# Multiplicative models for survival percentiles: estimating percentile ratios and multiplicative interaction in the metric of time

*Andrea Bellavia*[1], *Matteo Bottai*[1], *Nicola Orsini*[1]

*(1) Unit of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet*

***CORRESPONDING AUTHOR:*** *Dr. Andrea Bellavia - Institute of Environmental Medicine, Karolinska Institutet, 171 77, Stockholm, Sweden, Box 210 Telephone: +46-8-5248757 - E-mail: andrea.bellavia@ki.se*

***DOI:*** ***10.2427/11841***
*Accepted on July 4, 2016*

## ABSTRACT

Evaluating percentiles of survival was proposed as a possible method to analyse time-to-event outcomes. This approach sets the cumulative risk of the event of interest to a specific proportion and evaluates the time by which this proportion is attained. In this context, exposure-outcome associations can be expressed in terms of differences in survival percentiles, expressing the difference in survival time by which different subgroups of the study population experience the same proportion of events, or in terms of percentile ratios, expressing the strength of the exposure in accelerating the time to the event. Additive models for conditional survival percentiles have been introduced and their use to estimate multivariable-adjusted percentile differences and additive interaction on the metric of time has been described. On the other hand, the percentile ratio has never been fully described, neither statistical methods have been presented for its models-based estimation. To bridge this gap, we provide a detailed presentation of the percentile ratio as a relative measure to assess exposure-outcome associations in the context of time-to-event analysis, discussing its interpretation and advantages. We then introduce multiplicative statistical models for conditional survival percentiles and present their use in estimating percentile ratios and multiplicative interactions in the metric of time. The introduction of multiplicative models for survival percentiles allows researchers to apply this approach in a large variety of context where multivariable adjustment is required, enriching the potentials of the percentile approach as a flexible and valuable tool to evaluate time-to-event outcomes in medical research.

*Key words: survival percentiles, prospective cohort studies, quantile regression, time metric, multiplicative interaction*

## INTRODUCTION

Survival data are commonly evaluated by fixing an observational time within which quantities of interest (hazard, rates, or risks of the event) are estimated. Different authors have underlined the need to complement these common approaches providing additional measures to present the time dimension of the association [1-3]. A possible suggested approach is to set the risk/probability of the outcome to a specific value and to evaluate survival percentiles, defined as the time-points by which that specific proportion of cases is achieved [2]. This approach provides considerable advantages, especially for inevitable health outcomes, such as death, when one is more interested in the time to occurrence of the event rather than its probability [3].

In the context of survival percentiles, measures of association can be presented in terms of percentile differences or percentile ratios [1] and express the effect of a given exposure in the unit of time in absolute or relative terms, respectively. Statistical modelling of survival percentiles can be carried out with methods to estimate conditional quantiles of censored outcomes, which allow directly modelling the percentiles of the time variable as a function of possible covariates [2]. The use of this approach to estimate multivariable adjusted percentile differences [4-6] and to assess additive interaction in the metric of survival time [7] has been described. On the other hand, to the best of our knowledge, a detailed description of the percentile ratio and its advantages has never been carried out. Moreover, there is no established statistical framework to estimate percentile ratios, strongly limiting the potentials and applicability of this useful measure of association [1, 8, 9]. A complementary presentation of relative and absolute measures has been extensively recommended, as this would provide a comprehensive summary of the exposure-outcome association [10].

In this paper we provide a detailed presentation of the percentile ratio as a relative measure to assess exposure-outcome associations in the context of survival analysis, discussing its interpretation and advantages. We then proceed by introducing multiplicative models for conditional survival percentiles, and present their use in estimating percentile ratios and multiplicative interactions in the metric of time.

