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Dose-Responses from Multi-Model Inference for the Non-cancer Disease Mortality of A-Bomb Survivors

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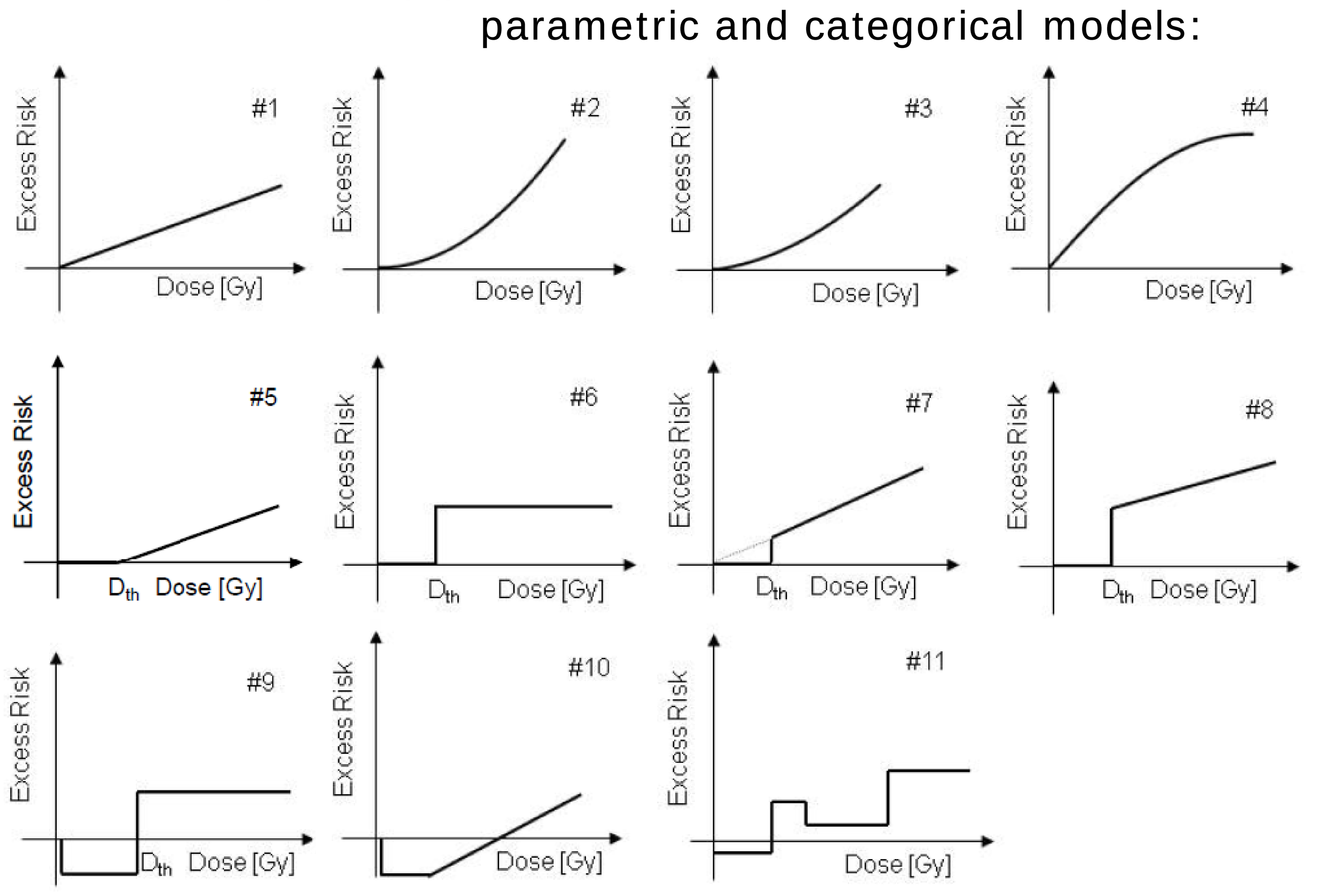
Aims of Research

Investigate the shape of the dose-responses related to the non-cancer data of the Lifespan Study (LSS). Special interest: shape at low doses.

