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Assessment of the Vitreomacular Interface Using High Resolution Optical Coherence Tomography in a Population Based Cohort Study of Older Adults.

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Running head: Vitreomacular interface features in NICOLA

vitreomacular adhesion (VMA), vitreomacular interface (VMI), Vitreomacular traction (VMT), full thickness macular hole (FTMH), lamellar macular hole (LMH), age-related macular degeneration (AMD), epiretinal membrane (ERM), optical coherent tomography (OCT), the International Vitreomacular Traction Study (IVTS), spectral domain OCT (SD-OCT), Northern Ireland Cohort Study for the Longitudinal Study of Ageing (NICOLA), computer assisted home interview (CAPI), self-completion questionnaires (SCQ), Northern Ireland Clinical Research Facility (NICRF), Early Treatment Diabetic Retinopathy (ETDRS), Colour fundus photography (CFP), multicolour (MC), Network of Ophthalmic Reading Centres UK (NetWORC UK), psuedo macular hole (PMH), macular hole (MH), body mass index (BMI),

37 systolic blood pressure (SBP), diastolic blood pressure (DBP), Choroidal neovascularisation
38 (CNV), geographic atrophy (GA), high-density lipoprotein cholesterol (HDL), confidence
39 intervals (CI), odds ratios (OR).

Abstract

Objective: To describe the prevalence of vitreomacular interface (VMI) features classified using spectral-domain optical coherence tomography (SD-OCT) and their associated risk factors in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA Study).

Design: Cross-sectional population-based study

Participants: Non-institutionalised Northern Irish adults aged ≥ 40 years.

Methods: Using geographic stratification, a representative sample of people in Northern Ireland was invited to participate in the NICOLA Study. SD-OCT images of participants were graded for vitreomacular traction (VMT), macular hole (MH) and epiretinal membrane (ERM) according to the International Vitreomacular Traction Study (IVTS) Group. A subsample was graded in more detail to estimate the prevalence of VMA and VMA area detailing size and location of VMA. Descriptive analysis and risk factors for each VMI feature was determined, using generalised estimating equations. Results were standardised to the Northern Ireland population census (2011).

Main outcome measures: Cohort profile, standardised prevalence and risk factor associations of each VMI feature.

Results: 3,358 NICOLA participants who attended the health assessment had gradable SD-OCT images available for at least one eye. The prevalence of VMT was 0.5% (CI 0.31%-0.70%), MH 0.4% (CI 0.23%-0.52%) and ERM 7.6% (CI 7.0%-8.3%). The more detailed VMA analysis was done on a subsample consisting of the first 1,481 participants. The prevalence of VMA was 22.6%, (CI 21.1-24.2), VMA area ranged

from 0.25mm²-42.7mm² (mean=12.53, S.D = 6.90). In multivariate analysis increased age was associated with an increased odds ratio of VMT, MH and ERM. A lower visual acuity was associated with an increased odds ratio of VMT, MH and ERM. VMA area was positively associated with younger age and normal blood pressure. ERM and MH were more often present in more myopic eyes, an increase in levels of high-density lipoprotein (HDL)-cholesterol and triglycerides.

Conclusion: The epidemiology of VMI features within a Northern Irish population was reported and indicate VMI interactions throughout life are age dependent. Vitreous separation reduced to a greater extent in the horizontal meridians compared to the vertical, differing to previous studies. Future longitudinal studies of the evolution of these VMI changes over time would be of great interest.

83 As part of normal human ageing, vitreous liquefaction occurs with loss of the
84 homogenous gel structure present in early life. As a consequence of liquefaction and
85 perhaps degradation of the normal mechanisms of vitreoretinal attachment, vitreous
86 separation starts to occur first peripheral to the fovea, with later spontaneous
87 vitreofoveal separation and finally vitreopapillary separation. A phase of vitreomacular
88 adhesion (VMA) with gradually increasing perifoveal vitreous separation before
89 complete posterior vitreous detachment, is thus a normal part of ageing. Due to the
90 difficulty in detecting it clinically, age-related posterior vitreous detachment was initially
91 thought to have quick onset and rapid progression however with the introduction of B-
92 scan ultrasonography and optical coherence tomography (OCT) it is now known to
93 progress slowly over a long period of time before complete separation of the vitreous
94 occurs.¹ Unfortunately, pathological alterations in this sequence of events can results
95 in a variety of disorders, collectively known as vitreomacular interface (VMI) features.
96 Vitreomacular traction (VMT) is the term given to the tractional changes observed
97 when there is persistent and pathological attachment of the vitreous cortex to the fovea
98 during the process of VMA resolution. This can lead full thickness macular hole
99 (FTMH), but also in some cases lamellar macular hole (LMH), and has been implicated
100 in the aetiology of other disease processes including diabetic maculopathy and wet
101 age-related macular degeneration (AMD). Anomalous and incomplete vitreoretinal
102 separation is also thought to be key to the process responsible for epiretinal
103 membrane (ERM) formation.²⁻⁴

104 Recent advances in OCT has evoked considerable interest in the VMI as it now much
105 better visualised and evaluated in a non-invasive manner. Evaluation of OCT images
106 has revolutionised the understanding of VMI diseases and has increased in
107 importance with the introduction of pharmacologic vitreolysis for the treatment of VMT

or FTMH and focal VMA.⁵ A number of studies have described features of the VMI however there is heterogeneity in the definitions and classification of abnormalities making comparisons difficult.⁶⁻⁹ In 2013, to address variations and inconsistencies in nomenclature, the International Vitreomacular Traction Study (IVTS) Group published a classification system for diseases of the VMI.¹⁰ It was designed with clinical applicability in mind as well as for use in research studies. Some studies have estimated VMI features using data obtained on attenders at hospital clinics¹¹⁻¹⁵ which has the potential for introducing bias. The purpose of the present study is to report the prevalence of VMI features on spectral domain OCT (SD-OCT) images captured in a population setting using the definitions of the IVTS group. Furthermore, this is the first study to examine VMA area and dimensions in an aging population based study to better understand the natural progression of VMA as seen on SD-OCT.

Methods

Participants

In brief, the **Northern Ireland Cohort Study for the Longitudinal Study of Ageing** (NICOLA) is a multidisciplinary prospective population-based cohort study of the ageing population in Northern Ireland. The sampling strategy identified addresses within postcode-based geographic regions. A systematic sample was drawn from each postcode-based geographical stratum.¹⁶ Participation involved a computer assisted home interview (CAPI) conducted at the participant's home, a series of self-completion questionnaires (SCQ) and a health assessment conducted at the Northern Ireland Clinical Research Facility (NICRF) at Belfast City Hospital. Wave 1 of the study commenced in December 2013 and ended in April 2018. A total of 8452 persons completed the CAPI. Of these, 3420 (40.5%) attended for the health assessment,

consisting of anthropometric, cardiac, respiratory, cognitive and ophthalmic tests.

