Childhood Cancer 2012 - Early exposures and childhood cancer
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# Maternal and offspring dietary intake in association with leukemia risk among children

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# Presentation axes and key points

Content

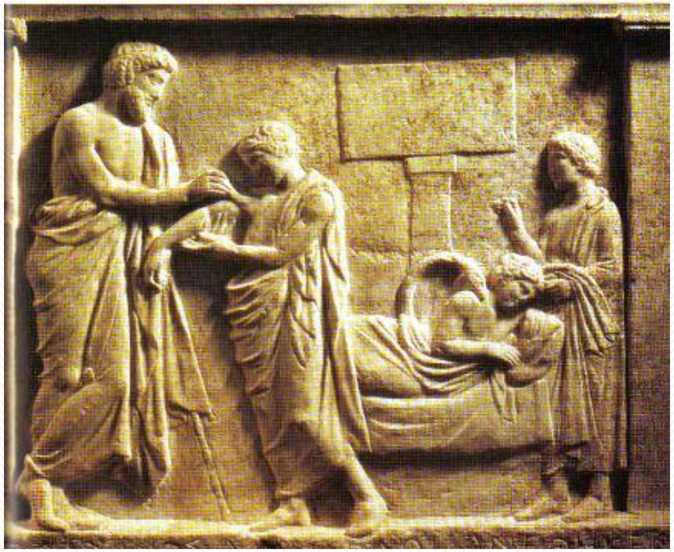
1. **Maternal dietary intake** during or just before pregnancy & **Paternal dietary intake**
2. **Index child nutrition,** including breastfeeding,

in association with **leukemia**

Mode:

- Sharing experiences with **un/published NARECHEM data, and methodological concerns**
- Attempting **critical reappraisal of published literature**

# Tracing the origins of childhood nutrition



*'' growing creatures have most innate heat, and it is for this reason that they need most food, deprived of which their body pines away''* Hippocrates (Aphorisms, I. XIV)

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# Icie Macy (USA) & Elsie Widdowson (UK): pioneers

**Played major roles in shaping our understanding on the complex associations of food with child growth**

- ***’health care and nutritional influences may affect or change the normal course of health, growth and development of children–the world’s most precious asset”***

- ***“One of the great mysteries of life is the power of growth, that harmonious development of complete organs and tissues from simple protoplasmic cells, with the ultimate formation of a complex organism with its orderly adjustment of structure and function”***




# A natural experiment on the effects of extreme dietary restrictions:
## the Dutch Famine of 1944 (Hunger Winter) & the later infant health/survival

*'' nutritional deprivation severe enough to result in maternal weight loss or reduced weight gain results in a corresponding reduction in offspring length and ponderal index (and hence also birth weight), that is directly related to infant survival.''  Stein et al. 1995*

*''prenatal exposure to famine is linked to decreased glucose tolerance in adults'' Ravelli et al, 1998*

*'' Acute famine exposure in utero appears to have no adverse consequences for a woman's fertility. [...] the excess of perinatal deaths occurred among offspring of famine exposed women is unexplained.'' Lumey et al. 1997*

*''Women whose mothers were malnourished during the early stages of pregnancy stand a greater chance of becoming overweight in middle age' Malnourished Mothers Breed Obese Daughters ,The Independent, 1999*



# Diet during pregnancy or just before





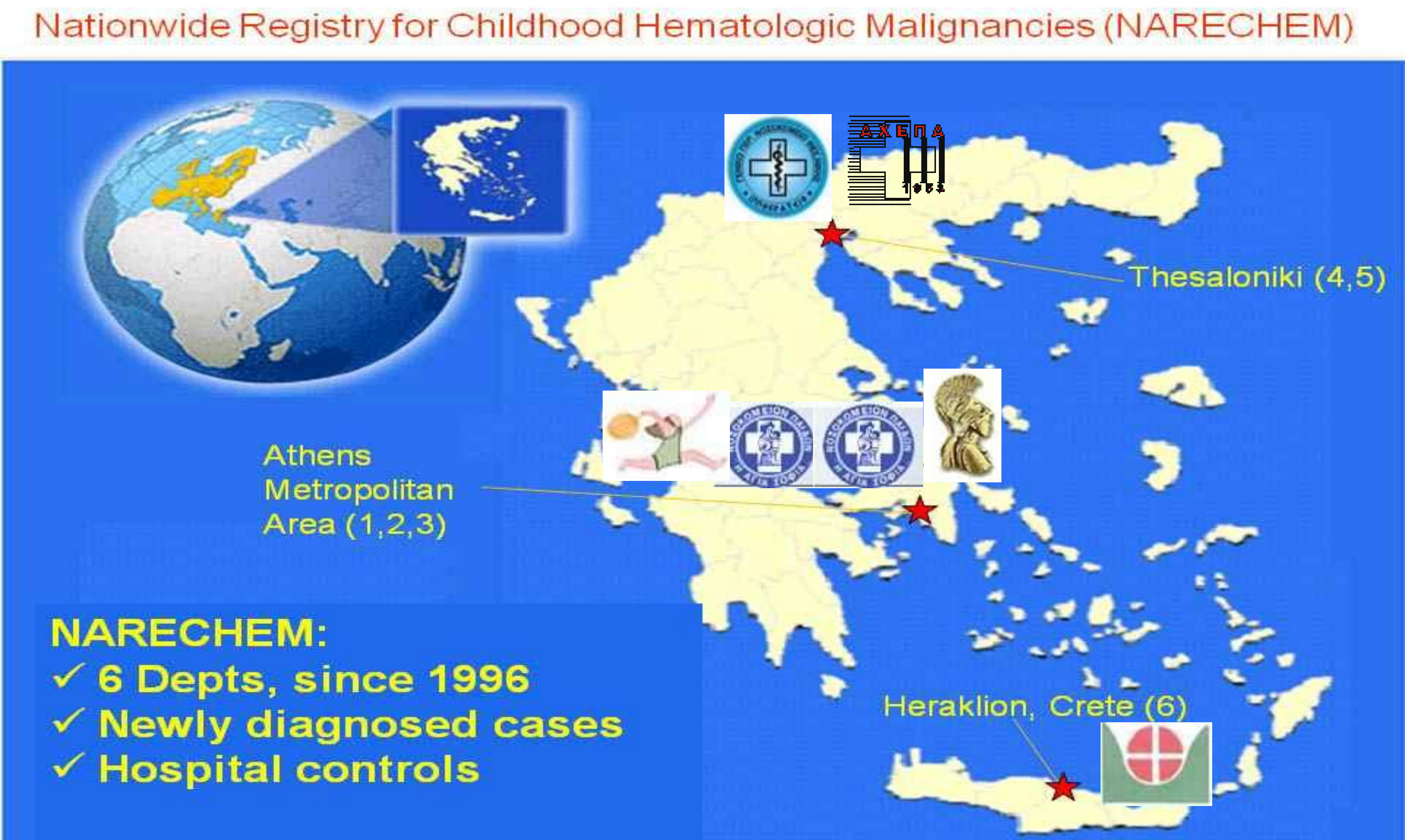
# Maternal dietary intake

## Maternal Diet and Acute Lymphoblastic Leukemia in Young Children

Eleni Petridou,[1,2] Evangelos Ntouvelis,[1] Nick Dessypris,[1] Agapios Terzidis,[1] Dimitrios Trichopoulos,[1,2] and the Childhood Hematology-Oncology Group

