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RESEARCH ARTICLE

Associations of inner retinal layers with risk of incident dementia: An individual participant data analysis of four prospective cohort studies

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Abstract

INTRODUCTION: Our main objective was to investigate whether retinal neurodegeneration, estimated from lower thickness of inner retinal layers, was associated with incident all-cause dementia and Alzheimer's disease (AD).

METHODS: We performed an individual participant data meta-analysis using unpublished data from four prospective cohort studies with a total of 69,955 participants ($n = 1087$ cases of incident all-cause dementia; $n = 520$ cases incident AD; follow-up time median [interquartile range] 11.3 [8.8–11.5] years).

RESULTS: General baseline characteristics of the study population were mean (standard deviation) age, 58.1 (8.8) years; 47% women. After adjustment, lower baseline macular retinal nerve fiber layer thickness was significantly associated with a 10% and 11% higher incidence of all-cause dementia and AD, respectively. Lower baseline macular ganglion cell-inner plexiform layer thickness was not significantly associated with these outcomes.

DISCUSSION: These findings suggest that retinal neurodegeneration precedes the onset of clinical dementia. Retinal imaging tools may be informative biomarkers for the study of the early pathophysiology of dementia.

KEYWORDS

Alzheimer's disease, dementia, E3 consortium, early-onset dementia cohort, epidemiology, frontotemporal dementia, OCT, optical coherence tomography, retinal imaging, retinal neurodegeneration, The Alienor Study, The Maastricht Study, The Tromsø Study, The UK Biobank, UK Biobank Eye & Vision Consortium, vascular dementia

1 | BACKGROUND

There is an imperative for the development of novel methods for the study of the early pathophysiology of dementia.^{1,2} Currently available methods have important limitations. For example, limitations of magnetic resonance imaging and biochemical quantification of proteins in cerebrospinal fluid are that these methods are expensive, invasive, time consuming, and/or do not allow for direct quantification of neuronal structures.^{3,4}

The retina has been postulated to be a window to the brain and hence may provide opportunity for the study of neurodegeneration in the early pathophysiology of clinical dementia.⁵ Indeed, retinal neurodegenerative changes have been found to be associated with cognitive decline and lower brain volume.⁵ In the retina subtle neurodegenerative changes can be non-invasively, inexpensively, and rapidly assessed with optical coherence tomography (OCT; up to a semi-histological resolution).⁵ Such changes include thinning of inner retinal layers, that is, the macular retinal nerve fiber layer (mRNFL) and the macular ganglion cell inner plexiform layer (mGCIPL); and may be detectable before the onset of clinical dementia.⁵ Lower mRNFL thickness is presumed to reflect loss of retinal ganglion cell axons; and lower mGCIPL thickness is presumed to reflect loss of retinal ganglion cells (soma and dendrites).⁵

At present there is a widely held belief that retinal imaging tools may be useful biomarkers for the study of the early pathobiology

of dementia; however, there are few prospective population-based data available to support this belief.⁵ Indeed, only one population-based study has analyzed the association of the thickness of inner retinal layers with incident dementia (<90 cases).⁶ This study found that lower peripapillary RNFL thickness was significantly associated with a higher risk of incident dementia and Alzheimer's disease (AD) and had directionally similar, though less strong, findings for mGCIPL thickness.⁶

In view of the above, the aim of this study is to investigate in an individual patient data meta-analysis, using prospective population-based data from four cohorts, (1) whether retinal neurodegeneration, estimated from lower thickness of inner retinal layers, is associated with incident all-cause dementia and AD (primary outcomes); and vascular dementia and late-onset dementia (secondary outcomes); and (2) whether these associations differ with age, sex, or apolipoprotein E (APOE) genotype status.

2 | METHODS**2.1 | Study population and design**

Prospective data from the following four observational, population-based cohort studies were used: The UK Biobank ($n = 82,860$; United Kingdom),⁷ The Tromsø Study ($n = 10,180$; Norway),⁸ The Maastricht

Study ($n = 7689$; the Netherlands),⁹ and The Alienor Study ($n = 613$; part of the Three-City Study; France).¹⁰ General characteristics (mean age \pm standard deviation [SD]; % men; median [interquartile range (IQR)] follow-up time) of the study populations are: 57.7 ± 8.3 years, 46% men, 11.3 [9.1; 11.5] years in the UK Biobank; 61.2 ± 9.9 years, 45% men, 11.0 [4.0; 11.6] years in The Tromsø Study; 60.0 ± 8.7 years, 50% men, 6.0 [5.2; 6.8] years in The Maastricht Study; and 81.9 ± 4.2 years, 37% men, 7.3 [6.1; 7.6] years in The Alienor Study). More details are presented in the [Supporting Information](#).