The ophthalmic tests included multi-modal retinal imaging using a standard retinal fundus camera (Canon CX-1 Fundus Camera (Canon U.S.A., Inc.), wide-field retinal imaging (Optos plc, Dunfermline, UK) and SD-OCT imaging (Heidelberg Engineering, Heidelberg, Germany). The Early Treatment Diabetic Retinopathy (ETDRS) chart was used to test visual acuity.¹⁷ Visual acuity was recorded as the number of letters correctly identified from either the 4m chart or the 1m chart using a pinhole occluder. Autorefraction was measured using the auto-refractometer (Shin Nippon Accuref K-900, Rexam, Japan). Spherical equivalent was calculated using the standard formula (Spherical equivalent= sphere + (cylinder/2)).

Ethical approval for the study was obtained from the School of Medicine, Dentistry and Biomedical Sciences Ethics Committee, Queen's University Belfast (Ref: 12/23). The study adhered to the Declaration of Helsinki and all participants gave informed written consent.

Image acquisition

Participants were given the option of having the pupils of neither (2592/6840, 37.9%) one eye (right eye =832/6840, 12.2%, left eye = 1424/6840, 20.8%) or both eyes dilated (1992/6840, 29.1%). Colour fundus photography (CFP), and SD-OCT images were captured irrespective of pupillary dilation, whereas multicolour (MC) images were only captured in dilated eyes. CFP of the disc and macula with 50° field of view was

performed on the Canon CX-1 Digital Fundus Camera (Canon U.S.A., Inc, Tokyo, Japan). MC images had a 30° field of view and a single macula centred image was obtained. Tomographic images (768 x768 pixels) were captured on the Spectralis SD-OCT/cSLO (Heidelberg Engineering, Heidelberg, Germany). OCT was performed at a resolution of approximately 11µm per pixel. Each OCT volume scan was composed of 61 horizontal B-scan lines with a spacing of approximately 125µm on a 30° x 25° (horizontal x vertical) scan angle and was acquired using active eye tracking and automatic real-time mean image, an averaging of 8 scans per B-scan. The macula was well positioned at the centre of the image.

VMI Grading

NICOLA Study VMI assessment

Grading was conducted to a standardised protocol with screen settings at the highest available resolution (1920 x 1080). CFP were viewed on Oculab (V3.7.98.0). OCT and MC images were graded using the Heidelberg Eye Explorer Viewing Module 6.0.13.0 (Heidelberg Engineering, Heidelberg, Germany).

Trained graders within the Network of Ophthalmic Reading Centres UK (NetWORC UK) graded repository of images from the NICOLA study. All graders were certified for study specific grading achieving 70% concordance with the grading outcomes in the standard set and subsequently checked every 3 months for drift. The average certification score for graders was 87.9% concordance. The nomenclature and definitions of the IVTS Group classification,¹⁰ was used and graders recorded the features of VMT and macular hole (MH). MHs were subdivided into, 1) FTMH 2) LMH

and 3) pseudomacular hole. VMT was further classified as, 1) inner retinal profile change only, 2) inner retinal changes with schitic spaces and 3) outer retinal change with sub retinal fluid. ERM were defined based on the Handan Eye Study,¹⁸ where an ERM was definitely present if detected on any part of the macula on either OCT or CFP (Supplementary material Table 1) (Figure 1).

VMI assessment of sub sample

In addition to the grading described above a more detailed evaluation of the VMI of the first 1500 consecutively enrolled NICOLA participants was undertaken by two independent masked trained graders:

Definition of VMA: Evidence of perifoveal vitreous cortex detachment from the retinal surface with no detectable change in foveal contour or underlying retinal tissues.¹⁰ within an area of diameter of 3000µm measured on the maximum foveal depression scan (Figure 1).

Determination of the area of VMA: All 61 B scans of the raster were scrutinized for evidence of vitreous detachment in either horizontal or vertical planes. The horizontal extent of VMA was measured on the B scan at the maximum foveal depression. To obtain this metric we determined the distance from the fovea to the nasal and temporal limits of the VMA (Figure 2A). The vertical extent of the VMA was obtained by identifying the most superior and inferior limits of the separation of the vitreous from the inner retina on the raster and recording the scan numbers (Figure 2B & 2C). The number of B scans enclosed within this set was multiplied by the distance between each B scan to obtain the vertical dimension of the VMA. Distance between each B scan was ascertained using the “image information” tab in the Heidelberg Eye Explorer Viewing Module 6.0.13.0 (Heidelberg Engineering, Heidelberg, Germany). The vertical

and horizontal extents were multiplied to compute an approximate area of the VMA. If the VMA limits extended beyond the length of the foveal scan in any meridian or if the VMA did not involve the fovea the area of the VMA was not calculated.

Quality Control

NICOLA Study

All images exhibiting features of VMT and MH were reviewed by a retinal specialist. If ERM was recorded as present on both OCT and CFP no additional arbitration was performed. Arbitration was undertaken in eyes with ERM detected on a single imaging modality with no detection on any other modality.

Subsample

Inter-observer reliability was assessed in a subset of 100 images. There was near perfect inter-observer agreement for presence of VMA (Kappa statistic 0.92). Every 1 in 20 images were double regraded for presence of VMA. Using Bland-Altman plots inter-observer reliability for temporal measurements produced 95% limits of agreement of 13.92 to -114.6, mean difference of 13.92 and no significant bias ($p=0.05$). For nasal measurements the 95% limits of agreement were -96.08 to 131.44, a mean difference of 17.68 and significant bias ($p<0.004$).

Statistical analysis

Covariate selection and categorisation

Potential risk factors were selected based on a literature search or those related to putative mechanisms proposed by the study team, they included age, sex,⁷ body mass index (BMI; kg/m²), smoking,¹⁹ hypertension, spherical equivalent,²⁰ visual acuity,²¹ plasma high-density lipoprotein (HDL)-cholesterol, triglycerides, HbA1c²² and cataract.¹¹ HbA1c, triglycerides and HDL were measured on blood samples collected at the health assessment. Age was divided into three categories; 40-59 years, 60-69 years, and > 70 years. Hypertension was defined as normal (systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg); elevated (SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (SBP 130-139 mm Hg or DBP 80-89 mm Hg); stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg).²³ Cataract status was categorised as pseudophakic, phakic cataract present and clear lens. Participants were categorised based on the HbA1c as no diabetes <42mmol/mol (<6%) -, impaired glucose regulation 42 to 47 mmol/mol (6%-6.4%) – and diabetes ≥48mmol/mol (≥6.5%).²⁴ Smoking status was categorised as never, ex-smokers and current. Choroidal neovascularisation (CNV), geographic atrophy (GA), retinal vein occlusions and diabetic retinopathy were considered as potentially confounding retinal diseases.