[1]Department of Hygiene and Epidemiology, Athens University Medical School, Athens, Greece and
[2]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts

- Nationwide Coverage: All 6 case reporting sites



# The study:

- 131 children 1-4 years with ALL
- 1:1 gender and age-matched controls
- Food frequency questionnaire addressing maternal diet during the index pregnancy
- Multivariate adjustment for confounders

# Maternal dietary intake - food groups:

**Table 4. Conditional logistic regression–derived ORs and 95% CIs for ALL at ages 1 to 4 years by maternal intake of specified food groups**

| Variable | Increment | OR (95% CI) | P |
|---|---|---|---|
| Cereals and starchy roots | One quintile more | 1.23 (0.94-1.60) | 0.13 |
| Sugars and syrups | One quintile more | 1.32 (1.05-1.67) | 0.02 |
| Pulses and nuts | One quintile more | 0.96 (0.77-1.20) | 0.73 |
| Vegetables | One quintile more | 0.76 (0.60-0.95) | 0.01 |
| Fruits | One quintile more | 0.72 (0.57-0.91) | 0.007 |
| Meat and meat products | One quintile more | 1.25 (1.00-1.57) | 0.05 |
| Fish and seafood | One quintile more | 0.72 (0.59-0.89) | 0.003 |
| Milk and dairy products | One quintile more | 0.82 (0.66-1.02) | 0.08 |
| Butter/margarine | One tertile more | 1.41 (0.97-2.06) | 0.07 |

NOTE: Controlling for matching variables, maternal age at birth, birth weight, maternal smoking during pregnancy, maternal years of schooling, maternal occupation, and maternal daily energy intake during pregnancy but not mutually among food groups.

# Integrating our study in the wider context…

Kwan et al, 2009; 282 children with ALL- 359 controls

**Maternal dietary intake -12 months prior to pregnancy**

- Significant **protective associations** (ORs 0.55- 0.81) with **ALL** for increased consumption of:

-**Vegetables**

-**Fruit** (borderline significance)

-**Legumes**

-**Protein sources (sources of glutathione)**

- **Non significant associations**: cured meat, grain and dairy products

# Integrating our study in the wider context…

Specifically, individual foods **inversely related** to **ALL**:

-Carrots

-Cantaloupe

-Oranges

-Green beans

-Other beans

Beef : a controversial entity

(Kwan et al, 2009, same study)

# YES


# Meat-related controversies

**Non significant association between :**

- consumption of **5 meat groups** during pregnancy and **ALL** - ORs tended to increase for **cured meat** consumption among those not taking vitamin supplements

(Sarasua & Savitz,1994 )

- usual maternal consumption of **different meat/meat products** and childhood leukemia

(Peters et al,1994)

# A need for quantitative synthesis is evident






# Maternal dietary intake - Tea

Maternal consumption of coffee/tea
**during the last 6 months of pregnancy**
337 children with ALL- 697 controls (Aus-ALL study)

- **Tea:** overall, inverse non significant associations with both Pre-B and T-cell ALL
- Associations modified after **control for gene translocations**

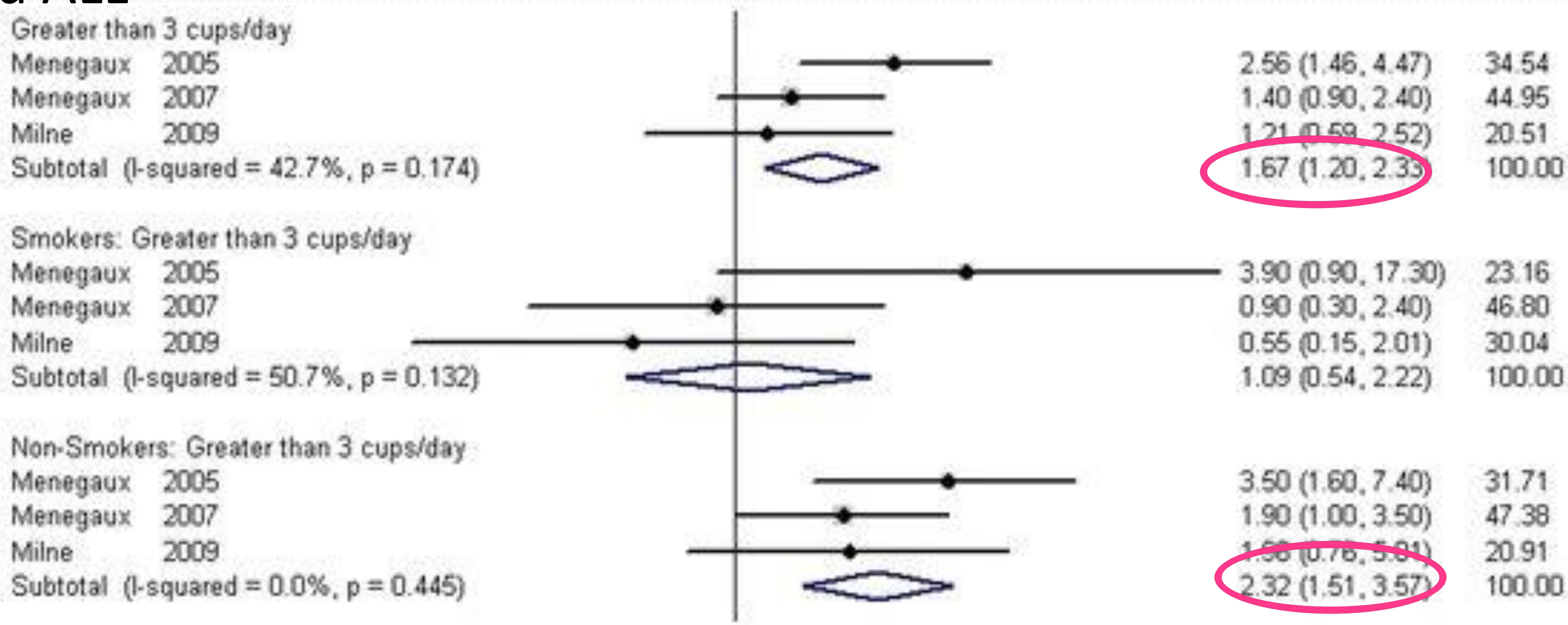
- **MA:** overall protective effect of tea consumption, although there was some evidence of heterogeneity

