HelmholtzZentrum münchen
German Research Center for Environmental Health

Department of Radiation Sciences

Institute of Radiation Protection

Dose-responses for cerebrovascular and heart diseases in atomic bomb survivors - an analysis involving multi-model inference techniques

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HELMHOLTZ ASSOCIATION

Overview of presentation

- HMGU/ISS studies on cardiovascular diseases in A-bomb survivors
  - Data
  - Models used
  - Data fitting techniques
  - Multi-model inference
  - Results + Conclusions

Data

LSS Circulatory Disease Mortality Data (lsscvd10.dat; Shimizu et al. 2010)

All circulatory diseases (ICD-9 390-459)

“Stroke” (correct: cerebrovascular diseases (CbVD), 430-438)

Heart diseases (393-429, excl. 401, 403, 405)

Follow-up: 1950 – 2003

86611 survivors with 3294282 person-years

9622 deaths from CbVD

8463 deaths from heart diseases

Models used..

ERR model $h = h_0(c, s, a, b) \times (1 + ERR(D, s, a, e))$

EAR model $h = h_0(c, s, a, b) + EAR(D, s, a, e))$

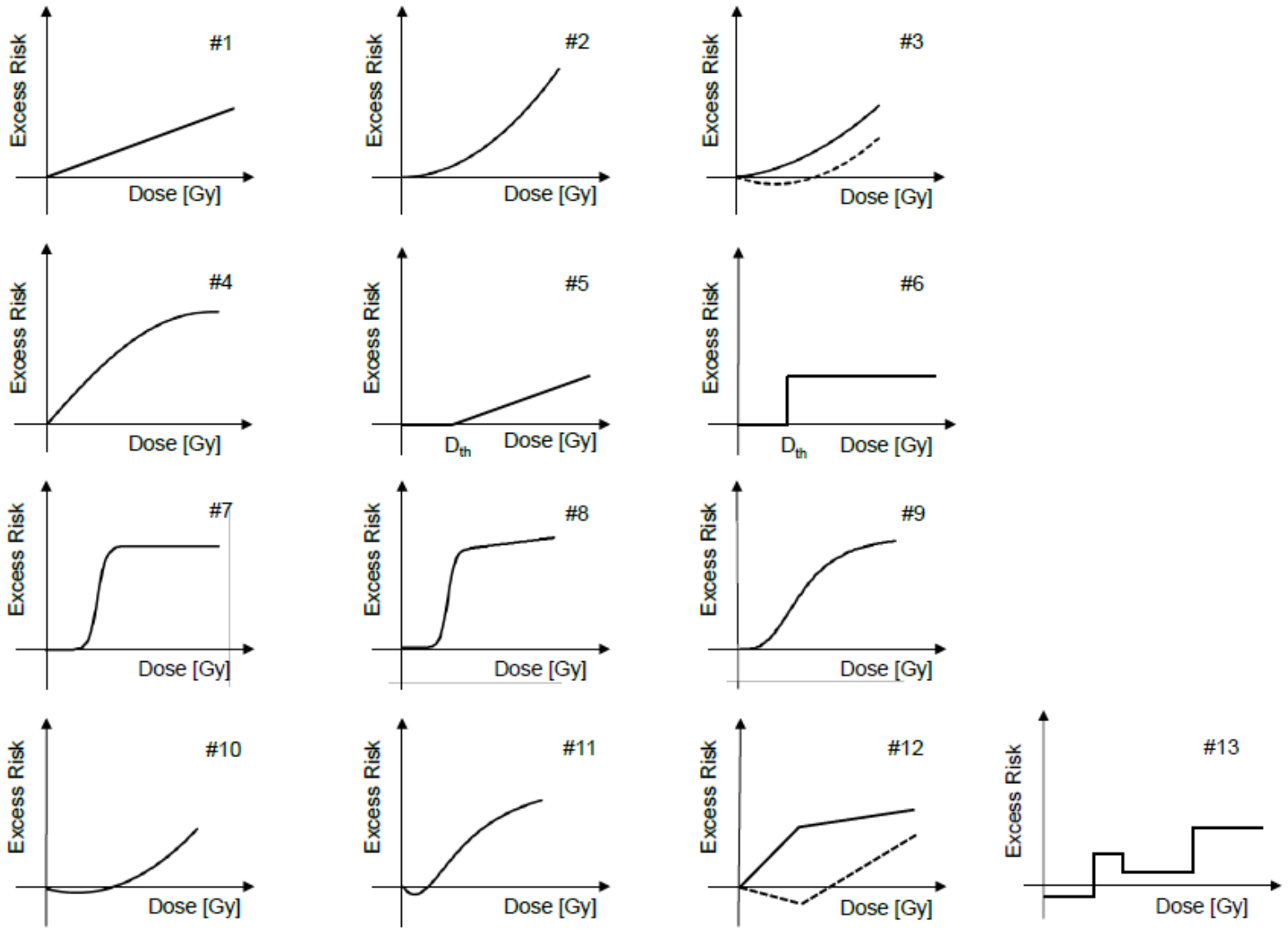
$h_0(c, s, a, b)$ "Preston baseline model": modified exp-function that depends on city c, sex s, attained age a and birth year b

