Pediatric RESEARCH
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POPULATION STUDY ARTICLE

Risk factors for recurrent respiratory tract infection in preschool-aged children

Bo Zhou[1,2,3], Wenquan Niu[4], Fangyu Liu[1], Yuan Yuan[1,2,3], Kundi Wang[3], Jing Zhang[3], Yunfeng Wang[3] and Zhixin Zhang[2,3]

BACKGROUND: We aimed to identify potential risk factors for recurrent respiratory tract infection among Chinese preschool-aged children, and further to construct a nomogram prediction model.

METHODS: This is a cross-sectional survey conducted in Beijing. Utilizing a stratified cluster random sampling strategy, a total of 7222 children from 20 kindergartens were enrolled. Data are analyzed by STATA software and R language.

RESULTS: Five independent factors were identified to be significantly associated with recurrent respiratory tract infection risk overall and by pathogenic sites. The significant odds of recurrent respiratory tract infection was 8.31 (95% confidence interval [CI]: 5.69–12.12, $P < 0.001$), 2.31 (2.06–2.58, $P < 0.001$), 1.72 (1.48–1.99, $P < 0.001$), 1.24 (1.08–1.43, $P = 0.002$), and 1.19 (1.09–1.31, $P <$ 0.001) for asthma, allergy, initial use of antibiotics <6 months, breastfeeding duration <6 months, and maternal body mass index, respectively. Besides the leading role played by asthma, allergy, initial use of antibiotics, and breastfeeding might exert a graded, dose-dependent effect on recurrent respiratory tract infection susceptibility.

CONCLUSIONS: We have identified five potential risk factors for the risk of recurrent respiratory tract infection from 7222 preschool-aged Chinese children. Notably, asthma plays a leading role, and allergy, initial use of antibiotics, and breastfeeding might exert a graded, dose-dependent effect on recurrent respiratory tract infection susceptibility.

Pediatric Research (2021) 90:223–231; https://doi.org/10.1038/s41390-020-01233-4

IMPACT:

- This is the first report of examining the joint contribution of multiple potential risk factors to recurrent respiratory tract infection among Chinese preschool-aged children.
- We have identified five potential risk factors for the risk of recurrent respiratory tract infection via analyzing survey data from 7222 preschool-aged Chinese children.
- Asthma plays a leading role, and allergy, initial use of antibiotics, and breastfeeding might exert a graded, dose-dependent effect on recurrent respiratory tract infection susceptibility.

INTRODUCTION

Respiratory tract infection constitutes a major load in pediatric outpatient services and hospitalizations, especially in developing countries,[1] and thereof recurrent respiratory tract infection is commonly seen among young children.[2] Both upper and lower respiratory tracts may get infected, and recurrent lower respiratory tract infection, such as pneumonia, remains the leading infectious cause of pediatric fatality under the age of 5 years. According to the Global Burden of Disease Study 2016, an estimated 0.65 million children died from lower respiratory tract infection,[3] in sharp contrast to 0.94 million in 2013[4] and 1.3 million in 2011.[1] Despite a declining trend in the recent decade, the actual fatality figure is still high. In addition, epidemiologic statistics in 2010 revealed that the incidence of community-acquired childhood pneumonia was ~0.22 (interquartile range: 0.11–0.51) episodes per child-year in low- and middle-income countries, and it ranged from 0.015 to 0.060 in high-income countries.[5,6] As there are currently no reliable tools to distinguish which children are at enhanced risk for recurrent respiratory tract infection, higher priority should be given to research that identify potential risk predictors to enable risk stratification, optimize prevention strategies, and ensure timely therapeutics.

Clinically, deficiencies in the defense system or in the pulmonary pathways often confer susceptibility to recurrent respiratory tract infection.[7] Several epidemiologic risk factors have been acknowledged for the development of recurrent respiratory tract infection in children, such as parental smoking and asthma,[8,9] yet no consensus has been reached. For example, Jopje and colleagues[10] found that exposure to environmental tobacco smoke had a strongly increased risk for recurrent respiratory tract infection, yet no effect of maternal smoking during pregnancy was reported by Liesbeth and colleagues.[11] Because the underlying pathogenesis of recurrent respiratory tract infection is proposed to be multifactorial, it is unlikely that any one single factor would

[1]Graduate School, Beijing University of Chinese Medicine, Beijing, China; [2]International Medical Services, China-Japan Friendship Hospital, Beijing, China; [3]Department of Pediatrics, China-Japan Friendship Hospital, Beijing, China and [4]Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing, China
Correspondence: Zhixin Zhang (zhangzhixin032@163.com)
These authors contributed equally: Bo Zhou, Wenquan Niu, Fangyu Liu, Yuan Yuan

Received: 16 May 2020 Revised: 12 August 2020 Accepted: 11 October 2020
Published online: 10 November 2020

exert a dominant impact on recurrent respiratory tract infection. Given its complexity, it is of interest to interrogate the possible interaction of major risk factors, and if allowed, construct a multivariate risk prediction model. In addition, given that the incidence of recurrent respiratory tract infection varies considerably in different countries and across ethnic groups, it is of public health importance to construct a database of risk profiles related to this disease in each ethnic group.

To fill this gap in our knowledge and generate more information for future studies, we conducted a large-scale cross-sectional investigation among preschool-aged children randomly selected from 20 kindergartens in Beijing, aiming to identity potential risk factors responsible for recurrent respiratory tract infection, both in isolation and in combination, and further to construct a risk nomogram prediction model on the basis of significant risk factors identified.

METHODS

Study design

This is a cross-sectional survey conducted in Beijing from September to November 2019 following the guidelines of the Declaration of Helsinki. The conduct of this study got approval from the Ethics Committee of China-Japan Friendship Hospital, and written informed consent was obtained from the parents or guardians of study children prior to participation.

Study children

A stratified cluster random sampling strategy was utilized to select four (including two urban and two suburban) districts from 16 districts in Beijing, and further select five kindergartens, either public or private, from each designated district. Study subjects were restricted to preschool-aged children currently attending junior to senior classes in kindergartens. Children with unhealthy conditions, such as airway malformations, chronic respiratory disease, or congenital heart disease, were excluded from this present study.

In this survey, a self-designed structured electronic questionnaire was administered to the parents or guardians of 7524 children, and 7469 questionnaires were answered (response rate: 99.3%). After excluding 247 questionnaires with incomplete or missing information of interest, data from 7222 valid questionnaires were left in the final analysis.

Data collection and quality control

Data on possible risk factors of both children and their parents for pediatric recurrent respiratory tract infection were exported from qualified electronic questionnaires to a Microsoft Office Excel™ spreadsheet. From children, data were collected on date of birth, sex, region, birth weight, history of respiratory diseases, sleep duration, and time of adding complementary foods, as well as the episodes of upper and lower respiratory tract infection over the past year, diagnosis of asthma by physicians, frequency of snoring during sleeping, allergy (including food, drug, dust, flower, or chemicals), and the initial use of antibiotics. For children, body height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg) were measured by trained health physicians. From parents, data were collected on date of birth, sex, body height and weight, maternal pre-pregnancy weight, gestational weight gain (GWG), delivery mode, education, family income, breastfeeding duration, cigarette smoking, gestational diabetes mellitus, and gestational hypertension.

To ensure quality control, one health physician was invited from each designated kindergarten, and received training on the methodology of this survey. Questionnaires were handed out by kindergarten teachers, and were completed online. Data from questionnaires were cross-checked by health physicians and investigators, and missing or extreme data were returned to kindergarten teachers in charge for further confirmation, and if necessary contacting parents or guardians.

