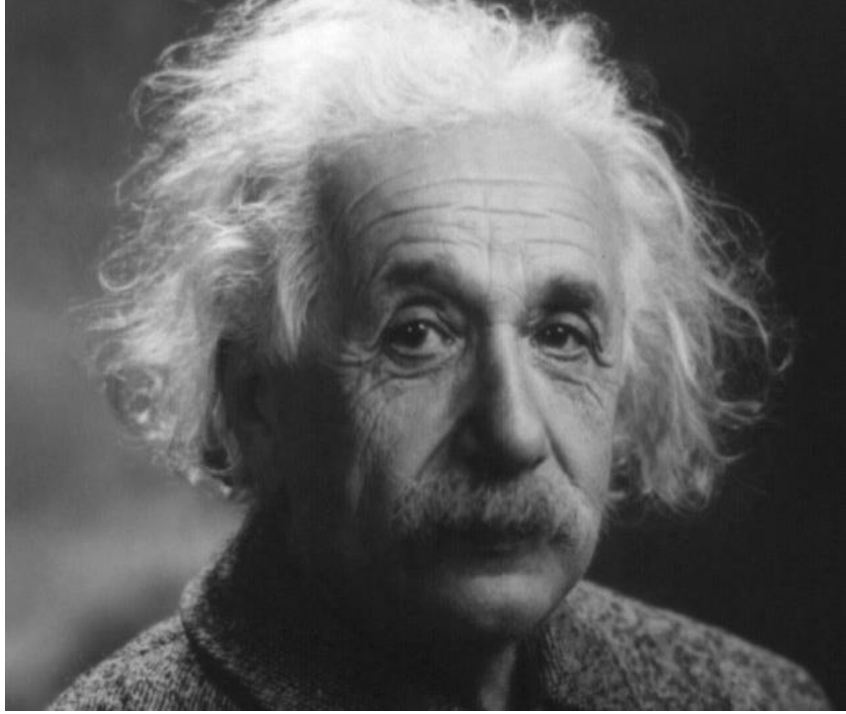
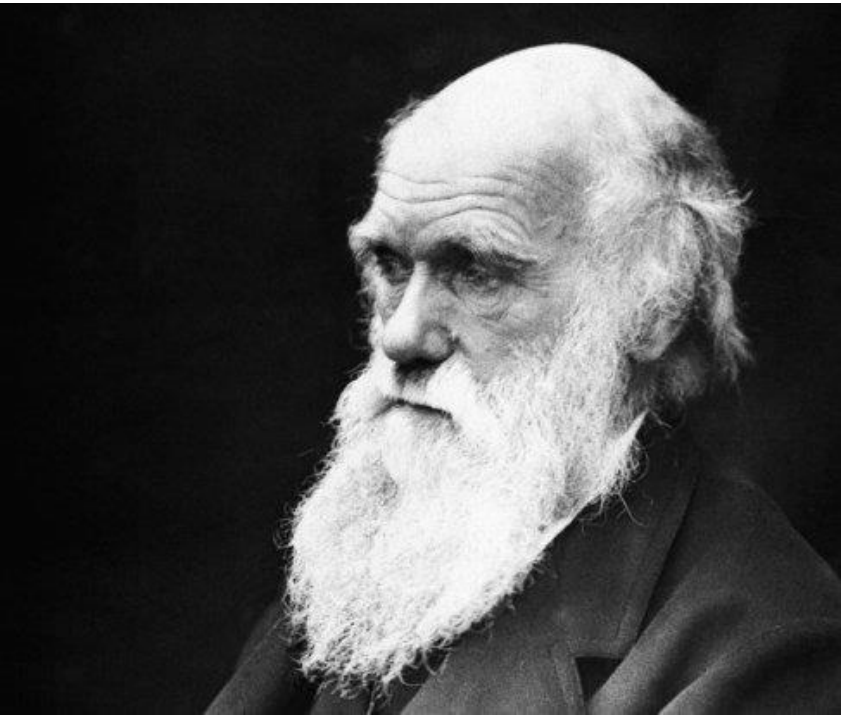
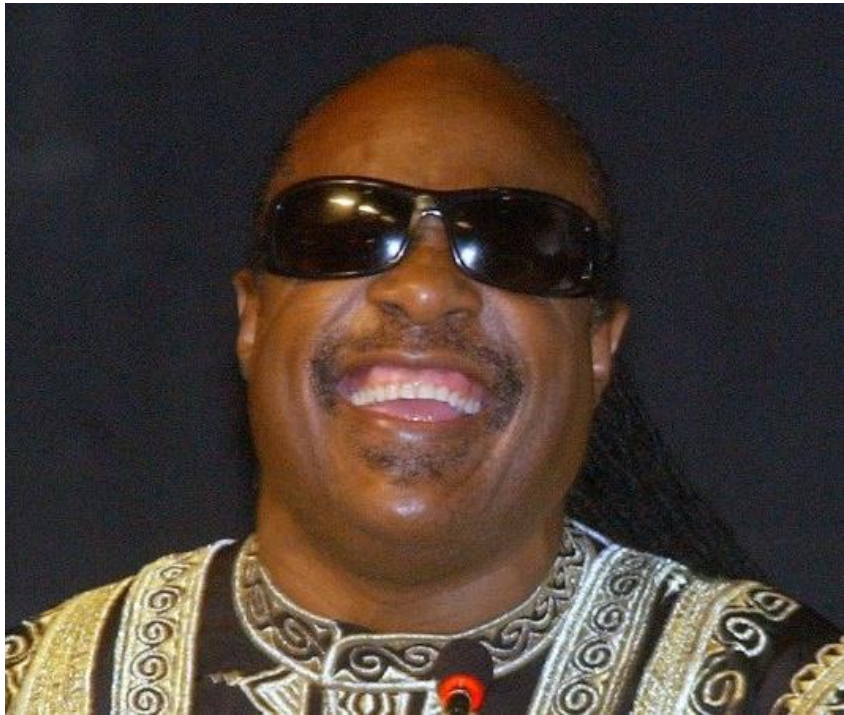
Targeting fetal Hemoglobin percentages to improve outcome in preterm infants