Analysis

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 25. Armonk, NY: IBM Corp). Inter-observer reliability was evaluated using kappa (κ) statistics²⁵ and Bland-Altman plot analyses.²⁶ Data was weighted by age and gender using the 2011 Census for Northern Ireland.²⁷ All statistics are given as a representative of the Northern Ireland population unless “unweighted” is stated. Frequency, prevalence and confidence intervals (CI) of

each VMI feature was calculated. All variables were checked for normal distribution and collinearity. Chi-squared test or Fischer exact tests (parametric categorical variables), independent sample t-test (parametric continuous variables) or Mann-Whitney (non-parametric) were used to examine differences in characteristics according to gradable and ungradable OCT images, presence or absence of each VMI feature and VMA area. Adjusted odds ratios (OR) with 95% CIs were then estimated for right and left eyes combined, using generalised estimating equations models to account for correlation between the 2 eyes. Interactions of each variable with age and sex was tested. Multivariate models included all variables that was significant in univariate analysis. Statistical significance was defined as $p < 0.05$ (2-sided).

Results

In the current analysis the health assessment was undertaken by 3420 participants. Of these, 68(2%) participants refused imaging and in 1(0.03%) participant the images of both eyes were ungradable. Data from 3351(99.97%) participants were available for analysis (Supplementary Figure 1); 3264(97.4%) had images from both eyes and in 87(2.6%) images were available from one eye only 67(77%) had no left eye images captured and 15(17%) no right eye images captured). A further 5(6%) left eye images were deemed ungradable) resulting in 6615(96.7%) images available for analysis (3336(50.4%) right eye and 3279(49.6%) left eye).

The weighted data characteristics of NICOLA participants with gradable images were compared with those without gradable images (Supplementary material Table 2). Participants with missing or ungradable images were significantly older and had poorer visual acuity. Table 1 shows the overall characteristics of participants as well as those subdivided by the presence of VMT, MH and ERM in the NICOLA Study. In participants

with gradable images the mean age was 62 (9.33), 57.3% of participants were aged 40-59 years, of which 42.6% were aged 60 years and over. 53.1% of participants were female, there was a mean spherical equivalent of 0.60 (2.41) and 13.2% were pseudophakic. On univariate analysis participants with VMT, MH and ERM were older, had a lower visual acuity and had cataracts present compared with participants without these features. VMT were also more often present in participants that had cataract surgery, a higher spherical equivalent refraction whereas MHs and ERMs were more often present in participants with a lower spherical equivalent. ERMs were more often present in males, participants with lower levels of HDL and triglycerides, participants with stage 2 hypertension, pre diabetes and diabetes (Table 1).

Prevalence of VMT, MH and ERM

Table 2 shows the estimated age stratified prevalence of VMT, MH and ERM in eyes of participants in the unweighted and weighted datasets. Unweighted represents the study sample prevalence whereas weighted represents the estimated prevalence for the Northern Ireland population.

Vitreomacular Traction

VMT was detected in 30 eyes (0.5%, CI 0.31-0.70), and in 24 of these VMA was present in the fellow eye (80%). The frequency of VMT in right eyes (53%, 16/30) was similar to that in left eyes (47%, 14/30, $p=0.75$). VMT was bilateral in 3 participants and unilateral in 24 participants. 26 VMT cases only had a change in the inner retinal profile present, whilst 4 also had inner retinal changes with schitic spaces present.

VMT prevalence increased with age, from 0.1% in those aged 40-59 years to 1.5% in those aged 70 or more years ($p<0.001$). There was no difference in the prevalence of VMT between females (14/27, 51.9%) and males (13/27, 48.1%, $p=0.89$). In the multivariable model (Table 3), the odds of VMT increased with older age [60-69 =OR = 7.07 (95% CI 1.53-32.6, $p=0.01$), 70+ = OR = 25.2 (95% CI 5.92-107.7, $p<0.001$)] and a lower visual acuity OR = 0.97 (95% CI 0.95-0.99, $p=0.001$).

Macular holes

Macular holes were seen in a total of 23 eyes (0.4%, CI 0.23-0.52). There was 7(30.4%) pseudomacular holes, 14(60.9%) LMHs and 2(8.7%) FTMH present. The FTMHs detected were classified as large (range 529 μ m - 665 μ m), none had a VMT present in their fellow eye and all were present in participants aged 70 and over. The frequency of MHs in left eyes (11/23, 48%) was similar to that of right eyes (12/23, 52%, $p=0.86$). MHs were bilateral in one participant and unilateral in 21 participants. In the multivariate model (Table 3) the odds of MH increased with older age [60-69 =OR = 4.62 (95% CI 1.54-13.88, $p=0.01$), 70+ = OR = 4.65 (95% CI 1.28-16.85, $p=0.02$)], HDL OR = 3.33 (95% CI 1.64-6.53, $p<0.001$), higher serum triglycerides OR = 22.3 (95% CI 2.90-171.2, $p=0.003$), lower visual acuity OR = 0.95 (95% CI 0.94-0.97, $p<0.001$) and a more myopic refractive error, OR = 0.89 (95% CI 0.85-0.95, $p<0.001$).

Epiretinal membranes

319 ERMs were detected in a total of 503 eyes (7.6%, CI 7.0-8.3). The frequency of ERMs
320 found in left eyes (61% 308/503) was higher than that of right eyes (196/503, 39%,
321 $p<0.001$). ERMs were bilateral in 178 participants and unilateral in the rest. Prevalence
322 of ERMs increased with age, from 3.1% in those aged 40-59 years to 18.9% in those
323 aged 70 years or more ($p<0.001$). ERMs were found in 176 (54.2%) males and 149
324 (45.8%) females ($p=0.01$). In the multivariate model (Table 3) the odds of ERM
325 increased with older age [60-69 =OR = 1.97 (95% CI 1.34-2.89, $p=0.001$), 70+ =
326 OR = 4.61 (95% CI 3.08-6.90, $p<0.001$)], higher serum triglycerides OR = 2.11 (95%
327 CI 1.06-4.21, $p=0.03$), participants with cataracts OR = 1.83 (95% CI 1.26-2.64,
328 $p=0.001$), participants that have had cataract surgery OR = 3.55 (95% CI 2.30-5.50,
329 $p<0.001$), a lower visual acuity OR = 0.97 (95% CI 0.97-0.98, $p<0.001$) and a more
330 myopic refractive error OR = 0.92 (95% CI 0.88-0.96, $p=0.001$). The odds of ERM
331 decreased with female gender OR = 0.69 (95% CI 0.52-0.91, $p=0.01$).

Relationships with other retinal conditions

VMT and ERM were more likely present in eyes with other retinal diseases including those with CNV and retinal occlusions. MHs and ERM were more often present in eyes with GA present and VMT were more often present in eyes with diabetic retinopathy present (Supplementary table 3).

