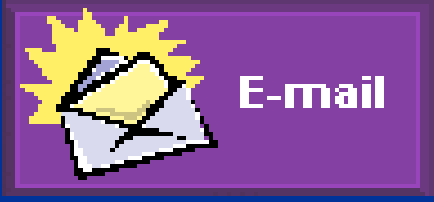
CAP TRIAL

Dear Peter:

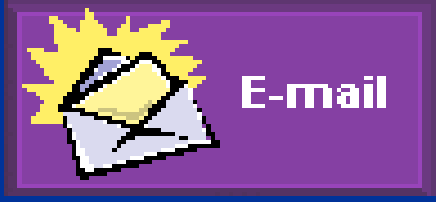
Remember, we were going to create a shortlist of important questions for future joint trials? Well, here is one potential candidate:

Barbara Schmidt; February 18, 1998



I was just browsing through the neonatal Cochrane website… I was absolutely horrified to see how few infants have ever been randomized to theophylline or caffeine,

Barbara Schmidt; February 18, 1998



and that all we know is that these drugs reduce short-term apnea.

I did not honestly know that the evidence was quite this flimsy.

Barbara Schmidt; February 18, 1998

METHYLXANTHINE THERAPY IN PRETERM INFANTS

Total no. of infants randomized to a methylxanthine (17 trials)	267
Median no. per trial	14

METHYLXANTHINE THERAPY IN PRETERM INFANTS

Duration of follow-up in17 RCTs

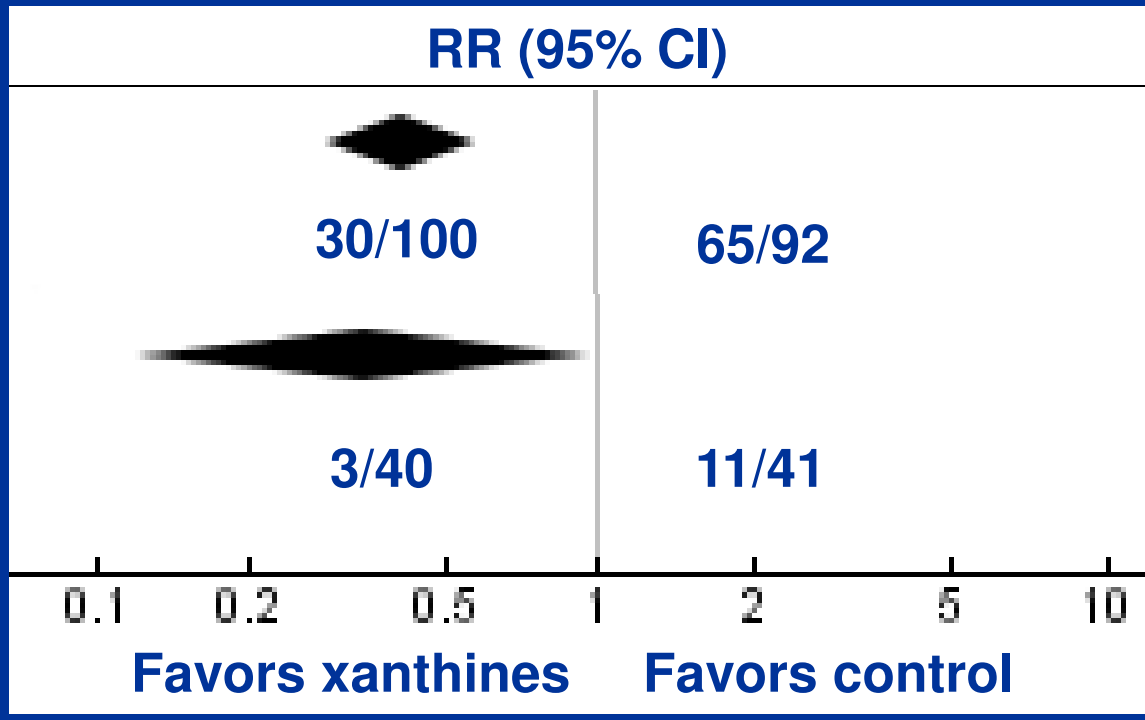
7 days

Median

COCHRANE LIBRARY

Methylxanthines reduce:

- Apnea of prematurity
- Mechanical ventilation



Safety of xanthine therapy is uncertain

Henderson-Smart DJ et al. In: The Cochrane Library, Issue 3, 2001.

