Quantiles of the marginal and conditional dose-response relation based on weighted mixed-effects models

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Outline

- Examples, data, and challenges
- Weighted mixed-effects model
- Quantiles of marginal and conditional dose-response
- Statistical software
- Visualizations of quantiles
- Applications to simulated and real data
- Final remarks

Blood Pressure Effects of Sodium Reduction: Dose–Response Meta-Analysis of Experimental Studies. *Circulation* 2021

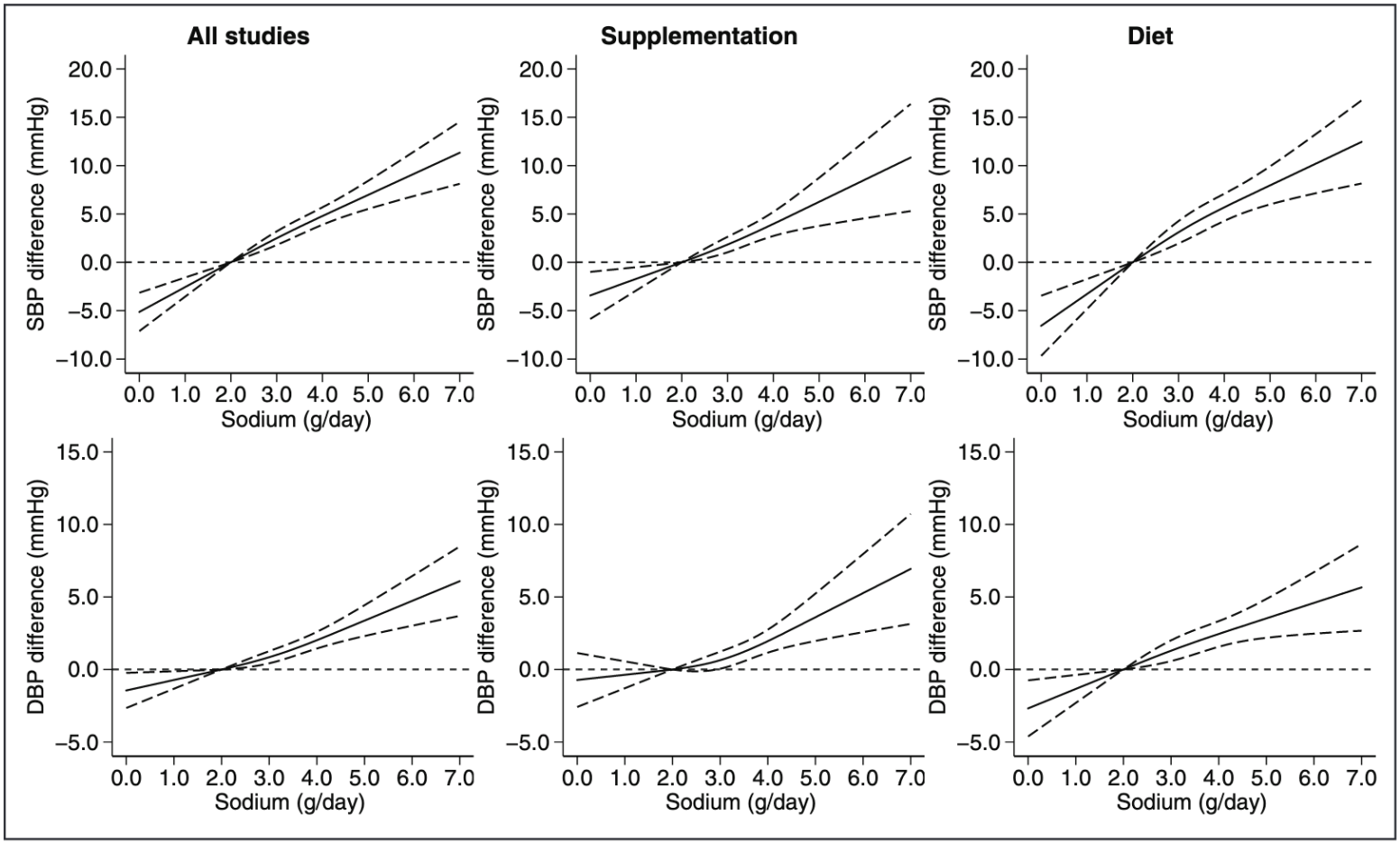
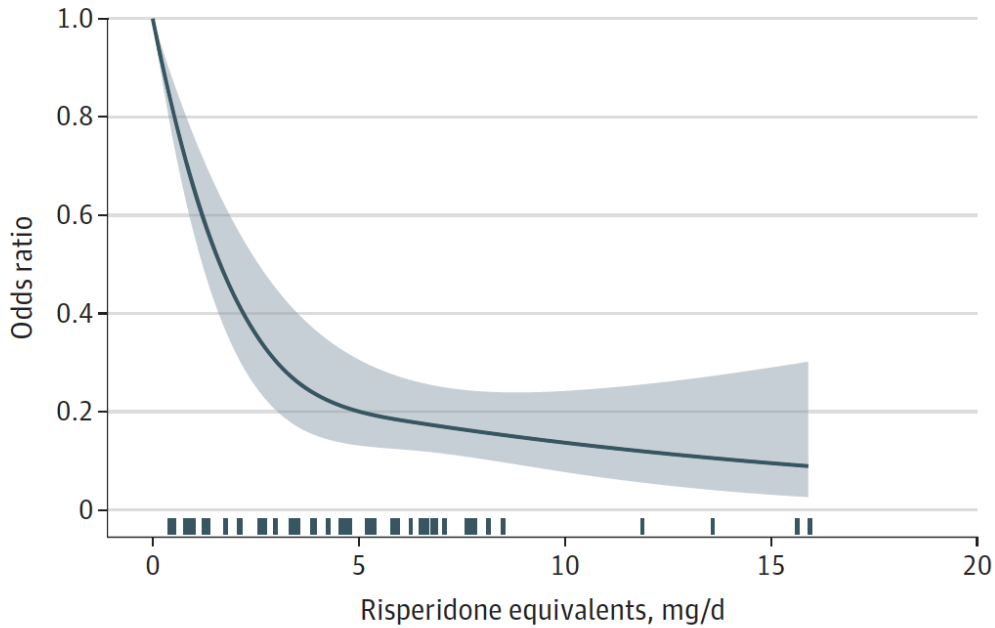


Figure 2. Dose–response meta-analysis of changes in SBP and DBP levels (mm Hg) according to achieved sodium excretion in the treatment and control groups at the end of the trials (all studies) and by type of intervention (supplementation or diet).
The average curve (solid line) with 95% confidence limits (dashed lines) was estimated with a 1-stage random-effects restricted cubic spline model, using 2 g/d as referent. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

Examination of Dosing of Antipsychotic Drugs for Relapse Prevention in Patients With Stable Schizophrenia. *JAMA Psychiatry* 2021

Figure 1. Relapse



The dose-response curve for the primary outcome relapse after pooling all drugs using the primary scientific dose-equivalence method (the maximum effective dose method). The marks on the x-axis indicate for which doses data from study arms were available. A total of 26 studies with 71 individual dose arms including 4749 patients were included (1 publication reported on 2 studies).[27,32-55] The shaded areas indicate 95% CIs for the primary outcome.

Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. *Lancet Public Health* 2022

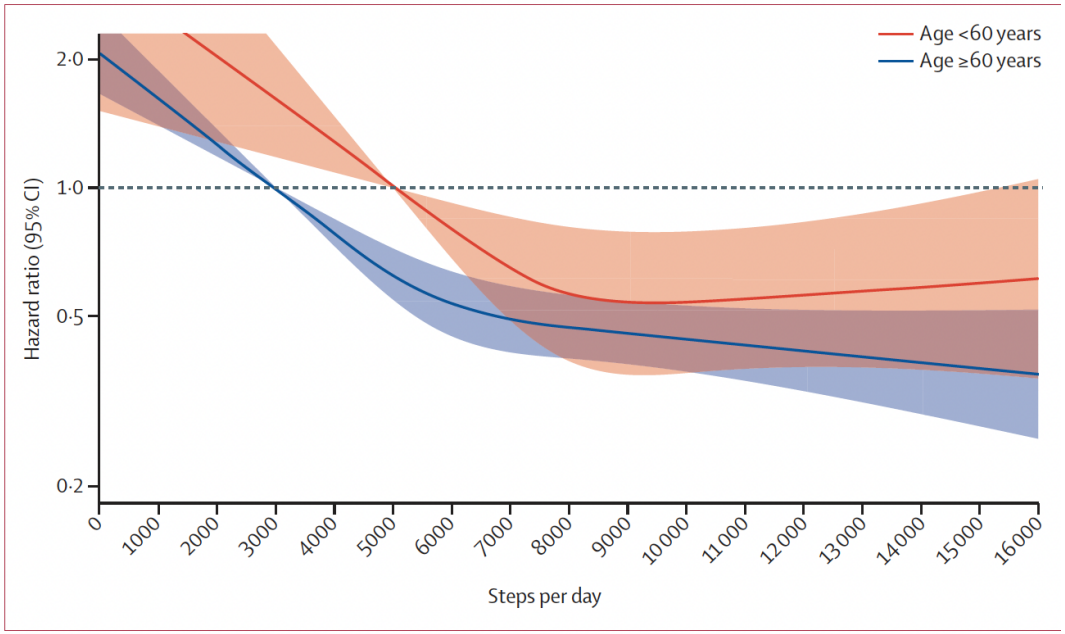


Figure 3: **Dose-response association between steps per day and all-cause mortality, by age group**
Thick lines indicate hazard ratio estimates, with shaded areas showing 95% CIs. Reference set at the median of the medians in the lowest quartile group (age ≥60 years = 3000 steps per day and <60 years = 5000 steps per day). Model is adjusted for age, accelerometer wear time, race and ethnicity (if applicable), sex (if applicable), education or income, body-mass index, and study-specific variables for lifestyle, chronic conditions or risk factors, and general health status. $p_{interaction}$=0·012 by age group. 14 studies included in spline analysis, excluded Baltimore Longitudinal Study of Aging.[19] The y-axis is on a log scale.

Diet, Nutrition, Physical Activity and Cancer Risk

Dose-response analysis in health risk assessment

- Consortium of researchers from 4 EU Member States (Italy, Sweden, Greece, Portugal)

The effect of exposure to radiofrequency fields on cancer risk in the general and working population: A protocol for a systematic review of human observational studies. *Environment International* 2021 - WHO ongoing project

c. We will perform dose–response *meta*-analyses of neoplasm risks per cumulative call time and total number of calls. We will use weighted mixed effects models suitable for table of correlated estimates (Crippa et al. 2019; Orsini 2021). A single exposure value is assigned to each category based on what has been reported (mean, median, midpoint) within each study. In case the typical exposure value within each exposure interval is not available from the publication, it will be assigned according to its distribution. We will use regression splines of different degrees to answer specific questions about the dose–response relationships (Orsini 2021; Orsini and Spiegelman 2020). The heterogeneity of dose–response gradients across studies is taken into account by using random-effects for the regression coefficients of the exposure transformations. The main target of statistical inference (test of hypothesis, confidence intervals) is the pointwise dose–response relationship for the average study. To examine the magnitude of heterogeneity across studies, the best linear unbiased predictions (BLUP) of the random effects will be used. A comparison of alternative candidate dose–response models will be done using the Akaike Information Criteria, balancing goodness of fit and overall number of parameters. Stratified analyses according to relevant design or scientific factors (e.g., gradient of susceptibility to systematic and differential exposure measurement

What's in common in these examples?