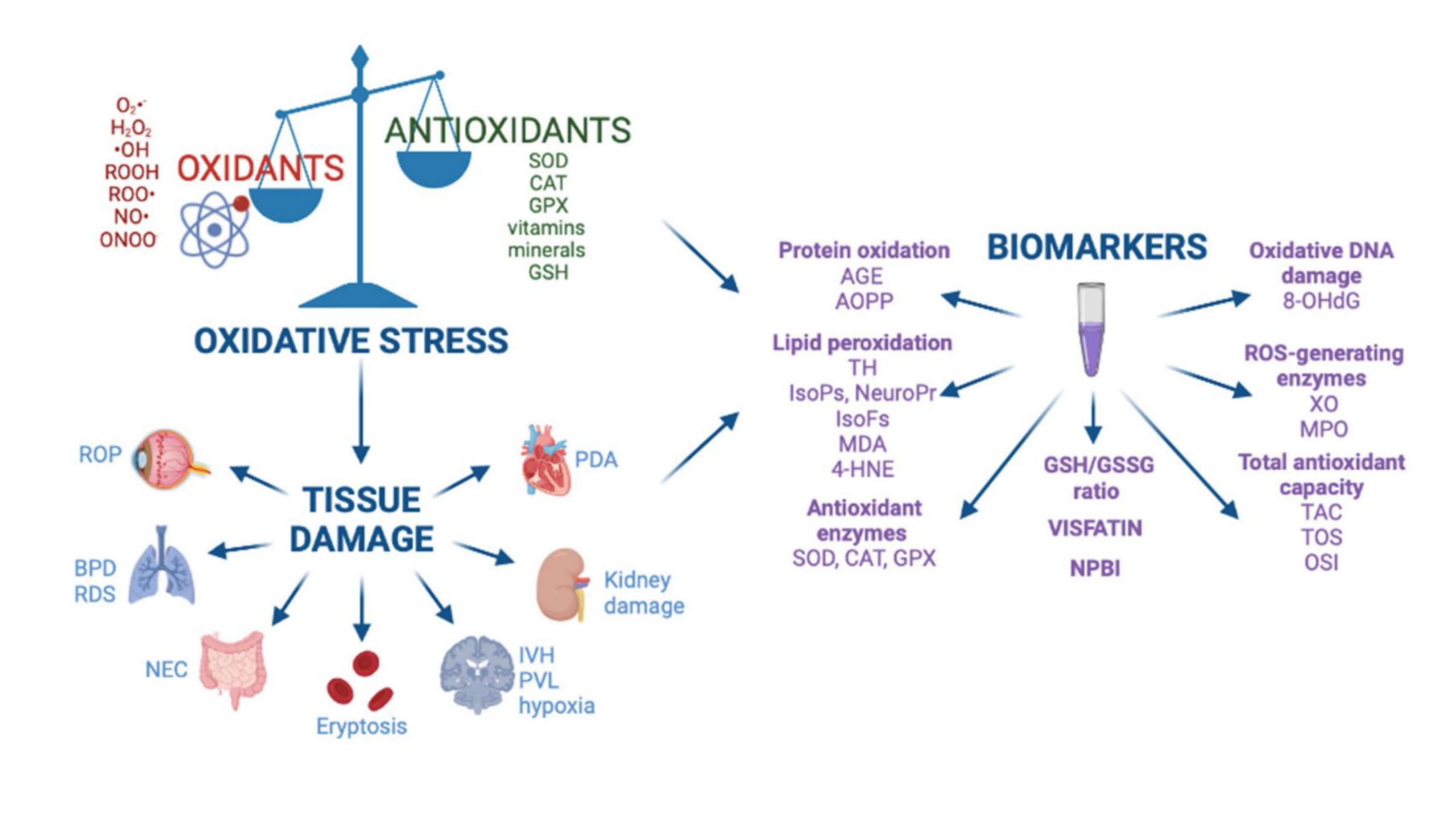
Irwin Reiss

i.reiss@erasmusmc.nl



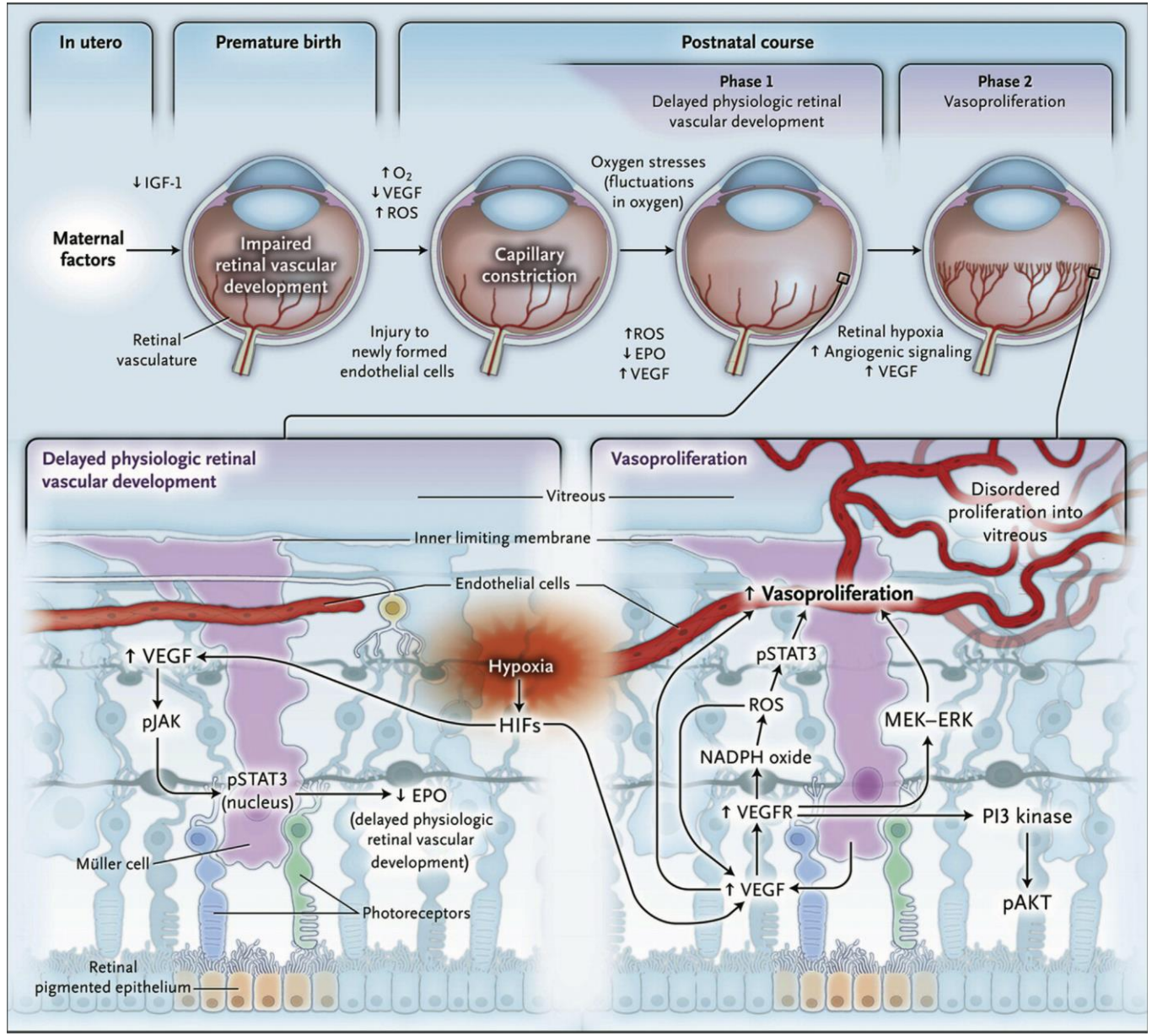



$O_2^{\bullet-}$
H_2O_2
•OH
ROOH
ROO•
NO•
ONOO
OXIDANTS
ANTIOXIDANTS
SOD
CAT
GPX
vitamins
minerals
GSH
OXIDATIVE STRESS
TISSUE DAMAGE
ROP
PDA
BPD
RDS
Kidney damage
NEC
Eryptosis
IVH
PVL
hypoxia
BIOMARKERS
Protein oxidation
AGE
AOPP
Lipid peroxidation
TH
IsoPs, NeuroPr
IsoFs
MDA
4-HNE
Antioxidant enzymes
SOD, CAT, GPX
GSH/GSSG ratio
VISFATIN
NPBI
Oxidative DNA damage
8-OHdG
ROS-generating enzymes
XO
MPO
Total antioxidant capacity
TAC
TOS
OSI

Erasmus MC 2018-2021

	24		**25**		**26**		**27**		**28**		**29**	
N=	71		72		108		80		143		142	
Geslacht jongen	40	56%	44	61%	56	52%	42	53%	82	57%	81	57%
Geboorte gewicht*	695	[600; 740]	803	[721; 878]	902	[746; 1000]	1000	[892; 1140]	1135	[970; 1260]	1300	[1050; 1470]
Inborn	62	87%	66	92%	96	89%	61	76%	117	82%	114	80%
Infectie EO	4	6%	1	1%	4	4%	1	1%	3	2%	5	4%
Infectie LO	27	38%	38	53%	45	42%	19	24%	25	17%	16	11%
NEC	9	13%	22	31%	20	19%	13	16%	11	8%	5	4%
ROP laser	21	30%	7	10%	12	11%	1	1%	0	0%	1	1%
≥28dagen O2	41	58%	41	57%	58	54%	20	25%	16	11%	11	8%
BPD (mild, matig of ernstig)	31	44%	30	42%	43	40%	12	15%	9	6%	13	9%
IVH >1	27	38%	25	35%	25	23%	8	10%	14	10%	10	7%
IVH >2	10	14%	13	18%	11	10%	4	5%	6	4%	5	4%
Beademd ja	67	94%	66	92%	79	73%	43	54%	64	45%	52	37%
Beademingsduur (dagen)*	16	[6; 32]	12	[5; 19]	9	[4; 19]	4	[2; 10]	4	[2; 8]	3	[2; 8]
Opname duur (dagen)*	66	[8; 100]	56	[14; 82]	51	[29; 75]	30	[19; 49]	17	[13; 34]	11	[7;27]
Overlijdens dag*	7	[3; 13]	8	[6; 15]	6	[3; 10]	6	[6; 82]	8	[4; 23]	1	[0,3; 6]
Overlijden	26	37%	25	35%	22	20%	8	10%	10	7%	4	3%

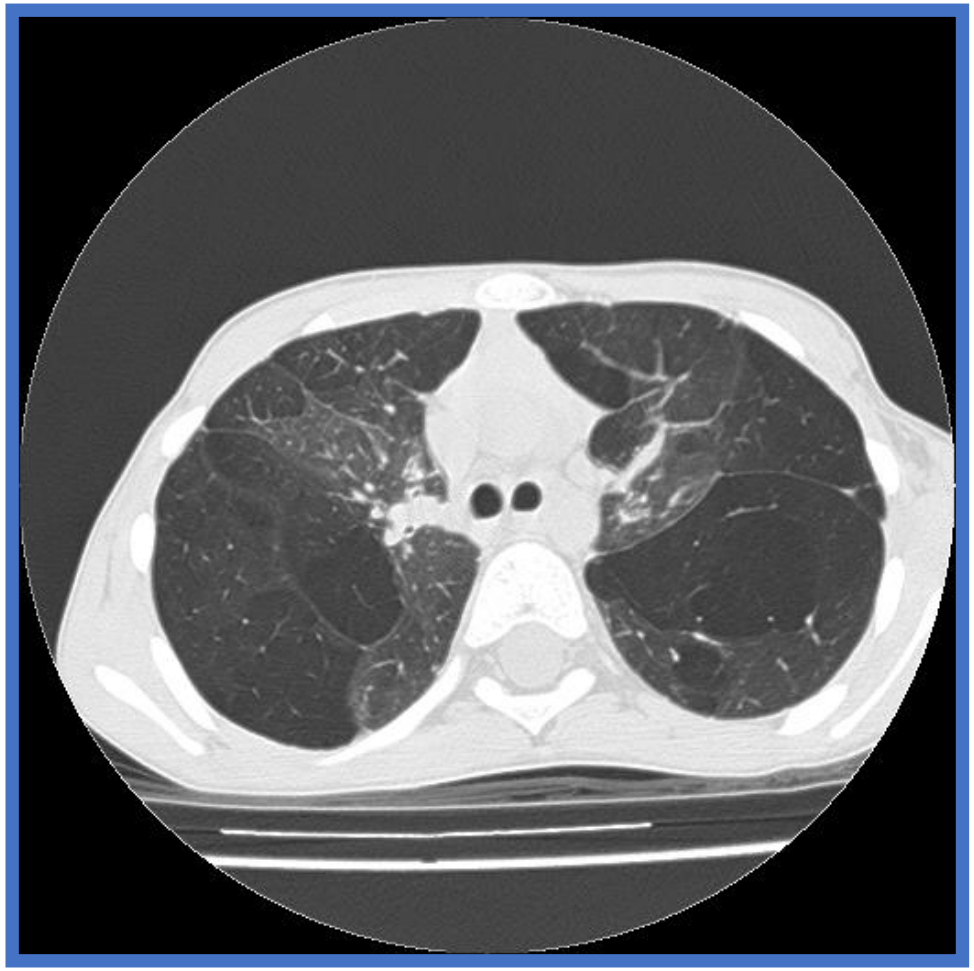
*Mediaan [IQR]


In utero
Premature birth
Postnatal course
Phase 1
Delayed physiologic retinal vascular development
Phase 2
Vasoproliferation
↓ IGF-1
Maternal factors
Impaired retinal vascular development
Retinal vasculature
↑ O_2
↓ VEGF
↑ ROS
Injury to newly formed endothelial cells
Capillary constriction
Oxygen stresses (fluctuations in oxygen)
↑ROS
↓ EPO
↑ VEGF
Retinal hypoxia
↑ Angiogenic signaling
↑ VEGF
Delayed physiologic retinal vascular development
Vasoproliferation
Vitreous
Inner limiting membrane
Endothelial cells
Disordered proliferation into vitreous
↑ Vasoproliferation
↑ VEGF
pJAK
pSTAT3 (nucleus)
↓ EPO
(delayed physiologic retinal vascular development)
Müller cell
Photoreceptors
Retinal pigmented epithelium
Hypoxia
HIFs
pSTAT3
ROS
NADPH oxide
MEK–ERK
↑ VEGFR
PI3 kinase
↑ VEGF
pAKT

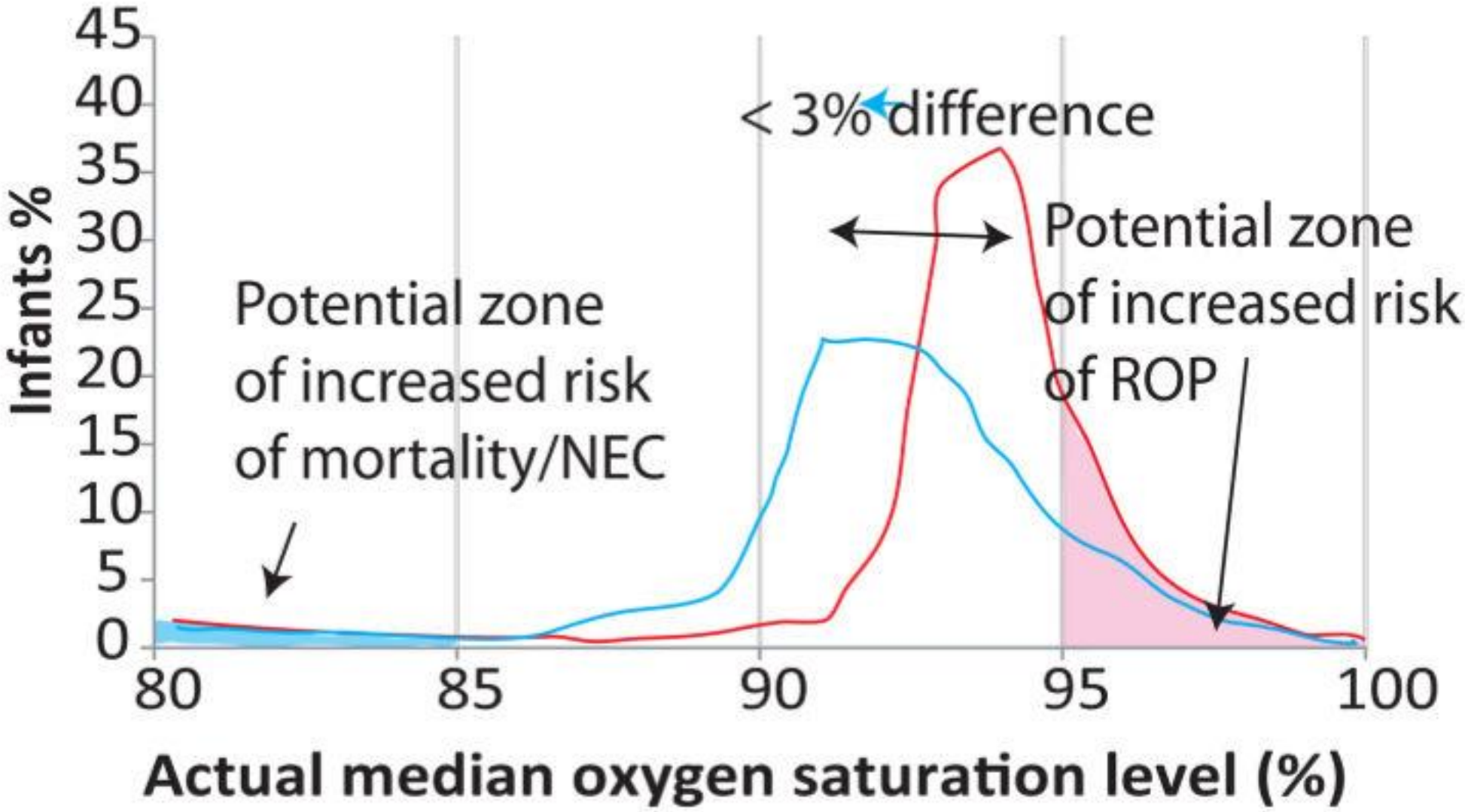
Structural and functional ventilatory impairment in infants with severe bronchopulmonary dysplasia