Diagnosis of recurrent respiratory tract infection

There is currently no consensus about the accepted definition of recurrent respiratory tract infection in children, and in most cases, it is defined according to a certain number of annual infection episodes or specific diagnoses.[12] Clinically, recurrent lower respiratory tract infection includes pneumonia and acute bronchitis, and recurrent upper respiratory tract infection includes common cold, tonsillitis, sinusitis, and otitis media. In this study, we employed the definition of recurrent respiratory tract infection recommended by Martino and Ballotti.[13] In detail, a child is diagnosed to have recurrent respiratory tract infection if any pathological underlying condition justifying the recurrence of infections is absent, and at least one of the following conditions is met, that is, (i) six or more upper or lower respiratory tract infection episodes per year, (ii) one or more respiratory tract infection episodes per month from October to February, and (iii) two or more lower respiratory tract infection episodes per year. Recurrent upper respiratory tract infection is defined as one of the following two conditions: (i) six or more upper respiratory tract infection episodes per year, and (ii) one or more upper respiratory infection episodes per month from October to February. Recurrent lower respiratory tract infection is defined as two or more lower respiratory tract infection episodes per year.

Other definitions

Parental and maternal body mass index (BMI) (kg/m^2) were calculated from self-reported height and weight (including the present and prior to pregnancy) and used to classify mothers as underweight ($BMI < 18.5\ kg/m^2$), normal weight ($18.5\ kg/m^2 \leq BMI \leq 24\ kg/m^2$), and overweight/obesity ($BMI \geq 24\ kg/m^2$).[14] GWG was calculated by subtracting maternal pre-pregnancy weight from maternal weight at delivery.

Education level was categorized as graduate degree or above, college (or equivalent) degree, high school (or equivalent) degree, or middle school degree or below. Family income level (RMB per year) was categorized as ≥500,000, 200,000–500,000, 100,000–200,000, or <100,000. Gestational diabetes mellitus and gestational hypertension, diagnosed by doctors from second-class or above hospitals, were recorded. Maternal pregnancy smoking was defined as smoking and non-smoking. Maternal pre-pregnancy smoking and paternal smoking were grouped into never smoking and ever (current or former) smoking. Delivery mode included natural birth and cesarean section.

For children, breastfeeding duration and time of adding complementary foods were self-reported and recorded in months. Breastfeeding duration was classified as <6 months and ≥6 months. Sleep duration was calculated as the sum of both sleep time on work days × 5 and sleep time on weekends × 2 divided by 7. Birth weight was classified as “low weight” (≤2.5 kg), “normal weight” (2.6–3.9 kg), or “high weight” (≥4.0 kg).[15] Asthma was self-reported to be diagnosed by a doctor or health professional. Allergy was self-reported, including food, drug, dust, flower, or chemicals allergies. Snoring during sleeping was self-reported yes or no. Initial use of antibiotics was self-reported and classified as <6 months and ≥6 months.

Statistical analysis

Based on the diagnosis of recurrent respiratory tract infection and by pathogenic sites, all study children were classified into two groups. The distributions of continuous variables were assessed for normality by use of the skewness and kurtosis test. Skewed continuous variables are expressed as median (interquartile range), and normally distributed variables as mean (SD). Categorical variables are expressed as number (percentage). Between-group comparisons were implemented by *t* test or rank-sum test or χ^2 test, where appropriate. Potential risk factors for recurrent respiratory tract infection were selected by both forward and backward logistic regression analyses at a statistical significance level of 5%, before and after adjusting for confounding factors, including age of children, sex, and region. The magnitude of risk association is quantified by odds ratio (OR) and 95% confidence interval (95% CI). The difference between two effect-size estimates was assessed using the Z test as recommended by Altman and Bland.[16]

Prediction accuracy of significant risk factors was appraised from calibration and discrimination aspects. Calibration statistics includes Akaike information criterion (AIC) and Bayesian information criterion (BIC), as well as the −2 log-likelihood ratio test. Discrimination statistics includes the area under the receiver-operating characteristic (ROC) to justify the improvement in prediction performance. In addition, the net benefit for adding significant risk factors was justified by decision curve analysis.[17]

Finally, on the basis of significant risk factors, a risk prediction nomogram model was constructed to enhance clinical and public health application, and this model was generated by the R language version 3.5.2 for Windows.

Unless otherwise reported, statistical analyses were completed using the STATA software version 14.0 (Stata Corp, TX) for Windows. Two-sided P value < 5% was reported to be statistically significant. Statistical power was estimated using the PS Power and Sample Size Calculations software version 3.0.

RESULTS

Baseline characteristics

In total, data from 7222 qualified questionnaires from 7222 preschool-aged children were extracted for analysis. The mean age of all children was 4.63 years old, and there are 3601 boys and 3621 girls. The percentage of recurrent respiratory tract infection was 23.91%, and that of recurrent upper and lower respiratory tract infection was 11.73% and 17.64%, respectively.

Shown in Table 1 are the baseline characteristics of study children upon stratification by recurrent respiratory tract infection overall and by pathogenic sites. The distributions of region, maternal BMI, paternal BMI, maternal pre-pregnancy BMI, GWG, gestational diabetes mellitus, breastfeeding duration, asthma, snore during sleeping, allergy, and initial use of antibiotics differed significantly between children with and without recurrent respiratory tract infection (all $P < 0.05$).

Identification of potential risk factors

Both forward and backward logistic regression analyses were used to potential risk factors in association with the risk for recurrent respiratory tract infection overall and by pathogenic sites among preschool-aged children (Table 2). Of note, six factors, including asthma, allergy, initial use of antibiotics, breastfeeding duration, maternal BMI, and GWG, were found to be associated with the significant risk of recurrent respiratory tract infection overall and at the lower site before adjustment (all $P < 0.05$), and at the upper site, significance remained for asthma, allergy, initial use of antibiotics, and maternal BMI only ($P < 0.001$, <0.001, <0.001, and 0.014, respectively).

After adjusting for age, sex, and region, all six, except GWG, factors were significantly associated with recurrent respiratory tract infection overall and at the lower site (all $P < 0.05$), and for recurrent upper respiratory tract infection, breastfeeding duration was additionally insignificant ($P = 0.159$). For example, the significant odds of having recurrent respiratory tract infection was 8.31 (95% CI: 5.69–12.12, $P < 0.001$), 2.31 (95% CI: 2.06–2.58, $P < 0.001$), 1.72 (95% CI: 1.48–1.99, $P < 0.001$), 1.24 (95% CI: 1.08–1.43, $P = 0.002$), and 1.19 (95% CI: 1.09–1.31, $P < 0.001$), respectively, for asthma, allergy, initial use of antibiotics <6 months, breastfeeding duration <6 months, and maternal BMI, which were retained for further explorations. The power to detect significance was >90% for above comparisons.

The difference between the effect-size estimates in children with recurrent upper and lower respiratory tract infection was nonsignificant ($P > 0.05$) as reflected by the Z test (Table 2).

Prediction performance assessment

Prediction performance for five aforementioned significant risk factors associated with recurrent respiratory tract infection overall and by pathogenic sites was assessed by comparing two models —basic model (without five risk factors) and full model (all variables with five risk factors), from calibration and discrimination aspects (Table 3). Significant improvement was seen after adding the five significant factors under three disease classifications. For example, the full model was significantly superior to the basic model as reflected by the goodness-of-fit test (all $P < 0.001$), which was further reinforced by decision curve analysis (Fig. 1).

