**Appendix A**

**Comparing spirometric reference values from childhood to old age estimated by LMS and linear regression models**

This supplemental material contains additional results on Z-scores and the lower limit of normal (LLN). Likewise, we describe the method to compute the spline values in each equation from LMS models, and how to calculate L, M, S, predicted values (PV), LLN, Z-scores (Z) and percentage of predicted (%P). Finally, we compare the residual from LMS and linear regression models.

**Results**

In order to proof the goodness of fit of the international spirometric reference equations, Z-score were calculated. The closer mean (SD) to 0 (1) the better fit. Table A.1 shows the Z-scores from the reference equations by Pérez Padilla and GLI equations.

Table A.1. Mean (SD) of reported spirometric values expressed as Z-scores from the reference equations by Pérez Padilla and GLI equations

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   | Pérez Padilla | P value | GLI | P value |
| Variable | Mean (SD) |   | Mean (SD) |   |
| **Females** |  |  |  |  |
| FEV1 | 0.07 (0.92) | <0.001 | 0.46 (1.07) | <0.001 |
| FVC | 0.02 (0.98) | 0.183 | 0.41 (1.03) | <0.001 |
| FEV1/FVC | 0.01 (0.95) | 0.49 | 0.05 (0.92) | 0.0027 |
| **Males** |  |  |  |  |
| FEV1 | -0.01 (0.97) | 0.479 | 0.52 (1.11) | <0.001 |
| FVC | 0.07 (0.98) | <0.001 | 0.47 (1.03) | <0.001 |
| FEV1/FVC | -0.03 (1.01) | 0.0254 | 0.07 (0.88) | <0.001 |

*P* value testing the hypothesis that the mean of Z-scores is equal to zero.

FEV1: Forced expiratory volume in 1s. FVC: Forced vital capacity. FEV1/FVC: ratio of FEV1 to FVC.

A perfect adjustment would be shown if means were 0 and SD=1. The closer to these values, the better the adjustment.

It was expected 5% or less of individuals were below lower limit of normal for each spirometric variable. The results with both models LMS and linear were very similar as shown in e-Table 2.

Table A.2. Percentage of subjects <LLN by model type and gender

|  |  |  |  |
| --- | --- | --- | --- |
|  | Females (n=3054) |  | Males (n=6575) |
| Variable | LMS | LR |   | LMS | LR |
| FEV1 | 5.1 | 5.7 |  | 5.1 | 5.9 |
| FVC | 5.1 | 5.5 |  | 4.9 | 5.9 |
| FEV1/FVC | 5.4 | 6.4 |   | 5.1 | 5.9 |

LLN: Lower limit of normal.

LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: Linear regression model.

FEV1: Forced expiratory volume in 1s. FVC: Forced vital capacity. FEV1/FVC: ratio of FEV1 to FVC.

**Spline**

Spline values are useful when the dependent variable varies in a complex manner with one independent variable. We used penalized B-spline method in order to generate spline values for age in each model. These values were generated for each quarter of year. Therefore, the effect of age is explained by a fix effect (linear coefficient) and an age spline. The dataset LookupMexico contains the L, M and S splines for FEV1, FVC and FEV1/FVC by gender.

 **L, M and S values**

The mean (mu, M), variation (sigma, S) and the skewness (nu, L) values are computed using the equations in tables 3 and 4 of the paper.

 Eq. (A.1)

 Eq. (A.2)

 Eq. (A.3)

In order to show an example to calculate L, M and S for FEV1 in females, we used the equations Eq. (A.1)-(A.3). Considering a woman with 9.3 years old and height of 125 cm. First, we have to narrow the variable age to the closest value to 0.25, in this case 9.25. Then, we have to replace the values of age, height and splines corresponding to a woman of 9.25 years old as following:

 = **1.6795**

**Calculating predicted values, lower limit of normal and Z-scores**

Predicted values (PV), the lower limit of normal (LLN), the Z-score (Z) depend and percentage of predicted (%P) on L, M and S. The following formulas show how to calculate each value.

Predicted value = M Eq. (A.4)

) Eq. (A.5)

 Eq. (A.6)

 Eq. (A.7)

Replacing the age, height, L, M, S values from previous section and FEV1 of 1.40 L on Eq. (A.4)-(A.7), we calculate PV, LLN, Z and %P.