Subsample

In the unweighted subsample of the first 1500 consecutive participants whose images were subjected to a more detailed grading, 2933(97.8%) images were available for analysis (53(1.7%) not captured and 14(0.5%) ungradable). The weighted prevalence of VMA was 22.6%, (CI 21.1-24.2), VMT, 0.3% (CI 0.14-0.54), MH, 0.1% (CI 0.00-0.20) and ERM, 9.7% (CI 8.66-10.80). For VMT, MH and ERMs similar prevalence was found to that observed in the overall NICOLA sample.

Vitreomacular Adhesions and Area

Table 4 shows the characteristics of participants with and without VMA in at least one eye on univariate analysis. Participants with a VMA were older than those without in the 60-69 age group (26.5% vs 19.2%) however in the 70+ age group participants without a VMA were older than participants with a VMA (26.5% vs 14.6%). VMA was more likely to be undetected in eyes with a past history of cataract surgery. On univariate analysis participants with and without VMA did not differ for other characteristics (gender, BMI, HDL, triglycerides, visual acuity, spherical equivalent, HbA1c, hypertension status and smoking) (Table 4).

The frequency of VMA in right eyes (51.0%, 342/670) was similar to that in left eyes (49.0%, 328/670, $p=0.54$). VMA was bilateral in 269 participants and unilateral in the rest. In the multivariate model (Table 4) the odds of VMA increased in participants age 60-69 [60-69 =OR = 1.27 (95% CI 1.05-1.55, $p=0.02$) and becomes less common in the 70+ age group [70+ = OR = 0.57 (95% CI 0.42-0.76, $p<0.0001$)], and participants with impaired glucose regulation OR = 1.32 (95% CI 1.04-1.67, $p=0.02$). The odds of VMA decreased with female gender OR = 0.79 (95% CI 0.66-0.94, $p=0.01$) and pseudophakic eyes OR = 0.50 (95% CI 0.30-0.83, $p=0.01$).

On examining the area of VMA in the 1040 participants with evidence of vitreous separation on both horizontal and vertical meridians. The minimum area was 0.25mm² and the maximum was 42.7mm² (mean=12.53, S.D = 6.90). The presence of VMA was the highest in the superior region (96.3%) followed by the nasal region (94.4%), temporal region (90.9%) and finally the inferior region (58.6%). The mean measurements for superior, nasal, temporal, and inferior sectors was 2.27mm (S.D = 0.56), 1.92mm (S.D = 0.73), 1.89mm (S.D = 0.68) and 2.22mm (S.D = 0.58) respectively. Extent of vitreous separation with age groups shows a consistent effect of nasal and temporal adhesions reducing throughout age groups whilst superior and inferior adhesions remained constant (Figure 3A). Figure 3B shows the extent of VMA area by age and gender. VMA area decreased and was the similar between male and females in each age group. In the 80+ age group female participants had a smaller VMA area when compared to participants in the 40-49 and 50-59 age groups.

An increase in VMA area was associated with younger age [60-69 =OR = 0.03 (95% CI 0.01-0.09, $p<0.001$), 70+ = OR = 0.001 (95% CI 0.00-0.01, $p<0.001$)]. VMA area increased in participants with a higher spherical acuity OR = 1.23 (95% CI 1.02-1.48,

p=0.03) and normal blood pressure compared to participants with stage 2 hypertension OR = 0.21 (95% CI 0.06-0.67, p=0.01) (Table 4).

Discussion

The purpose of this study was to report on the epidemiology of VMI features in a population based study. Most population based study prevalence estimates of VMI abnormalities are based on detection using fundus images.^{28,29} In this study we used multimodal imaging and particularly relied on the SD-OCT to report on the status of the VMI. To the best of our knowledge this is the first population study that provides estimates of the dimensions of VMA in an older population, and the first study that examines its dimensions in a Caucasian population.

VMA was defined as evidence of perifoveal vitreous cortex detachment from the retinal surface with no detectable change in foveal contour or underlying retinal tissues. VMA was measured on the maximum foveal depression scan and recorded as present if the sum of the nasal and/or temporal limits did not exceed 3000µm. The overall prevalence of VMA within the present study was 22.6%, a similar prevalence of VMA was found in the Beaver Dam Eye Study (26%) where SDOCT was also used.³⁰ The information on prevalence of VMI features on SD-OCT within a population based study is largely lacking with most data coming from hospital based studies or disease specific studies.^{11-15,31-33} Previous prevalence data on VMA varies greatly (14.74%-40.6%);^{31,34,35} with differences between VMA prevalence reported in the current study and other published literature likely due to the significant heterogeneity in the definitions, classification of conditions used, methods of detection and/or the study sample analysed.⁹ In keeping with other studies, we found participants with impaired

403 glucose regulation more often had a VMA present,³⁶⁻³⁸ VMA has been shown to be a
404 characteristic change in proliferative diabetic retinopathy causing worsening of the
405 proliferative process compared to eyes with no detachment or complete
406 detachment.^{38,39} Although participants classified as having diabetes in this study
407 showed no association with VMA, participants with impaired glucose regulation did,
408 few studies have examined the pre diabetes stage and its association with VMA using
409 HbA1c therefore perhaps VMA manifests earlier in the disease process than initially
410 thought. In this study VMA increased with age in the 60-69 age group and decreased
411 in the 70+ age group compared to the 40-59 age group. The decrease in odds of VMA
412 found in the 70+ age group supports the view that the VMA in these participants
413 progress to complete posterior vitreous detachment. The lower prevalence in the 70+
414 age group may be related to the timing of vitreous detachment. The process of
415 detachment begins around the macula, then the centre of the macula, followed by the
416 disc, and finally there is a complete posterior vitreous detachment in older subjects.⁹
417 The lack of gender difference for VMA is interesting and agrees with the lack of gender
418 difference with VMT, however different to that of FTMH which has a higher incidence
419 in females.⁴⁰ VMA was less likely found in phakic eyes and pseudophakic eyes in the
420 NICOLA Study, supporting the findings in the Alienor Study.¹¹ This supports the view
421 that movement and biochemical changes in the vitreous during and after cataract
422 surgery can result in the vitreous becoming fully detached.⁴¹ In this study VMA was
423 more likely present in males than females. If we believe a VMA is considered as a
424 precursor of complete posterior vitreous detachment of the vitreous the results in this
425 study are concordant with previous studies^{6,42} where complete detachment of the
426 vitreous was associated with female gender.

