Nonlinear Trajectory of GFR in Children before RRT

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ABSTRACT

GFR decline in patients with CKD has been widely approximated using linear models, but this linearity assumption is not well validated. We conducted a matched case-control study in children from the Chronic Kidney Disease in Children (CKiD) cohort ages 1–16 years with mild to moderate CKD to assess whether GFR decline follows a nonlinear trajectory as CKD approaches ESRD. Children (n=125) who initiated RRT (cases) during follow-up were individually matched by CKD stage at baseline and glomerular/nonglomerular diagnosis with children (n=125) who remained RRT-free when the corresponding case initiated RRT (controls). GFR trajectories were compared using log-linear and piecewise log-linear mixed effects models adjusted for baseline characteristics. From study entry to 18 months before RRT, GFR declined 7% faster among cases compared with controls. However, GFR declined 26% faster among cases compared with controls (P<0.001) during the 18 months before RRT. Nonlinearity in the rate of kidney function loss, which was shown in this cohort, may preclude accurate clinical prediction of the timing of RRT and adequate patient preparation. This study should prompt the characterization of predictive factors that may contribute to an acceleration of kidney function decline.


GFR is a key measurement of kidney function, and the degree of GFR decline over time is a reflection of the severity of CKD progression. GFR decline has been approximated as linear or log-linear in most analyses of progression, an assumption that has been consistent with available data.1–4 However, many studies rely on relatively short follow-up periods and few repeated measures. Given the convenience of assuming a linear GFR trajectory, which results from the ease of modeling and interpreting linear slopes, few studies have sought to validate the linearity assumption and explore the possibility of nonlinear GFR decline. However, nonlinearity in GFR decline has been observed in some epidemiologic studies,5–7 and the implications on the risk for adverse outcomes have generated interest.8 A CKD cohort study in France found that about one half of its patients experienced nonlinear GFR decline during the last year before dialysis.9 A study by Li et al.9 used a flexible approach to model nonlinearity in GFR trajectories. Li et al.9 found evidence of nonlinear GFR trajectory behavior in adult patients with CKD, and furthermore, the probability of having nonlinear features in an individual trajectory was associated with known risk factors for CKD progression. O’Hare et al.10 found several distinct nonlinear patterns of GFR decline in the 2 years before dialysis initiation in Veterans Affairs patients.

Clinical strategies and subsequent patient response to care could potentially benefit from new insights into the variable paths of progression in patients with CKD.10,11 The question of whether characterizing the nonlinearity in the GFR trajectory can assist the identification of risk groups for outcomes, such as ESRD, remains unexplored. The implications on future outcomes of an increased rate of GFR decline could inform clinical decisions about screening frequencies, treatment, or preparation for RRT.

The Chronic Kidney Disease in Children (CKiD) study is an ongoing cohort study of children with CKD who, at baseline, had an eGFR between 30 and 90 ml/min per 1.73 m² and were ages 1–16 years. An end point of the study is RRT defined as transplant or dialysis. To determine whether trajectories of GFR accelerate before RRT, we nested a case-control study, in which cases were children observed to have received RRT and controls were children with CKD who remained RRT-free at the time...
when the corresponding case initiated RRT.

There were 147 children who experienced RRT during follow-up. Each case was matched individually to an eligible control at the time of the case occurrence. The matching factors included baseline CKD stage, glomerular/nonglomerular diagnosis, and, through design, the amount of follow-up time from study entry. Matching was done without replacement, and 22 cases were excluded from the analyses, because no appropriate control was available. We used a random sequence to determine the order of matching. The analysis was, thus, based on 125 matched case-control pairs. Demographic and clinical characteristics of cases and controls at baseline are shown in Table 1. The case and control groups did not differ by age, but differences were observed in sex, race, and urine protein/creatinine ratio. Specifically, the case group had a higher median protein/creatinine ratio and a substantially higher proportion with nephrotic proteinuria (defined as urine protein/creatinine ratio $\geq 2$).

