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Duration of neonatal oxygen supplementation, erythropoiesis and blood pressure in young adults born preterm.

Adrien Flahault[1] MD PhD, Camille Girard-Bock[1] MSc, Rafael Oliveira Fernandes[1] PT PhD, Anik Cloutier[1] MSc, Yves D. Pastore MD[1,2], Thuy Mai Luu[1,3] MD MSc, Anne Monique Nuyt[1,4]* MD, HAPI collaborating group.

For the **HAPI collaborating group**: Nathalie Alos MD, Mariane Bertagnolli PhD, Jean-Luc Bigras MD, Daniel Curnier PhD, Daniela Ravizzoni Dartora PhD, Jacques Delfrate MSc, Ramy El-Jalbout MD MSc, Geneviève Gyger MD, Patrick Hamel MD, Mélanie Henderson MD PhD, Anne-Laure Lapeyraque MD, Jean-Claude Lavoie PhD, Benoît Mâsse PhD, Muhammad Oneeb Rehman Mian PhD, Valérie Orlando MSc, Katryn Paquette MD, Li Feng Xie RD MSc

[1]Sainte-Justine University Hospital Research Center, University of Montreal, Montreal, Quebec, Canada

[2]Division of hematology and oncology, [3]Division of general pediatrics, [4]Division of neonatology, Department of Pediatrics, Sainte-Justine University Hospital, University of Montreal, Montreal, Quebec, Canada

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*Correspondence to: Dr. Anne Monique Nuyt, Sainte-Justine University Hospital and Research Center, 3175 Chemin de la Côte-Sainte-Catherine, Montréal (Québec) H3T 1C5 Canada. Tel.: +1 514 345 4931, ext 6146; E-mail: anne.monique.nuyt@umontreal.ca

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Supplemental methods

Study population

We obtained data from a cross-sectional observational study, the *Health of Adults born Preterm Investigation (*HAPI) project, that evaluated the health of young adults (18-29 years) born at ≤29 weeks of gestational age (GA) between 1987 and 1997 and compared them to individuals born full-term (≥37 weeks GA) matched for sex and age (± 2 years) and recruited among friends and siblings. Participants from the preterm group were admitted to one of the three main neonatal intensive care units in Montreal, Quebec: Sainte-Justine University Hospital (Centre hospitalier universitaire Sainte-Justine (CHUSJ)), and the McGill University affiliated Royal Victoria Hospital and Sir Mortimer B. Davis Jewish General Hospital. Participants with severe neurocognitive impairment and pregnancy were excluded. The study began in September 2014, and 176 participants were recruited by December 2016. Five participants were excluded due to misclassification based on GA (three in term group with GA <37 weeks and two in preterm group with GA >29 completed weeks) after review of medical records. In order to achieve a sample size of 200, on which power calculations had been performed, we decided to include in the study 40 participants from the pilot study (term=20, preterm=20) that were also matched on sex and age, but were not recruited from friends or siblings. The pilot study took place between December 2011 and March 2013 and had the exact same protocol, procedures and evaluations used in this research. Five participants from the pilot study were called back to participate in the main study and were only analyzed once. Ethics approval was obtained from the Sainte-Justine University Hospital and Research Center (Comité d'éthique de la recherche, number 3901), the Royal Victoria Hospital, and the Sir Mortimer B. Davis Jewish General Hospital Research Ethics Boards (Comité d'éthique de la recherche, number 2139), and all participants gave written informed consent to participate to the study. All authors had access to primary clinical data; AF, TML and AMN analyzed the data.

Clinical outcomes

On the day of the visit, each participant underwent clinical assessment. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automated

oscillometric device (DINAMAP model DPC300M-CF, GE Medical Systems Information Technologies Inc. Milwaukee, WI, USA). BP measurements were taken after seated rest for 5 minutes, in duplicate. All BP measurements were obtained prior to blood collection. Spirometry was performed according to the American Thoracic Society / European Respiratory Society guidelines[1], by a trained technician, using the Jaeger – CareFusion Oxycon Pro Spirometer (York Linda, CA) compact stress unit. Forced Expiratory Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC) were measured in seated position. Consecutive FVC manoeuvres were performed until repeatability criteria was met for three acceptable manoeuvres. FVC and FEV_1 were measured from at least three forced expiratory curves that had an acceptable start of test and were free from artefact, and the largest FVC and FEV_1 were recorded after examining data from all usable curves, even if they did not come from the same curve, according to the guidelines[1]. FEV_1 and FVC Z-scores were calculated using the Global Lung Initiative (GLI) 2012 reference values[2]. Neonatal characteristics were obtained from the participant's medical records. Dietary intakes of iron, vitamin B6 and B12 were estimated using a validated food frequency questionnaire[3].

