Analisis Efecto de la menopausia 2019

CEMCAT

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Effect of menopause in EDSS trajectories for menopausic women

Data are available for a total of490 women in the databases. In this analyis 74 women have been selected for evaluating changes after menopause in EDSS trajectories

All measurements during first year after CIS have not been considered in the analysis

Model of EDSS before-after Menopause

In this section we can found the results related to effect of time before and after menopause . The equation is shown below. The model include time since menopause and time after menopause . The first coefficient is the slope along time and the second is the change of the slope after the menopause There is an increase of EDSS since the beginning but not change after menopause as can be seen in the figure and in the equation

edss=\beta_{0}+\beta_{1}(t_{since\quad menopause})+\beta_{2}(t_{after \quad menopause})

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Model modmenop1
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Mixed-effects REML regression                   Number of obs     =      2,062
Group variable: nhc                             Number of groups  =         73

                                                Obs per group:
                                                              min =          5
                                                              avg =       28.2
                                                              max =        108

                                                Wald chi2(2)      =      15.69
Log restricted-likelihood = -1660.0962          Prob > chi2       =     0.0004

------------------------------------------------------------------------------
         edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
      tmesura |   .0598102   .0199764     2.99   0.003     .0206572    .0989631
tmesura_after |  -.0096909    .028589    -0.34   0.735    -.0657242    .0463425
        _cons |    1.73579   .1665705    10.42   0.000     1.409318    2.062262
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  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
               var(tmesura) |   .0220553   .0048391      .0143467    .0339059
              var(tmesur~r) |   .0390898   .0101225      .0235311     .064936
                var(_cons) |   1.967701   .3359568      1.408085    2.749728
       cov(tmesura,tmesur~r) |  -.0203062   .0060359     -.0321364    -.008476
          cov(tmesura,_cons) |   .1774655   .0357257      .1074445    .2474865
         cov(tmesur~r,_cons) |  -.1687275   .0478373     -.2624869   -.0749681
-----------------------------+------------------------------------------------
              var(Residual) |   .2183107   .0071685      .2047034    .2328226
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LR test vs. linear model: chi2(6) = 4070.54               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

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Model modmenop1g
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This is the same model but rearranging the coding , and tmesura is the slope after menopause and tmesura-before the change

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Mixed-effects REML regression                   Number of obs     =      2,062
Group variable: nhc                             Number of groups  =         73

                                                Obs per group:
                                                              min =          5
                                                              avg =       28.2
                                                              max =        108

                                                Wald chi2(2)      =      15.69
Log restricted-likelihood = -1660.0962          Prob > chi2       =     0.0004

