A Meta-Analytic Evaluation of Day Care Attendance and Risk of Childhood ALL

International Workshop on Risk Factors for Childhood Leukemia (ICNIRP/WHO/BfS)

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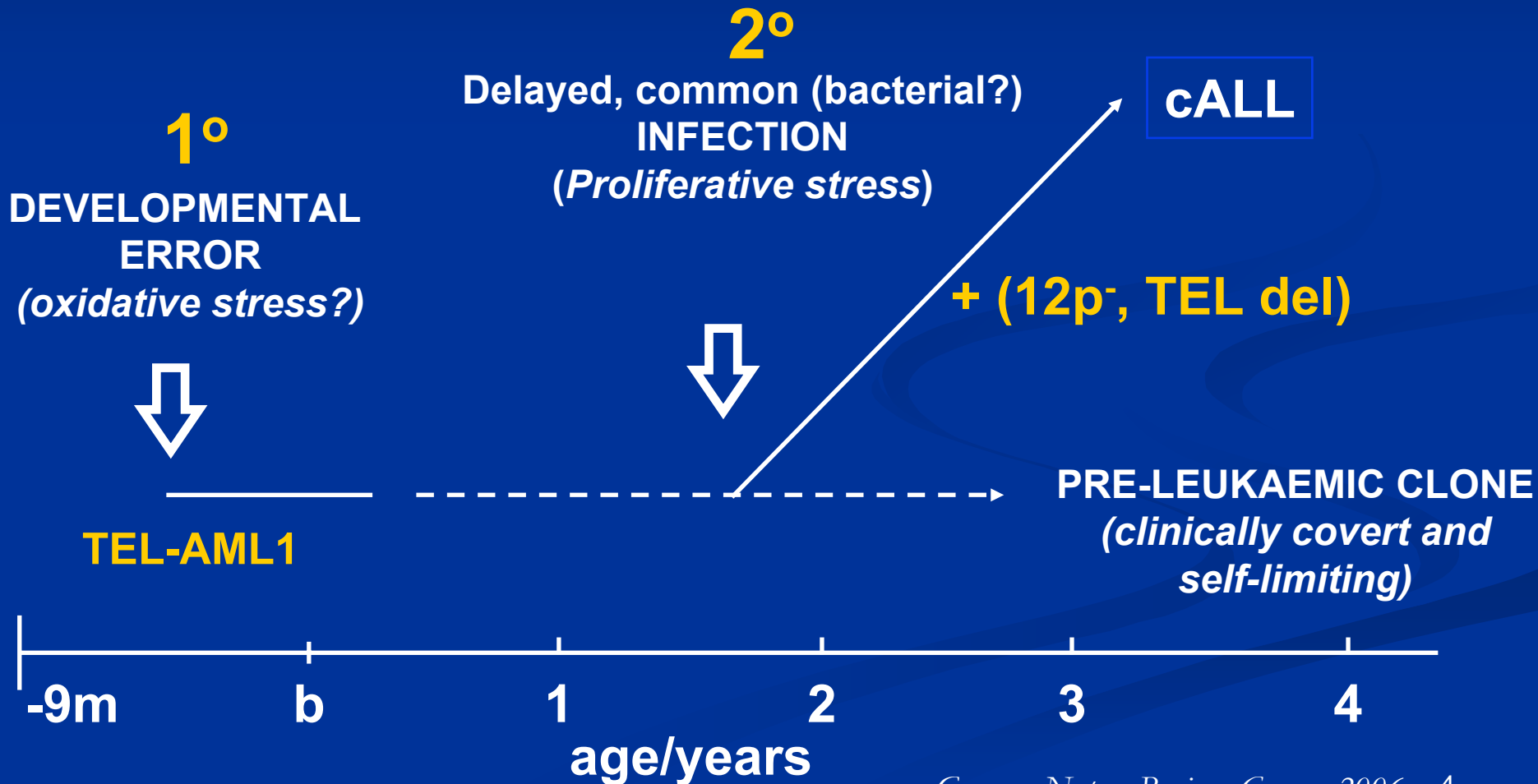School of Public Health

Outline of Presentation

- Hypotheses on the role of infections in childhood leukemia

- Day care attendance finding in the Northern California Childhood Leukemia Study (NCCLS)

- Meta-analysis of studies of day care attendance/social activity and risk of childhood leukemia

Hypotheses on Infections

- Describes childhood leukemia as a rare response to one or more common infections acquired by personal contact

- <u>Kinlen's Hypothesis ('population mixing')</u>
  - Childhood leukemia may be caused by a viral infection or infections, the transmission of which is promoted by population-mixing.

- <u>Greaves' Hypothesis ('delayed infections')</u>
  - Childhood leukemia, especially cALL, may arise as a consequence of a rare abnormal response due to a delay in the of exposure to common infection(s)

A 2 Step Model for the Natural History of cALL

2º
Delayed, common (bacterial?) INFECTION
(*Proliferative stress*)

1º
DEVELOPMENTAL ERROR
(*oxidative stress?*)

cALL

+ (12p⁻, TEL del)

TEL-AML1

PRE-LEUKAEMIC CLONE
(*clinically covert and self-limiting*)

| -9m | b | 1 | 2 | 3 | 4 |

age/years

Surrogate measures used to assess the role of infections in childhood leukemia

Social Contacts

• Child's birth order/family structure

• **Child's social contacts through day care, playgroups, etc.**

• Parental social contacts at work

• Population mixing

Infections

• Childs infections

• Maternal infections during pregnancy

Immune modulating

• Breastfeeding

• Vaccinations

QUESTION
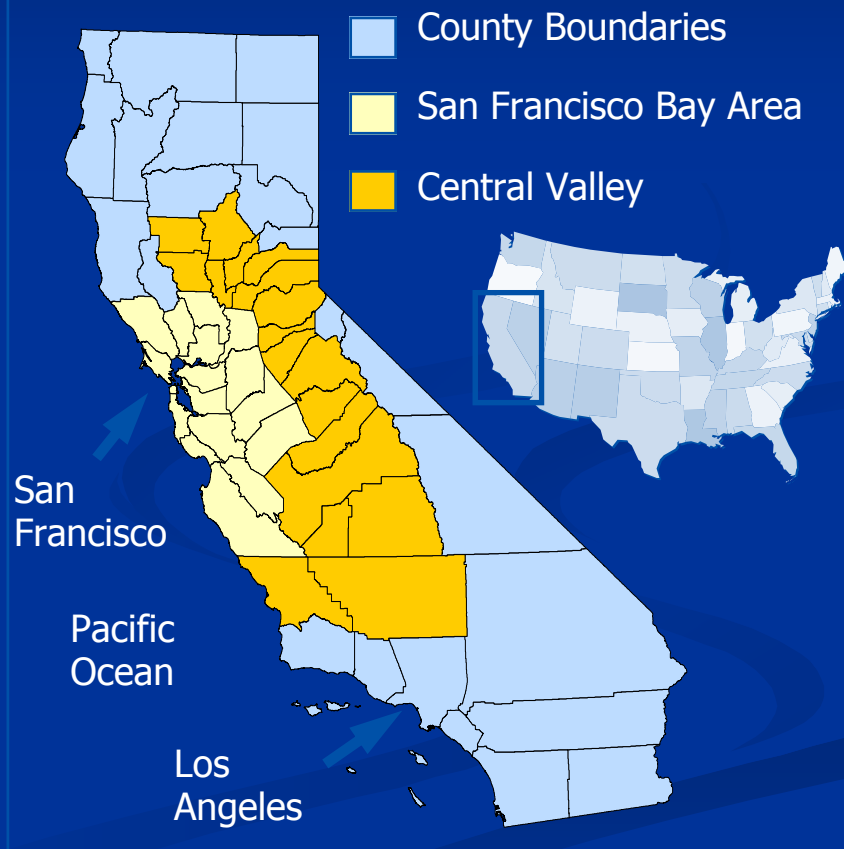Are infections associated with childhood leukemia?

