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# Progression from ocular hypertension to visual field loss in the English hospital eye service

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## ABSTRACT

**Background** There are more than one million National Health Service visits in England and Wales each year for patients with glaucoma or ocular hypertension (OHT). With the ageing population and an increase in optometric testing, the economic burden of glaucoma-related visits is predicted to increase. We examined the conversion rates of OHT to primary open-angle glaucoma (POAG) in England and assessed factors associated with risk of conversion.

**Methods** Electronic medical records of 45 309 patients from five regionally different glaucoma clinics in England were retrospectively examined. Conversion to POAG from OHT was defined by deterioration in visual field (two consecutive tests classified as stage 1 or worse as per the glaucoma staging system 2). Cox proportional hazards models were used to examine factors (age, sex, treatment status and baseline intraocular pressure (IOP)) associated with conversion.

**Results** The cumulative risk of conversion to POAG was 17.5% (95% CI 15.4% to 19.6%) at 5 years. Older age (HR 1.35 per decade, 95% CI 1.22 to 1.50,  $p < 0.001$ ) was associated with a higher risk of conversion. IOP-lowering therapy (HR 0.45, 95% CI 0.35 to 0.57,  $p < 0.001$ ) was associated with a lower risk of conversion. Predicted 5-year conversion rates for treated and untreated groups were 14.0% and 26.9%, respectively.

**Conclusion** Less than one-fifth of OHT patients managed in glaucoma clinics in the UK converted to POAG over a 5-year period, suggesting many patients may require less intensive follow-up. Our study provides real-world evidence for the efficacy of current management (including IOP-lowering treatment) at reducing risk of conversion.

## INTRODUCTION

Referral guidelines for ocular hypertension (OHT) or other glaucoma-related conditions in England currently require a repeated applanation tonometry intraocular pressure (IOP) measurement of above 24 mm Hg if referring on IOP alone.<sup>1</sup> Previously guidelines set the IOP threshold for referral at 21 mm Hg and the EPIC-Norfolk study reported a prevalence of 10% for OHT in the English county of Norfolk using this IOP cut-off.<sup>2</sup> Current guidance recommends that IOP-lowering eye-drops may be offered to patients with high IOP if they are at risk of visual impairment in their lifetime.<sup>1</sup> The reported rate of conversion from OHT to primary open-angle glaucoma (POAG) is variable in the literature with, for example, a 5-year conversion rate of anywhere between 4.4% and 25%.<sup>3–6</sup> Robust data on the likelihood of developing glaucoma for those with OHT are required to inform monitoring guidelines in terms

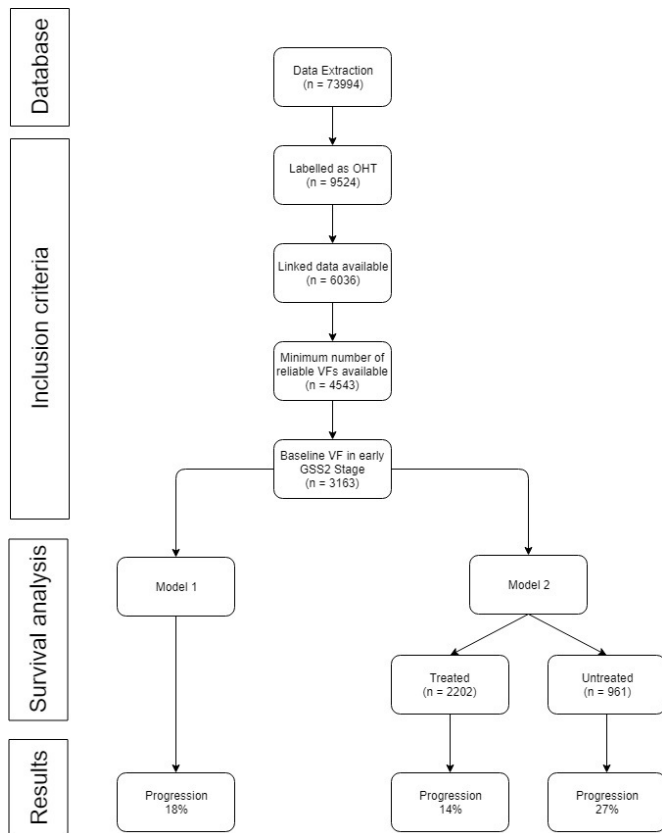
of cost-effectiveness and acceptability to patients, eye care providers and commissioners of National Health Service (NHS) services.