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          edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+----------------------------------------------------------------
       tmesura |   .0501193   .0199345     2.51   0.012     .0110484    .0891901
tmesura_before |   .0096909    .028589     0.34   0.735    -.0463425    .0657243
         _cons |    1.73579   .1665705    10.42   0.000     1.409318    2.062262
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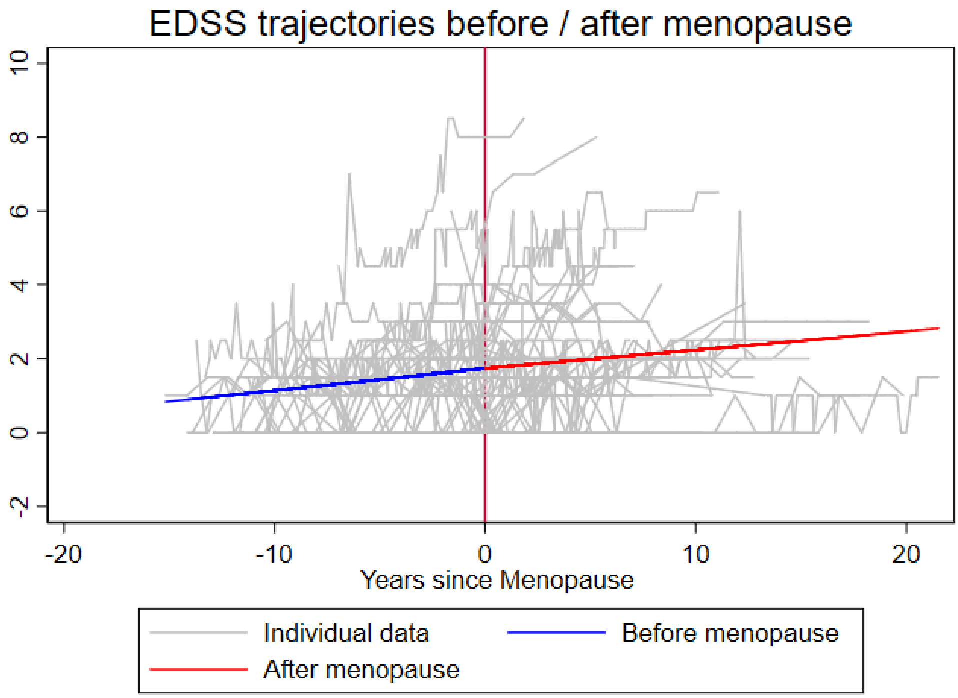
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
                var(tmesura) |   .0205328   .0050347      .0126979     .033202
               var(tmesur~e) |   .0390898   .0101241      .0235292    .0649413
                 var(_cons) |   1.967703   .3359608      1.408081     2.74974
      cov(tmesura,tmesur~e) |  -.0187836   .0062725     -.0310774   -.0064898
         cov(tmesura,_cons) |    .008738   .0306074     -.0512513    .0687274
        cov(tmesur~e,_cons) |   .1687276   .0478585      .0749268    .2625285
-----------------------------+------------------------------------------------
               var(Residual) |   .2183107   .0071685      .2047034    .2328226
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 4070.54               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Next table show the differences before/after relapse

Variable	Effect
Time before menopause	0.0598 (95%CI 0.0207; 0.0990)
Slope after menopause	-0.0097 (95%CI -0.0657; 0.0463)
Time after menopause	0.0501 (95%CI 0.0110; 0.0892)



In next tables a polynomial fractional model has been fitted to relax the linear hypothesis of previous model. All the possible models tested are shown in the list . As it can be see no changes are identified around menopause. The polynomial fractional model suggests only a plateau at the end of follow up after 10 years since menopause. Obviously an infinite increase of EDSS is not reliable

```
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = X^-2*ln(X)-.1830064713
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = X^-1-.6368315999
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = X^-0.5-.798017293
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = ln(X)-.4512500228
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = X^0.5-1.253105677
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = X-1.570273837
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = X^2-2.465759924
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-2-.4055544866
-> gen double x_2 = X^3-3.871918297
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-1-.6368315999
-> gen double x_2 = X^-1*ln(X)-.2873702739
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-1-.6368315999
-> gen double x_2 = X^-0.5-.798017293
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-1-.6368315999
-> gen double x_2 = ln(X)-.4512500228
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-1-.6368315999
-> gen double x_2 = X^0.5-1.253105677
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-1-.6368315999
-> gen double x_2 = X-1.570273837
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-1-.6368315999
-> gen double x_2 = X^2-2.465759924
```

```
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-1-.6368315999
-> gen double x_2 = X^3-3.871918297
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-0.5-.798017293
-> gen double x_2 = X^-0.5*ln(X)-.3601053216
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-0.5-.798017293
-> gen double x_2 = ln(X)-.4512500228
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-0.5-.798017293
-> gen double x_2 = X^0.5-1.253105677
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-0.5-.798017293
-> gen double x_2 = X-1.570273837
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-0.5-.798017293
-> gen double x_2 = X^2-2.465759924
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^-0.5-.798017293
-> gen double x_2 = X^3-3.871918297
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = ln(X)-.4512500228
-> gen double x_2 = ln(X)^2-.203626583
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = ln(X)-.4512500228
-> gen double x_2 = X^0.5-1.253105677
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = ln(X)-.4512500228
-> gen double x_2 = X-1.570273837
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = ln(X)-.4512500228
-> gen double x_2 = X^2-2.465759924
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = ln(X)-.4512500228
-> gen double x_2 = X^3-3.871918297
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^0.5-1.253105677
-> gen double x_2 = X^0.5*ln(X)-.5654639652
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^0.5-1.253105677
-> gen double x_2 = X-1.570273837
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^0.5-1.253105677
-> gen double x_2 = X^2-2.465759924
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^0.5-1.253105677
-> gen double x_2 = X^3-3.871918297
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X-1.570273837
-> gen double x_2 = X*ln(X)-.7085861048
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X-1.570273837
-> gen double x_2 = X^2-2.465759924
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X-1.570273837
-> gen double x_2 = X^3-3.871918297
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^2-2.465759924
-> gen double x_2 = X^2*ln(X)-1.112674222
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^2-2.465759924
-> gen double x_2 = X^3-3.871918297
   (where: X = (x+15.15674161911011)/10)
-> gen double x_1 = X^3-3.871918297
-> gen double x_2 = X^3*ln(X)-1.74720322
   (where: X = (x+15.15674161911011)/10)
```


