Birth Weight and Childhood Cancer and Leukemia

Update from the I4C

Environmental Working Group on Birth Weight and Childhood Cancer

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Oxford, November 2015

Manuscript submitted

Birth weight and childhood cancer: an analysis of pooled data from 380000 live births-the International Childhood Cancer Cohort Consortium (I4C)

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Background- Big babies and leukemia

J. A. Ross et al

Table 1. Epidemiologic studies examining birthweight and childhood leukemia

Author (year)	Study type (*n* = leukemia cases)	Definition of high birthweight	Birthweight findings with leukemia (comments)
MacMahon (1962)[1]	Birth and death certificates: childhood cancer overall and by leukemia (*n* = 1,323)	Not applicable[a]	Positive association; no age stratification provided
Iversen (1966)[2]	Birth and death certificates: leukemia only (*n* = 258)	Not applicable[a]	Deficit of low birthweights in children with leukemia
Jackson (1968)[3]	Twins: leukemia only (*n* = 50)	Not available	Nearly 70 percent of the leukemic twins were heavier than the non-leukemic co-twin[b,c]
Fasal (1971)[4]	Case-control: leukemia only (*n* = 802)	Males (> 9 lb); Females (> 8.5 lb)	Overall odds ratio (OR) = 1.40; males 1.10, females 2.07[d]

American Journal of Epidemiology
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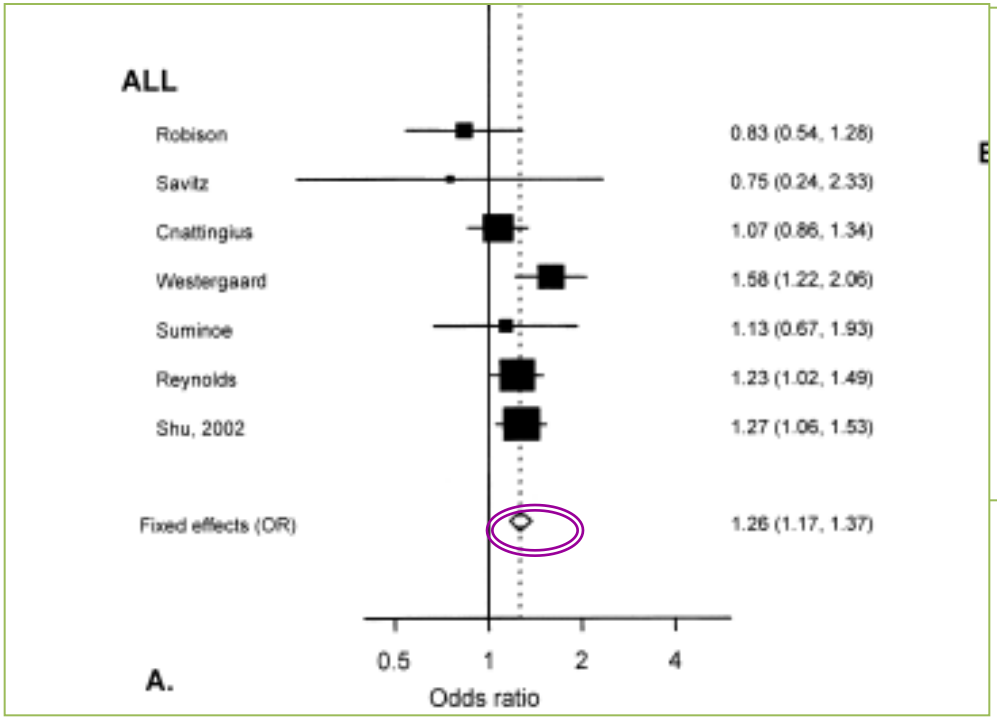
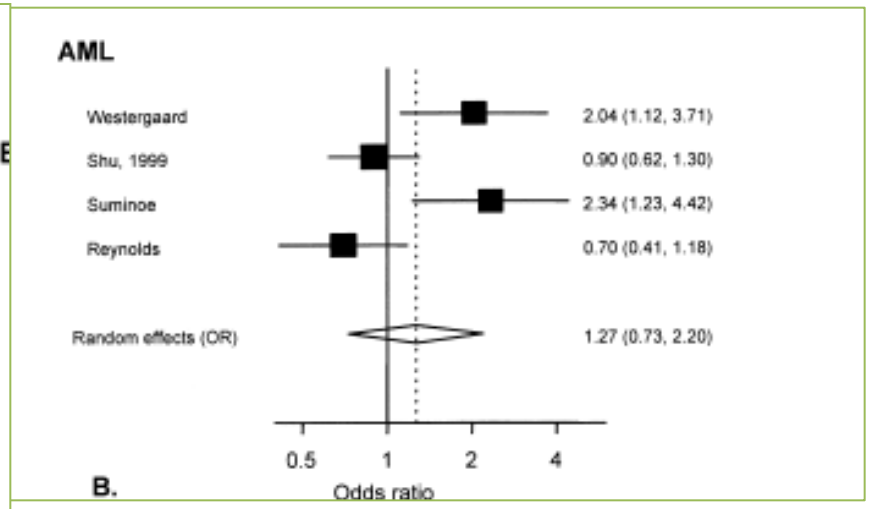
Vol. 158, No. 9
Printed in U.S.A.
DOI: 10.1093/aje/kwg210

META-ANALYSIS

Birth Weight as a Risk Factor for Childhood Leukemia: A Meta-Analysis of 18 Epidemiologic Studies

Lisa Lyngsie Hjalgrim[1], Tine Westergaard[1], Klaus Rostgaard[1], Kjeld Schmiegelow[2], Mads Melbye[1], Henrik Hjalgrim[1], and Eric A. Engels[3]





Determinants of birth weight

- Gestational age
- Birth length
- Child gender
- Altitude
- Birth order

- SES
- Ethnicity
- Smoking
- Gestational diabetes
- Maternal height
- Pre-pregnancy BMI
- Gestational weight gain

Beyond BWT – Fetal Growth- BWT corrected for gestational age

Pediatr Blood Cancer 2010;54:242–249

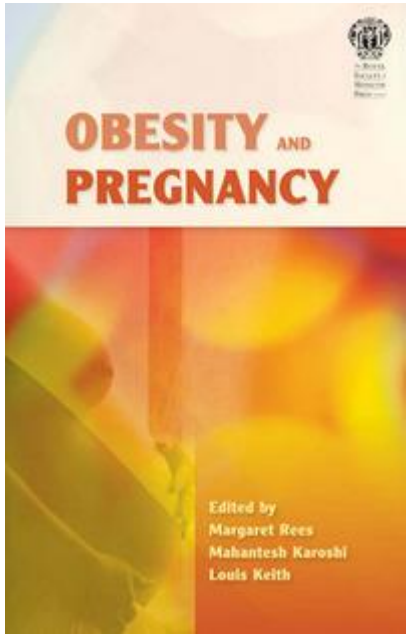
Comparison of Birth Weight Corrected for Gestational Age and Birth Weight Alone in Prediction of Development of Childhood Leukemia and Central Nervous System Tumors

