PREDICTION EQUATIONS FOR SINGLE BREATH DIFFUSING CAPACITY $D_LCO$ ($T_LCO$) IN A MIDDLE AGED CAUCASIAN POPULATION

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Abstract

**Rationale:** There are many reference equations for the measurement of $D_L CO$. However, the testing methodologies vary and there are no well-documented studies that develop reference equations for $D_L CO$ and alveolar volume ($V_A$) in middle-aged and older populations.

**Objectives:** 1. Develop reference equations for $D_L CO$ in a middle-aged population using the current ATS/ERS guidelines; 2. Compare the equations with those commonly used in laboratories around the world.

**Methods:** Healthy subjects (498 male and 474 female) aged 45 to 71 years were recruited as part of a larger epidemiological study. All participants completed a respiratory questionnaire and had spirometry and single breath $D_L CO$ (corrected for haemoglobin) measurements following ATS/ERS guidelines.

**Results:** The mean age was 58 years for males and 57 years for females. For males, factors that predicted $D_L CO$ were: Height, Age and Age * Height interaction and being an ex-smoker. For females, factors that predicted $D_L CO$ were: Height, Age, Weight and an Age * Height interaction.

**Conclusion:** We have described new prediction equations for $D_L CO$ in a middle-aged population that require validation in other populations.

**Number of Words:** 175

**Key words:** Diffusion capacity, Transfer factor, Carbon monoxide, Reference equations, Middle age, Epidemiology
INTRODUCTION
There are many studies describing prediction equations for the measurement of single breath carbon monoxide diffusing capacity of the lung (DLCO) (1-6). These studies have demonstrated that the main predictors of DLCO are height, gender and age. Significant limitations of the previous studies include small sample sizes (3, 7), non-standardised equipment (1, 3, 5), and different concentrations of inspired oxygen (1, 3-7). Importantly, previous prediction equations have been based on populations that included only relatively few subjects older than 55 years. However in clinical practice, DLCO is most likely to be measured in this age group as many respiratory diseases such as chronic obstructive pulmonary disease (COPD) are predominantly confined to older patients.

Despite evidence of increasing morbidity in older people with respiratory disease, knowledge of normal respiratory function in older people is limited. Diffusing capacity along with spirometry is the cornerstone of the clinical guidelines for the diagnoses of COPD and other pulmonary conditions (8, 9). Current measurements are compared with “normal” values which have been calculated using algorithms derived from population studies of healthy volunteers. Only relatively recently have publications reported normal values for spirometry in those aged over 70 years in European (10) and American (11) populations, which show departures of 20% or more obtained in predictive values compared to those obtained from extrapolations of equations derived in younger people. Neither of these studies included DLCO measurements.

The existing studies on DLCO normative values have a number of methodological differences. All existing studies have used manual or semi-automated DLCO measurement equipment (1-7). However currently used testing systems are fully computerised and depending on the manufacturer, differ in the methodology of the gas analysers, flow measuring devices, analogue to digital converters and sample rates. All these factors can affect the measured DLCO (12, 13, 15).

Finally, the population sampled has a significant effect on the outcomes of the study. In a recent study (1), weight was shown to be a significant predictor of DLCO and DLCO/VA (Kco) in the female population. However in this Spanish study, the distribution of weight was limited, again making the equations susceptible to extrapolation errors in broader clinical populations.

To address the above methodological issues, we set out to develop a set of prediction equations for DLCO and alveolar volume (VA) in a large “normal” middle aged and older population using modern computerised equipment, specifically following guidelines produced by the ERS/ATS (9).

METHODS
Subject selection
DLCO and VA were obtained in Caucasian subjects with no history of lung disease based on questionnaires, who either never smoked or were former smokers. Lung function was not used to define normality, as it can become a circular argument when creating new prediction equations for “normal” subjects. The subjects were recruited as part of another larger epidemiological study of COPD (16). All patients had DLCO and spirometry measured, and were administered the European Community Respiratory Health Study (ECRHS) questionnaire (17 - 19) – see on line repository for further details. Smoking status was based
on standard Australian smoking questions (20). Anyone with serum cotinine > 100 µmol/L was reclassified as a current smoker and excluded from the analysis. We further excluded any subject who met Global Obstructive Lung Disease (GOLD) (21) criteria for COPD stage 2 or greater. The study was approved by the Ethics Committee at The Alfred, Melbourne. All participants gave written informed consent.