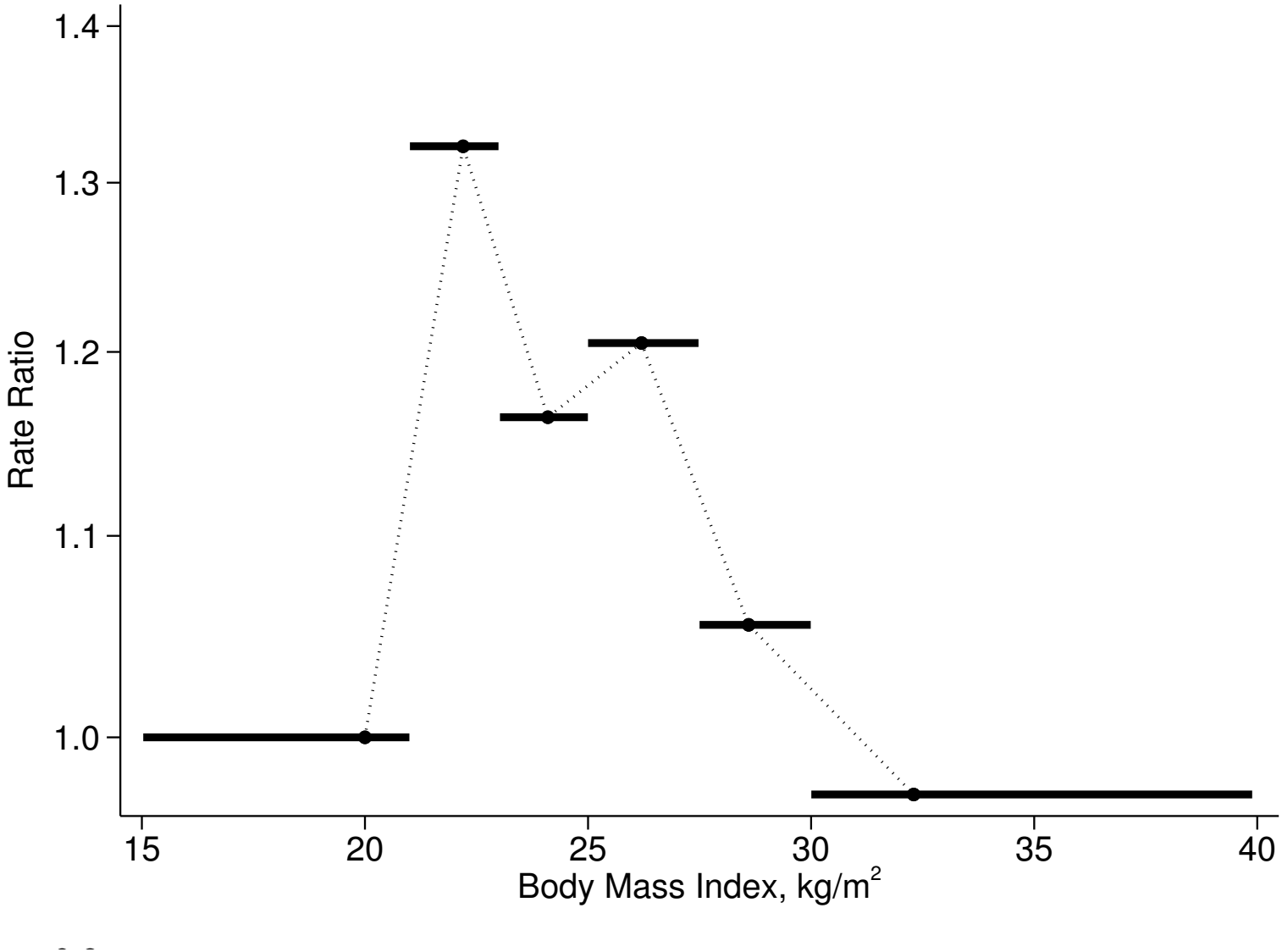
- There is a quantitative factor measured in either experimental or observational studies
- Effect measures can be of any type (mean difference, odds ratios, hazard ratios).
- Research questions are about the shape of the dose-response relationship or some specific less known aspects of it
- Design of the meta-analysis can be either retrospective (previously published) or prospective (pooling projects)
- A statistical model is used to learn from multiple tables of empirical estimates

Observational data from one prospective study #1

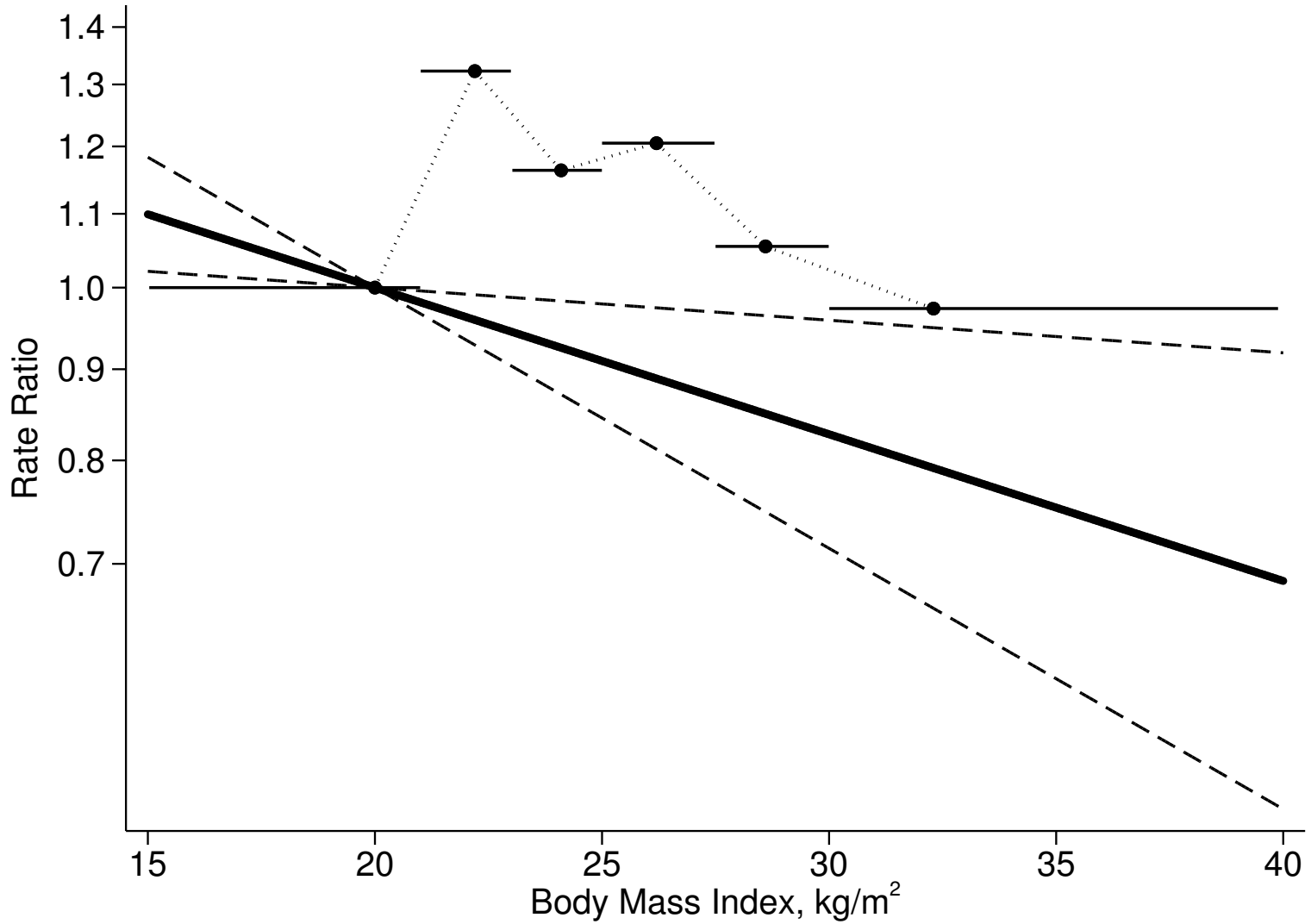
Table: Rate ratios of prostate cancer according to categories of body mass index (kg/m^2). Data from a cohort of 36,143 middle-age and elderly men followed for 446,699 person-years during which 2,037 were diagnosed with prostate cancer.

BMI	Median, kg/m^2	No. of cases	Person-years	Rate Ratio (95% CI)
< 21.00	20.0	84	21,289	1.00 Ref.
$[21.00; 23.00)$	22.2	323	61,895	1.32 (1.04, 1.68)
$[23.00; 25.00)$	24.1	532	115,885	1.16 (0.92, 1.46)
$[25.00; 27.50)$	26.2	651	136,917	1.21 (0.96, 1.51)
$[27.50; 30.00)$	28.6	283	68,008	1.05 (0.83, 1.35)
≥ 30	32.3	164	42,704	0.97 (0.75, 1.27)

Plot of the data for a single study



Alternative parametrizations of the exposure may not be graphically comparable



Observational data from one prospective study #2

Table: Incidence rate of colorectal cancer in relation to alcohol intake (grams/day) in the Health Professionals Follow-up Study. Rate ratios were adjusted for age, energy intake (kcal/day), multivitamin use, family history of colorectal cancer, current smoking, past smoking, red meat intake, total milk intake, and dietary folate intake.

Alcohol Intake	Median, grams/day	No. of cases	Person-years	Rate per 10,000	Adjusted Rate Ratio (95% CI)
0	0	100	103,002	9.7	1.00 Ref.
>0 to <5	2.1	65	106,826	6.1	0.66 (0.48, 0.90)
5 to <15	9.5	104	119,846	8.7	0.91 (0.69, 1.20)
15 to <30	18.8	63	58,034	10.9	1.10 (0.79, 1.52)
30 to <45	36.7	46	33,081	13.9	1.23 (0.85, 1.76)
≥ 45	59.4	30	18,455	16.3	1.41 (0.92, 2.17)