TABLE 2 PRAGMA-BPD chest CT scores

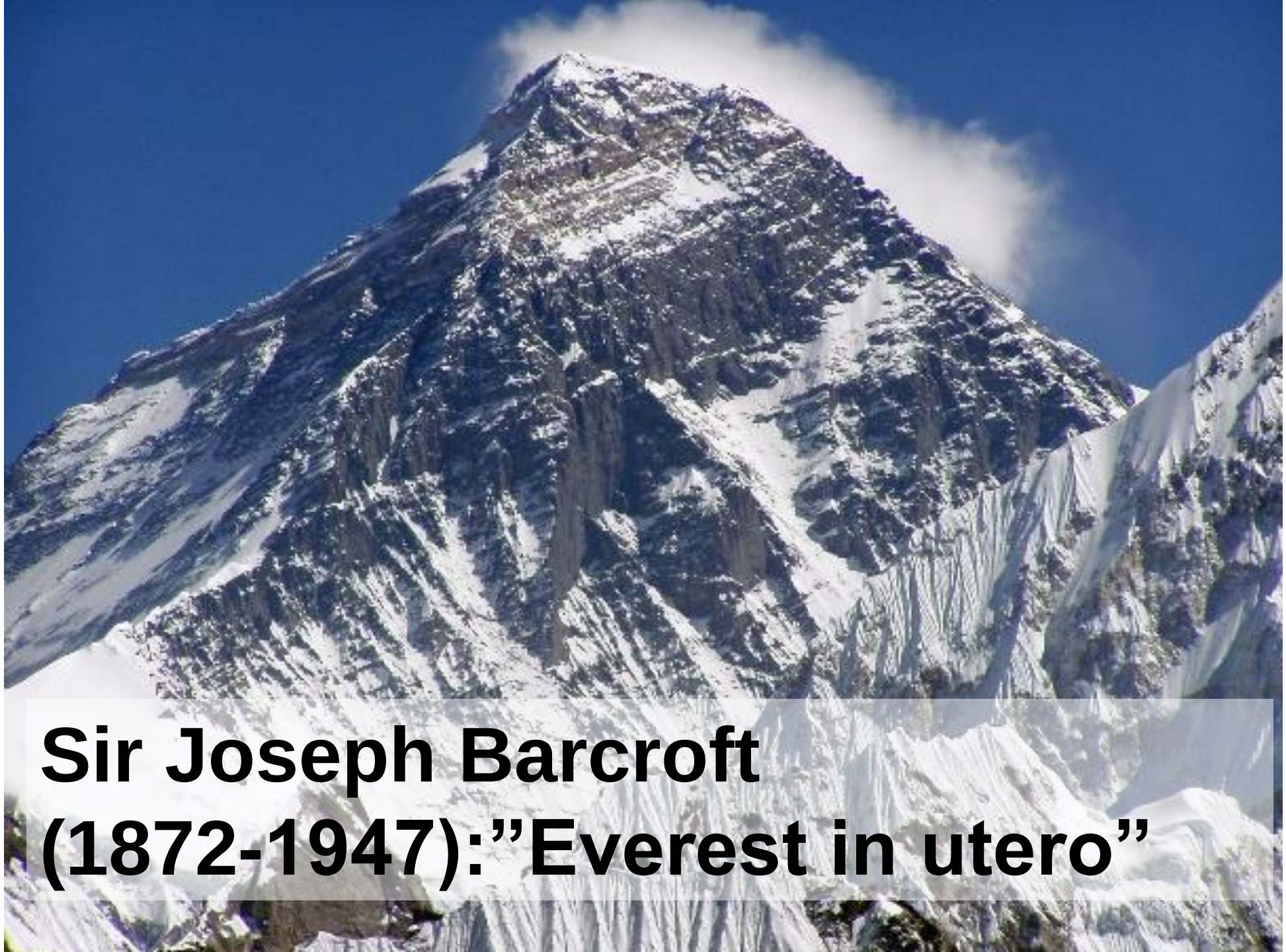
	Severe BPD ($n = 45$)
Total lung volume (mL)	264 (219-327)
Normal lung volume (mL/% total volume)	231 (197-307)/89.7 (85.6-93.2)
Hypoattenuation (mL/% total volume)	4 (1-10)/1.6 (0.5-3.8)
Hyperattenuation (mL/% total volume)	11 (5-27)/4.2 (2.0-9.1)
Bronchial wall thickening (mL/% total volume)	5 (2-9)/2.1 (0.8-2.9)
Number of affected segments	6 ± 3
Percentage of affected segments of total number of segments	29.8 ± 16.8
Architectural distortion	
Absent	2 (4.5%)
Mild	24 (53.3%)
Moderate	18 (40.0%)
Severe	1 (2.2%)



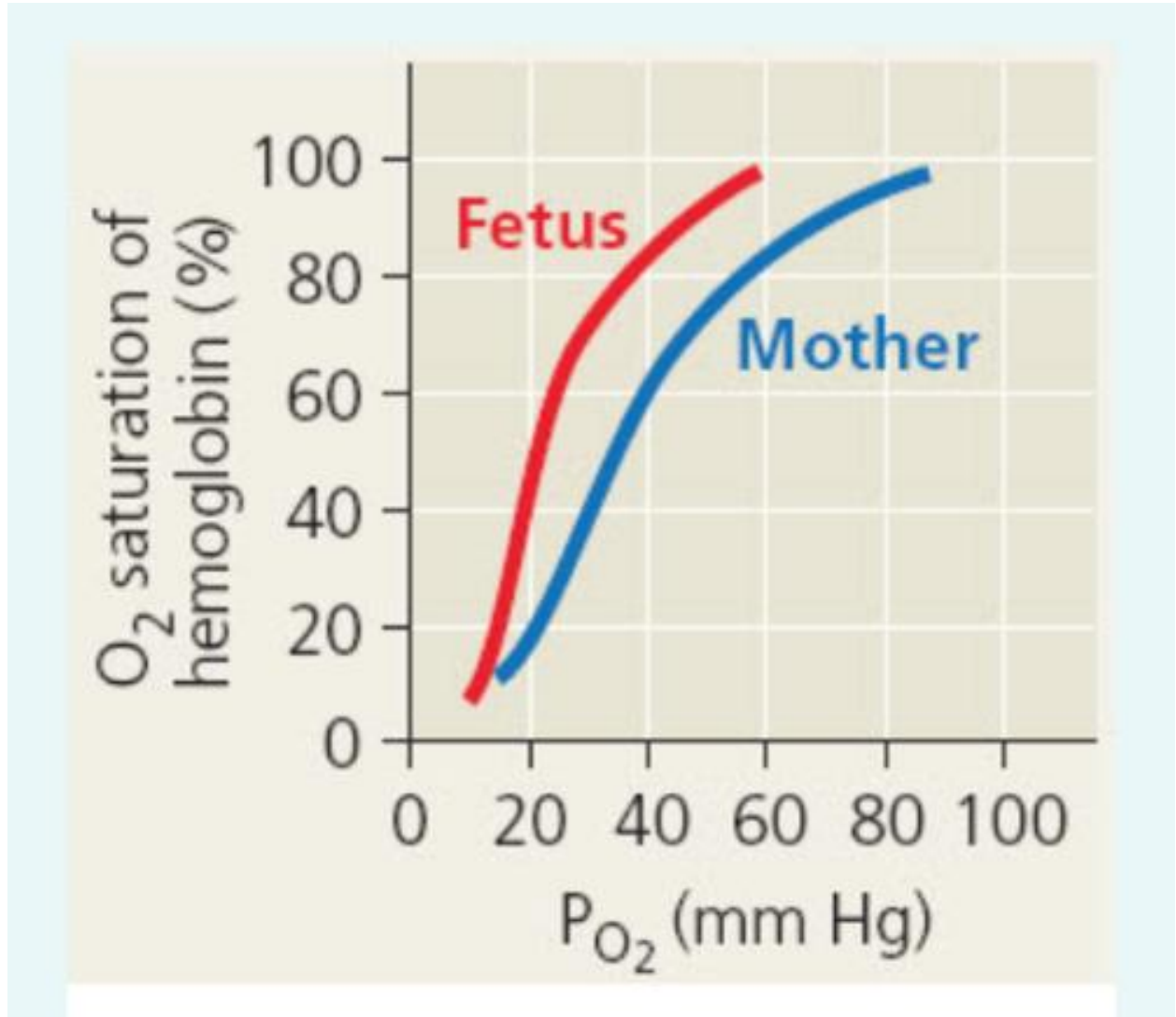
Van Mastrigt E et al. Ped Pulm 2017



Lakshminrushima S et al. J Perinatol 2015



Sir Joseph Barcroft (1872-1947):”Everest in utero”

