1 A randomised controlled trial investigating the effect of lutein, zinc and antioxidant dietary

2 supplementation on visual function in healthy eyes

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Abstract

Background and aims

It has been suggested that retinal lutein may improve visual acuity for images that are illuminated by white light. Our aim was to determine the effect of a lutein and antioxidant dietary supplement on visual function.

Methods

A prospective, nine- and eighteen-month, double-masked randomised controlled trial. For the nine-month trial, 46 healthy participants were randomised (using a random number generator) to placebo (n = 25) or active (n = 21) groups. Twenty-nine of these subjects went on to complete 18 months of supplementation, 15 from the placebo group, and 14 from the active group. The active group supplemented daily with 6 mg lutein combined with zinc and antioxidants. Outcome measures were distance and near visual acuity, contrast sensitivity, and photostress recovery time. The study had 80 % power at the 5 % significance level for each outcome measure. Data were collected at baseline, nine, and 18 months.

Results

There were no statistically significant differences between groups for any of the outcome measures over nine or 18 months.

Conclusion

There was no evidence of effect of nine or 18 months of daily supplementation with 6 mg lutein combined with zinc and antioxidants on visual function in this group of people with healthy eyes. ISRCTN78467674.

Keywords: lutein, visual function, randomised controlled trial, antioxidants

59 **Introduction**

60 The role of lutein supplementation in the improvement in visual function for patients with age-

61 related macular degeneration (AMD) has been established via a randomised controlled trial [1]. It

62 has been suggested that lutein and its isomers, zeaxanthin and meso-zeaxanthin play a similar

63 role in humans as in plants, as antioxidants and screeners of high-energy blue light [2].

64

65 With respect to healthy eyes, the blue-light filter effect of lutein/zeaxanthin may reduce

66 longitudinal chromatic aberration [3-5]. In addition, the acuity hypothesis states that these nutrients

67 may improve visual acuity for images that are illuminated with white light by absorbing poorly

68 focussed short wavelengths before this light is processed by the retina [6, 7]. In theory, if an

69 emmetropic eye views a mid-wavelength object (approximately 550 nm) in blue-dominated

70 sunlight, shorter wavelengths will focus in front of the retina, and longer wavelengths will focus

71 behind such that there is a range of focus of approximately 1.20 dioptres [5]. The fact that images

72 are not degraded may be explained in part by the pre-retinal filtering effect of the

73 lutein/zeaxanthin. Lutein and its isomers are collectively known as macular pigment (MP) within

74 the retina.

75

76 During the design of the trial, 6 mg daily intake of lutein from food had been reported to be

77 associated with a reduced risk of AMD (57 % lower risk for the highest quintile of lutein intake, 6

78 mg per day, relative to the lowest quintile, 0.5 mg per day) [8]. The reasons for using a multi-

79 ingredient formulation include the fact that AMD has a multifactorial aetiology, and so may be

80 affected by more than one nutrient, and also that nutrients are thought to work synergistically

81 together.

82

83 Despite a lack of empirical evidence, lutein/zeaxanthin supplements are being taken by the

84 public in an attempt to improve retinal health and vision in the absence of disease [9].The aim of

85 this RCT was to determine the effect of a lutein and antioxidant dietary on measures of visual

86 function in healthy eyes.

87

88 **Materials and methods**

89 The study was approved by the Aston University Human Sciences Ethical Committee (code

90 02/M). The tenets of the Declaration of Helsinki were followed [10]. The trial was registered for an

91 International Standard Randomised Controlled Trial Number (ISRCTN 78467674), and the

92 method has been published [11]. Reporting of this RCT adheres to the guidelines set out in the

93 revised CONSORT statement [12].

94

95 *Recruitment*

96 Recruitment methods included an editorial in the regional press and advertising throughout the

97 Aston University Campus.

98

99 *Research centres*

100 The main research centre was Aston University, Birmingham. A secondary research centre was

101 a UK optometric clinical practice. Data collection took place in standard consulting rooms at

102 both centres. Investigators and participants were masked to group assignment.

