THE UNIVERSITY OF MELBOURNE

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Cancers following diagnostic radiation

What do we know about the dose-response curve following low-dose radiation?

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CSRP 2015

21 September 2015

Acknowledgments

Particular thanks are due to the 15 co-authors of our BMJ publication.

Data access and linkage was facilitated by

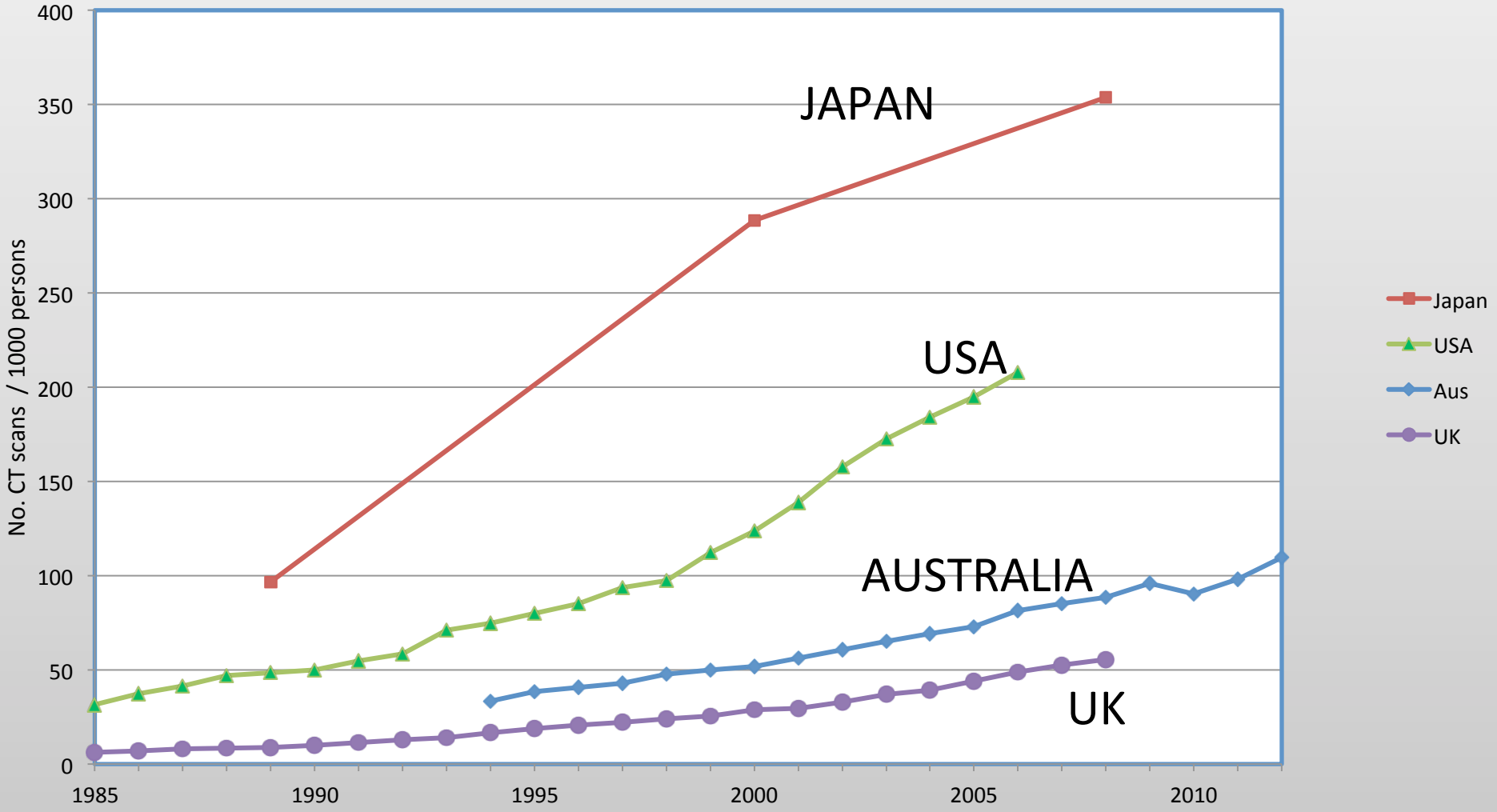
- Health & Ageing, Medicare Australia
- Australian Institute of Health and Welfare
- State and Territory governments and cancer registrars

This report includes valuable contributions from Darren Wraith (now at the Queensland University of Technology), Marissa Bartlett (Queensland Health), Anna Forsythe, and Zoe Brady

Themes for the talk

1. Cancer risks following diagnostic CT scan radiation before the age of 20 years.
2. Potential biases such as reverse causation.
3. Preliminary results – cancer risks following diagnostic nuclear medicine procedures.
4. Comparison of risk estimates for low-dose radiation from the LSS, from diagnostic exposures and other studies.
5. Implications of old and new data and new models for the shape of the dose-response curve.
6. Predicting future risks of diagnostic radiation.

Per capita CT usage varies by Country



Context and significance of CT exposed cohorts

- Theoretical papers by Brenner and others from 2000 predicted an increased risk following childhood CT based on results from the Life Span Study (LSS) of atomic survivors.
- Pearce et al (2012) used UK data to show an actual increase in brain cancer & leukaemia following childhood CT
- Our Australian study (Mathews et al, 2013) showed actual increases in brain cancer, leukaemia, and other solid cancers. Our study had:
  - About 4 times the exposure of the UK study
  - About 4-5 times as much low dose exposure as LSS
- **Longer follow-up of medically-exposed cohorts will soon answer the "low-dose" radiation question.**

Cancer after CT scans - Study design

Exposure

Records of CT scans funded by Medicare for all persons aged 0-19 years in 1985-2005

Outcome

First diagnoses of cancer more than 12 months after CT exposure

Data linkage in high security unit of the Australian Institute of Health & Welfare

