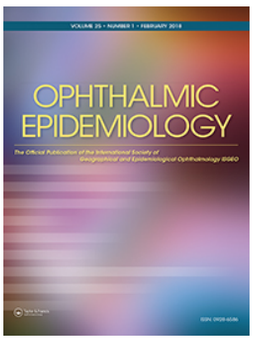

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Can ultra-wide field retinal imaging replace colour digital stereoscopy for glaucoma detection?

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ABSTRACT

Purpose: Ultra-wide field (UWF) retinal imaging (Optomap, Optos plc, Dunfermline, UK) is a novel technique to image the peripheral fundus. The goal of this study was to explore the potential use of UWF imaging to detect glaucoma, and specifically to evaluate the reproducibility of measures of vertical cup-to-disc ratio (VCDR) using ultra-wide field (UWF), and the agreement between UWF and standard colour digital stereoscopy (CDS).

Methods: An observational study. From a population-based epidemiological study we selected 100 eyes from 100 consecutive participants who were imaged using both standard CDS and UWF retinal imaging. Estimation of the VCDR using both modalities was made by a masked glaucoma specialist and two masked independent observers. Reliability and agreement between colour digital stereoscopy and the UWF imaging was assessed by Bland-Altman scatterplots.

Results: Intra-observer reproducibility of the UWF imaging in estimating VCDRs produced Limits of Agreement (LOA) ranging from −0.13 to 0.1 (mean 0.02) and −0.14 to 0.14 (mean 0.0004) for observer 1 and 2 respectively. Inter-observer reliability between observer 1 and the glaucoma specialist for VCDR measurements using CDS and UWF produced LOA ranging from −0.37 to 0.15 (mean −0.11) and −0.24 to 0.26 (mean 0.0005) respectively. Bland Altman plots produced LOA of −0.16 to 0.20 (mean 0.02) between the two imaging methods for assessing VCDR when carried out by a glaucoma specialist.

Conclusion: Grading of UWF imaging has high reproducibility in evaluating VCDR and agreement with stereoscopic optic disc imaging and may be suitable for glaucoma diagnosis in situations where CDS is not available.

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Glaucoma; Optos; colour fundus photography; comparison

Introduction

Glaucoma is a degenerative, sight-threatening disease regarded as one of the major causes of blindness, accounting for an estimated 60 million people worldwide. By the year 2020 this number is thought to increase to around 80 million people globally.[1] At present, according to current clinical guidelines,[2,3] combinations of tests are used to detect the presence of glaucoma, mainly visual field tests and optic disc examination.

The gold standard tool for optic disc assessment is a clinical examination with dilated slit-lamp bio-microscopy[2] carried out by a glaucoma specialist who will identify typical changes associated with glaucoma. However clinical examination by an expert clinician may not be feasible when evaluating large populations within epidemiology studies. For this purpose digital imaging of the optic nerve head (ONH) is more efficient, with methods including colour digital stereoscopic photography, retinal tomography (RT) and SD-OCT. As part of the optic disc/nerve head assessment, a commonly used structural parameter used to diagnose glaucoma is the vertical cup-to-disc ratio (VCDR). The VCDR indicates the diameter of the cup expressed as a fraction of the diameter of the disc along the vertical meridian and provides an estimate of the health of the optic disc. The VCDR is particularly useful because glaucoma preferentially thins the superior and inferior neuroretinal rim, although it has limitations mainly because VCDR is correlated with optic disc size. Previous studies have reported on intra- and inter-grader agreement on estimating vertical CDR (VCDR)[4,5] and area and radial CDR,[6] as well as comparing these estimations using different imaging modalities such as optical coherence tomography (OCT),[7] slit-lamp bio-microscopy,[8] confocal scanning laser tomography[9] and stereo disc images[10] in assessing glaucomatous changes at the optic disc. The Optomap (Optos plc, Dunfermline, UK) is increasingly being used in both optometric and ophthalmological contexts as well as in research cohort studies, and while its comparability with colour fundus photography has been confirmed for diabetic retinopathy[11] it is not known whether it can be used for optic disc/nerve head assessment.