Challenge of comparing observed vs predicted exposure effects

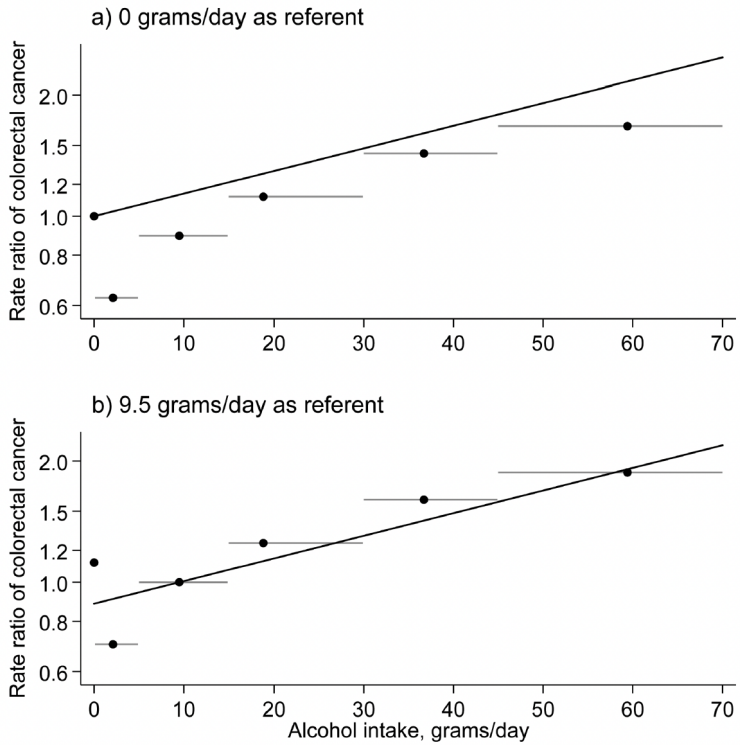


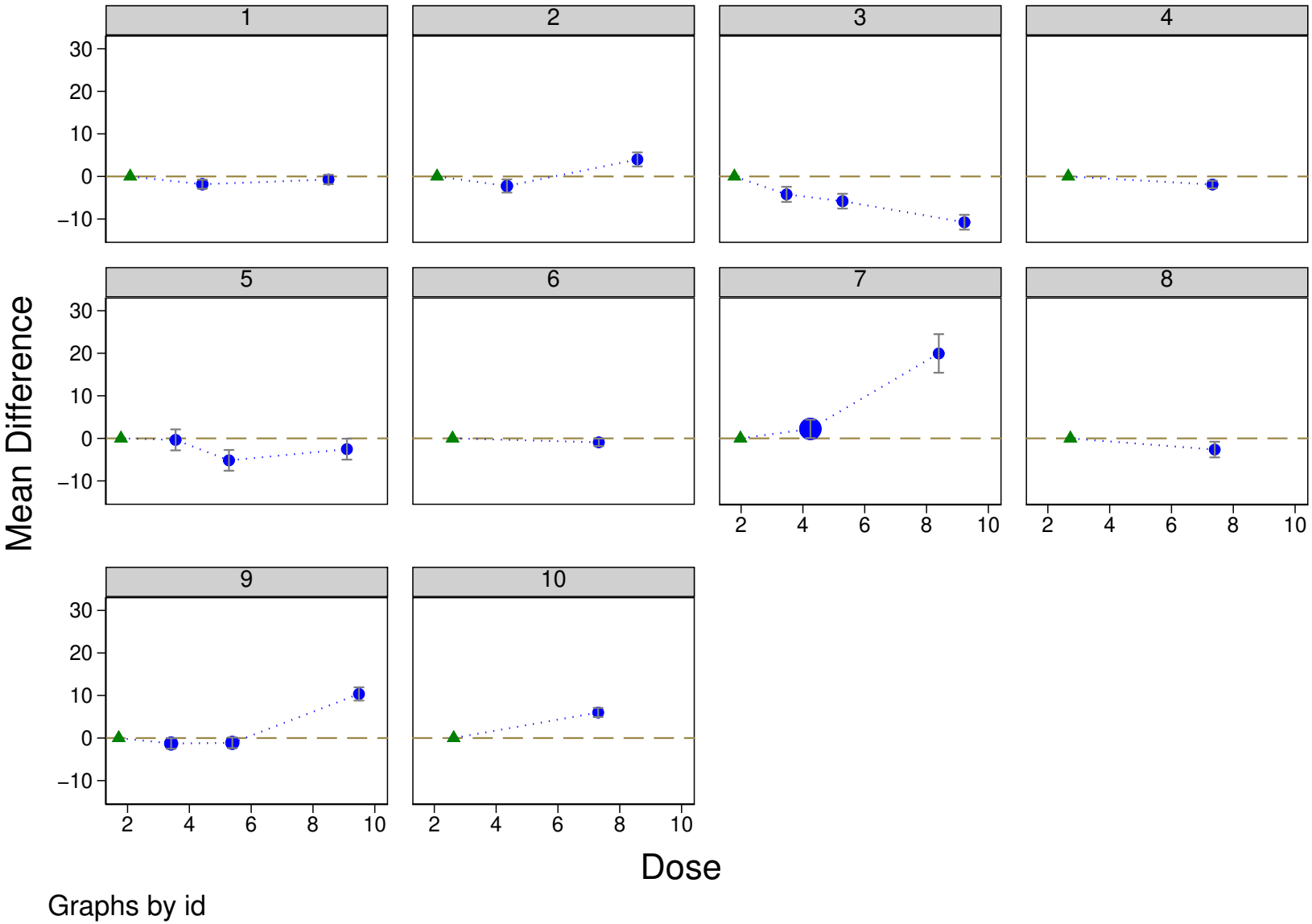
FIGURE 18.4
Alcohol intake and colorectal cancer rate ratios in the Health Professionals Follow-up Study using (a) 0 grams/day and (b) 9.5 grams/day as referent. Summarized data (dots) were fitted with a dose-response model assuming a linear trend (solid line). Horizontal gray lines represent the width of the exposure interval.

Orsini, N., and Spiegelman D. Meta-Analysis of Dose-Response Relationships. Chapter 18. in *Handbook of Meta-Analysis*. Chapman and Hall/CRC, 2020. 395-428.

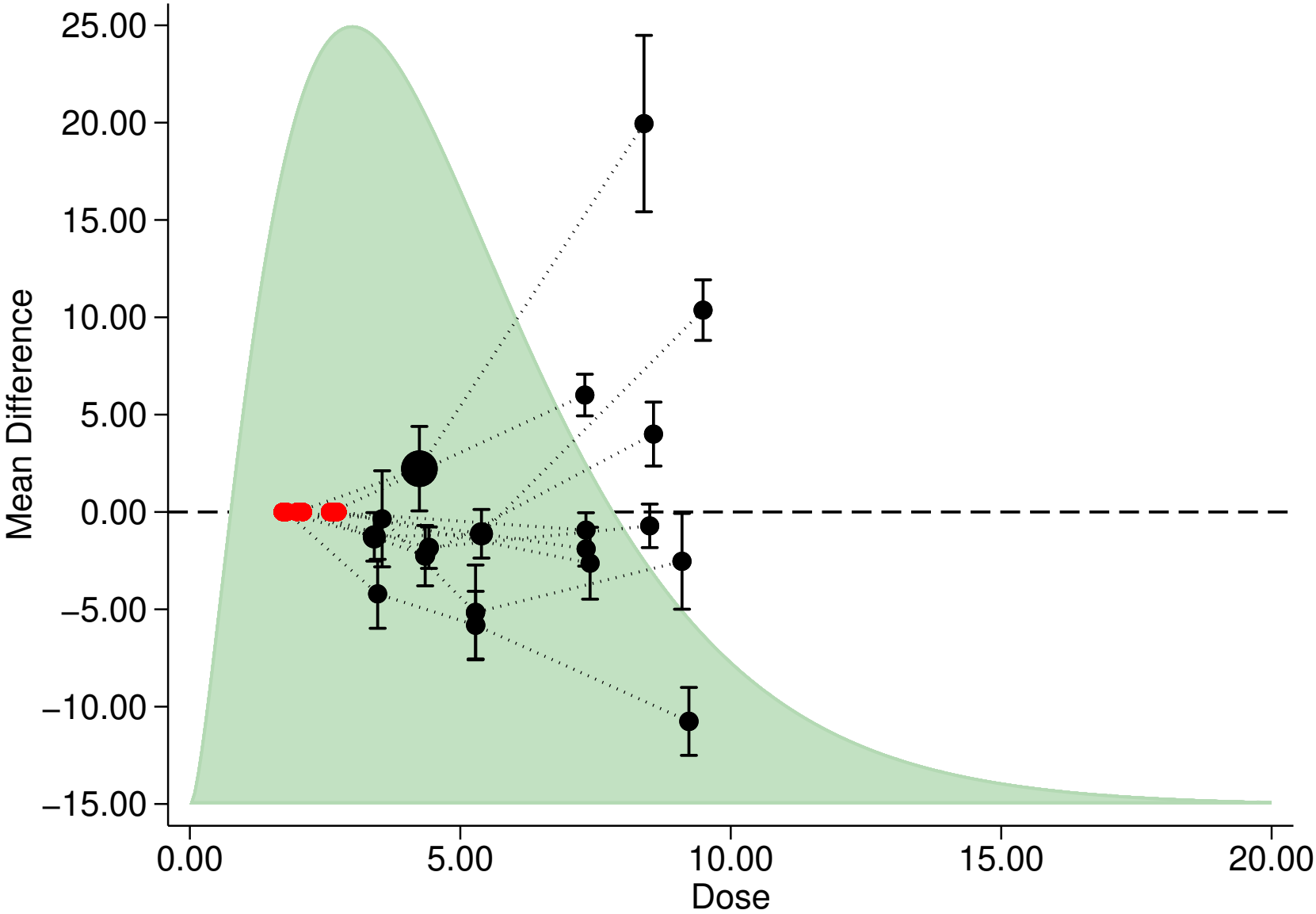
Experimental data, mean difference

id	dose	md	semd	sd	n
1	2.09	0.00	0.00	10.20	667
1	4.42	-1.83	0.54	9.63	667
1	8.50	-0.71	0.57	10.63	666
2	2.09	0.00	0.00	10.02	334
2	4.35	-2.24	0.79	10.39	333
2	8.57	4.00	0.84	11.56	333
3	1.78	0.00	0.00	9.93	250
3	3.47	-4.21	0.90	10.27	250
3	5.28	-5.81	0.89	9.90	250
3	9.23	-10.76	0.89	9.96	250
4	2.66	0.00	0.00	9.97	1000
4	7.33	-1.90	0.45	10.25	1000
5	1.79	0.00	0.00	10.20	125
5	3.55	-0.35	1.26	9.70	125
5	5.28	-5.16	1.24	9.42	125
5	9.10	-2.53	1.25	9.64	125

Visualization of data from 10 studies



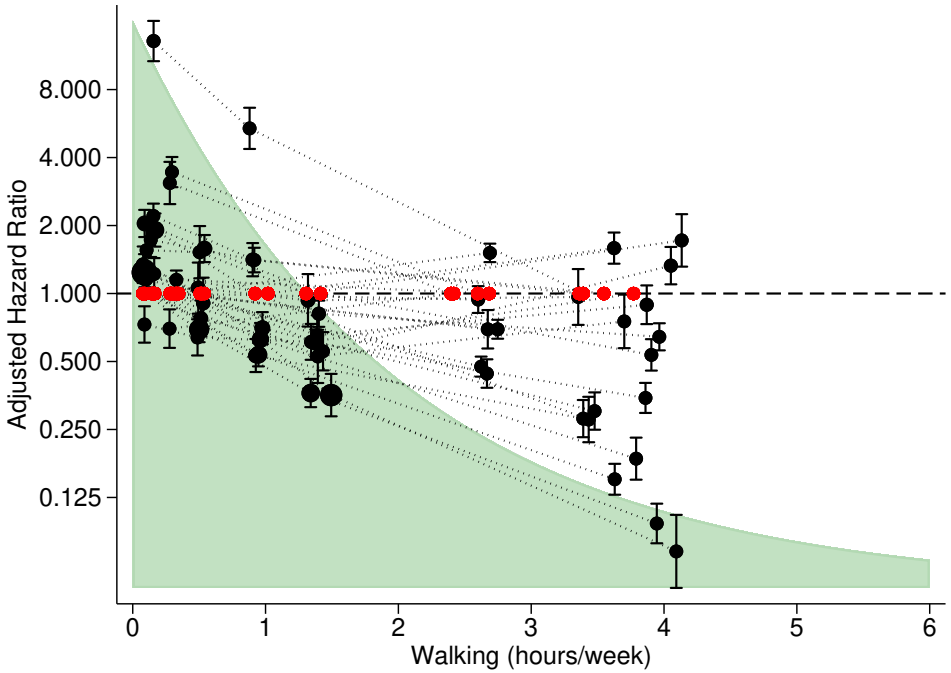
Overlay data on the same plot region



Main features of the data

- The response is typically exposure effect
- Exposure effects within a study are typically positively correlated
- Number of exposure contrasts may vary across studies
- Doses being compared may vary across studies
- Number of regression coefficients may be greater than the number of contrasts within a study

Challenge of balancing model complexity and aggregated data



Orsini, N. Weighted mixed-effects dose-response models for tables of correlated contrasts. *Stata Journal*. 2021, Vol.21 (2), p.320-347.

