LETTER TO THE EDITOR

MEASUREMENT OF INTERRUPTER RESPIRATORY RESISTANCE AND SPIROMETRY IN PRESCHOOL CHILDREN: INFLUENCE OF RESPIRATORY SYMPTOMS

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Pulmonary function tests play an important role in the diagnosis and management of respiratory diseases in children. The purpose of the study was to evaluate lung function using the interrupter resistance technique (Rint) and spirometry (flow-volume and volume-time) in preschool children and to correlate the findings with respiratory symptoms. We studied 103 children (65 males, 38 females; mean age 5.2±0.7 years; range 3.6–5.8). For each child we collected family history concerning: respiratory diseases, skin prick tests, smoking during maternal pregnancy, history of gestational and neonatal period. All children performed lung function tests (Rint and spirometry) and skin prick test for inhalant and food allergens. Twenty-eight subjects (27.2%) had respiratory symptoms (RS). Expiratory Rint were performed in all subjects and spirometry was carried out on 76 children (73.8%). Spirometric indices were not statistically different between subjects without respiratory symptoms (controls) and RS children except for FEF_{25-75} expressed as a percentage of the predicted value (RS: 81.5±13.7% *vs* controls: 94.5±15.8%; p <0.001). Rint mean values were significantly higher in RS children than in controls (RS: 135.6 ±24.8% *vs* controls: 102.4 ±21.7%; p< 0.0001). We found a statistically negative correlation between Rint and the following spirometric indices: $FEV_{0.5}$ (R= -0.696; p < 0.0001), FEV_1 (R= - 0.728; p < 0.0001) and FEF_{25-75} (R= -0.681; p <0.0001). In preschool children with respiratory disease we found significantly higher mean values of Rint and lower FEF_{25-75} than in the control group and a significant negative relationship between Rint and spirometric indices.

Pulmonary function tests are an essential tool in the instrumental assessment of respiratory diseases and for understanding respiratory physiology in older children. They are useful to determine the severity of respiratory illness, progress over time and response to treatment.

Many lung diseases begin in early life and, partly to address this issue, the ERS and ATS task force published a statement on measuring lung function in preschool children (1).

The interrupter resistance technique (Rint) is an ideal lung function test on preschool children because is a non-invasive method for measuring respiratory resistance during tidal breathing. It requires minimal subject cooperation, is quick and well tolerated in children as young as 3 years (2-4).

With regard to spirometry, important studies assessing the feasibility and repeatability of the tests in preschool children have been conducted and have demonstrated that many children are able to perform

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the required maneuvers (5-8). The latest guidelines on standardization of spirometry emphasize that, with appropriate coaching, children as young as 5 years of age are often able to perform acceptable spirometry tests (1, 9).

Few studies have evaluated Rint in preschool children in relation to respiratory symptoms (cough and wheezing). McKenzie compared Rint before and after administration of a bronchodilator in preschool children with a history of wheezing, isolated cough and without respiratory symptoms (10). Brussee measured interrupter resistance in 4-year-old children with different wheezing phenotypes to identify children at high risk of asthma (11). In their study Mele et al. measured Rint in preschool children with a history of recurrent wheezing and found that it differed in asymptomatic and symptomatic children at the time of testing (12). But none of these studies measured both Rint and spirometry in preschool children in relation to their respiratory symptoms.

The aim of our study was to measure the baseline Rint and spirometry values in preschool children with a history of respiratory symptoms (RS) but without symptoms for a period of three weeks prior to the test, and to compare the results with those of a control group.

MATERIALS AND METHODS

The study was performed between October 2009 and June 2010 on 103 children, 65 males (M) and 38 females (F), mean age 5.2±0.7 years (range 3.6–5.8) attending kindergartens in the third district of Rome.

The school principals of the chosen kindergartens were interviewed by the research team and details of the study were explained. The study was approved by the local Scientific Ethics Committee. An invitation letter and an informed consent form were distributed to all parents of the participating children. Of 112 children screened, the parents of 108 subjects gave written informed consent to the performance of lung function measurements and skin prick tests (SPT) for their children. Five children with upper respiratory tract infection in the previous three weeks, three of them with bronchial asthma, were excluded.