Primary care general practitioners do not generally have the appropriate training or equipment for monitoring patients with OHT. Standard UK practice as such is to monitor in secondary care in hospital eye services (HESs). This monitoring places a strain both on eye care services and patients, as monitoring in specialist eye clinics can be inconvenient, may lead to 'overtreatment' and is expensive for the NHS.<sup>2</sup> As up to half of POAG is characterised as normal tension glaucoma in Europeans, high IOP is neither a necessary nor a sufficient condition of glaucoma.<sup>2,7</sup> Therefore, it is likely that a proportion of patients with OHT are receiving unnecessarily intensive follow-up or treatment. With an ageing population and an increase in optometric testing, the number of patients being seen in clinics with glaucoma-related conditions is expected to rise, placing further strain on these services.<sup>8,9</sup> Currently, there are significant glaucoma clinic appointment backlog issues in many ophthalmology departments in England and Wales.<sup>10,11</sup>

HESs in the UK are transitioning to electronic medical record (EMR) systems to store structured patient data digitally, although progress is slow.<sup>12,13</sup> Glaucoma clinics, in particular, have the ability to store structured data relevant to OHT patients such as IOP readings, visual field (VF) test results and which medications (if any) they are taking. The aims of this study were to use EMR data from five glaucoma clinics in England to retrospectively analyse what happens to OHT patients. The primary aim was to estimate the proportion of OHT cases that converted to POAG within 5 years and to examine factors associated with this conversion. Our secondary objective was to consider the burden (number of unique scheduled appointments) that OHT patients place on glaucoma clinics, relative to other conditions such as POAG and suspected glaucoma.

## MATERIALS AND METHODS

Anonymised clinical data recorded between April 2000 and March 2015 were extracted from the Medisoft (Medisoft, Leeds, UK) EMR at five different NHS Hospital Trust glaucoma clinics in England. Commissioned to do so by the Healthcare Quality Improvement Partnership as part of the National Clinical Audit and Patient Outcomes Programme, the Royal College of Ophthalmologists collected this data as the National Ophthalmology Database Audit provider.<sup>14,15</sup> Details and summary statistics of these data are available elsewhere.<sup>16</sup> The data extraction



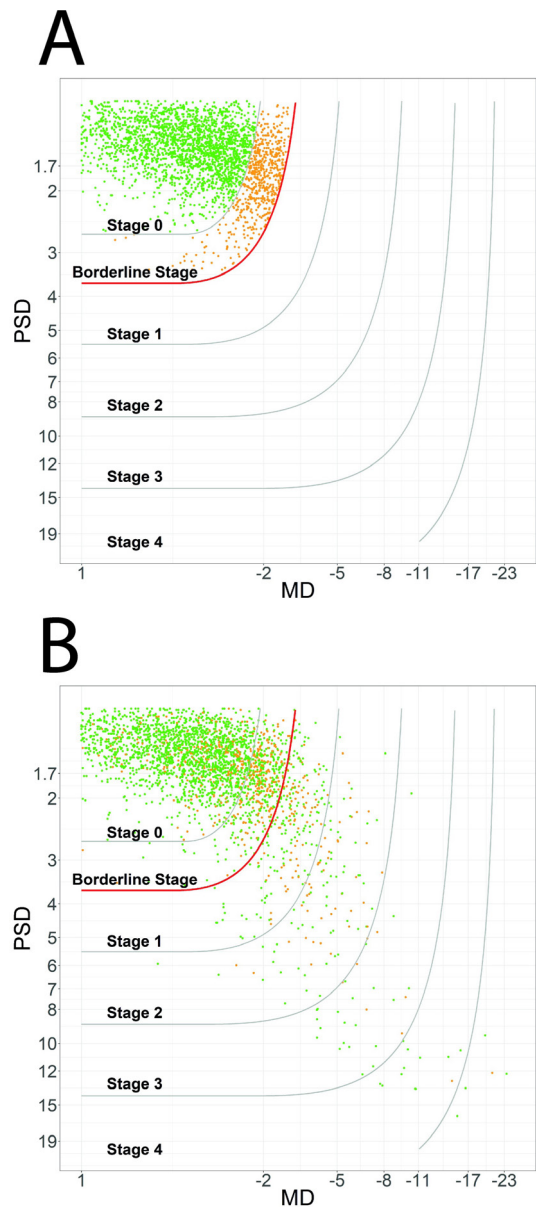
**Figure 1** Flow chart of patient eye selection. The flow chart also shows the predicted proportion of conversion for model 1 (all-cause survival analysis) and model 2 (stratified by treatment group).

