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**Do risk factors for asthma modify lung function in infants with recurrent wheeze?**

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4 **Do risk factors for persistent asthma modify lung function in infants and young**  
5 **children with recurrent wheeze?**  
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51 **Keywords:** wheezing, infant, child, asthma, respiratory function test  
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54 **Running title:** Lung function in wheezing infants with asthma risk  
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**ABSTRACT:**

**Background :** There is very limited information on how the risk of persistent asthma in recurrent wheezing (RW) infants modifies their lung function early in life. The aim of the present study is to compare lung function of RW infants and young children with a positive or negative asthma predictive index (API), an index previously used to anticipate asthma persistence into childhood and adolescence.

**Methods:** Two groups of RW infants and young children were recruited in two centres in Spain (Palma de Mallorca and Murcia). Lung function was measured according to the thoraco-abdominal compression technique (RCT), and values of the maximal flow at functional residual capacity ( $V'_{\max\text{FRC}}$ ) were expressed as Z-scores. Other variables included in the study, as independent factors, were: gender, age, length, weight and parental smoking habits together with information regarding API.

**Results:** Expressed as mean $\pm$ SD, API+ RW infants (n=50; age in months 11.9 $\pm$ 4.9) had a lower  $V'_{\max\text{FRC}}$  Z-score than API- RW ones (n=41; age in months 12.3 $\pm$ 6.2) (-2.01 $\pm$ 0.79 vs. -1.64 $\pm$ 0.77, p=0.026, respectively). Centre and tobacco exposition did not have an effect on lung function.

**Conclusion:** Among RW infants and young children, those having a positive API have a significant lower lung function as measured by  $V'_{\max\text{FRC}}$  very early in life at an early age.

## INTRODUCTION

Respiratory disorders associated to wheezing are very common in early ages. Wheezing is the manifestation of different conditions which provoke narrowing of the airways, but most of the time it is triggered by a viral infection. Among those infants who suffer from several episodes of wheezing during their first months or years of life, different groups can be identified: those who repeat episodes during the first 3 years but not after that age (transient wheezers); those who do not outgrow their wheezing, have an elevated IgE and typically a family history of asthma or allergies (atopic persistent wheezers, or asthmatics); and those who suffer episodes beyond the age of three but usually not beyond the age of 13, which usually started with a severe bronchiolitis at early age and do not have a family history of asthma or allergies (non-atopic wheezers).[1]

On the other hand, low lung function prior to any wheezing episode has been described in some infants (related to mother smoking during pregnancy, for example), leading to the hypothesis that the pre-existing impaired lung function may be the cause, rather than the effect, of the severe episodes of bronchiolitis which some infants suffer and which are associated with future recurrent episodes of wheezing. [2] However, the actual pathophysiology of frequent wheezing episodes in infants is not fully understood [3] and there is still much information lacking on lung mechanics in the early stages of the different phenotypes of wheeze. A recent study found that wheezing infants with high risk of suffering asthma have a lower lung function at early ages, as compared to frequent wheezers with low risk.[4] A different way of assessing the asthma risk is the so-called asthma predictive index (API), which includes major and minor criteria.[5] To the best of our knowledge, only the study by Borrego et al. [4] has compared lung

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4 function of infants with and without markers of future asthma, such as parental allergy.  
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7 The aim of the present study is to compare lung function of two groups of recurrent  
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9 wheezing infants and young children: positive and negative to the asthma predictive  
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11 index (API) described by Castro et al [5], hypothesizing that lung function might be –as  
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13 a group- be lower in those with a positive API index who are more prone to suffer from  
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16 future asthma.  
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## 21 MATERIAL AND METHODS

### 22 Population

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25 **Infants Children** up to 24 months of age who had wheezed at least 3 times in  
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27 their lives were selected from two different Paediatric Pulmonology clinics. Wheezing  
28  
29 was always diagnosed by a paediatric pulmonologist. **Infants Children** with chronic  
30  
31 respiratory disease or born preterm and/or with low birth-weight, were not included. A  
32  
33 total of 79 91 steroid naïve wheezing Caucasian infants children (58 male) aged 2 to 24  
34  
35 months were included in the study. Forty were attended to the Paediatric Pulmonology  
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37 unit at Palmaplanas Clinic, Palma de Mallorca, Spain; while 39 were studied at the  
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39 Paediatric Pulmonology unit, at the Virgen de la Arrixaca University Children's  
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41 Hospital, Murcia, Spain. **Infants Children** were recruited between 2004 and 2008.  
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48 Asthma predictive index was established as previously described; and the  
49  
50 stringent index was applied [5]. Tobacco exposure was considered positive when either  
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52 the father or the mother or both were smokers at the time of the lung function test.  
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54 Length and weight were measured at the time of the lung function measurement  
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56 according to standard procedures.  
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### 59 Lung function measurement