$ERR(D, s, a, e)$ Excess risk from radiation with dose-effect modifiers that depend on sex, age attained and age at exposure

$$ERR(D) \times \exp(\mathrm{dem}_1 \cdot \mathrm{sex} + \mathrm{dem}_2 \cdot \frac{e-30}{10} + \mathrm{dem}_3 \cdot \ln\frac{a}{70})$$

$ERR(D)$ 13 empirical models

Models used..


#1
Excess Risk
Dose [Gy]
#2
Excess Risk
Dose [Gy]
#3
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#4
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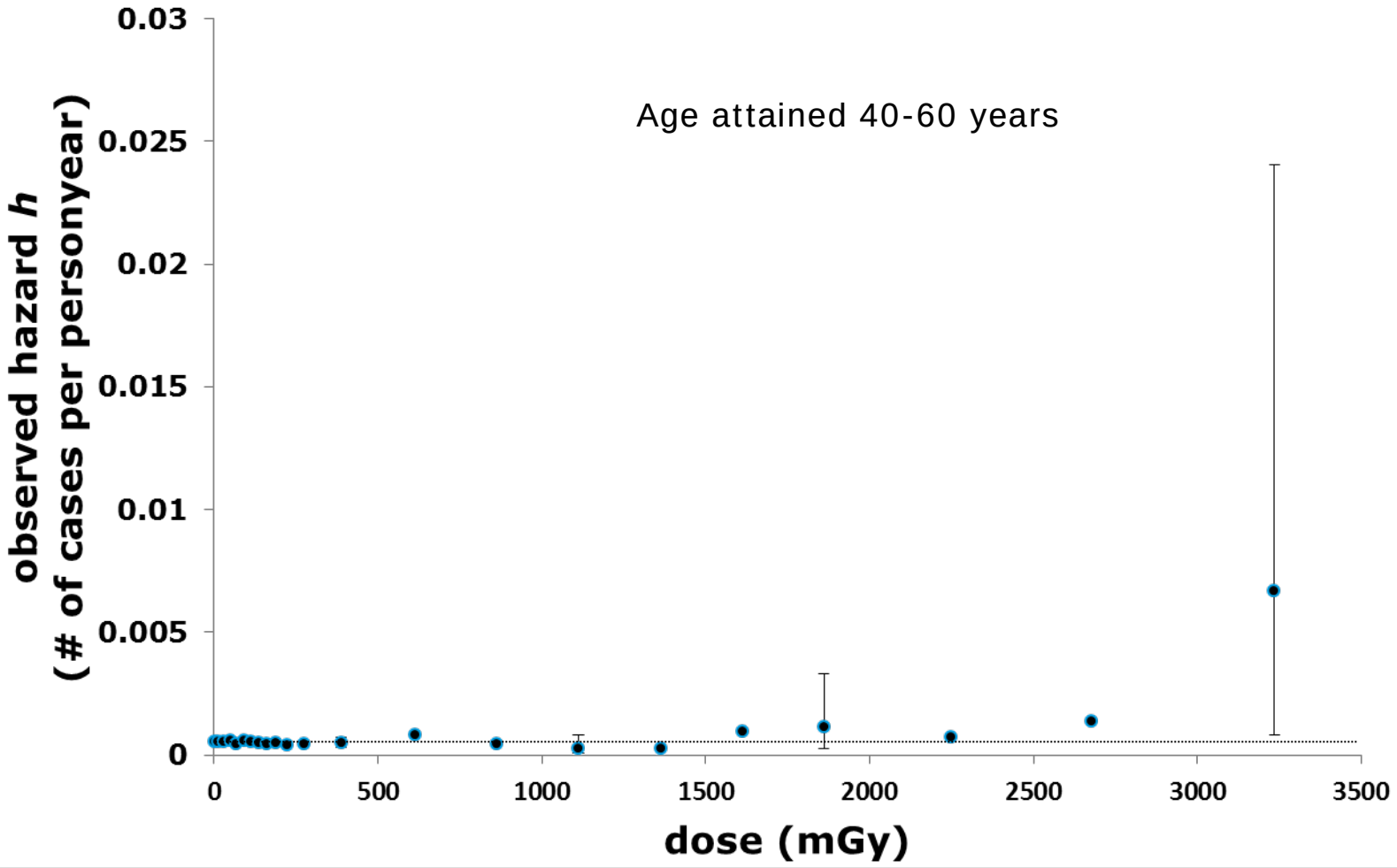
#13
Excess Risk
Dose [Gy]

Why so many models?