Best model has powers 2 2, deviance = 3332.87708144799

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active results
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-- This is the best polynomial model fit with powers 2, 2. Better than the equation is the figure of the predictions showed below.

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Mixed-effects ML regression                     Number of obs     =      2,062
Group variable: nhc                             Number of groups  =         73

                                                Obs per group:
                                                              min =          5
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                                                  avg =       28.2
                                                  max =        108

                                         Wald chi2(2)     =      14.85
Log likelihood = -1666.4385              Prob > chi2      =     0.0006

------------------------------------------------------------------------------
           y |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         x_1 |    .502703   .1643987     3.06   0.002     .1804874    .8249186
         x_2 |  -.3381193   .1494617    -2.26   0.024    -.631059   -.0451797
       _cons |   1.786862   .1592483    11.22   0.000     1.474741    2.098983
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
                     sd(x_1) |   1.198779          .             .           .
                     sd(x_2) |   1.030922          .             .           .
                   sd(_cons) |   1.348356          .             .           .
                corr(x_1,x_2) |  -.9558002          .             .           .
              corr(x_1,_cons) |     .79003          .             .           .
              corr(x_2,_cons) |  -.6931379          .             .           .
-----------------------------+------------------------------------------------
                sd(Residual) |   .4684917          .             .           .
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 4015.23               Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
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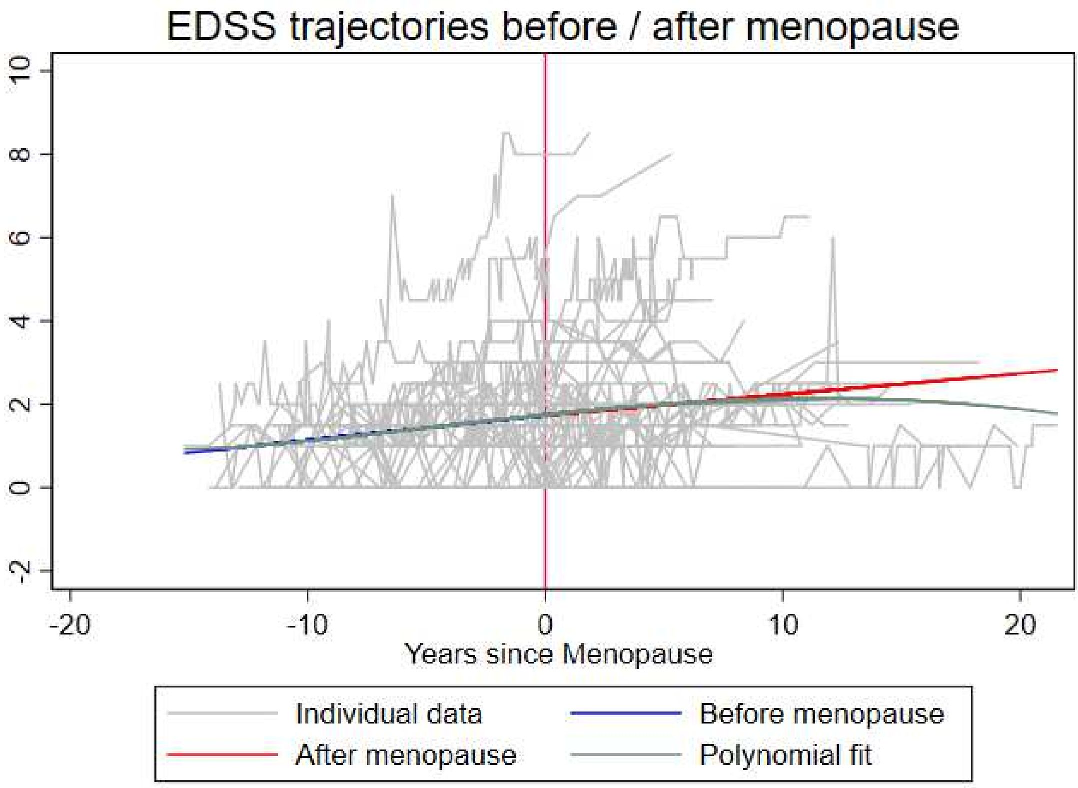

