USZ Universitäts Spital Zürich

Evidence based interventions for supporting neurodevelopment of preterm infants

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ANNUAL MEETING of the SSN 2022 in collaboration with the Swiss Neonatal Follow-up group

May 24, 2022, Kongresshaus Biel / Bienne

USZ neonatal department

University of Zurich[UZH]

During the next 20 minutes

1. Catch the PICOT

2. Intervention for supporting neurodevelopment of preterm infants
   a) Antenatal
   b) At birth
   c) In the NICU
   d) Once home

3. Take home message

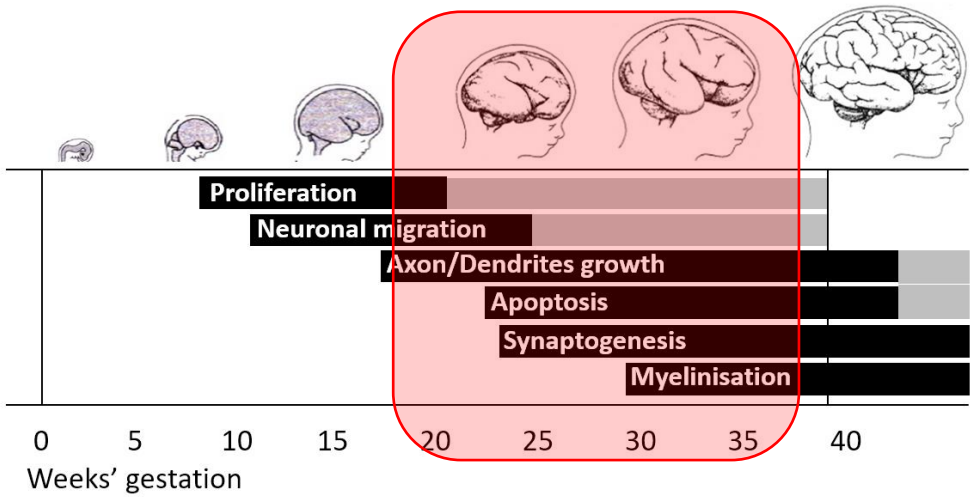
Catch the P in the PICOT

Preterm born infants (i.e., < 37 weeks‘ gestation)

- ca. 9% live births in Switzerland
- limits of viability trend downward
- survival rate increase
- rate of neurodevelopmental impairment constant

Issue and consequences

- ‚Interruption‘ of normal brain development



EPT, extreme preterm infants, i.e., born < 28 weeks’ gestation

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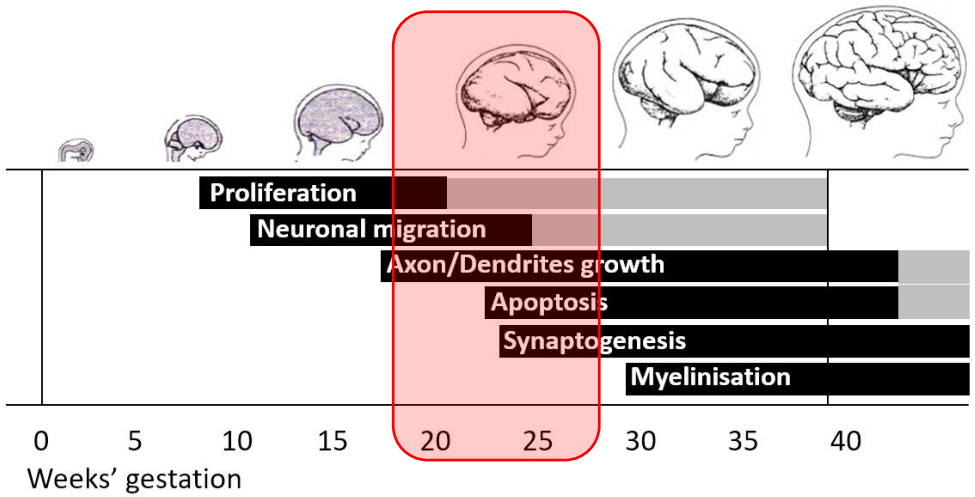