Challenge of statistical fallacies

Failing to reject the null hypothesis (either a $p > 0.05$ or equivalently a 95% confidence interval covering the null) is frequently and mistakenly interpreted as evidence for the null hypothesis.

In both test of hypothesis and confidence intervals some selected extreme quantiles (i.e. 0.025, 0.975) are routinely used to allocate a degree of trust about claims related to the unknown parameter of interest in light of the collected data and assumed statistical model.

The fact that in a dose-response meta-analysis there might be several contrasts of interest and the fact that uncertainty increases by definition with the distance from the chosen referent, there might be more occasions for this fallacy to occur.

Weighted Mixed Effects Model

A one-stage approach for meta-analysis of summarized dose-response data has been proposed in the general framework of linear mixed effects model (*Stat Meth Med Res*, 2019).

$$\hat{\boldsymbol{\gamma}}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\epsilon}_i$$

$$\mathbf{b}_i \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Psi})$$
$$\epsilon_i \sim \mathcal{N}(\mathbf{0}, \mathbf{S}_i)$$

$\hat{\boldsymbol{\gamma}}_i$ is the vector of empirical constrasts (i.e. mean differences, log odds ratios, log hazard ratios) estimated relative to a common referent in the i-th study

It is implemented in `Stata` (`drmeta` command) and `R` (`dosresmeta` package).

Design matrix

Since the $\hat{\gamma}_i$ is a set of response contrasts relative to the baseline dose x_{i0}, $\mathbf{X}_i$ needs to be constructed in a similar way by centering the p transformations of the dose levels to the corresponding values in x_{i0}.

Let consider, for example, a transformation f; the generic j-th row of $\mathbf{X}_i$ would be defined as $f(x_{ij}) - f(x_{i0})$.

As a consequence $\mathbf{X}_i$ does not contain the intercept term ($\hat{\gamma}_i = 0$ for $x = x_{i0}$).

Random effects and residual error term

$\mathbf{b}_i \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Psi})$

The random-effects $\mathbf{b}_i$ represent study-specific deviations from the average study regression coefficients $\boldsymbol{\beta}$.

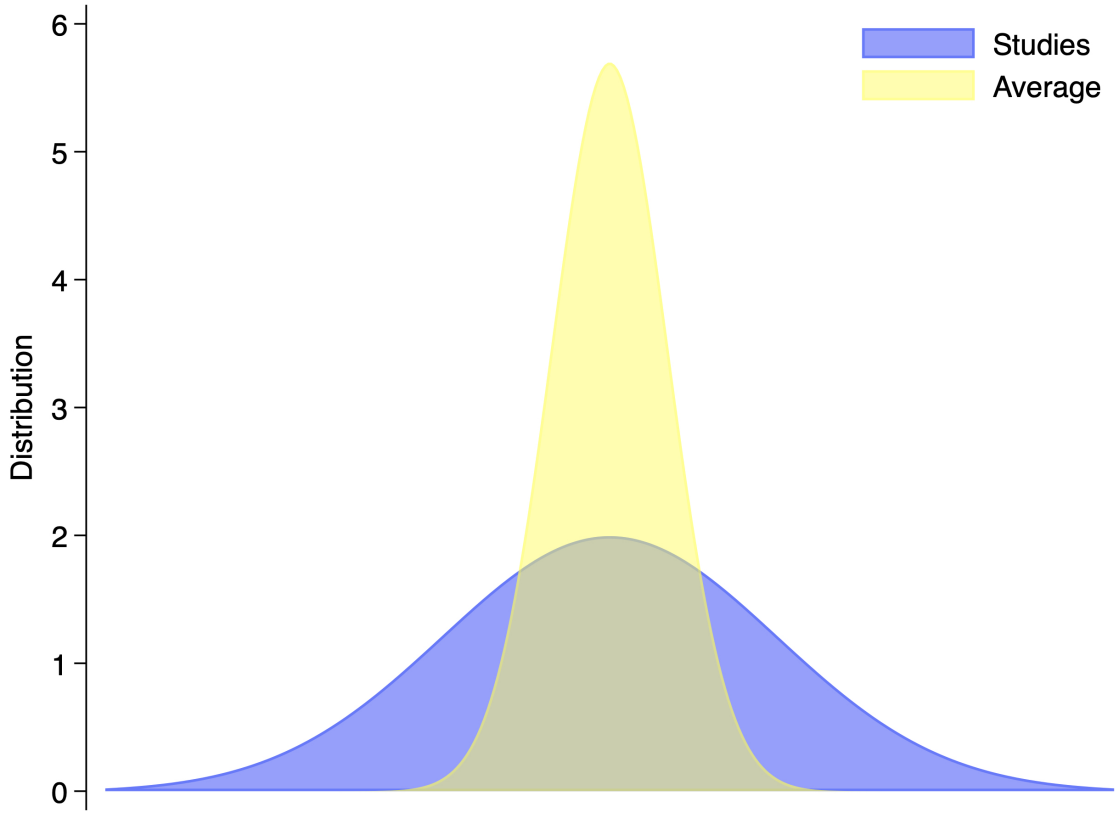
$\mathbf{Z}_i$ is the analogous design matrix for the random-effects.

The residual error term $\boldsymbol{\epsilon}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{S}_i)$, whose variance matrix $\mathbf{S}_i$ is assumed known.

$\mathbf{S}_i$ can be either given or approximated using available summarized data (*AJE*, 2012; *BMC Med Res Meth*, 2016).

Average study vs Individual studies

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



Uncertainty about the average study is smaller than the uncertainty of the individual studies.

Heterogeneity of a specific contrast

Let's get started by using a linear dose-response function in which one parameter, the slope β would be of primary interest.

$$\beta_i(x - x_0) \sim N(\beta(x - x_0), \tau(\beta_i(x - x_0)))$$

Consider a meta-analysis of I studies of the same size n, equal dose std deviation σ_{X_i}, and equal conditional outcome std deviation σ_{Y_i}

$$\tau(\beta_i(x - x_0)) = \sqrt{(x - x_0)^2(\widehat{SE}(\hat{\beta})^2 + \hat{\tau}^2)}$$

$$\widehat{SE}(\hat{\beta}) = 1/\sqrt{1/(\widehat{SE}(\hat{\beta}_i)^2 + \hat{\tau}^2)I}$$

$$\widehat{SE}(\hat{\beta}_i) = \sigma_{Y_i}/(\sigma_{X_i}\sqrt{n-1})$$

Quantiles of marginal and conditional dose-response

$$Q_p^C(\beta_i(x - x_0)) = \beta(x - x_0) + \phi^{-1}(p)\sqrt{(x - x_0)^2(\widehat{SE}(\hat{\beta})^2 + \hat{\tau}^2)}$$

$$Q_p^M(\beta(x - x_0)) = \beta(x - x_0) + \phi^{-1}(p)\sqrt{(x - x_0)^2\widehat{SE}(\hat{\beta})^2}$$

$\phi^{-1}(p)$ is the p-quantile of a standard normal distribution

$Q_{0.5}^M = Q_{0.5}^C$ because $\phi^{-1}(0.5) = 0$

If $\tau^2 > 0$, then $|Q_p^C| > |Q_p^M|$

Interpretation of Q_p^M and Q_p^C, however, is always different.

Post-data quantile approach for inference

- The degree of confidence in a claim (inequality) regarding the unknown exposure effect for an average study is a number between 0.01 and 0.99 based on empirical data and assumed model.

  The degree of confidence in the claim $\beta(x - x_0)) < Q_p^M$ is p

- The degree of confidence in a claim (inequality) regarding the unknown exposure effects for a population of studies is a number between 0.01 and 0.99 based on empirical data and assumed model.

  The degree of confidence in the claim $\beta_i(x - x_0)) < Q_p^C$ is p

Analytical example

The random-effect linear dose-response mechanism is $\beta_i \sim N(0.5, 0.2)$. Consider $I = 10$ studies of the same size $n = 1000$, equal dose distribution $X \sim \chi 2(5)$, and equal conditional outcome std deviation $\sigma_{Y_i} = 10$. Using a dose of 5 units as referent we have that

$$\beta_i(x - 5) \sim N(0.5(x - 5), 0.2(x - 5)))$$

the standard error of the slope in any similar study would be

$$\widehat{SE}(\hat{\beta}_i) = 10/(\sqrt{5(2)}\sqrt{1000 - 1}) = 0.1$$

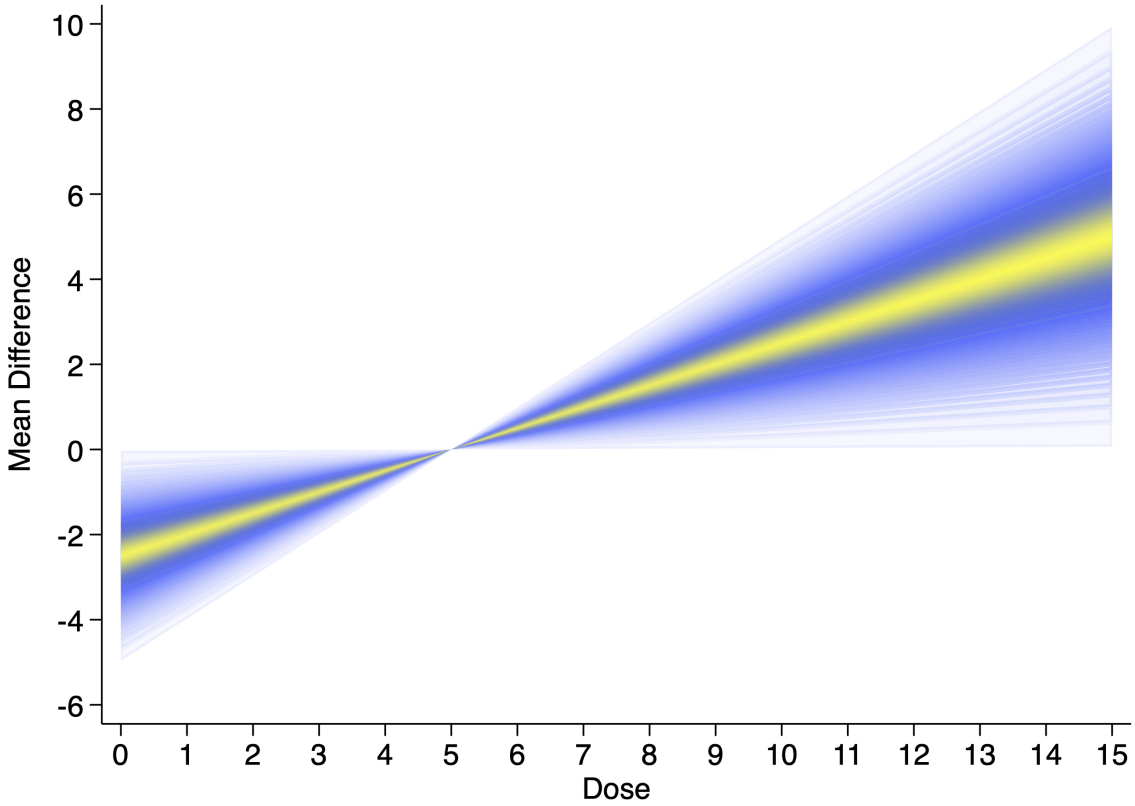
and the standard error of the slope for the average study would be

