Continuous Reference Ranges for Spirometry from Childhood to Adulthood

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The child first and always

Background

- Clinical interpretation of spirometry results requires appropriate reference data
- Reference equations based on the NHANES III survey (Hankinson, AJRCCM 1999) are amongst the most recent and representative 'all age' references available and are widely used across the USA.
- However,
  - the survey was limited to children >8 years of age, thereby limiting use of these equations in the paediatric population
  - a continuous reference equation could not be produced across the entire age range

Aims

To develop more appropriate spirometry reference equations, with a smooth transition from childhood to adulthood

Data

- Spirometry data (FEV_1 and FVC) from the Caucasian NHANES III survey were supplemented with three paediatric datasets to include children <8 years of age giving:
  - USA: n=2274, 8-80 years (Hankinson, AJRCCM1999)
  - Britain: n=769, 4-18 years (Rosenthal, Thorax 1993)
  - Belgium: n=316, 5-18 years (Lebeque, Ped Pulm 1991)
  - Canada: n=248, 5-20 years (Corey, Am Rev Respir Dis 1976)
- The final dataset comprised of 3607 Caucasians aged 4-80 yrs

Analysis

The LMS method, widely used to construct national growth references (Cole, Stat Med 1992) is an extension of regression analysis which includes three parameters 1) the median 2) the coefficient of variation (spread of values around the median) and 3) the skewness.

The LMS method was applied using the GAMLSS package (Rigby, Stat Med 2004) in the statistical programme R to allow for modelling of more than one co-variable, in this case height, age and between-centre differences.

The resulting median, variability and skewness were combined algebraically to determine a height-age-sex adjusted SD score (z-score or centile).

Results

The Effect of Height

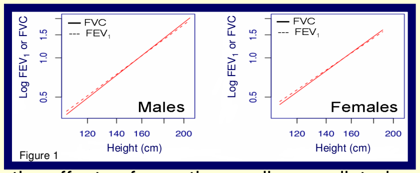

Figure 1

After adjusting for the effects of age, the median predicted values for FEV_1 and FVC had a strong and non-linear relationship with height. Using a log-log scale this relationship was linear with a slope of 2.5 (Figure 1).

The Effect of Age

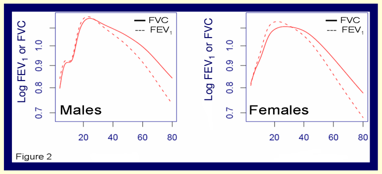

Figure 2

After adjusting for the effects of height, there was an important and **complex relationship with age**, such that lung function improves until early adulthood and subsequently declines (Figure 2), accompanied by age related changes in FEV_1/FVC

Between Subject Variability

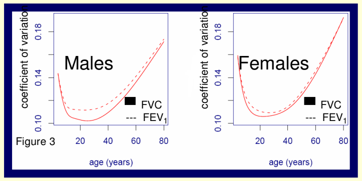

Figure 3

Age is also important for describing the between-subject variability. Expressed as the coefficient of variation (CV), variability decreases until puberty, plateaus in young adults and then increases in later life (Figure 3).

This finding has important implications with respect to age related differences in the lower limit of normal which are used to define clinically significant reductions in lung function. This is especially true in young children and the elderly where the range 80-120% predicted, corresponding to a CV of 0.11, is likely too narrow.

Discussion

We demonstrate how to construct child-to-adult reference curves using a single smoothly changing model to explain the complex relationship between lung function, height and age during puberty and early adulthood.

By extending NHANES III down to 4 years of age and developing smoothly changing curves, these models can be applied across both paediatric and adult settings to interpret spirometry results more accurately.

Using a log-log model to describe the combined effects of age and height we were able to model a proportional and biologically plausible relationship between age, height and lung function to make better adjustment for changes during puberty.




Future Work

Future work will include producing user-friendly and equipment-compatible software to interpret results. These methods can be applied to other datasets or populations and could be extended to the new NHANES IV survey.

Larger collaborative initiatives could further improve the precision and generalisability of these models by combining data from several population surveys.

Conclusions

GAMLSS provides an elegant solution to a complex and longstanding problem: fitting age-height trends to child-adult lung function data. Implementation, facilitated by user-friendly software, will allow for more meaningful interpretation of both cross-sectional and longitudinal pulmonary function results.

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