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A command for Laplace regression

Matteo Bottai
Unit of Biostatistics
Institute of Environmental Medicine
Karolinska Institutet
Stockholm, Sweden
matteo.bottai@ki.se

Nicola Orsini
Unit of Biostatistics and Unit of Nutritional Epidemiology
Institute of Environmental Medicine
Karolinska Institutet
Stockholm, Sweden
nicola.orsini@ki.se

Abstract. We present the new `laplace` command for estimating Laplace regression, which models quantiles of a possibly censored outcome variable given covariates. We illustrate `laplace` with an example from a clinical trial on survival in patients with metastatic renal carcinoma. We also report the results of a small simulation study.

Keywords: st0294, laplace, quantile regression, censored outcome, survival analysis, Kaplan–Meier

1 Introduction

Estimating percentiles for a time-to-event variable of interest conditionally on covariates may offer a useful complement to current approaches to survival analysis. For example, comparing survival across treatments or exposure levels in observational studies at various percentiles (for example, at the 50th or 10th percentiles) provides important insights. At the univariate level, this can be accomplished with the Kaplan–Meier estimator.

Laplace regression can be used to estimate the effect of risk factors and important predictors on survival percentiles while adjusting for other covariates. The user-written `clad` command (Jolliffe, Krushelnytskyy, and Semykina 2000) estimates conditional quantiles only when censoring times are fixed and known for all observations (Powell 1986), and its applicability is limited.

In this article, we present the `laplace` command for estimating Laplace regression (Bottai and Zhang 2010). In section 3, we describe the syntax and options. In section 3, we illustrate `laplace` with data from a randomized clinical trial. In section 4, we sketch the methods and formulas. In section 5, we present the results of a small simulation study.

 st0294

2 The laplace command

2.1 Syntax

`laplace` *depvar* [*indepvars*] [*if*] [*in*] [, `quantiles(`*numlist*`)` `failure(`*varname*`)` `sigma(`*varlist*`)` `reps(`#`)` `seed(`#`)` `tolerance(`#`)` `maxiter(`#`)` `level(`#`)`]

`by`, `statsby`, and `xi` are allowed with `laplace`; see [U] **11.1.10 Prefix commands**.

See [R] **qreg postestimation** for features available after estimation.

2.2 Options

`quantiles(`*numlist*`)` specifies the quantiles as numbers between 0 and 1; numbers larger than 1 are interpreted as percentages. The default is `quantiles(0.5)`, which corresponds to the median.

`failure(`*varname*`)` specifies the failure event; the value 0 indicates censored observations. If `failure()` is not specified, all observations are assumed to be uncensored.

`sigma(`*varlist*`)` specifies the variables to be included in the scale parameter model. The default is constant only.

`reps(`#`)` specifies the number of bootstrap replications to be performed for estimating the variance–covariance matrix and standard errors of the regression coefficients.

`seed(`#`)` sets the initial value of the random-number seed used by the bootstrap. If `seed()` is specified, the bootstrapped estimates are reproducible (see [R] **set seed**).

`tolerance(`#`)` specifies the tolerance for the optimization algorithm. When the absolute change in the log likelihood from one iteration to the next is less than or equal to #, the `tolerance()` convergence criterion is met. The default is `tolerance(1e-10)`.

`maxiter(`#`)` specifies the maximum number of iterations. When the number of iterations equals `maxiter()`, the optimizer stops, displays an `x`, and presents the current results. The default is `maxiter(2000)`.

`level(`#`)` specifies the confidence level, as a percentage, for confidence intervals. The default is `level(95)` or as set by `set level`.

2.3 Saved results

`laplace` saves the following in `e()`:

Scalars			
`e(N)`	number of observations	`e(n_q)`	number of estimated quantiles
`e(N_fail)`	number of failures	`e(reps)`	number of bootstrap replications
Macros			
`e(cmd)`	`laplace`	`e(qlist)`	requested quantiles
`e(cmdline)`	command as typed	`e(vcetype)`	title used to label Std. Err.
`e(depvar)`	name of dependent variable	`e(properties)`	`b V`
`e(eqnames)`	names of equations	`e(predict)`	program used to implement `predict`
Matrices			
`e(b)`	coefficient vector	`e(V)`	variance–covariance matrix of the estimators
Functions			
`e(sample)`	marks estimation sample		