Day Care Attendance

- In developed countries, contact with other children is the main source of exposure to common infections.

- Day care attendance increases the risk of infections.

- <u>Hypothesis</u>: Day care attendance, as a surrogate for exposure to infections during early childhood, is associated with a reduced risk of acute lymphoblastic leukemia

Northern California Childhood Leukemia Study (NCCLS)

- Population-based matched case-control study of childhood leukemia
- <u>Incident cases</u> ascertained from 9 major pediatric clinical centers in N. & C. California
- <u>Controls individually matched</u> (date of birth, sex, Hispanic status, and maternal race)
- 42% Hispanic

Map of NCCLS Study Area

- County Boundaries
- San Francisco Bay Area
- Central Valley

San Francisco

Pacific Ocean

Los Angeles

Day care Attendance Data

- Data collected through an in-home personal interview

- Information obtained for each day care attended:
  - Age started day care
  - Months attended
  - Mean hours per week attended
  - Number of other children at day care
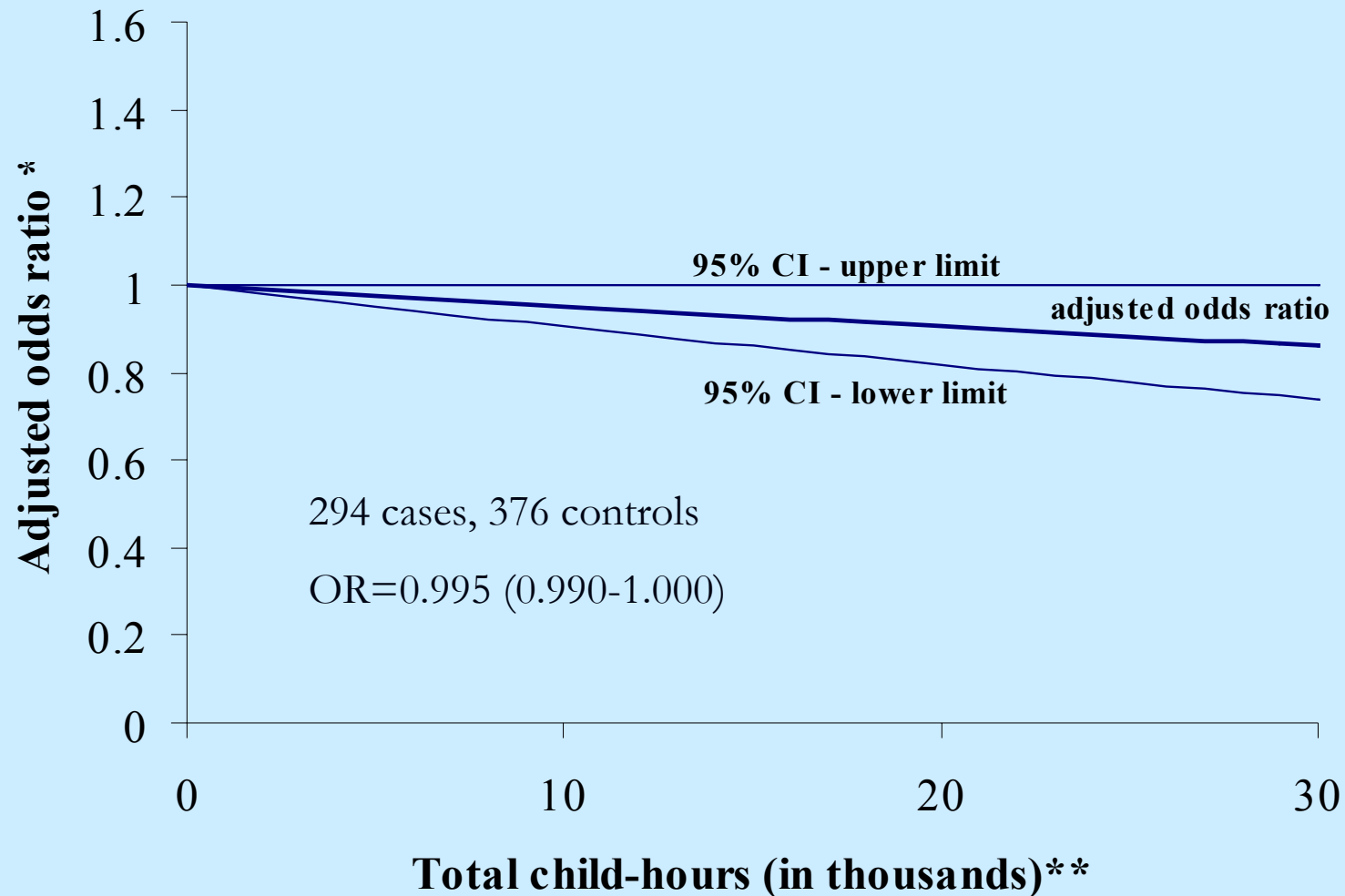- Total child-hours of exposure summary measure

Total Child-hours Calculation

	No. other children	X	Months attended	X	Mean hrs/wk	X	4.35 wks/mo	=	Child-hours
1st	10		5		5		4.35		1,087.5
2nd	6		4		7		4.35		730.8
3rd	13		6		6		4.35		2,035.8

Total child-hours   3,854.1

Total Child-hours and Risk of ALL

95% CI - upper limit

adjusted odds ratio

95% CI - lower limit

294 cases, 376 controls

OR=0.995 (0.990-1.000)

Adjusted odds ratio *
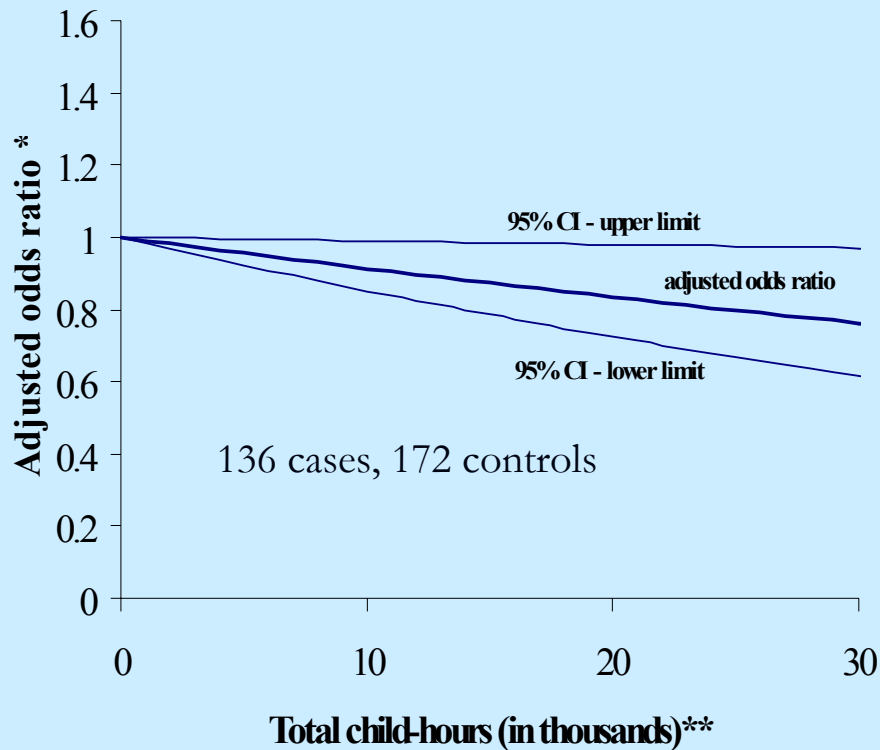
Total child-hours (in thousands)**

