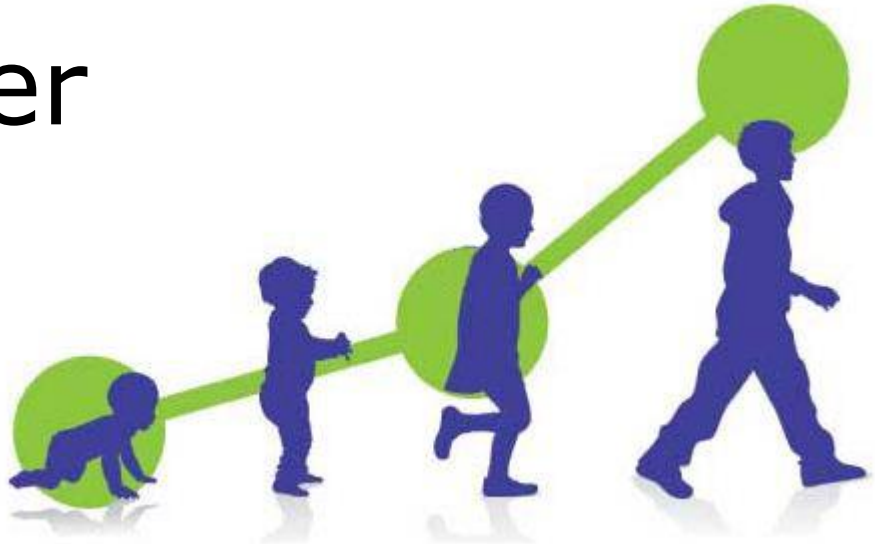
Birth order and childhood cancer

I4C Oxford, November 2015



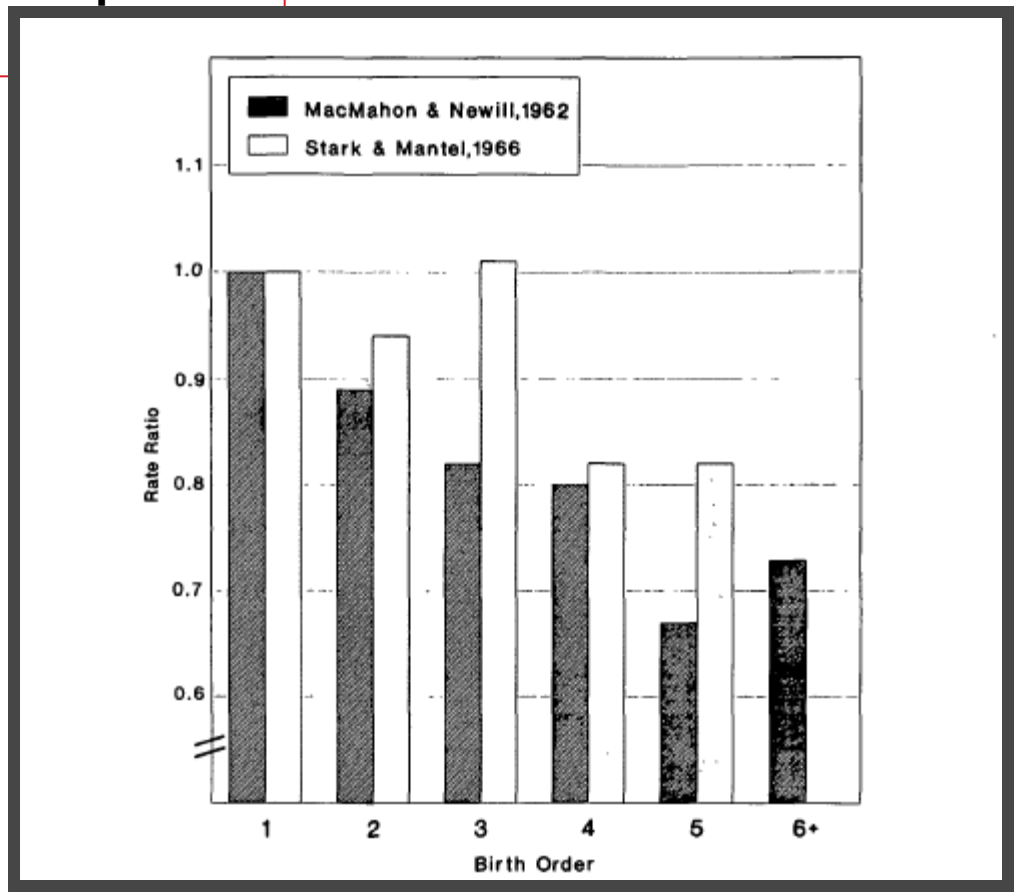
Ora Paltiel, Hadassah Medical Center, Jerusalem

Writing and analysis : Gary Phillips, Stan Lemeshow, Terry Dwyer
Data Pooling: Gabriella Tikellis
Data: The cohorts

Theoretical background and early literature

Greaves hypothesis:early infection exposure is protective for development of future overt leukemia.

Birth order and sibship size are considered proxies for exposure to infection



Radiation Protection Dosimetry (2008), Vol. 132, No. 2, pp. 267–272
Advance Access publication 22 October 2008
doi:10.1093/rpd/ncn263

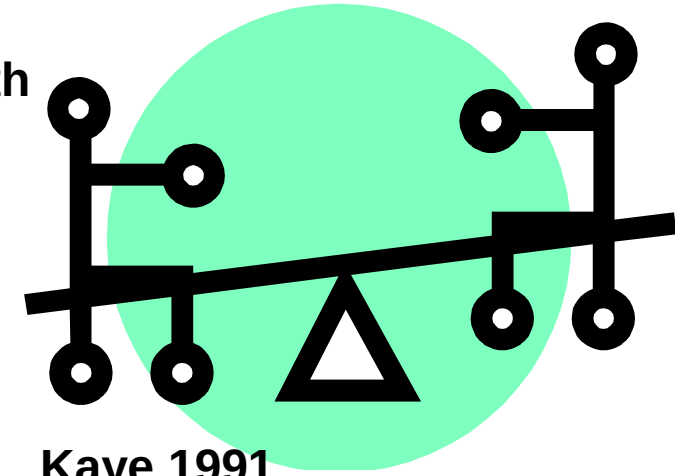
HOST, FAMILY AND COMMUNITY PROXIES FOR INFECTIONS POTENTIALLY ASSOCIATED WITH LEUKAEMIA