Interaction exploration

Considering the factor that asthma is an established risk factor for recurrent respiratory tract infection and the number of children with asthma was very limited, pairwise interaction analysis was undertaken for the rest four significant risk factors (allergy, initial use of antibiotics, breastfeeding duration, and maternal BMI). To maximize the power to detect significance, the four significant risk factors were divided into two or three subgroups. Specifically, both maternal BMI and maternal pre-pregnancy BMI were divided into the low (BMI < 18.5 kg/m^2), normal (BMI: 18.5–24 kg/m^2), and high (BMI ≥ 24 kg/m^2) groups.[18] Breastfeeding duration was binarized on the basis of 6 months according to the recommendation of the World Health Organization, that is, solids were introduced at 6 months.[19] Initial use of antibiotics was binarized on the basis of 6 months according to the study, which demonstrated that antibiotic use in the first 6 months preceded the manifestation of wheeze.[20]

As shown in Table 4, pairwise interaction of four significant risk factors was explored and presented. Of note, there was a graded increase in the odds of having recurrent respiratory tract infection overall and by pathogenic sites. For example, when compared with children without allergy and with initial use of antibiotics ≥6 months, children without allergy and initial use of antibiotics <6 months, with allergy and initial use of antibiotics ≥6 months, and with allergy and initial use of antibiotics <6 months were 1.81 (95% CI: 1.50–2.20; $P < 0.001$), 2.24 (95% CI: 1.97–2.54; $P < 0.001$), and 3.25 (95% CI: 2.56–4.13; $P < 0.001$) times more likely to suffer recurrent respiratory tract infection, respectively. The case was the same for the interaction between allergy and breastfeeding, as well as initial use of antibiotics and breastfeeding, indicating that allergy, initial use of antibiotics, and breastfeeding contributed to the development of recurrent respiratory tract infection in a dose-dependent manner. Relative to normal maternal BMI, low maternal BMI seemed to be a protective, albeit nonsignificant factor in the context of without allergy, initial use of antibiotics ≥6 months, or breastfeeding ≥6 months, and by contrast, high maternal BMI was a significant risk-conferring factor, especially in the present of with allergy, initial use of antibiotics <6 months, or breastfeeding <6 months for recurrent respiratory tract infection overall and by pathogenic sites.

Risk prediction nomogram model

For practical reasons, a nomogram was constructed and displayed in Fig. 2 to help visually predict the risk of having recurrent respiratory tract infection overall and by pathogenic sites among preschool-aged children by modeling promising and significant risk factors under investigation (Fig. 2). Overall accuracy for prediction was good, with the C-index over 80% for three nomogram models (all $P < 0.001$) and calibration curves (Supplementary Fig. 1).

Table 1. The baseline characteristics of study children according to recurrent respiratory tract infection overall and by sites.

Characteristics	Recurrent respiratory tract infection			Recurrent upper respiratory tract infection			Recurrent lower respiratory tract infection		
	No ($n = 5495$)	Yes ($n = 1727$)	P value	No ($n = 6375$)	Yes ($n = 847$)	P value	No ($n = 5948$)	Yes ($n = 1274$)	P value
From children									
Age									
≤5 years	3266 (59.4%)	1076 (62.3%)	0.034	3806 (59.7%)	536 (63.3%)	0.046	3565 (59.9%)	777 (61%)	0.486
>5 years	2229 (40.6%)	651 (37.7%)		2569 (40.3%)	311 (36.7%)		2383 (40.1%)	497 (39%)	
Age (months)	57.3 (44.87, 64.34)	56.81 (46.64, 63.59)	0.687	57.27 (45.03, 64.31)	56.38 (45.56, 63.29)	0.174	57.14 (44.85, 64.24)	57.27 (47.57, 63.68)	0.200
Males	2765 (50.3%)	836 (48.4%)	0.166	3179 (49.9%)	422 (49.8%)	0.981	2994 (50.3%)	607 (47.6%)	0.081
Region									
Urban area	3141 (57.2%)	802 (46.4%)	<0.001	3553 (55.7%)	390 (46%)	<0.001	3373 (56.7%)	570 (44.7%)	<0.001
Suburban area	2354 (42.8%)	925 (53.6%)		2822 (44.3%)	457 (54%)		2575 (43.3%)	704 (55.3%)	
BMI (kg/m^2)	15.38 (14.42, 16.53)	15.32 (14.42, 16.53)	0.318	15.39 (14.42, 16.53)	15.15 (14.36, 16.33)	0.005	15.38 (14.42, 16.53)	15.39 (14.46, 16.58)	0.839
Birth weight (g)	3350 (3050, 3650)	3350 (3050, 3630)	0.491	3350 (3050, 3650)	3355 (3050, 3600)	0.723	3355 (3050, 3650)	3350 (3050, 3630)	0.427
Sleep duration	10.43 (9.86, 11.29)	10.57 (10, 11.29)	0.736	10.5 (9.86, 11.29)	10.57 (10, 11.29)	0.362	10.57 (10, 11.29)	10.5 (10, 11.29)	0.811
Breastfeeding duration (months)	12 (7, 18)	12 (6, 18)	<0.001	12 (6.5, 18)	12 (6, 18)	0.749	12 (7, 18)	12 (6, 17)	<0.001
Breastfeeding duration									
≥6 months	4573 (83.2%)	1375 (79.6%)	0.001	5267 (82.6%)	681 (80.4%)	0.109	4948 (83.2%)	1000 (78.5%)	<0.001
<6 months	921 (16.8%)	352 (20.4%)		1107 (17.4%)	166 (19.6%)		999 (16.8%)	274 (21.5%)	
Add food supplement (months)	6 (6, 6)	6 (6, 6)	0.455	6 (6, 6)	6 (6, 6)	0.809	6 (6, 6)	6 (6, 6)	0.363
Asthma									
No	5455 (99.3%)	1634 (94.6%)	<0.001	6293 (98.7%)	796 (94%)	<0.001	5897 (99.1%)	1192 (93.6%)	<0.001
Yes	40 (0.7%)	93 (5.4%)		82 (1.3%)	51 (6%)		51 (0.9%)	82 (6.4%)	
Allergy									
No	4003 (72.8%)	927 (53.7%)	<0.001	4490 (70.4%)	440 (51.9%)	<0.001	4258 (71.6%)	672 (52.7%)	<0.001
Yes	1492 (27.2%)	800 (46.3%)		1885 (29.6%)	407 (48.1%)		1690 (28.4%)	602 (47.3%)	
Snoring during sleeping									
No	4641 (84.5%)	1401 (81.1%)	0.001	5378 (84.4%)	664 (78.4%)	<0.001	5001 (84.1%)	1041 (81.7%)	0.038
Yes	854 (15.5%)	326 (18.9%)		997 (15.6%)	183 (21.6%)		947 (15.9%)	233 (18.3%)	
Initial use of antibiotics									
≥6 months	4840 (88.1%)	1399 (81%)	<0.001	5567 (87.3%)	672 (79.3%)	<0.001	5210 (87.6%)	1029 (80.8%)	<0.001
<6 months	655 (11.9%)	328 (19%)		808 (12.7%)	175 (20.7%)		738 (12.4%)	245 (19.2%)	
From parents or guardians									
Maternal BMI (kg/m^2)	21.45 (19.71, 23.44)	21.77 (19.96, 24.03)	<0.001	21.48 (19.72, 23.5)	21.75 (19.84, 24.03)	0.052	21.45 (19.71, 23.44)	21.87 (19.98, 24.03)	<0.001
Paternal BMI (kg/m^2)	24.69 (22.86, 26.87)	25.11 (22.86, 27.68)	<0.001	24.69 (22.86, 27.04)	25.06 (22.86, 27.72)	0.018	24.69 (22.86, 26.99)	25.18 (22.86, 27.76)	<0.001
Maternal pre-pregnancy BMI (kg/m^2)	20.57 (18.96, 22.58)	20.7 (19.1, 22.86)	0.029	20.69 (19, 22.58)	20.57 (19.05, 22.76)	0.625	20.57 (18.97, 22.58)	20.76 (19.13, 22.86)	0.006
Gestational weight gain	15 (10, 19)	15 (11, 20)	0.011	15 (10, 19)	15 (11, 20)	0.355	15 (10, 19)	15 (11, 20)	0.004
Paternal education									
Graduate degree and above	1357 (24.7%)	400 (23.2%)	0.391	1552 (24.3%)	205 (24.2%)	0.999	1474 (24.8%)	283 (22.2%)	0.073
College degree	3409 (62%)	1077 (62.4%)		3959 (62.1%)	527 (62.2%)		3691 (62.1%)	795 (62.4%)	
High/technical school degree	614 (11.2%)	207 (12%)		724 (11.4%)	97 (11.5%)		659 (11.1%)	162 (12.7%)	
Middle school degree or below	115 (2.1%)	43 (2.5%)		140 (2.2%)	18 (2.1%)		124 (2.1%)	34 (2.7%)	
Maternal education									
Graduate degree and above	1182 (21.5%)	343 (19.9%)	0.492	1339 (21%)	186 (22%)	0.682	1295 (21.8%)	230 (18.1%)	0.014
College degree	3759 (68.4%)	1202 (69.6%)		4377 (68.7%)	584 (68.9%)		4065 (68.3%)	896 (70.3%)	
High/technical school degree	452 (8.2%)	146 (8.5%)		536 (8.4%)	62 (7.3%)		478 (8%)	120 (9.4%)	
Middle school degree or below	102 (1.9%)	36 (2.1%)		123 (1.9%)	15 (1.8%)		110 (1.8%)	28 (2.2%)	
Family income (RMB per year)									
>500,000	895 (16.3%)	252 (14.6%)	0.060	1027 (16.1%)	120 (14.2%)	0.065	961 (16.2%)	186 (14.6%)	0.005
200,000–500,000	2178 (39.6%)	658 (38.1%)		2513 (39.4%)	323 (38.1%)		2362 (39.7%)	474 (37.2%)	
100,000–200,000	1824 (33.2%)	600 (34.7%)		2107 (33.1%)	317 (37.4%)		1987 (33.4%)	437 (34.3%)	
<100,000	598 (10.9%)	217 (12.6%)		728 (11.4%)	87 (10.3%)		638 (10.7%)	177 (13.9%)	
Gestational diabetes mellitus	574 (10.4%)	225 (13%)	0.003	681 (10.7%)	118 (13.9%)	0.005	638 (10.7%)	161 (12.6%)	0.048
Gestational hypertension	176 (3.2%)	58 (3.4%)	0.750	206 (3.2%)	28 (3.3%)	0.909	196 (3.3%)	38 (3%)	0.568
Maternal pre-pregnancy smoking	111 (2%)	36 (2.1%)	0.868	130 (2%)	17 (2%)	0.950	120 (2%)	27 (2.1%)	0.815
Maternal pregnancy smoking	11 (0.2%)	8 (0.5%)	0.063	16 (0.3%)	3 (0.4%)	0.582	14 (0.2%)	5 (0.4%)	0.321
Paternal smoking	2244 (40.8%)	726 (42%)	0.376	2604 (40.8%)	366 (43.2%)	0.189	2444 (41.1%)	526 (41.3%)	0.896
Delivery mode: cesarean	2219 (40.4%)	729 (42.2%)	0.177	2604 (40.8%)	344 (40.6%)	0.897	2393 (40.2%)	555 (43.6%)	0.028

