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# Normal-tension glaucoma is associated with cognitive impairment

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## ABSTRACT

**Background/aims** Recent research suggests an association between normal-tension glaucoma (NTG) and dementia. This study investigated whether cognitive impairment is more strongly associated with NTG than high tension glaucoma (HTG) using cognitive screening within an Australiasian Glaucoma Disease Registry.

**Methods** The authors completed a case–control cross-sectional cognitive screening involving 290 age-matched and sex-matched NTG participants and HTG controls aged ≥65 randomly sampled from the Australian and New Zealand Registry of Advanced Glaucoma. Cognitive screening was performed using the Telephone Version of the Montreal Cognitive Assessment (T-MoCA). The T-MoCA omits points requiring visual interpretation, accounting for confounding factors related to vision loss in visually impaired participants. Cognitive impairment was defined by a T-MoCA score of <11/22. Cognition was compared between NTG and HTG participants using predetermined thresholds and absolute screening scores.

**Results** A total of 290 participants completed cognitive assessment. There were no differences in NTG (n=144) and HTG (n=146) cohort demographics or ocular parameters at baseline. Cognitive impairment was more prevalent in the NTG cohort than the HTG cohort (OR=2.2; 95% CI 1.1 to 6.7, p=0.030). Though a linear trend was also observed between lower absolute T-MoCA scores in the NTG cohort when compared with the HTG cohort, this association was not statistically significant (p=0.108).

**Conclusion** This study demonstrated an association between NTG status and poor cognition, supporting the hypothesis that there exists a disease association and shared pathoaetiological features between NTG and dementia.

## INTRODUCTION

Glaucoma encompasses a heterogeneous group of optic neuropathies characterised by pathological optic disc cupping, retinal ganglion cell death and specific patterns of irreversible visual field loss.[1] Elevated intraocular pressure (IOP) is the single modifiable risk factor in glaucoma.[2 3] Without treatment, glaucoma leads to irreversible vision loss and is the second leading cause of blindness worldwide.[4] Recent research suggests the existence of an association between primary open-angle glaucoma (POAG) and dementia-causing diseases such as Alzheimer's Disease (AD).[5] Dementia collectively describes a group of neurodegenerative diseases that are characterised by decreased cognitive function as result of progressive neuronal loss within the central nervous system.[6 7] The international disease burdens of both of POAG and dementia are predicted to increase in the coming decades corresponding with an ageing population.[4 7]

Though some studies suggest that POAG is associated with dementia,[8–13] others do not.[14–20] A recent study meta-analysed the existing studies investigating the relationship between POAG and AD, the most common cause of dementia, and demonstrated a small, positive disease association (relative risk=1.17; 95%CI 1.00 to 1.37, p<0.001).[5] The results of the individual meta-analysed studies were heterogeneous, however, with three reporting no association[18–20] and one reporting a negative association between POAG and AD.[15] Among the meta-analysed studies reporting positive associations were two studies performed in predominantly East Asian populations including Taiwan[12 13] and Japan.[11] A unique epidemiological feature of Asian POAG is that normal-tension glaucoma (NTG) is the dominant subphenotype, representing 52%–92% of cases.[21] Conversely, in European populations, the dominant POAG subphenotype is high tension glaucoma (HTG), with NTG representing only 30%–39% of cases.[21] The single meta-analysed study demonstrating a positive association between POAG and AD in Europeans reported a high prevalence of NTG in a case-controlled AD cohort.[10] It has, thus, been suggested that the association between POAG and dementia may be specific to NTG and AD.[11]

NTG is a subtype of POAG characterised by glaucomatous retinal degeneration in the absence of observed ocular hypertension. The pathophysiology of NTG is not completely understood with various pathoaetiological hypotheses, including vascular dysregulation,[22] altered cerebrospinal fluid mechanics[23] and increased IOP sensitivity[24] having been proposed. Furthermore, the discovery of the association between NTG and both *OPTN* and *TBK1*, two genes implicated in frontotemporal dementia, suggests the possibility of shared neurodegenerative pathways in NTG and dementia.[25–27]

Previous studies investigating an association between NTG and dementia include two retrospective case–control studies involving national registries[12 17] and a small cross-sectional study.[16] The results of these studies are limited, however, by retrospective study designs or small sample sizes. We hypothesised that NTG is associated with an increased prevalence of cognitive impairment and sought to elucidate this association through a cross-sectional comparison of cognition in older NTG and HTG participants randomly sampled from a large, multicentre glaucoma registry.