2.2 | Dementia

2.2.1 | Primary outcomes: All-cause dementia and AD

Data on primary outcomes were available in all cohorts. In The UK Biobank and The Tromsø studies, cases of incident dementia were identified via linkage to hospital episode statistics data (e.g., death registry and hospital inpatient records in the UK Biobank) and classified using the International Classification of Diseases, ninth and tenth revision (ICD-9 and ICD-10).¹¹ In The Maastricht Study, potential cases of incident dementia were identified via hospital records. Medical data were checked by a geriatric specialist and dementia cases were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. In The Alienor Study, potential cases of dementia were identified based on a neuropsychological test battery.¹² Those individuals who were identified as potential cases of dementia were referred to a neurologist for further diagnosis and classification of dementia according to the DSM-IV criteria.¹² More details are presented in the [Supporting Information](#).

2.2.2 | Secondary outcomes: vascular dementia and late-onset dementia

Late-onset dementia was defined as the onset of dementia at an age ≥ 65 years.¹³ Data on vascular dementia were available in all cohorts except for The Tromsø Study. Data on late-onset dementia were available in all cohorts.

2.3 | Retinal thickness indices

The thickness of inner retinal layers (i.e., mRNFL and mGCIPL) was assessed at the macula (peri-foveal) in both eyes with OCT. We calculated global mRNFL and mGCIPL thickness indices using data from both eyes (i.e., we calculated the mean thickness of both eyes), or, if data were only available for one eye, using data from that eye only. In The Alienor Study only, data on mRNFL and mIPL thickness were not presently available, hence, to be able to combine the data from all cohorts, we estimated mGCIPL thickness in The Alienor Study using mGCL thickness and reference data on the ratio between mGCL thick-

RESEARCH IN CONTEXT

- 1. Systematic review:** There is a widely held belief that retinal imaging tools may be useful biomarkers for the study of the early pathobiology of dementia; however, there are few prospective population-based data available to support this belief. Using Pubmed we identified one previous study that investigated this (up to January 1, 2023; search terms: retinal nerve fiber layer thickness, ganglion cell inner plexiform layer thickness, and incident dementia). This study found a significant association between lower retinal nerve fiber layer thickness with higher risk of incident all-cause dementia and Alzheimer's disease and weaker, non-significant, findings for lower ganglion cell-inner plexiform layer thickness ($n = 3289$ participants; 86 cases of incident dementia; 4.5-year follow-up).
- 2. Interpretation:** The present study contributes important novel data to the existing literature. Findings of this study are in line with the concept that retinal thickness biomarkers may be tools for the study of the early pathobiology of dementia.
- 3. Future directions:** Future studies may aim to further develop the concept of retinal imaging biomarkers as tools for the study of the early pathobiology of dementia. Future studies may seek to quantify the predictive value of retinal imaging biomarkers for prediction of onset and progression of dementia relative to existing risk scores. In addition, future studies may seek to evaluate to which extent retinal neurodegeneration is caused by damage to the retinal capillaries. The retinal capillary vasculature can be quantified in epidemiological studies with optical coherence tomography angiography.

ness and mIPL thickness (strongly correlated; $\rho = 0.94$) from The Maastricht Study. More details, including on the assessment of OCT image quality, are provided in the [Supporting Information](#).

In a subset of participants from The Tromsø Study ($n = 3309$ participants) OCT data were available at two moments in time (median [IQR] difference in time between OCT measurements was 7.7 [7.3, 8.0] years), allowing for the calculation of change in retinal thickness over time.

2.4 | Assessment of covariables

The following covariables were assessed at baseline (a detailed description of the assessment of all variables per cohort is provided in the [Supporting Information](#) section).

2.4.1 | Variables for the main analyses

Sociodemographic variables included age (years), sex (male/female), and educational level (higher [college/university degree or other professional qualification], upper secondary [second/final stage of secondary education], lower secondary [first stage of secondary education], vocational [work-related practical qualifications], or other).¹¹

Key dementia risk factors included body mass index (BMI; kg/m²), diabetes (presence/absence), alcohol consumption (none, moderate, high), smoking (never, former, current), antihypertensive medication (presence/absence), systolic and diastolic (office) blood pressure (mm Hg), and APOE genotype status (categorized as $\epsilon 2$ [$\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$]; $\epsilon 2/\epsilon 4$; $\epsilon 3/\epsilon 3$; $\epsilon 4$ [$\epsilon 3/\epsilon 4$ or $\epsilon 4/\epsilon 4$]).¹⁴

Eye variables were spherical equivalent (diopter) and other variables included time until death (only available in the UK Biobank, The Tromsø Study, and The Alienor Study).

2.4.2 | Variables for the additional analyses

Eye variables were the presence of any eye disease (age-related macular degeneration, glaucoma, retinopathy, cataract; presence/absence [in any eye]).