BMI body mass index.
Data are expressed as median (interquartile range) or count (percent). P value was calculated by the t test or the rank-sum test or the χ^2 test, where appropriate.

Table 2. Risk prediction of six significant factors for recurrent respiratory infection in preschool-aged children under three disease classifications.

Variables	Recurrent respiratory tract infection			Recurrent upper respiratory tract infection			Recurrent lower respiratory tract infection			$P_{Z\ test}$*
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	
Before adjustment										
Asthma	7.76	5.34–11.29	<0.001	4.92	3.44–7.03	<0.001	7.95	5.58–11.34	<0.001	0.063
Allergy	2.32	2.07–2.59	<0.001	2.20	1.91–2.55	<0.001	2.26	2.00–2.55	<0.001	0.780
Initial use of antibiotic <6 months	1.73	1.50–2.00	<0.001	1.79	1.50–2.15	<0.001	1.68	1.43–1.97	<0.001	0.606
Breastfeeding duration <6 months	1.27	1.11–1.46	0.001	1.16	0.97–1.39	0.110	1.36	1.17–1.58	<0.001	0.183
Maternal BMI per 3 kg/m^2 increment	1.05	1.03–1.07	<0.001	1.03	1.01–1.05	0.014	1.05	1.03–1.07	<0.001	0.166
Gestational weight gain	1.01	1.00–1.02	0.035	1.00	0.99–1.01	0.582	1.01	1.00–1.02	0.007	0.166
After adjustment for age, sex, and region										
Asthma	8.31	5.69–12.12	<0.001	5.26	3.67–7.54	<0.001	8.44	5.90–12.09	<0.001	0.068
Allergy	2.31	2.06–2.58	<0.001	2.21	1.91–2.56	<0.001	2.22	1.96–2.52	<0.001	0.963
Initial use of antibiotic <6 months	1.72	1.48–1.99	<0.001	1.78	1.48–2.14	<0.001	1.66	1.41–1.95	<0.001	0.577
Breastfeeding duration <6 months	1.24	1.08–1.43	0.002	1.14	0.95–1.37	0.159	1.32	1.13–1.53	<0.001	0.227
Maternal BMI per 3 kg/m^2 increment	1.19	1.09–1.31	<0.001	1.25	1.11–1.40	<0.001	1.26	1.13–1.40	<0.001	0.921
Gestational weight gain	1.01	1.00–1.01	0.261	1.00	0.99–1.01	0.952	1.01	1.00–1.02	0.105	0.166

OR odds ratio, *95% CI* 95% confidence interval, *BMI* body mass index.
*$P_{Z\ test}$ was calculated for comparing the difference in effect-size estimates between upper and lower respiratory tract infection.

Table 3. Prediction accuracy gained by adding five significant factors associated with recurrent respiratory tract infection overall and by sites in preschool children.

