An application of spline regression to dose-response analysis in observational study

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Outline

Dose-response in epidemiology

Definition:

"the shape of the exposure-outcome curve(whatever that shape may be)"

or

"a relationship in which a change in amount, intensity, or duration of exposure is associated with a change - either an increase or a decrease - in risk of a specified outcome"

Categorical approach

- Divide (categorize) continuous exposure by breaking the exposure range into k groups.

  Percentiles:

  controls in case-control study

  cohort population in cohort study

  Cut-points:

  based on distibution

  dataset specific
- Fit a logistic model, if binary outcome, as step function.

  logit(R|x)= $\alpha_1 + \alpha_2 i_2 + \ldots + K i_K(0)$

  with k-1 category indicator variables $i_2, \ldots i_K$ where $i_k = 1$ if x is in category k, 0 otherwise.
- Run a supplemental trend test

  ordinal scores (0,1,2,...) are assigned to the categories.

Advantages of categorical approach

- Usefulness in health promotion
  Risk management:
  e.g., blood pressure for risk of cardiovascular event
- No assumption about the dose-response curve
- Convenient and realistic in questionnaire design

Disadvantages of categorical approach

- Not using full information within category
  Loss of power, especially when exposure effects on tail or non-linear.
  Loss of precision
- Implied assumption of constant effect within categories while allowing for big jumps in risk at category boundaries
- Subjects at high risk category may be submerged into lower risk category by the mechanical grouping procedure.

Disadvantages of categorical approach

- Investigator-induced measurement error and residual confounding (for continuous covariates)

  when the adjusting variable is categorized, its confounding effect is not completely captured by the regression model.
- Biased or distorted exposure-response estimate.

  especially when the association is non-linear within category (for primary exposure)

A paper on categorization

Problems in the Average-Risk Interpretation of Categorical Dose-Response Analyses

Sander Greenland

In a recent article,[1] I commented that categorical risk models depended on the assumption of homogeneous within-category risks, a step-function assumption that I labeled absurd. I also dismissed the average-risk interpretation of such regressions as questionable. In an accompanying editorial, Weinberg[2] agreed that the step-function assumption was absurd but argued that the average-risk interpretation rendered the homogeneity assumption unnecessary. I here clarify the basis of my comment by illustrating how the apparent dose-response relation conveyed by a categorical analysis may be biased if there is substantial within-category heterogeneity of risk. The fact that the categorical relative risks are interpretable as ratios of average risks does not address this problem. I also comment on other justifications for categorical analysis of continuous variables.

How Categorization Can Distort Dose-Response

As a simple numeric illustration of the main points, Table 1 presents underlying distributions for a hypothetical study of the effect of an occupational exposure x on 10-year risk of lung cancer in 10,000 men. Of the total, 4,800 (48%) are unexposed; 1,400 (14%) are at each of $x = 1$, 1.5, and 2; and 200 (2%) are at each of $x = 3$, 4, 5, 6, and 7. Such skewed exposure patterns are not unusual in occupational and environmental studies, in which most subjects are unexposed or lightly exposed, but some are in various "dirty" tasks that involve high exposures. Such patterns can also occur in nutritional studies, in which typical subjects may have moderate micronutrient intakes, but some consume various supplements and so are spread across a range of high exposure levels.

The risks given in Table 1 are rounded values generated by the log quadratic risk function $\ln(\text{risk}) = -6 + 0.0473x^2$; this function yields a risk ratio of 10 for the highest exposure ($x = 7$) *vs* none. The function is highly nonlinear, yielding only small exposure effects below $x = 3$, but growing to substantial effects beyond $x = 3$, and so the function is equivalent to a quadratic logistic model.

The expected numbers of cases are too low for reliable dose-response estimation without some sort of grouping or modeling. Suppose that the cohort will be analyzed by collapsing $x = 1$ to 2 together and $x = 3$ to 7 together. The expected results will then be as in Table 2. Because exposure is distributed evenly within the categories, the mean and median exposures both equal the category midpoints, and the average risks for the categories are just the simple averages of the risks within the categories.

The risk ratio comparing the third and second categories is 111.9/27.9 = 4.0. Assuming that confounding is absent, this ratio has the following causal interpretation: It is the proportionate increase in the average risk that workers in the second category would experience if their exposure distribution was changed to match that of the third category (that is, if they were evenly redistributed among exposure levels 3 to 7). Although it is a causal parameter, this risk ratio is not a biological one because it depends on the exposure distributions within both categories, as well as on any biological exposure effects. Nor can it be interpreted as an occupational health parameter, because interventions generally would *not* involve changing exposure distributions in one category to match that in another. Rather, an intervention would seek to reduce exposure levels to conform to some maximum allowable level (for example, reduce all exposures above 2 to 2), and shifts in work tasks would generally produce a new exposure distribution.