We compared the GFR trajectories using log-linear and piecewise log-linear mixed effects models, with the piecewise model specified to allow a change of the GFR slope at 18 months before RRT. Models were adjusted for baseline characteristics, including age, race, sex, and proteinuria status. Tables 2 and 3 show the adjusted results from the mixed effects model analyses. The Akaike Information Criterion indicated that the piecewise log-linear model (including a spline or changing slope at 18 months) was a better fit to the data than the log-linear model that assumed a single slope across the entire period of observation. The GFR of cases declined at an adjusted rate of 6.8% per year ($P < 0.001$) during the time before the spline in the earlier period of observation and 32.4% per year ($P < 0.001$) after the spline within 18 months of RRT. The GFR of controls did not change significantly ($P = 1.00$) before the spline and declined at an adjusted rate of 9.0% ($P < 0.001$) after the spline. Although the rates of GFR decline comparing cases with controls differed by only 7% before the spline, the GFR of cases declined 26% faster ($P < 0.001$) compared with controls within 18 months of RRT, suggesting an acceleration in the GFR decline during this period in the case group. This acceleration, which was quantified by the piecewise log-linear mixed effects model, could be clearly seen from the data and nonparametric smooth fits (Figure 1). The variability around the piecewise log-linear fit was assessed by the root mean square error (RMSE) and found to be similar between cases and controls (RMSE for controls=0.303; RMSE for cases=0.303), indicating an equally good fit. When a single slope was fit to the data, the GFR decline rate for cases was overestimated before the spline and considerably underestimated within 18 months of RRT. To assess whether the acceleration in decline was a function of the log scale, models were rerun with GFR in the natural scale. The results showed similar nonlinear patterns but a poorer model fit to the data.

Our results show that, although linear or log-linear GFR decline is a convenient assumption for longitudinal studies of CKD progression, individuals experience periods of accelerated decline. Li et al. showed that patients in the African American Study of Kidney Disease and Hypertension experienced a variety of nonlinear progression patterns. O’Hare et al. classified CKD patients who progressed to dialysis into four GFR trajectory categories and found evidence that patients with mild to moderate CKD experienced more rapid renal function deterioration in the 2 years before reaching long-term dialysis. In the current study assessing progression in children with CKD, we found similar results, indicating that RRT events are preceded by a period of accelerated decline in GFR. It is likely that this period of precipitous loss in kidney function is a key factor in the determination of the timing of RRT. An acceleration of GFR decline may be a primary feature of a worsening clinical profile that prompts a clinician to initiate dialysis or transplant. The question arises as to what contributes to accelerated kidney function loss. A primary epidemiologic challenge is to find predictors that antecedes the acceleration and are amenable to intervention to prevent or delay such accelerated loss and RRT. Clearly, these results and the questions that they raise speak to a need for additional investigations of CKD progression in various populations, with care taken to appropriately

### Table 1. Demographic and clinical characteristics of cases and controls at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n=125)</th>
<th>Controls (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>12.64 (9.23–14.53)</td>
<td>12.33 (8.71–14.74)</td>
</tr>
<tr>
<td>Sex (girls), N (%)</td>
<td>38 (30.4)</td>
<td>57 (45.6)</td>
</tr>
<tr>
<td>Race (nonwhite), N (%)</td>
<td>51 (40.8)</td>
<td>36 (28.8)</td>
</tr>
<tr>
<td>Urine protein/creatinine ratio</td>
<td>1.74 (0.48–4.04)</td>
<td>0.60 (0.26–1.76)</td>
</tr>
<tr>
<td>Proteinuria, N (%)</td>
<td>0.2=protein/creatinine ratio&lt;2</td>
<td>56 (46.7)</td>
</tr>
<tr>
<td></td>
<td>Protein/creatinine ratio=2</td>
<td>51 (42.5)</td>
</tr>
<tr>
<td>Baseline GFR*</td>
<td>32.21 (26.43–39.64)</td>
<td>35.77 (27.86–43.78)</td>
</tr>
<tr>
<td>Glomerular diagnosis, N (%)*</td>
<td>47 (37.6)</td>
<td>47 (37.6)</td>
</tr>
</tbody>
</table>

Median (interquartile range) unless otherwise indicated.

