

Bronchodilator responses in Chinese children from asthma index families and the general population

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Background: Although airway hyperresponsiveness to bronchoconstrictors has been extensively investigated, epidemiologic studies on airway hyperresponsiveness to bronchodilators are limited.

Objective: Our goal was to characterize the distribution and determinants of bronchodilator response (BDR) and bronchodilator hyperresponsiveness (BDHR) in rural Chinese children age 8 to 15 years.

Methods: Our study included children with and without asthma from asthma index families (1131 boys, 1143 girls) and subjects without asthma from general population controls (457 boys, 377 girls). BDR was calculated as $[(\text{post bronchodilator FEV}_1 - \text{baseline FEV}_1)/\text{baseline FEV}_1] \times 100$. BDHR was defined as BDR greater than 12%. We investigated the distributions and major determinants of BDR and BDHR using scatterplots and multiple linear and logistic regression models.

Results: There was a gradient in BDR by asthma status and family history. The mean ($\pm$ SD) BDR was $7\% \pm 9\%$ in subjects with asthma, $4\% \pm 5\%$ in subjects without asthma from index families, and $3\% \pm 5\%$ in controls. This trend was also seen for BDHR. BDR generally decreased with age. There was a notable sex difference in BDR around puberty in subjects with asthma. Sex difference was also seen in the relationship of BDR with body mass index. Additional variables correlated with BDR included height and prebronchodilator FEV₁. Atopy was not correlated with BDR. In models accounting for these variables, chronic respiratory symptoms were associated with BDR and BDHR.

Conclusion: In these Chinese children, multiple factors affected BDR, including age, sex, height, body mass index, asthma status, and family history of asthma.

Clinical implications: Because BDR can be affected by multiple factors, interpretation of clinical or research findings on BDR

needs to take these factors into consideration. (J Allergy Clin Immunol 2006;117:1257-63.)

Keywords: Bronchodilator response, airway responsiveness, epidemiologic study, risk factors, Chinese

Despite intensive research, the morbidity and mortality of asthma remain relatively high.¹ Some of this difficulty ensues from the fact that asthma is a complex trait with multiple, variably defined intermediate phenotypes. These phenotypes themselves are not fully understood in terms of mechanism and are not fully characterized. Of these, airway responsiveness remains a central and standard assessment in asthma.² Airway reactivity to bronchoconstrictor agents has been assessed among populations with different age, ethnicity, and disease status.³

The conventional approach for assessing airway reactivity has been with the use of bronchoconstrictor agents. However, bronchodilator response (BDR or $[(\text{baseline FEV}_1 - \text{postbronchodilator FEV}_1)/\text{baseline FEV}_1] \times 100$) may be preferred over methacholine challenge in large-scale population-based studies. This is not only a result of the fact that methacholine challenges are time and labor intensive. They also entail more risk to the patient than may be accommodated in large-scale population-based studies in which the study visit often occurs in the community. Finally, it is not clear that BDR and methacholine challenges are necessarily equivalent. The relationship of β -receptor polymorphisms to methacholine responsiveness is present in some⁴⁻⁶ but not all^{7,8} studies. Therefore, it is important to evaluate the determinants of BDR to understand better this intermediate phenotype in asthma.

Bronchodilator response and bronchodilator hyperresponsiveness (BDHR) aggregate in families in both the general population and among families with asthma.^{9,10} BDR has been used as an epidemiologic parameter of asthma among different populations^{9,11-13} and is a characteristic finding in subjects with asthma.^{14,15} Given the variability of response,^{16,17} BDR distribution and variability patterns among various populations need to be described further to increase this central measure's utility as an intermediate phenotype.

The purpose of this report is to characterize the distribution of BDR and BDHR among a sample of children age 8 to 15 years including children with and without asthma (family history only) from asthma index families, and control children without asthma randomly selected

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Abbreviations used

BDHR: Bronchodilator hyperresponsiveness
BDR: Bronchodilator response
BMI: Body mass index

from the general population, respectively. Secondary aims included developing sex-specific predictive models of BDR among children of the control families to elucidate which of the epidemiologic demographic variables are important determinants of BDR and BDHR.