(Milne et al, 2011)

# Maternal dietary intake – MA coffee

**Consumption of $\geq$ 3cups/day: OR 1.67 (95% CI 1.20, 2.32)**

ORs varied by **smoking habits of mothers** suggesting that smoking may modify the association between coffee consumption and ALL




(Milne et al, Am J Epidemiol, 2011)

# Maternal dietary intake – **micronutrients**

- Micronutrients possibly **inversely** associated to ALL:

-provitamin A carotenoids, alpha-carotene

-vitamins A and D (Shu et al, 1988)

-total and reduced glutathione (found in protein-containing foods)

- **Possibly Not associated**:

- Flavonoids (Genistein, Quercetin)
- Folate
- Vitamins A & D

(Kwan et al,2009)

# Natural DNAt2 Inhibitors

**Dietary DNAt2 inhibitors**:

flavonoids (quercetin, genistein), caffeine, and catechins

**positively associated especially with infant AML (MLL+)**

- Ross et al,1996, Spector, CEBP, 2005

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# Folate and ALL: the hypothesis generating study

Thompson et al, 2001
Case control study of 83 children with ALL- 166 controls

→**Folate** supplementation **with or without iron** during pregnancy was **protective** for childhood **ALL**

OR=0·40 (0·21–0·73)

→**iron alone** was not significantly protective

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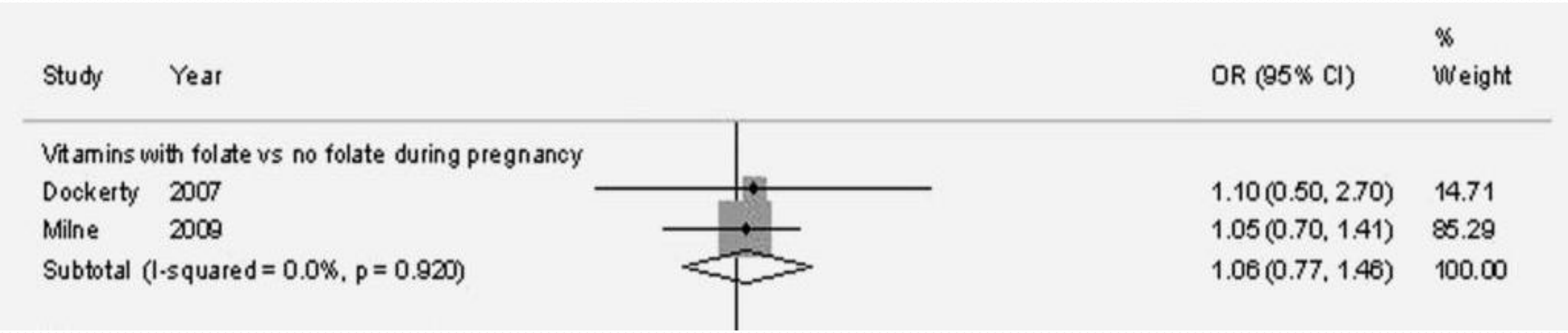
# Maternal dietary intake and ALL – folate




Milne et al, IJC, 2010

--Excluding the hypothesis-generating study. Why?

The ESCALE study: discrepancies and need for further, ongoing synthesis CLIC

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# Folate-related gene polymorphisms

- ESCALE data: Folate-related genetic polymorphisms may represent risk factors for CL (MTHFR C677T, MTRR A66G and C524T)
- Yin et al, MA PBC, 2012: a protective effect of the 677T allele

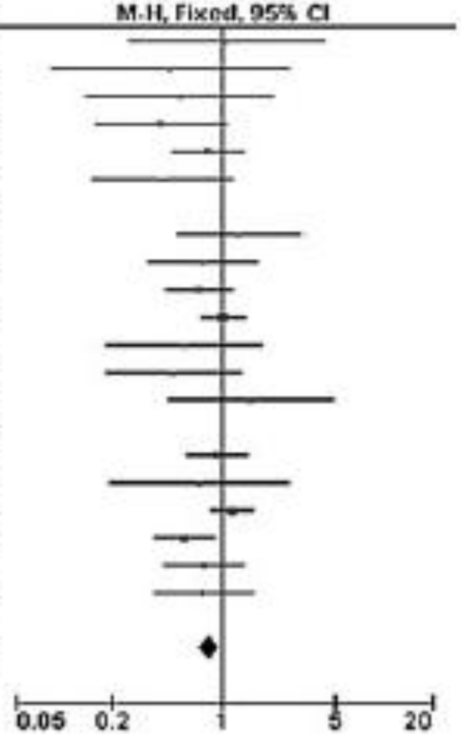
C677T

| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Alcasabas, 2008 | 3 | 189 | 6 | 394 | 0.8% | 1.04 [0.26, 4.22] |
| Chan 2010 | 2 | 185 | 4 | 177 | 0.9% | 0.47 [0.09, 2.61] |
| Chatzidakis, 2006 | 3 | 52 | 9 | 88 | 1.4% | 0.54 [0.14, 2.08] |
| Damnjanovic, 2010 | 5 | 78 | 59 | 412 | 3.8% | 0.41 [0.16, 1.06] |
| de Jonge, 2009 | 22 | 245 | 54 | 496 | 7.1% | 0.81 [0.48, 1.36] |
| Franco, 2001 | 6 | 70 | 13 | 71 | 2.6% | 0.42 [0.15, 1.17] |
| Giovannetti, 2008 | 3 | 65 | 0 | 32 | | Not estimable |
| Kamel, 2007 | 7 | 88 | 20 | 311 | 1.8% | 1.26 [0.51, 3.08] |
| Kim, 2006 | 11 | 66 | 21 | 100 | 3.0% | 0.75 [0.34, 1.69] |
| Krajinovic, 2004 | 31 | 270 | 46 | 300 | 8.4% | 0.72 [0.44, 1.17] |
| Lightfoot, 2010 | 90 | 805 | 84 | 760 | 16.7% | 1.01 [0.74, 1.39] |
| Oliveira, 2005 | 5 | 103 | 9 | 111 | 1.8% | 0.58 [0.19, 1.79] |
| Petra, 2007 | 5 | 68 | 36 | 258 | 3.0% | 0.49 [0.18, 1.30] |
| Reddy, 2006 | 7 | 135 | 5 | 142 | 1.0% | 1.50 [0.46, 4.84] |
| Sadananda, 2010 | 0 | 86 | 0 | 99 | | Not estimable |
| Schnakenberg, 2005 | 47 | 443 | 43 | 379 | 9.0% | 0.93 [0.60, 1.44] |
| Sood, 2010 | 3 | 95 | 11 | 255 | 1.3% | 0.72 [0.20, 2.65] |
| Thirumaran, 2005 | 50 | 453 | 167 | 1448 | 15.0% | 1.15 [0.84, 1.58] |
| Tong, 2010 | 34 | 361 | 78 | 508 | 12.7% | 0.57 [0.37, 0.88] |
| Yeoh, 2010 | 23 | 318 | 32 | 345 | 6.2% | 0.76 [0.44, 1.33] |
| Zanrosso, 2006 | 13 | 165 | 20 | 198 | 3.6% | 0.76 [0.37, 1.58] |
| Total (95% CI) | | 4340 | | 6884 | 100.0% | 0.83 [0.72, 0.95] |
| Total events | 376 | | 717 | | | |

