
National Health Statistics Reports

Number 156 ■ June 7, 2021

Using SAS/STAT to Understand the NCI Joinpoint Regression Software: Testing for a Zero Slope Using Rates of Drug Overdose Deaths Involving Fentanyl, 2011–2016

by Katherine E. Irimata, Ph.D., and Donald J. Malec, Ph.D., Division of Research and Methodology; Brigham A. Bastian, B.S., Division of Vital Statistics; and Merianne Rose Spencer, M.P.H., Division of Analysis and Epidemiology

Abstract

Background—The National Cancer Institute (NCI) Joinpoint regression software is a widely used software program for evaluating trends. In addition to producing model estimates for trend models, this software can search for changes in slope along the trend line. One component of the software, which tests whether line segment slopes are zero, is different from the usual t -test of zero slope that is used in linear models. This report will demonstrate this Joinpoint software procedure through replication using the SAS Institute’s statistical software (that is, SAS) and discuss the implications of the different assumptions used by Joinpoint and a typical SAS model for the test of zero slope.

Methods—First, Joinpoint’s procedure for testing a zero slope is compared with a typical test of zero slope using SAS, and the assumptions behind both approaches are evaluated. Second, the test from the Joinpoint software is replicated in SAS using its PROC REG procedure and additional SAS programming. Trend analyses of rates of drug overdose deaths involving fentanyl from the general population and among females are used as examples.

Results—In the evaluation of the trend of drug overdose deaths for the total population, Joinpoint produces a similar result to the linear model test in SAS. For the female subgroup, however, Joinpoint and SAS produce differing results for the test of zero slope. The replication of the Joinpoint test of zero slope using SAS demonstrates that Joinpoint’s procedure is based on fewer degrees of freedom, which results in a larger standard error estimate.

Conclusion—The Joinpoint approach accounts for the fact that the joinpoints are estimated and thus leads to a more conservative hypothesis test, particularly when the number of points in a trend analysis is small.

Keywords: trends analysis • mortality • t -test • National Vital Statistics System

Introduction

The National Cancer Institute (NCI) Joinpoint regression software (1) is a software program for evaluating trends

using joinpoint regression, which is also commonly referred to as piecewise, segmented, or linear spline regression. In cases where shifts in a trend line are uncertain, the software evaluates

the trend line to identify if there are any time points where a change in trend occurs and fits linear segments between the identified points. These inflection points, where a linear trend line changes direction and is replaced by a line with a different slope, are referred to as joinpoints. While other software programs can be used to estimate the slopes of the trend lines using user-specified joinpoints, the NCI Joinpoint regression software provides model selection procedures to estimate the locations of the joinpoints using user-specified parameters. After identifying the joinpoint locations, the software also estimates the slopes of the linear trend lines (that is, linear splines) to understand the trend for each segment. The software provides a test of zero slope to identify segments when the trend is nonzero (either increasing or decreasing). These capabilities make the Joinpoint software a widely used tool for evaluating trends, particularly at the National Center for Health Statistics (NCHS). However, users have noticed inconsistencies between the Joinpoint output for a test of zero slope and the output for a t -test of zero slope using standard linear models.

This report seeks to mitigate any potential confusion that can arise when an analyst compares the Joinpoint output to the standard linear model test. The statistical software SAS Version 9.4 (2)



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is used to demonstrate the usual test of zero slope for comparison. As will be shown, the standard linear model test assumes the joinpoints are known. However, in cases where the locations of the joinpoints are estimated, using a test of slope assuming that the locations of the joinpoints are known is an error-prone test because the variability related to the location of the joinpoint is ignored. NCI's procedure correctly considers the fact that the joinpoints are estimated by the Joinpoint software and their actual locations are subject to error. As will be explained in detail, the test of slope using NCI's Joinpoint procedure accounts for the additional variability in the estimation of the endpoints. This procedure has been evaluated using simulation studies and has been shown to be accurate (3,4). Currently, there does not seem to be an available test that perfectly fits within the standard hypothesis testing framework. This particular Joinpoint procedure, which is only one part of Joinpoint's suite of procedures, is highlighted because it is different from the usual *t*-test of zero slope that is used in linear models.

This report addresses two questions: 1) How does the test of zero slope in Joinpoint compare to the test of zero slope in SAS? and 2) How does Joinpoint test the hypothesis that a slope of a segment is zero? The first question provides motivation for this investigation by demonstrating cases where the Joinpoint procedure and the typical test of zero slope used in most software packages may result in similar or differing conclusions. The second question examines why the Joinpoint approach can differ from the usual test of zero slope by closely examining Joinpoint's procedure for the test of zero slope. Joinpoint's approach to the test of zero slope is demonstrated by replicating the Joinpoint procedure in SAS through step-by-step examples. Although the Joinpoint software's method for performing this test is thoroughly documented in the online NCI Joinpoint help guide (5) and several papers published in the literature (3,4), this report uses two real examples from NCHS data to reproduce estimates using SAS so that an analyst can see the impact of the underlying assumptions of the Joinpoint software approach.

For both questions, two examples using NCHS data are evaluated: drug overdose death rates involving fentanyl for the total population and for a specific subpopulation (among females). The examples are used to demonstrate agreement and disagreement between the Joinpoint software approach and the linear test of slope in SAS, and to clarify the assumptions behind Joinpoint's procedure. This report assumes familiarity with the Joinpoint software and is not intended to be a primer on the software. For a general reading on the Joinpoint model and estimation procedures, refer to the NCI Joinpoint manual (5). For a general reading on how Joinpoint is used to estimate trends at NCHS, see the NCHS Series 2 report "National Center for Health Statistics Guidelines for Analysis of Trends" (6).