METHODS**Study site and population**

This study was conducted by the Harvard School of Public Health in collaboration with Anhui Medical University and Anqing Health Bureau in a rural area in Anqing, China. The purpose of the main study was to evaluate gene-environment interactions as they relate to the development of asthma and familial aggregation of lung function in this rural Chinese cohort. This report used the data from 1131 boys and 1143 girls age 8 to 15 years from 2756 asthma index families and 457 boys and 377 girls from 935 random control families.

The study protocols were reviewed and approved by the local Chinese human subjects committees and the Institutional Review Board of Harvard School of Public Health. All of the subjects have given their written informed consent. The detailed description of protocols for informed consent and multilayer screening procedures have been published elsewhere.^{9,11,18}

Definition of asthma (American Thoracic Society–Questionnaire)

Asthma was determined by a previous doctor diagnosis of asthma (subject report) along with the following criteria: (1) there is a history of repeated episodes of wheeze and dyspnea, but the subject is asymptomatic between episodes; and (2) the obstructive symptoms can be significantly improved by a bronchodilator.^{9,11,18}

Identification of asthma index families and random control families

Asthma index families were identified in the 8 counties through a multistage process described elsewhere.¹⁸ Index families were chosen by using the following criteria: (1) the presence of an index patient with asthma who was at least 8 years old; (2) the existence of 1 or more siblings of the asthma index case, at least 8 years old; (3) the availability of both parents; and (4) no more than 1 parent with a history of asthma. These criteria were determined by the purpose of the main study, which was to evaluate gene-environment interactions around the development of asthma. To perform family-based association testing, we required heterozygous parent pairs for the trait of asthma. Random families were recruited from the general population of the rural communities of Anqing (from which the asthma index families were ascertained) on the basis of the 1992 census data by a 2-stage random sampling technique as described previously.^{9,11} Asthma index families were excluded from potential recruitment as controls.

Pulmonary function tests and definition of BDR and BDHR

Standardized pulmonary function tests were conducted with American Thoracic Society “Snowbird Guideline”–approved equipment and procedures (Schiller, Switzerland), as described

previously.¹⁸ The BDR is based on pulmonary function measurements before and after administration of 200 μ g albuterol.¹⁸ BDR was calculated as $[(\text{postbronchodilator FEV}_1 - \text{baseline FEV}_1)/\text{baseline FEV}_1] \times 100$. BDHR was defined as a change of at least 12% from baseline FEV_{1,0}.^{2,19}

Statistical analysis

In this report, the primary outcome variables were BDR (a continuous variable) and BDHR (a binary variable). We first examined the distributions of BDR and BDHR among children from random control families and among children from the asthma index families (with and without physician-diagnosed asthma). We further explored association of BDR with sex, age, height, body mass index (BMI), and parental smoking. All children in the study were younger than 15 years, with a mean age of 11 years. Active smoking was present in only 1 child, and this subject was excluded from analysis.

We first explored the functional relationships between BDR and the important variables listed using smoothing plots. These programs perform this function by smoothing out the described curve without constraining the data to a pattern that does not adequately describe the relationship. All plots were stratified by sex and plotted separately for each of the subgroups of subjects using locally weighted least squares (LOESS) regression as a nonparametric method for smoothing with SAS procedure LOESS (SAS Institute, Cary, NC).^{20,21} On the basis of the findings of the plots, we determined the relationship between variables and used this to aid in regression analysis to develop a predictive model for BDR.

For the predictive model of BDR and BDHR, we used multiple linear and logistic regression models, respectively. We stratified all of the analyses by sex and adjusted them for covariates significant in univariate analyses, including age, height, BMI, and parental smoking. We also evaluated the effect of atopy. Other variables such as smoking and age were kept because they have been well established as important determinants in multiple previous epidemiologic studies. Finally, we evaluated the model with and without inclusion of baseline FEV₁ as a covariate. We performed the same analyses in the subjects with and without asthma from asthma index families. We examined the goodness of fit of the model by plotting the residual of BDR by age for male and female subjects separately. The results confirm that the model fits our data very well. We presented the resulting plots are in this article's Fig E1 in the Online Repository at www.jacionline.org.

In addition, we examined association of BDR and BDHR with clinical characteristics including chronic cough (more than 3 months per year), chronic phlegm (more than 3 months per year), breathlessness, persistent wheeze, physician-diagnosed asthma, and family history of asthma.