Issue and consequences

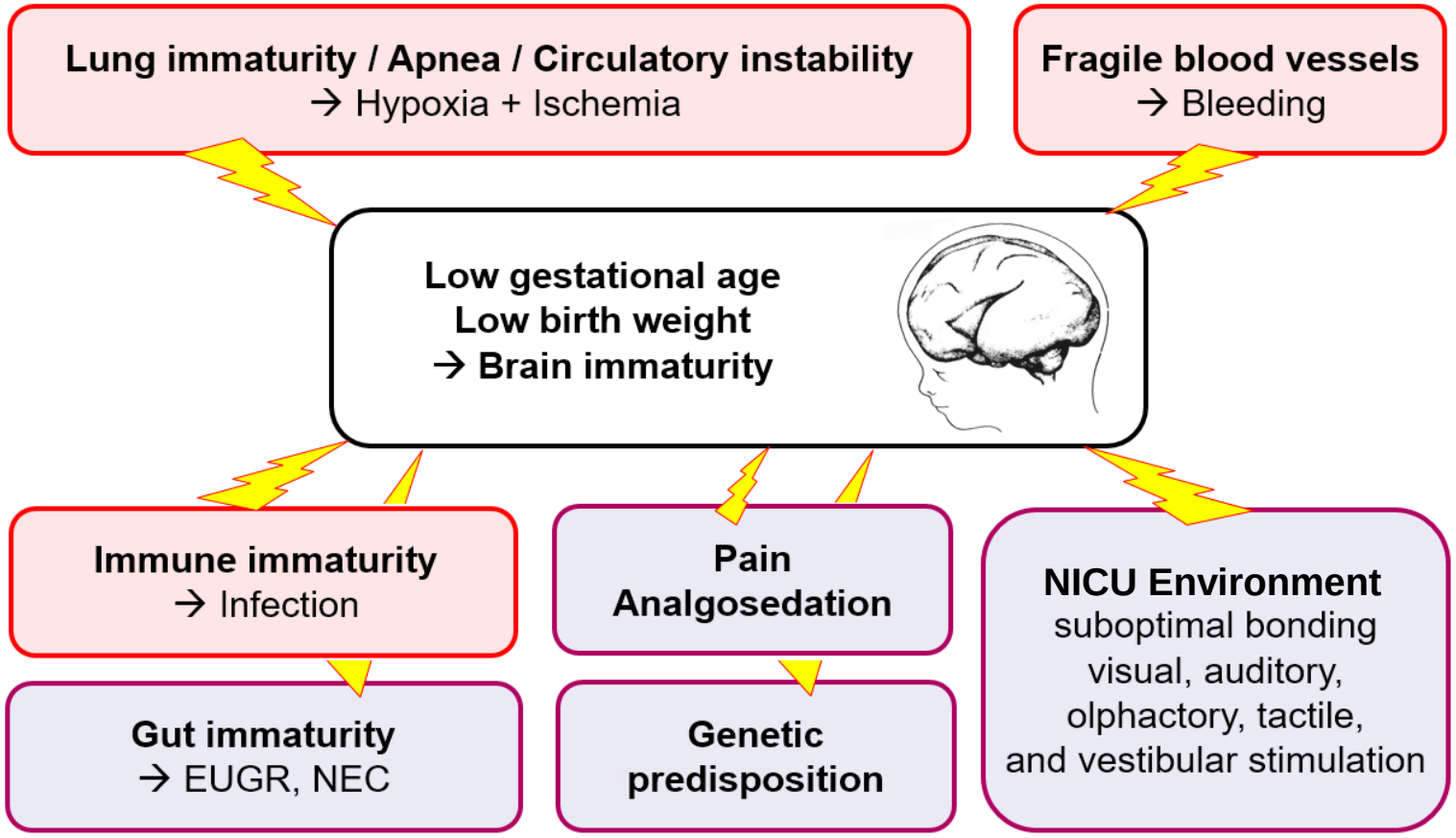
- ‚Interruption‘ of normal brain development
  → severe disabilities in 10% - 15% of EPT infants
  → mild to moderate disabilities in 50-60% of EPT infants

EPT, extreme preterm infants, i.e., born < 28 weeks’ gestation

Catch the P in the PICOT

Multiple risk factors for poor neurodevelopment

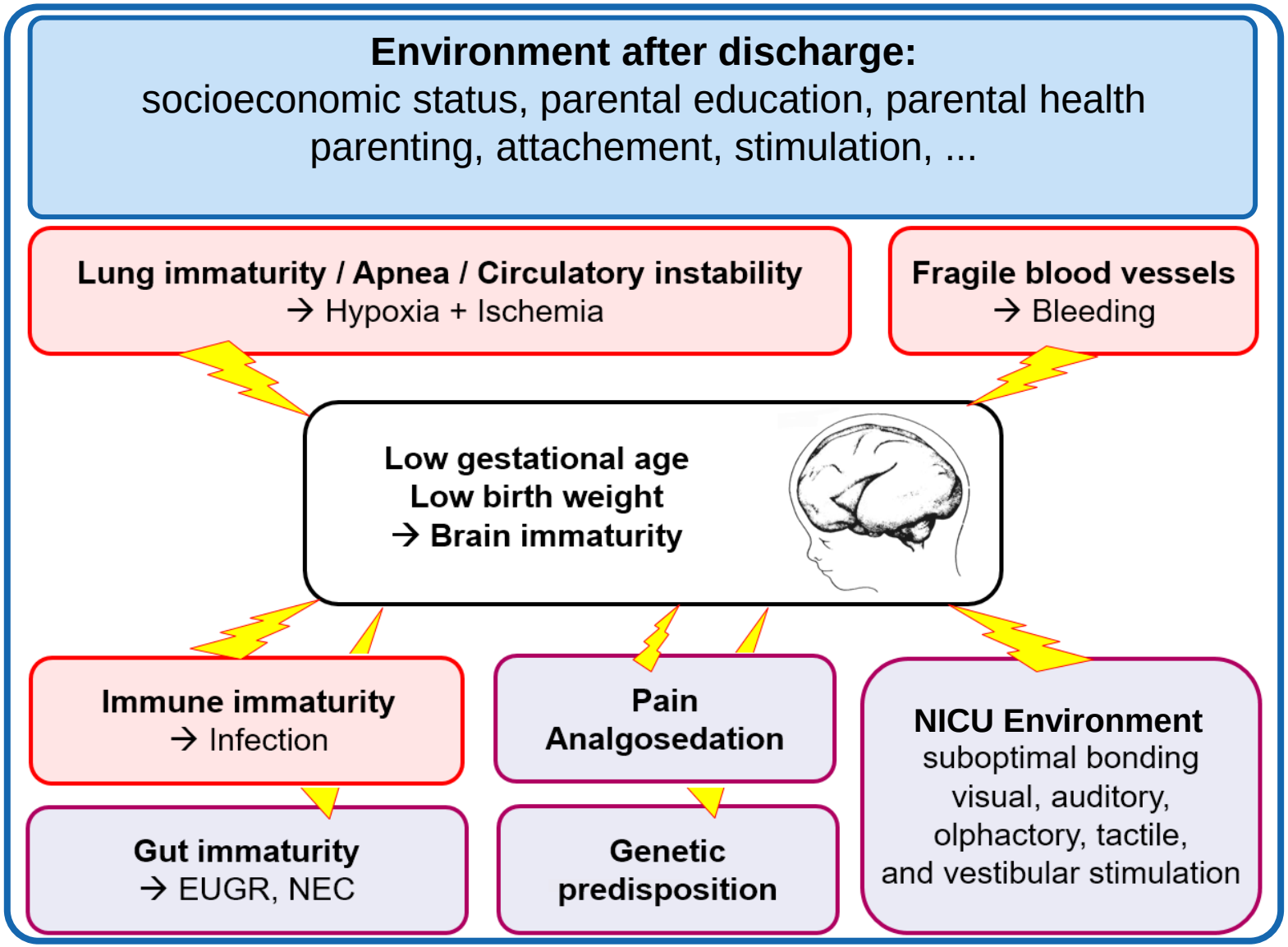
- predominant role of early biological risk factors
- only a few are modifiable