2.5 | Statistical analyses

We used Cox proportional hazards regression analyses to study the associations of baseline mRNFL and mGCIPL thickness with hazard of incident dementia (i.e., all-cause dementia; AD; vascular dementia; and late-onset dementia). We expressed associations per SD lower thickness (indicating higher levels of presumed neurodegeneration). Before we performed formal analyses, we checked whether proportional hazards assumption was not violated and whether associations were linear (both were the case; more details in the [Supporting Information](#)). We expressed results as hazard ratio (HR) with corresponding 95% confidence interval [CI].

Follow-up time was calculated as the time between OCT measurement and censoring (the date of incident dementia, the date of death, or the last date at which data on dementia and death status were available). For analyses with individual types of dementia, we censored participants who developed other types of dementia than the type of dementia of interest.¹⁵

We used the following models. In the crude model, we adjusted for cohort to account for differences in the assessment of variables between cohorts. In Model 1, we additionally adjusted for age, sex, educational level, and spherical equivalent, as these variables are key determinants of risk of dementia (age, sex, educational level [the latter is a proxy of social economic status])² or retinal thickness (spherical equivalent can affect the assessment of retinal thickness).¹⁶ In Model 2, we additionally adjusted for important risk factors for dementia that are also associated with retinal thickness (potential confounders), that is, BMI, diabetes (presence/absence), alcohol consumption (none [ref-

erence], moderate, high), smoking (never [reference], former, current), antihypertensive medication (with/without), and systolic blood pressure (continuous variable).² We adjusted for covariables in Model 2 in a separate model as these factors are weaker determinants of dementia than the covariables entered in Model 1. We did not include APOE genotype status in the model because the association of APOE genotype status with retinal thickness remains largely unknown as few data are available on this association.^{17,18} Missing data on covariables were imputed using multiple imputation analysis (more details in the [Supporting Information](#)).¹⁹

To visualize the associations between retinal thickness indices and incident dementia we plotted Kaplan–Meier curves. For these curves, retinal thickness was entered as a dichotomized variable (i.e., thick, thin, dichotomized by median thickness [i.e., < median thickness; \geq median thickness]).

To assess whether the associations differed in strength by key demographic variables (age, sex, and educational level) or by APOE genotype status, we tested for interaction with these covariables. For APOE genotype status, we hypothesized that individuals with APOE $\epsilon 4$ versus APOE $\epsilon 3$ may be more susceptible to microvascular dysfunction, and therefore also may be more susceptible to the development of clinical dementia.²⁰ To test for interaction, interaction terms were entered with the determinant in the fully adjusted model (e.g., sex x mRNFL thickness).

2.6 | Additional analyses

We performed a range of additional analyses. First, we analyzed associations in individual cohorts. Second, we analyzed the association of change in retinal thickness over time with incident dementia. Third, we repeated analyses after exclusion of individuals with eye diseases. Fourth, we analyzed the association of APOE genotype status with retinal thickness. Fifth, we performed competing risk analyses to account for risk of death.²¹ Other analyses are reported in the [Supporting Information](#).

Main analyses were performed using Statistical Package for Social Sciences version 28.0 (IBM SPSS, IBM Corp.). For all analyses (including interaction analyses) a *P*-value < 0.05 was considered statistically significant in two-sided tests.

3 | RESULTS

3.1 | Baseline retinal thickness and incident dementia

3.1.1 | Characteristics of the study population

Figure 1 shows the selection of participants for inclusion in analyses. The study population for mGCIPL thickness consisted of $N = 69,955$ participants ($N = 1087$ and $n = 520$ cases of incident all-cause dementia and AD, respectively). The study population for mRNFL thickness