3 Example: Survival in metastatic renal carcinoma

We illustrate the use of `laplace` with data from a clinical trial on 347 patients with metastatic renal carcinoma. The patients were randomly assigned to either interferon-α (IFN) or oral medroxyprogesterone (MPA) (Medical Research Council Renal Cancer Collaborators 1999). A total of 322 patients died during follow-up. The outcome of primary research interest is overall survival.

```
. use kidney_ca_l
(kidney cancer data)
. quietly stset months, failure(cens)
```

The numeric variable `months` represents the time to event or censoring, and the binary variable `cens` indicates the failure status (0 = censored, 1 = death).

3.1 Median survival

We estimate a Laplace regression model where the response variable is time to death or censoring (`months`) and the binary indicator for treatment (`trt`) is the only covariate. We specify the event status with the option `failure()`. The default percentile is the median (`q50`).

```
. laplace months trt, failure(cens)
Laplace regression                              No. of subjects  =        347
                                                No. of failures  =        322

------------------------------------------------------------------------------
             |               Robust
      months |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
q50          |
         trt |   3.130258   1.195938     2.62   0.009     .7862628    5.474254
       _cons |    6.80548   .7188408     9.47   0.000     5.396578    8.214382
------------------------------------------------------------------------------
```

The estimated median survival in the MPA group is 6.8 months (95% confidence interval: [5.4, 8.2]). The difference (`trt`) in median survival between the treatment groups is 3.1 months (95% confidence interval: [0.8, 5.5]). Median survival among patients on IFN can be obtained with the postestimation command `lincom`.

```
. lincom _cons + trt
 ( 1)  [q50]trt + [q50]_cons = 0

------------------------------------------------------------------------------
      months |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   9.935738   .9557906    10.40   0.000     8.062423    11.80905
------------------------------------------------------------------------------
```

Percentiles of survival time by treatment group can also be obtained from the Kaplan–Meier estimate of the survivor function by using the command `stci`.

```
. stci, by(trt)
         failure _d:  cens
   analysis time _t:  months

             |    no. of
trt          |  subjects         50%      Std. Err.      [95% Conf. Interval]
-------------+-------------------------------------------------------------
         MPA |       175     6.80548       .8902896       4.86575    8.15342
         IFN |       172    9.830137       .8982793        7.7589    11.7041
-------------+-------------------------------------------------------------
       total |       347    7.956164       .5699226       6.90411     9.1726
```

The estimated median in the IFN group (9.8 months) differs slightly from the `laplace` estimate (9.9 months) shown above. The Kaplan–Meier curve in the IFN group is flat at the 50th percentile between 9.83 and 9.96 months of follow-up. The command `stci` shows the lower limit of this interval while `laplace` shows a middle value.

3.2 Multiple survival percentiles

When it is relevant to estimate multiple percentiles of the distribution of survival time, these can be specified with the option `quantiles()`.

```
. laplace months trt, failure(cens) quantiles(25 50 75) rep(100) seed(123)
Laplace regression                              No. of subjects  =        347
                                                No. of failures  =        322

------------------------------------------------------------------------------
             |              Bootstrap
      months |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
q25          |
         trt |   1.509151   .8289345     1.82   0.069    -.1155312    3.133832
       _cons |    2.49863    .399623     6.25   0.000     1.715384    3.281877
-------------+----------------------------------------------------------------
q50          |
         trt |   3.130258   1.209658     2.59   0.010     .7593719    5.501145
       _cons |    6.80548   .9100921     7.48   0.000     5.021732    8.589227
-------------+----------------------------------------------------------------
q75          |
         trt |   3.663238   3.482536     1.05   0.293    -3.162407    10.48888
       _cons |   15.87945   1.714295     9.26   0.000      12.5195    19.23941
------------------------------------------------------------------------------
```

The treatment effect is larger at higher percentiles of survival time. The difference between the two treatment groups at the 25th, 50th, and 75th percentiles is 1.5, 3.1, and 3.7 months, respectively. When bootstrap is requested, one can test for differences in treatment effects across survival percentiles with the postestimation command `test`.

```
. test [q25]trt = [q50]trt
 ( 1)  [q25]trt - [q50]trt = 0
           chi2(  1) =    2.59
         Prob > chi2 =    0.1076
```

We fail to reject the hypothesis that the treatment effects at the 25th and 50th survival percentiles are equal (p-value > 0.05).