Catch the P in the PICOT

Multiple risk factors for poor neurodevelopment

- social / environmental factors become increasingly important over time



Catch the I in the PICOT

The strategies of the neuroprotective interventions are

- Preserve Brain integrity (e.g., reduce bleeding / encephalopathy of prematurity)
- Sustain Brain Development (e.g., promote growth)

The targets of the neuroprotective interventions are

- Prevent preterm birth
- Impact perinatal/neonatal morbidities
- Support infant development and her/his environment

Catch the O in the PICOT

What is the outcome measure?

QUALITY

PERFORMANCE

Pippi Långstrump, 1969, Warner Bros. Television Distribution ©

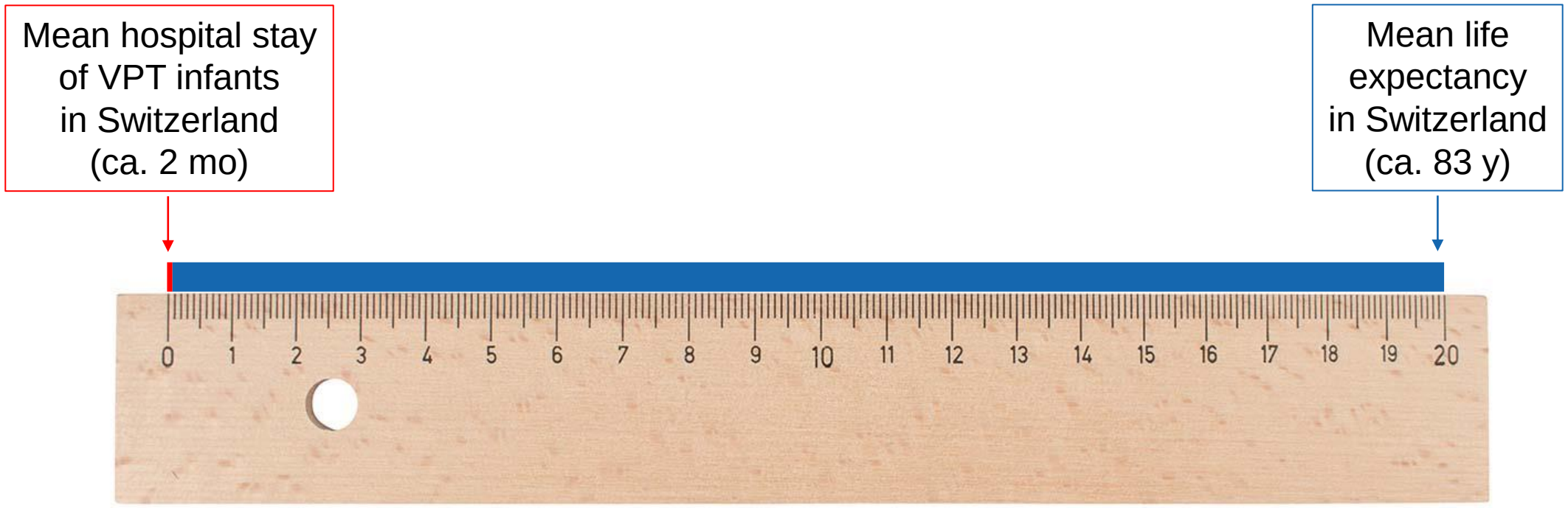
Catch the O in the PICOT

What is the neurodevelopmental outcome of the intervention?

- mostly based on performance (e.g., cognitive, motor)
- often defined as a composite of different measures, e.g.:
  - death or neurodevelopmental impairment (NDI)
  - NDI: severe cognitive or motor development score or cerebral palsy, blindness, deafness
- although pragmatic may not be appropriate on a scientific basis for all interventions
- relevant for clinicians and potentially confusing for families
- the reported long-term outcomes are rarely the primary goal of investigation

Catch the T in the PICOT

When is the neurodevelopmental outcome of the intervention measured?



Rüegger et al., BMC Pediatrics 2010; www.bfs.admin.ch

Catch the T in the PICOT

When is the neurodevelopmental outcome of the intervention measured?