$$\widehat{SE}(\hat{\beta}) = 1/\sqrt{1/(0.1^2 + 0.2^2)10} = 0.07$$

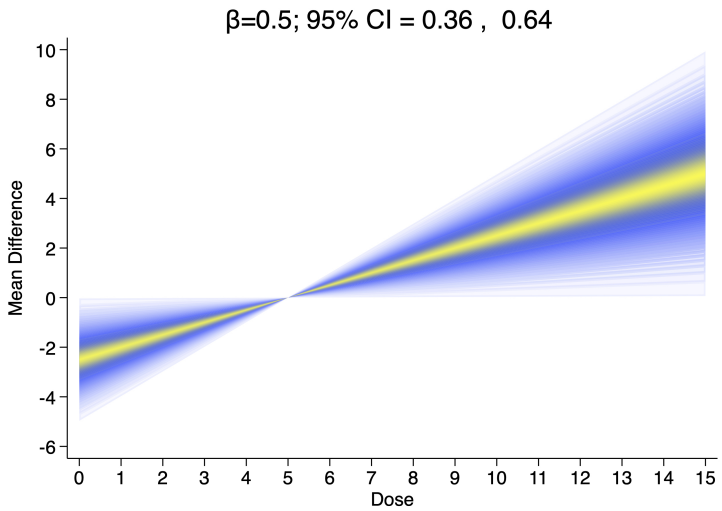
Marginal vs Conditional Quantiles

$$Q_p^C(\beta_i(x-5)) = 0.5(x-5) + \phi^{-1}(p)\sqrt{(0.07^2 + 0.2^2)(x-5)^2}$$

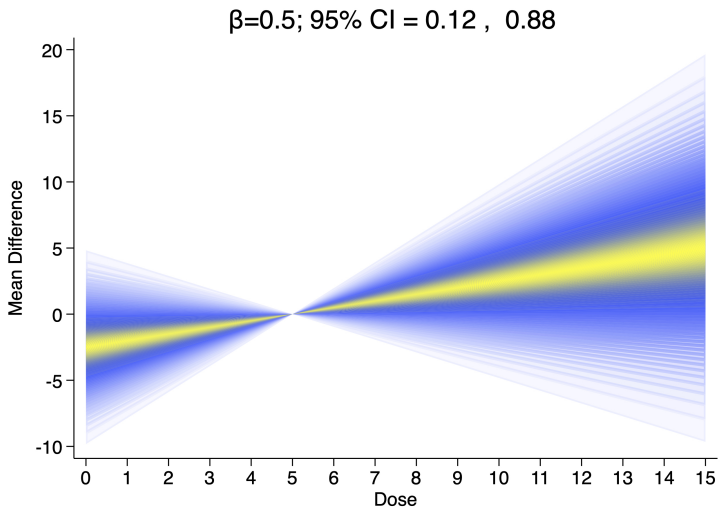
$$Q_p^M(\beta(x-5)) = 0.5(x-5) + \phi^{-1}(p)\sqrt{(0.07^2)(x-5)^2}$$



And so what?



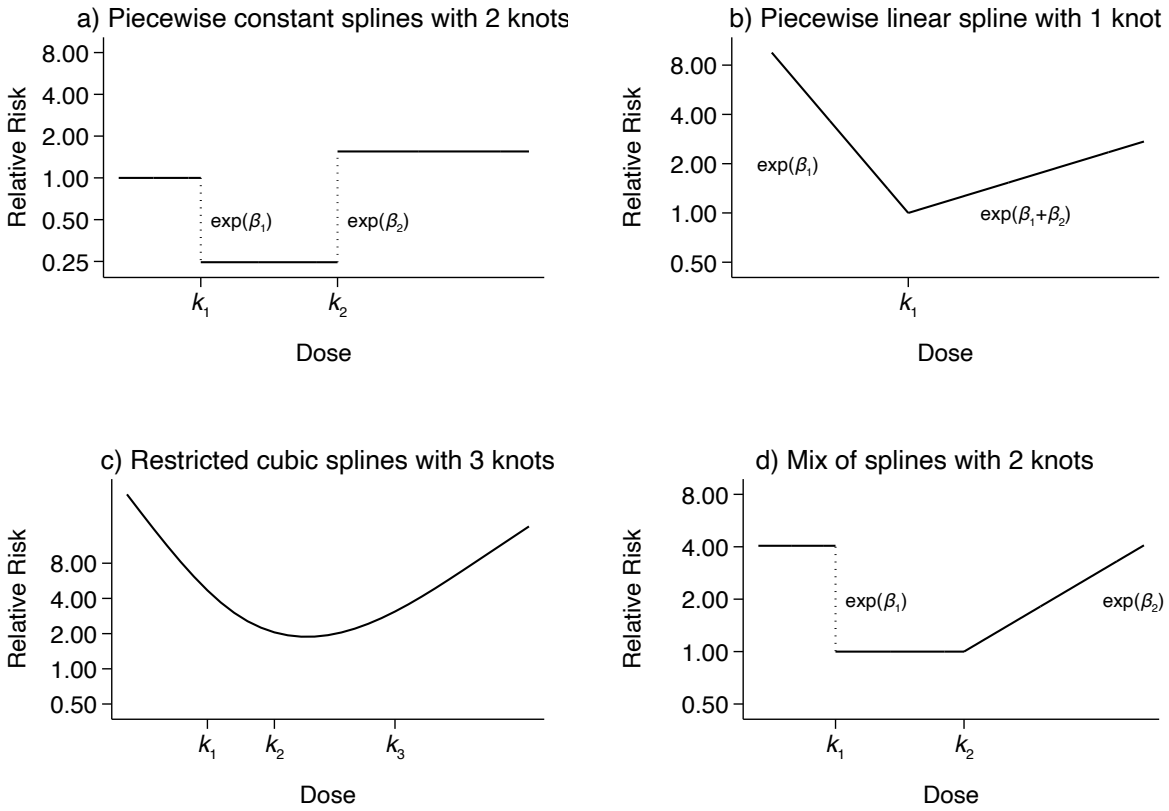
(a) $\tau = 0.2$



(b) $\tau = 0.6$

Figure: In Scenario b) a large number of conditional quantiles are in opposite direction relative to marginal quantiles

Moving beyond linear dose-response relationships



Orsini N, and Spiegelman D. *Meta-Analysis of Dose-Response Relationships*. Chapter 18. Handbook of Meta-Analysis. Ed. Schmid CH, Stijnen T, White, I. 2020. CRC Press.

Extend the reasoning

Let's consider two transformations (i.e. splines, fractional polynomials), saying $f_1(x)$ and $f_2(x)$, of the original dose.

$$\beta_{1i}(f_1(x) - f_2(x_0)) + \beta_{2i}(f_2(x) - f_2(x_0))$$

$$\begin{pmatrix} \beta_{1i} \\ \beta_{2i} \end{pmatrix} \sim \mathcal{N}\left(\begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix}, \begin{bmatrix} \xi_1 & \\ \xi_3 & \xi_2 \end{bmatrix} \right)$$

The model is in terms of 2 fixed-effects plus 2 variances and 1 covariance of the 2 random-effects.

At this point, it helps to use a compact matrix notation

$$\boldsymbol{\beta_i} \sim \mathcal{N}(\boldsymbol{\beta}, \boldsymbol{\Psi})$$

Quantiles for the marginal and conditional dose-response relationship

Marginal

$$Q_p^M = (\mathbf{X}^* - \mathbf{x}_0^*)\hat{\boldsymbol{\beta}} + \phi^{-1}(p)\mathrm{diag}[(\mathbf{X}^* - \mathbf{x}_0^*)V(\hat{\boldsymbol{\beta}})(\mathbf{X}^* - \mathbf{x}_0^*)']^{1/2}$$

Conditional

$$Q_p^C = (\mathbf{X}^* - \mathbf{x}_0^*)\hat{\boldsymbol{\beta}} + \phi^{-1}(p)\mathrm{diag}[(\mathbf{X}^* - \mathbf{x}_0^*)(V(\hat{\boldsymbol{\beta}}) + \hat{\boldsymbol{\Psi}})(\mathbf{X}^* - \mathbf{x}_0^*)']^{1/2}$$

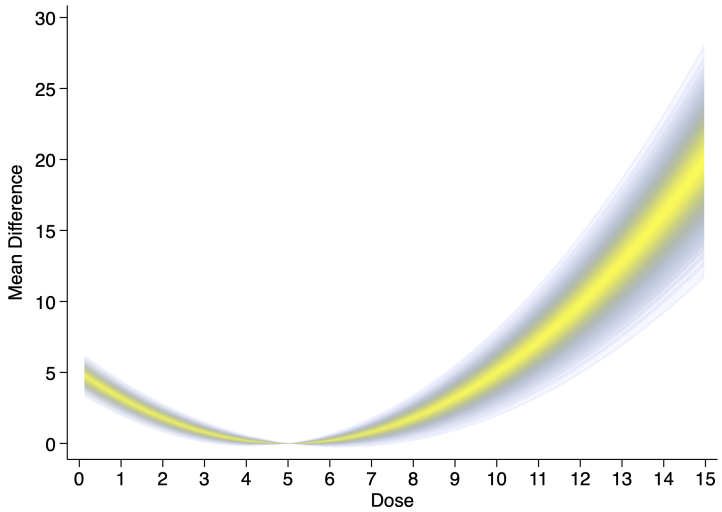
where

$\mathbf{X}^*$ indicates a matrix of user specified transformations

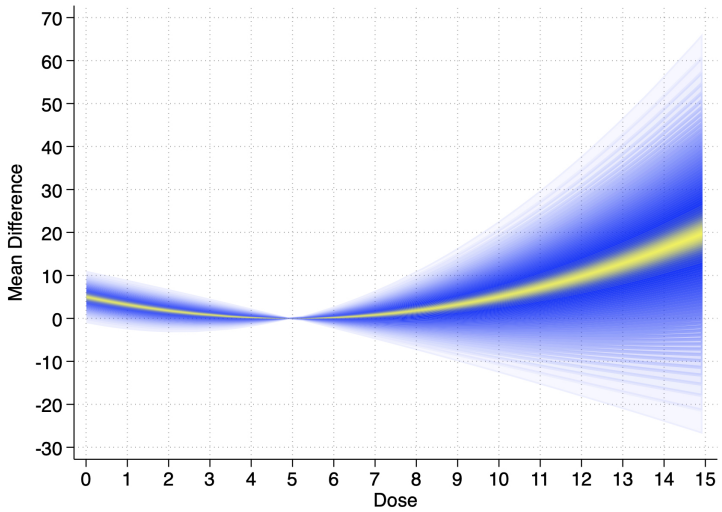
$\mathbf{x}_0^*$ indicates a matrix of reference values