Heterogeneity: $Chi^2 = 17.35$, $df = 18$ ($P = 0.50$); $I^2 = 0\%$

Test for overall effect: $Z = 2.67$ ($P = 0.008$)

Odds Ratio M-H, Fixed, 95% CI



**Inversely associated food groups/foods**

Vegetables
Fruit - Oranges, carrots, cantaloupe
Legumes
Fish and seafood
Tea

**Positively associated food groups/foods**

Sugar and Syrups
Coffee (>3 cups/day)
Total energy intake

**Equivocal results**

Protein Sources - beans, beef
Fiber from fruit/vegetables

Meat products
Fiber Cereals

**Inversely associated micronutrients**

- Provitamin A Carotenoids
- Alpha- carotene
- Total/reduced glutathione
- Vitamins A & D (cod liver oil)
- Folate (?)

# You Are What Your Dad Ate

Cell Metabolism (Previews) AC Ferguson-Smith, ME Patti 2011

- Metabolic Risk Can Be Conferred via the Paternal Lineage

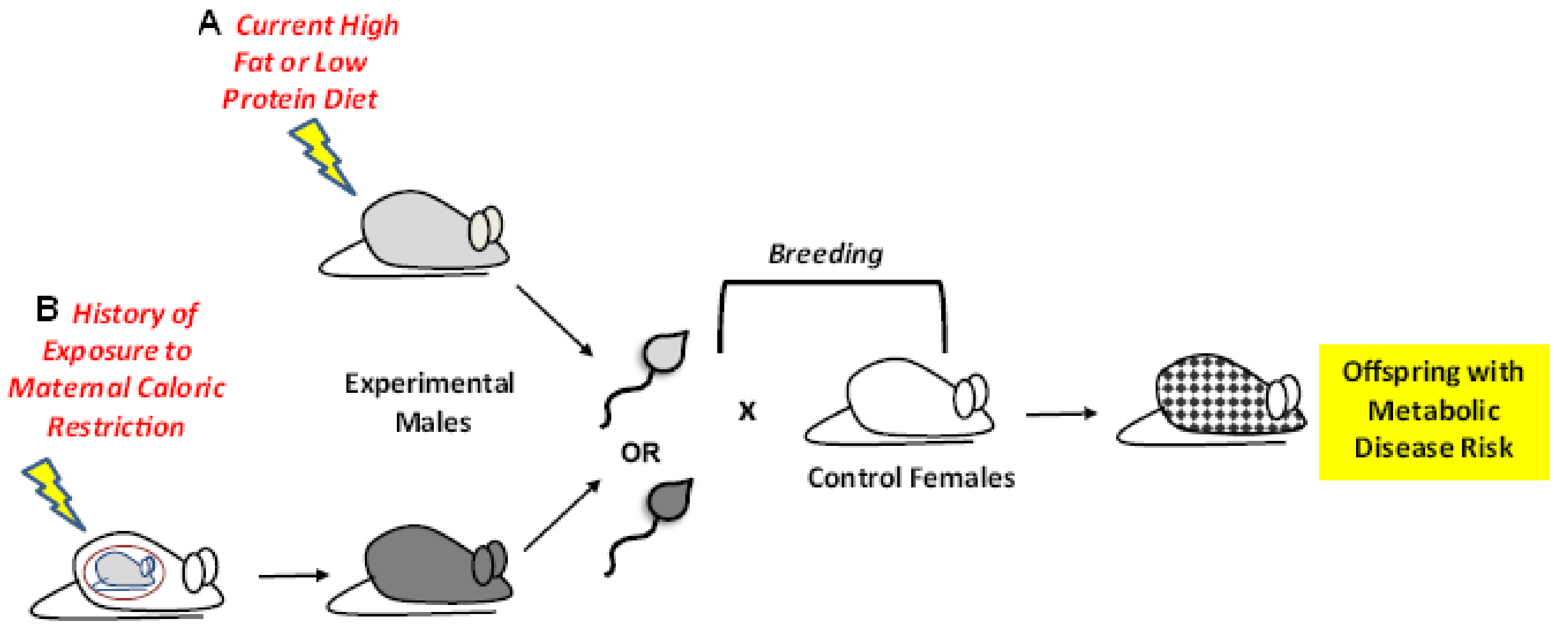
Adverse offspring outcomes associated with the father's diet, indicating nongenetic inheritance of paternal experience

Determining underlying mechanisms may require reconsideration of our understanding of the heritability of epigenetic states

# Paternal diet and offspring metabolic outcome

(A) Male mice were fed a reduced-protein (and bred with female with normal diet) had offsprings with increased hepatic expression of lipid and cholesterol synthesis genes
(B) male mice with a history of intrauterine exposure to maternal undernutrition could influence metabolism in their offspring

A+B →dietary or metabolic history of males **affects metabolism in offspring**, even in cases of normal diet at breeding.