Michael R. Sprehe, MD, MPH,[1] Nadia Barahmani, MD, MS,[1,2] Yumei Cao, PhD,[3] Tao Wang, MS,[4] Michele R. Forman, PhD,[1,3] Melissa Bondy, PhD,[2,3] and M. Fatih Okcu, MD, MPH[1,2]*

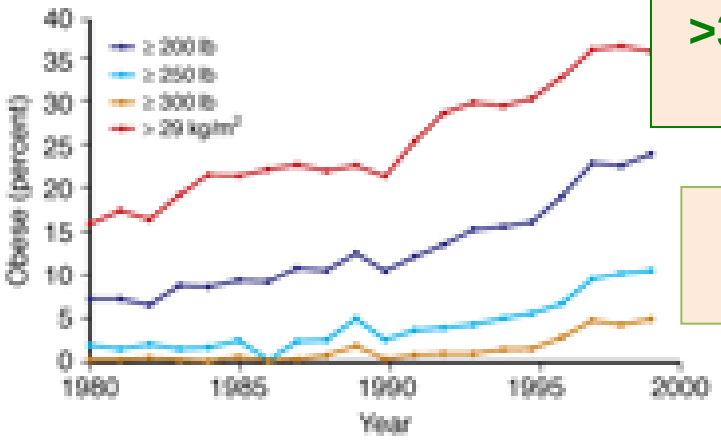
Birth certificate data of 2,254 children with cancer <5 years old at diagnosis and registered at Texas Cancer Registry 1995-2003 were compared to 11,734 age-matched controls.

	Total cases (n = 2,500[a]) OR (95% CI)	Total leukemia (n = 899) OR (95% CI)	ALL (n = 717) OR (95% CI)	AML (n = 120) OR (95% CI)
Weight-for-Age				
SGA	0.94 (0.81–1.09)	0.84 (0.65–1.08)	0.73 (0.54–0.98)	1.13 (0.63–2.04)
AGA[b]	1.0	1.0	1.0	1.0
LGA	1.24 (1.08–1.43)	1.39 (1.12–1.73)	1.57 (1.25–1.97)	0.76 (0.37–1.57)
Birth weight (g)				
Continuous (unit = 1 kg)	1.13 (1.04–1.22)	1.28 (1.12–1.44)	1.42 (1.23–1.63)	0.82 (0.60–1.12)
Categorical				
≤2,500	1.06 (0.88–1.27)	0.89 (0.65–1.22)	0.80 (0.56–1.16)	1.28 (0.64–2.53)
2,501–3,999[b]	1.0	1.0	1.0	1.0
≥4,000	1.27 (1.11–1.45)	1.44 (1.18–1.75)	1.59 (1.28–1.96)	0.74 (0.37–1.46)

- **BW corrected-for-gestational age was a better predictor than the model with BW alone**



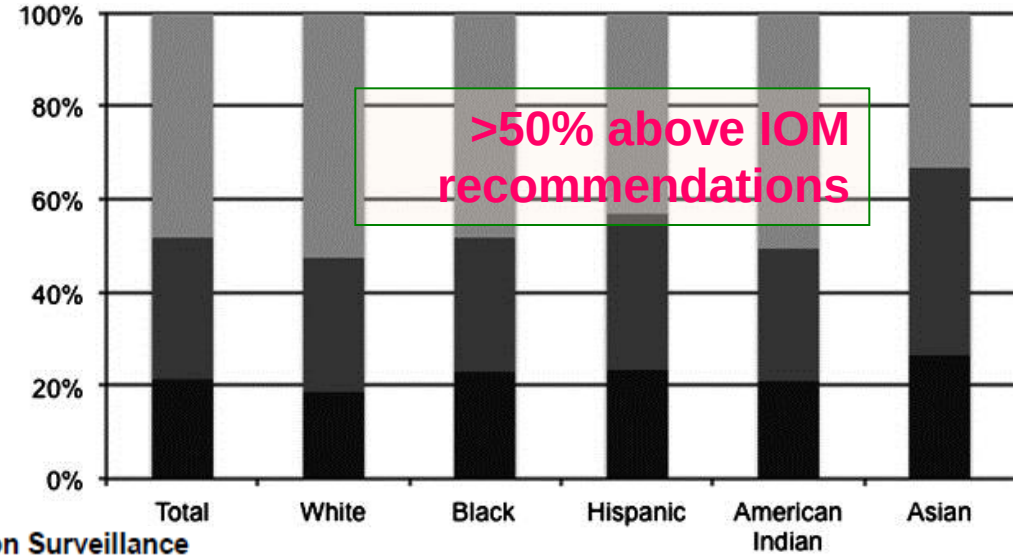
New case for action….



>30% BMI>29 kg/m2

Prevalence of obesity among pregnant women

Pre-pregnancy BMI	Recommended weight gain (pounds)	Recommended total gain (kg)
Low BMI (<19.8)	28 - 40 pounds	12.5 - 18 kg
Normal BMI (19.8 - 26.0)	25 - 35 pounds	11.5 - 16 kg
Hi BMI (26 - 29.0)	15 - 25 pounds	7 - 11.5 kg
Highest BMI (> 30)	≥12 pounds	≥6 kg



Maternal adiposity- important determinant of BW

Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy[1–3]

Ellen A Nohr, Michael Vaeth, Jennifer L Baker, Thorkild IA Sørensen, Jorn Olsen, and Kathleen M Rasmussen

TABLE 4

Neonatal outcomes according to prepregnancy BMI and gestational weight gain categories[1]