**Measurement of DLCO and Alveolar Volume**

Single breath DLCO was measured in duplicate on a fully computerised system (Medgraphics Profiler, Minnesota, USA, software version 4a) according to ATS/ERS guidelines (9). This testing system uses gas chromatography for the measurement of gas concentrations and a pitot tube for measurement of flow. The inspired gas mixture contained 0.3% carbon monoxide, 0.5% neon, 20.6% oxygen with the balance, nitrogen. Breath-hold time was calculated as described by Jones-Meade (22), washout and sample volumes were set to 0.9 L, and an interval between repeat tests was at least 4 minutes. At least two measurements were performed which had to agree to within 1 mmol/min/kPa or 10%, whichever was greater, otherwise further measurements were made until repeatable results were obtained. All DLCO results were corrected to a standard haemoglobin concentration of 14.6 g/dL using the method described by Cotes (13). Standing height (metres) and body weight (kilograms) were measured without shoes.

**Quality control of equipment**

The quality control of the flow and volume signals was performed using a pulmonary waveform generator initially, an explosion decompression device monthly and biological control weekly. The flow sensor was also calibrated prior to each testing session using a 3 litre certified syringe. The accuracy of the DLCO and VA measurements was determined monthly using a custom built validator. The DLCO and VA validator consisted of a 3L certified syringe and two accurately known concentrations of inspired and expired CO and Ne to simulate typical inspired and expired gas concentrations. With the two gas mixtures it was possible to simulate a measured DLCO and VA value with known limits of agreement (7.20 – 7.43 mmol/min/kPa for DLCO and 3.15 - 3.25 L for VA). DLCO measurements were taken at ATPS and subject dead space correction was not included (30). Further detail of the methods is supplied in the on-line repository including the results of the quality assurance program for the testing equipment.

**Statistical analysis**

All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) or SPSS version 15.0 (SPSS Inc, Chicago, IL 2006). Multivariate linear regression models were constructed using a stepwise selection technique and validated using a backwards elimination technique. Each model was then assessed for clinical and biological plausibility. A two-sided p-value of 0.05 was considered statistically significant.

**RESULTS**

We recruited 1201 subjects in to the study; 147 were excluded as current smokers, 41 had doctor diagnosed COPD, 1 was excluded for dwarfism. We then excluded a further 4 subjects with incomplete smoking data, and 36 with undiagnosed COPD (GOLD stage 2 or greater) leaving a total of 972 subjects (498 male and 474 female)

Table 1 shows the demographic details of the sample. All subjects were aged between 45 and 71 years with a relatively even distribution across the ages up to 70 years. Of the 498 males,
248 (50%) were ex-smokers, and of the 491 females, 159 (34%) were ex-smokers. The mean pack year history of the ex-smokers was 13 and the range was 5 - 28.

<table>
<thead>
<tr>
<th></th>
<th>Males median (5-95%le)</th>
<th>Females median (5-95%le)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>498</td>
<td>474</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>3.75 (2.57 – 4.84)</td>
<td>2.71 (1.96 – 3.61)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>4.92 (3.61 – 6.33)</td>
<td>3.48 (2.60 – 4.57)</td>
</tr>
<tr>
<td>FER (%)</td>
<td>77.0 (65 – 85)</td>
<td>78.0 (68 – 85.3)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.75 (1.64 – 1.87)</td>
<td>1.62 (1.52 – 1.71)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.0 (66 – 109)</td>
<td>69.0 (53.8 – 92.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 (22.5 – 34.6)</td>
<td>26 (20.9 – 36)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>57.0 (47 – 70)</td>
<td>57.0 (47 -70)</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>15.2 (13.7 – 16.9)</td>
<td>13.7 (12.1 – 15.5)</td>
</tr>
<tr>
<td>DLCO (mmol/min/KPa)</td>
<td>9.17 (6.80 - 12.0)</td>
<td>6.63 (4.97 – 8.61)</td>
</tr>
<tr>
<td>VA (L)</td>
<td>6.71 (5.06 – 8.29)</td>
<td>4.88 (3.82 – 6.09)</td>
</tr>
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</table>