was done in November 2015. All patient data were anonymised and stored on a database securely held at the university.

### Inclusion criteria

**Figure 1** presents a flow chart for patient eye selection. With this EMR (Medisoft) every diagnosis entry is associated with a diagnosis code. As such, it is possible to search and filter for specific conditions by filtering for the associated code or codes. We included patients with a clinical diagnosis label of OHT in at least one eye with no prior glaucoma-related diagnoses for either eye and with no significant ocular comorbidities. Specifically, eyes with a visual acuity (VA) of 6/18 or worse, or a diagnosis label of cataract, corneal pathology or eye casualty attendance were excluded. Eyes with age-related macular degeneration were included if they had a VA better than 6/18. As we are considering the risk of VF loss at a patient level, we are concerned with VF loss to either eye. As such, if both eyes were eligible, the eye with the higher baseline IOP was chosen for this analysis as it is potentially at a higher risk of VF loss. If both eyes had the same baseline IOP, one eye was chosen at random. For the purpose of this study, only VFs tested by using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, California, USA) with the 24–2, white-on-white test strategy acquired with the Swedish Interactive Testing Algorithm (SITA Standard or SITA Fast) were included in the analysis. A minimum of three reliable VF tests were required; one at baseline and two consecutive reliable examinations to enable detection of repeated VF loss if present.

To classify patients into different levels of VF damage, we used the glaucoma staging system 2 (GSS2) described by Brusini and Filacorda.<sup>17</sup> The system classifies VF damage into one of seven progressively worsening categories. As we wanted to consider

