EPI-CT – statistical challenges in a European study of radiation exposure from pediatric CTs and cancer risk

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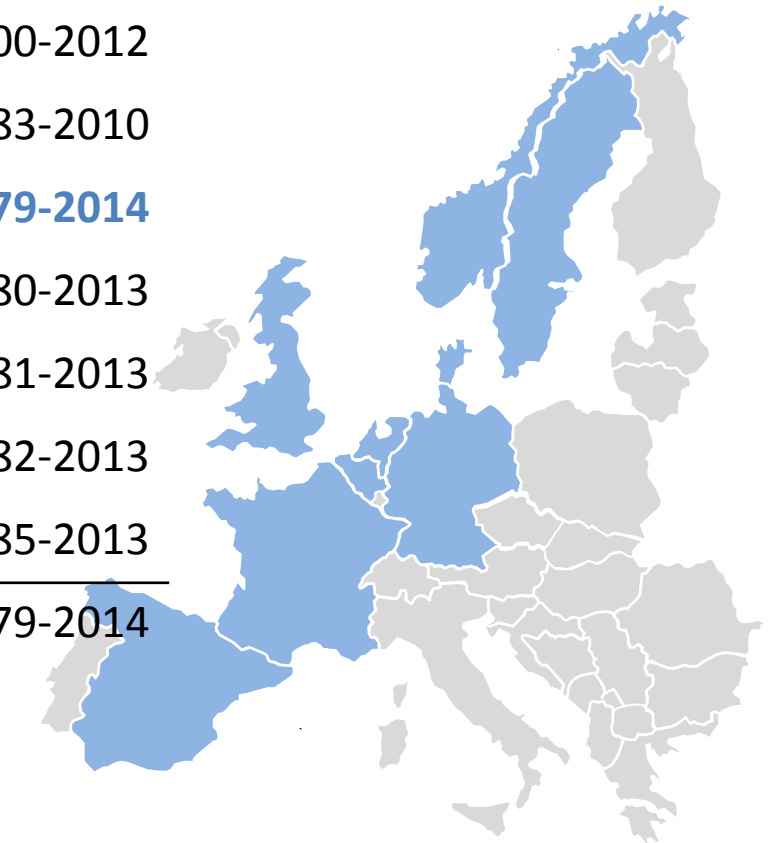
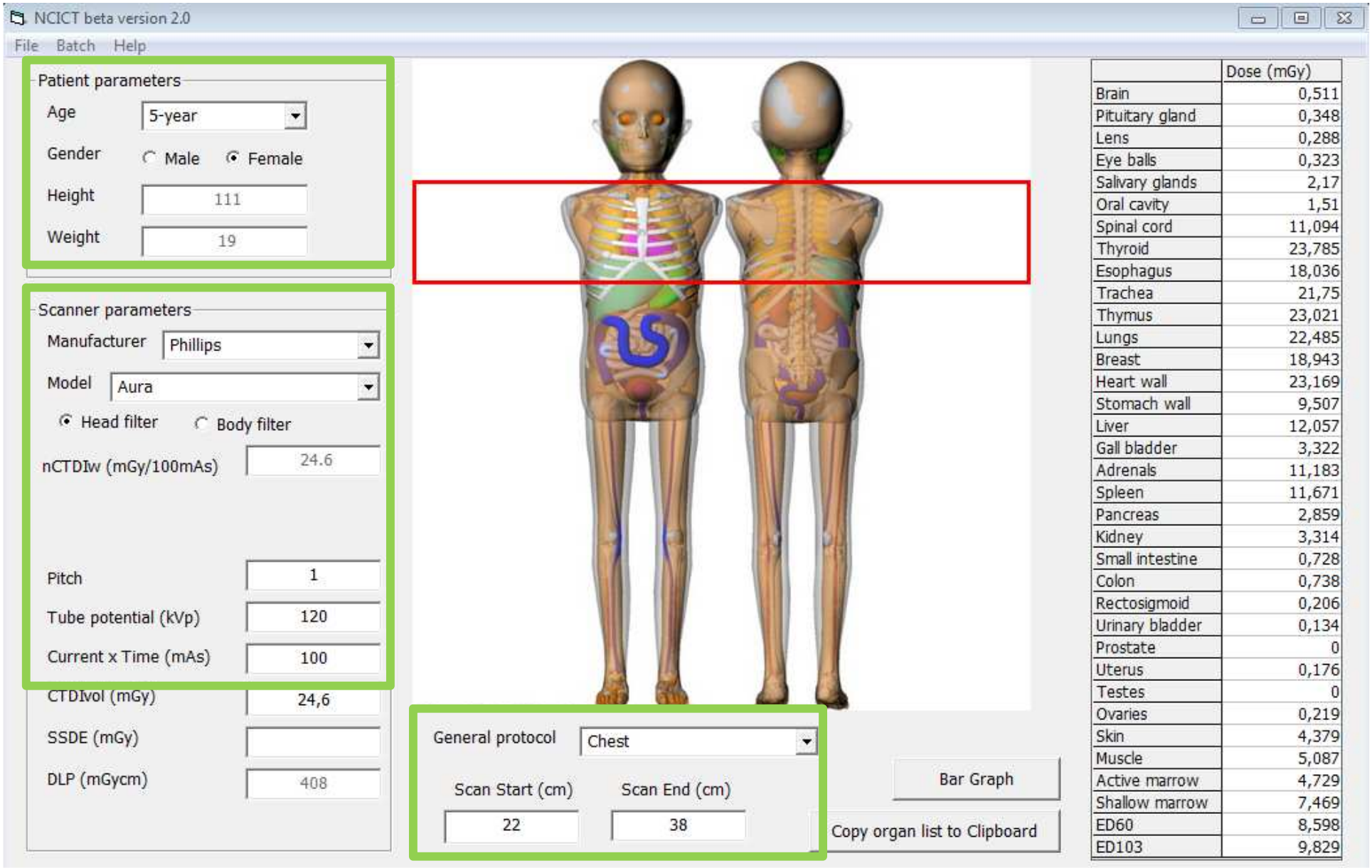
Country	Hospitals	Patients	Period
Belgium	2	17,506	2000-2012
Denmark	2	9,800	2001-2012
France	23	136,138	2000-2012
Germany	20	83,000	1983-2010
Netherlands	**37**	**162,886**	**1979-2014**
Norway	19	87,477	1980-2013
Spain	18	139,483	1981-2013
Sweden	7	96,229	1982-2013
UK	89	405,211	1985-2013
Total	217	1,137,730	1979-2014