The second categorical risk ratio also provides a biased impression of the causal (dose-response) dependence of risk on exposure, in the following sense: The ratio makes it appear that moving from an exposure of 1.5 (the second category mean) to 5 (the third category mean) will increase a worker's risk by 4-fold. But from Table 1 we can see that such a change would increase

A paper on categorizatio: dichotomizing

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Dichotomizing continuous predictors in multiple regression: a bad idea

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A paper on categorization of BMI

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ORIGINAL ARTICLE

Categorizing BMI may lead to biased results in studies investigating in-hospital mortality after isolated CABG

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Abstract

Objective: To investigate how categorizing body mass index (BMI) into weight classes can impact the assessment of the relationship between BMI and in-hospital mortality after coronary artery bypass graft (CABG) surgery.

Study Design and Setting: BMI–mortality (in-hospital) relationship was assessed in 5,762 patients who underwent isolated CABG at Baylor University Medical Center (Dallas, TX) from January 1, 1997 to November 30, 2003. Different ways of modeling BMI were used to investigate this association in a propensity-adjusted model, controlling for risk factors identified by the Society of Thoracic Surgeons (STS) and other clinical/nonclinical details.

Results: A highly significant ($P = 0.003$) association between BMI (modeled with a restricted cubic spline) and mortality was found. Reduced risk of in-hospital mortality was observed for subjects with BMI in the low-30s as compared with patients with BMI in the mid-20s or over 40 kg/m^2. Results were strongly affected by the way BMI was specified in the multivariable model. Only five of the 10 BMI categorizations considered produced significant results, and these results did not fully determine the effect of BMI on mortality.

Conclusions: BMI categorization critically impacts study results. Conceivably, findings of other studies investigating BMI and adverse outcomes after CABG may be similarly affected. Investigators should consider smoothing techniques to avoid categorization.

Keywords: Body mass index; Coronary artery bypass; Postoperative adverse outcomes; In-hospital mortality; Epidemiologic methods; Smoothing methods

1. Introduction

With the rising incidence of obesity in the U.S. population, there has been increasing interest in how obesity affects the risk of disease as well as the risk of adverse

categorization of BMI may be partly responsible for the variable and often conflicting findings regarding the effect of BMI on risk for adverse events after coronary artery bypass graft (CABG) surgery [1]. Specifically, the way BMI is

Properties of categorical approach

Different categorization schemes

Table 1
Findings for the adjusted association between BMI (kg/m^2) and operative/in-hospital mortality, and BMI categorization schemes/analytic methods for studies investigating adverse operative outcomes in patients undergoing CABG surgery

		Studies' weight class cutoff points and labels					Study findings for operative/in-hospital mortality
Authors	Cohort size	Underweight (UW)	Normal (N)	Overweight (OW)	Obese (O)	Severely obese (SO)	OR (95% CI)
Reeves et al., 2003 [8]	4,372	<20	20–24.9	25–29.9	30–34.9	≥35	UW vs. N = 4.12 (1.48, 11.10)
Engelman et al., 1999 [9]	5,168	<20	20–30		>30		UW vs. N = 2.00 (1.20, 3.60)
Prabhakar et al., 2002 [10]	559,004		18.5–24.9	25–34.9[a]	35–39.9	≥40	O vs. N + OW = 1.21 (1.13, 1.29) SO vs. N + OW = 1.58 (1.45, 1.73)
Habib et al., 2005 [11]	6,068		22–32[b]		32.1–35.9[c]	≥36	NS[d]
Kuduvalli et al., 2002 [12]	4,713		<30		30–34.9	≥35	NS
Birkmeyer et al., 1998 [19]	11,101		≤30		30.1–36	>36	NS
Koshal et al., 1985 [13]	200		≤27		>27		NS
Lindhout et al., 2004 [14]	1,130		<30		≥30		NS
Brandt et al., 2001[e] [17]	500						NS
Moulton et al., 1996 [15]	2,299		≤30		>30		NS
Rockx et al., 2004 [16]	1,310						NS
Ranucci et al., 1999 [1]	345		Men, ≤30, women, ≤28.6		Men, >30; women, >28.6		NS
Jin et al., 2005 [20]	15,999	BMI[f] (continuous) and other transformations in the adjusted analysis					NS

Abbreviation: NS = not significant at $\alpha = 0.05$.
[a] Defined by investigators as "mildly obese."
[b] Also required a body surface area >1.85.
[c] Also required a body surface area >1.85—this category is defined by investigators as "moderately obese."
[d] Authors found a significant association between body surface area and mortality but not between BMI and mortality.
[e] Subjects with BMI ≥30 were defined by investigators as "severely obese."
[f] Investigators studied BMI in various ways, including as a linear effect, in the adjusted analysis.