*Baseline GFR and glomerular/nonglomerular diagnosis were matching factors.

### Table 2. The adjusted expected percent GFR change rates in the log-linear mixed effects model

<table>
<thead>
<tr>
<th>Case Group</th>
<th>Adjusted % GFR Change per Year</th>
<th>SEM (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>–3.2</td>
<td>1.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Cases</td>
<td>–18.2</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cases-controls</td>
<td>–15.5</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIC</td>
<td>260.78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Parameter estimates from the models are provided in Supplemental Appendix II. All results were adjusted for baseline characteristics, including age, race, sex, and proteinuria status. AIC, Akaike Information Criterion.
characterize changing levels of factors that are known predictors of CKD progression. The timing of potential insults to the kidney (e.g., loss of control of BP) may hold important information concerning the patterns of CKD progression and nonprogression. O’Hare et al. found that rates of recommended pre-ESRD care were lower for those patients experiencing the most rapid progression before dialysis initiation. Ambrogi et al. suggested that nonlinear patterns in

Table 3. The adjusted expected percent GFR change rates in the piecewise log-linear mixed effects model

<table>
<thead>
<tr>
<th>Case Group</th>
<th>Before 18 mo before RRT of Cases</th>
<th>After 18 mo before RRT of Cases</th>
<th>Difference between Early and Late Slopes*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted % GFR Change per Year</td>
<td>SEM (%)</td>
<td>P Value</td>
</tr>
<tr>
<td>Controls</td>
<td>0.3</td>
<td>1.5</td>
<td>0.87</td>
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<tr>
<td>Cases</td>
<td>−6.8</td>
<td>1.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Cases-controls</td>
<td>−7.0</td>
<td>1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Adjusted % GFR Change per Year</td>
<td>SEM (%)</td>
<td>P Value</td>
</tr>
<tr>
<td>Controls</td>
<td>−9.0</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cases</td>
<td>−32.4</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cases-controls</td>
<td>−25.7</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Adjusted % GFR Change per Year</td>
<td>SEM (%)</td>
<td>P Value</td>
</tr>
<tr>
<td>Controls</td>
<td>9.2</td>
<td>3.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Cases</td>
<td>27.4</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>AIC</td>
<td>149.14</td>
<td></td>
</tr>
</tbody>
</table>

Parameter estimates from the models are provided in Supplemental Appendix II. All results were adjusted for baseline characteristics, including age, race, sex, and proteinuria status.

*Difference resulting from the piecewise linear mixed effects model estimated in the log scale and then exponentiated.

Figure 1. Nonlinear GFR decline before RRT can be approximated with a piece-wise log-linear model. A and B show the smooth fit of log GFR over time for cases of RRT and matched controls anchoring at the RRT onset time of cases. C and D show the fit from the adjusted log-linear and adjusted piecewise log-linear mixed effects models for cases of RRT and matched controls anchoring at the RRT onset time of cases. Models were adjusted for baseline characteristics including age, race, sex, and proteinuria status.
GFR decline might create difficulty in estimating the timing of dialysis.

These results may also highlight the coarseness of current methods for assessing the impact of risk factors on CKD progression, which mainly rely on the assumption of linear decline in kidney function. Analyses assuming linear decline average over nonlinear patterns that speak to the true nature of the exposure-outcome relationships. More sensitive analyses may be needed to characterize the heterogeneity in the patterns that describe CKD progression and assess the impact of often changing values of the exposure. Improvements in how we characterize patterns of progression could lead to new approaches to clinical care, because accelerations in kidney function loss may complicate the timing of RRT and pre-ESRD care.

There are several strengths of this study. We drew from a well characterized cohort of children with CKD with directly measured GFR at the first two annual study visits and all even visits thereafter. The CKiD study also has an internally derived estimating equation for GFR to capture kidney function in odd visit years of the study, thereby providing regular GFR assessments for characterizing nonlinear patterns of GFR decline. The CKiD study has longitudinal data for up to 6 years of follow-up, and the multicenter setting with 43 clinical sites provides a sample of children highly representative of the pediatric CKD population in care in the United States. By adopting the case-control design, we were able to compare the nonlinearity of the GFR trajectory before RRT with the expected trajectory in comparable children who had not yet experienced RRT.

