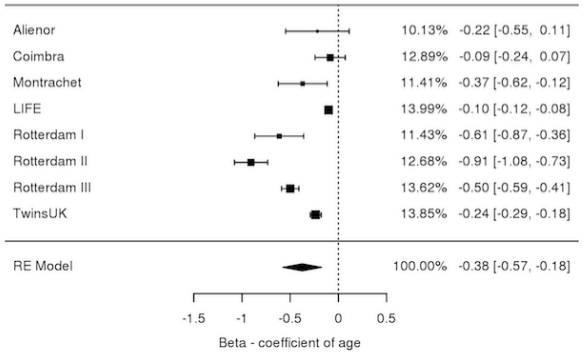
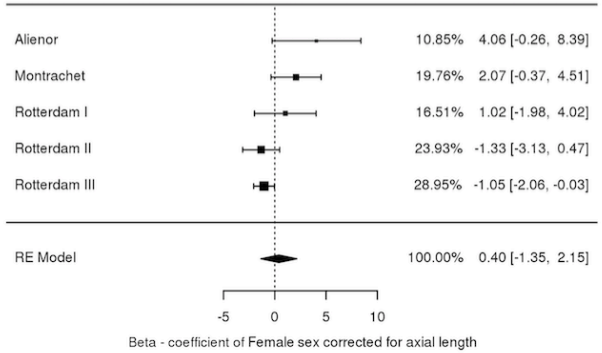
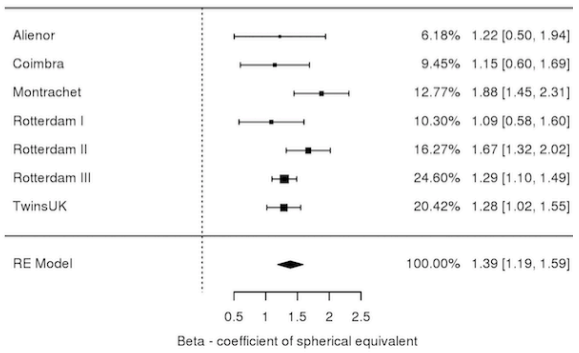
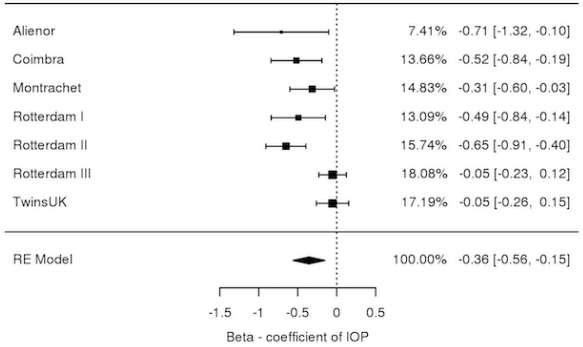
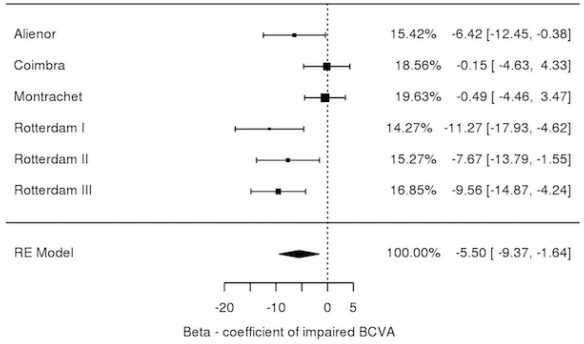
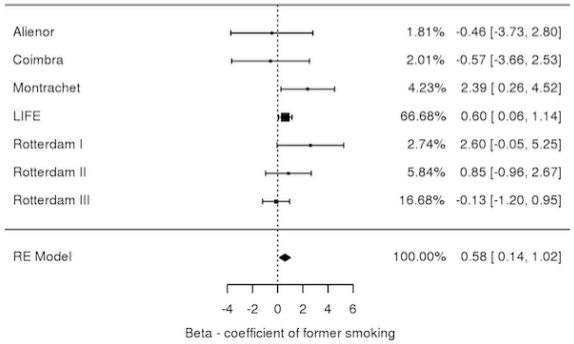

Alienor 10.13% -0.22 [-0.55, 0.11]
Coimbra 12.89% -0.09 [-0.24, 0.07]
Montrachet 11.41% -0.37 [-0.62, -0.12]
LIFE 13.99% -0.10 [-0.12, -0.08]
Rotterdam I 11.43% -0.61 [-0.87, -0.36]
Rotterdam II 12.68% -0.91 [-1.08, -0.73]
Rotterdam III 13.62% -0.50 [-0.59, -0.41]
TwinsUK 13.85% -0.24 [-0.29, -0.18]
RE Model 100.00% -0.38 [-0.57, -0.18]
-1.5 -1 -0.5 0 0.5
Beta - coefficient of age