Analysis of de-identified data at the University of Melbourne

A large study

CT exposed

680,211

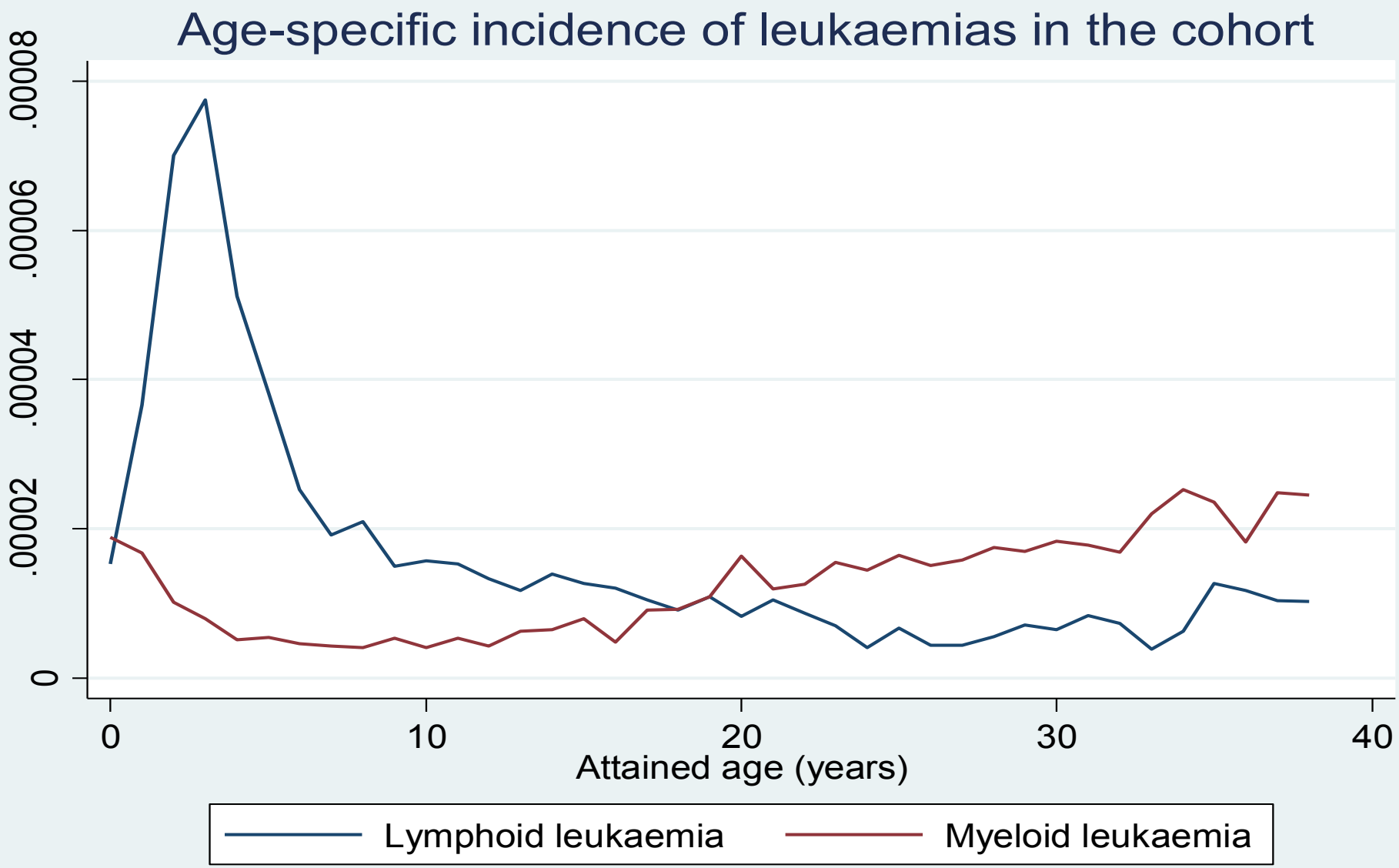
- Exposure more than 12 months prior to any cancer diagnosis
- When aged 0-19 years
- In period 1985-2005
- Follow-up to 31/12/2007

Non-exposed

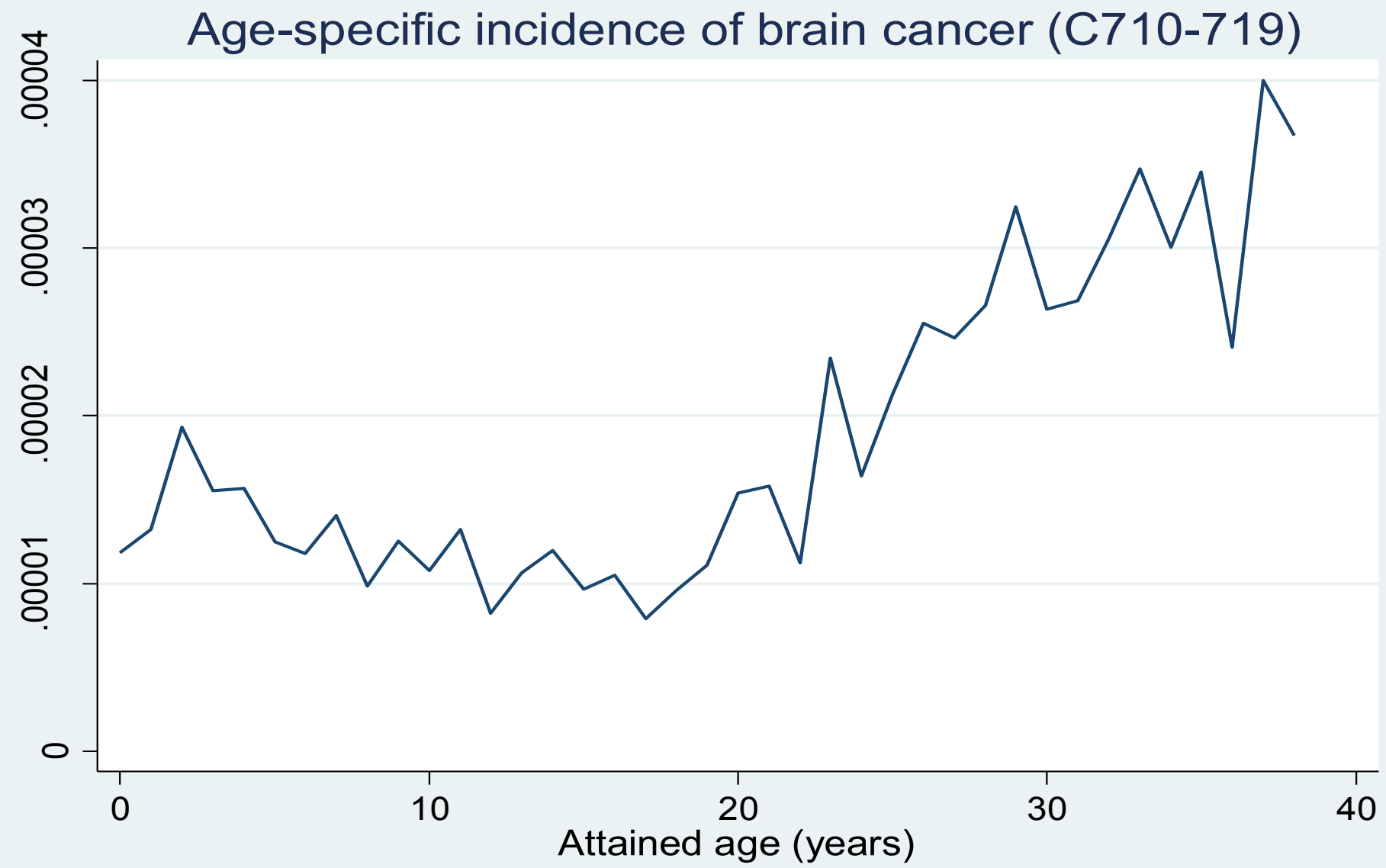
10,259,469

- No Medicare record of any CT scan
- When aged 0-19 years
- In period 1985-2005
- Follow-up to 31/12/2007