Materials and Methods

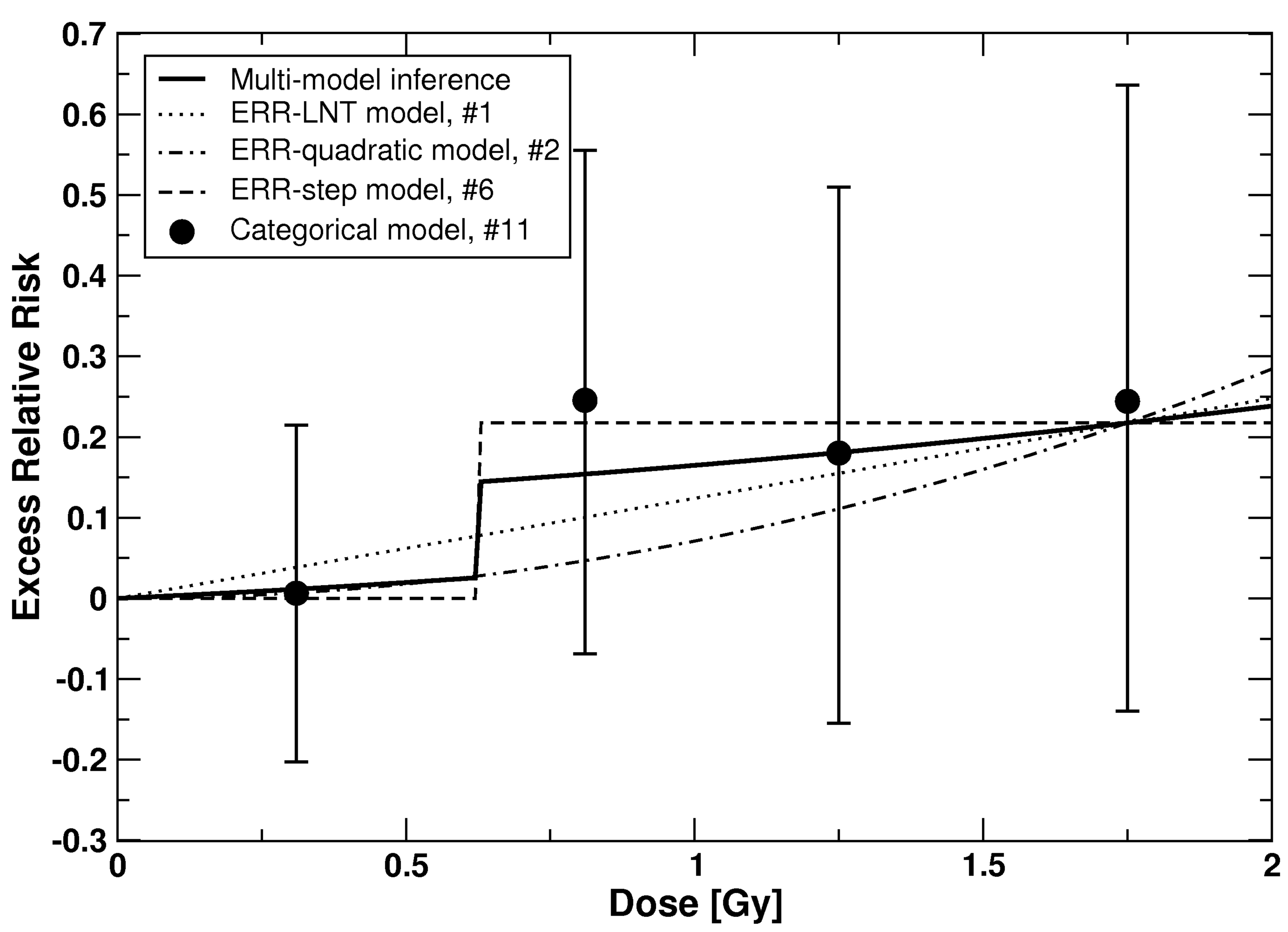
Data: LSS Report 13 (Preston et al. Radiat. Res. 2003)
Cerebrovascular disease (CVD, ICD-9 430-438)
Cardiovascular diseases excl. CVD (ICD-9 390-429, 440-459)
Follow-up: 1/1/1968 – 31/12/1997
50364 survivors (19467 men, 30897 women)
3954 deaths from CVD (1434 men, 2520 women)
4477 deaths from cardiovasc. diseases (1614 men, 2863 women)

Models used:
- ERR model: $h = h_0 \times (1 + ERR(D))$
- EAR model: $h = h_0 + EAR(D)$
- h_0: baseline model
- $ERR(D)$, $EAR(D)$: describe excess risk from radiation; 11 parametric and categorical models:



Results for CVD

	Δdev	N_{par}	ΔAIC	Weight
ERR-LNT model	3.46	22	1.46	0.2628
ERR-quadratic model	4.09	22	2.09	0.1918
ERR-step model, D_{th}=0.62 Gy	0	23	0	0.5454
Preston's ERR-LNT model	33.53	30	47.53	-



Age at exposure: 30 yr
Age attained: 70 yr

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Materials and Methods

Determination of dose-responses via multi-model inference (MMI):

1.) Reproduce Preston's fit of data for CVD and cardiovascular diseases excl. CVD using his baseline model (Preston et al. 2003) combined with ERR-LNT model.