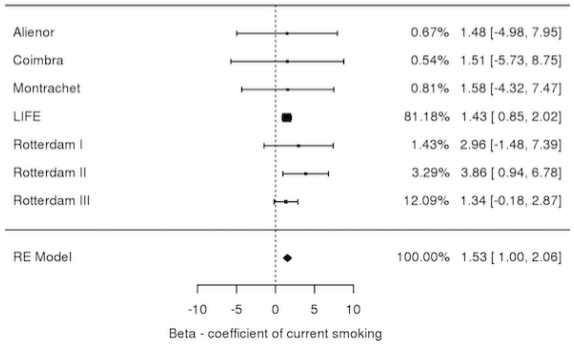

Alienor 10.85% 4.06 [-0.26, 8.39]
Montrachet 19.76% 2.07 [-0.37, 4.51]
Rotterdam I 16.51% 1.02 [-1.98, 4.02]
Rotterdam II 23.93% -1.33 [-3.13, 0.47]
Rotterdam III 28.95% -1.05 [-2.06, -0.03]
RE Model 100.00% 0.40 [-1.35, 2.15]
-5 0 5 10
Beta - coefficient of Female sex corrected for axial length

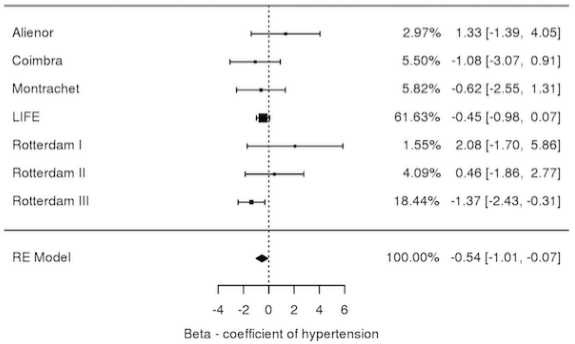

Alienor 6.18% 1.22 [0.50, 1.94]
Coimbra 9.45% 1.15 [0.60, 1.69]
Montrachet 12.77% 1.88 [1.45, 2.31]
Rotterdam I 10.30% 1.09 [0.58, 1.60]
Rotterdam II 16.27% 1.67 [1.32, 2.02]
Rotterdam III 24.60% 1.29 [1.10, 1.49]
TwinsUK 20.42% 1.28 [1.02, 1.55]
RE Model 100.00% 1.39 [1.19, 1.59]
0.5 1 1.5 2 2.5
Beta - coefficient of spherical equivalent

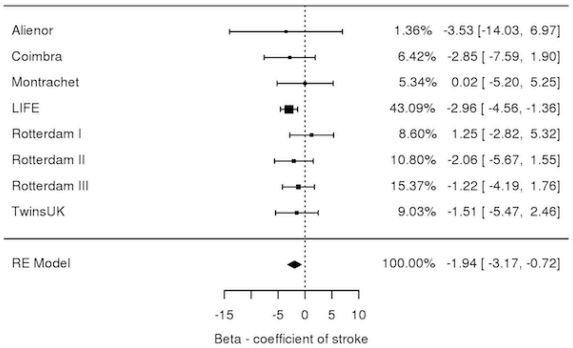

Alienor 7.41% -0.71 [-1.32, -0.10]
Coimbra 13.66% -0.52 [-0.84, -0.19]
Montrachet 14.83% -0.31 [-0.60, -0.03]
Rotterdam I 13.09% -0.49 [-0.84, -0.14]
Rotterdam II 15.74% -0.65 [-0.91, -0.40]
Rotterdam III 18.08% -0.05 [-0.23, 0.12]
TwinsUK 17.19% -0.05 [-0.26, 0.15]
RE Model 100.00% -0.36 [-0.56, -0.15]
-1.5 -1 -0.5 0 0.5
Beta - coefficient of IOP


Alienor 15.42% -6.42 [-12.45, -0.38]
Coimbra 18.56% -0.15 [-4.63, 4.33]
Montrachet 19.63% -0.49 [-4.46, 3.47]
Rotterdam I 14.27% -11.27 [-17.93, -4.62]
Rotterdam II 15.27% -7.67 [-13.79, -1.55]
Rotterdam III 16.85% -9.56 [-14.87, -4.24]
RE Model 100.00% -5.50 [-9.37, -1.64]
-20 -10 0 5
Beta - coefficient of impaired BCVA


