Taylor & Francis
Taylor & Francis Group

Inhalation Toxicology

International Forum for Respiratory Research

ISSN: 0895-8378 (Print) 1091-7691 (Online) Journal homepage: http://www.tandfonline.com/loi/iiht20

Ozone exposure-response model for lung function changes: an alternate variability structure

William F. McDonnell, Paul W. Stewart & Marjo V. Smith

To cite this article: William F. McDonnell, Paul W. Stewart & Marjo V. Smith (2013) Ozone exposure-response model for lung function changes: an alternate variability structure, Inhalation Toxicology, 25:6, 348-353, DOI: 10.3109/08958378.2013.790523

To link to this article: https://doi.org/10.3109/08958378.2013.790523

http://informahealthcare.com/iht
ISSN: 0895-8378 (print), 1091-7691 (electronic)

Inhalation Toxicology

Inhal Toxicol, 2013; 25(6): 348–353

DOI: 10.3109/08958378.2013.790523

informa healthcare

RESEARCH ARTICLE

Ozone exposure-response model for lung function changes: an alternate variability structure

William F. McDonnell[1], Paul W. Stewart[2], and Marjo V. Smith[3]

[1]*William F. McDonnell Consulting, Chapel Hill, NC, USA,* [2]*Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA, and* [3]*SRA International, Durham, NC, USA*

Abstract

Context: A statistical model that accurately predicts human forced expiratory volume in one second (FEV_1) response to ozone exposure has been identified and proposed as the foundation for future risk assessments for ambient ozone. We believe that the assumptions about intra-subject variability in the published model can be improved and hypothesize that more realistic assumptions will improve the fit of the model and the accuracy of risk assessments based on the model.
Objective: Identify alternate assumptions about intra-subject variability and compare goodness-of-fit for models with various variability structures.
Materials and methods: Models were fit to an existing data set using a statistical program for fitting nonlinear mixed models. Goodness-of-fit was assessed using Akaike's Information Criteria (AIC) and visual examination of graphical figures showing observed and predicted values.
Results: The AIC indicated that a model that assumed intra-subject variability was related to the magnitude of individual response fit the data better than a model that assumes intra-subject variability is constant across individuals and exposures (the original model). This finding was consistent with the variability of observed responses for filtered air exposures and for exposures predicted to be below the threshold for response.
Conclusion: An ozone exposure-response model that assumes intra-subject variability increases with individual mean FEV_1 response appears to fit the data better than one that assumes constant variability.

Keywords

Air pollution, exposure-response, lung function, model evaluation, ozone, risk assessment, variability

History

Received 24 February 2013
Revised 25 March 2013
Accepted 25 March 2013
Published online 6 June 2013

Introduction

We have recently identified a statistical model that accurately describes the exposure-response (E-R) characteristics of volunteers exposed to a wide range of controlled ozone exposure conditions for changes in forced expiratory volume in one second (FEV_1) (McDonnell et al., 2012). We have also established that this model accurately predicts responses of individuals whose data were not used to estimate the parameters of the model (McDonnell et al., 2010). The model, which is described in the Methods and in Appendix A of this manuscript, completely specifies a well-defined functional form for central tendency, for between-subject variability and for within-subject variability.

Our efforts in the earlier manuscripts were focused upon identification of the functional form for central tendency of response, identification of a proper inter-subject variability structure and estimation of the primary parameters of the model. We selected a typical within-subject error structure that was additive and that assumed constant variance for intra-subject variability at all levels of exposure and response. In retrospect, however, it seems clear to us that intra-subject variability is more complex than was originally specified and that its misspecification can result in less accurate assessment of risk when an adverse outcome is defined as a decrement in FEV_1 that exceeds some given magnitude. Rather than being constant across all individuals and all exposures, it seems likely that intra-subject variability increases with increasing response. It is well known that differences exist among individuals in the magnitude of FEV_1 response to similar ozone exposures and that the range of these differences in response increases at higher levels of exposure and response (McDonnell et al., 1983). If the ozone E-R functions were linear, the individual differences in responsiveness to ozone would be defined by differences in slope with the arithmetic differences in FEV_1 response increasing in proportion to both the level of response and the level of exposure (which are linearly related in this example). In reality, the ozone–FEV_1 relationship is best represented by a sigmoid-shaped curve where variability among individuals in ozone responsiveness