Small and large non-linear heterogeneity

$$MD = -2(x - 5) + 0.2(x^2 - 5^2)$$



(a) $\xi_1 = 0.0001$, $\xi_2 = 0.0001$, $\xi_3 = 0$



(b) $\xi_1 = 0.01$, $\xi_2 = 0.01$, $\xi_3 = 0$

Figure: Apparently small differences in variance components can lead to large heterogeneity for extreme comparisons

Some informative post-estimation procedure would help

Ideally, it would be great to have a post-estimation command that

- works with a variety of dose transformations and outcome measures
- allows the user to choose between quantile of the conditional, marginal, or both
- allows the user to overlay the study-specific BLUPs
- easily provides both static and interactive visualizations

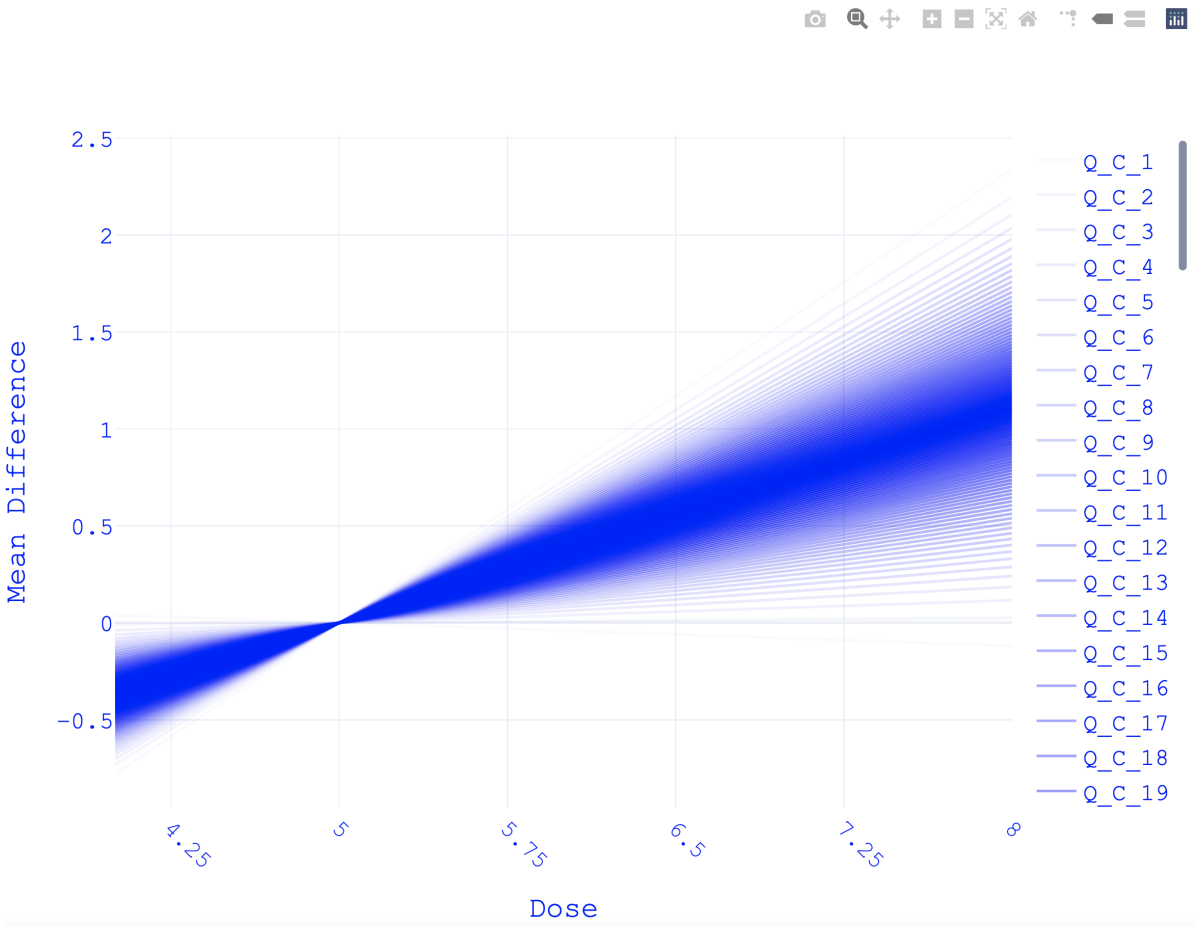
So I wrote `drmeta_het` using Plotly Python Graphing Library taking advantage of the recent Stata/Python integration.

Simulated Example

	id	md	dose	semd	n	sd
1.	1	0	2.020252	0	334	9.458647
2.	1	-.6599554	4.426369	.7682979	333	10.36173
3.	1	.9591057	8.731555	.7440263	333	9.754083
4.	2	-3.207253	1.784821	.8826443	250	9.898886
5.	2	-1.717937	3.514592	.8673572	250	9.555094
6.	2	0	5.421488	0	250	9.837545
7.	2	1.940711	9.397936	.8920666	250	10.10784
8.	3	0	1.801217	0	250	9.401782
9.	3	.627276	3.494548	.8673193	250	9.983344
10.	3	2.376793	5.359765	.862201	250	9.871885
11.	3	2.563129	9.262744	.8850933	250	10.366
12.	4	-.3530243	2.018016	.7970039	334	9.713749
13.	4	0	4.214327	0	333	10.83753
14.	4	.1312752	8.515213	.8070071	333	9.970876

Syntax of drmeta_het #1

```
drmeta_het , dose(4(.5)8) ref(5) eq(d) iqc
```



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Syntax of drmeta_het #2

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drmeta_het , dose(4(.5)8) ref(5) eq(d) iqc iqm
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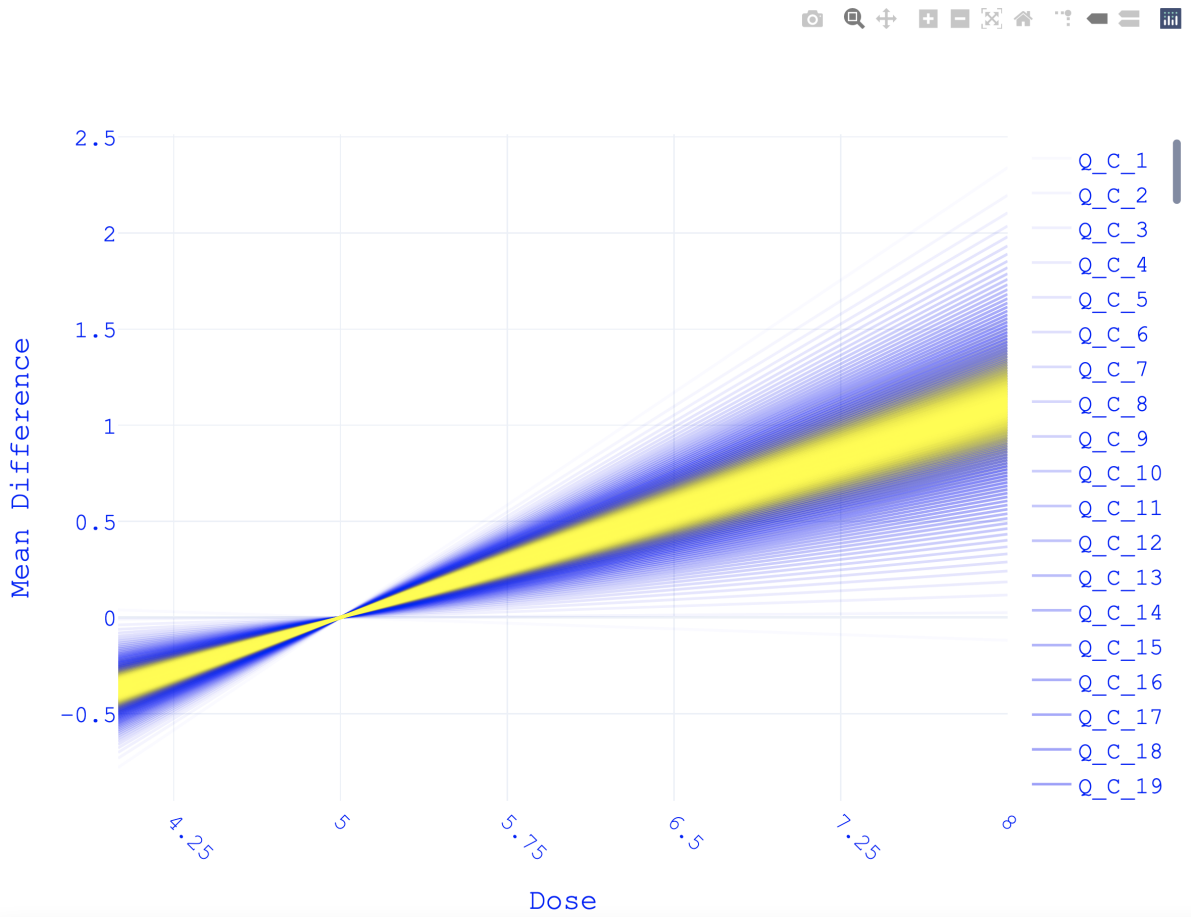