Graham Richard Law*

Infection	Raises risk of infection	Infection assessment
Virus		
Herpes simplex virus type 1	↑ younger siblings	Blood sample
Epstein–Barr virus	→ younger siblings	Blood sample
Respiratory syncytial virus	↑ birth order	Nasopharyngeal sample
	↑ birth order	Nasopharyngeal sample
Bacteria		
Helicobacter pylori	↑ number of siblings	Breath test
	↑ birth order	Blood sample
	↑ birth order	Blood sample
Protozoa		
Giardia duodenalis	↑ birth order	Faecal sample
'General' infections	↓ birth order	Medical notes
	→ birth order	Medical notes

Historical Seesaw- Birth order and Leukemia

Shaw 1984 AmJEpi "Cases less likely to be birth order 1



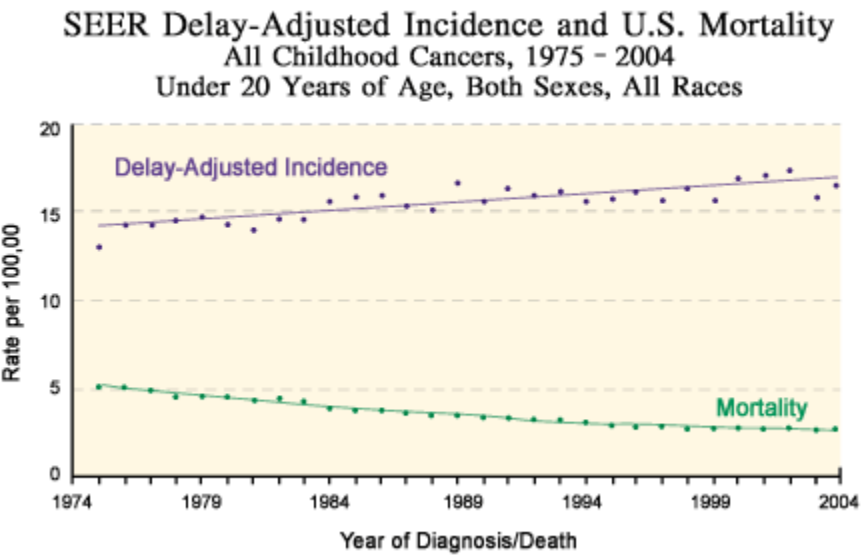
Van Steensel-Moll AmJ Epi 1986 "RR first born 1.8(1-2.7)"

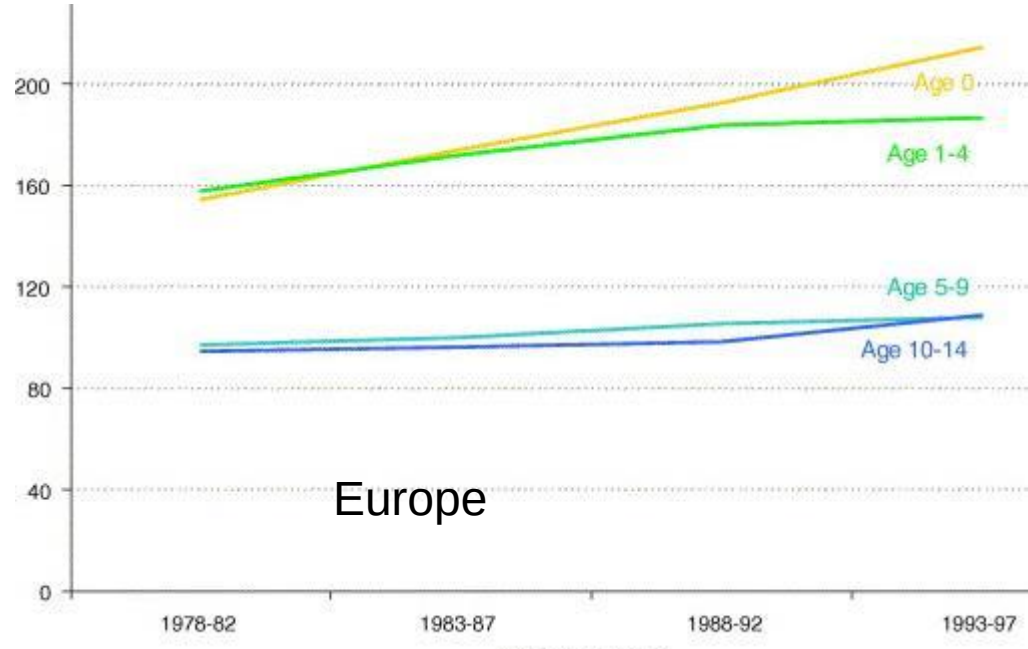
Kaye 1991 Cancer "No association with birth order"

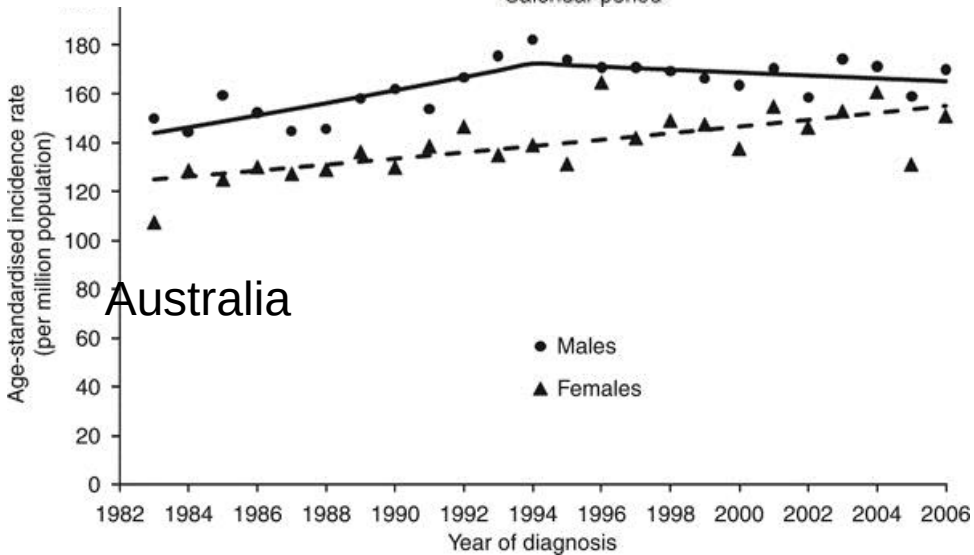
Table 1. Number of publications (references in parentheses) for risk of disease with increasing birth order in publications 1997–2007.