Statistics	Recurrent respiratory tract infection		Recurrent upper respiratory tract infection		Recurrent lower respiratory tract infection	
	Basic model	Full model	Basic model	Full model	Basic model	Full model
Calibration						
AIC	7131.5	6932.2	4780.6	4687.5	5998.3	5821.6
BIC	7295.2	7136.7	4944.2	4892.0	6161.9	6026.1
LR test (χ^2)	210.99		97.96		186.99	
LR test (*P* value)	<0.0001		<0.0001		<0.0001	
Discrimination						
AUROC (*P* value)	<0.0001		<0.0001		<0.0001	

AIC Akaike information criterion, *BIC* Bayesian information criterion, *BMI* body mass index, *LR* likelihood ratio, *AUROC* area under the receiver-operating characteristic.
Basic model included age, sex, region, BMI, paternal BMI, pre-pregnancy BMI, gestational weight gain, paternal education, maternal education, family income, gestational diabetes mellitus, gestational hypertension, maternal smoking pre-pregnancy, maternal smoking pregnancy, paternal smoking, delivery mode, birthweight, sleep duration, food supplement, and snoring during sleeping. Full model additionally included asthma, allergy, initial use of antibiotics, breastfeeding duration, and maternal BMI.

Taking the risk prediction nomogram model for recurrent respiratory tract infection as an example, assuming a child in suburban region (27 points), aged 60 months (7.5 points), with BMI at 15 kg/m^2 (55 points), maternal BMI of 30 kg/m^2 (36 points), paternal BMI of 30 kg/m^2 (12.5 points), asthma (100 points), without allergy (0 point), birth weight of 3 kg (12.5 points), breastfeeding duration of 5 months (18 points), initial use of antibiotics ≥6 months (0 point), and GWG of 20 kg (5 points), the probability of having recurrent respiratory tract infection was estimated to be 70%.

DISCUSSION

To identify potential risk factors responsible for the development of recurrent respiratory tract infection, we, in a large-scale cross-sectional survey of 7222 Chinese preschool-aged children, explored the individual and interactive effects of these factors. Importantly, five independent factors, including asthma, allergy, initial use of antibiotics, maternal obesity, and breastfeeding duration, were significantly associated with the risk of recurrent respiratory tract infection overall and by pathogenic sites. Moreover, besides the leading role played by asthma, allergy, initial use of antibiotics, and breastfeeding might exert a graded, dose-dependent effect on recurrent respiratory tract infection susceptibility. To our knowledge, this is the first report of examining the joint contribution of multiple potential risk factors to recurrent respiratory tract infection among Chinese preschool-aged children.

Currently, the burden of recurrent respiratory tract infection is high in China, infected children frequently use supportive care services or antibiotics, or undergo surgical procedures for severe

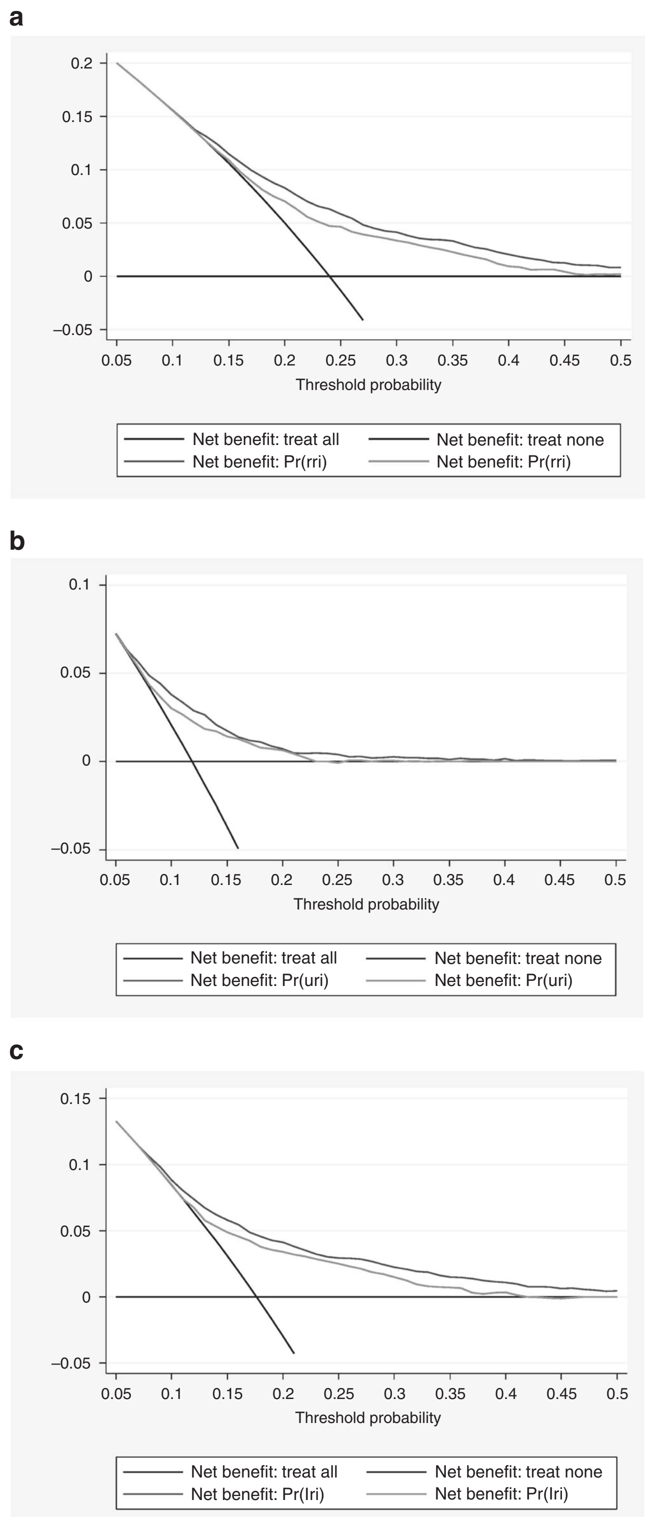

Fig. 1 Decision curve analysis for recurrent respiratory tract infection overall and by pathogenic sites. a Recurrent respiratory tract infection overall, **b** recurrent upper respiratory tract infection, and **c** recurrent lower respiratory tract infection.

cases of infection in clinical practice.[21] In such situation, it is imperative to take more practical and effective actions to prevent or control pediatric recurrent respiratory tract infection around the globe.

The implication of asthma in the development of recurrent respiratory tract infection is subject to much debate. Some studies have shown that asthma is the most common underlying illness for recurrent pneumonia,[22,23] an acute and common lower respiratory tract infection in pediatrics. By contrast, Hoving and Brand[24] deemed that asthma was more likely a differential diagnostic consideration than an underlying cause of recurrent pneumonia in children. Another study by Heffelfinger et al.[25] reported that asthma was infrequently present with recurrent pneumonia, and whether their coexistence represents a causality or merely coincides by chance, was not always clear. The findings of this study supported the leading predominant role of asthma with the risk of having recurrent respiratory tract infection overall and by pathogenic sites, consistent with that of previous studies.[22,26] However, the cross-sectional nature of our study prevents us from evaluating the direction of the association, such as whether asthma contributes to recurrent respiratory tract infection or vice versa. Considering the limited number of children with asthma and the association paradox, further exploration is restricted to the rest four significant factors in this study.

