

A RANDOM-EFFECTS META-REGRESSION MODEL FOR STUDYING NONLINEAR DOSE- RESPONSE RELATIONSHIP

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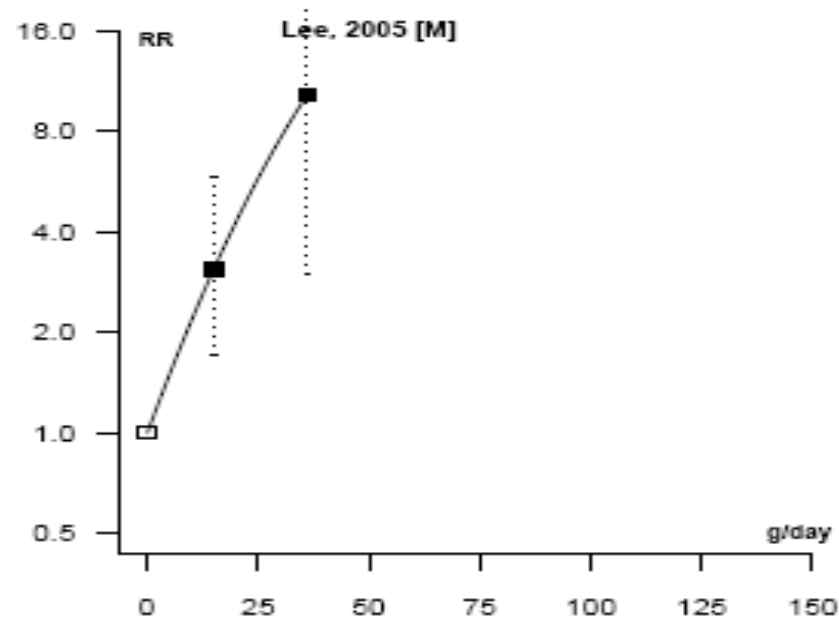
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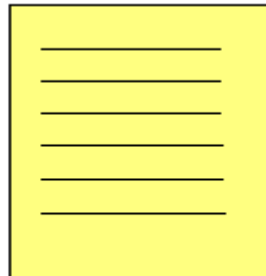
V Congresso Nazionale SISMEC, Pavia 16-19 Settembre 2009

DOSE-RISK RELATION

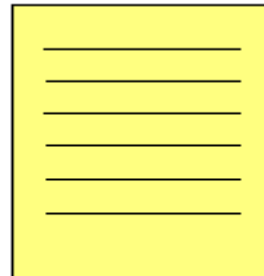
Estimation of the function describing how the risk of disease varies across different levels of a given exposure.



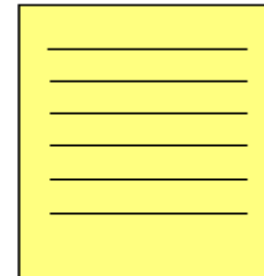
META-ANALYSIS



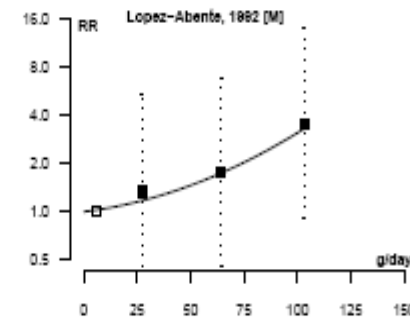
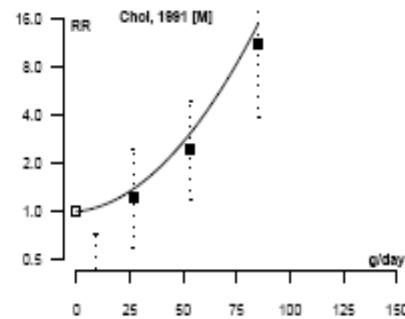
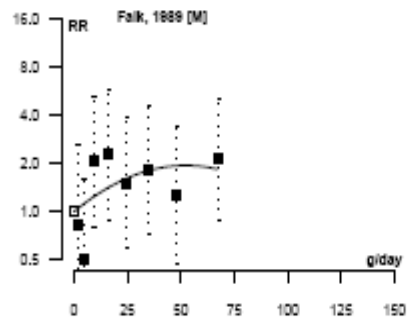
STUDY 1



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STUDY N



Summarize the results from different epidemiological studies to investigate the shape of the dose-risk relation.