*Adjusted for annual household income and maternal education
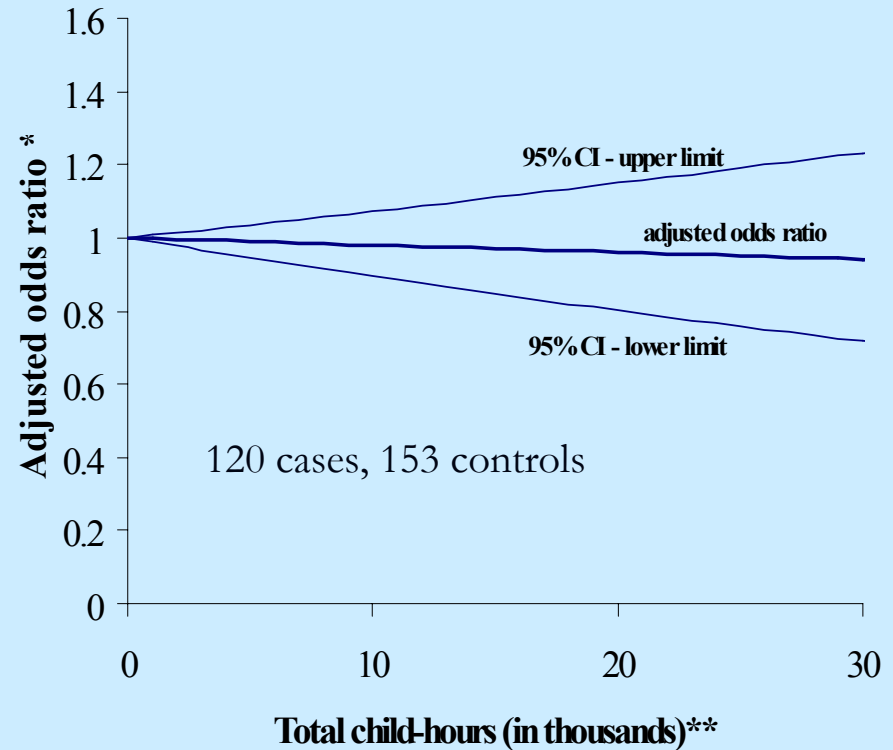
**Total child-hours censored at reference date

Data from Ma et al., Cancer Epidemiology Biomarkers and Prevention, 2005.

Total Child-hours and Risk of ALL by Race/Ethnicity

*Adjusted for annual household income and maternal education

**Total child-hours censored at reference date

Data from Ma et al., Cancer Epidemiology Biomarkers and Prevention, 2005.

Day Care Attendance Characteristics in NH-Whites & Hispanics

Variables	Cases			Controls			Case vs cont.
	White	Hisp	P	White	Hisp	P	in Whites
Total child-hrs, k	8.0	1.9	0.01	12.3	2.1	<0.001	0.06
Age started, mo.	30.0	54.0	<0.001				
Mo. of stay	12.5	3.0	<0.001				
Hrs/week	8.5	6.8	0.21				
# children at day care	9.4	3.8	<0.01				
# children in household	1.0	2.0	<0.001				

Median values are presented; Data censored on reference data

P-values are from nonparametric Wilcoxon rank-sum tests. *(From Ma et al., CEBP, 2005)*

Day Care Attendance Characteristics in NH-Whites & Hispanics

Variables	Cases			Controls			Case vs cont. in Whites
	White	Hisp	P	White	Hisp	P	
Total child-hrs, k	9.0	1.9	0.001	12.3	2.1	<0.001	0.06
Age started, mo.				30.0	49.0	<0.001	
Mo. of stay				18.8	3.0	<0.001	
Hrs/week				13.7	8.0	<0.01	0.01
# children at day care				10.1	5.0	<0.01	
# children in household				1.0	2.0	<0.001	

Median values are presented; Data censored on reference data

P-values are from nonparametric Wilcoxon rank-sum tests. *(From Ma et al., CEBP, 2005)*

13

Day Care Attendance Characteristics in NH-Whites & Hispanics

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	White	Hisp	P	White	Hisp	P	
Total child-hrs, k	8.0			12.3			**0.06**
Age started, mo.	30.0			30.0			**0.06**
Mo. of stay	12.5			18.8			0.32
Hrs/week	8.5			13.7			**0.01**
# children at day care	9.4			10.1			0.26
# children in household	1.0			1.0			0.72

Median values are presented; Data censored on reference data

P-values are from nonparametric Wilcoxon rank-sum tests. *(From Ma et al., CEBP, 2005)*

Total Child-hours during Infancy and Risk of ALL and cALL in NH-Whites
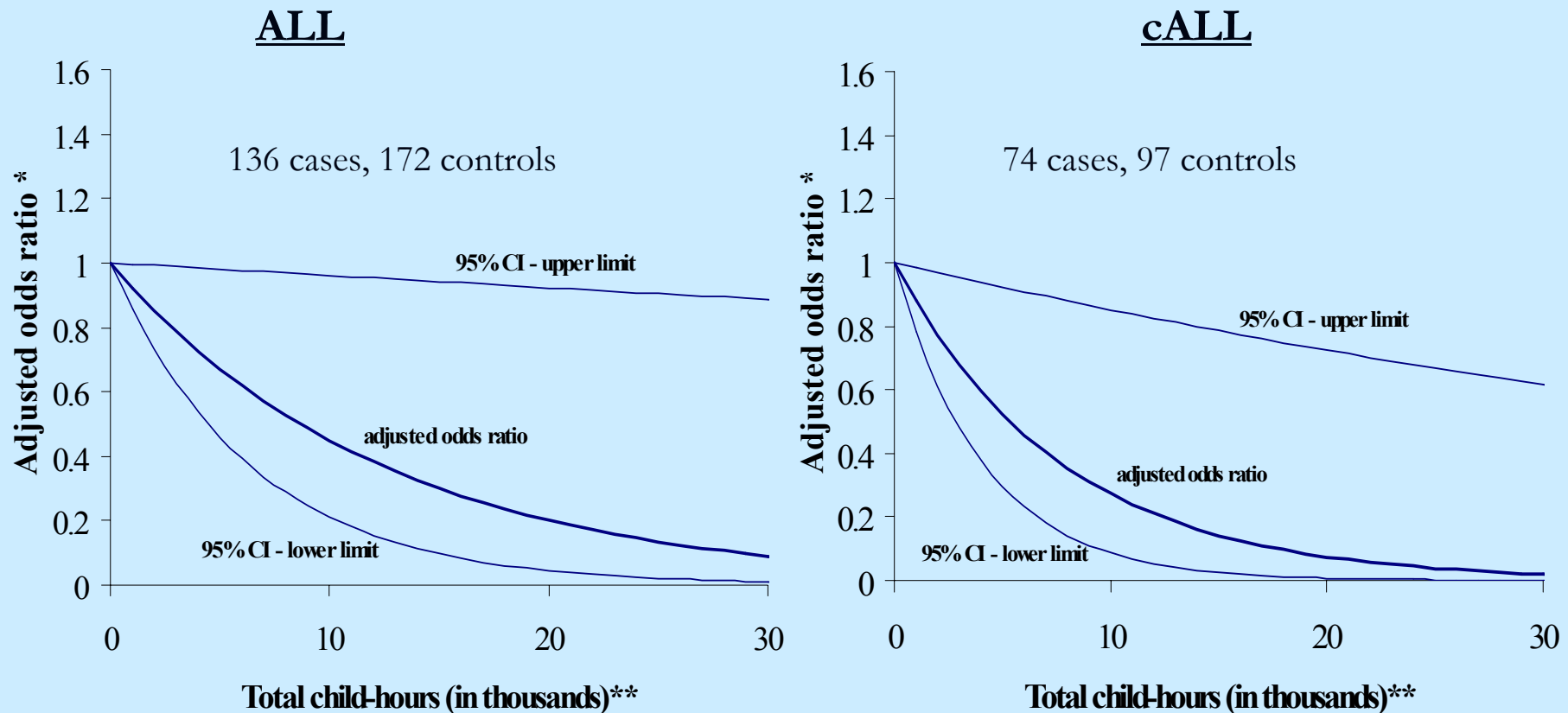
*Adjusted for annual household income and maternal education

**Total child-hours censored at 1 year of age

Data from Ma et al., Cancer Epidemiology Biomarkers and Prevention, 2005.