Biology and ultrasonography measurements

Blood was collected on the morning of the assessment. Erythropoietin was measured in the serum at the Maisonneuve-Rosemont University Hospital on a Dynex DX system (Dynex Technologies, Chantilly, VA, USA) using the Human Erythropoietin Quantikine IVD ELISA Kit (R&D Systems, Minneapolis, MN, USA). Enzyme-linked immunosorbent assays (ELISAs) were used for determination of circulating levels of soluble vascular endothelial growth factor receptor 1 (VEGF-R1 or sFlt-1), human soluble endoglin (CD105) and vascular endothelial growth factor (VEGF) using magnetic Luminex screening assays (R&D Systems, Minneapolis, MN, USA). These biomarkers were measured in the serum. Total blood count, as well as other biologic assessments, were measured at the Sainte-Justine University Hospital clinical biochemistry laboratory. Estimated glomerular filtration rate was calculated from serum creatinine values using the CKD-EPI 2009 formula.

Statistical analysis

All statistical analyses were performed using R version 3.5.1. For continuous variables, data were presented as mean ± standard deviation or median (interquartile range, 25% - 75%) and between-group comparisons were performed using Student's t or Mann-Whitney U tests for normally-distributed and non-normally distributed variables, respectively. Categorical variables were presented as n (%) with between-group comparisons done with the Fisher's exact test. For sex-stratified analysis of hemoglobin levels, group sample sizes of 43 achieved 82% power to reject the null hypothesis of equal means when the population mean difference is 5.0 g/l with a standard deviation for both groups of 8.0 and with a significance level of 0.05 using a two-sided two-sample equal-variance t-test.

Correlations between continuous variables were assessed using Spearman's rho coefficient and test. In order to identify and adjust for potential confounders (including age, sex, body mass index, tobacco smoking and neonatal comorbidities), we performed univariate and multivariate linear regressions for continuous parameters (including SBP, DBP, FEV_1 Z-score hemoglobin and EPO levels). For these assessments, individuals for whom data was missing were excluded from the analysis. Normality of the distribution of quantitative variables and of residuals of the linear regression models was verified visually.

We performed a mediation analysis using the "mediation" package in R[4]. Since hemoglobin and BP levels were higher in males, mediation analyses were adjusted for sex. We first tested if an association between exposure (preterm birth) and hemoglobin (as a mediator), and between the mediator and the outcome (SBP and DBP) were observed. We then used mediation analysis to estimate the direct and mediated (indirect) effects of exposure on the outcome. The proportion of the effect of the mediator on outcome was estimated by the ratio of the mediated effect over the sum of the mediated and direct effects, using non-parametric bootstrap with 1,000 Monte-Carlo simulations. P values < 0.05 were considered statistically significant.

Sensitivity analyses for missing data

Number (percent) of missing data for each measured variable in this study is provided in the tables. The number of missing data for complete blood count (n=7, 3%, due to inability to collect blood) and for blood pressure (n=5, 2%, measured but not reported in the case

report form) was very low. A higher proportion of data was missing for spirometry results (n=17, 8%) and for pulse oximetry results (n=57, 28%) due to machine unavailability during a part of the study. Thus, data was most likely missing completely at random. We restricted our main statistical analysis to participants with no missing data for the parameters of interest, since a the small proportion of participants had missing data (<5% except for spirometry) and because missing data for other parameters of interest (including spirometry) was most likely completely missing at random.

We further performed sensitivity analysis for missing data using Multivariate Imputation by Chained Equations (MICE), conducted using the "mice" package in R[5]. We performed 20 iterations of 20 imputations. Convergence and distribution of imputed data was verified visually. Pooled estimates obtained from imputations are provided in a supplemental file.