Shimizu et al. 2010 data: mortality from heart diseases; data stratified according to dose and age attained



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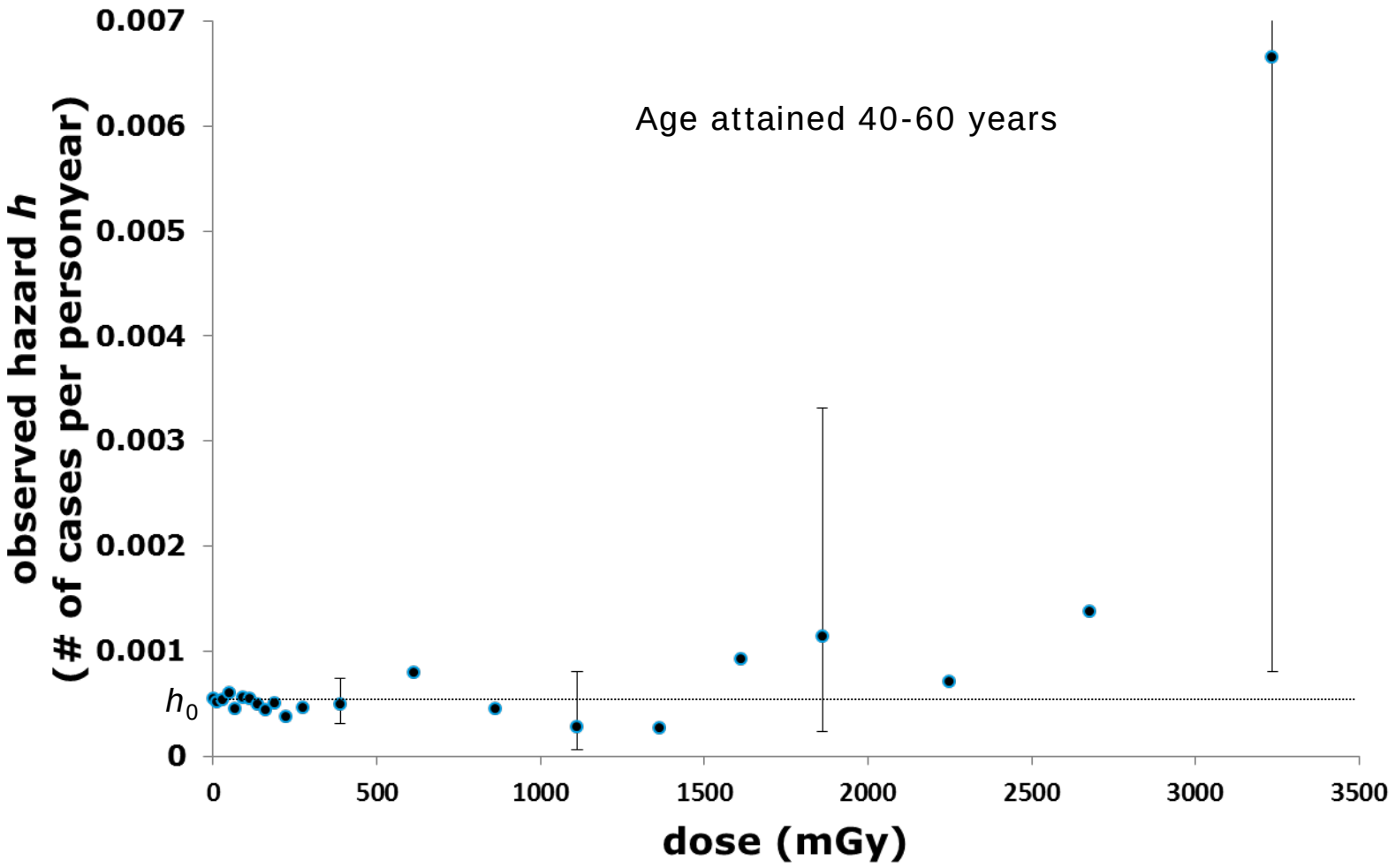

