Detection of anaemia from retinal fundus images via deep learning

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Supplementary information

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Supplementary methods

We trained each model on a single Google TPUv2 unit (8 cores across 4 chips, 8 GB memory per core, 180 teraFLOPS in total) with the following hyperparameters:
– Inception-v4 architecture
– Input image resolution: 587 × 587
– Learning rate: 0.0008
     – Learning rate was initially 0.0001, and linearly increased at each step until it reached 0.0008 after 3 epochs[59].
– Batch size: 64 (8 per core, and 8 cores ran synchronously)
– Batch size for batch normalization: 8 (batch normalization was performed at each core)
– Weight decay: 0.00004
– Mini-batch stochastic gradient descent optimizer with momentum[58]
– Data augmentation (in order):
  • Random vertical and horizontal reflections
  • Random brightness changes with a max delta of 0.1147528
  • Random saturation changes between 0.5597273 and 1.2748845
  • Random hue changes between -0.0251488 and 0.0251488
  • Random contrast changes between 0.9996807 and 1.7704824
– For classification tasks, each class was weighted in proportion to the number of examples of the class to the power of -0.9.
– Model evaluations were performed using a running average of parameters, with an exponential decay factor of 0.9999.

Table S1. Prediction of complete blood count components.

The metadata-only model, the fundus-only model, and the combined model were trained to predict all the complete blood components. Note that the difference from Figure 1 is due to being trained for additional components at the same time and using a smaller subset of subjects who had all the components measured. R^2, coefficient of determination.

Complete blood count components	R^2			Mean absolute error			
	Metadata-only	Fundus-only	Combined	Metadata-only	Fundus-only	Combined	unit
Hemooglobin concentration	0.43 (0.41-0.44)	0.51 (0.50-0.52)	0.52 (0.51-0.53)	0.95 (0.93-0.96)	0.69 (0.68-0.70)	0.67 (0.66-0.68)	g/dL
Hemoatocrit percentage	0.41 (0.40-0.42)	0.47 (0.46-0.48)	0.49 (0.48-0.50)	2.70 (2.66-2.74)	2.02 (1.99-2.05)	1.96 (1.93-1.99)	%
Red blood cell count	0.32 (0.31-0.33)	0.35 (0.34-0.36)	0.36 (0.34-0.37)	0.34 (0.33-0.34)	0.26 (0.25-0.26)	0.26 (0.25-0.26)	10^{12}/L
High light scatter reticulocyte count	0.18 (0.16-0.19)	0.05 (0.04-0.06)	0.18 (0.17-0.20)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)	10^{12}/L
Reticulocyte count	0.16 (0.15-0.17)	0.05 (0.04-0.06)	0.17 (0.15-0.18)	0.02 (0.02-0.02)	0.02 (0.02-0.02)	0.02 (0.02-0.02)	10^{12}/L
High light scatter reticulocyte percentage	0.14 (0.13-0.16)	0.03 (0.02-0.04)	0.15 (0.13-0.16)	0.20 (0.19-0.21)	0.15 (0.15-0.16)	0.14 (0.14-0.15)	%
Mean corpuscular haemooglobin	0.11 (0.09-0.12)	0.09 (0.08-0.11)	0.12 (0.11-0.14)	1.79 (1.73-1.85)	1.29 (1.26-1.31)	1.27 (1.24-1.29)	pg
Neutrophill count	0.11 (0.10-0.12)	0.04 (0.03-0.05)	0.12 (0.11-0.13)	1.33 (1.30-1.36)	1.08 (1.06-1.10)	1.00 (0.99-1.02)	10^9/L