Exposure

- CT-related radiation doses absorbed by
  - red bone marrow for leukemia analysis
  - brain for brain tumor analysis
- Estimated as function of scanner- and patient-related factors (e.g. scanner model and associated scanner settings, body part scanned, patient's age, sex and body size)

Organ dose estimation from a CT: NCICT



	Dose (mGy)
Brain	0,511
Pituitary gland	0,348
Lens	0,288
Eye balls	0,323
Salivary glands	2,17
Oral cavity	1,51
Spinal cord	11,094
Thyroid	23,785
Esophagus	18,036
Trachea	21,75
Thymus	23,021
Lungs	22,485
Breast	18,943
Heart wall	23,169
Stomach wall	9,507
Liver	12,057
Gall bladder	3,322
Adrenals	11,183
Spleen	11,671
Pancreas	2,859
Kidney	3,314
Small intestine	0,728
Colon	0,738
Rectosigmoid	0,206
Urinary bladder	0,134
Prostate	0
Uterus	0,176
Testes	0
Ovaries	0,219
Skin	4,379
Muscle	5,087
Active marrow	4,729
Shallow marrow	7,469
ED60	8,598
ED103	9,829

Risk analysis

- Internal comparison:
  - 2 time-dependent and lagged exposure metrics:
    (1) Number of (relevant) CTs
    (2) Cumulative absorbed organ dose
  - Survival analysis risk model: $RR = 1+\beta \cdot D$
  - Covariates: sex, calendar year, country, SES
- Additional analyses:
  (1) SIR
  (2) Assessment of curvature
  (3) Effect modification
  (4) Uncertainty

Previous results – are they true?

- Better: Is entire observed effect due to CT-related radiation exposure?
- Legitimate reasons for caution
  - Record-linkage design: lack of information on potential confounders
  - Dose estimation: relatively crude stratified single imputation based on survey (Kim et al. 2012) & uncertainty ignored
- Criticism: Letters, NCRP, UNSCEAR, Walsh et al.
- Concern: possible overestimation of risks due to
  - Underestimation of dose (CTs prior to enrollment or in non-participating hospitals, repeat CTs, other imaging)
  - Confounding by reason for scan
- Critics did not provide any data

Confounding by indication

- Undiagnosed cancer or precancerous condition that causes symptoms warranting a CT examination (prodromal disease)

  Example: headache caused by tiny & slow-growing brain tumor

- Medical condition that increases both the probability of having a CT scan & of developing cancer