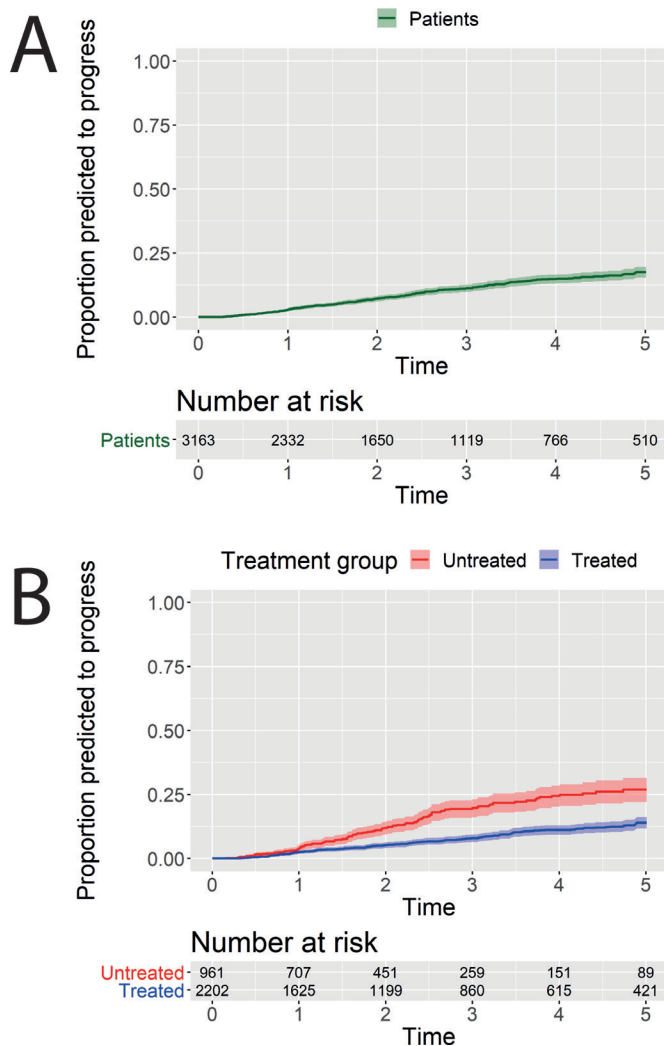


**Figure 2** A glaucoma staging system 2 (GSS2) scatterplot showing the eyes included for analysis. Only eyes with a baseline measurement in the early stages (stage 0 (green) or borderline (orange) stage, demarked by a red curve) were included (A). A second scatterplot illustrating the GSS2 stage of the last recorded follow-up visit for the same eyes is also shown (B). OHT, ocular hypertension; VF, visual field.

‘true’ OHT patients, we opted to only include eyes with little-to-no VF damage at baseline, as defined by the GSS2 (stage 0 or borderline stage). Baseline VF was defined as the VF closest to the time of diagnosis labelling, with a maximum of 1 year between the diagnosis and VF test. Baseline stages as measured by the GSS2 for all included eyes can be seen in **figure 2A**. The GSS2 stage at the last recorded follow-up visit is also shown in **figure 2B**.

### Statistical analysis

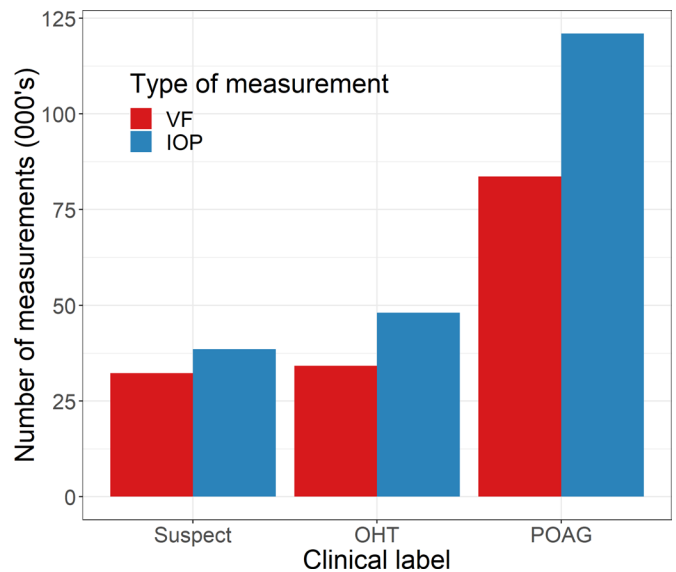
We considered follow-up VF data for up to 5 years following diagnosis of OHT. Any visits after this 5-year window were excluded. Two consecutive reliable VF exams with a GSS2 classification of stage 1 or worse were used to define VF loss. An unreliable VF was determined by the standard HFA criteria for false-positive errors (>15%) or fixation-loss errors (>20%). The VF with the earlier



**Figure 3** Cox PH survival curve of 5-year conversion predictions for (A) all patients (green) and (B) the treated (blue) and untreated (red) groups with the 95% CIs. The risk table shows the number of patients still included in the analysis for a group over time (1-year intervals). The cumulative probability of conversion was higher in the untreated group than the treated group ( $p < 0.01$ ), (B). PH, proportional hazard.

date was considered as the date of conversion. Patients with less than 5 years follow-up were included in the analysis but censored. The risk of conversion was calculated by computing the predicted survival function for a Cox proportional hazard (PH) model. The predicted survival functions were computed for a simple model (all-case conversion) and a model with IOP treatment as a predictor (figure 3).

Cox PH regression analysis was used to examine the baseline factors associated with incident conversion. Age, sex, baseline IOP (mm Hg) and treatment group (treated vs untreated) were examined both crudely and then together in a multivariable model. The treated group was defined as eyes that had a record of IOP-lowering medication, laser or surgery, while being labelled as an OHT patient (ie, before conversion in patients that developed POAG). The untreated group was defined as eyes that were recorded in the linked medications database but did not have any glaucoma medication listed and had no recorded glaucoma laser or surgery. To determine whether our results are affected by the choice of eye selected in patients with two eligible eyes, we repeated analyses for the fellow eye for bilaterally eligible patients instead of the



**Figure 4** Number of recorded patient visits for IOP measurements (red) and VF testing (blue) by primary diagnosis (glaucoma suspect, OHT and POAG) across the full-time period in the dataset. IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma; VF, visual field.

originally included eye; results were very similar (online supplementary materials).