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Supplemental tables

	Preterm: no BPD (n=33)		Preterm: BPD (n=66)		P-value
	Missing n (%)	Mean (SD) or n (%)	Missing n (%)	Mean (SD) or n (%)	
Gestational age	0 (0)	27.8 ± 1.1	0 (0)	26.8 ± 1.4	0.0002
Number of red blood cells transfusions in the neonatal period	4 (12)	2.79 ± 3.96	3 (5)	8.68 ± 6.35	< 0.0001
SpO2≥95%	9 (27)	24 (100)	18 (27)	48 (100)	1.00
Spirometry					
FEV1, L	4 (12)	3.29 ± 0.78	4 (6)	3.24 ± 0.73	0.791
FEV1, percent predicted	4 (12)	93.6 ± 12.3	4 (6)	87.4 ± 12.4	0.030
FEV1, Z-score	4 (12)	-0.532 ± 1.039	4 (6)	-1.061 ± 1.047	0.028
FVC, L	4 (12)	4.2 ± 1.1	4 (6)	4.2 ± 1	0.823
FVC, percent predicted	4 (12)	101.4 ± 10.6	4 (6)	97.3 ± 11.8	0.102
FVC, Z-score	4 (12)	0.112 ± 0.879	4 (6)	-0.227 ± 0.993	0.105
FEV1/FVC	4 (12)	0.799 ± 0.094	4 (6)	0.774 ± 0.087	0.240
FEV1/FVC, Z-score	4 (12)	-0.911 ± 1.095	4 (6)	-1.216 ± 1.043	0.200
Venous blood gas					
Venous pH	5 (15)	7.38 ± 0.03	21 (32)	7.39 ± 0.03	0.458
Venous pCO_2, mmHg	5 (15)	43.3 ± 4.5	21 (32)	42.5 ± 4	0.413
Venous bicarbonate, mmol/L	5 (15)	23.7 ± 1.9	21 (32)	24.6 ± 1.7	0.038
Chronic use of asthma medication, n (%)	0 (0)	2 (6)	0 (0)	11 (17)	0.209
Systolic blood pressure, mmHg	1 (3)	119.1 ± 14.1	3 (5)	120.0 ± 13.8	0.773
Diastolic blood pressure, mmHg	1 (3)	72.6 ± 9.7	3 (5)	71.4 ± 7.9	0.563
eGFR, mL/min/1.73m2	1 (3)	117 ± 12	4 (6)	119 ± 12	0.570
Total serum protein, g/L	0 (0)	66 ± 4	6 (9)	66.9 ± 4.7	0.360

Supplemental Table 1. Clinical characteristics in individuals born preterm, according to BPD status. Results shown as mean ± SD or n (%). Comparisons were performed using Student's t tests or the Fisher exact test. FEV_1: Forced Expiratory Volume in 1 second. FVC: Forced vital capacity. eGFR: estimated glomerular filtration rate, using the CKD-Epi formula. BPD: Bronchopulmonary dysplasia (mild, moderate or severe).

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	Term			Preterm			
	Low	Normal	High	Low	Normal	High	Normal range
Hemoglobin, g/L							
Males	5 (12)	37 (88)	0 (0)	3 (7)	41 (91)	1 (2)	135-175
Females	13 (22)	47 (78)	0 (0)	7 (13)	45 (87)	0 (0)	120-160
Hematocrit, %							
Males	10 (24)	32 (76)	0 (0)	5 (11)	40 (89)	0 (0)	41-53
Females	10 (17)	50 (83)	0 (0)	6 (12)	46 (88)	0 (0)	36-46
Mean globular volume, µ	3 (3)	99 (97)	0 (0)	0 (0)	97 (100)	0 (0)	80-100
Mean corpuscular hemoglobin concentration	0 (0)	102 (100)	0 (0)	0 (0)	97 (100)	0 (0)	310-370
Red blood cell distribution width, %	0 (0)	100 (98)	2 (2)	0 (0)	96 (99)	1 (1)	11.5-14.5
Red blood cells, per mm^3							
Males	12 (29)	30 (71)	0 (0)	6 (13)	39 (87)	0 (0)	4.5-5.9
Females	18 (30)	42 (70)	0 (0)	9 (17)	43 (83)	0 (0)	4.0-5.2
Leucocytes, per mm^3	11 (11)	88 (86)	3 (3)	9 (9)	87 (90)	1 (1)	4.5-11
Neutrophils, per mm^3	4 (4)	95 (93)	3 (3)	5 (5)	91 (94)	1 (1)	1.8-7.0
Lymphocytes, per mm^3	1 (1)	98 (96)	3 (3)	0 (0)	97 (98)	2 (2)	1.0-4.0
Eosinophils, per mm^3	-	97 (95)	5 (5)	-	92 (95)	5 (5)	0.0-0.4
Basophils, per mm^3	-	101 (99)	1 (1)	-	96 (99)	1 (1)	0.0-0.1
Monocytes, per mm^3	-	100 (98)	2 (2)	-	92 (95)	5 (5)	0.0-0.9
Platelets (/mm^3)	2 (2)	100 (98)	0 (0)	2 (2)	95 (98)	0 (0)	140-440
Erythropoietin, U/L	4 (4)	95 (93)	3 (3)	3 (3)	85 (93)	4 (4)	3.3-16.6