Summary of NCCLS Results

- In Non-Hispanic White children, increasing child-hours of exposure is associated with reduced risk of ALL.

- In Non-Hispanic White children, the reduction in risk is stronger in cALL and when censoring day care on the 1st year of life.

Meta-analysis of Studies of Day Care Attendance and Risk of Childhood ALL

<u>Objectives</u>:

1) Identify all previous studies on day care attendance/social activity and risk of childhood leukemia

2) Calculate combined risk estimates and 95% confidence intervals

3) Evaluate the overall consistency and strength of association while identifying the various sources of between-study heterogeneity
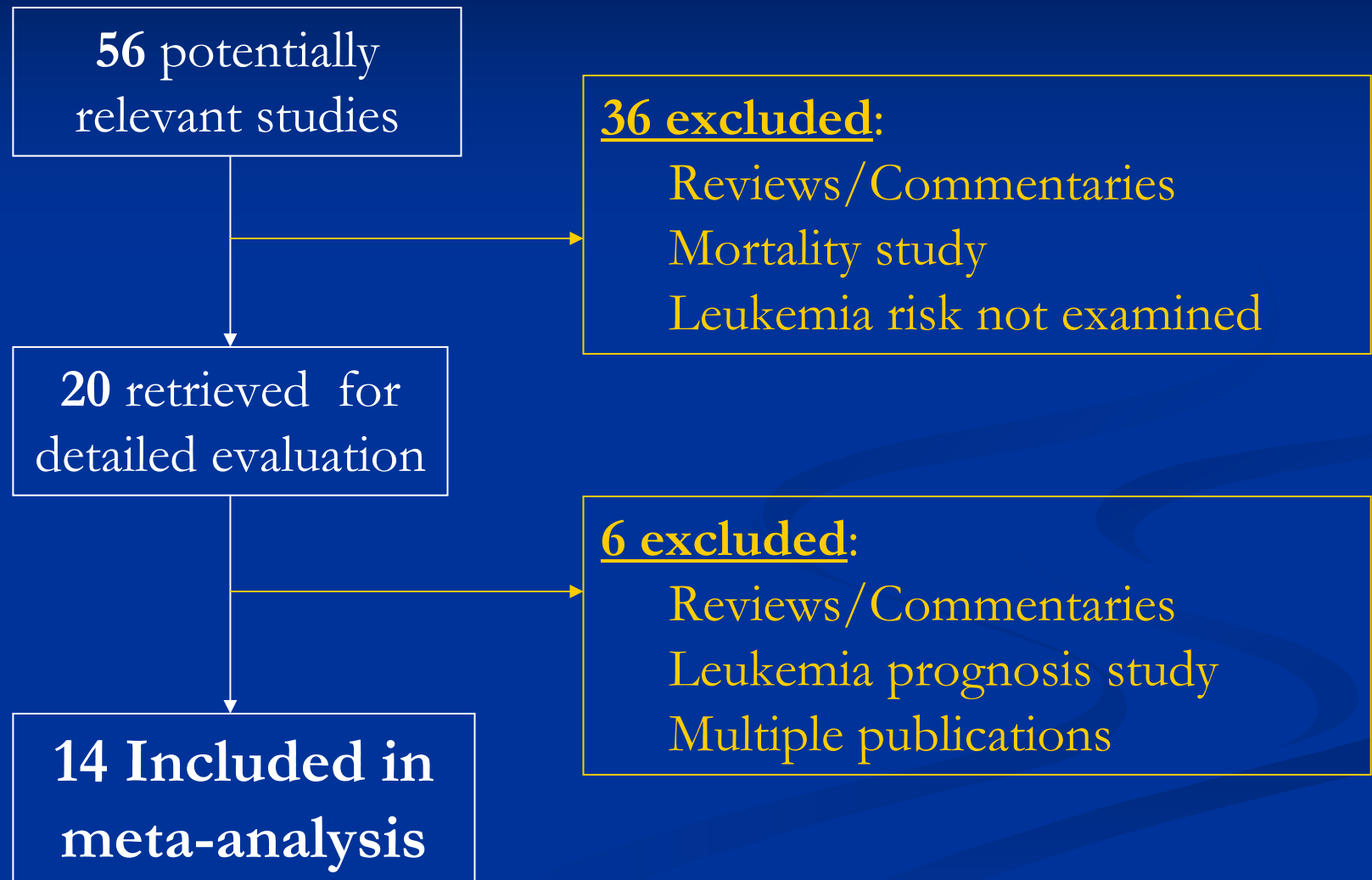
Definitions

- <u>Outcome</u>: Clinically diagnosed ALL, acute leukemia or leukemia in children between 0 and 19 years of age.

- <u>Exposure</u>: Day care attendance and/or social activity

  - Such as formal day care, nursery school, play groups, mother and toddler groups, preschool, "social activity", etc.

Search Method

- Searched the PubMed database using the terms "childhood leukemia" and "childhood cancer" in combination with terms including:
    - Infections
    - Day care
    - Child care
    - Social contact
- Bibliographies of publications on infections and childhood leukemia

Flow Diagram of Inclusion/Exclusion

56 potentially relevant studies

36 excluded:

Reviews/Commentaries

Mortality study

Leukemia risk not examined

20 retrieved for detailed evaluation

6 excluded:

Reviews/Commentaries

Leukemia prognosis study

Multiple publications

14 Included in meta-analysis

14 Studies Included in Analysis

Study, Year	Location	Disease	Age	Case/cont
Petridou et al., 1993	Greece	Leukemia	0-14	136/187
Roman et al., 1994	UK	ALL	0-4	38/112
Petridou et al., 1997	Greece	Leukemia	0-14	153/300
Schuz et al., 1999	Germany	AL, c-ALL	1.5-14	921/921
Dockerty et al., 1999	New Zealand	ALL	15 mo – 14	90/266
Infante-Rivard et al., 2000	Canada	ALL	0-9	433/416
Rosenbaum et al., 2000	USA	ALL	0-14	158/499
Neglia et al., 2000	USA	ALL, c-ALL	1-14	1744/1879
Chan et al., 2002	Hong Kong	AL, c-ALL	2-14	98/228
Perrillat et al., 2002	France	AL	2-15	246/237
Jourdan-Da Silva et al., 2004	France	AL, ALL	1-15	387/525
Gilham et al., 2005	UK	ALL, c-ALL	2-14	1272/6238
Ma et al., 2005 (NH-Whites)	USA	ALL, c-ALL	1-14	136/172
Ma et al., 2005 (Hispanics)	USA	ALL, c-ALL	1-14	120/153
Kamper-Jorgensen et al., 2008	Denmark	ALL, c-ALL	0-15	176/1571