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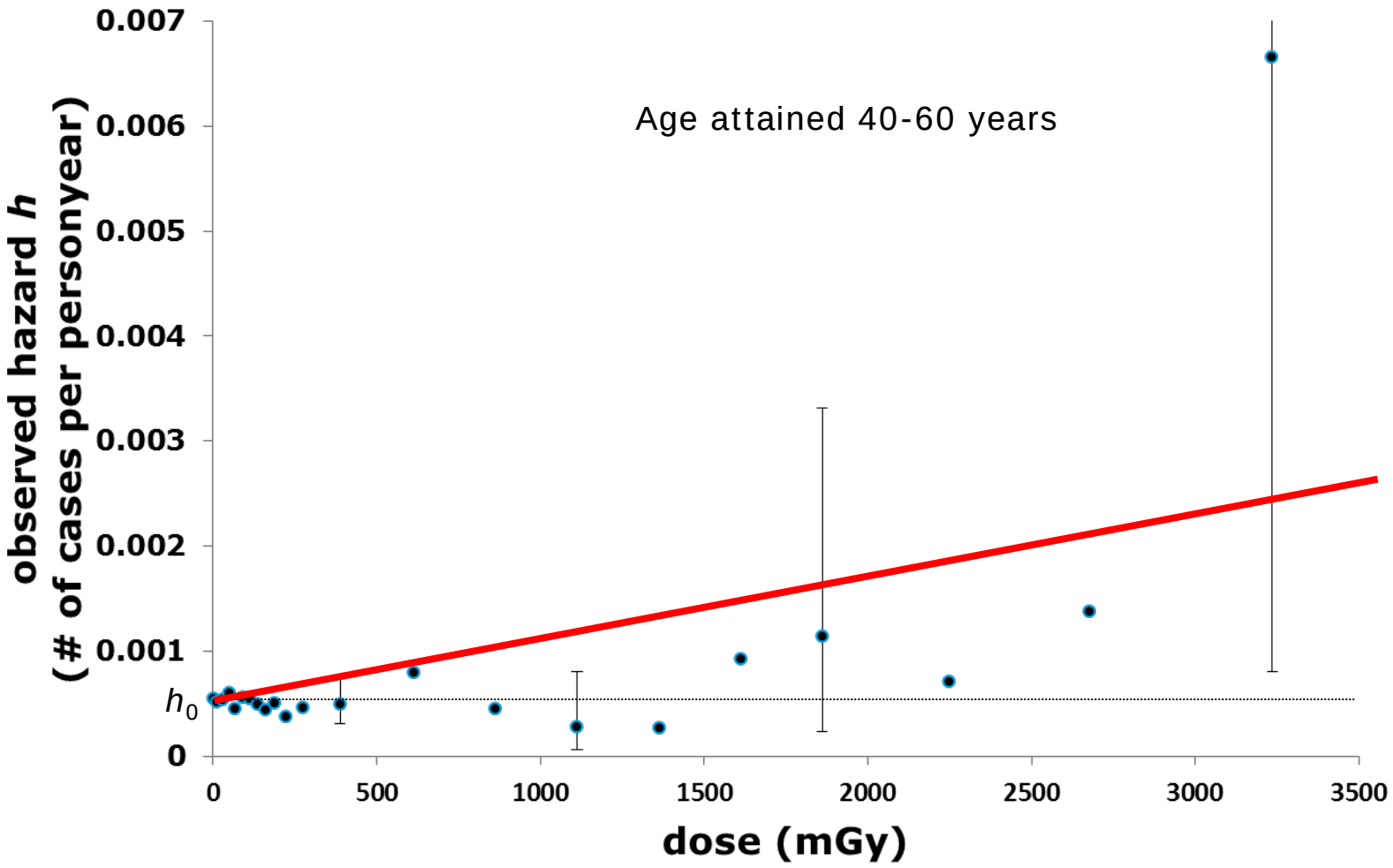