Figure 1 shows the predicted percentiles from the 1st to the 99th in each treatment group. The difference of 3 months in median survival between groups is represented by the horizontal distance between the points A and B. Approximately 30% and 40% of the patients on MPA and IFN, respectively, are estimated to live longer than 12 months. The absolute difference of about 10% in the probability of surviving 12 months is represented by the vertical distance between the points C and D.

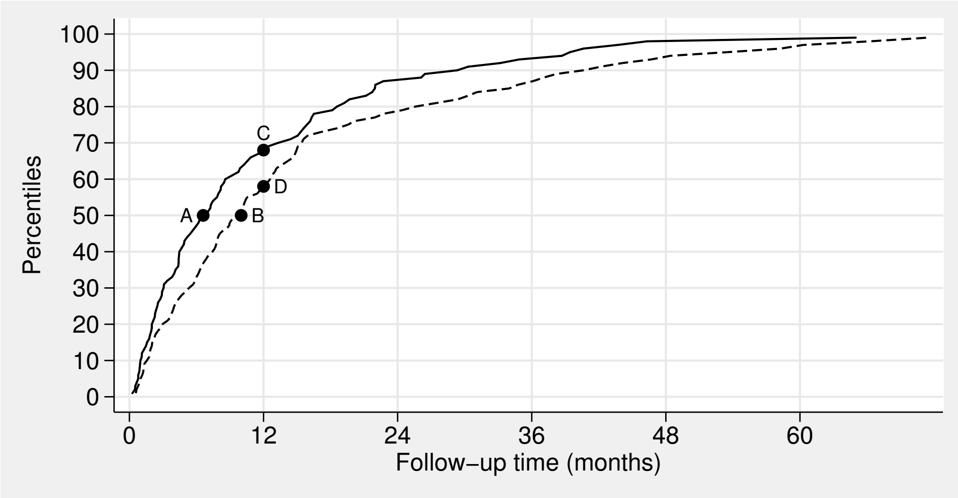

Figure 1. Survival percentiles in the MPA (solid line) and IFN (dashed line) groups estimated with Laplace regression. The horizontal distance between the points A and B (3.1 months) indicates the difference in median survival between groups. The vertical distance between C and D (about 10%) indicates the difference in the proportion of patients estimated to survive 12 months.

3.3 Interactions between covariates

Royston, Sauerbrei, and Ritchie (2004) analyzed the same data and described how a continuous prognostic factor, white cell count (`wcc`), affects the treatment effect as measured by a relative hazard. We now perform a similar analysis by using Laplace regression for the median survival. We include as covariates the treatment indicator (`trt`), three equally sized classes of white cell counts (`cwcc`) by means of two indicator variables, and their interactions.

```
. xi: laplace months i.trt*i.cwcc, failure(cens)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.cwcc            _Icwcc_0-2          (naturally coded; _Icwcc_0 omitted)
i.trt*i.cwcc      _ItrtXcwc_#_#       (coded as above)
Laplace regression                              No. of subjects  =       347
                                                No. of failures  =       322
```

months	Coef.	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
q50						
_Itrt_1	8.01462	2.270786	3.53	0.000	3.563962	12.46528
_Icwcc_1	2.262442	2.068403	1.09	0.274	-1.791554	6.316438
_Icwcc_2	-2.496523	1.645959	-1.52	0.129	-5.722544	.7294982
_ItrtXcwc_1_1	-5.737988	3.241483	-1.77	0.077	-12.09118	.6152021
_ItrtXcwc_1_2	-7.751629	2.645534	-2.93	0.003	-12.93678	-2.566478
_cons	6.90203	1.658547	4.16	0.000	3.651337	10.15272

The predicted median survival can be obtained with standard postestimation commands such as `predict` or `adjust`.

```
. adjust, by(trt cwcc) format(%2.0f) noheader
```

treatment	White Cell Counts Low	Medium	High
MPA	7	9	4
IFN	15	11	5

```
     Key:  Linear Prediction
```

The between-treatment-group difference in median survival varies from 8 months in the low white cell count category to 1 month in the high white cell count category. We test for interaction between treatment and white cell counts with the postestimation command `testparm`.

```
. testparm _ItrtX*
 ( 1)  [q50]_ItrtXcwc_1_1 = 0
 ( 2)  [q50]_ItrtXcwc_1_2 = 0
           chi2(  2) =    8.59
         Prob > chi2 =    0.0137
```

We reject the null hypothesis of equal treatment effect across categories of white cell counts ($p = 0.0137$). The treatment effect seems to be largest in patients with low white cell counts.