FUNDAMENTAL ISSUES

- i. Correlation within the same study among reported dose-specific logRR estimates due to the common reference group (usually nondrinkers);
- ii. Between studies heterogeneity;
- iii. Nonlinear trend components of the dose-risk relation.

i. WITHIN STUDY CORRELATION

Data reported in the original article				Data transformed for the meta-analysis		
Reported alcohol dose	Cases (No.)	Controls (No.)	Adjusted OR (95% CI)	Assigned dose x (g/day)	log OR	Var(logOR)
Non drinkers	56	204	1.0	0	-	-
≤ 750	52	46	3.1 (1.7-5.8)	15	1.13	0.098
> 750	15	4	10.3 (3.0-42.5)	36	2.33	0.460

The reported ORs are calculated versus a common reference group [usually non drinkers].

GREENLAND & LONGNECKER APPROACH [1992]:

$$\log OR_j = \beta x_j + s_j \varepsilon_j \quad j = 1, \dots, n \quad \hat{\beta} = (X' \Sigma_{GL}^{-1} X)^{-1} X' \Sigma_{GL}^{-1} y$$

Σ_{GL} approximate covariance matrix of the reported log ORs calculated through an iterative algorithm.

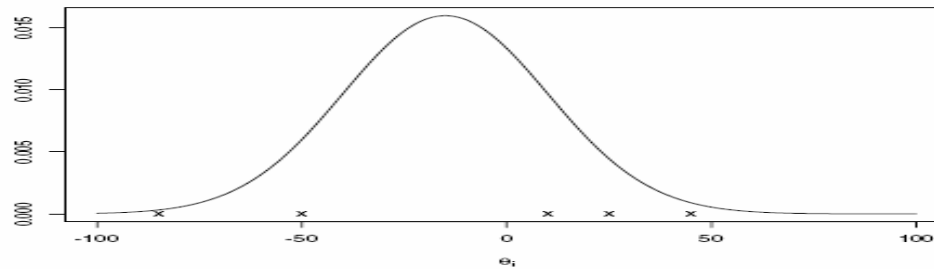
[Greenland & Longnecker Am J Epidemiol 1992, 135:1301-1309]

ii. BETWEEN STUDIES HETEROGENEITY

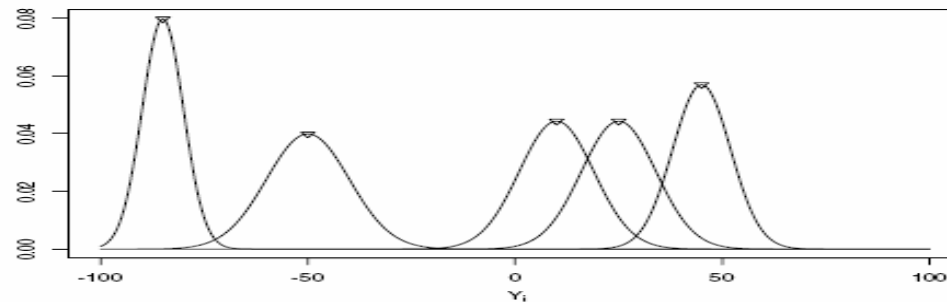
The appropriateness of a pooled summary:

$$\hat{\beta} = \frac{\sum_i \hat{\beta}_i w_i}{\sum_i w_i} \quad w_i = \frac{1}{s_i^2}$$

depends on a stringent **homogeneity** assumption.



Is the true relative risk constant across studies?