Immature reticulocyte fraction	0.12 (0.11-0.13)	0.04 (0.03-0.04)	0.12 (0.11-0.13)	0.06 (0.06-0.06)	0.05 (0.05-0.05)	0.04 (0.04-0.05)	ratio
Reticulocyte percentage	0.12 (0.10-0.13)	0.01 (0.00-0.02)	0.12 (0.10-0.13)	0.49 (0.48-0.51)	0.39 (0.38-0.40)	0.37 (0.36-0.38)	%
Mean corpuscular volume	0.11 (0.09-0.12)	0.07 (0.06-0.08)	0.12 (0.10-0.13)	4.35 (4.24-4.47)	3.26 (3.20-3.32)	3.17 (3.11-3.23)	fL
Platelet crit	0.11 (0.10-0.12)	0.07 (0.06-0.08)	0.12 (0.10-0.13)	0.04 (0.04-0.04)	0.03 (0.03-0.03)	0.03 (0.03-0.03)	%
Lymphocyte percentage	0.09 (0.08-0.10)	0.04 (0.02-0.05)	0.09 (0.08-0.10)	7.27 (7.14-7.41)	5.81 (5.72-5.90)	5.64 (5.55-5.73)	%
Platelet count	0.09 (0.08-0.10)	0.04 (0.03-0.05)	0.09 (0.08-0.10)	52.89 (51.86-53.94)	41.34 (40.69-42.00)	40.19 (39.58-40.83)	10^9/L
White blood cell count	0.08 (0.04-0.12)	0.03 (0.02-0.05)	0.08 (0.04-0.13)	2.16 (1.71-2.78)	1.41 (1.38-1.44)	1.31 (1.28-1.35)	10^9/L
Neutrophill percentage	0.07 (0.06-0.08)	0.02 (0.01-0.03)	0.07 (0.06-0.08)	8.24 (8.09-8.39)	6.56 (6.46-6.66)	6.38 (6.28-6.47)	%
Red blood cell distribution width	0.03 (0.02-0.04)	0.08 (0.07-0.10)	0.07 (0.06-0.08)	0.99 (0.95-1.04)	0.65 (0.64-0.66)	0.64 (0.63-0.65)	%
Mean sphered cell volume	0.07 (0.06-0.07)	-0.00 (-0.01-0.01)	0.07 (0.06-0.08)	5.10 (4.99-5.21)	4.12 (4.06-4.18)	3.91 (3.84-3.97)	fL
Mean corpuscular haemoglobin concentration	0.05 (0.04-0.06)	0.06 (0.05-0.07)	0.06 (0.05-0.07)	0.79 (0.74-0.85)	0.56 (0.55-0.57)	0.56 (0.55-0.57)	g/dL
Monocyte count	0.06 (0.04-0.07)	0.03 (0.02-0.04)	0.06 (0.04-0.08)	0.20 (0.18-0.22)	0.13 (0.13-0.13)	0.12 (0.12-0.13)	10^9/L
Monocyte percentage	0.04 (0.03-0.05)	0.02 (0.01-0.02)	0.04 (0.03-0.06)	2.60 (2.30-2.93)	1.63 (1.60-1.68)	1.59 (1.56-1.63)	%
Platelet distribution width	0.03 (0.02-0.04)	0.02 (0.02-0.03)	0.03 (0.03-0.04)	0.51 (0.50-0.52)	0.40 (0.39-0.41)	0.40 (0.39-0.40)	%
Nucleated red blood cell percentage	0.02 (0.01-0.03)	-0.01 (-0.02-0.00)	0.02 (0.01-0.03)	0.34 (0.27-0.41)	0.05 (0.04-0.06)	0.06 (0.05-0.07)	%
Mean reticulocyte volume	0.02 (0.01-0.03)	0.00 (-0.01-0.01)	0.02 (0.02-0.03)	8.05 (7.87-8.25)	6.21 (6.11-6.32)	6.12 (6.02-6.22)	fL
Nucleated red blood cell count	0.02 (0.01-0.03)	-0.02 (-0.03--0.01)	0.02 (0.01-0.03)	0.02 (0.02-0.03)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	10^9/L
Eosinophill count	0.02 (0.01-0.03)	0.01 (0.01-0.02)	0.02 (0.01-0.03)	0.13 (0.12-0.14)	0.09 (0.09-0.09)	0.09 (0.08-0.09)	10^9/L
Eosinophill percentage	0.01 (0.01-0.02)	0.00 (0.00-0.01)	0.01 (0.01-0.02)	1.72 (1.65-1.79)	1.22 (1.20-1.25)	1.20 (1.18-1.23)	%
Lymphocyte count	0.02 (0.00-0.07)	0.00 (-0.00-0.02)	0.01 (0.00-0.07)	1.44 (0.72-2.22)	0.52 (0.49-0.55)	0.50 (0.48-0.53)	10^9/L
Mean platelet volume	0.01 (0.01-0.02)	0.01 (0.00-0.01)	0.01 (0.01-0.02)	1.08 (1.06-1.10)	0.85 (0.84-0.87)	0.85 (0.83-0.86)	fL
Basophill count	0.01 (0.00-0.01)	0.00 (0.00-0.01)	0.01 (0.01-0.01)	0.05 (0.05-0.06)	0.03 (0.02-0.03)	0.02 (0.02-0.03)	10^9/L
Basophill percentage	0.00 (0.00-0.01)	0.00 (0.00-0.00)	0.00 (0.00-0.01)	0.70 (0.61-0.79)	0.34 (0.32-0.35)	0.33 (0.32-0.34)	%