FEV1 predicted = M = = **1.6796 L**

 = **1.3816 L**

**Model evaluation**

In order to evaluate the models, the quantile residuals were estimated. Box-plot graphs were plotted by age group in order to verify the goodness of fitness by type of model (Figure A.1-A.6). Comparisons of error between types of model by age group were developed as well (Table A.3 and A.4).

Figure A.1. Box plot of quantile (standardized) residual FEV1 by type of model and age group for women



LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

FVC: Forced vital capacity.

FEV1/FVC: ratio of FEV1 and FVC.

Figure A.2. Box plot of quantile (standardized) residual FEV1 by type of model and age group for men



LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

FVC: Forced vital capacity.

FEV1/FVC: ratio of FEV1 and FVC.

Figure A.3. Box plot of quantile (standardized) residual FVC by type of model and age group for women



LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

FVC: Forced vital capacity.

FEV1/FVC: ratio of FEV1 and FVC.

Figure A.4. Box plot of quantile (standardized) residual FVC by type of model and age group for men



LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

FVC: Forced vital capacity.

FEV1/FVC: ratio of FEV1 and FVC.

Figure A.5. Box plot of quantile (standardized) residual FEV1/FVC by type of model and age group for women



LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

FVC: Forced vital capacity.

FEV1/FVC: ratio of FEV1 and FVC.

Figure A.6. Box plot of quantile (standardized) residual FEV1/FVC by type of model and age group for men



LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

FVC: Forced vital capacity.

FEV1/FVC: ratio of FEV1 and FVC.

Table A.3. Comparisons of medians\* (p25, p75) of quantile error by type of model and age group for women

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Age group | ln(FEV1) |   | Ln(FVC) |   | Ln(FEV1/FVC) |
| LMS | LR | P value |   | LMS | LR | P value |   | LMS | LR | P value |
| 0-5 | -0.014 (-0.708, 0.733) |  0.012 (-1.088, 1.163) | 0.179 |  | -0.094 (-1.126, 0.719) |  0.055 (-1.188, 0.873) | 0.999 |  |  0.042 (-0.696, 0.808) |  0.016 (-0.751, 1.531) | 0.486 |
| 6-10 | -0.015 (-0.638, 0.659) | -0.189 (-0.776, 0.435) | <0.001 |  |  0.024 (-0.657, 0.661) | -0.053 (-0.694, 0.486) | <0.001 |  | -0.040 (-0.590, 0.611) | -0.042 (-0.645, 0.532) | <0.001 |
| 11-15 | -0.044 ( -0.677, 0.665) |  0.073 (-0.560, 0.715) | <0.001 |  | -0.028 (-0.689, 0.680) |  0.036 (-0.647, 0.681) | 0.053 |  | -0.010 (-0.680, 0.739) |  0.201 (-0.444, 0.855) | <0.001 |
