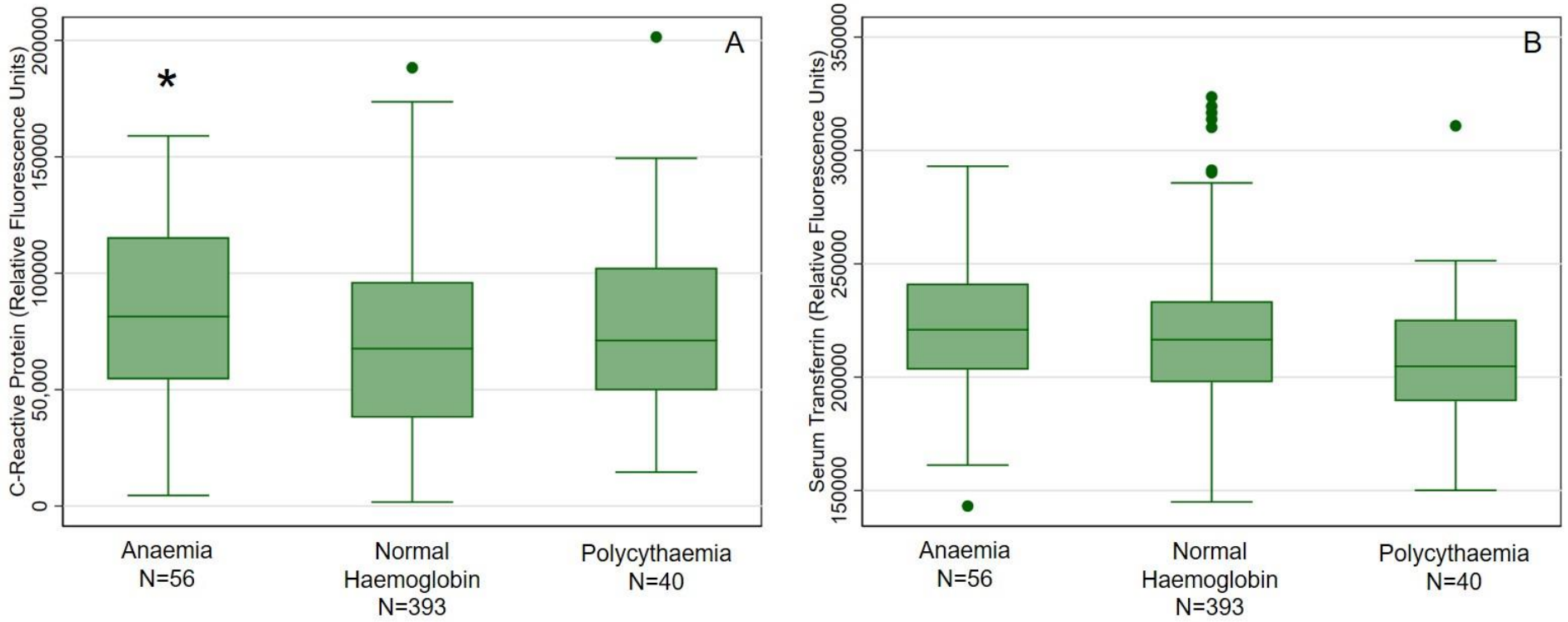
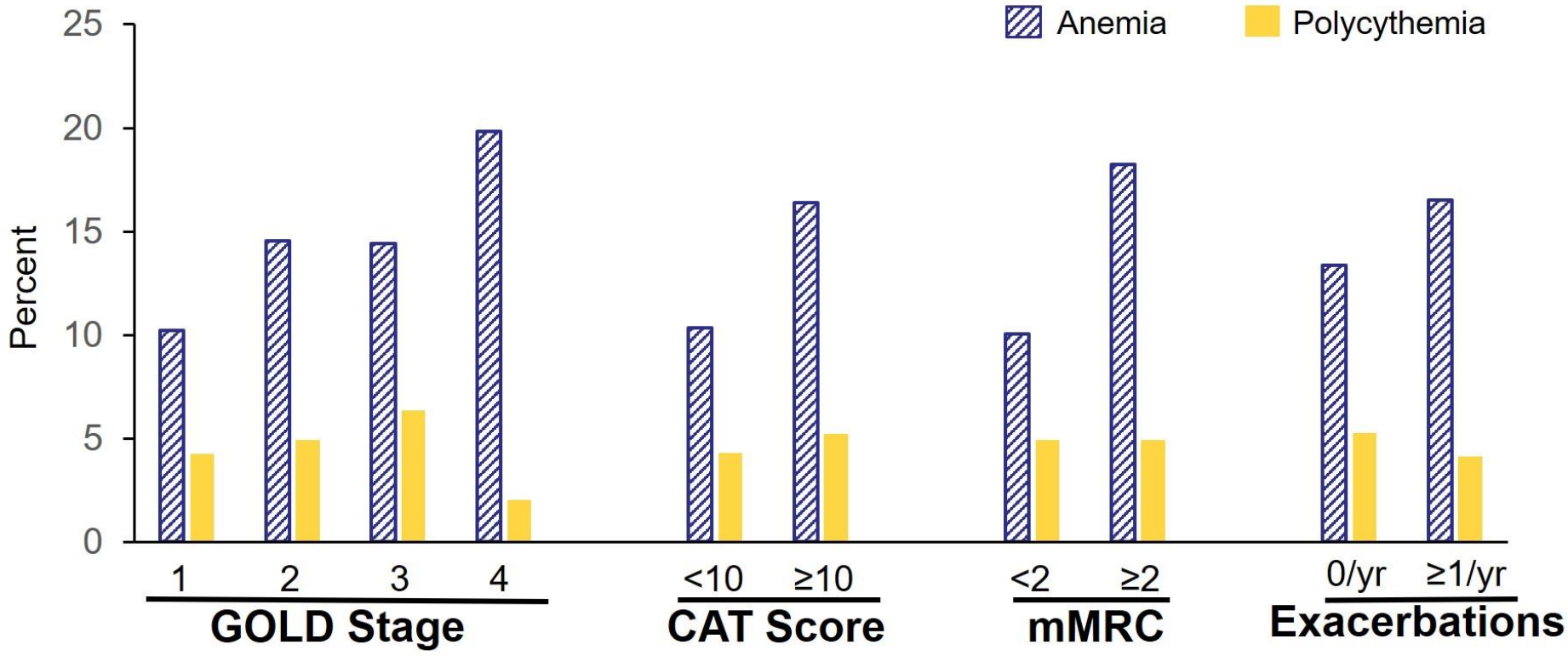
Supplemental Figure 1. Distributions of C-reactive protein and transferrin by Anaemia, Normal Haemoglobin, and Polycythaemia groups