Table 1. Anthropometric and respiratory measurements of the study sample. Abbreviations: FEV1 = Forced expired volume in one second (L), FVC = Forced vital capacity (L), FER = Forced expired ratio (%), BMI = Body Mass Index (Kg/m²), DLCO = Carbon monoxide transfer factor (mmol/min/kPa), VA = Alveolar volume (L).

**Prediction equations for DLCO and VA in males**

Both linear and more complex higher order models and interactions between variables were explored. The model that gave the best fit was one in which the height was cubed, age squared and included an interaction between age and being an ex-smoker (Table 2). This model explained over a third of the variance in DLCO. Predicted VA was a simpler linear equation which included the terms height and weight which described nearly half of the variance in VA.

**Prediction equations for DLCO and VA in females**

The model that gave the best fit for DLCO in the female population was one that included height, height cubed, age, weight and an age-height interaction (Table 2). Similar to the equations for males this model explained 36% of the variance. The equation for VA was also similar to the male equation including height and weight, however it also included an age-height interaction term and explained a third of the variance.

**Age-Height Interaction**

In our sample, there was an interaction between age and height that was a significant predictor for all outcomes in females. The effect of an age height interaction was a greater rate of decline in age-related DLCO with increasing height. That is, the taller the subject the more rapid the decline in DLCO with age (see Figure 1 in on line repository). This interaction is a novel finding which significantly increases the total explanatory power of the model.

<table>
<thead>
<tr>
<th></th>
<th>Prediction equation</th>
<th>R²</th>
<th>SD</th>
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<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO</td>
<td>1.109<em>Ht³ - 0.000402</em>A² - 0.035<em>A</em>ExSm + 1.805*ExSm +4.696</td>
<td>36.0%</td>
<td>3.71</td>
</tr>
<tr>
<td>DLCO⁹⁵th</td>
<td>1.109<em>Ht³ - 0.000402</em>A² - 0.035<em>A</em>ExSm + 1.805*ExSm +6.741</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO⁵th</td>
<td>1.109<em>Ht³ - 0.000402</em>A² - 0.035<em>A</em>ExSm + 1.805*ExSm +2.651</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td>10.155<em>Ht - 0.013</em>Wt - 0.0000943*A² - 9.628</td>
<td>47.8%</td>
<td>0.69</td>
</tr>
<tr>
<td>VA⁹⁵th</td>
<td>10.155<em>Ht - 0.013</em>Wt - 0.0000943*A² - 8.501</td>
<td></td>
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</tr>
</tbody>
</table>
Table 2. Abbreviations: Ht = Height (metres), A = Age (years), ExSm = Ex Smoker. Ex-smoker is a binary term in which ex-smoker is one and never-smoker is zero, BMI = Body Mass Index (Kg/m²).

Comparison with other equations
Table 3 gives the mean predicted DlCO for other published prediction equations using our data set. In our sample, DlCO expressed as a percent predicted was systematically lower using all the previous commonly used prediction equations. This is highly likely to reflect the older population included in our study. The previous prediction equations that best fitted our sample were those of Miller (5). Conversely, the equations of Knudson (7) substantially overestimated the observed mean DlCO in both males and females.

DISCUSSION
We have developed a new set of prediction equations for the measurement of DlCO and VA for a middle aged and older population using current computerised equipment and methods. We have shown that there are major differences in our equations compared with previous studies that were mainly developed in younger populations (Table 3). The importance is that a significant proportion of patients seen in a clinical lung function laboratory are in this particular age group, making our new equations more clinically relevant.

Table 3. Comparison of mean percent predicted DlCO in this sample using other published equations.