Survival of 3 - 9 day old mice exposed to nitrogen

Aminophylline	Control
0 of 16 0%	10 of 16 63%

Science 1978; 201: 649-51

MAIN STUDY QUESTION

P Among very-low-birth-weight infants who are at risk of apnea of prematurity,

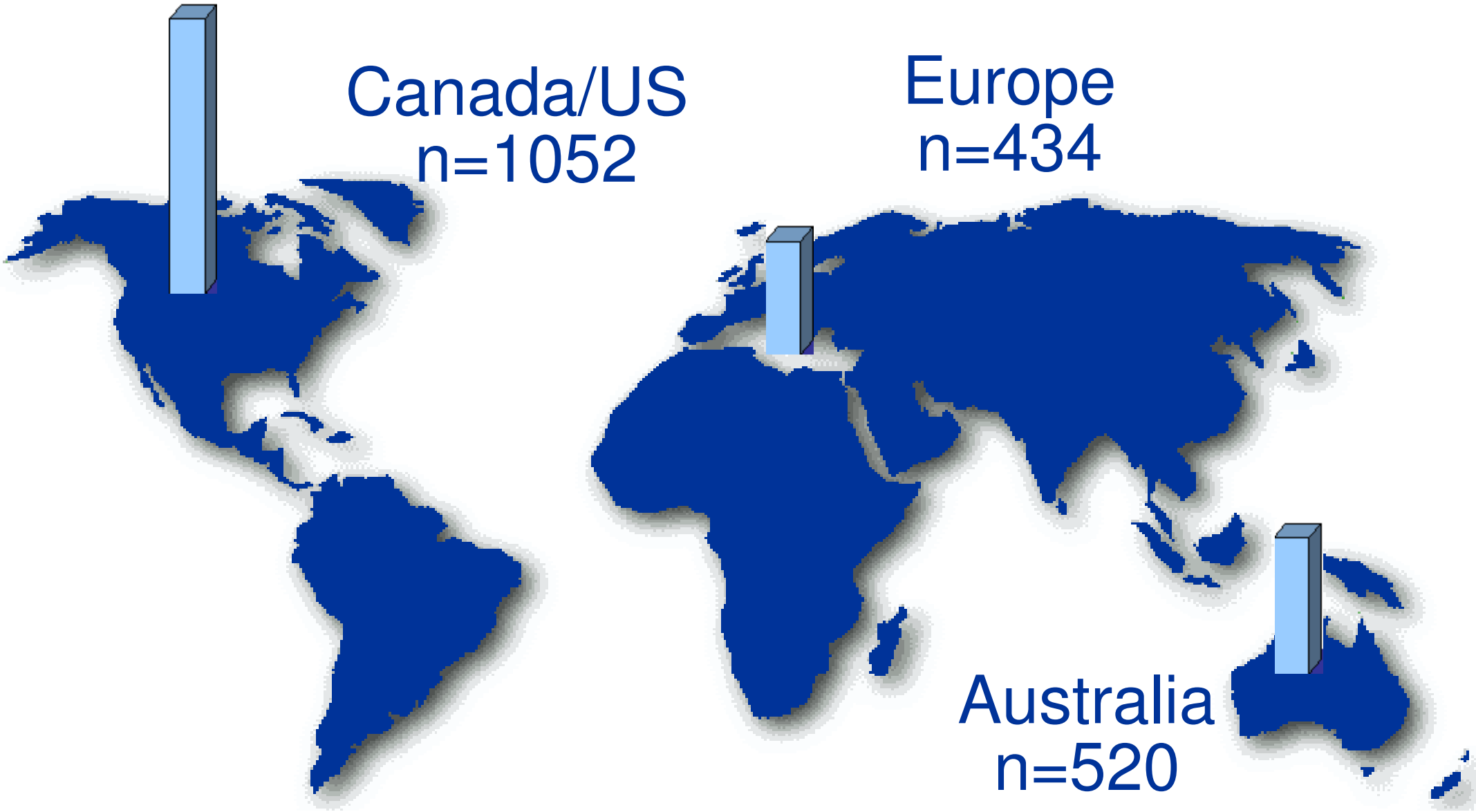
I does the use of caffeine

C compared with placebo

O increase the risk of death or neurosensory disability

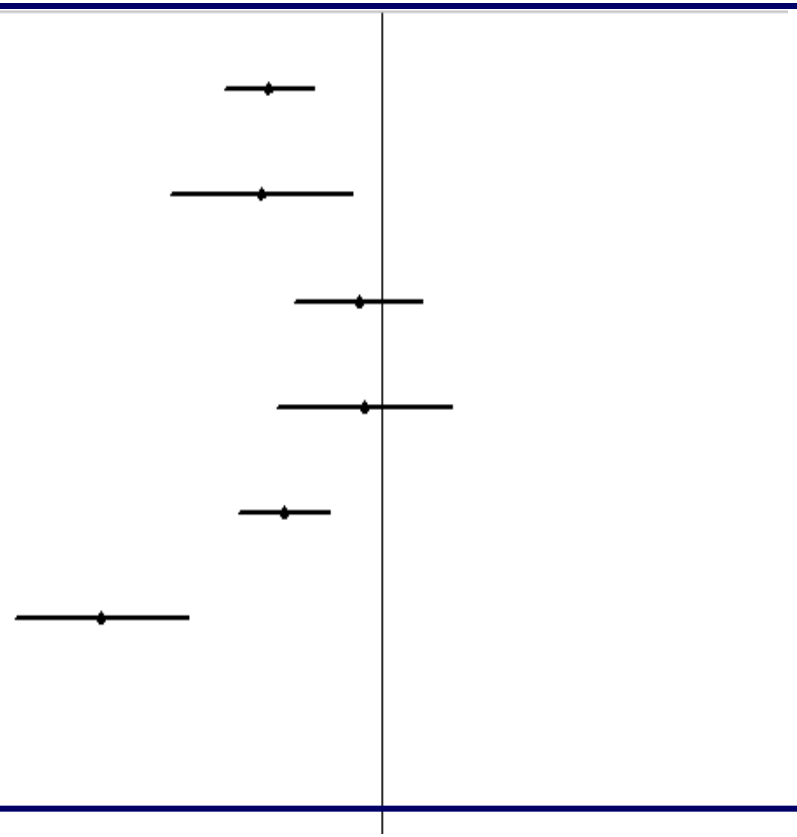
T at a corrected age of 18 months

PATIENT ACCRUAL



Short Term Outcomes of the Caffeine Trial

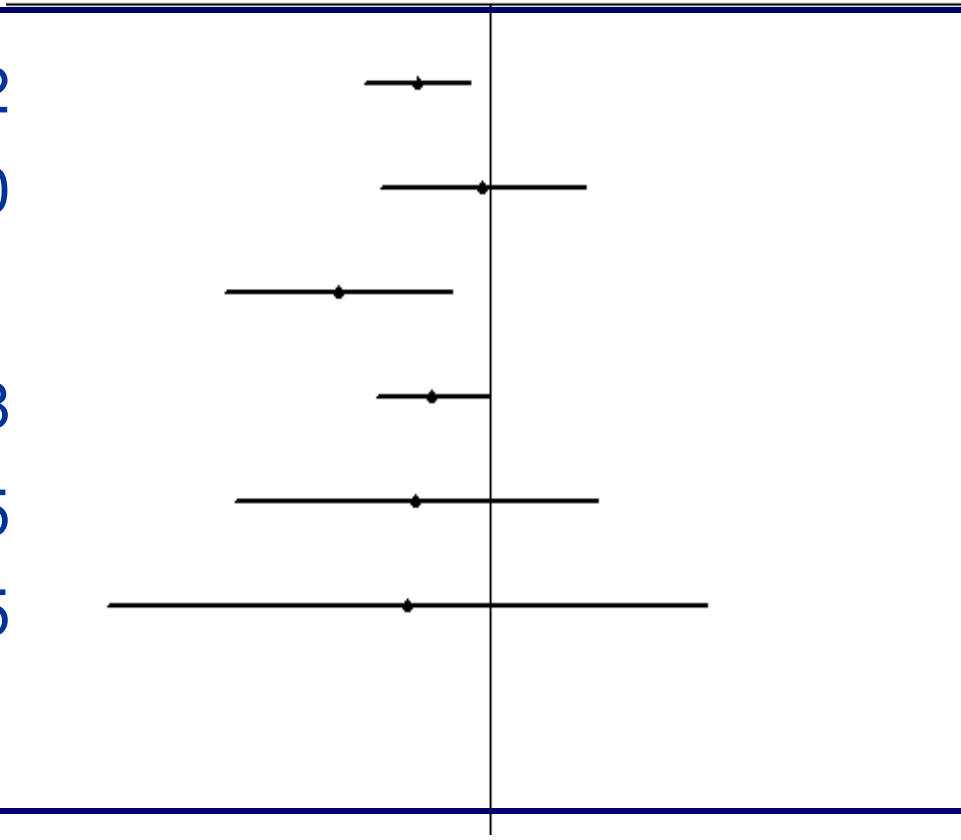
Outcome	Caffeine n/N	Placebo n/N	Odds Ratio (95% CI)
BPD	350/963	447/954	