There are also notable limitations to the current analysis. There were only 125 case-control pairs, and our GFR assessments were annual, limiting the degree to which heterogeneity in progression to RRT could be assessed among the case group. As has been reported previously, there is likely variation in GFR patterns before RRT. However, what is clear from the current study is that, on average, children approaching RRT experience acceleration in their loss of kidney function. Another consideration is the assumption of a break in linearity at 18 months before RRT, which provided sufficient data before and after the spline for our analyses but is an oversimplification of what is likely a more prolonged period of acceleration in GFR decline. However, our choice of 18 months before RRT to examine changes in the rate of GFR decline is consistent with other studies that have noted similar rapid declines in kidney function within 2 years of dialysis.

Finally, it should be noted that, although cases and controls were matched, the models in Tables 2 and 3 did not cluster on the matched pairs. Our final model provided practically identical results to a model including an additional random effect for case-control pair, and it had modestly higher precision.

CO N C I S E M E T H O D S

Participants and Design
The CKiD study has been described previously. In brief, children ages 1–16 years with mild to moderate CKD were recruited based on an eGFR from 30 to 90 ml/min per 1.73 m² using the original Schwartz formula from 43 participating pediatric nephrology centers. Only children who, at baseline, had never been dialyzed or undergone organ transplant were eligible for the study. GFR was measured in participants at baseline, 1 year later, and every other year thereafter using plasma iohexol disappearance. When a directly measured GFR was unavailable, GFR was estimated using the CKiD equation. A nested case-control study was used to assess whether acceleration of GFR decline was a risk factor for RRT, which was defined as either dialysis or transplant. Eligible cases were children who experienced RRT while under observation. These children were individually matched to study participants who had not yet experienced RRT as of the time of the case RRT but could later experience RRT and become a case using the following characteristics: CKD stage at baseline and glomerular/nonglomerular diagnosis. The period of observation for the controls was from CKiD study entry to the time point of RRT for the matched case.

Statistical Analyses
GFR trajectories of cases and controls were modeled using a log-linear mixed effects model, which allowed for individual intercepts and slopes of GFR over time to deviate from the population averages using random effects. The model was adjusted for age (continuous), race (white versus nonwhite), sex (boys versus girls), and baseline proteinuria status (categorized as urine protein to creatinine ratio <0.2, 0.2–2.0, and ≥2.0). Time was specified in the model to be anchored at the event of RRT and proceed back in years to study entry. Thus, time was negative in the model, with the intercept describing the GFR at RRT (for cases) or the equivalent follow-up time (for controls).

To assess whether an accelerated kidney function decline was present in cases versus controls, we added a spline term to the log-linear model described above that quantified the change in the slope of GFR decline at 18 months before RRT (t = −1.5 years). This piecewise log-linear model, thus, allowed the GFR trajectory for cases and controls to be described by two slopes: a slope from study entry to 18 months before RRT (t = −1.5 years) and a (possibly different) slope from −18 months to RRT or the equivalent follow-up time for the controls.

Akaike Information Criterion was used to assess the fit of both models described above. All analyses were conducted using STATA/MP 11.2 (Statacorp LP), and the graphics were produced using SAS 9.3 (SAS Institute, Inc.). More details of the design and statistical methods can be found in Supplemental Appendix I.

ACKNOWLEDGMENTS

We are grateful to GE Healthcare, Amersham Division, for providing the Chronic Kidney Disease in Children Prospective Cohort (CKiD) study with iohexol (Omnipaque) for the GFR measurements.

The CKiD study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases, with additional funding from the National Institute of Child Health and Human Development and National Heart, Lung, and Blood Institute Grants U01-DK
DISCLOSURES
None.