Many of the respiratory disorders that use DlCO to help diagnosis, such as parenchymal and pulmonary vascular lung diseases, occur predominantly in an older population. Previous equations (1, 3, 4, 5, 7) have had relatively few subjects (eg, 8 males (3)) in older age groups (>60 years) compared with younger (<40 years) age groups. The inclusion of relatively few older subjects has led to the equations being susceptible to error in this group. Moreover, extrapolating the equations to patients with an age greater than those included in a specific study can lead to considerable error, especially if the data are biased to a younger population.
Previous studies looking at spirometric prediction equations in an older population have shown differences of up to 20% when compared with extrapolating equations generated from a younger population (10, 11). The mean age of the subjects in our study was substantially older than other recent studies of normal DLCO ranges, where the mean age has been as young as 35 years (1). Over half the subjects in our sample were more than 55 years of age.

**Smoking status**

A substantial minority of the subjects included in our study were classified as ex-smokers which improves the generalisability of our prediction equations. Although most of these subjects had only a limited smoking history, separate analyses to develop separate prediction equations for DLCO based on the never smokers and ex-smokers were performed. Whilst the regression curves were slightly different (figure 2 on-line repository), especially in the older subjects, this was not statistically significant. Nonetheless, being an ex-smoker was a significant predictor of DLCO in our male population. There may have been some under-reporting of previous smoking in this population, or there may have been some other confounding factor such as passive smoking/occupational exposures to explain the results. Furthermore, there was an interaction between age and being an ex-smoker. Ex-smoker status was only a significant predictor for DLCO in the males and not the females, who may have smoked less.

**Comparison with other equations**

This is the first study to describe a set of prediction equations for the measurement of DLCO and VA in a middle aged and older population. Moreover we have shown a number of interactions between predictors that had significant effects on the outcome. Previous studies have mainly confined predictors to Height and Age (1, 3, 4, 5, 7). However some other authors have used terms including weight (1). Previous studies have also tested for non-linear effects and also performed various transformations, which have added little to the strength of the models (1, 5). We confirmed that the improvement in R² using complex higher order terms was small compared to the use of simple linear equations. However, we believe it makes little difference to the end user as most equations are now incorporated within the software of the measuring device.

The subjects studied were sampled randomly for another larger epidemiological study (17). There is much controversy in the literature regarding the inclusion of ex-smokers. Some studies have found statistically different measurements of DLCO in smokers versus non-smokers, but we did not find this in our group. Ex-smokers would be expected to have a lower DLCO than never smokers. As a high proportion of patients presenting to a pulmonary function laboratory are former smokers, the ability to adjust for this factor improves the likelihood of detecting pulmonary disease.

One methodological difference between various prediction equation studies is the FiO₂ of the inspired mixture. It is well known that higher the FiO₂ the lower the measured DLCO (29). The various published studies have used a FiO₂ ranging from 18% (1) to 25% (4). For the study that used 25% the reason for the higher FiO₂ was to counteract the effect of that study being performed at an altitude of 1520m. However the majority of the studies have used a FiO₂ of approximately 21%. Nevertheless, there are still large differences in measured DLCO across the various equations that use the same FiO₂ (figures 1a and b). One exception is the equations published by Roca (1), if these were corrected to an FiO₂ of 21% this would reduce the overall DLCO, leading to similar results obtained in the current study and the equations published by Miller (5).
An important consideration when using prediction equations is the cross over age from one set of equations to another. Although rarely a problem in an adult population, this issue is highlighted when changing from equations based on children to equations from an adult population as an individual patient reaches adulthood. From Figures 1a and b the issue is highlighted at an age of 45 years where the equations for the current study start. The equations that minimise the difference in DLCO at an age of 45 years are those published by Miller (5), Quanjer (31), Crapo (4) and Roca (1).

Weight term
Weight was first demonstrated by Roca et al (1) to be a significant predictor of DLCO in females. However the weight term may falsely elevate the predicted DLCO especially in overweight and obese subjects. Part of this is likely due to the narrow weight range that was included in the population studied (60 – 75Kg (1)). Therefore previously published equations need to be extrapolated on a relatively frequent basis making the predicted value unreliable. This is especially the case with the documented increase in obesity in the population (32). Not including the weight term would lead to increase numbers of people with reduced DLCO relative to their predicted values solely based on their weight.

