Dear Miss Chan

Manuscript ID BMJ.2016.036789 entitled "Defining a new threshold for ocular hypertension and estimating referral burden from the EPIC-Norfolk Eye Study: a cross-sectional study of the potential impact on referrals to the Hospital Eye Services"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Jose Merino
jmerino@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Richard Riley (statistical consultant), Rubin Minhas, John Fletcher, Georg Roeggla, Daoxin Yin, Amy Price, Tiago Villanueva, José Merino

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- We liked the topic of the paper. But along with the reviewers did not find that a paper that identifies a specific threshold suitable for The BMJ. Age and gender appear to vary the threshold considerably. Yet the paper consider single thresholds of 24 (or 22 etc) and the impact of using these rather the current value of 21. Surely the decision about threshold will have to take different factors into account. The ideal cut-off point will have to take into account risks and benefits. The decision of the optimal threshold is best made by multiple stakeholders including clinicians, patients and policy makers.

- We recognize the value of your dataset.

- Rather than a paper that identifies a specific threshold, we are interested in a revised paper that describes the distribution of IOP in the general population and then by age and sex. We are interested in a revised "prevalence" paper that avoids making value judgements about the optimal threshold with the best trade-off between risks and benefits and is along the line of "this is the distribution of IOP in the population... and this is the associated prevalence of glaucoma....". If you agree that a paper along those lines will be of value, we look forward to considering the revised version.

All references to IOP referral thresholds have been removed, and the paper is now re-written with the focus being glaucoma frequency and IOP distribution. The new title is “Glaucoma and intraocular pressure in the EPIC-Norfolk Eye Study: a cross-sectional cohort study”

- At the manuscript meeting some editors thought that it may be possible for you to develop a prediction model for development of glaucoma taking into account IOP, age, sex and other clinical covariates. Is this possible, considering the available data? This prediction model does not have to be a part of the revised manuscript but this is an idea for another paper. The BMJ may be interested in such a paper if you could externally validate the model. The model could enable individualized predictions of the risk of having glaucoma. Decisions about referrals could then be based on individual risk, rather than an arbitrary threshold of 24, which corresponds to a different risk in different individuals.

- Some additional concerns:
* In Table 6, the authors do slightly refine sens and spec by age group, and say: “Table 6 and figure 4 show the sensitivity and specificity of glaucoma detection at different IOP thresholds. Overall, sensitivity for glaucoma detection was poor at all IOP levels shown, regardless of the additional refining parameters of age and sex…” – but age and sex are considered separately, and no tailored PPV or NPV are given for each (as prevalence would change for each).
The original Table 6 (Intraocular pressure level among glaucoma cases and glaucoma suspects in the EPC-Norfolk cohort) has been removed as the main aim of the study has changed

* Why categorize age into 5-year age groups? Within a prediction model, age could be considered as fully continuous, with potentially non-linear associations with IOP.
Age group is used for the purpose of the tables, but we agree that should a prediction model be used, IOP as continuous variable could be more appropriate.

* The abstract is very confusing. The current 21 threshold is only mentioned at the end, and it is hard to ascertain what proportion of people in the study truly had OHT or subsequent glaucoma. No CIs are given for projects %s of glaucoma patients missed
This study has now deleted references to IOP referral threshold.
CI for projected percentages are now included.

* Methods does not explain how CIs were generated

* P8 says: “To understand the potential referral burden for different IOP thresholds, Table 3 shows the distribution of subjects above or below various IOP thresholds, using the higher IOP of either eye (mean of three values) to reflect clinical referral practices, excluding glaucoma cases and those on ocular hypotensive eyedrops.” – but why exclude these patients? Surely we want to include glaucoma patients, as these are the ones we are trying to detect?
This study has now deleted references to IOP referral threshold.

*Table 4: crucial numbers, yet no CIs.
The original Table 4 (Impact of varying the ocular hypertension threshold on referral numbers from 21mmHg extrapolating EPIC Norfolk data to England and Wales) has been removed as the main aim of the study has changed.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.
Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Comments to authors:

General comments:

The authors have done a thorough job of analyzing intraocular pressure data from the EPIC-Norfolk Eye Study. The motivation for the study was that the population norms for establishing statistical elevation of intraocular pressure are fifty years old, and were established using Goldmann applanation tonometry. Evidently most optometrists in the UK, however, use some form of non-contact tonometry today, which tends to read higher than Goldmann, and also tends to have higher variability. Therefore, the authors determined the statistical limits of "normal" intraocular pressure using non-contact tonometry, thinking that the results might lead to a reassessment of the recommendations by which individuals are referred for glaucoma evaluation.