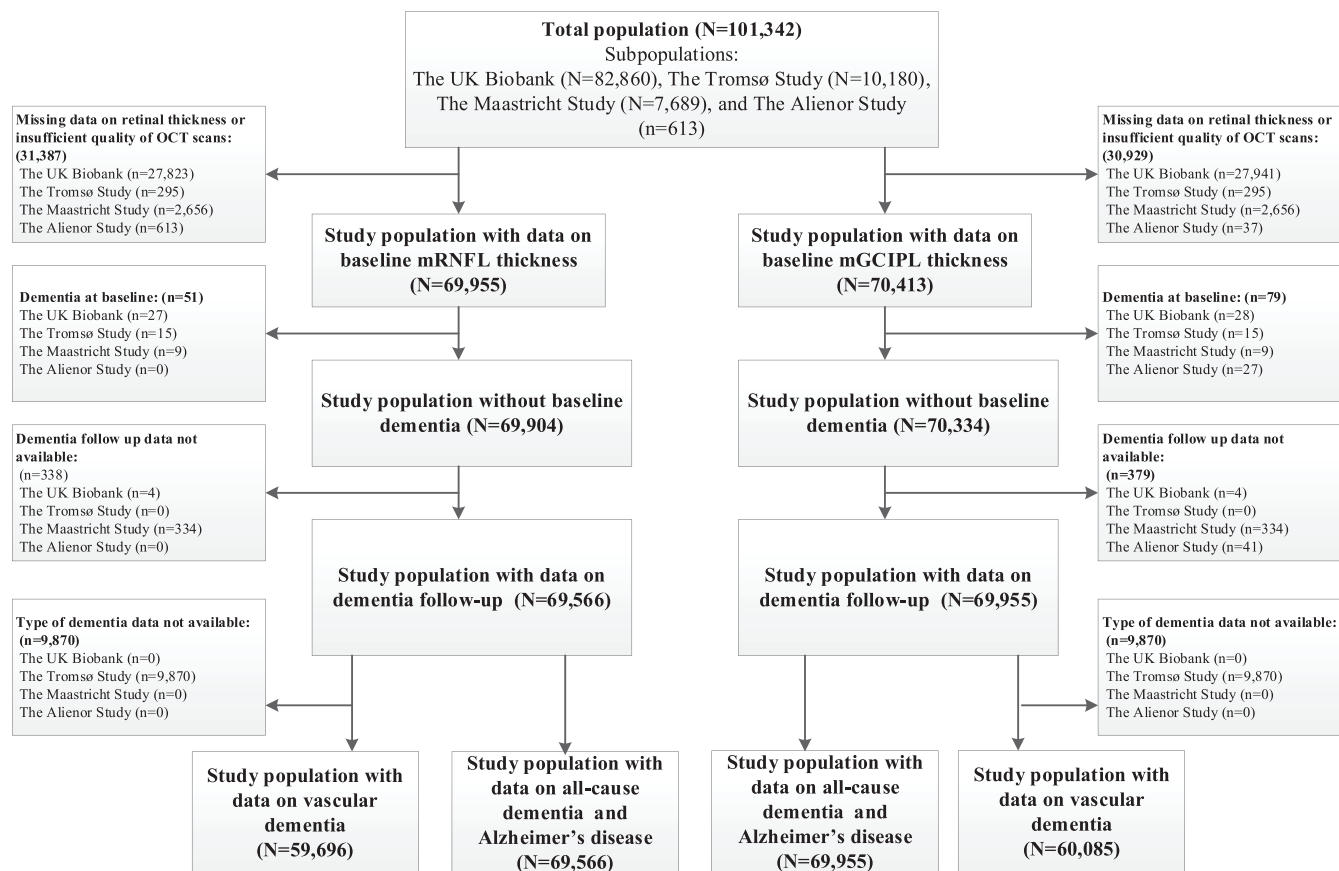


FIGURE 1 Selection of the study population with data on baseline retinal thickness. Data on covariables required for models 1 and 2 was missing for $\approx 11\%$ of the study populations. This data was imputed. Abbreviations: mRNFL, macular retinal nerve fiber layer thickness; mGCIPL, macular ganglion cell-inner plexiform layer thickness; OCT, optical coherence tomography.

consisted of $N = 69,566$ participants ($N = 985$ and $n = 450$ cases of incident all-cause dementia and AD, respectively). The median follow-up time for both study populations was 11.3 years (IQR 8.8–11.5 years).

General characteristics of the participants of the mGCIPL study population according to incident dementia status are provided in Table 1 and Table S1 in Supporting Information. Table S2 in Supporting Information shows general characteristics of the participants of the mRNFL study population. Overall, participants with incident dementia were older and had a more adverse dementia risk profile (e.g., higher blood pressure at baseline) compared to individuals without incident dementia. Characteristics of the participants included in the analyses were highly comparable to those of participants excluded from analyses due to missing data (Table S3 in Supporting Information).

3.1.2 | mRNFL

After full adjustment (Model 2), lower baseline mRNFL thickness was significantly associated with a higher incidence of all-cause dementia and AD (per SD, hazard risk [95% CI], 1.10 [1.02; 1.17] and 1.11 [1.001; 1.23], respectively; Table 2). Figure 2 in shows the Kaplan–Meier curve.

3.1.3 | mGCIPL

After full adjustment (Model 2), lower baseline mGCIPL thickness was not significantly associated with a higher incidence of all-cause dementia and AD (1.04 [0.99; 1.10] and 1.01 [0.94; 1.09], respectively; Table 2). Figure 2 shows the Kaplan–Meier curve.

3.2 | Tests for interaction

Age, sex, and APOE genotype status did not modify any of the above associations. Educational level did not consistently modify associations. *P*-values for interaction are presented in Table S4 in Supporting Information.