Before performing the tests, a physician collected a medical history of each child, including habitual smoking in parents and smoking during the mother's pregnancy, neonatal period, atopy and respiratory disease (wheezing, recurrent or chronic cough). In particular, we classified subjects with respiratory symptoms: children known to have wheezed in past years and receiving no treatment; children with three episodes of recurrent cough in the last 6 months, but with no fever, upper respiratory tract infection, snoring or other illness and not receiving treatment. Chronic cough was defined as coughing every day for more than four consecutive weeks (13).

Twenty children were affected by persistent wheeze, one of whom had had bronchiolitis at six months of age, 6 children had recurrent cough and 2 children chronic cough. Seventy-five children had no history of wheeze, or of recurrent or chronic cough. No child enrolled in the study had previously been diagnosed as having asthma or used bronchodilators. All children were free from respiratory symptoms and had not been receiving treatment for at least 3 weeks prior to undergoing the lung function tests.

SPT for common aero (house dust mites, grass pollens, cupressus, mould, olea, cat and dog danders) and food (fish, milk, eggs, wheat and soya) allergens and histamine and saline controls (Lofarma, Milan) were carried out on the children prior to performing the lung function tests. A wheal of > 3 mm to one prick classified a subject as SPT-positive. Height and weight were measured prior to carrying out Rint and spirometry. Standing height without shoes was measured using the standard stadiometer to the nearest 0.1 cm. Body weight was measured with the lightest clothing to the nearest 0.1 Kg on a mechanical scale. Lung function tests were performed using a commercial device, Cosmed Quark PFT4 Ergo (Rome, Italy) in accordance with ATS-ERS statements (1). Before each Rint and spirometry test, volume and flow were calibrated using a precision 3-liter syringe. After giving a few simple explanations, the procedure was demonstrated to each child by the physician. The Rint measurement was taken with the child sitting comfortably and willingly, during quiet spontaneous respiration, using a disposable mouthpiece with an antibacterial filter device with a dead space of 30 ml (Cosmed, Rome, Italy). The child was instructed to put the nasal clip in place, close the lips around the mouthpiece and place the tongue under the mouthpiece. The researcher supported the child's face and chin in order to avoid energy loss and reduce the effect of upper airway compliance. The head was held in a neutral position. The measurements were taken by researchers trained in the method. During the test the children watched a cartoon. This was intended to reduce anxiety and avoid abnormal respiration. All children, enrolled in the study, performed Rint correctly.

The respiratory resistance measured by Rint was calculated as the ratio of alveolar pressure, estimated from mouth pressure during occlusion, to flow before interruption. Ten-fifteen airflow interruptions were performed sequentially at the peak flow of an unforced expiration, in ten consecutive respiratory cycles, and obtained during a technically satisfactory measurement session.

After a period of quiet breathing, in response to a trigger during expiration at the peak of tidal flow, a single shutter closed automatically within 10 msec and stayed closed for 100 msec. In this study 10-15 occlusions were performed and the median of five technically acceptable values was considered a measurement of Rint. Measurements were excluded when there was an air leakage or when children, instead of quietly breathing, inspired or expired vigorously.

Rint was performed during expiration before spirometry, as the deep inspiration preceding the forced expiratory maneuver required to perform spirometry could influence the bronchial tone.

The children performed spirometry whilst standing, using mouthpieces with a disposable antibacterial filter device (dead space, 30 ml) and a nose clip. With computer incentive games we obtained for each child: forced expiratory vital capacity (FVC), forced expiratory volume in 0.5 second ($FEV_{0.5}$), forced expiratory volume in the first second (FEV_1), $FEV_{0.5}$/FVC ratio, FEV_1/FVC ratio, forced expiratory flow between 25 and 75 % of FVC (FEF_{25-75}) and maximal peak expiratory flow (PEF). The session ended after three technically acceptable maneuvers or a maximum of 15 minutes. From all the acceptable curves, we considered those in which the sum of FVC and FEV_1 was greatest, and where the maximum forced expiratory time was longer than 1 second in order to reach the residual volume or at least approach it. Overall, 76 children performed the spirometry correctly, while 27 children (26.2%) failed to do so, 18 of whom were aged under 4 years. Two children refused to perform or complete the test; the session was terminated immediately and no further attempt was made to complete the test.

All statistical calculations were performed using SPSS for Windows version 18.0 (SPSS, Inc., Chicago, Illinois, USA).