Age and menopause analysis for all women

The model evaluates the EDSS trajectories by age in a linear way. The first coefficient is the slope along age and the second is the difference of level between menopausic and no menopausic women. We did not find any difference for menopause variables. Age was centered at 45 years so the zero has a meaning

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edss=\beta_{0}+\beta_{1}(t_{since\quad age})

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Model modprineffect
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Mixed-effects REML regression                   Number of obs     =     13,718
Group variable: nhc                             Number of groups  =        490

                                                Obs per group:
                                                              min =          1
                                                              avg =       28.0
                                                              max =        110

                                                Wald chi2(2)      =      23.07
Log restricted-likelihood = -13806.368          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
        edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     edat_45 |   .0249001   .0052084     4.78   0.000     .0146919    .0351084
             |
       menop |
   Menopause |  -.0853178   .1337793    -0.64   0.524    -.3475203    .1768847
       _cons |    1.62141   .0806567    20.10   0.000     1.463326    1.779494
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
                   var(edat) |   .0100385   .0008092      .0085715    .0117566
                  var(_cons) |   11.24632   .9592961      9.514899    13.29281
             cov(edat,_cons) |  -.3228327   .0272597     -.3762607   -.2694047
-----------------------------+------------------------------------------------
               var(Residual) |   .3564031   .0044698      .3477492    .3652723
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 19079.92          Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

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The model evaluates the existence of interaction among age and menopause. The p value for
interaction is 0.02 indicating a higher slope for menopause group.

Model modintera
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Mixed-effects REML regression                   Number of obs     =     13,718
Group variable: nhc                             Number of groups  =        490

                                                Obs per group:
                                                              min =          1
                                                              avg =       28.0
                                                              max =        110

                                                Wald chi2(3)      =      28.23
Log restricted-likelihood = -13807.261          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
        edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     edat_45 |   .0195063   .0057318     3.40   0.001     .0082722    .0307404
             |
       menop |
  Menopause  |    .260536   .2048803     1.27   0.203    -.141022     .6620939
  intermenop |   .0302737   .0135525     2.23   0.025     .0037114    .0568361
       _cons |   1.555431   .0858697    18.11   0.000     1.387129    1.723732
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  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
                var(edat_45) |   .0099746   .0008037      .0085174    .0116811
                  var(_cons) |   2.514731   .1834704      2.179663    2.901307
            cov(edat_45,_cons) |   .128433   .0109022      .1070651    .1498009
-----------------------------+------------------------------------------------
               var(Residual) |   .3563939   .0044695      .3477406    .3652625
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 18770.84              Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

