

Supplementary Table 1. Multivariable linear model for factors associated with basal OCR in the entire cohort and non-glaucomatous controls

	Entire cohort		Controls	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value
HTG	-5.586 (0.822)	<0.001		
NTG	-8.494 (0.776)	<0.001		
Age, decades	0.893 (0.315)	0.005	1.010 (0.883)	0.26
Male sex	-0.534 (0.607)	0.38	0.393 (1.918)	0.84
Number of systemic diseases	-0.405 (0.310)	0.19	0.810 (0.956)	0.40
Diabetes	-1.381 (1.274)	0.28	-1.247 (4.019)	0.76
Migraine	1.329 (0.839)	0.11	0.540 (3.251)	0.87
Vasospasm	1.199 (0.787)	0.13	2.711 (3.517)	0.44
Alcohol consumption	0.927 (0.704)	0.19	-0.283 (2.486)	0.91
Systemic betablocker	-0.952 (0.847)	0.26	-4.306 (3.119)	0.17

Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. Diagnostic status reference: control subject.

HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.

Supplementary Table 2. Multivariable linear model for factors associated with ATP-linked OCR in the entire cohort and non-glaucomatous controls				
	Entire cohort		Controls	
Variable	<i>β Estimate (SE)</i>	<i>P-value</i>	<i>β Estimate (SE)</i>	<i>P-value</i>
HTG	-3.751 (0.692)	<0.001		
NTG	-6.170 (0.639)	<0.001		
Age, decades	0.891 (0.263)	<0.001	1.222 (0.747)	0.11
Male gender	-0.743 (0.515)	0.15	-1.059 (1.617)	0.52
Number of systemic diseases	-0.405 (0.310)	0.19	-0.556 (0.897)	0.54
Diabetes	-0.716 (1.085)	0.51	-1.409 (3.519)	0.69
Alcohol consumption	0.678 (0.599)	0.26	0.549 (2.004)	0.79
Statins use	0.440 (0.638)	0.49	1.302 (2.197)	0.56
Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. Diagnostic status reference: control subject. ATP: adenosine triphosphate; HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.				

Supplementary Table 3. Multivariable linear model for factors associated with Maximal OCR in the entire cohort and non-glaucomatous controls

	Entire cohort		Controls	
Variable	β Estimate (SE)	P-value	β Estimate (SE)	P-value
HTG	-22.344 (6.125)	<0.001		
NTG	-35.903 (5.659)	<0.001		
Age, decades	2.460 (2.328)	<0.001	0.726 (4.745)	0.88
Number of systemic diseases	-7.962 (2.573)	0.002	-0.792 (5.537)	0.89
Diabetes	-11.333 (9.560)	0.24	-46.739 (20.809)	0.030
Alcohol consumption	10.504 (5.192)	0.044	2.906 (12.327)	0.81
Statins use	13.501 (5.649)	0.018	7.604 (13.199)	0.57
Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. Diagnostic status reference: control subject. HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.				

Supplementary Table 4. Multivariable linear model for factors associated with Reserve OCR in the entire cohort and non-glaucomatous controls

	Entire cohort		Controls	
Variable	β Estimate (SE)	P-value	β Estimate (SE)	P-value
HTG	-17.065 (5.671)	0.003		
NTG	-27.994 (5.240)	<0.001		
Age, decades	1.623 (2.155)	0.45	-0.429 (4.355)	0.92
Number of systemic diseases	-7.292 (2.382)	0.003	-0.106 (5.082)	0.98
Diabetes	-10.004 (8.852)	0.26	-43.997 (19.098)	0.026
Alcohol consumption	9.936 (4.807)	0.040	2.246 (11.313)	0.84
Statins use	12.874 (5.231)	0.015	5.562 (12.113)	0.65
Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. Diagnostic status reference: control subject. HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.				