103

104 *Inclusion/exclusion criteria*

105 For inclusion, participants had to 1) provide written informed consent, 2) be available to attend

106 one of the research centres, 3) present with no ocular pathology in either eye. Absence of

107 pathology was assessed through dilated pupils using slit lamp binocular indirect

108 ophthalmoscopy. Exclusion criteria relate to the inclusion of zinc and vitamin E in the study

109 formulation. The exclusion criteria included type I and II diabetes as diabetic retinopathy may

110 confound the results. Those taking anti-platelet or anti-coagulant medication were excluded

111 because of possible interaction with vitamin E, as were those who used nutritional supplements

112 that potentially raised vitamin and mineral intake above the recommended safe limits. People

113 with conditions that affect dietary absorption, such as Crohn's disease, were also excluded.

114

115 A dilated fundus examination was carried out prior to enrolment. Fundus photographs were

116 taken using Topcon non-mydriatic TRC-NW5S retinal camera (Topcon House, Bone Lane,

117 Kennet Side, Newbury, Berkshire RG14 2PX, UK) at baseline and at each subsequent visit.

118

119 *Masking*

120 The study formulation and placebo tablets were produced by Quest Vitamins Ltd, and were

121 identical in external and internal appearance, and taste. The manufacturer allocated

122 distinguishing symbols, μ and λ to the tablet containers. The trial was double-masked; and the

123 manufacturer revealed the code only when all data had been collected and analysed.

124 Throughout this manuscript, the letters P and A will be used to refer to the placebo and active

125 formulation respectively.

126

127 *Intervention*

128 The study formulation contained the following:

129 Lutein   6mg

130 Vitamin A   750μg

131 Vitamin C   250mg

132 Vitamin E   34mg

133 Zinc   10mg

134 Copper   0.5mg

135 The placebo tablets contained cellulose and were identical in appearance to the active tablets.

136

137 Participants in both groups were instructed to take one tablet, at the same time every day, with

138 food. They were encouraged not to alter their diets, or to change their current supplementation

139 regime. A contact telephone number was provided.

140

141 *Randomisation*

142 Only one investigator was involved in the randomisation process, which employed the random-

143 number generator in Microsoft Excel for Windows XP. Odd and even numbers indicated group.

144   *Outcome measures*

145   At the first visit, refractive error was neutralised with lenses for both eyes, and the eye with the

146   best logMAR (minimum angle of resolution) score for visual acuity was included in the study.

147   Only one eye of each participant was included. Refractive error was neutralised with lenses at

148   each subsequent visit and the resulting trial lenses were used for all visual function tests.

149   Distance visual acuity (DVA) was measured using Early-Treatment Diabetic Retinopathy Study

150   (EDTRS) logMAR charts and near visual acuity (NVA) was measured using Bailey-Lovie

151   reading cards.

152

153   Contrast sensitivity (CS) provides additional information about vision and was measured using a

154   Pelli-Robson chart (Clement Clarke International, Edinburgh Way, Harlow, Essex, CM20 2TT,

155   UK). The Pelli-Robson chart determines the contrast required to read large letters and is

156   designed to test mid- to low-spatial frequencies [13].

157

158   The Eger Macular Stressometer (EMS) (Gulden Ophthalmics, Elkins Park, PA 19027) was used

159   to measure photostress recovery time (PSRT). This is the time taken for the regeneration of

160   photopigments in bleached photoreceptors to a level that allows resolution of, for example, a

161   letter at near. The EMS has been found to be reliable to within ± 7 seconds [14]. The instrument is

162   hand-held and consists of a flash bulb and a near reading chart. It houses a 40.6 cm length of

163   string, which, when extended, maintains a constant working distance while the subject

164   determines the smallest letter size that can be read on the integrated VA chart monocularly. The

165   test types range from Snellen equivalents of 6/6 to 6/30, with letter size decreasing from the top

166   to the bottom of the chart. The working distance is then reduced to 15.2 cm (measured using a

167   marker on the string) and the patient is directed to look at the centre of the flash tube, situated

168   just above the test type. A third button press simultaneously activates the flash and starts the

169   timer. The device is then returned to 40.6 cm and the patient is asked to read the line of letters

170   above the smallest line read before bleaching as soon as it becomes visible. A fourth button

171   press stops the timer when the patient has recovered enough macular function to correctly

172   identify three from the five letters on the designated line. A note of this PSRT is made and a fifth

173   press of the button resets the instrument.

