Use of the bayesmh command in Stata to calculate excess relative and excess absolute risk for radiation health risk estimates

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Overview

Describe excess relative risk (ERR) and excess absolute risk (EAR)

- Definitions
- Example from the radiation epidemiology literature
- Standard model fitting (uses software called Epicure)

Fit models within a Bayesian framework using the bayesmh command in Stata

- Describe data
- Provide code
- Show results

Describe excess relative risk (ERR) and excess absolute risk (EAR)

Risk is modeled on the excess risk scale

EXCESS RELATIVE RISK (ERR)

$h_0 \cdot (1 + ERR)$

where

- h_0 is the background hazard function
  - Baseline rates for those not exposed
  - Can be defined using spline functions in log-attained age
    - See “Flexible Parametric Survival Analysis Using Stata…” Royston and Lambert
  - Can be modified by sex or other descriptive variables
- ERR is the excess relative risk
  - Risk is **multiplicate** relative to the background
  - Main outcome is the dose-response function
  - Can be modified by sex, age, or other descriptive variables

EXCESS ABSOLUTE RISK (EAR)

$h_0 + EAR$

where

- h_0 is the background hazard function
  - Baseline rates for those not exposed
  - Can be defined using spline functions in log-attained age
    - See “Flexible Parametric Survival Analysis Using Stata…” Royston and Lambert
  - Can be modified by sex or other descriptive variables
- EAR is the excess absolute risk
  - Risk is **additive** relative to the background
  - Main outcome is the dose-response function
  - Can be modified by sex, age, or other descriptive variables

Example from the radiation epidemiology literature

Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009

Gy = typical unit of absorbed dose in J/kg

Eric J. Grant,[a,1] Alina Brenner,[d] Hiromi Sugiyama,[a] Ritsu Sakata,[a] Atsuko Sadakane,[a] Mai Utada,[a] Elizabeth K. Cahoon,[d] Caitlin M. Milder,[c] Midori Soda,[a] Harry M. Cullings,[b] Dale L. Preston,[e] Kiyohiko Mabuchi[d] and Kotaro Ozasa[a]

TABLE 5

All Solid Cancer Linear ERR per Gy Adjusted for Modifying Effects of Age at Exposure and Attained Age with or without Adjustment for Smoking: LSS Solid Cancer Incidence Cohort with Known Doses, 1958–2009

ERR per Gy[a]				Age at exposure[b]	Attained age[c]
Sex-averaged (95% CI)	Males (95% CI)	Females (95% CI)	F:M ratio (95% CI)	(percentage change per 10-year increase) (95% CI)	(power) (95% CI)
Unadjusted for smoking (deviation = 57,404.131, 17 parameters)					
0.50 (0.42 to 0.59)	0.36 (0.28 to 0.45)	0.65 (0.53 to 0.77)	1.80 (1.42 to 2.33)	–19% (–27% to –12%)	–1.57 (–2.01 to –1.11)
Adjusted for smoking, additive joint effect (deviation = 56,950.969, 21 parameters)					
0.56 (0.46 to 0.66)	0.48 (0.36 to 0.61)	0.64 (0.52 to 0.76)	1.33 (1.04 to 1.74)	–21% (–29% to –13%)	–1.53 (–1.98 to –1.07)
Adjusted for smoking, multiplicative joint effect (deviation = 56,959.086, 21 parameters)					
0.47 (0.39 to 0.55)	0.33 (0.25 to 0.42)	0.60 (0.49 to 0.72)	1.81 (1.42 to 2.35)	–21% (–29% to –12%)	–1.66 (–2.11 to –1.20)

[a] Estimates were centered and scaled to correspond with an attained age of 70 years after exposure at age 30 years.
[b] The age-at-exposure effect was expressed as percentage change per decade increase (e.g., in the top row, the per decade decrease is calculated as: $-19\% = \exp[-0.21 \times (age_{exp} - 30)/10] - 1$, where –0.21 is the model parameter estimate and age_{exp} is age 40).
[c] The effect of attained age was modeled as power of attained age (e.g., in the top row: $[age_{attained}/70]^{-1.57}$)

Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, et al. Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009. Radiation Research. 2017 Mar 20; Available from: http://www.rrjournal.org/doi/abs/10.1667/RR14492.1

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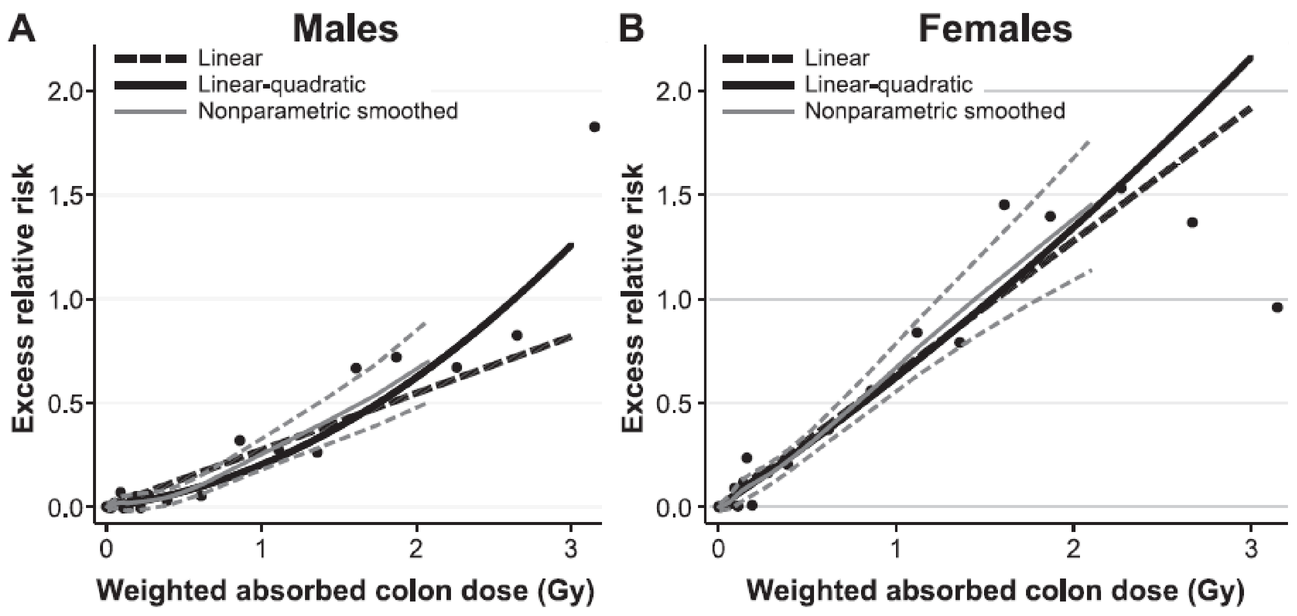