## REVIEW OF THE PERCENTILE APPROACH: ESTIMATING PERCENTILE DIFFERENCES WITH ADDITIVE MODELS

In time-to-event analysis we are interested in assessing the occurrence of an event $D$ and the time $T$ by which that event is achieved. Survival percentiles, which are visually summarised in the survival curve, link these two quantities, as they represent the time points by which different proportions of the study population have experienced the event of interest [2]. Figure 1 depicts the survival curves for two populations of individuals (e.g. exposed and non-exposed). In the figure, survival percentiles are identified corresponding to a given proportion $p$ and by calculating the time points. $t_0$ is the time by which $p$% of non-exposed individuals experience the event, while $t_1$ is the time by which the same fraction of events is attained by exposed participants.

In the context of survival percentiles, an intuitive measure of association is given by $t_1 - t_0$, defined as the difference in the $p$th survival percentile (PD=percentile difference). This absolute measure of association represents the difference in time by which exposed and non-exposed participants experience the same fraction of events. For example, when $p$=0.5, the measure corresponds to the difference in median survival between exposed and non-exposed.

Estimators of the survival function, such as the non-parametric Kaplan-Meier method, can be used to calculate survival percentiles with standard errors and confidence intervals. Statistical methods for quantiles of censored outcomes can be used to model survival percentiles conditional on covariates [11-14]. These statistical approaches offer all the advantages of multivariable regression modelling, such as the possibility of adjusting for confounders and assessing interactions. Among the available methods, Laplace regression offers additional advantages in terms of modelling flexibility and computational speed [11,15]. In brief, Laplace models the percentiles of the time variable of interest as a function of a set of predictors. The errors are assumed to follow an asymmetric Laplace distribution, assumption that has been shown to have minimal influence on the model performances under different scenarios [11, 16-20]. Model estimation is performed by maximising the likelihood through a gradient search algorithm [21], and standard errors and confidence intervals can be either derived numerically or via bootstrap [22].

In its basic form, a Laplace regression model establishes a linear association between a predictor E and the $p$th survival percentile of the time variable T

$$T(p|E=e) = \beta_{p0} + \beta_{p1} \cdot e \qquad (1)$$

$\beta_{p0}$ estimates the time by which $p$% of participants with $E=0$ experience the event ($t_0$ from figure 1). $\beta_{p1}$ is an estimate of the pth PD $t_1 - t_0$, as it indicates the difference in time by which participants with $E=1$ experience the same fraction of events of participants with $E=0$.

Model (1) can be extended by inclusion of additional covariates to estimate multivariable-adjusted PDs. Inclusion of a product term between two exposures of interest will serve as a test of additive interaction in the metric of time [7].