174   *Sample size calculation*

175   Reliability data from previous studies was used to determine effect sizes for use in sample size

176   calculations for visual acuity (± 0.1 logMAR) [15], CS (± 0.15 log units) [13], and PSRT (± 7

177   seconds) [14]. The largest group size required for 80% power at the 5% significance level was for

178   DVA (n = 13), indicating that a total minimum of 26 participants was required for the study.

179

180   *Follow up*

181   Data collection took place at baseline, nine, and 18 months. Recruitment started in December

182   2002 and ended in March 2004.

183

184   *Statistical analysis*

185   For each outcome measure the change between baseline, nine month, and 18-month values

186   was calculated. Each data set was checked for normality of distribution using SPSS software

187   (version 11) for Microsoft Windows XP. When the data set was normally distributed, a two-tailed

188   independent samples t-test was used to determine whether the means of these values differed

189   at the 5% significance level between the placebo and antioxidant formulation. When the data

190   set was not normally distributed, the non-parametric Mann-Whitney U test was used. A mixed

191   ANOVA was used to assess the effect of the between-subjects variable (group), and the within-

192   subjects variable (time), on the outcome measures (dependent variable).

193

194   *Enrolment, duration and compliance*

195   Out of the 66 people that completed enrolment questionnaires, eight did not meet the inclusion

196   criteria or decided not to enrol. The remaining 58 individuals were randomised to active or

197   placebo groups: a breakdown is shown the Consort flowchart (figure 1).

198

199   Insert figure 1 about here.

200

201 Enrolment continued until nine months before the end of the data collection period, and this

202 accounts for the difference in numbers between the nine- and 18-month cohorts. Of the 12

203 participants that were lost to follow up, one became pregnant, two moved out of the area, four

204 had difficulty taking the tablets, and five developed illnesses unrelated to the project. These

205 subjects were not included for analysis. Of the 46 participants who took part for nine months, 29

206 went on to take part for 18 months.

207

208 Statistical analysis was carried out on a per protocol basis. Compliance was assessed by

209 counting remaining tablets at the follow-up visits, and averaged 92.3 %. The difference in

210 compliance was not significant for either cohort.

211

212 *Baseline data*

213 Although it is not usually considered necessary to test for statistical differences between two

214 randomly allocated groups, since any differences will have arisen by chance alone, we

215 acknowledge that our small sample size could have resulted in some baseline differences

216 between groups. The cohort ranged in age from 22 to 73 years (mean ± SD: 50.0 ± 15.9), and

217 seventy-four percent were female. For the nine-month trial, twenty-five participants were

218 randomised to the placebo (mean ± SD age: 50.1 ± 15.1 years) and 21 (mean ± SD age: 49.8 ±

219 16.4 years) to the active group. For the 18-month trial, 15 subjects were randomised to the

220 placebo (mean ± SD age: 48.3 ± 15.8 years) and 14 to the active group (mean ± SD age: 46.7 ±

221 16.0). There was no significant difference in age or gender between groups for the nine-month

222 comparison. For the 18-month comparison, the P group contained two males and 13 females

223 and the A group contained seven males and seven females (X^2 = 4.71, p = 0.03); there was no

224 significant difference in age.

225

226 All participants were White British. There was no significant difference in eye colour or baseline

227 DVA, NVA, CS, or EMS scores between groups. A Student's t-test was used to assess

228 differences between groups in age, smoking history (pack years), and years spent living abroad.

229 Dietary intake of lutein, vitamins C and E, retinol equivalents, and zinc was assessed using food

230   frequency questionnaires and food diaries. Analysis of food diaries was carried out using

231   FoodBase 2000 (Institute of Brain Chemistry and Human Nutrition, London) for Microsoft

232   Windows XP. There was no significant difference between groups for any of these

233   characteristics. In the A group, one person was taking thyroxine and one person was taking

234   codeine. In the P group, one person was taking diazepam, one was taking thyroxine, and one

235   was taking bendrofluazide. Participants were asked to provide details of additional nutritional

236   supplementation. There was no difference in supplementation between groups (see table 1).

237

238   Insert table 1 about here.

239

240   The baseline characteristics are shown in table 2 for the nine-month group, and table 3 for the

241   18-month group.

242   Insert tables 2 and 3 about here

243

244   *Assessment of change in characteristics*

245   All participants were asked to fill out end-of-trial food diaries and food frequency questionnaires

246   in order to assess any change in dietary habits over the trial period. Eighty percent were

247   returned by the nine and 18-month P groups, 86 % by the nine month A group, and 79 % by the

248   18 month A group.

