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Original Article: Diagnostic Testing

Correcting standardised expiratory flows for prematurity in ex-preterm survivors – is it necessary?[1]

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in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Keywords: lung function, correction for prematurity, infant

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Abstract

Objective: To determine the effect of correcting for prematurity on standardised values for expiratory flow rates for participants from 5 years through to 70 years of age.

Methods: In a theoretical model we assumed starting values for expiratory flows that were expected to give ranges within +/-2 SD. Keeping expiratory flows, ethnicity and height constant, we then determined how z-scores varied between 5 and 16.9 years, and, with two different fixed values for height and expiratory flows, between 16 and 70 years of ages, for both sexes. In a clinical example, we compared expiratory flows with age both corrected and uncorrected for prematurity between 144 survivors born extremely preterm and 141 term-born controls at both 8 and 18 years of age.

Results: In the theoretical models, z-scores mostly declined through childhood until the late teenage years, and then began to rise through later life. The maximum difference in z-scores between corrected and uncorrected scores for a participant born 4 months' preterm would occur in the early teenage years, and for the forced vital capacity would be approximately -0.09 SD wider. In the clinical example not correcting for prematurity resulted in a maximum gap between preterm and term cohorts 0.06 SD wider for the forced vital capacity at 8 years than if age was corrected for prematurity.

Conclusions: Correction for prematurity is not necessary in clinical practice, and is probably not required for research in studies of respiratory airflow through childhood or adulthood.

Word count: 241

As more extremely preterm infants (those born before 28 weeks of pregnancy, or more than 12 weeks too early) survive into adulthood, it is becoming clear that they have higher rates of

various health problems, including more respiratory disease. In particular, expiratory flow rates in adulthood are reduced in ex-preterm survivors compared with those not born preterm[1], and even more so in preterm survivors who had bronchopulmonary dysplasia in the newborn period[1-5].

When considering outcomes such as growth or cognitive function, the age of ex-preterm survivors is corrected for the degree of prematurity, particularly in early childhood. This makes sense, for example, when assessing a child born at 23 weeks of gestation (which is 4 months too early) at say 6 months after birth, which would be at 2 months of age corrected for prematurity. One would not expect a baby born at 23 weeks to be the same size, have the same level of development, or have values for expiratory flows as a child born at full-term at the age of 6 months after birth, and hence for this scenario correction for prematurity makes sense from both clinical and research perspectives. From a clinical viewpoint, the older the child and the further away from birth, the issue of correction becomes less relevant; some in clinical practice would argue that the issue of preterm birth can be ignored after the first few years of age and the child should then be compared with all other similar-aged peers, regardless of prematurity. However, from a research perspective, not correcting for prematurity introduces a bias; we have shown for cognitive scores, for example, that such a bias persists even into the teenage years.[6] The amount of bias can be as large as 3-4 IQ points in the teenage years for a child born 4 months preterm, which represents a 3-4% difference for an expected IQ of 100.

The issue of correction for prematurity has not been discussed with respect to respiratory function testing later in childhood or into adulthood, perhaps because most clinical respiratory function testing does not occur until children reach school-age or later, an age when correction for prematurity occurs rarely, even in research. However, with increasing numbers of surviving extremely preterm infants, it is relevant to consider the magnitude of

the effect of correction for prematurity on respiratory function results, because if it is large it might affect clinical care. This is also relevant because airway growth is not linear – it is rapid in early life, slows in middle childhood, increases again at puberty, peaks in the early 20s and then gradually declines[7]. Consequently, the effect, if any, of correction for prematurity will vary with the age of testing. Moreover, since the growth of the airways differs between males and females[7], there are likely to be different effects of age correction between the sexes at the same age of testing.

The aim of this study was to determine the effect of correcting for prematurity on expected values for expiratory flow rates for participants from early childhood through to 70 years of age using not only a theoretical model but also real-life lung function values to assess the influence of age alone, and then prematurity, on lung function Z-scores. We hypothesised that there would be a small bias in expected values if age was not corrected for prematurity, but that the size of the bias would vary with age and with sex, and possibly with the flow variable under consideration.

Methods

We took both a theoretical approach, and provide a clinical example.