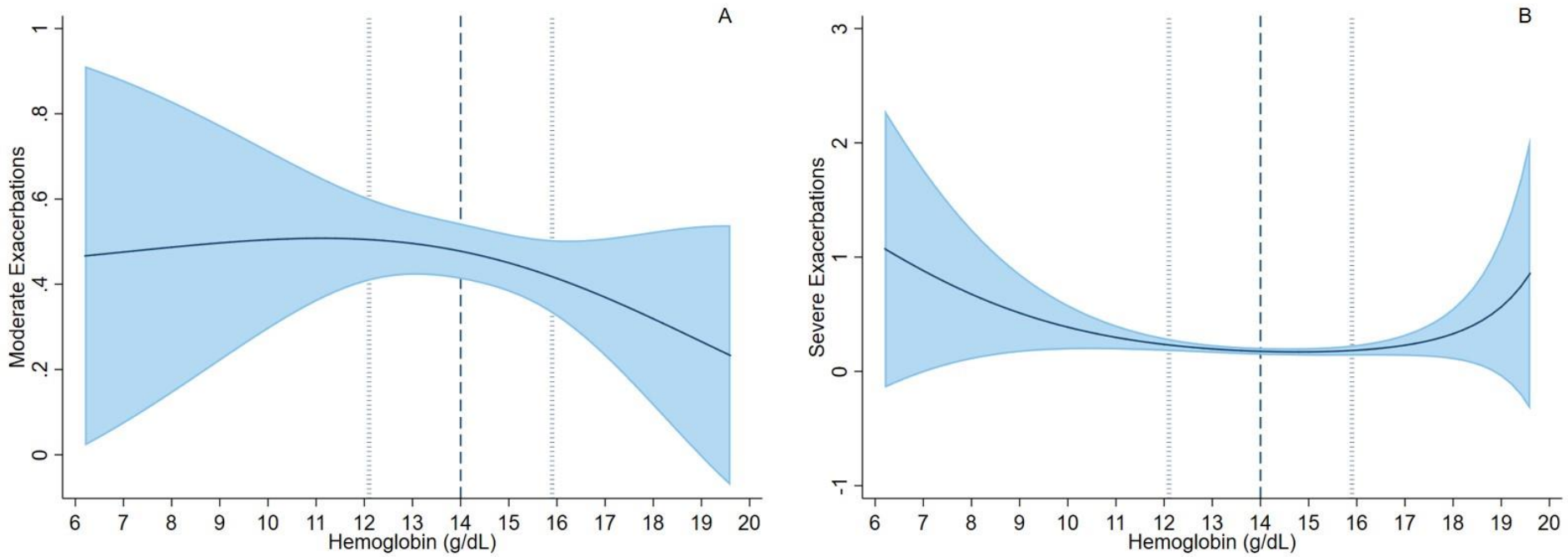
Proteomic analyses using SOMAScan assay performed in a subset of individuals. Panel A describing distributions of C-reactive protein and Panel B with distributions of Serum Transferrin. * represents $p<0.05$ for comparison to Normal Haemoglobin group.