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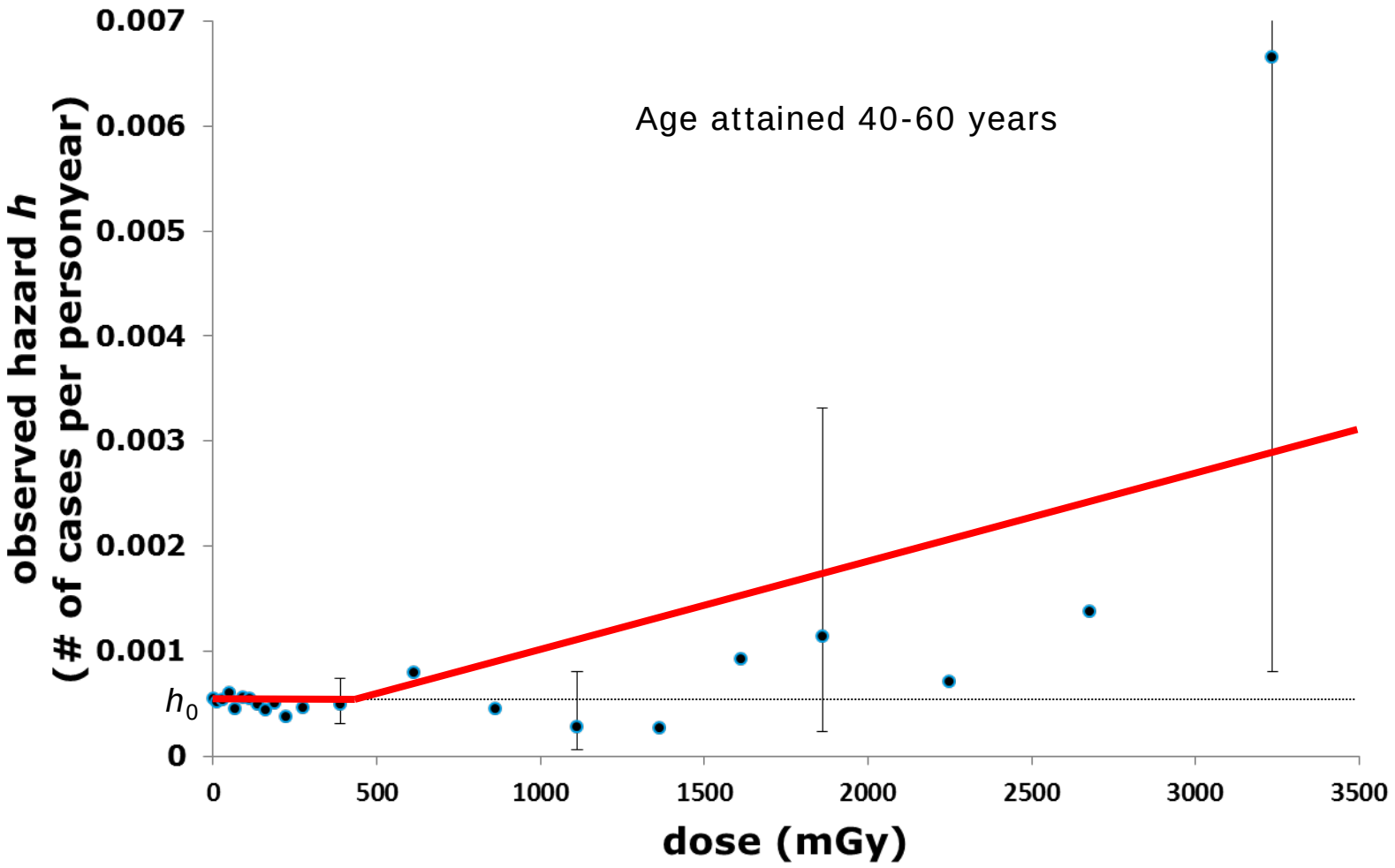

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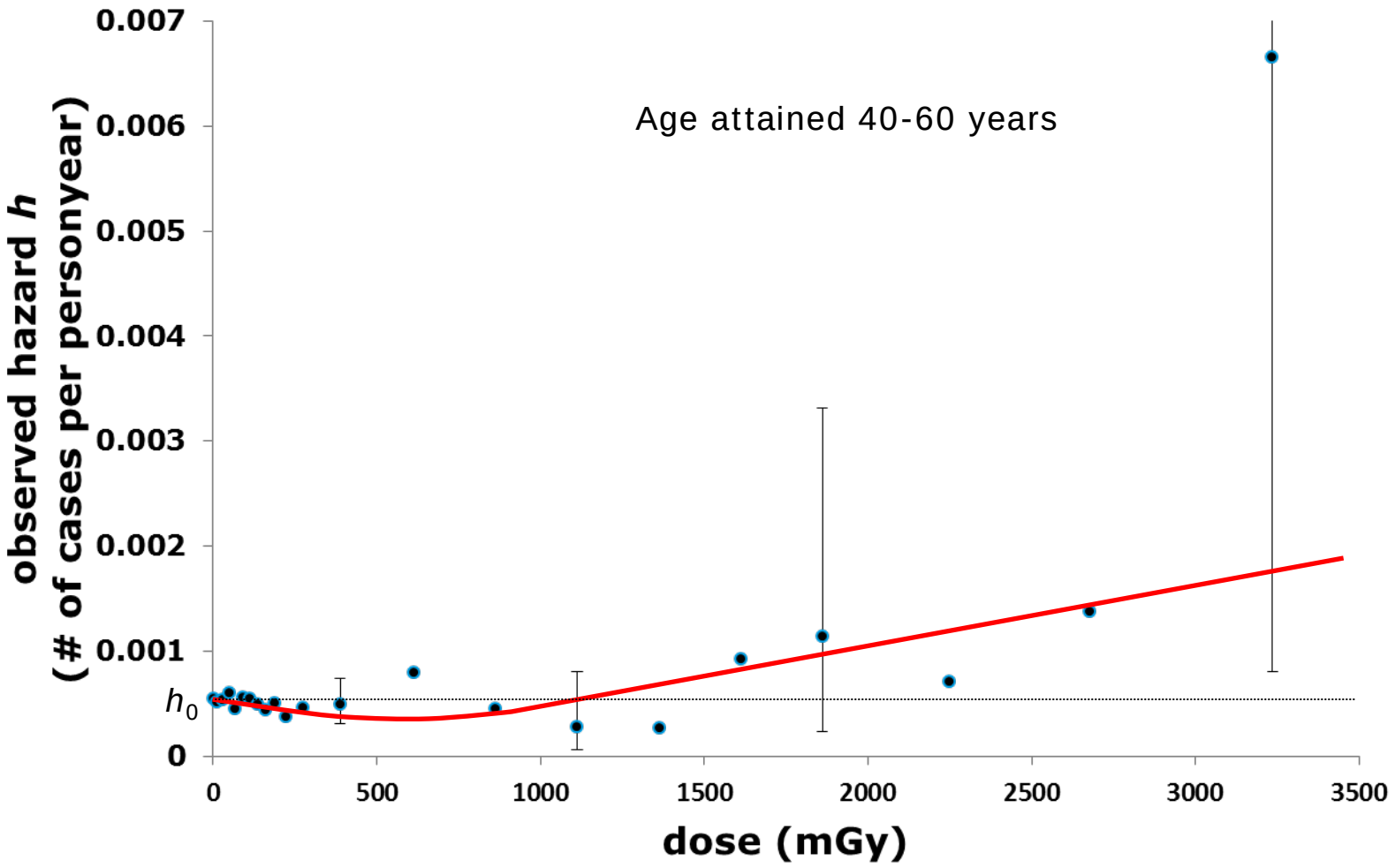