## METHODS AND MATERIALS

### Ethical approval

Ethics approval was obtained through the Southern Adelaide Clinical Human Research Ethics Committee. This study adhered to the tenets of the Declaration of Helsinki and followed the National Health and Medical Research Council statement of ethical conduct in research involving humans. This was a blinded, randomised population study. Participants were part of the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) as previously described.[28]

### Sampling and inclusion criteria

ANZRAG is a large disease registry of individuals with well-phenotyped glaucoma, which was developed to identify genetic and clinical risk factors associated with glaucoma. ANZRAG currently comprises more than 7000 participants, including over 3200 with POAG. Participants in this study were sampled from ANZRAG. Selected participants were aged ≥65 years with a diagnosis of POAG defined by glaucomatous visual field defects on a reliable Humphrey 24–2 field with corresponding optic disc rim thinning, an enlarged vertical cup-to-disc ratio (≥0.7) or cup to disc asymmetry (≥0.2) between both eyes. HTG inclusion required a highest recorded IOP ≥25 mm Hg, while NTG inclusion required a highest recorded IOP ≤21 mm Hg before treatment or at diagnosis. Participants with a highest recorded IOP of 22–24 mm Hg were excluded to demarcate NTG and HTG phenotypes according to IOP. Individuals with secondary glaucoma were excluded.

Age-matched and sex-matched NTG and HTG participants were randomly sampled from ANZRAG. Selected participants were mailed invitational letters and contacted by telephone to request participation in a health questionnaire and cognitive assessment screen. If participants were unwilling to participate, or unable to complete screening, reasons were recorded when possible. If participants could not be contacted following three attempts, no further attempts were made. Two hundred and ninety participants (48.5%) completed cognitive screening (figure 1).

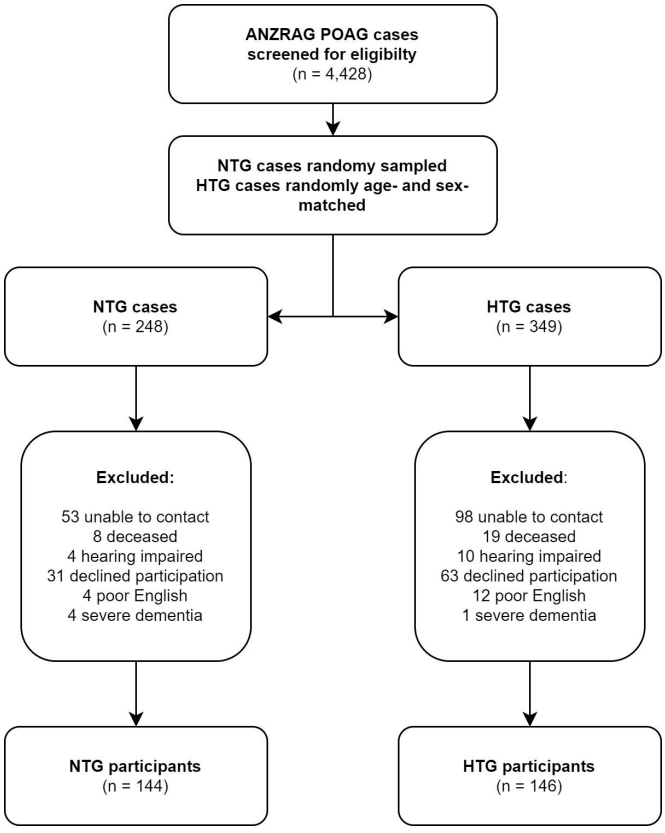


**Figure 1** Sample response profile. ANZRAG, Australian and New Zealand Registry of Advanced Glaucoma; HTG, high tension glaucoma (maximum intraocular pressure ≥25 mm Hg); NTG, normal-tension glaucoma (maximum recorded intraocular pressure ≤21 mm Hg); POAG, primary open-angle glaucoma.