Methods

Data

Data from an NCHS report (7) on drug overdose deaths involving fentanyl were used for illustrative purposes in this report. The data include frequencies, rates per 100,000 standard population, and standard errors for drug overdose deaths where fentanyl, fentanyl analogs, and misspellings of fentanyl and fentanyl analogs were mentioned on death record literal text fields from the National Vital Statistics System multiple cause-of-death 2011–2016 data. As with the NCHS report, any mention in this report using the label "drug overdose deaths involving fentanyl" includes both prescribed or illicitly manufactured fentanyl, as well as deaths involving any fentanyl metabolites, precursors, or analogs as identified in the death certificate literal text (7). Bridged-race vintage postcensal resident population estimates were used to calculate death rates (8). Age-adjusted death rates were calculated using the direct method and the 2000 standard U.S. population (8). Trends in these data were also examined (7). For additional detail on the methods used to identify drug overdose deaths involving fentanyl, see [Technical Notes](#) or refer to the National Vital Statistics Reports (NVSR) (7,9). Fentanyl overdose deaths for the total

population ([Table 1](#)) and among females ([Table 2](#)) from 2011 through 2016 were considered in this report.

Analysis

The NCI Joinpoint regression software, Version 4.8.0.1 (1) was used to perform trend analyses in this report. The specified parameter settings in the Joinpoint software used for both examples are shown in [Figures 1](#) and [2](#).

On the input file tab ([Figure 1](#)), the log transformation was specified for the Joinpoint regression models in this report as this was previously used in the evaluation of trends of drug overdose deaths involving fentanyl (7) and is useful for evaluating and describing relative differences in trends.

Specifications related to the number and locations of the joinpoints were indicated on the method and parameters tab ([Figure 2](#)). The grid search method, which identifies all possible locations for joinpoints using the specified settings and evaluates each location to identify the best possible fit, was specified. For these analyses, a minimum of one observation from a joinpoint to either end of the data and a minimum of zero observations between two joinpoints are specified since these allow for more possible joinpoint locations in the evaluation of shorter trends. The defaults were used for the number of points to place between adjacent observed values in the grid search (0 points) and for the minimum number of joinpoints (0 points). A maximum of one joinpoint was specified as a simple setup to illustrate the approach for the test of zero slope for both examples. Note that this analysis differs from the trend analysis for the total population in the published NVSR (7). In the NVSR, a maximum of two joinpoints were specified in the software to investigate up to two possible changes over the entire time period and thus the results cannot be directly compared. The permutation test (10), one of the oldest and perhaps most commonly used methods in the Joinpoint software, was used to select the location of the joinpoints. The permutation test is a nonparametric approach, which shuffles the sampled observations and evaluates the likelihood of the observed sample

Figure 1. Joinpoint regression software Input File tab with log transformation

year	rate	se
2011	0.5264	0.0131
2012	0.5235	0.01328
2013	0.6135	0.01429
2014	1.3371	0.02088
2015	2.6381	0.02948

NOTES: SE is standard error. National Cancer Institute Joinpoint Regression Software, Version 4.8.0.1; based on age-adjusted rates of drug overdose deaths involving fentanyl.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

compared with the possible permutations of the sampled observations. For these examples, permutation tests were used with an overall significance level of 0.05 and 4,499 permutations (default options) to select the final models. Guidance as to how to choose these settings can be found in the “National Center for Health Statistics Guidelines for Analysis of Trends” report (6).

The statistical software SAS Version 9.4 (2) was used to perform the usual linear model *t*-test of zero slope for comparison (Question 1) and to reproduce the results of the Joinpoint software regression approach (Question 2). SAS data steps were used to transform and reparameterize the data. The SAS procedure PROC REG was used to obtain slope, standard error, and degrees of freedom estimates for the test for zero slope.

Results

Question 1: How does the test of zero slope in Joinpoint compare to the test of zero slope in SAS?

Both the Joinpoint and SAS software can be used to perform the test of zero slope, although confusion has arisen as the results from these two software programs are not always in agreement. Comparisons of the Joinpoint approach and the linear model approach in SAS, or the naive model, for the fentanyl overdose age-adjusted death rate trends for the total population and for the female subgroup are provided. As shown below, the Joinpoint and SAS approaches for the test of zero slope differ although the two software programs may produce similar results in some cases. In the examples shown, Joinpoint and SAS produce comparable findings in the evaluation of the trend of fentanyl overdose deaths in the total population but produce differing

conclusions in the evaluation of the trend for the female subgroup.

Example 1: Trend for the total population

Conducting the analysis in the Joinpoint software

For the evaluation of the trend of drug overdose deaths involving fentanyl for the total population, the Joinpoint program produced a plot of the estimated trend (Figure 3) and estimated regression coefficients under two parameterizations (Table A). The Joinpoint software graphs the trend line on the original scale, even when a log-transformed model is used.

The Joinpoint software’s standard output produces trend model estimates under two parameterizations, the standard parameterization and the general parameterization (Table A). The estimates reported correspond to two ways of looking at the slopes. The standard parameterization presents estimates to test whether the change in slope between segments is zero. In this example, *Slope 2–Slope 1* in the standard parameterization reports the change in slope between the second segment (2013–2016) and the first segment (2011–2013). Although the standard parameterization reports the statistical test for the change in trend between the two segments, users should defer to the result of the model selection methods (Table A, Estimated joinpoints) as the most reliable locations of where the line changes direction as these approaches appropriately account for the degrees of freedom. In this example, the difference in slopes between the first and second segments is not found to be statistically significant ($p = 0.1475$); however, the permutation test identifies a statistically significant ($\alpha = 0.05$) joinpoint at 2013 (Table A, Estimated joinpoints).