Models used..

Hazard rates $h > h_0$ represent radiation-induced cases (mortalities)

Hazard rates $h < h_0$ represent negative excess rates

The classical way to describe the radiation-induced excess rate (and also moderate negative excess rates) are ERR- and EAR-models:

ERR-model $h = h_0(c, s, a, b) \times (1 + ERR(D, s, a, e))$

EAR-model $h = h_0(c, s, a, b) + EAR(D, s, a, e))$

Data fitting techniques

MECAN software (by Ch. Kaiser): model fitting and MMI in one run;
C++ code

- Maximum likelihood method → maximum likelihood estimates (MLE)
- Poisson regression because data are grouped

$$-\ln(L) = \sum_i \left[\Lambda_i - n_i + n_i \ln\left(\frac{n_i}{\Lambda_i}\right) \right]$$

n_i observed # of cases in group i

Λ_i calculated (expected) # of cases in group i: $PY_i \times h_{i,M}(\theta)$

ERR model $h = h_0(c, s, a, b) \times (1 + ERR(D, s, a, e))$

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- Search algorithm: MINUIT2
- deviance: = -2 × ln(Max$L$)

Multi-model inference

- A heuristic method for superposing different models that fit the data about equally well

- Burnham and Anderson 2002, Model selection and multimodel inference, Springer

- Claesken and Hjort 2008, Model selection and model averaging, Cambridge Univ. Press

$$\hat{\mu} = \sum_{i=1}^{m} w_i \hat{\mu}_i \qquad w_i \propto \exp(-0.5\,\mathrm{AIC}_i)$$

$$SE(\hat{\mu}) = \sum_{i=1}^{m} w_i \sqrt{Var(\hat{\mu}) + (\hat{\mu}_i - \hat{\mu})^2}$$

Determination of dose-responses via MMI

1.) Reproduce Preston's fit of data for CbVD and heart diseases using his baseline model h_0 combined with ERR-LNT model.

2.) Streamline Preston's baseline model: test each baseline parameter for its significance by setting it to zero and refitting all others. Use likelihood-ratio test (LRT) to decide.
→2 streamlined baseline models:

15 baseline parameters for CbVD (-14 compared to Preston)
20 baseline parameters for heart diseases (-9)

3.) Combine all 13 empirical models with the streamlined baseline-models either as ERR or EAR models and fit them to the data. Use LRT to eliminate nested models
→ 2 sets of non-nested models

4.) For each non-nested model calculate $AIC = dev + 2 \times N_{par}$ & AIC-weight w_i. Perform Monte Carlo simulations of ERR or EAR using the MLEs of all non-nested models taking account of AIC-weights. Then, for each set of preselected values of age attained, age at exposure and dose, the created model-specific probability density functions are merged.