3.3 | Analyses with secondary outcomes

Figure 1 shows the selection of participants for inclusion in analyses. The study population for late-onset dementia was the same as for all-cause dementia and AD. For vascular dementia the study

TABLE 1 General characteristics of the study population for baseline mGCIPL thickness.

Characteristic	All-cause dementia			
	N	Overall, N = 69,955 ^a	Without, N = 68,868	With, N = 1087
Age (years), mean ± SD	N = 69,955	58.11 ± 8.82	57.93 ± 8.71	69.48 ± 8.16
Sex, n (%)	N = 69,955			
Women		36,889 (53)	36,314 (53)	575 (53)
Men		33,066 (47)	32,554 (47)	512 (47)
Educational status, n (%)	N = 69,221			
Higher		33,644 (49)	33,344 (49)	300 (28)
Upper secondary		5750 (8.3)	5687 (8.3)	63 (5.9)
Lower secondary		13,903 (20)	13,744 (20)	159 (15)
Vocational		5628 (8.1)	5485 (8.0)	143 (13)
Other		10,296 (15)	9894 (15)	402 (38)
Diabetes, n (%)	N = 69,726			
Without diabetes		65,016 (93)	64,087 (93)	929 (86)
With diabetes		4710 (6.8)	4564 (6.6)	146 (14)
Spherical equivalent (dpt), median (IQR)	N = 69,543	0.22 (−0.83–1.16)	0.22 (−0.84–1.15)	0.81 (−0.26–1.93)
Office systolic blood pressure (mmHg), mean ± SD	N = 69,736	136.90 ± 18.95	136.77 ± 18.88	145.21 ± 21.48
Office diastolic blood pressure (mmHg), mean ± SD	N = 69,734	80.50 ± 10.25	80.53 ± 10.24	78.99 ± 10.94
Antihypertensive medication use, n (%)	N = 69,955			
Without antihypertensive medication at baseline		53,366 (76)	52,770 (77)	596 (55)
With antihypertensive medication at baseline		16,589 (24)	16,098 (23)	491 (45)
Body-mass index (kg/m ²), mean ± SD	N = 69,719	27.23 ± 4.64	27.24 ± 4.64	27.08 ± 4.71
Alcohol consumption, n (%)	N = 63,892			
None		11,271 (18)	10,907 (17)	364 (37)
Moderate		29,665 (46)	29,239 (46)	426 (43)
High		22,956 (36)	22,758 (36)	198 (20)
Smoking status, n (%)	N = 69,712			
Never		36,211 (52)	35,721 (52)	490 (45)
Former		26,258 (38)	25,792 (38)	466 (43)
Current		7243 (10)	7122 (10)	121 (11)
APOE genotype status				
ε2/ε2, n (%)	N = 55,615	352 (0.6)	349 (0.6)	3 (0.5)
ε2/ε3, n (%)	N = 55,615	6711 (12)	6658 (12)	53 (8.1)
ε2/ε4, n (%)	N = 55,615	1398 (2.5)	1381 (2.5)	17 (2.6)
ε3/ε3, n (%)	N = 55,615	32,840 (59)	32,561 (59)	279 (43)
ε3/ε4, n (%)	N = 55,615	13,011 (23)	12,770 (23)	241 (37)
ε4/ε4, n (%)	N = 55,615	1300 (2.3)	1238 (2.3)	62 (9.5)
Baseline retinal thickness indices				
mRNFL thickness* (μm), mean ± SD	N = 69,566	29.27 ± 4.90	29.26 ± 4.90	29.36 ± 4.85
mGCIPL thickness (μm), mean ± SD	N = 69,955	74.55 ± 6.95	74.56 ± 6.91	73.89 ± 9.16
Types of dementia				
Alzheimer's disease, n (%)	N = 69,955	520 (0.7)	0 (0)	520 (48)
Vascular dementia, n (%)	N = 60,085	109 (0.2)	0 (0)	109 (16)
Frontotemporal dementia, n (%)	N = 60,085	14 (<0.1)	0 (0)	14 (2.1)
Early-onset dementia, n (%)	N = 69,955	70 (0.1)	0 (0)	70 (6)
Late-onset dementia, n (%)	N = 69,955	1017 (1.5)	0 (0)	1017 (94)

