Flexible piecewise linear model for investigating dose-response relationship in meta-analysis: methodology, examples, and comparison

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Objectives: Dose-response meta-analysis (DRMA) is widely employed to establishing the potential dose-response relationship between continuous exposures and disease outcomes. However, no method is readily available for exploring the relation between a discrete exposure and a binary or continuous outcome. We proposed a piecewise linear (PL) DRMA model as a solution to this issue.

Methods: We illustrated the methodology of PL model in both one-stage DRMA approach and two-stage DRMA approach. The method by testing the equality of slopes of each piecewise was employed to judge if there is “piecewise effect” against simple linear trend. We then used sleep (continuous exposure) and parity (discrete exposure) data as examples to illustrate how to apply PL model in DRMA using the Stata code attached. We also empirically compared the slopes of PL model with simple linear as well as restricted cubic spline (RCS) model.

Results: Both one-stage and two-stage PL DRMA model fitted well in our examples, and the results were similar. Obvious “piecewise effects” were detected in both the two examples by the method we used. In our example, the PL model showed better fitting effect and practical reliable results compared to simple linear model, while similar results for to RCS model.

Conclusion: Piecewise linear function is a simple and valid method for DRMA and can be used for discrete exposures. It also represents a superior model to linear model in DRMA and may be an alternative model to non-linear model.

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Abstract

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Keywords piecewise linear function, dose-response meta-analysis, discrete exposure

Introduction

In epidemiological research, one of the important tasks is the investigation of potential dose-response relationship between exposures and disease outcomes. In order to establish the evidence of dose-specific effects, dose-response meta-analysis (DRMA) may be used [1]. In recent years, DRMA has gained increasing attention and has been put in practice in evidence-based medicine. A survey has found that there were nearly 400 DRMAs were published by alone over the past five years, and the number continues increasing [2].

One critical methodological issue remains in DRMA is how to fit dose-specific effects. Both continuous and discrete variables may be used as the exposure in DRMA. Several regression methods have been developed for exploring relationship between continuous exposures and binary outcomes in DRMA, including the simple linear model [3], the natural quadratic model [4], the flexible polynomial model [5], and the restricted cubic spline model [6]. These models, covering both simple linear and non-linear trend approximation, have been proven to be valid.

However, no model is readily available for investigating dose-response relation for discrete exposures due to their nature of discontinuous. Some have used non-linear DRMA model to assess the relationship between discrete exposure and disease outcomes [7, 8]. Although their results tend to be correct, the method is questionable because discrete variable cannot be directly smooth as a curve (but can be line) between two specified points due to the disjoint nature and nonconvex property [9]. Simple linear model is an alternative. However, in many cases, simple linear model tend to be at risk of under fit and wrong prediction. For example, for J-shaped or U-shaped curves, simple linear model may lead to unrealistic conclusion since the slopes differ across piecewise [10].

In this article, we described piecewise linear (PL) model, which can be fitted in both one-stage and two-stage approach, to solve the problem. The model may represent a valid solution to establish dose-specific relation between discrete exposures and binary outcomes. In the following sections, we firstly describe the expression of PL function and the methodology of pooling interested estimators; we subsequently use the parity and sleep data for illustration of discrete and continuous variables and compare them with simple linear and nonlinear spline model; we finally offer an extension of the model and include our discussion. The main

command using for model implementation in Stata is presented in the supplementary file.

Methods

Piecewise linear regression model

A collection of $\boldsymbol{j}$ $(1, 2, 3...,n)$ is assumed as included studies and $\boldsymbol{k}(1, 2, 3..., \boldsymbol{i}-1)$ as the knots assigned for the data distribution within a study. Then the data can be divided to $\boldsymbol{i}$ pieces. The expression of the model within each study can be written as

$$\boldsymbol{logY} = \boldsymbol{\alpha} + \boldsymbol{\beta_i X} + \boldsymbol{\varepsilon} \ \textbf{(1)}$$

Where $\boldsymbol{\alpha}$ is the intercept (not always needed), $\boldsymbol{\beta}_{\mathrm{i}}$ are slopes or regression coefficients of assigned pieces (i) cut by knots. $\boldsymbol{\varepsilon}$ is the random error. $\boldsymbol{Y}$ is the relative risk of interested outcome, including odds ratio (OR), relative risk (RR), or hazard ratio (HR) [6]. A natural logarithm transformation is made to achieve an approximate normal distribution. For continuous outcomes, $\boldsymbol{Y}$ is the mean difference (MD) or the standard mean difference (SMD), and the log-transformation is not usually needed. $\boldsymbol{X}$ is the exposure, referring to continuous or discrete variables. If we insert one knot (50^{th}) of the distribution of $\boldsymbol{X}$, the slope would be divided into two pieces: 0~50^{th} on the left side of the knot and 50^{th}~100^{th} on the right side. The integers should be chosen as cut points if $\boldsymbol{X}$ is a discrete variable. When $\boldsymbol{\alpha}$ equals zero (generally forced to be zero in binary outcome DRMA [6]), the expression (1) changes to

$$\boldsymbol{logY} = \boldsymbol{\beta}_{\mathrm{i}}\boldsymbol{X} + \boldsymbol{\varepsilon} \ \textbf{(2)}$$