249

250   There was no change in dietary lutein, vitamin C, vitamin, E, or vitamin A for any of the groups

251   (9P, 9A, 18P, or 18A). The normal nine month P group, however, had a significant change in

252   mean zinc intake from (mean ± SD) 6.82 ± 2.15 mg to 10.26 ± 4.39 mg (t = -3.54, df = 24, p =

253   0.002). There was no significant change in dietary zinc over time for any other group. There

254   were no changes in ocular health or smoking habits, and no participants developed AMD-

255   related ocular changes.

256

257   *Adverse effects*

258   There were no reported adverse events or side effects from any of the study participants.

259 **Results**

260 *Masking success*

261 An end of trial, assessment was made of masking success by asking participants if they thought

262 they knew which tablet they were taking, and if so, which one. Out of those participants taking

263 the placebo tablet, 12 % correctly guessed which tablet they were taking, and 10 % incorrectly

264 guessed. Out of those taking the nutritional supplement, 9 % guessed correctly which tablet

265 they were taking, and 11% incorrectly guessed. The remaining participants were not prepared

266 to make a guess indicating masking success.

267

268

269 *Outcomes: between groups*

270 There was no significant difference between groups at nine or 18 months for any of the outcome

271 measures. Results are shown in tables 4 and 5, where the p value refers to the analysis of the

272 difference in the amount of change between active and placebo groups for each outcome

273 measure.

274

275 Insert tables 4 and 5 about here.

276

277 *Outcomes: within groups*

278 In order to assess the effect of time on the outcome measures over nine months, paired

279 samples t-tests were carried out for DVA, NVA, CS, and EMS score. There were significant

280 improvements over nine months in DVA (p = 0.047, eta squared = 0.15), and NVA (p = 0.007,

281 eta squared = 0.27) in the P group. Eta squared describes the effect size and the following

282 guidelines can be used for interpretation: 0.01 = small effect, 0.06 = moderate effect, 0.14 =

283 large effect. Although the eta squared values for DVA and NVA suggest a large effect these

284 changes are not clinically significant, [15].

285

286 For those participants who attended two follow-up visits, a mixed between-within subjects

287 ANOVA was carried out to determine whether there was a change in each outcome measure

288   over time (main effect for time), if there was a difference in the effect on each outcome measure

289   between the two interventions (main effect for group), and also whether there is the same

290   change in scores over time for the two groups (interaction effect). The ANOVA results are

291   shown in table 6 and the change in outcome measures over 18 months are shown graphically in

292   figures 2 to 5.

293

294   Insert table 6 and figures 2 to 5 about here.

295

296   There was a significant change in CS and EMS score over time, but there was no difference

297   between the P and A groups, and no difference in the change in these outcome measures over

298   time between the two groups. The effect size for the change over time was moderate for CS

299   (Eta squared = 0.119) and large for the EMS (Eta squared = 0.149). In the A group, the

300   changes were not clinically significant for CS (less than ± 0.15 log units) [13] or EMS (less than ±

301   7 seconds) [14]. In the P group, the change in EMS was not clinically significant but the change in

302   CS of + 0.15 log units is the limit for clinical significance. Apart from chance, the only

303   explanation for this change in CS is that the scores did in fact improve in the P group over time.

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317 **Discussion**

318 This clinical trial was designed to evaluate the effect of a nutritional supplement containing 6mg

319 lutein, 750 μg vitamin A, 250 mg vitamin C, 34 mg vitamin E, 10 mg zinc, and 0.5 mg copper on

320 clinical measures of visual function. The study demonstrated that this nutritional supplement

321 had no effect on clinical visual outcome measures over nine or 18 months in healthy eyes. The

322 same formulation was assessed in a randomised control trial of people with age-related

323 maculopathy, which was powered for CS as an outcome measure [16]. The formulation had no

324 significant effect in this group either. Other combined-nutrient formulations have been effective

325 in improving visual function for people with age-related macular disease, including those used in

326 the Age-Related Eye Disease Study (AREDS) [17] and the Lutein Antioxidant Supplementation

327 trial (LAST) [1]. A full review of randomised controlled trials investigating the effect of nutritional

328 supplementation on age-related macular disease has been published by the authors [18].