Results of the categorization schemes

Table 3
Results of multivariable analysis (logistic regression) based on each of the categorizations identified in the literature and other analytic methods estimating the propensity-adjusted association between BMI and in-hospital mortality ($n = 176$) after CABG for 5,762 patients who underwent surgery at Baylor University Medical Center (Dallas, TX) between January 1997 and November 2003

	Propensity-adjusted association of BMI with in-hospital mortality							
	Underweight vs. normal[a]		Overweight vs. normal[a]		Obese vs. normal[a]		Severely obese vs. normal[a]	
BMI	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)
Reeves et al., 2003 [8]	0.163	0.54 (0.23, 1.28)	0.003	0.57 (0.39, 0.83)	0.001	0.44 (0.27, 0.72)	0.917	1.03 (0.61, 1.75)
Engelman et al., 1999 [9]	0.440	0.72 (0.31, 1.70)			0.350	0.84 (0.59, 1.20)		
Prabhakar et al., 2002 [10]			0.001	0.55 (0.39, 0.78)	0.640	0.86 (0.45, 1.63)	0.167	1.65 (0.81, 3.35)
Habib et al., 2005 [11]					0.010	0.38 (0.19, 0.79)	0.100	1.53 (0.92, 2.57)
Kuduvalli et al., 2002 [12]					0.038	0.61 (0.39, 0.97)	0.115	1.47 (0.91, 2.39)
Birkmeyer et al., 1998 [19]					0.063	0.66 (0.43, 1.00)	0.112	1.53 (0.91, 2.60)
Koshal et al., 1985 [13]					0.028	0.69 (0.50, 0.96)		
Lindhout et al., 2004 [14]					0.390	0.85 (0.59, 1.22)		
Moulton et al., 1996 [15]					0.390	0.85 (0.59, 1.22)		
Rockx et al., 2004 [16]								
Ranucci et al., 1999 [1]					0.620	0.92 (0.65, 1.30)[b]		
Brandt et al., 2001 [17]							0.390	0.85 (0.59, 1.22)
Linear	*P*-value for association of BMI with in-hospital mortality = 0.846 (OR = 1.00; 95% CI: 0.97, 1.03)							
Cubic spline	*P*-value for association of BMI with in-hospital mortality = 0.003[c]							

[a] Refer to Table 1 for cutoff values used to define the weight class categories.
[b] Estimate based on Ranucci et al. [1] categorization of different BMI cutoffs for men and women.
[c] Estimate based on restricted cubic spline (see Fig. 3).

The risk shape of BMI example

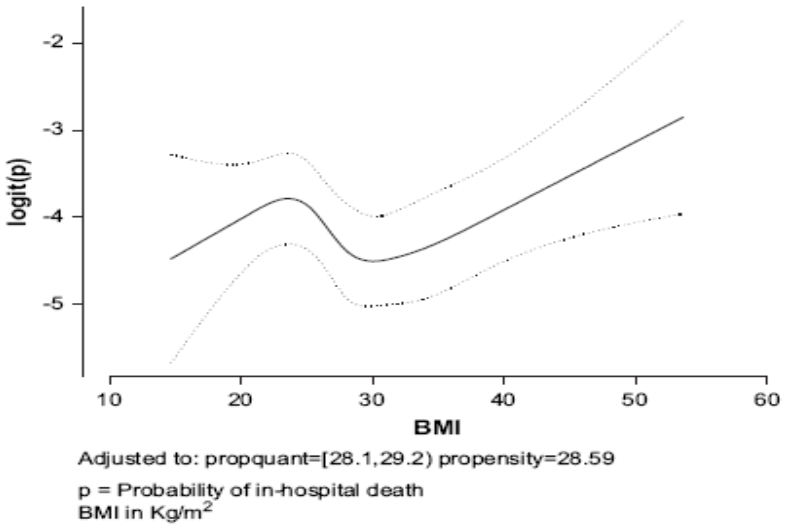


Fig. 4. Propensity-adjusted logit of the probability of in-hospital mortality (with 95% CIs) by BMI for 5,762 patients who underwent CABG surgery at Baylor University Medical Center (Dallas, TX) between January 1997 and November 2003.

Spline regressions

Spline regression can be a solution or an alternative for the issues that categorical regression can not solve. Spline regression is a smoothly joined piecewise regression which can be performed with any regression program simply by adding some transformed exposure variables to the regression. Spline regression has the following properties.

Properties of spline regressions

- fit complex distribution as well as linear association.
- examine both strength and shape of associations.
- Beneficial for skewed data.
- Use all information on risk variation within categories and avoid power loss.
- Restrict tails to linearity, if restricted form is used, and provide conservative estimates for the tail regions so to reduce the influence of outliers.

Linear spline regression

- A simple form of spline regression and a simple solution for the problems of categorization.
- Allows for non-zero slope within category and has no sudden jump between categories.
- Problems of linear spline regression
  still not biologically plausible with sharp bends at joining boundaries.

Procedure of linear spline regression

- The general idea is to simultaneously fit the K category-specific linear models.
  We would like these K models to fit together and the adjacent pair of category-specific models to predict the same risk at their boundaries.
- These ideas can be expressed in linear spline model:

$$logit(R|x) = \alpha + \beta_1 x + \beta_2 s_2 + \ldots + \beta_K s_K \quad (1)$$

  where
  $s_k = 0$ *if* $x \leq c_k$,
  x-c_k *if* $x > c_k$.
  s_k: positive part of $x - c_k$. c_k: boundary value.
- 2K coeficients(K intercepts and K slopes) are reduced to K+1.