In such situation, the function is expected to go through the origin. The mathematical expectation of $\boldsymbol{logY}$ is the estimator of interested, as $(\boldsymbol{\alpha} + \boldsymbol{\beta_i X})$ in formula (1) and $\boldsymbol{\beta_i X}$ in formula (2). The key problem of the function is the estimation of $\boldsymbol{\beta}$. Generally, ordinary least squares (OLS) estimation can reach the best linear unbiased evaluation (BLUE) for $\boldsymbol{\beta}$. However, in meta-analysis of dose-response data, correlations between logRRs cannot be ignored. Orsini et al [13] proposed a generalized least square (GLS) method to satisfy BLUE property for $\boldsymbol{\beta}$ in DRMA. With the OLS method, the estimation of $\boldsymbol{\beta}$, $\widehat{\boldsymbol{\beta_0}}$ could be estimated using the following formula:

$$\widehat{\boldsymbol{\beta_0}} = (\boldsymbol{X}^{'}\boldsymbol{X})^{-1}(\boldsymbol{X}^{'}\boldsymbol{Y}) \ \textbf{(3)}$$

While in the GLS method, the formula for estimation of $\boldsymbol{\beta}$, $\widehat{\boldsymbol{\beta}_{\boldsymbol{G}}}$ is

$$\widehat{\boldsymbol{\beta}_{\boldsymbol{G}}} = (\boldsymbol{X}^{'}\boldsymbol{C}^{-1}\boldsymbol{X})^{-1}(\boldsymbol{X}^{'}\boldsymbol{C}^{-1}\boldsymbol{Y}) \quad (4)$$

Where $\boldsymbol{C}$ is the covariance matrix of $\boldsymbol{Y}$, which generally needed to be estimated according to group sizes information——that is, numbers of cases and controls/total of category levels within each study [4]. When the group size information is missing, the GLS approach is hard to be applied. An alternative way in this situation is to use the weighted least squares (WLS) estimation [11]. Likewise, the WLS estimation of $\boldsymbol{\beta}$, $\widehat{\boldsymbol{\beta}_{\boldsymbol{W}}}$ could be conducted as below

$$\widehat{\boldsymbol{\beta}_{\boldsymbol{W}}} = (\boldsymbol{X}^{'}\boldsymbol{W}^{-1}\boldsymbol{X})^{-1}(\boldsymbol{X}^{'}\boldsymbol{W}^{-1}\boldsymbol{Y}) \quad (5)$$

$\boldsymbol{W}$ is the weight and is usually set as inverse variance in meta-analysis**.** The variance can be generally written as

$$\boldsymbol{Var} = (\boldsymbol{X}^{'}\boldsymbol{\Omega}^{-1}\boldsymbol{X})^{-1} \quad (6)$$

With $\boldsymbol{\Omega}$ indicates the identity matrix for OLS, covariance matrix for GLS, and weighted variance matrix for WLS of Y.

Synthesis methods of piecewise relationship

Two methods are available to pool the regression estimators ($\boldsymbol{\beta}$), which refer to, the one-stage approach and the two-stage approach. For the one-stage approach, all studies were treated as a whole while each study was treated as a cluster [11]. This method was first described by Doi and Chang [11], which based on WLS for the estimation and refers to random effect model, and known as the robust-error meta-regression (REMR).. We did slight modification on it that forced the intercept as zero in this model. Under the REMR model, the estimation of variance becomes:

$$\boldsymbol{Var} = (\boldsymbol{X}^{'}\boldsymbol{W}\boldsymbol{X})^{-1}\left(\sum_{\boldsymbol{j}=1}^{\boldsymbol{n}}\sum_{\boldsymbol{i}\in\boldsymbol{c_j}}\boldsymbol{X}^{'}\boldsymbol{W}\hat{\boldsymbol{\Sigma}}\boldsymbol{W}\boldsymbol{X}\right)(\boldsymbol{X}^{'}\boldsymbol{W}\boldsymbol{X})^{-1} \quad (7)$$

The synthesis of $\boldsymbol{\beta}$ in one-stage model is the actually the estimation of $\boldsymbol{\beta}$ of the regression due to the nature of one-stage approach. Details were illustrated elsewhere [11].