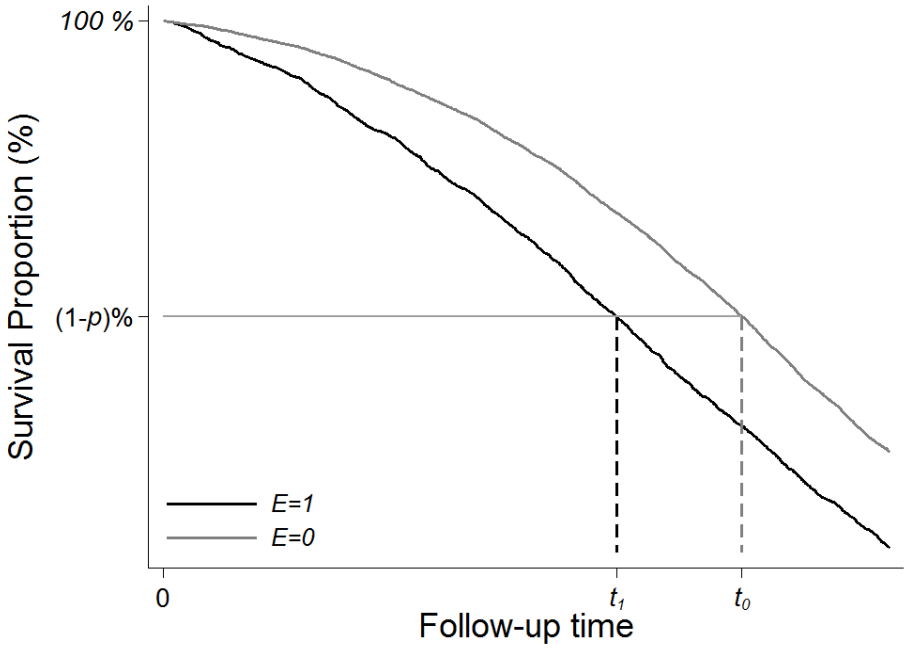
## PERCENTILE RATIOS

Given the fixed percentile $p$, another measure of association between the exposure $E$ and the $p$th survival percentile can be defined by taking the ratio of survival percentiles (PR=percentile ratio) $t_1$ and $t_0$ [1, 8, 9].

$$PRp = t_1 / t_0 \qquad (2)$$

This measure indicates how much faster/slower exposed participants attain the fixed proportion of $p$% of cases. For example, a PR of 0.5 would indicate that non-exposed participants achieve that proportion 50% slower - that is - the time by which exposed subjects experience the fixed proportion of cases is half of the time by which the same proportion is achieved by non-exposed participants. As any ratio measure, PR$p$ requires $t_0 \rightarrow 0$, implying that the time by which $p$% of non-exposed participants

**FIGURE 1. Survival curves for two groups of subjects. The fixed percentile is showed by the horizontal line and the corresponding survival percentiles are indicated on the x-axis.**




experience the event *D* must be larger than 0. A PR ranges from zero (in the extreme case of $t_1$ =0) to infinity (when $t_0 \rightarrow 0$). The null association occurs in the case of PR=1, when exposed and non-exposed participants achieve the fraction of events *p* at the same time *t*.

Both PRs and PDs can be calculated for any observed percentile and the statistical model for a given percentile is not making any assumption on the behaviour of the survival curve at other levels of *p*. This property is not shared by common statistical methods for the analysis of survival data. The exposure-outcome measures of association can be evaluated as a function of *p*, thus reflecting the percentile-varying and, equivalently, time-varying dimension of the association [23].

## MODEL-BASED ESTIMATION OF PERCENTILE RATIOS

A possible procedure to estimate the $PR_p$ is to fit model (1) and subsequently predict the survival percentiles $t_0$ and $t_1$ as a nonlinear combinations of the estimated $\beta_{p0}$ and $\beta_{p1}$. An alternative approach is to build a multiplicative model on the *p*th survival percentile directly estimating the percentile ratio. Thanks to the property of equivariance to monotone transformations (EMT) [24], peculiar of quantiles and not shared by the mean, this second alternative is straightforward. Let *h*(.) be a non-decreasing function. The property of EMT implies that for any random variable *T* the quantiles of the transformed random variable *h(T)* are the transformed quantiles of the original *T*.

To define a multiplicative model for survival percentiles an intuitive approach is to specify a model that is linear on the logarithm of time. The property of EMT assures that this can be achieved by simply operating a logarithmic transformation on the original time variable and by fitting a linear model on this new outcome.

$$log[T(p|E=e)] = \beta_{p0}^* + \beta_{p1}^* \cdot e \qquad (3)$$

Coefficients estimated from this log-linear model can be used to back-calculate survival percentiles by applying the exponential transformation

$$T(p|E=e) = exp(\beta_{p0}^* + \beta_{p1}^* \cdot e) = exp(\beta_{p0}^*) \cdot exp(\beta_{p1}^* \cdot e) \qquad (4)$$

The *p*th survival percentile among exposed ($t_1$ of Figure 1) is therefore estimated by,

$$[T(p|E=1)] = exp(\beta_{p0}^*) \cdot exp(\beta_{p1}^*)$$

and the same survival percentile among non-exposed ($t_0$ of Figure 1) by

$$[T(p|E=0)] = exp(\beta_{p0}^*)$$

It simply follows that an estimate of the PR is given by

$$t_1 / t_0 = [exp(\beta_{p0}^*) \cdot exp(\beta_{p1}^*)] / [exp(\beta_{p0}^*)] = exp(\beta_{p1}^*) \qquad (5)$$

An estimate of the PR associated with the exposure *E* only requires a logarithmic transformation of the time variable. After fitting a regression model on the percentile of interest of the logarithm of time, the PR is estimated by the exponential of the coefficient associated with the exposure *E*. The Stata command for Laplace regression [22] simplify this step by allowing the inclusion of the option *link(log)*, which automatically transforms the time variable of interest and gives back the percentile ratios associated with the included covariates. Caution must be taken when using the logarithm of individual times exactly equal to 0. Zero survival time values could be eventually replaced with small positive values.