Further analysis of BMI demonstrated that 1.9% of the subjects were classified as underweight (BMI < 20kg/m²), 29.2% were of ideal weight (BMI 20 – 25), 47.3% were classified as overweight (BMI 26 – 30) and 21.6% subjects were classified as obese (BMI>30). There was a positive relationship between weight and DLCO. However the maximum difference in mean DLCO between the groups was only 0.60 mmol/min/KPa. Furthermore it was the overweight not the obese group that lead to the significant weight term in the equation. The mean DLCO for the overweight group was 0.60 mmol/min/KPa higher than the ideal weight (p<0.001) whereas in the obese subjects the DLCO was only 0.35 higher than the ideal weight group.

Effect of equipment and testing methodology on the measurement.
There are relatively few studies that have entirely complied with the ATS/ERS criteria (9) for the measurement of DLCO. Importantly, existing studies have significant methodological differences in the measurement of DLCO relating to the calculation of breath-hold time, FiO₂ and dead space correction. Moreover there have not been any published prediction equations using fully computerised equipment. The type of analyser used for the CO analysis, the type of insoluble inert marker gas used for the calculation of VA and estimating the initial alveolar CO concentration may all play a part in contributing to the variability of the measurement of DLCO. Our study is up to date, using modern equipment and methods.

Calculation of breath hold time has also shown to be important leading to differences of up 6.8% in measured DLCO (23) between the method described by the Epidemiology Standardisation Project (24) and Ogilvie et al (25). Using the breath-hold time calculation as described by Jones and Meade (22) gives a similar measured DLCO to that of Ogilvie et al (25). The ATS criteria stipulate the Jones-Meade calculation, which is what was used in the current study.

The Medgraphics system uses gas chromatography for the analysis of tracer gases. Also peculiar to this system is the use of Neon as the insoluble inert tracer gas. Neon has a relatively low diffusivity and therefore likely to distribute further throughout the lung leading a higher measured alveolar volume than Helium (26). Even though the latest ATS/ERS (9)
document states that the tracer should have a diffusivity closer to that of Helium, there are now large numbers of computerised devices that use different gases such Methane and Helium.

**Conclusion**
We have developed a set of prediction equations for an older population using modern computerised equipment. The equations generated gave a significantly higher predicted $D_{L}CO$ than most of those previously published (1, 3, 6, 7). Most of the differences are likely to be explained by the older population, but methodological differences cannot be excluded. The latest ATS/ERS guidelines for the performance of $D_{L}CO$ state that prediction equations need to be selected carefully taking into account important methodological differences. This is one of the few studies using fully computerised equipment, gas chromatography for the gas analysis and Neon as the tracer gas. Furthermore we have developed a set of predictions equations more specific to an older population which are therefore, likely to be the most clinically relevant available.
Acknowledgments

This study was supported by the National Health & Medical Research Council of Australia. Biljana Skoric and Melanie Matheson assisted with data collection and management.
REFERENCES


18. ECRHS questionnaire (http://www.ecrhs.org/Quests/mainquest.pdf)


Legends

Figure 1a and b. DLCO vs Age for males (a) and females. Height for the males was assumed to be the mean height in our sample (1.75meters for the males and 1.62meters for the females). The weight in the females was assumed to be the mean measured weight of the sample 70.4Kgs. The Miller equations were those of the non-smoking group.
ON-LINE DATA REPOSITORY