The two-stage approach, which based on GLS, is first described by Orsini and known as GLST [6]. It estimate the regression coefficients within each study first and then combine the coefficients in fixed-, random-effect, or other weighting schemes. Let us assume one knot of the function as illustration of two-stage method; consequently, we could obtain two piece of slopes (

β_1 *and* β_2) in each study produced by the knot. Then formula

$$\begin{pmatrix}\beta_{1j}\\ \beta_{2j}\end{pmatrix} \sim N\left(\begin{pmatrix}\theta_1\\ \theta_2\end{pmatrix}, \boldsymbol{\Sigma} + \boldsymbol{\Phi}\right); \boldsymbol{\Sigma} = \begin{pmatrix}\sigma_{1j}^2 & \sigma_1\sigma_2\rho_1\\ \sigma_1\sigma_2\rho_1 & \sigma_{2j}^2\end{pmatrix}; \boldsymbol{\Phi} = \begin{pmatrix}\tau_1^2 & \tau_1\tau_2\rho_2\\ \tau_1\tau_2\rho_2 & \tau_2^2\end{pmatrix} \quad (8)$$

indicate the fixed- ($\boldsymbol{\Phi} = \mathbf{0}$) or random-effect model ($\boldsymbol{\Phi} \neq \mathbf{0}$) of the two-stage DRMA. Here $\boldsymbol{\theta_1}$ and $\boldsymbol{\theta_2}$ are the summarized estimators of $\boldsymbol{\beta_{1j}}$ and $\boldsymbol{\beta_{2j}}$. $\boldsymbol{\Sigma_j}$ is the within-study variance matrix while $\boldsymbol{\Phi}$ is the between-study variance matrix which need to be estimated. $\boldsymbol{\rho_1}$ and $\boldsymbol{\rho_2}$ are correlation coefficients within $\boldsymbol{\sigma}$ $(\boldsymbol{\sigma_{1j}}, \boldsymbol{\sigma_{2j}})$ and $\boldsymbol{\tau}$ $(\boldsymbol{\tau_1}, \boldsymbol{\tau_2})$ respectively. Details of the algorithm have been illustrated by White [12] and Matteo [5].

Examples

We used both the GLST approach (two-stage) and the REMR approach (one-stage) for PL DRMA as examples. We tested the equality of the slopes (e.g. β_1 *and* β_2) of each piecewise as a judgment of whether there is "piecewise effect" against the simple linear effect, and considered P < 0.1 was statistical significance due to the lower power of the test. Random-effect model were used due to the potential heterogeneity. All the analyses were illustrated in Stata/SE 14 (Stata Corp, College Station, TX, USA). The code we used was presented in Table 1.

Dose-response meta-analysis for continuous data

In a large cohort-based dose-response meta-regression, Liu et al [13] has investigated the relationship between sleep duration and all-cause mortality. We used their data as an example but since we knew that sleep duration tends to have a grossly non-linear association with mortality the dose needed to be centred but this time keeping the reference dose conceptually constant. A look at the range of reference values for sleep duration revealed that in most cases this was between 4.5 and 5.5 h with a mean of 5 h and thus we excluded all studies with a reference of 6+ h (five studies). We also excluded a sixth study with an error that did not allow computation of covariance required for the GLST model. Although the reference varied slightly in the remaining studies, they were all assumed to have conceptually constant reference duration of sleep at 5h. We centred by subtracting the actual reference dose from each non-reference dose

and thus modelled increments but considered all these increments to conceptually start from the 5h sleep duration baseline.

Our meta-analysis showed that, based on GLST approach, significant "piecewise effect" was observed ($P < 0.01$), the relative risk (RR) of all-cause mortality was 1.02 (95%CI: 1.00, 1.04) for every 1-hour reduction of sleep duration among people who slept less than 7 hours; the RR was 1.09 (95%CI: 1.09, 1.10) for every 1-hour increase of sleep duration among people who slept more than 7 hours (Figure 1a); based on REMR approach, the "piecewise effect" test was significant ($P < 0.01$) and the RRs were 1.01 (95%CI: 1.01, 1.02) for each hour reduction when sleep less than 7 hours and 1.08 (95%CI: 1.05, 1.10) for each hour increase when sleep more than 7 hours, respectively (Figure 1b).

Dose-response meta-analysis for discrete data

Epidemiological studies suggested parity (number of birth) may relate to the risk of rheumatoid arthritis. We searched PubMed and Embase and crudely included 4 case-control or cohort studies about parity and risk of rheumatoid arthritis. We then used the parity data as an example of analyzing response of a discrete exposure with an outcome in DRMA (Table S2). We choose 3 as the cut point of number of birth refers to evidence from previous similar publications [14, 15]. This not need centered since all the studies with "doses" start from zero.

Our results showed that, based on GLST approach, for women with 3 or less births, the RR of rheumatoid arthritis was 0.94 (95%CI: 0.87, 1.01) for every 1-birth increment (P for "piecewise effect" was 0.03); for women with 3 or more births, the RR of rheumatoid arthritis was 1.13 (95%CI: 1.01, 1.26) for every 1-birth increment (Figure 2a). Based on REMR approach, the RRs were 0.92 (95%CI: 0.83, 1.03) for every 1-birth increment for women with 3 or less births (P for "piecewise effect" was 0.06), and 1.15 (95%CI: 1.10, 1.32) for women with 3 or more births (Figure 2b).