Alienor 1.81% -0.46 [-3.73, 2.80]
Coimbra 2.01% -0.57 [-3.66, 2.53]
Montrachet 4.23% 2.39 [0.26, 4.52]
LIFE 66.68% 0.60 [0.06, 1.14]
Rotterdam I 2.74% 2.60 [-0.05, 5.25]
Rotterdam II 5.84% 0.85 [-0.96, 2.67]
Rotterdam III 16.68% -0.13 [-1.20, 0.95]
RE Model 100.00% 0.58 [0.14, 1.02]
-4 -2 0 2 4 6
Beta - coefficient of former smoking


Alienor 0.67% 1.48 [-4.98, 7.95]
Coimbra 0.54% 1.51 [-5.73, 8.75]
Montrachet 0.81% 1.58 [-4.32, 7.47]
LIFE 81.18% 1.43 [0.85, 2.02]
Rotterdam I 1.43% 2.96 [-1.48, 7.39]
Rotterdam II 3.29% 3.86 [0.94, 6.78]
Rotterdam III 12.09% 1.34 [-0.18, 2.87]
RE Model 100.00% 1.53 [1.00, 2.06]
-10 -5 0 5 10
Beta - coefficient of current smoking


Alienor 2.97% 1.33 [-1.39, 4.05]
Coimbra 5.50% -1.08 [-3.07, 0.91]
Montrachet 5.82% -0.62 [-2.55, 1.31]
LIFE 61.63% -0.45 [-0.98, 0.07]
Rotterdam I 1.55% 2.08 [-1.70, 5.86]
Rotterdam II 4.09% 0.46 [-1.86, 2.77]
Rotterdam III 18.44% -1.37 [-2.43, -0.31]
RE Model 100.00% -0.54 [-1.01, -0.07]
-4 -2 0 2 4 6
Beta - coefficient of hypertension


Alienor 1.36% -3.53 [-14.03, 6.97]
Coimbra 6.42% -2.85 [-7.59, 1.90]
Montrachet 5.34% 0.02 [-5.20, 5.25]
LIFE 43.09% -2.96 [-4.56, -1.36]
Rotterdam I 8.60% 1.25 [-2.82, 5.32]
Rotterdam II 10.80% -2.06 [-5.67, 1.55]
Rotterdam III 15.37% -1.22 [-4.19, 1.76]
TwinsUK 9.03% -1.51 [-5.47, 2.46]
RE Model 100.00% -1.94 [-3.17, -0.72]
-15 -5 0 5 10
Beta - coefficient of stroke

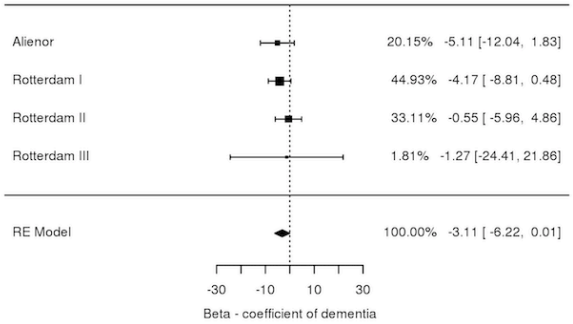

Alienor 20.15% -5.11 [-12.04, 1.83]
Rotterdam I 44.93% -4.17 [-8.81, 0.48]
Rotterdam II 33.11% -0.55 [-5.96, 4.86]
Rotterdam III 1.81% -1.27 [-24.41, 21.86]
RE Model 100.00% -3.11 [-6.22, 0.01]
-30 -10 10 30
Beta - coefficient of dementia

Table 1. Descriptive data for participating studies

Study	Years	City/country	pRNFLT measurements		N	Women (%)	Mean age in years ± SD	Mean global pRNFLT microns ± SD
			OCT - Device	Details				
Alienor Study	2009-2011	Bordeaux, France	Spectralis OCT, Heidelberg Engineering	12° / 3.4mm diameter ring scan on ONH	529	62%	82.1±4.2	89.2±16.0
Coimbra Eye Study	2016-2017	Coimbra, Portugal			618	54%	71.8±6.2	96.8±12.0
Montrachet Study	2009-2013	Dijon, France			803	60%	82.0±3.7	90.3±13.7
LIFE Study	2011-2014	Leipzig, Germany			8351	52%	56.9±12.3	97.4±10.6
Rotterdam Study I	2009-2011	Rotterdam, the Netherlands	3D OCT 1000, Topcon Medical Systems	6.0 x 6.0mm on ONH	1287	57%	79.3±4.6	86.8±21.4
Rotterdam Study II	2011-2012		3D OCT 1000 and 2000, Topcon Medical Systems		1376	55%	72.4±4.9	98.2±17.2
Rotterdam Study III	2012-2013				2267	56%	62.2±5.6	104.7±12.5
Twins UK Study	2014-2016	UK (multiple cities)	iVue, Optovue	3.45 mm diameter ring scan on ONH	853	98%	61.8±12.2	96.4±9.8