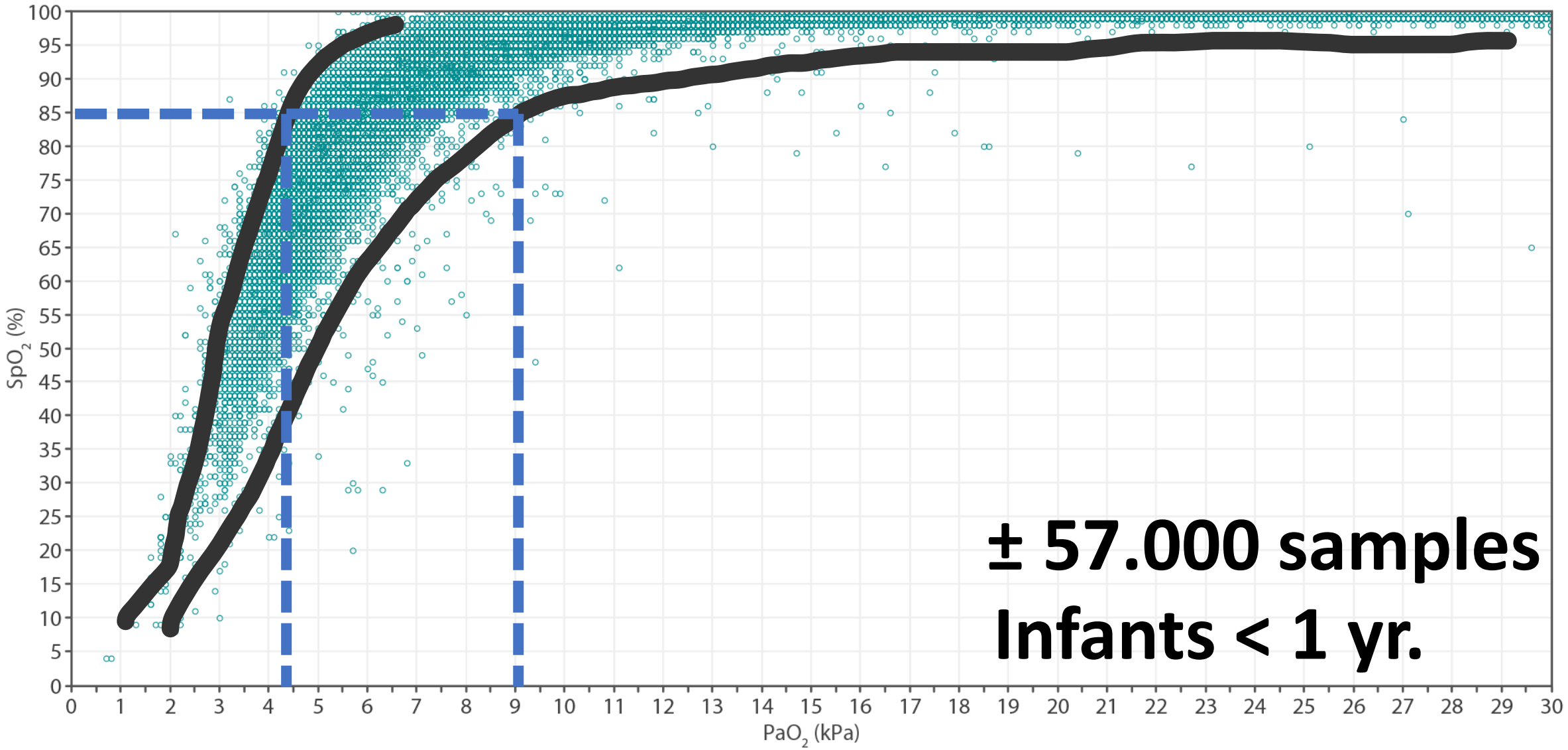

Fetus
Mother
O_2 saturation of hemoglobin (%)
100
80
60
40
20
0
0 20 40 60 80 100
P_{O_2} (mm Hg)

Oxygen saturation in arterial blood (SaO_2)

