.31)	10 784 (41.79)	61 352 (51.81)	1268 (44.81)				
Antibiotics no bronchiolitis	49 909 (41.16)	38 212 (40.03)	9422 (44.73)	2275 (48.02)	38 212 (40.03)	9422 (44.73)	2275 (48.02)	38 212 (40.03)	38 212 (40.03)	11 697 (45.33)	48 625 (41.06)	1284 (45.37)				
Bronchiolitis no antibiotics	2731 (2.25)	1746 (1.83)	759 (3.60)	226 (4.77)	1746 (1.83)	759 (3.60)	226 (4.77)	1746 (1.83)	1746 (1.83)	985 (3.82)	2642 (2.23)	89 (3.14)				
Antibiotics and bronchiolitis	5995 (4.94)	3658 (3.83)	1765 (8.38)	572 (12.07)	3658 (3.83)	1765 (8.38)	572 (12.07)	3658 (3.83)	3658 (3.83)	2337 (9.06)	5806 (4.90)	189 (6.68)				



**Figure 3** Mediation diagram for the association between at least one antibiotic prescription and bronchiolitis in the first year of life, recurrent wheezing between the second and fourth years of life, and asthma onset after the fifth year of life. PE, percentage eliminated; PM, portion mediated; pNDE, pure natural direct effect; tNIE, total natural indirect effect; TE, total effect.

Among children with wheezing, including only those with isolated wheezing but excluding recurrent wheezing cases, no association was found between the exposure levels of interest and asthma onset. In contrast, among wheezing-free children, the results confirmed the estimates observed in the overall cohort, showing an increasing asthma risk with higher exposure levels.

Specifically, HR was 1.23 (95% CI 1.11 to 1.36) for children exposed only to antibiotics, 1.24 (95% CI 0.86 to 1.77) for those exposed only to bronchiolitis, and 1.17 (95% CI 0.91 to 1.50) for those exposed to both antibiotics and bronchiolitis. Results were also consistent in the sensitivity analysis, in which exposure was defined as having filled at least two antibiotic prescriptions within



**Figure 4** Forest plot showing HRs with corresponding 95% CIs for the risk of developing asthma, adjusted for sex, area deprivation index, history of atopy or asthma and diagnosis of eczema or atopic dermatitis in the first year of life. The analysis was conducted in (1) the entire cohort, (2) children without wheezing, (3) children with wheezing and (4) wheezing children excluding those with recurrent wheezing.

the first year of life, alone or in combination with bronchiolitis (online supplemental eFigure 1).

## DISCUSSION

In our Italian paediatric cohort of 121 255 children followed for at least 5 years, early-life exposure to antibiotics and bronchiolitis was common; 41% received antibiotics alone, and 5% experienced both exposures. Wheezing between the ages of 2 and 5 was reported in 21% of children, with 18% experiencing recurrent episodes. Asthma was diagnosed in 2.3% of the cohort. After adjusting for sex, atopy, eczema and socioeconomic status, asthma risk increased by 24% in children exposed only to antibiotics and by 48% in those exposed to both antibiotics and bronchiolitis, compared with unexposed peers. Moreover, although the combined exposure to antibiotic use and bronchiolitis showed a slightly lower point estimate than bronchiolitis alone, the overlapping CIs indicate that these effects are not meaningfully different. Recurrent wheezing emerged as a key mediator, accounting for 29%–74% of the excess asthma risk. These findings emphasise the central role of recurrent wheezing in the transition from early-life exposures to asthma and suggest that preventing bronchiolitis and antibiotic prescriptions could reduce asthma risk by up to 70%.

Both antibiotic use and bronchiolitis are recognised risk factors for wheezing and asthma, with preschool wheezing being a major contributor to asthma onset.<sup>27–29</sup> While previous studies explored these associations separately, our analysis is among the first to assess their combined effect and quantify the mediating role of recurrent wheezing to asthma onset after age five. Using mediation analysis, we show that recurrent wheezing explains more than half of asthma risk in children exposed to bronchiolitis, highlighting its pivotal role in this pathway.

Previous research supports these findings. Teijeiro and Gómez reported that respiratory viruses responsible for bronchiolitis, such as RSV and rhinovirus, along with timing and severity of infection, and a child's atopic status, are key determinants of asthma risk.<sup>30</sup> Recurrent wheezing following bronchiolitis episodes significantly increases the likelihood of later asthma.<sup>31</sup> RSV causes 60%–80% of bronchiolitis cases in infancy, particularly in winter, while rhinovirus circulates year-round.<sup>32–34</sup> RSV is more likely to have a causal role in asthma development, whereas rhinovirus may act as a marker of susceptibility.<sup>27</sup> Rhinovirus-induced bronchiolitis has also been identified as a strong predictor of recurrent wheezing, which itself is closely associated with later asthma.<sup>33 35 36</sup>