pRNFLT=Peripapillary retinal nerve fiber layer thickness, SD=Standard deviation, OCT=Optical coherence tomography, ONH=Optic nerve head

Table 2a. Associations with peripapillary retinal nerve fiber layer thickness (pRNFLT) for each individual study

	Alienor (n=529)		**Coimbra (n=618)**		**Montrachet (n=803)**		**LIFE (n=8351)**	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Age (per year)	-0.22 (-0.55; 0.11)	0.12	-0.09 (-0.24; 0.07)	0.28	-0.37 (-0.62; -0.12)	0.004	-0.10 (-0.12; -0.08)	<0.001
Female sex	3.98 (0.84; 7.11)	0.01	2.78 (0.70; 4.85)	0.01	3.85 (1.78; 5.92)	<0.001	1.36 (0.90; 1.82)	<0.001
BMI (per kg/m^2)	0.13 (-0.22; 0.48)	0.46	-0.10 (-0.30; 0.11)	0.37	0.33 (0.09; 0.57)	0.006	0.08 (0.03; 0.13)	0.002
SE (per diopter)	1.22 (0.50; 1.94)	<0.001	1.15 (0.60; 1.69)	<0.001	1.88 (1.44; 2.31)	<0.001	N/A	N/A
IOP (per mmHg)	-0.71 (-1.32; -0.10)	0.02	-0.52 (-0.84; -0.19)	0.002	-0.31 (-0.60; -0.03)	0.03	N/A	N/A
Visual impairment*	-6.42 (-12.47; -0.37)	0.04	-0.15 (-4.64; 4.34)	0.95	-0.49 (-4.46; 3.48)	0.81	N/A	N/A
Former smoker	-0.47 (-3.74; 2.81)	0.78	-0.57 (-3.67; 2.53)	0.72	2.39 (0.25; 4.53)	0.03	0.60 (0.06; 1.14)	0.03
Current smoker	1.48 (-4.99; 7.96)	0.65	1.51 (-5.74; 8.77)	0.68	1.58 (-4.33; 7.48)	0.60	1.43 (0.85; 2.02)	<0.001
Hypertension	1.33 (-1.40; 4.05)	0.34	-1.08 (-3.07; 0.91)	0.29	-0.62 (-2.55; 1.32)	0.53	-0.46 (-0.98; 0.07)	0.09
Diabetes	2.11 (-2.30; 6.52)	0.35	1.34 (-0.88; 3.55)	0.24	-2.08 (-5.29; 1.13)	0.21	-1.25 (-2.03; -0.46)	0.002
Stroke	-3.53 (-14.05; 6.99)	0.51	-2.85 (-7.60; 1.91)	0.24	0.02 (-5.20; 5.25)	0.99	-2.96 (4.56; -1.36)	<0.001
Dementia	-5.11 (-12.06; 1.84)	0.15	N/A	N/A	N/A	N/A	N/A	N/A

Results from the multivariable regression models; N/A= not available

*Visual impairment as defined by the World Health Organization (<0.3 decimal BCVA); BMI=Body Mass Index, SE=Spherical equivalent, IOP=Intraocular pressure

Table 2b. Associations with peripapillary retinal nerve fiber layer thickness (pRNFLT) for each individual study (continued)

