Can changes in spirometry over time be interpreted using cross-sectional reference data?

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Background

Serial spirometry measurements can facilitate identification of individuals with rapid lung function decline. Cross-sectional reference data describe a population at one point in time and do not necessarily reflect how individuals change over time. In clinical practice, repeated measurements are commonly interpreted using cross-sectional reference data.

Aims

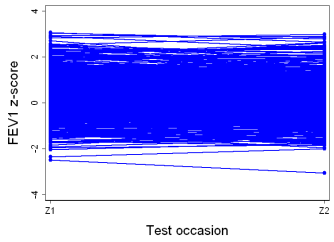
To adjust for the correlated nature of repeated measurements in order to interpret changes over time using cross-sectional reference data.

Study Population

938 healthy white subjects (age 6-18y) were measured twice. FEV_1 z-scores were calculated using "all-age" reference equations (Stanojevic et al., AJRCCM 2008)

Variability within subjects

Normal lung growth can be viewed as roughly a constant Z-score ($Z_1 = Z_2$) over time. The change in Z-score is described as Z_2-Z_1. The graph shows time changes in the subjects.



Mean (SD)
Z_1 0.4 (0.9)
Z_2 0.2 (0.9)
Z_2-Z_1 -0.2 (0.4)

Tracking

The uncertainty (SD) around the change ($Z_2 - Z_1$) is normally distributed around a mean change of ~ 0 Z-scores and depends on the correlation (r) between Z_1 and Z_2

The correlation coefficient (r) depends on:
1) The measurement error and biological variability
2) The time interval between Z_1 and Z_2

In this study **r = 0.89** over a one year interval, indicating strong tracking

Z-score for change (Z_c)

From this we can calculate a Z-score for change (Z_c). This can be used to identify individuals whose lung function changes more than that observed in health

The Z_c considers:
- the **change in Z-score**
- the baseline result (Z_1)
- the correlation (r) expected for the specific time interval

$$Z_c = \frac{(Z_2 - Z_1) + (1-r) \times Z_1}{\sqrt{1-r^2}}$$

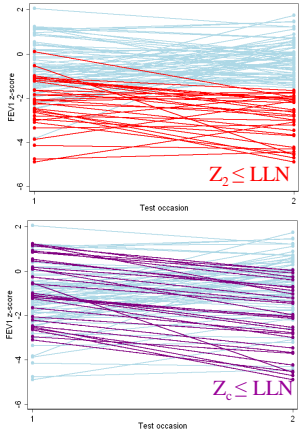
This includes an adjustment for **regression to the mean,** whereby extreme values are expected to be nearer to the median on the second test occasion

It also incorporates a scaling factor to give an SD of 1, such that Z_c is normally distributed (mean (0), SD (1)) and the **lower limit of normal (LLN) for Z_c is -1.645**

Clinical Application

Data from 98 children with cystic fibrosis (age 6 -16y) measured on two occasions one year apart were used to demonstrate the clinical application of Z_c

Z_c identifies changes in lung function



	Abnormal $Z_c \leq$ LLN	Normal $Z_c >$ LLN
Abnormal $Z_2 \leq$ LLN	17	14
Normal $Z_2 >$ LLN	14	53

Z_2 and Z_c each identified 31 subjects as abnormal (≤ LLN). A combination of both cut-offs identified 45 subjects as abnormal

14 subjects classified as 'normal' using Z_2 (cross-sectional cut-off) had significant lung function decline using Z_c (longitudinal cut-off)

An additional 14 subjects had abnormal spirometry ($Z_2 \leq$ LLN) but did not

Clinical Example

Test 1
Age: 10 years
Height: 140cm
FEV_1 = 2.07 L
Z_1 = 0.19
%predicted = 102%

Test 2
Age: 11 years
Height: 150cm
FEV_1 = 2.22 L
Z_2 = -0.65
%predicted = 93%

Z_2-Z_1 = 0.84
Z_2 = -0.65 > LLN
Z_c = -1.81< LLN

The subject appears to be normal (Z_2>LLN) but had significant lung function decline (Z_c<LLN) between the two test occasions

Conclusions

Z-score for change (Z_c) is an additional tool for interpreting repeated spirometry results

Z_c takes into account the expected within-subject variability in health as well as the patient's prior lung function

Zc is more sensitive than cross-sectional Z-scores for detecting lung function deterioration

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