Risk with increasing birth order	Leukaemia	ALL
Increased	2 (24,25)	4 (24,26–28)
No change	5 (27,29–32)	4 (33–36)
Decreased	1 (37)	2 (28,38)

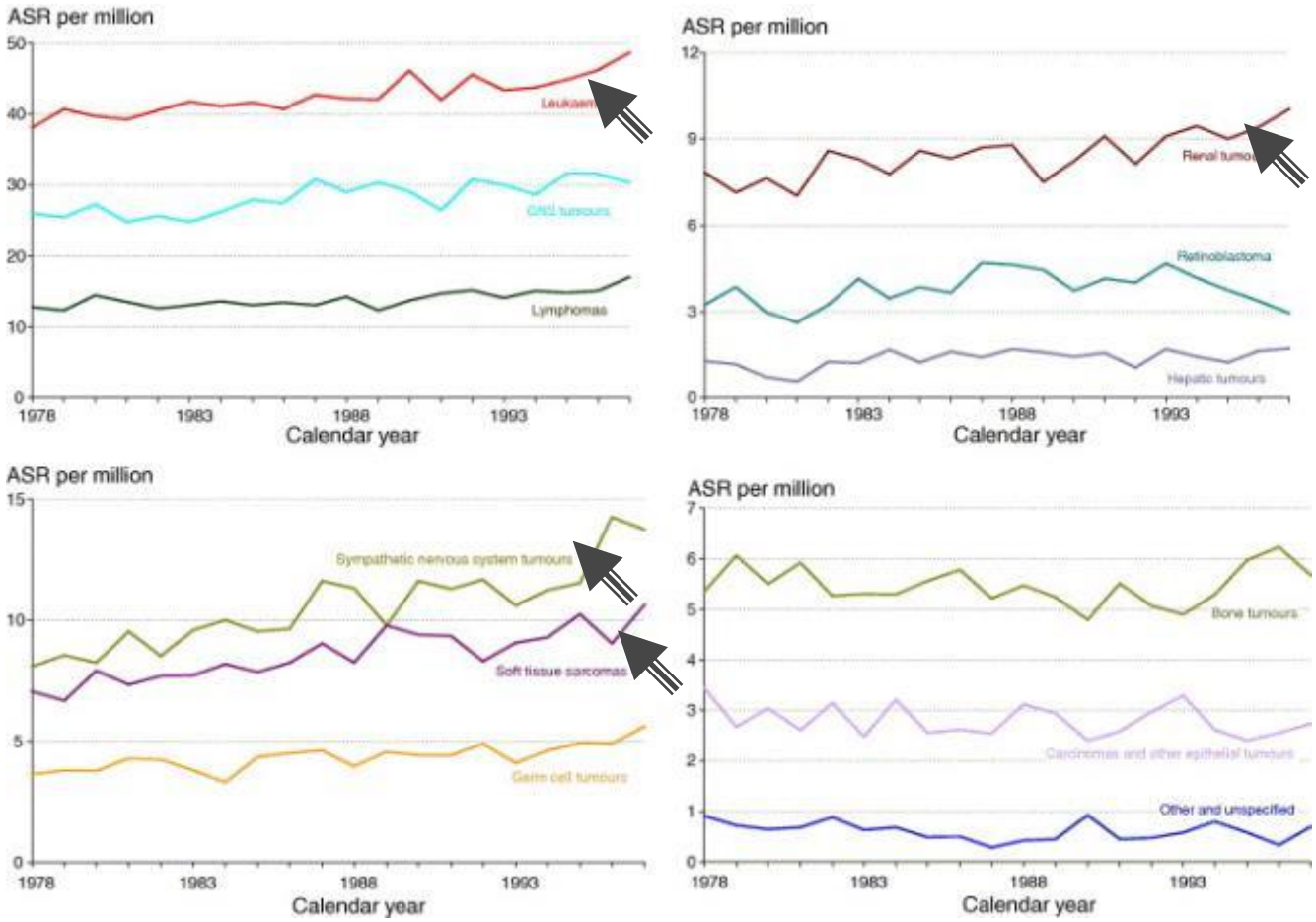
Case for action
1. Rising childhood cancer incidence







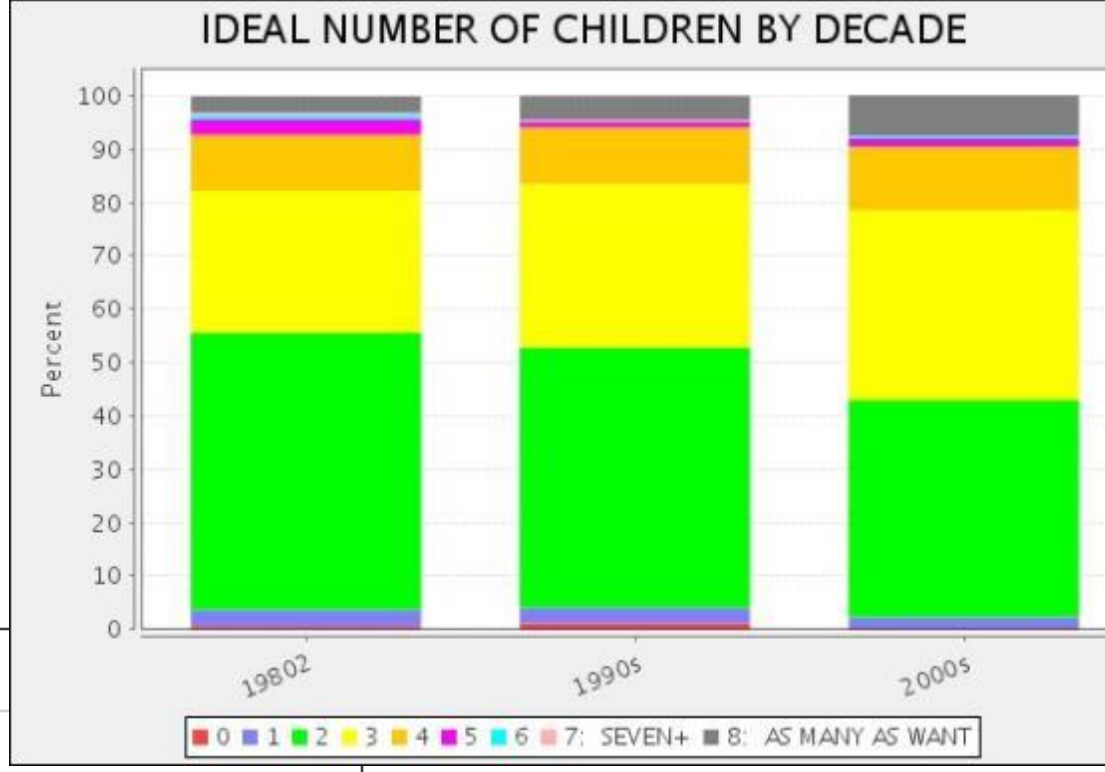
Case for action
1. Rising childhood cancer incidence