- trend from short-term mortality and morbidity endpoints to composite outcomes at 2 years

  → vague demarcation between safety and long-term neurodevelopment endpoints

  → possible discordance between short-term and long-term outcomes

  → important outcomes may not be manifest until many years after intervention
  e.g., language, executive functions, psychiatric conditions

- Randomization does not necessarily influence the balance of confounders that may arise subsequently (months-years) after the intervention

Supporting neurodevelopment of preterm infants

Intra utero

→ Antenatal interventions

In the delivery room

→ Perinatal interventions

In the NICU

→ Postnatal interventions

Once home

→ Postdischarge interventions

SpaceX's Crew-4, mission for SpaceX NASA, SpaceX ©

Antenatal interventions to support neurodevelopment

Intervention before birth	Certainty GRADE
Prevention of preterm birth (e.g., progesterone)	Low / Insufficient [1]
Antenatal corticosteroids	Moderate [2]
Magnesium sulfate ($MgSO_4$)	High [3]
Intrauterine transport in level-III centre	Low [4] (↓ IVH, no RCTs)
Prompt antibiotics for chorioamnionitis / PPROM	Low (↓ brain lesion) [5]

1) Medley et al., Cochrane 2018; 2) McGoldrick et al., Cochrane 2020; 3) Doyle et al., Cochrane 2009; 4) Lasswell et al., JAMA 2010
5) Conde-Agudelo et al., Am J Obstet Gynecol 2021

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Antenatal interventions to support neurodevelopment

Antenatal steroids

- Probably **reduce any IVH: RR 0.58 (0.45 to 0.75)**, 8475 PT; 12 Trials [1]
- Probably **reduce developmental delay at 2y-12y: RR 0.51 (0.27 to 0.97)**, 600 PT; 3 RCTs [1]
- Probably **no effect on cerebral palsy**: RR 0.60 (0.34 to 1.03), 904 PT, 5 Trials [1]

1) McGoldrick et al., Cochrane 2020; 2) Chawla et al., JAMA Pediatr 2016; 3) Norman et al., JAMA Pediatr 2017; 4) Walters et al., Cochrane 2022
5) Ninan et al., JAMA Pediatr 2022 / Räikkonen et al., JAMA 2020; 6) Ehret et al., JAMA Netw Open 2018; 6) Backers et al., Am J Obstet Gynecol 2021

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- Most widley studied strategies: Bethamesone (2x12mg/24h i.m), Dexamethasone (4x6mg/12h i.m.)
- **Dose-dependent protective effect** against neurodevelopmental impairment [2]
- **Timing of last dose (<48h before birth)** influence risk of brain injury (vs <24h before birth) [3]
- Repeated courses probably do not influence neurodevelopment [4]

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- Possibly **harmful for infants > 32 - 34** weeks' gestation [5]
  → higher risk for adverse neurodev. and psychological outcomes in late preterm and full term infants
- Possibly **increase survival without major morbidities in infants 22-23** weeks' gestation [6]
  → little overall impact on survival

1) McGoldrick et al., Cochrane 2020; 2) Chawla et al., JAMA Pediatr 2016; 3) Norman et al., JAMA Pediatr 2017; 4) Walters et al., Cochrane 2022
5) Ninan et al., JAMA Pediatr 2022 / Räikkonen et al., JAMA 2020; 6) Ehret et al., JAMA Netw Open 2018; 6) Backers et al., Am J Obstet Gynecol 2021

Antenatal interventions to support neurodevelopment

Magnesium sulfate

- **Reduce the rate of cerebral palsy up to 2y: RR 0.69 (0.55 to 0.88)**, 6145 PT; 5 RCTs [1] (NNT 46) [2]
- Probably no effect on cerebral palsy at age > 2y [1,2,3]
- Probably no effect on cognitive and behavioral outcomes [1,2,3]

- No studies compared dosage/duration strategies (LD 4g-6g; MD 1-2g/h for 12h-24h)

1) Doyle et al., Cochrane 2009; 2) Doyle et al., JAMA 2014; 3) Crowther et al., Plos Med 2017

Perinatal interventions to support neurodevelopment

Intervention at birth	Certainty GRADE
Delivery mode, timing and location	Low (no RCTs) [1,2]
Delayed cord clamping (30” - 120”)	High (↓ IVH) [3]
Stantdardised management	Low (↓ mortality / IVH; no RCTs) [4,5]
- avoid Hypothermia	Low (↓ mortality / IVH; no RCTs) [6,7]
- empiric antibiotics when chorioamnionitis susp.	Low (↓ mortality / IVH/PVL, no RCTs) [8]
- see postnatal ‘Bundle of measures’	

1) Wolff et al., 2021; 2) Stock et al., 2016; 3) Rabe et al., Cochrane 2019; 4) Schmid et al., 2013
5) Travers et al., 2022 6) Miller et al., J Pediatr 2011; 7) Yu et al., 2020 8) Maisonneuve et al., 2020

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Perinatal interventions to support neurodevelopment

Mode of delivery

Unclear evidence for benefits/harms of CS (vs vaginal) unless fetus is malpresenting

- possibly **reduce severe IVH**: OR 1.61 (1.01 to 2.58), 1575 VPT, 1 study (VON) [1]
- in breech position probably reduces any IVH: OR 0.51 (0.29–0.91), 12335 EPT, 15 studies [2]
- in vertex position possibly not associated with neurodevelopment at 2y, 1966 VPT, 1 study [3]
- vaginal delivery and emergency CS possibly increases any IVH, 2203 VLBW, 1 study [4]

1) Gamaleldin et al., 2019; 2) Grabovac et al., 2018; 3) Wolff et al., 2021; 4) Humberg et al., 2017; 5) Stock et al., 2016
6) Helenius et al., BMJ 2019; 7) Sasaki et al., 2019 (Amer et al., 2018); 8) Mohamed & Aly, 2010; 9) Hirata et al., 2022