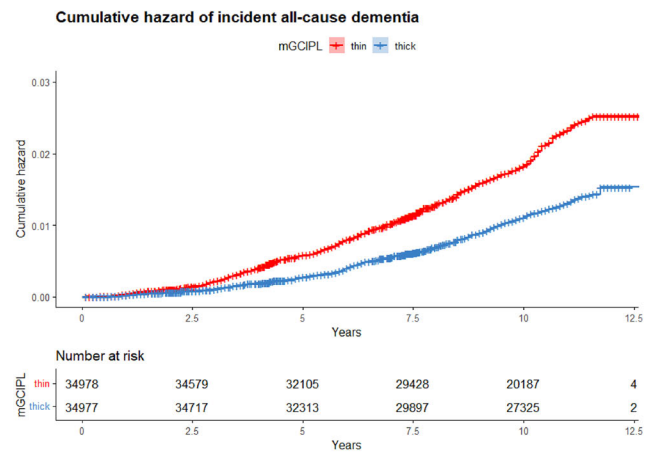
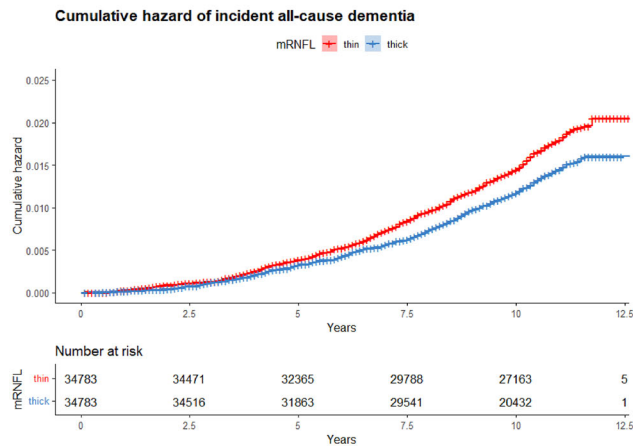
Abbreviations: APOE, apolipoprotein E; IQR, interquartile range; mGCIPL, macular ganglion cell-inner plexiform layer; mRNFL, macular retinal nerve fiber layer; SD, standard deviation.

^aMean ± SD; n (%); median (IQR).

*Shown for the population with complete data on mRNFL thickness (n = 69,566).

mRNFL

mGCIPL



S2.1 mRNFL

S2.2 mGCIPL

FIGURE 2 Kaplan–Meier plots for all-cause incident dementia according to mRNFL thickness and mGCIPL thickness. Figure S2 in Supporting Information shows the hazard of incident all-cause dementia according to median thickness (thin [in red]; lower than median thickness) or thick [in blue]; median thickness or larger than median retinal thickness). Data are shown for the study populations with complete data on mRNFL thickness (2.1) or mGCIPL thickness (2.2) and incident all-cause dementia. Abbreviations: mRNFL, macular retinal nerve fiber layer; mGCIPL, macular ganglion cell-inner plexiform layer.

TABLE 2 Associations of baseline retinal thickness indices with incident dementia.

		Incident dementia	
		All-cause dementia	Alzheimer's disease
Model		<i>n</i> = 69,566 (985 cases)	<i>n</i> = 69,566 (450 cases)
		HR (95% CI)	HR (95% CI)
mRNFL, per SD lower	Crude	1.29 (1.20 to 1.40)	1.31 (1.17 to 1.46)
	1	1.10 (1.03 to 1.18)	1.11 (1.004 to 1.23)
	2	1.10 (1.02 to 1.17)	1.11 (1.001 to 1.23)
		All cause dementia	Alzheimer's disease
		<i>n</i> = 69,955 (1087 cases)	<i>n</i> = 69,955 (520 cases)
		HR (95% CI)	HR (95% CI)
mGCIPL, per SD lower	Crude	1.30 (1.25 to 1.36)	1.24 (1.17 to 1.32)
	1	1.04 (0.99 to 1.10)	1.01 (0.94 to 1.09)
	2	1.04 (0.99 to 1.10)	1.01 (0.94 to 1.09)

Notes: Variables entered in models: Crude: cohort; model 1: Crude + age, sex, educational level, and spherical equivalent; model 2: model 1 + BMI, diabetes, alcohol consumption, smoking status, antihypertensive medication, and systolic blood pressure. Bold indicates *P*-value < 0.05. Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; mGCIPL, macular ganglion cell-inner plexiform layer; mRNFL, macular retinal nerve fiber layer; SD, standard deviation.

populations for mGCIPL thickness consisted of *N* = 60,085 participants (*N* = 109) and for mRNFL thickness the study population consisted of and *N* = 59,696 participants (*N* = 97 cases). The

median follow-up time for both study populations was 11.3 years (IQR 8.8–11.5 years).

3.3.1 | mRNFL

After full adjustment (Model 2), lower baseline mRNFL thickness was significantly associated with a higher incidence of late-onset dementia (1.08 [1.01; 1.16]), and was numerically identically, though not statistically significantly, associated with a higher incidence of vascular dementia (1.08 [0.85; 1.36]; Table 3).