Supplemental Table 2. Proportion of participants with laboratory values outside reference ranges. Values shown are the number n (%) of participants meeting criteria for low, normal or high complete blood count values.

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	FEV_1 Z-score < -1			FEV_1 Z-score ≥ -1		
	Term	Preterm	P-value	Term	Preterm	P-value
Hemoglobin, g/L	129.2 ± 11.2	139.8 ± 12.8	0.019	131.0 ± 11.8	136.2 ± 14.4	0.039
Erythropoietin, U/L	8.77 ± 4.47	8.76 ± 3.57	0.993	7.10 ± 3.36	7.76 ± 3.00	0.260
Soluble endoglin, ng/mL	1600 (1470, 2090)	1420 (1150, 1840)	0.298	1500 (1220, 1820)	1280 (1010, 1630)	0.009
VEGF, ng/mL	53.9 (39.2, 97)	77.4 (47.4, 113)	0.456	70.6 (38.6, 97)	71.1 (45.7, 90.5)	0.913
sFlt-1, ng/mL	213 (175, 263)	176 (153, 235)	0.617	199 (165, 230)	187 (153, 234)	0.360

Supplemental Table 3. Hemoglobin, erythropoietin and angiogenesis markers levels according to respiratory function. Results shown as mean ± SD or medians (25%-75%) and comparisons were performed using Student's t test or Mann-Whitney U test, when appropriate.

	SBP, mmHg			DBP, mmHg		
	B (unadjusted)	B (Model 1)	B (Model 2)	B (unadjusted)	B (Model 1)	B (Model 2)
Hemoglobin, g/L	0.45* (0.32, 0.58)	0.23* (0.05, 0.41)	0.20* (0.01, 0.39)	0.15* (0.07, 0.24)	0.26* (0.13, 0.38)	0.22* (0.09, 0.35)
EPO, U/L	-0.01 (-0.57, 0.54)	0.22 (-0.27, 0.72)	0.18 (-0.32, 0.67)	0.04 (-0.30, 0.38)	0.07 (-0.27, 0.41)	0.01 (-0.33, 0.35)
eGFR, 10 ml/min/1.73m^2	0.29 (-1.34, 1.92)	0.06 (-1.39, 1.50)	-0.04 (-1.48, 1.41)	0.38 (-0.61, 1.38)	0.36 (-0.64, 1.35)	0.24 (-0.74, 1.21)
Fasting glucose, mmol/L	6.48 * (2.35, 10.61)	2.79 (-1.12, 6.69)	2.72 (-1.18, 6.61)	1.41 (-1.19, 4.01)	1.12 (-1.60, 3.83)	1.02 (-1.63, 3.67)
LDL-cholesterol, mmol/L	4.10 * (1.17, 7.03)	3.59 * (0.99, 6.20)	3.74 * (1.15, 6.34)	1.63 (-0.19, 3.44)	1.57 (-0.24, 3.39)	1.76 (-0.02, 3.54)
Soluble endoglin, ng/mL	3.63* (0.33, 6.93)	-0.65 (-3.91, 2.61)	-0.34 (-3.62, 2.94)	-1.53 (-3.54, 0.47)	-2.20 (-4.39, 0.00)	-1.84 (-4.02, 0.33)
VEGF, ng/mL	-3.90 (-45.6, 37.8)	-10.2 (-46.8, 26.3)	-11.8 (-48.3, 24.8)	-10.5 (-35.8, 14.9)	-11.1 (-36.5, 14.2)	-13.05 (-38.0, 11.9)
sFlt-1, ng/mL	36.3 (-15.3, 87.9)	9.54 (-36.8, 55.9)	12.1 (-34.1, 58.3)	-4.66 (-35.3, 26.0)	-10.9 (-41.7, 20.0)	-8.56 (-39.1, 22.0)

Supplemental Table 4. Associations of hemoglobin, erythropoietin and angiogenesis markers levels with blood pressure. Estimated effect of an increase in 1 unit of hemoglobin, EPO, metabolic and angiogenesis biomarkers on systolic (SBP) and diastolic (DBP) blood pressure, obtained using univariate and multivariate linear regression. Model 1: Adjustment for sex. Model 2: Adjustment for sex and term/preterm status. Results are shown as the unstandardized regression coefficient B (95% confidence interval). * $p<0.05$.