3.4 Laplace regression with uncensored data

Suppose all the values for the variable `months` were uncensored times at death. The `laplace` command can be used with uncensored observation by omitting the `failure()` option. In this case, `laplace` is simply an alternative to the standard quantile regression commands `qreg` and `sqreg`.

```
. qui laplace months trt
. adjust, by(trt) format(%3.2f) noheader
```

treatment	xb
MPA	6.77
IFN	9.89

```
     Key:  xb  =  Linear Prediction
. qui qreg months trt
. adjust, by(trt) format(%3.2f) noheader
```

treatment	xb
MPA	6.77
IFN	9.96

```
     Key:  xb  =  Linear Prediction
```

The number of observations in the MPA group is odd (175 patients), and the sample median survival is 6.77 months. The number of observations in the IFN group is even (172 patients), and the median is not uniquely defined. The two nearest values are 9.83 and 9.96 months. The command `qreg` picks the larger of the two, while `laplace` picks a value in between.

4 Methods and formulas

In this section, we follow the description provided by Bottai and Zhang (2010). Suppose we have a sample of size n. Let t_i, $i = 1, \ldots, n$, be a continuous outcome variable, c_i be a continuous censoring variable, and $x_i = \{x_{1,i}, \ldots, x_{r,i}\}'$ and $z_i = \{z_{1,i}, \ldots, z_{s,i}\}'$ be two vectors of covariates. The sets of covariates contained in x_i and z_i may partially or entirely overlap. We assume that c_i is independent of t_i conditionally on the covariates. Suppose we observe (y_i, d_i, x_i', z_i'), with $y_i = \min(t_i, c_i)$ and $d_i = I(t_i \leq c_i)$, where $I(A)$ denotes the indicator function of the event A. We assume that

$$t_i = x_i'\beta_p + \exp(z_i'\sigma_p)\varepsilon_i \tag{1}$$

where $\beta_p = \{\beta_{p,1}, \ldots, \beta_{p,r}\}'$ and $\sigma_p = \{\sigma_{p,1}, \ldots, \sigma_{p,s}\}'$ indicate the unknown parameter vectors, and ε_i are independent and identically distributed error terms that follow a standard Laplace distribution, $f(\varepsilon_i) = p(1-p)\exp\{[I(\varepsilon_i \leq 0) - p]\varepsilon_i\}$. For any given $p \in (0, 1)$, the p-quantile of the conditional distribution of t_i given x_i and z_i is $x_i'\beta_p$ because $P(t_i \leq x_i'\beta_p | x_i, z_i) = p$.

The command `laplace` estimates the $(r+s)$-dimensional parameter vector $\{\beta_p', \sigma_p'\}$ by maximizing the Laplace likelihood function described by Bottai and Zhang (2010). It uses an iterative maximization algorithm based on the gradient of the log likelihood that generates a finite sequence of parameter values along which the likelihood increases. Briefly, from a current parameter value, the algorithm searches the positive semiline in the direction of the gradient for a new parameter value where the likelihood is larger.

The algorithm stops when the change in the likelihood is less than the specified tolerance. Convergence is guaranteed by the continuity and concavity of the likelihood.