Based upon these data, the authors were able to calculate the 97.5 percentile intraocular pressure level among normal using non-contact tonometry, and found that it was about 2 mm Hg higher than that currently adopted by NICE of 21 mmHg. They reason that policy makers should consider a shift from a cutoff of 21 mm Hg for referral up to 23 or even 24 mm Hg.
The novelty of the study is limited. The authors state that theirs is the "first study to reexamine" the statistical basis for the definition of an abnormally high IOP. So, obviously it has been examined before. Their finding that the non-contact tonometers used by optometrists read higher than Goldman applanation raises the 97.5 percentile by a couple of mm Hg. This is not surprising.

It has been realized for decades that IOP is an invalid screening method for glaucoma detection. It is clear from the Baltimore Eye Survey (ref 8) data that there is no level of IOP with acceptable sensitivity and specificity that would serve as an appropriate level for referral. This is beautifully illustrated in the current submission's Table 7 and Figure 4. The authors state in the Abstract that raising the referral cutoff from 21-24 mm Hg would reduce the number of referred patients by 70%, with a loss in case detection of 16%. What is not obvious from the Abstract is that this case loss of 16% is from a case detection of only 32% down to 16%. If one is proposing an IOP cutoff that misses 84% of cases, one might consider giving up on IOP entirely?

Having said the above, the analysis is sound, and if IOP is going to remain a referral criterion, the authors have provided valuable data to help decision makers perform a cost-benefit analysis of different IOP thresholds. What we really need is a better screening tool. The authors might include a paragraph in the Discussion about the need for a better screening algorithm.

For a general medical audience, I think that there are too many tables and that the reader make get lost in the trees rather than appreciate the forest.
I hope that the authors find these comments useful in further improving their solid work.

Specific comments:

The Methods section should discuss how ORA pressure values were calibrated against GAT to produce IOPg and the Discussion section should further elaborate on the relationship between GAT/IOPg differences as a function of IOP.

According to a publication by DA Luce from the manufacturers of ORA, IOPg was derived from an average of the two applanation pressures (P1 and P2) and then calibrated linearly against GAT (J Cataract Refract Surg 2005:31:156-162., Many studies have attempted to examine the relation between different tonometers yielding variable results. A systematic review published in 2012 (Cook JA et al, Ophthalmology 2012;119:1552-1557) showed that among 12 studies that directly compared the agreement of IOPg and GAT, the mean difference between the two (IOPg-GAT) is 1.5mmHg (95% predictived interval -0.6 to 3.7mmHg), We have now included these information in the methods section.

Please consider a cost-effectiveness analysis for IOP referral threshold adjustment

All references to IOP referral threshold are now removed from the paper

What is the effect of inclusion of peripapillary RNFL data in the sensitivity/specificity for glaucoma detection across IOP range?

Diagnostic effects of RNFL data is not included in this paper as it will be more thoroughly examined in a separate manuscript exploring combinations of several different diagnostic tests and their performances on glaucoma detection.

Confidential comments to Editor:

With the target audience being GPs and hospital clinicians, the manuscript may not be particularly suited for this journal audience. If you are favorably inclined, consider relegating many of the Tables to on line or appendix.

Additional Questions:
Please enter your name: Henry Jampel

Job Title: Professor of Ophthalmology

Institution: Johns Hopkins University School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 2

Recommendation:

Comments:
As a patient diagnosed with glaucoma based on a single GAT measurement of 22mmHg in one eye in 1984, I find this study fascinating and hugely relevant to patients diagnosed with ocular hypertension by their Optometrist (<21mmHg) and referred to a Hospital Eye Service or Consultant Ophthalmologist.