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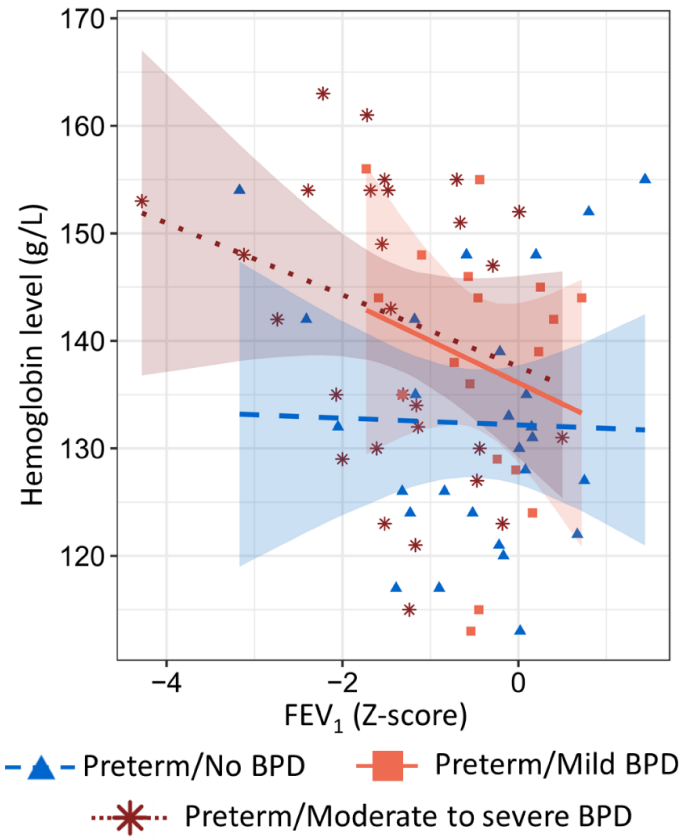
Supplemental Figures



Supplemental Figure 1. Association of hemoglobin and respiratory function in adults born preterm, according to bronchopulmonary dysplasia (BPD) status. FEV_1: Forced Expiratory Volume in 1 second. Participants using chronic asthma medication (inhaled corticosteroids including fluticasone propionate, ciclesonide, budesonide; long-acting β2 adrenergic receptor agonist including salmeterol xinafoate, formoterol fumarate; and montelukast) excluded.

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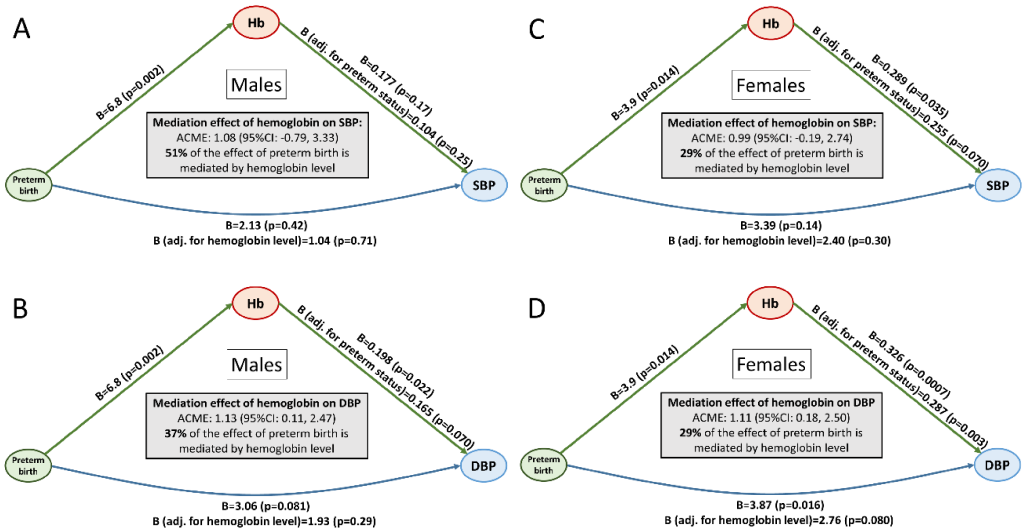