3.3.2 | mGCIPL

After full adjustment (Model 2), lower baseline mGCIPL thickness was not significantly associated with vascular dementia (1.17 [0.98; 1.40]) or late-onset dementia (1.02 [0.97; 1.08]; Table 3).

3.4 | Additional analyses

We had quantitatively similar results in a range of additional analyses (Tables S5–S13 in Supporting Information). Here we highlight main findings, all results of additional analyses reported in the Supporting Information section. First, we found that associations did not statistically differ according to cohort (*P* interaction-value for cohort > 0.05). Second, greater change in mRNFL and mGCIPL thickness over time (i.e., retinal thinning) was significantly associated with a higher risk of

TABLE 3 Associations of baseline retinal thickness indices with vascular dementia and late-onset dementia.

		Incident dementia	
		Vascular dementia	Late-onset disease
Model		<i>n</i> = 59,696 (97 cases)	<i>n</i> = 69,566 (914 cases)
		HR (95% CI)	HR (95% CI)
mRNFL, per SD lower	Crude	1.28 (1.003 to 1.63)	1.29 (1.19 to 1.39)
	1	1.13 (0.89 to 1.42)	1.08 (1.01 to 1.16)
	2	1.08 (0.85 to 1.36)	1.08 (1.01 to 1.16)
		Vascular dementia	Late-onset disease
		<i>n</i> = 60,085 (109 cases)	<i>n</i> = 69,955 (1017 cases)
		HR (95% CI)	HR (95% CI)
mGCIPL, per SD lower	Crude	1.32 (1.13 to 1.56)	1.31 (1.25 to 1.37)
	1	1.16 (0.97 to 1.39)	1.02 (0.97 to 1.08)
	2	1.17 (0.98 to 1.40)	1.02 (0.97 to 1.08)

Notes: Variables entered in models: Crude: cohort; model 1: Crude + age, sex, educational level, and spherical equivalent; model 2: model 1 + BMI, diabetes, alcohol consumption, smoking status, antihypertensive medication, and systolic blood pressure. Bold indicates *P*-value < 0.05. Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard risk; mGCIPL, macular ganglion cell-inner plexiform layer; mRNFL, macular retinal nerve fiber layer; SD, standard deviation.

incident dementia (*n* = 3309; *n* = 64 cases of incident all-cause dementia; per SD greater mRNFL and GCIPL thickness change, HR [95%CI] for incident all-cause dementia 1.19 [1.05; 1.35] and 1.17 [0.999; 1.39], respectively; Table S6). Findings were similar for incident AD (*n* = 34 cases). Third, associations remained similar when we repeated analyses after exclusion of individuals with eye diseases (Table S11). Fourth, a higher number of $\epsilon 4$ alleles was significantly associated with lower mRNFL thickness (per allele, -0.02 [-0.03 ; -0.001] SD mRNFL thickness) but not lower mGCIPL thickness (beta per allele increase, -0.01 [-0.03 ; 0.01] SD; Table S10). Last, we had similar findings to those shown in Table 2 when we used competing risk analyses (Table S13).

4 | DISCUSSION

The present individual participant data meta-analysis, using data from *n* = 70,000 participants followed over *n* = 10 years (>1000 cases of incident all-cause dementia), has four main findings. First, lower mRNFL thickness was significantly associated with an approximately 10% higher risk per SD of incident all-cause dementia and AD. Second, lower mGCIPL thickness was associated with an $\approx 5\%$ increase per SD in risk of all-cause dementia and AD, though not reaching statistical significance. Third, associations of mRNFL and mGCIPL thickness with dementia other than AD dementia were generally similar to our findings for AD. Fourth, associations of mRNFL and mGCIPL thickness with incident dementia did not differ with age, sex, educational level, or APOE genotype status.

Findings of the present study contribute important novel data to the existing literature. Indeed, this is the largest study to date on the prospective association of retinal thickness with incident dementia (providing considerably more data than the existing literature [$>70,000$ participants and >1000 cases of incident dementia versus *n* = 3289 participants; 86 cases of incident dementia]).⁶ Moreover, it is the first study to (1) investigate the associations of retinal thickness with other types of dementia than AD, (2) investigate the association of change in retinal thickness over time with incident dementia, and (3) investigate whether associations of retinal thickness with incident dementia differ according to APOE genotype status.