a Metadata-only, ICC=0.57 (0.55, 0.58), slope=-0.56 (-0.58, -0.54), MAE=2.10 (2.07-2.13)

+1.96 SD: 5.46, (5.31, 5.63)
mean: 0.09, (0.04, 0.14)
-1.96 SD: -5.29, (-5.44, -5.16)

b Fundus-only, ICC=0.66 (0.64, 0.67), slope=-0.45 (-0.48, -0.43), MAE=1.94 (1.91-1.97)

+1.96 SD: 4.94, (4.80, 5.12)
mean: 0.06, (0.02, 0.10)
-1.96 SD: -4.82, (-4.98, -4.70)

c Combined, ICC=0.71 (0.70, 0.72), slope=-0.33 (-0.35, -0.31), MAE=1.83 (1.80-1.86)

+1.96 SD: 5.02, (4.88, 5.21)
mean: 0.46, (0.42, 0.50)
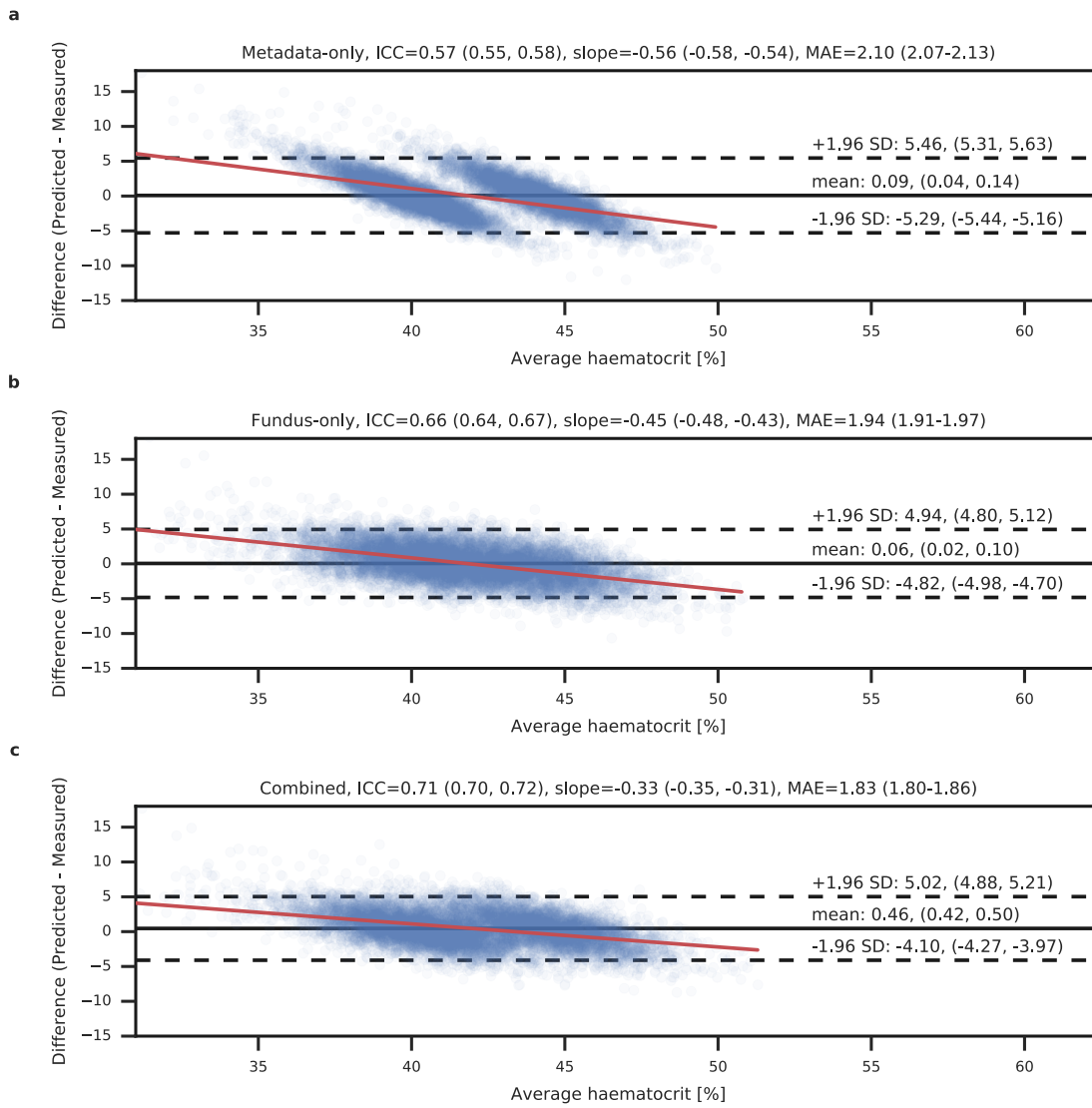-1.96 SD: -4.10, (-4.27, -3.97)

Figure S1. Bland-Altman plot for predicted and measured haematocrit.
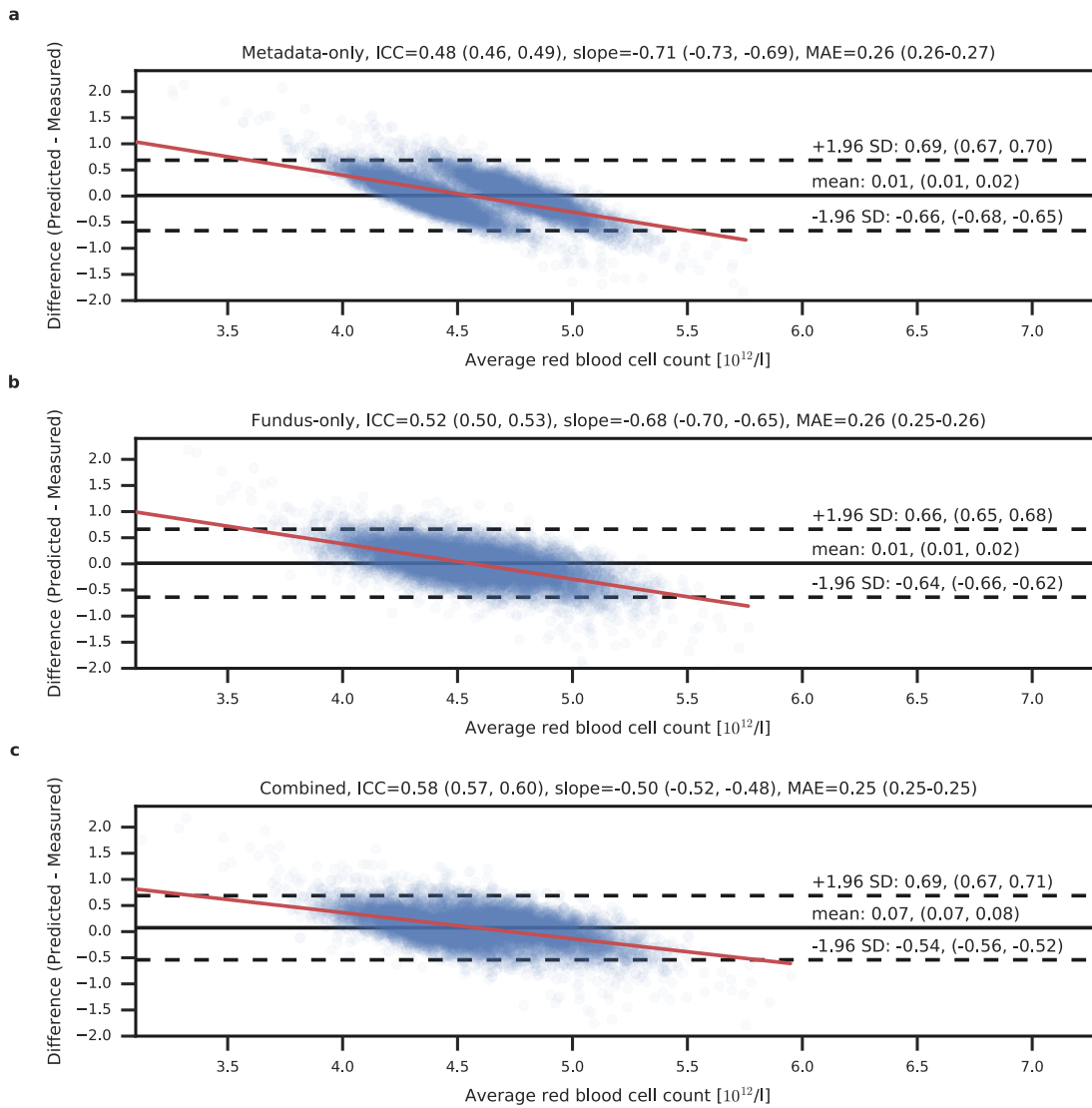Same as Figure 1 but for haematocrit.