	Small-for-gestational-age (n = 58 342 with 5418 cases)		Large-for-gestational-age (n = 58 342 with 7206 cases)	
	Crude risk	Adjusted OR[2]	Crude risk	Adjusted OR[2]
	%		%	
Prepregnancy BMI				
Underweight	17.1	1.9 (1.7, 2.1)[4]	5.1	0.5 (0.4, 0.5)
Normal-weight	9.5	1.0 (ref.)	11.0	1.0 (ref.)
Overweight	7.7	0.7 (0.6, 0.8)	15.9	1.7 (1.6, 1.8)
Obese	7.4	0.5 (0.4, 0.6)	19.6	2.9 (2.7, 3.2)
Weight gain				
<10 kg	14.8	1.8 (1.6, 2.0)	9.1	0.7 (0.6, 0.8)
10–15 kg	10.1	1.0 (ref.)	9.7	1.0 (ref.)
16–19 kg	7.8	0.7 (0.7, 0.8)	13.3	1.6 (1.5, 1.7)
>20 kg	6.1	0.5 (0.5, 0.5)	18.8	2.6 (2.4, 2.8)
P^5		<0.01		

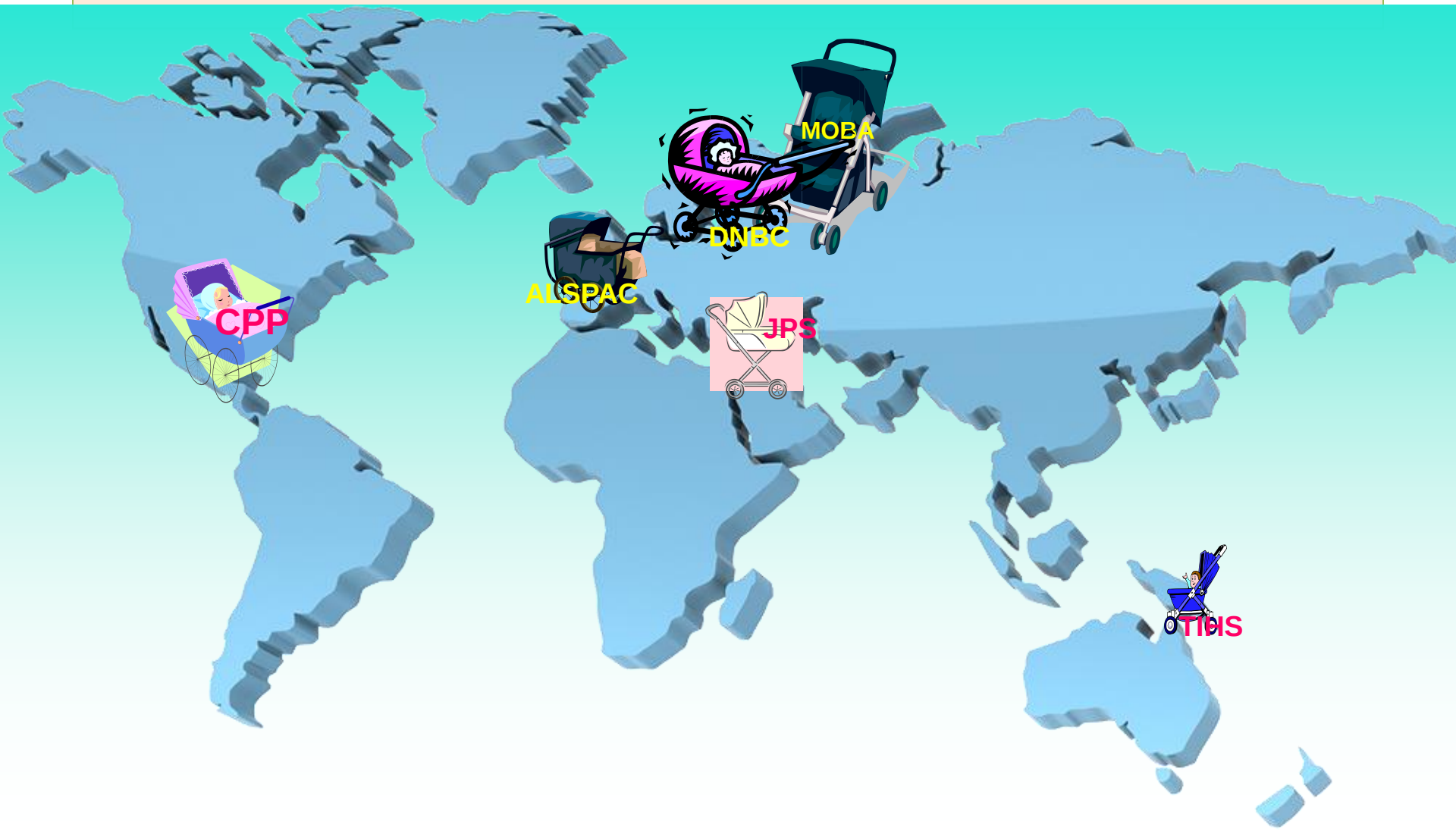
Am J Clin Nutr 2008;87:1750–9.

Aims

Using the pooled database of the International Childhood Cancer Cohort Consortium (I4C)….

- To investigate the association between BW and childhood cancer, and the potential modifying role of
  - age at diagnosis
  - maternal anthropometrics
- To take advantage of the rich set of covariates which are included in each cohort's database

Participating cohorts



Study design and population

- A **pooled cohort study** ascertaining cancer cases from 380,000 live births in the six participating cohorts.
- **Included:** All live births for ALSPAC, CPP and TIHS.
  - For MoBa and DNBC all cases and a random 10% sample of the non-cases were included.
  - For JPS all infants with recorded GA were included, comprising all those born 1974-1976, and a subset born 1964-1973 (n=20,944).
- **Excluded:** multiple births (low BW), and children with Down Syndrome (childhood leukemia)
- **In total**, the pooled dataset comprises **112,781 live births**

Cancer ascertainment
Childhood cancer (diagnosed < 15 years of age)

- Linkage to national registries for ALSPAC, DNBC, JPS and MoBa.
- For TIHS, linkage was with the Tasmanian Cancer Registry.
- For CPP -via examination of diagnostic summaries and other indirect methods. Each potential case was reviewed by two board-certified pediatricians.

- Tumors were classified into 4 groups based on the ICD-0 3rd Ed.:
  - **all cancers** (C-code 42),
  - **leukemia** (morphology codes 9800-9941),
  - **ALL** (codes 9820-9827, 9850) and
  - **non-leukemia cancer** (C-code 42, excluding 9800-9991).

Birth weight metrics- 3 approaches

- First, dichotomized as **≥4.0 kg versus <4.0 kg.**

- Second approach took into account differing BW distributions across populations* and time .**Top decile considered the "exposed" group while the lower 90% of children comprised the reference group.**

- Third, BW was assessed as a **continuous variable in 0.5 and 1.0 kg increments**

*eg. ≥90th percentile of BW was as follows: ALSPAC: 4129, CPP: 3827, DNBC: 4320, JPS: 3880, MoBa: 4260, and TIHS: 4030 grams.