For the theoretical approach we considered how varying age, while keeping other predictors of lung function constant, affects lung function z-scores. We studied two age ranges; 3-16.9 years, and 16-70 years. We assumed values for forced expired volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow between 25-75% of vital capacity ($FEF_{25-75\%}$), for both males and females. We chose two arbitrary values for height and each expiratory flow variable that would result in initial z-scores within the range of +/- 2 SD (Table 1); two different ages were chosen because no single set of values of height and expiratory flow for each sex would result in z-scores that would be mostly within the range

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+/-2 SD for all ages from 5 years to 70 years. Then, by keeping the height constant for each sex, we varied age to determine if the patterns of the relationships with age differed between the higher or lower value for the expiratory variables. We varied the age of the participants from 5.0 to 16.9 years, and from 16.0 years up to 70.0 years, in 0.1-year increments. The values assumed for the two different age bands are shown in Table 1. Ethnicity was assumed to be Caucasian for all values. Z-scores for each variable were calculated using the reference equations from the Global Lung Initiative[7]. We then plotted the z-scores against age of testing for each of the flow variables for each sex separately, for each of the two age bands to demonstrate figuratively how age alone influences lung function z-scores. For the older age band, we determined the age at the nadirs for each expiratory flow variable for each sex. We also assessed the linear relationship between the four expiratory flow variables with age for each sex in four age brackets; 7-9 years, 12-14 years, 16-18 years, and 30-40 years, to estimate the rate of change in z-scores per year within those age ranges.

The clinical example used data that we have previously reported for two cohorts of participants who had expiratory flows measured at both 8 and 18 years of age[8]. The first cohort comprised 144 participants who had been born extremely preterm, (<28 weeks' gestational age) in the state of Victoria in 1991-92; they were derived from 224 consecutive infants born over the two-year period who survived to 18 years of age. There were no exclusions. The second cohort comprised 141 contemporaneous term-born (37-42 weeks' gestational age) controls. Controls were derived from 251 children randomly selected from one of three level-III maternity hospitals in the state, matched with the preterm survivors for sex, maternal health insurance status, and mother's country of birth (primarily English-speaking or not) who also survived to 18 years. These cohorts have been assessed for various outcomes at 2, 5, 8 and 18 years and we have always corrected age for gestational age for all of our research studies, to be consistent at the different ages that the cohorts have been

assessed. Expiratory flows were measured only at 8 and 18 years. When we originally computed z-scores for expiratory flows at 8 and 18 years of age using the reference equations from the Global Lung Initiative, we had corrected age at the time of testing for prematurity. We then recomputed the expiratory z-scores and % predicted values with age not corrected for prematurity.

Statistical Methods

The statistical methods are largely descriptive. We compared both corrected and uncorrected z-scores and % predicted values between preterm and term cohorts by t-test.

Results

Theoretical modelling

The patterns of the associations of z-scores with age for each expiratory variable are shown in Figure 1 for 5-16.9 years, and Figure 2 for 16-70 years. The y-axes have the same ranges to aid interpretation.

From 5-16.9 years of age, the patterns differed for each variable (Fig 1). For FEV_1 and FVC the z-scores were stable between 5-8 years, then declined, earlier in females than males, but steepest between 12-14 years of age for both sexes. The FEV_1/FVC z-scores did not change much over time. The $FEF_{25-75\%}$ z-scores initially rose in both sexes with increasing age, then stabilised around 6-7 years, then declined earlier in females, but the rate of decline was not as marked as for the FEV_1 or the FVC z-scores.

From 16-70 years of age, the z-scores for FEV_1 for both sexes continued to decline with age initially, until a nadir was reached in the late teens or early 20s, and then the values steadily increased throughout the remaining years (Fig 2). The changes at around 20 years of age were more marked in males than females. The z-scores for FVC for both sexes followed a similar

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pattern to those for the FEV_1, except that the nadirs were slightly later and the changes at older ages were more gradual with age. Males again had more marked changes around 20 years of age than females. In contrast with the z-scores for FEV_1 and FVC, the z-scores for FEV_1/FVC for both sexes barely declined with age in the males initially, and not at all in females. There was then a steady increase with age for both sexes, with a plateauing in later decades. The patterns in z-scores for $FEF_{25-75\%}$ for both sexes were similar to those for the FEV_1, but the initial decline with age was less obvious, and the nadir was reached a little earlier, in the late teens. The early changes were slightly more marked in males than females.

For all variables in both age bands the patterns were similar within each sex, and for both the higher and the lower theoretical lung function values.