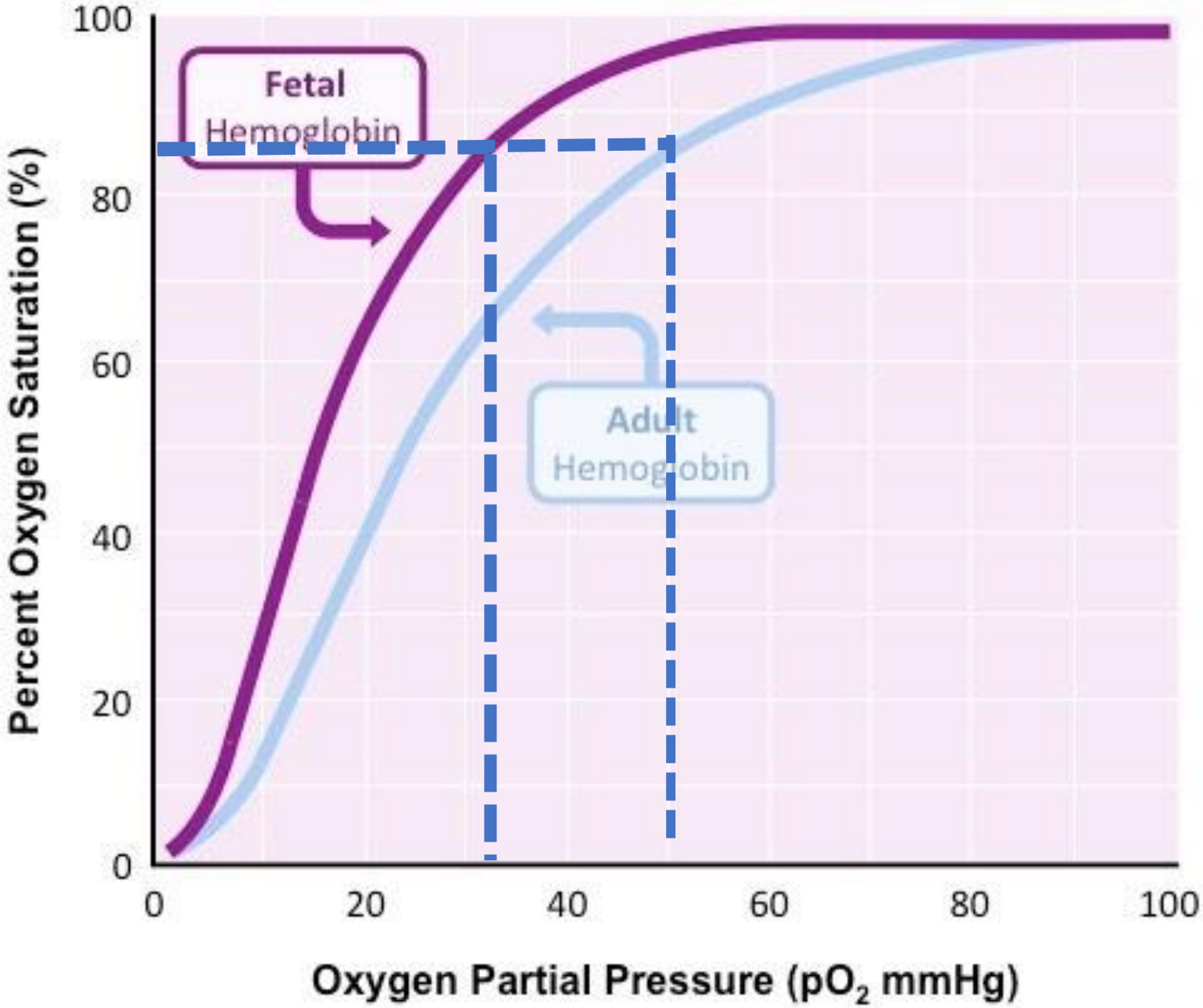
$$SaO_2 = [HbO_2]/([HbO_2] + [Hb])$$

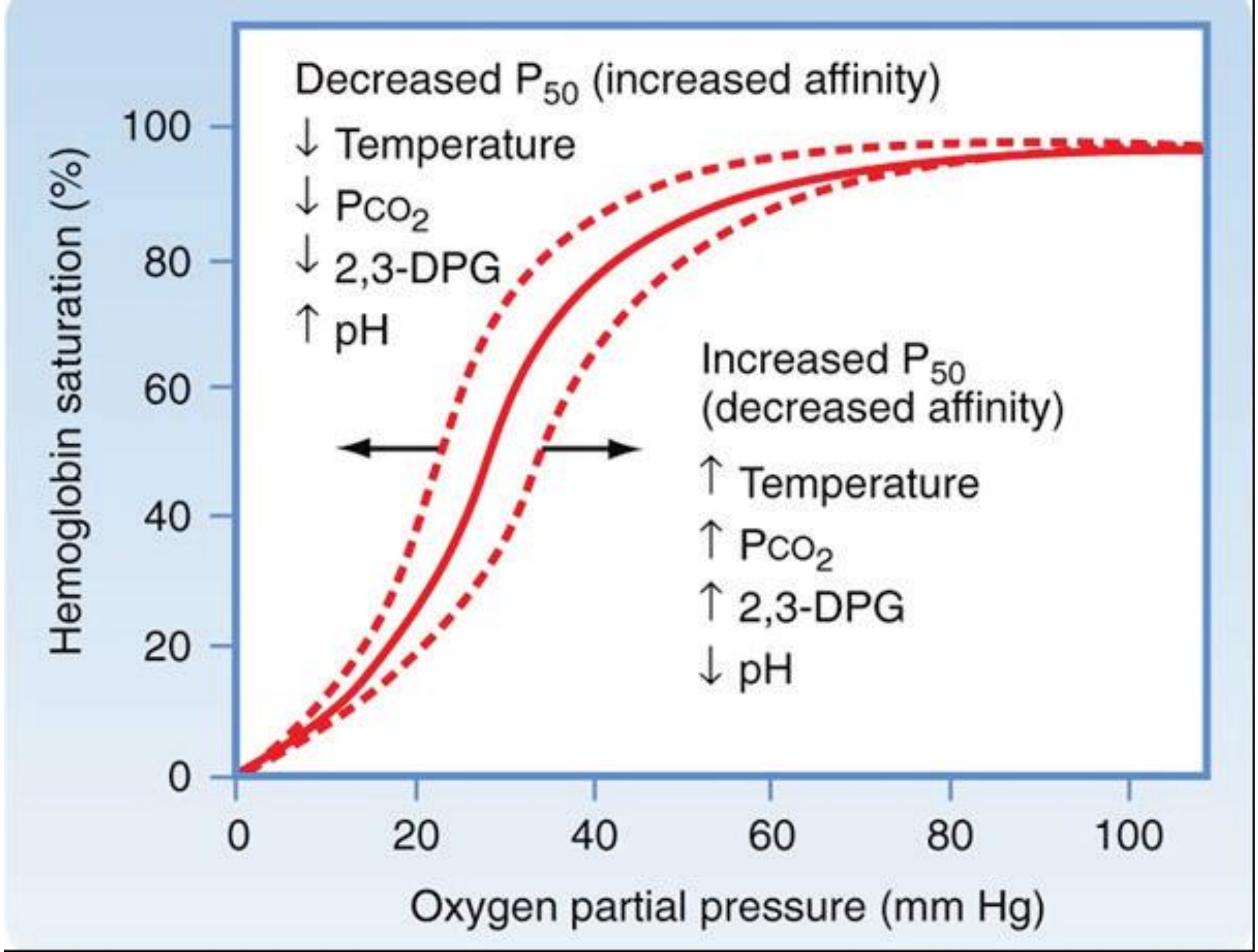
Oxygen Content of Arterial Blood

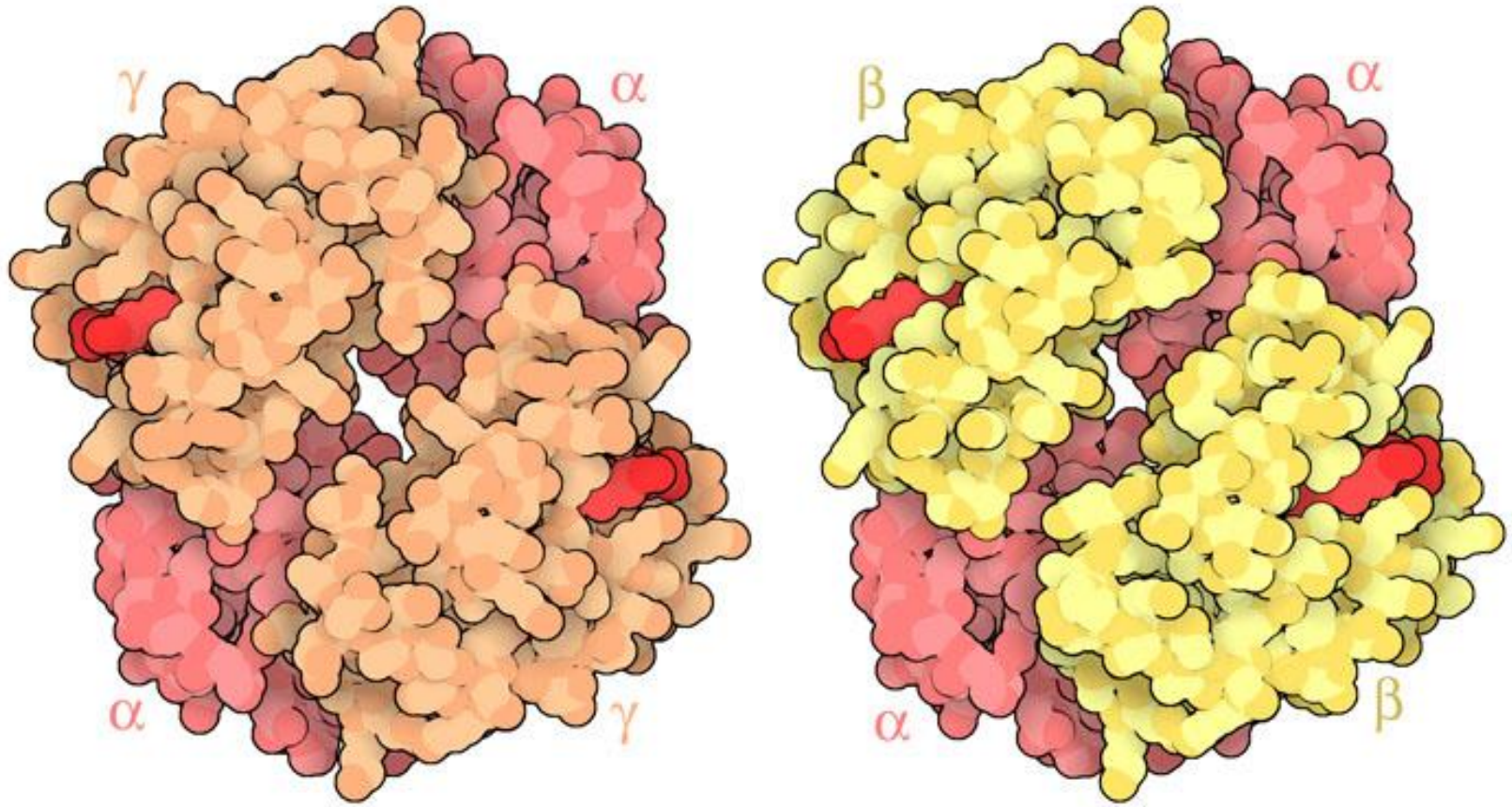
$$CaO_2 = (Hb \times 1.39 \times SaO_2) + (PaO_2 \times 0.003)$$



Van Weteringen W , Gangaram-Panday N, (unplished data)


Fetal
Hemoglobin
Adult
Hemoglobin
Percent Oxygen Saturation (%)
100
80
60
40
20
0
0
20
40
60
80
100
Oxygen Partial Pressure (pO_2 mmHg)

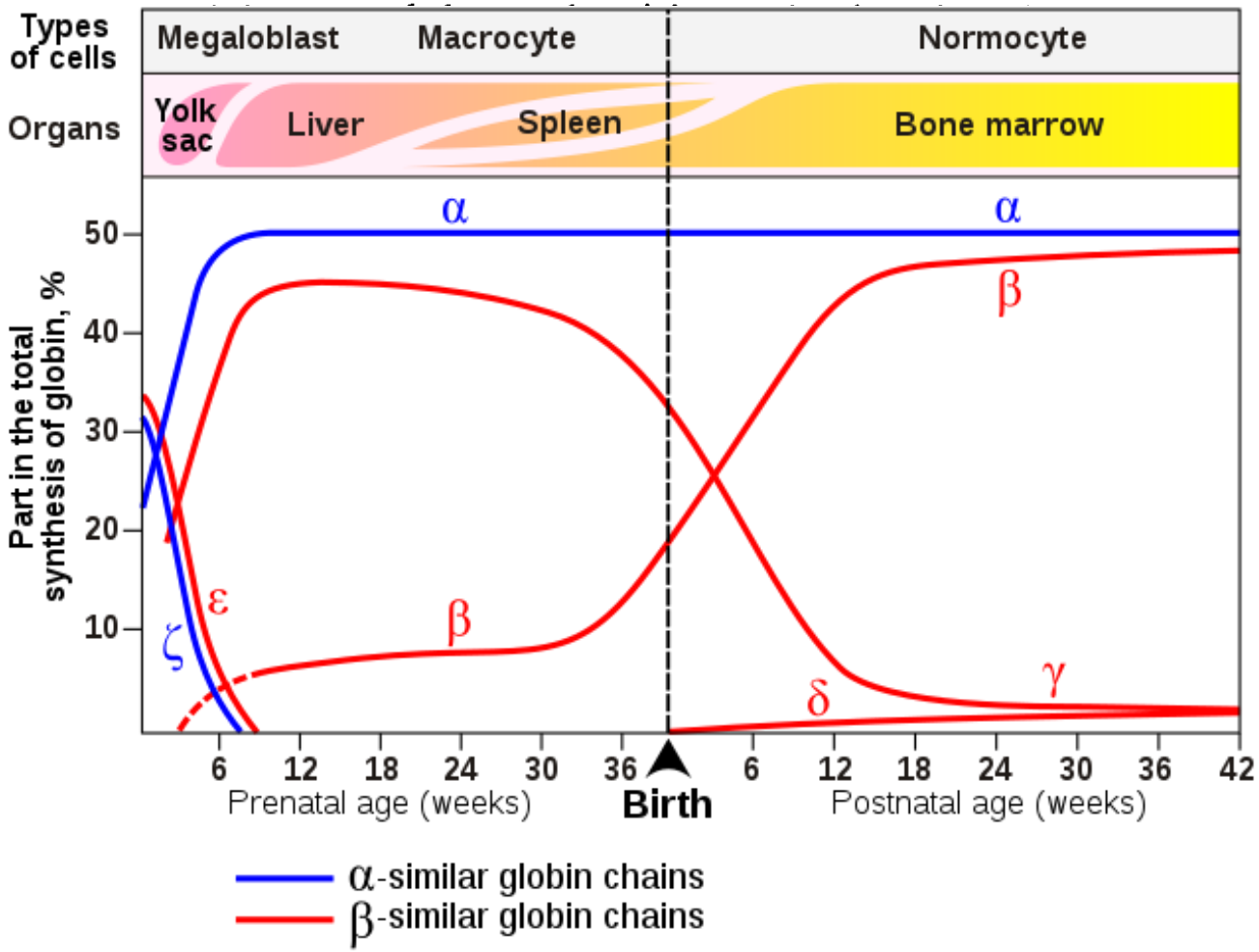

Decreased P_{50} (increased affinity)
↓ Temperature
↓ PCO_2
↓ 2,3-DPG
↑ pH
Increased P_{50}
(decreased affinity)
↑ Temperature
↑ PCO_2
↑ 2,3-DPG
↓ pH
Hemoglobin saturation (%)
0
20
40
60
80
100
Oxygen partial pressure (mm Hg)


γ
α
α
γ
β
α
α
β

aspects of Hb F and its persistence or reactivation in adult life have been the subject of several recent reviews (Lorkin, 1973; Kazazian, 1974; Weatherall *et al.* 1974).

1. Erythropoiesis during Development

The first haemoglobin-containing cells in the human fetus are produced in the mesenchyme of the yolk sac at about two weeks' gestation. The cells produced are morphol[illegible] distinct from erythrocytes of hepatic or medullary



previously published, the complete switchover from F to Hb A synthesis can be described in humans elation to postconceptional age. It follows a sig- l curve; the steep portion, which lies between the and 52nd postconceptional week, is preceded and wed by plateaus averaging 95% and 7% Hb F hesis, respectively.

INTRODUCTION

orderly appearance and disappearance of adult and

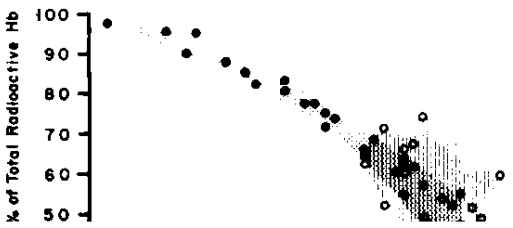
METHODS

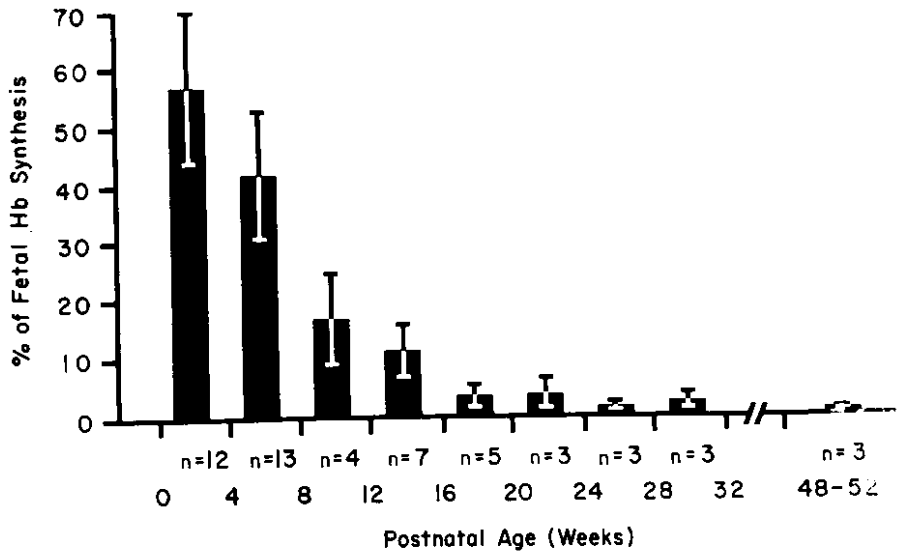
The study was carried out with th serially Hb F and Hb A synthesis full-term infants. 37 healthy, normal between 38 and 42 wk gestation) for gestational age (5) were selecte were all chosen at birth on the basi between the gestational age determ history and the clinical assessment neurological examination. These infa drawn during follow-up for their ro

The synthesis of Hb F and Hb measuring the incorporation of [^{14}C]

significant. $Hb A_1$ may well be a product of the normal ageing of erythrocytes, as there appear to be insignificant amounts present in newly synthesized Hb F.