Leukaemias in our cohort



Brain cancer in our cohort



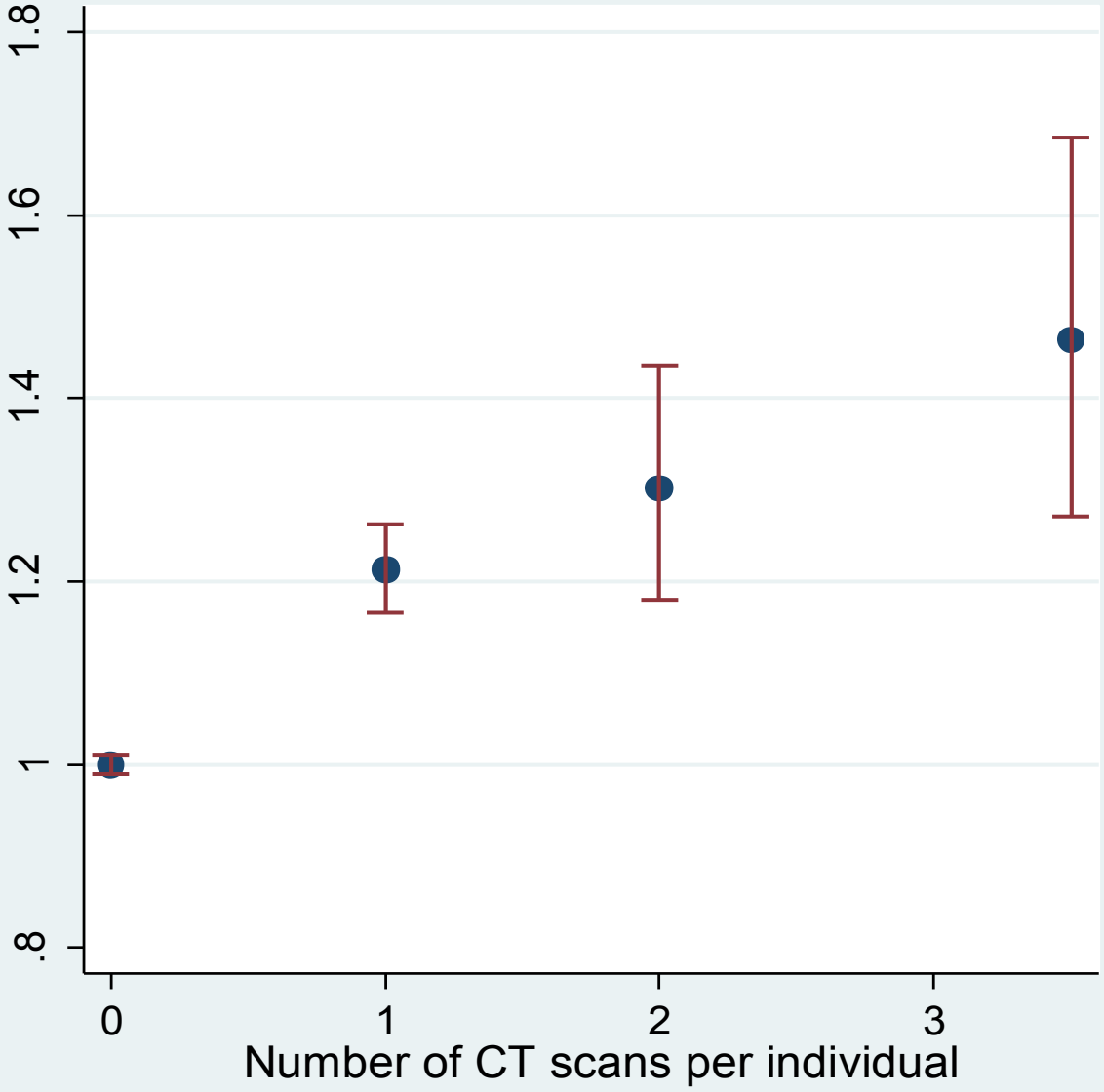
Cohort follow-up details

Characteristic (at one year lag)	Exposed persons	Unexposed persons
Number of person years of follow-up	6 486 548	177 191 342
Mean length of follow-up (years)	9.5	17.3
Number of cancers	3150	57 524

So what did we find?

	1 year lag	5 year lag	10 year lag
Observed cancers in exposed	3,150	2,365	1,405
Expected cancers in exposed	2,542	1,963	1,196
Incidence rate ratio (IRR) & 95 % CI	**1.24 (1.20,1.29)**	**1.21 (1.16,1.26)**	**1.18 (1.11,1.24)**

Cancer risk by number of CT scans (All cancers & all exposures)



The incidence rate ratio increased by 0.16 (95% CI 0.13 to 0.19) for each additional CT scan, calculated after stratification for age, sex, and year of birth

(χ^2 for trend: 131.4 , $p<0.0001$).

If unexposed persons are excluded the trend remains significant

(χ^2 for trend: 5.79, $p = 0.02$).

Cancers after head CT – 5 year lag

Type of cancer	No. exposed cancers	Incidence rate ratio (IRR)	IRR 95% confidence interval
Brain cancer	123	2.03	(1.69-2.43)
Soft tissue	46	1.55	(1.15-2.08)
Thyroid	130	1.36	(1.14-1.62)
Leukaemia	100	1.25	(1.02-1.53)
Other solid	536	1.12	(1.03-1.22)
All cancers	**1532**	**1.21**	**(1.15-1.27)**

Different measures of CT risk

Measure	Average risk	More extreme risk
Excess relative risk	16% increase per CT	200% per CT after exposure at an early age
Absolute increase	1 extra cancer per 2000 scans	Will continue to increase over time
Attributable risk for a person with cancer after exposure	14 % per CT	67% for a person with brain cancer after exposure at a young age

Understanding Attributable Risk

An example

If a child is exposed to a CT head scan before the age of 5 years, then in the years that follow, the average rate of brain cancer is 3 times as great as for "unexposed".