Besides asthma, the significant contribution of other four significant factors identified to the risk of recurrent respiratory tract infection in this study merits special discussion, and they are epidemiologically and biologically plausible. Population studies showed that allergic children had more and longer-lasting respiratory tract infection, in the upper and lower respiratory airways, than children free of allergies.[26–28] Allergy is featured by the immune mechanism inducing the T-helper type 2 (Th2) lymphocyte pathway, which reduces Th1 response. Some cytokines such as interferon-γ, typical of the Th1 response, are essential to control infection, and they are lowered in allergic patients,[28,29] which is posed as a possible reason for the involvement of allergy in recurrent respiratory tract infection. In addition, allergic mucosal inflammation can trigger the expression of adhesion molecules on epithelial cells such as intercellular adhesion molecule-1,[30] the important receptor for rhinovirus,[31] which may predispose to upper airway infection as a result. As a crucial cytokine in allergic inflammation, interleukin-13 is able to reduce mucociliary clearance and facilitate viral adhesion to airway epithelial cells.[32]

As for breastfeeding, growing evidence indicated its protective role in respiratory tract infection, and this role is dominant with the increase of breastfeeding duration.[33,34] Breastmilk de facto contains many protective factors such as immunoglobulins, lactoferrin, and lymphocytes, as well as other factors that may contribute to reduced infant mortality.[35] In addition, breastfeeding is reported to be influenced by maternal obesity.[36] Maternal obesity is a significant risk factor for recurrent refractory tract infection in this study. There is evidence that maternal pre-pregnancy obesity and GWG may impact the fetus on the intrauterine environment with the 'fuel-mediated teratogenesis' and 'developmental origin of health and disease' hypotheses.[37–39]

With regard to the use of antibiotics, approximately one in five children aged over 1 month to 18 years have received antibiotics due to bacterial lower respiratory tract infection,[40] with around four in five children using antibiotics in the first years of life.[41] Interestingly, our findings indicate that initial use of antibiotics <6 months was associated with an increased risk of recurrent respiratory tract infection. Several possible reasons are behind this association. First, antibiotics can cause immunomodulatory changes in intestinal bacterial diversity during the first months of life, and influence immune system, Th, and regulatory T cell balance accordingly.[42–44] As evidenced, gut microbiomes plays a key role in the maturation of the neonatal immune system, and further precipitates the development of respiratory tract infection.[42–44] Second, children in need of antibiotics early in life have Th1/Th2 imbalance caused by infection, which makes them more

Table 4. The interaction of allergy, first use of antibiotic, breast feeding, and maternal BMI in predicting the risk of recurrent respiratory infection in preschool-aged children under three disease classifications.

Interaction items	Recurrent respiratory tract infection			Recurrent upper respiratory tract infection			Recurrent lower respiratory tract infection		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Without allergy/Initial use of antibiotics ≥6 months	Ref.			Ref.			Ref.		
Without allergy/initial use of antibiotics <6 months	1.81	1.50 to 2.20	<0.001	1.91	1.49–2.45	<0.001	1.65	1.33–2.05	<0.001
Allergy/initial use of antibiotics ≥6 months	2.24	1.97–2.54	<0.001	2.19	1.85–2.59	<0.001	2.07	1.80–2.39	<0.001
Allergy/initial use of antibiotics <6 months	3.25	2.56–4.13	<0.001	3.31	2.48–4.42	<0.001	3.32	2.57–4.27	<0.001
Without allergy/breast feeding ≥6 months	Ref.			Ref.			Ref.		
Without allergy/breast feeding <6 months	1.25	1.04–1.51	0.018	1.12	0.86–1.45	0.394	1.39	1.13–1.71	0.002
Allergy/breast feeding ≥6 months	2.22	1.95–2.52	<0.001	2.15	1.82–2.54	<0.001	2.17	1.88–2.50	<0.001
Allergy/breast feeding <6 months	2.38	1.92–2.96	<0.001	2.11	1.60–2.79	<0.001	2.32	1.83–2.94	<0.001
Without allergy/normal maternal BMI	Ref.			Ref.			Ref.		
Without allergy/low maternal BMI	0.80	0.61–1.04	0.1	0.91	0.64–1.31	0.625	0.73	0.53–1.01	0.057
Without allergy/high maternal BMI	1.37	1.16–1.62	<0.001	1.31	1.04–1.65	0.022	1.31	1.08–1.58	0.006
Allergy/normal maternal BMI	2.24	1.95–2.58	<0.001	2.12	1.76–2.56	<0.001	2.16	1.85–2.53	<0.001
Allergy/low maternal BMI	2.14	1.59–2.87	<0.001	2.40	1.67–3.46	<0.001	1.67	1.18–2.35	0.004
Allergy/high maternal BMI	2.46	2.00–3.01	<0.001	2.42	1.87–3.13	<0.001	2.31	1.85–2.89	<0.001
Initial use of antibiotics ≥6 months months/breast feeding ≥6 months	Ref.			Ref.			Ref.		
Initial use of antibiotics ≥6 months/breast feeding <6 months	1.14	0.97–1.34	0.109	1.02	0.82–1.27	0.835	1.20	1.00–1.43	0.045
Initial use of antibiotics <6 months/breast feeding ≥6 months	1.59	1.34–1.88	<0.001	1.68	1.36–2.09	<0.001	1.55	1.28–1.87	<0.001
Initial use of antibiotics <6 months/breast feeding <6 months	2.20	1.65–2.94	<0.001	2.00	1.40–2.86	<0.001	2.27	1.67–3.08	<0.001
Initial use of antibiotics ≥6 months/normal maternal BMI	Ref.			Ref.			Ref.		
Initial use of antibiotics ≥6 months/low maternal BMI	0.88	0.71–1.09	0.233	0.99	0.75–1.31	0.925	0.79	0.62–1.02	0.067
Initial use of antibiotics ≥6 months/high maternal BMI	1.26	1.09–1.45	0.002	1.18	0.97–1.44	0.098	1.21	1.03–1.43	0.020
Initial use of antibiotics <6 months/normal maternal BMI	1.64	1.36–1.97	<0.001	1.58	1.24–2.01	<0.001	1.64	1.34–2.01	<0.001
Initial use of antibiotics <6 months/low maternal BMI	1.71	1.01–2.88	0.045	2.34	1.29–4.26	0.005	1.20	0.64–2.26	0.574
Initial use of antibiotics <6 months/high maternal BMI	2.09	1.58–2.76	<0.001	2.36	1.69–3.28	<0.001	1.95	1.44–2.64	<0.001
Breast feeding ≥6 months/normal maternal BMI	Ref.			Ref.			Ref.		
Breast feeding ≥6 months/low maternal BMI	0.86	0.69–1.07	0.177	1.04	0.78–1.38	0.794	0.75	0.57–0.98	0.034
Breast feeding ≥6 m/high maternal BMI	1.19	1.02–1.38	0.024	1.11	0.91–1.35	0.299	1.16	0.98–1.37	0.082
Breast feeding <6 months/normal maternal BMI	1.10	0.92–1.32	0.304	0.92	0.72–1.19	0.534	1.20	0.99–1.47	0.067
Breast feeding <6 m/low maternal BMI	1.05	0.70–1.57	0.810	0.93	0.53–1.63	0.793	0.97	0.61–1.54	0.895
Breast feeding <6 months/high maternal BMI	1.75	1.37–2.24	<0.001	1.74	1.28–2.37	<0.001	1.68	1.28–2.20	<0.001

OR odds ratio, *95% CI* 95% confidence interval, *BMI* body mass index, *Ref.* reference group.
All effect-size estimates were adjusted for age, sex, and region.

susceptible to respiratory tract infection later in life.[45] Third, the antibiotic-related suppression of inflammatory responses in the course of treatment may lead to enhanced immune response among Th2-shifted children or impaired Th1 immune responses in early childhood.[46] Based on above evidence, it is reasonable to speculate that the five factors identified in this study might be responsible for the development of recurrent respiratory tract infection among Chinese preschool-aged children.