Data were expressed as absolute values and percentages of normal values compared with predicted reference equations obtained by algorithms based on age, sex, height and weight (14). Baseline Rint is reported as measured values, percentages of predicted values and Z-scores calculated using published reference values (15).

Values were further calculated as z scores from healthy children (z score is the number of Standard Deviations that a value deviates from the expected mean value of healthy subjects).

The significance of differences between the two study groups was tested using Student's two-tailed unpaired *t*-test. Results were expressed as mean ± standard deviation and range. Linear regression tests assessed with Spearman's rank test were used to search for relationships between the lung function indices in children with respiratory symptoms and controls.

RESULTS

One hundred and three children were studied, 28 of whom were RS children (F: 10 – M: 18) and 75 were controls (F: 28 – M: 47). No statistically significant age and anthropometric parameters differences were observed between RS and Control group. In particular the mean values, standard deviations and range were: age (years) = RS: 5.2±0.7 (3.8-5.9) *vs*

Table I. *Baseline Rint values measured in all subjects.*

Variable	**MEASURED VALUES**		
	RS 28	**Controls 75**	**p <**
Rint kPa · L^{-1} · s^{-1}	1.48±0.34 (0.87-2.10)	1.05±0.32 (0.38-1.70)	0.0001
Rint % predicted	135.6±24.8 (83.2-214.5)	102.4 ±21.7 (86.7-120.3)	0.0001
Rint Z-score	1.12±0.97 (- 0.05 +1.29)	0.21±0.82 (-0.29 +0.98)	0.0001

Data are expressed as Mean ± SD (range)

Table II. *Baseline Spirometry values measured in 76 subjects.*

Variable	MEASURED VALUES		
	RS 21	Controls 55	p <
FVC (L)	1.32±0.24 (0.9-1.9)	1.38±0.27 (0.8-1.9)	n.s
FVC (% predicted)	91.8±9.8 (66.5-108.6)	93.8±12.6 (72.5-117.6)	n.s
FVC (z-score)	0.08±1.3 (-0.16 +1.2)	0.19±0.19 (-0.18 +1.3)	n.s
$FEV_{0.5}$ (L)	0.96±0.25 (0.5 - 1.6)	1.02±0.29 (0.4 - 1.7)	n.s
$FEV_{0.5}$ (% predicted)	87.4±5.20 (78-98.8)	91.7±10.6 (74-111.6)	n.s
$FEV_{0.5}$ (z-score)	0.31±1.5 (-0.23 +1.4)	0.12±1.6 (0.14 +1.3)	n.s
FEV_1 (L)	1.24±0.25 (0.8-1.8)	1.28±0.28 (0.5-1.8)	n.s
FEV_1 (% predicted)	91.9±10.02 (68.9-108.6)	92.9±11.6 (71.5-115.1)	n.s
FEV_1 (z-score)	-0.12±1.3 (-0.25 +1.2)	0.10±1.2 (- 0.11 +1.4)	n.s
$FEV_{0.5}$/ FVC	0.74±0.7 (0.68- 0.87)	0.72±0.6 (0.65-0.85)	n.s
$FEV_{0.5}$/ FVC (z-score)	0.32±1.6 (-0.29 +1.4)	0.23±1.4 (-0.21 +1.3)	n.s
FEV_1/ FVC	0.88±0.9 (0.74-0.93)	0.91±0.8 (0.79-0.95)	n.s
(FEV_1/ FVC (z-score)	-0.23±0.78 (-0.33 +1.4)	-0.06±0.45 (-0.12 + 0.9)	n.s
PEF (L/s)	2.22±0.85 (0.9-4.3)	2.33±0.69 (1.1-4)	n.s
PEF (% predicted)	92.5±8.5 (68.5-107.8)	93.2±11.1 (61.5-110)	n.s
PEF (z-score)	1.5±0.89 (-0.22 +1.5)	1.8±0.78 (-0.31+1.4)	n.s
$FEF_{25-75\%}$ (L/s)	1.07±0.50 (0.5-2.3)	1.48±0.37 (0.7-2.5)	0.0002
$FEF_{25-75\%}$ (% predicted)	81.5±13.7 (45.7-100.1)	94.5±15.8 (40.0-114.3)	0.001
FEF25-75% (z-score)	-1.25±1.19 (-2.23 +1.76)	0.12±1.16 (-0.51 +1.23)	0.0001