We are interested in the **attributable risk -** probability that the cancer was caused by exposure. This is calculated as:

A.R. = Excess rate in exposed/Overall rate in exposed

= (3 -1)/3 = 2/3 = 67%

Cancer risk and site of radiation

Cancer risks tended to be increased most in the tissues actually irradiated

e.g. Brain cancers after head CT

This is consistent with the causal hypothesis, but a devil's advocate could also argue that it might also be due to the use of CT to investigate early symptoms of brain cancer or a pre-cancerous condition.

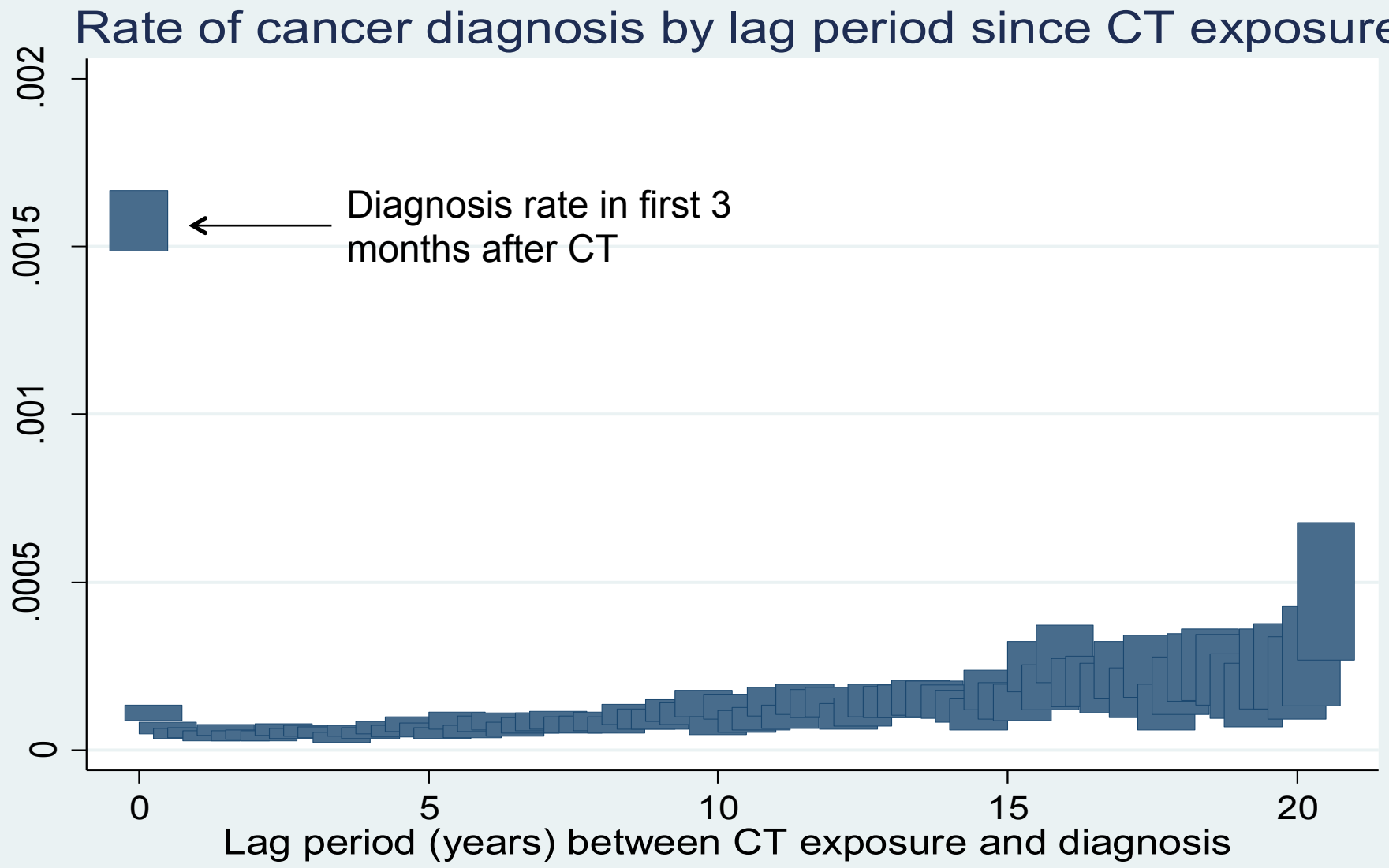
What about “reverse causation”?

Cancers at the shortest lag periods following CT scans are almost certainly due to **“reverse causation”,** as when symptoms of cancer or a pre-cancerous condition prompt the CT scan.

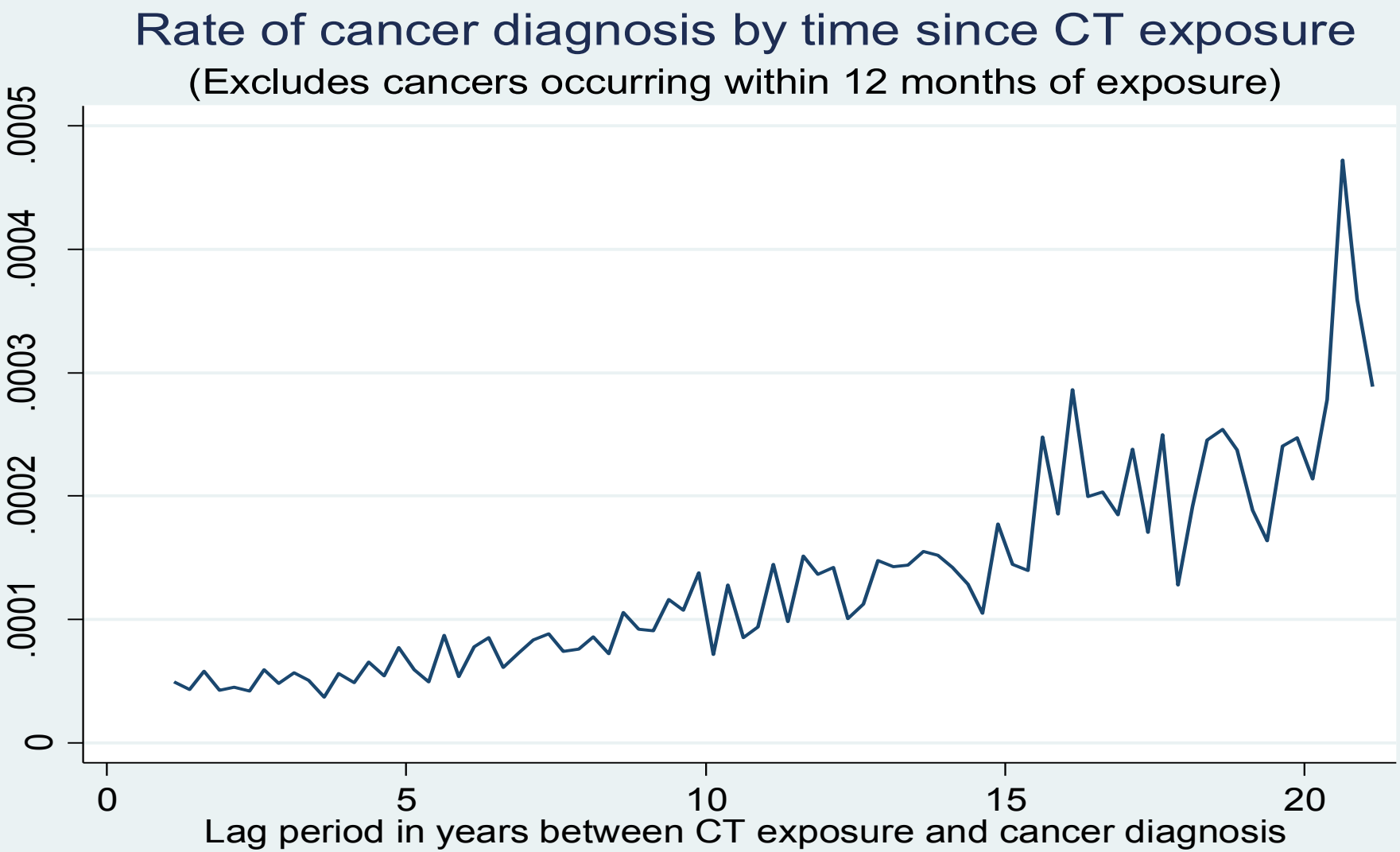
It was for this reason that in our BMJ paper we chose to exclude cancers occurring at a lag of less than 12 months after exposure.