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Timing of delivery

Insufficient evidence for benefits/harms of immediate (vs expectative) delivery [5]

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Outborn delivery

- possibly **increases cerebral palsy**: aOR 1.9 (1.1 to 3.3), 2951 VPT 1 study [6]
- possibly **increases cognitive impairment**: aOR 1.49 (1.01 to 2.20), 12164 EPT, 1 study [7]

Neonatal transfer

- possibly **increases severe IVH**: aOR 1.44 (1.22 to 1.70), 67596 VLBW (US); 1 study [8]
- possibly **increases NDI at 3y**: OR 1.75 (1.17 to 2.62), 2647 PT, 1 study (ASQ) [9]

1) Gamaleldin et al., 2019; 2) Grabovac et al., 2018; 3) Wolff et al., 2021; 4) Humberg et al., 2017; 5) Stock et al., 2016
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Perinatal interventions to support neurodevelopment

Delayed umbilical cord clamping (DCC)

- Probably **reduces any IVH: aRR 0.83 (0.70 to 0.99)**, 2333 PT; 15 Trials [1]
- Possibly no benefits/harms for neurodevelopmental outcomes (insufficient data)
- DCC range 30'' to 180''; most widely studied strategy: DCC 30'' to 60''

- **Umbilical cord milking (UCM) is probably harmful in infants < 28-32 weeks' gestation**

  → < 32 weeks: higher risk for severe IVH [RD 5% (1% to 9%) vs DCC], 477/540 VPT, 1 RCT [2]

  → 23-27 weeks: higher risk for severe IVH [RD 16% (6% to 26%) vs DCC], 182/540 VPT, 1 RCT [2]

1) Rabe et al., Cochrane 2019; 2) Katheria et al., JAMA 2019
IVH, intraventricular haemorrhage; VPT, very preterm infants

Postnatal interventions to support neurodevelopment

Intervention in the NICU		Certainty GRADE
Bundle of measures		Low (↓ brain lesion; no RCTs) [1]
- Caffeine citrate		Moderate [2]
- Avoid $PaCO_2$ fluctuations		Low [3] (↓ brain lesion)
- Volume tergated ventilation		Moderate [4] (↓ brain lesion)
- Avoid blood pressure fluctuations		Low [5] (↓ brain lesion, no RCTs)
- Avoid glycaemia fluctuations		Low [6] (no RCTs)
- Neutral head positioning		Insufficient [7]
- Prophylactic indomethacine/Ibuprofene		Moderate [8] (↓ IVH)
Nurturing environment	- 'Optimise' nutrition	Low [9]
	- Human milk	Low [10] (no RCTs)
	- Developmental care	Low [11]
Emerging treatments	- Erythropoietin	*Debated effect* [12]

1)Travers et al., 2022; 2) Schmidt et al, 2007; 3) Fabres et al., 2007; 4) Klingenberger et al., 2017; 5) Fowlie et al., 2010; 6) Shah et al., 2019; 7) Romantsik et al., 2017; 8) Ohlsson & Shah, 2020; 9) Harding et al., 2017; 10) Lechner & Vohr, 2017; 11) Aita et al., 2021; 12) Fischer et al., 2021

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Postnatal interventions to support neurodevelopment

Caffeine citrate

- Probably **reduces cognitive delay at 18-21mt: OR 0.66 (0.66 to 0.99)**, 1869 VLBW; 1 RCT [1]
- Probably **reduces cerebral palsy at 18-21mt: OR, 0.58 (0.39 to 0.87)**, 1869 VLBW, 1 RCT [1]
- Probably **reduces motor dysfunction at 5y to 11y: aOR 0.70 to 0.66**, 1640 [2] and 1202 [3] VLBW, 1 RCT [1]
- Probably no effect on cognition, behavior and cerebral palsy at 5y to 11y, 1640 [4] and 870 [5] VLBW, 1 RCT [1]

- Most widely studied strategy: LD 20 mg/kg, MD 5mg/kg/24h

- Probably **harmful at higher doses, e.g., 80mg/kg** [6]
  → higher risk for cerebellar injury and alteration in early motor performance

1) Schmidt et al., NEJM 2007; 2) Doyle et al., J Pediatr 2014; 3) Schmidt et al., JAMA Pediatr 2017; 4) Schmidt et al., JAMA 2012
5) Mürmer-Levanchy et al., Pediatrics 2018; 6) McPherson et al., Pediatr Res 2015; Handerson-Smart et al., Cochrane 2010

Postnatal interventions to support neurodevelopment

Nutrition *facts*

- High nutritional need in preterm infants relates to rapid brain growth during the last trimester
- Postnatal growth of EPT lags behind fetal growth curves [1]
- Infants experiencing EUGR show delayed brain maturation and impaired neurodevelopment [2]
- Catch-up growth through fat mass accretion predisposes to metabolic syndrome [3]

Strategies to otpimise nutrition [4]

- Protein supplementation
- Lipid supplementation
- Multi-nutrient fortification
- Timing of fortification
- Individualised fortification

1) Cormack et al., Nutrients 2019; 2) Ehrenkranz et al., 2006; 3) Chan et al. Acta Paediatr 2016; 4) Soll et al., 2020

