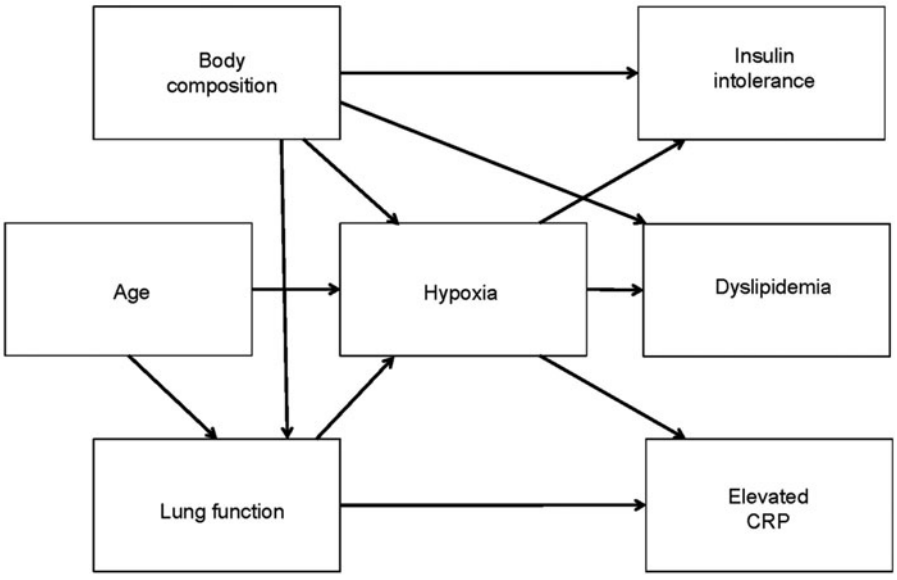
Supplementary Data

Biostatistical Methods

We have demonstrated that increased waist circumference (which is reflective of body mass index [BMI]) was directly associated with a lower oxyhemoglobin saturation (Table 3). Similarly, BMI is a well-known risk factor for cardiovascular disease (CVD). Since a higher BMI is associated with both a lower oxyhemoglobin saturation and CVD, as we have presented in our directed acyclic graph, BMI and oxyhemoglobin saturation are collinear variables and thus should not be included together in a regression. However, given the fact that both BMI independently affects CVD and we are trying to show that hypoxemia can also have direct affect on CVD independent of BMI, we needed to find a way to adjust for BMI while taking into account this collinearity. To make this adjustment, we orthoganalized BMI and oxyhemoglobin saturation. This essentially means that we regressed oxyhemoglobin saturation on BMI. We then used the residuals of this regression in our analyses. The residuals represent the difference between the observed values for the dependent variable (BMI) and predicted value for the dependent variable. This is a way to define the component of BMI that is independent from (or not directly related to) oxyhemoglobin saturation.



SUPPLEMENTARY FIG. S1. Assumed directed acyclic graph of cause and effects of hypoxemia. Description of how hypoxemia may be related to various cardiovascular disease risk factors.

Supplementary Table S1. Unadjusted Odds of the Relationship Between Individual Components of Metabolic Syndrome and a 5% Decrease in Resting Daytime Oxyhemoglobin Saturation

	OR	*95% CI*	p
Metabolic syndrome	1.51	1.24–1.83	<0.001
Waist circumference ≥90 cm in men and ≥80 in women	1.54	1.24–1.92	<0.01
Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg	0.95	0.75–1.20	0.67
HDL <40 mg/dL in males and <50 mg/dL in females	1.30	1.05–1.61	0.02
Triglycerides ≥150 mg/dL	1.05	0.83–1.33	0.68
Fasting glucose ≥100 mg/dL	1.36	1.07–1.71	0.01
Other cardiovascular risk factors			
Systolic blood pressure ≥140 mmHg	1.29	0.94–1.77	0.11
Diastolic blood pressure ≥90 mmHg	0.97	0.70–1.34	0.84
LDL ≥160 mg/dL	1.11	0.85–1.43	0.44
hs-CRP ≥3 mg/L	2.10	1.66–2.66	<0.001
Fasting insulin >25 mIU/L	1.62	0.98–2.68	0.06
Fasting glucose ≥126 mg/dL	1.34	0.88–2.04	0.17
Hemoglobin A1c ≥6.5%	2.65	1.94–3.60	<0.001
HOMA-IR >2 mass units	1.38	1.13–1.69	<0.001
Diabetes	1.55	1.07–2.26	<0.04

HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein.

Supplementary Table S2. Single and Multivariable Analysis Evaluating Patient-Specific Traits Associated with Resting Daytime Oxyhemoglobin Saturation <85%

	Oxyhemoglobin saturation <85%					
	Single variable analysis			*Multivariable analysis*		
	OR	*95% CI*	p	*OR*	*95% CI*	p
Older age per 5 years	1.38	1.24–1.54	<0.001	1.37	1.20–1.56	<0.001
Sex male vs. female	0.86	0.48–1.53	0.60	1.14	0.60–2.16	0.69
Higher BMI per 5 kg/m^2 increments	1.43	1.09–1.89	<0.02	2.08	1.47–2.94	<0.001
Rural vs. urban setting	0.68	0.41–1.14	0.15	0.69	0.32–1.49	0.35
Percent predicted FVC <80%	3.62	1.31–10.00	<0.02	4.16	1.35–12.76	0.01
Wealth index						
Middle vs. low	0.65	0.34–1.26	0.20	0.64	0.27–1.50	0.30
High vs. low	0.82	0.45–1.50	0.52	0.59	0.25–1.39	0.23

BMI, body mass index.