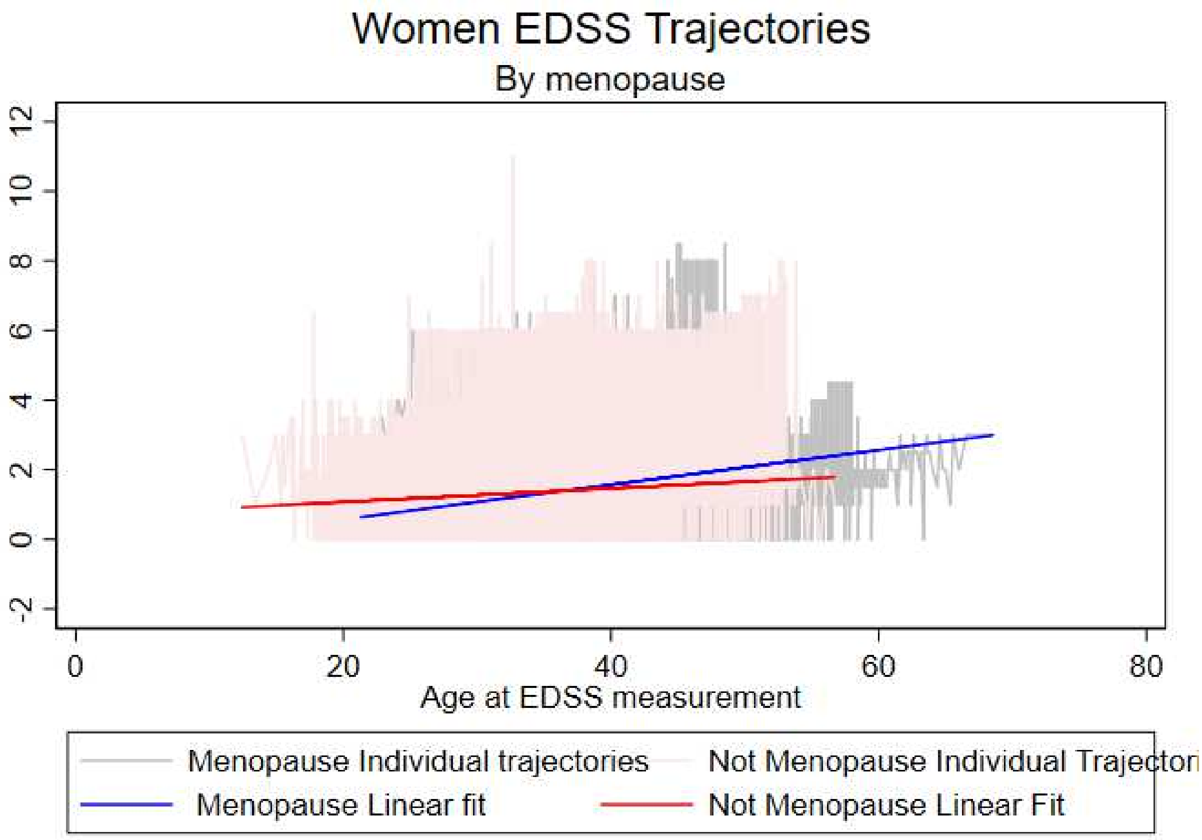
Akaike's information criterion and Bayesian information criterion