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Figure S2. Bland-Altman plot for predicted and measured red blood cell count. Same as Figure 1 but for red blood cell count.
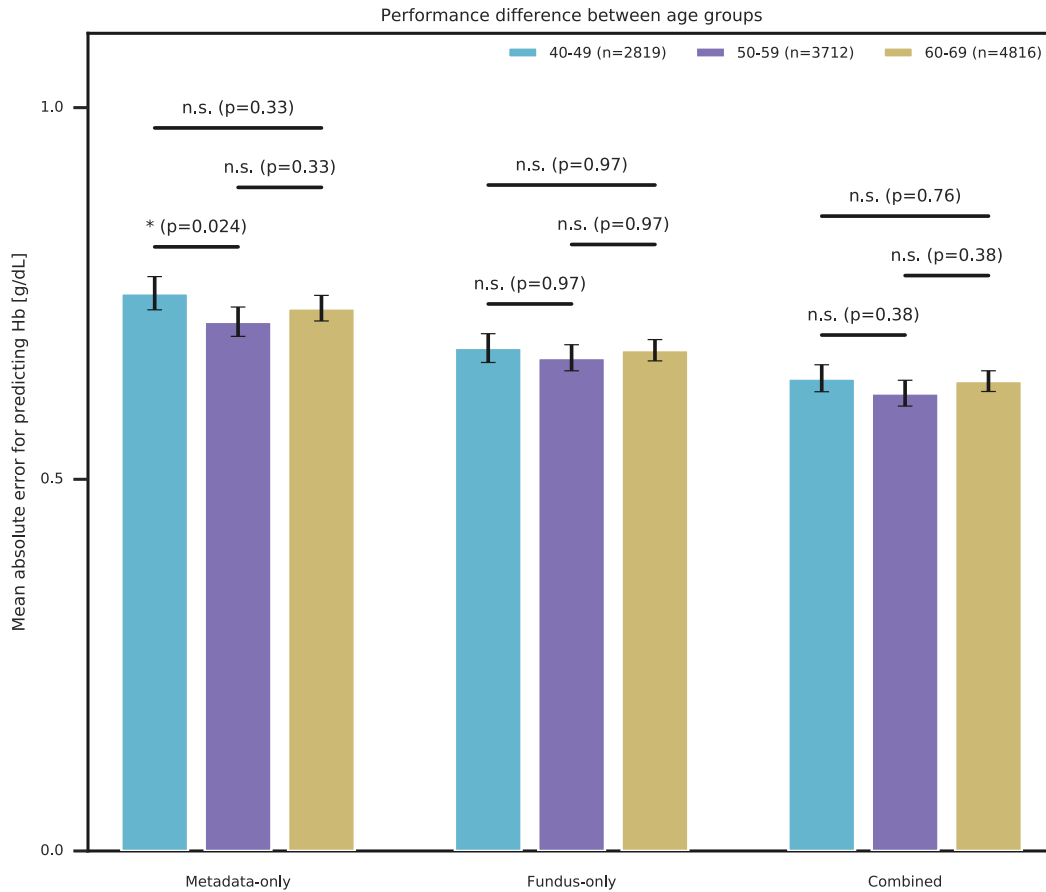
Figure S3. Performance difference in regression tasks between age groups.