Covariates and potential confounders

Variables associated with BW or childhood cancer were assessed as **potential confounders or effect modifiers** including:

Y/N=yes/no

(a)Maternal factors: age at time of index child's birth (years); married/cohabitating at time of enrollment (Y/N); at least 12 years of education completed (Y/N); any smoking during pregnancy (Y/N); exposure to any smoking at home during pregnancy (Y/N); parity- defined as the number of previous live births (for all cohorts except DNBC which includes number of previous pregnancies and stillbirths), grouped as 0/1-2/≥3; pre-existing or gestational diabetes (Y/N); **pre-pregnancy body mass index (BMI= kg/height (m^2); and total pregnancy weight gain (kg).**

(b) Factors relating to the index child: GA (weeks), determined by date of last menstrual period (or ultrasound in a subgroup from MoBa); sex; first born (Y/N), birth length (cm); placental weight (g); and **age at diagnosis of primary cancer (years**).

(c) Paternal factors: *age at time of index child's birth (years), and completion of at least 12 years of education (Y/N). *non- linear-thus transformed to quadratic expression.

Missing data

- Missing covariate data: **0% to nearly 40%.**
- To construct MV models with maximal sets of covariates, we **used chained multiple imputation to impute 20 complete datasets**.
- **Cox regression** performed separately on each imputation *m* = 1, … , 20 and results were pooled into a single multiple-imputation result.
  - Used truncated **linear regression for continuous variables** (paternal age, maternal height, pregnancy weight gain, and pre-pregnancy BMI)
  - imputations limited to lower and upper boundaries set at the minimum and maximum values of non-missing observations
  - **logistic regression for dichotomous variables** (first born and maternal smoking).
- **Variables used to impute missing data: maternal age, GA, BW, sex of child, and cohort.**

Statistical analysis

Stata Statistical Software, Version 12.1 (StataCorp, College Station, TX).

- We report hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazards model, stratified by cohort.
- **Model 1 - unadjusted.**
- **Model 2- adjusted for GA and child's sex.**
- **Model 3 -a parsimonious multivariable model** adjusted for GA, child's sex, as well as different combinations of covariates (chosen on the basis of P value and influence coefficients of BW and other covariates (15% change)
- Schoenfeld residuals were used to assess the proportional hazard assumption with all covariates entered into the model

Statistical analysis – effect modification

- Maternal anthropometric measurements (pre-pregnancy BMI and pregnancy weight gain), we **introduced interaction terms**
  - BW * maternal pre-pregnancy BMI using a cut-off of normal or underweight (up to 25 kg/m^2) versus overweight (≥25 kg/m^2).
  - BW * pregnancy weight gain, dichotomized according to the WHO recommendation of ≤16 kg versus >16 kg
- Age at diagnosis: **Time-varying coefficient approach** used to assess association between BW and cancer .This allowed for the estimation of two HRs, before and after a particular age at diagnosis:
  - the HRs for BW were significantly different before and after age 3 years, ~stable for years 4-7. Thus cut-off at age 3 was used.
- To assess heterogeneity effects by cohort we **generated random-effects (shared frailty) Cox** models. Results were similar to those obtained using a **stratified analysis with each cohort serving as a stratum.**

Covariates: Example

JPS: Association between Covariates and Birthweight (cont)

Characteristic	β	95% CI		*p*-value
Maternal age (years)	10.8	9.6	11.9	< 0.001
Marital status married/partner	201.7	85.5	317.8	0.001
Maternal education (≥ 12 years)	-17.6	-30.2	-4.9	0.006
Maternal smoking, Yes	-98.0	-116.8	-79.2	< 0.001
Maternal passive smoking*, Yes	-29.2	-43.0	-15.4	< 0.001
Maternal pre-pregnancy BMI (kg/m^2)	21.8	19.5	24.0	< 0.001
Maternal pregnancy weight change (kg)	18.1	16.5	19.6	< 0.001
Maternal height (cm)	11.5	10.3	12.7	< 0.001
Maternal diabetes*, Yes	433.3	359.4	507.1	< 0.001
Paternal age (years)	8.8	7.8	9.7	< 0.001
Paternal education (≥ 12 years)	-2.7	-15.4	10.0	0.675
Gestational age (weeks)	104.1	101.3	107.0	< 0.001
Gender, female	-126.5	-138.9	-114.1	< 0.001
Placental weight* (grams)				
First born child, Yes	-133.3	-146.8	-119.9	< 0.001
Birth length* (cm)				
Parity*(referent: no living children)				
1-2 living children	106.4	91.8	121.0	< 0.001
3-4 living children	150.5	131.6	169.4	< 0.001
5-6 living children	175.6	147.2	204.0	< 0.001
≥7 living children	292.3	259.5	325.1	< 0.001

TABLE 1: Descriptive characteristics of sub-cohorts in 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
Singleton, live births with no DS in sub-cohort	221	249	616	239	457	224
Maternal age (years)						
Mean ± SD	28.0 ± 4.7	24.0 ± 5.8	30.3 ± 4.1	26.7 ± 5.0	29.8 ± 4.7	23.5 ± 4.4
Missing (%)	*0*	*0*	*2 (0.3)*	*0*	*0*	*0*
Marital status, married %	73.3	74.3	94.6	99.2	93.2	81.3
Missing (%)	*6.3*	*0*	*3.9*	*0.4*	*5.0*	*0.0*
Mother completed secondary school (≥12 years) **n (%)**	58 (26.2)	105 (42.2)	298 (48.4)	114 (47.7)	278 (60.8)	36 (16.1)
Missing %	*11.7*	*0.8*	*27.6*	*0 (0.0)*	*52 (11.4)*	*0 (0.0)*

Table 2: Distribution of All Cancers, Leukemia and ALL by cohort, gender and age of diagnosis