The relative burden of OHT, POAG and glaucoma suspect patients on the glaucoma clinics was estimated (figure 4). This was defined as the relative proportion of unique clinic visits (for IOP or VF measurements) for each of the three clinical diagnosis labels. A visit for one of the labels, say OHT, was defined as a visit date that occurred in the range of dates while the eye of interest was labelled as OHT. If the diagnosis label was updated at a later date, for example, from OHT to POAG, then subsequent visits would be counted as POAG visits. A visit where both eyes had the same label, would be counted as one visit for that label. A visit where both eyes had different labels, would be counted as a visit for the more 'serious' label (where POAG > glaucoma suspect > OHT). The average number of months between VF tests for patients with at least four visits was calculated. All VF visits (including those with unreliable results) were included to better determine resource usage. All analyses were performed within the open-source statistical programming environment R.<sup>18 19</sup>

## RESULTS

### Baseline characteristics

From the initial cohort of 9524 patients with a clinician diagnosis label of OHT, we included 3163 eyes from 3163 patients for our analysis (see figure 1 for inclusion flow chart). Of these, 1716 (54%) were women, 2202 (70%) were on IOP-lowering treatment during their OHT diagnosis and 1531 (48%) were right eyes. For the included eyes, 4551/22 896 (20%) of VF examinations were excluded due to unreliability. Other descriptive statistics can be found in table 1.

### Cox PH analysis

Survival analysis curves are shown in figure 3. Overall predicted conversion after 5 years was 17.5% (95% CI 15.4% to 19.6%) (figure 3A). When stratified by treated and untreated groups, the predicted conversion after 5 years was 14.0% (95% CI 11.7% to 16.1%) and 26.9% (95% CI 22.0% to 31.4%), respectively



**Table 1** Statistics of included patient eyes

Included (n)	Median (IQR) age at diagnosis (years)	Median (IQR) baseline IOP (mm Hg)	Median (IQR) follow-up IOP (mm Hg)	Median (IQR) Baseline visual field mean deviation (dB)
3163	60 (51–66)	24 (20–27)	20.75 (18.33–23.00)	–0.45 (–1.32–0.34)

IOP, intraocular pressure.

(figure 3B). Of those that converted, 90% had mild or moderate VF loss (GSS stage 1 or Stage 2) and 10% had severe (GSS stage 3 or Stage 4). Results of the Cox regressions (univariable and multivariable) are shown in table 2. Use of IOP-lowering treatment was associated with a reduced chance of conversion; HR 0.45 (95% CI 0.35 to 0.57,  $p < 0.001$ ). Older age was associated with an increased risk of conversion (HR 1.35 per decade, 95% CI 1.22 to 1.50,  $p < 0.001$ ). There was no statistically significant association between risk of conversion and baseline IOP or sex.

### Burden on clinics

Of the total number of unique visits (recording either a VF or IOP measurement or both) for the three clinical labels included for analysis, 21% were recorded for glaucoma suspect patients, 22% for OHT patients and 57% for POAG patients. Considering only VF measurements, the distribution was 23%, 23% and 54% for glaucoma suspects, OHT and POAG patients, respectively. For IOP measurements only, the distribution was 20%, 23% and 57% (absolute numbers are shown in figure 4).

If we only consider the 3163 patients who were included in the survival analysis, 11 727 of 15 464 (76%) of the visits within the 5-year study window were recorded while the eye was receiving IOP-lowering treatment. This corresponds to 76% and 74% of the IOP and VF measurements, respectively. For patients with at least four VF visits, the average time between VF tests was 10.9, 9.7 and 9.6 months for glaucoma suspects, OHT patients and POAG patients, respectively.