Pairwise comparisons between age groups were conducted for each model with the bootstrap method (two-sided), and p-values were corrected for multiple comparisons with the Holm-bonferroni method. Error bars, 95% confidence interval (bootstrap method). *, statistically significant ($p < 0.05$). n.s., not statistically significant. Hb, haemoglobin concentration.

a

Metadata-only, ICC=0.49 (0.43, 0.54), slope=-0.68 (-0.76, -0.61), MAE=0.85 (0.79-0.90)

+1.96 SD: 2.29, (2.12, 2.47)

mean: 0.19, (0.10, 0.29)

-1.96 SD: -1.91, (-2.07, -1.75)

b

Fundus-only, ICC=0.63 (0.59, 0.67), slope=-0.52 (-0.59, -0.45), MAE=0.74 (0.69-0.79)

+1.96 SD: 1.90, (1.76, 2.04)

mean: 0.06, (-0.02, 0.14)

-1.96 SD: -1.78, (-1.92, -1.65)

c

Combined, ICC=0.66 (0.61, 0.70), slope=-0.45 (-0.51, -0.39), MAE=0.73 (0.68-0.78)

+1.96 SD: 2.00, (1.86, 2.16)

mean: 0.25, (0.17, 0.33)
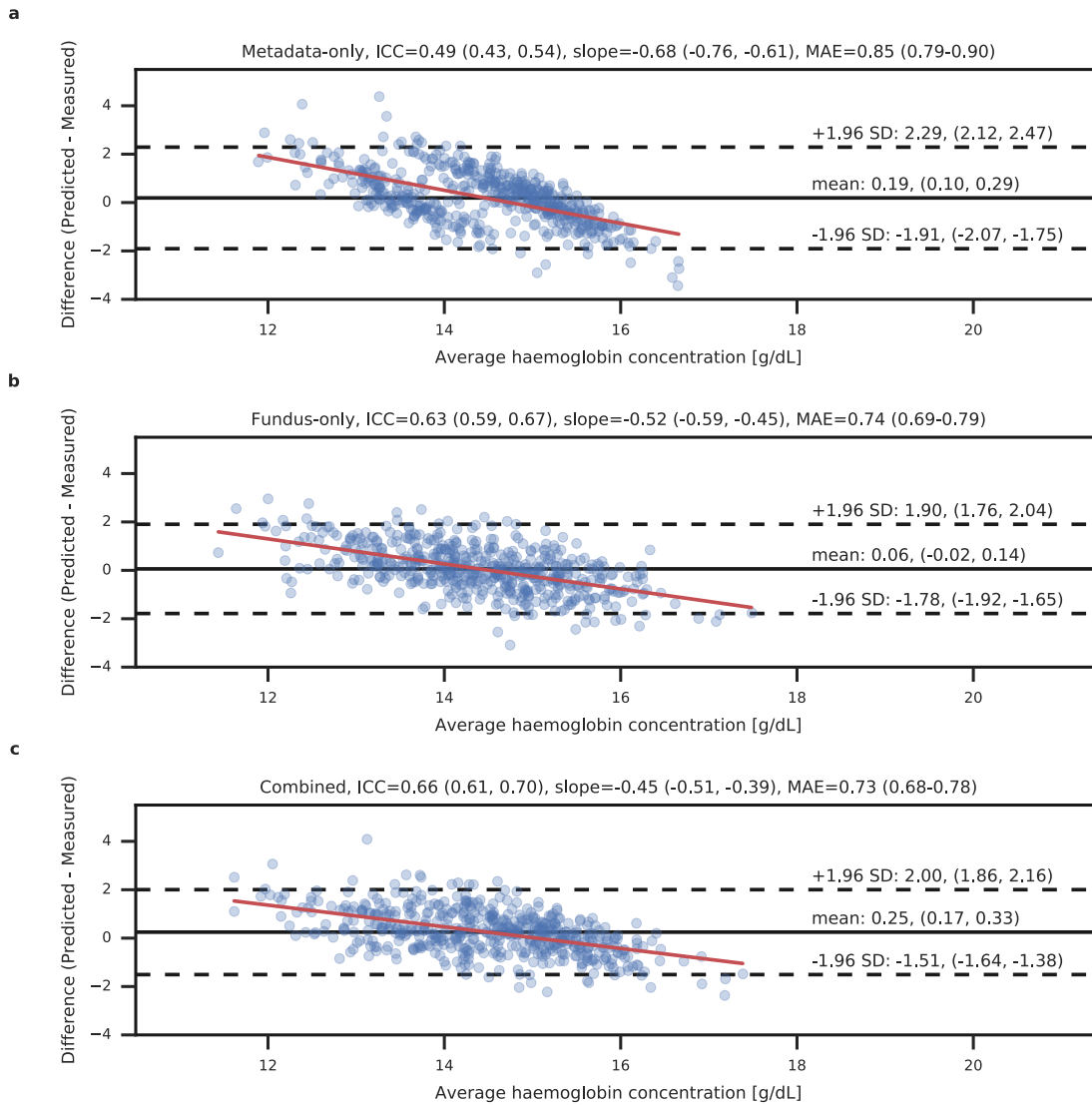
-1.96 SD: -1.51, (-1.64, -1.38)

Figure S4. Bland-Altman plot for predicted and measured haemoglobin concentration in a subgroup with self-reported diabetes.