Address for correspondence: William F. McDonnell, MD, PhD, 1207 Hillview Road, Chapel Hill, NC 27514, USA. Tel: 919-967-1219. E-mail: McDonnell.William@Earthlink.Net

is defined by differences in the parameter representing the FEV_1 response plateau. This results in a series of individual sigmoid curves for which FEV_1 response differs proportionately at respective points on the individual curves. This constant proportionality difference implies that at very low exposures, the arithmetic differences in response are small and increase with both exposure and response until the upper plateau in response is reached at which point the absolute differences in response become constant even if exposure continues to increase. Although responsiveness to ozone is generally stable over time for a given individual (McDonnell et al., 1985), there is likely to be some day-to-day variability. Similar to the effect of differences in between-subject responsiveness described above, the effect of day-to-day changes in within-subject responsiveness will result in a family of sigmoid curves for each individual for which the arithmetic differences in response are proportional to the level of response for that individual. In addition, although spirometry was performed and FEV_1 data were reduced according to American Thoracic Society criteria for all studies from which data were obtained, it is possible that the presence of respiratory symptoms such as pain upon deep inspiration may have resulted in somewhat more variability in FEV_1 at higher levels of response. If the above are true, use of our current model, with its assumption of constant intra-subject variance, may result in an over-prediction of the variability of response (and consequently the risk of experiencing a 10% FEV_1 decrement) for low level exposures and an under-prediction of variability for high level exposures. The purpose of this manuscript is to identify several alternate structures for intra-subject variability and to determine whether any of these improve the fit of the model to the data.

Methods

The data for this analysis are identical to those used in our previous publication (McDonnell et al., 2012) and include the FEV_1 responses of 741 individuals (637 males and 104 females) exposed one or more times to ozone and/or filtered air (FA). These individuals contributed 11 415 measures of lung function (8477 during ozone exposures and 2938 for FA exposures). The exposure and response data as well as the participant characteristics were gathered from 23 controlled ozone exposure studies conducted either at the US EPA laboratory in Chapel Hill, NC or the Human Performance Laboratory in Davis, CA, and are described in detail in previous publications (McDonnell et al., 2007, 2012). All studies from which data were collected were approved by the governing institutional review boards, and all volunteers provided informed consent prior to participation.

The outcome of interest ($\%\Delta FEV_{1ijk}$) is the percent decrement in FEV_1 from baseline calculated for the *i*th participant at the *j*th time in the *k*th ozone exposure protocol and adjusted for any effect of FA by subtracting the observed mean percent decrement in FEV_1 during the FA control exposures (McDonnell et al., 2012). The statistical model characterizing the relationship between ozone exposure and this FA-adjusted lung function response is described in Equation (1).

$$\%\Delta FEV_{1ijk} = e^{(U_i)} \times M_{ijk} + E_{ijk} \quad (1)$$

in which M_{ijk} represents the median response of the population for a given set of demographic and exposure conditions and is fully defined in Equations (A1)–(A3) in Appendix A in terms of ozone concentration (C), minute ventilation ($\dot{V}_E$), body surface area (BSA), age and body mass index (BMI). The random effect variable U_i represents inter-subject variability in responsiveness of individuals to ozone and is assumed to be normally distributed with mean zero. The product of $e^{(U_i)} \times M_{ijk}$ is the central tendency of response for the *i*th individual for a given set of demographic and exposure conditions. The variability around this central tendency of response for an individual (the intra-subject variability) is represented by E_{ijk} which, in the original model (McDonnell et al., 2012), was assumed to be normally distributed with mean zero and with constant variance. Together, Equations (1), (A1), (A2) and (A3) comprise a parametric, nonlinear statistical model for clustered data and completely specify a well-defined functional form for central tendency and for variance and correlation.