Data are expressed as Mean ± SD (range)

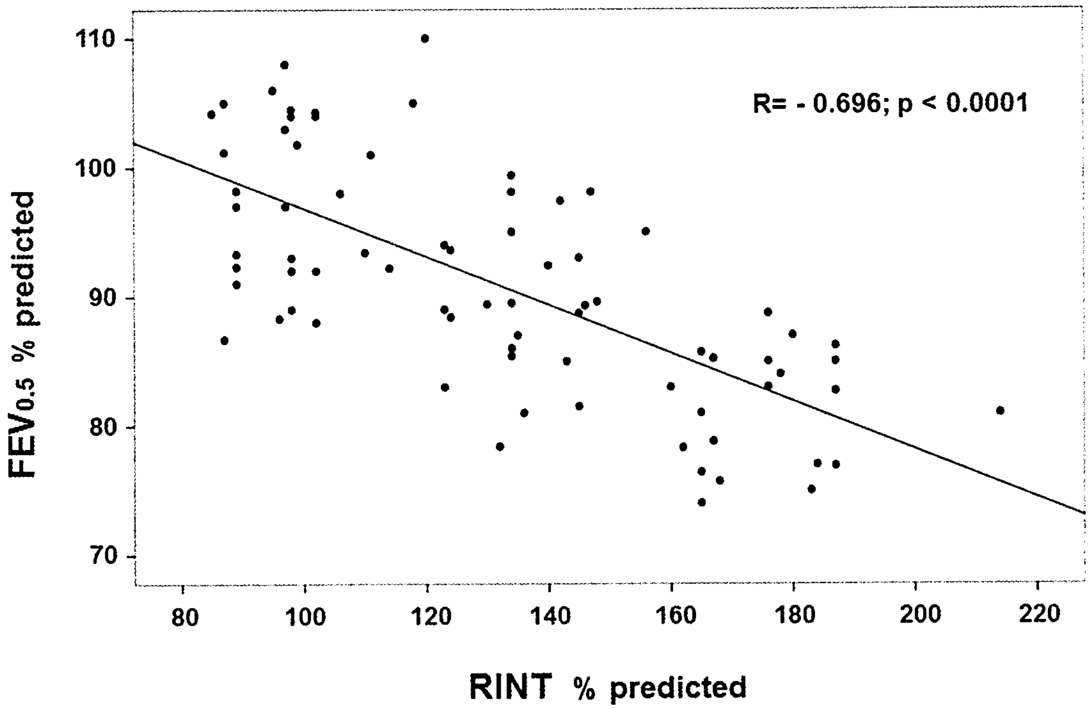

Fig. 1. *Correlation between FEV0.5 and Rint in 76 children.*

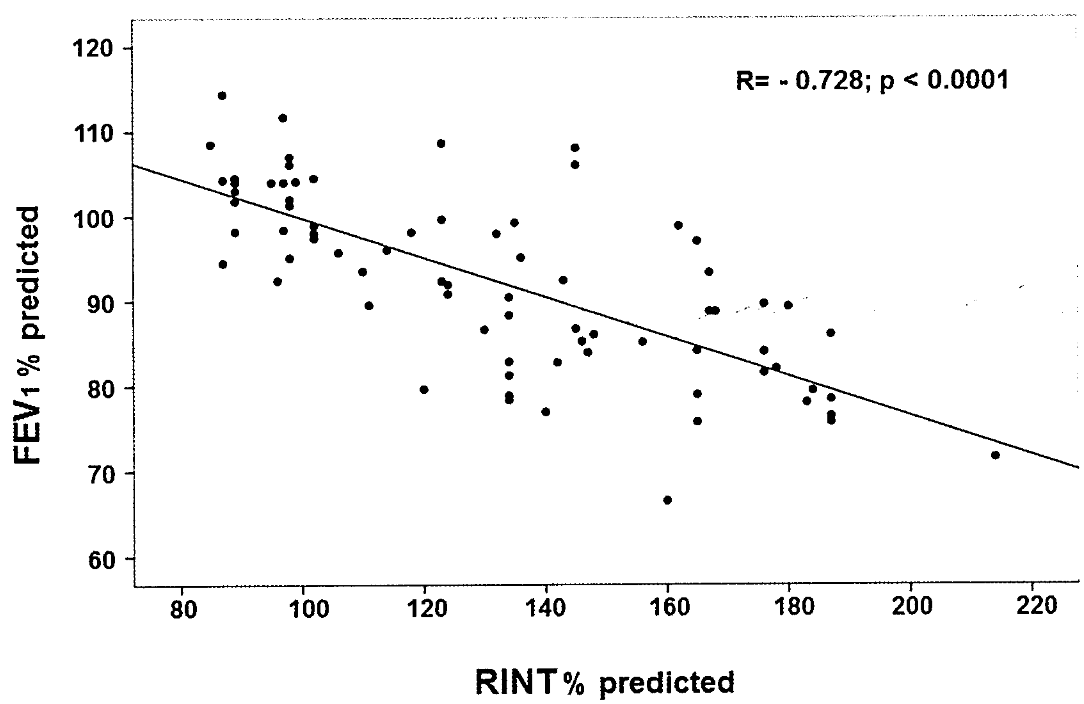

Fig. 2. *Correlation between FEV1 and Rint in 76 children.*

Controls: 5.1±0.7(3.6-5.8) p =n.s.; Height (cm) = RS: 112.4±8.7 (97-128) *vs* Controls: 112.6±8.5 (97-125) p=n.s.; Weight (kg)= RS:19.9±3.9 (14.8-31) *vs* Controls: 20.9±4.2 (14-33) p=n.s.; Body Mass Index (Kg/m^2) = RS:15.63±1.5 (13-18.2) *vs* Controls: 16.5±2.2 (12-22.5) p=n.s.

Of all subjects 29 children (28.1%) had positive skin prick tests, 20 of whom had respiratory symptoms. The most common allergens were dust mites (in 70% of the subjects), followed by grass pollens in 35% and cupressus in 25%. We observed no differences in lung function tests in relation to atopy. In particular, the mean Rint, expressed as percentages of predicted values, did not differ significantly between children with positive and negative skin prick tests, which were respectively 105.5±12.3% *vs* 97.4±13.4 %; p = ns. In all subjects the gestational birth age was between 37 and 42 weeks. Birth weights were similar in both groups (RS: 3231±399 g and control: 3242±461 g; p = n.s.). Only three parents of control group and one parent of RS children declared habitual smoking.

The spirometric indices (Rint, FVC, $FEV_{0.5}$, FEV_1, $FEV_{0.5}$/FVC ratio, FEV_1/FVC ratio, FEF_{25-75}) were all normally distributed.