Results

Comparison to simple linear model

A simple linear model was used to fit the dose-response relationship of the sleep duration and

all-cause mortality and compared it with the PL model. The results by simple linear model showed that RR for each-hour increment of sleep duration was 1.00 (95%CI: 0.97, 1.03) based on GLST approach and 0.99 (95%CI: 0.99, 1.00) based on REMR approach, respectively (Table 2). Compared to PL model, these results obviously under fit and failed to in line with clinical practice.

Comparison to non-linear spline model

We used the restricted cubic spline (RCS) model [6] to fit a non-linear trend for sleep duration and all-cause mortality and compared it with the PL model. We insert 3 knots of the distribution of sleep duration in the RCS model. For non-linear relationship between sleep duration and risk of all-cause mortality, the slopes of PL model fitted well to RCS curve for both GLST and REMR approaches. The dose-specific results were similar for PL model and RCS model of the two approaches (Table 2).

Discussion

In this article, we proposed a new model for dose-response meta-analysis exploring relation between discrete variables and outcomes. To the best of our knowledge, few previous articles clearly address summarized dose-specific effects on discrete exposures. In our examples, this model fitted well and the results were reasonable. Our PL model is useful when non-linear association cannot be directly employed and linear association is not sufficient.

Previous models for DRMA have been well developed for continuous exposures, but are limited when discrete exposures are used. In practice, however, discrete variables are often used as exposures in DRMAs. While such types of exposure were usually misused. A cross-sectional study showed that 5.7% of published DRMAs inappropriately used discrete exposures to fit non-linear association [2]. This fact may result from the absence of usable model. Our model thus offers a solution for discrete exposures in DRMAs.

Generally, in a dose-response meta-analysis, the doses (e.g. 1-5 cup/day) were extracted from source publications and have to be changed into an acceptable form [6, 16]. Briefly, for closed

interval, the median or mean value of each exposure level is assigned to a corresponding relative risk [17]; for the open-ended interval (e.g. >5 cup/day), the assigned dose is estimated by multiplying 1.2 of cut-off point [18] or by assuming the range to be the same as the adjacent interval. However, these approaches are inappropriate for discrete variables because of which would result in decimals that are not allowed for discrete variables – the assigned doses for discrete variables are expected to be integer. Future studies are needed to focus this problem.

In DRMAs, it is important to decide a best-fit model among non-linear, piecewise linear, and simple linear procedures. For linear and non-linear association, the common approach often sets the coefficients of non-linear term as zero and test the probability of this null hypothesis. If $P < 0.1$ (assuming α=0.1), we have reasonable evidence to reject the null hypothesis and treat the potential trend as non-linear. A linear model would be chosen, otherwise. When non-linear association is not significant or cannot be directly used, it is reasonable to consider the piecewise or the simple linear model. We use the method of testing the equality of the slopes, which allows us to detect if there is "piecewise effect" against simple linear model. And the piecewise linear model should be chose when there is obvious "piecewise effect".

In our examples, we presented the application of one-stage approach as were as the two-stage approach based on the PL model. We found that the results were mostly similar between one-stage and two-stage approach. One advantages of one-stage approach is it do not need the group size information of included studies while still allows a valid estimation; another advantages of one-stage approach is the exempt assumption of normal distribution of the regression coefficients. While for two-stage approach allows for the estimation of heterogeneity between studies and correlation between regression coefficients. Both these two approaches can be easily applied by the STATA code we attached.

The proposed method has a few limitations. First, the piecewise linear model is a special type of linear function; the results are less precise and flexible compared to higher order function (e.g. third order). Although adding more knots may improve precision, the results remain to be at risk of under fit when a non-linear association is significant. Second, inverse variance or other weighting schemes according to sample sizes were used in current methods; such methods, however, do not address the issue of study quality. Suhail A.R et al [19] proposed a quality effect

(QE) model that included study quality for adjusting pooled effect estimates from meta-analysis of observational studies may serve as a potential solution. Third, a valid approach to determining the best cut point of the distribution of exposure has yet to be established, although adjusted R-squared may offer some suggestions.

In conclusion, piecewise linear function is a simple and valid method for DRMA. It is useful for assessing relation between discrete exposures and outcomes, and represents an alternative model to the non-linear model, and it may also be a superior model to linear model in DRMA. Further studies should focus on improving the precision of cut point selection as well as the flexibility of PL model.

Conflicts of interests

None.

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Author Contributions: Proposed the method: Chang Xu; Data analysis: Chang Xu; Draft the manuscript: Chang Xu; Revise the manuscript: Xin Sun, Lehana Thabane.

Data Sharing Statement: All the data we used were shared in the supplementary file.

