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GENERALIZABILITY OF REGRESSION MODELS FOR THE FEV_1-MEASUREMENTS IN ASTHMATIC CHILDREN

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Abstract

Large scale asthma studies often rely on measurements of lung function such as the forced expiratory volume in one second (FEV_1) to assess severity of asthma. However, it is generally accepted that prediction equations derived in populations from one ethnic group are not generalizable to other self designated ethnic populations (reference PubMed ID 1952453). It is therefore possible that using percent of predicted FEV_1 as a metric of lung function may not be optimal for population-based studies. We examined this formally using data from the Childhood Asthma Management Program (CAMP), a multicenter, randomized, clinical trial including 1,041 children with mild to moderate asthma. New prediction equations for FEV_1 were developed for each of three self designated ethnicities (Caucasian, African American, and Hispanic). The correlations between residuals for each of the new regression models and the standard percent of predicted FEV_1 based on normal self designated Caucasians were examined. There was a strong correlation among the residuals of all of the percent

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predicted models based on this data set; however, correlation between the standard percent of predicted FEV_1 based on normal subjects and all ethnic specific models was low. Therefore, percent of predicted FEV_1 based on normal subjects is not an optimal phenotype for this study. Since FEV_1 depends on a variety of factors such as height, weight, environmental exposures, genetics, etc., direct adjustment for the relevant covariates rather than indirect adjustment using percent of predicted FEV_1 may be the most useful measurement in large scale asthma studies.

Introduction

In the US, ten million children under 16 have asthma [1]. A defining characteristic of asthma is intermittent bronchoconstriction and airway inflammation with subsequent small airway obstruction, characterized by episodes of wheeze and breathlessness. Asthma is a heterogeneous disorder, caused by complex interactions between genetic and environmental factors. For researchers searching for genetic components that increase risk for this disease, it is helpful to identify more homogenous subsets of patients, for example, based on asthma severity. Moreover, in order to have sufficient power for their statistical tests, researchers often do initial screening by dividing subjects into the two groups to be tested separately.

One of the tests of lung function frequently used to measure severity is forced expiratory volume in one second (FEV_1). FEV_1 is the volume of air that one can forcefully exhale in a sustained breath measured at one second. FEV_1 is used to diagnose airway obstruction, to assess the effectiveness of treatment, and for the general monitoring of lung function. FEV_1 is also used in the evaluation of airways responsiveness. Due to the dependency of FEV_1 on age, sex, and height, FEV_1 is typically expressed as percent of predicted values, based on sex stratified regression equations derived in large populations. Percent of predicted FEV_1 is determined by the equation

$$\text{Percent of Predicted } FEV_1 = \frac{FEV_1}{\text{Predicted } FEV_1} \times 100,$$

where general form of the regression equation for predicted FEV_1 is

$$Y = \beta_0 + \beta_1 \text{ age} + \beta_2 \text{ height} + \beta_3 \text{ height}^2.$$

Despite relying on this calculation to determine whether children are within the normal limits of lung function, separate models are required for distinct self designated ethnic groups. As a result, it is unclear whether percent of predicted FEV_1 can reliably be used to perform large scale population based studies of lung function in cohorts of mixed ethnicity.

In this study, data from the Childhood Asthma Management Program were used to compare percent of predicted FEV_1 based on normal Caucasian children to other prediction equations in asthmatic children of three ethnicities (Caucasian, African American, and Hispanic) with mild to moderate asthma. The goal was to determine the usefulness of percent of predicted FEV_1 as a measurement of lung function in large scale asthma studies. If percent of predicted FEV_1 is a valid measurement of lung function, then there should be a high correlation between it and the residuals of FEV_1 predicted by regression models based on this well defined study population, that is, both percent of predicted FEV_1 and the new regression models should rank subjects' lung function similarly.

Methods

The design and methods of the research program have been described previously by Childhood Asthma Management Program Research Group [1].