REFERENCES

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2013050487/-/DCSupplemental.
Appendix I: Full Methods

Participants and Design

The Chronic Kidney Disease in Children (CKiD) study enrolled children aged 1 to 16 years with a Schwartz-estimated GFR of 30 to 90 ml/min\(\text{m}^2\) who had never been dialyzed or undergone organ transplant. Participants were drawn from 43 participating tertiary care pediatric nephrology programs across the U.S. and 2 sites in Canada. The baseline study visits occurred between January 19, 2005 and August 3, 2009, with annual follow-up visits. Institutional Review Boards for each participating site approved the study protocol and the study has been described previously.13

At the baseline and first annual one year follow-up visits, GFR was determined by directly measured plasma iohexol (GE Healthcare, Amersham Division, Princeton, NJ) disappearance curves; details of the GFR assessment methods have been published previously.18 An estimated GFR value was used when a directly measured value was unavailable.17 Basic metabolic profile, including measurement of creatinine, was assessed using an enzymatic method on the Bayer Advia 2400 analyzer (Siemens Diagnostics, Tarrytown NY). For the present study we nested a case-control design within the CKiD cohort by matching children who had been observed to initiate dialysis or undergo kidney transplant (renal replacement therapy [RRT] cases) to children who, at the time of the case event, had not yet experienced an RRT event. Controls, however, could become cases in the study at a later time point. Thus the design matched cases to controls on time on study. We also matched on CKD stage at baseline and glomerular/non-glomerular diagnosis. Cases were matched to one control without replacement such that each case had a unique control and cases for which an appropriate match was unavailable were removed from the analysis. The order of matching was determined by a random computer generated sequence.

Statistical Analysis

GFR trajectories of cases and controls were modeled using a log-linear mixed effects model of the form

\[
\log(GFR_{ij}) = (a_0 + a_i) + a_1 \text{case}_i + a_2 \text{age}_i + a_3 \text{race}_i + a_4 \text{sex}_i + a_5 \text{proteinuria status}_i
+ (\beta_0 + b_i)t_{ij} + \beta_1 t_{ij}\text{case}_i + \epsilon_{ij},
\]

where \(\beta_0\) is the rate of log(GFR) change in controls, and \(\beta_1\) is difference in the rates of change of log(GFR) comparing cases and controls. The intercept, \(a_0\), represented the log(GFR) at the time of RRT for the case (or comparable time from baseline for the controls) and time proceeded negatively in years such that -1 represented 1 year prior to RRT. Thus all case GFR trajectories were anchored at RRT with their matched control GFR trajectories anchored at the same time from baseline as the respective cases. The model included subject-specific random effects for the intercept and slope (\(a_i\) and \(b_i\)) distributed according to \(\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N \left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau_1^2 & \rho \tau_1 \tau_2 \\ \rho \tau_1 \tau_2 & \tau_2^2 \end{pmatrix} \right)\). Finally \(\epsilon_{ij}\) represented the random error with a distribution of \(\epsilon_{ij} \sim N (0, \sigma^2)\). The model was adjusted for age (continuous), race (white versus nonwhite), sex (male versus female) and baseline proteinuria status (categorized as urine protein to creatinine ratio<0.2, 0.2 to 2.0, and ≥2.0).

To address the study hypothesis that cases experienced an acceleration of their kidney function decline prior to RRT, the above model was refined to allow a change in slope (spline)
proximate to the RRT event. The spline term in this piecewise log-linear mixed effects was positioned at 18 months prior to the date of RRT (t = -1.5). The model was of the form

\[
\log(GFR_{ij}) = (a_0 + a_i) + \alpha_{case} + \alpha_{age} + \alpha_{race} + \alpha_{sex} + \alpha_{proteinuria\ status} + (\beta_0 + h_i)t_{ij} + \beta_1t_{ij}case_i + \beta_2(t_{ij} - (-1.5)) + \beta_3(t_{ij} - (-1.5))case_i + \epsilon_{ij}
\]

with a slope parameter for the spline term (\(\beta_2\)) and the interaction between case status and the spline (\(\beta_3\)) added to the log-linear mixed effects model to form the piecewise log-linear model. The breakpoint for the change in slope was set at 18 months prior to RRT to balance the desire to look for slope changes proximate to RRT with the limitations of the data and the need to have at least two GFR measurements from most participants to robustly fit a slope representative of the individual GFR trajectories.