### Data collection

Cognitive function was assessed using the Telephone Version of the Montreal Cognitive Assessment (T-MoCA)[29] (www.mocatest.org). Permission to use the T-MoCA was provided by Dr Ziad Nasreddine at MoCA Test Montreal. The T-MoCA is a modified version of the MoCA, which screens cognition in specific cognitive domains including attention, calculation, language, conceptual thinking, memory and orientation.[30] The advantage of using the T-MoCA to assess cognition in visually impaired patients is that it omits eight points requiring visual interpretation (including visuospatial and visual-naming functions). Key differences between the T-MoCA and the MoCA include:

- Lowering the maximal possible score from 30 to 22 (due to omission of points requiring visual interpretation).
- During the attention task in which participants are instructed to tap a pen on a table whenever the letter 'A' is read out, participants were instructed to tap the mouthpiece of the phone to facilitate accurate registration by the researcher.
- During the orientation task in which participants are instructed to provide details of their location, they were instead instructed to provide details of their current address. These details were matched against the details to which the invitation letter was posted.

All T-MoCAs were administered by one of the two investigators (SM, LX), who were blinded to participant NTG/HTG status. Within our study, 'cognitive impairment' was defined by a T-MoCA cut-off score of <11/22, as determined from a Cochrane meta-analysis of MoCA score thresholds in dementia.[31] Within this meta-analysis, two independent studies demonstrated a MoCA score threshold of <19/30 to result in the highest levels of specificity and sensitivity for the diagnosis of dementia. Our T-MoCA score threshold of <11/22 (which subtracted the eight points omitted within the T-MoCA) was selected following the premise that our results would be at least as specific as the MoCA <19/30 threshold.

During telephone interviews, information regarding the highest level of education, history of smoking (defined as ≥20 pack year history), hypertension, prior cerebrovascular accidents, diabetes and mental health issues (specifically history of depression or psychosis) was collected. Participants unable to perform cognitive screening due to poor hearing or poor English were excluded. Participants with known dementia (declared by family members at the time of telephone contact), who were sufficiently cognitively impaired that they were unable to engage in T-MoCA screening, were excluded. To account for the effect of education bias on cognitive performance, participants who had completed less than or equal to 12 years of formal education were assigned an additional point to their total T-MoCA score, as per the T-MoCA evaluation protocol.[29] Additional glaucoma-specific data including highest-recorded IOP, vertical cup-to-disk ratio, visual acuity and central corneal thickness (CCT) were obtained from the ANZRAG clinical database. All clinical information were gathered by the treating ophthalmologists, and IOP was measured using Goldmann applanation tonometry.

### Statistical analysis

All statistical analyses were performed using 'R' (V.4.0.3, RCore Team, Austria). T-MoCA scores, demographic data and ocular indices such as IOP, CCT and visual acuity were compared between NTG and HTG cohorts. T-MoCA scores were categorised according to specific cut-off scores. The absolute T-MoCA score was also assessed as a continuous variable. As age, gender and ethnicity are known to be associated with dementia and thus cognitive impairment, linear and logistic regression analyses were performed using these data as covariates. Based on a previously reported association between myopia status and cognitive impairment, this analysis was repeated using the additional covariate of mean spherical equivalence between eyes for each participant for whom these data were available.[32] As severely demented participants did not undergo cognitive screening, they were excluded from analyses. To account for potential confounding, the association between HTG/NTG status and cognitive impairment was assessed within a multivariate logistic regression analysis including dementia risk factors including age and self-reported history of smoking, stroke, hypertension and diabetes mellitus. Clinical ophthalmic data were assessed using independent-sample unpaired t-tests and Fisher's exact tests. ORs were expressed with 95% CIs. The cut-off for statistical significance (alpha) was set at 0.05.

## RESULTS

### Sample statistics

A total of 248 NTG and 349 age-matched and sex-matched HTG participants aged ≥65 were sampled from the ANZRAG database and contacted by invitational letters followed by telephone between June 2016 and July 2019 to request participation. No significant differences in self-reported clinical parameters were observed between NTG and HTG cohorts (table 1).