Alternatively, the general parameterization presents estimates of the actual slope of the trend line starting at the last joinpoint. For example, the parameter estimate for *Slope 1* (0.08108) is the slope of the trend for the first segment from 2011 to 2013 and the parameter estimate for *Slope 2* (0.75769) is the slope of the trend line from 2013 to 2016. The general parameterization

Figure 2. Joinpoint regression software Method and Parameters tab, Permutation Test selection method with log transformation and a maximum of one joinpoint

Joinpoint Session - 3

Input File Method and Parameters Advanced Analysis Tools

Method

Grid Search [Why did some default settings change?](#) Hudson's [Why is Hudson's Method disabled?](#)

Min. number of observations from a joinpoint to either end of the data (excluding first or last joinpoint if it falls on an observation)

Min. number of observations between two joinpoints (excluding any joinpoint if it falls on an observation)

Number of points to place between adjacent observed x values in the grid search:

Min. percentage points difference (PPD) between consecutive APC segments™ (MADWD) Min. PPD

Number of Joinpoints

Number of Joinpoints: Minimum: Maximum:

[How are Maximum Joinpoints determined?](#)

Autocorrelated Errors Options

Fit an uncorrelated errors model

Fit an autocorrelated errors model based on the data

Fit an autocorrelated errors model with parameter =

Model Selection Method [Which method should I choose?](#)

Permutation Test

Overall significance level

Number of permutations:

Early Stopping Options

B-Value Curtailed Fixed

Data Driven BIC Methods

Weighted BIC*

Weighted BIC-Alt*

Data Dependent Selection*

Traditional BIC Methods

Bayesian Information Criterion (BIC)

BIC3

Modified BIC

APC/AAPC/Tau Confidence Intervals

Parametric Method

Empirical Quantile™ ([Learn More](#))

Method 1

Method 2

of Resamples:

AAPC Segment Ranges

Entire Range Other range:

The last Other range:

The last Other range:

Note: These features are ~ Alpha and * Beta versions

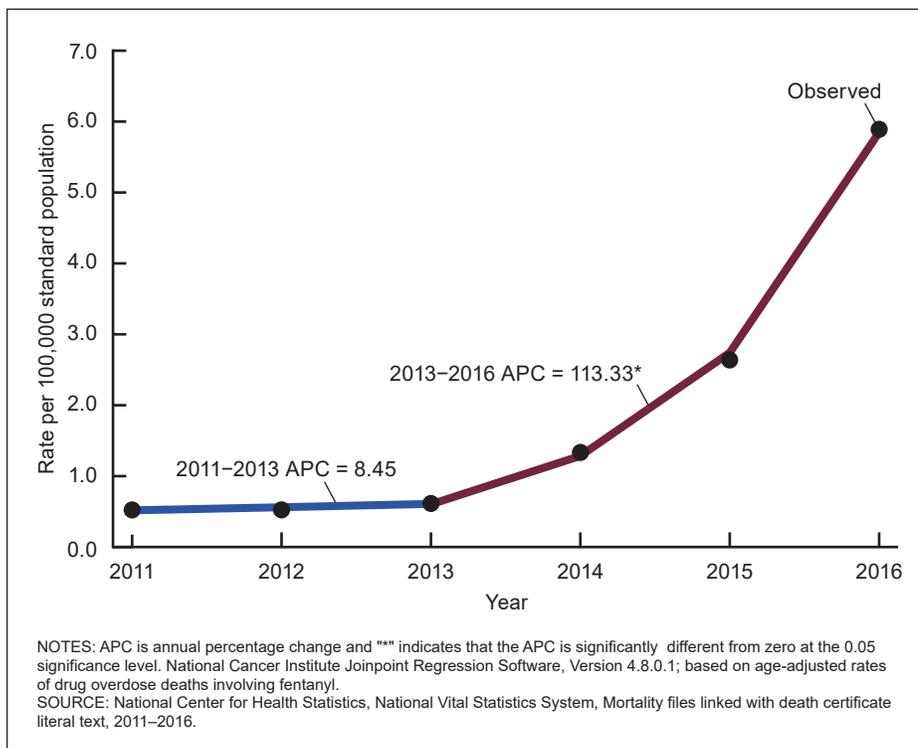
Session Note:

Created by Joinpoint Version 4.8.0.1

NOTE: National Cancer Institute Joinpoint Regression Software, Version 4.8.0.1; based on age-adjusted rates of drug overdose deaths involving fentanyl.

SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

Figure 3. Linear plot from Joinpoint, age-adjusted rates of drug overdose deaths involving fentanyl, total population: United States, 2011–2016



can be used to assess whether there is a flat trend (the test of zero slope), which is the focus of this report. This report evaluates the test of zero slope using the second line segment, which has a slope of 0.75769 and standard error of 0.03508. The statistical test from Joinpoint suggests that the second slope for the segment from 2013 to 2016 is nonzero (p -value = 0.0294).

Conducting the analysis in SAS

Alternatively, the test of zero slope can be evaluated in SAS. The data are log-transformed for consistency with the model set up in the Joinpoint software. The log transformation on a given rate (r) and standard error (se) is performed as follows: the log-transformed outcome is the natural log of the rate ($\ln(r)$) and the standard error of the log-transformed outcome is the provided standard error divided by the rate (se/r). The data are also parameterized as shown in Table B to perform the test of zero slope in SAS. This parameterization is set up so that the second coefficient can be used to directly perform the same test (that is, the general parameterization). See parameterizations A and B in the “National Center for Health Statistics Guidelines for Analysis of Trends” report (6) for more details on the equivalence of this parameterization or see Kim, et al. (3).