$$\beta_i \sim N(\beta, \tau^2)$$

RANDOM EFFECTS

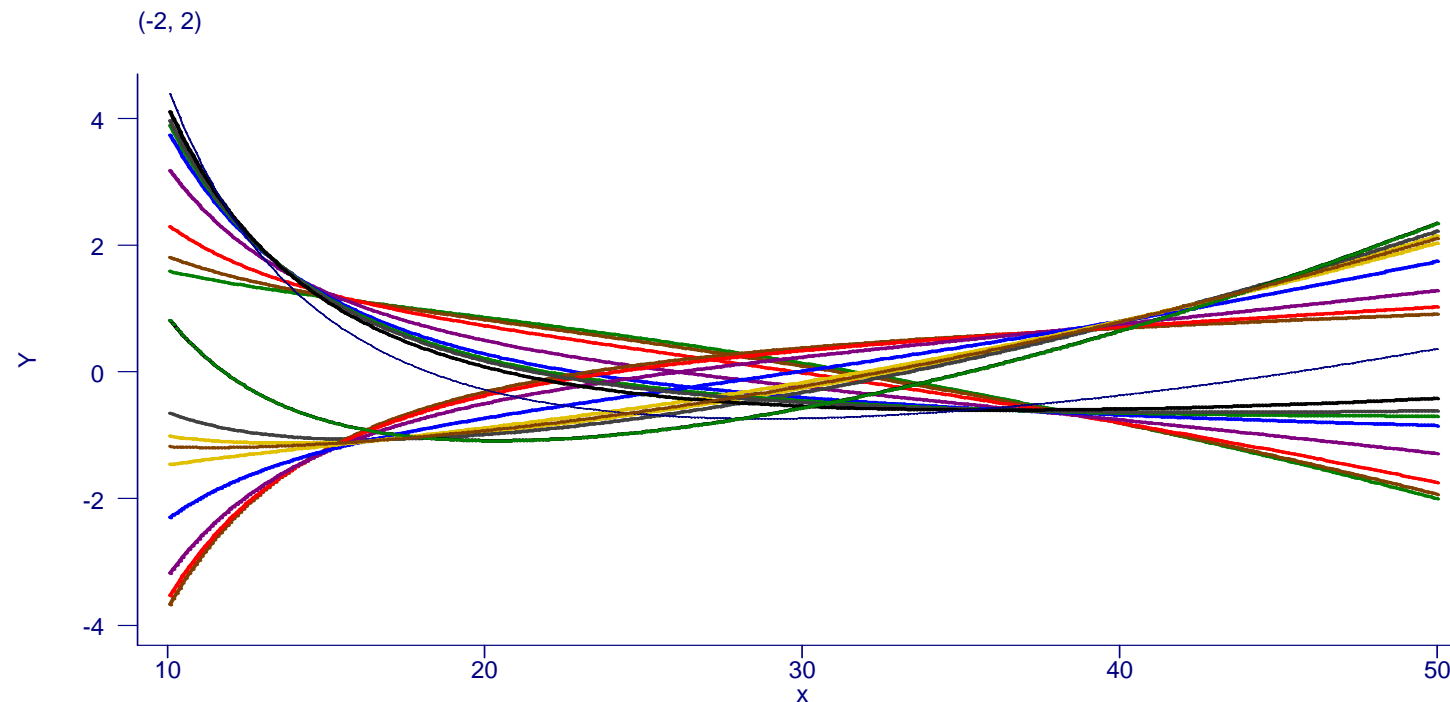
iii. NONLINEAR TREND COMPONENTS

SECOND ORDER FRACTIONAL POLYNOMIAL [FP2]:

$$\log RR_j = \beta_1 x^{p_1} + \beta_2 x^{p_2}$$

$$p_1, p_2 \in P = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}.$$

Several trends: J-shaped and U-shaped



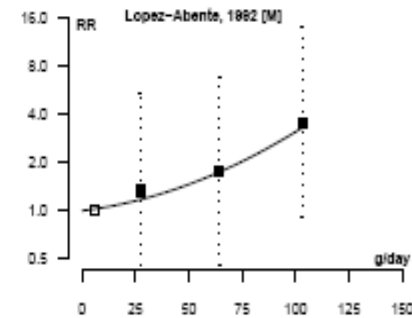
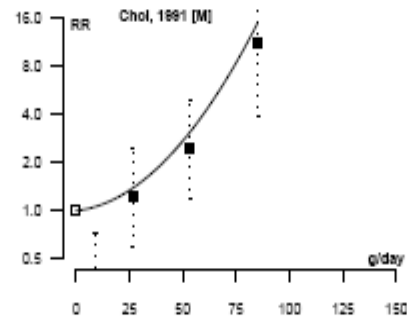
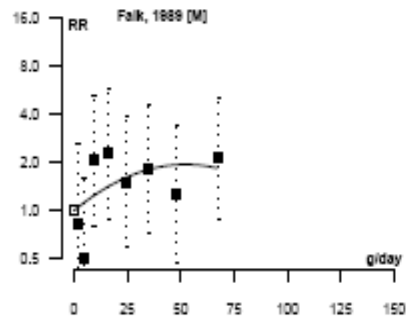
[Royston & Altman Applied Statistics 1994, 43:429-467]