The Childhood Asthma Management Program was a multicenter, randomized, clinical trial including 1041 children. Children between 5 and 13 years of age with mild to moderate asthma were enrolled. Data on the subjects' gender, age, ethnicity, weight, height, FEV_1, and percent of predicted FEV_1 were used to create prediction equations. Percent of predicted FEV_1 values were derived using the equations derived by Coultas et al. [2] for normal Hispanic subjects and equations derived by Knudson et al. [3] for normal Caucasian and normal African American

subjects. Multiple regression was done separately for Caucasian asthmatic children ($n = 711$), African American asthmatic children ($n = 138$), and Hispanic asthmatic children ($n = 98$). The covariates tested were gender, age, age^2, weight, weight^2, height, and height^2. Height and height^2 were centralized by subtracting the mean to reduce colinearity. Prediction equations were produced using forward regression, backwards regression, adjusted R^2 regression, and using the set of covariates that percent of predicted uses (i.e., age, height, and height^2) with an additional term for gender. The residuals of each model were graphed against every other model's residuals and against percent of predicted FEV_1 to assess correlation visually. All analyses were performed using the Statistical Analysis System.

Results

Some variation among ethnicities can be seen in the coefficients of the prediction equations using the covariates of the percent of predicted model (Table 1). Table 2 presents the correlation between predicted FEV_1 and each covariate for each of these models. The correlation between predicted FEV_1 and the height squared covariate varies considerably across the models, indicating that the relative importance of this covariate depends on ethnicity. Similarly, age and gender also vary across ethnicity. The age coefficient also changes sign; it is positive in the Africa American model and negative in both the Caucasian and Hispanic models.

Table 1. Regression equations for FEV_1 in asthmatic children 5-13 years of age by ethnicity

Ethnicity	Constant	Coefficient for Height-Mean Height (cm)	Coefficient for (Height-Mean Height)^2 (cm^2)	Coefficient for Gender	Coefficient for Age
Caucasian	1.61734	0.02979	0.00021479	0.03549	0.01957
African American	1.77943	0.03699	0.0001846	0.02821	– 0.02603
Hispanic	1.6091	0.03081	0.00025498	0.07205	0.01542

Table 2. Correlation between predicted FEV_1 and each covariate for models with height, gender, and age fitted to each ethnicity

Ethnicity	Coefficient for Height-Mean Height (cm)	Coefficient for (Height-Mean Height)^2 (cm^2)	Coefficient for Gender	Coefficient for Age
Caucasian	0.9937	0.20103	0.00611	0.91354
African American	0.99482	0.49587	– 0.00208	0.86293
Hispanic	0.98249	0.53145	0.13199	0.82146

The regression equations from three selection methods for each ethnicity are given in Table 3. Notice that the adjusted R^2 selection method and the forward selection method yielded the same model (Table 3). The stability in models for Caucasian asthmatic children may be a result of the very large sample size $(n = 711)$.

Table 3. Regression equations for FEV_1 in asthmatic children 5-13 years of age by ethnicity using three selection methods

Selection Procedure	Constant	Coefficient for Height-Mean Height (cm)	Coefficient for (Height-Mean Height)^2 (cm^2)	Coefficient for Gender	Coefficient for Age	Coefficient for Age^2	Coefficient for Weight (kg)	Coefficient for Weight^2 (kg^2)
Caucasian								
Adjusted R^2	1.31818	0.02624	0.00023982	0.03893	0.02217	-	0.01191	–0.00010201
Forward	1.31818	0.02624	0.00023982	0.03893	0.02217	-	0.01191	–0.00010201
Backward	1.48415	0.02713	0.00019746	0.0382	0.02197	-	0.00345	-
African American								
Adjusted R^2	1.67793	0.03677	0.00020011	-	-	–0.00139	-	-
Forward	1.73578	0.03871	0.00022982	0.02648	-	–0.0015	–0.00201	-
Backward	1.56831	0.03323	0.000188	-	-	-	-	-
Hispanic								
Adjusted R^2	1.75362	0.0328	0.00024346	0.06913	-	-	-	-
Forward	1.67695	0.03082	0.00024473	0.07152	-	0.00086	-	-
Backward	1.79792	0.03279	0.00025576	-	-	-	-	-

Standardized residuals from the adjusted R^2, forward, and backward selected models were plotted against each other for each ethnicity (see figures at end of document). All the models built using the CAMP data had linearly related residuals, that is, they would rank the children in nearly the same order with respect to predicted FEV_1. None of the models showed nearly the same degree of correlation with percent of predicted FEV_1. The greater variability in the African American models and especially the Hispanic models in comparison to the Caucasian models is a result of smaller sample size.