The nadirs were reached a little earlier for females for all variables except zFVC, and the ages at which the nadir occurred were similar for both sexes whether the values were lower or higher (Table 2). The lowest point for the $zFEV_1$/FVC for females was approximately 15.5 years of age, whereas it was later by 1.2 to 2.2 years for males, varying with the flow rates.

The rates of change averaged over both flow rates were negative in the early years for all variables, except for $zFEV_1$/FVC (Table 3). The rates of change were more negative for females than males for all variables between 7-9 years. The rates of change increased between 12-14 years of age; the largest negative rates of change were for males, at -0.227 SD per year for the $zFEV_1$ and -0.275 for zFVC. For a participant born 4 months' preterm (at 23 weeks' gestation), this translates into a z-score that would be -0.275/3 = -0.092 SD lower for zFVC if age was not corrected between 12 and 14 years of age. The rate of change was lower between 16-18 years of age compared with 12-14 years of age. Between 30-40 years of age, the rates of change over time for all variables were similar, were all positive, and were similar between males and females. The largest rate of change was in FEV_1 for females at

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0.057/year, which translates into a difference of 0.019 SD between uncorrected and corrected ages for a participant born 4 months' preterm.

Clinical example

The corrected mean ages for the preterm and term groups at testing around 8 years were 8.6 (SD 0.3) years and 8.8 (0.4) years, respectively, and around 18 years were 17.9 (SD 0.8) years and 18.1 (SD 0.9) years, respectively. The different values for z-scores and % predicted scores, both corrected and uncorrected for gestational age at birth, in the preterm and term cohorts are shown in Table 4. Survivors born extremely preterm had considerably lower values for expiratory airflows compared with controls, consistent with what is reported in the literature.[9-12] Correcting for prematurity resulted in only small changes in mean scores overall. When age was uncorrected for preterm birth, compared with corrected for prematurity, both z-scores and % predicted for FEV_1, FVC and $FEF_{25-75\%}$ were lower in the preterm cohorts, and the gaps between the preterm and term cohorts were wider for these variables, whereas the z-scores for FEV_1/FVC went in the opposite direction. The widest gap by not correcting for prematurity was at 8 years in the FVC, where it was wider by 0.06 SD for the z-score, and by 0.65% for % predicted. The differences between corrected and uncorrected values were not as wide at 18 years as they were at 8 years.

Discussion

The major findings of this study are that correcting for prematurity has a small and varying effect on z-scores for expiratory flow variables from 5 to 70 years of age. In the late teenage years correcting for prematurity results in only a small improvement in z-scores for the most preterm of survivors. The effects are mostly in the opposite direction beyond the mid-20s for all variables, but the absolute magnitude is smaller. At a clinical level comparing airway flows between an extremely preterm cohort and a term cohort at 18 years of age, the

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differences when comparing airflows that were corrected for prematurity with those that were not corrected for prematurity were trivial.

Our findings were in the directions expected, given the known changes in airway growth, and the known differences between males and females[7]. The FEV_1 and FVC both increase through childhood, peaking around 20 years of age, and then gradually decline, which means that adjusting age upwards before 20 years of age but keeping height and measured volume constant would result in a drop in z-scores for FEV_1 and FVC. On the contrary, later in life, an increase in age with other things kept constant would mean that z-scores for both would rise. Starting in early childhood, the FEV_1/FVC declines with increasing age in both sexes, except for an upward spurt corresponding with puberty. Consequently, increasing age, keeping height and volume constant, would lead to a progressive rise in z-score for FEV_1/FVC at all ages, apart from around puberty, which typically occurs later in males than females. What is novel about our study is that we have calculated the size of the effects of correcting for prematurity, and they are not large.

There is no clear definition of what might comprise a clinically important difference in z-scores by not correcting for prematurity. In clinical practice, patient care would not be determined solely based on a single z-score for any expiratory flow variable, but rather on the patient's overall symptoms and health, as well as on responses to bronchodilation and to changes over time in z-scores for expiratory flows. In the absence of any definition, we suggest that if it made a difference in z-scores of more than 0.25 SD, then correcting for prematurity might be worthwhile in clinical practice. However, since correcting for prematurity has an effect less than 0.1 SD on any flow variable at any age, prematurity does not have to be factored into the interpretation of expiratory flows in clinical practice and can be ignored.