-----------------------------------------------------------------------------
       Model |        Obs  ll(null)  ll(model)      df         AIC        BIC
-------------+---------------------------------------------------------------
           . |     13,718         .  -13807.26       8    27630.52   27690.73
-----------------------------------------------------------------------------
               Note: N=Obs used in calculating BIC; see [R] BIC note.
```

Next table shows the slopes and differences of trajectories between menopause and no menopause. It seems menopause are more accelarated than non menopause. In the second part of the table it can bi seen that the slop is .019 for non menopausic women and 0.049 for menopause women.

Variable	Effect
Principal effect age	0.0249 (95%CI 0.0147; 0.0351)
Principal effect menopause	-0.0853 (95%CI -0.3475; 0.1769)
Interaction model	
Age effect no menopause	0.0195 (95%CI 0.0083; 0.0307)
Menopause difference at 45	0.2605 (95%CI -0.1410; 0.6621)
Interaction (change in slope for menopause)	0.0303 (95%CI 0.0037; 0.0568)
Age effect menopause	0.0498 (95%CI 0.0257; 0.0738)

This figure have the results of the two slopes for both groups.



If we fit separated models by group the results are similar, In the next models we add age at cis in order to control differences in slope. There results are simila but confidence interval crosses each other.

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Model modnotmenop
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Mixed-effects REML regression                   Number of obs     =     11,483
Group variable: nhc                             Number of groups  =        416

                                                Obs per group:
                                                              min =          1
                                                              avg =       27.6
                                                              max =        107

                                                Wald chi2(2)      =      16.97
Log restricted-likelihood = -11603.485          Prob > chi2       =     0.0002

------------------------------------------------------------------------------
        edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     edat_45 |   .0221992   .0056832     3.91   0.000     .0110603    .0333381
  age_at_cis |   .1395424   .0667987     2.09   0.037     .0086193    .2704654
       _cons |    1.23265   .1774878     6.94   0.000       .88478    1.580519
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
               var(edat_45) |   .0093225   .0008267      .0078351    .0110922
                 var(_cons) |   2.432053   .1968176      2.075335    2.850085
```

```
          cov(edat_45,_cons) |   .1251733   .0115837      .1024696     .147877
-----------------------------+------------------------------------------------
               var(Residual) |   .3628917   .0049718      .3532768    .3727683
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 14812.69          Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
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Menopause

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Model modmenop
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Mixed-effects REML regression                   Number of obs     =      2,235
Group variable: nhc                             Number of groups  =         74

                                                Obs per group:
                                                              min =          2
                                                              avg =       30.2
                                                              max =        110

                                                Wald chi2(2)      =      13.14
Log restricted-likelihood = -2189.0935          Prob > chi2       =     0.0014

------------------------------------------------------------------------------
        edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     edat_45 |   .0483314   .0141408     3.42   0.001     .0206159    .0760469
  age_at_cis |   .3469604   .2452486     1.41   0.157     -.133718    .8276388
       _cons |   1.311061   .4197655     3.12   0.002     .4883363    2.133787
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
                var(edat_45) |   .0134166   .0025857      .0091959    .0195745
                  var(_cons) |   2.724464   .4748581      1.936072    3.833897
          cov(edat_45,_cons) |   .1250286   .0291663      .0678636    .1821935
-----------------------------+------------------------------------------------
               var(Residual) |   .3221485   .0100314      .3030752    .3424221
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 3265.59           Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
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Analysis change 50 years

In this analysis data from all women EDSS trajectories have been collected. The aim is to test the change of Eddss trajectories before and after 50 years.

For the analysis we kept women that have a CIS between 18 and 55 five years old. and we compare menopause and not menopause data

All measurements during first year after CIS have not been considered in the analysis

The model include time since age 50 and time after age 50. The first coefficient is the slope along time and the second is the change of the slope after the age 50.

edss=\beta_{0}+\beta_{1}(t_{since\quad age})+\beta_{2}(t_{after \quad age})

This first model fits the change of EDSS trend after 50 years for all the women groups

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Model mod_501
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Mixed-effects REML regression                   Number of obs     =     11,701
Group variable: nhc                             Number of groups  =        445

                                                Obs per group:
                                                              min =          1
                                                              avg =       26.3
                                                              max =        108

                                                Wald chi2(2)      =      65.44
Log restricted-likelihood = -10515.653          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
        edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     tmesura |   .0469072   .0058893     7.96   0.000     .0353644    .0584499
tmesura_after |  -.055515   .0209388    -2.65   0.008    -.0965542   -.0144758
       _cons |   1.985081   .1043908    19.02   0.000     1.780479    2.189684
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
               var(tmesura) |   .0113488   .0009695      .0095991    .0134173
              var(tmesur~r) |   .0480606   .0143522      .0267669    .0862941
                 var(_cons) |   4.025592    .312853      3.456828    4.687937
      cov(tmesura,tmesur~r) |    -.01645   .0032418     -.0228038   -.0100962
         cov(tmesura,_cons) |   .1833124   .0160679        .15182    .2148049
        cov(tmesur~r,_cons) |  -.3968059   .0729744     -.5398331   -.2537786
-----------------------------+------------------------------------------------
              var(Residual) |   .2788844   .0038014      .2715324    .2864354
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 19371.97          Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.

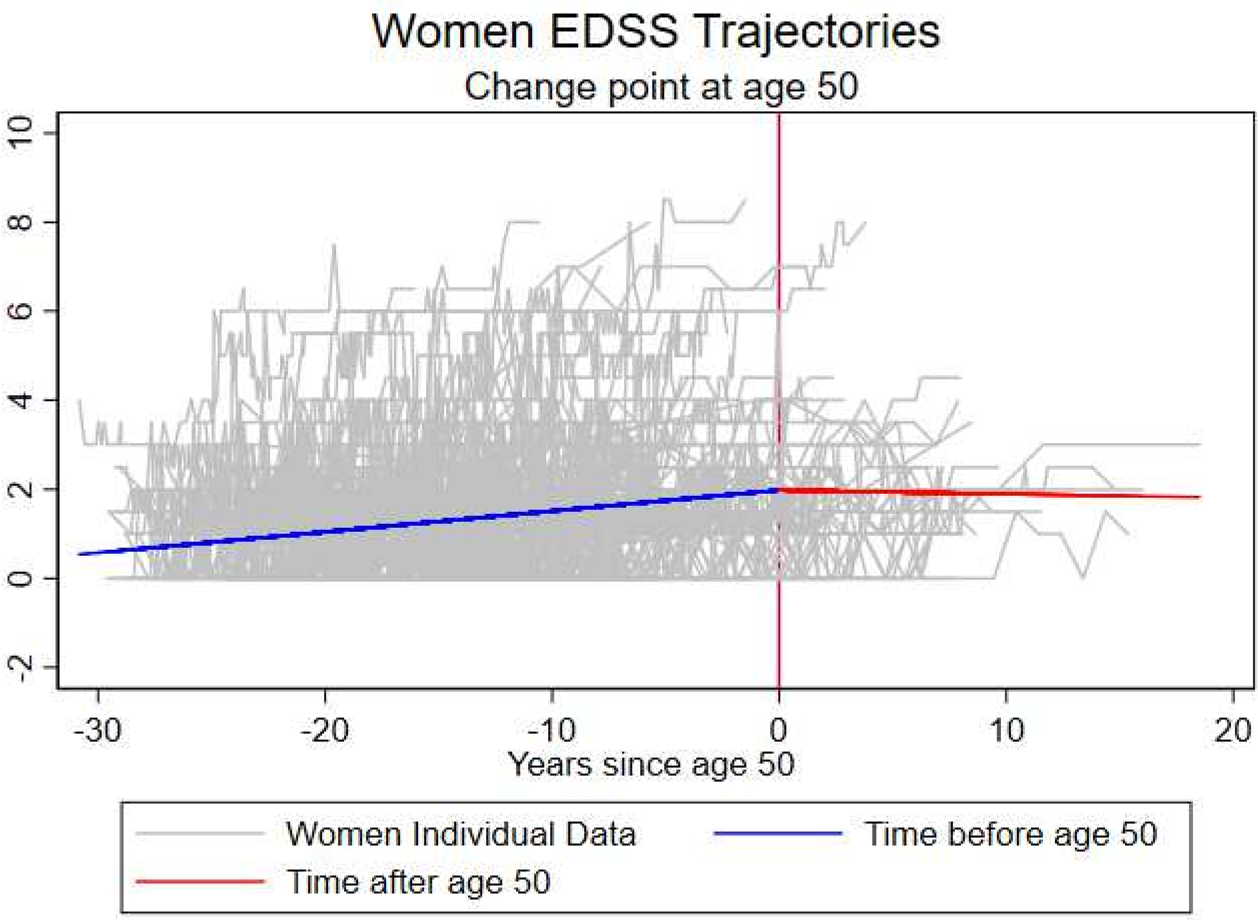
Akaike's information criterion and Bayesian information criterion

-----------------------------------------------------------------------------
       Model |        Obs  ll(null)  ll(model)      df         AIC        BIC
-------------+---------------------------------------------------------------
           . |     11,701         .  -10515.65      10    21051.31   21124.98
-----------------------------------------------------------------------------
               Note: N=Obs used in calculating BIC; see [R] BIC note.
```