| 16-20 | -0.021 (-0.639, 0.732) |  0.447 (-0.088, 1.120) | <0.001 |  |  0.045 (-0.688, 0.756) |  0.407 (-0.299, 1.079) | <0.001 |  | -0.011 (-0.628, 0.736) |  0.317 (-0.316, 0.915) | <0.001 |
| 21-25 | -0.107 (-0.764, 0.470) |  0.052 (-0.513, 0.512) | <0.001 |  | -0.249 (-0.675, 0.542) |  0.069 (-0.390, 0.612) | <0.001 |  | -0.237 (-0.951, 0.458) | -0.221 (-0.913, 0.446) | <0.001 |
| 26-30 | 0.013 (-0.555, 0.537) | -0.188 (-0.805, 0.328) | <0.001 |  | -0.011 (-0.541, 0.400) | -0.161 (-0.569, 0.448) | <0.001 |  | -0.138 (-0.655, 0.553) | -0.371 (-0.892, 0.150) | <0.001 |
| 31-35 |  0.050 (-0.736, 0-.704) | -0.161 (-0.925, 0.451) | <0.001 |  | -0.050 (-0.836, 0.908) | -0.236 (-0.889, 0.618) | <0.001 |  |  0.080 (-0.808, 0.987) | -0.316 (-1.143, 0.420) | <0.001 |
| 36-40 | -0.072 (-0.980, 0.651) | -0.260 (-1.298, 0.426) | <0.001 |  | -0.083 (-0.756, 0.597) | -0.088 (-0.989, 0.545) | <0.001 |  | -0.006 (-0.569, 0.665) | -0.184 (-0.778, 0.325) | <0.001 |
| 41-45 | 0.056 (-0.612, 0.724) | -0.065 (-0.740, 0.601) | <0.001 |  |  0.088 (-0.540, 0.657) | -0.017 (-0.602, 0.561) | <0.001 |  | -0.194 (-0.813, 0.609) | -0.249 (-0.909, 0.457) | <0.001 |
| 46-50 | 0.033 (-0.740, 0.734) | -0.013 (-0.934, 0.596) | <0.001 |  | -0.054 (-0.803, 0.604) | -0.188 (-0.919, 0.519) | <0.001 |  |  0.171 (-0.522, 0.777) |  0.233 (-0.484, 0.731) | <0.001 |
| 51-55 | 0.007 (-0.626, 0.640) | -0.111 (-0.755, 0.692) | <0.001 |  |  0.024 (-0.529, 0.604) | -0.092 (-0.683, 0.476) | <0.001 |  | -0.013 (-0.706, 0.593) |  0.146 (-0.625, 0.729) | <0.001 |
| 56-60 | -0.033 (-0.669, 0.779) | -0.005 (-0.551, 0.877) | 0.242 |  |  0.039 (-0.621, 0.696) | -0.010 (-0.691, 0.707) | <0.001 |  |  0.141 (-0.582, 0.659) |  0.361 (-0.394, 0.895) | <0.001 |
| 61-65 | 0.075 (-0.765, 0.638) |  0.488 (-0.646, 0.994) | <0.001 |  | -0.175 (-0.998, 0.722) |  0.084 (-1.036, 0.968) | <0.001 |  |  0.076 (-0.673, 0.999) |  0.468 (-0.486, 1.324) | <0.001 |
| 66-70 |  -0.014 (-0.754, 0.508) |  0.555 (-0.617, 1.296) | <0.001 |  |  0.139 (-1.197, 0.716) |  0.651 (-1.007, 1.377) | <0.001 |  | -0.353 (-1.105, 0.100) |  0.122 (-0.816, 0.618) | 0.003 |
| 71-75 | 0.650 (0.211, 0.826) |  1.825 (1.234, 2.075) | 0.005 |  |  0.196 (-0.149, 0.493) |  1.265 (0.618, 1.684) | 0.005 |  |  0.559 (-0.252, 1.074) |  1.135 ( 0.279, 1.648) | 0.005 |
| 76+ |  0.220 (-1.324, 0.290) |  1.467 (-0.633, 2.209) | 0.138 |   |  0.290 (-0.785, 0.688) |  1.436 (0.379, 2.451) | 0.080 |   | -1.024 (-1.285, -0.051) | -0.547 (-1.131, 0.474) | 0.080 |