All of the infants included in this study were normal, born after a term gestation, and healthy during their postnatal follow up. This selection of subjects thus differed from those included in a similar investigation performed by Garby, Sjölin, and Vuille (8). They used two methods, one based on the relative rate of the appearance of i.v. injected radioactive iron in circulating Hb F and the other based on the semi-





JCI 1975

Article

Activation of γ-globin expression by hypoxia-inducible factor 1α

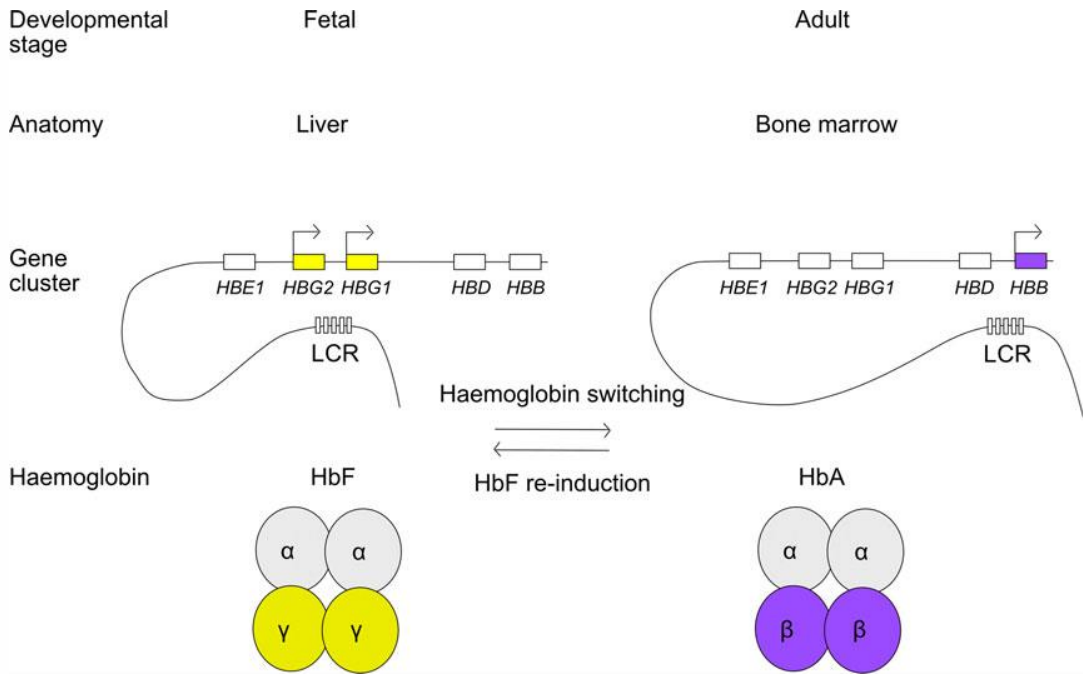
https://doi.org/10.1038/s41586-022-05312-w

Received: 15 October 2021

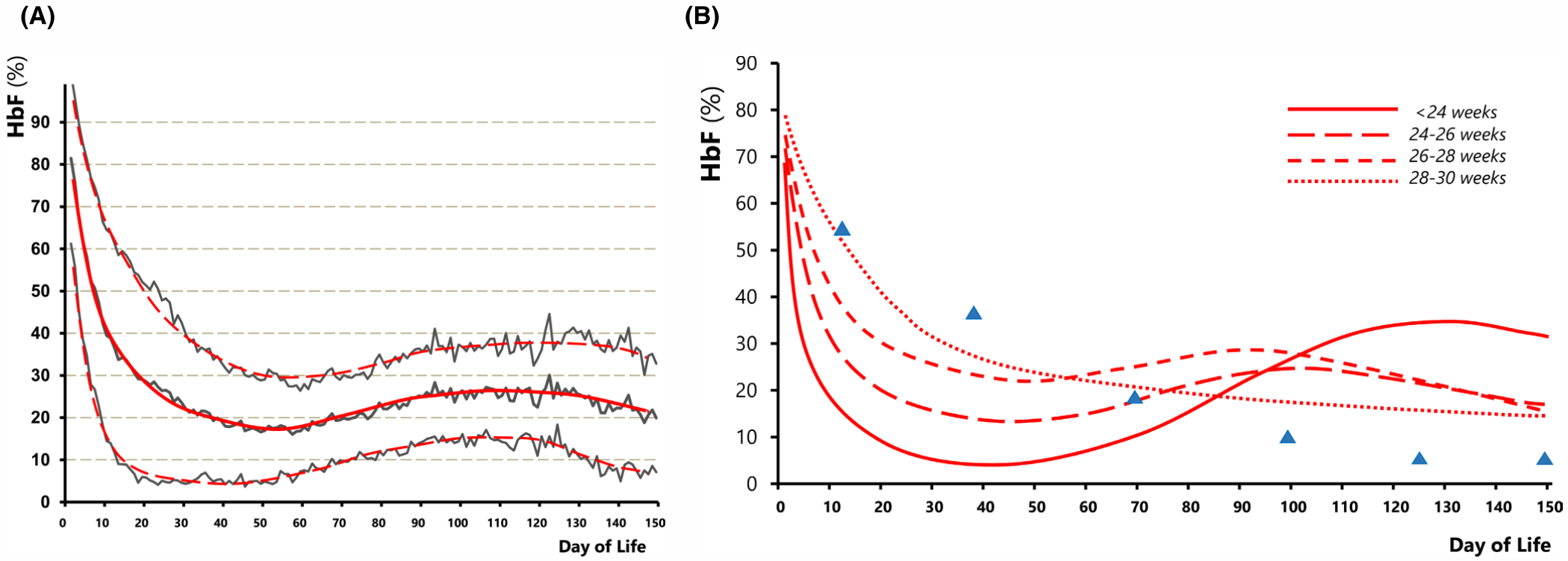
Accepted: 2 September 2022

Published online: 12 October 2022

Ruopeng Feng[1], Thiyagaraj Mayuranathan[1], Peng Huang[2], Phillip A. Doerfler[1], Yichao Li[1], Yu Yao[1], Jingjing Zhang[1], Lance E. Palmer[1], Kalin Mayberry[1], Georgios E. Christakopoulos[1], Peng Xu[1], Chunliang Li[3], Yong Cheng[1], Gerd A. Blobel[2], M. Celeste Simon[4] & Mitchell J. Weiss[1]✉



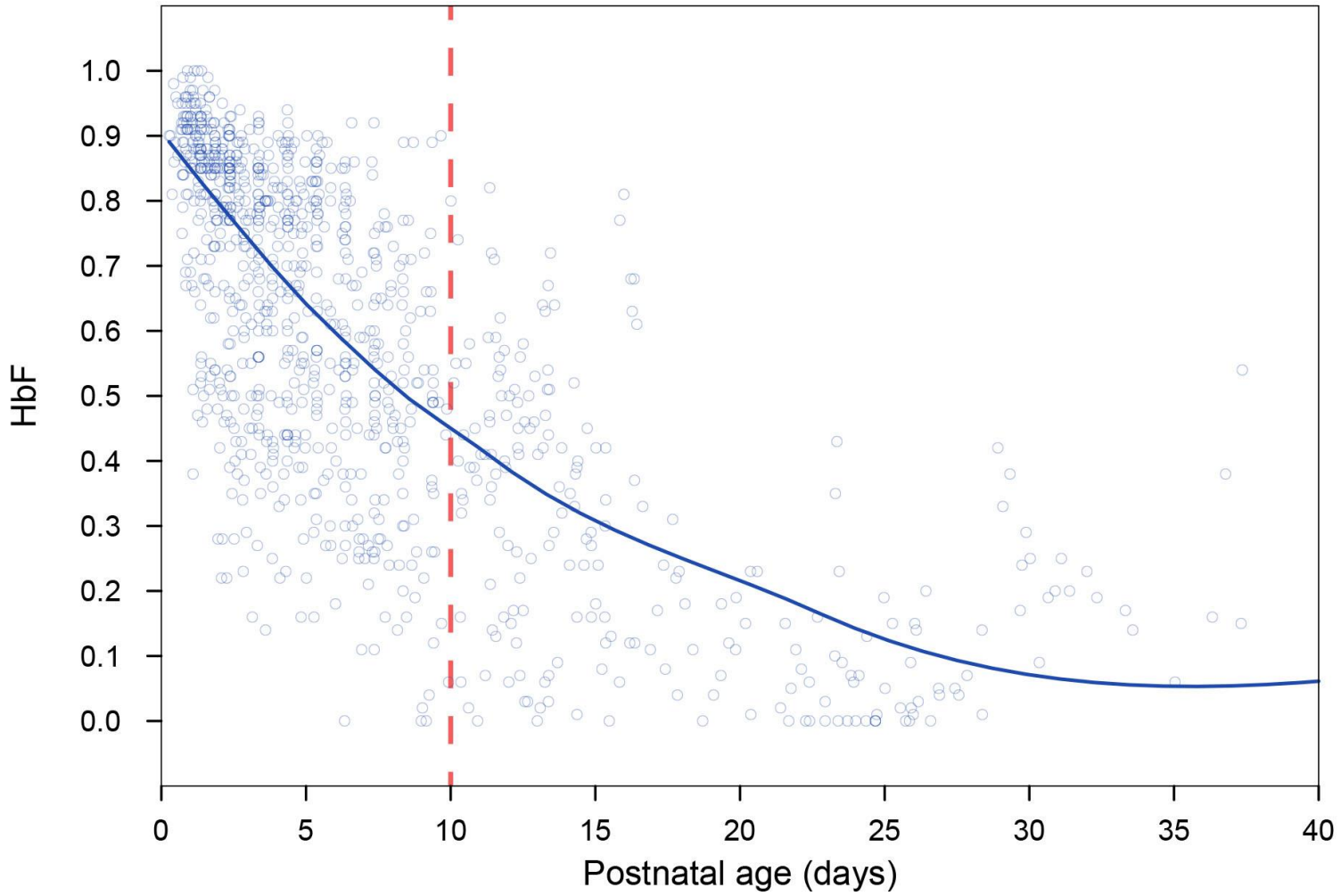
Postnatal temporal changes of foetal haemoglobin in prematurely born infants