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Quanjer et al[13] discussed biases in computed z-scores that arise from measurement inaccuracy, particularly in height, and because of rounding of age to whole years. Both of these sources of bias can be much larger than we have been able to show by correcting or not for prematurity, ranging from -8% to 7% by using age in whole years, and from 1% to 40% by overestimating height by 1%[13]. What we have shown is that an age difference of up to 4 months caused by extreme prematurity has much less effect, less than 1%, even in the late teenage years when airway growth is relatively rapid, and any effect of correcting for prematurity would have a larger effect than at any other age between 5 and 70 years

Correcting for prematurity has large effects on non-lung variables, such as height and weight during childhood, and developmental test scores and IQ[6], with larger effects earlier in life. The reason it might have a smaller effect on expiratory flows than for non-respiratory variables is because the standardised expiratory flows are all corrected for height; since height is lower in ex-preterm survivors than controls[14], z-scores for ex-preterm survivors will already be partly "corrected" upwards.

In conclusion, as the absolute sizes of the differences in flow rates are not clinically important, correction for prematurity is not necessary in clinical practice. In research, the effect of correcting for prematurity would reduce a bias, but as the magnitude of the bias is small in even the most extreme cases of prematurity, it can be largely ignored and is unlikely to change any major conclusions from the research being performed. Most researchers do not correct lung function results for prematurity. On the other hand, if researchers do correct for prematurity, to be consistent with what they have done when assessing extremely preterm survivors through childhood, they need not be criticised for doing so, as correcting for prematurity will have little effect on any conclusions arising from the research.

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Table 1. Assumed values for theoretical modelling

Age range (years)	Height (cm)		FEV_1 (l)		FVC (l)		FEV_1/FVC (%)		$FEF_{25-75\%}$ (l)	
	Male	Female	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
5-16.9	127	127	1.6	1.8	1.8	2.0	88.0	91.9	1.9	2.3
16-20	161	158	3.0	3.5	3.3	3.8	90.9	92.1	3.0	3.5

Table 2. Ages (years) at the nadir for each variable from the teenage years onwards, for each sex, and for lower and higher flow rates.

	$zFEV_1$	zFVC	$zFEV_1$/FVC	$zFEF_{25-75\%}$
lower flow rates				
Males	21.5	22.7	16.9	19.2
Females	19.7	23.5	15.7	18.4
higher flow rates				
Males	21.7	22.8	17.5	19.5
Females	19.8	23.5	15.3	18.5

Table 3. Rates of change in expiratory flow rate z-scores between various ages for each sex, averaged over lower and higher flow rates

	$zFEV_1$	zFVC	$zFEV_1$/FVC	$zFEF_{25-75\%}$

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7-9 years of age				
Males	-0.094/yr	-0.115/yr	0.038/yr	-0.056/yr
Females	-0.144/yr	-0.139/yr	0.028/yr	-0.183/yr
12-14 years of age				
Males	-0.227/yr	-0.275/yr	-0.140/yr	-0.253/yr
Females	-0.085/yr	-0.253/yr	-0.096/yr	-0.162/yr
16-18 years of age				
Males	-0.214/yr	-0.211/yr	-0.011/yr	-0.096/yr
Females	-0.076/yr	-0.096/yr	0.035/yr	-0.029/yr
30-40 years of age				
Males	0.047/yr	0.032/yr	0.045/yr	0.040/yr
Females	0.057/yr	0.025/yr	0.052/yr	0.048/yr

Table 4. Expiratory flow values for preterm and term groups, both corrected for prematurity and not corrected for prematurity.