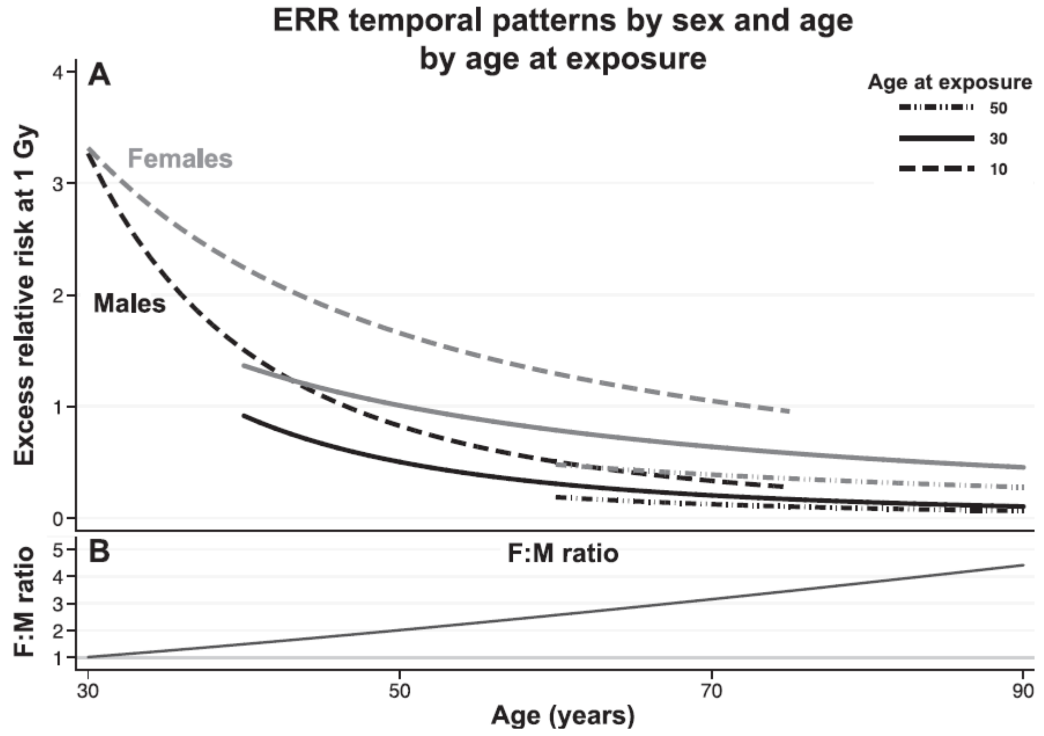

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Standard model fitting

EPICURE software package: https://risksciences.com/epicure/

- Developed by D. Preston and D. Pierce
- Modules available
  - GMBO – binomial data
  - PECAN – case-control matched data
  - PEANUTS – survival data
  - DATAB – person year tables for Poisson analyses
  - AMFIT – grouped Poisson data
    - Includes the ERR and EAR models

Fit models within a Bayesian framework using the bayesmh command in Stata

Data for example model fitting

Population description:

- HS/Npt stock mice of both sexes
  - Heterogeneous stock originated from eight strains: A/J, AKR/J, BALB/cJ, C3H/HeJ, C57BL/6J, CBA/J, DBA/2J and LP/J
  - 71st generation
  - 603 males and 594 females
- Followed until death, moribund, or to age 26.7 months

Outcome of interest:

- Mortality rates for all solid tumors
  - All tissues were grossly evaluated after death
  - Solid tumors found in 516 mice

Radiation description

- Whole body irradiated evenly
- Irradiated between ages 1.5 and 3 months
- Focus on the subset of mice exposed to sham irradiation and Gamma irradiation
  - Type of radiation similar to atomic bomb exposures

Edmondson EF, Gatti DM, Ray FA, Garcia EL, Fallgren CM, Kamstock DA, et al. Genomic mapping in outbred mice reveals overlap in genetic susceptibility for HZE ion– and γ-ray–induced tumors. Science Advances. 2020 Apr 1;6(16):eaax5940.