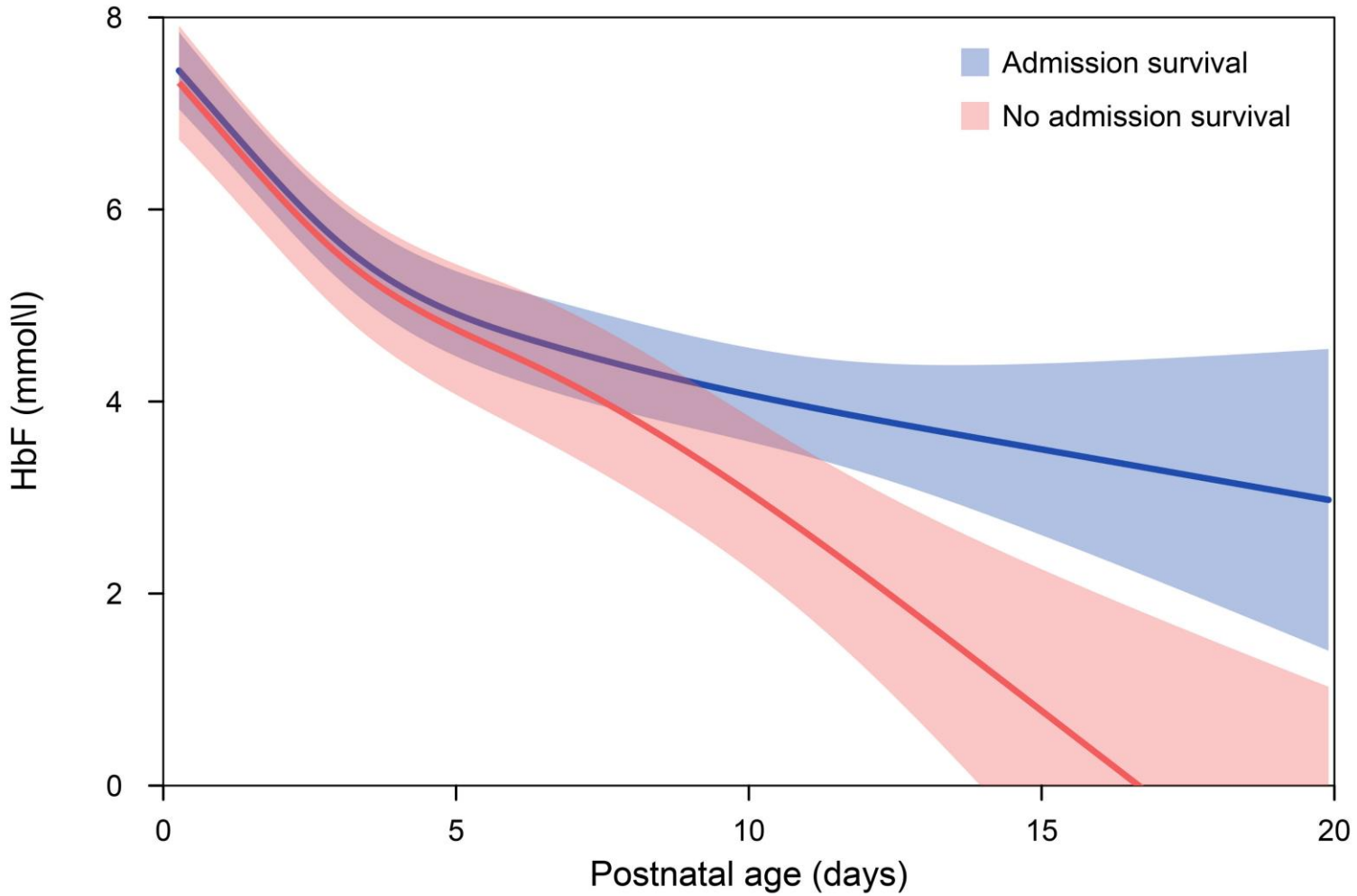


4,631 blood gas samples ; n=103 infants

Bednarczuk N et al., Acta Pediatrica 2022

Fetal hemoglobin (GA < 28 weken)




Admission survival
No admission survival
HbF (mmol\l)
0
2
4
6
8
0
5
10
15
20
Postnatal age (days)

Foetal haemoglobin, blood transfusion, and retinopathy of prematurity in very preterm infants

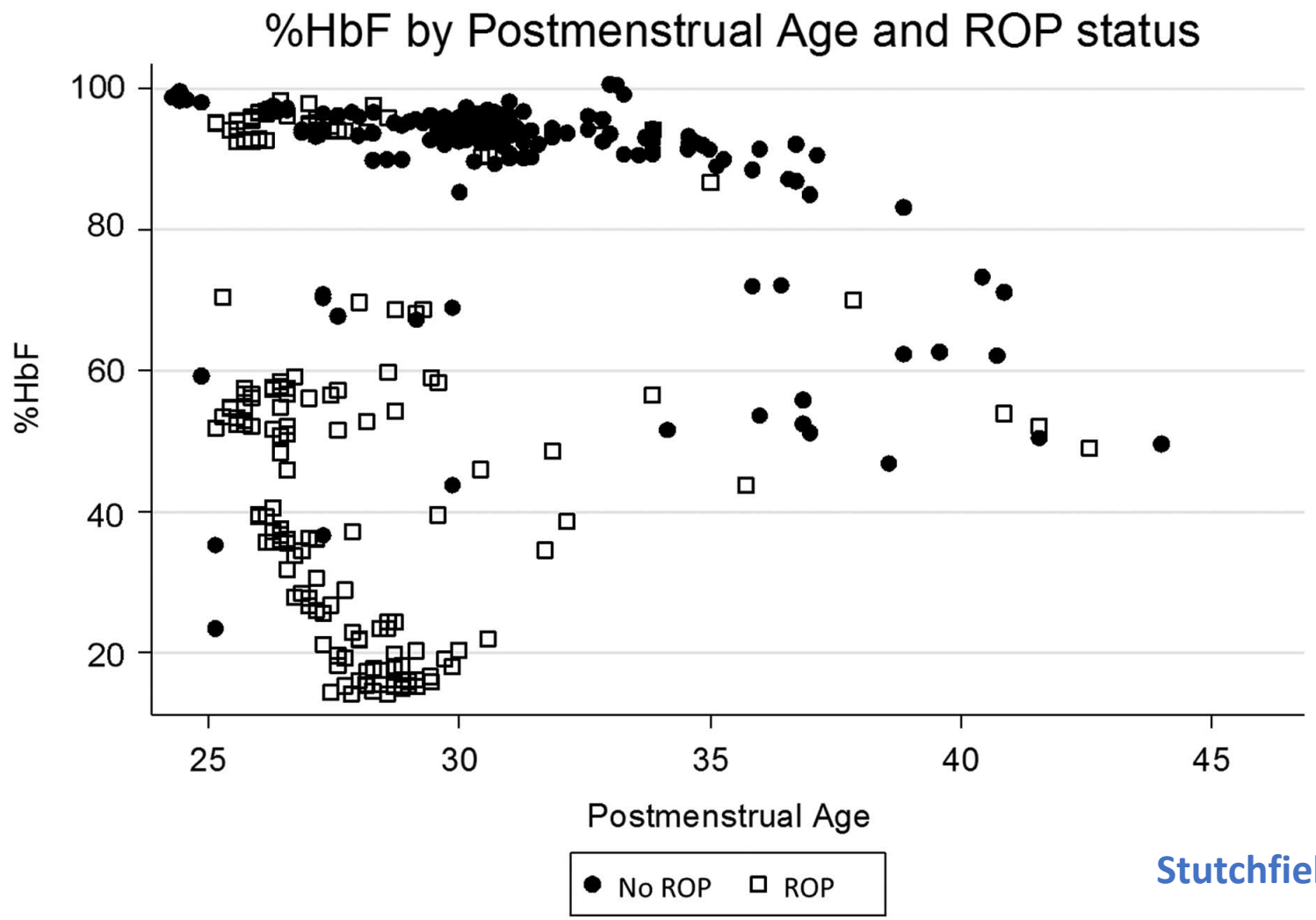
Table 1 Demographics and ROP[a] outcome data

Variable	*No ROP*	*ROP*	P
Male	9 (40.9%)	5 (35.7%)	0.441
Non-White ethnicity	2 (9.1%)	0 (0%)	0.411
Multiple birth	11 (50.0%)	1 (7.1%)	0.027
RBC[b] transfusions	0 (0–1)	3 (1–5)	<0.001
Total RBC transfusion (ml/kg)	0 (0–20)	53 (20–103)	<0.001
Culture-positive sepsis	2 (9.1%)	3 (21.4%)	0.297
Gestation (weeks)	29.2 (1.1)	26.6 (1.6)	<0.001
Birth weight (g)	1160 (261)	924 (205)	0.007
Days on ventilator	1 (0–2)	6 (2–20)	<0.001
Days on CPAP	10 (6–27)	30 (14–39)	0.028
Days on supplementary O_2	28 (7–51)	50 (21–73)	0.051

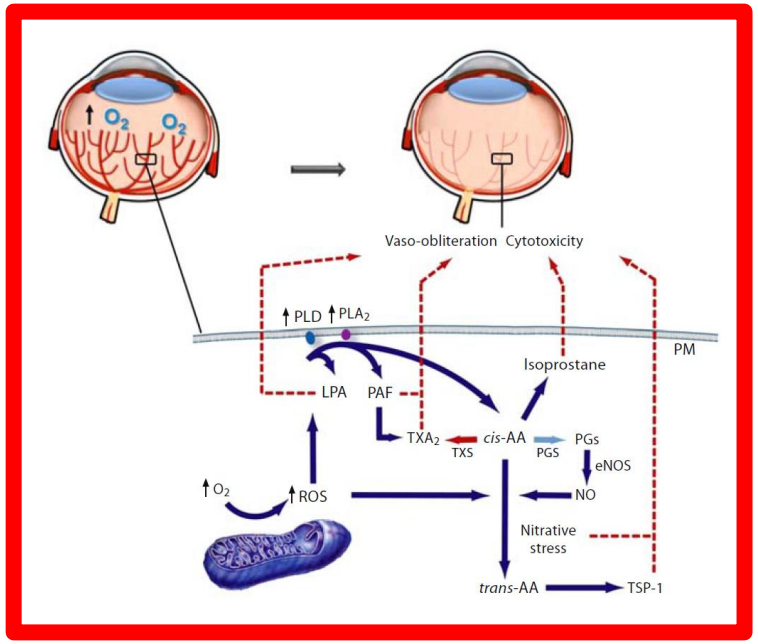
Values are mean (SD), median (IQR), or *n*(%) as appropriate. [a]Retinopathy of prematurity. [b]Red blood cell.

Stutchfield CJ et al , Eye 2017

Foetal haemoglobin, blood transfusion, and retinopathy of prematurity in very preterm infants



Effects of oxidant stress on premature retinal vasculature



Stutchfield CJ et al , Eye 2017

Foetal haemoglobin, blood transfusion, and retinopathy of prematurity in very preterm infants: a pilot prospective cohort study

Table 2 Comparison of haematological values between those infants who developed ROP and those that did not

	No ROP (95% CI) (n = *22*)	*ROP (95% CI)* (n = *14*)	P-*value*
Initial Hb (g/l)	162.5 (153.2, 171.8)	143.6 (133.3, 153.9)	0.009
Mean Hb (g/l)	134.9 (116.0, 153.7)	112.4 (102.8, 122.1)	0.06
Initial %HbF	92.3 (89.9, 94.7)	83.3 (71.1, 95.5)	0.06
Mean %HbF	91.87 (87.2, 96.5)	61.75 (44.5, 79.0)	0.0001

Table 3 Association between haematological values and ROP

Variable	*OR (95% CI)*	*Adjusted*[a] *OR (95% CI)*
Initial HbF%	0.96 (0.93–1.00)	0.97 (0.91–1.03)
Mean HbF%	0.94 (0.90–0.97)	0.94 (0.90–0.99)

Abbreviations: CI, confidence interval; OR, odds ratio. [a]Adjusted for birth weight, gestation, and total transfusion volume.