Supplemental Figure 2. Mediation analysis to assess the role of hemoglobin levels in the increase in blood pressure observed in young adults born preterm, stratified by sex. A. Systolic blood pressure (SBP), males. **B.** Diastolic blood pressure (DBP), males. **C.** SBP, females. **D.** DBP, females Hb: hemoglobin. ACME: Average Causal Mediation Effect. B: unstandardized regression coefficient. All estimations are adjusted for sex.

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Sensitivity analyses

Sensitivity analyses for missing data were conducted using multiple imputations for missing data (see supplemental methods for details concerning analysis).

Sensitivity analysis of Table 4 for missing data. Influence of neonatal comorbidities on hemoglobin and EPO levels.

Sensitivity analysis of Table 5 for missing data. Association of hemoglobin and EPO to current clinical characteristics.

Sensitivity analysis of Supplemental Table 4 for missing data. Associations of hemoglobin, erythropoietin and angiogenesis markers levels with blood pressure.

Sensitivity analysis of Figure 2 for missing data. Mediation analysis to assess the participation of hemoglobin levels to the increase in blood pressure observed in young adults born preterm.

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	Hemoglobin, g/L		Erythropoietin, U/L		
	B (unadjusted)	B (Model 1)	B (unadjusted)	B (Model 1)	B (Model 2)
Term					
Birth weight percentile (per 1% increase)‡	-0.02 (-0.12, 0.08)	0.01 (-0.06, 0.08)	0.02 (-0.01, 0.04)	0.01 (-0.01, 0.04)	0.02 (-0.01, 0.04)
Preeclampsia	3.2 (-6.49, 12.89)	2.99 (-3.86, 9.83)	-0.92 (-3.63, 1.8)	-0.9 (-3.63, 1.84)	-0.58 (-3.24, 2.08)
Preterm					
Gestational age	-0.12 (-2.11, 1.86)	-0.14 (-1.41, 1.13)	0.21 (-0.32, 0.74)	0.21 (-0.31, 0.72)	0.2 (-0.32, 0.71)
Birth weight percentile (per 1% increase)‡	0.16 * (0.00, 0.31)	0.01 (-0.1, 0.11)	0.01 (-0.03, 0.06)	0.03 (-0.02, 0.07)	0.03 (-0.02, 0.07)
Preeclampsia	0.30 (-6.19, 6.79)	1.73 (-2.46, 5.93)	-1.28 (-3.02, 0.45)	-1.53 (-3.22, 0.17)	-1.46 (-3.16, 0.25)
Antenatal corticosteroids	-2.24 (-7.7, 3.22)	0.38 (-3.12, 3.88)	-0.73 (-2.21, 0.75)	-1.03 (-2.51, 0.44)	-1.02 (-2.49, 0.46)
Neonatal oxygen supplementation (per 10 days)	0.81 * (0.3, 1.33)	0.46 * (0.11, 0.81)	-0.08 (-0.22, 0.06)	-0.08 (-0.22, 0.07)	-0.06 (-0.21, 0.09)
Red blood cells transfusions (per 5 transfusions)	3.42 * (1.35, 5.49)	1.71 * (0.36, 3.06)	-0.33 (-0.9, 0.24)	-0.21 (-0.78, 0.37)	-0.14 (-0.73, 0.46)

Sensitivity analysis of Table 4 for missing data. Influence of neonatal comorbidities on hemoglobin and EPO levels. Estimated effects of antenatal factors on hemoglobin and erythropoietin levels, obtained using univariate and multivariate linear regression with imputation of missing data. Model 1: adjustment for sex and tobacco use. Model 2: adjustment for sex, tobacco use and hemoglobin level. ‡ birth weight percentiles according to Hadlock (preterm group) or Kramer (term group). Results are shown as the unstandardized regression coefficient B (95% confidence interval).* $p<0.05$