	ALSPAC		CPP		DNBC		JPS		MoBA		TIHS	
CANCERS	N	Age diagnosis Mean (yrs)	N	Age diagnosis Mean (yrs)	N	Age diagnosis Mean (yrs)	N	Age diagnosis Mean (yrs)	N	Age diagnosis Mean (yrs)	N	Age diagnosis Mean (yrs)
Boys	12	8.48	27	2.90	70	3.82	23	7.33	56	1.94	17	7.64
Girls	10	8.53	22	3.00	73	4.28	16	6.05	45	2.25	7	6.23
Total	22	8.50	49	2.94	143	4.05	39	6.08	101	2.08	24	7.23
CHILDHOOD LEUKEMIA												
Boys	3	5.99	7	2.67	22	3.77	5	6.28	18	2.46	3	7.25
Girls	0		9	2.69	26	4.14	3	1.44	18	3.17	1	5.23
Total	**3**	**5.99**	**16**	**2.68**	**48**	**3.97**	**8**	**4.46**	**36**	**2.71**	**4**	**6.75**
ALL												
Boys	3	5.99	6	2.82	21	3.88	5	6.28	14	2.35	2	8.61
Girls	0		5	3.03	22	4.12	3	1.44	17	3.17	1	5.23
Total	3	5.99	11	2.92	43	4.00	8	4.46	31	2.79	3	7.48

Based on singleton births, Down Syndrome excluded

NEW RESULTS SINCE LAST I4C

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*	*1.533*	*1.248*	*2.121*	*1.745*	*1.125*
LEUKEMIA							
	0.147	*0.495*	*0.518*	*0.263*	*0.787*	*0.291*	*0.397*
ACUTE LYMPHOBLASTIC 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*

BW Metrics and cancer subtypes: unadjusted, adjusted and full models

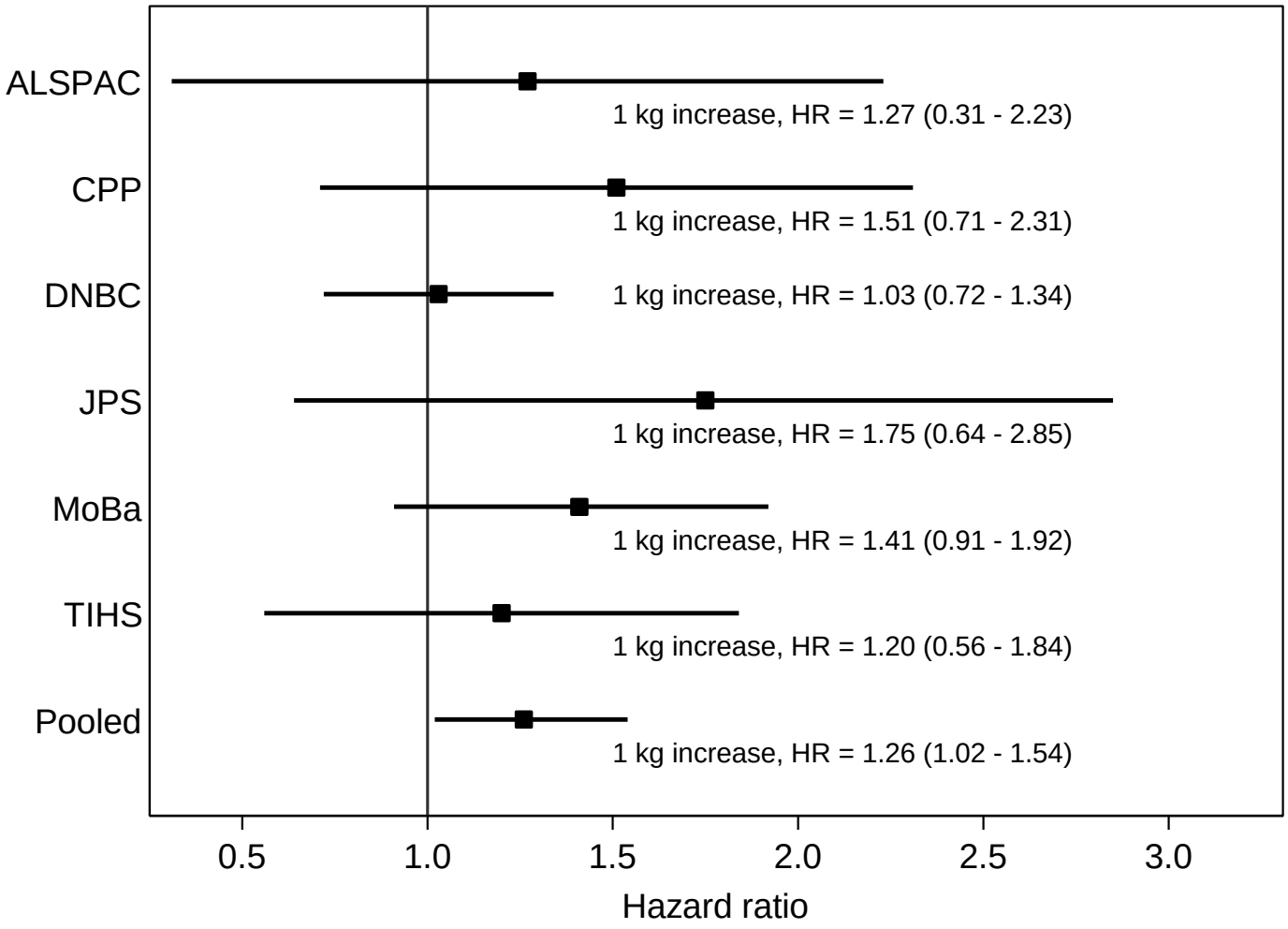
Birthweight metric (N)	Model 1*				Model 2*				Model 3*			
	HR[1]	95% CI		*p*-value	HR[2]	95% CI		*p*-value	HR[3]	95% CI		*p*-value
Birth weight ≥ 4.0kg[1]												
Cancer (377)	1.14	0.88	1.48	0.317	1.19	0.91	1.55	0.197	1.17	0.89	1.54	0.255
Leukemia (115)	1.25	0.80	1.96	0.324	1.31	0.83	2.08	0.249	1.21	0.74	1.96	0.443
ALL (98)	1.21	0.74	1.96	0.449	1.25	0.76	2.06	0.379	1.21	0.72	2.04	0.472
Non-leukemia (262)	1.09	0.79	1.50	0.589	1.14	0.82	1.58	0.438	1.11	0.79	1.56	0.549
Top 10% of birth weights in each cohort												
Cancer (377)	1.17	0.85	1.61	0.324	1.22	0.88	1.69	0.228	1.18	0.84	1.65	0.340
Leukemia (115)	1.25	0.72	2.19	0.430	1.31	0.74	2.31	0.358	1.16	0.63	2.12	0.639
ALL (98)	1.14	0.61	2.13	0.684	1.17	0.62	2.23	0.622	1.08	0.55	2.14	0.818
Non-leukemia (262)	1.14	0.77	1.68	0.509	1.18	0.80	1.75	0.402	1.14	0.75	1.71	0.540
Continuous birth weight, kg												
Cancer (377)	1.10	0.91	1.31	0.326	1.26	1.02	1.54	0.031	1.26	1.02	1.56	0.033
Leukemia (115)	1.25	0.89	1.75	0.192	1.42	0.98	2.06	0.064	1.35	0.90	2.02	0.145
ALL (98)	1.16	0.81	1.67	0.419	1.29	0.85	1.93	0.228	1.29	0.83	1.99	0.258
Non-leukemia (262)	1.04	0.83	1.28	0.750	1.19	0.93	1.52	0.172	1.18	0.91	1.54	0.219

