# Bidirectional retinal oculomics in Parkinson disease: A cross-sectional and longitudinal analysis of two cohort studies

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## Background

**Background:**

- Parkinson Disease (PD) and Nigrostriatal dopaminergic degeneration
- Evidence of detectable brain degeneration decades before diagnosis
- Dopaminergic content in the retina is reduced in Parkinson disease in cadaveric study[1]

**However, it remains unclear whether this can be reliably detected with in vivo imaging.**

## Objective

**Objective:** We want to know

- Do individuals with prevalent Parkinson disease have thinner Retinal Nerve Fiber Layer(RNFL), Ganglion Cell-Inner Plexiform Layer (GCIPL) and/or Inner Nuclear Layer (INL)?
- Are any differences in these inner retinal layers also associated with incident / developing Parkinson disease?

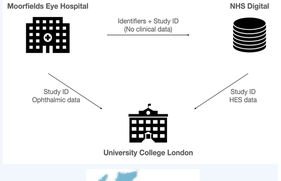
**How?** We investigated inner retinal anatomy, measured using Optical Coherence Tomography (OCT)

- prevalent PD in a retrospective cohort
- incident (developing) PD using a prospective cohort

## Methods part 1

**AlzEye Cohort[2]:** used for prevalent PD

- Retrospective cohort of patients aged 40+ years attending Moorfields Eye Hospital between 2008 and 2018
- 154,830 patients with retinal imaging
- Individual-level ophthalmic data linked with all UK hospital admissions
- PD case definition = ICD-10 code of G20 (positive predictive value of 84%[3])
- Those with all-cause dementia excluded






**UK Biobank[4]:** used for incident / developing PD

- Prospective cohort study
- >500,000 participants
- 22 assessment centres across UK
- Ophthalmic assessment (n=67,320)
- Parkinson disease case definition = ICD-10 code G20 and self-report
- Excluded those who self-reported any eye disease

**Retinal Imaging:** Macula-centered OCT

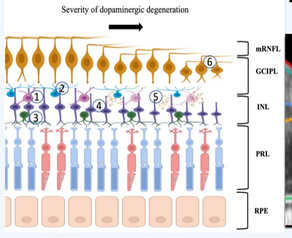
- AlzEye - 5 different Topcon devices (80% on the Topcon 3D-OCT 2000)
- UK Biobank - Topcon 3D-OCT 1000 MK II
- Segmentation via TABS *('Topcon Advanced Boundary Segmentation Tool')*
- Parafoveal segments analyzed
- Quality control based on image metadata

**Statistical Analysis:** models adjusted for age, sex, ethnicity, diabetes & hypertension

- AlzEye (Prevalent Parkinson disease)
  - Linear mixed effects models
  - Multiple imputation used for ethnicity (missing for 19.4%)
- UK Biobank (Incident Parkinson disease)
  - Frailty models
  - Removed those with prevalent Parkinson disease, and incomplete cases

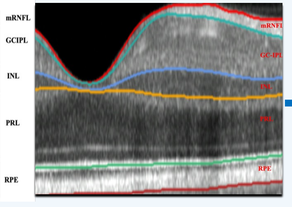
## Methods part 2

### Cell Types in the retina



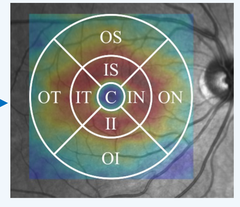

(1) Dopaminergic cells (in IPL and INL)
(2) amacrine AII cells (pre-synaptic)
(3) horizontal cells
(4) bipolar cells (postsynaptic)
(5) INL (aggregation of proteins α synuclein)