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A factor to consider when estimating VCDRs using different ophthalmic techniques is the dimension of the image it produces. When observing stereo disc images a three-dimensional (3D) image is visible, allowing detection of elevation and depression at different points across the optic disc. In addition to this, improved optic disc vessel pathways and contouring can be seen. Overall, this information on depth in combination with "true colour" capturing the stereoscopic image of the optic disc gives a "true life like" image. In contrast to this, the optic disc image seen using UWF imaging is a two-dimensional (2D) image, potentially losing valuable information in regards to cup depression, elevation and vessel contours. It also produces a pseudocolour image, possibly altering the appearance of the neuro retinal rim which is integral to the interpretation and grading of the optic disc. However, in saying this previous studies have reported on the value of non-stereo fundus images to evaluate disc cupping[12,13] with Sharma and colleagues reporting no differences in diagnostic performance between monoscopic and stereoscopic images when detecting glaucoma.[14]

Therefore we have evaluated the potential use of ultra-wide field (UWF) retinal imaging (Optomap Optos plc, Dunfermline, UK) for glaucoma detection by evaluating the reproducibility of VCDR data and agreement between UWF and the standard colour digital stereoscopy (CDS) from 100 consecutive participants from the Northern Ireland Cohort for the Longitudinal Study of Aging (NICOLA). We also evaluated how many patients underwent successful testing and explored the sensitivity of the UWF in detecting pathological discs according to a standard epidemiological definition.[15]

Materials and methods

Participants

Stereoscopic optic disc and UWF images from 100 consecutive participants who participated in the NICOLA study were selected. The NICOLA study is an epidemiological study of aging started in February 2014. A representative sample of persons over the age of 50 has been recruited from across Northern Ireland. The study consists of a computer-assisted home interview and health assessment which is carried out at The Wellcome Trust-Wolfson Northern Ireland Clinical Research Facility (NICRF) at Belfast City Hospital. The health assessment consists of a variety of anthropometric, cardiac, respiratory, cognitive, and ophthalmic tests. The ophthalmic tests include 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). For the purposes of the current study we have selected 100 consecutive participants who chose to have at least one eye dilated from the cohort. Institutional review board approval was obtained from the School of Medicine, Dentistry and Biomedical Sciences Ethics Committee, Queen's University Belfast (Ref: 12/23).

Image acquisition

Images were captured using a standard protocol by trained research nurses according to standardised protocols. In brief, stereoscopic 45° colour fundus photographs were taken using the Canon CX-1 Fundus Camera (Canon U.S.A., Inc.) for all NICOLA participants. In each photograph, the optic disc was well positioned at the centre of the photograph.

UWF colour images were captured using the Optomap Panoramic 200Tx scanning laser ophthalmoscope (SLO) (Optos plc, Dunfermline, UK). Two central colour images per eye were acquired. All digital images were stored and then transferred to the Central Angiographic Resource Facility (CARF) based at Queen's University, Belfast.

Grading methods

All colour fundus disc photographs and UWF retinal images were graded by two masked trained observers and one masked glaucoma specialist (AAB) (expert observer). There was approximately 1 month between grading the first (CDS) and second (UWF) measurements to reduce the possibility of remembering previous data. The dilated eye was chosen as the study eye, if both eyes were dilated one eye was chosen at random. Observers 1 and 2 regraded 50 Optomap images to assess intra-observer reliability independently of each other.

Colour digital stereoscopy grading

Disc photographs were opened in the Oculab (V3.7.98.0) imaging platform and graded by measuring the diameter of the optic cup to the diameter of the optic disc in the vertical meridian to the nearest first decimal place from the stereoscopic photograph using a stereo slide viewer. All observers measured the VCDR with the cup being defined on contour and not pallor and the optic disc border being defined as the inner border of the peripapillary scleral ring or the outer border of the neural rim if the scleral ring was not visible.[16]

Ultra-wide field grading

Optomap images were graded using the 'measure distance' tool on the Optomap Vantage software. The VCDR was measured in a similar way using the 'measure distance' tool to record cup and disc size. This involved

the observer measuring the vertical length of the cup and disc respectively. The outputs of both the cup and disc measurements were given in pixel size. This was then divided in order to give the VCDR value.