Severe ROP	49/965	75/955*	
Brain injury	126/967	138/966	
NEC	63/1006	67/1000	
PDA drug Tx	293/1001	381/999	
PDA surgery	45/1001	126/999	



NEJM 2006;354:2112 and *2007;357:1893

18-Months Outcomes of the Caffeine Trial

Outcome	Caffeine n/N	Placebo n/N
Death or disability	377/937	431/932
Death	62/974	63/970
Cerebral Palsy	40/909	66/901
Cognitive delay	293/867	329/858
Hearing loss	17/909	22/905
Blindness	6/911	8/905



N Engl J Med 2007;357:1893

SOCIETY FOR CLINICAL TRIALS

project ImpACT
IMPORTANT ACHIEVEMENTS OF CLINICAL TRIALS

2008 SCT/IMPACT CLINICAL TRIAL OF THE YEAR AWARD

Long Term Effects of Caffeine for Apnea of Prematurity Trial

PI: Barbara Schmidt, MD, MSc

In recognition of a landmark randomized clinical trial
to improve the lives of premature infants.

Eleanor McFadden, MA
President, Society for Clinical Trials

Steven Goodman, MD, PhD
Project ImpACT

Caffeine for Apnea of Prematurity (CAP)Trial: Outcomes at 5 Years

Barbara Schmidt, Peter Anderson, Lex Doyle, Deborah Dewey, Ruth Grunau, Elizabeth Asztalos, Peter Davis, Win Tin, Diane Moddemann, Alfonso Solimano, Arne Ohlsson, Keith Barrington, Robin Roberts and The CAP Investigators

McMaster University

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Penn
University of Pennsylvania