### In-Vivo OCT Layer Segmentation on B-scan



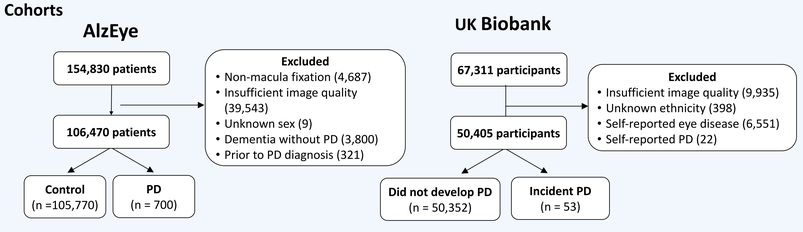

RNFL: myelinated retinal nerve fiber layer
GCIPL: macular ganglion cell-inner plexiform layer
INL: inner nuclear layer
PRL: photoreceptor layer
RPE: retinal pigment epithelium

### En-Face Thickness per Layer per ETDRS region




O: Outer I : Inner C: Center
T: Temporal N: Nasal
S: Superior I: Inferior

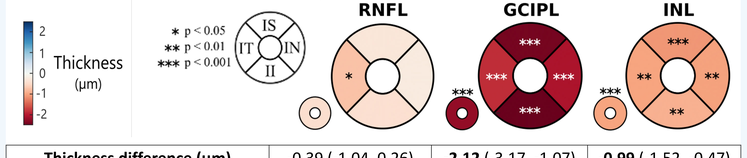
### Cohorts




## Results 1. Prevalent Parkinson Disease (=current PD)

In AlzEye cohort

- 700 individuals with prevalent PD and 105,770 controls (mean age 65.5 ± 13.5 years, 51.7% female).
- **individuals with prevalent PD had**
  - **thinner GCIPL** (-2.12 µm, 95% confidence interval: -3.17, -1.07, p = 8.2 × 10-5)
  - **thinner INL** (-0.99 µm, 95% confidence interval: -1.52, -0.47, p = 2.1 × 10-4)

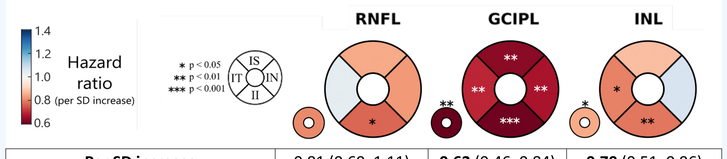



| Thickness difference (µm) | -0.39 (-1.04, 0.26) | **-2.12** (-3.17, -1.07) | **-0.99** (-1.52, -0.47) |
|---|---|---|---|
| ***P*-value** | 0.24 | **8.2 x 10$^{-5}$** | **2.1 x 10$^{-4}$** |

## Results 2. Incident Parkinson Disease (=developing PD)

In United Kingdom Biobank

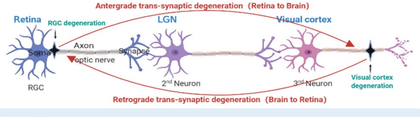
- 53 developed PD at a mean of 2653 ± 851 days
- out of 50,405 participants (mean age 56.1 ± 8.2 years, 54.7% female)
- **incident PD was associated with**
  - **thinner GCIPL** (hazard ratio: 0.62 per SD increase, 95% confidence interval: 0.46, 0.84, p=0.002)
  - **thinner INL** (hazard ratio: 0.70 per SD increase, 95% confidence interval: 0.51, 0.96, p=0.026)




| Per SD increase | 0.81 (0.60, 1.11) | **0.62** (0.46, 0.84) | **0.70** (0.51, 0.96) |
|---|---|---|---|
| ***P*-value** | 0.19 | **0.002** | **0.026** |

## Discussion

- Thinner INL: Dopaminergic degeneration?
- Thinner mGC-IPL: Retrograde or anterograde?
- Prognostic factor? Prodromal disease?




## Conclusion

- Results: Thinner mGC-IPL and INL in those with PD and those developing PD
- Differences detectable several years before clinical presentation
  ➞ highlights potential role for retinal imaging for at-risk stratification of PD
- Individual-level prediction unclear given magnitude of difference

## Miscellaneous

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