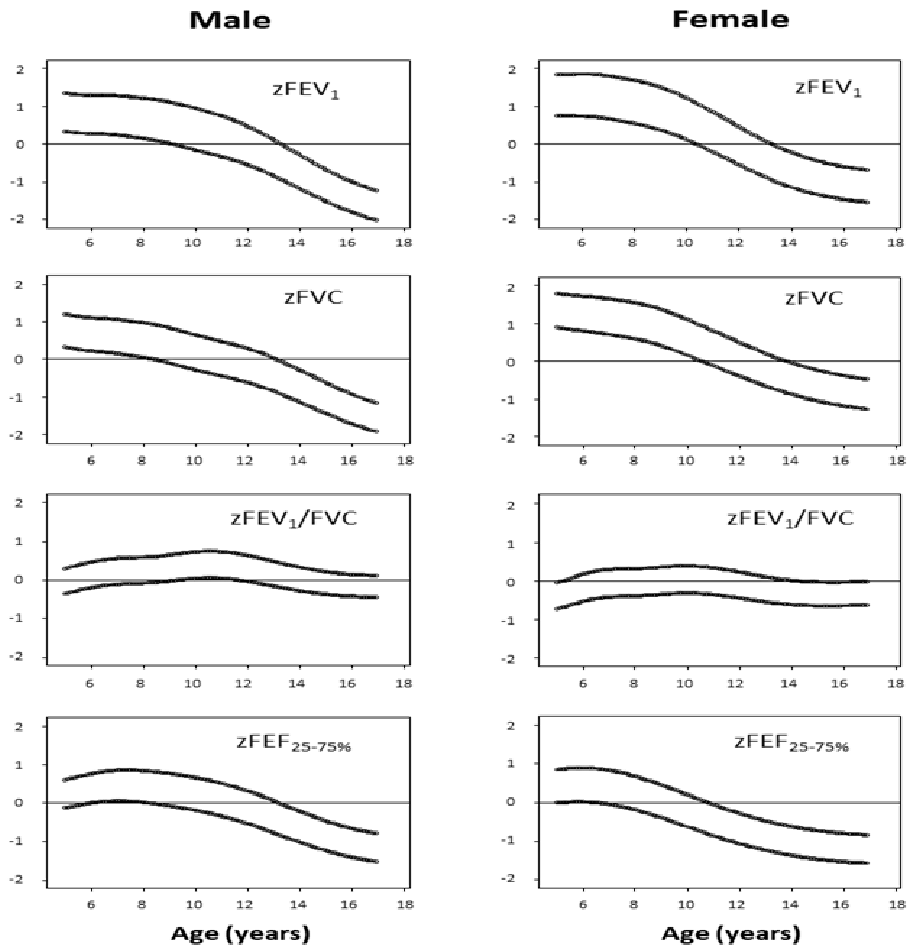
Variable	Preterm; n=144 mean (SD)	Term; n=141 mean (SD)	Mean difference (95% CI)	Δ*
at 8 years				
FEV_1				
z-scores – corrected	-0.952 (1.085)	0.027 (1.065)	-0.979 (-1.230, -0.729)	
– not corrected	-1.001 (1.089)	0.023 (1.065)	-1.024 (-1.275, -0.773)	-0.045
% predicted – corrected	88.61 (13.09)	100.2 (12.45)	-11.60 (-14.58, -8.62)	
– not corrected	88.13 (13.02)	100.17 (12.45)	-12.04 (-15.01, -9.07)	-0.44
FVC				
z-scores – corrected	-0.807 (1.245)	-0.250 (1.085)	-0.558 (-0.830, -0.285)	
uncorrected	-0.872 (1.260)	-0.254 (1.085)	-0.618 (-0.892, -0.344)	-0.060