Because our analyses included multiple offspring from the same parents, the SEs were estimated by the generalized estimation equation²² for correction of the interfamilial correlation of BDR. All of the analyses used statistical software SAS for Windows 8.20 (SAS Institute).

RESULTS

Table 1 presents the baseline characteristics among 3 subgroups: children from random control families and children with and without asthma from asthma index families. The 3 groups did not differ significantly in age, sex, height, weight, BMI, atopy, and parents smoking.

There was a difference in BDR by group. Compared with the control group, the group with asthma had much higher prevalence of respiratory symptoms, lower baseline

FEV_{1,0}, and higher BDR and BDHR. The subjects without asthma from asthma index families (family history only) had a lesser degree of BDR ($4\% \pm 5\%$) compared with the subjects with asthma ($7\% \pm 9\%$), but a greater degree compared with the control families ($3\% \pm 5\%$). This was not a result of inclusion of undiagnosed subjects with asthma in the subjects without asthma from index families. The distribution of BDR was not bimodal as might be expected if this sample included a significant number of undiagnosed subjects with asthma (see this article's Fig E2 in the Online Repository at www.jacionline.org). The proportion of subjects with hyperresponsiveness was 21%, 10%, and 9%, respectively, for the subjects with asthma, the subjects without asthma from index families, and random control subjects.

We sought to elucidate further the relationships between the clinical and epidemiologic variables in Table I and BDR. Table II presents the sex-specific predictive models for BDR among 713 nonsmoking healthy individuals from random control families ages 8 to 15 years. The covariates in the models included age, height, BMI, parental smoking status, atopy, and baseline FEV₁. There were significant relationships of BDR with height and baseline FEV₁ in both male and female subjects.

However, we recognize that the BDR variable includes baseline FEV₁ and first developed a model without baseline FEV₁. We then created a model with baseline FEV₁. The results of the analysis were no different, and FEV₁ was not included in the predictive models. We did assess the relationship of BDR and prebronchodilator FEV₁ despite the fact that it was not included in the model. This was done to ensure that the data did not vary from the expected inverse relationship. We performed S-plus (Mathsoft, Cambridge, Mass) graphic plots of BDR with prebronchodilator FEV_{1,0}, stratified by sex (see this article's Fig E3 in the Online Repository at www.jacionline.org). This relationship was not linear on the basis of the output of the s-plus program. The S-plus program is a scatterplot smoother that will not constrain data to a function it does not fit. We adjusted age and BMI both as background variables. BDR was inversely related to prebronchodilator FEV_{1,0}. The slope of the curve was much steeper at the lower end of FEV_{1,0} (<2.0 L).

Body mass index was significantly associated with BDR in male subjects only. However, because of previous studies showing a relationship between BMI and asthma, this was included in the predictive models for both male and female subjects. We analyzed BMI in tertiles as noted in Table I. There was no association with BDR and BDHR and atopy. We further evaluated whether individual allergens were associated with BDR and BDHR and did not find a relationship (data not shown).

On the basis of these findings in the control populations, we evaluated the relationships between these epidemiologic variables and BDR. All plots were stratified by sex and plotted separately for each of the groups of subjects. We first plotted the relation of age with BDR, adjusted for height. We then plotted BDR against BMI with adjustment for age.

TABLE I. Epidemiologic and clinical characteristics of children from asthma index families and random control families

Characteristics	Asthma index families (N = 2286)		Random control families (N = 766)
	With asthma (n = 697)	Without asthma (n = 1589)	
N (%)			
Male	348 (50)	794 (50)	421 (55)
BMI			
Low tertile	242 (35)	540 (34)	231 (30)
Mid tertile	240 (35)	526 (33)	246 (32)
High tertile	212 (31)	512 (32)	289 (38)
Parents' education (both at elementary or lower)	152 (23)	337 (22)	76 (11)
Parents' smoking			
None	105 (16)	253 (17)	104 (15)
Former smoker	47 (7)	128 (9)	33 (5)
Current smoker	505 (77)	1132 (75)	538 (80)
Chronic cough	146 (21)	87 (6)	19 (3)
Chronic phlegm	160 (23)	95 (6)	17 (2)
Breathlessness	290 (42)	198 (13)	31 (4)
Persistent wheeze	178 (26)	89 (6)	5 (1)
BDHR	148 (21)	167 (11)	70 (9)
Atopy	289 (49)	571 (42)	317 (48)
Mean $\pm$ SD			
Age, y	11.3 $\pm$ 1.9	11.3 $\pm$ 1.9	11.5 $\pm$ 1.9
Height, m	1.35 $\pm$ 0.12	1.36 $\pm$ 0.12	1.37 $\pm$ 0.13
Weight, kg	29.8 $\pm$ 7.5	30.3 $\pm$ 8.0	31.6 $\pm$ 8.5
FEV ₁ , prebronchodilator, L	1.90 $\pm$ 0.53	2.00 $\pm$ 0.56	2.05 $\pm$ 0.59
FEV ₁ , postbronchodilator, L	2.00 $\pm$ 0.55	2.08 $\pm$ 0.57	2.12 $\pm$ 0.60
BDR, %	6.5 $\pm$ 9.4	4.4 $\pm$ 4.8	3.4 $\pm$ 4.6