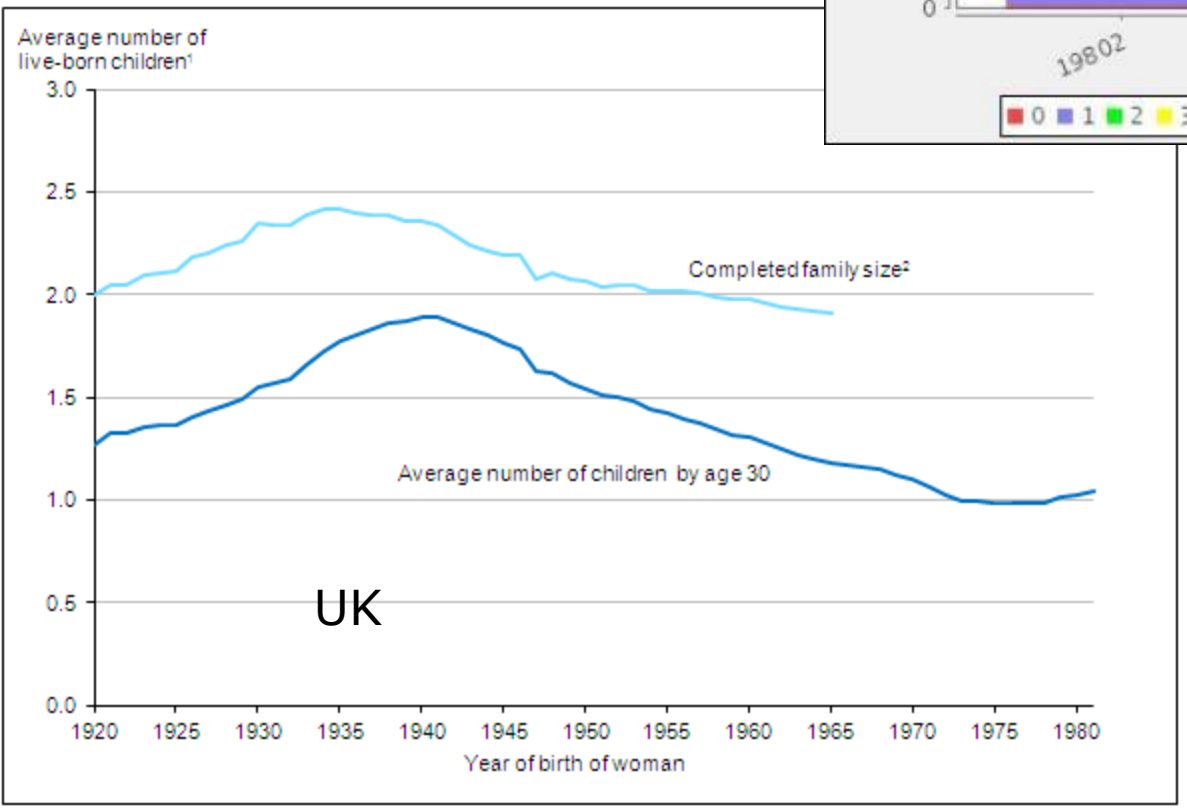


Time trends of cancer incidence in European children (1978–1997): Report from the Automated Childhood Cancer Information System project

European Journal of Cancer **Volume 42, Issue 13, September 2006, Pages 1961–1971**

Case for action 2: Decreasing family size





Current Decade: Northern Californian Case-control study- refinement of exposures

Published in final edited form as:
Int J Cancer. 2011 April 1; 128(7): 1632–1643. doi:10.1002/ijc.25752.

Early life exposure to infections and risk of childhood acute lymphoblastic leukemia

Kevin Y. Urayama[1], **Xiaomei Ma**[2], **Steve Selvin**[1], **Catherine Metayer**[1], **Anand P. Chokkalingam**[1], **Joseph L. Wiemels**[3], **Monique Does**[1], **Jeffrey Chang**[4], **Alan Wong**[5], **Elizabeth Trachtenberg**[6], and **Patricia A. Buffler**[1]

- 669 ALL cases, 977 controls
- >50% hispanic

- Excluded infant leukemias
- C-ALL age 2-5 CD10 and CD19+

Int J Cancer. Author manuscript; available in PMC 2012 April 1.

Strong effect of Birth Order on ALL and c-ALL

Social contact measures [daycare attendance (thousand child-hours) and birth order
Northern California Childhood Leukemia Study, 1995–2008

	ALL	c-ALL	Controls	OR (95% CI)[1]	
	n (%)	*n* (%)	*n* (%)	ALL	c-ALL
Birth order					
First	131 (46.8)	67 (47.5)	171 (38.1)	1.00 (Ref)	1.00 (Ref)
Second	93 (33.2)	43 (30.5)	164 (36.5)	0.75 (0.53–1.06)	0.65 (0.41–1.04)
Third	45 (16.1)	25 (17.7)	84 (18.7)	0.62 (0.40–0.97)	0.68 (0.39–1.20)
≥Fourth	11 (3.9)	6 (4.3)	30 (6.7)	0.44 (0.21–0.92)	0.43 (0.17–1.14)
p trend				0.004	0.038
Non-firstborn	149 (53.2)	74 (52.5)	278 (61.9)	0.68 (0.50–0.92)	0.64 (0.42–0.96)

California study – effect of having a sibling, controlling for day care hours, infections