In the Online Supplementary Material we also show that model (4) is an accelerated failure time model [25] for the pth survival percentile and that the PR associated with the exposure of interest shares the same interpretation of an acceleration factor. Also, an extension to continuous exposures is presented in the Online Supplementary Material.

## MULTIPLICATIVE INTERACTION IN THE METRIC OF TIME

Inclusion of a product term in a linear model for survival percentiles, such as Laplace regression, serves as a test for additive interaction in the metric of time [7]. We here explore the meaning and estimation of multiplicative interaction in the context of survival percentiles. Let *G* and *E* be two binary predictors, which can take values 0 or 1 and are associated with the outcome *D*. Given a fixed proportion of events p we can defined the pth survival percentile $t_{00}$, $t_{10}$, $t_{01}$, and $t_{11}$, which depict the time by which participants in all the possible combinations of *G* and E (respectively *G*=0, *E*=0; *G*=1, *E*=0; *G*=0, *E*=1; *G*=1, *E*=1) achieve the fraction of events *p*. Following the common notation used in terms of risk [26], we can define a measure of multiplicative interaction between *G* and *E* at the pth survival percentiles as

$$I_p=(t_{11} \cdot t_{00})/(t_{10} \cdot t_{01}) \qquad (7)$$

If $t_{11}/t_{01}=t_{00}/t_{10}$ then $I_p=1$ and we are in the presence of multiplicativity of the effect. If $I_p>1$ there is a positive interaction on the multiplicative scale, while a situation of $I_p<1$ implies that the combined effect of *G* and *E* on *D* is minor than the product of the two main effects. In the Online Supplementary Material we show that inclusion of a product term in a multiplicative model for survival percentiles will serve as a test for the presence of multiplicative interaction as defined in equation (7).

## ILLUSTRATIVE EXAMPLE

To illustrate the meaning, interpretation and estimation of PRs we used data from 14.786 old participants (70-83 years at baseline) of the Cohort of Swedish Men and the Swedish Mammography Cohort, largely described elsewhere [27]. These cohorts were established in 1997 in central Sweden and followed-up for 15 years (1 January 1998 - 31 December 2013) during which 8415 participants of the subcohort herein evaluated died (58%). For illustrative purpose we considered the self-reported information on smoking status (current/never), body mass index (BMI, continuous), total physical activity (summarised in MET-hrs/day and categorised as low, if <42, or high, if >42) and age at baseline (continuous), investigating time to death from all-causes as primary outcome.