FIRST STEP

For every set of powers $(p_1, p_2) \in P$:

STUDY	β_1	β_2
1	β_{11}	β_{12}
...
j	β_{j1}	β_{j2}
n	β_{n1}	β_{n2}

$$\Sigma_j = \begin{bmatrix} \sigma_{\beta_1}^2 & \sigma_{\beta_1, \beta_2} \\ \sigma_{\beta_2, \beta_1} & \sigma_{\beta_2}^2 \end{bmatrix}$$



SECOND STEP: THE POOLED DOSE-RISK RELATION

The pooled dose-risk relation is estimated accordingly to the bivariate random effects model:

$$\begin{pmatrix} \beta_{1,i} \\ \beta_{2,i} \end{pmatrix} \sim N \left(\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Sigma_i + \Delta \right)$$

Best fitting model of powers (p_1^*, p_2^*) : min (AIC).

The optimal predicted pooled dose-risk relations is:

$$\log RR = u_1 x^{p_1^*} + u_2 x^{p_2^*}$$

with 95% confidence limits:

$$\mathbf{u}'\mathbf{x} \pm 1.96\sqrt{\mathbf{X}'\text{Cov}(\mathbf{u})\mathbf{X}}$$

APPLICATION

A meta-analysis of epidemiological data on dose-risk relation between **alcohol consumption** and the risk of **esophageal cancer** [ICD-IX 150].

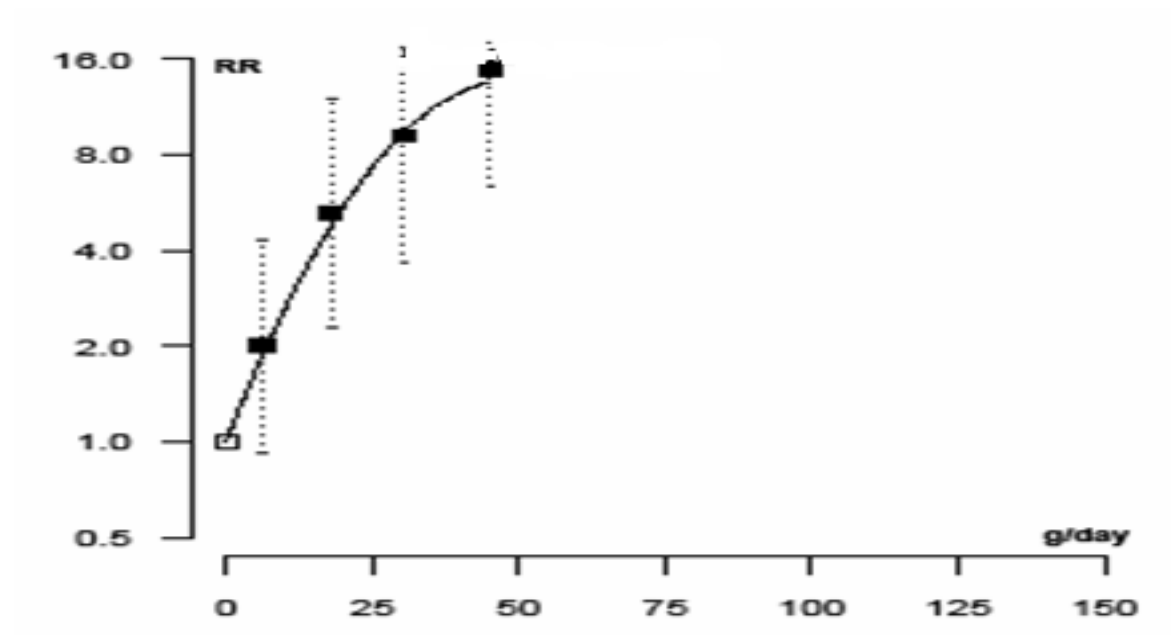
44 studies included:

- 38 case-control studies;
- 6 cohort studies.