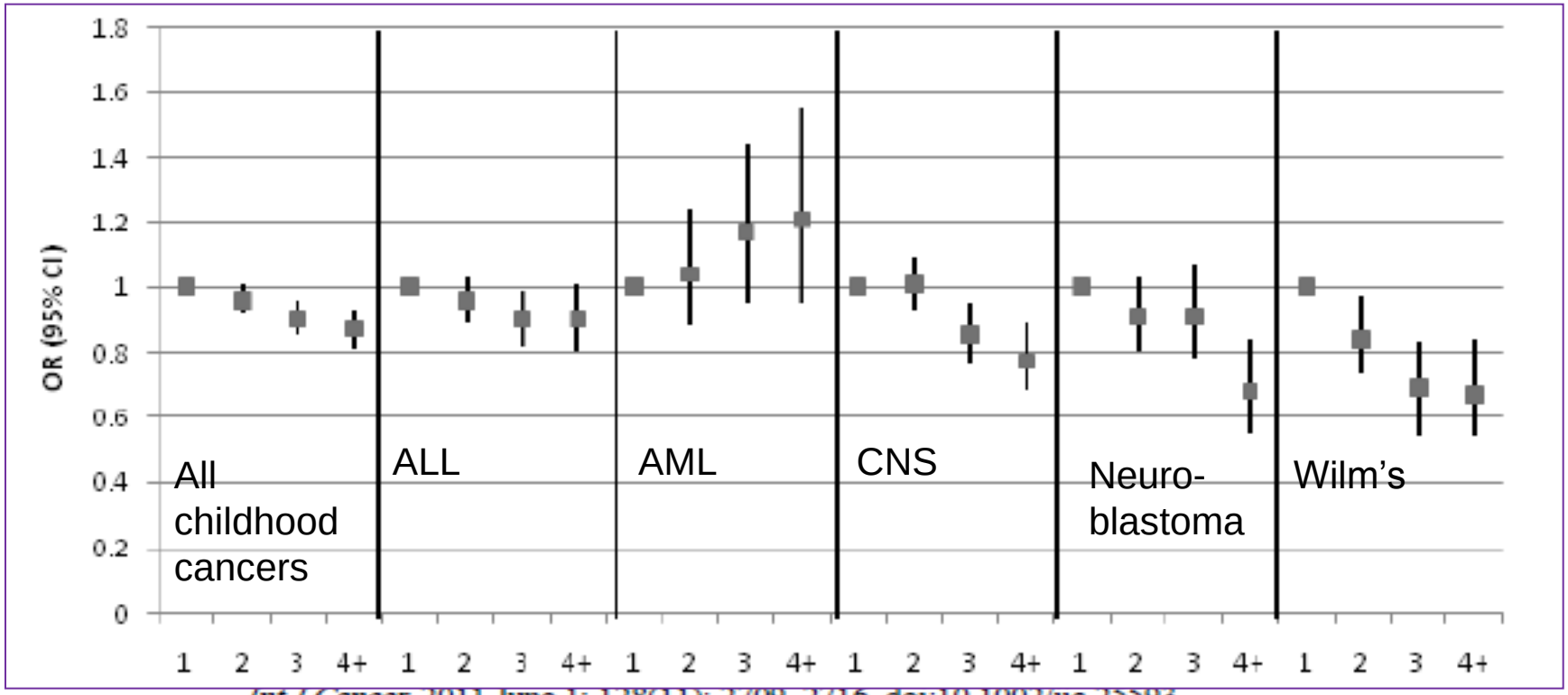
Multivariable analyses of social contact measures, ear infections during the first year of life, and risk o
Leukemia Study, 1995–2008

Social contacts and ear infection variables	Model 1[1] OR (95% CI)	Model 1[1] *p*	Model 2[1] OR (95% CI)	Model 2[1] *p*	Model 3[1] OR (95% CI)	Model 3[1] *p*
Non-Hispanic White						
Daycare child-hours[2] by age 6 months	0.91 (0.80–1.03)	0.142	0.89 (0.80–0.98)	0.024	0.83 (0.73–0.94)	0.004
Older siblings (yes *vs.* no)	0.67 (0.48–0.93)	0.016	0.65 (0.48–0.89)	0.006	0.59 (0.43–0.83)	0.002
Daycare child-hours*older siblings interaction	0.94 (0.75–1.18)	0.590	–	–	–	–
Ear infections (*vs.* none during 1st year)						
Age <6 months only	–	–	–	–	0.44 (0.19–1.02)	0.056
Age 6–11 months only	–	–	–	–	0.71 (0.46–1.08)	0.110
Both time periods (<6 and 6–11 months)	–	–	–	–	1.32 (0.83–2.11)	0.247

Int J Cancer. Author manuscript; available in PMC 2012 April 1.

Birth order and Risk of Childhood Cancer: A Pooled Analysis from Five U.S. States

Julie Von Behren[1], Logan G. Spector[2,3], Beth A. Mueller[4], Susan E. Carozza[5], Eric J. Chow[4], Erin E. Fox[6], Scott Horel[5], Kimberly J. Johnson[2], Colleen McLaughlin[7], Susan E. Puumala[2], Julie A. Ross[2,3], and Peggy Reynolds[1]



Int J Cancer. 2011 June 1; 128(11): 2709–2716. doi:10.1002/ijc.25593.

Details of the Five Studies included in the Pooled Analysis

State	Ages of Diagnosis	Years of Diagnosis	Years of Birth	No. of Cases (%)	No. of Controls (%)	Matching factors
California	28 days to 4 yrs	1988-1997	1983-1997	4177 (23.6)	8730 (15.1)	Birth year, sex
Minnesota	28 days to 14 yrs	1988-2004	1976-2004	2170 (12.3)	8735 (15.1)	Birth year
New York	28 days to 14 yrs	1985-2001	1970-2001	4357 (24.7)	12041 (20.8)	Birth year
Texas	28 days to 14 yrs	1990-1998	1975-1998	4647 (26.3)	4732 (8.2)	Birth year
Washington	28 days to 14 yrs	1980-2004	1980-2004	2321 (13.1)	23728 (40.9)	Birth year, sex

RESEARCH ARTICLE Open Access

Influence of family size and birth order on risk of cancer: a population-based study