Bayesian Poisson regression model

Data stratified
- By sex
  - male = 0
  - female = 1
- By attained age
  - < 14 months
  - 2 month categories from ages 14 months to 24 months
  - ≥ 24 months

Priors
- Uninformed priors for the background hazard
  - $\{\theta_0, \theta_1, \theta_2, \theta_s\} \sim \text{normal}(0{,}10000)$
- Atomic bomb results inform ERR priors
  - $\beta_\gamma \sim \text{lognormal}(0.33{,}2)$
  - $\delta_s \sim \text{normal}(0.59{,}0.5)$
  - $\delta_e \sim \text{normal}(-0.21{,}0.5)$
  - $\delta_a \sim \text{normal}(-1.66{,}0.5)$

Model equations:

$$MM\ h_0(a,s)(1 + ERR(s,e,a,D,r))$$

where

$$ERR(s,e,a,D,r) = \exp(\delta_s 1_{s=female} + \delta_e(e-1) + \delta_a \ln(\tfrac{a}{20}))(\beta_\gamma D)$$

and

$$h_0(\mathrm{a,s}) = \exp\left(\theta_0 + \theta_1 \cdot \ln\left(\frac{a}{20}\right) + \theta_2 \cdot \frac{\left(\ln\left(\frac{a}{15}\right)\right)_+^3}{\ln\left(\frac{23}{15}\right)^2} - \theta_2 \cdot \frac{\left(\ln\left(\frac{a}{20}\right)\right)_+^3}{\ln\left(\frac{23}{15}\right) \cdot \ln\left(\frac{23}{20}\right)} - \theta_2 \cdot \frac{\left(\ln\left(\frac{a}{23}\right)\right)_+^3 \cdot \ln\left(\frac{15}{20}\right)}{\ln\left(\frac{23}{15}\right)^2 \cdot \ln\left(\frac{23}{20}\right)} + \theta_s 1_{s=female}\right)$$