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% predicted – corrected	90.51 (14.56)	97.13 (12.98)	-6.62 (-9.84, -3.40)	
– not corrected	89.81 (14.64)	97.09 (12.97)	-7.27 (-10.50, -4.05)	-0.65
FEV_1/FVC				
z-scores – corrected	-0.119 (1.469)	0.605 (1.170)	-0.724 (-1.034, -0.413)	
– not corrected	-0.107 (1.474)	0.606 (1.170)	-0.712 (-1.023, -0.402)	0.012
$FEF_{25-75\%}$				
z-scores – corrected	-1.454 (1.051)	-0.434 (0.984)	-1.020 (-1.259, -0.780)	
– not corrected	-1.499 (1.054)	-0.438 (0.984)	-1.062 (-1.302, -0.822)	-0.042
% predicted – corrected	69.12 (21.88)	90.93 (22.34)	-21.81 (-27.02, -16.61)	
– not corrected	68.41 (21.68)	90.86 (22.33)	-22.45 (-27.63, -17.27)	-0.64
at 18 years				
FEV_1				
z-scores – corrected	-1.034 (1.124)	-0.102 (0.924)	-0.932 (-1.172, -0.691)	
– not corrected	-1.058 (1.123)	-0.104 (0.924)	-0.955 (-1.195, -0.715)	-0.023
% predicted – corrected	87.73 (13.40	98.71 (10.79)	-10.98 (-13.82, -8.14)	
– not corrected	87.46 (13.37)	98.69 (10.79)	-11.23 (-14.07, -8.40)	-0.25
FVC				
z-scores – corrected	-0.417 (1.039)	-0.106 (0.880)	-0.311 (-0.536, -0.087)	
– not corrected	-0.449 (1.035)	-0.108 (0. 880)	-0.342 (-0.566, -0.118)	-0.031
% predicted – corrected	95.15 (12.18)	98.82 (10.58)	-3.67 (-6.34, -1.01)	
– not corrected	94.77 (12.14)	98.80 (10.59)	-4.03 (-6.69, -1.37)	-0.36
FEV_1/FVC				
z-scores – corrected	-0.934 (1.285)	-0.034 (0.987)	-0.900 (-1.167, -0.632)	
– not corrected	-0.925 (1.284)	-0.034 (0.987)	-0.891 (-1.158, -0.623)	0.009
$FEF_{25-75\%}$				
z-scores – corrected	-1.426 (1.261)	-0.243 (0.980)	-1.183 (-1.447, -0.919)	
– not corrected	-1.433 (1.257)	-0.243 (0.980)	-1.190 (-1.453, -0.927)	-0.007
% predicted – corrected	72.19 (24.26)	95.70 (21.36)	-23.52 (-28.85, -18.18)	
– not corrected	72.01 (24.18)	95.69 (21.36)	-23.68 (-29.01, -18.37)	-0.16

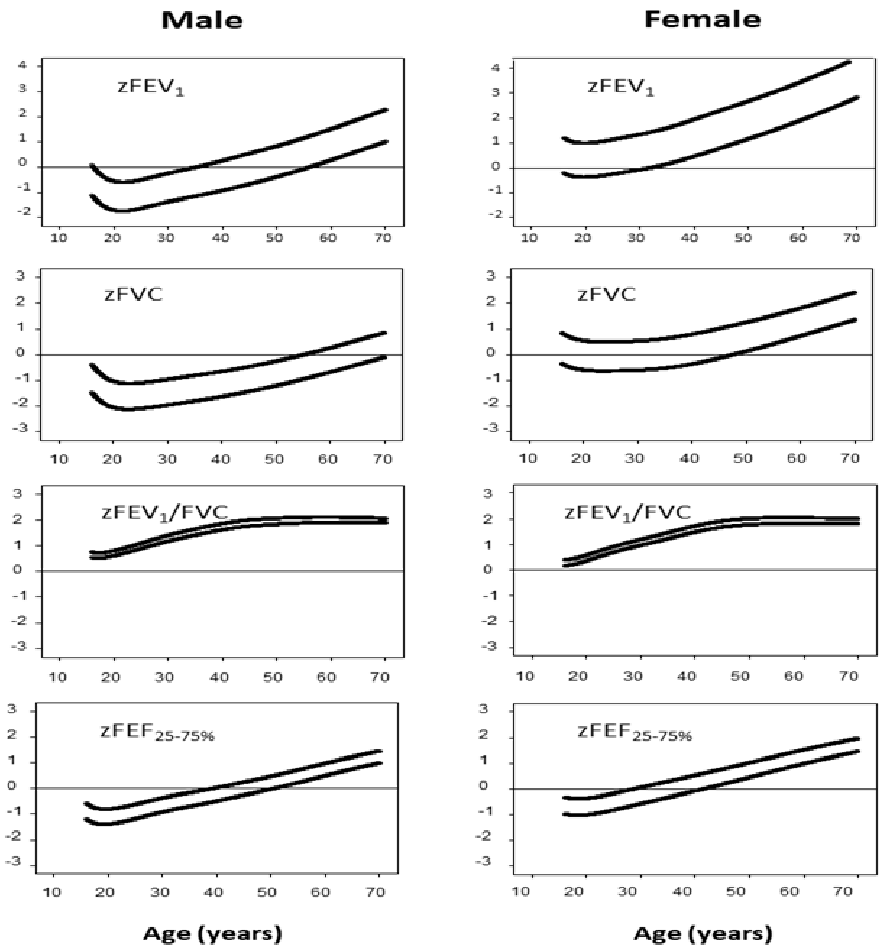
*Δ=differences between corrected and uncorrected mean differences between preterm and term groups

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correcting for prematurity fig 1 .

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correcting for prematurity fig 2 .

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