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4 Lung function was studied by means of the rapid thoraco-abdominal compression  
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6 technique [6]. With the sedated infant breathing at tidal volume through a face mask  
7  
8 connected to a pneumotachometer, a rapid thoraco-abdominal compression is made  
9  
10 by means of a jacket which is instantly inflated at a given pressure. This pressure is  
11  
12 increased in successive manoeuvres until the flow at functional residual capacity is  
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14 maximal. This flow is the maximal flow at functional residual capacity ( $V'_{\max\text{FRC}}$ ).  
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18 The best (highest flow from a minimum of three technically acceptable curves) value  
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20 is reported, provided it is within 10% or  $10 \text{ mL}\cdot\text{s}^{-1}$  (whichever is greater) of the next  
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22 highest value [6]. Tests were performed with two different systems: a custom-built  
23  
24 system following the guidelines of the ATS/ERS Working Group on Standardization  
25  
26 of Infant Pulmonary Function Tests [6] in Palmaplanas Clinic and a MasterScreen  
27  
28 BabyBody Plethysmograph from Jaeger (Germany) (Virgen de la Arrixaca University  
29  
30 Children's Hospital). Lung function was performed after sedation with chloral hydrate  
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32 (50-100 mg/Kg). Studies were performed in asymptomatic patients at least 3 weeks  
33  
34 after the last wheezing episode. The same protocol was followed in both centers. Both  
35  
36 systems used the same ~~typemodel~~ of face mask, and ~~similar~~ pneumotachometergraph  
37  
38 types ~~models~~ (Jaeger's original in Murcia and Hans Rudolf, non heated 0-35 l/min  
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40 [Shawnee, KS 66227, USA] in Palma de Mallorca); and they share the same dead  
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48 space and resistance.

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Investigators performing lung function tests were not aware to the API (positive or negative) of each infant.

### Statistical analysis

Continuous variables, including  $V'_{\max\text{FRC}}$  (Z-scores calculated according to published regression formulas) [7] were compared by means of Student "t" test. Proportions were compared with the Pearson Chi-square. A factorial analysis of variance analysis was performed in order to know the effect of API on  $V'_{\max\text{FRC}}$  Z-scores including age, sex, tobacco exposure and center as a covariate. The relative contribution of each studied variables (age, sex, length, weight, API, tobacco exposure and center) to the variability of  $V'_{\max\text{FRC}}$  was calculated by the sum of squares in the analysis of variance. All statistical calculations were carried out using the SPSS v15 software (Chicago, IL, USA).

### Ethics

The study was approved by the two ethics committees of the two hospitals involved, Virgen de la Arrixaca University Children's Hospital and Palmaplanas Clinic, and informed consent was obtained before testing. Parents were asked for consent to perform a lung function study as part of the follow-up of their children.

### RESULTS

Lung function studies were performed in a total 91 children. With this sample the estimated power of the study to ascertain a difference between the two wheezy groups was 60%. There were no differences in gender, age, weight, length, percentage of smokers parents, or z-score of  $V'_{\max\text{FRC}}$  between the infants children recruited in both centers (Table 1 and Figure 1). Among the 91 wheezing infants children, 51 had a positive asthma predictive index (API+) while 40 had it negative (API-), and no statistical difference was found in proportion of API (+) between both centers (55% vs 54.9%;  $p=0.99$ ).

As ~~is~~ shown in Table 2 ~~and Figure 2~~, no differences were found in age, length, weight and tobacco exposure between API+ and API- wheezing children. However, the API+ group had a  $V'_{\max\text{FRC}}$  Z-score significantly ( $p < 0.026$ ) lower than the API – one (~~mean±SD: -2.01±0.79 vs. -1.64±0.77 respectively~~) (Figure 2).

In the factorial variance analysis, which included age, gender, center and smoke habits, as covariates and API as factor, the difference in z-score of  $V'_{\max\text{FRC}}$  between the API+ and the API- groups persisted significant ( $F=5.153$ ;  $p=0.026$ ).

Finally, the main contributors for the variability of  $V'_{\max\text{FRC}}$  was length (83.04%;  $p < 0.001$ ) and API (9.39%;  $p=0.038$ ). The contribution of the others variables was not statistically significant (Figure 3).

## DISCUSSION

The results of this study show that lung function is significantly lower, at a mean age of one year, in recurrent wheezing children with a positive asthma predictive index, ~~than in those without these risk factors~~ as compared to those with a negative one.

~~In the present study, wheezing infants and young children were recruited in two centres in Spain. In all instances, lung function tests were performed by two trained pulmonologists following the same protocol. There was no statistically significant difference in any of the variables between the two centers (Table 1), and the factorial variance analysis did not find that the effect of center modified the difference between  $V'_{\max\text{FRC}}$  Z-score of API+ and API- groups. This suggests that the effect of risk of suffering from asthma is the more most important factor that explains the loss explaining the reduced in lung function.~~ Although the use of the sum of squares is a method of establishing the relative contribution of several variables could be