Reference

1. Bagnardi V, Zambon A, Quatto P, et al. Flexible meta-regression functions for modeling aggregate dose–response data, with an application to alcohol and mortality. American Journal of Epidemiology 2004; 159(11): 1077–1086.
2. Xu C, Doi SA, Zhang C, et al. Proposed Reporting Guidelines for dose-response Meta-analysis (Chinese Edition). Chinese journal of evidence-based medicine 2016; 16(10): 1221-1226.
3. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. American Journal of Epidemiology 1992; 135(11): 1301–1309.
4. Liu Q, Cook NR, BergströmA, et al. A two-stage hierarchical regression model for meta-analysis of epidemiologic nonlinear dose–response data. Comput Stat Data An 2009; 53(12): 4157-4167.
5. Rota M, Bellocco R, Scotti L, et al. Random-effects meta-regression models for studying nonlinear dose–response relationship, with an application to alcohol and esophageal squamous cell carcinoma. Statistics in Medicine 2010; 29(26): 2679–2687.
6. Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose–response relations: examples, an evaluation of approximations, and software. American Journal of Epidemiology 2012; (175): 66–73.
7. Guo P, Xu C, Zhou Q, et al. Number of parity and the risk of gallbladder cancer: a systematic review and dose-response meta-analysis of observational studies. Arch Gynecol Obstet 2016; 293(5): 1087-96.
8. Rong Y, Chen L, Zhu T, et al. Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. BMJ 2013; 346:e8539.
9. Arora JS, Huang MW, Hsieh CC. Methods for optimization of nonlinear problems with discrete variables: A review. Structural Optimization 1994; 8: 69.
10. Zhang C, Jia P, Yu L, et al. Introduction to methodology of dose-response meta-analysis for binary outcome: With application on software. J Evid Based Med 2018. doi: 10.1111/jebm.12267.
11. Xu C, Doi SA. The robust-error meta-regression method for dose-response meta-analysis. International Journal of Evidence-Based Healthcare 2018; 16(3):138-144.

12. White IR. Multivariate random-effects meta-regression: Updates to mvmeta. Stata Journal 2011; 11(2): 255-270.
13. Liu TZ, Xu C, Matteo R, et al. Sleep duration and risk of all-cause mortality: A flexible non-linear meta-regression of 40 prospective cohort studies. Sleep Medicine Reviews 2017; 32:28-36.
14. Konishi S, Ng CFS, Watanabe C. U-shaped association between fertility and mortality in a community-based sample of Japanese women. J Epidemiol Community Health 2018. pii: jech-2017-209809. doi: 10.1136/jech-2017-209809.
15. Sung HK, Ma SH1, Choi JY, et al. The Effect of Breastfeeding Duration and Parity on the Risk of Epithelial Ovarian Cancer: A Systematic Review and Meta-analysis. J Prev Med Public Health 2016; 49(6):349-366.
16. Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008; 27(7): 954-70.
17. Bekkering GE, Harris RJ, Thomas S, et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol 2008; 167(9): 1017-26.
18. Xu C, Zeng XT, Liu TZ, et al. Fruits and Vegetables Intake and Risk of Bladder Cancer: A PRISMA-Compliant Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. Medicine (Baltimore) 2015; 94(17): e759.
19. Doi SA, Barendregt JJ, Khan S, et al. Advances in the meta-analysis of heterogeneous clinical trials II: The quality effects model. Contemp Clin Trials 2015; 45(Pt A): 123-9.

Figure legends

Figure 1. Piecewise linear prediction for sleep duration and risk of all-cause mortality: a) based on random-effect GLST approach ($P < 0.01$ for "piecewise effect" test); b) based on REMR approach ($P < 0.01$ for "piecewise effect" test).

Figure 2. Piecewise linear prediction for parity and risk of rheumatoid arthritis: a) based on random-effect GLST approach ($P = 0.03$ for "piecewise effect" test); b) based on REMR approach ($P = 0.06$ for "piecewise effect" test).

Figure 1(on next page)

Figure 1

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a) based on random-effect GLST approach ($P < 0.01$ for “piecewise effect” test);

b) based on REMR approach ($P < 0.01$ for “piecewise effect” test).