Lower mRNFL thickness was approximately twice as strongly associated with incident all-cause dementia and AD than lower mGCIPL thickness. Possibly this may be because lower mRNFL thickness reflects loss of synapses whereas lower mGCIPL thickness (mainly) reflects loss of neuronal gray matter atrophy; and synaptic deterioration precedes gray matter atrophy.⁵ Indeed, consistent with this concept, synaptic loss is a stronger predictor of cognitive decline and dementia than gray matter atrophy.^{22,23}

We hypothesized that the associations of mRNFL thickness and mGCIPL thickness with incident dementia may be stronger in individuals with one or two APOE $\epsilon 4$ alleles because the APOE $\epsilon 4$ genotype is associated with cerebral vascular disease.²⁰ However, we did not find evidence for such an interaction, possibly because it may be difficult to show such an interaction. APOE $\epsilon 4$ genotype status can predispose to an increased risk for dementia via other mechanisms in which APOE genotype is not an effect modifier.²⁰ For example, APOE $\epsilon 4$ genotype can directly predispose to neurodegeneration because the APOE $\epsilon 4$ genotype is associated with an impaired removal of neurotoxins such as amyloid beta in neuronal tissue.²⁰

This study has many strengths. First, the use of data from multiple large European, population-based cohort studies enables us to draw conclusions that are valid in the general population and reduces the chance that our results are affected by selection bias.²⁴ Second, due to the prospective nature of the data, we could account for temporality and, thus, can conclude that mRNFL and mGCIPL thinning precedes incident clinical dementia.²⁴ Third, we adjusted for a large number of potential confounders, which reduces the chance that unmeasured confounding spuriously affects the strength of associations under study (i.e., confounding bias).²⁴ Fourth, many variables included in this study were assessed in a standardized manner with state-of-the-art methods (e.g., mRNFL and mGCIPL thickness), which reduces the chance that measurement error affects associations under study (i.e., information bias).²⁴

This study also has certain limitations. First, in most cohorts the cases of incident dementia were identified from medical records, which is a less precise method to determine the diagnosis of dementia than via neuropsychological tests.¹² This may have resulted in misclassification, which may have reduced statistical power to detect an association.²⁴ Individuals with earlier (subclinical) stages of dementia may not have been detected from hospital records. In addition, the false positive classification of individuals as dementia cases may also have resulted in an underestimation of the strength of the

associations under study.²⁴ Second, we had relatively low numbers of cases for other types of dementia than AD and were not able to investigate all subtypes of dementia (e.g., Lewy body dementia and Parkinson's disease dementia).²⁴ Third, there were relatively few cases of incident dementia among participants with the *APOE* ϵ 2 genotype (<50 cases); hence there was limited statistical power to detect whether the associations under study differed between participants with *APOE* ϵ 2 versus *APOE* ϵ 3 genotype. Fourth, even though we took an extensive set of confounders into account, we cannot fully exclude unmeasured confounding.²⁴ For example, we did not account for other genetic factors than *APOE* genotype status in the analyses. Last, the study population mainly consisted of White individuals; whether findings are generalizable to populations with other ethnicities requires further study.²⁴

5 | CONCLUSION

The present individual participant data meta-analysis found that retinal neurodegeneration, estimated from lower inner retinal layer thickness, was associated with a 5% to 10% higher risk of incident all-cause dementia and AD. These findings support the concept that retinal neurodegeneration precedes the onset of clinical dementia and that retinal imaging tools may be informative biomarkers for the study of the early pathophysiology of dementia.

AUTHOR CONTRIBUTIONS

Frank C. T. van der Heide contributed to conception and design, participated in acquisition of data, analyzed and interpreted data, coordinated the acquisition of data, drafted the manuscript (with Coen D. A. Stehouwer [Netherlands], Anthony Khawaja [UK], Geir Bertelsen [Norway], and Catherine Helmer [France]), revised the manuscript critically for important intellectual content, and provided final approval of the version to be published. Frank C. T. van der Heide also is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Tos T. J. M. Berendschot, Thomas J. Littlejohns, Elżbieta Kuźma, Robert Luben, Therese von Hanno, Sara C. L. Rebouças, Leslie Grasset, Cécile Delcourt, Carroll A. Webers, Anthony Khajawa, Martien C. J. M. van Dongen, Simone J. P. M. Eussen, Casper Schalkwijk, Henrik Schirmer, Sebastian Koehler, Miranda Schram, Gabriella A. M. Blokland, David E. J. Linden, Praveen J. Patel, Paul J. Foster, Bente Johnsen, and Anke Wesselius, contributed to conception and design, revised the manuscript critically for important intellectual content, and provided final approval of the version to be published. The E3 consortium and the UK Biobank Eye & Vision Consortium contributed to data collection and combining data. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

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CONFLICT OF INTEREST STATEMENT

A.P.K. has acted as a consultant to Abbvie, Aerie, Google Health, Novartis, Reichert, Santen, and Thea. For all other authors, no potential conflicts of interest relevant to this article were reported. Author disclosures are available in the Supporting Information 2.

DATA AVAILABILITY STATEMENT

Data are available for any researcher who meets the criteria for access to confidential data; the corresponding author may be contacted to request data.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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