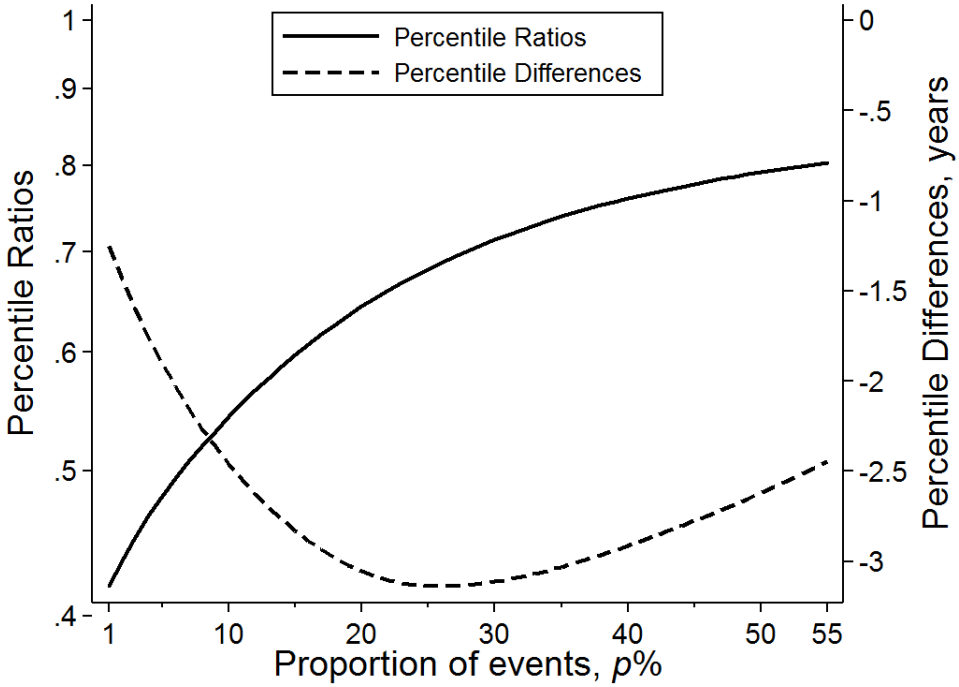
First, we evaluated differences in the 50th survival percentile (median survival) according to categories of smoking status. The crude estimates of median survival, calculated with the Kaplan-Meier estimator, were 11.7 years for current smokers ($t_1$) and 14.4, years for never smokers ($t_0$). The PD and PR between current and never smokers, calculated by taking the difference and the ratio of this two quantities, were $PD_{50}$= - 2.7 years and $PR_{50}$=0.81. Median survival was attained 19% slower in non-smokers than in smokers. This acceleration resulted in a median survival difference of 2.7 years.

We also evaluated the impact of smoking on median survival further adjusting for age at baseline, by fitting a Laplace regression model on the 50$^{th}$ survival percentile with smoking status and age at baseline as predictors. We fit two models on the original survival time and on its logarithmic transformation. The 50$^{th}$ PD between current and never smokers and the corresponding PR, were similar to the crude estimates (50$^{th}$ PD= -2.6 years, 95% CI: -3.0, -2.3; 50$^{th}$ PR=0.79, 95% CI: 0.76, 0.81)

To investigate how the association is changing over time, Figure 2 presents age-adjusted PDs and PRs for smoking status for all observed percentiles (1$^{st}$ - 55$^{th}$). The absolute difference in survival between current and never smokers increased up to 3 years before slowly shortening. On the other hand smoking showed a strong relative effect at low percentiles, representing the early deaths, (1$^{st}$ PR=0.4) and progressively decreased from 60% to 19% at higher percentiles (55$^{th}$ PR=0.81), thus reflecting a weakening of the relative strength of the exposure.

Next, the age-adjusted association between the continuous predictor of BMI and median survival (50$^{th}$ percentile) was evaluated in a multiplicative model. To relax the linear assumption in the dose-response relationship we evaluated BMI by means of restricted cubic splines, with 3 knots at fixed percentiles of the distribution (Figure 3), and we observed that the association between BMI and the median ratio (50$^{th}$ PR) was strongly inverse U-shaped. Comparing to participants with median BMI (24.8 kg/m$^2$), the time by which 50% mortality risk was attained was accelerated by up to 19% (PR=0.81, 95% CI: 0.75-0.87) for those with BMI=15, and 17% (PR=0.83, 95% CI: 0.76-0.90) for those with BMI=40.

**FIGURE 2. Percentile ratios (straight line) and percentile differences (dashed line) between smokers and non-smokers calculated for the observed range of percentiles.**




We finally fitted an additive and a multiplicative model to estimate age-adjusted median survival as a function of smoking and physical activity, including an interaction term between the two dichotomous predictors. Current smoking and low physical activity were both associated with shorter survival either in the additive and multiplicative model. When looking at the multiplicative scale the interaction effect was negligible, as the presence of both exposures only increased by 2% the strength of the two main effects (50th PR associated with the product term =0.98). However, evaluating interaction on the additive scale showed that median survival among participants with both exposures was shortened by additional 5 months (50th PD associated with the product term =-0.4 years).