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4 controversial, only two variables contributed significantly to  $V'_{\max FRC}$ : length  
5 (83.04%), as expected, and API (9.39%), suggesting that ~~very early in life the~~ lung  
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7 function may be influenced ~~early in life~~, in some way, by the risk of suffering from  
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9 asthma.  
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14 The impact of the “asthma predictive index” [5] on the airway obstruction has  
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16 not been fully studied. The present ~~study results~~ shows that there is a difference in the  
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18 size of the impairment between children with and without risk factors of suffering from  
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20 asthma. Considering that children with risk of ~~suffering having future~~ asthma are more  
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22 likely to be persistent wheezers in late childhood, our findings emphasize the loss of  
23  
24 lung function at ~~very-an~~ early age.  
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29 With a very similar aim, a recent study by Borrego et al. [4] compared lung  
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31 function (raised volume RTC technique, and tidal RTC technique) between wheezing  
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33 infants with high and low risk of suffering from asthma. High risk was defined as  
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35 parental history of asthma or wheezing without a cold, plus eosinophilia >4%; while low  
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37 risk was defined as the absence of both such features. In contrast, the present study  
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39 defined risk factors according to a stringent index published previously [5] which  
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41 include major (medical diagnosis of asthma in one parent or medical diagnosis of atopic  
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43 dermatitis in the children) and minor (allergic rhinitis in the child, wheezing without  
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45 colds, eosinophilia >4%) criteria. A positive asthma risk index requires at least one  
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47 positive major criterion or two minor ones. Although very similar, the criteria used in  
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49 the present study and that used in the one by Borrego et al. [4] are not exactly the same,  
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51 as –for example- children diagnosed of atopic dermatitis would have been in different  
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53 risk groups (API+ in the present study and low risk in that by Borrego et al. [4]). What  
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55 is important to underline is that, the mean value of  $V'_{\max FRC}$  Z-score among all  
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4 wheezing children is fairly similar in the present study and in the aforementioned study  
5 by Borrego et al. [4] ( $-1.84 \pm 0.8$  vs.  $-1.9 \pm 1.0$ , respectively). These authors ~~do not~~  
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7 ~~found~~ ~~did not find~~ significant differences in  $V'_{\max\text{FRC}}$  Z-score between high and low risk  
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9 weezhing infants, ~~perhaps~~ ~~probably~~ because the number of children in the wheezing  
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11 group (n=50) was ~~relatively~~ ~~too~~ low to have a high statistical power, ~~thus~~ it is not  
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13 striking that the difference was not statistically significant (although there was a trend  
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15 for it:  $p=0.1$ ). In the present study, the number of children in the wheezing group was  
16  
17 ~~relatively~~ larger. ~~This fact, and~~ together with the somewhat different method to classify  
18  
19 ~~the~~ asthma risk ~~are probably enough to explain~~ ~~may account for~~ the apparent discordant  
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21 results when comparing  $V'_{\max\text{FRC}}$  Z-scores between high and low risk wheezing children  
22  
23 in the two studies. The estimated powers of the study by Borrego et al. [4] and that of  
24  
25 the present one are ~~respectively~~ 33% and 60% respectively. However, as compared with  
26  
27 the aforementioned study, we acknowledge ~~the main limitation of our own study is~~ that  
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29 tidal RTC technique is less discriminative than ~~the~~ raised volume RTC to evaluate  
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31 airway obstruction.  
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40 Lung function in transient wheezing children has been shown to be lower than in  
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42 non-wheezing ones prior to the first wheezing episode. This lower lung function persists  
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44 until the age of 16 years. In contrast, children with persistent wheezing have normal  
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46 lung function before their first wheezing episode but this is reduced with time, and is  
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48 lower at the age of 6 years [9]. Low lung function during the first months of life is  
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50 associated with an increased prevalence of asthma in late childhood [10,11] and even  
51  
52 with low lung function in adulthood [12,13]. In fact, low Z-scores of  $V'_{\max\text{FRC}}$  at one  
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54 month of life are associated with persistent wheezing at 11 years of age, and this loss of  
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56 lung function has not been related to an increased airway reactivity or atopy in  
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4 childhood [10]. It has been hypothesized that small airways size could explain this[14].  
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7 However, and very interestingly, no difference was found in small-airway size between  
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10 recurrent wheezing infants and normal controls when analyzed by high-resolution  
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12 computed tomography images[15].

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14 As shown here, with  $V'_{\max\text{FRC}}$ , and previously by Borrego et al.,[4] with forced  
15  
16 expiratory lung volumes and flows (FVC and  $\text{FEF}_{25-75}$ ), atopic risk is associated with  
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18 lower lung function at an early age. Whether atopic children are born with structurally  
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20 and/or functionally different airways, or respond to viral infections with greater tissue  
21  
22 disorganisation and/or repair is not possible to say. What is known is that persistent  
23  
24 wheezing infants respond differently than transient wheezing ones to lower respiratory  
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26 tract infections[16]. As atopy is the most important risk factor for persistent wheeze it  
27  
28 could be hypothesized that –independently of the differences in lung tissue architecture  
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30 at the time of birth- a distinct response to viral infections may affect lung tissue in a  
31  
32 different way in API+ ~~infants~~ children as compared to API- ones.