Fig 1 presents sex-specific relationships between BDR and age among the 3 subgroups (subjects with asthma in index families, subjects without asthma in index families, and control subjects). In general, BDR decreased with age. The association of BDR with age was nonlinear in subjects with and without asthma from index families. In subjects from control families, there was a more linear decrease of the BDR with increasing age from 8 to 15 years, but there was still a relative plateau in the peripubertal period around 10 to 12 years.

There were interesting sex differences in the effects of pubertal age on BDR and the effect of BMI on BDR. Female subjects with and without asthma from index families showed a nonlinear pattern, which was more pronounced in the subjects with asthma. BDR dramatically decreased between 8 and 10 years of age, with a plateau between age 10 to 12 years; finally, it decreased linearly in the age range of 12 to 15 years. In male subjects, BDR also decreased with age. As with the girls, there was a nonlinear relationship in the peripubertal age range in boys with and without from index families. However, the male subjects with asthma from index families had an actual increase in BDR between 10 and 12 years of age. There is

TABLE II. Sex-specific epidemiologic determinants of BDR among children from the random control families

	Male				Female			
	N	Regression coefficient	SE	P	N	Regression coefficient	SE	P
Age, y	1170	1.34	2.78	.63	1329	2.99	2.35	.20
Age squared	1170	−0.09	0.12	.43	1329	−0.16	0.10	.12
Height, m	1166	10.05	63.74	.88	1323	−187.66	72.0	<.01
Height squared	1166	−2.22	21.96	.92	1323	70.40	26.21	<.01
Atopy	456	−0.82	0.53	.12	472	−0.13	0.64	.84
BMI								
Low tertile	361		Ref		467		Ref	
Mid tertile	408	0.77	0.75	.31	423	−0.19	0.83	.82
High tertile	396	1.64	0.77	.03	431	0.07	0.84	.93
Parents' smoking								
None	184		Ref		202		Ref	
Former smoker	85	1.40	2.07	.50	73	−0.92	1.20	.44
Current smoker	831	0.32	0.58	.58	955	0.08	0.79	.92

a plateau in the boys with asthma from index families between 12 to 14 and followed by a linear decrease in BDR. The boys without asthma from index families do not show the same degree of increase in BDR after the initial decline in BDR until age 10 years. They do plateau, and they have a level of BDR between that of subjects with asthma and controls. The peripubertal changes were more marked in male than female subjects.

Fig 2 presents the Splup graphics plots of BDR against BMI in the 3 groups stratified by sex. The presentation has age factored in as a background variable given the findings noted in Fig 2. The response of BDR to BMI was different in male and female subjects. Specifically, in male subjects, there was a linear increase in BDR with increasing BMI in all 3 groups. In female subjects, BDR had a roughly U-shaped relationship in subjects with asthma and to a lesser extent in controls. There was greater BDR at lower and higher ranges of the BMI spectrum with less BDR at the mid range. In subjects without asthma from index families, BDR showed a different pattern with BMI than the other 2 groups. BDR increased to a BMI of 16 and then plateaued with a gradual decrease at higher BMI levels. As such, the response in female subjects was nonlinear and differed between the 3 groups.

There was a linear relationship between BDR and height. However, as noted, the relationships between BDR and BMI were not linear.