Determination of dose-responses via MMI

Ad 4. *AIC*-weight: $w_i \propto \exp(-0.5AIC_i)$

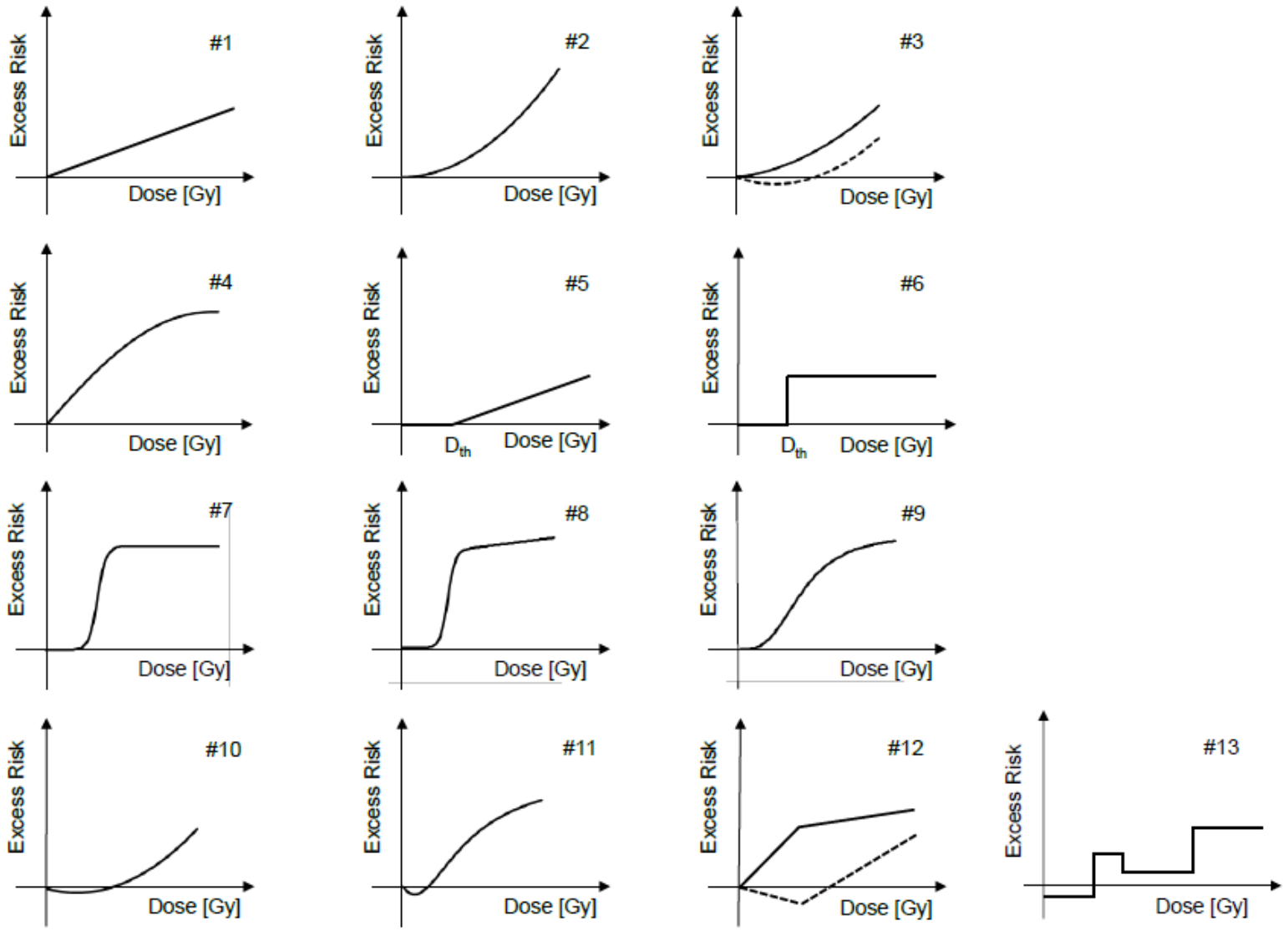
Multiply *AIC*-weight with 10^4 → gives number of iterations for the Monte Carlo simulations to be performed for MMI.

For example: for agex = 30 yrs, age = 70 yrs and for range of doses (0 to 3 Gy) perform MC sims with e.g. 3000 calculations using best estimates of 1st non-nested model → 3000 *ERR*-values that make up 1 pdf for agex=30, age=70, dose=0.01 Gy
3000 *ERR*-values that make up 1 pdf for agex=30, age=70, dose=0.02 Gy
…

Perform MC simulation with 7000 calculations with best estimates of 2nd non-nested model → 7000 *ERR*-values that make up 1 pdf for agex=30, age=70, dose=0.01
7000 *ERR*-values that make up 1 pdf for agex=30, age=70, dose=0.02 Gy
…

Then, for each preselected value of agex, age, and dose merge the pdf's and calculate mean ERR-values, the median ERR-values, percentiles etc.