  Intercept $\alpha_2, \ldots, \alpha_K$ are eliminated because of the continuity (no jump) constraint, leaving only one

  intercept.

How the exposure variable is transformed for spline function

If the boundaries are 2, 5, and 7 servings of fruit and vegetable intake per day,

$$
\begin{aligned}
s_2 &= \begin{cases} x-2, & \text{if } x > 2, \\ 0, & \text{if } x \leq 2, \end{cases} \\
s_3 &= \begin{cases} x-5, & \text{if } x > 5, \\ 0, & \text{if } x \leq 5, \end{cases} \\
s_4 &= \begin{cases} x-7, & \text{if } x > 7, \\ 0, & \text{if } x \leq 7, \end{cases}
\end{aligned} \tag{2}
$$

A graphic on linear spline

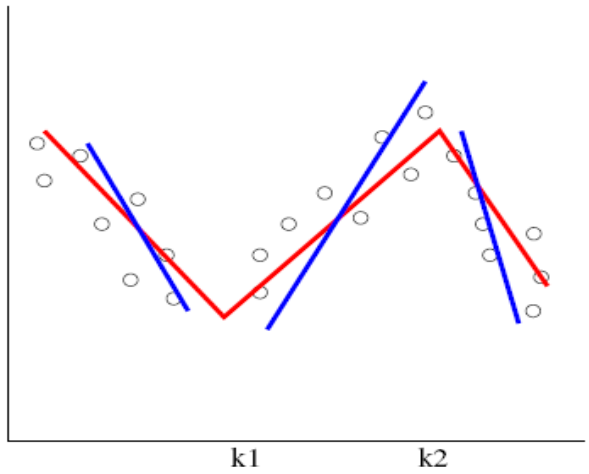


Figure 2: The aim of linear splines is to fit a piece-wise linear function such as the one shown in red. We can imagine splitting the data points up into three groups using the given knots k_1 and k_2 and solve three separate regression problems. This, however, does not assure continuity.

Quadratic spline regression

- Allows for the same slope for the adjacent models at their common boundaries to have a smooth appearance
  by adding a quadratic term to each category-specific model,
  and fit them together as linear spline regression to have the same slope at their common boundaries.
- The summarized model will be:

$$logit(R|x) = \alpha + \beta x + \gamma_1 x^2 + \gamma_2 s_2^2 + \ldots + \gamma_K s_K^2 \quad (3)$$

- One more parameter than linear spline regression

A graphic on quatratic spline

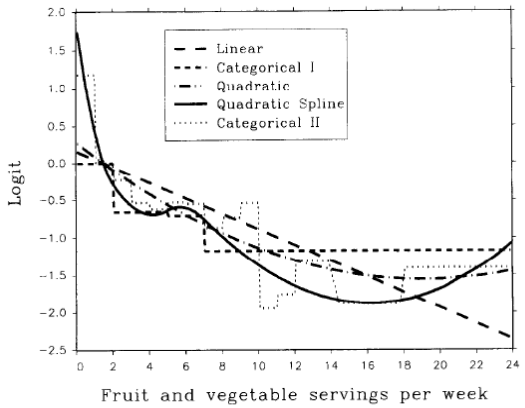


FIGURE 1. Dose-response models for the relation between fruit and vegetable consumption and colorectal polyps: linear (short dashes); categorical I—using four categories given in the Conventional Dose-Response and Trend section (dots and dashes); quadratic (dashes); quadratic spline (solid line); and categorical II—using the categories given in Table 1 (dotted line).

Cubic spline regression

- Further smooths the curve

  by adding a cubic term $\delta_k x^3$ to the category-specific quadratic models.
- Problem of cublic spline regression

  not stable at tails
- The model will look like:

$$logit(R|x) = \alpha + \beta x + \gamma x^2 + \delta_1 x^3 + \delta_2 s_2^3 + \ldots + \delta_K s_K^3 \quad (4)$$

- will have K+3 coefficients including intercept.

Restricted cubic spline regression

- Restrict the fitted curve to be linear in open-ended categories by dropping γx^2 and $\delta_1 x^3$ at lower tail and $\delta_K s_K^3$ at upper tail.
- The model will be written:

$$logit(R|x) = \alpha + \beta x + \delta_2 s_2^3 + \ldots + \delta_{K-1}(s_{K-1})^3 \quad (5)$$

- will have K coefficients including intercept.