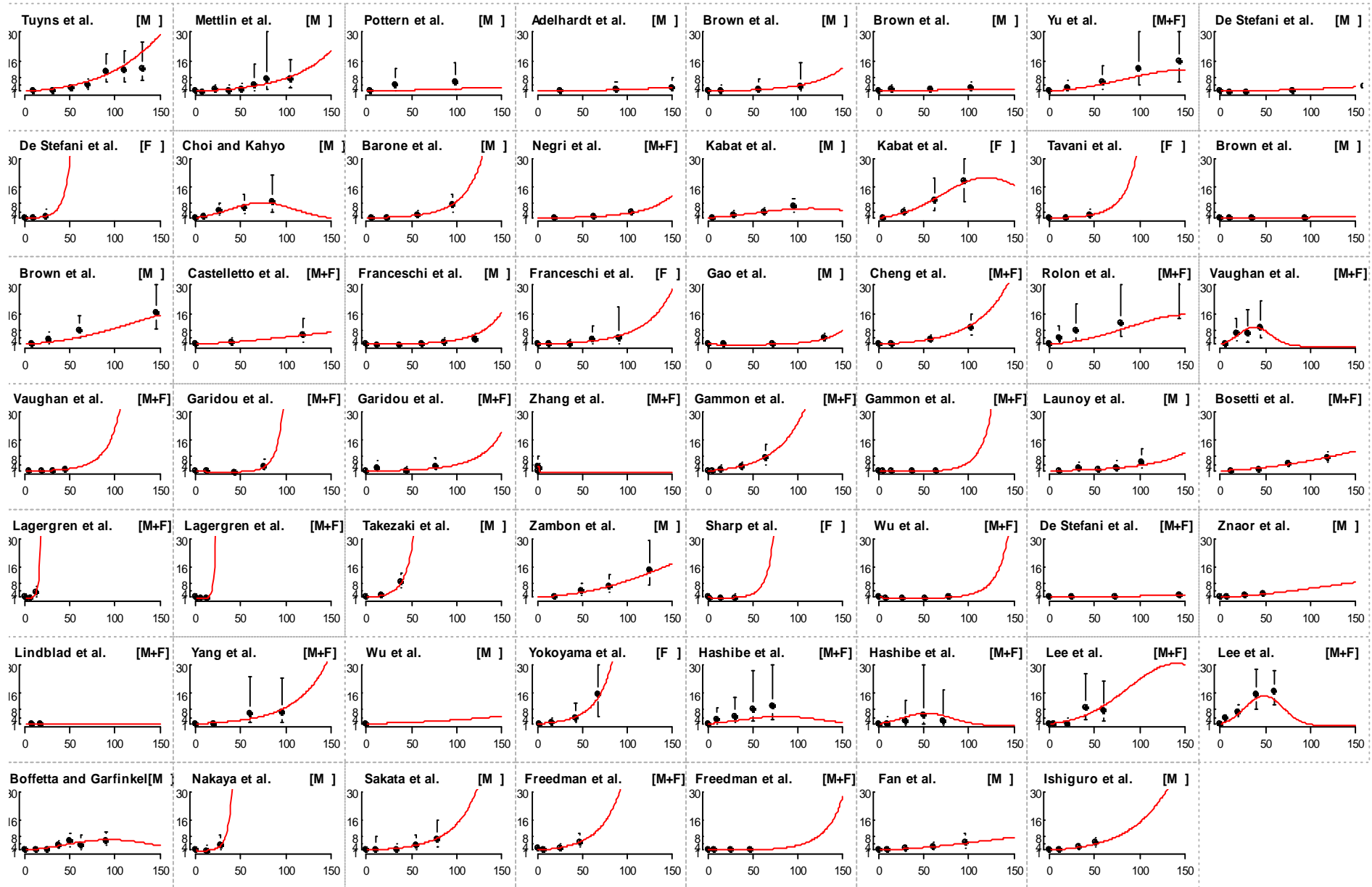
10,762 cases of esophageal cancer.