In addition we have provided metrics on the limits of attachment and the patterns of separation. We showed that the area of VMA was larger in younger participants which is consistent with findings by Palacio et al where they looked at healthy subjects without clinical pathology over nine decades of life.⁴³ VMA area was also found to be larger in participants with a higher spherical equivalent and normal blood pressure. It is uncertain if the association between larger VMA area and normal blood pressure is a real or coincidental as it hasn't been found before and we do not have a hypothesis for the mechanism underlying this finding. This is the first study to look at multiple associations with VMA area and while some are easily explained mechanistically, others are not and will require replication and further investigation in other cohorts. Few studies have charted the sequence of vitreous separation in normal eyes. We found that evidence of vitreous separation was greatest superiorly followed by nasally, temporally and inferiorly. Superior vitreous separation has been consistently recorded at higher levels than inferiorly in other studies, presumably secondary to gravity.^{9,44} We found however that the length of persistent VMA was lowest horizontally, the opposite of previous studies^{6,45} from east Asian countries suggesting ethnic differences may affect the pattern of vitreous separation.

The prevalence of VMT using the definition provided in the IVTS Group¹⁰ was similar in the NICOLA Study (0.5%) compared to that seen by a hospital based study carried out in Spain (0.6%).⁴⁶ When compared to other population based studies the prevalence of VMT in the NICOLA Study was noticeably lower to that reported by the Beaver Dam Eye Study (1.6%) which in turn was different from that of the Beijing Eye Study (2.4%). The higher prevalence in the Beijing Eye Study may be related to the fact that myopia which is highly prevalent in China is associated with VMT. We also observed an association between older age and lower visual acuity with the presence

of VMT consistent with the Beaver Dam Eye Study and other studies.^{6,7} The higher prevalence of VMT found in the Beaver Dam Eye Study compared to the NICOLA Study may be due to the age profile used in each study. In the Beaver Dam Eye Study the mean age was 74.1 years (range 43-84 years) compared to a mean age of 62 years (range 40-96 years) in the NICOLA Study.

The overall prevalence of MHs, which included FTMH, LMH and pseudomacular holes within the NICOLA Study was 0.4%. Currently available prevalence data on MHs varies.^{28,29,47} In the NICOLA Study all cases of full thickness MH (n=3) occurred in the older participants (>70+ years)⁴⁸ and had reduced visual acuity.⁴⁹ Although the numbers were few we found a weak association with high HDL, triglycerides and highly myopic eyes. Vitreous liquefaction and degeneration with development of traction, lower concentrations of collagen, proteins and hyaluronic acid in myopic eyes are likely factors in the developments of macular holes of all three subtypes.⁵⁰

ERMs were observed at a prevalence of 7.6% and similar to that seen in the Blue Mountains Study (7%)²⁸, the Melbourne Visual Impairment Project (6%)⁵¹ and the Maastricht Study.⁵² When compared to some of the other population based studies the rate observed in the NICOLA Study is considerably higher^{53,18} but lower than of the Beaver Dam Eye Study (34.1%)⁷ and Los Angeles Latino Eye Study (19.9%).⁵⁴ These differences likely attributable to the imaging methods and the definitions used to grade ERMs. Nonetheless we observed similarities in that the prevalence of ERMs increased strongly with age from 23% in those aged 40-59 years to 54% in those aged 70 years or more ($p<0.001$).^{46,52,55} Not surprisingly, we found that presenting visual acuity was significantly worse in participants with an ERM than those without,^{28,29} and the prevalence of ERM was higher in pseudophakes when compared to participants with a clear lens and those with retinal vascular occlusions and CNV.^{18,29} Interestingly

the prevalence of ERM was also higher in phakic eyes with cataract when compared to clear lens perhaps suggesting a genetic association. Our study also showed that more myopic eyes were at risk of ERM, similar to that reported in the Singapore Indian Eye Study and The Handan Eye Study and Melbourne Visual Impairment Project.^{18,20,51}

Our study has several strengths. It is the first population based study to report on the health of the VMI and associations with risk factors. We used standardised protocols to acquire and grade SD-OCT images. A limitation of our study in common with other studies previously undertaken was our inability to identify a complete vitreous detachment from a complete attachment of the vitreous as only a small area of the retina is included in the scan area and ultrasound was not performed. Another limitation was the low response rate with only some 40.5% of the participants who completed the CAPI willing to attend the clinical assessment. When comparing the attending group (40.5%) to the non-attending group there was a higher percentage of females in the non-attending group (57.5%) compared to the attending group (52.1%) ($p<0.001$) with non-attending participants being older (70+ age group= 37.8% vs 25%, $p<0.001$). There was also a higher percentage of current smokers in the non-attending group (21.1%) when compared to the attending group (10.1%) ($p<0.001$). However, we attempted to minimise the potential impact through the use of population based weightings of age and gender.

In conclusion, we have described normal and pathological changes in the VMI in an ageing Caucasian population. Vitreomacular adhesion is shown to reduce gradually with age after onset, and reduced in prevalence with vitreous separation in pseudophakic eyes and females. In this population it reduced to a greater extent in the

horizontal meridians compared to the vertical, in contradistinction to previous studies in other ethnic groups. ERMs increased in prevalence with age reaching a prevalence of 19% in those over 70 years old, and were commoner in men and pseudophakic eyes. VMT and macular holes were much rarer at 0.5% overall, but again increasing in prevalence with age. The study was a cross sectional population based study and longitudinal studies of the evolution of these VMI changes over time would be of great interest.

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Figures

Figure 1 An example of a vitreomacular adhesion from the NICOLA study. A: White arrows shows the first point of vitreous separation from the surface of the retina at the nasal and temporal limits, B: White arrow shows attachment of the vitreous with distortion of the foveal surface. C: Lamellar macular hole with irregular foveal contour (white arrow), photoreceptor layer remains intact. D: Epiretinal membrane, white arrows point to the thin hyper reflective band on the neurosensory retina. In regions

where there is separation of the hyper reflective band from the retina puckering is seen.

Figure 2 A: Nasal (1903µm) and temporal (1918µm) limits of detachment (white arrows) measured on the B scan transecting the maximum foveal depression site. B: The superior most B scan (48/61) showing complete separation between the vitreous and the internal limiting membrane across the entire length of the scan. C: The inferior most B scan (8/61) showing complete separation between the vitreous and internal limiting membrane along the entire length of the scan.

Figure 3 A: Bar graph showing the extent of vitreomacular adhesion measured from the maximum foveal depression site for each sector on the retina (superior, inferior, nasal and temporal) with age. Superior and inferior measurements remained constant with age whereas the nasal and temporal measurements consistently decreased with increasing age. B: Graph showing the extent of vitreomacular adhesion area by age and gender. Area of vitreomacular adhesion decreased with age and was similar between male and females with the exception of females in the

80+ group where vitreomacular adhesion area was smaller than that of females aged 40-59 years.