### Cognitive impairment

NTG status was associated with a higher prevalence of impaired cognition than HTG status (p=0.030; OR=2.2 (95% CI 1.1 to 6.7)) in a multivariate analysis adjusting for age, gender and ethnicity (table 2). When repeating this analysis including an additional covariate of mean spherical equivalence between eyes which was available for 84% of respondents, the association between NTG status and cognitive impairment remained statistically significant (p=0.046; OR=2.0 (95% CI 1.1 to 8.0)). Within the same model, the outcome of cognitive impairment was not associated with mean spherical equivalence between eyes (p=0.562). NTG status was associated with a lower absolute T-MoCA score as a continuous variable, but this association was not statistically significant (p=0.108).

Within a multivariate analysis investigating possible confounding due to history of stroke, smoking, hypertension and diabetes demonstrated a persisting association between NTG status and cognitive impairment (p=0.034; OR=2.6 (1.1 to 6.7)). Within the same model, hypertension was also associated with cognitive impairment (p=0.038; OR=1.7 (95% CI 1.0 to 2.8); table 3).

**Table 1** Response group demographic and outcome parameters

| Risk factor | NTG | HTG | P value |
|---|---|---|---|
| Cohort size (n) | 144 | 146 | |
| Age (years, mean (SD)) | 78.6 (9.5) | 77.3 (9.9) | 0.26 |
| Sex (m:f) (percentage male) | 56:88 (39%) | 53:93 (36%) | 0.72 |
| Ethnicity (European:Asian) | 142:2 | 145:1 | 0.62 |
| Stroke history | 14 (10%) | 18 (12%) | 0.58 |
| Smoker | 31 (22%) | 39 (26%) | 0.87 |
| Diabetes | 23 (16%) | 22 (15%) | 0.87 |
| Hypertension | 70 (49%) | 88 (60%) | 0.06 |
| Psychiatric history | 7 (5%) | 6 (4%) | 0.79 |

Clinical data including history of stroke, smoking, diabetes, hypertension and psychiatric history were self-reported immediately prior to T-MoCA assessment; p values were determined using independent-sample unpaired t-tests and Fisher's exact tests.
HTG, high tension glaucoma (maximum intraocular pressure ≥25 mm Hg); NTG, normal-tension glaucoma (maximum recorded intraocular pressure ≤21 mm Hg); T-MoCA, Telephone Version of the Montreal Cognitive Assessment.

### Ocular parameters

Although participants in the cognitively impaired group had lower highest-measured IOP compared with those in the cognitively normal group, the difference was not statistically significant (p=0.16) possibly due to study power. Cognitive status across all individuals with NTG and HTG was not associated with any other glaucoma disease parameters (table 4).

## DISCUSSION

This study sought to investigate the association between NTG and cognitive impairment through cognitive screening of participants with NTG randomly sampled from a national glaucoma registry. Our results demonstrated a statistically significant higher prevalence of cognitive impairment in participants with known NTG, compared with randomly matched participants with known HTG. To the best of our knowledge, this is the largest study to date assessing cognition in a glaucoma cohort and the first cross-sectional study demonstrating an association between NTG and impaired cognition when compared with a matched HTG cohort in a random sample of patients with glaucoma of predominantly European ancestry.

Our study used a validated cognitive screening tool, the T-MoCA, to assess cognition in NTG and HTG participants. Whether the impaired cognition observed in our NTG cohort was due to AD or alternative dementia syndromes, such as vascular dementia, frontotemporal dementia or Lewy body dementia, is unclear. Common dementia phenotypes are known to be difficult to distinguish clinically, as their cognitive manifestations are variable, and they commonly coexist in patients with dementia.[33] Therefore, cognitive screening tools are not diagnostic for dementia phenotypes. Test-specific cognitive screening score thresholds can be used, however, to infer a high likelihood that a patient has some form of dementia.[34] We chose the T-MoCA in this study for several reasons, including the omission of vision-dependant cues which are known to confound cognitive screening results in the visually impaired,[35] and the fact that this tool is otherwise identical to the MoCA: an extensively validated test with specific cut-off scores known to be associated with cognitive impairment and dementia.[36]