Strategy	Procedure	Study	Neurodevelopment Outcome
Protein supplement. in human milk [1]	≥ 1.4 g/100ml human milk **vs** [1.0 - 1.4] g/100ml human milk	861 PT 9 Trials	Insufficient data
Protein supplement. in formula milk [2]	[3.0 - 4.0] g/kg/day **vs** < 3.0 g/kg/day (very high ≥ 4 g/kg/day)	218 LBW 6 Trials	Insufficient data
Lipid supplementation [3]	30% MCT formula by weight **vs** < 30% MCT formula by weight	253 PT 10 Trials	Insufficient data
Lipid supplementation [4]	LCPUFA fortified formula **vs** standard formula milk	2160 PT 17 Trials	Probably no benefits/harms
Multi-nutrient fortification [5]	Fortified human milk **vs** unfortified human milk	1456 PT 18 trials	Insufficient data
Multi-nutrient fortification [6]	Human milk-derived fortification **vs** bovine- derived fortification	127 PT 1 Trial	Insufficient data
Timing of fortification [7]	Fortification started at < 100 mL/kg/d enteral feed volume or < 7 days postnatal age **vs** fortification started at ≥ 100 mL/kg/d feeds or ≥ 7 days postnatal age.	237 PT 2 Trials	Insufficient data
Individualised fortification [8]	exclusive breast milk nutrition with non-individualized **vs** individualized (any) fortification for min. 2 weeks	521 7 Trials	Insufficient data

Cochrane Database Syst Rev: 1) Gao et al. Cochrane 2020; 2) Fenton et al., 2020; 3) Perretta et al., 2003; 4) Dorling et al, 2020
5) Brown et al., 2020; 6) Premkumar et al., 2019; 7) Thanigainathan & Abiramalatha 2020; 8) Fabrizio et al., 2020

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Postnatal interventions to support neurodevelopment

Human milk (HM) *facts*

- Human milk feeding is the regulatory standard for feeding infants
- **Numerous observational studies have showed beneficial effects of HM on preterm outcomes including measurable advantage in neurodevelopment up to adolescence** [1]

- The mechanisms by which HM provides neuroprotection are unknown

  → effect of **high concentration of specific macronutrients** (e.g., LCPUFAs) ?

  → effect of **high concentration of specific micronutrients** (e.g., HMOs, choline, active proteins) ?

  → effect through **reduction of preterm morbidities** (e.g., sepsis and necrotizing) ?

  → **epigenetic effect** (components of human milk, that could influence gene expression) ?

  → effect of **non-biological factors** (e.g. social and behavioural determinants) ?

1) Belfort, Breastfeed Med 2017; 2) Chiurazzi, et al., Repr Med 2021

Postnatal interventions to support neurodevelopment

Human milk (HM) *facts*

- Discordant reports from systematic reviews published in the last 10 years, e.g.:

  Lerchner & Vohr, 2017: HM associated with favourable neurodevelopmental outcome [1]
  Systematic review: 14 studies, N=8859

  Miller et al., 2017: HM not associated with benefits/harms in neurodevelopmental outcome [2]
  Systematic review and meta-analysis: 13 studies (1 trial), N=1744, low to very low certainty of evidence

- Experimental setting ethically unsustainable *(random allocation to human vs control milk)*
  → **the relationship between HM exposition and neurodevelopment remains controversial**

- No difference between neurodevelopmental outcome after donor milk vs formula in PT infants [3]

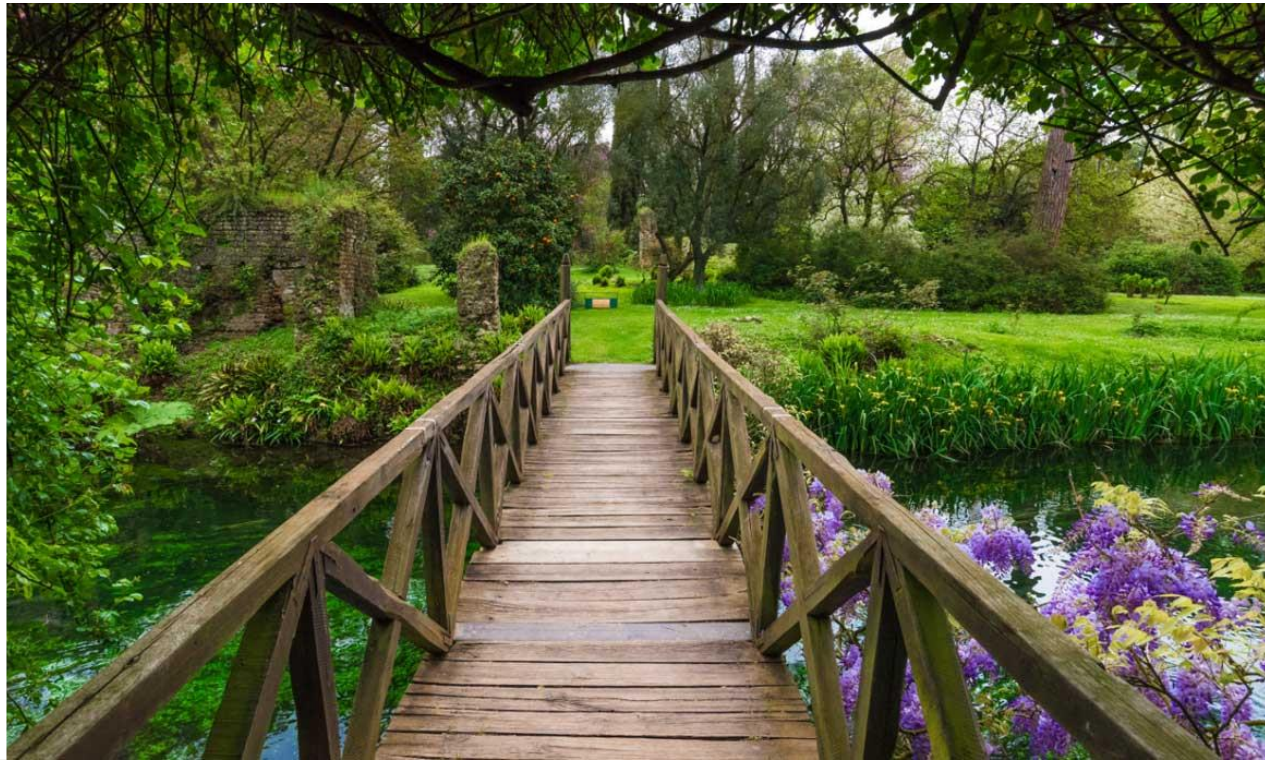
1) Lerchner & Vohr, Clin Perinatol 2017; Miller et al., Nutrients 2019; 3) Quigley et al. Cochrane Database Syst Rev 2019