Definitions of Exposure in Analysis

Study, Year	Exposure Type	Time of Exposure
Petridou et al., 1993	Attendance at creche (No/Yes)	< 2 yrs of age
Roman et al., 1994	Preschool playgroup (No/Yes)	Year before dx
Petridou et al., 1997	Day care (No/Yes)	Birth to dx
Schuz et al., 1999	Deficit in social contacts (No/Yes)	< 2 yrs of age
Dockerty et al., 1999	Reg. contact outside home (No/Yes)	< 1 yr of age
Infante-Rivard et al., 2000	Entry ≤2 yrs old vs. no day care	< 2 yrs of age
Rosenbaum et al., 2000	>36 mo. of care vs. stayed home	Birth to dx
Neglia et al., 2000	Day care before age 2 (No/Yes)	< 2 yrs of age
Chan et al., 2002	Index & family day care measure	< 1 yr of age
Perrillat et al., 2002	Day care (No/Yes)	Birth to dx
Jourdan-Da Silva et al., 2004	Day care (No/Yes)	Birth to dx
Gilham et al., 2005	Social activity (No/Yes)	< 1 yr of age
Ma et al., 2005 (NH-Whites)	Day care (No/Yes)	< 1 yr of age
Ma et al., 2005 (Hispanics)	Day care (No/Yes)	< 1 yr of age
Kamper-Jorgensen et al., 2008	Child care (No/Yes)	< 2 yrs of age

Main Meta-analysis

- Random effects model

- <u>Main analysis</u>:
  - Day care/social activity and ALL (14 studies)
  - If study reported multiple ORs by time period of day care attendance/social activity, then OR for earliest time period was used

Day care Attendance/Social Activity (ever/never) & Childhood ALL
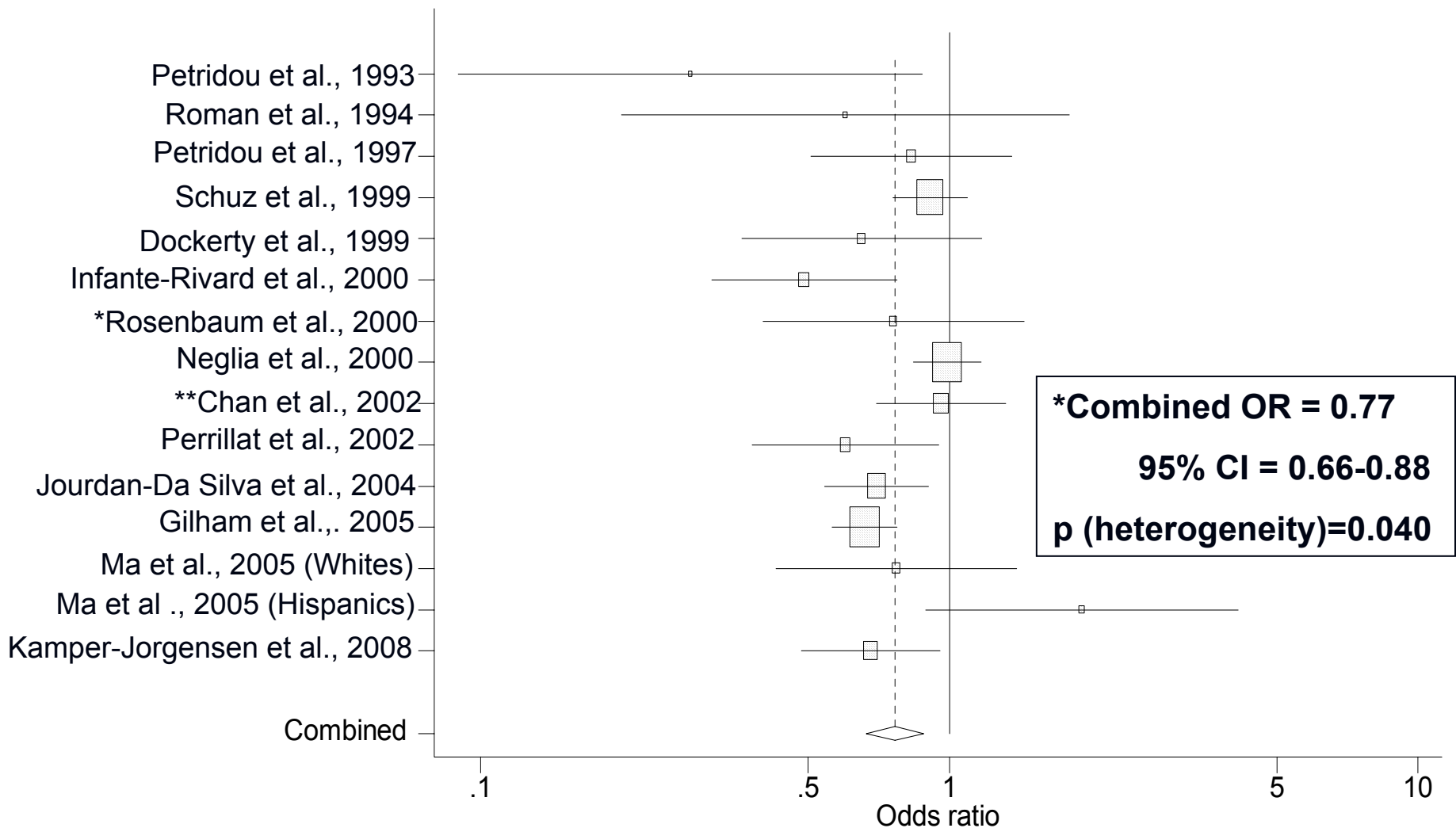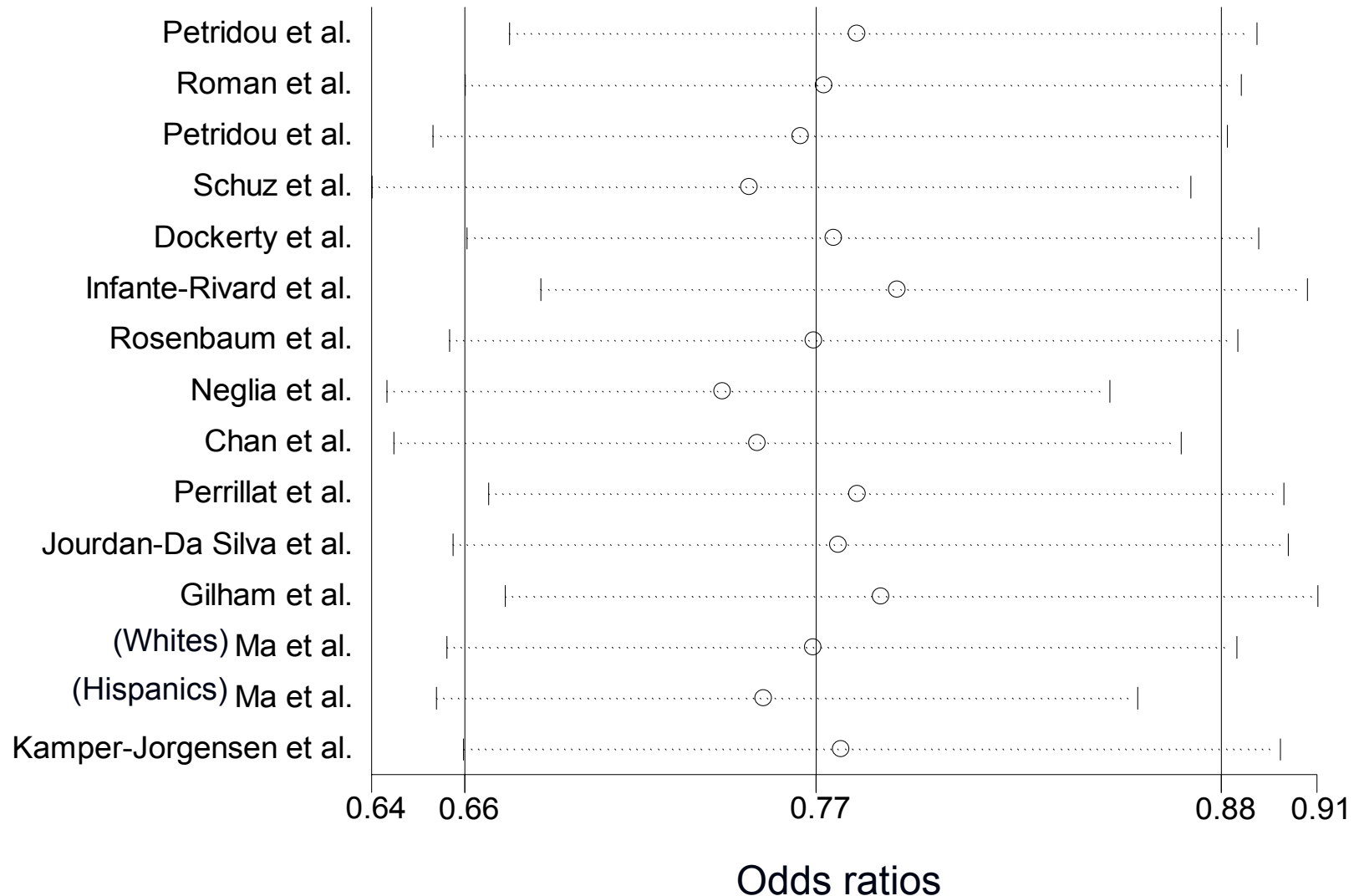