Next table show the differences before/after relapse

Variable	Effect

Slope Time before age 50	0.0469 (95%CI 0.0354; 0.0584)
Slope change after age 50	-0.0555 (95%CI -0.0966; -0.0145)
Slope Time after age 50	-0.0086 (95%CI -0.0454; 0.0282)



The second model model include time since age 50 and time after age 50 and the interaction with menopause cases . The first coefficient is the slope along time and the second is the change of the slope for menopausic before 50. The third is the change of the slope for Non menopausic after 50 and forth is the change after 50 for menopuasic

edss=\beta_{0}+\beta_{1}(t_{since\quad age})+\beta_{1menop}(t_{since\quad age_menop})+\beta_{2}(t_{after \quad age}) +\beta_{2menop}(t_{after \quad age_menop}) +\beta_{3}menop

```
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Model mod_502
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Mixed-effects REML regression                   Number of obs     =     11,701
Group variable: nhc                             Number of groups  =        445

                                                Obs per group:
                                                              min =          1
                                                              avg =       26.3
                                                              max =        108

                                                Wald chi2(5)      =      67.16
Log restricted-likelihood =  -10509.82          Prob > chi2       =     0.0000

--------------------------------------------------------------------------------
          edss |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------+----------------------------------------------------------------
       tmesura |   .0426002   .0063552     6.70   0.000     .0301442    .0550562
      mtmesura |   .0250607   .0174326     1.44   0.151    -.0091065    .0592279
 tmesura_after |  -.0710376   .0403965    -1.76   0.079    -.1502132     .008138
mtmesura_after |  -.0041706   .0526933    -0.08   0.937    -.1074475    .0991063
         menop |   .1376491   .2639848     0.52   0.602    -.3797515    .6550497
         _cons |   1.951056   .1160924    16.81   0.000     1.723519    2.178593
--------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects Parameters  |   Estimate   Std. Err.     [95% Conf. Interval]
-----------------------------+------------------------------------------------
nhc: Unstructured            |
               var(tmesura) |   .0108214    .000964      .0090878    .0128857
               var(tmesur~r) |   .0354614   .0211234      .0110336    .1139708
              var(mtmesura) |   .0074835          .             .           .
              var(mtmesu~r) |   .0163814          .             .           .
                 var(_cons) |   4.028209   .3127148       3.45965    4.690205
       cov(tmesura,tmesur~r) |  -.0131156   .0042378     -.0214215   -.0048096
       cov(tmesura,mtmesura) |  -.0018245          .             .           .
       cov(tmesura,mtmesu~r) |  -.0062389          .             .           .
          cov(tmesura,_cons) |   .1826928   .0160457      .1512438    .2141419
      cov(tmesur~r,mtmesura) |  -.0024425          .             .           .
      cov(tmesur~r,mtmesu~r) |   .0029211          .             .           .
         cov(tmesur~r,_cons) |  -.3571311   .1013281     -.5557306   -.1585316
      cov(mtmesura,mtmesu~r) |  -.0004263          .             .           .
         cov(mtmesura,_cons) |    .000429          .             .           .
         cov(mtmesu~r,_cons) |  -.0746024          .             .           .
-----------------------------+------------------------------------------------
               var(Residual) |   .2789247   .0038008      .2715738    .2864746
------------------------------------------------------------------------------
LR test vs. linear model: chi2(15) = 19054.99             Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
Warning: convergence not achieved

Akaike's information criterion and Bayesian information criterion

-----------------------------------------------------------------------------
       Model |        Obs  ll(null)  ll(model)      df         AIC        BIC
-------------+---------------------------------------------------------------
           . |     11,701         .  -10509.82      19    21057.64   21197.62
-----------------------------------------------------------------------------
               Note: N=Obs used in calculating BIC; see [R] BIC note.
```

Next table show the slopes by menopause group before and after 50 years

Variable	Effect
Slope Time before age 50 no menopausic	0.0426 (95%CI 0.0301; 0.0551)
Change slope before age 50 for menopausic (interaction)	0.0251 (95%CI -0.0091; 0.0592)
Change slope Time after age 50	-0.0710 (95%CI -0.1502; 0.0081)
Change slope after age 50 for menopausic (interaction)	-0.0042 (95%CI -0.1074; 0.0991)
Menopause diffferences at age 50	0.1376 (95%CI -0.3798; 0.6550)