unselected consecutive series of 223 secondary and tertiary periocular BCC referrals to a UK regional oculoplastic service. Our case mix should therefore be representative of that in other similar UK units and our results are therefore more relevant to them than those of the high risk biased Australian Mohs series and our results can be used as an audit benchmark. Although we have used conventional non-Mohs treatment, we achieved a very low recurrence rate.

We fully support that full histological margin control, as in Mohs micrographic surgery, is the best treatment option in recurrent, high risk cases. Our study shows that careful non-Mohs BBC excision remains a valuable, safe and cost effective option. Our technique offered the patients with primary non-infiltrative BCC excellent cure rates and functional and cosmetic outcomes with no recurrence over the 5 year follow up.

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NAION and treatment of erectile dysfunction: reply from Pfizer

McGwin *et al*[1] suggest that treatment of erectile dysfunction with sildenafil (Viagra) or tadalafil (Cialis), two phosphodiesterase inhibitors (PDE5-I), may increase the odds of non-arteritic anterior ischaemic optic neuropathy (NAION) in men with a history of myocardial infarction (MI) or hypertension (HTN). We believe, however, that this study is fraught with significant limitations (as the authors acknowledge) that preclude drawing any conclusions about this relation.

Case-control studies are susceptible to several biases that must be carefully considered and controlled for in the study design, implementation, and analysis.[2] For example, accurate and complete ascertainment of exposure is critical in a retrospective case-control study because both disease and exposure occur before study initiation. The authors note that the interviewers were *not* blinded to the case or control status of the patient, making it possible that the interviewer may, even unconsciously, probe cases differently from controls for exposure to a PDE5-I (interviewer bias). Another obstacle is that patients were not consistently interviewed at the time of the NAION event (or index date for controls) about their PDE5-I usage. Hence, NAION patients may have been more likely to remember drug usage (recall bias). Furthermore, exposure misclassification may have occurred as timing, dose, and duration of drug use relative to event onset were not captured (exposure bias). This information is crucial for drugs used as needed such as PDE5-I, and particularly for short half life drugs like sildenafil.

Perhaps, the most troublesome weakness of the study was the limited sample size and differential participation rates of cases and controls, likely resulting in selection bias that distorts the conclusion. The authors note that almost one fifth of the cases and one third of the controls refused to participate. The baseline cardiovascular characteristics, while not significantly different (with the exception of MI) between cases and controls, were consistently more prevalent in the NAION group. This finding is not surprising given that these cardiovascular conditions, especially in combination, are also risk factors for NAION.[3] Thus, the MI and HTN subgroup analyses presented in table 3 should be interpreted with scepticism.

Exacerbating the inherent problems are subgroup analyses that had no a priori hypothesis. The dangers of unplanned subgroup analyses in research are well documented.[4] Compounding matters is the sparse number of patients, reflected in the exceptionally wide confidence intervals (table 3). The robustness of such extremely small cell numbers must also be questioned, as the observed statistical significance for patients with MI can be eliminated if only one or two patients are switched to an alternative category. The authors also did not provide individual patient totals by exposure group with and without MI, rendering it impossible to replicate their results. Furthermore, there appear to be errors in the numbers/percentages and crude odds ratios presented in table 2.

In summary, the methodological limitations call into serious question the authors' conclusions. For men with a history of MI or HTN, therefore, this study does not provide any valid evidence that the use of Viagra or Cialis may increase the risk of NAION.

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Surgical characteristics of the retinal inner limiting membrane

In a recent issue of the *BJO* Steven *et al* describe secondary retinal holes after removal of the inner limiting membrane (ILM).[1] We consider this a key retinal publication and therefore wish to strengthen the importance of the authors' findings for modern surgery of the vitreoretinal interface.