A graphic on restricted cubic spline

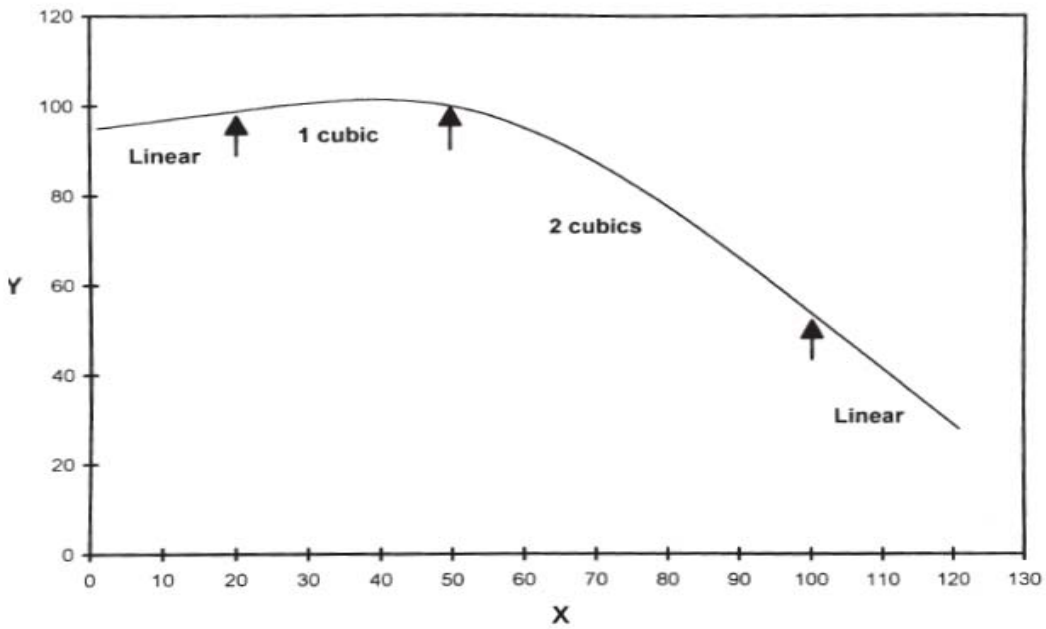


Figure 1: A cubic spline with three knots at X = 20, 50, 100.

S. Greenland (1995). Epidemiol 6:356

How to determine knot number

- General rule

  Usually between $k = 3,4$, or 5 based on sample size. For many datasets, $k = 4$ offers an adequate fit. When the sample size is large, k=5 is a good choice. Small sample size may require the use of k=3.

- Strengths of marginal relationships between predictors and response

  Estimated by using generalized Spearman $x^2 test.AIC$

  AIC can be used for data-based choice of k.

The specification of knot position

The location of the knots are usually specified in advance.
It has been found that the location of knots in a restricted cubic spline model is not very crucial in most situations; the fit depends much more on the choice of the number of knots.

the Tennessee Colorectal Polyp Study

- An on-going colonoscopy-based case-control study looking into risk factors for colorectal polyps starting at the year of 2000.
- Criteria for enrollment
  age 40-75
  free of genetic colorectal cancer syndromes or a prior history of inflammatory bowel disease, adenomas, or any cancer other than non-melanoma skin cancer.

  participants were recruited before colonoscopy was conducted.
- Case and control identification
  Case: with colonoscopy and pathology findings,as adenomatous polyps.