708 **Table 1. Characteristics of participants with gradable images and according to vitreomacular interface status. Weights were applied**
709 **to measure the number of people in the population that are represented by each member of the sample.**

710

Characteristic		Participants with gradable images	Vitreomacular Traction Present	Vitreomacular Traction Absent	p value	Macular Hole Present	Macular Hole Absent	p value	Epiretinal Membrane Present	Epiretinal Membrane Absent	p value
Number		N=3358	N=27	N=3331		N=22	N=3336		N=325	N=3033	
Age group n(%)	40 – 59	1926 (57.3)	2 (7.4)	1924 (57.8)	<0.001	3 (14.6)	1922 (57.6)	<0.001	79(24.3)	1847(60.9)	<0.001
	60 – 69	703 (20.9)	6 (22.2)	697(20.9)		8 (38.1)	695 (20.8)		75 (23.1)	628 (20.7)	
	70+	729 (21.7)	19 (70.4)	710 (21.3)		11 (47.3)	719 (21.6)		171 (52.6)	558(18.4)	
Gender n(%)	Female	1784 (53.1)	14 (52)	1770 (53.1)	0.89	13 (59.1)	1771 (53.1)	0.57	149 (45.8)	1635(53.9)	0.01
	Male	1574 (46.9)	13 (48)	1561 (46.9)		9 (40.9)	1565 (46.9)		176 (54.2)	1398 (46.1)	
BMI (Kg/m ²) median(IQR)		28.1(5.9)	27.5 (6.3)	28.2 (5.9)	0.29	27.3(6)	28.1 (5.9)	0.14	28.1(5.70)	28.2 (5.96)	0.67
High density lipoprotein (HDL) mean(SD)		1.62 (0.43)	1.51 (0.36)	1.62 (0.43)	0.10	1.74 (0.43)	1.62 (0.43)	0.19	1.57 (0.41)	1.63 (0.44)	0.002
Triglycerides median(IQR)		1.44 (0.99)	1.46 (1.66)	1.44 (0.99)	0.81	1.95 (1.67)	1.44 (0.98)	0.01	1.51(1.06)	1.44 (0.97)	0.03

Visual Acuity median (IQR)		83.00 (6.0)	76.8 (12)	82.0 (6)	<0.001	78.4 (18)	83.0 (6)	<0.001	79.0 (8)	83.0 (6)	<0.001
Spherical Equivalent mean(SD)		0.60 (2.41)	1.53 (1.93)	0.60 (2.41)	0.02	-0.05 (2.47)	0.61(2.41)	0.04	0.33 (2.41)	0.63 (2.41)	0.01
Cataract n(%)	Clear Lens	2836 (84.7)	17 (63)	2819 (84.9)	0.002	13 (61.9)	2823 (84.9)	0.01	194 (59.7)	2642(87.4)	<0.001
	Psuedophakic	174 (5.2)	2 (7.4)	171 (5.1)		4 (19.0)	170 (5.1)		65(20.0)	109 (3.6)	
	Phakic Cataract	339 (10.1)	8 (29.6)	331 (10)		4 (19.0)	334 (10.0)		66 (20.3)	273 (9.0)	
HbA1c n(%)	No Diabetes	2165(77.8)	14 (70)	2151 (81.9)	0.57	16 (84.2)	2149(77.8)	0.76	176 (69.3)	1989(78.7)	0.003
	Impaired glucose regulation	344(12.4)	4 (20)	340 (12.3)		2 (10.5)	342(12.4)		43(16.9)	301(11.9)	
	Diabetes	273(9.8)	2 (10)	271 (9.8)		1 (5.3)	272 (9.8)		35 (13.8)	238(9.4)	
Smoking n(%)	Never	1817 (54.3)	16 (57.1)	1802 (54.2)	0.48	11 (50.0)	1806 (54.3)	0.50	183 (56.3)	1635(54.0)	0.10
	Ex-smoker	1179 (35.2)	11 (39.3)	1168 (35.2)		7 (31.8)	1172 (35.2)		119 (36.6)	1060(35.0)	
	Current	352 (10.5)	1 (3.6)	352 (10.6)		4 (18.2)	349 (10.5)		23 (7.1)	330 (10.9)	
Hypertension n(%)	Normal	828 (24.8)	5 (20)	823 (24.9)	0.59	4 (18.2)	824 (24.9)	0.85	62 (19.3)	766 (25.4)	0.04
	Elevated	341 (10.2)	4 (16)	337 (10.2)		3 (13.6)	338 (10.2)		37 (11.5)	305 (10.1)	

	Stage 1	923 (27.7)	5 (20)	918 (27.7)		7 (31.8)	916 (27.6)		85 (26.4)	837 (27.8)	
	Stage 2	1243 (37.3)	11 (44)	1231 (37.2)		8 (36.4)	1235 (37.3)		138 (42.9)	1105 (36.7)	

Table 2. Prevalence of vitreomacular interface features at eye level in the overall sample and age group stratified prevalence using unweighted and weighted data. Number n, prevalence %, and confidence intervals CI.

Vitreomacular Interface feature	Age Groups	Unweighted Prevalence n eyes n(%,CI)	Weighted Prevalence n eyes n(%,CI)
Vitreomacular Traction	Total	39 (0.6, 0.43-0.81)	30 (0.5, 0.31-0.70)
	40-59	1 (2.6, 0.13-15.1)	2 (0.1, 0.0-0.2)
	60-69	11 (28.2, 15.6-45.1)	6 (0.4, 0.2-0.9)
	70+	27 (69.2, 52.3-82.5)	22 (1.5, 55.6-85.8)
Macular Hole	Total	31 (0.5, 0.33-0.67)	23 (0.3, 0.23-0.52)
	40-59	2 (6.5, 1.12-22.8)	3 (0.1, 0.0-0.2)
	60-69	17 (54.8, 36.3-72.2)	9 (0.6, 0.3-1.2)
	70+	12 (38.7, 22.4-57.7)	11 (0.8, 0.4-1.4)
Epiretinal Membrane	Total	602 (9.1, 8.42-9.82)	503 (7.6, 7.0-8.3)
	40-59	74 (12.3, 9.83-15.2)	117 (3.1, 2.5-3.7)
	60-69	211 (35.0, 31.3-39.0)	116 (8.3, 6.9-9.9)
	70+	317 (52.7, 48.6-56.7)	270 (18.9, 16.9-21.1)

716 **Table 3 Generalised estimating equation investigating associations between each vitreomacular feature and potential risk**
717 **factors. Each feature was adjusted for age* and gender† and multivariate adjustment.**