*Stayed home vs. >36 months of care

**3-part index and family day care measure (trend)

Influence Analysis of Individual Study Results

Meta-analysis random-effects estimates (exponential form)
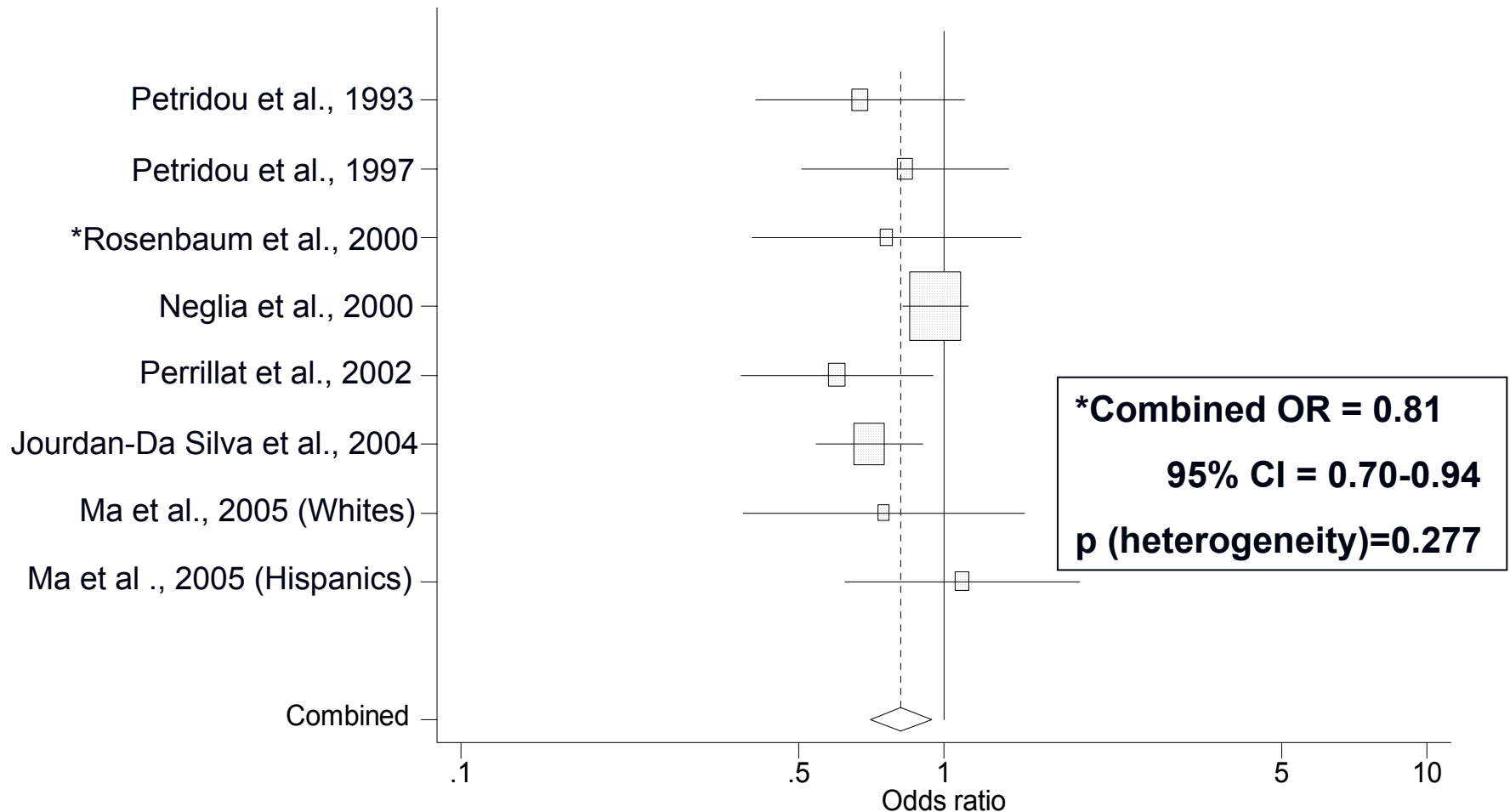Study ommited

Odds ratios

Subgroup Meta-analysis

■ Random effects model

■ <u>Subgroup analyses</u>:
- ■ Day care/social activity unspecified timing and ALL (7 studies)
- ■ Day care/social activity at age <1 or <2 and ALL (9 studies)

Day care attendance/social activity & childhood ALL
Unspecified Timing

Petridou et al., 1993

Petridou et al., 1997

*Rosenbaum et al., 2000

Neglia et al., 2000

Perrillat et al., 2002

Jourdan-Da Silva et al., 2004

Ma et al., 2005 (Whites)

Ma et al., 2005 (Hispanics)