Previous studies have reported conflicting evidence regarding a potential association between NTG and AD. Bach-Holm *et al*[17] observed a negative relationship between NTG and AD in a national registry retrospective case note review of 69 individuals with NTG diagnosed at a single glaucoma centre in Denmark. Such retrospective registry studies can be susceptible, however, to the under-reporting dementia prevalence, as dementia is known to be significantly underdiagnosed.[37] Bulut *et al* conversely demonstrated a positive association between NTG and impaired cognition in a cognitive screening study involving NTG, HTG and non-glaucoma controls cognitively screened using the standardised mini-mental state examination (MMSE).[16] NTG participants in this study demonstrated similar cognitive screening scores to HTG participants but lower cognitive screening scores than controls (mean MMSE score difference=3.1; p<0.001). No adjustment was made, however, for

**Table 2** Cognitive impairment in NTG and HTG cohorts

| Number of participants | T-MoCA score | NTG | HTG | ORs (95% CI) | P value |
|---|---|---|---|---|---|
| T-MoCA completed | | 144 | 146 | | |
| Cognitively impaired | <11/22 | 21 (14.8%) | 8 (5.4%) | 2.2 (1.1 to 6.7) | 0.030* |

P values were determined by multivariate logistic regression using age, gender and ethnicity as covariates; * $p < 0.05$.
HTG, high tension glaucoma (maximum intraocular pressure ≥25 mm Hg); NTG, normal-tension glaucoma (maximum recorded intraocular pressure ≤21 mm Hg); T-MoCA, Telephone Version of the Montreal Cognitive Assessment.

vision-dependent cognitive tasks that are known to influence cognitive screening scores in visually impaired patients.[35] Several additional study limitations included small sample sizes of 20 patients per group, exclusion of patients with known dementia and sampling from a younger age range (44–73 years) unlikely to represent the dementia-at-risk age demographics.

A positive association between NTG and AD was also observed in a large East-Asian population-based national registry study of the Taiwanese National Health Insurance Research Database. In this retrospective case-controlled cohort study, Chen *et al*[12] analysed 15 317 cases of NTG compared with 61 268 age-matched and sex-matched controls and demonstrated a strong association between NTG and AD, which remained after adjusting for important AD-associated risk factors including hypertension, hyperlipidaemia and diabetes (adjusted HR=1.52 (95% CI 1.41 to 1.63)).[38] Similarly, several case–control studies, investigating glaucoma incidence in AD samples, have demonstrated high prevalence of NTG in both East-Asian[11 13] and European[10] cohorts.

Our finding of an association between NTG and cognitive impairment supports a growing body of evidence suggesting an association between NTG and dementia. AD is clinically characterised by deficits in episodic memory, which are typically assessed through objective memory tasks.[39] Episodic memory is assessed in the T-MoCA through the ability to recall five words several minutes following word registration. Though no differences were observed in memory-task scores between NTG and HTG cohorts in this study, the T-MoCA is unlikely to be of use in differentiating AD from other causes of dementia. Comprehensive clinical assessments would be required to implicate specific dementia-causing diseases in this association.

Visual impairment has been shown to result in underestimation of cognition in studies using traditional cognitive screening tools.[35] Our study is the first to account for any confounding factors related to vision loss by using a tool developed for cognitive screening in blind patients. Moreover, visual impairment is unlikely to have confounded our results given the similarity in visual acuity between NTG and HTG cohorts at baseline. Of additional interest, the results of our multivariate analysis which demonstrated no association between mean spherical equivalence between eyes and cognitive impairment does not support the hypothesis that myopia is associated with cognitive impairment.[32]