Discussion

Different models are needed for predicting FEV_1 in different ethnicities. Table 2 shows that covariates varied in importance among the ethnicities studied. This implies that the raw percent of predicted FEV_1 cannot reliably be used for evaluation of the determinants of lung function in populations of mixed ethnicity. Height and Height^2 were the only covariates included in every model; they are likely the most important factors in predicting FEV_1 (Table 3).

Regardless of the selection method utilized, models based on the CAMP dataset provided similar rankings of residuals. This is apparent because there was a strong correlation between the residuals of any model based on CAMP data and any other model based on CAMP data for the same ethnicity.

Although all model selection procedures yielded regression models that strongly correlated with one another, none were strongly correlated with percent of predicted FEV_1 measurements for normal subjects. Thus, percent of predicted FEV_1 in normals is not an optimal model for this study. Raw FEV_1 is not an easy measurement to predict since it depends on so many different factors. Given the difficulty inherent in predicting FEV_1 percent predicted FEV_1 from normal regression equations may not be an ideal measure of lung function, unless it is

adjusted within the study. The applicability of FEV_1 should be further explored using other large datasets.

References

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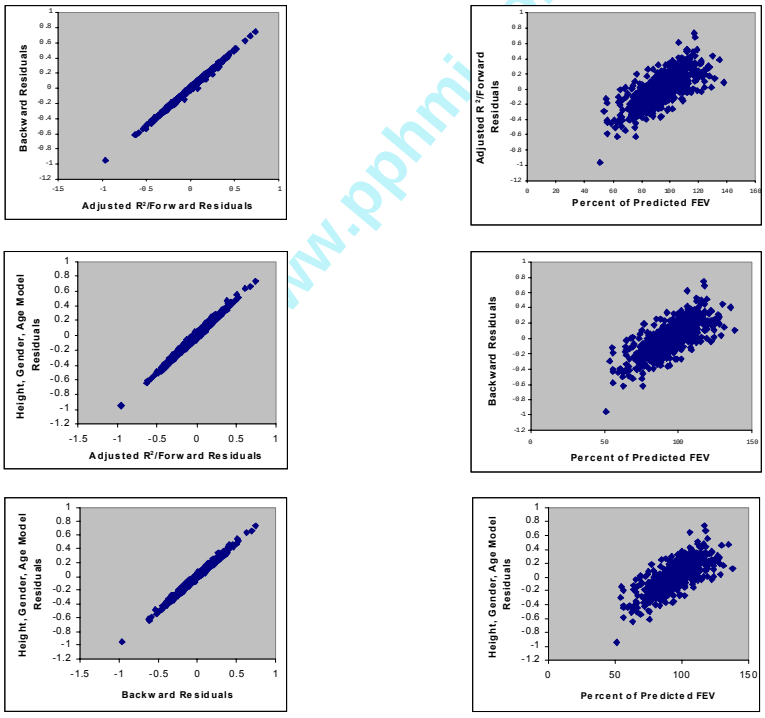
[3] R. F. Knudson, M. D. Lebowitz, C. J. Holberg and B. Burrows, Changes in the normal maximal expiratory flow-volume curve with growth and aging, Am. Rev. Respir. Dis. 127 (1983), 725-734.

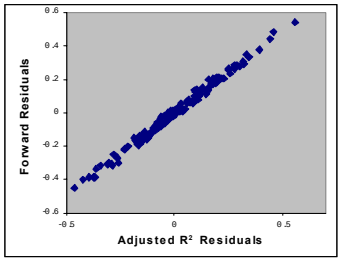
Figures

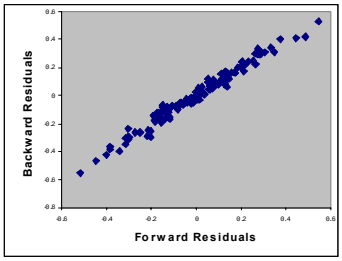
Correlation between **Caucasian** Model Residuals and PPFEV

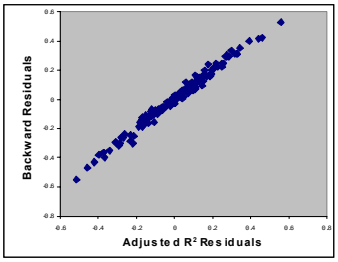
Note. Only 6 graphs are shown here since some of the models were the same (see text).