Supplementary Table 5. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in entire cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age	-0.090 (0.029)	0.002	-0.097 (0.029)	0.001	-0.076 (0.029)	0.010	-0.075 (0.030)	0.012
CCT	0.008 (0.033)	0.82	0.005 (0.029)	0.87	0.012 (0.034)	0.73	0.013 (0.035)	0.70
Mean IOP	-0.069 (0.034)	0.042	-0.076 (0.033)	0.025	-0.057 (0.035)	0.10	-0.056 (0.035)	0.11
Basal OCR	0.186 (0.035)	<0.001						
ATP- linked OCR			0.199 (0.034)	<0.001				
Maximal OCR					0.123 (0.036)	0.001		
Reserve Capacity							0.108 (0.036)	0.003

The current model has mean intraocular pressure (IOP) as IOP covariate. All covariates are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 6. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in the normal-tension glaucoma (NTG) cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age	-0.034 (0.040)	0.40	-0.040 (0.039)	0.31	-0.032 (0.040)	0.43	-0.031 (0.041)	0.44
CCT	-0.026 (0.046)	0.57	-0.025 (0.045)	0.59	-0.025 (0.047)	0.60	-0.024 (0.047)	0.62
Mean IOP	-0.108 (0.067)	0.11	-0.109 (0.066)	0.11	-0.133 (0.069)	0.056	-0.137 (0.069)	0.050
Basal OCR	0.176 (0.047)	<0.001						
ATP- linked OCR			0.187 (0.046)	<0.001				
Maximal OCR					0.102 (0.042)	0.018		
Reserve Capacity							0.092 (0.042)	0.033

The current model has mean intraocular pressure (IOP) as IOP covariate. All variables are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 7. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in the high-tension glaucoma (HTG) cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age	-0.195 (0.047)	<0.001	-0.198 (0.047)	<0.001	-0.179 (0.047)	<0.001	-0.179 (0.048)	<0.001
CCT	0.062 (0.052)	0.25	0.057 (0.052)	0.28	0.071 (0.055)	0.20	0.070 (0.055)	0.21
Mean IOP	-0.083 (0.058)	0.16	-0.088 (0.057)	0.13	-0.093 (0.060)	0.12	-0.095 (0.061)	0.12
Basal OCR	0.197 (0.061)	0.002						
ATP-linked OCR			0.211 (0.063)	0.002				
Maximal OCR					0.142 (0.079)	0.08		
Reserve Capacity							0.110 (0.079)	0.17

The current model has mean intraocular pressure (IOP) as IOP covariate. All variables are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 8. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in the entire cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age	-0.090 (0.029)	0.002	-0.097 (0.029)	0.001	-0.078 (0.029)	0.008	-0.076 (0.030)	0.010
CCT	0.008 (0.033)	0.82	0.005 (0.033)	0.87	0.013 (0.034)	0.71	0.014 (0.035)	0.68
Mean IOP	-0.069 (0.035)	0.047	-0.076 (0.034)	0.030	-0.059 (0.035)	0.09	-0.057 (0.035)	0.10
Basal OCR	0.186 (0.035)	<0.001						
ATP- linked OCR			0.199 (0.034)	<0.001				
Maximal OCR					0.126 (0.036)	<0.001		
Reserve Capacity							0.111 (0.036)	0.003
Mean IOP*OCR parameter	0.001 (0.031)	0.98	0.000 (0.028)	0.99	0.031 (0.037)	0.41	0.031 (0.038)	0.41

The current model has mean intraocular pressure (IOP) as IOP covariate. All variables are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 9. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in the entire cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age	-0.084 (0.028)	0.003	-0.090 (0.028)	0.001	-0.071 (0.029)	0.015	-0.069 (0.029)	0.018
CCT	0.003 (0.032)	0.93	0.000 (0.032)	0.99	0.007 (0.034)	0.84	0.008 (0.034)	0.81
Peak IOP	-0.075 (0.033)	0.024	-0.079 (0.033)	0.016	-0.051 (0.034)	0.14	-0.048 (0.034)	0.16
Basal OCR	0.190 (0.034)	<0.001						
ATP- linked OCR			0.202 (0.034)	<0.001				
Maximal OCR					0.122 (0.035)	0.001		
Reserve Capacity							0.107 (0.036)	0.003

The current model has peak intraocular pressure (IOP) as IOP covariate. All variables are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 10. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in the entire cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age	-0.076 (0.028)	0.007	-0.081 (0.028)	0.004	-0.066 (0.029)	0.022	-0.065 (0.029)	0.025
CCT	-0.007 (0.032)	0.84	-0.010 (0.032)	0.75	0.000 (0.034)	0.99	0.002 (0.034)	0.96
IOP Fluctuation	-0.039 (0.032)	0.22	-0.042 (0.031)	0.19	-0.015 (0.033)	0.65	-0.013 (0.033)	0.70
Basal OCR	0.184 (0.034)	<0.001						
ATP-linked OCR			0.194 (0.034)	<0.001				
Maximal OCR					0.120 (0.036)	0.001		
Reserve Capacity							0.106 (0.036)	0.004