The main limitation of our study was our inability to account for the 51.5% of our sample who could not be contacted or did not participate. Though we did observe similar baseline demographics and similar prevalence of self-reported disease features between our HTG and NTG cohorts, it is possible that our results were confounded by unobserved differences in clinical features or cognition within nonparticipant subcohorts. Motivation to participate in cognitive screening may also have introduced an element of self-selection bias. However, this study involved randomised sampling and, therefore, the same conditions were observed for both HTG and NTG cohorts. Similarly, the systemic disease features reported in our analyses were collected during a telephone interview and consequently subjected to self-reporting bias. Again, though these factors may have impacted our results, we expect that the effect would have been minimal given similar baseline demographics and similar prevalences of reported disease risk factor prevalence between our study cohorts. Though our analyses have accounted for major demographic and clinical risk factors for both POAG and dementia, they did not account for other potentially confounding dementia-associated risk factors such as socioeconomic status. To the best of our knowledge; however, this study represents the most statistically comprehensive cognitive screening study of POAG and cognitive impairment to date. This study was also limited by its inability to implicate a specific dementia-phenotype association with NTG. These clinical diagnoses would require more intensive clinical assessment including neuroimaging. Finally, nondisease controls were not used in this study. Therefore, no conclusions can be made regarding the relative prevalence of cognitive impairment or systemic disease risk factors in NTG or HTG compared with the general population. However, in considering the similarity in magnitude of our OR and the unadjusted HR observed by Chen *et al*[12] between dementia prevalence in NTG and nonglaucoma controls (HR=1.66; p<0.0001), we can hypothesise that the association between POAG and dementia may apply to NTG but not HTG. Given this strong association between NTG and

**Table 3** Multivariate analysis of cognitive status and associated risk variables

| Cognitive status | Risk variable | OR | 95% CI | P value |
|---|---|---|---|---|
| Cognitively impaired (T-MoCA <11/22) | NTG status | 2.6 | 1.1 to 6.7 | 0.034* |
| | Hypertension | 1.7 | 1.0 to 2.8 | 0.038* |
| | Age | 1.0 | 1.0 to 1.1 | 0.29 |
| | Stroke history | 0.8 | 0.3 to 1.6 | 0.47 |
| | Diabetes mellitus | 1.2 | 0.6 to 2.4 | 0.56 |
| | Smoking history | 0.8 | 0.5 to 1.4 | 0.43 |

Logistic regression analysis investigating possible associations between NTG status, and systemic disease risk factors and an outcome of cognitive impairment (<11/22 T-MoCA score); *p<0.05.
NTG, normal-tension glaucoma; T-MoCA, Telephone Version of the Montreal Cognitive Assessment.

**Table 4** Glaucoma parameters and cognitive impairment

| Glaucoma parameter (mean (SD)) | Cognitive stratification | | P value |
|---|---|---|---|
| | Impaired (<11/22) | Normal (≥11/22) | |
| Total number (n) | 29 | 261 | |
| Highest measured IOP (mm Hg) | 21.9 (8.7) | 25.5 (9.4) | 0.16 |
| LogMAR BCVA | 0.36 (0.31) | 0.29 (0.40) | 0.19 |
| VCDR worst eye | 0.86 (0.09) | 0.83 (0.12) | 0.55 |
| Mean deviation worst eye (dB) | −14.4 (9.3) | −12.9 (9.2) | 0.40 |
| CCT average (µm) | 519.2 (36.7) | 525.6 (39.1) | 0.57 |

P values were determined with linear regression using age as a covariate.
LogMAR BCVA, logarithm of the minimal angle of resolution best central visual acuity; CCT, central corneal thickness; IOP, intraocular pressure; VCDR, vertical cup-to-disc ratio.

dementia, clinicians should maintain a low threshold to refer older patients with NTG for cognitive assessment.

This study addressed potential confounding due to systemic disease features including history of stroke, smoking, hypertension and diabetes mellitus. These systemic cardiovascular disease risk factors that are strongly associated with dementia were accounted for in our analyses using self-reported data collected at the time of T-MoCA administration. Though such data would ideally be collected objectively within the clinical setting, such information was not available to this study. Regardless, our results demonstrated an association between NTG status and cognitive impairment, which withstood a strong association between hypertension and cognitive impairment.

Our study demonstrates that NTG is more strongly associated with cognitive impairment than HTG in older patients with POAG. This finding supports the hypothesis that a glaucoma–dementia association applies to the NTG phenotype. This NTG–dementia association has the potential to change our understanding of NTG and provide insight into future treatment directions. Further research is required to elucidate this NTG–dementia relationship more definitively.

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**Competing interests** None declared.

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