  Example: Down syndrome – lung problems – CT – leukemia

- Reverse causation

Cancer susceptibility syndromes

	General population CSS prevalence (per 100,000)				
RR (CSS–Cancer)	<1	1-<5	5-<25	25-<50	50-160
1-2	AT[L] Trisomy 8[L] Gorlin[B]	-	Sotos[L]	CF[L]	-
2-15	Biallelic Lynch[B,L]	NF type 2[B]	Turcot[B] Gardner's[B]	Turner[B]	Noonan[L]
15-50	-	-	Li-Fraumeni[B]	NF type 1[B]	**Down[L]**
>50	-	VHL[B]	**TSC[B]**	-	-

RR = Relative risk
NF = Neurofibromatosis
CF = Cystic fibrosis

CSS = Cancer susceptibility syndromes
AT = Ataxia teleangiectasia

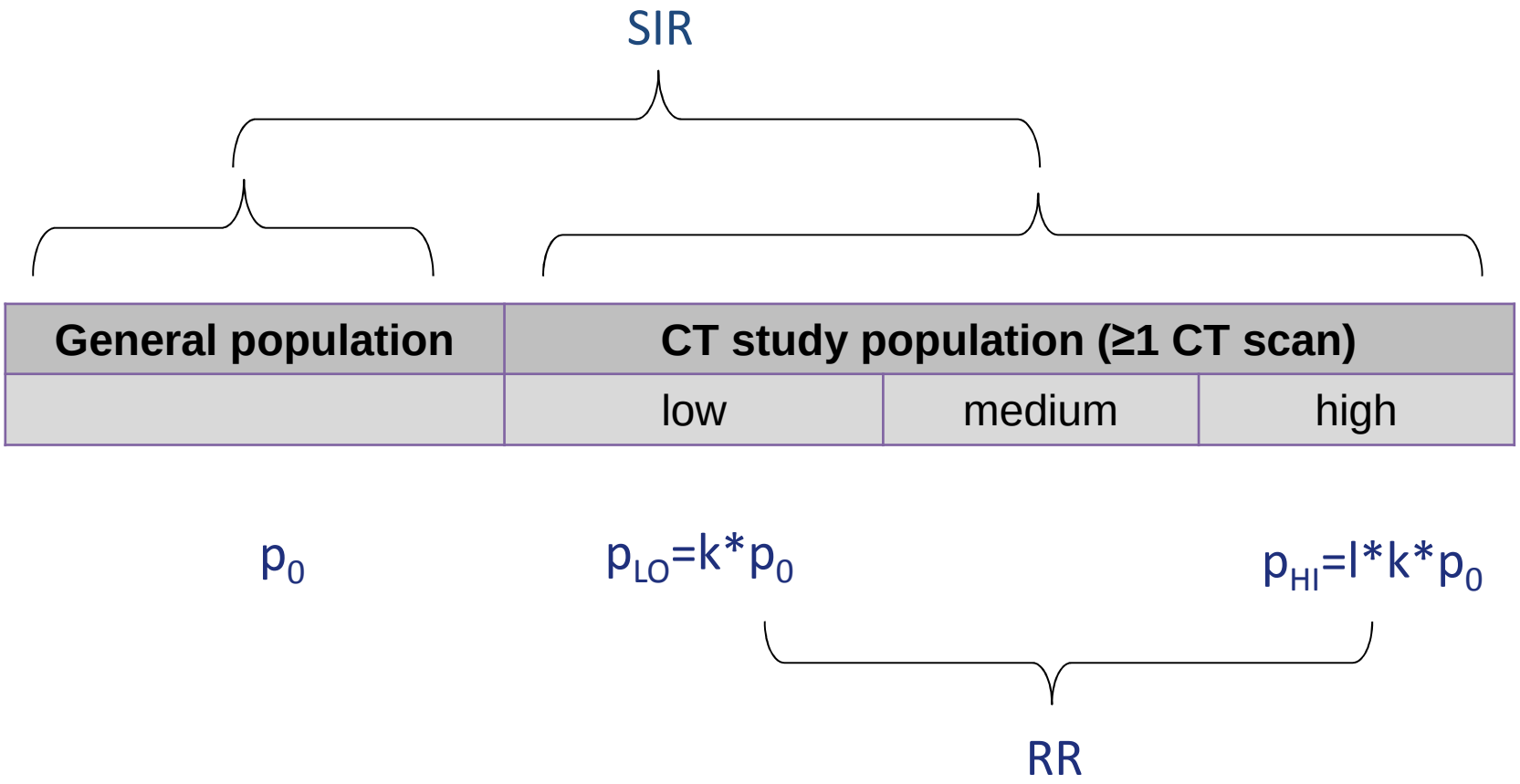
[B] Brain tumors
[L] Leukemia

Bias calculation

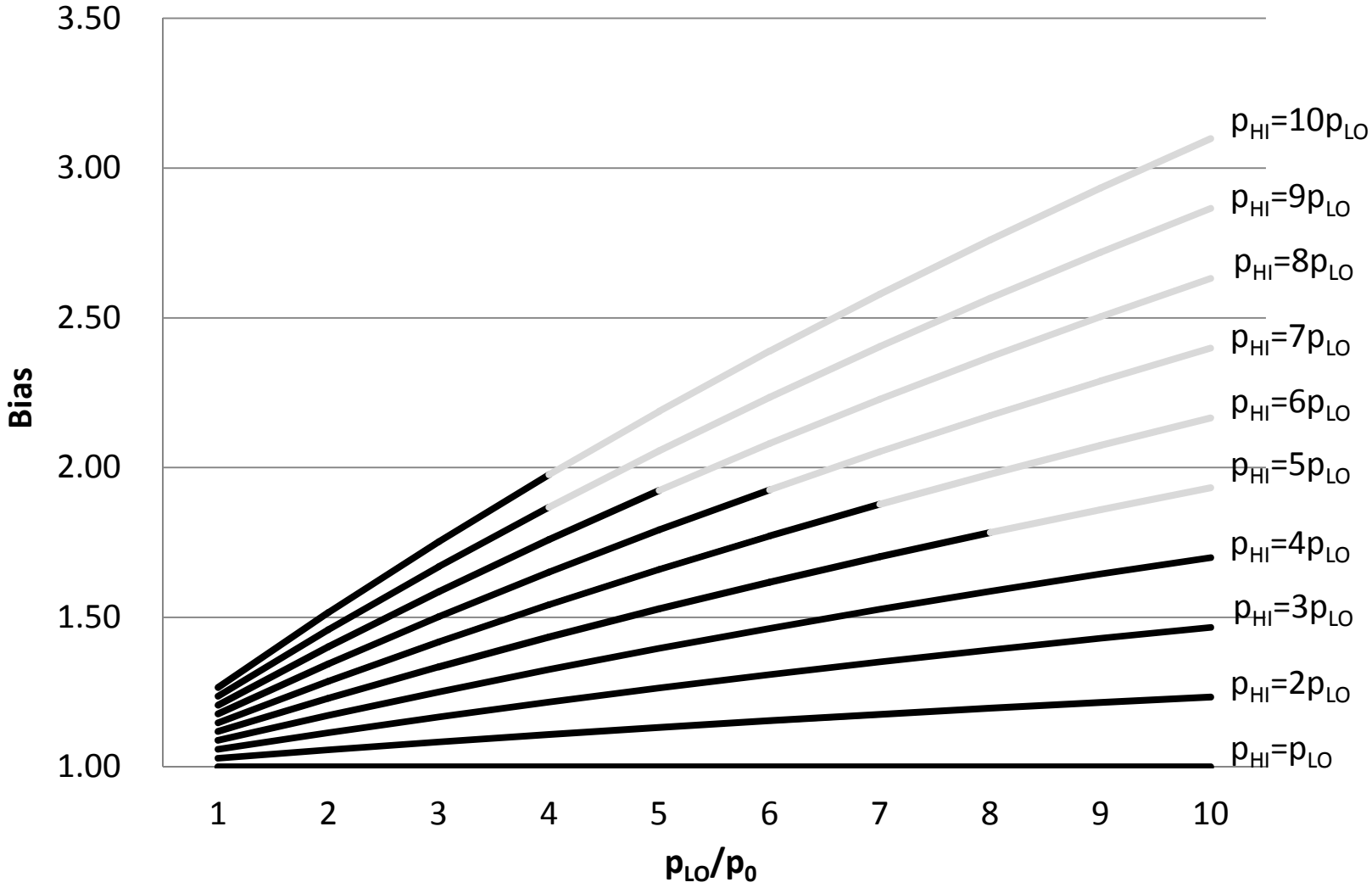
$$Bias = \frac{RR_{OBS}}{RR_{ADJ}} = \frac{RR_{CD} * p_{HI} + (1 - p_{HI})}{RR_{CD} * p_{LO} + (1 - p_{LO})}$$