Can we be more precise about cancers due to reverse causation at different lag periods?

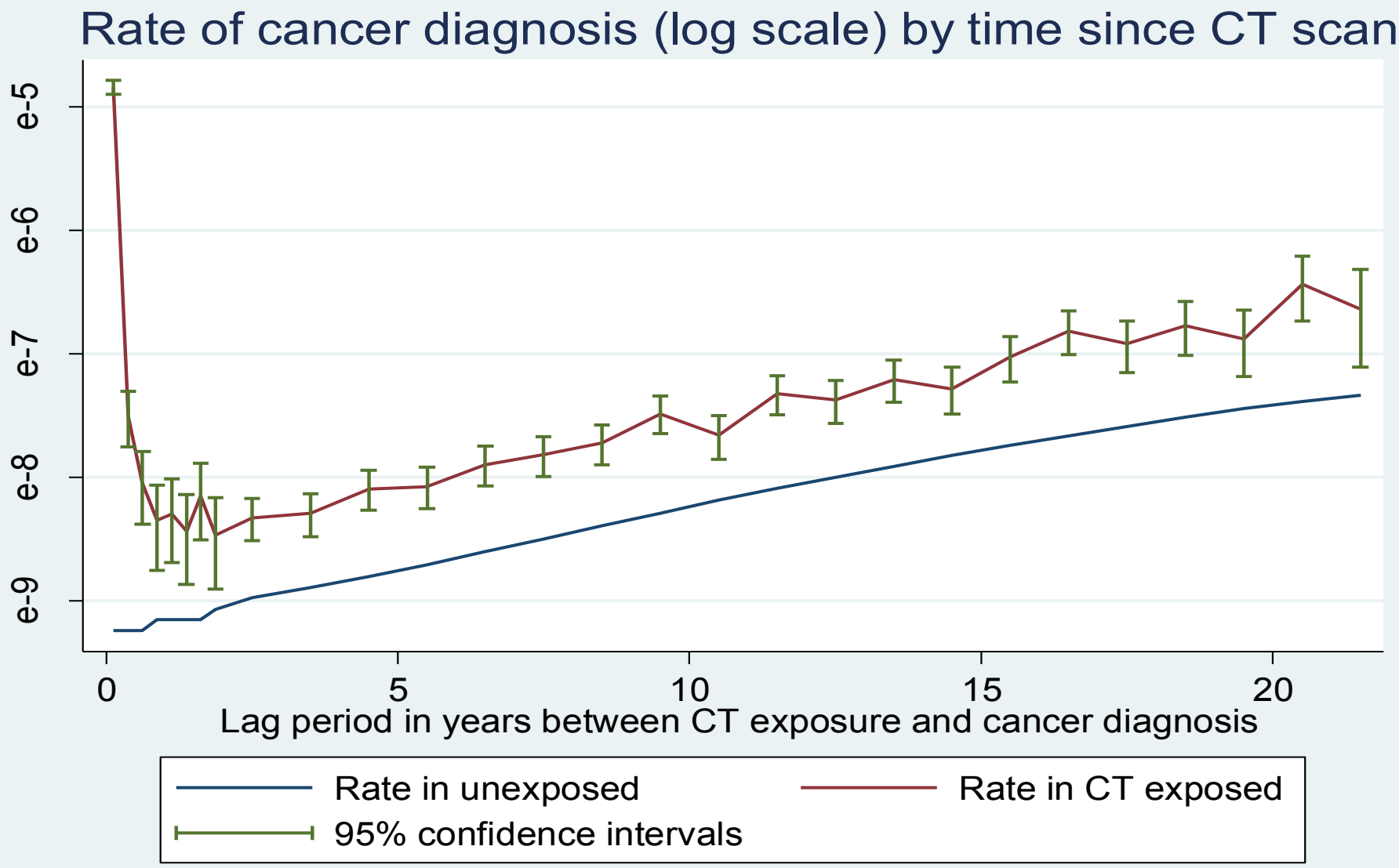
Cancer diagnosis rate by years since CT exposure