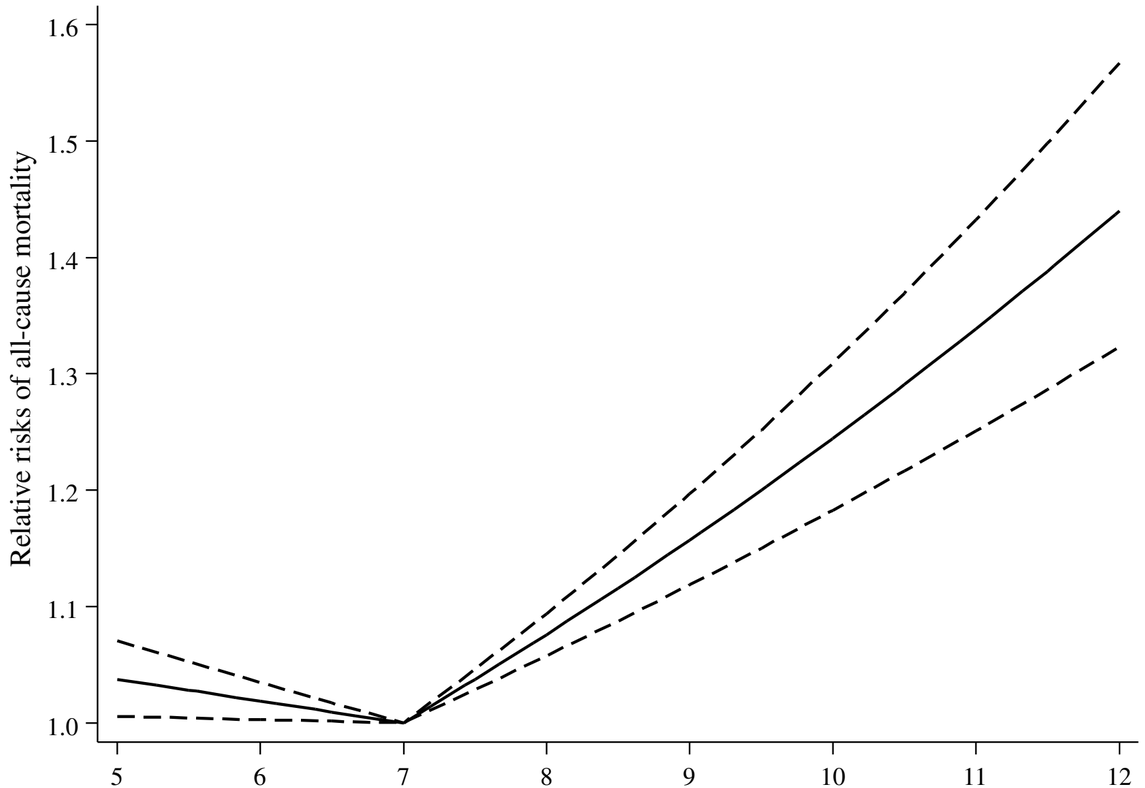

Figure 1a.Sleep duration,hours/day

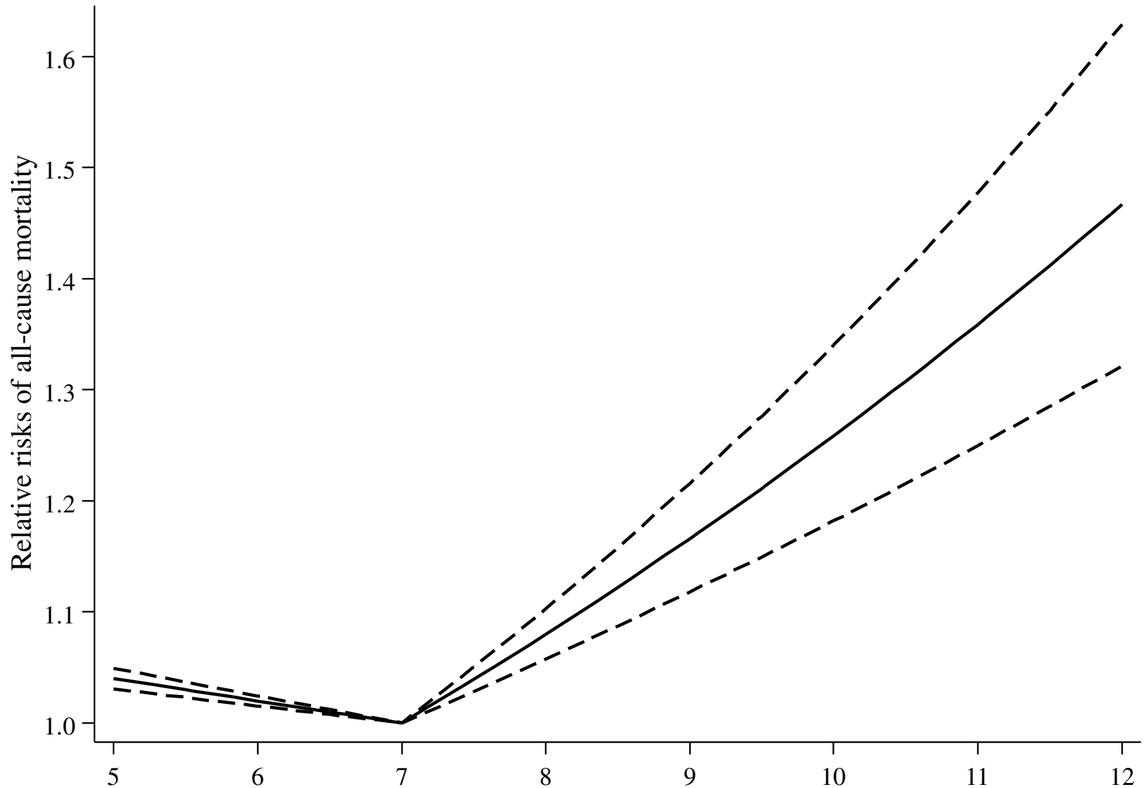

Figure 1b.Sleep duration, hours/day

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Figure 2(on next page)