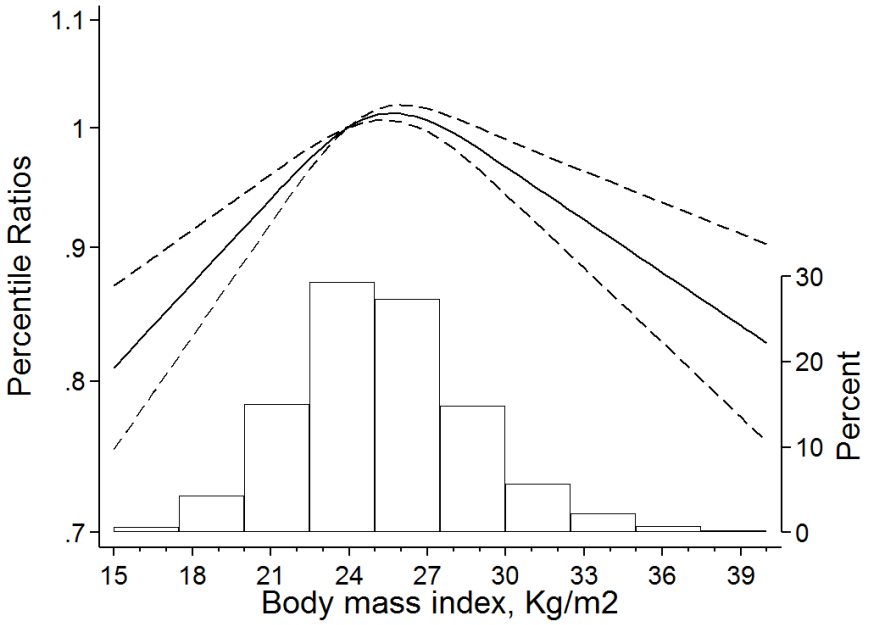
## DISCUSSION

In this paper we presented the percentile ratio as a relative measure of association in the context of survival percentiles and introduced multiplicative models for survival percentiles, presenting how these can be used to estimate multivariable adjusted percentile ratios and multiplicative interaction in the metric of time.

Evaluating survival percentiles was introduced as a possible approach to time-to-event outcomes [2]. The probability of the event and the time to its occurrence are the two equally critical quantities of interest in survival analysis. Nevertheless, all common statistical methods focus on the risk/rate/hazard of the event, while committing limited consideration to the time dimension [1, 28]. However, there are different situations in which the most relevant research question may be ''when is the event happening?'' rather than ''is the event happening?'' [1, 28, 29]. Percentiles describe the survival distribution thoroughly and provide valuable insights in understanding the link between the probability of the event and the time by which this is attained. Moreover, differently from other methods in survival analysis, such as the popular Cox regression, the assumption of a constant exposure-outcome association over follow-up is not required. On the contrary, by focusing on different percentiles one can evaluate how the association of interest is changing according to the proportion of cases occurring over time [2, 23].

When evaluating survival percentiles, exposure-outcome associations have been mainly expressed in terms of percentile differences [4-6, 30-32]. While this absolute measure provides advantages in understanding the magnitude of the association in terms of delayed survival, there are different situations in which evaluating the strength of the exposure in relative terms might be of greater interest. Both relative and absolute measures of association have their own advantages and their complementary use to present epidemiological results has been extensively recommended [10, 33]. This study, introducing a statistical technique to estimate percentile ratio in epidemiological studies, enriches the potentialities and advantages of evaluating survival percentiles in