To do this, the following SAS code may be used:

```
*Read in data;
data overall;
input year rate se;
datalines;
2011 0.52642221414374
0.01309819069566
2012 0.52348955303881
0.01327859444996
2013 0.61348908485145
0.01428634914743
2014 1.33709071629324
0.02088464305748
2015 2.63808606193993
0.02948388397648
2016 5.89191591137986
0.04418210644237
;
run;
*Log transform rates;
data overall;
```

Table A. Joinpoint regression software model estimates, age-adjusted rates of drug overdose deaths involving fentanyl, total population: United States, 2011–2016**Model statistics**

Number of joinpoints	Number of observations	Number of parameters	Degrees of freedom	Sum of squared errors	Mean squared error	Autocorrelation parameter
1	6	4	2	26.52509	13.26255	Uncorrelated

Estimated joinpoints

Joinpoint	Estimate	Lower confidence interval	Upper confidence interval
1	2013	2012	2014

Estimated regression coefficients (beta)

Parameter	Parameter estimate	Standard error	Test statistic (t)	Probability greater than t
Standard parameterization				
Intercept 1	-163.71073	313.36837	-0.52	0.6935
Slope 1	0.08108	0.15579	0.52	0.6945
Slope 2–Slope 1	0.67662	0.15969	4.24	0.1475
General parameterization				
Intercept 1	-163.71073	313.36837	-0.52	0.6935
Intercept 2	-1525.73712	70.69239	21.58	0.0295
Slope 1	0.08108	0.15579	0.52	0.6945
Slope 2	0.75769	0.03508	21.60	0.0294

NOTE: National Cancer Institute Joinpoint Regression Software, Version 4.8.0.1; based on log-transformed age-adjusted rates of drug overdose deaths involving fentanyl.

SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

Table B. Model set up to demonstrate a trend model in SAS

Year	x1	x2
2011	2011	0
2012	2012	0
2013	2013	0
2014	2013	1
2015	2013	2
2016	2013	3

```

set overall;
logy=log(rate); *Dependent
variable;
wy=rate**2/se**2; *Weight,
inverse variance of log-
transformed rate;
run;
*Create variable x2 which is
0 if year<=c, or year-c
otherwise (c=2013 is the
joinpoint);
data jp2013;
set overall;
x1=min(year,2013);
x2=max(0,year-2013);
run;
*Model log-transformed rates;
proc reg data= jp2013 all;
model logy=x1 x2;
weight wy;
run;

```

The resulting output is shown in [Table C](#).

From the PROC REG output, the estimated slope for the second segment x_2 (0.75770) is nearly identical to the slope estimates from the general parameterization in the Joinpoint software (0.75769, [Table A](#)). However, the standard error from SAS (0.01784) is smaller than the standard error of the slope obtained from Joinpoint (0.03508, [Table A](#)) and the test uses three degrees of freedom instead of one. Note that SAS displays one degree of freedom per variable estimated (*Intercept*, x_1 , and x_2), but the model has a total of three degrees of freedom as there are six data points and three estimated coefficients. SAS reports a p -value of less than 0.0001 for the slope of the second line segment.

The Joinpoint software's testing procedure previously reported a p -value of 0.0294. In this case, both the Joinpoint software's estimation approach and the naïve linear model approach lead to the same conclusion that the trend is not flat after 2013. Although similar results were obtained using both methods, the naïve test in SAS can be viewed as excluding variability as it is based on the a priori assumption that a shift occurred at 2013. Alternatively, the Joinpoint software's approach accounts for the estimation of

the joinpoint location at 2013 prior to fitting the trend line.

Example 2: Trend for females**Conducting the analysis in the Joinpoint software**

The comparison of the Joinpoint and SAS tests of zero slope is also performed for a second example, the trend of fentanyl overdose deaths for the female subpopulation. This example replicates the steps performed in Example 1; however, it is demonstrated that the two tests produce differing conclusions in this case. The plot of the estimated trend for the female subpopulation and the output from the Joinpoint program are displayed, respectively, in [Figure 4](#) and [Table D](#). Note that for this demonstration, the trend line ([Figure 4](#)) does not connect through all the points due to the small sample size and the restriction of a maximum of one joinpoint.

For this example, the estimate of the slope for the second line segment is 0.63711 and the estimated standard error is 0.07272. The statistical test from Joinpoint suggests that the second slope for the trend from 2013 to 2016 for females is not significantly different than zero (p -value = 0.0724).

Table C. SAS/STAT PROC REG output, overall age-adjusted death rates of drug overdose deaths involving fentanyl: United States, 2011–2016

Variable	Degrees of freedom	Parameter estimate	Standard error	t value	Probability greater than t
Intercept	1	-163.65063	85.32588	-1.92	0.1509
x1	1	0.08104	0.04240	1.91	0.1519
x2	1	0.75770	0.01784	42.46	Less than 0.0001

NOTE: SAS, Version 9.4; based on log-transformed, age-adjusted rates of drug overdose deaths involving fentanyl.
 SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

Conducting the analysis in SAS

The Joinpoint test of zero slope is compared with the naïve test of slope in SAS for the female subgroup. Like Example 1, the following SAS code is used to set up the data (see structure in Table B) and obtain the linear model estimates in PROC REG:

```
*Read in data;
data female;
input year rate se;
datalines;
2011 0.45663881229817
0.01708918272498
2012 0.42394702648993
0.01641024598534
2013 0.48517527324639
0.01738273665556
2014 0.88749374921809
```

```
0.02418202405264
2015 1.4638129148067
0.03098863268132
2016 3.13574208253773
0.04549312957479
```

```
;
run;
*Log transform rates;
data female;
set female;
logy=log(rate); *Dependent variable;
wy=rate**2/se**2; *Weight, inverse variance of log-transformed rate;
run;
*Create variable x2 which is 0 if year<=c, or year-c
```

```
otherwise (c=2013 is the joinpoint);
data jp2013;
set female;
x1=min(year,2013);
x2=max(0,year-2013);
run;
*Model log-transformed rates;
proc reg data= jp2013 all;
model logy=x1 x2;
weight wy;
run;
```

The PROC REG output in Table E shows that the estimated slope for x2 (0.63713) is close to the Joinpoint software slope (0.63711, Table D) although the estimated standard error from SAS (0.03427) is smaller than the standard error from Joinpoint (0.07272, Table D). In this example for the female subpopulation, the p-value for the test of slope in SAS is 0.0003, which indicates the slope is significantly different than zero. In the Joinpoint software, however, the p-value is 0.0724 (Table D), which suggests that the slope is not significantly different from zero (conflicting result with the usual linear model in SAS). This second example demonstrates that the naïve linear model approach can result in different results compared with the Joinpoint software approach.