329

330 A branch of the AREDS looked at the effect of antioxidant and zinc supplementation on visual

331 loss in people with age-related cataract and found no significant effect [19]. Conversely, in another

332 randomised controlled trial, supplementation with 15 mg of lutein three times per week for two

333 years was associated with improvements in visual acuity and glare sensitivity in patients with

334 age-related cataract. However, no effect was found using 100 mg alpha-tocopherol

335 supplementation three times weekly [20].

336

337 In a healthy group of 27 subjects aged between 60 and 84 years, those with higher levels of MP

338 did not have significantly different visual sensitivity than a group of younger subjects aged

339 between 24 and 36 years, whereas subjects in the older group with lower levels of MP did differ

340 from the younger group [21]. This suggests that retinal lutein levels may effect visual function.

341

342 The specific uptake of lutein and zeaxanthin at the macula has been investigated with respect to

343 the potential functional role of these carotenoids in normal visual function. The macula is

344 specialized for high spatial resolution and also for colour vision and it has been hypothesised

345 that lutein and zeaxanthin play a part in these processes. With any optical system defects in the

346   formation of the image occur and these aberrations can be classified as chromatic or

347   monochromatic. In the human eye longitudinal chromatic aberration results from the dispersion

348   characteristics of the ocular media, and a dioptric interval of around 0.9 D between the paraxial

349   foci for 656.3 nm red light and 486.1 nm blue light has been reported [22]. Transverse chromatic

350   aberration results in long-wavelength light being deviated less than short-wavelength light,

351   which has the effect of producing a red blur around the edge of an image. When viewing white

352   light, the combined effect of transverse and longitudinal chromatic aberration would be to create

353   a purple penumbra, or shadow, to the image.

354

355   Short-wavelength light is scattered more than long-wavelength light by air molecules and larger

356   atmospheric molecules. This scattering effect results in the blue coloration of the sky, as well as

357   the blue haze seen around objects viewed in the distance. Wooten and Hammond [7] hypothesize

358   that MP may increase visibility by reducing the luminance of the background with respect to the

359   object itself. This means that the contrast of the object is increased. A person with a macular

360   pigment optical density (MPOD, the amount of lutein or its isomers at any point in the retina) of

361   0.0 would only be able to see an object at 10 km that a person with an MPOD of 0.5 would be

362   able to see at 11.9 km.

363

364   In 1866 it was proposed that MP might reduce longitudinal chromatic aberration through

365   absorption of short-wavelength light [23]. It has been since been shown that a filter covering a

366   similar spectral range to MP can reduce the radiance of the short-wavelength blur circle to a

367   sub-threshold value [24]. The hypothesis that MP reduces short-wavelength chromatic blur and

368   therefore enhances spatial vision (often termed the acuity hypothesis) [7] has been tested under

369   different illumination conditions. One condition consisted of mid-wavelength yellow light that is

370   not absorbed by MP, and the other consisted of a white light that was subject to chromatic

371   aberration because the blue portion would be absorbed by MP [25]. No relationship between MP

372   and resolution acuity or between MP and hyperacuity in either illumination condition was found.

373   However, a marginal improvement in red-green discrimination with increased MPOD has been

374   reported, supporting the theory that increasing MP levels improves human chromatic

375   discrimination sensitivity [26].

376

377   Macular pigment is also thought to improve visual performance by reducing the strength of the

378   rod signals that are subject to large spatial summation and therefore more sluggish responses

379   [27]. Absorption of blue light by MP may extend high-acuity cone-mediated vision at low light

380   levels. Supplementation with 10 or 20 mg daily lutein or zeaxanthin over six months was

381   reported to lower contrast acuity thresholds in the mesopic range in a recent conference

382   abstract [27]. Similarly, a significant downward trend in contrast acuity thresholds was found with

383   10 mg or 20 mg daily lutein and zeaxanthin supplementation in a larger cohort, although MPOD

384   was not significantly correlated with either the amount of forward light scatter in the eye, or

385   contrast acuity thresholds [28].

386

387   Conflict in the literature may be explained by the acuity hypothesis. Although the MP filters the

388   out-of-focus short wavelength light, there is an associated reduction in luminance that may

389   effect acuity [29]. In other words, any improvement in visual acuity may be countered by

390   luminance reduction.