Another key finding of our study is that allergy, initial use of antibiotics, and breastfeeding predispose to recurrent respiratory tract infection in a graded, dose-dependent manner as revealed by our pairwise interactive analyses, highlighting the importance of joint analysis of multiple risk factors. To take one step forward and increase the application of our findings, we employed the nomogram technique, and fortunately the accuracy of prediction nomogram models constructed for recurrent respiratory tract infection overall and by pathogenic sites was very good. Despite the significant association, our findings presented here should be regarded as preliminary, and we agree that validation in other independent, well-designed, longitudinal studies are necessary to confirm or refute our conclusions.

Limitations

Finally, some limitations should be acknowledged for this present study. First, the cross-sectional design of this study restricted further comments on the causality of potential risk factors with recurrent respiratory tract infection. Second, our data were obtained through questionnaires filled in by the parents or guardians of study children, and hence a recall bias cannot be excluded. Third, all study children are living in Beijing and of Chinese origin, and extrapolation of our findings to other racial or ethnical groups should be done with caution.

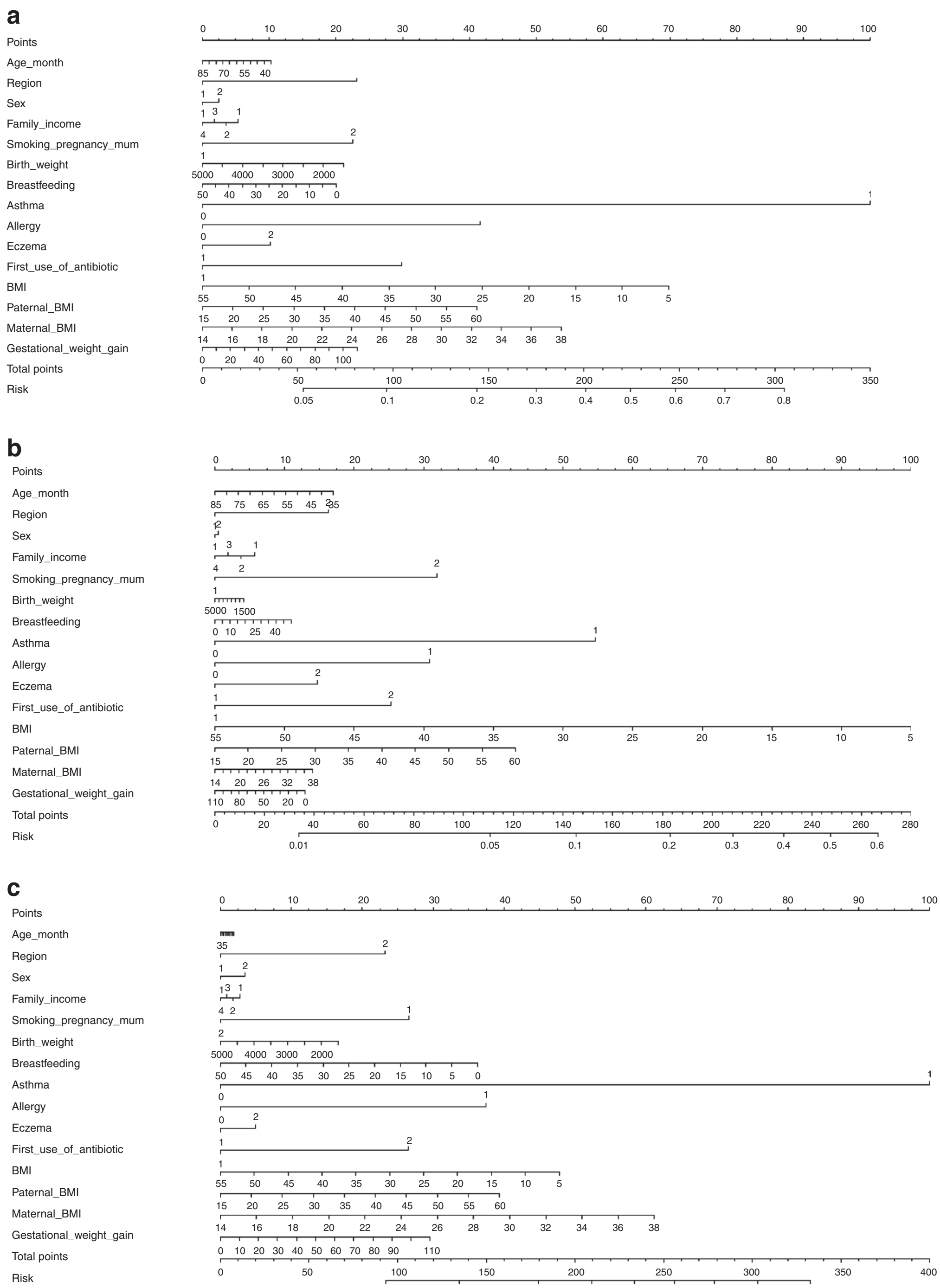

Fig. 2 Prediction nomograms for recurrent respiratory tract infection overall and by pathogenic sites. a Recurrent respiratory tract infection overall, **b** recurrent upper respiratory tract infection, and **c** recurrent lower respiratory tract infection.

Conclusions

To sum up, we have identified five potential risk factors responsible for the risk of having recurrent respiratory tract infection via an analysis of data from 7222 preschool-aged Chinese children. Notably, asthma plays a leading role, and allergy, initial use of antibiotics, and breastfeeding might exert a graded, dose-dependent effect on recurrent respiratory tract infection susceptibility. For practical reasons, we hope the present study will not remain just another endpoint of research instead of a beginning to establish background data to further explore potential risk factors of pediatric recurrent respiratory tract infection, as well as the possible underlying molecular mechanisms.

ACKNOWLEDGEMENTS

We are grateful to all participating children and their parents or guardians for their cooperation and willingness, as well as kindergarten teachers and health physicians for their great help.

AUTHOR CONTRIBUTIONS

Z.Z. planned and designed the study, and directed its implementation. Z.Z. drafted the protocol. B.Z., K.W., Y.Y., J.Z., and Z.Z. obtained statutory and ethics approvals. B.Z. and W.N. contributed to data acquisition. B.Z., F.L., and W.N. conducted statistical analyses. B.Z., K.W., Y.Y., Y.W., J.Z., F.L., and W.N. did the data preparation and quality control. B.Z. and W.N. wrote the manuscript. All authors read and approved the final manuscript prior to submission.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-020-01233-4) contains supplementary material, which is available to authorized users.

Competing interests: The authors declare no competing interests.

Patient consent: Written informed consent was obtained from the parents or guardians of study children prior to participation.