Postnatal interventions to support neurodevelopment

Developmental care	Certainty GRADE
Key components	
- Physiotherpy	Low [1]
- Music therapy	Low (no [2]
- Skin-to-skin care (e.g., Kangaroo)	Low [3]
- Parental coaching / involvement	Low [4]
- Control of external stimuli (vestib., audit., vis., tact.)	Very low [5,6]
- Clustering of nursery care activities	No data
- Positioning or swaddling of the infant	No data
- Encourage maternal voice exposure	Very low [7]
- Mitigate painful procedures / Decrease opioid use	Low [8]
Combined programs	
- e.g., NICAP	Low [9,10]

1) Meena et al., 2013 ; 2) Haslbeck et al., 2018; 3) Conde-Agudelo et al, Cochrane 2014; 5) Almadhoob & Ohlsson, Cochrane 2020; 6) Morag & Ohlsson, et al., Cochrane 2016; Krueger et al., 2010; 8) Grunau et al., 2013 9) Symington et al. Cochrane 2016; 10) Ohlsson & Jacobs, 2013;

Even with the best shoes, you still have to check the terrain ...



Giardino di Ninfa, Italy; Dash-e Lut, Iran (www.pixabay.com)

Postdischarge interventions to support neurodevelopment

Intervention after discharge	Certainty GRADE
Early intervention [1]	Moderate [2]
Therapeutic interventions targeting the infant - promotion of self-initiated appropriate motor activity - promotion of cognitive stimulation - supporting infant self-regulation	
Parent education - supporting positive parent-infant relationships - promotion of early communication skills - parent coaching - responsive parenting	
Psychosocial support - supporting parental mental wellbeing	Low (e.g., postpartum depression) [3, 4]

1) Benzies et al., BMC Pregnancy & Childbirth 2013; 2) Spittle et al., Cochrane Database Syst Rev 2015;
3) Koutra et al., Soc Psychiatry Psychiatr Epidemiol 2013; Girchenko et al., Sci Rep 2022

Postdischarge interventions to support neurodevelopment

Early intervention programs

- **probably improve cognitive quotient in infancy: SMD 0.32 (0.16 to 0.47) SDs**, 2372 PT, 16 trials
- **probably improve intelligent quotient at preschool age: SMD 0.43 (0.32 to 0.54) SDs**, 1436 PT, 8 trials
- probably do not improve intelligent quotient at school age: SMD 0.18 (-0.08 to 0.43) SDs, 1372 PT, 5 trials

Spittle et al., Cochrane Database Syst Rev 2015; 2) Hugues et al., Pediatrics 2016

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- **probably improve motor outcome in infancy: SMD 0.10 (0.01 to 0.19) SDs**, 1895 PT, 12 trials [1]
- possibly improve motor outcome at preschool and school age but data insufficient for MA [1,2]
- probably do not affect the rate of cerebral palsy: RR 0.82 (0.52 to 1.27), 985 PT, 7 trials [1]

Variability was evident with regard to:	focus and intensity of the intervention participant characteristics length of follow-up.
Heterogeneity between trials:	significant for cognitive outcomes at infancy and at school age

Spittle et al., Cochrane Database Syst Rev 2015; 2) Hugues et al., Pediatrics 2016

Take home message

In the preterm born infants

- Interventions with a favourable neurodevelopmental effect under an experimental study setting:
  - antenatal corticosteroids adminitration
  - antenatal magnesium sulfate adminitration
  - postnatal coffeine citrate adminitration
  - postdischarge early intervention

- **The level of evidence for many other neurodevelopmental interventions is low**
  due to lack of data (no long-term endpoints), quality and heterogeneity of studies.
  → *to answer a specific question, trials should be designed accordingly*

- **Developmental interventions are effective and needed not only in the NICU**
  but also during the first years of life to optimise outcomes.

- The **role of parents and their support** (competences + mental health)
  must be increasingly valued.