Through Examples 1 and 2, the test of zero slope in Joinpoint is compared with the test of zero slope in SAS. In the evaluation of the trend for the total population (Example 1), Joinpoint and SAS produce comparable findings (p-values of 0.0294 and less than 0.0001, respectively). Both tests suggest that trend was not flat after 2013. However, for the comparison of fentanyl overdose deaths in the female subgroup (Example 2), Joinpoint and SAS result in differing conclusions. Joinpoint finds that the slope was not significantly different from zero (p-value = 0.0724), suggesting a flat trend, while SAS finds that the slope was nonzero after 2013 (p-value = 0.0003).

Figure 4. Linear plot from Joinpoint, rates of drug overdose deaths involving fentanyl, females: United States, 2011–2016

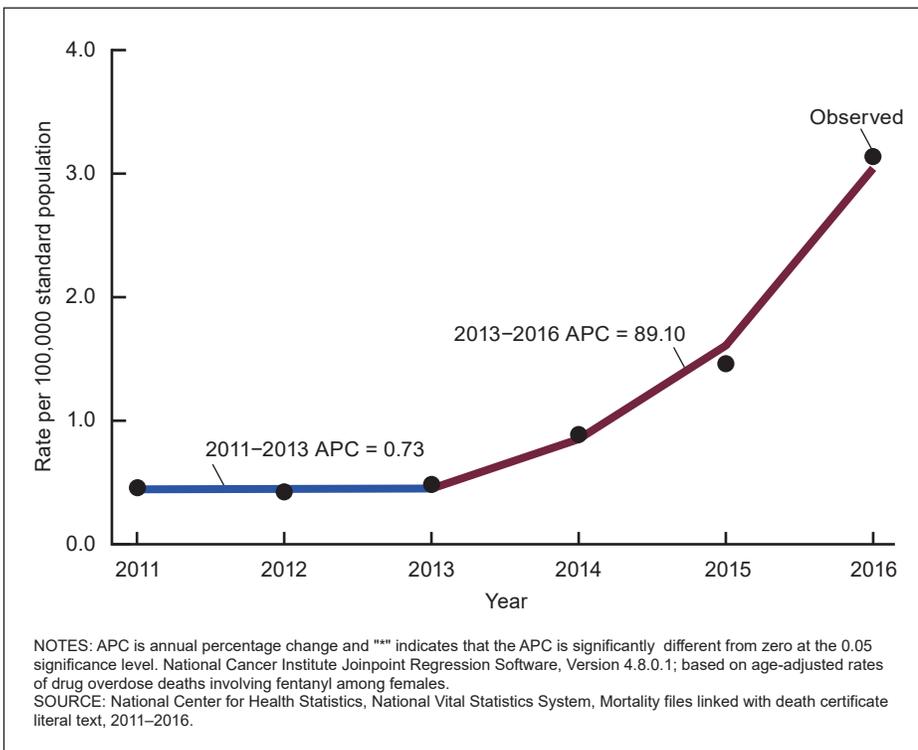


Table D. Joinpoint regression software model estimates, age-adjusted rates of drug overdose deaths involving fentanyl, females: United States, 2011–2016

Model statistics

Number of joinpoints	Number of observations	Number of parameters	Degrees of freedom	Sum of squared errors	Mean squared error	Autocorrelation parameter
1	6	4	2	33.42794	16.71397	Uncorrelated

Estimated joinpoints

Joinpoint	Estimate	Lower confidence interval	Upper confidence interval
1	2013	2012	2015

Estimated regression coefficients (beta)

Parameter	Parameter estimate	Standard error	Test statistic (t)	Probability greater than t
Standard parameterization				
Intercept 1	-15.41032	540.41245	-0.03	0.9819
Slope 1	0.00726	0.26866	0.03	0.9828
Slope 2–Slope 1	0.62985	0.27833	2.26	0.2649
General parameterization				
Intercept 1	-15.41032	540.41245	-0.03	0.9819
Intercept 2	-1283.30106	146.56108	-8.76	0.0724
Slope 1	0.00726	0.26866	0.03	0.9828
Slope 2	0.63711	0.07272	8.76	0.0724

NOTE: National Cancer Institute Joinpoint Regression Software, Version 4.8.0.1; based on log-transformed age-adjusted rates of drug overdose deaths involving fentanyl.
 SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

Question 2: How does Joinpoint test the hypothesis that a slope of a segment is zero?

To assess why the Joinpoint and SAS tests of zero slope differ in some cases, the procedure used in Joinpoint is evaluated by revisiting the two examples. As shown in Question 1, SAS can be used to log transform the data and SAS PROC REG can be used directly on the log-transformed data to provide the same estimates of slope as Joinpoint. However, the estimates of standard error and the degrees of freedom differed between Joinpoint and SAS in both examples. In Question 2, SAS is used to replicate the Joinpoint procedures of calculating the standard error, degrees of freedom, test statistic, and *p*-value to demonstrate the

approach used in the Joinpoint software. The estimates of standard error and the determination of a *p*-value cannot be achieved directly from SAS PROC REG but can still be accomplished within SAS. As will be shown, the estimated standard error and degrees of freedom differ in Joinpoint due to the treatment of joinpoint locations as estimated values. Refer to Examples 1 and 2 below for details.

Example 1: Trend for the total population

For the evaluation of the trend for the total population, the data must be log transformed since the Joinpoint analysis was run on the log-scale (that is, $\ln(y)$, Figure 1) and SAS PROC REG can be used to determine the estimated slope (see SAS code in Question 1, Example

1). As shown previously, the estimated slope of the second line segment from SAS PROC REG (0.75770, Table C) was nearly identical to the estimated slope from Joinpoint (0.75769, Table A), with a slight difference due to rounding. However, the estimate of standard error from SAS PROC REG (0.01784, Table C) differed from the estimated standard error from Joinpoint (0.03508, Table A) and the degrees of freedom for each approach differed (3 in SAS, 1 in Joinpoint). The approach to replicate the Joinpoint estimate of standard error for the second line segment in SAS follows. As will be seen, the Joinpoint software does not use all the data to estimate the standard error as SAS PROC REG does. The Joinpoint procedure for testing a regression coefficient can be found elsewhere (5).