We performed sex-specific analyses on BDR and BHDR, respectively, in relation to an array of clinical signs and symptoms in the subjects from all 3 groups. The variable of family history was included in the analysis, allowing us to adjust for membership in an asthma index family. Multiple linear regression is applied with adjustment for demographic variables from the analysis in Table II, including age, height, BMI in tertiles, parental smoking, and family history of asthma (subject from an asthma index family).

The mean BDR and the prevalence of BHDR increased among subjects with chronic respiratory symptoms and physician-diagnosed asthma. Family history of asthma

was significant for BDR. The associations were similar between male and female subjects (see this article's Tables E1 and E2 in the Online Repository at www.jacionline.org).

DISCUSSION

Impairment of lung function and increased airway responsiveness to bronchodilator can be observed from childhood through adult life in cohorts with asthma.^{12,23-25} Airway responsiveness was reported to predict the development of chronic respiratory symptoms in both adults and children in populations.²⁶⁻²⁸ By contrast with evaluation of bronchial hyperresponsiveness, bronchodilator reversibility is easily obtained, safe, and reliably measured in epidemiologic studies.^{17,29} However, there are few descriptive studies of BDR in general populations,³⁰ underscoring the importance of this study.

This report contributes new information that BDR varied by family history, age (with more pronounced changes in male subjects around puberty), sex, and BMI. With adjustment for these major covariates (age, height, BMI, parental smoking, and baseline FEV₁), BDR was significantly increased in subjects with chronic respiratory symptoms and physician-diagnosed asthma. These findings corroborate the clinical relevance of BDR in this population.

Our recent population-based study in China found significant familial aggregation of BDR.^{9,11} Similarly, in the current study, subjects without asthma from index families (subjects with a family history of asthma) had a distribution of bronchodilator response between that of subjects with asthma and random control subjects. The plots of these responses were all unimodal. This implies that the finding was not a function of misclassification of subjects and suggests the importance of inherited determinants of BDR. However, our current understanding of β -receptor polymorphisms^{31,32} does not sufficiently explain variability between populations^{33,34} and variability caused by factors including age,³⁵⁻³⁹ airway caliber,⁴⁰ and sex.⁴¹⁻⁴⁴ Given the effect of these factors, it becomes even more

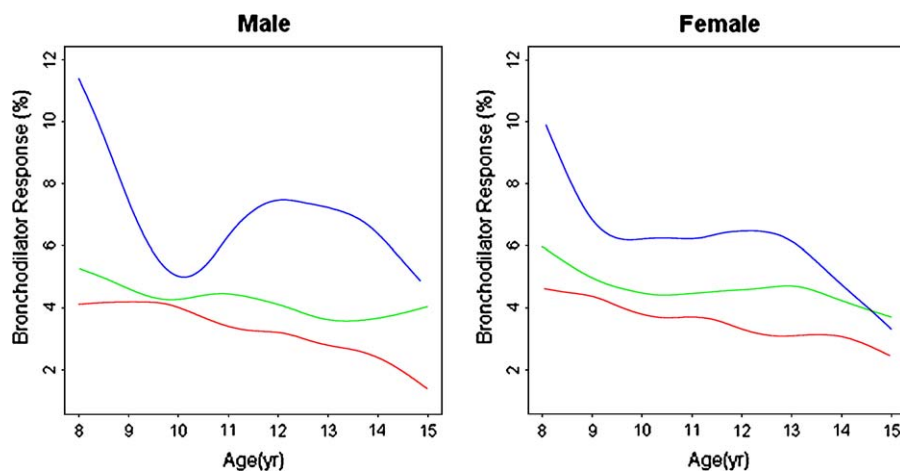


FIG 1. Smoothing plots of BDR in percent predicted change in FEV_1 against age in 3 study groups, stratified by sex. The y-axis represents Percent predicted change in FEV_1 , with the x-axis displaying age in years. Groups are as follows: subject with asthma from index family (blue line), subject without asthma from index family (green line), and control subjects (red line).