# Paternal diet and off-spring

**Mechanism**

• mediated by sperm, potentially via epigenetic marks in germ cells, but the changes must survive the important reprogramming events ( methylation) that occur immediately postfertilization

• can also be mediated posttranscriptionally via the action of microRNAs (alteration of chromatin modulation)

! The described models are examples of paternal germline effects rather than transgenerational effects

→true transgenerational effect would be manifest in offspring from sperm never exposed to dietary modification

# Paternal diet and risk for leukemia in the offspring

Peters JM et al. Processed meats and risk of childhood leukemia (California, USA). Cancer Causes Control. 1994

Fathers' intake of hot dogs risk of leukemia among children 0-10 years: OR = 11.0, CI = 1.2-98.7, P = 0.01

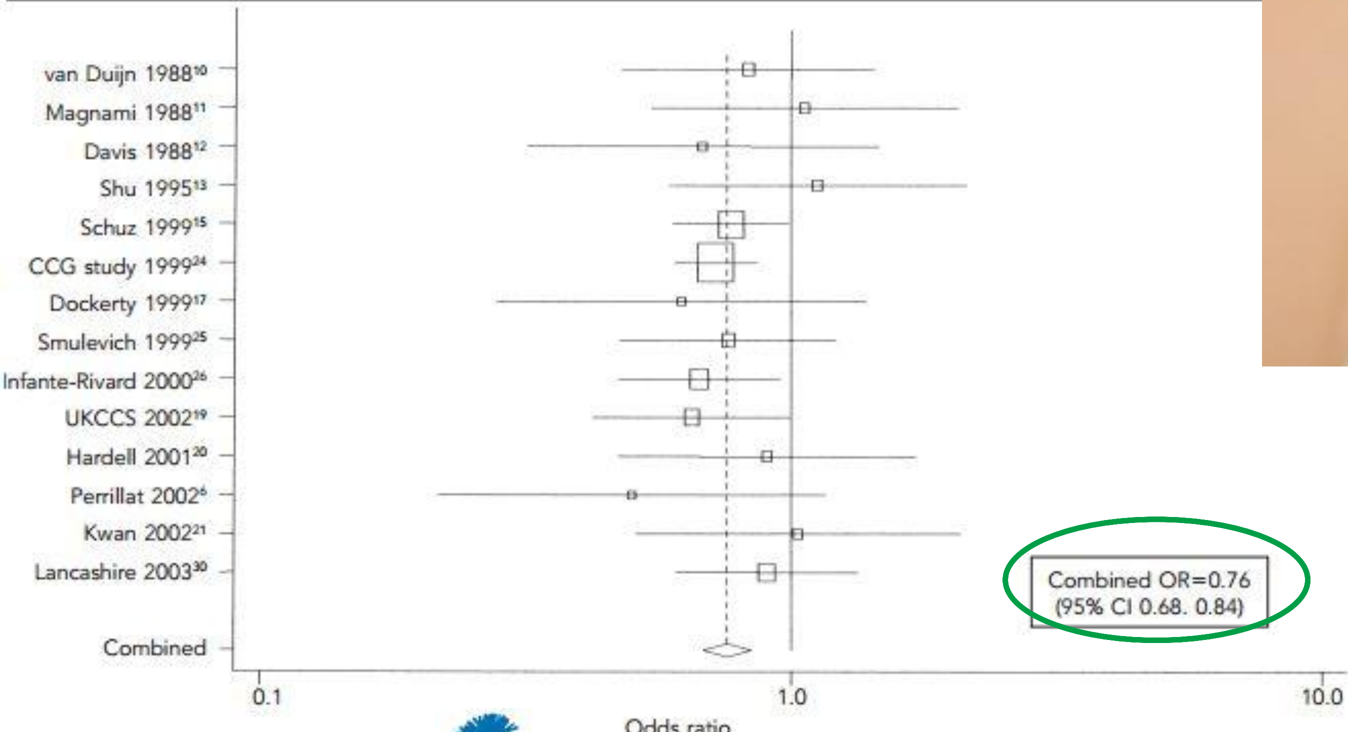
BUT small numbers of observations in the subgroups (only about 2% of the controls were reported to eat hot dogs/ $\geq$other day


# Breastfeeding

# Short and long term breastfeeding: ALL

Kwan et al, 2004 MA (14 studies)

**Figure 2. Odds ratios (ORs) and 95% confidence intervals (CIs) in studies of association between breastfeeding >6 months and risk of childhood ALL (*n*=14 studies)**

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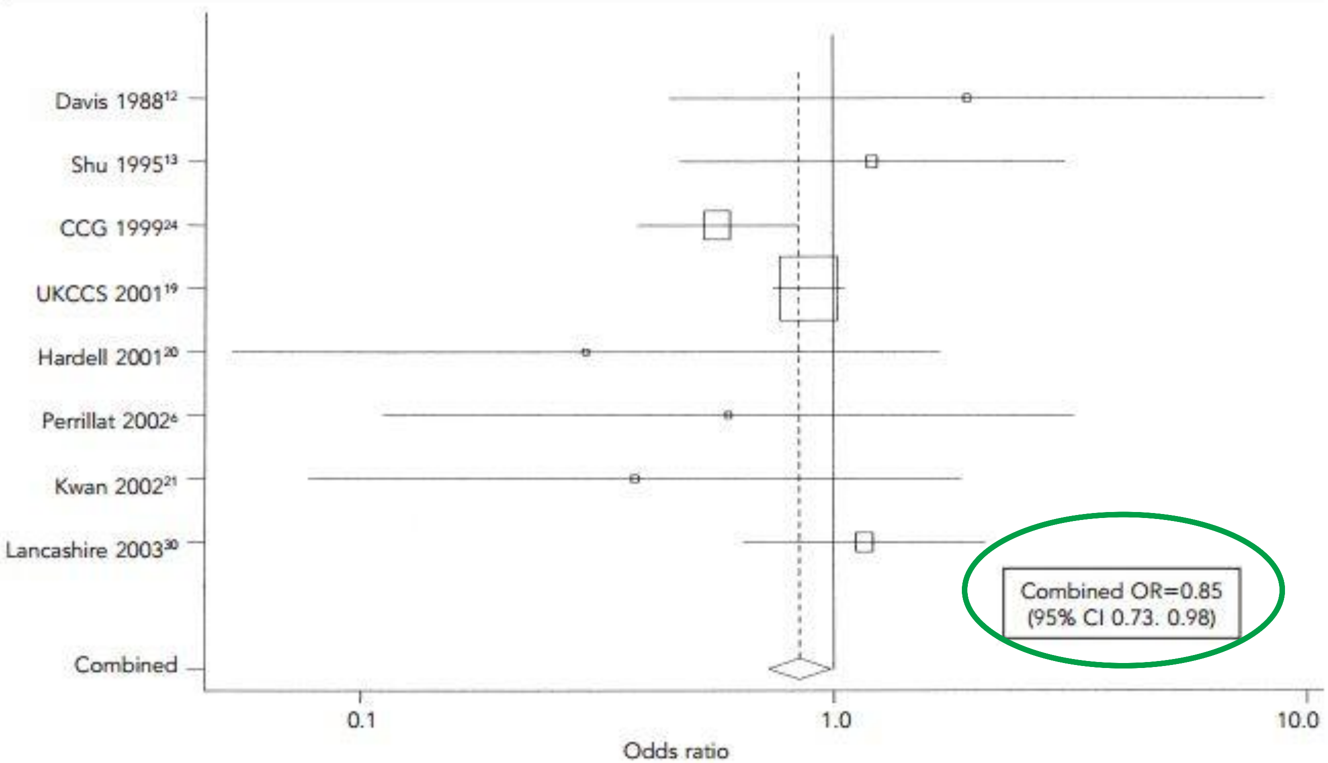
# Breastfeeding -AML