Gy = typical unit of absorbed dose in J/kg

Code to fit model

Variables in the data:

- agedays = attained age in days
- SolidTumor = indicator variable for solid tumors
- Animalnumber = animal identifier
- sex = indicator variable for females
- exposure_age_months = age at exposure in months
- dose_Gy = dose in Gy

```
stset agedays, failure(SolidTumor) id(Animalnumber)
  scale(30)
* Split the age variable into categories
stsplit agegroup, at(14(2)25)
* Calculate rates by age group, sex, and dose
strate agegroup dose_Gy sex, per(100)
generate time_exposed = _t - _t0
gen agemed = agegroup + 1
replace agemed = 7 if agegroup == 0
gen lnage = ln(agemed/20)
* Create a cubic spline with knots at ages 15 20 and 23
mkspline lnagesp = lnage, cubic knot(-.28768207 0
  .13976194)
```

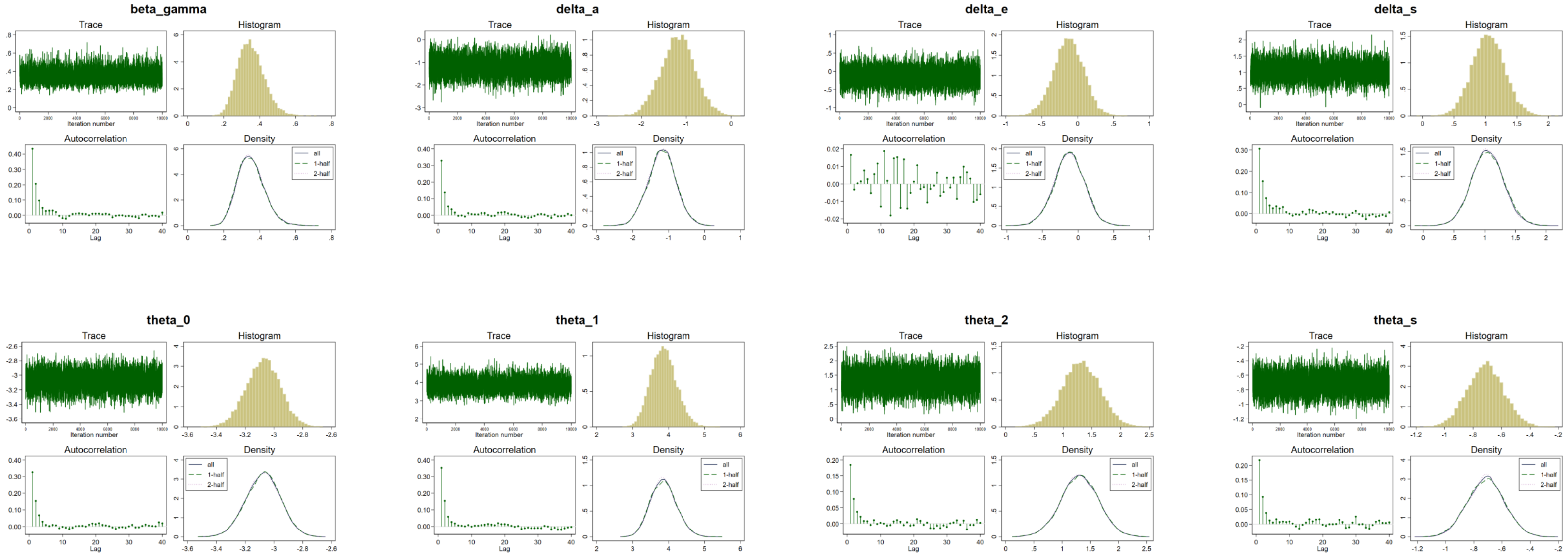
```
* Bayesian Poisson regression model
bayesmh (_d,
  likelihood(dpoisson(exp(ln(time_exposed) +
  lnagesp1*{theta_1=10} + lnagesp2*{theta_2=-3} +
  {theta_0=-2.5} + sex*{theta_s}) * (1 + exp({delta_s}*sex
  + {delta_e}*(exposure_age_months-2) + {delta_a}*lnage) *
  {beta_gamma=0.5}*dose_Gy)))),
  prior({theta_0} {theta_1} {theta_2} {theta_s},
  normal(0,10000))
  prior({beta_gamma}, lognormal(0.33,2))
  prior({delta_s}, normal(0.59,0.5))
  prior({delta_e}, normal(-0.21,0.5))
  prior({delta_a}, normal(-1.66,0.5))
  block({theta_0} {theta_1} {theta_2} {delta_a})
  block({theta_s} {delta_s})
  block({beta_gamma})
  block({delta_e})
  thinning(20) burnin(50000)
```