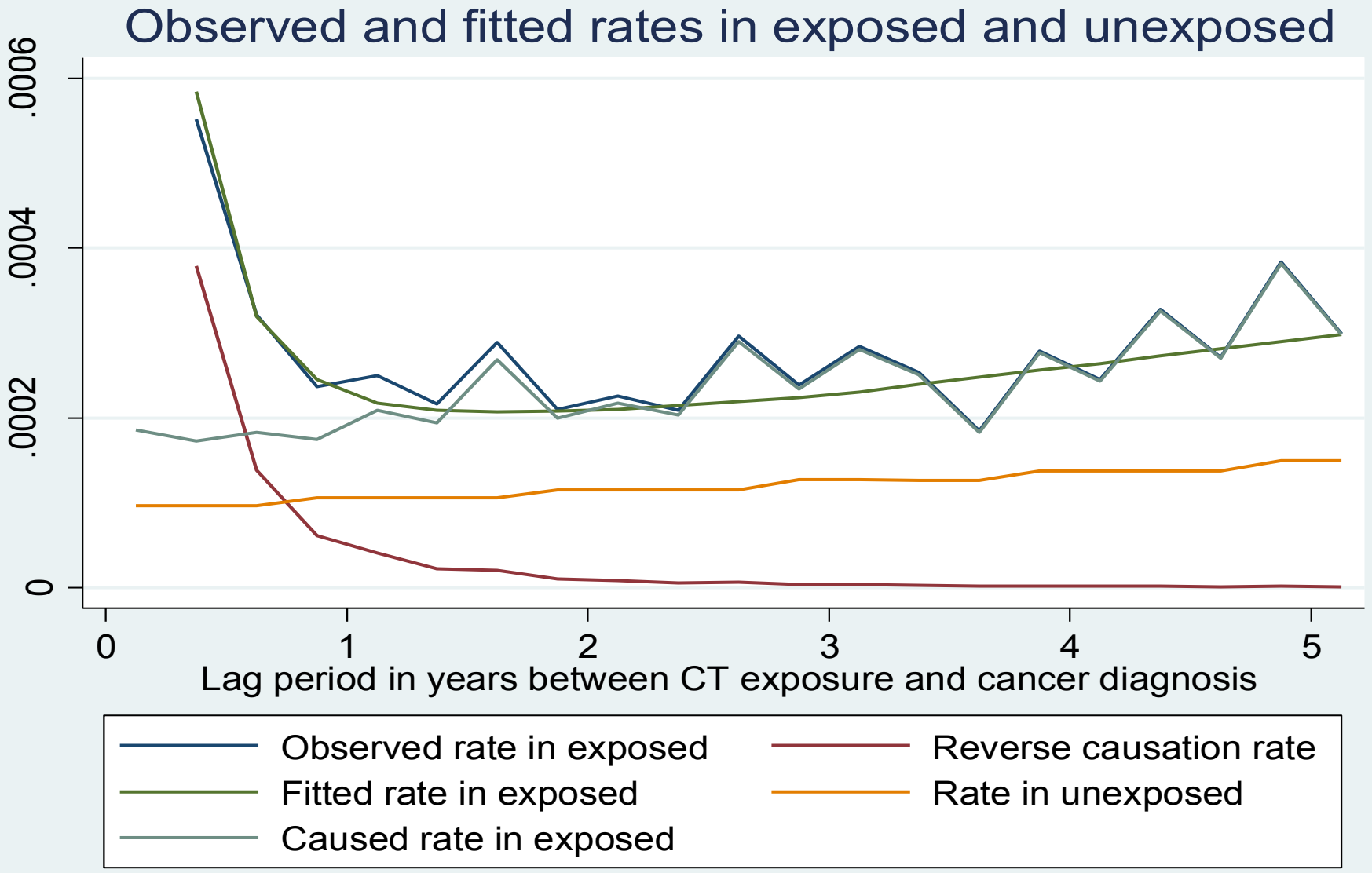
Diagnosis rate –excluding first year



The ERR model seems justified!



Modelled effects for first five years



Interpreting these findings

The reverse causation model has provided 95% credible interval estimates of the average dose response coefficient (ERR) for **young people in our cohort, where many lags are short**

ERR = 0.11-0.16 per mSv at age 10

ERR = 0.036-0.053 per mSv at age 30

These estimates, adjusted for reverse causation, are consistent with our BMJ results but **are higher than previous estimates in the literature.**

Are our results believable?

Potential explanation for the larger coefficients include:

1. Radiation doses in those actually getting cancer may have been greater than the estimated doses.
2. As our model E2 takes explicit account of age-related susceptibility (arising from stochastic factors) it may make more efficient use of the data.
3. The earliest cancers are likely to have occurred in persons who are most susceptible, for genetic reasons or because of stochastic selection.
4. The dose response curve could have a gradient (ERR/dose) that is greater at low average doses (after CT scans) than at the higher average doses which drove the estimates of ERR/mSv in the LSS of atomic survivors.

Nuclear medicine diagnostics Preliminary results

Algorithms to estimate individual effective doses from diagnostic nuclear medicine (NM) procedures in our Medicare cohort were developed by Dr Marissa Bartlett, using ICRP tables, and codified by Ms Anna Forsythe.

There were1635 cancers in persons with one or more NM procedures followed for 2.030 million person years, compared with 52020 cancers in persons without exposure to NM or CT procedures (followed for 168 million person years).

Nuclear medicine diagnostics
Preliminary results

Dr Darren Wraith has estimated the excess relative risk (ERR) per mSv (95% confidence intervals) as:

Over all exposed persons

ERR = 0.08 (0.06-0.11) per mSv

Excluding procedures possibly ordered for cancer detection

ERR = 0.06 (0.02-0.09) per mSv

Major discrepancies in ERR/dose

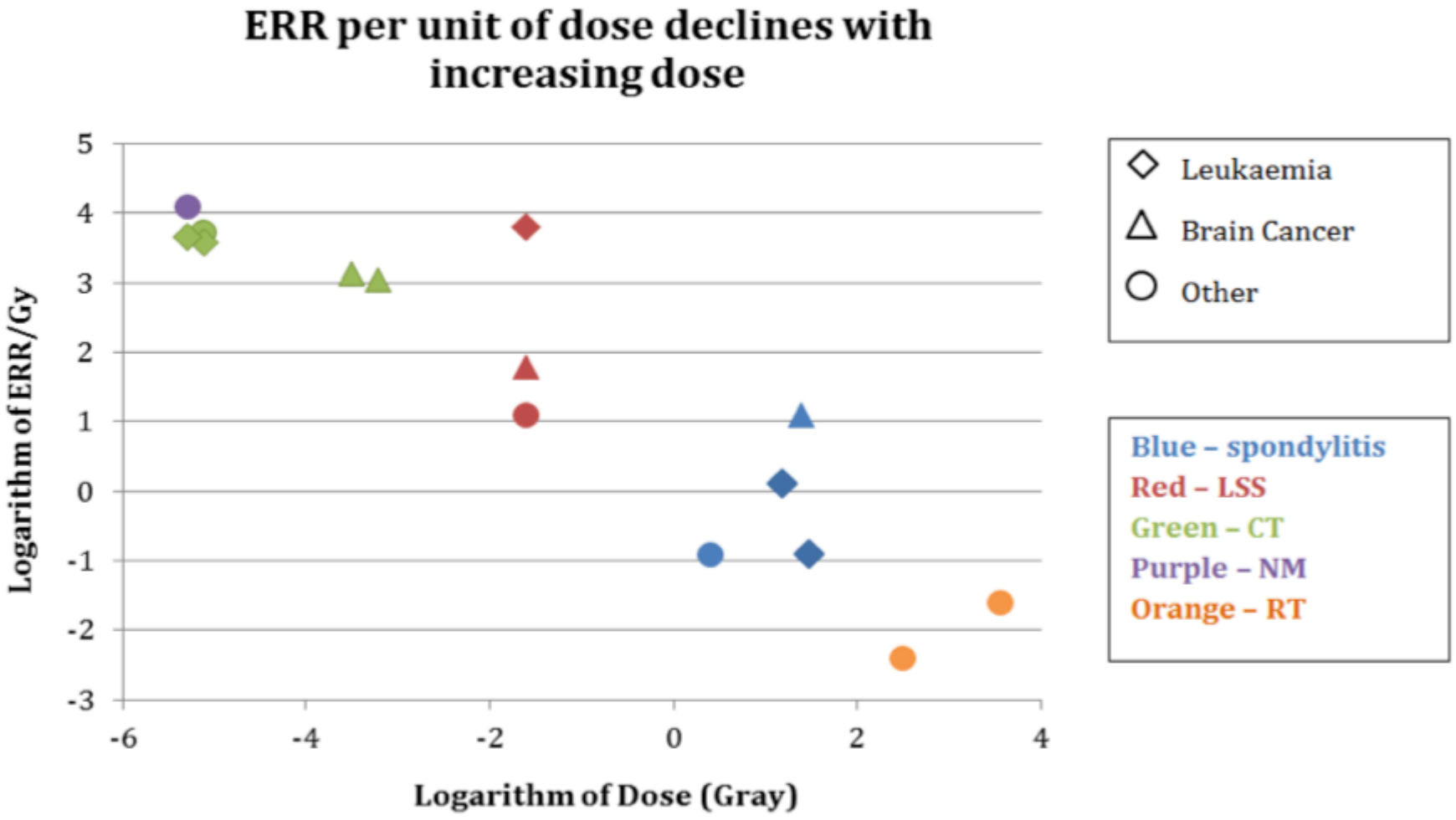
- ERR/dose estimates from CT and NM exposures are substantially greater than from LSS
- Is there bias inflating the CT/NM estimates?
  - Reverse causation/ confounding by indication
  - Under-estimation of CT doses in exposed cases
- What factors could explain a real difference?
  - Young age of exposure
  - Early cancer cases would be most susceptible
  - **Larger ERR/dose coefficient at low doses**
    - **Mean dose from CT scans is much lower than in LSS**
    - Cell killing at high doses
    - Bystander and other homeostatic effects at lower doses

Orders of magnitude in ERR/Gy

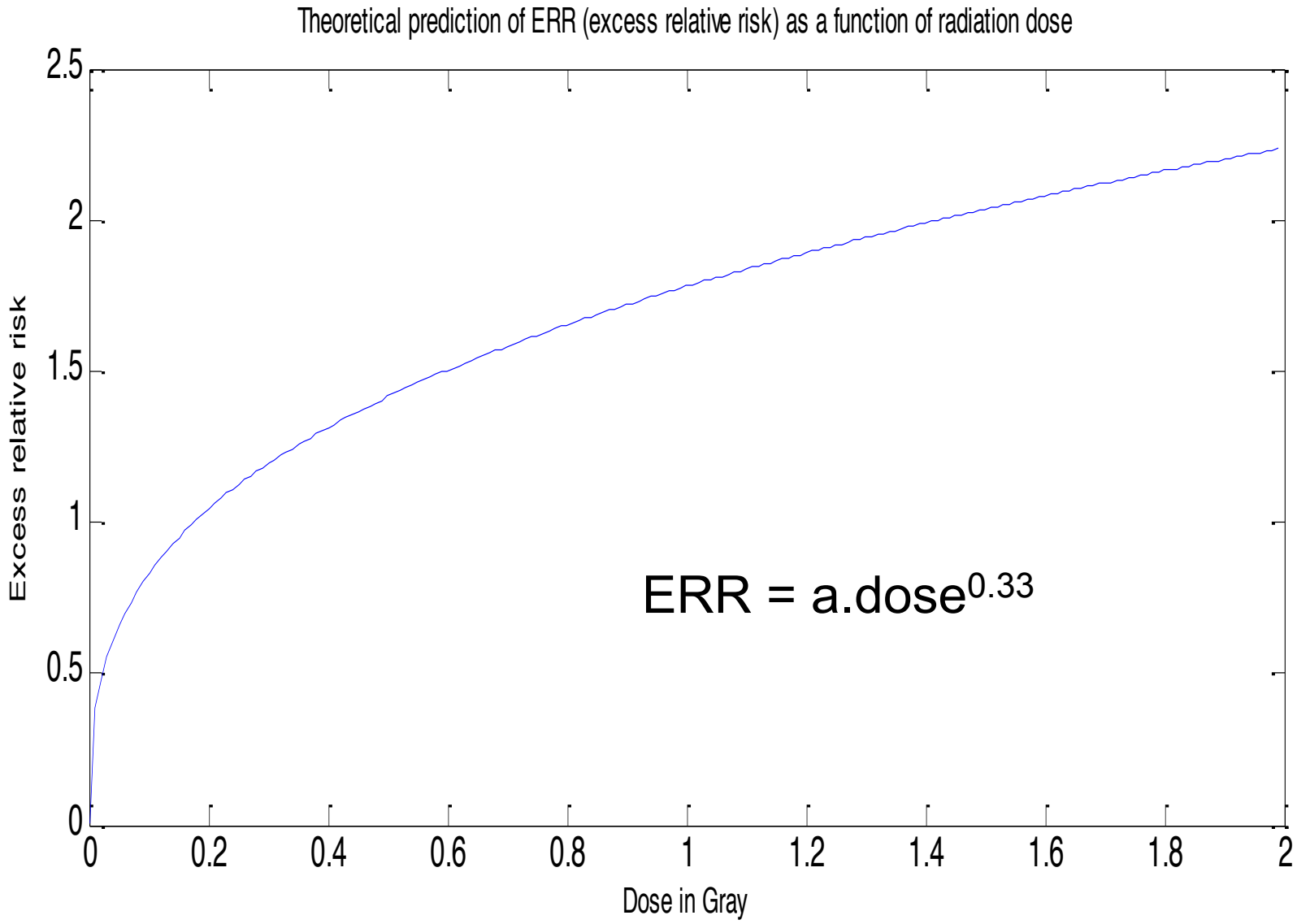
Type of exposure	DOSE RANGE	Estimated ERR/Gy
Radiotherapy	Up to 50+ Gy	0.10
Atomic survivors	Up to 5 Gy	0.60
CT scans	Up to 100 mGy	20
Nuclear medicine	Up to 20 mSv	60

These data are consistent with the idea that the dose-response curve is steepest at the lowest doses of radiation – arguably because of greater susceptibility of the few persons getting cancers at short lags, and because of the bystander response, cell killing and other biological responses.