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	Hemoglobin, g/L		Erythropoietin, U/L		
	B (unadjusted)	B (Model 1)	B (unadjusted)	B (Model 1)	B (Model 2)
Male sex	19.4 * (16.84, 21.96)	-	-0.98 * (-1.99, 0.02)	-	-
Preterm birth	6.27 * (2.69, 9.86)	5.47 * (3.04, 7.89)	0.84 (-0.17, 1.85)	0.9 (-0.11, 1.91)	1.34 * (0.3, 2.38)
Body Mass Index, kg/m^2	0.30 (-0.14, 0.75)	0.18 (-0.13, 0.48)	0.07 (-0.05, 0.19)	0.08 (-0.04, 0.2)	0.09 (-0.03, 0.21)
Age, year	0.32 (-0.47, 1.10)	-0.05 (-0.6, 0.49)	0.20 (-0.01, 0.41)	0.23 * (0.02, 0.43)	0.22 * (0.02, 0.43)
Current tobacco smoking	7.47 * (3.05, 11.88)	3.78 * (0.62, 6.95)	-0.79 (-1.99, 0.41)	-0.62 (-1.82, 0.59)	-0.4 (-1.61, 0.82)
Number of days since last periods†	0.04 (-0.24, 0.32)	-	0.01 (-0.04, 0.06)	-	-
eGFR, 10 $mL/min/1.73m^2$	-0.31 (-1.85, 1.24)	-0.66 (-1.71, 0.4)	0.3 (-0.14, 0.74)	0.32 (-0.12, 0.76)	0.29 (-0.15, 0.73)
Fasting glucose, mmol/L	4.97 * (0.94, 9.01)	-1.02 (-3.98, 1.94)	-1.21 * (-2.39, -0.03)	-0.98 (-2.18, 0.22)	-1.04 (-2.24, 0.16)
LDL-cholesterol, mmol/L	1.37 (-1.6, 4.34)	0.64 (-1.44, 2.71)	-0.52 (-1.31, 0.28)	-0.48 (-1.27, 0.31)	-0.45 (-1.23, 0.34)

Sensitivity analysis of Table 5 for missing data. Association of hemoglobin and EPO to current clinical characteristics. Estimated effects of current clinical characteristics on hemoglobin and erythropoietin levels, obtained using univariate and multivariate linear regression with imputation of missing data. Model 1: Adjusted for sex. Model 2: Adjusted for sex and hemoglobin level. Results are shown as the unstandardized regression coefficient B (95% confidence interval); eGFR: estimated Glomerular Filtration Rate. † females only, no adjustment for sex * $p<0.05$.

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	SBP, mmHg			DBP, mmHg		
	B (unadjusted)	B (Model 1)	B (Model 2)	B (unadjusted)	B (Model 1)	B (Model 2)
Hemoglobin, g/L	0.43 * (0.31, 0.56)	0.24 * (0.06, 0.43)	0.21 * (0.02, 0.40)	0.15 * (0.07, 0.23)	0.26 * (0.14, 0.38)	0.22 * (0.1, 0.35)
EPO, U/L	-0.01 (-0.54, 0.51)	0.22 (-0.26, 0.7)	0.16 (-0.32, 0.65)	0.08 (-0.25, 0.41)	0.1 (-0.24, 0.43)	0.03 (-0.30, 0.36)
eGFR, 10 mL/min/1.73m^2	0.25 (-1.34, 1.84)	0.06 (-1.38, 1.51)	-0.05 (-1.49, 1.39)	0.36 (-0.64, 1.36)	0.35 (-0.65, 1.34)	0.21 (-0.77, 1.19)
Fasting glucose, mmol/L	6.38 * (2.35, 10.41)	3.06 (-0.83, 6.96)	3.02 (-0.83, 6.88)	1.46 (-1.12, 4.04)	1.28 (-1.42, 3.97)	1.23 (-1.39, 3.85)
LDL-cholesterol, mmol/L	3.97 * (1.10, 6.84)	3.52 * (0.91, 6.13)	3.68 * (1.1, 6.27)	1.53 (-0.3, 3.37)	1.5 (-0.34, 3.34)	1.69 (-0.09, 3.47)
Soluble endoglin, ng/mL	3.25 * (0.22, 6.27)	-0.89 (-3.94, 2.16)	-0.58 (-3.61, 2.46)	-1.66 (-3.54, 0.22)	-2.4 * (-4.48, -0.32)	-2.05 (-4.07, -0.03)
VEGF, ng/mL	-3.39 (-43.0, 36.2)	-10.71 (-47.1, 25.7)	-12.56 (-48.6, 23.5)	-9.95 (-34.2, 14.3)	-10.56 (-34.9, 13.8)	-12.73 (-36.4, 11.0)
sFlt-1, ng/mL	36.8 (-8.87, 82.5)	14.57 (-27.5, 56.6)	16.71 (-26.0, 59.5)	-10.68 (-39.8, 18.4)	-12.96 (-43.1, 17.2)	-10.65 (-40.5, 19.2)