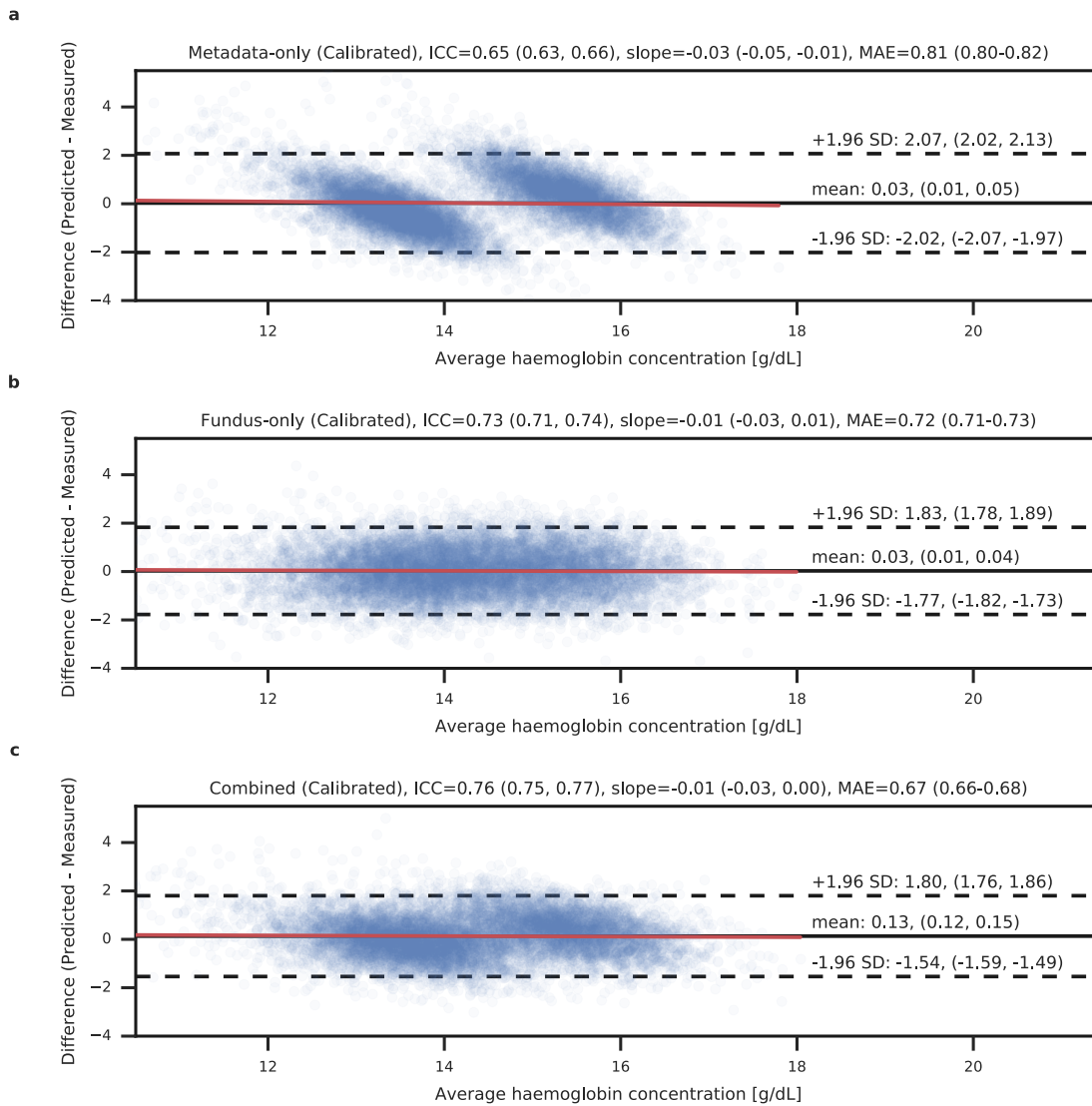Same as Figure 1, but applied to a subgroup with self-reported diabetes (n=539).

a Metadata-only (Calibrated), ICC=0.65 (0.63, 0.66), slope=-0.03 (-0.05, -0.01), MAE=0.81 (0.80-0.82)

+1.96 SD: 2.07, (2.02, 2.13)
mean: 0.03, (0.01, 0.05)
-1.96 SD: -2.02, (-2.07, -1.97)

b Fundus-only (Calibrated), ICC=0.73 (0.71, 0.74), slope=-0.01 (-0.03, 0.01), MAE=0.72 (0.71-0.73)

+1.96 SD: 1.83, (1.78, 1.89)
mean: 0.03, (0.01, 0.04)
-1.96 SD: -1.77, (-1.82, -1.73)

c Combined (Calibrated), ICC=0.76 (0.75, 0.77), slope=-0.01 (-0.03, 0.00), MAE=0.67 (0.66-0.68)

+1.96 SD: 1.80, (1.76, 1.86)
mean: 0.13, (0.12, 0.15)
-1.96 SD: -1.54, (-1.59, -1.49)

Figure S5. Bland-Altman plot for predicted and measured haemoglobin concentration after calibrating the model output.