### DISCUSSION

This is the first study to use large-scale, real-world EMR data from glaucoma clinics to model conversion from OHT to POAG. Our survival analysis predicts that around one in six (17.5%) OHT patients will have detectable VF loss within 5 years and the majority of those (67%) will have mild VF loss (GSS stage 1). In our study population, 70% of the OHT patients were receiving IOP-lowering treatment and these patients had a lower predicted rate of conversion of

around one in eight (14%). This indicates that there are many OHT patients in the clinics, especially those who are being treated, that are unlikely to lose much VF function within a 5-year window. Despite this, our data show that the average frequency of VF and IOP monitoring across OHT patients, POAG patients and glaucoma suspects is similar.

In a large multicentre clinical trial, the Ocular Hypertension Treatment Study (OHTS), the cumulative probability of developing POAG at 5 years was 4.4% in the treated group 9.5% and in the untreated group.<sup>20</sup> In another study, the European Glaucoma Prevention Study (EGPS), the conversion rates were 13.7% and 16.4%, respectively.<sup>4</sup> Our treated and untreated rates of conversion (14% and 26.9%) seem relatively high when compared with the above trials. There are several possible reasons for this discrepancy. First, we did not use any structure-based data (such as optic disc changes) for the inclusion or conversion criteria as was done in OHTS and EGPS, instead relying on the diagnostic labelling in the EMR.<sup>4 20</sup> Second, we may be overestimating the conversion rate if OHT patients with perceived low risk (eg, patients with thick corneas) were discharged to community review without treatment. Finally, it is possible that OHT patients being monitored in a hospital glaucoma clinic in England are a higher risk population than those in the studies described above, and so would have a higher likelihood of conversion to POAG.

Just over one in five (22%), glaucoma-related visits (OHT, POAG or glaucoma suspect visits) were for OHT patients. If only 17.5% of patients are predicted to have detectable VF loss within 5 years, is it necessary that they be seen in secondary care clinics this frequently, considering that the risk of significant vision loss is very low (only 1.75% of our study population reaching severe VF loss)? There are several alternative options available that would reduce the burden on hospitals and glaucoma clinics, such as monitoring patients in primary care practices or in virtual clinics. So-called ‘shared care’ schemes could be a possible approach for low risk OHT patients.<sup>8 21 22</sup> Notably, OHT patients had VF testing as frequently as both POAG and glaucoma suspect patients further emphasising that OHT patients are using a disproportionate amount of resources, relative to the immediate risk of VF loss. One suggestion to reduce the burden of OHT patients could be to increase the follow-up period between appointments.<sup>8</sup> Morley and Murdoch estimated that increasing time between follow-up visits by a factor of 1.5 could reduce the relative clinic workload by 30%. If the follow-up time was increased by a similar factor for stable, low-risk OHT patients, it could free up resources for high-risk or new patients.

A caveat of using this retrospective observational data is we cannot say for sure that the treatment caused a lower rate of conversion, as there may have been differential allocation of treatment by risk of conversion. However, it seems unlikely that eyes at lower risk of conversion would preferentially be given treatment. Another limitation of our approach is that we did not have data regarding other potential risk factors for conversion, such as family history, central corneal thickness or retinal nerve fibre defects. The OHTS reported an HR of 0.58 (95% CI 0.44 to 0.76) of IOP medication on conversion to POAG in the context of a randomised controlled trial. Our study illustrates the efficacy of treatment outside the context of a clinical trial. Age was also a significant predictor of conversion, both in our study and in the OHTS with our results being broadly in agreement with the OHTS HR of 1.22 (95% CI 1.01 to 1.49) per decade.<sup>3</sup> When designing the study protocol, one option was to consider a change of diagnosis

**Table 2** Results of COX PH survival univariable and multivariable analyses

Variable name	HR with 95% CI (univariable)	P value	HR with 95% CI (multivariable)	P value
Baseline age (decade)	1.36 (1.22 to 1.51)	<0.001	1.35 (1.22 to 1.50)	<0.001
Baseline IOP (mm Hg)	1.00 (0.97 to 1.02)	0.70	1.00 (0.98 to 1.03)	0.98
Sex (F)	1.07 (0.85 to 1.35)	0.56	0.99 (0.78 to 1.25)	0.93
Treatment (yes)	0.44 (0.35 to 0.56)	<0.001	0.45 (0.35 to 0.56)	<0.001