Table I shows that mean values of Rint were significantly lower in controls than in RS children. The mean Rint values, as absolute values and percentages of predicted values and z-scores, of RS children and controls were similar in both sexes.

Table II shows that mean values of FEF_{25-75}, expressed as absolute values and percentages of predicted values and z-scores, were significantly higher in controls than in RS children. Other mean spirometric values were not statistically different. We observed no differences between the sexes in the spirometric indices, expressed as absolute values and as percentages of predicted values and z-scores, for preschool children in this study.

We found a significant negative correlation between Rint and the following spirometric indices (expressed as percentages of predicted values): $FEV_{0.5}$ (R= -0.696; $p < 0.0001$), FEV_1 (R= -0.728; $p < 0.0001$) and FEF_{25-75} (R= -0.681; $p <0.0001$). Figs. 1 and 2 show the correlation between Rint and $FEV_{0.5}$ and FEV_1 (expressed as percentages of predicted values). When the two groups of children (21 RS and 55 controls) were examined separately the significant negative relationship between Rint and spirometric values (as percentages of predicted values) was confirmed: RS = $FEV_{0.5}$ (R= -0.549; $p < 0.01$), FEV_1 (R= -0.695; $p < 0.001$) and FEF_{25-75} (R= -0.522; $p <0.01$); control = $FEV_{0.5}$ (R= -0.612; $p < 0.001$), FEV_1 (R= -0.761; $p < 0.0001$) and FEF_{25-75} (R= -0.381; $p <0.01$).