The alternate models that we identified in this study are identical to the model above with one exception: in each case assumptions about the structure of the intra-subject variability differ. The following refer to those assumptions with E_{ijk} still being normally distributed with mean zero in all cases.

$$\begin{aligned}
\text{Model 1 (original)} \quad & \text{Var } E_{ijk} = \nu 1 \\
\text{Model 2} \quad & \text{Var } E_{ijk} = \nu 1 + \nu 2 \times (M_{ijk}) \\
\text{Model 3} \quad & \text{Var } E_{ijk} = \nu 1 + \nu 2 \times (e^{U_i} \times M_{ijk}) \\
\text{Model 4} \quad & \text{Var } E_{ijk} = \nu 1 + \nu 2 \times (e^{U_i} \times M_{ijk}) \\
& \qquad + \nu 3 \times (e^{U_i} \times M_{ijk})^2
\end{aligned}$$

where $\nu 1$, $\nu 2$ and $\nu 3$ are parameters whose values are to be estimated from the data.

Model 1 assumes that the variance of intra-subject variability is constant for all levels of exposure and response. This would be expected for the situation in which ozone responsiveness for an individual was invariate and FEV_1 was measured with equal precision under all conditions. Model 2 assumes that the intra-subject variance increases in proportion to M_{ijk} which represents the median response of the population for given exposure and demographic conditions. Model 3 assumes that the intra-subject variance increases as a linear function of $(e^{U_i} \times M_{ijk})$ which is the mean response of the *i*th individual for given exposure and demographic conditions. This model best reflects the effects of day-to-day changes in ozone responsiveness as outlined in the Introduction. Individuals experiencing small effects either because exposure was low, or because of demographics (e.g. older age) or because baseline value of responsiveness (U_i) was small would be expected to exhibit less variability in response than those with larger mean responses. Model 4 assumes a quadratic relationship between intra-subject variability and mean response for the individual for a given exposure. Other factors besides those identified in this manuscript may also contribute to intra-subject variability. This model allows for a more complex relationship than that reflected in Model 3 should the data indicate the need for it.

All models were fit using PROC NLMIXED, SAS 9.2 (SAS Institute, Inc., Cary, NC) a procedure specially designed

for fitting nonlinear random-effects models. Model fitting provided statistical estimates of the primary model parameters ($\beta 1 \ldots \beta 9$, $\nu 1 \ldots \nu 3$, and variance of U_i). These maximum likelihood estimators (MLEs) of the primary parameters were used to compute confidence intervals and to compute MLEs of secondary parameters such as expected values and the probability that an individual would experience an effect greater than a given magnitude. Akaike's Information Criteria (AIC) was calculated for comparison of goodness-of-fit of the models. Details of model fitting and calculation of predicted values are described in McDonnell et al. (2012). An example of NLMIXED programming statements for fitting the models is provided in Appendix B.

The overall goodness-of-fit of each model was evaluated by plotting the observed responses versus predicted responses for the central tendency of response as well as for the proportions of individuals experiencing FEV_1 decrements greater than 10%, 15% and 20%. Study-specific goodness-of-fit was evaluated for each exposure by plotted averages of observed values and averages of predicted values versus time. Agreement between different fitted models was evaluated by graphically comparing their sets of predicted values.

For purposes of comparison with the intra-subject variance estimated from Models 1 to 4 for low-level ozone exposures, we estimated the intra-subject variance of the FEV_1 responses for the FA exposures after adjusting for the mean FA response at each time point of each study, and we estimated the intra-subject variance for the observed responses of all ozone exposures that were predicted to be below the threshold for response as defined in Equation (A2) of Appendix A. The estimates were obtained by fitting linear repeated-measures analysis of variance models.