IOP, intraocular pressure; PH, proportional hazard.

label as an outcome for conversion. However, instead we opted for an objective measure using VF results that did not rely on a clinician updating the diagnosis label in the EMR. We rely on initial diagnostic labels, along with VF status to define our population when establishing baseline status, but not for detection of conversion. For added robustness, we also required a reliable baseline VF measurement indicating no VF damage, as classified by the GSS2. As the dataset did not include any objective structural data, this study did not examine OHT patients progressing to POAG in a strict clinical sense, but rather investigated the likelihood of developing VF loss in OHT patients. For the analysis on clinic burden, we faithfully reported visits as they appeared in the EMR and did not try to refine the labels based on, say, VF measurements. This is a minor limitation as it is possible that labels are not always updated as conscientiously they should be after status conversion.

The diagnosis labels and dates of diagnosis we used in this study to select OHT patients are to be interpreted as surrogates of disease presentation. For this analysis, we used the first recorded VF date as a surrogate of when the disease began. However, it is sometimes the case that patients come into a clinic previously diagnosed with OHT and already are being treated for some time before being entered into the EMR. Retrospective analyses such as ours are only possible if the data are accurately recorded in EMRs in a structured way. Today, many medical record systems are being digitised which makes the possibility of large, multicentre studies using 'big-data' much more feasible.<sup>12</sup> As these data are already being recorded routinely, there is an opportunity of relatively cheap and accessible healthcare research, and patient benefit, to be gained from exploring them. Moreover, as these data come straight from clinics, it can tell us more about what goes on in real-world scenarios, which could inform how we organise our healthcare systems.

According to the National Institute for Health and Care Excellence glaucoma guidelines, 1.3 million people over aged 40 in the UK have high eye pressure (above 24 mm Hg) and most of those who have this condition are monitored in HESs.<sup>1</sup> Less than one-fifth of OHT patients managed in the reported UK glaucoma clinics converted to POAG over a 5-year period. The majority of those conversions were to a mild disease stage. Simultaneously it is equally important to highlight results from those patients that were in clinics but were untreated. That is, more than 25% of the untreated OHT patients converted to POAG, although to a relatively mild disease stage within the time of follow-up. While it is difficult to extrapolate these findings to life-time risk of visual loss, since even mild disease can have an impact on quality of life, it is likely that these patients will be at an increased risk of sight-related harm during their lives. The results from this study highlight the issue of a 'one size fits all' approach in glaucoma clinics around the UK. Despite many of the referrals to secondary care being deemed as low risk, there is often a reluctance to discharge to community review.<sup>8</sup> Moreover, there are several potential barriers to discharging patients to primary care pertaining to agreement on professional boundaries and responsibilities.<sup>23</sup> Nevertheless, many people with OHT and without VF loss, are at a low risk of sight loss in the near future. Yet, according to our data, they take up a relatively large proportion of resources and are seen as frequently as POAG patients. Our results suggest that it would be reasonable to reduce the frequency of visits for OHT patients and perhaps this should be explored with prospective study incorporating a health economic and patient

preference element too, echoing a need for further work that has been reported before.<sup>24</sup> It would furthermore be reasonable for such patients, who are not at risk of imminent sight loss, to be monitored by suitably trained and equipped optometric primary care practitioners, thus reducing the burden on hospital secondary eye care services.

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**Contributors** SRK contributed to the design and implementation of the research, to the statistical analysis of the results and to the writing of the manuscript. APK contributed to the design and implementation of the research and to the writing of the manuscript. SRB contributed to the design and implementation of the research and to the writing of the manuscript. AA-B contributed to the design and implementation of the research and to the writing of the manuscript. JMS contributed to the design and implementation of the research and to the writing of the manuscript. DPC contributed to the design and implementation of the research, to the writing of the manuscript, and supervised the project. All authors discussed the results and contributed to the final manuscript.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** The current study was undertaken through a data-sharing agreement and adhered to the Declaration of Helsinki with all analyses approved by a research ethics committee of City, University of London.

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**Data availability statement** No data are available.

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