5.7 million offspring of parents without cancer first-born as reference

Swedish Family cancer database

Relative risks for birth order and age at diagnosis

		Age at diagnosis < 50 years		Age at diagnosis ≥ 50 years	
			Birth order		Birth order
Cancer site	**(ICD-7 code)**	**N**	**RR (95% CI)**	**N**	**RR (95% CI)**
Salivary glands	**(142)**	**119**	**0.79 (0.63-0.99)**	**59**	**0.93 (0.65-1.33)**
Lung	(163 ,162)	589	**1.17** (1.04-1.31)	2201	1.03 (0.97-1.09)
Endometrium	(172)	213	0.72 (0.64-0.81)	321	0.87 (0.83-0.92)
Other female genital	(176)	128	1.34 (1.09-1.64)	101	1.03 (0.85-1.26)
Testis	(178)	1668	**0.90** (0.84-0.97)	65	0.78 (0.60-1.02)
Melanoma	(190)	2789	**0.88 (0.83-0.95)**	**1310**	**0.87 (0.81-0.93)**
Squamous cell skin	(191)	412	0.97 (0.84-1.12)	638	**0.87** (0.79-0.95)
Thyroid gland	**(194)**	**821**	**0.86 (0.79-0.95)**	**156**	**0.79 (0.64-0.97)**
Endocrine glands	(195)	1013	0.99 (0.91-1.09)	568	**0.87** (0.78-0.98)
Connective tissue	(197)	572	**0.88** (0.78-0.98)	161	1.00 (0.82-1.21)
Hodgkin lymphoma	(201)	1001	0.92 (0.84-1.01)	76	1.00 (0.75-1.33)
Leukaemia	(209 - 204)	2208	0.98 (0.90-1.06)	709	1.02 (0.93-1.12)
Any site	**(any)**	**29574**	**0.97 (0.94-0.99)**	**29479**	**0.96 (0.93-1.00)**

Reference group: first born child. Bold type, 95% CI does not include 1.00. Poisson regression adjusted for age, sex, period, region, socioeconomic status., N:number of cases

Bevier et al BMC Cancer 2011;11:163

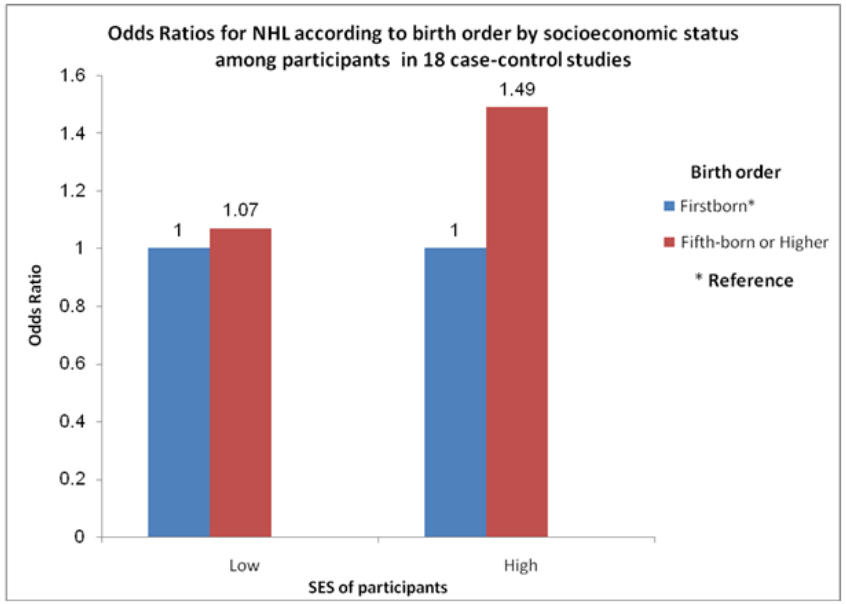
Study rationale

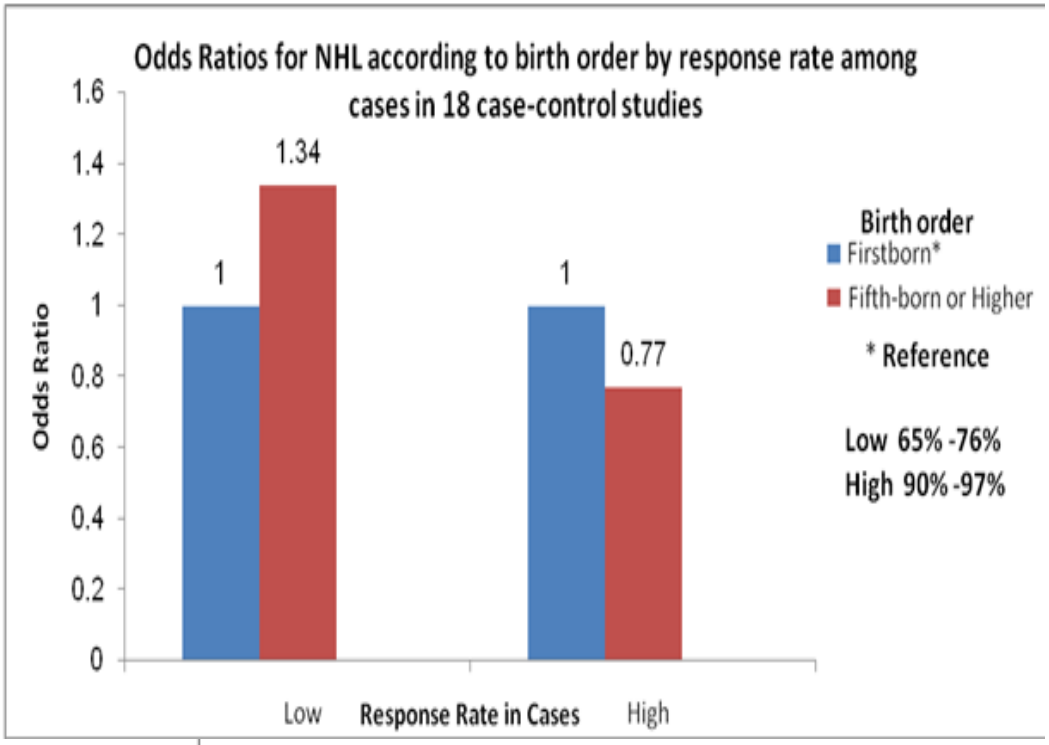
- Rising rates of childhood cancers
- Decreasing family size
- Uncertainty regarding the association

