Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: Randomized Clinical Trial

Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L.,

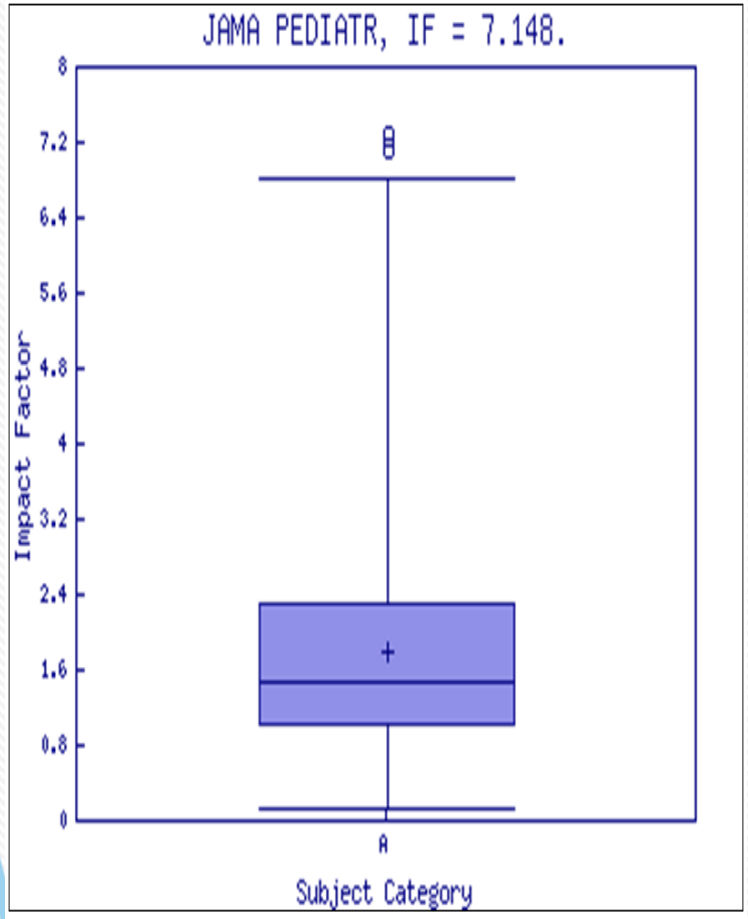
JAMA **Pediatr. 2015 Jul 1;169(7):631-8.**

doi: 10.1001/jamapediatrics.2015.0358.

報告者：周寶鈺

日　期：104.08.25

JAMA Pediatr



Category Name	Total Journals in Category	Journal Rank in Category	Quartile in Category
JAMA Pediatr	119	2	Q1

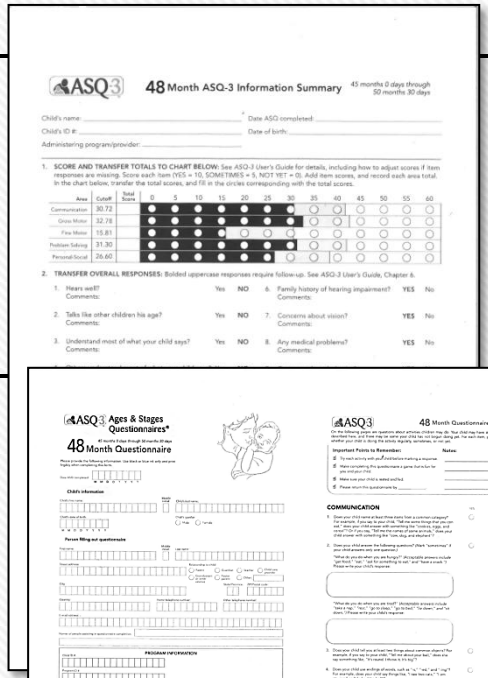
Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: Randomized Clinical Trial

https://youtu.be/eIEQH-7dVFA

步驟 1：研究探討的問題為何？

研究族群/問題 (Population/ Problem)	Full-term newborns with stational age of 37 to 41 weeks were eligible if the mother was healthy, was a nonsmoker, and had an uncomplicated pregnancy with expected vaginal delivery.
介入措施 (Intervention)	• Delayed umbilical cord clamping (≥180 second safter delivery)
比較 (Comparison)	• Early umbilical cord clamping (≤10 seconds after delivery).
結果 (Outcome)	primary outcome • Full-scale IQ as assessed by the WPPSI-III Secondary outcomes • Development as assessed by the scales from the WPPSI-III and Movement ABC • Development as recorded using the ASQ, and behavior using the Strengths and Difficulties Questionnaire.