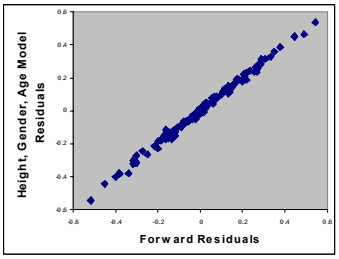


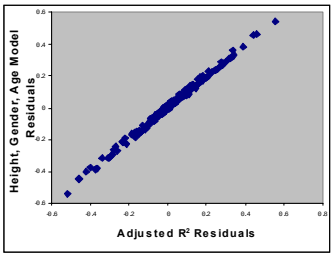
Correlation Between **African American** Model Residuals

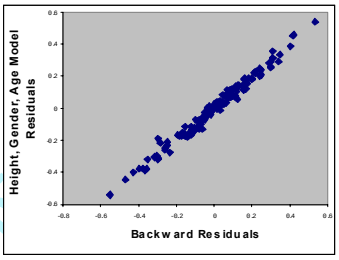




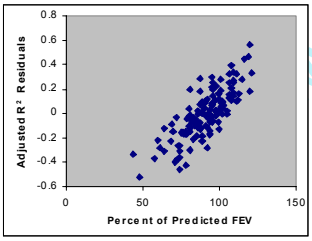


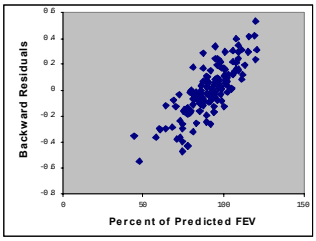


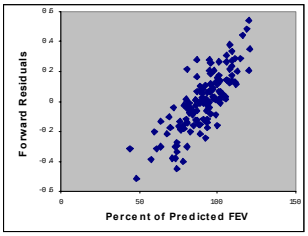


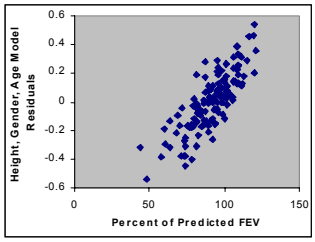


Correlation Between **African American** Model Residuals and PPFEV

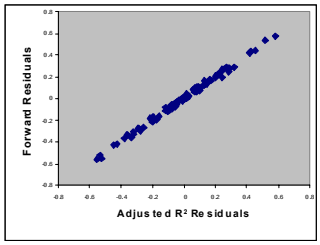


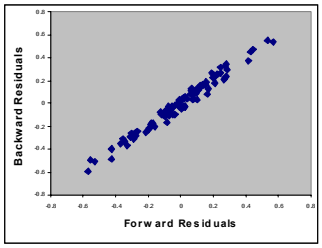


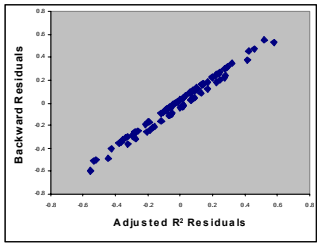


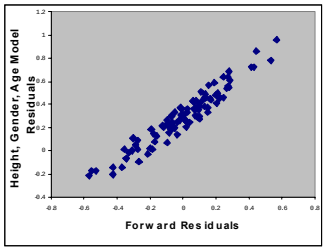


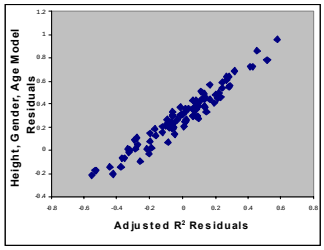
Correlation Between **Hispanic** Model Residuals

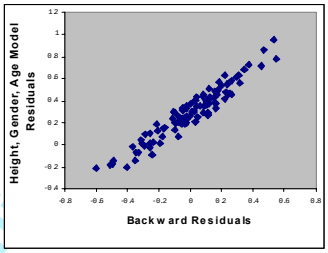












Correlation Between **Hispanic** Model Residuals and PPFEV