ILLUSTRATIVE EXAMPLE

Estimate the trend for each study included in the meta-analysis:



TREND ANALYSIS BY MEANS OF FP2



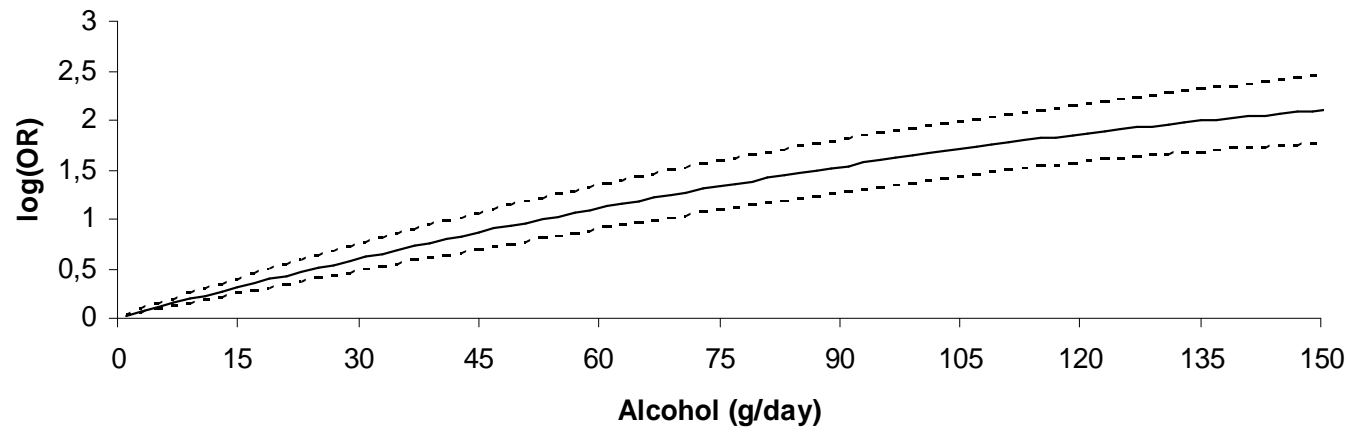
TREND ANALYSIS BY MEANS OF FP2

Powers				Powers				Powers			
p ₁	p ₂	AIC	G	p ₁	p ₂	AIC	G	p ₁	p ₂	AIC	G
-2	-2	2424	-1852.8	-1	1	945.3	-374.1	0	2	50.3	520.9
-2	-1	2323.1	-1751.9	-1	2	1060.9	-489.7	0	3	∞	-∞
-2	-0.5	2351.5	-1780.3	-1	3	∞	-∞	0.5	0.5	513.8	57.4
-2	0	1384.1	-812.9	-0.5	-0.5	1975	-1403.8	0.5	1	400.7	170.5
-2	0.5	1195.1	-623.9	-0.5	0	977.8	-406.6	0.5	2	-171.6	742.8
-2	1	1209.5	-638.3	-0.5	0.5	805.7	-234.5	0.5	3	∞	-∞
-2	2	1317.7	-746.5	-0.5	1	839.7	-268.5	1	1	27.5	543.7
-2	3	∞	-∞	-0.5	2	982.5	-411.3	1	2	-343.1	914.3
-1	-1	2264.8	-1693.6	-0.5	3	∞	-∞	1	3	∞	-∞
-1	-0.5	2309.8	-1738.6	0	0	568.5	2.7	2	2	∞	-∞
-1	0	1164.9	-593.7	0	0.5	722.3	-151.1	2	3	∞	-∞
-1	0.5	939.6	-368.4	0	1	476.9	94.3	3	3	∞	-∞

RESULTS

POOLED DOSE-RISK RELATION

Quadratic Random-Effects Meta-Regression Model



MODEL-BASED POOLED ESTIMATES OF RR

OR (95% CI)		
25 g/day	50 g/day	100 g/day
1.66 [1.48,1.87]	2.59 [2.12,3.15]	5.21 [3.95,6.86]

CONCLUSION

- Alcohol consumption is a risk factor for esophageal cancer;
- A strong positive non-linear dose-risk relation emerged;
- The fractional polynomial modeling allow us to test several trends: the best is the quadratic one;
- Significant heterogeneity between study-specific linear and quadratic terms was found.

ADVANTAGES

- A random effects meta-regression methodology has been found to perform satisfactorily in estimating the dose-risk relation;
- Addressing simultaneously for the first time three statistical issues in estimating the dose-response function:
 - i. Correlation among reported estimates within the same study;
 - ii. Between studies heterogeneity;
 - iii. Nonlinear trend components (FP2).

LIMITATIONS

- It is not possible to examine more complex models (i.e., cubic spline) since the results of published dose-response data are usually presented considering few levels of exposure;
- Publication bias;
- Meta-analysis is a useful alternative but not a substitute for single investigations.