The gut and respiratory microbiomes likely contribute to these associations. Early microbial colonisation and the development of the respiratory tract microbiota are critical for immune system maturation.<sup>37</sup> Delayed microbiota development has been linked to instability and increased susceptibility to infections.<sup>38</sup> Antibiotic use in infancy can disrupt microbial diversity, influencing

immune regulation, particularly the balance between T helper cells and regulatory T cells.<sup>39</sup> This disruption may increase the risk of allergic diseases, including asthma, supporting the hygiene hypothesis.<sup>10</sup> The Dutch KOALA cohort study demonstrated that infants exposed to antibiotics had gut microbiota patterns associated with eczema and wheezing by age two, reinforcing the connection between antibiotic-driven microbiome alterations and immune-related respiratory outcomes.<sup>40</sup>

Despite accumulating evidence, a 2022 review and a 2019 WHO expert panel concluded that evidence linking RSV lower respiratory tract infections to asthma remains inconclusive.<sup>18</sup> However, if a causal relationship does exist, preventive strategies must be prioritised globally. Our findings contribute to this evolving discussion. The recent nationwide rollout of nirsevimab in Italy marks an important step in RSV prevention. Real-world evidence from 2025 showed a 27% reduction in wheezing in the first year following nirsevimab introduction, demonstrating its effectiveness in preventing RSV infections and related complications. This effect reflects the decrease of bronchiolitis, which represents the main risk factor for subsequent wheezing development. These outcomes align with Advisory Committee on Immunization Practices (ACIP) recommendations supporting its use in all eligible infants.<sup>41</sup> Future studies should examine the long-term effects of RSV immunoprophylaxis not only on acute illness but also on downstream conditions such as asthma.

Our previous research during the COVID-19 lockdown, which effectively delayed bronchiolitis onset, revealed a 30% reduction in wheezing incidence.<sup>15</sup> Furthermore, this study showed that effective prevention of recurrent wheezing could reduce asthma risk by at least 70% in the general paediatric population. These results reinforce the importance of early-life interventions that target the underlying triggers of wheezing and asthma.

A major strength of our study is the use of real-world primary care data, which ensures comprehensive coverage and reflects actual clinical practice. Additionally, our methodological framework enabled exploration of complex interrelationships among exposures, mediators and outcomes, moving beyond simple exposure-outcome models to provide a more nuanced understanding of asthma development.

Nonetheless, some limitations must be acknowledged. First, the mediation analysis was constrained by software limitations, which prevented the use of isolated wheezing as a mediator in time-to-event models. To address this, we performed wheezing-stratified analyses, which consistently supported the role of wheezing as a mediator. Second, asthma diagnosis was based on clinical coding, which may have led to some degree of misclassification of undiagnosed cases. We deliberately chose not to include respiratory medication data to avoid further misclassification, a decision that may have led to conservative estimates. Third, the analysis was restricted to children followed from birth with at least 5 years of follow-up. This

restriction was implemented to ensure reliable ascertainment of incident asthma, as diagnoses made before the age of 5 may be less specific due to transient wheezing phenotypes in early childhood. Although this approach reduced the sample size and may have led to an overrepresentation of healthier children in the analytic cohort, such selection would be expected to bias results towards the null rather than inflate associations. Moreover, previous studies have shown that Pedianet birth cohorts are representative of national birth cohorts, thereby limiting the risk of substantial selection bias.<sup>42</sup> Finally, as with all observational studies, residual confounding cannot be excluded, particularly in relation to environmental exposures or unmeasured parental behaviours.

## CONCLUSIONS

Our findings highlight the crucial role of early-life events, specifically antibiotic use and bronchiolitis, in shaping long-term respiratory health. Recurrent wheezing serves as a key mediator linking these early exposures to asthma. Public health strategies aimed at preventing bronchiolitis through immunoprophylaxis and promoting judicious antibiotic use may significantly reduce the burden of asthma. These findings should inform future clinical guidelines and policy interventions targeting respiratory health in early childhood.

### Author affiliations

<sup>1</sup>Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, Università degli Studi di Milano-Bicocca, Milan, Italy

<sup>2</sup>Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padua Unit of Biostatistics, Epidemiology and Public Health, Padua, Italy

<sup>3</sup>Department of Women's and Children's Health, University of Padua, Padua, Italy

<sup>4</sup>Neonatal Intensive Care Unit, Department of Women's and Children's Health, Institute of Pediatric Research, University of Padua, Padua, Italy

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### ORCID iDs

Riccardo Boracchini <https://orcid.org/0009-0002-8339-9485>

Costanza Di Chiara <https://orcid.org/0000-0002-3586-0612>

Anna Cantarutti <https://orcid.org/0000-0002-3700-780X>

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