Analysis by age at diagnosis (<3 vs≥3 yrs)

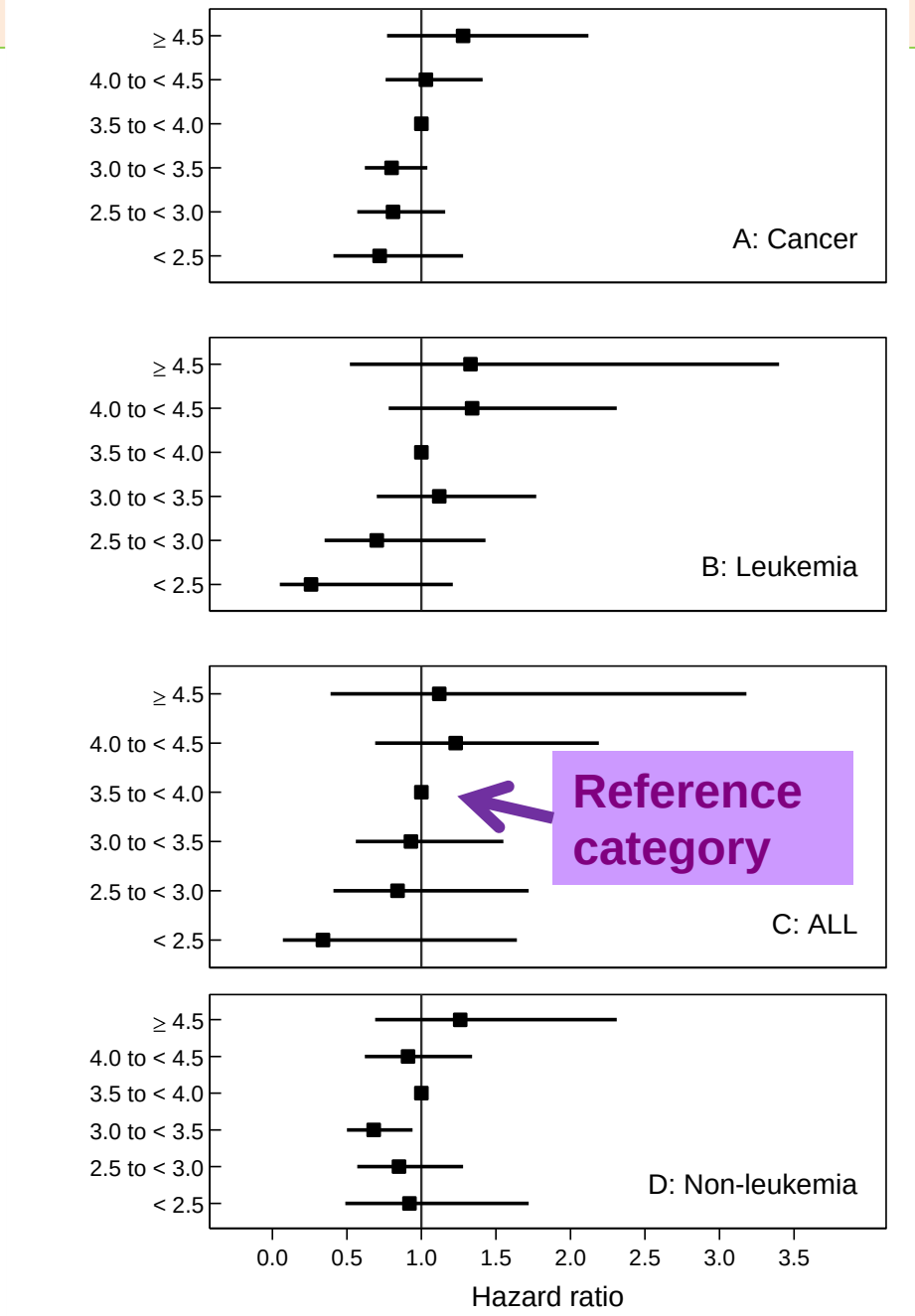
Birth weight	Diagnosis	<3 years old HR (95% CI) [*p*-value]	≥3 years old HR (95% CI) [*p*-value]	Comparison of HRs between time periods, *p*-value
≥ 4.0 kg	**Cancer**	0.84 (0.56 – 1.27) [0.418]	1.60 (1.13 – 2.26) [0.008]	0.018
Top 10%		0.80 (0.46 – 1.39) [0.426]	1.64 (1.10 – 2.44) [0.016]	0.037
Continuous		1.08 (0.82 – 1.42) [0.606]	1.44 (1.11 – 1.88) [0.007]	0.099
≥ 4.0kg	**Leukemia**	1.08 (0.55 – 2.13) [0.824]	1.56 (0.84 – 2.88) [0.156]	0.425
Top 10%		1.08 (0.46 – 2.54) [0.852]	1.55 (0.72 – 3.30) [0.260]	0.538
Continuous		1.29 (0.79 – 2.11) [0.308]	1.57 (0.96 – 2.57) [0.075]	0.556
≥ 4.0 kg	**ALL**	1.02 (0.48 – 2.15) [0.962]	1.49 (0.77 – 2.88) [0.235]	0.446
Top 10%		1.07 (0.42 – 2.73) [0.881]	1.28 (0.54 – 3.03) [0.581]	0.789
Continuous		1.23 (0.72 – 2.11) [0.455]	1.34 (0.78 – 2.30) [0.281]	0.805
≥ 4.0 kg	**Non leukemia**	0.75 (0.45 – 1.24) [0.261]	1.62 (1.06 – 2.46) [0.025]	0.020
Top 10%		0.67 (0.33 – 1.38) [0.274]	1.68 (1.05 – 2.68) [0.032]	0.035
Continuous		0.99 (0.71 – 1.38) [0.941]	1.39 (1.02 – 1.91) [0.039]	0.104

Heterogeneity: Hazard ratios for any cancer in each cohort and pooled overall for birth weight continuous (per kg increase)

Cox proportional hazards models adjusted for gestational age and sex of child



Hazard ratios for cancer by BW (500 gram increments)



Cox proportional hazards models adjusted for gestational age and sex of child

Spearman rank correlation (roh)=

0.943, p = 0.005 for all cancers;

for all leukemia rho= 0.886, p = 0.019 ;

for ALL rho-0.943, p = 0.005;

for non-leukemia cancers rho=0.486, p=0.329.