Spittle et al., Cochrane Database Syst Rev 2015; 2) Hugues et al., Pediatrics 2016

Thank you

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LRF Center for Neurodevelopment Growth and Nutrition of the Newborn

Postnatal interventions to support neurodevelopment

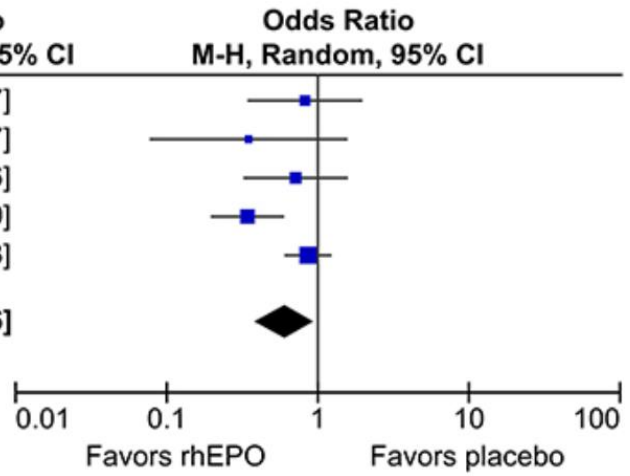
Erythopoietin (and erythropoiesis stimulant agents)

- Probably **reduces cognitive delay at 18-24mt: OR 0.61 (0.39 to 0.96)**, 1746 VLBW; 5 RCT [1,2]

A MDI <70 (BSID II) or composite cognitive score <85 (BSID III)

Study or Subgroup	rhEPO Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ohls 2004	14	45	16	45	16.1%	0.82 [0.34, 1.97]
Ohls 2014	3	29	6	24	7.3%	0.35 [0.08, 1.57]
Natalucci 2016	12	191	15	174	18.3%	0.71 [0.32, 1.56]
Song 2016	19	309	49	304	25.4%	0.34 [0.20, 0.59]
Juul 2020	77	311	87	314	32.9%	0.86 [0.60, 1.23]
Total	**125**	**885**	**173**	**861**	**100.0%**	**0.61 [0.39, 0.96]**

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 8.49$, df = 4 (P = 0.08); $I^2 = 53\%$
Test for overall effect: Z = 2.16 (P = 0.03)



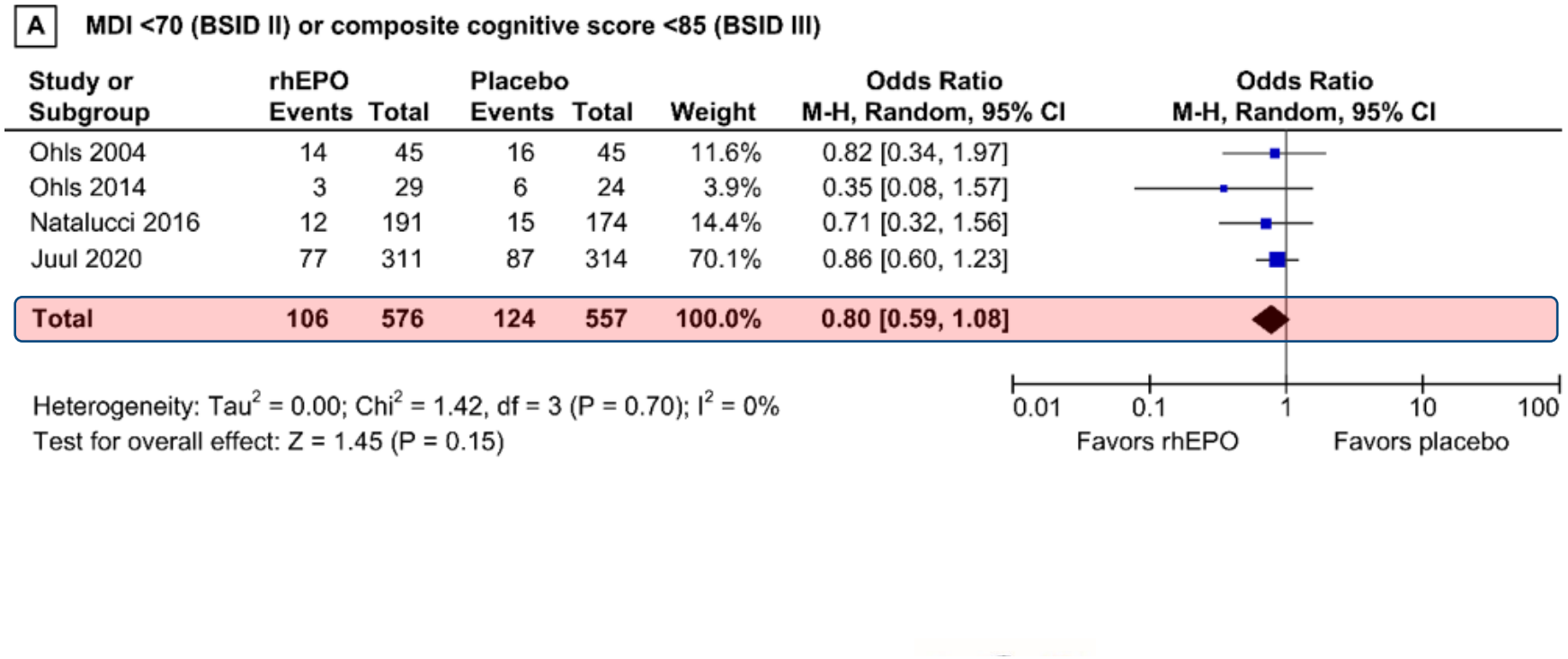
- **substantial heterogeneity** ascribed to a single trial featuring a **high risk of (performance and reporting) bias** [2]

1) Ohlsson & Aher, Cochrane 2020; 2) Fischer et al., Front. Pediatr 2021

Postnatal interventions to support neurodevelopment

Erythopoietin (and erythropoiesis stimulant agents)

- Probably **reduces cognitive delay at 18-24mt: OR 0.61 (0.39 to 0.96)**, 1746 VLBW; 5 RCT [1,2] **…but**



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- **exclusion of this trial abolished heterogeneity and any effects of rEPO** treatment at age 2y [2]

1) Ohlsson & Aher, Cochrane 2020; 2) Fischer et al., Front. Pediatr 2021