ERR/Gy is less at higher doses



A supralinear model for ERR



Significance of a supralinear model for ERR

- The slope of the curve is likely influenced by cell killing at high doses and homeostatic effects (DNA repair and bystander response) at lower doses.
- Calculation of credibility intervals is unlikely to change the generic shape of the curve.
- If **cancer risk per unit of dose is really greater at low doses**, it is likely that background radiation is contributing to background rates of cancer.
- ***Longer follow-up of CT-exposed cohorts will help to answer these important "low-dose radiation" questions***.

SUMMARY 1

- The Australian CT scan study cohort was exposed to more low dose radiation (<100 mGy) than the LSS cohort of atomic survivors –and at a lower average dose and younger average age.
- Risks of leukaemia following CT scan radiation are quite consistent with the risks from the LSS of atomic bomb survivors.
- Some 60% of CT scans are scans of the head, with an average organ dose of 40 mGy, so that the increase in brain cancers in the CT cohorts is not surprising.

SUMMARY 2

- Modelling suggests that almost all of the excess cancers at more than 12 months after CT were actually caused by CT-scan radiation
- Excess cancer in the early years after exposure probably occur in persons who are most susceptible, for stochastic &/or genetic reasons.
- The dose response curve for radiation is **much** steeper at lower doses and at short lags because of:
  - Genetic susceptibility and stochastic selection
  - Homeostatic mechanisms such as the bystander response
  - Cell killing at higher doses
- Important implications for radiation protection!

Future work - questions

1. Finalise individual (organ) dosimetry
2. Explore cancer risks following nuclear medicine (NM) procedures in more detail
3. Explore “reverse causation” in more detail
4. Test biologically-based models for low-dose radiation effects
5. Assess ERR/dose, attributable risks, liability and compensation issues in more detail
6. Extend follow-up by 5 years to December 2012
7. Extend follow-up by 10 years to December 2017

SUMMARY OF MODEL RESULTS

	Model E1	Model E2
Posterior log likelihood at median parameter values	-24682	-24664
Estimated proportion of (incident) diagnosed cancers due to reverse causation	30.6% at 1 year lag 6.4% at 2 year lag 2.1% at 3 year lag	21.5% at 1 year lag 4.3% at 2 year lag 1.5% at 3 year lag
ERR per mSv (from 95% credibility estimates)	0.047-0.065 Assumed constant over all attained ages	Age 10 0.110-0.160 Age 20 0.055-0.080 Age 30 0.036-0.053

Modelling the lag period

Basic idea

The observed distribution of lag periods between CT exposure and diagnosis of cancer depends upon one or other of two processes

- **Reverse causation** – where the CT is prompted by early symptoms of cancer or by a pre-cancerous condition.
- **Excess cancers caused by radiation** from the CT scan

We model these two processes to compare their magnitudes at different lag periods.

Methods - data

- We used data from our follow-up of cancer incidence in almost 11 million young Australians, including more than 680,000 exposed to at least one diagnostic computed tomography (CT) scan .
- We examined diagnoses of any cancer (C00 to C96 – ICD 10);
- We defined the lag period as the interval between the date of any first recorded CT scan and the date of any later diagnosis of a new cancer.
- For categorical and ordinal analyses, lag period was measured to the nearest quarter year.

Model for reverse causation lags

We consider a process where an early symptom of cancer triggers a CT scan, and we are interested in the lag period between the scan and the date of cancer diagnosis.

The simplest model is to assume that the average rate of diagnosis (***r***) following the scan is constant, so that the lag period follows an exponential distribution.

$$flagR,r = Re\uparrow -r.lag$$

Models for reverse causation lags - 2

If the rate of diagnosis after a CT scan is not homogeneous, the distribution of reverse causation lag periods ***(x)*** will be different.

For example, if *r* varies between individuals, according to:

$$f(r|a)=a\uparrow i\, r\uparrow i-1\, e\uparrow -ar$$ then $$fxa = a\uparrow i /(a+x)\uparrow i$$.

An additional parameter R, measuring the notional rate at zero lag, is weighted by the population person years for the age and sex group at each lag period. In practice, R is defined to absorb *r* or *a* in the numerator. We tested several distributions, and found consistently better fits for *i* = 3.

Model: $$f\downarrow i\, xa,R = R/(a+x)\uparrow 3$$

Model for excess relative risk (ERR)

The simplest assumption is:

Model E1 $ERR = \beta . dose$

However, for most cancers, incidence increases with age. Evidence from the Life Span Study and from stochastic theory suggests that the ERR (excess rate ratio) can be modelled as a function of dose and attained age:

Model E2 $ERR = \beta . dose / age^{\uparrow}$

ERR is not directly dependent on *lag,* but as *age* = *age at exposure* + *lag,* this formula "explains" why ERR is greater after short lags and early ages of exposure.

Model Implementation

- If there were no effects of exposure, then within each stratum of age and sex, the expected risk of a cancer at a given lag would be proportional to the person years for the stratum that fell within that lag period since exposure, relative to the total person years for the stratum.
- If there were effects of causation and reverse causation, then the expected risk of cancer would be increased in proportion to the person years for each lag in each age and sex stratum.
- We used an iterative proportional fitting algorithm to calculate the likelihood of the observations given the model, and we used a Bayesian framework with non-informative priors and an MCMC algorithm to estimate credibility intervals for the parameters of interest.

Fitting the models

1. A mixture model, stratified by age and sex, was used to explain the incidence of excess cancers by lag period.
2. The model added estimated contributions from the separate effects of “reverse causation” and “causation”.
3. A Bayesian approach was used to estimate parameters of the model by Markov Chain Monte Carlo (MCMC), given the observed lag periods.

From the mixture model we derived the probability that an excess cancer (occurring at a particular lag within each age and sex stratum) was due to either to “reverse causation” or “causation”.

$$Pr(RC) = Reverse\ Causation\ incidence/Total\ incidence$$

Significance of a supralinear model for ERR

- The slope of the curve is likely influenced by cell killing at high doses and homeostatic effects (DNA repair and bystander response) at lower doses.
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