Designation of glaucomatous cupping

Previously, Foster and colleagues proposed a classification of glaucoma into three categories. Category 1 included structural (VCDR ≥97.5th percentile) and functional changes. Category 2 was based on advanced structural changes (VCDR ≥99.5th percentile) with no functional evidence and category 3 was based on people with a visual acuity <3/60 who had no visual fields or disc photographs available.[15] In the present study glaucoma will be defined using category 2 taking into consideration we have only images available. In many ophthalmic epidemiology studies visual field data or intra-ocular pressure information are not available. We used the classification proposed by Foster and colleagues in classifying glaucoma. In this study diagnosis was based on advanced structural evidence where the 99.5th percentile is used and there is no visual field examination available.[15] However, there was no 99.5th percentile computed. With the 97.5th percentile being VCDR > 0.75 only two participants had values higher than this; 0.76 and 0.78 thus a 99.5th percentile could not be computed, therefore the 97.5th percentile was used (VCDR of ≥0.75) for classification of glaucoma. Sensitivity and specificity was then calculated for UWF imaging with VCDR ≥0.75 using the CDS as the gold standard. The number of patients with successful testing was also compared between techniques.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Inter-modal, inter-grader, intra-grader reliability and reproducibility were assessed as well as the agreement between CDS and UWF retinal imaging to assess the effectiveness of evaluating the VCDR. For all pairs of comparisons Bland-Altman plot[17] analyses were used.

The glaucoma specialist (AAB) was used to assess inter-modal reliability between the colour digital stereoscopy and UWF imaging. Inter-grader reliability was assessed using observer 1 and the glaucoma specialist. Intra-grader reliability between colour digital stereoscopy and UWF imaging was assessed using observer 1. Observers 1 and 2 both repeated UWF assessment on 50 cases to evaluate intra-observer agreement, and thus the reproducibility of UWF imaging in detecting VCDRs. Sensitivity and specificity of UWF imaging in detecting glaucomatous discs was not officially assessed in this study due to the low overall prevalence of glaucoma in the population.

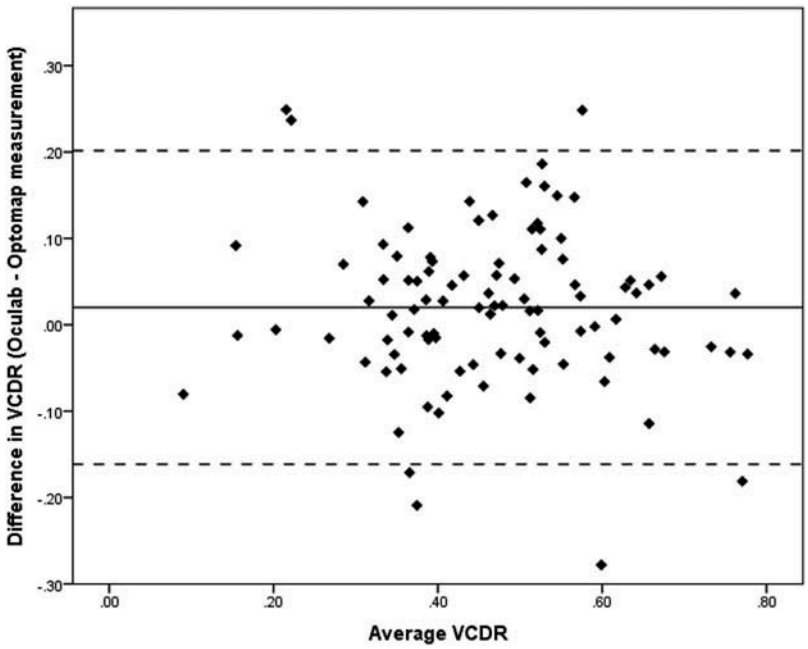

Figure 1. Similarity between Colour Digital Steroscopy (CDS) and Ultra Wide-Field (UWF) retinal imaging performed by the glaucoma specialist. The Bland-Altman plot for the glaucoma specialist shows 95% limits of agreement (LOA) of −0.16 to 0.20 with a mean difference of 0.02.

Results

Images from 100 participants were graded for VCDR, two participants were excluded as the disc was obscured in one UWF image and an UWF image wasn't available for the other participant, leaving 98 participants available for analysis. Of the 100 colour digital stereoscopy images, all had stereopsis available.