Figure 2

Figure 2. Piecewise linear prediction for parity and risk of rheumatoid arthritis: a) based on random-effect GLST approach (P = 0.03 for “piecewise effect” test); b) based on REMR approach (P = 0.06 for “piecewise effect” test)

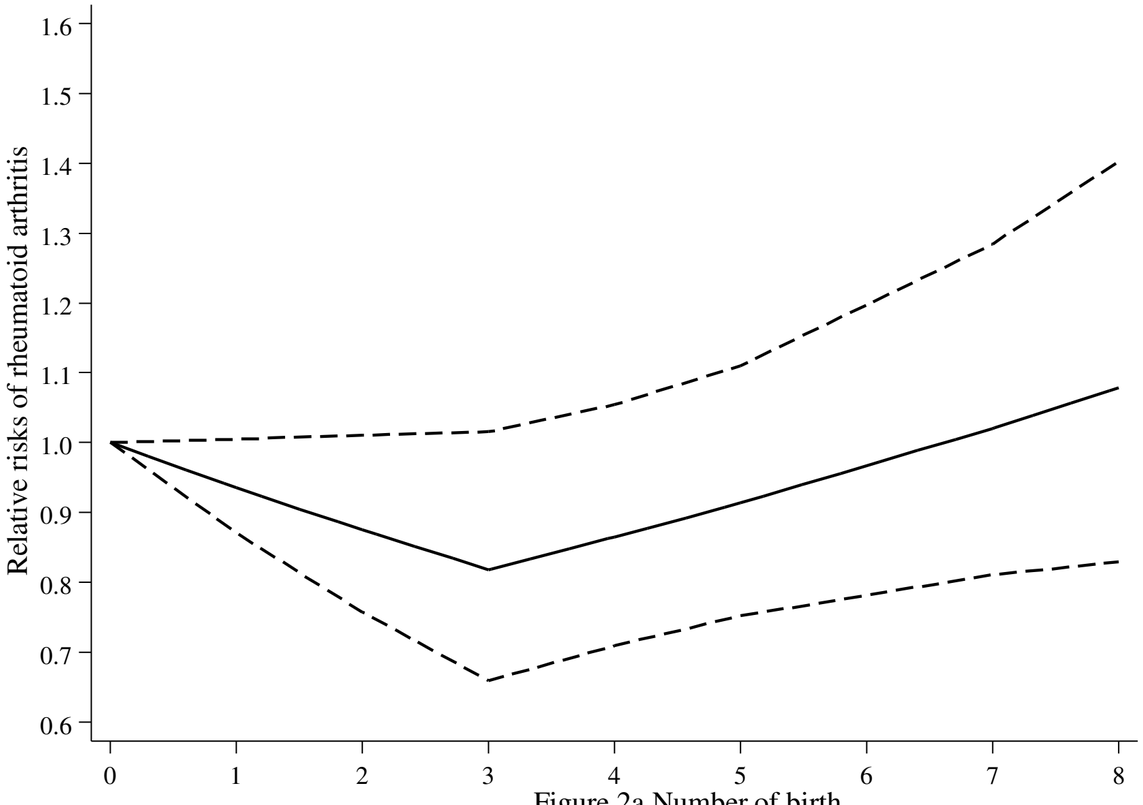

Figure 2a.Number of birth

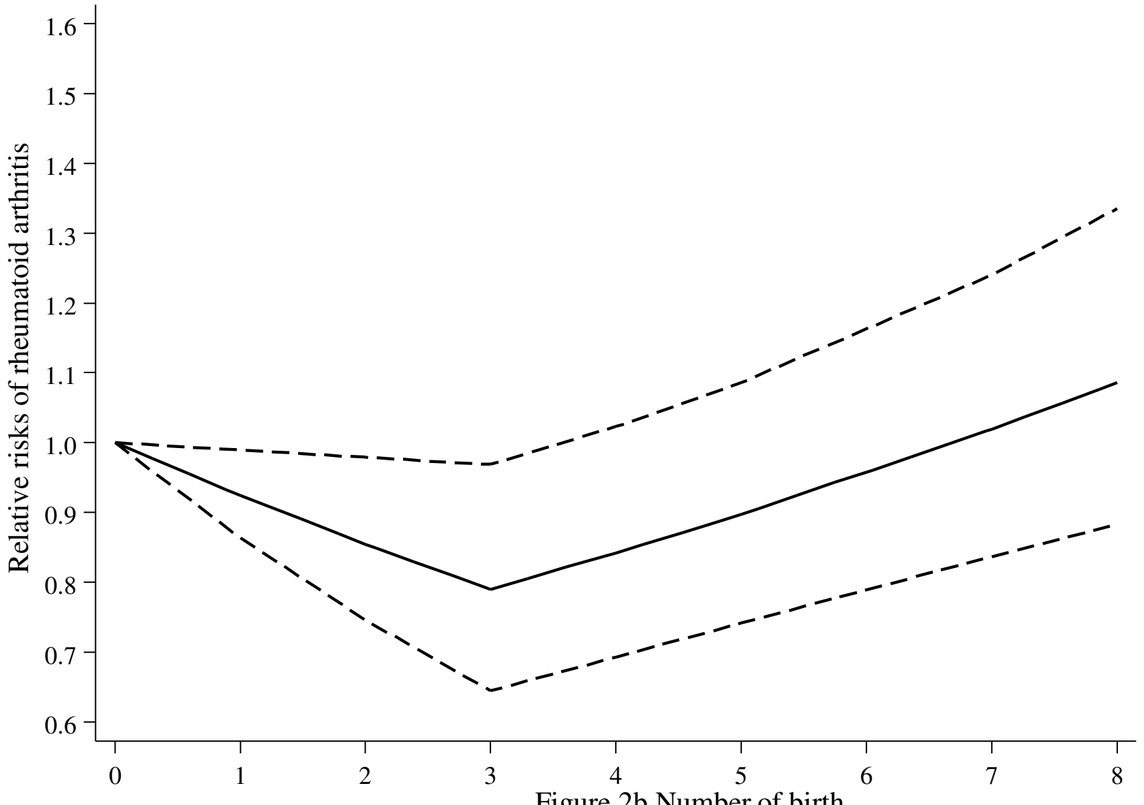

Figure 2b.Number of birth

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Table 1(on next page)

Table 1

Table 1. Stata commands for piecewise linear DRMA for sleep data.

1 **Table 1.** Stata commands for piecewise linear DRMA for sleep data.

GLST approach-random effect	***REMR approach without intercept***
******Data centering(if needed)***	******Data centering(if needed)***
bysort id: gen dosec =(dose- dose[1])+5	*bysort id: gen dosec =(dose- dose[1])+5*
****** Weighting***	******Weighting***
gen wt=1/(se^2)	*gen wt=1/(se^2)*
	bysort id: egen maxwt=max(wt)
	replace wt = maxwt if wt==.
******Regression***	******Regression***
mkspline linsp_dose1 7 linsp_dose2 = dosec, marginal displayknots	*mkspline linsp_dose1 7 linsp_dose2 = dosec, marginal displayknots*
glst logrr linsp_dose, cov(n case) se(se) pfirst(id studytype) r eform*	*regress logrr linsp_dose* [aweight=wt], nocons vce(cluster author) eform (exp beta)*
******test for piecewise effect***	******test for piecewise effect***
test linsp_dose1= linsp_dose2	*test linsp_dose1 =linsp_dose2*