	primary outcome	Secondary outcomes
WPPSI-III 標準化的智力評估方式	*Full-scale IQ	*Verbal IQ *Performance *Processing-speed quotient *General language composite
Movement ABC 動作協調功能評估		*Manual dexterity *Posting coins in box *Bead threading *Drawing bicycle trail
ASQ 由家長填寫，找出兒童是否有發展問題的最有效方法		*Communication *Motor skill(Gross/ Fine) *Problem solving *Personal-social



步驟 2：研究的品質有多好？
(內在效度)

招募(Recruitment)－受試者是否具有代表性？(p.632)

我們是否知道病人族群爲何(收案場所、納入／排除 條件)？在理想情況下，納入本研究之受試者應具有 連續性(有時爲隨機取樣)，了解符合收案條件的對象且簽署同意書。

- This study is a follow-up of a randomized clinical trial conducted at the Hospital of Halland from April 16, 2008 ,through May 21, 2010.
- **Follow-up** was conducted at the same location from April11 ,2012, through August 13 ,2013
- Full-term newborns with a gestational age of 37 to 41 weeks were eligible if the mother was **healthy**, was **a nonsmoker**, and had an **uncomplicated pregnancy** with expected vaginal delivery.
- The original trial and the follow-up study were approved by the **Regional Ethics Review Boardat Lund University** (protocols 41/2008 and 23 / 2012) ,and written patient consent was obtained from parents separately for the study and follow-up.
- Both studies were registered with Clinicaltrials.gov (NCT01245296 and NCT01581489).

評讀結果：■是　　否　　不清楚

步驟 2：研究的品質有多好？
(內在效度)

分派(Allocation)－分派方式是否隨機且具隱匿性…？ (p.632)

最理想的方式是以中央電腦進行隨機分配，此方式常用於多中心試驗，而較小型的試驗可由獨立人員(如：醫院藥師)「監督」隨機分配的過程。

- **Randomization assignments (1:1),** consisting of delayed (≥180 seconds after delivery) or early (≤10 seconds after delivery) CC, were contained in sealed, numbered, opaque envelopes that were opened by the midwife when delivery was imminent.

評讀結果：□是　□否　■不清楚

步驟 2：研究的品質有多好？
(內在效度)

…每個組別，在研究開始時的情況是否相同？(p.635)

若隨機分配順利，各組研究對象的條件應是相近、可互相比較的。每組研究對象的基本條件越相近越好。應有指標可確認各組研究對象之間的差異是否達到統計上顯著的差異(如 p 值)。

- Data from all 4 tests were acquired from 243 of 382 children (63.6%) and from at least 1 test from 263 children (68.8%) (Figure1). There was **no significant difference** in **response rates** between the delayed- an dearly- CC groups.
- **Baseline Characteristics of participants** in the follow-up did **not differ** between the 2 groups (Table1).
- As previously reported, **birth weights were higher** in the **delayed-CC group** as a result of the intervention. At 4 years, there were no group differences in the mean(SD) weight or height measurements ,which were17.3 (2.1)kg and 104(4)cm in the delayed-CC group(n=136) vs17.1 (2.1)kg and 104(4)cm in the early-CC group(n=120) (P=.45 and P=.90,respectively).

Table 1. Baseline and Background Characteristics by Intervention Group Comparing Infants With Delayed CC vs Early CC[a]