## Kwan et al, 2004 meta-analysis

**Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) in studies of association between breastfeeding >6 months and risk of childhood AML (*n*=8 studies)**



# Breastfeeding: any/exclusive breastfed vs. never breastfed

Martin et al, IJC 2005 meta-analysis:

- Significant **protective effect** of breastfeeding for **overall leukemia** (OR=0.87) and **ALL** (OR=0.91) but not for ANLL
- Significant **protection** for **Hodgkin's disease** (HD)
- No association with Non-Hodgkin Lymphoma (NHL)

# Breastfeeding: a multivalent factor

Early development of the immune system [vs] artificially fed infants

-**Protection from ALL**: <u>Early exposure</u> to infectious agents transferred from the mother's milk→ immune response via B-cell and <u>appropriate modulation of the immune system</u>

-(expansion , suppression, elimination of certain T-cell subsets)

The Greaves's hypothesis

- **Protection from AML:** implies a separate immunological mechanism that is operating via myeloid precursors, along with the mechanism suggested by Greaves

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# Childhood diet

# The NARECHEM study

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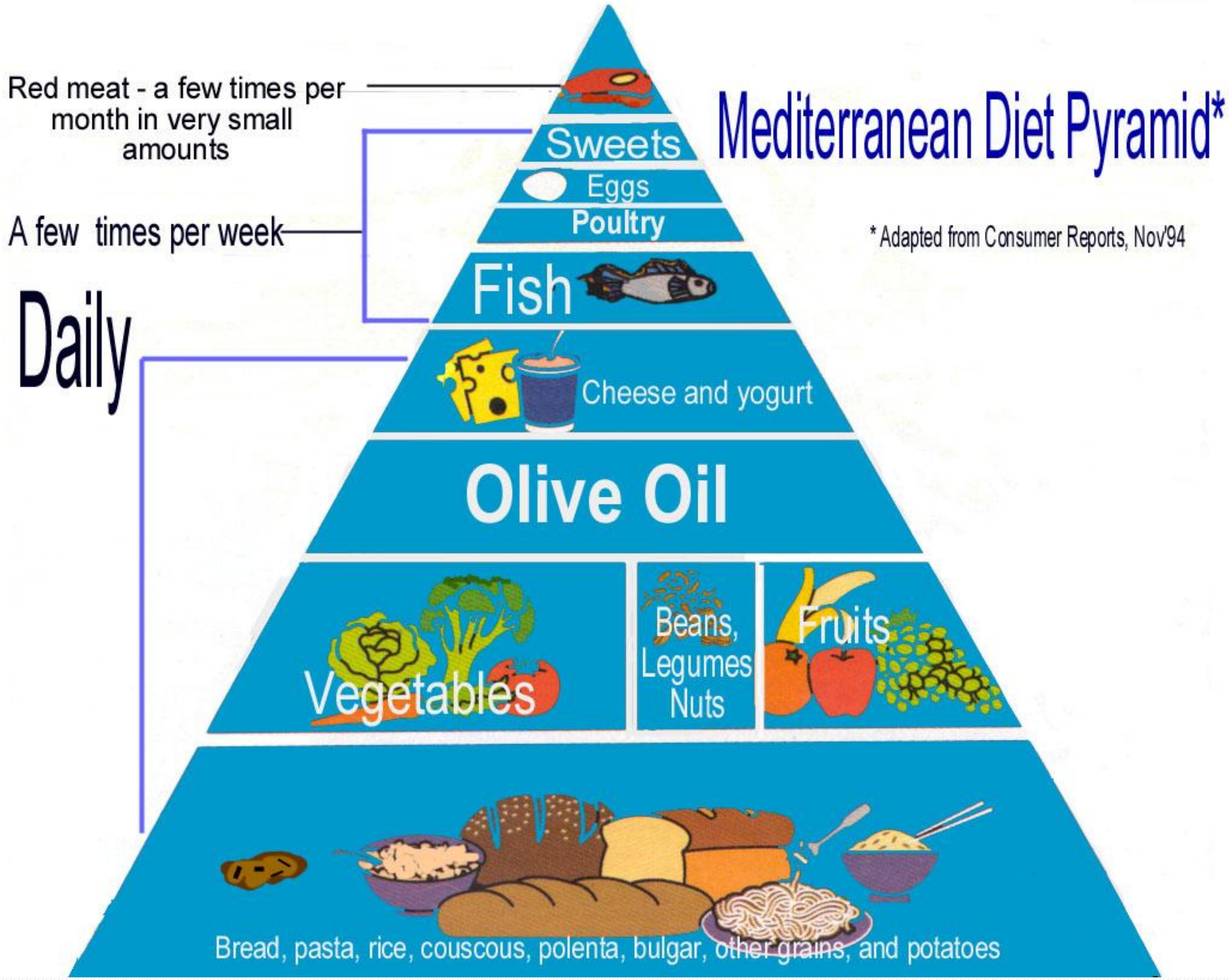
# Childhood diet and food groups:

- 139 children with ALL, aged 5-14 years
- 1:1 gender and age-matched controls
- Food frequency questionnaire addressing diet (157 items)
- Food groups, macronutrients, micronutrients
- Multivariate adjustment for confounding factors
- Adherence to Mediterranean diet



Mediterranean Diet Pyramid*
* Adapted from Consumer Reports, Nov'94
Red meat - a few times per month in very small amounts
A few times per week
Daily
Sweets
Eggs
Poultry
Fish
Cheese and yogurt
Olive Oil
Vegetables
Beans, Legumes Nuts
Fruits
Bread, pasta, rice, couscous, polenta, bulgar, other grains, and potatoes

# Mediterranean diet score

Range: 0-55, Eleven distinct food groups

- Olive oil
- Alcohol (inv)
- Non-refined cereals
- Potatoes
- Fruits
- Vegetables
- Legumes
- Fish
- Red meat products (inv)
- Poultry (inv)
- Full-fat dairy (inv)

# Adherence to Mediterranean diet

**OR for Med-diet score: 1.06, p=0.16**

## Assessment of impact of childhood diet: a core methodological consideration

## Is the exposure time frame adequate?

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# Food groups and ALL: NARECHEM data