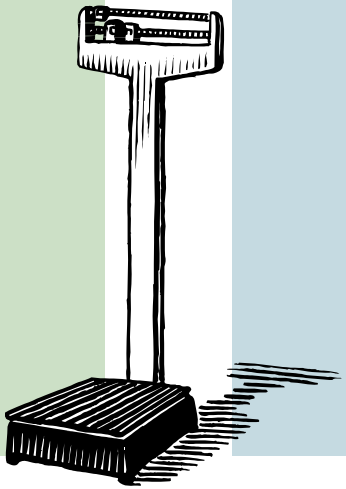
No effect modification by maternal anthropometrics (all cancer)

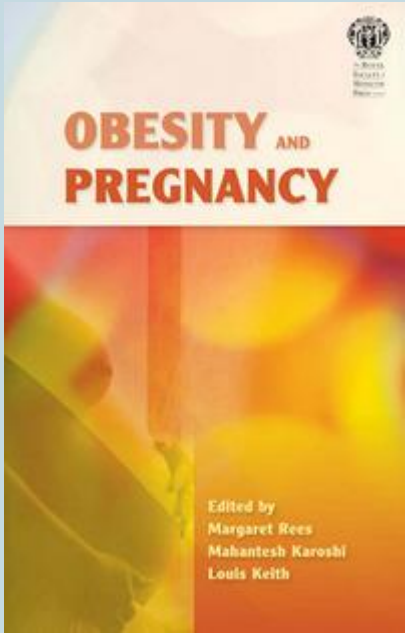
Pre-pregnancy BMI

- <25kg/m^2
- ≥25 kg/m^2

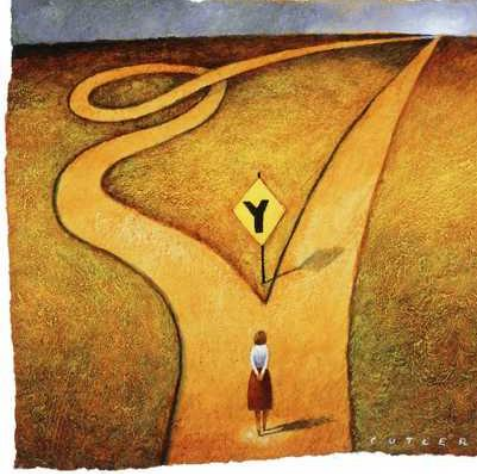
Pregnancy weight gain

- ≤16kg
- >16 kg



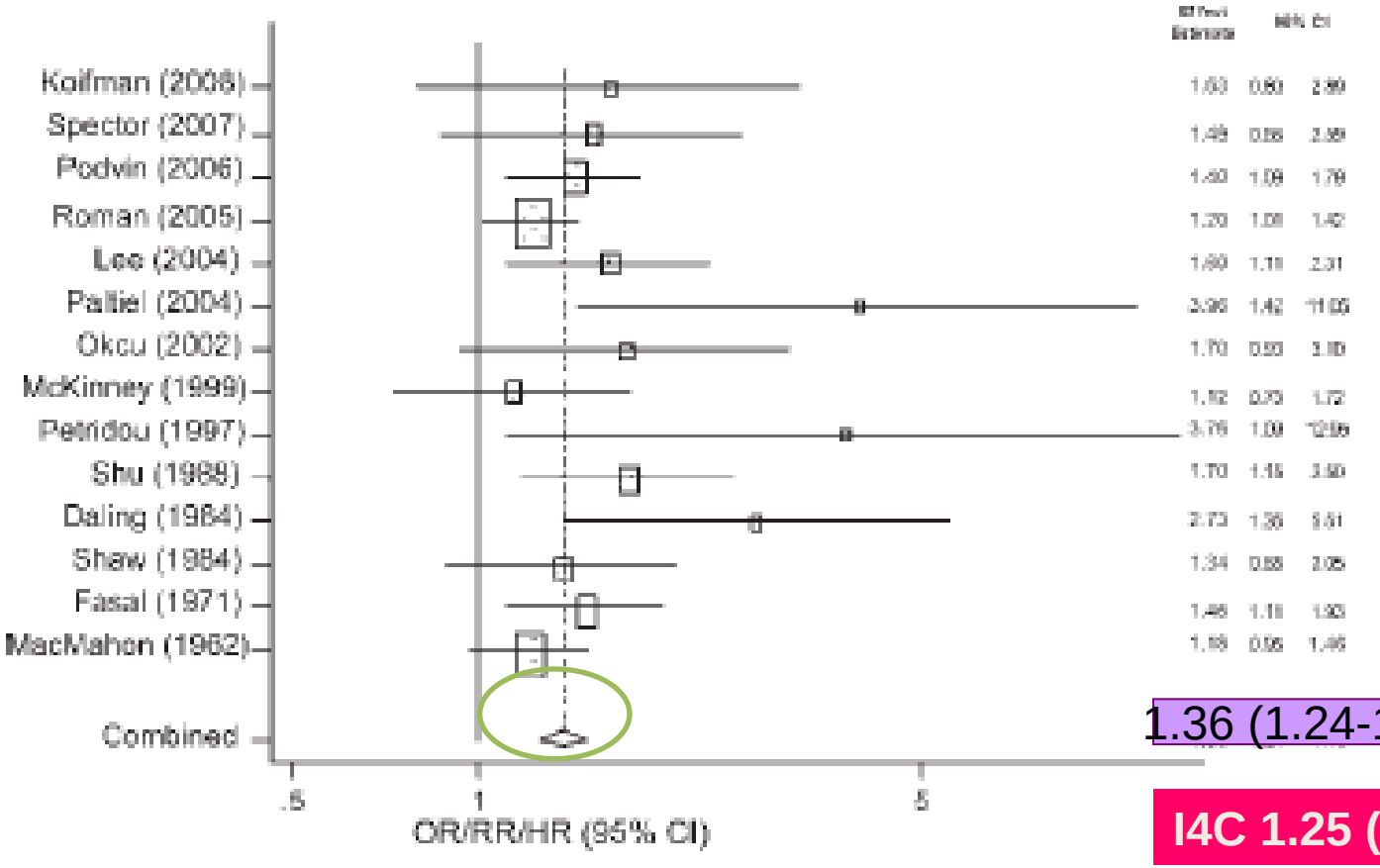


Decisions along the way



- Many decisions re: analysis strategy
- Journal type
- Authorship

Coherence with literature?
High Birth weight (categorical) and childhood leukemia
Caughey and Michels International Journal of Cancer 2009