(Axelson 1979)

RR_{OBS}	RR(cancer, high vs. low exposure) omitting CSS	
RR_{ADJ}	Ditto adjusted for CSS	
RR_{CD}	RR(cancer, CSS) in general population	Literature
p_0	General population CSS prevalence	Literature
$p_{LO} = k*p_0$	CSS prevalence in low exposed	k = 1,…, 10
$p_{HI} = l*p_{LO}$	CSS prevalence in high exposed	l = 1, …, 10


SIR
General population
CT study population (≥1 CT scan)
low
medium
high
p_0
$p_{LO}=k*p_0$
$p_{HI}=l*k*p_0$
RR

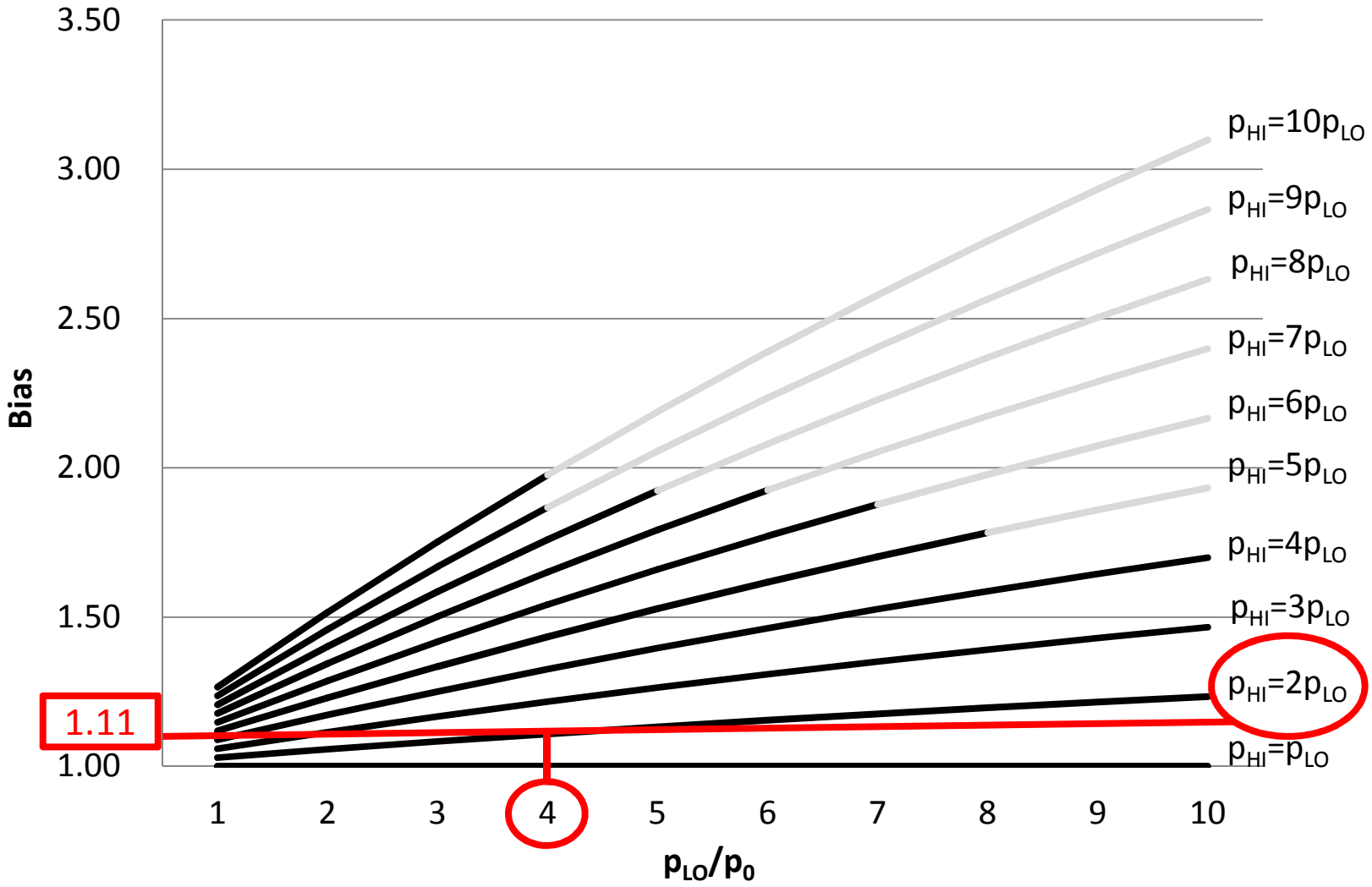
Down syndrome – leukemia



Scenario based on expert opinion

- 1 additional chest CT <10 years of age for 20% of all children with Down
- Several CTs due to Down-related morbidity very unlikely
- 20 CTs/1,000 Down patients/year due to Down
- Dutch general population: 7 CTs/1,000 children/year
- $p_{HI} \approx p_{LO}$ and $p_{LO}/p_0 = 27/7 \approx 4 \rightarrow$ bias < 20% for SIR & RR