Interestingly, the paper included only patients with macular puckers and cystoid macular oedema, but not macular holes. In cases of macular holes only a small sized central part of the ILM will usually be peeled. In contrast, macular puckers and cystoid oedemas will typically affect a larger region of the posterior pole. Thus a more extensive fraction of the ILM will be stripped if surgery is performed in such cases.

More than 30 years ago Foos[2] described two anatomical features of the ILM that might explain why current peeling of the peripheral ILM may be unsafe. Firstly, the ILM is thickest at the posterior pole and will become continuously thinner in the periphery. In the initiation of the ILM removal this may increase the risk for direct retinal trauma. Secondly, the Müller glia are more strongly attached to the ILM away from the macula. This may lead to indirect surgical trauma of the non-neuronal parts of the retina during the peeling process.

In conclusion, the more eccentric from the macula, the thinner and the more adherent to the retina is the ILM. As described by Steven *et al*, removal of these peripheral ILM fractions may lead to retinal hole formation.[1] Direct and/or indirect surgical trauma may be responsible for such injury, which may not be related to toxic effect of dyes used. One should therefore avoid stripping the peripheral ILM outside the macular region to prevent inadvertent retinal damage.

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Lutein and zeaxanthin dietary intake and age related macular degeneration

We read with interest the letter published by Vu *et al*[1] which investigated the risk of age related macular degeneration (AMD) and its association with the dietary carotenoids, lutein and zeaxanthin (LZ), stratified by linoleic acid intake. Vu *et al* reported a marked increase in the risk of both early and late AMD among people who consumed greater than the median intake of linoleic acid and higher dietary intakes of LZ.

We have a number of concerns in relation to the authors' letter and their conclusions. The letter used cross sectional data based on photographic macular assessments of 71.9% of their sample of 2448 people, who attended follow up examinations. The authors also included 212 people who did not have

photographic macular assessment (10.8% of those with dietary assessments). This is one area of concern. The dietary assessment method (food frequency questionnaire, FFQ) was not conducted at baseline, which only allows measurements of association from the follow up examination. Owing to the cross sectional nature of the data, it is plausible and even likely that participants with known signs of early macular degeneration or associated visual changes may have increased their dietary antioxidant intakes (indication bias)—for example, after being told about their signs at the first examination or at other times. This bias may have occurred in particular among those consuming higher linoleic acid diets as higher intakes of linoleic acid have been reported to increase the risk of AMD.[2] An excellent example of this indication bias can be seen in the finding of a significantly increased risk of poor night vision associated with increased consumption of carrots.[3]

The letter also states that a possible protection existed with high LZ intake on AMD among those with low levels of linoleic acid intake. We could, however, not see any data in the results or tables to support this statement.

We thought that these findings needed to be confirmed in other study populations. Given our concerns about the cross sectional data design we explored this association with the incidence of AMD in the Blue Mountains Eye Study cohort. Baseline data were collected in 1992–4 from 3654 residents of the Blue Mountains aged 49 years and over. Eye examinations were conducted on residents at baseline and at follow up using retinal photographs and the Wisconsin AMD grading system.[4] Dietary data were assessed at baseline (n = 2900) and follow up examinations using a 145 item food frequency questionnaire (FFQ).[5] Of the participants examined at either or both the 5 year and 10 year examinations, 2454 had retinal photographs available for the assessment of age related maculopathy (ARM) lesions. Of the 2454 participants 2083 had complete FFQ data, including 818 supplement users. We used the Willett method[6] to energy adjust the linoleic and LZ data and investigated those with less than and greater than median intake for linoleic acid (median = 6.6 g) and 1 standard deviation increases of LZ (mean intake of energy adjusted LZ intake was 819 μg, with an SD of 475 μg), using a multivariate adjusted discrete logistic model to assess factors associated with 10 year incident AMD.