  Control: polyp-free at colonoscopy.
- Dietary intake assessment

  FFQ within 13 days after colonoscopy

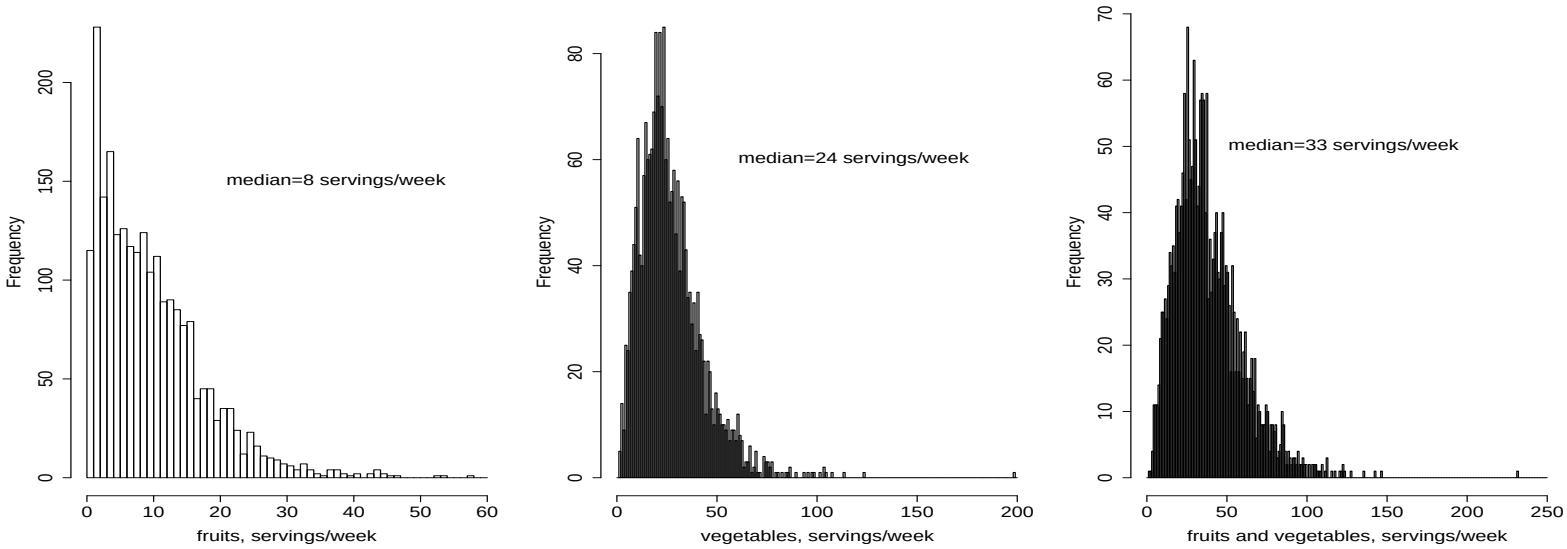
Study questions

- Whether there is an association between fruit and vegetable intakes and risk of colorectal adenomas.
- What is the shape of the association?

Participants characteristics

Characteristic	Case N=764	Control N=1517	P value
Age (years, median, 25th, 75th)	59.6 (54.9, 65.2)	56.7 (51.7, 63.1)	< 0.001
Female (%)	173 (23)	664 (44)	< 0.001
White (%)	645 (86)	1341 (89)	0.013
Study sites (%)			< 0.001
Veteran's Affairs	398 (51)	528 (35)	
Academic	368 (48)	994 (66)	
Education			< 0.001
High school or less	503 (66)	825 (55)	
College or higher	257 (34)	681 (45)	
Household Income (%)			< 0.001
<30,000	278 (38)	353 (25)	
30,0000 - <50,000	158 (22)	317 (22)	
>=50,000	288 (40)	759 (53)	
NSAID use (%)			0.957
Current	398 (56)	753 (56)	
Former	36 (5)	72 (5)	
Never	273 (39)	512 (38)	
Smoking status (%)			< 0.001
Current	215 (28)	188 (12)	
Former	298 (39)	558 (37)	
Never	250 (33)	768 (51)	
Alcohol drinking (%)			< 0.001
Current	157 (21)	260 (17)	
Former	217 (28)	348 (23)	
Never	388 (51)	905 (60)	
Regular physical activity past 10 years	382 (50)	876 (58)	< 0.001
Family history of colorectal cancer	107 (14)	199 (13)	0.887
BMI (kg/m^2 , median, 25th, 75th)	27.9 (24.7, 31.3)	27.3 (23.8, 30.9)	< 0.001
Dietary intake (median, 25th, 75th)			
Red meat (servings/week)	1.74 (1.03, 2.81)	1.50 (0.80, 2.39)	< 0.001
Total energy (kcal/day)	1611 (1249, 2016)	1554 (1221, 1955)	0.064

Exposure distribution



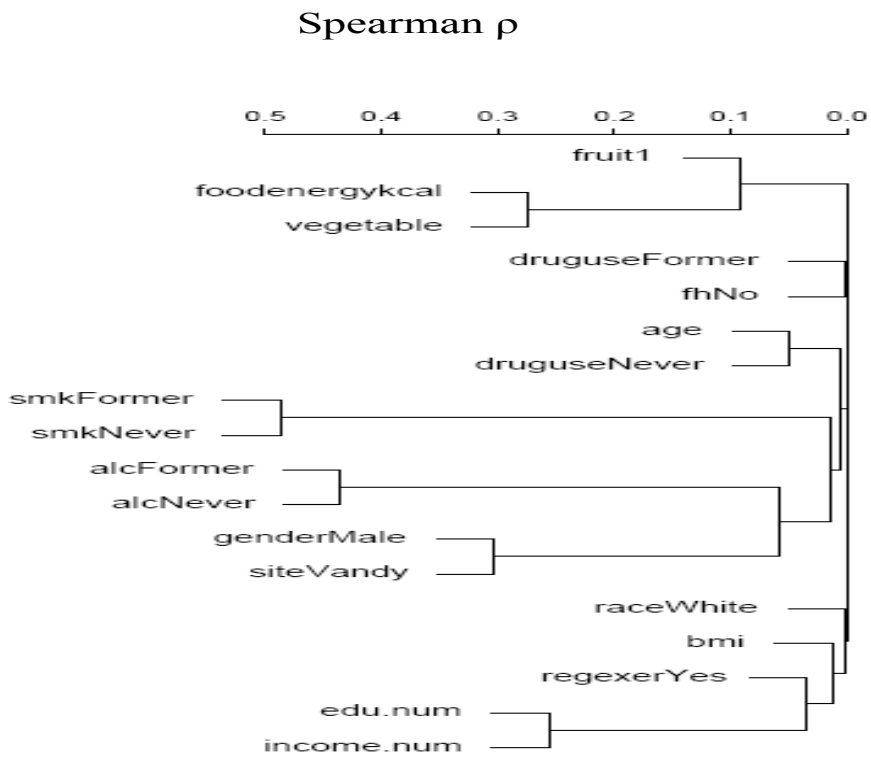
recommended daily intake for fruit and vegetable combined: 8 servings (56 servings/week)

Model building procedure

- Two models were built
  1. restricted cubic spline regression
     3 knots
  2. categorical regression
     tertiles
- The two models had the same d.f..
- Variable selection
  Known potential risk factors and confounders according to literature
- Interaction
  Sex and fruit and vegetable was pre-specified according to literature, and then deleted because of insignificance
- Variable collinearity
  see next slide

Variable collinearity

Moderate correlations (around 0.25) between vegetable and total energy intakes, gender and study site, and education and income.