Supplemental Figure 2. Increasing Prevalence of Anaemia by COPD Disease Severity



Blue dashed bars represent prevalence of anaemia, while solid filled yellow bars represent prevalence of polycythaemia. *GOLD Stage = spirometry stages established by Global Obstructive Lung Disease Committee, CAT = COPD Assessment Test score, mMRC = modified medical research council score*

Supplemental Figure 3. Moderate and Severe Exacerbations across Haemoglobin range



Models adjusted for age, sex, ethnicity, education, pack-years smoked, smoking status, BMI, CHF, HTN, DM, CKD, FEV1 % predicted, DLCO % predicted, and percent emphysema.

Supplemental Table 1. Micro-, Normo-, and Macrocytosis Percentages by Anaemia, Normal Haemoglobin, and Polycythaemia groups

	Anaemia (N=366)	**Normal Haemoglobin (N=2048)**	**Polycythaemia (N=125)**
Microcytosis	42 (11)	35 (2)	0 (0)
Normocytosis	306 (84)	1905 (93)	113 (90)
Macrocytosis	18 (5)	108 (5)	12 (10)

Cells are N (% of column). 77 (3%) of participants were microcytic, 2324 (92%) normocytic, and 138 (5%) macrocytic. χ^2 = 108.9, p<0.001. Microcytosis was defined as a mean corpuscular volume<80 fL, normocytosis as 80-100 fL, and macrocytosis as >100 fL.

Supplemental Table 2. Sensitivity analysis of associations between Anaemia or Polycythaemia with clinical outcomes among only normocytic individuals

	Anaemia (N=188)		**Polycythaemia (N=85)**	
	β (95% CI)	p-value	β (95% CI)	p-value
CAT Score	1.04 (-0.07 – 2.15)	0.068	-0.48 (-2.05 – 1.1)	0.56
mMRC Dyspnea Score	0.22 (0.04 – 0.39)	0.015	0.09 (-0.15 – 0.35)	0.45
SGRQ Score	3.17 (0.60 – 5.73)	0.016	0.53 (-3.12 – 4.17)	0.78
SF-36 General	-2.0 (-3.48 – -0.54)	0.007	1.18 (-0.91 – 3.27)	0.27
SF-36 Physical Function	-2.44 (-3.89 – -1.0)	0.001	0.33 (-1.74 – 2.40)	0.76
SF-36 Mental Health	-1.41 (-3.0 – 0.19)	0.08	-0.16 (-2.4 – 2.1)	0.89
6MWD (m)	-50.1 (-66 – -34)	<0.001	-3.8 (-26 – 18)	0.74
	RR (95% CI)	p-value	RR (95% CI)	p-value
Moderate Exacerbations	0.98 (0.67 – 1.43)	0.91	0.65 (0.36 – 1.19)	0.16
Severe Exacerbations	1.46 (0.94 – 2.27)	0.09	1.34 (0.68 – 2.7)	0.39

