		8	
Phenotype	Consortium	Diagnostic criteria/Method	
Iron status	GIS	Serum iron: colorimetric assay, ferrozine measurement. Ferritin: latex particle immunoturbidimetry. Transferrin: immunoturbidimetric, Electro-chemiluminescence immunoassay. Transferrin saturation: Serum iron/ Transferrin×100%	
Lung cancer	ILCCO	Histology, immunohistochemistry	
CIS. Constiss of Iron Status: II CCO. International Lung Conser Consertium			

Table S1 Diagnostic criteria used by databases about iron status and lung cancer

GIS, Genetics of Iron Status; ILCCO, International Lung Cancer Consortium.

Table S2 Heterogeneity test for the instrumental variables associated with the four iron status biomarkers and the risk of lung cancer overall and the histological subtypes

Outoomo	Iron		Ferritin		Transferrin		Transferrin saturation	
Outcome	Q	P value	Q	P value	Q	P value	Q	P value
Lung cancer overall	3.013	0.390	4.814	0.186	18.694	0.009*	2.750	0.432
Adenocarcinoma	5.207	0.157	5.453	0.141	16.055	0.025*	3.605	0.307
Squamous cell carcinoma	0.095	0.992	1.209	0.751	17.530	0.014*	0.768	0.857

*, P<0.05.

	Iron		
Exclude SNP		OR (95% CI)	P value
Lung cancer overall			
Inverse variance weighted			
rs1799945		0.88 (0.75, 1.03)	0.121
rs1800562		0.87 (0.73, 1.02)	0.085
rs7385804		0.88 (0.76, 1.01)	0.077
rs8177240		0.87 (0.76, 0.99)	0.030
rs855791		0.96 (0.82, 1.12)	0.591
Adenocarcinoma			
Inverse variance weighted			
rs1799945		0.90 (0.67, 1.20)	0.464
rs1800562		0.85 (0.65, 1.10)	0.214
rs7385804		0.91 (0.70, 1.19)	0.497
rs8177240		0.89 (0.71, 1.12)	0.315
rs855791		— 1.08 (0.84, 1.38)	0.563
Squamous cell carcinoma			
Inverse variance weighted			
rs1799945		0.74 (0.60, 0.91)	0.005
rs1800562		0.78 (0.62, 0.98)	0.034
rs7385804		0.74 (0.61, 0.89)	0.002
rs8177240		0.74 (0.61, 0.89)	0.002
rs855791	e	0.75 (0.60, 0.94)	0.014
0.	.60 0.80 1.0 1.2	1.4	

Figure S1 Leave-one-out analysis for the MR estimates for serum iron and the risk of lung cancer. The ORs of lung cancer and their histological subtypes risk per standard deviation increment in the level of serum iron excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.

	Ferritin		
Exclude SNP		OR (95% CI)	P value
Lung cancer overall			
Inverse variance weighted			
rs1799945		0.84 (0.60, 1.18)	0.307
rs1800562		0.77 (0.51, 1.18)	0.232
rs411988		0.79 (0.59, 1.06)	0.115
rs744653		0.81 (0.57, 1.16)	0.250
rs855791		0.92 (0.70, 1.20)	0.525
Adenocarcinoma			
Inverse variance weighted			
rs1799945		- 1.03 (0.56, 1.89)	0.915
rs1800562		- 0.91 (0.44, 1.89)	0.799
rs411988		0.98 (0.55, 1.75)	0.944
rs744653		0.93 (0.51, 1.69)	0.813
rs855791		- 1.24 (0.81, 1.89)	0.315
Squamous cell carcinoma			
Inverse variance weighted			
rs1799945		0.57 (0.39, 0.83)	0.003
rs1800562		0.57 (0.34, 0.94)	0.029
rs411988		0.54 (0.37, 0.78)	0.001
rs744653		0.53 (0.35, 0.79)	0.002
rs855791		0.59 (0.40, 0.86)	0.007
		7	
0.3	30 0.50 0.75 1.0 1.4 1	.9	

Figure S2 Leave-one-out analysis for the MR for between ferritin and the risk of lung cancer. The OR of lung cancer and their histological subtypes risk per standard deviation increment in the level of ferritin excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.