\* Comparision was made by Wilcoxon matched-pairs signed-ranks test

LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

FVC: Forced vital capacity.

FEV1/FVC: ratio of FEV1 and FVC.

Table A.4. Comparisons of medians\* (p25, p75) of quantile error by type of model and age group for men

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Age group | ln(FEV1) |   | ln(FVC) |   | FEV1/FVC |
| LMS | LR | P value |   | LMS | LR | P value |   | LMS | LR | P value |
| 0-5 |  0.004 (-0.790, 0.520) |  0.135 (-0.581, 0.787) | 0.050 |   | -0.034 (-0.596, 0.823) |  0.026 (-0.435, 0.499) | 0.274 |   | -0.421 (-0.782, 0.719) | -0.360 (-0.935, 1.008) | 0.838 |
| 6-10 |  0.012 (-0.675, 0.709) | -0.026 (-0.669, 0.491) | <0.001 |  |  0.012 (-0.652, 0.726) | -0.008 (-0.620, 0.561) | <0.001 |  |  0.058 (-0.653, 0.653) | -0.036 (-0.778, 0.542) | <0.001 |
| 11-15 | -0.018 (-0.700, 0.635) | -0.167 (-0.718, 0.390) | <0.001 |  | -0.024 (-0.709, 0.664) | -0.134 (-0.769, 0.431) | <0.001 |  | -0.079 (-0.687, 0.626) |  0.057 (-0.605, 0.725) | <0.001 |
| 16-20 |  0.027 (-0.705, 0.685) |  0.637 (-0.004, 1.239) | <0.001 |  | -0.006 (-0.656, 0.670) |  0.443 (-0.147, 1.009) | <0.001 |  |  0.059 (-0.655, 0.793) |  0.578 (-0.202, 1.257) | <0.001 |
| 21-25 | -0.094 (-0.738, 0.651) |  0.387 (-0.204, 1.036) | <0.001 |  |  0.116 (-0.775, 0.754) |  0.693 (-0.204, 1.163) | <0.001 |  | -0.264 (-0.782, 0.508) | -0.049 (-0.792, 0.600) | 0.035 |
| 26-30 | -0.112 (-0.708, 0.650) | -0.015 (-0.468, 0.609) | 0.044 |  | -0.014 (-0.688, 0.709) |  0.179 (-0.472, 0.861) | <0.001 |  |  0.007 (-0.786, 0.714) | -0.254 (-0.962, 0.318) | <0.001 |
| 31-35 |  0.004 (-0.722, 0.807) |  0.059 (-0.664, 0.675) | 0.119 |  | -0.115 (-0.780, 0.720) |  0.072 (-0.689, 0.751) | <0.001 |  |  0.086 (-0.666, 0.706) | -0.082 (-0.833, 0.374) | <0.001 |
| 36-40 | -0.024 (-0.648, 0.585) | -0.053 (-0.589, 0.558) | <0.001 |  | -0.005 (-0.692, 0.625) |  0.024 (-0.627, 0.597) | 0.319 |  |  0.096 (-0.578, 0.712) |  0.076 (-0.632, 0.563) | <0.001 |
| 41-45 |  0.037 (-0.707, 0.727) |  0.049 (-0.657, 0.674) | <0.001 |  |  0.053 (-0.682, 0.670) |  0.063 (-0.657, 0.672) | <0.001 |  | -0.004 (-0.618, 0.607) |  0.016 (-0.573, 0.530) | <0.001 |
| 46-50 | -0.024 (-0.633, 0.646) |  0.015 (-0.625, 0.642) | <0.001 |  | -0.005 (-0.645, 0.714) | -0.008 (-0.680, 0.668) | <0.001 |  |  0.016 (-0.657, 0.631) |  0.081 (-0.570, 0.620) | 0.003 |
| 51-55 |  0.002 (-0.657, 0.641) |  0.038 (-0.647, 0.708) | <0.001 |  | -0.010 (-0.657, 0.638) |  0.004 (-0.699, 0.641) | <0.001 |  |  0.028 (-0.660, 0.721) |  0.135 (-0.509, 0.785) | <0.001 |
| 56-60 | -0.064 (-0.685, 0.706) |  0.040 (-0.646, 0.818) | <0.001 |  | -0.023 (-0.703, 0.673) |  0.046 (-0.710, 0.728) | 0.526 |  |  0.001 (-0.675, 0.733) |  0.163 (-0.578, 0.777) | <0.001 |
| 61-65 |  0.057 (-0.610, 0.752) |  0.181 (-0.530, 0.963) | <0.001 |  |  0.007 (-0.613, 0.837) |  0.138 (-0.551, 0.968) | <0.001 |  | -0.100 (-0.819, 0.549) | -0.008 (-0.798, 0.610) | 0.976 |
| 66-70 | -0.180 (-0.728, 0.648) |  0.103 (-0.661, 0.860) | <0.001 |  | -0.081 (-0.805, 0.619) |  0.177 (-0.668, 0.933) | <0.001 |  | -0.087 (-0.712, 0.678) | -0.023 (-0.691, 0.672) | 0.005 |
| 71-75 | -0.356 (-1.011, 0.665) | -0.013 (-0.980, 1.110) | 0.003 |  | -0.351 (-0.990, 0.532) |  0.028 (-0.748, 0.955) | <0.001 |  | -0.077 (-0.662, 0.810) | -0.033 (-0.811, 0.783) | 0.001 |
| 76+ | -0.231 (-0.947, 0.621) |  0.360 (-0.734, 1.375) | 0.004 |   | -0.004 (-1.013, 0.998) |  0.720 (-0.596, 1.696) | <0.001 |   |  0.083 (-0.886, 0.575) | -0.055 (-1.068, 0.483) | <0.001 |

\* Comparision was made by Wilcoxon matched-pairs signed-ranks test

LMS model: Generalized additive model for location, scale and shape, LMS method.

LR: linear regression model

FEV1: Forced expiratory volume in 1s.

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