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Syntax of drmeta_het #3

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drmeta_het , dose(4(.5)8) ref(5) eq(d) iqc iqm iqcb
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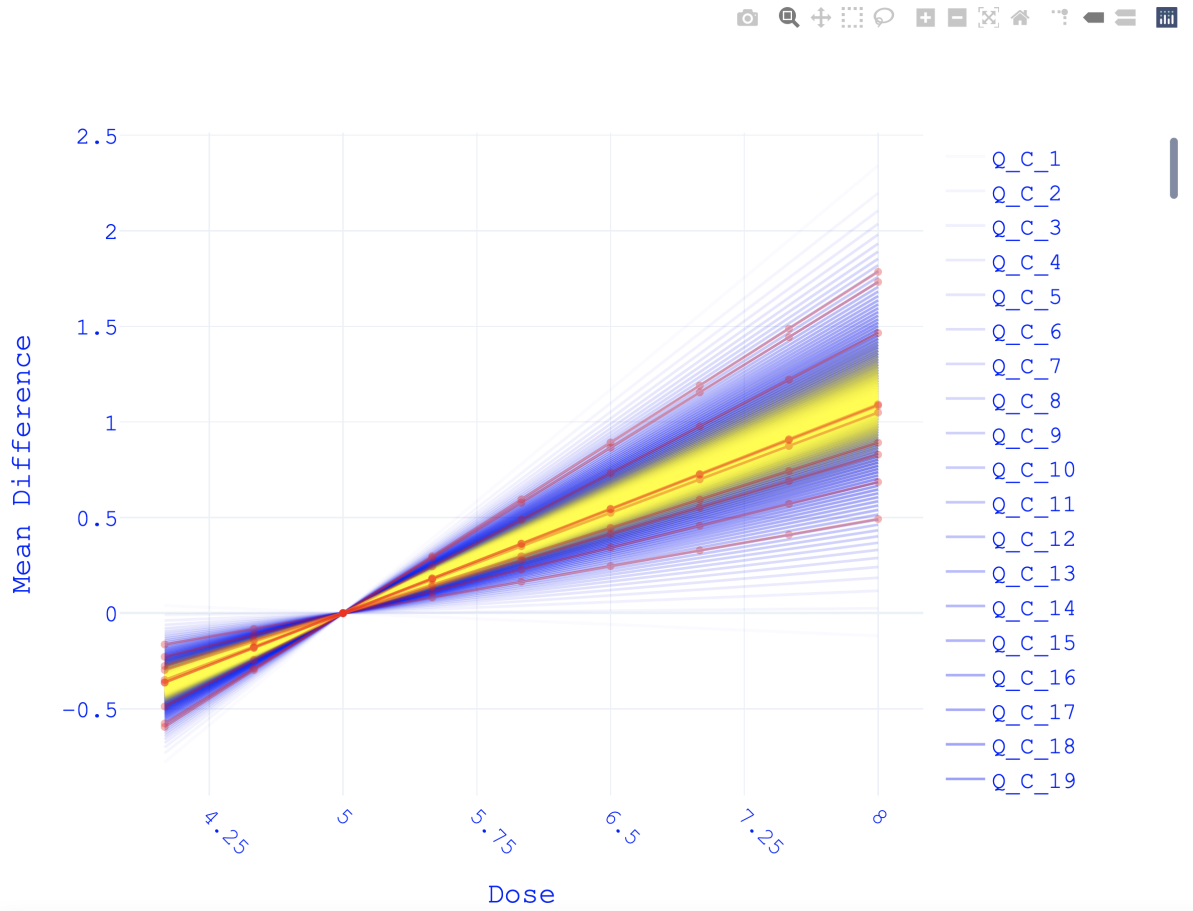

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Simulated Example: Walking and mortality

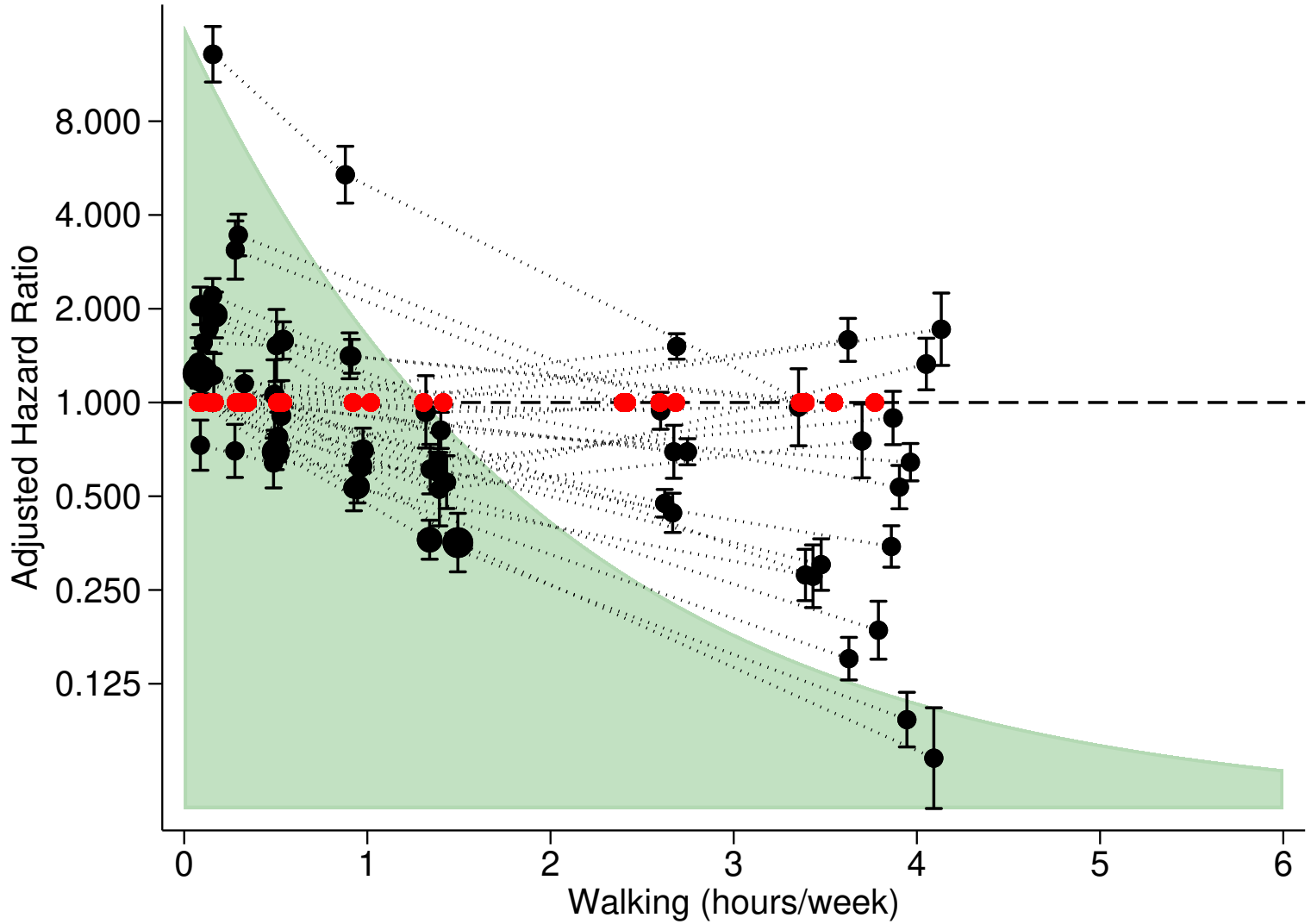
- Consider 30 prospective cohort studies investigating the association between baseline walking, measured in hours/week, and time until death, or end of follow-up (10 years), whichever came first.
- Age is inversely associated with walking levels and positively associated with higher mortality rates independently of walking levels.
- The true summary age-adjusted mortality hazard ratio is decreasing with higher walking levels with a threshold effect at 2 hours per week

$$HR = e^{-0.5(x-2)+0.5(x>2)(x-2)}$$

Snapshot of the aggregated data

id	walk	b	seb	case	py
1	0.3	1.13	0.11	229	777
1	2.4	0.00	0.00	137	1704
20	0.1	0.21	0.10	239	674
20	0.5	0.00	0.00	216	946
20	1.5	-1.04	0.11	133	1773
20	4.1	-2.63	0.19	32	2318
23	0.2	0.65	0.09	311	973
23	0.9	0.00	0.00	247	1765
23	3.4	-1.28	0.12	101	2752

Plotting the empirical contrasts



Piecewise linear weighted mixed-effects model

We specify a dose-response model with constant change for the age-adjusted log mortality hazard ratio associated with every 1 hour per week increase in walking before and after the knot at 2 hours per week.

$$\hat{\gamma}_{ij} = (\beta_1 + b_{1i})x_{ij} + (\beta_2 + b_{2i})I(x_{ij} > 2)(x_{ij} - 2) + \epsilon_{ij}$$

Stata output

```
. drmeta b walk walkplus, se(seb) data(py case) type(type)  id(id) ml

One-stage random-effects dose-response model     Number of studies =        30
Optimization   = ml                                  Number of obs =        61
           AIC = 37.55                               Model chi2(2) =    110.27
Log likelihood = -13.773298                            Prob > chi2 =    0.0000
```

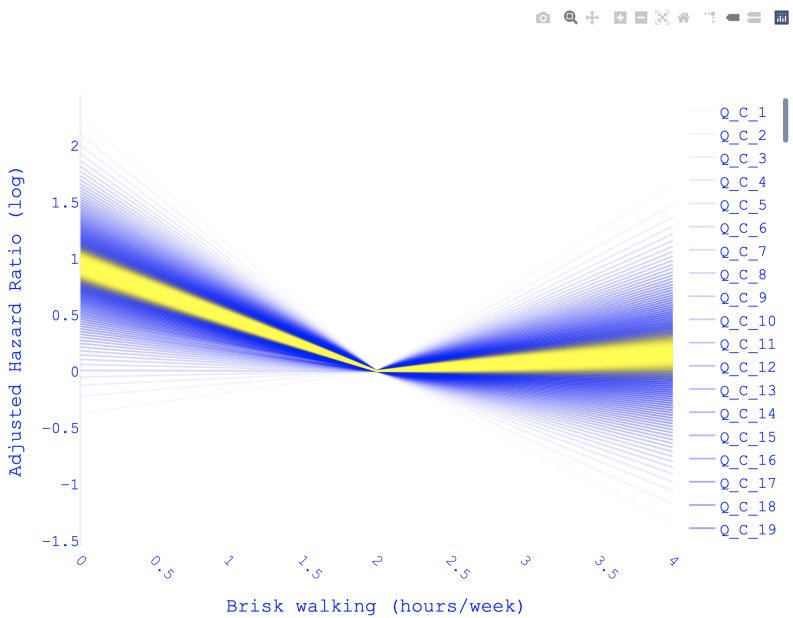
b	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
walk	-.4678671	.0536744	-8.72	0.000	-.573067	-.3626673
walkplus	.5432787	.0626324	8.67	0.000	.4205213	.666036

Random-effects parameters	Estimate
var(walk,walk)	.0766958
var(walkplus,walkplus)	.0507463
cov(walk,walkplus)	-.0136841

LR test vs. no random-effects model = **2713.6** Prob >= chi2(3) = **0.0000**

Syntax of drmeta_het

```
drmeta_het ,  eq(d  (d>2)*(d-2) ) dose(0(.1)4)  ///
    ref(2) ///
    yt("Adjusted Hazard Ratio (log)") ///
    xt("Brisk walking (hours/week)") ///
    iqm iqc  iqcbm
```



Click Here

Alcohol intake and colorectal cancer risk

We combine the dose-response relation between alcohol intake and colorectal cancer rate arising from 8 prospective cohort studies including 489,979 women and men participating in the Pooling Project of Prospective Studies of Diet and Cancer. A total of 3,646 cases and 2,511,424 person-years are included in this analysis.