	Transferrin		
Exclude SNP		OR (95% CI)	P value
Lung cancer overall			
Inverse variance weighted			
rs174577	- 	1.05 (0.96, 1.15)	0.282
rs1799945		1.03 (0.90, 1.17)	0.716
rs1800562		1.02 (0.88, 1.20)	0.757
rs4921915		1.03 (0.90, 1.18)	0.626
rs6486121		1.03 (0.90, 1.18)	0.655
rs744653		1.03 (0.90, 1.18)	0.681
rs8177240		1.00 (0.80, 1.24)	0.980
rs855791		1.02 (0.91, 1.14)	0.724
rs9990333		1.04 (0.91, 1.18)	0.574
Adenocarcinoma			
Inverse variance weighted			
rs174577		1.04 (0.91, 1.18)	0.570
rs1799945		1.01 (0.83, 1.22)	0.942
rs1800562		1.03 (0.84, 1.28)	0.759
rs4921915		1.02 (0.84, 1.23)	0.873
rs6486121		1.01 (0.83, 1.22)	0.934
rs744653		1.01 (0.84, 1.22)	0.881
rs8177240—		0.89 (0.66, 1.19)	0.440
rs855791		1.00 (0.85, 1.17)	0.953
rs9990333		1.01 (0.83, 1.22)	0.943
Squamous cell carcinoma			
Inverse variance weighted			
rs174577		1.07 (0.90, 1.27)	0.421
rs1799945		1.04 (0.86, 1.26)	0.682
rs1800562		0.97 (0.80, 1.19)	0.784
rs4921915		1.07 (0.89, 1.28)	0.474
rs6486121		1.06 (0.88, 1.28)	0.524
rs744653		1.05 (0.87, 1.27)	0.632
rs8177240	\longrightarrow	1.16 (0.87, 1.56)	0.312
rs855791		1.04 (0.87, 1.25)	0.637
rs9990333		1.06 (0.88, 1.28)	0.542
0	70 0.85 10 12 14		
0.			

Figure S3 Leave-one-out analysis for the MR estimates for transferrin and the risk of lung cancer. The OR of lung cancer and their histological subtypes risk per standard deviation increment in the level of transferrin excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.

	Transferrin satu	ration	
Exclude SNP		OR (95% CI)	P value
Lung cancer overall			
Inverse variance weighted			
rs1799945		0.90 (0.81, 1.00)	0.058
rs1800562		0.85 (0.75, 0.97)	0.017
rs7385804		- 0.90 (0.82, 0.99)	0.039
rs8177240		0.91 (0.83, 1.00)	0.059
rs855791		0.94 (0.85, 1.05)	0.288
Adenocarcinoma			
Inverse variance weighted			
rs1799945		0.92 (0.74, 1.14)	0.431
rs1800562		0.82 (0.67, 1.01)	0.057
rs7385804		0.93 (0.77, 1.13)	0.463
rs8177240		0.94 (0.78, 1.14)	0.551
rs855791		1.01 (0.85, 1.19)	0.918
Squamous cell carcinoma			
Inverse variance weighted			
rs1799945		0.81 (0.70, 0.94)	0.006
rs1800562		0.82 (0.67, 1.00)	0.049
rs7385804		0.81 (0.71, 0.93)	0.002
rs8177240		0.80 (0.70, 0.92)	0.002
rs855791	8	0.83 (0.71, 0.96)	0.013
	r r		
0.	65 0.80 ^r	1.0 1.2	

Figure S4 Leave-one-out analysis for the MR estimates for transferrin saturation and the risk of lung cancer. The OR of lung cancer and their histological subtypes risk per standard deviation increment in the level of transferrin saturation excluding one SNP at per time based on the inverse variance-weighted method. SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval; MR, Mendelian randomization.