The current model has intraocular pressure (IOP) fluctuation as IOP covariate. This is SD of IOPs over the visits in the study period. All variables are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 11. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in the entire cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age	-0.076 (0.028)	0.008	-0.080 (0.028)	0.005	-0.068 (0.029)	0.021	-0.067 (0.029)	0.023
CCT	-0.008 (0.033)	0.81	-0.012 (0.032)	0.71	0.000 (0.034)	0.99	0.002 (0.034)	0.94
Relative IOP reduction	-0.019 (0.034)	0.58	-0.026 (0.034)	0.44	0.003 (0.035)	0.94	0.007 (0.035)	0.84
Basal OCR	0.184 (0.036)	<0.001						
ATP-linked OCR			0.196 (0.035)	<0.001				
Maximal OCR					0.120 (0.036)	0.001		
Reserve Capacity							0.105 (0.037)	0.005

The current model has relative intraocular pressure (IOP) reduction from baseline as IOP covariate. All variables are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the independent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 12. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in subset of patients undergoing surgery.

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The current model has mean intraocular pressure (IOP) as IOP covariate. All covariates are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 13. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in subset of patients not undergoing surgery.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value	β Estimate (SE)	P- value
Age, per decade	-0.118 (0.041)	0.005	-0.015 (0.042)	0.007	-0.080 (0.042)	0.06	-0.075 (0.042)	0.08
CCT, per 10 μm	-0.046 (0.039)	0.25	-0.033 (0.040)	0.42	-0.007 (0.041)	0.86	-0.002 (0.041)	0.96
Mean IOP	-0.118 (0.041)	0.005	-0.121 (0.042)	0.005	-0.067 (0.041)	0.11	-0.061 (0.042)	0.15
Basal OCR	0.282 (0.047)	<0.001						
ATP-linked OCR			0.258 (0.047)	<0.001				
Maximal OCR					0.207 (0.047)	<0.001		
Reserve Capacity							0.190 (0.048)	<0.001

The current model has mean intraocular pressure (IOP) as IOP covariate. All covariates are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 14. Standardized multivariable linear mixed model for factors associated with visual field mean deviation (MD) rates of change in entire cohort.

	Model A		Model B		Model C		Model D	
Variable	β Estimate (SE)	P-value	β Estimate (SE)	P-value	β Estimate (SE)	P-value	β Estimate (SE)	P-value
Age, per decade	-0.135 (0.028)	<0.001	-0.138 (0.029)	<0.001	-0.119 (0.019)	<0.001	-0.117 (0.029)	<0.001
CCT, per 10 μm	-0.027 (0.031)	0.39	-0.023 (0.031)	0.47	-0.015 (0.032)	0.64	-0.013 (0.032)	0.69
Mean IOP	-0.079 (0.032)	0.013	-0.081 (0.032)	0.012	-0.056 (0.032)	0.08	-0.053 (0.032)	0.10
Glaucoma surgery (ref:no)	-0.401 (0.064)	<0.001	-0.393 (0.064)	<0.001	-0.426 (0.065)	<0.001	-0.428 (0.066)	<0.001
OCR*Surgey	-0.167 (0.063)	0.009	-0.114 (0.063)	0.07	-0.144 (0.064)	0.026	-0.135 (0.064)	0.037
Basal OCR	0.270 (0.047)	<0.001						
ATP-linked OCR			0.248 (0.045)	<0.001				
Maximal OCR					0.211 (0.047)	<0.001		
Reserve Capacity							0.193 (0.048)	<0.001

The current model has mean intraocular pressure (IOP) as IOP covariate. All covariates are standardized (i.e., zero mean and unit standard deviation), and coefficient effect should be interpreted as one standard deviation increase in the dependent variable.

ATP: adenosine triphosphate; CCT: central corneal thickness; OCR: oxygen consumption rate.