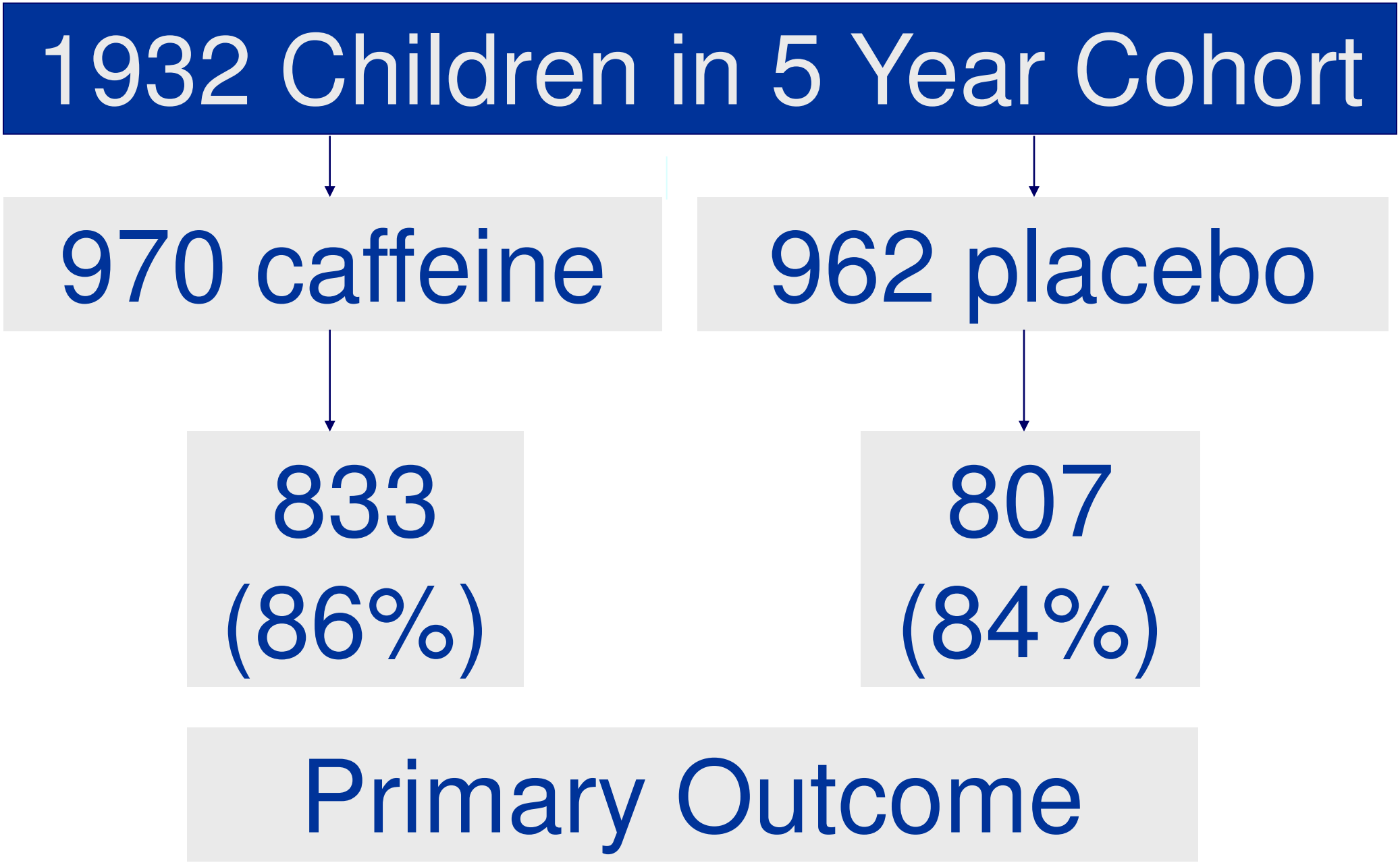
Primary Outcome at 5 Years

Death or survival with disability in at least 1 of 6 domains:

- Motor Function
- Cognition
- Behaviour
- General Health
- Hearing
- Vision

Definitions of Disability

- Gross Motor Function level > 2
- WPPSI III Full Scale IQ < 70
- CBCL Total Problem T score > 69
- O_2, pos. pressure, frequent seizures, IV or tube feeding, or ICU admission
- Serious hearing loss
- Bilateral blindness


1932 Children in 5 Year Cohort
970 caffeine
962 placebo
833
(86%)
807
(84%)
Primary Outcome

Characteristics of 5 Year Cohort

Infant	Caffeine	Placebo	P-value
BW - g	965 ±184	953 ±181	0.17
GA - wks	27.4 ±1.8	27.3 ±1.8	0.16
Female	51%	46%	0.07
Antenatal Steroids	89%	88%	0.31
Singleton	71%	70%	0.45

Characteristics of 5 Year Cohort

Mother	Caffeine	Placebo	P-value
Race			0.80
White	84%	82%	
Education			0.86
University	39%	38%	
Family			0.80
Single	9.9%	8.9%	
Employed	92%	94%	0.15

Death or Disability at 5 Years

Caffeine	Placebo
176 of 833	200 of 807
21.1%	24.8%

OR = 0.82 95% CI 0.65-1.03 p = 0.09

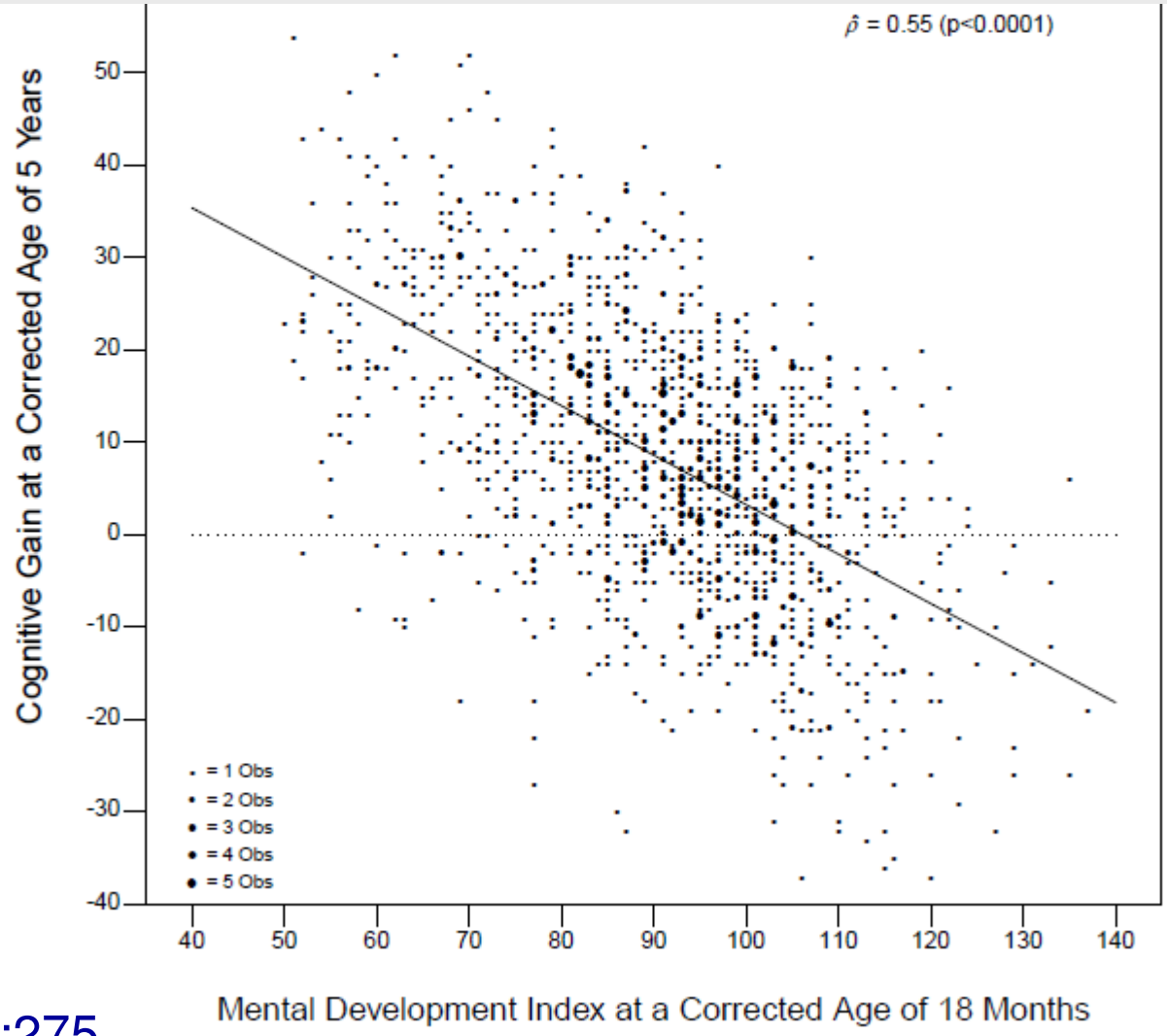
Disabilities at 5 years

Infant	Caffeine	Placebo	P-value
GMFCS>2	1.6%	2.7%	0.20
FSIQ<70	4.9%	5.1%	0.89
CBCL>69	5.4%	7.1%	0.18
Poor Health	4.0%	4.3%	0.75
Deafness	2.8%	3.2%	0.58
Blindness	0.9%	0.9%	0.94

Cognitive Impairment in the 5 Year Cohort

Outcome	Caffeine	Placebo	P-value
MDI < 85	31%	37%	0.03
MDI < 70	12%	16%	0.02
FSIQ<70	4.9%	5.1%	0.89

Relationship between MDI at 18 months and gain in cognitive scores between 18 months and 5 years



JAMA 2012;307:275

Conclusion I