Results

Models 1, 2 and 3 were successfully fit, and parameter estimates and the AIC for each model are presented in Table 1. We were unable to obtain convergence for Model 4 suggesting that either the model is not an optimal one or that the data are not adequate to evaluate this model. In Model 1 (the original model), the variance of E_{ijk} was assumed to be a constant with an estimated value (SE) of 17.08 (1.13) as was reported in McDonnell et al. (2012). In Model 2, the estimated variance of E_{ijk} was assumed to be a linear function of M_{ijk}, the predicted median population response for given demographic and exposure characteristics, and in Model 3, the estimated variance of E_{ijk} was assumed to be a linear function of $(e^{U_i} \times M_{ijk})$, the predicted central tendency of response for an individual with given demographic and exposure characteristics and a specific value of U_i. The AIC was progressively lower for the models in which the intra-subject variance was more closely related to an individual's predicted response, and estimated values of $\nu 1$ and $\nu 2$ were significantly different from zero for Models 2 and 3. The AIC indicated that Model 3 fits the data better than the other two models. The estimates of β1, β3, β5, β6 and the estimated variance of U_i were generally similar for all three models (Table 1) while estimates of other coefficients and their standard errors were sensitive to perturbations of model assumptions. Although some coefficients did vary across models, visual examination of graphs revealed little if any difference in predicted E-R characteristics among the models.

Plots of observed versus predicted responses exhibit small inconclusive differences from graph to graph, and plots of observed and predicted responses versus time revealed little, if any, visual difference in the fits of the three models to the data. The predicted values for all of the models were generally similar with no consistent pattern of differences across all endpoints.

The estimated intra-subject variance (SE) of the 2938 FA responses (adjusted for mean FA response) was 5.28 (0.15). The estimated intra-subject variance (SE) of the 253 responses for ozone exposures identified by Model 3 as being below threshold was 7.32 (0.81).

Discussion

The increasingly better fit of models (indicated by decreasing AIC) in which the variance of intra-subject variability is more closely related to magnitude of individual predicted response is consistent with our hypothesis that intra-subject variability increases with increasing levels of response which is most likely due to the existence of day-to-day variability in ozone responsiveness. This is further supported by comparison of

Table 1. Estimated coefficients and statistical parameters for models with three variability structures[a].

Model	Original (Model 1)	Model 2	Model 3
β1	11.091059 (0.847759)	9.356645 (0.725447)	9.763037 (0.848493)
β2	−0.287275 (0.256745)	−0.346580 (0.109620)	−0.431453 (0.123605)
β3	0.014862 (0.001169)	0.012763 (0.002826)	0.012808 (0.001139)
β4	13.449713 (2.355605)	52.609218 (27.180879)	30.920850 (6.213557)
β5	0.003224 (0.000209)	0.002825 (0.000192)	0.002921 (0.000198)
β6	0.886759 (0.001809)	0.988797 (0.060574)	0.952545 (0.000206)
β8	0.546653 (0.368904)	0.957210 (0.224196)	0.489014 (0.223399)
β9	59.949843 (0.034599)	7.494455 (25.694545)	32.944404 (0.189891)
$\nu 1$	17.075670 (1.130057)	10.243165 (1.121702)	9.111714 (0.944807)
$\nu 2$	–	2.513969 (0.331660)	2.166247 (0.235499)
Var (U)	0.916567 (0.070497)	1.008008 (0.093703)	1.122874 (0.101749)
AIC	49 583	49 161	48 460

AIC: Akaike's Information Criteria; Var: estimated variance of parameter.