DISCUSSION

The main results of the present study indicate that children with a history of respiratory disease show significantly higher mean values of Rint and lower FEF_{25-75} than controls, expressed as absolute values, as percentages of predicted values and as z-scores. We also observed a significant negative relationship between Rint and $FEV_{0.5}$, FEV_1 and FEF_{25-75} when expressed as absolute values and as percentages of predicted values.

In the present study only three parents of control group children and one parent of an RS child declared habitual smoking. An Italian study (SIDRIA) has shown that the proportion of families with at least one parent smoker is about 50%, and this is associated with a greater risk for respiratory diseases (16).

In our opinion the fact that only 3.9% of parents admitted to smoking cigarettes in the presence of their children appears somewhat implausible. A possible explanation is that some parents deny their smoking habit because of the associated negative cultural and social considerations and the known harmful effects on the health of their children.

The RS children also present high mean values for Rint because the airway obstruction, confirmed by a reduced FEF_{25-75}, can decrease the diameter of the intrapulmonary airways and contribute to the higher resistance during expiration.

It is important to underline that Rint and spirometry reflect different physiological bases of the two techniques, the former being obtained during tidal breathing and the latter from a forced expiratory maneuver. Rint measures a combination of the resistance of the airways, lung tissue and chest wall (the total respiratory resistance), while spirometry measures the volume and flow of air that can be inhaled and exhaled through the airways and, in particular, assesses the airway caliber (9). Measurements of respiratory mechanics during tidal breathing may not always correlate with those recorded during forced expiratory flow. These features could explain the absence of the relationship between Rint and some spirometric indices (FVC and PEF).

Moreover, Turner et al. found a relatively poor specificity of FEV_1 for asthma symptoms in 5-year-old children (17). Thus, the evidence suggests that FEV_1 may not be particularly sensitive to asthma symptoms in asymptomatic individuals across all age groups. Despite their increased variability, measurements of mid-expiratory flows (FEF_{50}) may be more clinically informative than FEV_1 in young children with asthma.

Spirometry is different in preschool children and in adults. Young children have small absolute lung volumes and large airway size relative to lung volume compared with older children and adults. The descending limb of the flow-volume curve is convex in young children, on account of the rapid interruption of flow towards the end of the forced expiration, which is completed in a shorter time (18, 19). For these reasons FEV_1 may not always be successfully obtained in preschool children. Other studies have explored the usefulness of $FEV_{0.5}$ or $FEV_{0.75}$ as outcome measures in this age group (14, 19). In the present study all preschool children were able to execute Rint correctly and the majority of children (73.8%) accurately performed a reproducible spirometry, with no prior training, that met the quality-control criteria recommended by the ATS/ERS guidelines. The latter data are consistent with the findings of other authors who have reported success rates of between 60% and 76% in preschool children (7, 14, 19, 20).

The major limiting factor in the use of spirometry in preschool children is the limited availability of reference values. The correct usage of appropriate reference equations is essential to an accurate interpretation of results, in order to separate the effects of disease from those of growth and development. Reference spirometry values in preschool children were recently published by Stanojevic et al. (21). It is necessary to specify that the reference equations for $FEV_{0.5}$ and PEF are based on a relatively small sample of children.

To our knowledge, the present study is the first to evaluate Rint and spirometry in preschool children in relation to respiratory symptoms, but the major limitation is the lack of an assessment bronchodilator response (BDR).

Mckenzie et al. measured Rint before and after salbutamol treatment in three groups of children: recurrent wheeze, isolated cough and no symptoms (control subjects). The mean values of Rint were significantly higher in children with wheezing, while children with recurrent cough did not differ significantly from control subjects. The authors suggest that the children with cough and with a high salbutamol response could represent a "cough-variant" asthma (10).

Brussee et al. compared Rint in 4-year-old children with different wheezing phenotypes. In this study children with persistent wheeze had significantly higher mean Rint values than children with no wheezing. The authors suggest that their findings are consistent with the hypothesis that children with persistent wheeze are at high risk of asthma, with increased resistance (11).

In conclusion, we confirm that the interrupter resistance technique can be performed easily in preschool children and that reproducible spirometry values can be obtained in the majority of preschool children. We found that preschool children with a history of respiratory disease show significantly higher mean values of Rint and lower FEF_{25-75} than the control group, and we also observed a significant negative relationship between Rint and spirometric values ($FEV_{0.5}$ and FEV_1).

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