Same as Figure 1, but the model output was calibrated to have the same mean and standard deviation to the measured values. Calibration was determined using the tune set.
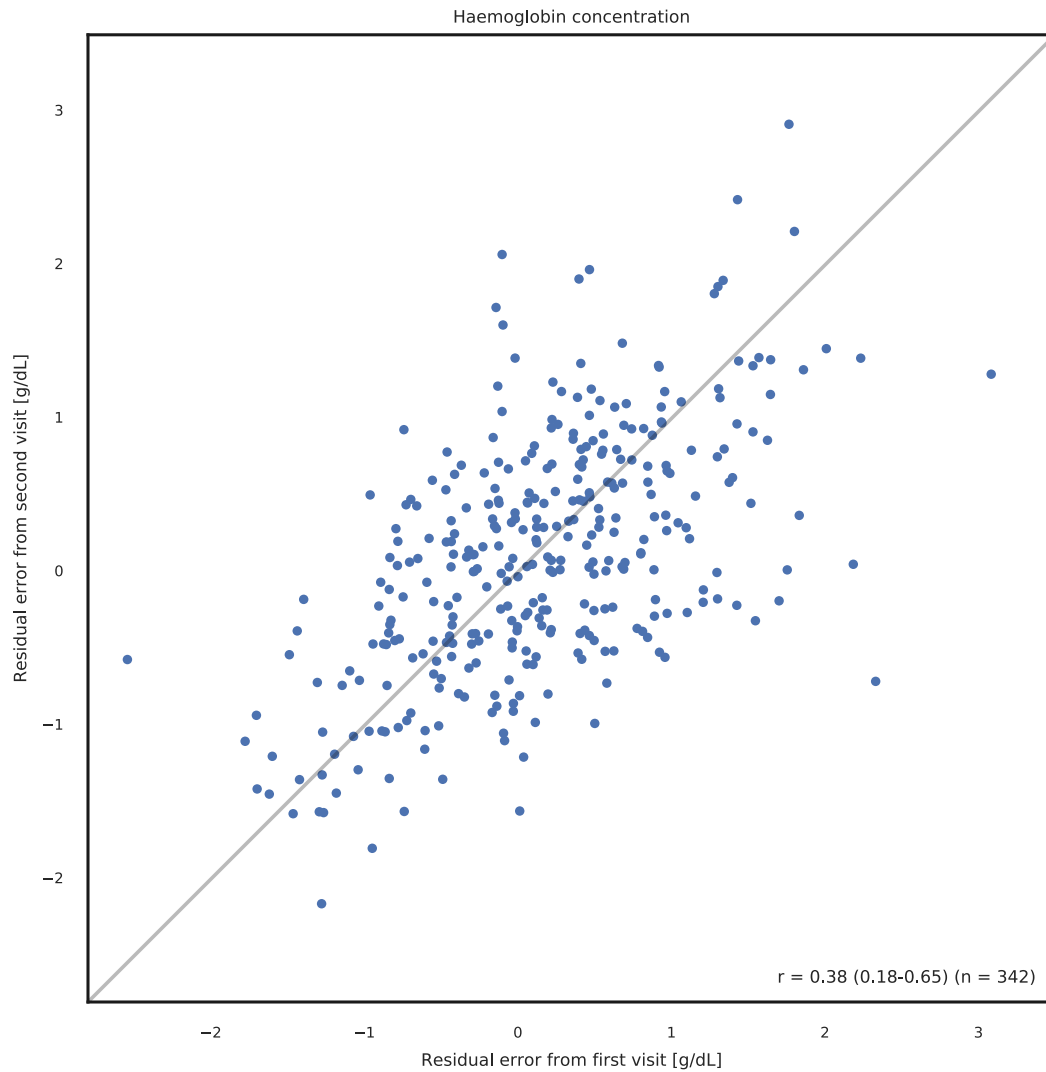
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Figure S6. Correlation between residual errors of the combined model from multiple visits.

Each blue dot represents each subject that had multiple visits with fundus photographs in this dataset (n=342). Residual error is the difference between measured haemoglobin concentration and prediction by the combined model. Gray line represents the identity line. Pearson's correlation coefficient r = 0.38 (95% confidence interval: 0.18-0.65).
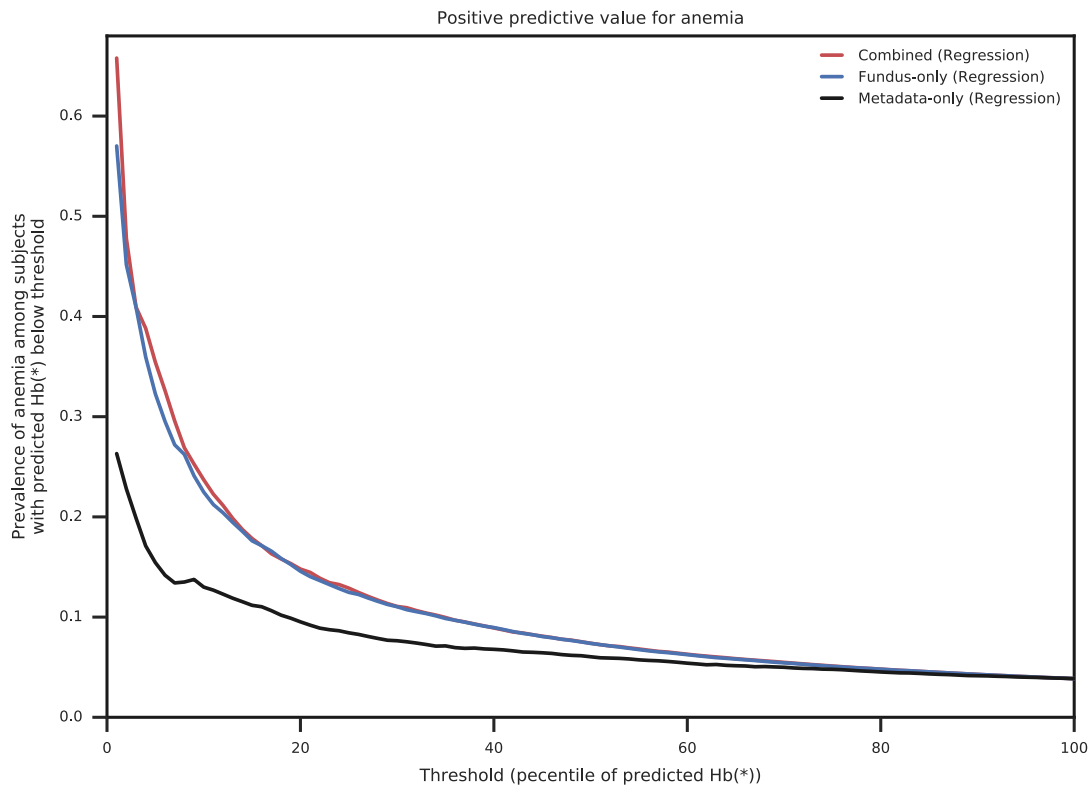
Figure S7. Positive predictive value curves for anemia by regression models.