Agreement between the colour digital stereoscopy and the UWF retinal imaging performed by the glaucoma specialist

Figure 1 shows the Bland Altman scatter plot for VCDR estimates between colour digital stereoscopy and UWF imaging when carried out by a single masked glaucoma specialist. The Bland-Altman plot showed the 95% LOA of −0.16 to 0.20 with a mean difference of 0.02. The mean difference value of 0.02 indicates the bias present (p = 0.03) and given it is a

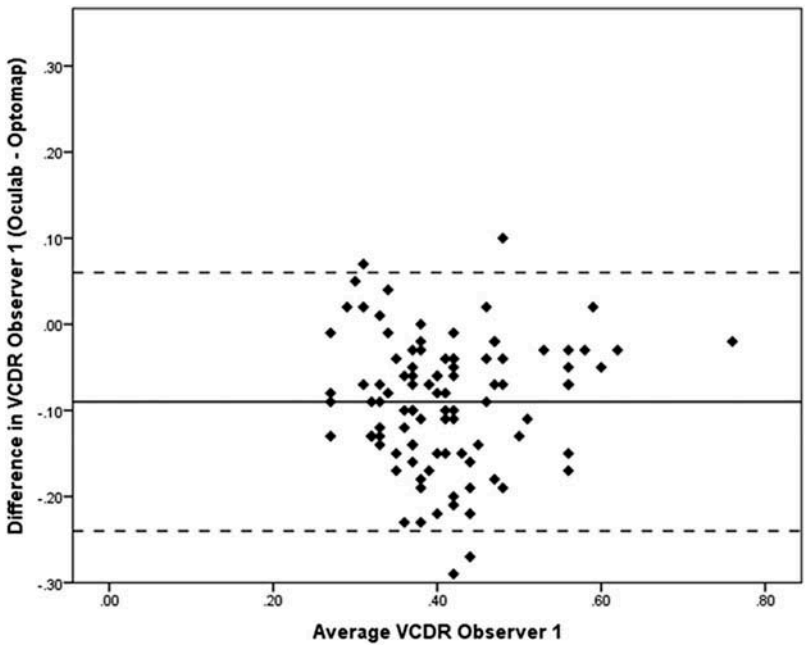

Figure 2. Bland-Altman plot showing the variation between Colour Digital Stereoscopy and Ultra Wide-Field imaging when carried out by Observer 1. The Bland-Altman plot shows 95% limits of agreement (LOA) of −0.24 to 0.06 with a mean difference of −0.09.

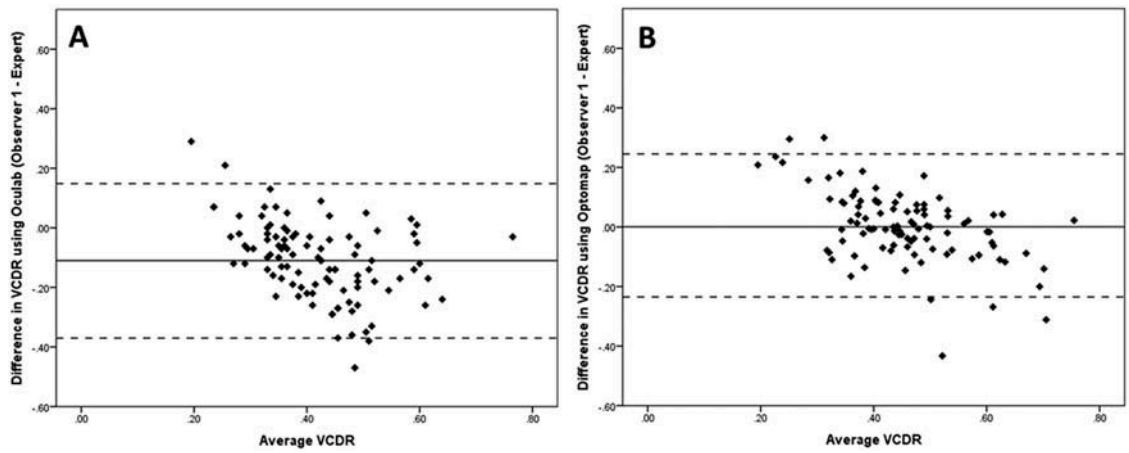

Figure 3. Inter-grader reliability illustrated by Bland-Altman plots between Observer 1 and the glaucoma specialist. Bland-Altman plots using colour digital stereoscopy (CDS) (A) and ultra-wide field imaging (UWF) (B). (A) 95% limits of agreement (LOA) of −0.37 to 0.15 with a mean difference of −0.11 (A). (B) 95% LOA of −0.24 to 0.26 with a mean difference of 0.0005.