Akaike Information Criterion (AIC) was used to assess the fit of both models described above. All of the analyses were conducted using STATA/MP 11.2 (Statacorp LP) and the graphics were produced using SAS 9.3 (SAS Institute, Inc).
Appendix II. Coefficient estimates from the log-linear and piecewise log-linear model

Log-linear model:
\[ \log \text{GFR}_{ij} = (\alpha_0 + \alpha_i) + \alpha_1 \text{case}_i + \alpha_2 \text{age}_i + \alpha_3 \text{race}_i + \alpha_4 \text{sex}_i + \alpha_5 \text{proteinuria status}_i \\
+ (\beta_0 + \beta_i) t_{ij} + \beta_i \text{case}_i + \epsilon_{ij}, \]

Piecewise log-linear model:
\[ \log \text{GFR}_{ij} = (\alpha_0 + \alpha_i) + \alpha_1 \text{case}_i + \alpha_2 \text{age}_i + \alpha_3 \text{race}_i + \alpha_4 \text{sex}_i + \alpha_5 \text{proteinuria status}_i \\
+ (\beta_0 + \beta_i) t_{ij} + \beta_i \text{case}_i + \epsilon_{ij} + \tilde{\beta}_1 (t_{ij} - (-1.5))_{t_{ij}} + \tilde{\beta}_2 (t_{ij} - (-1.5))_{t_{ij}} \text{case}_i + \epsilon_{ij}. \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient Estimate</th>
<th>SE</th>
<th>P-value</th>
<th>Coefficient Estimate</th>
<th>SE</th>
<th>P-value</th>
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<td>(\alpha_0)</td>
<td>3.493</td>
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<td>3.456</td>
<td>0.074</td>
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<tr>
<td>(\alpha_1)</td>
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<td>&lt;0.001</td>
<td>-0.570</td>
<td>0.040</td>
<td>&lt;0.001</td>
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<tr>
<td>(\alpha_2)</td>
<td>0.010</td>
<td>0.005</td>
<td>0.033</td>
<td>0.009</td>
<td>0.005</td>
<td>0.068</td>
</tr>
<tr>
<td>(\alpha_3)</td>
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<td>0.061</td>
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<td>(\alpha_4)</td>
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<td>(\alpha_5)</td>
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<td>0.224</td>
<td>0.046</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AIC = 260.78

*In the log-linear mixed effects model:
Slope for controls: \(\beta_0=-0.032\) (SE=0.012; P-value=0.009)
Slope for cases: \(\beta_0+\beta_1=-0.201\) (SE=0.011; P-value<0.001)
Difference in slopes comparing cases and controls: \(\beta_1=-0.169\) (SE=0.015; p-value<0.001)

¶In the piecewise log-linear mixed effects model:
Slope before -1.5 years for controls: \(\beta_0+\beta_1=-0.003\) (SE=0.015; P-value=0.866)
Slope after -1.5 years for controls: \(\beta_0=-0.094\) (SE=0.028; P-value<0.001)
Slope before -1.5 years for cases: \(\beta_0+\beta_1+\beta_2+\beta_3=-0.070\) (SE=0.015; P-value<0.001)
Slope after -1.5 years for cases: \(\beta_0+\beta_1=-0.391\) (SE=0.019; P-value<0.001)
Difference in slopes comparing cases and controls before -1.5 years: \(\beta_1+\beta_3=-0.073\) (SE=0.021; P-value<0.001)
Difference in slopes comparing cases and controls after -1.5 years: \(\beta_1=-0.297\) (SE=0.033; P-value<0.001)
Difference in early and late slopes of controls: \(-\beta_3=-0.097\) (SE=0.037; P-value=0.008)
Difference in early and late slopes of cases: \(-\beta_3=-0.320\) (SE=0.028; P-value<0.001)

AIC = 149.14