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37 The present study has two main potential limitations. Firstly, we do not have a  
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39 prospective healthy control group; however, as our objective was to compare lung  
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41 function between API+ and API- recurrent wheezing children, so a healthy control  
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43 group does not seem strictly necessary, as device variability –if any- is most probably  
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45 random and if having any effect it would have pushed the results towards the null  
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47 hypothesis. Secondly, we used two different devices for measuring lung function.  
48  
49 However, face masks and dead spaces were the same, pneumotacometers were of the  
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51 same type, values obtained from children were very similar between centers (Figure 1)  
52  
53 and no centre effect was found in the regression analysis, thus making any bias derived  
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55 from this limitation unlikely.  
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4 In summary, the present study shows that among recurrent wheezing infants and  
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6 young children, those having a positive API have a significant lower lung function at an  
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8 early age.~~very early on in life.~~  
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For Peer Review

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7 Figure legends:  
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11 Figure 1.- VmaxFRC (z-score) in Palma de Mallorca and Murcia. There were no  
12 differences statistically significant between both centers:  $p=0.36$  (see Table 1).  
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18  
19 Figure 2.- VmaxFRC (z-score) in wheezing infants. Difference between API+ and  
20 API- is statistically significant ( $p=0.026$ ).  
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27 Figure 3.- Percentage contribution of the different factors to the total explained  
28 variability of  $V'_{\max\text{FRC}}$  according to the sum of squares in the ANOVA analysis. Of the  
29 total variability, total explained variability was 35.7%.  
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33 \* $p=0.038$ ; \*\* $p<0.001$ .  
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4 **Do risk factors for persistent asthma modify lung function in infants and young**  
5 **children with recurrent wheeze?**  
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52 **Keywords:** wheezing, infant, child, asthma, respiratory function test  
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54 **Running title:** Lung function in wheezing infants with asthma risk  
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**ABSTRACT:**

**Background :** There is very limited information on how the risk of persistent asthma in recurrent wheezing (RW) infants modifies their lung function early in life. The aim of the present study is to compare lung function of RW infants and young children with a positive or negative asthma predictive index (API), an index previously used to anticipate asthma persistence into childhood and adolescence.

**Methods:** Two groups of RW infants and young children were recruited in two centres in Spain (Palma de Mallorca and Murcia). Lung function was measured according to the thoraco-abdominal compression technique (RCT), and values of the maximal flow at functional residual capacity ( $V'_{\max\text{FRC}}$ ) were expressed as Z-scores. Other variables included in the study, as independent factors, were: gender, age, length, weight and parental smoking habits together with information regarding API.

**Results:** Expressed as mean $\pm$ SD, API+ RW infants (n=50; age in months 11.9 $\pm$ 4.9) had a lower  $V'_{\max\text{FRC}}$  Z-score than API- RW ones (n=41; age in months 12.3 $\pm$ 6.2) (-2.01 $\pm$ 0.79 vs. -1.64 $\pm$ 0.77, p=0.026, respectively). Centre and tobacco exposition did not have an effect on lung function.

**Conclusion:** Among RW infants and young children, those having a positive API have a significant lower lung function as measured by  $V'_{\max\text{FRC}}$  at an early age.

## INTRODUCTION

Respiratory disorders associated to wheezing are very common in early ages. Wheezing is the manifestation of different conditions which provoke narrowing of the airways, but most of the time it is triggered by a viral infection. Among those infants who suffer from several episodes of wheezing during their first months or years of life, different groups can be identified: those who repeat episodes during the first 3 years but not after that age (transient wheezers); those who do not outgrow their wheezing, have an elevated IgE and typically a family history of asthma or allergies (atopic persistent wheezers, or asthmatics); and those who suffer episodes beyond the age of three but usually not beyond the age of 13, which usually started with a severe bronchiolitis at early age and do not have a family history of asthma or allergies (non-atopic wheezers).[1]

On the other hand, low lung function prior to any wheezing episode has been described in some infants (related to mother smoking during pregnancy, for example), leading to the hypothesis that the pre-existing impaired lung function may be the cause, rather than the effect, of the severe episodes of bronchiolitis which some infants suffer and which are associated with future recurrent episodes of wheezing. [2] However, the actual pathophysiology of frequent wheezing episodes in infants is not fully understood [3] and there is still much information lacking on lung mechanics in the early stages of the different phenotypes of wheeze. A recent study found that wheezing infants with high risk of suffering asthma have a lower lung function at early ages, as compared to frequent wheezers with low risk.[4] A different way of assessing asthma risk is the so-called asthma predictive index (API), which includes major and minor criteria.[5] To the best of our knowledge, only the study by Borrego et al. [4] has compared lung

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4 function of infants with and without markers of future asthma, such as parental allergy.  
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7 The aim of the present study is to compare lung function of two groups of recurrent  
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9 wheezing infants and young children: positive and negative to the asthma predictive  
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11 index (API) described by Castro et al [5], hypothesizing that lung function might be –as  
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13 a group- lower in those with a positive API index who are more prone to suffer from  
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16 future asthma.  
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## 21 MATERIAL AND METHODS