Characteristic	Delayed CC		Early CC	
	Value[b]	Patients, No.	Value[b]	Patients, No.
Maternal data				
Age, y	31.4 (4.4)	141	32.0 (4.2)	122
Weight, kg	67.6 (11.9)	141	66.9 (12.3)	119
Hemoglobin level at first antenatal visit, g/dL	12.8 (1.1)	141	12.9 (0.9)	116
Parity (including newborn child)	1.7 (0.7)	141	1.7 (0.8)	122
College education, No. (%)	90 (66.7)	135	85 (70.2)	121
Newborn data				
Male sex, No. (%)	60 (42.6)	141	57 (46.7)	122
Gestational age, wk	40.1 (1.0)	141	40.1 (1.1)	122
Apgar score, min				
1	8.8 (0.8)	141	8.7 (1.0)	122
5	9.8 (0.5)	141	9.8 (0.7)	122
Measurement at birth				
Weight, kg[c]	3.64 (0.48)	141	3.50 (0.52)	122
Length, cm	50.9 (1.9)	141	50.6 (2.1)	120
Head circumference, cm	34.8 (1.4)	141	34.5 (1.4)	122
Umbilical cord blood sample tests				
pH	7.26 (0.08)	117	7.26 (0.09)	117
Base deficit	4.8 (3.5)	116	5.1 (3.6)	116
Hemoglobin level, g/dL	16.0 (1.8)	122	16.3 (1.6)	109
Mean cell volume, fL	105 (5)	122	106 (5)	109
Ferritin level, ng/mL	225 (140)	136	232 (163)	119
Transferrin				
Saturation, %	54.3 (16.6)	132	53.4 (17.6)	115
Level, mg/L	5.26 (1.85)	140	5.33 (1.96)	122
Condition 1 h after birth, No. (%)				
Respiratory symptoms[d]	12 (9.0)			
Breastfed	95 (72.0)			
Exclusively breastfed at 4 mo, No. (%)	80 (56.7)			

評讀結果：
■是　□否　□不清楚

步驟 2：研究的品質有多好？
(內在效度)

維持(Maintenance)－各組是否給予相同的治療？(P.632)

各研究組別之間，除了對病人的介入之外，其餘的治療應完全相同(即爲了執行本研究所增加的治療、檢驗或評估應相同)。

- **Follow-up** was conducted at the same location from April 11 ,2012, through August 13 ,2013
- All children included in the original study (n=382) were eligible for the follow-up. An invitation letter for the follow-up study was sent 1 month before the child's fourth birthday.
- The children were assessed by a psychologist(B.L.) at 48 to 51 months of age.
- WPPSI-III；Movement ABC；ASQ