Down syndrome – leukemia



Preliminary conclusion

- CSS unlikely to substantially confound radiation-related leukemia risks
- Potentially substantial confounding of brain tumor risks by TSC
- Empirical data on uptake of CT among CSS patients urgently needed
- Bias of ERR?

Simulation study

- Generate data from Dutch Pediatric CT study
- Outcome: leukemia
- Risk model: linear ERR model

Life table-based approach to data simulation

- Described by Richardson (2003) and Shuryak et al (2014)

- 3 steps:

1. Specify size of cohort

2. Assign to each cohort member his/her gender, year of first CT, age at first CT, type of first CT & associated RBM dose

3. Track each subject year after year until occurrence of: leukemia Dx, other cancer Dx, death, end of study

Richardson (2003). Power calculations for survival analyses via Monte Carlo estimation. Am J Ind Med 44:532-539.

Shuryak, Lubin, Brenner (2014). Potential for adult-based epidemiological studies to characterize overall cancer risks associated with a lifetime of CT scans. Rad Res 181(6), 584–591.

Preliminary simulation results

N=150,000, exponential RR (Cox) model, 500 generated datasets

	ERR per mGy		
	0	**0.04**	**0.1**
Mean	-0.003	0.039	0.101
Standard deviation	0.030	0.023	0.013
Mean relative bias	-	2.5%	1%
Mean no. of leukemias	41	60	119.9
Mean computing time (min)	3.2	3.58	4.92

* Computing time = time to generate & analyze a single dataset.

N=150,000, linear ERR model, 500 generated datasets

	ERR per mGy		
	0	**0.04**	**0.1**
Mean	0.026	0.065	0.141
Standard deviation	0.060	0.092	0.160
Mean relative bias	-	62.5%	41%
Mean no. of leukemias	41	55.9	77.3
Mean computing time* (min)	4.1	3.9	3.3

* Computing time = time to generate & analyze a single dataset.

N=150,000, linear ERR model, 500 generated datasets

10-fold background incidence

	ERR per mGy		
	0	**0.04**	**0.1**
Mean	0.001	0.042	0.105
Standard deviation	0.010	0.018	0.030
Mean relative bias	-	5%	5%
Mean no. of leukemias	403.5	547.3	765.2
Mean computing time* (min)	9.7	12.8	17.7

* Computing time = time to generate & analyze a single dataset.

N=1,000,000, linear ERR model, 15 generated datasets

	ERR per mGy		
	0	**0.04**	**0.1**
Mean	0.003	0.040	0.102
Standard deviation	0.013	0.021	0.036
Mean relative bias	-	0%	2%
Mean no. of leukemias	279.13	337.47	513.87
Mean data simulation time (min)	15.08	15.08	14.23
Mean model fitting time (min)	20.01	29.57	43.67
Mean total simulation time (min)	35.69	45.26	58.50

Preliminary results for DS

- DS patients twice as common among children w/ 1+ CT vs general population
- DS patients have a 25% higher chance to undergo a chest CT vs non-DS patients

N=150,000, linear ERR model, 50 generated datasets

	ERR per mGy	
	0.04	**0.1**
Unadjusted mean	0.053	0.186
Adjusted mean	0.058	0.203
Mean relative bias	8.6%	8.4%
Mean no. of leukemias	63.6	90
Mean no. of DS subjects	479.4	482.6

Plans

- Refine simulation (>1 CT/yr, CT exams other than head/chest/abdomen, body parts by age, etc.)
- Confounding scenarios (CSS, SES, missing data)
- Reduce computer time

Uncertainty in dose estimation

- 2DMC method to create realizations of doses which represent uncertainty
- Naïve approach: arithmetic mean of realizations
- Monte Carlo Maximum Likelihood method (Stayner et al 2007)
- Bayesian model averaging-type approach (Kwon et al 2015)

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worldwide
cancer research
formerly known as AICR