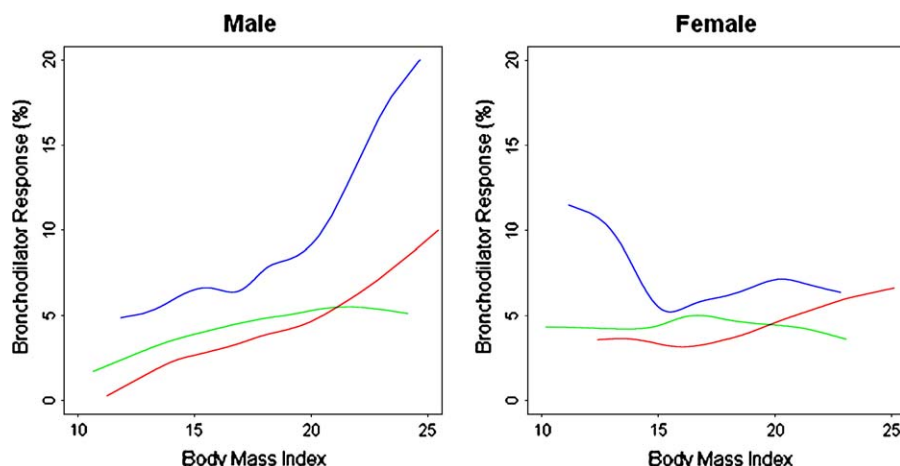


FIG 2. Smoothing plots of BDR in percent change in FEV_1 postbronchodilator on the y-axis against BMI on the x-axis in 3 study groups, stratified by sex and adjusted by age. Groups are as follows: subject with asthma from index family (blue line), subject without asthma from index family (green line), and control subjects (red line).

important to determine the epidemiologic characteristics and determinants of bronchodilator response in individuals with and without asthma to understand better variation of BDR and its utility as an intermediate phenotype of asthma in studies. We discuss each of the determinants of BDR in this population in turn.

There was an inverse, approximately linear relationship between age and BDR in control subjects. However, in subjects with and without asthma from asthma index families, there was a nonlinear relationship with a plateau at puberty. The peripubertal changes were more pronounced for male subjects. There was an actual increase in bronchodilator responsiveness in male subjects for the first part of the pubertal age range. The importance of this is that the use of a single definition of bronchodilator hyperresponsiveness would not take this variability into

account. If this were used as 1 criterion for the diagnosis of asthma, it would result in differences in the frequency of asthma diagnosis at different ages. There have been reports examining the effects of age on bronchodilator response in the past, although most studies focused on the elderly age range.^{36,37,39,45,46} Pediatric data are limited with small sample size and limited age range.³⁶ In-depth investigations are clearly needed to explore further the relation between age and BDR.

After age adjustment, BMI seemed to vary linearly with BDR in male subjects but had a nonlinear response in female subjects. Female subjects with asthma had higher levels of BDR at both higher and lower levels of BMI. This U-shaped relationship would imply that both low and high BMI is associated with increased responsiveness to bronchodilator in female subjects. In both male and

female subjects, higher BMI was associated with increased response to BDR, suggesting that one of the factors that may account for the association of the diagnosis of asthma with obesity is airway responsiveness.

Sex played an interesting role in BDR. We did not detect a significant difference in BDR between men and women. However, other predictors of BDR varied in their effect by sex, including BMI and age (especially peripubertally). With respect to sex effects, there is previous evidence that there is an interaction between the sympathetic system and ovarian response in puberty.^{47,48} Sex hormones may also have an effect on the asthmatic response.^{41,42} In this regard, there may be an interaction of weight, puberty, and sympathoadrenal hormones.⁴⁹ This interplay may also play a role in bronchodilator responses in subjects with asthma.⁴⁴ This might bear on the findings of our study in the female subjects, but would not provide a clear explanation for the findings in the male subjects.

Finally, there was no association of atopy with methacholine responsiveness and lower lung function in our cohort. This unusual finding may be a result of our mixed population of subjects with and without asthma where there are other determinants of BDR and BDHR as noted. Also, there is some evidence that these 2 phenotypes (atopy and BDR) may have some independent inheritance patterns.^{50,51}

This study highlights that the response to bronchodilator is different in male and female subjects, and varies according to age, especially around puberty. Furthermore, BDR varies not only according to the presence of asthma in the subject but also with family history. This may imply that some of the mechanisms predisposing to BDR are heritable in a continuous fashion and present in family members without asthma more than in the general population without a family history. These critical observations provide important insights into our understanding of the biological mechanisms underlying BDR. However, these findings were established in a Chinese population, and caution must be exercised in generalizing these findings to other populations. Replication in other large populations will be important. Finally, this paper underscores the utility of BDR as an important intermediate asthma phenotype in large-scale population studies in which methacholine challenges are less feasible.

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