[a]Models and parameters definitions are as described in Equations (1) and (A1)–(A3). Model 1 assumes that intra-subject error has constant variance. Model 2 assumes that intra-subject error variance is a linear function of population median response. Model 3 assumes that intra-subject error variance is a linear function of individual mean response. Values in parentheses are standard errors. Confidence limits (95%) for each parameter are approximately equal to the estimate ±2 SE.

the estimates for variance of intra-subject error for low-level ozone exposures from Models 1 and 3 with observations of responses for below-threshold ozone exposures and FA exposures. The value of $\nu 1$ from Model 3 (9.1) is an estimate of the variance of intra-subject error for the lowest level ozone exposures (those with $e^{U_i} \times M_{ijk} = 0$) and is consistent with the observed intra-subject variance (7.3) of the smaller data set of 253 responses from ozone exposures which were predicted to be below threshold. In contrast, the estimate of $\nu 1$ for Model 1 is 17.1. The intra-subject variance of the observed FA responses (5.3) provides another estimate of intra-subject variability of below-threshold ozone exposures which is also consistent with the estimate of $\nu 1$ from Model 3. Estimates based upon the FA responses are expected to be smaller than those based upon ozone exposures as the FA exposures were based upon a single day's measurements while ozone exposures were conducted on one day and corrected for FA exposures which occurred on a second day.

Changes in assumptions about the intra-subject variance structure had small, inconsistent effects on graphs of central tendency of response and proportions of individuals expected to experience FEV_1 changes in a given magnitude, and the improved fit of Models 2 and 3 was difficult to detect by simple examination of plots or linear regression of observed and predicted values. This suggests that the improvements in fit are modest.

Ozone risk assessment involves estimation of the number of individuals living in a metropolitan area with a given set of ambient ozone concentrations who would be expected to experience an FEV_1 decrement of some magnitude (e.g. 10%) over some period of time. This requires simulation of a large number of exposures for a population of interest using models such as proposed here and summation of the numbers of exposures producing a 10% FEV_1 decrement. Each simulation requires specification of demographic characteristics and exposure conditions and selection of a value for individual responsiveness (U_i from Equation 1) to ozone from the estimated distribution of possible values as well as a value for the intra-subject variability (E_{ijk}) from its distribution of possible values. Most simulated exposures are to low levels of ozone with small predicted central tendencies of response. An overestimate of the variance of the distribution of possible values for intra-subject variability will result in selection of larger positive and negative values of E_{ijk} and an overestimate of the variability of predicted responses. This lack of precision is unlikely to bias estimates of the central tendency of response; however, it will result in an overestimate of the number of responses greater than 10% for low-level ozone exposures.

The current study indicates that Model 3 fits the data better and provides more accurate estimates of intra-subject variability for low-level ozone exposures than Model 1. Although the estimated variance of the between-subject variability is larger in Model 3 than in Model 1 and may contribute to increased variability in population response, we expect that this reflects a more accurate partitioning of inter-subject and intra-subject variability. We expect that the use of Model 3 parameters will result in more accurate estimates of risk. Use of Model 3 in simulating exposures for risk assessment does require that the intra-subject variance be calculated for each level of response which is computationally trivial. The confidence intervals around each estimate of intra-subject variance will be larger than the confidence interval around a constant variance due to the smaller numbers of observations for each level of response.

In conclusion, the AIC and the statistical significance of $\nu 2$ indicate that Model 3, in which intra-subject variability increases with increased predicted individual response, fits the data better than our previous model in which variability is assumed to be constant. Although plots of the data are not informative regarding how much of an effect using Model 3 rather than Model 1 will have on risk assessment, we believe that the logic underlying the assumptions of Model 3 is compelling. Furthermore, the observed intra-subject variability in the FA data and the below-threshold ozone exposure data are consistent with the estimate of $\nu 1$ in Model 3.

Acknowledgements

The authors thank Dr. William Adams, Dr. Edward Schelegle and Dr. Chong Kim for providing E-R data for their studies.

Declaration of interest

The authors received funding to conduct this modeling research from the American Petroleum Institute and have previously received funding from API to conduct related modeling research. Dr. McDonnell has previously consulted for API and the US EPA.

References

McDonnell WF, Horstman DH, Abdul-Salaam S, House DE. (1985). Reproducibility of individual responses to ozone exposure. Am Rev Respir Dis 131:36–40.