Combined

*Combined OR = 0.81

95% CI = 0.70-0.94

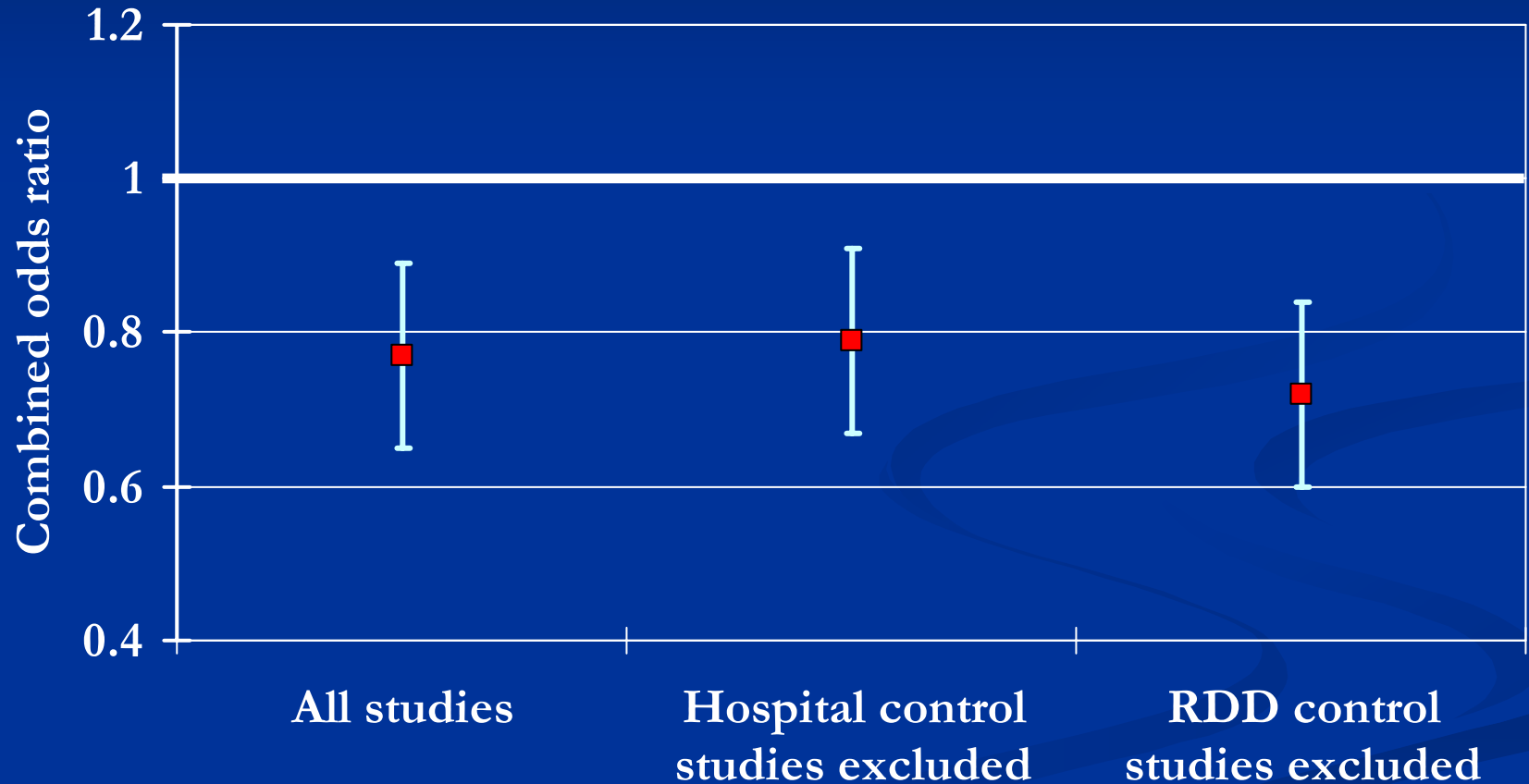**p (heterogeneity)=0.277**

.1   .5   1   5   10

Odds ratio

*Stayed home vs. >36 months of care

Day care attendance/social activity & Childhood ALL <1 or <2 years of age
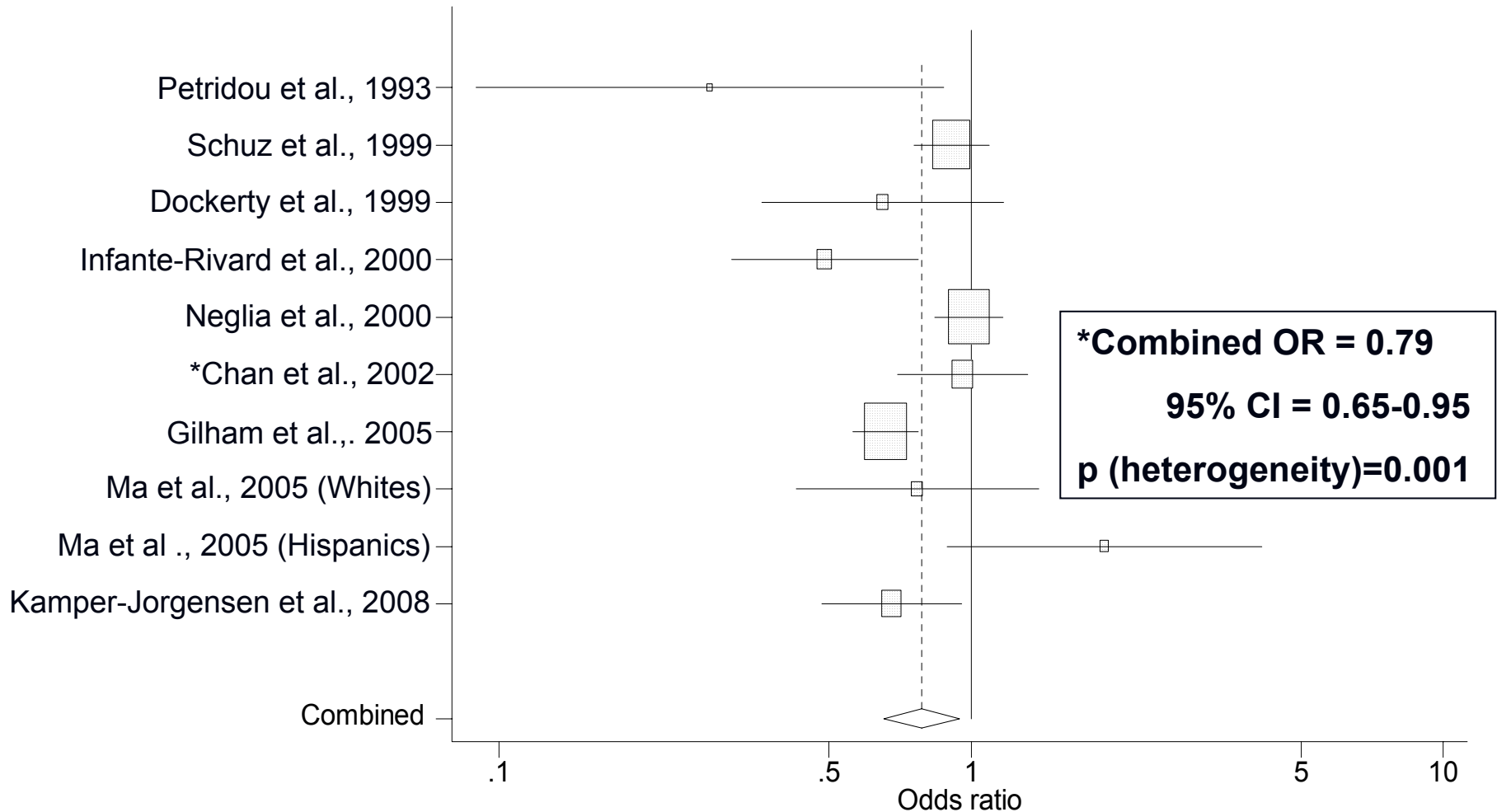
*3-part index and family day care measure (trend)

Heterogeneity: *Selection Bias*

Heterogeneity: *Information Bias*

- Recall bias
  - All studies are case-control in design
  - The 1 records-based study showed a reduced risk OR= 0.68, 95% CI=0.48-0.95
- Exposure misclassification
  - Only day care attendance (4 studies excluded)
- Disease misclassification
  - Infants in study pop. (6 studies excluded)
  - Only ALL studies (5 studies excluded)