Results for CbVD



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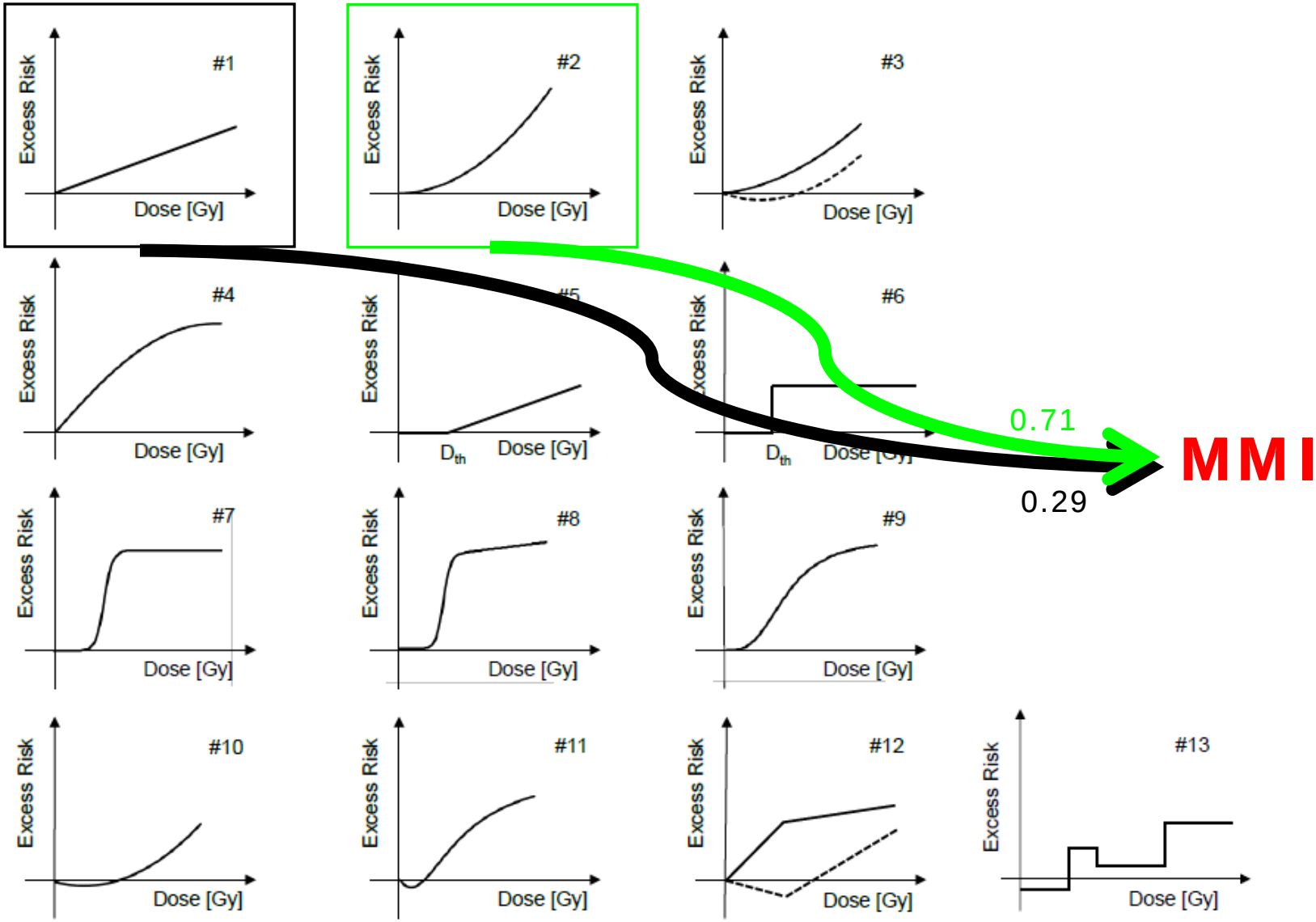

Conclusions

- Shapes of dose responses need to be analyzed with great care
- Besides LNT model, other models must also be tested
- MMI is an efficient tool to mathematically superpose different models that fit the data about equally well

- Three essential differences in our approach compared to Preston et al. 2003:

  1. We streamlined Preston's baseline model (to eliminate model parameters that are not significant; to get a smaller AIC; to reduce the size of error bars related to our MMI-curve)
  2. Age-knots related to the baseline model were allowed to be free
  3. We used more dose-response models for the excess risk

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