The asymptotic variance of the estimator $\widehat{\beta}_p$ for the parameter β_p is derived by considering the estimating condition reported by Bottai and Zhang (2010, eq. 4), $S(\widehat{\beta}_p)=0$, where

$$S\left(\widehat{\beta}_p\right)=\frac{1}{\exp\left(z_i'\widehat{\sigma}\right)}\sum_{i=1}^{n}x_i\left\{p-I\left(y_i\leq x_i'\beta_p\right)-I\left(y_i\leq x_i'\beta_p\right)\left(1-d_i\right)\frac{p-1}{1-\widehat{F}\left(y_i|x_i\right)}\right\}$$

with $\widehat{F}(y_i|x_i)=p\exp\{(1-p)(y_i-x_i'\widehat{\beta}_p)/\exp(z_i'\widehat{\sigma}_p)\}$. Following the standard asymptotic theory for method of moments estimators, $\widehat{\beta}_p$ approximately follows a normal distribution with mean β_p^* and variance $\widehat{V}$, where β_p^* indicates the expected value of β_p, $\widehat{V}=H(\widehat{\beta}_p)^{-1}S(\widehat{\beta}_p)'S(\widehat{\beta}_p)H(\widehat{\beta}_p)^{-1}$, and $H(\widehat{\beta}_p)=\partial S(\beta_p)/\partial\beta_p'|_{\beta_p=\widehat{\beta}_p}$. The derivative in $H(\widehat{\beta}_p)$ is evaluated numerically. Alternatively, the standard errors can be obtained with bootstrap by specifying the `reps()` option.

5 Simulation

In this section, we present the setup and results of a small simulation study to assess the finite sample performance of the Laplace regression estimator under different data-generating mechanisms. We contrast the performance of Laplace with that of the Kaplan–Meier estimator, a standard, nonparametric, uniformly consistent, and asymptotically normal estimator of the survival function. To generate the survival estimates, we used the `sts` command.

We generated 500 samples from (1) in each of the six different simulation scenarios that arose from the combination of two sample sizes and three data-generating mechanisms. In each scenario, we estimated five percentiles ($p=0.10, 0.30, 0.50, 0.70, 0.90$) with Laplace regression and the Kaplan–Meier estimator. The two sample sizes were $n=100$ and $n=1{,}000$. The three different data-generating mechanisms were obtained by changing the values of z_i, σ_p, and the censoring variable c_i. In all simulation scenarios, $x_i=(1,x_{1,i})'$, with $x_{1,i}\sim\text{Bernoulli}(0.5)$, $\beta_p=(5,3)'$, and ε_i was a standard normal centered at the quantile being estimated.

In scenario number 1, $z_i=1$, $\sigma_p=1$, and the censoring variable was set equal to a constant $c_i=1{,}000$ for all individuals. In this scenario, no observations were censored, and Laplace regression was equivalent to ordinary quantile regression. In scenario number 2, $z_i=1$, $\sigma_p=1$, and the censoring variable was generated from the same distribution as the outcome variable t_i. This ensured an expected censoring rate of 50% in both covariate patterns ($x_{1,i}=0,1$). In scenario number 3, $z_i=(1,x_{1,i})'$ and $\sigma_p=(0.5,0.5)'$. The censoring variable c_i was generated from the same distribution as the outcome variable t_i. In this scenario, the standard deviation of t_i was equal to 0.5 when $x_{1,i}=0$ and equal to 1 when $x_{1,i}=1$.

The following table shows the observed relative mean squared error multiplied by 1,000 for the predicted quantile in the group $x_{1,i} = 1$ in each combination of sample size (`obs`), data-generating scenario (`scenario`), and percentile (`percentile`) for Laplace (top entry) and Kaplan–Meier (bottom entry).

```
. table percentile scenario obs, contents(mean msel mean msekm) format(%4.3f)
> stubwidth(12)
```

	obs and scenario					
	100			1000		
percentile	1	2	3	1	2	3
10	1.187	1.395	1.268	0.129	0.136	0.126
	1.233	1.496	1.320	0.132	0.140	0.132
30	0.597	0.685	0.680	0.064	0.073	0.067
	0.606	0.792	0.831	0.064	0.078	0.075
50	0.496	0.570	0.653	0.053	0.065	0.073
	0.505	0.860	0.941	0.053	0.074	0.075
70	0.513	0.639	0.711	0.050	0.131	0.144
	0.518	1.329	1.050	0.050	0.113	0.094
90	0.728	1.661	1.930	0.063	0.876	0.955
	0.731	1.835	1.701	0.063	0.478	0.450

The relative mean squared error was smaller for Laplace than for Kaplan–Meier at lower quantiles and with the smaller sample size.

Figure 2 shows the relative mean squared error of Laplace (x axis) and Kaplan–Meier (y axis) estimators of the quantile in group $x_{1,i} = 1$ over all simulation scenarios.