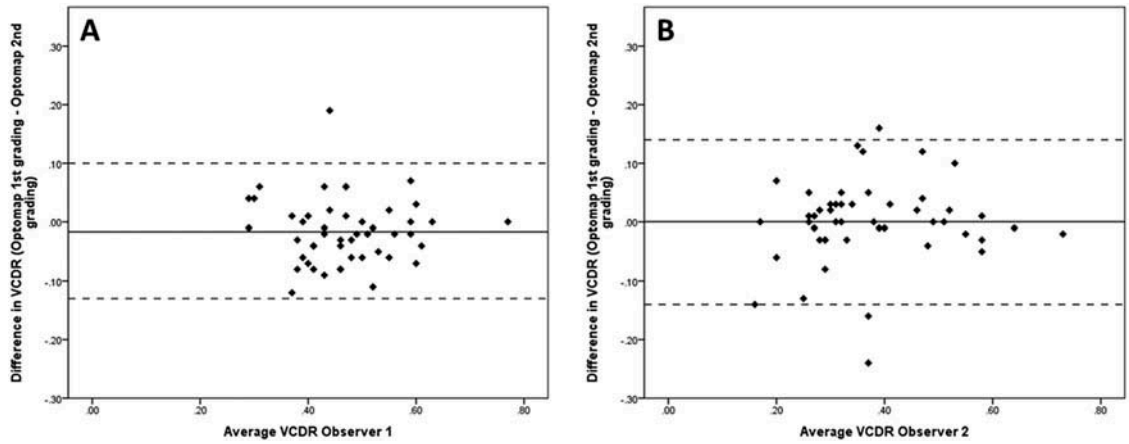

Figure 4. Reproducibility of the Ultra Wide-Field imaging technique in estimating vertical cup-to-disc ratio carried out by two independent graders. (A) Bland-Altman plot of vertical cup-to-disc ratio (VCDR) for Observer 1 shows 95% limits of agreement (LOA) of −0.13 to 0.1 and −0.14 to 0.14 with a mean difference of −0.02. (B) The Bland-Altman plot of vertical cup-to-disc ratio (VCDR) for Observer 2 shows 95% LOA of −0.14 to 0.14 with a mean difference of 0.0004.

positive value we can state that colour digital stereoscopy values were 0.02 units more compared to the UWF measurements. Of the 98 images available for analysis colour digital stereoscopy detected two glaucomatous cases and UWF imaging detected four. The two detected using the colour digital stereoscopy were also detected in the UWF imaging. The further two detected using UWF imaging were false positives.

Agreement between UWF and colour digital stereoscopy by non-glaucoma specialist

For Observer 1 intra-grader reliability, the Bland-Altman plot showed the 95% LOA of −0.24 to 0.06 with a mean difference of −0.09 (Figure 2). There was a statistically significant negative bias present ($p \leq 0.01$). It revealed that UWF VCDR measurements tended to be larger than VCDR measurements from the colour digital stereoscopy.

Inter-grader agreement

Inter-grader reliability between Observer 1 and the glaucoma specialist for VCDR measurements using the colour digital stereoscopy and UWF was shown using Bland Altman plots. The analyses of VCDR using the colour digital stereoscopy show 95% LOA of −0.37 to 0.15, a mean difference of −0.11 and a significant bias ($p \leq 0.01$) (Figure 3A). The Bland-Altman analyses of VCDR using the UWF show 95% LOA of −0.24 to 0.26 with a mean difference of 0.0005. There was no significant bias reported. From Figure 3A we can conclude Observer 1 measured VCDR −0.11 units lower than the glaucoma specialist when using the colour digital stereoscopy technique. Figure 3B indicates Observer 1 measured VCDR 0.0005 times higher than the glaucoma specialist when using UWF imaging.

Reproducibility of the UWF imaging using observer 1 and observer 2

Bland-Altman plots analyses for VCDR intra-grader reliability are shown in Figure 4A and B. The Bland-Altman plot of VCDR for Observer 1 shows 95% LOA of −0.13 to 0.1 with a mean difference of −0.02. The Bland-Altman plot of VCDR for Observer 2 shows 95% LOA of −0.14 to 0.14 with a mean difference of 0.0004. No significant bias from both Observer 1 (−0.02) and Observer 2 (0.0004) was present. As well as this, there was no significant difference in the first and second UWF grading for Observer 1 ($p = 0.05$) and Observer 2 ($p = 0.97$).