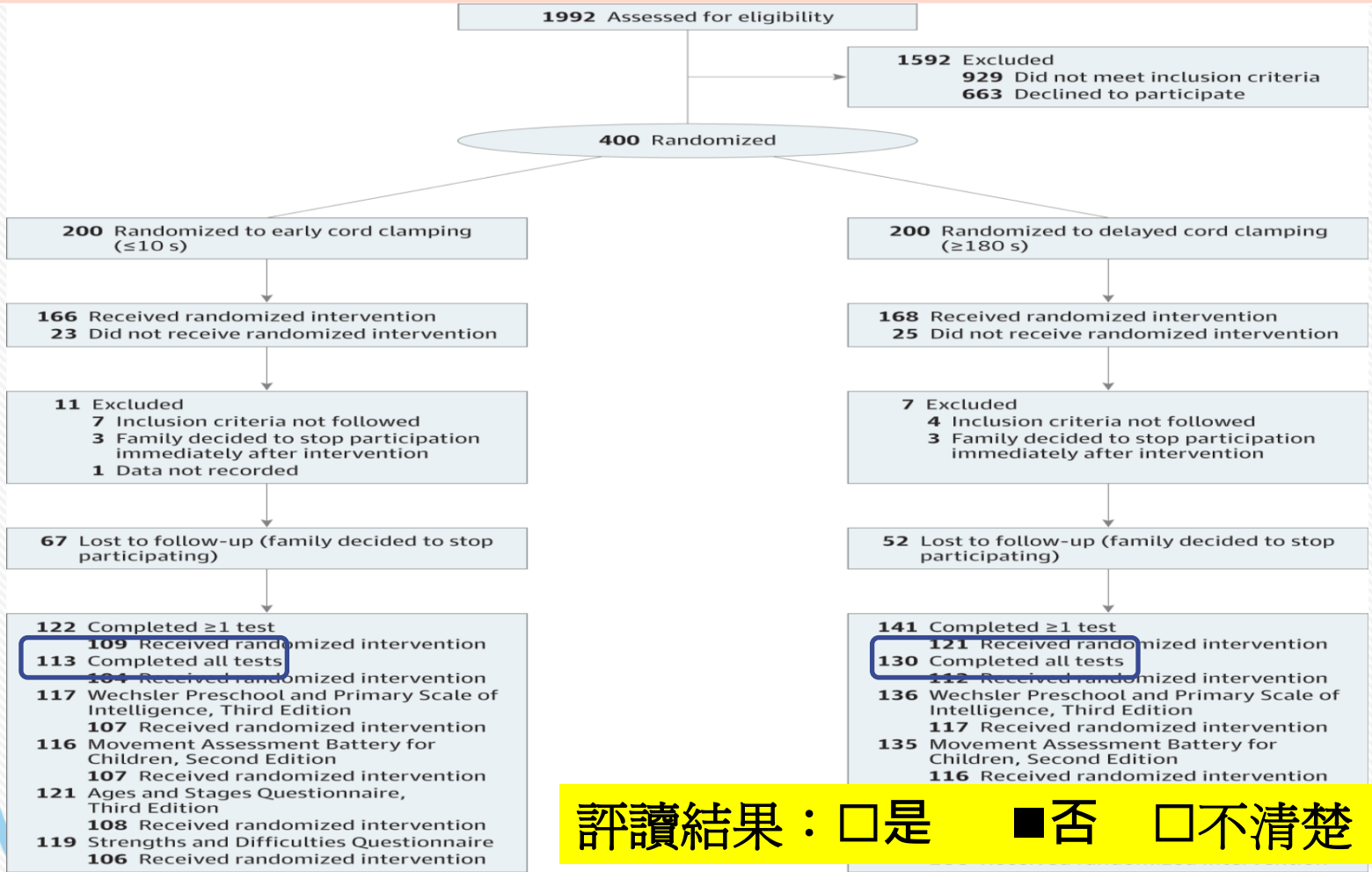
評讀結果：■是　□否　□不清楚

步驟 2：研究的品質有多好？

(內在效度)

...是否有足夠的追蹤(Follow up)？ (P.636)

研究中流失(無法繼續追蹤)的病人，最好少於 20%。 病人應依照隨機分配的組別進行統計分析(即「治療意向分析法」Intention – to-treat , ITT analysis)。



評讀結果：□是　■否　□不清楚

步驟 2：研究的品質有多好？
(內在效度)

評估(Measurement)－受試者與評估者是否對治療方式及(或)評估目的維持盲法(blind)？ (p.632)

在客觀結果(如：死亡)方面，盲法的重要性較低，但在主觀結果(如：症狀或功能)方面，評估者維持盲法非常重要。

- The mother and the midwife could not be masked, but all staff and researchers involved in the collection or analysis of data were blinded to the allocation group.

評讀結果：■是　□否　□不清楚

步驟 3：研究結果的意義為何？

使用何種評估方式，療效有多大？ NNT (=1/ARR)

這個研究結果是否可能隨機(巧合)發生？
p值/ 信賴區間 (Confident Interval, CI)

Table 2. Neurodevelopment at 48 Months of Age in Children Born at Term Who Were Randomized to Delayed CC or Early CC[a]

Characteristic	Delayed CC		Early CC		Unadjusted		Adjusted[b]	
	Mean (SD)	Patients, No.	Mean (SD)	Patients, No.	Mean Difference (95% CI)	*P* Value[c]	Mean Difference (95% CI)	*P* Value[d]
WPPSI-III								
Full-scale IQ	117.1 (9.7)	135	117.1 (9.7)	116	0.1 (−2.4 to 2.5)	0.95	0.6 (−1.8 to 2.9)	0.65
Verbal IQ	121.2 (13.8)	136	121.7 (12.5)	116	−0.5 (−3.8 to 2.7)	0.74	0.3 (−3.0 to 3.5)	0.87
Performance	115.0 (7.9)	135	115.3 (12.5)	117	−0.3 (−2.4 to 1.7)	0.74	−0.1 (−2.1 to 1.9)	0.92
Processing-speed quotient	100.7 (7.9)	129	98.9 (10.0)	111	1.8 (−0.5 to 4.1)	0.12	2.2 (−0.1 to 4.5)	0.06
General language composite	112.1 (12.8)	133	112.9 (10.2)	108	−0.8 (−3.7 to 2.2)	0.62	−0.4 (−3.5 to 2.7)	0.81

無差異

Table 3. Proportion of 4-Year-Old Children With Neurodevelopmental Test Scores Below Cutoff Levels[a]