	Rotterdam 1 (n=1287)		**Rotterdam 2 (n=1376)**		**Rotterdam 3 (n=2267)**		**Twins UK (n=853)**	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Age (per year)	-0.61 (-0.87; -0.36)	<0.001	-0.91 (-1.08; -0.73)	<0.001	-0.50 (-0.59; -0.41)	<0.001	-0.24 (-0.29; -0.18)	<0.001
Female sex	3.70 (1.23; 6.16)	0.003	1.36 (-0.31; 3.03)	0.11	0.49 (-0.50; 1.48)	0.33	3.58 (-1.01; 8.16)	0.13
BMI (per kg/m^2)	0.11 (-0.18; 0.40)	0.46	0.00 (-0.002; 0.002)	1.00	0.12 (0.00; 0.24)	0.05	-0.07 (-0.19; 0.05)	0.27
SE (per diopter)	1.09 (0.58; 1.60)	<0.001	1.67 (1.32; 2.02)	<0.001	1.29 (1.10; 1.49)	<0.001	1.28 (1.02; 1.55)	<0.001
IOP (per mmHg)	-0.49 (-0.84; -0.14)	0.005	-0.65 (-0.91; -0.39)	<0.001	-0.05 (-0.23; 0.12)	0.56	-0.05 (-0.26; 0.16)	0.62
Visual impairment*	-11.27 (-17.93; -4.61)	<0.001	-7.68 (-13.80; -1.55)	0.01	-9.56 (-14.87; -4.24)	<0.001	N/A	N/A
Former smoker	2.60 (-0.05; 5.25)	0.06	0.87 (-0.95; 2.68)	0.36	-0.13 (-1.20; 0.95)	0.82	N/A	N/A
Current smoker	2.96 (-1.48; 7.40)	0.19	3.86 (0.94; 6.78)	0.009	1.34 (-0.18; 2.87)	0.08	N/A	N/A
Hypertension	2.08 (-1.71; 5.86)	0.28	0.46 (-1.86; 2.77)	0.70	-1.37 (-2.43; -0.31)	0.01	N/A	N/A
Diabetes	-0.54 (-3.45; 2.36)	0.71	-1.72 (-3.92; 0.48)	0.12	0.40 (-1.30; 2.10)	0.65	-4.29 (-8.34; -0.24)	0.04
Stroke	1.25 (-2.83; 5.32)	0.55	-2.06 (-5.67; 1.55)	0.26	-1.22 (-4.19; 1.76)	0.42	-1.51 (-5.49; 2.48)	0.46
Dementia	-4.17 (-8.82; 0.48)	0.08	-0.55 (-5.96; 4.86)	0.84	-1.27 (-24.41; 21.86)	0.91	N/A	N/A

Results from the multivariable regression models; N/A= not available

*Visual impairment as defined by the World Health Organization (<0.3 decimal BCVA); BMI=Body Mass Index, SE=Spherical equivalent, IOP=Intraocular pressure

Table 3. Meta-analyzed associations with peripapillary retinal nerve fiber layer thickness (pRNFLT)

	All participants			**Excluding known glaucoma**		
	β (95% CI)	p	I^2	β (95% CI)	p	I^2
Age (per year)	-0.38 (-0.57; -0.18)	<0.001	97%	-0.35 (-0.60; -0.10)	0.006	97%
Female sex	2.17 (1.15; 3.20)	<0.001	69%	1.79 (0.93; 2.65)	<0.001	59%
BMI (per kg/m^2)	0.06 (-0.02; 0.14)	0.15	54%	0.09 (0.00; 0.18)	0.05	53%
SE (per diopter)	1.39 (1.19; 1.59)	<0.001	49%	1.36 (1.16; 1.57)	<0.001	40%
IOP (per mmHg)	-0.36 (-0.56; -0.15)	<0.001	74%	-0.42 (-0.65; -0.20)	<0.001	71%
Visual impairment*	-5.50 (-9.37; -1.64)	0.005	69%	-4.75 (-9.12; -0.38)	0.03	77%
Former smoker	0.58 (0.14; 1.02)	0.009	0%	0.79 (-0.01; 1.60)	0.05	43%
Current smoker	1.53 (1.00; 2.06)	<0.001	0%	1.49 (0.97; 2.02)	<0.001	0%
Hypertension	-0.54 (-1.01; -0.07)	0.03	4%	-0.62 (-1.11; -0.13)	0.01	7%
Diabetes	-0.69 (-1.69; 0.31)	0.18	40%	-0.33 (-1.32; 0.67)	0.52	40%
Stroke	-1.94 (-3.17; -0.72)	0.002	7%	-2.06 (-3.27; -0.84)	<0.001	2%
Dementia	-3.11 (-6.22; 0.01)	0.05	0%	-2.66 (-5.86; 0.55)	0.10	0%

All participants – results of the meta analysis of the multivariable regression models including all participants (n=16084)
Excluding known glaucoma – results of the meta analysis of the multivariable regression models excluding the 619 known glaucoma patients (n= 14695, without TwinsUK Study data, since no data on glaucoma were available); I^2=Heterogeneity of covariate in the meta-analysis;
*Visual impairment as defined by the World Health Organization (<0.3 decimal BCVA); BMI=Body Mass Index, SE=Spherical equivalent, IOP=Intraocular pressure