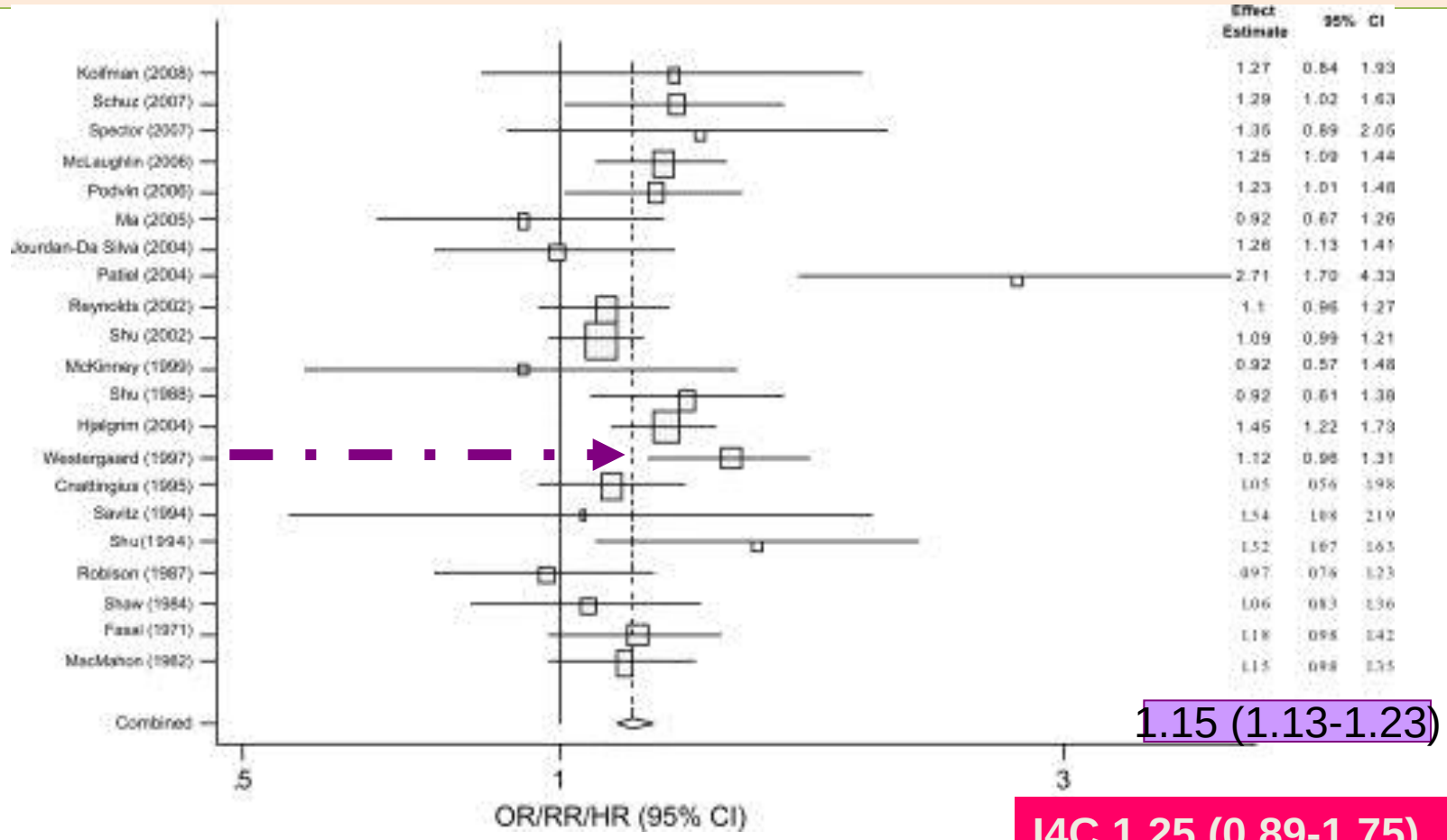
1.36 (1.24-1.49)

I4C 1.25 (0.80-1.96)

FIGURE 1 – Studies on the risk of overall leukemia associated with high birth weight. OR, odds ratio; RR, relative risk; HR, hazard ratio;

Birth weight per kg and childhood leukemia: Millions of observations

International Journal of Cancer
Volume 124, Issue 11, pages 2658-2670,



I4C 1.25 (0.89-1.75)

Samuelsen (Epidemiology 2009) Norwegian Cancer Registry including 1,842,113 live-born infants born 1967 -1998 : increase in leukemia risk of 29% per 1000g increase in birth weight after adjustment for gestational age

I4C 1.42 (0.98-2.06)

What this study adds

- Confirms BW-cancer and BW- leukemia association, when adjusted for child sex and GA
- Effect modification by age at diagnosis with stronger findings above age 3 yrs (for all cancer and non-leukemia)
- Heterogeneity among cohorts dealt with in analysis and minimal for BW cont.
- Maternal obesity and weight gain do not appear to alter the association btwn BW and cancer (power?)
- Comparable to literature (more or less)

Major limitations

- Small sample size –still!
  - most MV associations N.
  - inadequate power for individual solid tumors and AML (use of non-leukemia cancers), subgroups
- Validity of imputation?
- Novelty- large pooled case control studies and registry studies recently published

Merci

- Gabriella Tikellis
- Terry Dwyer
- Stan Lemeshow
- Gary Phillips
- Karen Lamb
- Working group members
- All participating cohorts
- Mothers and babies

Adjusted analyses

- Cancer hazard ratio is adjusted for gestational age, maternal age, paternal age (rescaled as quadratic), maternal height, first born, and maternal pre-pregnancy BMI.
- Leukemia hazard ratio is adjusted for gestational age, maternal age, total pregnancy weight change, maternal pre-pregnancy BMI, first born, and any maternal smoking.
- ALL hazard ratio is adjusted for gestational age, paternal age (rescaled as quadratic), total pregnancy weight change, and any maternal smoking.
- Non leukemia cancer hazard ratio is adjusted for gestational age, paternal age (rescaled as quadratic), maternal height, total pregnancy weight change, first born, and maternal pre-pregnancy BMI.