*Similar results for total childhood leukemia*

| Variable | OR (95%CI) | p |
|---|---|---|
| Cereals and starchy roots | 1.17 (0.92-1.49) | 0.20 |
| Sugars and syrups | 1.10 (0.88-1.38) | 0.38 |
| Pulses, nuts and seeds | 0.94 (0.76-1.15) | 0.55 |
| Vegetables | 1.09 (0.90-1.33) | 0.37 |
| Fruits | 1.05 (0.88-1.25) | 0.60 |
| Meats and meat products | 0.96 (0.78-1.18) | 0.69 |
| Fish and shellfish | 1.00 (0.82-1.21) | 0.98 |
| Milk and milk products | 0.94 (0.77-1.14) | 0.53 |
| **Added lipids** | **1.31 (1.04-1.64)** | **0.02** |

*Unpublished NARECHEM data (not to be quoted)*

# Micronutrients and ALL *Unpublished NARECHEM data not to be quoted*

| Variable | OR (95%CI) | p |
|---|---|---|
| Thiamin | 0.62 (0.39-0.99) | 0.05 |
| Nicotinic Acid | 0.38 (0.17-0.85) | 0.02 |
| Riboflavin | 0.68 (0.44-1.05) | 0.08 |

**Non significant associations with:**

- fiber
- retinol
- carotene
- vitamin C, vitamin B6
- sodium, potassium, calcium, magnesium, phosphorus
- iron

# Micronutrients and carcinogenesis

De Vogel, J Nutr, 2008g

**Riboflavin &** vitamin B6 are involved in the folate mediated1-carbon metabolism, may therefore **modulate the bioavailability of methyl groups**

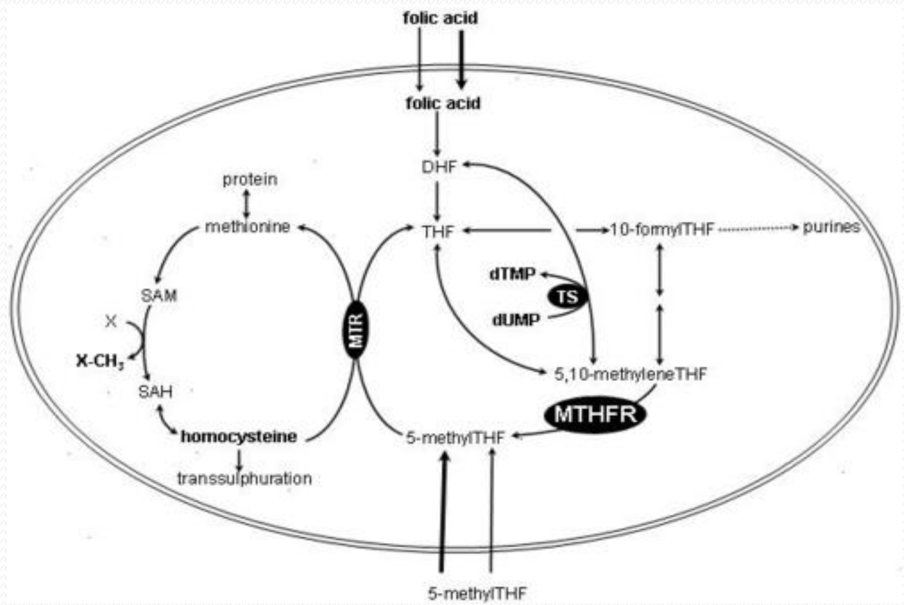
Low riboflavin status is associated

with increased

homocysteine concentration,

possibly resulting in lower

availability of methyl groups



# Convergence with other studies

Liu et al, 2009: Dietary intake before diagnosis; 145 leukemia cases (2-20 years old); 370 controls

**Table 3: Frequencies and adjusted odds ratios of diet effects on acute leukemia risk**

| | 2–5 years old | | | 2–20 years old | | |
|---|---|---|---|---|---|---|
| | Cases | Controls | | Cases | Controls | |
| Consumption of food | (n = 50) | (n = 118) | OR (95% CI)[a] | (n = 145) | (n = 370) | OR (95% CI)[a] |
| **Cured meat/fish** | | | | | | |
| Rare or occasional | 34 | 90 | 1.00 | 94 | 282 | 1.00 |
| Frequent | 16 | 28 | 1.52 (0.75–3.09) | 51 | 88 | **1.74 (1.15–2.64)[c]** |
| **Pickled vegetables** | | | | | | |
| Rare or occasional | 44 | 103 | 1.00 | 124 | 322 | 1.00 |
| Frequent | 6 | 15 | 1.07 (0.41–2.79) | 20 | 48 | 1.10 (0.62–1.93) |
| **Bean-curd food** | | | | | | |
| Rare or occasional | 17 | 21 | 1.00 | 34 | 53 | 1.00 |
| Frequent | 33 | 97 | **0.47 (0.22–0.99)[b]** | 111 | 317 | **0.55 (0.34–0.89)[b]** |
| **Vegetables** | | | | | | |
| Rare or occasional | 27 | 39 | 1.00 | 57 | 97 | 1.00 |
| Frequent | 23 | 79 | **0.44 (0.22–0.85)[b]** | 88 | 273 | **0.55 (0.37–0.83)[c]** |
| **Fruits** | | | | | | |
| Rare or occasional | 29 | 46 | 1.00 | 75 | 178 | 1.00 |
| Frequent | 21 | 72 | 0.53 (0.28–1.01) | 70 | 192 | 0.86 (0.58–1.26) |
| **Tea** | | | | | | |
| No | 34 | 80 | 1.00 | 100 | 237 | 1.00 |
| Yes | 16 | 38 | 0.98 (0.49–1.95) | 45 | 133 | 0.80 (0.53–1.22) |

[a]Odds ratios and 95% confidence intervals derived from logistic regression adjusted for age and sex
[b]$p < 0.05$; [c]$p < 0.01$

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# Convergence with other studies

Kwan et al. 2004:

- 328 children with leukemia >2 years of age – 415 controls
- Childhood diet in the **first 2 years** of life
- **Oranges**/**bananas** ($\geq$4-6 days/week): **lower CL risk**, OR = 0.49 (95%CI: 0.26-0.94)
- **Orange juice** ($\geq$1-3 days/week): OR= 0.54 (95%CI: 0.31-0.94)
- Non significant positive associations for hot-dogs/lunch meat and beef/hamburger






# Convergence with other studies

- Precursors or inhibitors of N-nitroso compounds (NOC): 14 cases- 3 controls

  Significant **positive** association of **>12 hot-dogs/month** with CL

  (Peters et al, CCC, 1994)

- Positive non-significant associations of different meats/meat products (especially combination of no vitamins and meat) with ALL
- (Sarasua & Savitz, CCC, 1994)

# Double controversy???

# The future

# Perspectives (qualitative aspects of diet)

- A systematic review – meta-analysis aiming to clarify comparability of studies in different time windows and synthesize available evidence *(in preparation, Athens, GR)*

- Large consortia studies needed to maximize statistical power in the detection of subtle effects

  -- > local particularities regarding nutritional habits?