******Get linear results of each pieces***	******Get linear results of each pieces***
lincom linsp_dose1-1, eform*	*lincom linsp_dose1*-1, eform*
*lincom linsp_dose2*1, eform*	*lincom linsp_dose2*1, eform*
******Dose-specific results and plots***	******Dose-specific results and plots***
quietly levelsof dosec, local(levels)	*quietly levelsof dosec, local(levels)*
xblc linsp_dose , covname (dosec) at(`r(levels)')*	*xblc linsp_dose* , covname (dosec) at(`r(levels)')*
ref (7) eform line	*ref (7) eform line*

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Table 2(on next page)

Table 2

Table 2. Comparison between piecewise linear and linear as well as cubic spline model.

Table 2. Comparison between piecewise linear and linear as well as cubic spline model.

Examples	**GLST**		**REMR**	
Sleep duration	***Piecewise linear***	***Simple linear***	***Piecewise linear***	***Simple linear***
<7, 1-hour decrease	1.02 (1.004, 1.04)	—	1.01 (1.01, 1.02)	—
>=7, 1-hour increase	1.09 (1.09, 1.10)	—	1.08 (1.05, 1.10)	—
1-hour increase	—	1.00 (0.97, 1.03)	—	0.99 (0.99, 1.00)
Sleep duration(continuous)	***Piecewise linear***	***Cubic spline***	***Piecewise linear***	***Cubic spline***
5 h	1.04 (1.01-1.07)	1.01 (0.99-1.04)	1.04 (1.03-1.05)	1.01 (1.00-1.02)
6 h	1.02 (1.00-1.03)	0.99 (0.98-1.01)	1.02 (1.02-1.02)	0.99 (0.99-1.00)
7 h	Reference	Reference	Reference	Reference
8 h	1.08 (1.06-1.09)	1.05 (1.03-1.06)	1.08 (1.06-1.10)	1.05 (1.03-1.06)
9 h	1.16 (1.12-1.20)	1.14 (1.10-1.17)	1.17 (1.12-1.22)	1.13 (1.09-1.17)