**FIGURE 3. 50th percentile ratios (acceleration factors by which half of the cohort has died) as a function of BMI. Data were fitted by age-adjusted Laplace regression on the 50th percentile of the logarithm of time. Dashed lines represent 95% CIs. The reference value is the median BMI and the histogram represents the distribution of BMI in the study population.**




time-to-event analysis. The percentile ratio, which was introduced in the clinical trials literature [8], and suggested as a possible measure to summarise literature data [9], can be interpreted as the acceleration factor of an accelerated failure time model, as it represents the strength of the exposure in accelerating the time to the event. A complementary presentation of relative and absolute measures of association allows illustrating the exposure-outcome relationship in two different and equally meaningful ways. For example, a constant difference in survival over time would imply a decreasing relative strength of the exposure. In our illustrative example smoking had a progressively lower relative effect on survival, while the absolute effect increased over the first quartile of the survival distribution and decreased in the remaining observed percentiles.

We also addressed the relevant topic of interaction in survival analysis [26]. Interaction is commonly assessed as a departure from additivity or multiplicativity of the effects and it has been showed that absence of interaction on one scale is likely to imply the presence of interaction on the other scale [34]. In general, presenting both additive and multiplicative interaction would provide a complete picture of how two exposures interact in predicting the outcome and this procedure has been widely recommended [35, 36]. For instance, in the illustrative example that we presented we documented a considerable combined effect on the additive scale, despite observing a negligible multiplicative interaction. To the best of our knowledge, the method herein presented to estimate multiplicative interaction, together with the one recently introduced to derive additive interaction [7], make evaluating survival percentiles the only approach that allows, in survival analysis, to estimate, interpret and present interaction between two predictors according to both scales.

Evaluating survival percentiles in epidemiological studies was eased by the introduction of statistical methods for conditional quantiles of possibly censored outcomes, which provide all regression modelling advantages such as adjusting for confounders and assessing interaction [7, 15]. Thanks to their unique properties, statistical approaches based on quantile estimation offer considerable advantages [24], and their regular application in epidemiology has been recommended [37]. In this study we have shown another remarkable added value of the percentile approach, as the same statistical model can be used to provide a relative and an absolute measure of association with a simple outcome transformation. Among the possible methods for censored quantile regression we have used Laplace regression [11], which is available in Stata [22], and provides various advantages in terms of computational speed and modelling flexibility [15, 21]. Other methods are available in main statistical software and can represent valid alternatives to Laplace [12-14].

In conclusion, the introduction of multiplicative models for survival percentiles allows researchers to apply this approach in a large variety of context where multivariable adjustment is required, enriching the potentials of the percentile approach as a flexible and valuable tool to evaluate time-to-event outcomes in medical research.

## Funding

This work was partly supported by a Young Scholar Award from the Karolinska Institutet's Strategic Program in Epidemiology. The study was also supported by the Swedish Research Council.