- Gene-environment interactions

  (the paradigm of folate and MTHFR/MTRR polymorphisms)

# Impact of quantitative  vs. qualitative of dietary intake aspects at population level?

# Is birth weight a summarizing proxy or a confounding factor?

*Int. J. Cancer*: **124**, 2658–2670 (2009)


**Birth weight and childhood leukemia: A meta-analysis and review of the current evidence**

**Robert W. Caughey[1] and Karin B. Michels[1,2*]**

uicc
global cancer control

IJC
International Journal of Cancer

**Is birth weight associated with childhood lymphoma? A meta-analysis**

C. Papadopoulou, C.N. Antonopoulos, T.N. Sergentanis, P. Panagopoulou, M. Belechri and E.T. Petridou

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# Intrauterine exposure to pregnancy diabetes (GDM) & risk of obesity/diabetes II in the adolescent offspring

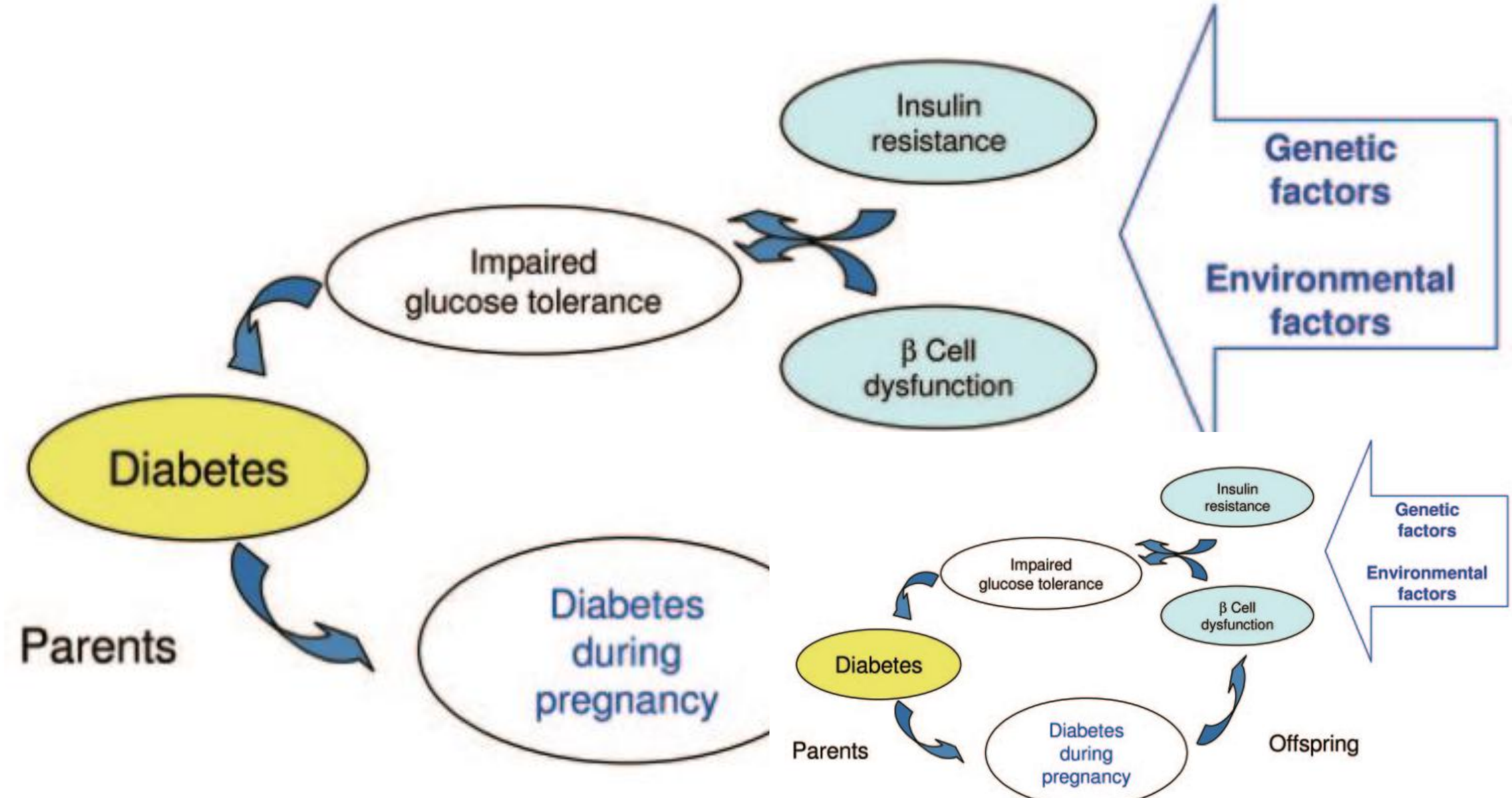
Hyperglycemic intrauterine environment: **predisposes** to earlier onset of diabetes II in the offspring; ~1.7 years earlier among those exposed to diabetes *in utero* than when maternal diabetes was diagnosed later

Intrauterine exposure **to maternal diabetes and obesity:** associated with diabetes II in youth (50%)

Inconsistent evidence: an association between GDM and offspring overweight/obesity (methodological limitations in 12 eligible studies)

- Preconception paternal diabetes: not associated with age at diagnosis

# Intrauterine exposure to maternal diabetes & risk of obesity-diabetes II in the adolescent offspring



# Dietary intake components in the CLIC studies panorama

**Table 3.** CLIC Pooled Analyses, as of December 2011

| Risk factors | Outcome |
|---|---|
| Fetal growth | Risk of ALL |
| Maternal vitamin and folate intake during pregnancy, alcohol consumption, and MTHFR variants | Risk of ALL, AML |
| Tobacco smoking, and *NQ01* variants | Risk of ALL |
| Markers of early infections and allergies | Risk of ALL |
| Indoor sources of benzene and hydrocarbons, xenobiotic transport and metabolic genes | Risk of AML |
| Assisted reproductive technologies; time to pregancy | Risk of ALL |
| Exposure to pesticides at home and work, xenobiotic transport and metabolic genes | Risk of ALL, AML |
| Exposure to paints at home and work, xenobiotic transport and metabolic genes | Risk of ALL, AML |
| Geographic distribution of AML, APL and cytogenetic subtypes | Risk of AML |
| Socio-demograhic and clinical characteristics | Survival of ALL, AML |
| Maternal consumption of coffee and tea | Risk of ALL, AML |

Abbreviations: ALL; acute lymphocytic leukemia; AML=acute myelpid leukemia; APL= acute promyelocytic leukemia