From the Bland-Altman plots carried out to show intermodal, intra- and inter-grader reliability and the reproducibility of the UWF retinal imaging, a number of outliers can be seen that fall outside the LOA. After further investigation all these outliers had plausible explanations including abnormal optic discs, i.e., tilted and anomalous discs, the presence of large peripapillary atrophy and very small cups making the VCDR difficult to estimate, or poor photographic quality of images.

Discussion

The purpose of this study was to evaluate the reproducibility and validity of UWF imaging in estimating VCDR measurements. For this purpose the reliability of VCDR measurements and the agreement with stereoscopic pictures of the optic disc was assessed. This study is the first of

its kind to investigate if UWF with the Optomap can be used as a possible diagnostic tool for glaucoma. The Optomap Panoramic 200Tx is a scanning laser ophthalmoscope (SLO) which captures approximately 200 degrees of the retina. This provides an image representing approximately 82.5% of the total retina compared to the 11% a traditional fundus image would show. In the present study, when comparing colour digital stereoscopy and UWF VCDR measurements carried out by a masked glaucoma specialist, the Bland-Altman plot displayed 95% LOA of −0.16 to 0.20 with a mean difference of 0.02. Since there is little variation around the zero-difference line (y-axis) between techniques this indicates the glaucoma specialist produced similar VCDR measurements when using the colour digital stereoscopy and UWF imaging. Additionally when the reproducibility of the UWF in grading VCDRs was assessed, Observer 1 and 2 showed (−0.13 to 0.1) and (−0.14 to 0.14) 95% LOA respectively. Again little variation was seen around the zero difference line and minimal dispersion above and below the line indicating low levels of bias. These favourable levels, terms of agreement and reproducibility of the UWF imaging are important in the follow-up of patients with glaucoma and clinical studies.

However when intra-grader reliability was analysed for Observer 1 between colour digital stereoscopy and UWF measurements, a mean difference of −0.09 was found indicating significant negative bias ($p \leq 0.01$). Observer 1 measured UWF VCDRs larger than VCDR measurements from the colour digital stereoscopy. This differs from the more similar VCDR measurements produced by the glaucoma specialist for both the colour digital stereoscopy and UWF imaging. This difference may be due to the fact Observer 1 did not have the same level of clinical experience and was relying solely on their skills of pattern recognition. From our results Observer 1 underestimated and overestimated VCDR measurements when using the colour digital stereoscopy and UWF imaging respectively. The bias reported in this study ranged from 0.0005 to 0.11. Although statistically significant it may not have clinical significance in diagnosing glaucoma. A difference in CDR of 0.2 or more would be considered to be clinically significant.[18]

The majority of participants had successful imaging, although UWF was not possible in two participants. As the overall prevalence of glaucoma is low in the population, the sensitivity and specificity was not formally evaluated in this study as it offers only a small sample size of 100 images. Of the images graded using the colour digital stereoscopy and UWF imaging, two and four images were detected as glaucomatous respectively. The two images detected using the colour digital stereoscopy were also detected using the UWF imaging with a further two being detected by UWF imaging.

The advantages of this study are the data available from an experienced glaucoma specialist, and a population-based consecutive sample drawn randomly from the community with little risk of selection bias.

This study has some limitations. Images were graded by non-glaucoma specialists as well as by only one glaucoma specialist. However regarding the possible use of UWF imaging for epidemiological studies, it is important to report on the findings of non-glaucoma specialists as these are likely to be the people grading the images in these studies. In addition, with a modest sample size and a low overall prevalence of glaucoma, this study was not powered to evaluate the diagnostic performance (sensitivity and specificity) of UWF for diagnosing glaucoma.

A small number of images (11) within this study were difficult to grade using either UWF and CDS. These made up the outliers when reliability and reproducibility were being assessed. These difficulties were down to the quality of the image taken at the time of image acquisition, pathology present at the optic disc (peripapillary atrophy), tilted discs and very small optic disc cups. Establishing the cup-to-disc ratio in these cases can be very difficult and not only challenged the non-glaucoma specialists but also the glaucoma specialist.

In conclusion, this study demonstrated almost perfect agreement between colour digital stereoscopy and the Optomap, an ultra-wide field imaging technique when assessed by a glaucoma specialist. It also showed the UWF technique was reproducible in VCDR estimates. Our data suggest that UWF imaging may be suitable for diagnosing glaucoma in situations in which slit-lamp biomicroscopy or digital colour stereoscopy are not available and further research about the comparative diagnostic performance of UWF and other imaging technologies may be warranted.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the writing and content of this article.

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