Stutchfield CJ et al , Eye 2017

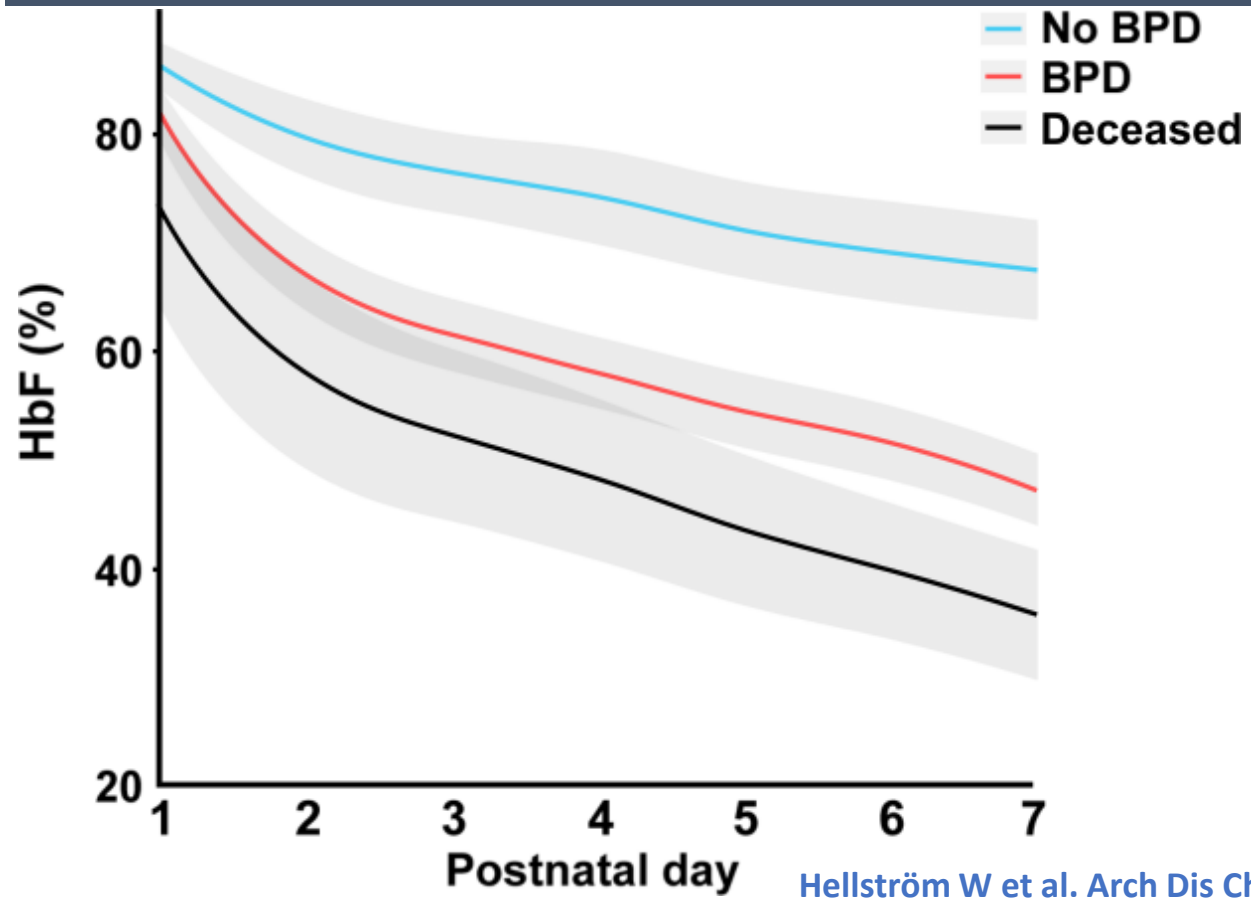
Original research

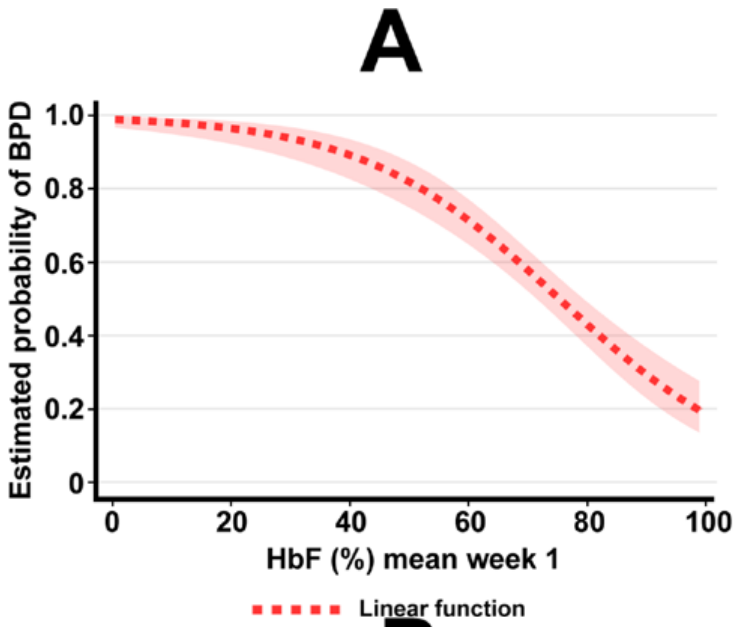
OPEN ACCESS

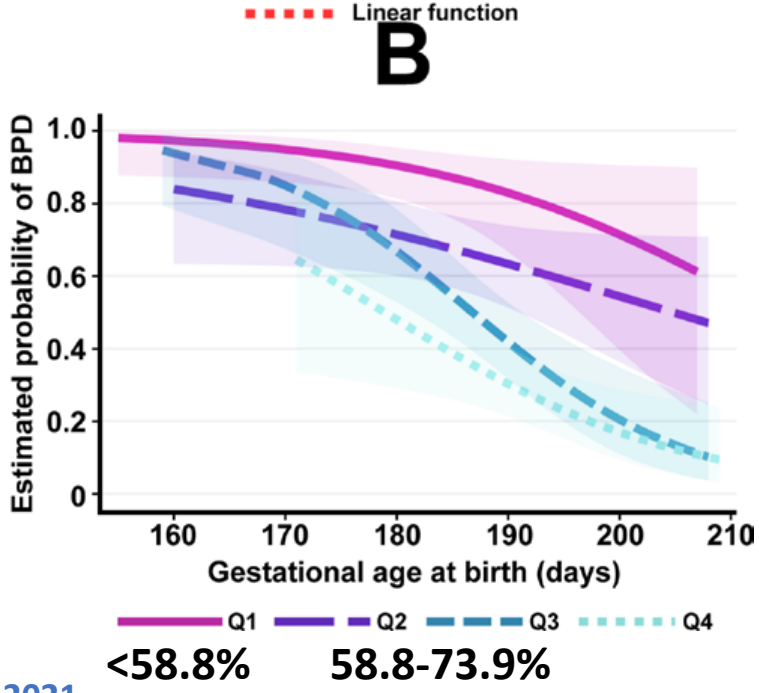
Fetal haemoglobin and bronchopulmonary dysplasia in neonates: an observational study

William Hellström ,[1] Tobias Martinsson,[2] Ann Hellstrom,[3] Eva Morsing,[2] David Ley[2]

452 very preterm infants (<30 gestational weeks) born 2009–2015







Hellström W et al. Arch Dis Child Fetal Neonatal Ed 2021

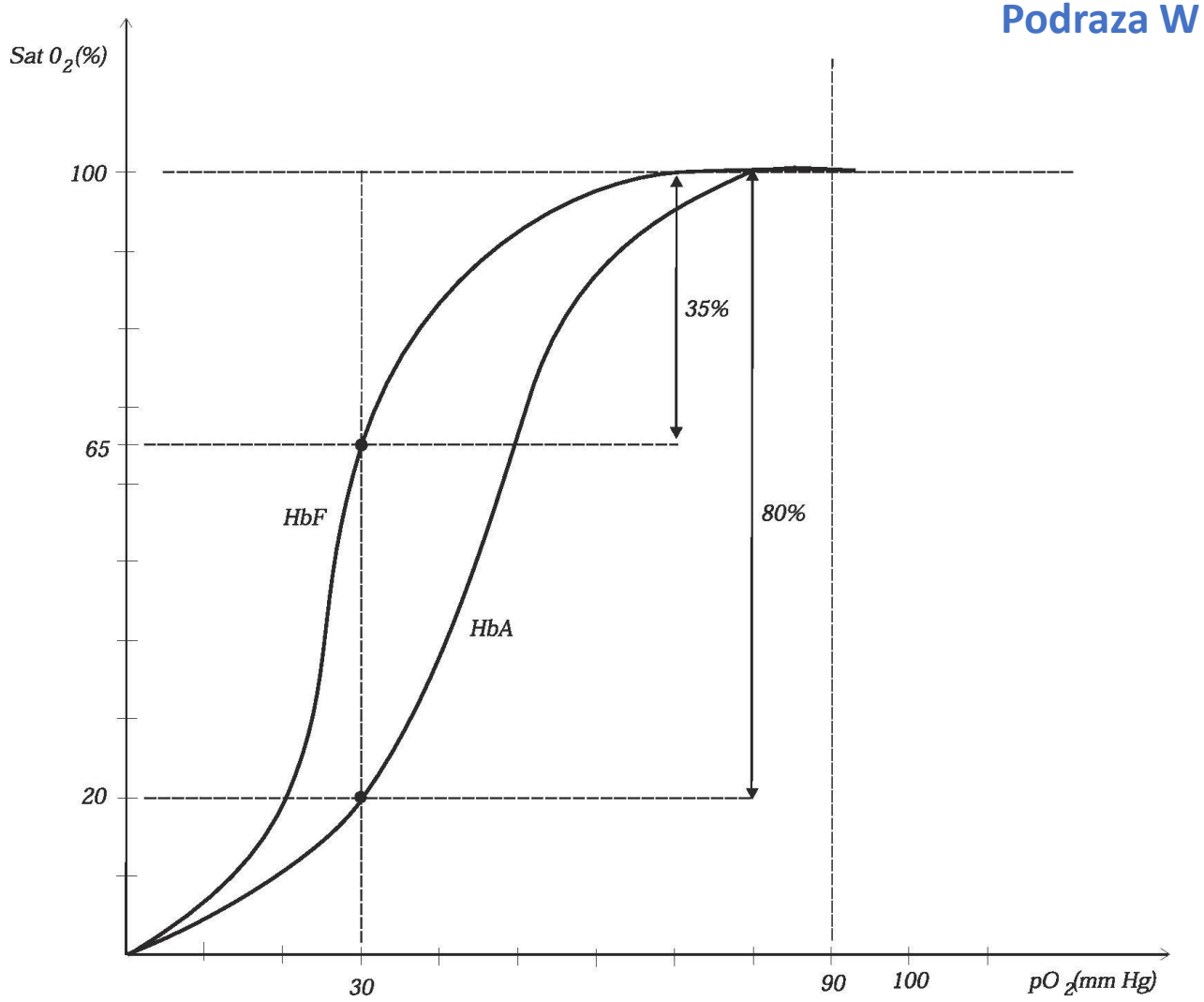
Table 1. Incidence of RBC and platelet transfusions in neonates with a hospital stay >3 days, per gestational age

Gestational age (weeks)	Number	Any RBC % (95% CI)	Any platelet % (95% CI)
<27	295	71 (66–76)	34 (28–39)
27–28	277	45 (39–51)	11 (7–14)
29–32	987	13 (11–15)	5.8 (4.3–7.2)
33–36	3063	3.1 (2.5–3.7)	1.6 (1.2–2.0)
37+	8199	2.5 (2.2–2.8)	1.7 (1.4–2.0)

CI, confidence interval; RBC, red blood cell.
Adapted from Patel *et al.* [1].

A new approach to neonatal medical management that could transform the prevention of retinopathy of prematurity: Theoretical consideration

Podraza W Med Hypothesis2020



bjh commentary

Allogeneic cord blood transfusions for extremely preterm neonates: an extremely promising proof of concept

Enrico Lopriore,[1] Elise Huisman,[2] Jaap Jan Zwaginga,[3] Pauline M. Snijder,[4] Irwin K. Reiss[4] and Simon Stanworth[5]

[1]Department of Paediatrics, Division of Neonatology, Leiden University Medical Centre, Leiden, [2]Department of Haematology, Erasmus Medical Centre, Rotterdam, [3]Jon J van Rood Center for Clinical Transfusion Medicine, Sanquin/LUMC, and Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, [4]Department of Paediatrics, Division of Neonatology, Erasmus Medical Centre, Rotterdam, and [5]NHS Blood and Transplant, John Raddiffe Hospital, Oxford

Linked article: This is a commentary on Luciana Teofili. et al., Allogeneic cord blood transfusions prevent fetal haemoglobin depletion in preterm neonates. Results of the CB-TrIP study. Br J Haematol. 2020;191:263–268.