## Disclaimer

The authors declare no conflict of interest

## REFERENCES

1. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol 2014;32(22):2380-2385.
2. Orsini N, Wolk A, Bottai M. Evaluating percentiles of survival. Epidemiology 2012;23(5):770-771.
3. Lytsy P, Berglund L, Sundstrom J. A proposal for an additional clinical trial outcome measure assessing preventive effect as delay of events. Eur J Epidemiol 2012;27(12):903-909.
4. Bellavia A, Larsson SC, Bottai M, Wolk A, Orsini N. Fruit and vegetable consumption and all-cause mortality: a dose-response analysis. Am J Clin Nutr 2013;98(2):454-459.
5. Rizzuto D, Orsini N, Qiu C, Wang HX, Fratiglioni L. Lifestyle, social factors, and survival after age 75: population based study. BMJ 2012;345:e5568.
6. Bellavia A, Akerstedt T, Bottai M, Wolk A, Orsini N. Sleep duration and survival percentiles across categories of physical activity. Am J Epidemiol 2014;179(4):484-491.
7. Bellavia A, Bottai M, Orsini N. Evaluating additive interaction using survival percentiles. Epidemiology 2016; 27(3): 360–364.
8. Friedman LM, Furberg C, DeMets DL. Fundamentals of clinical trials. Springer 2010.
9. Barrett JK, Farewell VT, Siannis F, Tierney J, Higgins J. Two-stage meta-analysis of survival data from individual participants using percentile ratios. Statistics in medicine 2012;31(30):4296-4308.
10. Rothman KJ, Greenland S, Lash TL. Modern epidemiology: Lippincott Williams & Wilkins 2008.
11. Bottai M, Zhang J. Laplace regression with censored data. Biom J 2010;52(4):487-503.
12. Peng L, Huang Y. Survival analysis with quantile regression models. Journal of the American statistical association 2008;103(482).
13. Portnoy S. Censored regression quantiles. Journal of the American statistical association 2003;98(464):1001-1012.
14. Powell JL. Censored regression quantiles. Journal of econometrics 1986;32(1):143-155.
15. Bellavia A, Discacciati A, Bottai M, Wolk A, Orsini N. Using Laplace Regression to model and predict percentiles of age at death when age is the primary time scale. Am J Epidemiol 2015; 182 (3): 271-277.
16. Farcomeni A. Quantile regression for longitudinal data based on latent Markov subject-specific parameters. Statistics and Computing 2012;22(1):141-152.
17. Geraci M, Bottai M. Quantile regression for longitudinal data using the asymmetric Laplace distribution. Biostatistics 2007;8(1):140-154.
18. Lee D, Neocleous T. Bayesian quantile regression for count data with application to environmental epidemiology. Journal of the Royal Statistical Society: Series C (Applied Statistics) 2010;59(5):905-920.
19. Liu Y, Bottai M. Mixed-effects models for conditional quantiles with longitudinal data. The International Journal of Biostatistics 2009;5(1).
20. Yuan Y, Yin G. Bayesian quantile regression for longitudinal studies with nonignorable missing data. Biometrics 2010;66(1):105-114.
21. Bottai M, Orsini N, Geraci M. A gradient search maximization algorithm for the asymmetric Laplace likelihood. Journal of Statistical Computation and Simulation 2014:1-7.
22. Bottai M, Orsini N. A command for Laplace regression. Stata J 2013;13(2):302-314.
23. Bellavia A, Bottai M, Discacciati A, Orsini N. Adjusted Survival Curves with Multivariable Laplace Regression. Epidemiology 2015;26(2):e17-e18.
24. Koenker R, Bassett Jr G. Regression quantiles. Econometrica: journal of the Econometric Society 1978:33-50.
25. Wei LJ. The accelerated failure time model: a useful alternative to the Cox regression model in survival analysis. Stat Med 1992;11(14-15):1871-1879.
26. VanderWeele TJ, Knol MJ. A tutorial on interaction. Epidemiologic Methods 2013.
27. Harris H, Håkansson N, Olofsson C, Julin B, Åkesson A, Wolk A. The Swedish mammography cohort and the cohort of Swedish men: Study design and characteristics of 2 population-based longitudinal cohorts. OA Epidemiology 2013;1 (2):16.
28. Hernan MA. The hazards of hazard ratios. Epidemiology 2010;21(1):13-15.
29. Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. American Journal of Epidemiology 1988;128(6):1185-1197.
30. Bellavia A, Bottai M, Wolk A, Orsini N. Alcohol consumption and mortality: a dose-response analysis in terms of time. Ann Epidemiol 2014;24(4):291-296.
31. Carlsson AC, Riserus U, Arnlov J, et al. Prediction of cardiovascular disease by abdominal obesity measures is dependent on body weight and sex - Results from two community based cohort studies. Nutr Metab Cardiovasc Dis 2014.
32. Johannessen A, Skorge TD, Bottai M, et al. Mortality by level of emphysema and airway wall thickness. Am J Respir Crit Care Med 2013;187(6):602-608.
33. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007;147(8):W163-194.
34. Greenland S. Interactions in epidemiology: relevance, identification, and estimation. Epidemiology 2009;20(1):14-17.
35. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol 2012;41(2):514-520.
36. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007;147(8):573-577.
37. Beyerlein A. Quantile regression-opportunities and challenges from a user's perspective. Am J Epidemiol 2014;180(3):330-331