Supplementary Table S3. Unadjusted and Adjusted Odds for the Individual Components of Metabolic Syndrome Per 5% Decrease in Resting Daytime Oxyhemoglobin Saturation in Urban Puno

	Model adjusted for age, sex, excessive erythrocytosis, and wealth index			*Model adjusted for age, sex, excessive erythrocytosis, wealth index, and residuals of BMI*		
Urban Puno	*OR*	*95% CI*	p	*OR*	*95% CI*	p
Metabolic syndrome	1.21	0.87–1.68	0.25	1.18	0.82–1.68	0.37
Waist circumference ≥90 cm in men and ≥80 in women	1.25	0.85–1.85	0.26			
Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg	0.75	0.48–1.15	0.19	0.68	0.43–1.07	0.10
HDL <40 mg/dL in males and <50 mg/dL in females	1.45	1.01–2.08	<0.5	1.45	0.00–2.10	<0.05
Triglycerides ≥150 mg/dL	0.82	0.55–1.21	0.32	0.81	0.55–1.20	0.30
Fasting glucose ≥100 mg/dL	1.01	0.69–1.48	0.96	0.99	0.67–1.46	0.74
Other cardiovascular risk factors						
Systolic blood pressure ≥140 mmHg	1.00	0.59–1.71	0.98	0.95	0.54–1.68	0.87
Diastolic blood pressure ≥90 mmHg	0.87	0.51–1.50	0.63	0.81	0.46–1.44	0.47
LDL ≥160 mg/dL	0.93	0.61–1.42	0.73	0.92	0.60–1.41	0.71
hs-CRP ≥3 mg/L	1.55	1.05–2.29	<0.04	1.52	1.01–2.26	0.04
Fasting insulin >25 mIU/L	1.42	0.60–3.35	0.43	0.97	0.36–2.58	0.95
Fasting glucose ≥126 mg/dL	0.76	0.38–1.50	0.43	0.71	0.35–1.44	0.35
Hemoglobin A1c ≥6.5%	1.69	0.99–2.89	0.06	1.68	0.97–2.91	0.06
HOMA-IR >2 mass units	1.18	0.84–1.66	0.34	1.10	0.75–1.62	0.62
Diabetes	0.80	0.42–1.50	0.48	0.73	0.38–1.41	0.36

Supplementary Table S4. Unadjusted and Adjusted Odds for the Individual Components of Metabolic Syndrome Per 5% Decrease in Resting Daytime Oxyhemoglobin Saturation in Rural Puno

	Model adjusted for age, sex, excessive erythrocytosis, and wealth index			*Model adjusted for age, sex, excessive erythrocytosis, wealth index, and residuals of BMI*		
Rural Puno	*OR*	*95% CI*	p	*OR*	*95% CI*	p
Metabolic syndrome	1.54	1.08–2.19	0.02	2.03	1.29–3.19	<0.01
Waist circumference ≥90 cm in men and ≥80 in women	1.34	0.96–1.88	0.09	—	—	—
Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg	0.79	0.54–1.16	0.23	0.82	0.55–1.21	0.31
HDL <40 mg/dL in males and <50 mg/dL in females	1.03	0.73–1.44	0.86	1.13	0.79–1.62	0.51
Triglycerides ≥150 mg/dL	1.45	0.92–2.28	0.11	1.51	0.95–2.42	0.08
Fasting glucose ≥100 mg/dL	1.17	0.71–1.93	0.53	1.22	0.74–2.02	0.44
Other cardiovascular risk factors						
Systolic blood pressure ≥140 mmHg	1.06	0.57–1.99	0.85	1.09	0.56–2.12	0.80
Diastolic blood pressure ≥90 mmHg	0.77	0.43–1.35	0.36	0.78	0.43–1.42	0.42
LDL ≥160 mg/dL	1.44	0.86–2.44	0.17	1.48	0.87–2.53	0.15
hs-CRP ≥3 mg/L	1.71	1.08–2.71	0.02	1.75	1.10–2.79	0.02
Fasting insulin >25 mIU/L	2.15	0.61–7.59	0.24	2.29	0.61–8.58	0.22
Fasting glucose ≥126 mg/dL	1.52	0.61–3.83	0.38	1.47	0.59–3.65	0.40
Hemoglobin A1c ≥6.5%	1.70	0.86–3.35	0.12	1.73	0.87–3.45	0.12
HOMA-IR >2 mass units	1.42	0.96–2.09	0.08	1.53	0.98–2.41	0.06
Diabetes	2.13	0.90–5.06	0.09	1.99	0.82–4.84	0.13