Test Score	Delayed CC		Early CC		Unadjusted[b]		Adjusted[b,c]	
	Value, No. (%)	Patients, No.	Value, No. (%)	Patients, No.	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
WPPSI-III								
Full-scale IQ<85	1 (0.7)	135	0	116	NA	>.99	NA	>.99
Verbal IQ<85	2 (1.5)	136	1 (0.9)	116	1.7 (0.2 to 19.2)	.66	1.7 (0.1 to 18.7)	.68
Performance	1 (0.7)	135	0 (0)	117	NA	>.99	NA	>.99
Processing-speed quotient <85	2 (1.6)	129	7 (6.3)	111	0.2 (0.0 to 1.2)	.07	0.2 (0.0 to 1.1)	.06
General language composite <85	4 (3.0)	133	2 (1.9)	108	1.6 (0.2 to 9.1)	.57	1.3 (0.2 to 8.3)	.76

無差異

步驟 3：研究結果的意義為何？

Table 2. Neurodevelopment at 48 Months of Age in Children Born at Term Who Were Randomized to Delayed CC or Early CC[a]

Characteristic	Delayed CC		Early CC		Unadjusted		Adjusted[b]	
	Mean (SD)	Patients, No.	Mean (SD)	Patients, No.	Mean Difference (95% CI)	*P* Value[c]	Mean Difference (95% CI)	*P* Value[d]
WPPSI-III								
Full-scale IQ	117.1 (9.7)	135	117.1 (9.7)	116	0.1 (−2.4 to 2.5)	0.95	0.6 (−1.8 to 2.9)	0.65
Verbal IQ	121.2 (13.8)	136	121.7 (12.5)	116	−0.5 (−3.8 to 2.7)	0.74	0.3 (−3.0 to 3.5)	0.87
Performance	115.0 (7.9)	135	115.3 (12.5)	117	−0.3 (−2.4 to 1.7)	0.74	−0.1 (−2.1 to 1.9)	0.92
Processing-speed quotient	100.7 (7.9)	129	98.9 (10.0)	111	1.8 (−0.5 to 4.1)	0.12	2.2 (−0.1 to 4.5)	0.06
General language composite	112.1 (12.8)	133	112.9 (10.2)	108	−0.8 (−3.7 to 2.2)	0.62	−0.4 (−3.5 to 2.7)	0.81
Movement ABC								
Manual dexterity	8.4 (2.4)	133	8.2 (2.5)	116	0.2 (−0.4 to 0.8)	0.53	0.3 (−0.2 to 0.9)	0.25
Posting coins in box	8.1 (2.7)	134	8.1 (2.7)	116	0.0 (−0.6 to 0.7)	0.92	0.3 (−0.4 to 1.0)	0.44
Bead threading	8.3 (3.1)	134	7.8 (3.4)	116	0.4 (−0.3 to 1.3)	0.28	0.5 (−0.2 to 1.3)	0.17
Drawing bicycle trail	9.3 (1.6)	133	9.1 (1.8)	116	0.2 (−0.3 to 0.6)	0.42	0.3 (−0.2 to 0.7)	0.23
ASQ								
Total score	278.9 (21.6)	130	275.5 (27.6)	115	3.5 (−2.7 to 9.7)	0.27	4.7 (−1.3 to 10.6)	0.12
Communication	56.6 (5.3)	132	57.7 (5.5)	117	−1.0 (−2.4 to 0.3)	0.13	−0.9 (−2.2 to 0.5)	0.22
Motor skill								
Gross	56.1 (6.5)	134	55.7 (7.9)	119	0.4 (−1.4 to 2.1)	0.07	0.2 (−1.6 to 2.0)	0.82
Fine	54.2 (7.3)	134	52.3 (9.4)	118	1.9 (−0.2 to 4.1)	0.07	2.1 (0.2 to 4.0)	0.03 *
Problem solving	56.1 (7.1)	134	55.8 (6.9)	117	0.3 (−1.4 to 2.1)	0.72	0.8 (−0.9 to 2.4)	0.35
Personal-social	55.5 (7.0)	135	53.1 (8.6)	119	2.4 (0.4 to 4.4)	0.02	2.8 (0.8 to 4.7)	0.006 *

無差異

Abbreviations: ASQ, Ages and Stages Questionnaire, Third Edition; CC, umbilical cord clamping; Movement ABC, Movement Assessment Battery for Children, Second Edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

[a] Delayed CC was defined as 180 s or more after delivery; early CC, 10 s or less.