The rates of cognitive impairment were lower at 5 years than at 18 months and no longer reduced by neonatal caffeine therapy

Gross Motor Function (GMFCS)

Level	Caffeine	Placebo	P-value
Normal	91%	86%	0.006
1	7.0%	10.1%	
2	0.7%	1.0%	
3	0.6%	0.6%	
4	0.5%	1.3%	
5	0.5%	0.8%	

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Reduction in Developmental Coordination Disorder with Neonatal Caffeine Therapy

Lex W. Doyle, MD[1,2], Barbara Schmidt, MD, MSc[3,9], Peter J. Anderson, PhD[2], Peter G. Davis, MD[1,2], Diane Moddemann, MD[4], Ruth E. Grunau, PhD[5], Karel O'Brien, MB BCh BAO[6], Koravangattu Sankaran, MD[7], Eric Herlenius, MD, PhD[8], and Robin Roberts, MSc[9], on behalf of the Caffeine for Apnea of Prematurity Trial investigators*

Objective To determine the effect of neonatal caffeine treatment on rates of developmental coordination disorder (DCD).

Study design Children in the Caffeine for Apnea of Prematurity trial were assessed for motor performance (Movement Assessment Battery for Children [MABC]), clinical signs of cerebral palsy, and Full-Scale IQ at 5 years of age

Definition of DCD in CAP Trial

Movement ABC < 5th Percentile

Full scale IQ > 69

No cerebral palsy

Rates of DCD at 5 Years

Caffeine	Placebo
83 of 735	106 of 698
11.3%	15.2%

OR = 0.70 95% CI 0.51-0.95 p =.024

Conclusion II

Caffeine therapy for apnea of prematurity reduces the severity of motor disorders at 5 years

Evidence-based therapy of apnea

Caffeine

Oxygen:
Not too high
Not too low

Temperature:
Not too hot
Not too cold

Nasal CPAP

Prone position