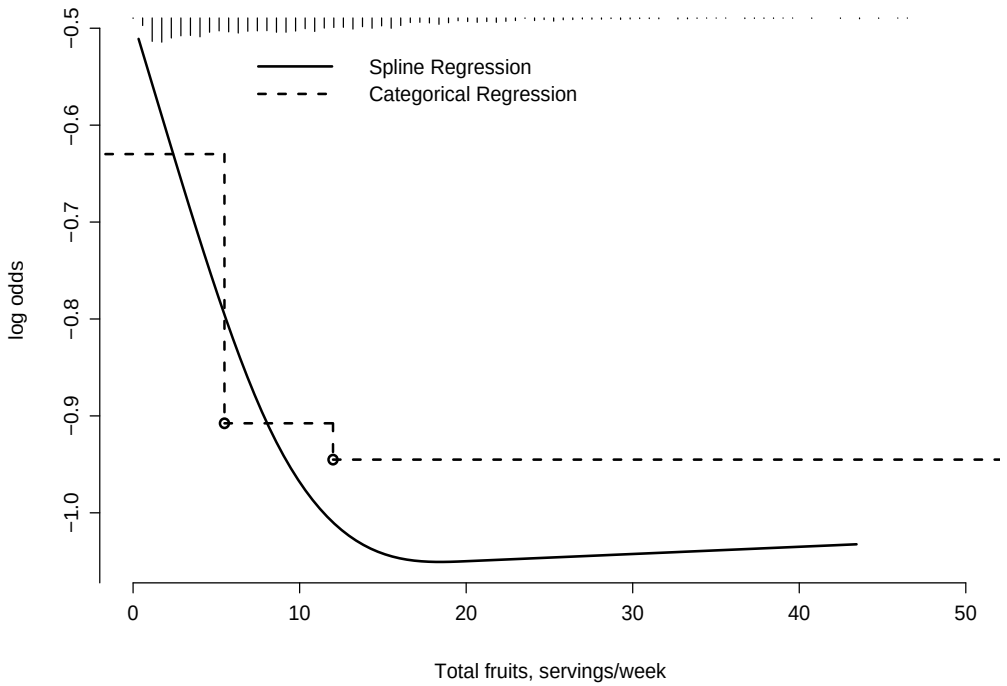
Model in R

```
ff = lrm (case - rcs(age,5)+reasons +
race+site+rcs(bmi,3)+regexer+druguse+smk+alc+rcs(redmeat,3)+fh+edu.num+income.num+rcs(foodenergykcal,3)+
rcs(vegetable,3)+ gender+rcs(fruit1,3),data=t3)
```

Fitted models

Monotonic relationship with the two models, somewhat nonlinear with restricted cubic spline regression.

Risk still increases when intake approaches 0, and decreases more with intake at after 10 relative to categorical regression.



Output of the models

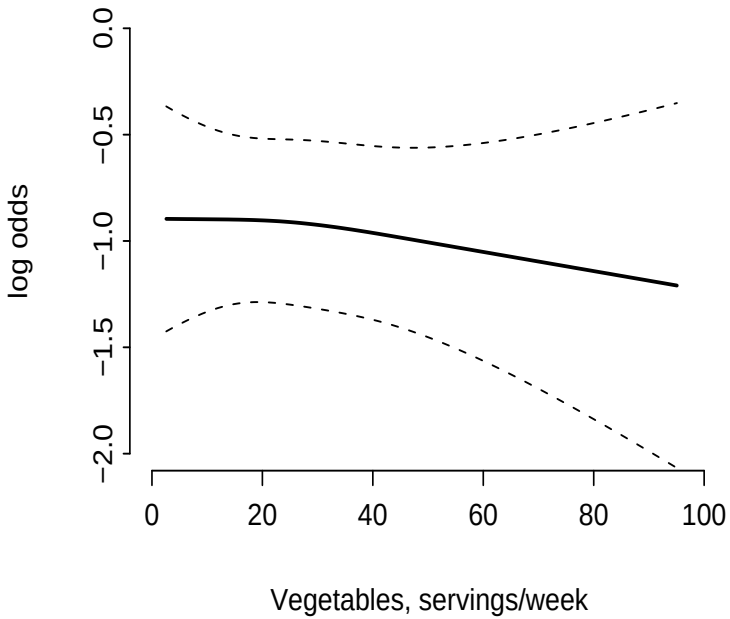
ORs and ANOVA including non-linearity can be computed with spline regression.