[b] Adjusted for the child's sex, mother's educational level, father's educational level, and child's age at testing.

[c] *P* values were calculated using the *t* test.

[d] *P* values were calculated using analysis of covariance.

步驟 3：研究結果的意義為何？

Table 3. Proportion of 4-Year-Old Children With Neurodevelopmental Test Scores Below Cutoff Levels[a]

	Delayed CC		Early CC		Unadjusted[b]		Adjusted[b,c]	
Test Score	Value, No. (%)	Patients, No.	Value, No. (%)	Patients, No.	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
WPPSI-III								
Full-scale IQ<85	1 (0.7)	135	0	116	NA	>.99	NA	>.99
Verbal IQ<85	2 (1.5)	136	1 (0.9)	116	1.7 (0.2 to 19.2)	.66	1.7 (0.1 to 18.7)	.68
Performance	1 (0.7)	135	0 (0)	117	NA	>.99	NA	>.99
Processing-speed quotient <85	2 (1.6)	129	7 (6.3)	111	0.2 (0.0 to 1.2)	.07	0.2 (0.0 to 1.1)	.06
General language composite <85	4 (3.0)	133	2 (1.9)	108	1.6 (0.2 to 9.1)	.57	1.3 (0.2 to 8.3)	.76
Movement ABC								
Manual dexterity <7 (15th percentile)	24 (18.0)	133	30 (25.9)	116	0.6 (0.3 to 1.2)	.14	0.6 (0.3 to 1.2)	.15
Posting coins in box <7 (15th percentile)	40 (29.9)	134	41 (35.3)	116	0.8 (0.5 to 1.3)	.36	0.7 (0.4 to 1.2)	.16
Bead threading <7 (15th percentile)	21 (15.7)	134	23 (19.8)	116	0.8 (0.4 to 1.4)	.39	0.7 (0.4 to 1.5)	.41
Drawing bicycle trail <7 (15th percentile)	5 (3.8)	133	15 (12.9)	116	0.3 (0.1 to 0.7)	.01	0.3 (0.1 to 0.8)	.02 *
ASQ								
Communication <46.2	11 (8.3)	132	5 (4.3)	117	2.0 (0.7 to 6.0)	.20	1.8 (0.6 to 5.8)	.32
Gross motor <41.7	7 (5.2)	134	8 (6.7)	119	0.8 (0.3 to 2.2)	.62	0.9 (0.3 to 3.2)	.88
Fine motor <36.7	5 (3.7)	134	13 (11.0)	118	0.3 (0.1 to 0.9)	.03	0.2 (0.1 to 0.8)	.02 *
Problem solving <42.3	7 (5.2)	134	10 (8.5)	117	0.6 (0.2 to 1.6)	.30	0.3 (0.1 to <1.0)	.05
Personal-social <38.7	4 (3.0)	135	10 (8.4)	119	0.3 (0.1 to 1.1)	.07	0.3 (0.1 to 1.2)	.10
Immature pencil grip[d]	18 (13.2)	136	30 (25.6)	117	0.4 (0.2 to 0.8)	.01	0.4 (0.2 to 0.8)	.01 *

Abbreviations: ASQ, Ages and Stages Questionnaire, Third Edition; CC, umbilical cord clamping; Movement ABC, Movement Assessment Battery for Children, Second Edition; NA, not analyzed because n = 0 in 1 group; OR, odds ratio; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

[a] The children were born at term and randomized to delayed (≥180 s after delivery) or early (≤10 s) umbilical CC.