### 22 23 Population

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25 Children up to 24 months of age who had wheezed at least 3 times in their lives  
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27 were selected from two different Paediatric Pulmonology clinics. Wheezing was always  
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29 diagnosed by a paediatric pulmonologist. Children with chronic respiratory disease or  
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31 born preterm and/or with low birth-weight, were not included. A total of 91 steroid  
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33 naïve wheezing Caucasian children (58 male) aged 2 to 24 months were included in the  
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35 study. Forty attended to the Paediatric Pulmonology unit at Palmaplanas Clinic, Palma  
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37 de Mallorca, Spain; while 39 were studied at the Paediatric Pulmonology unit, at the  
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39 Virgen de la Arrixaca University Children's Hospital, Murcia, Spain. Children were  
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41 recruited between 2004 and 2008.  
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47 Asthma predictive index was established as previously described; and the  
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49 stringent index was applied [5]. Tobacco exposure was considered positive when either  
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51 the father or the mother or both were smokers at the time of the lung function test.  
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53 Length and weight were measured at the time of the lung function measurement  
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55 according to standard procedures.  
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### 58 Lung function measurement

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4 Lung function was studied by means of the rapid thoraco-abdominal compression  
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6 technique [6]. With the sedated infant breathing at tidal volume through a face mask  
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8 connected to a pneumotachometer, a rapid thoraco-abdominal compression is made  
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10 by means of a jacket which is instantly inflated at a given pressure. This pressure is  
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12 increased in successive manoeuvres until the flow at functional residual capacity is  
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14 maximal. This flow is the maximal flow at functional residual capacity ( $V'_{\max\text{FRC}}$ ).  
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18 The best (highest flow from a minimum of three technically acceptable curves) value  
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20 is reported, provided it is within 10% or  $10 \text{ mL}\cdot\text{s}^{-1}$  (whichever is greater) of the next  
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22 highest value [6]. Tests were performed with two different systems: a custom-built  
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24 system following the guidelines of the ATS/ERS Working Group on Standardization  
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26 of Infant Pulmonary Function Tests [6] in Palmaplanas Clinic and a MasterScreen  
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28 BabyBody Plethysmograph from Jaeger (Germany) (Virgen de la Arrixaca University  
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30 Children's Hospital). Lung function was performed after sedation with chloral hydrate  
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32 (50-100 mg/Kg). Studies were performed in asymptomatic patients at least 3 weeks  
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34 after the last wheezing episode. The same protocol was followed in both centers. Both  
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36 systems used the same model of face mask, and similar pneumotachometer types  
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38 (Jaeger's original in Murcia and Hans Rudolf, non heated 0-35 l/min [Shawnee, KS  
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40 66227, USA] in Palma de Mallorca); and they share the same dead space and  
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48 resistance.

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50 Investigators performing lung function tests were not aware to the API (positive  
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52 or negative) of each infant.

### 53 54 55 56 57 **Statistical analysis** 58 59 60

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Continuous variables, including  $V'_{\max\text{FRC}}$  (Z-scores calculated according to published regression formulas) [7] were compared by means of Student “t” test . Proportions were compared with the Pearson Chi-square. A factorial analysis of variance analysis was performed in order to know the effect of API on  $V'_{\max\text{FRC}}$  Z-scores including age, sex, tobacco exposure and center as a covariate. The relative contribution of each studied variable (age, sex, length, weight, API, tobacco exposure and center) to the variability of  $V'_{\max\text{FRC}}$  was calculated by the sum of squares in the analysis of variance. All statistical calculations were carried out using the SPSS v15 software (Chicago, IL, USA).

### Ethics

The study was approved by the two ethic committees of the two hospitals involved, Virgen de la Arrixaca University Children’s Hospital and Palmaplanas Clinic, and informed consent was obtained before testing. Parents were asked for consent to perform a lung function study as part of the follow-up of their children.

### RESULTS

Lung function studies were performed in a total 91 children. With this sample the estimated power of the study to ascertain a difference between the two wheezy groups was 60%. There were no differences in gender, age, weight, length, percentage of smoker parents, or z-score of  $V'_{\max\text{FRC}}$  between children recruited in both centers (Table 1 and Figure 1). Among the 91 wheezing children, 51 had a positive asthma predictive index (API+) while 40 had it negative (API-), and no statistical difference was found in proportion of API (+) between both centers (55% vs 54.9%;  $p=0.99$ ).

As shown in Table 2, no differences were found in age, length, weight and

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4 tobacco exposure between API+ and API- wheezing children. However, the API+  
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6 group had a  $V'_{\max\text{FRC}}$  z-score significantly ( $p<0.026$ ) lower than the API – one  
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9 (mean $\pm$ SD:  $-2.01\pm 0.79$  vs.  $-1.64\pm 0.77$  respectively) (Figure 2).

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11 In the factorial variance analysis, which included age, gender, center and smoke  
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13 habits, as covariates and API as factor, the difference in z-score of  $V'_{\max\text{FRC}}$  between the  
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15 API+ and the API- groups persisted significant ( $F=5.153$ ;  $p=0.026$ ).