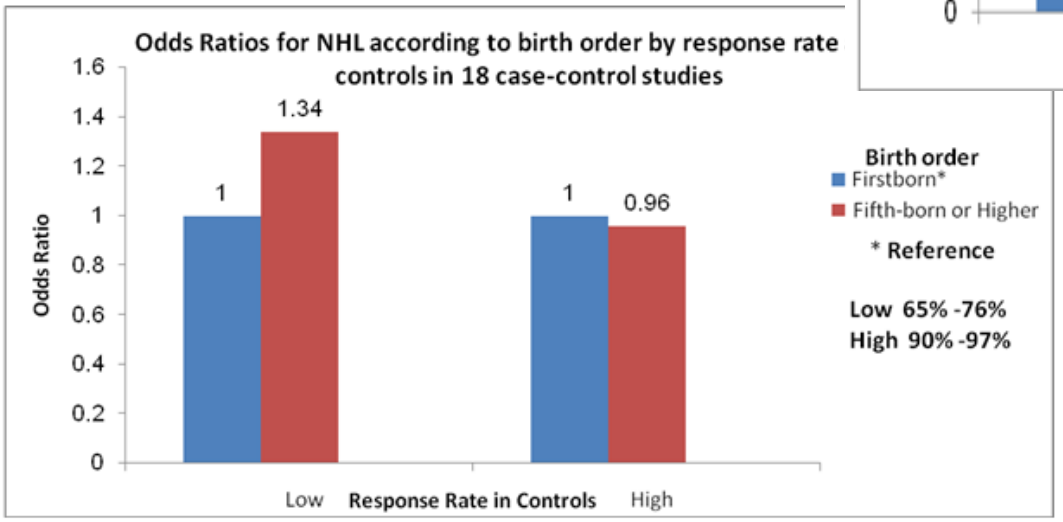
Potential strengths of pooled study I4C

- Few data from cohorts; bias in case-control studies
- Extensive exposure and socioeconomic data potentially available; potential to explore interactions
- Geographic and temporal representation
- Pooled data set exists

Bias in case control studies- by SES and response rates



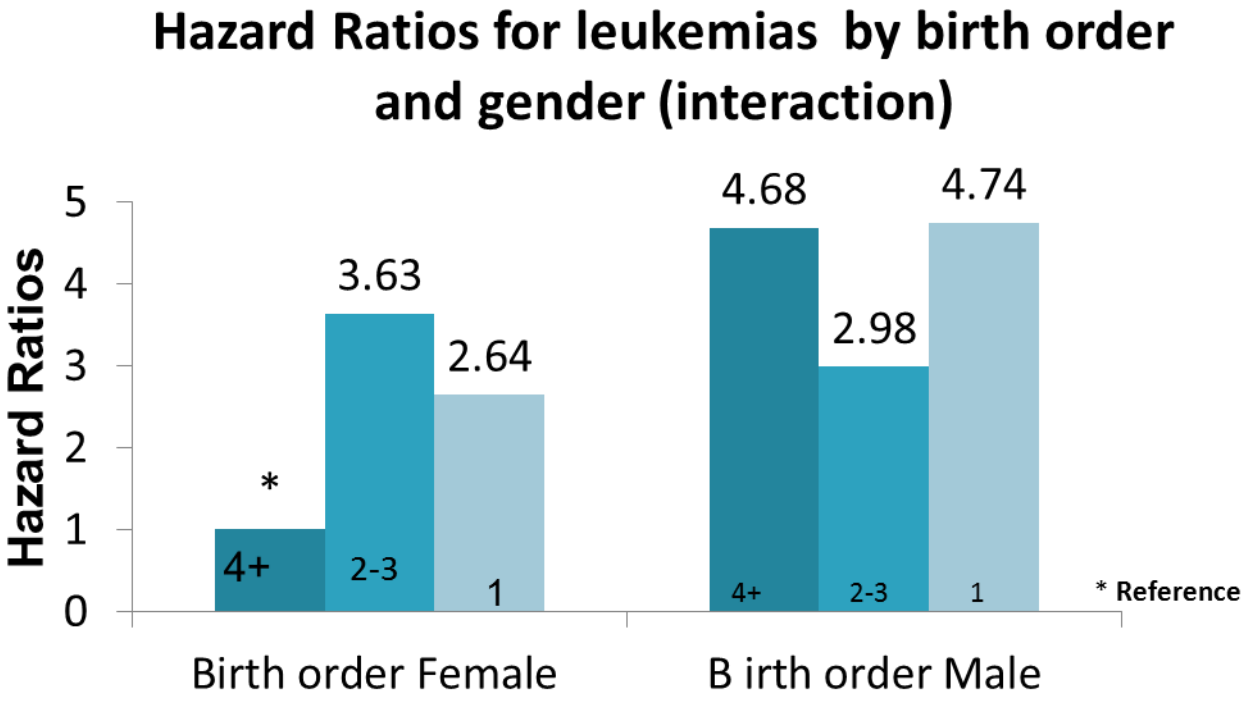




Source: Grulich et al ***Birth order and risk of Non-Hodgkin Lymphoma–True association or Bias***

Am J Epidemiol 2010;172:621–630

Preliminary data JPS: Significant interaction between birth order and gender



Males -higher risk of leukemia than females except in birth order 2-3 where females had greater risk

Females- being of higher birth order (4+) had a protective effect while in males higher birth order (4+) was associated with increased leukemia risk

Objective

- to assess the association between birth order and childhood cancer, leukemia, ALL, non-leukemia cancer in the pooled I4 C data base and to determine whether the association is modified by gender

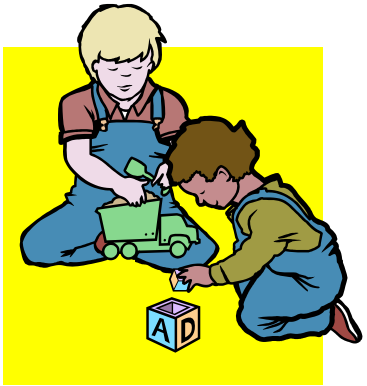
Methods

- Used pooled data set constructed for birth weight analysis (incl. imputed covariates); Cox regression, look at heterogeneity; stratified for study
- **Exposure variable** – first born or later born; continuous parity
- **Covariates**: study, year of birth, maternal age, paternal age, parental smoking, parental education, gest. age*, birth weight, (Day care attendance, childhood infection, breast feeding)
- **Outcomes:** All cancer, leukemia, ALL, non leukemia cancer
- **Modifiers**- gender of child and age at diagnosis