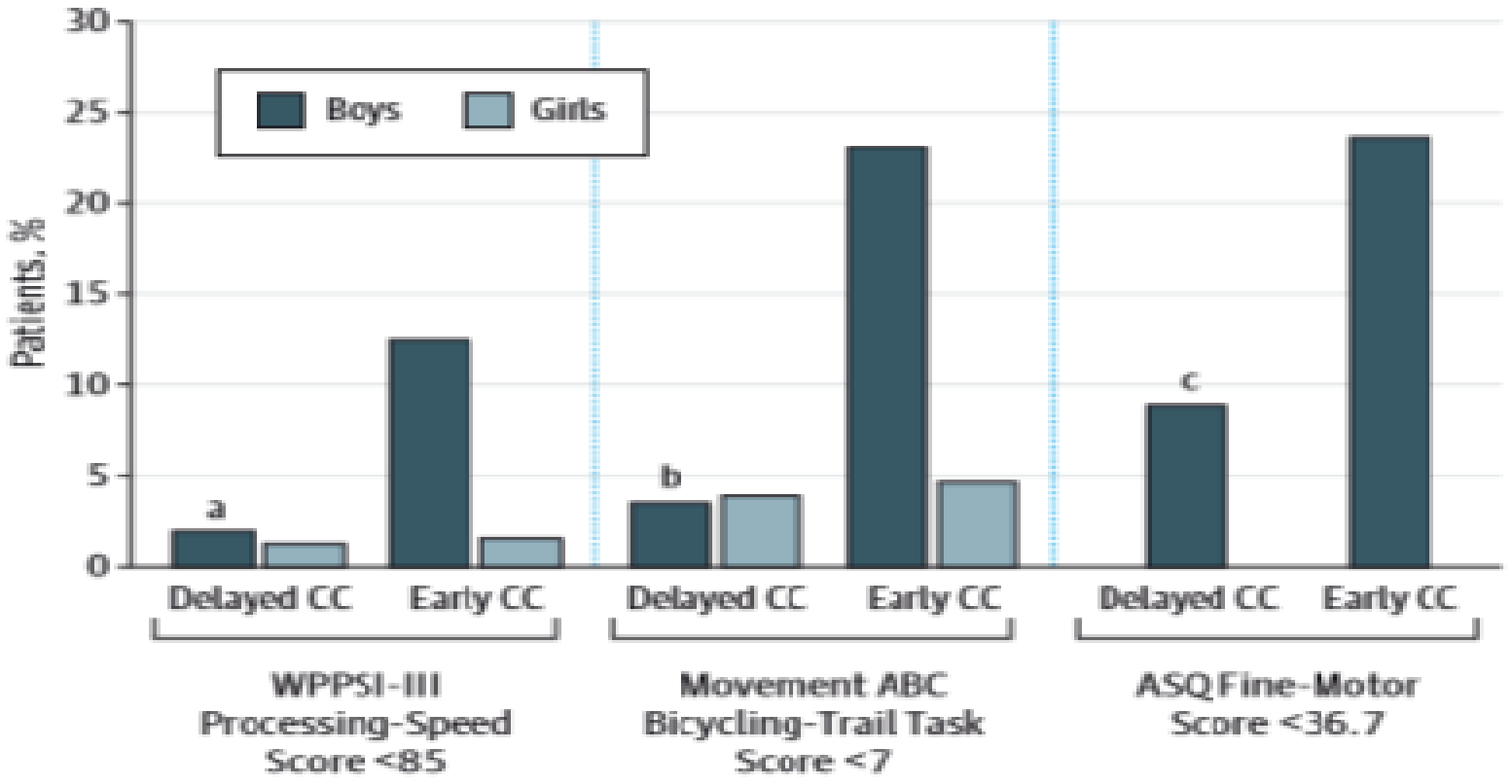
[b] Unadjusted and adjusted ORs were analyzed by logistic regression.

[c] Adjusted for the child's sex, mother's educational level, father's educational level, and child's age at testing.

[d] Palmar supinate or digital pronate grip.

步驟 3：研究結果的意義為何？

Figure 2. Proportion of Children With a Neurodevelopmental Score Below the Normal Range at 48 Months of Age



(2.0%vs12.5%;P=.06)　(3.6% vs 23.1%; P = .008)　(8.9%vs23.6%; P=.03)

結 論

- Delayed CC compared with early CC improved scores in the fine-motor and social domains at 4 years of age, especially in boys, indicating that optimizing the time to CC may affect neurodevelopment in a low-risk population of children born in a high-income country.
- 分娩後延遲夾住臍帶對於孩子的人際社交（社會領域）及精細動作發展有較高的分數，尤其是男生。在高收入國家的低風險族群中，延遲夾住臍帶是會影響孩子的日後的神經發育。

臨床現況?

討論

- 是否建議日後延遲夾住臍帶的時間？

- 同意：2人
- 懷疑：12人
- 不同意：7人

謝謝您的聆聽