718

		Vitreomacular Traction				Macular Hole				Epiretinal Membrane			
		Age and Sex adjusted		Multivariate adjusted		Age and Sex adjusted		Multivariate adjusted		Age and Sex adjusted		Multivariate adjusted	
		OR(95%CI)	p-value	OR(95%CI)	p-value	OR(95%CI)	p-value	OR(95%CI)	p-value	OR(95%CI)	p-value	OR(95%CI)	p-value
Age group	40-59	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	60-69	10.67(2.38-47.91)	0.002†	7.07(1.53-32.6)	0.01	8.47(2.75-26.11)	<0.001†	4.62(1.54-13.88)	0.01	2.85(2.16-3.77)	<0.001†	1.97(1.34-2.89)	0.001
	70+	40.52(9.59-171.14)	<0.001†	25.2(5.92-107.7)	<0.001	9.44(3.04-29.29)	<0.001†	4.65(1.28-16.85)	0.02	7.20(5.53-9.38)	<0.001†	4.61(3.08-6.90)	<0.001
Sex	Female	1.23(0.62-2.42)	0.56*	1.20(0.59-2.44)	0.62	2.02(0.97-4.19)	0.06*	1.49(0.65-3.42)	0.35	0.79(0.64-0.98)	0.03*	0.69(0.52-0.91)	0.01
	Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
BMI (Kg/m²)		0.10(0.00-20.7)	0.40			0.06(0.00-5.33)	0.22			0.77(0.18-3.42)	0.74		
HDL		0.57(0.25-1.28)	0.17			1.67(0.85-3.29)	0.14	3.33(1.64-6.53)	<0.001	0.94(0.72-1.23)	0.66	1.00(0.69-1.44)	0.99
Triglycerides		1.02(0.11-9.37)	0.98			10.93(1.40-85.47)	0.02	22.3(2.90-171.2)	0.003	1.90(1.09-3.29)	0.02	2.11(1.06-4.21)	0.03

Visual Acuity		0.97(0.95-0.99)	<0.001	0.97(0.95-0.99)	0.001	0.96(0.94-0.97)	<0.001	0.95(0.94-0.97)	<0.001	0.98(0.97-0.98)	<0.001	0.97(0.97-0.98)	<0.001
Spherical Equivalent		1.07(0.95-1.21)	0.25	1.06(0.96-1.17)	0.29	0.88(0.83-0.94)	<0.001	0.89(0.85-0.95)	<0.001	0.90(0.87-0.93)	<0.001	0.92(0.88-0.96)	0.001
Cataract	Clear Lens	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Psuedophakic	0.61(1.17-2.21)	0.45	0.71(1.19-2.70)	0.61	2.75(0.93-8.17)	0.07	1.77(0.57-5.55)	0.33	3.83(2.70-5.42)	<0.001	3.55(2.30-5.50)	<0.001
	Phakic Cataract	1.24(0.56-2.75)	0.59	1.34(0.58-3.13)	0.49	2.07(0.72-5.92)	0.18	1.86(0.67-5.19)	0.24	1.71(1.26-2.31)	0.001	1.83(1.26-2.64)	0.001
HbA1c	No Diabetes	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Impaired glucose regulation	1.26(0.45-3.52)	0.66			0.59(0.18-1.96)	0.39			1.15(0.84-1.58)	0.39	0.89(0.61-1.30)	0.56
	Diabetes	0.69(0.20-2.42)	0.56			0.23(0.03-1.72)	0.15			1.15(0.80-1.66)	0.45	0.93(0.61-1.42)	0.73
Smoking	Never	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Ex-smoker	0.98(0.49-1.96)	0.96			1.18(0.52-2.68)	0.68			0.85(0.68-1.06)	0.15	0.92(0.69-1.23)	0.59
	Current	0.34(0.05-2.48)	0.29			2.64(0.89-7.79)	0.08			0.77(0.51-1.16)	0.21	0.86(0.51-1.43)	0.55
Hypertension	Normal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Elevated	1.63(0.35-3.88)	0.81			1.01(0.29-3.51)	0.99			0.91(0.62-1.35)	0.63	1.11(0.68-1.80)	0.69

	Stage 1	0.53(0.17-1.69)	0.28			1.30(0.45-3.72)	0.63			1.03(0.76-1.41)	0.83	1.15(0.77-1.73)	0.49
	Stage 2	0.89(0.32-2.45)	0.83			0.87(0.32-2.39)	0.79			1.02(0.76-1.37)	0.91	1.12(0.76-1.66)	0.55

Table 4. Characteristics of sub-sample of participants included in analysis according to vitreomacular adhesion status and vitreomacular adhesion area. Generalised estimating equation investigating associations between vitreomacular adhesion and potential risk factors and vitreomacular adhesion area and potential risk factors. Each feature was adjusted for age* and gender† and multivariate adjustment.

		Vitreomacular Adhesion				Vitreomacular Adhesion				Vitreomacular Adhesion Area mm ²				
Characteristic		Participants with gradable images	Participants with VMA Present	Participants with VMA Absent	p value	Age and Sex adjusted		Multivariate adjusted		VMA Area mm ²	Age and Sex adjusted		Multivariate adjusted	
Number		N=1481	N=514	N=967		OR (95%CI)	p-value	OR (95%CI)	p-value	N=395	OR (95%CI)	p-value	OR(95%CI)	p-value
Age group n(%)	40 – 59	829 (55.9)	303 (58.9)	525 (54.3)	<0.001	Ref	Ref	Ref	Ref	289 (73.2)	Ref	Ref	Ref	Ref
	60 – 69	321 (21.7)	136 (26.5)	186 (19.2)		1.22(1.01-1.46)	0.04†	1.27(1.05-1.55)	0.02	69 (17.7)	0.001(0.00-0.01)	<0.001†	0.03(0.01-0.09)	<0.001
	70+	331 (22.4)	75 (14.6)	256 (26.5)		0.52(0.41-0.68)	<0.001†	0.57(0.42-0.76)	<0.001	37 (9.1)	0.03(0.01-0.08)	<0.001†	0.001(0.00-0.01)	<0.001
Gender n(%)	Female	791 (53.4)	260 (50.6)	532 (55.0)	0.10	0.80(0.68-0.95)	0.01*	0.79(0.66-0.94)	0.01	216 (54.7)	0.85(0.37-1.92)	0.69	1.24(0.48-3.21)	0.66