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18 Finally, the main contributors for the variability of  $V'_{\max\text{FRC}}$  was length (83.04%;  
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20  $p<0.001$ ) and API (9.39%;  $p=0.038$ ). The contribution of the others variables was not  
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22 statistically significant (Figure 3).  
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## 28 DISCUSSION

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30 The results of this study show that lung function is significantly lower, at a mean  
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32 age of one year, in recurrent wheezing children with a positive asthma predictive index,  
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34 as compared to those with a negative one. Although the use of the sum of squares is a  
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36 method of establishing the relative contribution of several variables could be  
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38 controversial, only two variables contributed significantly to  $V'_{\max\text{FRC}}$ : length (83.04%),  
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40 as expected, and API (9.39%), suggesting that lung function may be influenced early in  
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42 life, in some way, by the risk of suffering from asthma.  
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47 The impact of the “asthma predictive index” [5] on the airway obstruction has  
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49 not been fully studied. The present results show that there is a difference in the size of  
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51 the impairment between children with and without risk factors of suffering from asthma.  
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53 Considering that children with risk of having future asthma are more likely to be  
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55 persistent wheezers in late childhood, our findings emphasize the loss of lung function  
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57 at an early age.  
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5 With a very similar aim, a recent study by Borrego et al. [4] compared lung  
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7 function (raised volume RTC technique, and tidal RTC technique) between wheezing  
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9 infants with high and low risk of suffering from asthma. High risk was defined as  
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11 parental history of asthma or wheezing without a cold, plus eosinophilia>4%; while low  
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13 risk was defined as the absence of both such features. In contrast, the present study  
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15 defined risk factors according to a stringent index published previously [5] which  
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17 include major (medical diagnosis of asthma in one parent or medical diagnosis of atopic  
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19 dermatitis in the children) and minor (allergic rhinitis in the child, wheezing without  
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21 colds, eosinophilia>4%) criteria. A positive asthma risk index requires at least one  
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23 positive major criterion or two minor ones. Although very similar, the criteria used in  
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25 the present study and that used in the one by Borrego et al. [4] are not exactly the same,  
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27 as –for example- children diagnosed of atopic dermatitis would have been in different  
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29 risk groups (API+ in the present study and low risk in that by Borrego et al. [4]). What  
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31 is important to underline is that, the mean value of  $V'_{\max\text{FRC}}$  Z-score among all  
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33 wheezing children is fairly similar in the present study and in the aforementioned study  
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35 by Borrego et al. [4] ( $-1.84\pm 0.8$  vs.  $-1.9\pm 1.0$ , respectively). These authors did not find  
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37 significant differences in  $V'_{\max\text{FRC}}$  Z-score between high and low risk weezhing infants,  
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39 probably because the number of children in the wheezing group (n=50) was too low to  
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41 have a high statistical power, thus it is not striking that the difference was not  
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43 statistically significant (although there was a trend for it:  $p=0.1$ ). In the present study,  
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45 the number of children in the wheezing group was larger. This fact, together with the  
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47 somewhat different method to classify asthma risk may account for the apparent  
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49 discordant results when comparing  $V'_{\max\text{FRC}}$  Z-scores between high and low risk  
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51 wheezing children in the two studies. The estimated powers of the study by Borrego et  
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4 al. [4] and that of the present one are 33% and 60% respectively. However, as compared  
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6 with the aforementioned study, we acknowledge that tidal RTC technique is less  
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8 discriminative than raised volume RTC to evaluate airway obstruction.  
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11 Lung function in transient wheezing children has been shown to be lower than in  
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13 non-wheezing ones prior to the first wheezing episode. This lower lung function persists  
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15 until the age of 16 years. In contrast, children with persistent wheezing have normal  
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17 lung function before their first wheezing episode but this is reduced with time, and is  
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19 lower at the age of 6 years [9]. Low lung function during the first months of life is  
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21 associated with an increased prevalence of asthma in late childhood [10,11] and even  
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23 with low lung function in adulthood[12,13]. In fact, low Z-scores of  $V'_{\max\text{FRC}}$  at one  
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25 month of life are associated with persistent wheezing at 11 years of age, and this loss of  
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27 lung function has not been related to an increased airway reactivity or atopy in  
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29 childhood [10]. It has been hypothesized that small airways size could explain this[14].  
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31 However, and very interestingly, no difference was found in small-airway size between  
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33 recurrent wheezing infants and normal controls when analyzed by high-resolution  
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35 computed tomography images[15].  
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42 As shown here, with  $V'_{\max\text{FRC}}$ , and previously by Borrego et al.,[4] with forced  
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44 expiratory lung volumes and flows (FVC and FEF<sub>25-75</sub>), atopic risk is associated with  
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46 lower lung function at an early age. Whether atopic children are born with structurally  
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48 and/or functionally different airways, or respond to viral infections with greater tissue  
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50 disorganisation and/or repair is not possible to say. What is known is that persistent  
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52 wheezing infants respond differently than transient wheezing ones to lower respiratory  
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54 tract infections[16]. As atopy is the most important risk factor for persistent wheeze it  
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56 could be hypothesized that –independently of the differences in lung tissue architecture  
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4 at the time of birth- a distinct response to viral infections may affect lung tissue in a  
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6 different way in API+ children as compared to API- ones.  
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9 The present study has two main potential limitations. Firstly, we do not have a  
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11 prospective healthy control group; however, as our objective was to compare lung  
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13 function between API+ and API- recurrent wheezing children, so a healthy control  
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15 group does not seem strictly necessary, as device variability –if any- is most probably  
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17 random and if having any effect it would have pushed the results towards the null  
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19 hypothesis. Secondly, we used two different devices for measuring lung function.  
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21 However, face masks and dead spaces were the same, pneumotacometers were of the  
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23 same type, values obtained from children were very similar between centers (Figure 1)  
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25 and no centre effect was found in the regression analysis, thus making any bias derived  
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27 from this limitation unlikely.  
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33 In summary, the present study shows that among recurrent wheezing infants and  
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35 young children, those having a positive API have a significant lower lung function at an  
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37 early age.  
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7 Figure legends:  
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11 Figure 1.- VmaxFRC (z-score) in Palma de Mallorca and Murcia. There were no  
12 differences statistically significant between both centers:  $p=0.36$  (see Table 1).  
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18 Figure 2.- VmaxFRC (z-score) in wheezing infants. Difference between API+ and  
19 API- is statistically significant ( $p=0.026$ ).  
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25 Figure 3.- Percentage contribution of the different factors to the total explained  
26 variability of  $V'_{\max\text{FRC}}$  according to the sum of squares in the ANOVA analysis. Of the  
27 total variability, total explained variability was 35.7%.  
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33 \* $p=0.038$ ; \*\* $p<0.001$ .  
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Table 1.- Demographic characteristics and lung function of wheezing infants from Palma de Mallorca and Murcia.