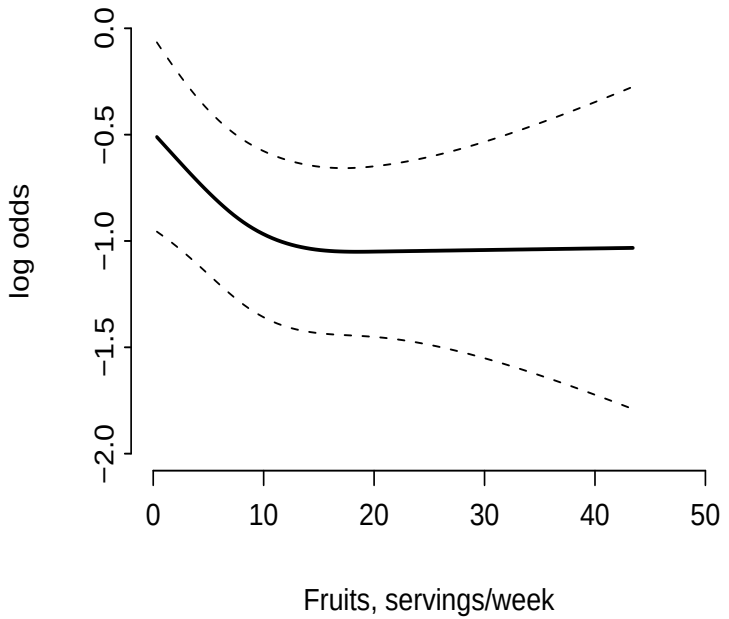
Table 2. Association of fruit and vegetable intake with the risk of colorectal adenoma risk, The Tennessee Colorectal Polyp Study 2003-2005

	Logistic regression with categorical intake					Logistic regression with spline function intake			
	Intake Tertile					Intake Tertile			
Fruits and Vegetables[3]	T1 (Lower)	T2 OR (95% CI)	T3 (Upper) OR (95% CI)	p ANOVA	p trend	T2 OR (95% CI)	T3 (Upper) OR (95% CI)	p ANOVA	P nonlinear
Total fruits	1.0 (ref)	0.75 (0.59-0.97)	.72 (0.54-0.95)	0.03	0.02	.75 (0.62-0.91)	0.66 (0.51-0.86)	0.01 (9.23)	0.05 (3.84)
Total vegetables	1.0 (ref)	0.74 (0.57-0.97)	0.87 (0.65-1.16)	0.08	0.36	0.99 (0.82-1.19)	0.94 (0.72-1.22)	0.73 (0.62)	0.77 (0.08)

Vegetable intake and risk

Total vegetable intake was not associated with risk for adenoma. The plot below shows the risk across the total vegetable intake.





Summary of the two models

- Similar point estimates, but narrower 95% confidence interval with spline regression.
- Underestimated risk reduction of further increase in fruit intake with categorical analysis.
- Overall,significant association for fruit intake, not for vegetable intake. Non-linear relationship for fruit with spline regression whereas significant trend test with categorical analysis.

A similar study

Witte et al tried categorical, linear, quadratic and quadratic spline regressions in analyzing the association between fruit and vegetable intake and adenoma risk. Only quadratic splne regression was satisfactory for describing the association for their data.

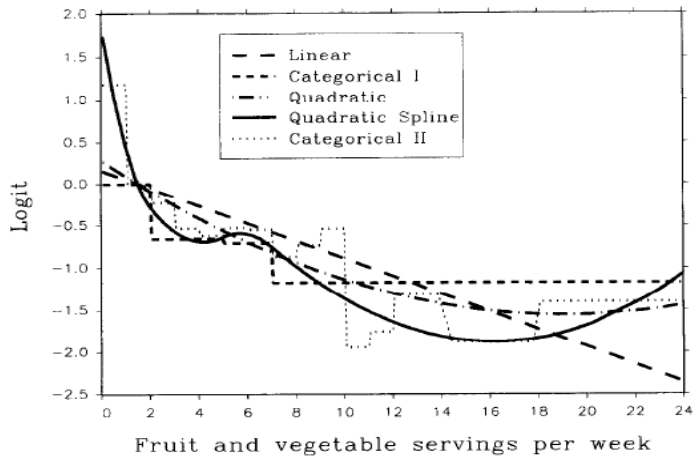


FIGURE 1. Dose-response models for the relation between fruit and vegetable consumption and colorectal polyps: linear (short dashes); categorical I—using four categories given in the Conventional Dose-Response and Trend section (dots and dashes); quadratic (dashes); quadratic spline (solid line); and categorical II—using the categories given in Table 1 (dotted line).

Model validation

with 26 d.f and 764 cases, overfitting won't be a major concern.

Fruits vs. vegetables

Why fruits, not vegetables?

Conclusions

- Nonlinearity does occur in nutritional epidemiology and categorical regression may not address this dose-response appropriately.
- Techniques are avaiable to deal with it.
- Restricted cubic spline regression has many advantages,both for checking nonlinearity and for checking overall trend.
- Restricted cubic spline regression can be used for dealing with primary exposure and covariates, and easily implemented in almost any software.

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Thank you and have a nice day!