Output from code

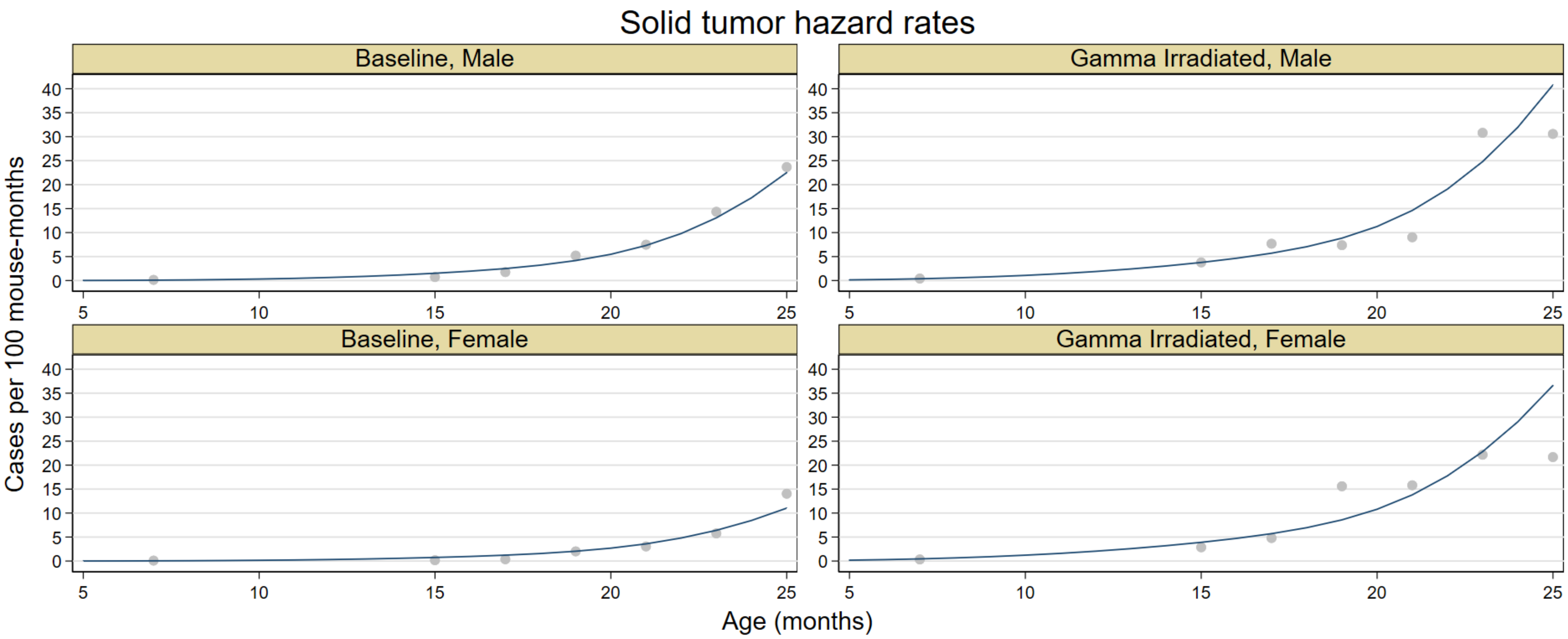
```
note: discarding every 19 sample observations; using observations 1,21,41,...

Burn-in ...
note: invalid initial state
Simulation ...

Model summary
------------------------------------------------------------------------------
Likelihood:
  _d ~ poisson(<expr1>)

Priors:
  {theta_s} ~ normal(0,10000)
  {delta_s} ~ normal(0.59,0.5)
  {delta_e} ~ normal(-0.21,0.5)
  {delta_a} ~ normal(-1.66,0.5)

Hyperpriors:
  {theta_0 theta_1 theta_2} ~ normal(0,10000)
              {beta_gamma} ~ lognormal(0.33,2)

Expression:
  expr1 : exp(ln(time_exposed) + lnagesp1*{theta_1=10} + lnagesp2*{theta_2=-3} + {theta_0=-2.5} +
          sex*{theta_s})*(1 + exp({delta_s}*sex + {delta_e }*(exposure_age_months-2) + {delta_a}*lnage) *
          {beta_gamma=0.5}*dose _Gy)
------------------------------------------------------------------------------
```

```
Bayesian Poisson model                          MCMC iterations  =    249,981
Random-walk Metropolis-Hastings sampling        Burn-in          =     50,000
                                                MCMC sample size =     10,000
                                                Number of obs    =      5,364
                                                Acceptance rate  =      .3486
                                                Efficiency:  min =      .3581
                                                             avg =      .5394
Log marginal likelihood = -1869.5654                         max =       .968

------------------------------------------------------------------------------
             |                                                Equal-tailed
             |      Mean   Std. Dev.     MCSE     Median  [95% Cred. Interval]
-------------+----------------------------------------------------------------
  beta_gamma |  .3523971    .0740951   .001238    .347643   .2218528   .5130183
     delta_a | -1.184415    .3838861   .005625  -1.179685  -1.943432  -.4291951
     delta_e |  -.125632     .211929   .002154  -.1246816  -.5465446   .2803918
     delta_s |  1.048715    .2600569   .004006   1.045351   .5465176   1.571688
     theta_0 |  -3.07478     .119328   .001752  -3.073381  -3.310085  -2.842623
     theta_1 |  3.863657     .356535   .005316   3.851435   3.199128   4.599245
     theta_2 |  1.311634    .3317564   .004253   1.311573    .654233   1.957713
     theta_s | -.7127724     .129681   .001704  -.7116233  -.9656503  -.4610413
------------------------------------------------------------------------------
```