	All wheezing infants	Palma de Mallorca	Murcia	mean difference (95% CI)	p
Number of cases	91	40	51	--	--
Male gender	72(79.1%)	30(75%)	42(82.4%)	--	0.39
Smoker parents	34(37.4%)	15(37.5%)	19(37.3%)	--	0.98
Asthma predictive index (+)	50(54.9%)	22(55%)	28(54.9%)	--	0.99
Age at study (months)	12.05±5.5	11.1±4.6	12.8±6.1	1.6 (-0.7;3.9)	0.17
Weight (Kg)	9.9±2.0	9.6±1.8	10.2±2.1	0.6 (-0.3;1.4)	0.19
Length (cm)	75.6±6.8	74.5±5.7	76.5±7.4	2.01 (-0.8;4.8)	0.16
V <sub>maxFRC</sub> (z-score)	-1.84±0.80	-1.92±0.87	-1.77±0.74	0.15 (-1.8;0.5)	0.36

Values are expressed as N(%) or as mean±SD

Table 2.- Demographic characteristics and lung function of wheezing infants. All wheezing infants split in API (+) and API (-).

	API (-) n=41	API (+) n=50	Mean difference (95% CI)	p
Male gender	33(80.5%)	39(78%)	--	0.77
Smoker parents	14(34.1%)	20(40.0%)	--	0.57
Age at study (months)	12.3±6.2	11.9±4.9	-0.4 (-2.8;1.9)	0.71
Weight (Kg)	9.8±2.0	10.1±2.0	0.4 (-0.5;1.2)	0.39
Length (cm)	75.2±7.5	76.0±6.2	0.7 (-2.1;3.6)	0.60
V <sub>maxFRC</sub> (z-score)	-1.64±0.77	-2.01±0.79	-0.4 (-0.7;-0.05)	0.026

Values are expressed as N(%) or as mean±SD

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Figure 1

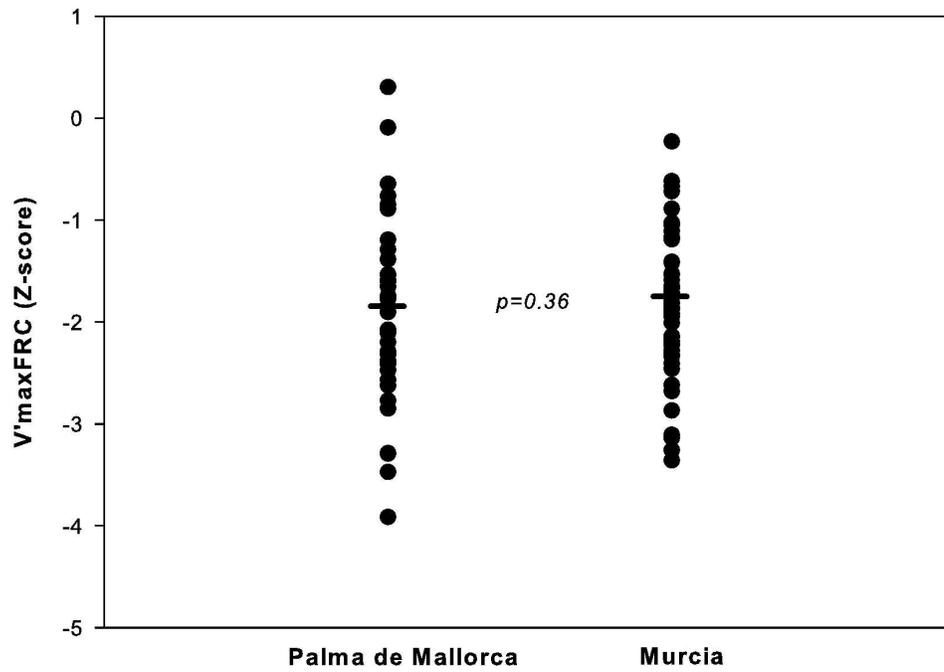


Figure 1.- VmaxFRC (z-score) in Palma de Mallorca and Murcia. There were no differences statistically significant between both centers:  $p=0.36$  (see Table 1).  
146x148mm (600 x 600 DPI)