To obtain the standard error of the slope in SAS, the data occurring at the joinpoint location(s) (in this example, in the year 2013) is removed and the data is reparameterized to fit the trend lines on either side of the joinpoint. This is accomplished by adding a separate intercept for each trend line (that is, do not force the trend to be continuous, but allow it to have breaks) and defining the slope for each segment, as shown in Table F. This results in the same model

Table E. SAS/STAT PROC REG output, age-adjusted rates of drug overdose deaths involving fentanyl, females: United States, 2011–2016

Variable	Degrees of freedom	Parameter estimate	Standard error	t value	Probability greater than t
Intercept	1	-15.24806	149.82788	-0.10	0.9254
x1	1	0.00718	0.07446	0.10	0.9283
x2	1	0.63713	0.03427	18.59	0.0003

NOTE: SAS, Version 9.4; based on log-transformed, age-adjusted rates of drug overdose deaths involving fentanyl among females.
 SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

estimates as those obtained by fitting two separate trend lines (2011–2012 and 2014–2016), although in this example there are not enough degrees of freedom to estimate the standard errors of the first intercept (*int1*) and slope (*year1*) using a separate model. Note that in general, one can obtain the appropriate standard error using SAS by eliminating all data points that fall on joinpoints and adding an intercept at the beginning of each new segment. For this example, there is only one joinpoint.

The following SAS statements are used to reparameterize the data as shown in Table F and fit the corresponding model. The output from the SAS code is used to obtain the standard error from the Joinpoint software to test the slope of the trend line.

```
*Create intercepts for each
  joinpoint, slope for segment
  before 2013;
data jp2013_SE;
set overall;
if year = 2013 then DELETE;
int1=1;
if year > 2013 then int1=0;
year1=year;
if year > 2013 then year1=0;
int2=1;
if year < 2013 then int2=0;
x=year;
if year < 2013 then x=0;
run;

*Model log-transformed rates =
  int1 + year1 + int2 + x;
proc reg data=jp2013_SE;
model logy=int1 year1 int2 x/
  noint;
weight wy;
run;
```

The SAS statements will result in the output shown in Table G, in which the standard error used to test the second slope in the Joinpoint software is the standard error of *x* (that is, 0.03508), which matches the standard error estimate from the Joinpoint output (Table A). Note that the coefficient of *x* is not equal to the second slope in the Joinpoint general parameterization model (0.75769, Table A) because not all the data are used and an extra intercept (*int2*) is included.

Table F. Model set up to reproduce the Joinpoint standard error estimate in SAS

Year	Intercept 1 (<i>int1</i>)	Slope 1 (<i>year1</i>)	Intercept 2 (<i>int2</i>)	Slope 2 (<i>x</i>)
2011	1	2011	0	0
2012	1	2012	0	0
2013	---	---	---	---
2014	0	0	1	2014
2015	0	0	1	2015
2016	0	0	1	2016

--- Data not available.

NOTE: The intercepts and slopes for 2013 are missing in this parameterization as the data for this year have been removed.

After obtaining the standard error used in the Joinpoint software, the test of zero slope for the second line segment can be evaluated using SAS. The test that the slope of the second line segment is zero in Joinpoint is located in the general parameterization section of the Joinpoint output for the parameter *Slope 2* (Table A). From Table A, the parameter estimate is 0.75769, the standard error is 0.03508, the test statistic (*t*) is 21.60 and the *p*-value is 0.0294.

Replicating this approach using SAS, the estimate for the second slope is 0.75770 (Table C) and the standard error is 0.03508 (Table G). For this test, there is one degree of freedom, as it can be seen that in this formulation only three data points (2014, 2015, and 2016) are used for estimating the slope of the second line segment and two degrees of freedom are used to estimate the intercept and slope for the second trend line. The test statistic and the *p*-value can be calculated using the values obtained in SAS. The test statistic is calculated as Parameter Estimate/Standard Error = 0.75770/0.03508 = 21.60 (rounded, unrounded test statistic used in SAS code below). In SAS, the *p*-value based on a 2-sided *t*-test with one degree of freedom is calculated as follows:

```
data pvalue;
p=probt(-21.59913,1)*2;
proc print data=pvalue;
run;
```

Note that the negative test statistic (–21.59913) is used to obtain the *p*-value since *probt* calculates the probability under the distribution to the left of the specified test statistic. SAS produces a *p*-value of 0.0295, which is consistent with the *p*-value in the Joinpoint output (0.0294, Table A). The slight difference between the *p*-values in Joinpoint and SAS can be attributed to rounding. Thus, the Joinpoint test of zero slope, including the estimate of the standard error and degrees of freedom, can be replicated in SAS by removing data at the joinpoint to account for the variability in the joinpoint location since it was estimated in the software prior to evaluating the trend.

Example 2: Trend for females

Like Example 1, the Joinpoint estimate of standard error for the test of zero slope is replicated using SAS for the female subpopulation. The age-adjusted rates of drug overdose deaths involving females are first log transformed and the estimate of slope is obtained using SAS PROC REG (see SAS code in Question 1, Example 2). As seen previously, the estimated slope of the second segment (after 2013) in SAS (0.63713, Table E) is nearly identical to the estimated slope from Joinpoint (0.63711, Table D), although the estimated standard errors differ between the two software programs (0.03427 in SAS, Table E; 0.07272 in Joinpoint, Table D). The Joinpoint estimate of standard error is replicated by reparameterizing the model in SAS, as shown below.