Positive predictive value curves for anemia by the metadata-only model (black line), the fundus-only model (blue line), and the combined model (red line). (*) 1 [g/dL] was added to predicted haemoglobin concentration (Hb) of female subjects to account for the World Health Organization's threshold difference.
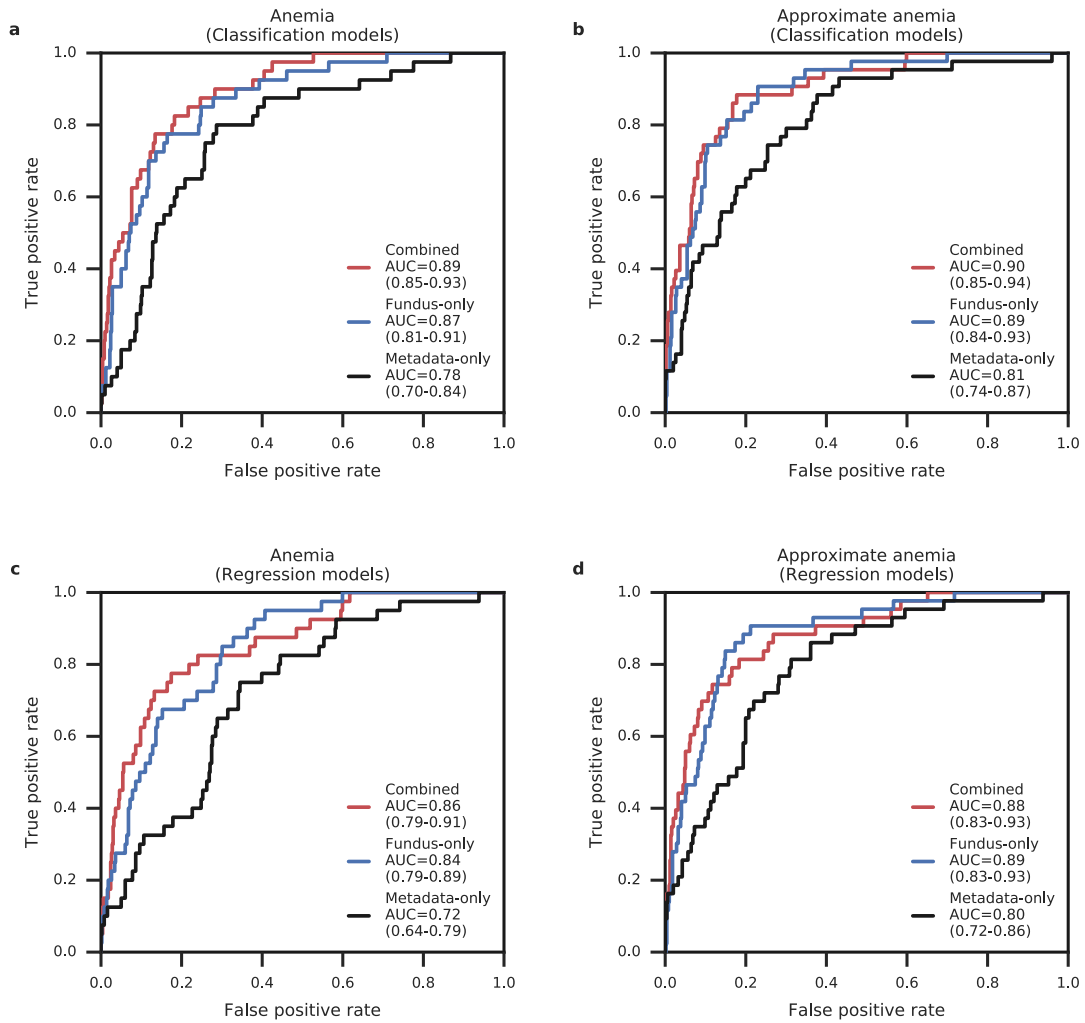
Figure S8. Prediction of anemia classifications in a subgroup with self-reported diabetes.

Prediction of anemia classifications similar to Figure 2, but applied to a subgroup with self-reported diabetes (n=539). There were no subjects who met the moderate anemia cutoff in this subgroup.