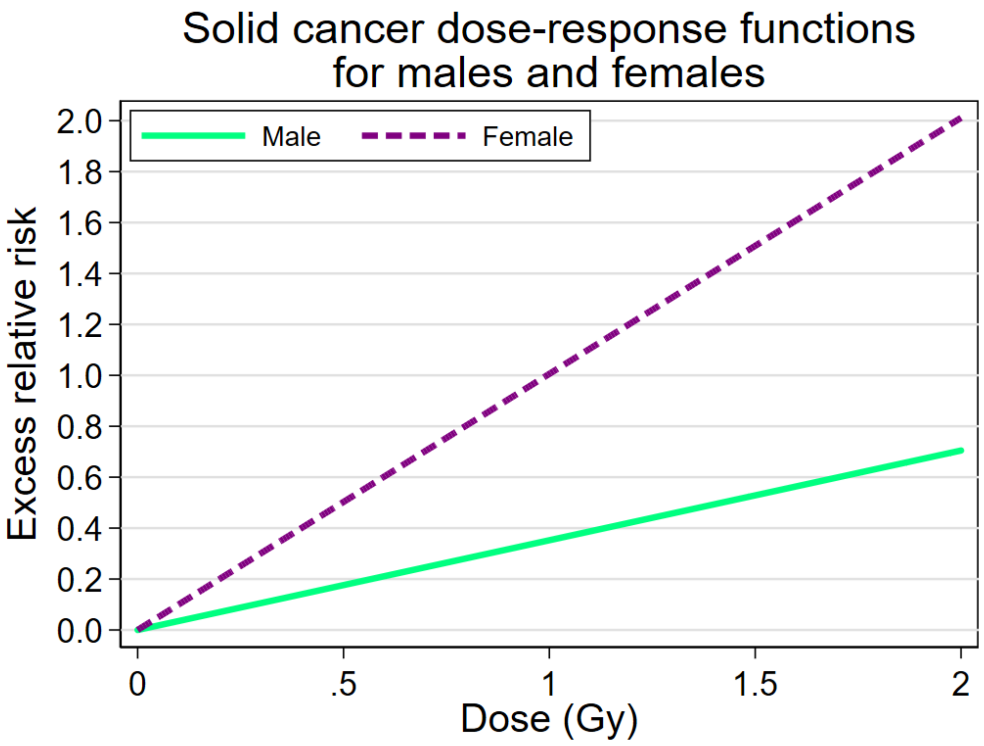
Confirm parameter convergence

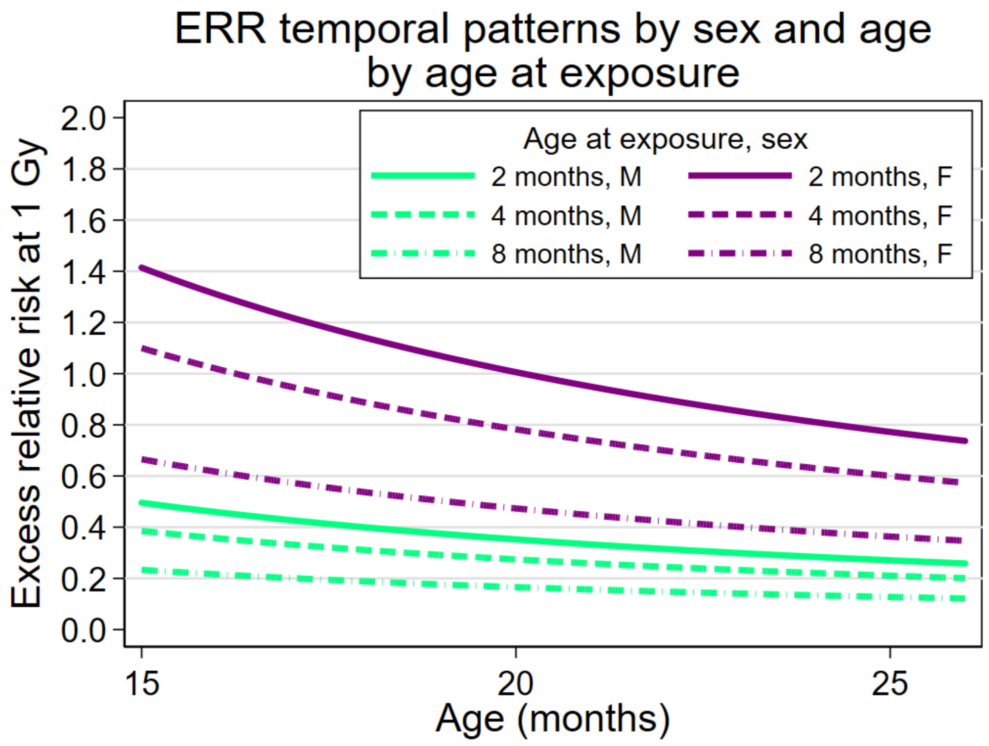


Solid tumor hazard rates figure



Dose-response and temporal patterns





ERR and EAR model benefits

Provides an alternative model to the Cox proportional hazard model

- Adding age modification to the hazard function models divergence from the hazard assumption

Focus on parameters of interest

- Dose-response functions can be emphasized
- Background hazard and modifying parameters can be factored out of the equation easily
  - Useful for comparing differences in doses across radiation type

Applying similar models to both human epidemiology data and animal experiment data may help translate across species

Questions?