McDonnell WF, Horstman DH, Hazucha MJ, et al. (1983). Pulmonary effects of ozone exposure during exercise: dose-response characteristics. J Appl Physiol: Respir Environ Exercise Physiol 54:1345–52.

McDonnell WF, Stewart PW, Smith MV. (2007). The temporal dynamics of ozone-induced FEV_1 changes in humans: an exposure-response model. Inhal Toxicol 19:483–94.

McDonnell WF, Stewart PW, Smith MV. (2010). Prediction of ozone-induced lung function responses in humans. Inhal Toxicol 22:160–8.

McDonnell WF, Stewart PW, Smith MJ, et al. (2012). Prediction of lung function response for populations exposed to a wide range of ozone conditions. Inhal Toxicol 24:619–33.

Appendix A

Model details

Equation (1) in the main body of the manuscript contains the term M_{ijk} which represents the population median FEV_1 response to ozone via the variable X_{ijk}. Equations (A1)–(A3) define the relationship between M_{ijk} and exposure conditions for a given set of demographic characteristics.

$$\mathrm{d}(X_{ijk})/\mathrm{d}t = C_{ijk} \times \left[(\dot{V}_E/\mathrm{BSA})^{\beta 6}\right]_{ijk} - (\beta 5 \times X_{ijk}) \qquad (A1)$$

Here, X_{ijk} is the value of an intervening variable X for the ith person, at the jth time, in the kth exposure protocol. The value of X increases over time as a function of the dose rate $(C \times \dot{V}_E)$ and decreases over time according to first order reaction kinetics. One could interpret X to represent the level of oxidant stress resulting from accumulation and removal of ozone or its reactive byproducts, although the validity of the model is not dependent upon this interpretation. The initial ($t = 0$) value of $X_{ijk} = 0$. Time is in minutes, C is the instantaneous concentration in ppm, $\dot{V}_E$ is the instantaneous minute ventilation in $\mathrm{l\,min^{-1}}$, BSA is body surface area in $\mathrm{m^2}$, the coefficient β5 is the inverse of the time constant for this differential equation and β6 allows response to differ in sensitivity to C and $\dot{V}_E$. Note that for any given temporal profile of C and $\dot{V}_E/\mathrm{BSA}$, this differential equation can be integrated over time and the temporal profile of X can be calculated if β5 and β6 are known.

$$(X_{ijk})_{\mathrm{Th}} = (X_{ijk} - \beta 9) \times I \qquad (A2)$$

in which I has a value of 1 if $X_{ijk} > \beta 9$; otherwise, I has a value of 0.

β9 is a threshold level of X below which no response is observed.

$$M_{ijk} = \left\{\left(\beta 1 + \beta 2\left[\mathrm{Age}_{ijk} - 23.8\right] + \beta 8[\mathrm{BMI} - 23.1]\right) \Big/ \left[1 + \beta 4 e^{-\beta 3\left(X_{ijk}\right)_{\mathrm{Th}}}\right] - \left(\beta 1 + \beta 2\left[\mathrm{Age}_{ijk} - 23.8\right] + \beta 8[\mathrm{BMI} - 23.1]\right)/[1 + \beta 4]\right\} \qquad (A3)$$

and is equal to the median of the population response distribution.

The right hand side of Equation (A3) is an algebraic function of X_{Th} which is modified by age (centered on 23.8 years, the mean age of the sample) and body mass index (BMI) (centered on $23.1\,\mathrm{kgm^{-2}}$, the mean BMI of the sample). It contains a mathematical adjustment to allow predictions of zero ozone-induced effect when $X_{\mathrm{Th}} = 0$ (e.g. at time = 0 and during FA exposures). One could interpret this equation as representing the neurally mediated lung function response to the oxidant stress described in Equation (A1), although again, the validity of the model is not dependent upon this interpretation. Note that for any given temporal profile of X values calculated from Equation (A1), one can calculate the temporal profile of the population median predicted $\%\Delta FEV_1$ for a volunteer of given age and BMI.