Table G. SAS/STAT PROC REG output to reproduce the Joinpoint standard error estimate and age-adjusted rates of drug overdose deaths involving fentanyl, total population: United States, 2011–2016

Variable	Degrees of freedom	Parameter estimate	Standard error	<i>t</i> value	Probability greater than <i>t</i>
<i>int1</i>	1	10.59281	313.29316	0.03	0.9785
<i>year1</i>	1	–0.00559	0.15575	–0.04	0.9772
<i>int2</i>	1	–1522.51585	70.69592	–21.54	0.0295
<i>x</i>	1	0.75609	0.03508	21.56	0.0295

NOTE: SAS, Version 9.4; based on log-transformed, age-adjusted rates of drug overdose deaths involving fentanyl.

SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

To estimate the standard error, the same procedure used in Example 1 is applied below. The data occurring in the year 2013 is removed and two separate trend lines are defined using a separate intercept and slope for each line (see structure in Table F for additional details).

```
*Create intercepts for each
  joinpoint, slope for segment
  before 2013;
data jp2013_SE;
set female;
if year = 2013 then DELETE;
int1=1;
if year > 2013 then int1=0;
year1=year;
if year > 2013 then year1=0;
int2=1;
if year < 2013 then int2=0;
x=year;
if year < 2013 then x=0;
run;

*Model log-transformed rates =
  int1 + year1 + int2 + x;
proc reg data=jp2013_SE;
model logy=int1 year1 int2 x/
  noint;
weight wy;
run;
```

The output from these steps is shown in Table H, in which the standard error for the second slope (that is, 0.07272) matches the standard error estimated by the Joinpoint software (Table D). This estimate of standard error, along with the estimate of the slope of the second line segment (obtained in Question 1, Example 2), can be used to replicate the test of zero slope in Joinpoint.

From the Joinpoint software output for the test of the slope of the

second line segment, the parameter estimate is 0.63711, the standard error is 0.07272, the test statistic (t) is 8.76, and the p -value is 0.0724 (Table D). To replicate this test using SAS, the parameter estimate for the second slope (0.63713, Table E) and the standard error (0.07272, Table H) are used. There is one degree of freedom as three data points are used to estimate the slope of the second line segment (2014, 2015, and 2016) but the extra intercept and slope require two degrees of freedom to estimate. The test statistic is calculated as Parameter Estimate/Standard Error = $0.63713/0.07272 = 8.76$ (rounded, unrounded test statistic used in SAS code below) and the p -value based on a 2-sided t -test with one degree of freedom can be calculated in SAS as follows:

```
data pvalue;
p=probt(-8.76141,1)*2;
proc print data=pvalue;
run;
```

Note that the negative test statistic (-8.76141) is used to obtain the p -value since *probt* calculates the probability under the distribution to the left of the specified test statistic. SAS produces a p -value of 0.0723, which is consistent with the p -value in the Joinpoint general parameterization output (Table D, 0.0724). The slight difference between the p -values in Joinpoint and SAS can be attributed to rounding. Again, the Joinpoint procedure for performing the test of zero slope is replicated using SAS. The step-by-step procedure demonstrates that the Joinpoint procedure uses an estimate of standard error that has been adjusted for the estimation of the joinpoint location.

While Question 1 demonstrated that the tests of zero slope in Joinpoint

and SAS can differ, Question 2 provides further details about the procedure used in Joinpoint. As shown through the two examples, although the estimated slopes in SAS and Joinpoint are nearly identical, the estimated standard errors from the two software programs differ. To replicate Joinpoint's estimate of standard error for the slope of the line segment, the user must remove the data occurring at the joinpoints to account for the variability due to estimating the joinpoint locations. In both examples, SAS was used to reparameterize the data, produce Joinpoint's estimate of standard error, and replicate the test of zero slope provided in Joinpoint.

Conclusion

In this report, the test of zero slope in NCI's Joinpoint software is explored by addressing two questions: 1) How does the test of zero slope in Joinpoint compare to the test of zero slope in SAS? and 2) How does Joinpoint test the hypothesis that a slope of a segment is zero? For Question 1, the results from the Joinpoint software test of zero slope were compared with the results from the linear model approach using SAS PROC REG through the evaluation of two examples, including fentanyl overdose deaths in the total population and the female subgroup. Although the Joinpoint software estimate of slope corresponded to the slope from a usual linear model, Joinpoint and SAS resulted in different standard error estimates. For the evaluation of the general trend of fentanyl overdose deaths, the usual test of slope performed in SAS resulted in the similar conclusion to the Joinpoint software that the trend in the fentanyl death rate significantly increased after 2013 (p -value = 0.0294 in Joinpoint, p -value less than 0.0001 in SAS). However, in the female subgroup, the Joinpoint software and SAS produced different conclusions. While the evaluation in the Joinpoint software did not identify a significant slope after 2013 (p -value = 0.0724), the naïve analysis in SAS identified a statistically significant increase (p -value = 0.0003).

These examples motivated further investigation into Joinpoint's approach to the test of zero slope through Question 2. SAS was used to demonstrate how

Table H. SAS/STAT PROC REG output to reproduce the Joinpoint standard error estimate and age-adjusted rates of drug overdose deaths involving fentanyl, females: United States, 2011–2016

Variable	Degrees of freedom	Parameter estimate	Standard error	t value	Probability greater than $ t $
<i>int1</i>	1	148.60171	540.33080	0.28	0.8291
<i>year1</i>	1	-0.07428	0.26862	-0.28	0.8282
<i>int2</i>	1	-1322.25028	146.56541	-9.02	0.0703
<i>x</i>	1	0.65644	0.07272	9.03	0.0702

NOTE: SAS, Version 9.4; based on log-transformed, age-adjusted rates of drug overdose deaths involving fentanyl among females.

SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

the Joinpoint software tests whether the line segment slopes are zero. Through the evaluation of the two fentanyl overdose death trends, it was illustrated that the Joinpoint test of slope can be reproduced by removing data at the joinpoints to estimate the standard errors. This step-by-step application of SAS illustrates how the Joinpoint approach to estimating the standard error and degrees of freedom accounts for the estimation of the joinpoints prior to estimating the trend model and differs from a straightforward application of SAS PROC REG. One should use caution when comparing trend results obtained from the Joinpoint software and SAS as the two software programs use different estimation approaches and are based on different assumptions. In practice, when locations of joinpoints are unknown and identification of the joinpoints is part of explanatory analysis, the Joinpoint approach may be useful because it accounts for the estimation of the joinpoints whereas the linear model approach (demonstrated in SAS PROC REG) with fixed joinpoints does not. Currently, there is no known method that uses all the data and considers that the joinpoint locations are unknown. This issue may become less important as the sample size gets larger relative to the number of joinpoints. However, simulations with sample sizes as low as 10 with one joinpoint have demonstrated accurate confidence interval coverage using the Joinpoint method (4).

This report has focused solely on the use of Joinpoint for analyzing trends using point estimates that do not include variability due to survey sampling, such as vital statistics. For the test of zero slope using survey data, a similar issue exists as standard survey-based software do not account for the uncertainty in the joinpoint locations when the joinpoints are estimated. However, as stated in Issue 5 of the “National Center for Health Statistics Guidelines for Analysis of Trends” report (6), it is still recommended to use survey-based software to test slopes because it can correctly account for between year correlation based on the survey design as well as use the survey-based degrees of freedom, which are typically much larger than those used by Joinpoint. The

guidelines further state that estimates of standard error are typically similar whether Joinpoint or a survey-based procedure is used in the estimation so performing the entire test using the survey approach may be preferable to using the Joinpoint software. However, one could mimic the Joinpoint approach described in this report and adapt it to the survey approach while still accounting for correlation between years and the survey-based degrees of freedom. Specifically, this could be accomplished using the following steps: 1) obtain the joinpoint locations using the Joinpoint software, 2) code the Joinpoint model into the survey approach and estimate the slope or slopes of interest (see structure in [Table B](#)), 3) remove all data that fall on any of the joinpoints and include an additional intercept at each join to follow the Joinpoint procedure (see structure in [Table F](#)), 4) use the resulting estimate of the standard error of the slope from this model and obtain the resulting design-based degrees of freedom (they may change slightly), and 5) perform a *t*-test by dividing the estimated slope by the estimated standard error of the slope to obtain the test statistic and use the resulting degrees of freedom to obtain the *p*-value.

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Table 1. Age-adjusted rates and standard errors for drug overdose deaths involving fentanyl, total population: United States, 2011–2016

Year	Rate	Standard error
2011	0.52642221414374	0.01309819069566
2012	0.52348955303881	0.01327859444996
2013	0.61348908485145	0.01428634914743
2014	1.33709071629324	0.02088464305748
2015	2.63808606193993	0.02948388397648
2016	5.89191591137986	0.04418210644237

SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

Table 2. Age-adjusted rates and standard errors for drug overdose deaths involving fentanyl, females: United States, 2011–2016

Year	Rate	Standard error
2011	0.45663881229817	0.01708918272498
2012	0.42394702648993	0.01641024598534
2013	0.48517527324639	0.01738273665556
2014	0.88749374921809	0.02418202405264
2015	1.46381291480670	0.03098863268132
2016	3.13574208253773	0.04549312957479

SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality files linked with death certificate literal text, 2011–2016.

Technical Notes

Data source and study population

The examples used to answer these questions use the National Vital Statistics System multiple cause-of-death mortality data (NVSS-M) from 2011 through 2016. NVSS-M contains information extracted from death certificates on cause of death, demographic, and geographic factors (8). The study population was limited to U.S. residents. Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. These underlying codes identify the deaths due to acute toxicity from drugs (that is, drug overdose) as opposed to chronic exposure leading to death (for example, liver toxicity) or adverse effects from therapeutic or prophylactic dosages of drugs. Drug overdose deaths include all intents (that is, unintentional, suicide, homicide, and undetermined intent). Use of these underlying cause-of-death codes is consistent with other NCHS publications on drug overdose deaths and facilitates comparisons with other analyses using ICD–10 coded data (7,9,11–13).

NVSS-M records for drug overdose deaths were linked to literal text data from death certificates. The literal text is the written information provided by the medical certifier, usually a medical examiner or coroner in the case of drug overdose deaths, that describes the cause of death as well as other factors or circumstances that contributed to the death (14,15). Literal text from three fields of the death certificate: 1) the causes of death from Part I, 2) the other significant conditions contributing to death from Part II, and 3) the description of how the injury occurred, was analyzed to identify the specific drugs involved in the overdose death.

Identification of drug overdose deaths involving fentanyl used the Drugs Mentioned with Involvement (DMI) methodology (9) informed by the results from an exploratory analysis of the literal text using SAS Contextual Analysis software (16). The DMI methodology (9) searches the literal text fields of NVSS-M data for mentions of drugs and for terms that provide context about involvement

of the drug in the death (that is, whether the drug contributed to the death). Drugs mentioned in the death certificate literal text are assumed to be involved in the death unless contextual information suggests otherwise (9).

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National Health Statistics Reports ■ Number 156 ■ June 7, 2021

Acknowledgments

The authors would like to acknowledge Huann-Sheng Chen of the National Cancer Institute for reviewing this report and providing valuable comments.

Suggested citation

Irimata KE, Malec DJ, Bastian BA, Spencer MR. Using SAS/STAT to understand the NCI Joinpoint Regression Software: Testing for a zero slope using rates of drug overdose deaths involving fentanyl, 2011–2016. National Health Statistics Reports; no 156. Hyattsville, MD: National Center for Health Statistics. 2021. DOI: <https://doi.org/10.15620/cdc:105105>.

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