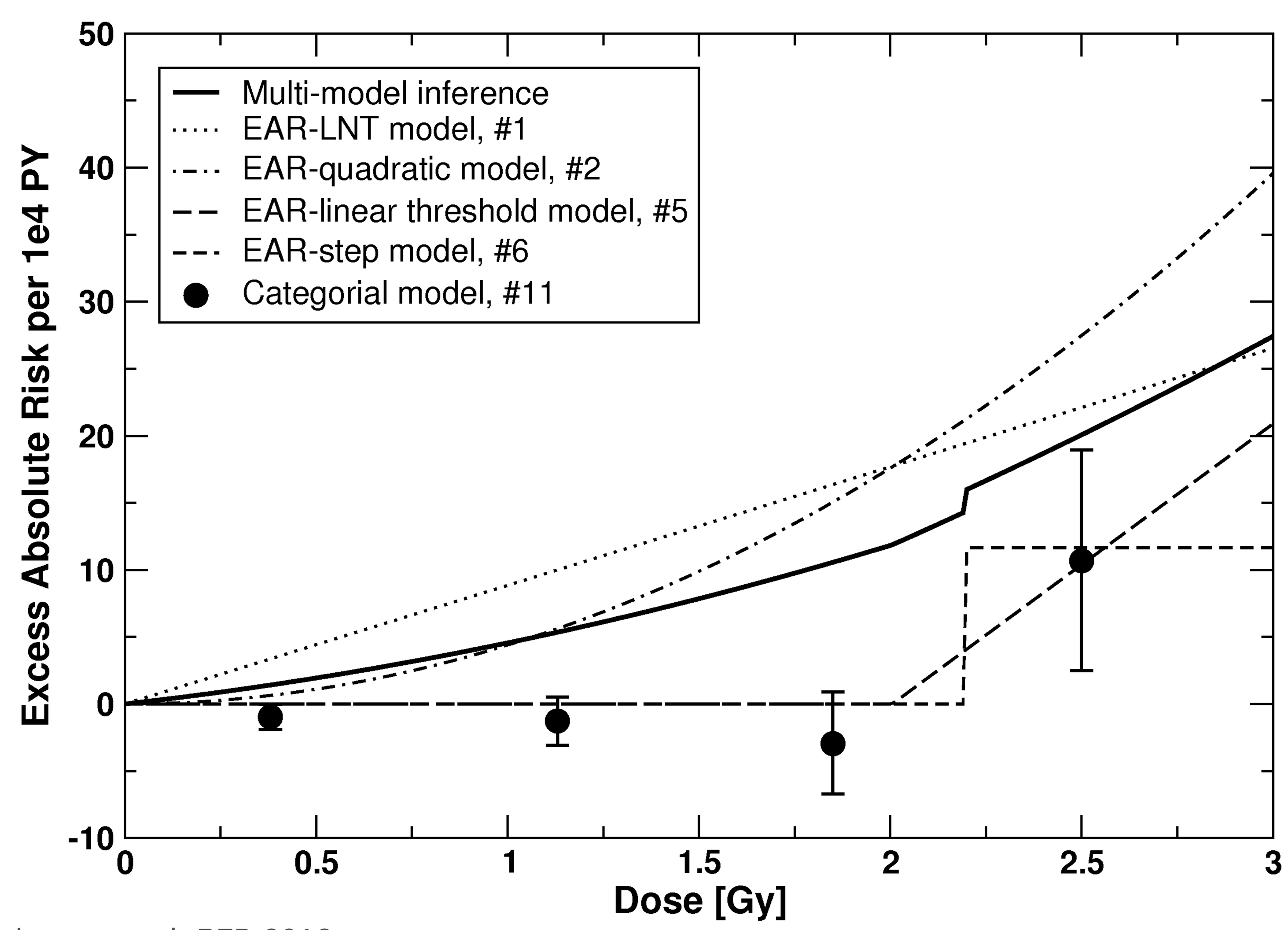
2.) Optimize Preston's baseline model: test each baseline parameter for its statistical significance by setting it to zero and refitting all others. Use likelihood-ratio tests (LRT) to decide.
→2 optimized baseline models:
21 baseline parameters for CVD (-8 compared to Preston)
15 baseline parameters for cardiovascular diseases (-14)

3.) Combine all 11 parametric and categorical models with the optimized baseline-models either as ERR or EAR models and fit them to the data. Use LRTs to get rid off nested models
→ 2 sets of non-nested models.

4.) For each non-nested model calculate AIC = dev + 2×N_{par} and AIC-weight. Perform Monte Carlo simulations of ERR or EAR using the best estimates 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.

Results for cardiovascular diseases excluding CVD

	Δdev	N_{par}	ΔAIC	Weight
EAR-LNT model	0	17	0	0.3619
ERR-quadratic model	0.32	17	0.32	0.3084
EAR-threshold model, D_{th}=2.0 Gy	1.27	17	1.27	0.1918
EAR-step model, D_{th}=2.19 Gy	1.93	17	1.93	0.1379
Preston's ERR-LNT model	15.98	30	41.98	-



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Conclusions

- For those A-bomb survivors who died from CVD, MMI shows – because of the contribution of the step model – that the LNT model overpredicts the radiation risk below the threshold dose of 0.62 Gy.
- For deaths from cardiovascular diseases excl. CVD, MMI shows that the LNT model overpredicts the risk below the threshold dose of 2.19 Gy. The reason for this is again the contribution from the step model.

Ongoing work

- Analysis of latest non-cancer LSS data (Shimizu et al. 2010) is ongoing. Results for CVD confirm the findings reported above.
- Fit of new mechanistic model (deterministic and stochastic) for atherosclerosis to the Shimizu data is under way.

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