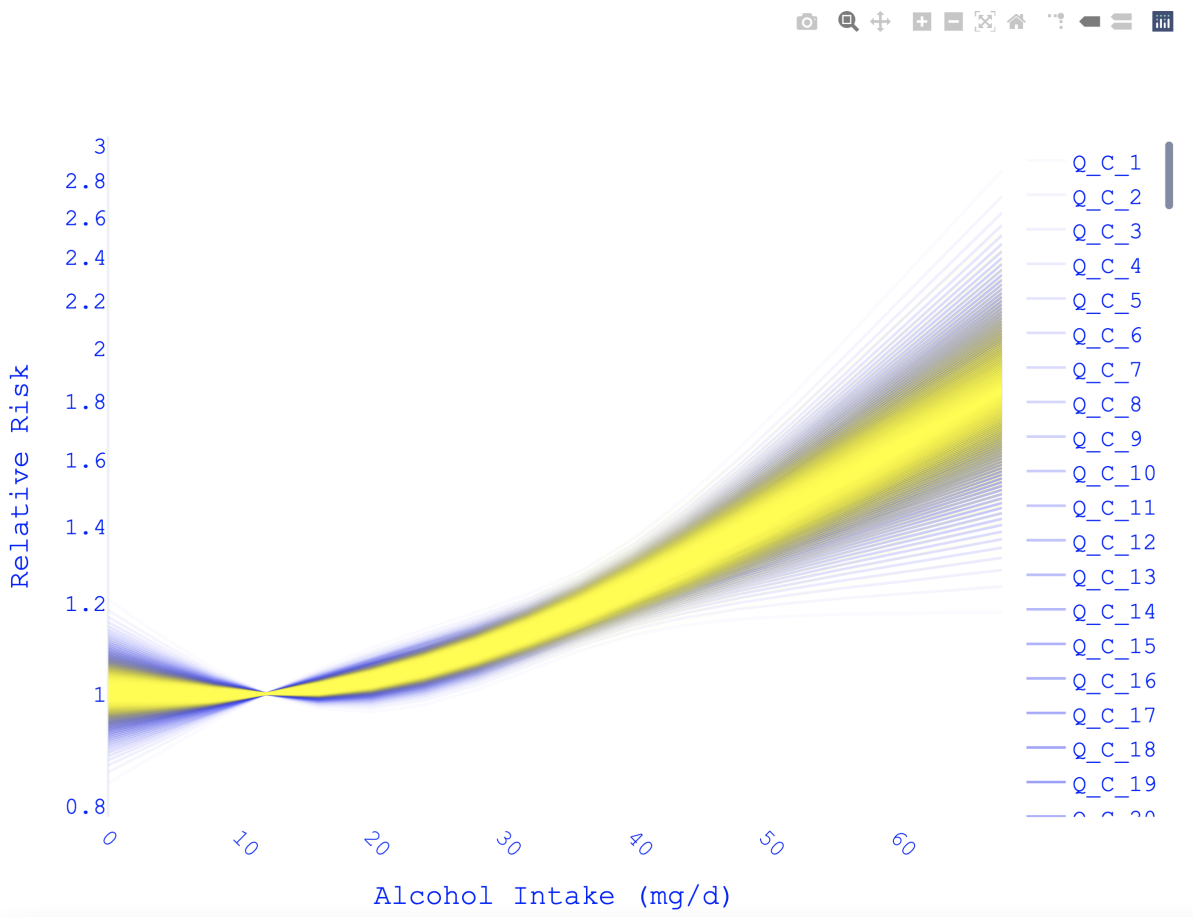
```
use ex_alcohol_crc.dta, clear
* Restricted cubic splines

mkspline doses = dose, nk(3) cubic
mat knots = r(knots)

drmeta logrr doses1 doses2 , data(peryears cases) ///
id(study) type(type) se(se) ml

drmeta_het , dose(0(4)70) ref(12) matk(knots) eform ///
yt("Relative Risk") xt("Alcohol Intake (mg/d)") iqc iqm
```

Alcohol intake and colorectal cancer risk



Click Here

Alcohol intake and colorectal cancer risk

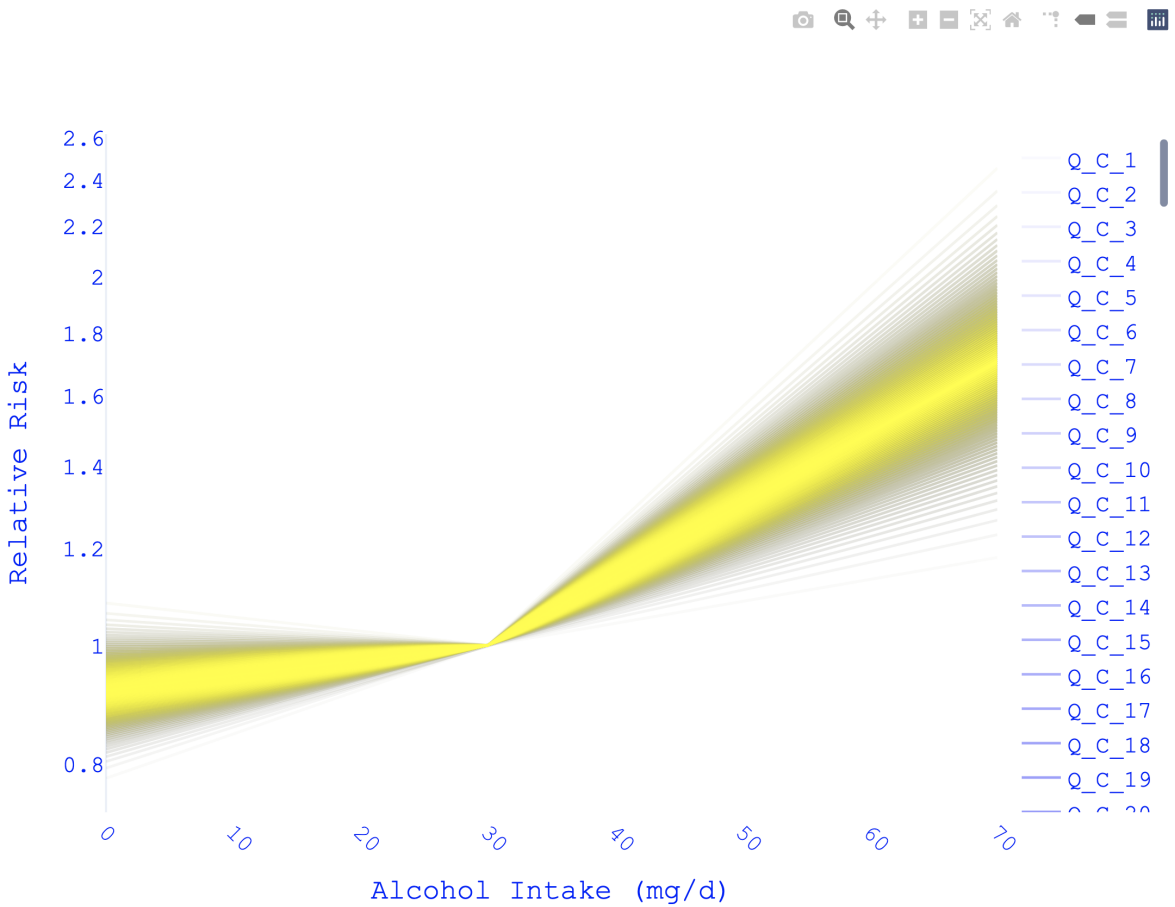
The drmeta_het command works even for piecewise linear splines.

```
gen dose_plus = (dose>30)*(dose-30)^1

drmeta logrr dose dose_plus,  se(se) ///
 data(peryears cases)  id(study) type(type) ml

drmeta_het , dose(0(1)70) ref(30) eform iqc iqm  ///
  eq(d (d>30)*(d-30)) ///
yt("Relative Risk") ///
xt("Alcohol Intake (mg/d)") iqc iqm
```

Alcohol intake and colorectal cancer risk



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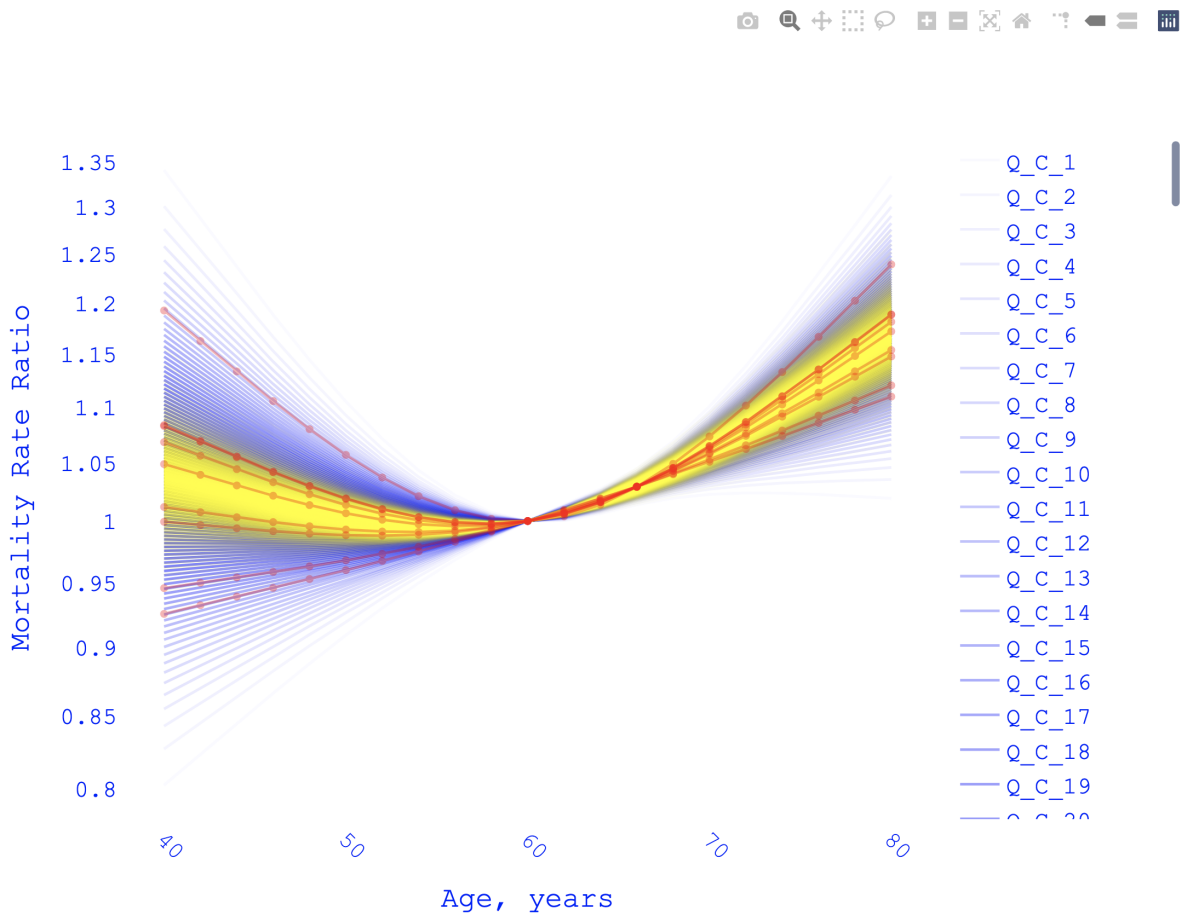
Age and and breast cancer mortality

We use data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The SEER program provides data about cancer statistics from several population-based registries in the USA (http://seer.cancer.gov) from San Francisco- Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Metropolitan Atlanta that here are considered as different studies. Analysis are based on 9 studies on prognostic factors for breast cancer survival including a total of 84,404 women. During 554,812 person-years, 8,520 women died from breast cancer.

Age and and breast cancer mortality



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Final remarks

- key assumption for deriving quantiles was a) a mixed model and b) the normal distribution of the random-effects
- key advantage of a quantile approach for inference is to learn in a continuous fashion from the data
- it can mitigate common statistical fallacies related to binary interpretation of inferential results (p-value, CI).
- the extent of heterogeneity can be explored point-by-point using quantiles of the conditional and marginal predicted dose-response
- interactive visualizations can help to identify exposure contrasts affected by more or less uncertainties

Selected References

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