The Laplace estimator had fewer extreme values than Kaplan–Meier. The overall concordance correlation coefficient (command `concord`) was 72.2%. After the 10% largest differences were excluded, the coefficient was 99.1%.

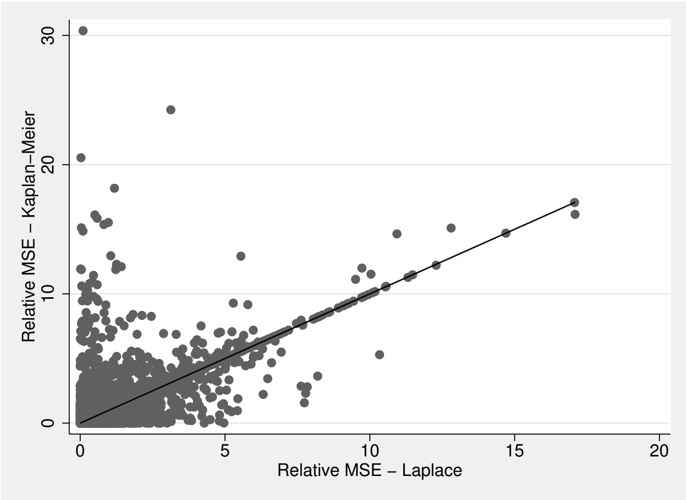

Figure 2. Relative mean squared error of Laplace (x axis) and Kaplan–Meier (y axis) estimators of the percentiles in group $x_{1,i} = 1$ over all simulation scenarios. The solid 45-degree line indicates the equal relative mean squared error of the two estimators.

The following two tables show the performance of the estimator of the asymptotic standard error for the regression coefficients $\widehat{\beta}_{p,0}$ (first table) and $\widehat{\beta}_{p,1}$ (second table). In each cell of each table, the top entry is the average estimated asymptotic standard error, and the bottom entry is the corresponding observed standard deviation across the simulated samples.

```
. table percentile scenario obs, contents(mean s0 mean ms0) format(%4.3f)
> stubwidth(12)
```

	obs and scenario					
	100			1000		
percentile	1	2	3	1	2	3
10	0.237	0.228	0.131	0.076	0.077	0.039
	0.235	0.251	0.123	0.073	0.082	0.039
30	0.185	0.200	0.098	0.059	0.062	0.031
	0.182	0.193	0.097	0.058	0.067	0.032
50	0.176	0.194	0.097	0.056	0.060	0.030
	0.169	0.185	0.093	0.053	0.064	0.032
70	0.188	0.198	0.098	0.059	0.064	0.032
	0.185	0.207	0.103	0.057	0.071	0.035
90	0.225	0.227	0.114	0.077	0.076	0.038
	0.231	0.255	0.141	0.072	0.087	0.046

```
. table percentile scenario obs, contents(mean s1 mean ms1) format(%4.3f)
> stubwidth(12)
```

percentile	100: 1	100: 2	100: 3	1000: 1	1000: 2	1000: 3
10	0.349	0.353	0.276	0.109	0.110	0.087
	0.330	0.351	0.263	0.104	0.113	0.088
30	0.277	0.292	0.232	0.084	0.089	0.070
	0.265	0.269	0.216	0.079	0.092	0.066
50	0.255	0.279	0.219	0.080	0.086	0.068
	0.250	0.257	0.226	0.077	0.086	0.073
70	0.272	0.293	0.227	0.084	0.090	0.070
	0.265	0.277	0.236	0.081	0.094	0.076
90	0.337	0.339	0.246	0.109	0.108	0.085
	0.325	0.320	0.284	0.104	0.109	0.098

The estimated standard errors were similar to the observed standard deviation across all cells for both regression coefficients.

6 Acknowledgment

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7 References

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About the author

Matteo Bottai is a professor of biostatistics in the Unit of Biostatistics at the Institute of Environmental Medicine at Karolinska Institutet in Stockholm, Sweden.

Nicola Orsini is an associate professor of medical statistics and an assistant professor of epidemiology in the Unit of Biostatistics and the Unit of Nutritional Epidemiology at the Institute of Environmental Medicine at Karolinska Institutet in Stockholm, Sweden.