This study clearly shows that this threshold is (yet another) surrogate marker, arbitrarily introduced many years and incorporated into guidelines imposed upon community optometrists. In fact, most if not all would be viewed as negligent if they failed in this protocol. It is the result of the of the promulgation from the now 50-year-old Rhondda Valley population study. Diagnostic tools and measures have progressed enormously in the intervening years and the diagnosis

of Primary Open Angle Glaucoma (POAG) is more cheaply and easily addressed at optometrist level using visual field testing; more accurate tonometry instruments and optic head assessment by Fundus Photography.
The community optometrists have the tools and the ability to screen for 'real' glaucoma but not the authority, which the raising of the referral threshold would resolve and thereby reduce the significant burden on secondary care in Eye Hospitals. Restricting this resource by imposing such a guideline, on a single None-Contact Tonometry (NCT) reading is both wasteful and condescending to a body of experts more than equipped and (usually) adequately resourced to fulfil this need. Increasing the level for referral would also increase the specificity of detection more likely to 'catch' those with POAG but IOP in the 'normal' range, which is said to be 50% of sufferers.
The study could have explored the fact that optometrists, given the freedom to use a higher referral marker, could then undertake such unconstrained by an unrealistic number and treat their patients as 'real people' referring those with a more comprehensive litany of symptoms other than an IOP over 21mmHg. This modification of referral level would in addition, prospectively work well in practice and is feasible, with patients only being referred that reach the revised IOP level OR are seen with other POAG symptoms that more reflect a diagnosis that is vision threatening, within the primary care provided by optometrists'. The overtreatment and over diagnosis of patients would be considerably reduced by this and the burden imposed on the hospital eye services reduced by almost 70%; prescriptions for hypotensive eyedrops, with their attendant side-effects, would be considerably reduced; the fear of vision loss by the elderly would also be ameliorated.
This is an outcome that most patients; Clinicians and the Taxpayer would welcome, allowing funds to be diverted into 'true' POAG; cataracts and age related vision problems.
The paper might have been further strengthened by referral to this valuable community resource and not wishing to oversell this protocol, I have been impressed often by my own experience with optometrists who have often been more than helpful with my own sight battles. They are a valuable resource that is currently undervalued and often underused (except of course for the conglomerates that have been gifted with 'contract services' by CCG's).
The lowering of the 'marker' for suspected POAG could prospectively bring about a minor revolution in eyecare unencumbered by short sighted (sic) guidelines that dominate and restrict resources.
Patient involvement in this study seems to have been quite proactive which is commendable. I would dearly love to see both this all studies to include a 'plain language summary' as the Cochrane Collaboration does.

We appreciate Mr Berry's favourable comments and agree with him on many levels. Please note however that the paper has now been revised substantially on the recommendation of the editorial team, and no longer refers to IOP referral thresholds.

Additional Questions:
Please enter your name: Ernest Berry

Job Title: Security Systems Engineer and Consultant. Patient Advocate. Carer and Glaucoma Sufferer.

Institution: None

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

Comments:
The authors describe the intraocular pressure (IOP) distribution of a large population in South East England from the EPIC study. Using the IOP data the authors challenged the rationale for the current definition of ocular hypertension (OHT), i.e., two standard deviations above average IOP (i.e., IOP over 21 mmHg), based on a 1966 study.
Changing the threshold for defining OHT has substantial policy implications due to the large number of unnecessary referrals from community to hospital eye services based on IOP measurements. Thus this paper is of great relevance for the NHS. This is also a topic of timely interest because NICE glaucoma guidelines are under review and this topic is within the scope of the reviewed guidelines
The authors also evaluated the diagnostic performance of IOP to detect glaucoma at different thresholds.
The methodology is solid and the statistical analysis appropriate. Overall the conclusions are justified.
In the appendix 1 it was unclear why a subgroup of patients underwent automated perimetry as part of the screening test. Perhaps it would be useful to add a footnote.
Would the authors add some potential limitations for the Discussion section? E.g., the sensitivity of HRT and GDx is not perfect, and it is possible some people with glaucoma may not have been detected? Could the ORA results be generalizable to other NCT tonometers?

We agree with Prof Azuara-Blanco's comments and have included in the discussion limitations of glaucoma diagnosis, especially since the focus of the paper is now fully on glaucoma diagnosis of the cohort. However, HRT and GDx results were used only as a screening tool to identify high risk individuals. HRT or GDX did not form part of the diagnostic criteria of glaucoma. Further safeguard were in place to look for possible missed diagnosis among those who did not meet the criteria for further examination. The limitations of HRT and GDx in detecting glaucoma would not have been a major factor in the overall outcome.

The issue whether ORA can be generalizable to other NCT tonometers it not relevant anymore as the focus of the study is no longer on IOP referral thresholds.

Overall this is a high quality article with large potential impact. It will help inform decision making by policy makers and clinicians

Additional Questions:
Please enter your name: Augusto Azuara-Blanco

Job Title: Professor of Ophthalmology

Institution: Queen's University Belfast

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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END