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Figure 2

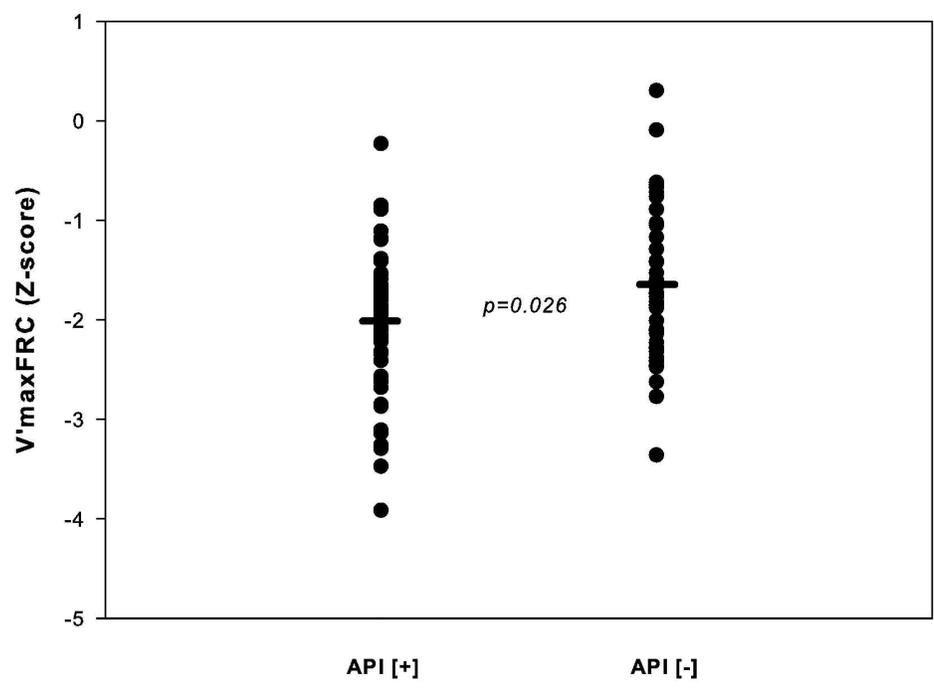


Figure 2.- VmaxFRC (z-score) in wheezing infants. Difference between API [+] and API [-] is statistically significant ( $p=0.026$ ).  
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Figure 3

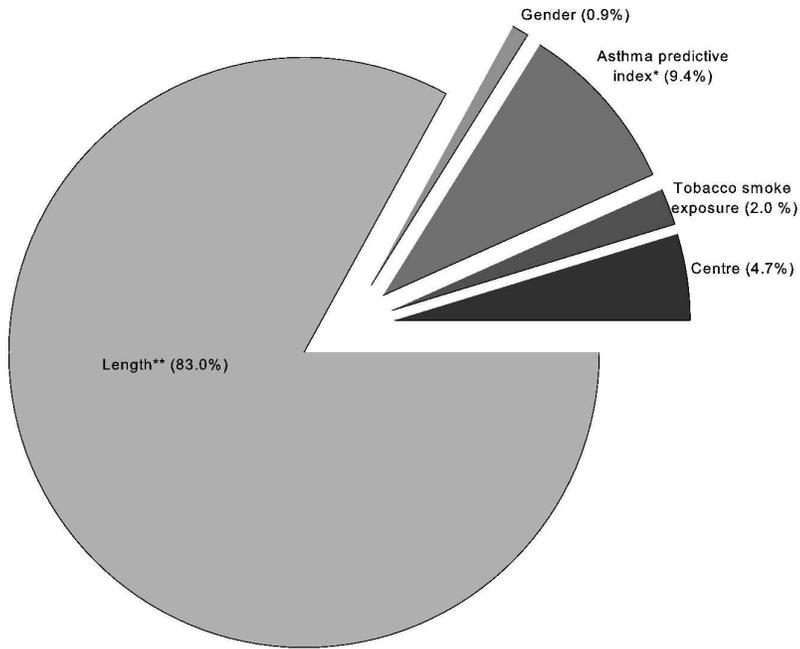


Figure 3.- Percentage contribution of the different factors to the total explained variability of V'maxFRC according to the sum of squares in the ANOVA analysis. Of the total variability, total explained variability was 35.7%.

\*p=0.038; \*\*p< 0.001.

210x212mm (600 x 600 DPI)