Appendix B

Example of Proc NLMIXED programming statements

```
proc sort      data=work.formodel;
     by        id study exposure time_id ;
     run;
proc nlmixed   data=work.formodel
       gconv  = 1e-11        technique = nrridg
     absgconv  = 1e-7         qpoints   = 30
         qtol  = 1e-4         qmax      = 100
     empirical corr           maxiter   = 900;
     ods       output nlmixed.parameterestimates  = work.betahat;
     ods       output nlmixed.fitstatistics       = work.fitstat;
     parms     B1       =  25.4750
               B2       =  -0.4847
               B3       =   0.0068
               B4       =  49.2633
               B5       =   0.0042
               B6       =   1.000
               B8       =   0.0001
               B9       =   10
               VAR_U    =   0.0001
               NU1      =   15
               NU2      =   0.0001;    /* NU2 could be omitted here  */
           ** NU2=0;                   /* and set to zero here       */
     bounds  0 <= B9;
     *** Tims is partitioned into small intervals ***;
     array      T_[48]        T_1 - T_48          ;  /* time intervals defined       */
     array     Ve_[48]       Ve_1 - Ve_48         ;  /* Ve in each time interval     */
     array    BSA_[48]      BSA_1 - BSA_48        ;  /* BSA on each occasion         */
     array     Cm_[48]  O3_mean_1 - O3_mean_48    ;  /* Ozone concentration fixed or */
     array     Cs_[48] O3_slope_1 - O3_slope_48   ;  /*   changing linearly          */
     *** recursive computation of X across time intervals as a function of B5  ***;
     XB5=   0;
     do J=1 to Time_ID;
        If (J > 1) then Ta= T_[J-1]; else Ta=0;  Tb=  T_[J];  TD= ( Tb - Ta );
        Cm= Cm_[J];   Cs= Cs_[J];
        Vs= 0; Vm= (( Ve_[J] )**B6) / (( BSA_[J] )**B6);
                 /* Ve/BSA is fixed in this example */
        XB5= XB5 * (  exp( -B5*TD ) )
             + ( Cm * Vm * (B5**(-1)) ) * ( 1 - exp(-B5*TD) )
             + ( Cm * Vs * (B5**(-2)) ) * ( ((1-B5*Ta )*exp(-B5*TD)) - (1-B5*Tb  ) )
             + ( Cs * Vm * (B5**(-2)) ) * ( ((1-B5*Ta )*exp(-B5*TD)) - (1-B5*Tb  ) )
             + ( Cs * Vs * (B5**(-3)) ) * ( ((-2+(2*B5*Ta)-(B5*B5*Ta*Ta))*exp(-B5*TD))
                        - (-2+(2*B5*Tb)-(B5*B5*Tb*Tb)) ) ;
     end;
```

```
*** Threshold is B9 ***;
XB5G=  (XB5 - B9) * ( B9  <= XB5 );
*** Nonlinear regression model for central tendency, variance and correlation ***;
Median=  0;
if (XB5G > 0) then do;
      F1=      B1 +  B2*(age-23.8) + B8*(BMI-23.1);
      T1=      1 + B4*exp( -B3 * XB5G );
      T2=      1 + B4;
      Median=  F1*( 1/T1 - 1/T2 );
end;
Yhat=     Median * exp(U);
var_E=    nu1 + nu2*Yhat;
model     DELFEV1 ~ normal( Yhat , var_E );
random          U ~ normal(    0 , var_U )    Subject = ID;
pop_mean= Median * exp(0.5*var_U);
ID       U XB5;
predict pop_mean  out=work.pop_mean
                    (rename=(pred=pop_mean   lower=pop_mean_l95m upper=pop_mean_u95m));
predict Median    out=work.Median
                    (rename=(pred=median     lower=median_l95m   upper=median_u95m  ));
predict Yhat      out=work.Yhat
                    (rename=(pred=Yhat       lower=Yhat_l95m     upper=Yhat_u95m    ));
run; quit;
```