391

392   Studies investigating retinal response (as opposed to serum response) to lutein

393   supplementation have found a range of responses, including no retinal response in three out of

394   11 people over 14 weeks [30], and no retinal response overall in a cohort of 12 young and 17

395   elderly subjects following 5 weeks of supplementation [31]. .Increases in MPOD of 15 – 23 %

396   have been found in some studies [32-34], while increases of around 40 % have been reported in

397   others [1, 35-37].

398

399   A putative lutein-binding protein which binds with high affinity and specificity to lutein and other

400   xanthophylls has been discovered in the retinae of human eyes [38], It has been suggested that

401   people who are less responsive to lutein supplementation may be so because of genetic

402   differences that result in reduced or less efficient binding proteins [39]. It is possible that this factor

403 may have had an effect on our results but we believe it is unlikely that all participants would

404 have been non-responders.

405

406 The fact that MPOD was not measured in this study means that we do not know how

407 responsive the participants were to the lutein supplementation. It would also have been

408 interesting to track MP levels over the nine and eighteen month intervention periods.

409 Unfortunately we did not have access to an MPOD measurement device at the start of the trial.

410

411 Studies have been carried out to investigate differences in bioavailability between pure and

412 esterified lutein. One study reported no significant difference in serum lutein response between

413 6 mg lutein from spinach, 6 mg pure lutein, and 10.23 mg lutein esters [40]. In another study,

414 serum response was greater from lutein esters than pure lutein [41]. Although these studies

415 suggest that the use of lutein esters in our formulation should not have hindered bioavailability,

416 it is important to note that they recorded serum response rather than retinal response. Although

417 the retinal response is related to serum response, and dietary modification affects both, there is

418 some variability in retinal response between subjects [30, 32, 42].

419

420 The use of a mixed antioxidant and mineral formulation does not permit assessment of the

421 effect of specific nutrients on visual function. The rationale for using a mixed formulation is that

422 nutrients are thought to work synergistically together. A relevant example of this synergism is

423 the facilitation of vitamin A transport from the liver by zinc [43]. Although serum concentrations of

424 lutein, zeaxanthin and antioxidants have been found to be responsive to dietary modifications [30,

425 36], they were not measured during this trial. Non-invasive compliance assessment was

426 undertaken as blood analysis was considered likely to hinder recruitment.

427

428 At baseline the nine-month P group consumed significantly more dietary vitamin C than the A

429 group. End of trial dietary analysis was carried out on at least 75 % of the participants in each

430 group. There was no change with time in dietary lutein, vitamins C and E, and retinol

431 equivalents in any of the groups. A mean increase in dietary zinc intake was shown in the nine

432 month P group. These differences could confound the results, although this would be of greater

433 concern if a significant difference in improvement of any of the outcome measures had been

434 found between the P and A groups in the nine-month cohort.

435

436 The results of this study add to the debate within the literature. Nutritional supplementation that

437 includes 10 mg lutein daily has been associated with improved visual function in people with

438 AMD [1] and supplementation with 15 mg of lutein three times per week for two years was

439 associated with improvements in visual acuity and glare sensitivity in patients with age-related

440 cataract [20]. A significant trend for improvement in CS was found with 10 mg or 20 mg daily lutein

441 and zeaxanthin supplementation in people with healthy eyes [28]. The results of this study

442 suggest that daily supplementation with 6 mg lutein combined with zinc and antioxidants is not

443 sufficient to effect a change in visual function. The results of other studies suggest that daily

444 supplementation with at least 10 mg of lutein may result an improvement in visual function in

445 people with age-related macular disease, age-related cataract, or healthy eyes. Lutein dosage

446 may be an important factor in the effectiveness of ocular nutritional supplements.

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619 **Figure legends**

620 Figure 1: CONSORT flow diagram

621 Figure 2: Mean distance visual acuity (DVA) recorded for the 18 month cohort at baseline, nine,

622 and eighteen months. Error bars represent standard deviation.

623 Figure 3: Mean near visual acuity (NVA) recorded for the 18 month cohort at baseline, nine, and

624 eighteen months. Error bars represent standard deviation.

625 Figure 4: Mean contrast sensitivity (CS) recorded for the 18 month cohort at baseline, nine, and

626 eighteen months. Error bars represent standard deviation.

627 Figure 5: Mean Eger macular stressometer (EMS) score recorded for the 18 month cohort at

628 baseline, nine, and eighteen months. Error bars represent standard deviation.

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