Models adjusted for age, sex, ethnicity, education, BMI, pack-years, smoking status, CHF, HTN, DM, CKD, % emphysema, FEV_1 % predicted, and DLCO % predicted. Total N=1735 for all models. Coefficients and p-values are in comparison to normal haemoglobin. β coefficient units are points for CAT, mMRC, SGRQ, and SF-36 scores, and meters for 6MWD.

Supplemental Table 3. Sensitivity analysis of associations between Anaemia and Polycythaemia with clinical outcomes, including oxygen use and resting oxygen saturation as confounders

	Anaemia		**Polycythaemia**	
	β (95% CI)	p-value	β (95% CI)	p-value
CAT Score	1.29 (0.29 – 2.29)	0.01	-0.39 (-1.9 – 1.1)	0.60
mMRC Dyspnea Score	0.26 (0.09 – 0.41)	0.001	0.06 (-0.18 – 0.29)	0.63
SGRQ Score	3.76 (1.47 – 6.04)	0.001	0.32 (-3.07 – 3.71)	0.85
SF-36 General	-1.9 (-3.21 – -0.59)	0.004	1.29 (-0.65 – 3.25)	0.19
SF-36 Physical Function	-2.65 (-3.9 – -1.3)	<0.001	0.61 (-1.33 – 2.56)	0.54
SF-36 Mental Health	-1.29 (-2.7 – 0.16)	0.08	-0.46 (-2.6 – 1.7)	0.67
6MWD (m)	-49.6 (-64 – -35)	<0.001	2.1 (-18.8 – 23.1)	0.84
	RR (95% CI)	p-value	RR (95% CI)	p-value
Moderate Exacerbations	1.03 (0.74 – 1.45)	0.85	0.74 (0.42 – 1.29)	0.29
Severe Exacerbations	1.46 (0.99 – 2.16)	0.05	1.29 (0.68 – 2.44)	0.44

Models adjusted for age, sex, ethnicity, education, BMI, pack-years, smoking status, resting oxygen saturation, long term oxygen use, CHF, HTN, DM, CKD, % emphysema, FEV_1 % predicted, and DLCO % predicted. Coefficients and p-values are in comparison to normal haemoglobin. β coefficient units are points for CAT, mMRC, SGRQ, and SF-36 scores, and meters for 6MWD.

Supplemental Table 4. Haemoglobin treated as a continuous variable is associated with COPD morbidity

	Fractional Polynomial Powers for Haemoglobin Terms	**p-value**
CAT Score	**0.5, 1**	**0.031**
mMRC Dyspnea Score	**1, 3**	**<0.001**
SGRQ Score	**-0.5, 3**	**<0.001**
SF-36 General	1, 1	0.05
SF-36 Physical Function	**0.5, 3**	**<0.001**
SF-36 Mental Health	-1, 3	0.018
6MWD (m)	**3, 3**	**<0.001**
Moderate Exacerbations	3, 3	0.664
Severe Exacerbations	**3, 3**	**0.003**

Fractional polynomial models (m=2) were used for all outcomes. Models were adjusted for age, sex, ethnicity, education, BMI, pack-years, smoking status, CHF, HTN, DM, CKD, % emphysema, FEV_1 % predicted, and DLCO % predicted all as linear terms. Exacerbation models were negative binomial regressions for rate of exacerbations. Fractional polynomial powers for haemoglobin terms, and the linear combination p-value for a non-zero haemoglobin coefficient are displayed in the above table. Bolded rows represent models where t-tests for all haemoglobin terms were significant at $p<0.05$.