REFERENCES

1. Walker, C. L. F. et al. Global burden of childhood pneumonia and diarrhoea. *Lancet* **381**, 1405–1416 (2013).
2. Marengo, R., Ortega Martell, J. A. & Esposito, S. Paediatric recurrent ear, nose and throat infections and complications: can we do more? *Infect. Dis. Ther.* **9**, 275–290 (2020).
3. Collaborators, G. B. D. L. R. I. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect. Dis.* **18**, 1191–1210 (2018).
4. Liu, L. et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* **385**, 430–440 (2015).
5. Rudan, I. et al. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J. Glob. Health* **3**, 010401 (2013).
6. Shi, T. et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. *J. Glob. Health* **5**, 020416 (2015).
7. Patria, M. F. & Esposito, S. Recurrent lower respiratory tract infections in children: a practical approach to diagnosis. *Paediatr. Respir. Rev.* **14**, 53–60 (2013).
8. Karevold, G., Kvestad, E., Nafstad, P. & Kvaerner, K. J. Respiratory infections in schoolchildren: co-morbidity and risk factors. *Arch. Dis. Child* **91**, 391–395 (2006).
9. Forssell, G., Hakansson, A. & Mansson, N. O. Risk factors for respiratory tract infections in children aged 2-5 years. *Scand. J. Prim. Health Care* **19**, 122–125 (2001).
10. Ruskamp, J. et al. Neonatal total IgE and respiratory tract infections in children with intrauterine smoke exposure. *Arch. Dis. Child* **95**, 427–431 (2010).
11. Duijts, L. et al. Maternal smoking in prenatal and early postnatal life and the risk of respiratory tract infections in infancy. The Generation R study. *Eur. J. Epidemiol.* **23**, 547–555 (2008).
12. de Benedictis, F. M. & Bush, A. Recurrent lower respiratory tract infections in children. *BMJ* **362**, k2698 (2018).
13. de Martino, M. & Ballotti, S. The child with recurrent respiratory infections: normal or not? *Pediatr. Allergy Immunol.* **18**(Suppl. 18), 13–18 (2007).
14. Li, H., Ji, C. Y., Zong, X. N. & Zhang, Y. Q. Body mass index growth curves for Chinese children and adolescents aged 0 to 18 years. *Zhonghua Er Ke Za Zhi* **47**, 493–498 (2009).
15. Oldroyd, J., Renzaho, A. & Skouteris, H. Low and high birth weight as risk factors for obesity among 4 to 5-year-old Australian children: does gender matter? *Eur. J. Pediatr.* **170**, 899–906 (2011).
16. Altman, D. G. & Bland, J. M. Interaction revisited: the difference between two estimates. *BMJ* **326**, 219 (2003).
17. Vickers, A. J. & Elkin, E. B. Decision curve analysis: a novel method for evaluating prediction models. *Med. Decis. Making* **26**, 565–574 (2006).
18. Zhou, B. F. & Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults-study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed. Environ. Sci.* **15**, 83–96 (2002).
19. World Health Organization. *The Optimal Duration of Exclusive Breastfeeding: Report of an Expert Consultation* (World Health Organization, Geneva, 2001).
20. Kummeling, I. et al. Early life exposure to antibiotics and the subsequent development of eczema, wheeze, and allergic sensitization in the first 2 years of life: the KOALA Birth Cohort Study. *Pediatrics* **119**, e225–e231 (2007).
21. Toivonen, L. et al. Burden of recurrent respiratory tract infections in children: a prospective cohort study. *Pediatr. Infect. Dis. J.* **35**, e362–e369 (2016).
22. Ciftci, E. et al. Underlying causes of recurrent pneumonia in Turkish children in a university hospital. *J. Trop. Pediatr.* **49**, 212–215 (2003).
23. Cabezuelo Huerta, G., Vidal Mico, S., Abeledo, Gomez, A. & Frontera Izquierdo, P. Underlying causes of recurrent pneumoni. *Pediatrics* **63**, 409–412 (2005).
24. Hoving, M. F. & Brand, P. L. Causes of recurrent pneumonia in children in a general hospital. *J. Paediatr. Child Health* **49**, E208–E212 (2013).
25. Heffelfinger, J. D. et al. Evaluation of children with recurrent pneumonia diagnosed by World Health Organization criteria. *Pediatr. Infect. Dis. J.* **21**, 108–112 (2002).
26. de Oliveira, T. B., Klering, E. A. & da Veiga, A. B. G. Is recurrent respiratory infection associated with allergic respiratory disease? *J. Asthma* **56**, 160–166 (2019).
27. Dellepiane, R. M. et al. Atopy in preschool Italian children with recurrent respiratory infections. *Pediatr. Med. Chir.* **31**, 161–164 (2009).
28. Ciprandi, G., Tosca, M. A. & Fasce, L. Allergic children have more numerous and severe respiratory infections than non-allergic children. *Pediatr. Allergy Immunol.* **17**, 389–391 (2006).
29. Rantala, A., Jaakkola, J. J. & Jaakkola, M. S. Respiratory infections in adults with atopic disease and IgE antibodies to common aeroallergens. *PLoS ONE* **8**, e68582 (2013).
30. Bartlett, N. W. et al. Mouse models of rhinovirus-induced disease and exacerbation of allergic airway inflammation. *Nat. Med.* **14**, 199–204 (2008).
31. Bossios, A. et al. Rhinovirus infection and house dust mite exposure synergize in inducing bronchial epithelial cell interleukin-8 release. *Clin. Exp. Allergy* **38**, 1615–1626 (2008).
32. Laoukili, J. et al. IL-13 alters mucociliary differentiation and ciliary beating of human respiratory epithelial cells. *J. Clin. Invest.* **108**, 1817–1824 (2001).
33. Chantry, C. J., Howard, C. R. & Auinger, P. Full breastfeeding duration and associated decrease in respiratory tract infection in US children. *Pediatrics* **117**, 425–432 (2006).
34. Lopez-Alarcon, M., Villalpando, S. & Fajardo, A. Breast-feeding lowers the frequency and duration of acute respiratory infection and diarrhea in infants under six months of age. *J. Nutr.* **127**, 436–443 (1997).
35. Kovar, M. G., Serdula, M. K., Marks, J. S. & Fraser, D. W. Review of the epidemiologic evidence for an association between infant feeding and infant health. *Pediatrics* **74**, 615–638 (1984).
36. Nutrition, E. C. O. et al. Breast-feeding: a commentary by the ESPGHAN Committee on Nutrition. *J. Pediatr. Gastroenterol. Nutr.* **49**, 112–125 (2009).
37. Freinkel, N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes* **29**, 1023–1035 (1980).
38. Barker, D. J. The origins of the developmental origins theory. *J. Intern. Med.* **261**, 412–417 (2007).
39. Alfaradhi, M. Z. & Ozanne, S. E. Developmental programming in response to maternal overnutrition. *Front. Genet.* **2**, 27 (2011).
40. Versporten, A. et al. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. *J. Antimicrob. Chemother.* **71**, 1106–1117 (2016).
41. Ahmadizar, F. et al. Early life antibiotic use and the risk of asthma and asthma exacerbations in children. *Pediatr. Allergy Immunol.* **28**, 430–437 (2017).
42. O'Dwyer, D. N., Dickson, R. P. & Moore, B. B. The lung microbiome, immunity, and the pathogenesis of chronic lung disease. *J. Immunol.* **196**, 4839–4847 (2016).
43. Gollwitzer, E. S. & Marsland, B. J. Impact of early-life exposures on immune maturation and susceptibility to disease. *Trends Immunol.* **36**, 684–696 (2015).
44. McFadden, J. P. et al. T helper cell 2 immune skewing in pregnancy/early life: chemical exposure and the development of atopic disease and allergy. *Br. J. Dermatol* **172**, 584–591 (2015).
45. Jordan, S., Storey, M. & Morgan, G. Antibiotics and allergic disorders in childhood. *Open Nurs. J.* **2**, 48–57 (2008).
46. Jedrychowski, W. et al. Wheezing and asthma may be enhanced by broad spectrum antibiotics used in early childhood. Concept and results of a pharmacoepidemiology study. *J. Physiol. Pharmacol.* **62**, 189–195 (2011).