Sensitivity analysis of Supplemental Table 4 for missing data. Associations of hemoglobin, erythropoietin and angiogenesis markers levels with blood pressure. Estimated effect of an increase in 1 unit of hemoglobin, EPO and angiogenesis biomarkers on systolic (SBP) and diastolic (DBP) blood pressure, obtained using univariate and multivariate linear regression with imputation of missing data. Model 1: Adjustment for sex. Model 2: Adjustment for sex and term/preterm status. Results are shown as the unstandardized regression coefficient B (95% confidence interval). * $p<0.05$.

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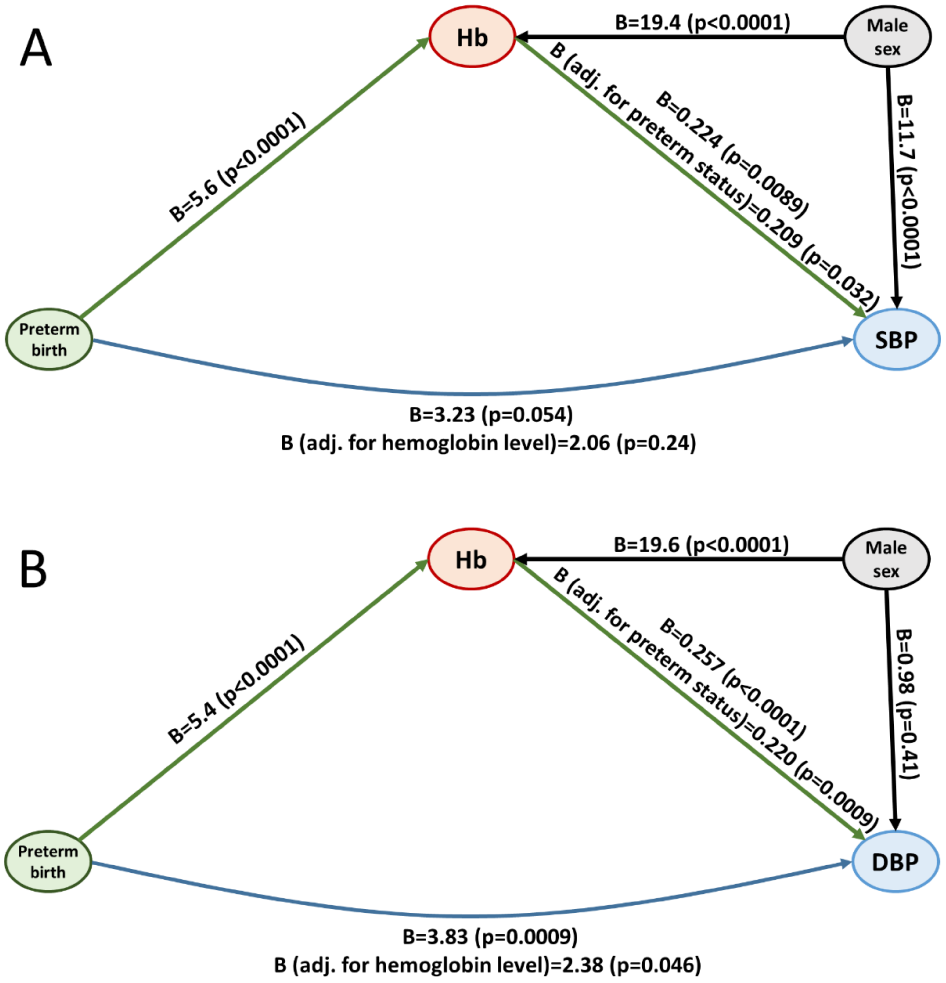

Sensitivity analysis of Figure 2 for missing data. Mediation analysis to assess the participation of hemoglobin levels to the increase in blood pressure observed in young adults born preterm. Results obtained using univariate and multivariate linear regression with imputation of missing data A. Systolic blood pressure (SBP). B. Diastolic blood pressure (DBP). Hb: hemoglobin. B: unstandardized regression coefficient. All estimations are adjusted for sex.

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