We found no association with energy adjusted LZ intake and the incidence of early, late, or any AMD, whether or not this was stratified by linoleic acid intake (table 1). Given that our median linoleic acid intake was less than the median used by Vu *et al*[1] (6.6 g verses 7.2 g) we also stratified the data by the highest tertile of linoleic acid intakes (cut point 8.5 g) and also found no association between LZ and incident AMD (data not shown).

While the examination of cross sectional data to investigate associations with disease may be useful, conclusions drawn from such data need to be made with care in the light of other known literature. Other data have demonstrated a potential protective effect from foods containing LZ[7] and foods and supplements rich in LZ are known to increase (protective) macular pigment density.[8] In addition, dietary guidelines[9] include recommendations to increase vegetables and fruit that are rich in LZ (for example, broccoli, green beans, silverbeet, brussel sprouts, oranges).[10] The authors' conclusions, based on their very limited data, are non-intuitive and we are concerned that they are potentially misleading. Care needs to be taken to continue to encourage the vegetable and fruit intakes of populations.

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Do retinopathy signs in non-diabetic individuals predict the subsequent risk of diabetes?

We read with interest the article by Wong *et al*,[1] which studied a non-diabetic population consisting of 7992 people aged 49–73 years. Non-mydriatic retinal photographs of one eye were taken and graded for retinopathy lesions using standardised protocols. Surprisingly, the presence of typical retinopathy lesions (microaneurysms or retinal haemorrhages) in people without diabetes did not significantly predict subsequent development of diabetes over a period of 3.5 years. Incident diabetes developed in 4.7% and 3.6% of people with and without retinopathy lesions at baseline, respectively, with a multivariate adjusted odds ratio, OR, 1.1, 95% confidence interval, CI, 0.7 to 1.9. However, in people with a family history of diabetes, presence of retinopathy lesions at baseline predicted a doubling of the risk of incident diabetes (OR 2.0, CI 1.1 to 3.8).

We previously reported findings from the Blue Mountains Eye Study cohort (BMES, n = 3654) that the 5 year risk of developing diabetes in people without diabetes but with retinopathy lesions at baseline was 3.5% (7/202).[2] The BMES examined 3654 participants at baseline (1992–4) and re-examined 2335 participants (75% of survivors) 5 years later (1997–9). Dilated six field retinal photographs of all participants were taken at the baseline and follow up examinations. Diabetes was diagnosed either from medical

Table 1 Odds ratio between baseline dietary lutein and zexanthin (LZ) intake, stratified by linoleic acid (LA) intake (less than and greater than median intake), and 10 year incident AMD in the Blue Mountains Eye Study

	Any AMD OR* (95% CI)	p Value	Early AMD OR* (95% CI) (n = 220)	p Value	Late AMD OR* (95% CI) (n = 59)	p Value
All participants						
Daily energy adj LZ intake	0.94 (0.71 to 1.24)	0.668	0.95 (0.71 to 1.28)	0.758	0.81 (0.45 to 1.50)	0.475
Energy adj LZ intake, <6.6 g LA	1.01 (0.71 to 1.45)	0.943	1.06 (0.73 to 1.53)	0.771	0.66 (0.30 to 1.46)	0.306
Energy adj LZ intake, ≥6.6 g LA	0.85 (0.54 to 1.34)	0.487	0.82 (0.51 to 1.32)	0.820	1.18 (0.51 to 2.77)	0.698
Excluding those who took supplements						
Daily energy adj LZ intake	1.06 (0.74 to 1.52)	0.749	1.11 (0.76 to 1.61)	0.596	0.85 (0.41 to 1.77)	0.666
Energy adj LZ intake, <6.6 g LA	1.10 (0.70 to 1.72)	0.675	1.15 (0.72 to 1.83)	0.559	0.62 (0.23 to 1.68)	0.349
Energy adj LZ intake ≥6.6 g LA	0.98 (0.54 to 1.79)	0.949	1.01 (0.54 to 1.89)	0.975	1.40 (0.49 to 3.96)	0.528

*Adjusted for age, sex, and smoking.