PREDICTION EQUATIONS FOR SINGLE BREATH DIFFUSING CAPACITY IN A MIDDLE AGED AUSTRALIAN POPULATION

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METHODS

Subject selection

$D_L CO$ and $V_A$ were obtained in Caucasian subjects with no history of lung disease who either never smoked or were minimal ex-smokers. The subjects were recruited as part of another larger epidemiological study of COPD (1). All patients had $D_L CO$ and spirometry measured, and were administered a respiratory health questionnaire (2). The interviewer-administered questionnaire comprised validated items on bronchial symptoms from the IUATLD questionnaire (3), British Medical Research Council items on cough, sputum and shortness of breath (4), demographics, past and family history and environmental risk factors from the main ECRHS questionnaire. Smoking status was based on standard Australian smoking questions (5). Only subjects in two categories were included: Firstly ex-smokers who did not smoke at all now, but have smoked at least 100 cigarettes or a similar amount of other tobacco products in their lifetimes. Secondly never smokers were defined as people who did not smoke now and have smoked fewer than 100 cigarettes or similar amount of other tobacco products in their lifetimes. Subject with a serum cotinine > 100 µmol/L were reclassified as current smokers and excluded from the analysis. To avoid including any subjects with undiagnosed COPD based on their lung function tests, we further excluded any subject who met Global Obstructive Lung Disease (GOLD) (6) criteria for stage 2 or greater. The study was approved by the Ethics Committee at The Alfred, Melbourne. All participants gave written informed consent.

Measurement of $D_L CO$ and Alveolar Volume

Single breath $D_L CO$ was measured in duplicate on a fully computerised system (Medgraphics Profiler, Minnesota, U.S.A) according to ATS/ERS guidelines (7). This testing system uses gas chromatography for the measurement of gas concentrations and a pitot tube for measurement of flow. The inspired gas mixture contained 0.3% carbon monoxide, 0.5% neon, 20.6% oxygen with the balance, nitrogen. Breath-hold time was calculated as described by Jones-Meade (8), washout and sample volumes were set to 0.9 L, and an interval between repeat tests was at least 4 minutes. At least two measurements were performed which had to agree to within 1 mmol/min/kPa or 10%, whichever was greater, otherwise a further measurement was made until repeatable results were obtained. All $D_L CO$ results were corrected to a standard haemoglobin concentration of 14.6 g/dl using the method described by Cotes (9). Standing height (meters) and body weight (kilograms) were measured without shoes.

Quality control of equipment

The quality control of the flow and volume signals was performed using a pulmonary waveform generator initially, an explosion decompression device monthly and biological control performed weekly. The flow sensor was also calibrated prior to each testing session using a 3 litre certified syringe. The accuracy of the $D_L CO$ and $V_A$ measurements was determined monthly using a custom built validator. The $D_L CO$ and $V_A$ validator consisted of a 3L certified syringe and two accurately known concentrations of inspired and expired CO and Ne to simulate typical inspired and expired gas concentrations. With the two gas mixtures it was possible to simulate a measured $D_L CO$ and $V_A$ value with known limits of agreement (7.20 – 7.43 mmol/min/kPa for $D_L CO$ and 3.15 - 3.25 L for $V_A$). All measurements were reported at ATPS and subject dead space correction was not included.
Results of the quality assurance program

The equipment remained within specification throughout the study and at no stage were any faults identified. There was no evidence of drift during the study. Based on the custom built validator, the inspiratory vital capacity, D\textsubscript{i}CO and V\textsubscript{A} were all within specification. The coefficient of variation for D\textsubscript{i}CO and V\textsubscript{A} from the custom built validator was 3.08% and 2.13% respectively. The coefficient of variation for D\textsubscript{i}CO and V\textsubscript{A} for the biological controls was 3.81% and 1.14% respectively.

Statistical analysis

All analysis was performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) or SPSS version 15.0 (SPSS Inc, Chicago, IL 2006). Multivariate linear regression models were constructed using a stepwise selection technique and validated using a backwards elimination technique. Each model was then assessed for clinical and biological plausibility. A two-sided p-value of 0.05 was considered statistically significant.
Predicted DLCO vs Age for 2 fixed heights within the female sample. Solid line is for a subject whose height is 1.5 meters, and the dotted line is for a subject whose height is 1.7 meters.
Measured DLCO vs Age for men. Subjects who never smoked are represented by dots (…) and subjects classified as ex-smokers are represented by xxx. The regression curve for the never smokers is represented by the dashed line and the regression curve for the ex-smokers is represented by the solid line.
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Prediction equations for single breath diffusing capacity (dlco) in a middle aged caucasian population

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