Supplementary Table 15. Demographic and clinical characteristics of the placebo group included in the UKGTS trial

Variable	Entire cohort
Number of eyes/patients	213/213
Baseline Age, mean ($\pm$ SD)	66.5 ($\pm$ 10.3)
Sex (female/male)	108/105
Laterality, right/left	92/121
CCT, mean ($\pm$ SD), micron	544 ($\pm$ 34)
Baseline MD, median (IQR), dB	-3.4 (-2.0 to -5.6)
Baseline IOP, median (IQR), mmHg	19.5 (16.0 to 22.8)
Number of VF, median (IQR)	13 (10 to 16)
Follow-up time, median (IQR), years	1.6 (1.0 to 2.0)
CCT: central corneal thickness; dB: decibel; IOP: intraocular pressure; IQR: interquartile range; MD: mean deviation; SD: standard deviation; UKGTS: United Kingdom Glaucoma Treatment Study; VF: visual field.	

Supplementary Table 16. Multivariable linear model for factors associated with basal OCR in the entire cohort and non-glaucomatous controls				
	Entire cohort		Controls	
Variable	<i>β Estimate (SE)</i>	<i>P-value</i>	<i>β Estimate (SE)</i>	<i>P-value</i>
Age, decades	0.400 (0.730)	0.59	1.397 (0.980)	0.17
Statins use	1.585 (1.871)	0.40	2.029 (3.549)	0.58
Number of systemic diseases	-0.817 (0.898)	0.37	-1.132 (1.612)	0.49
Diabetes	-4.262 (2.998)	0.16	-1.962 (5.678)	0.74
Alcohol consumption	2.363 (1.786)	0.19	-0.263 (3.081)	0.93
NAD levels	11.601 (2.120)	<0.001	6.467 (3.358)	0.07
Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.				

Supplementary Table 17. Multivariable linear model for factors associated with ATP-linked OCR in the entire cohort and non-glaucomatous controls

	Entire cohort		Controls	
Variable	β Estimate (SE)	P-value	β Estimate (SE)	P-value
Age, decades	0.788 (0.648)	0.23	1.698 (0.920)	0.08
Statins use	0.870 (1.660)	0.60	0.012 (3.333)	0.99
Number of systemic diseases	-0.756 (0.797)	0.35	-0.390 (1.514)	0.80
Diabetes	-3.158 (2.661)	0.24	-0.162 (5.333)	0.98
Alcohol consumption	1.681 (1.585)	0.29	0.207 (2.894)	0.94
NAD levels	10.024 (1.882)	<0.001	4.561 (3.154)	0.17
Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.				

Supplementary Table 18. Multivariable linear model for factors associated with maximal OCR in the entire cohort and non-glaucomatous controls				
	Entire cohort		Controls	
Variable	<i>β Estimate</i> (SE)	<i>P-value</i>	<i>β Estimate</i> (SE)	<i>P-value</i>
Age, decades	0.895 (5.268)	0.87	-0.619 (6.421)	0.92
Statins use	10.500 (13.501)	0.44	-0.966 (23.260)	0.98
Number of systemic diseases	-3.318 (6.483)	0.61	2.644 (10.566)	0.81
Diabetes	-13.595 (21.636)	0.53	-23.525 (37.217)	0.54
Alcohol consumption	18.690 (12.888)	0.15	13.651 (20.195)	0.51
NAD levels	35.207 (15.302)	0.026	-7.692 (22.009)	0.73
Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.				

Supplementary Table 19. Multivariable linear model for factors associated with reserve OCR in the entire cohort and non-glaucomatous controls

	Entire cohort		Controls	
Variable	β Estimate (SE)	P-value	β Estimate (SE)	P-value
Age, decades	0.895 (5.268)	0.87	-0.619 (6.421)	0.92
Statins use	10.500 (13.501)	0.44	-0.966 (23.260)	0.97
Number of systemic diseases	-3.318 (6.483)	0.61	2.644 (10.566)	0.81
Diabetes	-13.595 (21.636)	0.53	-23.525 (37.217)	0.54
Alcohol consumption	18.690 (12.888)	0.15	13.651 (20.195)	0.51
NAD levels	35.207 (15.302)	0.026	-7.692 (22.009)	0.73
Estimates for continuous variables are intended for 1-unit increase unless specified otherwise. HTG: high-tension glaucoma; NTG: normal-tension glaucoma; OCR: oxygen consumption rate; SE: standard error.				