- *JPS with and without GA

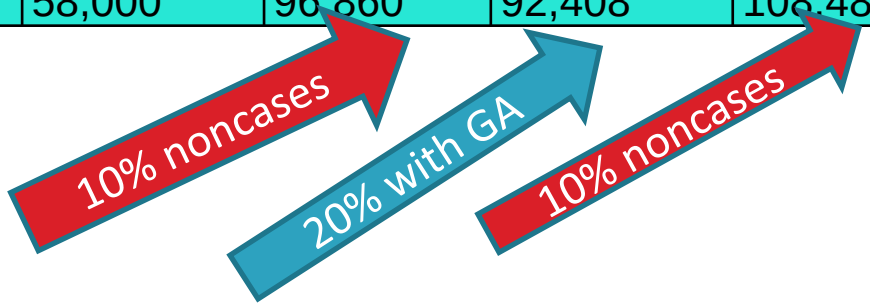
Power calculation

- For hazard ratio 1.7 (0.59), alpha 0.05, 110-117 events needed, power 0.8, presuming ~ 1/3 to 1/2 the children are first born



Pooled database

	ALSPAC	CPP	DNBC	JPS	MoBa	TIHS
Recruitment years	1991-1992	1959-1966	1996-2002	1964-1976	1999-2007	1987-1995
Total number of live births in cohort	14,062	58,000	96,860	92,408	108,487	10,628



Preliminary results: Case numbers and person-years

185,244 Subjects

Full data set

Cancer Type	Person-years	Cases	Incidence rate per 10,000 years	95% CI
Cancer	2,206,046	526	2.38	2.19 – 2.60
Leukemia	2,208,270	172	0.78	0.67 – 0.90
ALL	2,208,542	135	0.61	0.52 – 0.72
Non-leukemia	2,207,080	354	1.60	1.45 – 1.78

Subjects with data on gestational age and "later born"

Cancer Type	Person-years	Cases	Incidence rate per 10,000 years	95% CI
Cancer	1,144,459	372	3.25	2.94 – 3.60
Leukemia	1,145,791	133	1.16	0.98 – 1.38
ALL	1,145,915	110	0.96	0.80 – 1.16
Non-leukemia	1,145,155	239	2.09	1.84 – 2.37

Variables, covariates, and need for imputation

Variable	Missing	
	Yes	No
Gestational age	324	116,144
Paternal age	16,319	100,149
Maternal education ≥ 12	5,232	111,236
Any maternal DM	12,440	104,028
Any maternal smoking	4,776	111,692
Maternal height	13,982	102,486
Pre-pregnancy BMI ≥ 25	17,708	98,760
Total pregnancy weight change	17,856	98,612
Birth order	8,491	107,977
Maternal married	2,026	114,442

Absolute cancer risks vary by cohort

Absolute risk (cases per 10,000 person-years)	**ALSPAC**	**CPP**	**DNBC**	**JPS**	**MoBA**	**TIHS**	**Total**
ALL CANCERS	*1.079*	*1.517*	*1.5*				*1.125*
LEUKE							
							97
ACUTE LYMPHO LEUKEMIA							
	0.147	*0.340*	*0.464*	*0.263*	*0.678*	*0.145*	*0.341*
NON-LEUKEMIA CANCERS							
	0.931	*1.021*	*1.014*	*0.985*	*1.334*	*1.454*	*0.728*

But no significant heterogeneity for Birth order-cancer relationship

Main effect of later born vs first born

Cancer type	N	Model contains gestation-al age	Later born HR	95% CI	p-value
Cancer	113,409	Yes	0.827	0.671-1.019	0.075
Leukemia	113,409	Yes	0.762	0.537-1.080	0.127
ALL	113,409	Yes	**0.631**	**0.430-0.927**	0.019
Non-leukemia	113,409	Yes	0.867	0.667-1.126	0.284
Cancer	181,960	No	0.895	0.746-1.074	0.235
Leukemia	181,960	No	0.779	0.569-1.068	0.121
ALL	181,960	No	**0.622**	**0.465-0.944**	0.023
Non-leukemia	181,960	No	0.960	0.767-1.201	0.719

Main effect for continuous birth order

Cancer type	N	Model contains gestational age	Continuous birth order HR	95% CI	p-value
Cancer	107,669	YES	0.928	0.849-1.016	0.105
Leukemia	107,669		0.871	0.736-1.032	0.110
ALL	107,669		**0.814**	**0.666-0.994**	0.043
Non-leukemia	107,669		0.954	0.859-1.060	0.381
Cancer	176,206	No	0.991	0.938-1.046	0.738
Leukemia	176,206		0.910	0.808-1.024	0.116
ALL	176,206		**0.851**	**0.731-0.991**	0.038
Non-leukemia	176,206		1.018	0.958-1.082	0.568

Hazard ratio for later born with sex*LB interaction-Models without gestational age

Cancer type	N	Later born HR Female/ Male	95% CI Female/ Male	*p*-value Female/ Male
Cancer	181,960	0.937 0.864	0.714-1.229 0.679-1.099	0.637 0.235
Leukemia	181,960	0.928 0.665	0.589-1.462 0.433-1.022	0.748 0.063
ALL	181,960	0.850 **0.533**	0.507-1.425 **0.329-0.865**	0.538 0.010
Non-leukemia	181,960	0.943 0.972	0.672-1.324 0.725-1.302	0.737 0.848

Hazard ratio for later born sex*LB interaction models **with gestational age**

Cancer type	N	Later born HR Female/ Male	95% CI Female/ Male	*p*-value Female/ Male
Cancer	113,409	0.865 0.796	0.637-1.174 0.601-1.054	0.352 0.112
Leukemia	113,409	0.947 **0.607**	0.582-1.541 **0.370-0.996**	0.824 0.048
ALL	113,409	0.870 **0.449**	0.510-1.484 **0.258-0.781**	0.610 0.005
Non-leukemia	113,409	0.817 0.906	0.552-1.211 0.642-1.279	0.314 0.574

Summary and conclusions

- Protective effect of increasing birth order (or not being first born) on childhood leukemia, esp ALL
- Stronger effect for categorical variable

(misclassification of total parity)

- Significant interaction by gender of child –stronger effect in boys
- In sex stratified models, despite lower sample size, adjustment for GA strengthens the association

Mostly unstudied
Spector et al 2007; MLL no intxn

Next steps

- Obtain updated Scandinavian cases
- Look at specific nonleukemia sites?
- Biological or social explanation for gender interaction?
- Further adjustment for maternal age
- Suggestions?

Thank you!