	Male	690 (46.6)	254 (49.4)	435 (45.0)		Ref	Ref	Ref	Ref	179 (45.3)	Ref	Ref	Ref	Ref
BMI (Kg/m ²) median(IQR)		28.0 (5.9)	27.9 (5.6)	27.9 (5.9)	0.84	0.69(0.22-2.18)	0.53			28.1 (5.96)	7.88(0.01-6091)	0.54		
High density lipoprotein (HDL) mean(SD)		1.60 (0.44)	1.59 (0.44)	1.60 (0.44)	0.47	0.97(0.78-1.20)	0.78			1.61(0.42)	0.54(0.1+-1.55)	0.25		
Triglycerides median(IQR)		1.45 (1.00)	1.42 (0.90)	1.45 (1.02)	0.99	0.87(0.59-1.27)	0.46			1.48(0.99)	3.35(0.55-20.2)	0.19		
Visual Acuity median (IQR)		83.0 (6)	83.0 (5)	83.0 (6)	0.06	1.00(0.99-1.00)	0.86			84.0(6.0)	1.01(0.98-1.04)	0.50	1.00(0.97-1.04)	0.98
Spherical Equivalent mean(SD)		0.51 (2.60)	0.60 (2.62)	0.49 (2.60)	0.37	1.03(0.99-1.08)	0.11			0.24(2.40)	1.25(1.04-1.50)	0.02	1.23(1.02-1.48)	0.03
Cataract n(%)	Clear Lens	1262 (85.3)	463 (90.1)	799 (82.7)	<0.001	Ref	Ref	Ref	Ref	370(93.7)	Ref	Ref	Ref	Ref
	Psuedophakic	88(5.9)	15 (2.9)	73 (7.6)		0.50(0.31-0.81)	0.01	0.50(0.30-0.83)	0.01	7(1.8)	0.14(0.01-1.61)	0.11	1.51(0.30-7.66)	0.62
	Phakic Cataract	129 (8.7)	36 (7.0)	94 (9.7)		0.83(0.60-1.16)	0.27	0.84(0.60-1.19)	0.33	18(4.6)	0.23(0.04-1.45)	0.12	2.42(0.57-10.3)	0.23
HbA1c n(%)	No Diabetes	1015(72.7)	341 (71.3)	674 (73.3)	0.24	Ref	Ref	Ref	Ref	288 (78.3)	Ref	Ref	Ref	Ref
	Impaired glucose regulation	218 (15.6)	85(17.8)	133 (14.5)		1.30(1.03-1.65)	0.03	1.32(1.04-1.67)	0.02	54(14.7)	1.00(0.27-3.70)	0.99		
	Diabetes	164 (11.7)	52 (10.9)	112 (12.2)		1.02(0.77-1.34)	0.92	1.02(0.77-1.34)	0.91	26 (7.0)	0.93(0.17-5.16)	0.93		

Smoking n(%)	Never	805 (54.4)	269 (52.3)	536 (55.5)	0.22	Ref	Ref	Ref	Ref	212 (53.8)	Ref	Ref	Ref	Ref
	Ex-smoker	528 (35.7)	185 (36.0)	343 (35.5)		1.07(0.89-1.29)	0.45			139 (35.1)	0.81(0.35-1.87)	0.61		
	Current	147 (10.0)	60 (11.7)	87 (9.0)		1.02(0.78-1.29)	0.45			44 (11.1)	1.65(0.40-6.89)	0.49		
Hypertension n(%)	Normal	373 (25.3)	135 (26.3)	238 (24.7)	0.37	Ref	Ref	Ref	Ref	103 (26.1)	Ref	Ref	Ref	Ref
	Elevated	135 (9.1)	38 (7.4)	97 (10.1)		0.80(0.57-1.13)	0.21			40 (10.2)	4.56(0.82-25.5)	0.09	2.67(0.41-17.40)	0.31
	Stage 1	393 (26.6)	136 (26.5)	257 (26.7)		0.92(0.72-1.16)	0.46			123(31.2)	1.25(0.40-3.87)	0.70	0.77(0.21-2.78)	0.69
	Stage 2	575 (39.0)	205 (39.9)	370 (38.5)		0.96(0.77-1.21)	0.73			129 (32.5)	0.32(0.11-0.92)	0.03	0.21(0.06-0.67)	0.01

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726 **Table 2 Characteristics of participants with gradable and ungradable images, NICOLA Study 2013-2018. Weights were**
727 **applied to measure the number of people in the population that are represented by each member of the sample.**

		Participants with gradable images n(%)	Participants with ungradable images n(%)	P value
Number		3358 (98)	62 (2)	
Age group n(%)	40 – 59	1926 (57.3)	24 (38.6)	0.01
	60 – 69	703 (20.9)	15 (24.1)	
	70+	729 (21.7)	23 (37.3)	

Gender n(%)	Female	1784 (53.1)	29 (46.5)	0.30
	Male	1574 (46.9)	33 (53.5)	
BMI (Kg/m²) median(IQR)		28.9(5.15)	29.5 (5.6)	0.41
High density lipoprotein (HDL) mean(SD)		1.62 (0.44)	1.57 (0.4)	0.40
Triglycerides median(IQR)		1.63 (0.95)	1.67 (1.08)	0.80
Visual Acuity median (IQR)		82.00 (6.0)	80.0 (10.0)	<0.001
Spherical Equivalent mean(SD)		0.60 (2.41)	0.53 (4.03)	0.82
Cataract n (%)	Clear Lens	2213 (65.9)	42 (68.0)	0.20
	Psuedophakic	442(13.2)	4 (5.9)	
	Phakic Cataract	703 (20.9)	16 (26.1)	
HbA1c n(%)	No Diabetes	2275(81.8)	32 (71.0)	0.15
	Impaired glucose regulation	233 (8.4)	5 (11.6)	
	Diabetes	273(9.8)	8 (17.4)	
Smoking n(%)	Never	1817 (54.3)	26 (42.3)	0.18
	Ex-smoker	1179 (35.2)	28 (44.9)	

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	Current	352 (10.5)	8 (12.8)	0.47
Hypertension n(%)	Normal	828 (24.7)	15 (23.4)	
	Elevated	341 (10.2)	8 (12.6)	
	Stage 1	923 (27.6)	12 (19.6)	
	Stage 2	1253 (37.5)	27 (44.4)	

745 **Table 3 Relationship of other ocular diseases and conditions to prevalence of vitreomacular interface features.**

746 ***Too few participants to obtain reliable estimate. CA = Condition Absent. CP = Condition Present.**

			VMT			MH			ERM		
Condition	CA(N)	CP(N)	CA N(%)	CP N(%)	P value	CA N(%)	CP N(%)	P value	CA N(%)	CP N(%)	P value
GA	6217	14	14(0.2)	0(0.0)	‡	13(0.2)	1(5.3)	<0.001	(10)0.2	3(0.7)	0.03
CNV	6218	13	12(0.2)	1(3.4)	<0.001	13(0.2)	0(0.0)	‡	(7)0.1	6(1.4)	<0.001
DR	6153	77	75(1.2)	2(6.9)	0.01	77(1.2)	0(0.0)	‡	(69)1.2	9(2.0)	0.13
Occlusion	6219	12	11(0.2)	1(3.4)	<0.001	12(0.2)	0(0.0)	‡	(8)0.1	4(0.9)	<0.001

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755 **Table 4. Relationship of other ocular diseases and conditions to presence of VMA and VMA area measurement calculated**
756 **in participants.**

757 **‡Too few participants to obtain reliable estimate. CA = Condition Absent. CP = Condition Present.**

			VMA		
Condition	CA(N)	CP(N)	CA N(%)	CP N(%)	P value
GA	2730	3	2(0.1)	1(0.1)	0.78
CNV	2726	7	7(0.3)	0(0.0)	‡
DR	2691	40	30(1.5)	10(1.4)	0.86
Occlusion	2726	6	4(0.2)	2(0.3)	0.69

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