Heterogeneity: *Information Bias*
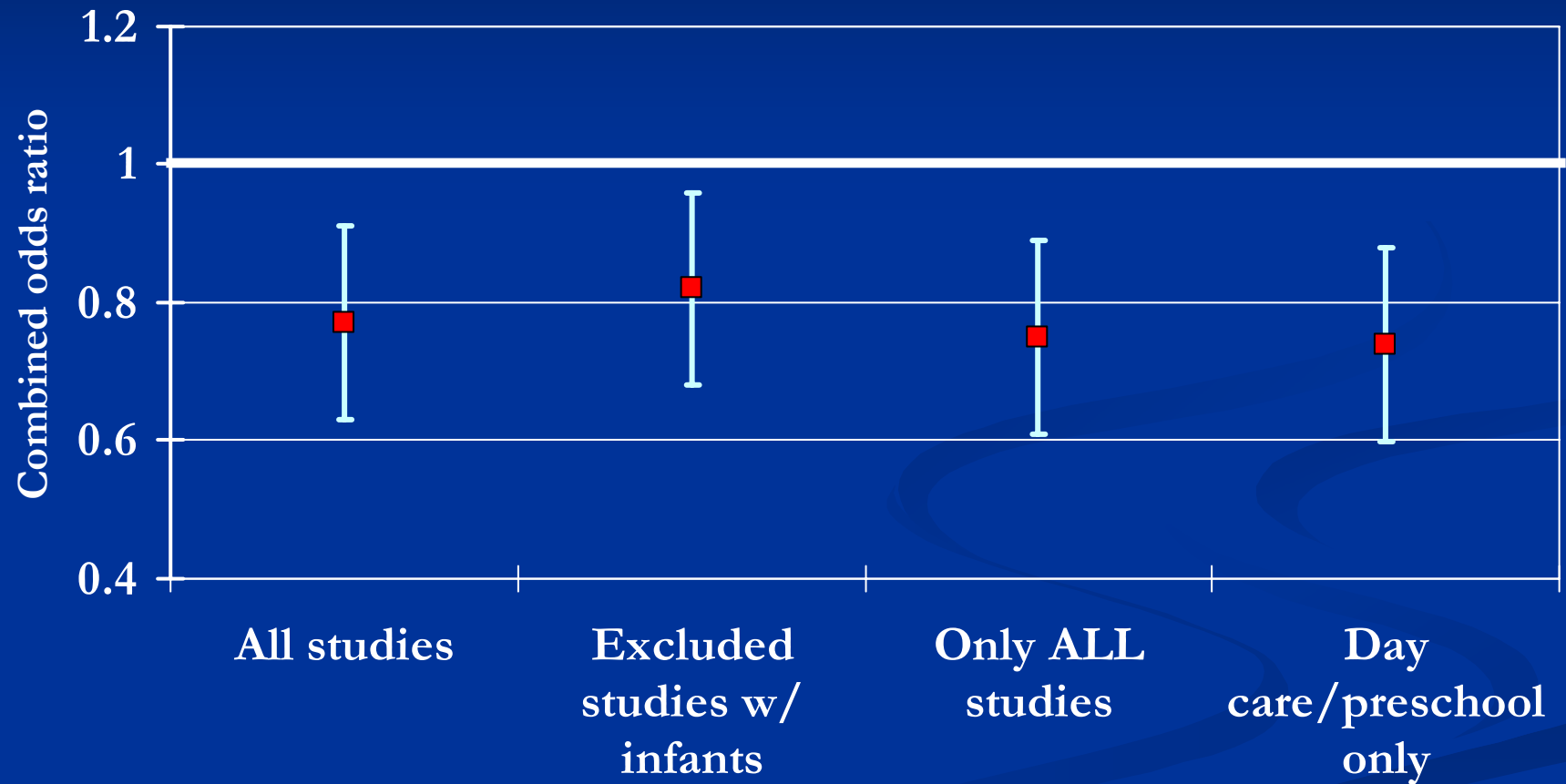
Heterogeneity: *Others*

Confounding

- All studies adjusted for major confounders (e.g. age, sex, SES and race/ethnicity if applicable)

Publication bias

- None observed based on visual evaluation of funnel graphs and the Begg and Mazumdar adjusted rank correlation test

Summary of Results

- Day care attendance/social activity is associated with a statistically significant reduced risk of childhood ALL

- Similar results were found for cALL, although based on a smaller number of studies (7)

Summary of Results

- Age at start of daycare/social activity does not appear to significantly affect results

- Individual study biases do appear to contribute to study heterogeneity, but do not completely account for the reduced risk observed.

Future Directions

- Studies should attempt to obtain detailed accounts of the extent of social contacts in the day care setting.

- Understand the relationships and contributions of the various sources of exposure to infections.

- Evaluate the influence of genetic susceptibility on the relationship between exposure to infections and childhood ALL.

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<u>University of California, San Francisco</u>

Joseph Wiemels, John Wiencke

Sponsors

Thank you for your attention!

Inclusion/Exclusion Criteria

- Language: English
- Publication date: Jan. 1966 to April 2008
- Study design: Cohort or case-control
- Exposure: day care attendance or social activity
- Outcome: leukemia in children aged 0-19 years
- Location: any
- Race/ethnicity: any
- Used most recent for multiple publications

Sources of Heterogeneity

- Exposure assessment and classification
- Timing of exposure
- Disease classification
- Age groups
- Location of study
- Control selection
- Adjustment for confounding

Statistical Analysis

- <u>Fixed effects model</u>: assumes that the true effect of the exposure is the same value in each study; differences due to random variation

  -ORs are weighted according to a measure of the quantity of information they contain

- <u>Random effects model</u>: assumes a different underlying effect for each study

  -Relatively more weight is given to smaller studies

14 Studies Included in Analysis

Study, Year	Location	Disease	Years Dx	Age
Petridou et al., 1993	Greece	Leukemia	1987-1992	0-14
Roman et al., 1994	UK	ALL	1972-1989	0-4
Petridou et al., 1997	Greece	Leukemia	1993-1994	0-14
Schuz et al., 1999	Germany	AL, c-ALL	1980-1997	1.5-14
Dockerty et al., 1999	New Zealand	ALL	1990-1993	15 mo – 14
Infante-Rivard et al., 2000	Canada	ALL	1989-1995	0-9
Rosenbaum et al., 2000	USA	ALL	1980-1991	0-14
Neglia et al., 2000	USA	ALL, c-ALL	1989-1993	1-14
Chan et al., 2002	Hong Kong	AL, c-ALL	1994-1997	2-14
Perrillat et al., 2002	France	AL	1995-1999	2-15
Jourdan-Da Silva et al., 2004	France	AL, ALL	1995-1998	1-15
Gilham et al., 2005	UK	ALL, c-ALL	1991-1996	2-14
Ma et al., 2005 (NH-Whites)	USA	ALL, c-ALL	1995-2002	1-14
Ma et al., 2005 (Hispanics)	USA	ALL, c-ALL	1995-2002	1-14
Kamper-Jorgensen et al., 2008	Denmark	ALL, c-ALL	1989-2004	0-15

Characteristics of Studies

Study	Exposure	Timing	Cases (n)	OR (95% CI)
Petridou	Attendance at creche	Before age 2	136	**0.28 (0.09-0.88)**
Roman	Preschool playgroup	Year before dx	38	0.60 (0.20-1.80)
Petridou	Day care	Birth to dx	153	0.83 (0.51-1.37)
Schuz	Deficit in social contacts	Before age 2	921	0.91 (0.90-1.30)
Dockerty	Contact outside home	First year of life	90	0.65 (0.36-1.17)
Infante-Rivard	Day care	Birth to age 2	433	**0.49 (0.31-0.77)**
Rosenbaum	Duration of care	Birth to dx	158	0.76 (0.70-2.52)
Neglia	Day care	Before age 2	1,744	0.99 (0.84-1.17)
Chan	Day care measure	First year of life	98	0.96 (0.70-1.32)
Perrillat	Day care	Birth to dx	246	**0.6 (0.4-1.0)**
Jourdan-Da Silva	Day care	Birth to dx	387	**0.7 (0.6-1.0)**
Gilham	Social activity	First year of life	1,272	**0.66 (0.56-0.77)**
Ma (White)	Day care	First year of life	136	0.77 (0.43-1.40)
Ma (Hispanic)	Day care	First year of life	120	1.92 (0.89-4.13)
Kamper-Jorgensen	Childcare	Birth to age 2	176	**0.68 (0.48-0.95)**